Concepts and Controversies in Haemostasis and Thrombosis Associated with Liver Disease: Proceedings of the 7th International Coagulation in Liver Disease Conference

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Introduction

Patients with acute and chronic liver disease frequently acquire unique changes in haemodynamic and haemostatic pathways that may result in life-threatening bleeding and thrombosis. Additionally, activation of haemostatic pathways may play a role in disease progression through parenchymal extinction, organ atrophy, recruitment of inflammatory cells and activation of stellate cells. In the setting of a previously entrenched set of clinical perceptions, the slowly evolving evidence-based paradigms of haemostasis in cirrhosis are now more carefully scrutinized.

The 7th International Conference on Coagulation in Liver Disease (held biennially since 2005) met in October of 2017 in Rome, Italy, to discuss and debate important topics in this field. This document provides a statement-based thematic summary of the meeting presented here amid a framework of the most current evidence. The review of the literature, preparation of the document and presentation of each summary statement below are based on systematic approaches used in published guidance documents.[1]

In particular, recognition of the potential disconnect between existing evidence and actual practice, we utilized a questionnaire and real-time poll of the conference attendees to compare actual clinical practice to the evidence-based support for each statement. The final section summarizes the results of the most salient results of the poll.

Laboratory Testing of the Coagulation System in Patients with Cirrhosis

1. *Traditional coagulation measures, including pro-thrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR) and bleeding time (BT) do not measure bleeding risk in cirrhosis.*

Conventional in vitro tests of the coagulation system are of limited value in estimating haemostatic competency in cirrhosis and current literature emphasizes these limitations when compared with global assays of coagulation.[2–5] PT/INR, aPTT and BT are generally prolonged in patients with cirrhosis in direct relationship to the degree of hepatic decompensation. While useful for predicting prognosis in chronic liver disease, these tests do not predict bleeding or thrombosis in patients with chronic liver disease.

For the PT/INR and aPTT, a trigger reagent (tissue factor for extrinsic pathway or kaolin for the intrinsic pathway),

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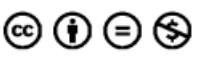

phospholipids and calcium are added to patient plasma in a test tube and the time to the formation of fibrin is recorded. The PT/INR test performs poorly in assessing coagulation capacity in patients with liver disease[6] and suffers from high inter-laboratory variability.[7,8] The PT/INR measures only pro-thrombotic pathways without measuring counter-balancing anticoagulation (AC) pathways including protein C. Numerous studies and clinical experience now clearly demonstrate that these tests do not measure in vivo activity of the coagulation system in cirrhosis.[9–13]

2. *Platelet count alone provides an incomplete guide to bleeding risk in cirrhosis. However, values below 50,000/μL may be associated with higher risk of bleeding.*

Thrombocytopenia is common in patients with advanced cirrhosis and indirectly correlates with the degree of portal hypertension and hepatic decompensation.[14] In vitro evidence indicates that platelet-dependent thrombin generation is preserved in patients with cirrhosis with platelet levels 56,000/μL or greater.[15] Notably, however, other important aspects of platelet function are not assessed by thrombin generation assay (TGA). Severe thrombocytopenia is associated with procedural-related bleeding events in some, but not all studies.[16,17] While there is no evidence that prophylactic platelet transfusion improves haemostatic potential,[18] current guidelines and expert opinion recommend consideration of platelet transfusion prior to high-risk procedures or when active bleeding is encountered in patients with platelet counts below 50,000/μL.[4,19] A notable exception is liver transplant surgery, in which platelet counts below 50,000/μl are accepted by many centres.

3. *Global viscoelastic tests (VETs) provide a more physiologic assessment of coagulation, VETs are not standardized in patients with liver disease and do not appear to predict bleeding or thrombosis. Application of VETs in patients with liver disease remains controversial.*

VETs measure clot strength and integrity in whole blood under low shear conditions, attempting to more closely recreate the environment in vivo during clot formation.[20] VETs are considered point-of-care tests and provide the clinician with information regarding the kinetics of clot formation and strength of the clot with the ability to distinguish contributions from fibrinogen, platelets and the fibrinolytic system. VETs are most extensively studied in patients with cirrhosis undergoing liver transplantation.[20–39]

More recently VETs have been employed to examine the haemostatic system in a wide variety of patients with liver disease, including well-compensated patients,[40–42] patients with acute liver failure[43] and in acutely ill patients with liver disease.[44–46] A recent randomized control trial compared transfusion-directed prophylactic therapy in patients with cirrhosis undergoing procedures using VETs as a guide *versus* standard coagulation tests.[47] While significantly less blood product was used in the group undergoing VETs screening, the low rate of bleeding events, lack of control arm and inclusion of relatively low risk procedures significantly limits conclusions from these data.[48] Specific nuances of VETs such as test performance without stimulators ('native' VETs) and optimal duration of test remain uncertain in cirrhosis.

4. *TGA provides a more comprehensive assessment of the haemostatic system in cirrhosis. However, the clinical utility of TGA in patients with cirrhosis is unexplored with current use confined mainly to research.*

TGA is a valuable research tool that has led to important insights in liver disease and coagulation.[9–13,15,18,49–54] It measures the rate of production and decay of thrombin after introduction of a triggering agent (tissue factor and phospholipid).[55–58] With the addition of thrombomodulin (required for thrombin-mediated activation of protein C), the integrity of the protein C anticoagulant system is measured. Tripodi et al demonstrated that thrombin generation is preserved in cirrhosis despite prolonged conventional coagulation assays due to decreased protein C.[10,13] Automation and standardization of TGA is incomplete and clinical use is not currently available. Efforts at standardization and development of a point-of-care whole blood thrombin generation test are in progress with the hope for future clinical utility.[52,59,60]

5. *Available laboratory tests of hyperfibrinolysis are of limited value in cirrhosis and clinical diagnosis is often necessary (see also anti-fibrinolytic therapy below).*

Identifying the presence of hyperfibrinolysis in cirrhosis is challenging with limited clinically available and laboratory testing.[61–65] Reliance on clinical assessment and empiric therapy are currently recommend (see the "Pre-Procedure Prophylaxis and Treatment of Non-Portal Hypertension-Related Bleeding in Patients with Cirrhosis" section).

The fibrinolytic system regulates clot remodelling and breakdown and is likely rebalanced in cirrhosis. With exogenous disruption (e.g. infection), hyperfibrinolysis, a state of abnormal fibrin degradation mediated by plasmin, can lead to delayed bleeding and has been a recognized clinical feature of cirrhosis for over a century.[66–74] Joist, who coined the term 'AICF' or 'accelerated intravascular coagulation and fibrinolysis', recognized the entity of bleeding in cirrhosis similar to, but distinct, from disseminated intravascular coagulation (DIC).[75] This condition was seen in a clinical series where laboratory evidence of hyperfibrinolysis was detectable in a third of hospitalized cirrhosis patients, but clinically evident in only 6% of patients.[76] However, the divergent results of two key studies which examined the mechanistic role of liver synthesized thrombin activatable fibrinolysis inhibitor has resulted in ongoing controversy regarding the clinical significance of AICF.[61,62] These studies have failed to resolve the long known and clinically evident occurrence of diffuse mucosal bleeding or delayed post-procedure bleeding and efficacy of anti-fibrinolytic therapy.[71,77] On the other hand, further laboratory-based studies have shown increased fibrinolytic capacity in cirrhosis patients[64] suggesting a precariously balanced system more prone to clot lysis. Both endotoxemia[78] and ascites fluid egress into the systemic circulation[79] have been postulated as mechanisms of increased clot lysis.

Pre-Procedure Prophylaxis and Treatment of Non-Portal Hypertension-Related Bleeding in Patients with Cirrhosis

Procedure-related bleeding is common in cirrhosis patients, but estimates of incidence vary widely.[16] For many years, the PT/INR served as a surrogate marker for estimating bleeding risk in cirrhosis. However, use of the INR and arbitrary 'cut-offs' as a clinical target is not recommended or supported by scientific evidence. Nonetheless, medical-legal concerns have dominated this field over scientific considerations for many years. This situation is exacerbated by the limited connection between the detached clinician performing the procedure and the ordering provider. This issue likely contributed to early termination of the well-conceived S.H.I.P. trial (Study of Hemostasis and Invasive Procedures NCT00233246) which did not enroll any patients. However, the field has substantially evolved since 2005.[80] This now allows for more refined recommendations based on recent data.

Assessment of individual patient characteristics is also essential as clinical factors, such as acute kidney injury[81] or infection[82] may alter bleeding risk in certain clinical scenarios. Global tests, such as VETs, have offered particular insight into potential pathophysiologic mechanism in patients with cirrhosis and active bacterial infection where release of endogenous heparinoids may contribute to an anticoagulant effect placing patients at higher risk to bleed.[83,84] Large clinical studies examining bleeding outcomes are needed to provide clinicians with better data to assess risk.

6. *Pre-procedure testing of plasma fibrinogen and platelet level is recommended for high-risk procedures (see ►**Table 1**) and pre-procedure correction is recommended for high risk procedures. Clinicians performing the procedure should define the level of risk.*

Single test assessments and even multi-parameter measures are unlikely to capture the nuances of a complicated physiology. Nonetheless, there are data suggesting that platelet level and the level of fibrinogen correlates to effective haemostasis, although it has not been established whether correction of low levels actually reduces bleeding risk.[85] Evidence is very limited regarding any measure as a guide to prophylactic measures and is mainly inferred from bleeding risk associative studies. Again, many centres do not correct low fibrinogen or platelets prior to liver transplantation, and a clinical trial has failed to demonstrate a beneficial effect of pre-emptive fibrinogen supplementation.[60] Despite the limitations and lack of firm data, with our current knowledge in the field, these parameters are currently considered to be useful in predicting bleeding in cirrhosis patients.

7. *Routine prophylaxis for low or moderate risk procedures (see ►**Table 1**) is generally not recommended. However, individualized approaches are often necessary.*

The most consistent finding with whole blood VETs (such as thromboelastography or rotational thromboelastometry) has been the demonstration of intact haemostatic mechanisms in cirrhosis with evidence that haemostatic support with blood products is not required despite abnormal PT or platelet count.[86,87] Unfortunately, the majority of studies in this field have lacked a placebo control arm which limits our understanding of the overall baseline risk in patients without prophylaxis. To this end, we conducted a poll to assess actual current practice in potential contradistinction to rational-based therapy—see below. The most important point to remember is that prophylactic measures PT/INR can paradoxically increase bleeding risk by engorging the collateral bed without any haemostatic benefit. Greater recognition of the baseline bleeding risk *and* the limitations of prediction, by both clinicians that perform procedures and other clinicians, will improve patient outcomes.

Specific Therapeutic Agents

8. *Platelet transfusion prior to high-risk procedures or with active bleeding has a rational in vitro basis, but lacks high level supportive data. Within the same limitations, thrombopoetin agonists may have a role in pre-planned procedural prophylaxis.*

Table 1 Examples of procedure risk[a]

Higher risk procedures	Intermediate risk procedures	Lower risk procedures
Brain or spinal surgery	Lumbar puncture	Paracentesis
All major surgery (cardiac, intra-abdominal and orthopaedic)	Percutaneous or transjugular liver biopsy	Thoracentesis
Intra-cranial pressure catheter insertion	Transjugular intrahepatic portosystemic shunt	Dental extraction
Endoscopy (large polypectomy with endoscopic mucosal or sub-mucosal resection, NOTES)	Endoscopy (e.g. percutaneous gastrostomy placement, cystgastrostomy, biliary sphincterotomy)	Endoscopy (e.g. diagnostic, variceal band ligation, uncomplicated polypectomy)
	Percutaneous biopsy of extra-hepatic organ or lesions	Cardiac catheterization
	Trans-arterial or percutaneous HCC therapies	Central line placement

Abbreviations: HCC, hepatocellular cancer; NOTES, natural orifice transluminal endoscopy.
[a]Risk is estimated here based on relative vascularity, degree of expected vascular breech and potential clinical consequences, but risk should always be defined by clinician preforming the procedure.

Conflicting data exists regarding bleeding risk and cirrhosis-related thrombocytopenia. The divergence in the literature likely reflects the complexity of haemostasis in cirrhosis and marked study design variation. Among patients undergoing liver transplant evaluation, procedure-related bleeding in one study was closely correlated to platelet levels < 75,000/μL.[16] Similarly, bleeding risk was higher in a retrospective study of cirrhosis patients undergoing dental extractions when platelets were < 40,000/μL.[88] Platelet levels < 30,000/μL were also an independent predictor of major bleeding among critically ill cirrhosis patients in the intensive care unit setting.[89] On the other hand, post-procedure bleeding in cirrhosis was not predicted by baseline platelet levels in another prospective study[90] and the platelet-related risk of post-banding ulcer bleeding has been variably reported.[91,92] Compensatory mechanisms which may alter overall platelet performance, such as elevated von Willebrand factor (VWF),[93] increased circulating activated platelets[94] and platelet-derived microvesicles,[95] may also be significant factors which balance the bleeding risk related to thrombocytopenia. Additional factors may also contribute to platelet physiology.[96–98] Limited yield of platelet infusion in cirrhosis is well known and raises the question of whether platelet transfusion prior to high-risk procedures is more 'cosmetic' to cover procedure-related liability or an actual effective strategy—this is an understandable conundrum that remains unresolved. More definitive studies require placebo-controlled trials which present clinical investigators with almost insurmountable ethical hurdles at the current state of the art.

In elective and planned settings, such as planned dental extractions or other invasive procedures with moderate or high risk, oral thrombopoetin agonists are an alternative means to increase platelets prior to invasive procedures. Concern for a transient hypercoagulable state due to thrombocytosis with eltrombopag, with early reports of increased risk of portal vein thrombosis (PVT), have tempered enthusiasm for these agents.[99–101] However, new agents are in development, such as avatrombopag and lusutrombopag, which appear to predictably raise platelets to a range associated with improved thrombin production without apparent increased thrombosis risk.[102,103]

9. *The use of desmopressin in patients with cirrhosis lacks a sound physiological basis and does not appear to significantly alter risk of bleeding.*

Desmopressin (1-deamino-8-arginine vasopressin or DDAVP) has been shown to be as effective as human blood products in cirrhosis patients undergoing dental extractions.[104] Notably, bleeding was very infrequent in both groups raising the question of actual efficacy and no control arm without prophylaxis was studied. Other studies show no benefit in variceal bleeding, liver biopsy in dialysis patients with chronic hepatitis C and with partial hepatectomy.[105–107] A recent report further demonstrated lack of significant pro-haemostatic effects in cirrhosis patients receiving a conventional dose of intravenous DDAVP compared with a control group of patients with haemophilia A.[108] These concerns raise the question again of the need for placebo controls to more definitively define the utility of various prophylactic strategies.

10. *Fibrinogen replacement, pro-thrombin complex concentrates (PCC), and recombinant factor VIIa (rVIIa) may have a role in treatment of significant bleeding in patients with cirrhosis in specific clinical scenarios, but the utility of these agents is undefined.*

Fibrinogen replacement: The clearest data regarding fibrinogen replacement in clinical bleeding is associated with non-cirrhosis conditions of severe trauma where fibrinogen levels > 200 mg/dL are associated with more effective haemostasis.[109] Although based on very limited data, levels below 120 mg/dL in active bleeding patients with cirrhosis have historically required correction. However, much remains to be learned about fibrinogen replacement in cirrhosis.[110] Replacement has conventionally involved cryoprecipitate, a plasma-derived product rich in VWF, fibrinogen and fibronectin, made by freezing and slow thawing human plasma and reconstituting the precipitate in 10 to 20 mL plasma. In contrast, fibrinogen concentrates are derived from a similar cryoprecipitation process of pooled plasma which then undergo isolation, viral exclusion and lyophilization.[111] The very low volume, standardization of fibrinogen content and lack of need for cross matching favour its use in cirrhosis. Recent in vitro data also suggests a clear improvement in haemostasis in cirrhosis.[112] However, further clinical studies are needed to justify the expense which currently limits wider application.

PCC: PCC have been studied in cirrhosis sporadically for over 40 years.[113,114] However, recommended dosing is linked to AC therapy as the dose is based on factor IX content of the agent, INR (while on vitamin K antagonist [VKA]) and body weight. Data are emerging that lower doses may be effective in cirrhosis, but needs further study.[112] A typical dose is 25 to 30 units of factor IX per kilogram of body weight. The low volume needed for VKA-treated patients is attractive to avoid volume overload and collateral bed engorgement in cirrhosis, however concerns over increasing the risk of thrombosis remain.

rFVIIa: rFVIIa has mainly been studied in cirrhosis and variceal bleeding. No definitive survival benefit was evident in patients treated with rFVIIa as an adjunct in variceal bleeding.[115,116] However, the use of this agent as a rescue agent in uncontrolled haemorrhage in cirrhosis remains unsettled by randomized trials.[117]

11. *In delayed and diffuse mucosal bleeding in decompensated cirrhosis (hyperfibrinolysis physiology), consider use of anti-fibrinolytic therapy.*

Optimal treatment of patients with suspected hyperfibrinolysis lacks well-controlled prospective trials to delineate risks and points of effective intervention. There are two available anti-fibrinolytics that block the lysine binding site on plasminogen preventing its attachment to fibrin and subsequent activation: trans-p-aminomethyl-cyclohexane carboxylic acid or tranexamic acid and epsilon-aminocaproic acid (EACA).[118,119] Both agents can be given orally or intravenously. Neither are felt to be significantly pro-thrombotic

based on studies in cardiac surgery of EACA versus placebo.[120] Several points of caution include the possibility of thrombotic issues if there is superimposed DIC, possible increased risk of central line related thrombosis[121] and the high concentration of the agent excreted in urine. A third agent, aprotinin, is a serine protease inhibitor that binds to plasmin to block its activity and also blocks thrombin-induced platelet aggregation. The agent decreased the need for blood transfusion in liver transplantation,[122] but remained controversial in that application[123] and was associated with increased mortality in cardiac surgery ultimately leading to marked restrictions in its clinical availability.[124]

Diagnosis and Screening for Non-Tumoural Portal Vein Thrombosis in Patients with Cirrhosis

12. *Patients with advanced cirrhosis and low portal blood flow (< 15 cm/s) are at the highest risk to develop portal or splanchnic vein thrombosis.*

The risk for PVT in cirrhosis parallels the severity of liver disease and hepatic decompensation. The prevalence of PVT is approximately 1% in compensated cirrhosis patients as opposed to 8 to 25% in decompensated, liver transplant candidates,[125,126] and up to 40% in patients with hepatocellular carcinoma (HCC).[124] Of the three pathophysiologic factors predisposing to thromboembolism—slow blood flow, endothelial damage and hypercoagulability, portal flow is the most influential.[128,129] Portal vein (PV) blood flow is inversely related to severity of liver disease as measured by the Child-Turcotte-Pugh (CTP) score,[130] and rates < 10 cm/s are associated with increased mortality.[131] Patients with underlying thrombophilia are likely at increased risk for PVT, but inherited deficiencies in natural anticoagulants can be difficult to detect in decompensated cirrhosis.[132] Emerging data suggest that cirrhosis aetiology may also have predictive power in determining which patients will develop future PVT. In particular, non-alcoholic steatohepatitis may be an independent risk factor for clinically significant thrombotic events, including PVT, in patients with decompensated cirrhosis.[133–135] The presence of a spontaneous portosystemic shunt is an under-appreciated risk for PVT as a result of a 'steal' syndrome and resulting PV stasis.[136]

13. *Patients with cirrhosis and portal hypertension should be screened for development of PVT every 6 months with Doppler ultrasound (US).*

In 2015, a systematic review concluded that PVT was associated with poorer survival in patients with cirrhosis.[137] Although hampered by heterogeneity, a recent meta-analysis similarly showed that PVT was associated with more frequent portal hypertension decompensation and higher mortality rates.[138] Furthermore, several studies indicate that PVT is associated with poorer outcomes related to variceal bleeding.[139–141] However, a large, multi-centre trial of over 1,200 subjects utilizing screening US in CTP class A and B cirrhosis demonstrated that PVT was not an independent predictor of mortality or hepatic decompensation.[142] Larger prospective studies are needed to better delineate the effect of PVT on patients with cirrhosis. As patients with cirrhosis should undergo screening US for HCC every 6 months, assessment of the PV can be performed simultaneously with Doppler US without significant additional cost and is recommended.

14. *Patients with cirrhosis listed for liver transplantation should be screened at least every 6 months with Doppler US for PVT.*

In general, the pre-operative presence of higher grade PVT leads to worse outcomes after liver transplantation.[126,135,143–147] However, some studies suggest that the presence of PVT may not necessarily alter the outcome for patient survival.[148,149] These studies are challenging to compare due to the frequency of PVT in this population, selection bias and multiple confounding factors. The ability of a surgeon to establish a physiologic anastomosis for portal flow to the graft is the most important factor in predicting outcome and often related to the degree of thrombus burden.[126,150,151]

Detection of PVT prior to liver transplantation aids in surgical planning and allows for potential pre-operative therapy to re-canalize the PV. Detection of higher grade PVT may identify patients that are not appropriate candidates for transplantation. Re-canalization of the main PV is a high priority in transplant eligible patients.[143,151] As treatment for PVT has a proportionally higher rate success early after diagnosis, timely recognition and prompt treatment is highly desirable (discussed below).

15. *Patients with cirrhosis diagnosed with PVT by abdominal Doppler US should be assessed with cross-sectional imaging to confirm and stage the extent of thrombus.*

While Doppler US is generally the initial screening modality to assess cirrhosis patients for PVT, it is limited by variation in sensitivity and specificity due in part to operator technique and experience.[152,153] Despite this imprecision, Doppler US has a high negative predictive value (98%).[154] Contrast-enhanced computed tomography and magnetic resonance imaging have comparable sensitivity in verifying the presence of PVT seen on Doppler US, and both are equally effective in characterizing the extent of splanchnic involvement, evaluating for underlying malignancy and other sequelae.[154–156] There are several systems of grading PVT severity, yet none are widely adopted in clinical practice.[150,157,158] To date, the Yerdel system remains the most frequently utilized PVT classification system in clinical research.[150]

16. *Testing for acquired and inherited thrombophilia in cirrhosis can be considered in patients with PVT on an individual basis, but universal screening is not currently recommended.*

Inherited thrombophilia is reported in as many as 5.6% of patients with cirrhosis and PVT.[132] Several study cohorts have demonstrated more frequent occurrence of the prothrombin G20210A gene mutation in cirrhosis patients with PVT.[159,160] Additional hypercoagulable risk factors may occur in patients with cirrhosis. The JAK2 V617F mutation is found in increased prevalence in patients with cirrhosis and PVT.[161] When a myeloproliferative neoplasm is suspected, consultation with a haematologist is recommended for further testing. Inherited protein C, protein S or antithrombin deficiencies may also predispose to PVT; however,

these are difficult to detect due to co-existent liver synthetic dysfunction.[5,11,162]

Treatment of Portal Vein Thrombosis in Patients with Cirrhosis

17. *Prior to AC, patients should be assessed for portal or systemic bleeding risk.*

Assessment of bleeding risk and benefit of therapy is imperative when considering AC, but not yet well-defined in this population. Contraindications to AC include recent unexplained gastrointestinal (GI) bleeding, active alcohol abuse and poor functional status due to fall risk. Severe thrombocytopenia ($< 50 \times 10^9$/L) may be predictive of bleeding events in cirrhosis patients treated with AC for PVT and thus special consideration should be given to this particular group.[163] Prior to AC, patients should ideally undergo upper endoscopy to assess for the presence of gastroesophageal varices.[164] If high-risk stigmata are found, endoscopic or pharmacologic therapy with non-selective β blockade should be utilized as per guideline recommendations.[165,166]

18. *AC appears to be a safe and effective treatment strategy in selected patients with compensated cirrhosis and splanchnic vein thrombosis.*

Safety: AC in patients with cirrhosis and splanchnic vein thrombosis is an area of increasing interest in research.[165–167] Several series examining AC in PVT are currently published, the majority of which have been retrospective evaluating low molecular weight heparin (LMWH), VKA and direct-acting oral anti-coagulants (DOACs).[126,163,168–179] Bleeding rates among treated and non-treated patients are similar in these highly selected patient populations.[180,181] Rates of major bleeding range from 5 to 20% and minor bleeding rates range from 1 to 13%, but definitions of bleeding are not uniform. A recent meta-analysis examined AC for patients with cirrhosis and PVT and demonstrated a pooled bleeding rate of all bleeding events (both major and minor) of 3.3% for LMWH or VKA.[182] Remarkably, the administration of AC did not affect outcomes of upper GI bleeding events in patients with cirrhosis.[183] While overall bleeding rates appear acceptable, it is important to note the high rate of variability, the disparate outcome definitions and lack of prospective randomized studies. Caution must be maintained when considering patients with cirrhosis for treatment with AC, particularly in patients with more advanced cirrhosis (CTP B and C). Multi-disciplinary approaches on a case-by-case basis are needed.

Efficacy: Comparing studies examining the efficacy or safety of AC is challenging secondary to the heterogeneity of study design, patient population and variety of types of AC used. In general, response rates are variable and range from 42 to 82% in terms of either a partial or a complete re-canalization of the splanchnic veins.[126,163,168–170,172–174,176] Factors associated with successful therapy (re-canalization of the PV) include recent time of onset, early initiation of AC (< 6 months) and the degree of thrombus burden (partial vs. complete).[163,184,185] Recurrence after discontinuing therapy for PVT following clot resolution ranges from 27 to 38%.[163,174]

19. *VKAs, LMWH or direct oral anticoagulants can be considered for therapy in patients with compensated cirrhosis (CTP class A and B).*

Patients with cirrhosis are no longer considered auto-anticoagulated and evidence clearly indicates risk of splanchnic and non-splanchnic thrombosis in this population. As patients with known liver disease have been excluded from clinical trials of these agents, current treatment paradigms are based on data and experience in smaller studies in cirrhosis populations.

Vitamin K antagonists: VKAs have been a cornerstone to AC therapy over many years. VKAs act through inhibition of vitamin K epoxide reductase which inhibits post-translational modification required for the function of factors II, VII, IX, X, protein C and protein S. Patients with liver dysfunction represent a particular challenge when using VKA as the INR is often elevated secondary to hepatic dysfunction. Therefore, determining the appropriate therapeutic target is problematic. Moreover, use of VKA in patients listed for transplant artificially inflates the MELD score and adversely affects organ allocation. Reversal agents for VKA include administration of vitamin K, FFP and PCC. Major advantages to VKA include familiarity through extensive clinical use over many years, low cost and oral formulation. Disadvantages include unclear therapeutic goal in liver disease patients, the requirement of routine monitoring with uncertain target levels and an apparent increase in bleeding risk.[186]

Low molecular weight heparin: LMWH is a short chain polysaccharide heparin which acts through anti-thrombin to inhibit factor Xa and thus the production of thrombin. LMWH is the most widely studied AC in patients with cirrhosis and appears safe and effective for treatment of PVT. However, studies in cirrhosis are generally small and retrospective with variation in dose and inclusion/exclusion characteristics. Expense and subcutaneous injections remain a significant disadvantage to long-term use. Monitoring therapy of LMWH to determine dosing efficacy is also controversial. Anti-Xa assays are routinely used for hospitalized patients on heparin-based AC; however, these assays can be misleading in liver disease.[181,187,188] TGA may offer a more reliable tool in cirrhosis to determine efficacy; however, these are not widely available.[50] In vitro studies using TGA suggest that the anti-coagulant effect of LMWH may be altered in patients with cirrhosis.[50,189] While no proven method for complete neutralization of the anticoagulant effect of LMWH is known, partial reversal of LMWH can be accomplished with protamine sulfate administration in severe hemorrhage.[190]

Direct oral anticoagulants: DOACs act to directly inhibit coagulation factors, factor IIa (dabigatran) and factor Xa (apixaban, edoxaban, rivaroxaban). DOACs are now routinely used in patients without liver function impairment with favourable safety and efficacy profiles. However, DOACs remain largely investigational in patients with cirrhosis with experience limited to in vitro studies and small case series.[177,189,191–194] The largest series comparing DOAC to traditional AC shows similar bleeding risks.[195] In vitro data suggest that DOAC may have variable effects in patients with cirrhosis depending on the degree of hepatic decompensation present.[188,189,192]

Notably, cirrhosis patients have been consistently excluded from DOAC clinical trials and data on pharmacodynamics is limited to in vitro studies with caution in CTP B and C cirrhosis advised. Currently, in the United States only dabigatran has an available direct reversal agent (idarucizumab).[196,197] A recent report demonstrated successful reversal of dabigatran prior to liver transplantation without major bleeding or new thrombosis highlighting the practical use of this newly available reversal agent.[198] Clinical trials investigating andexanet α and ciraparantag as reversal agents of factor Xa inhibitors are awaiting potential approval.[196,199] PCC may be considered for emergent reversal in the setting of DOAC therapy; however, the approach retains the possibility of inducing hypercoagulability compared with direct reversal agents.[200,201] Use of DOAC in patients with cirrhosis should be restricted to well-compensated patients (CTP A or B) with platelet count $>$ 50,000, and consultation with haematology is advised.

20. *Liver transplant candidates with PVT should be considered for AC therapy. Non-transplant candidates may also benefit.*

The indication for treatment of acute and chronic PVT in patients with cirrhosis remains controversial. The vast majority of literature focuses on the natural history, outcome and therapy of PVT in the context of liver transplantation.[143,202] Studies outside of liver transplantation are limited and the risks and benefits of AC therapy are more difficult to estimate.

Transplant population: Significant PVT (Yerdel Grade 2 and higher) is associated with higher morbidity and mortality in patients undergoing liver transplantation.[126,135,144–146,150,203] Maintaining physiologic blood flow through the PV preferably via end-to-end anastomosis is imperative.[151] The ability to achieve physiologic inflow to the graft is generally dependent on the extent of the PVT prior to surgery. Patients with low grade PVT (Yerdel Grade 1) and non-occlusive branch PVT have similar outcomes to patients without PVT. With more advanced thrombus (Yerdel Grade 2 or higher) promoting re-canalization of the main PVT or superior mesenteric vein (SMV) thrombosis prior to transplantation is desirable. Liver transplant candidates with occlusive main PVT with or without proximal extension into the SMV should be prioritized for treatment with AC.

Non-transplant population: While prevention of PVT with AC may delay hepatic decompensation,[204] a recent study suggests PVT is not related to liver disease progression.[142] Patients with acute PVT can develop significant portal hypertension complications and progression of thrombosis may be a risk for intestinal ischemia or eventual cavernous transformation. Prospective trials are currently lacking; however, certain patients may benefit from AC therapy for acute PVT, particularly those with Yerdel Grade 2 PVT or higher where AC therapy should be considered on an individual basis after careful deliberation and multi-disciplinary review.

21. *Trans-jugular intrahepatic portosystemic shunt (TIPS) is a potentially effective treatment of acute and chronic PVT in patients with cirrhosis requiring treatment for significant portal hypertension.*

Historically, the presence of PVT in patients with cirrhosis was a contraindication for TIPS. However, more recent experience suggests that TIPS is safe and effective for the treatment of PVT when performed in the presence of significant portal hypertension or symptomatic complete occlusion of the main PV.[205–207] Rates of re-canalization are similar to reports from AC trials and range from 60 to 92% depending on the vascular access technique.[208–210] Recent reports suggest that TIPS alone may be adequate for re-canalization and no immediate chronic AC is required to maintain stent patency.[209–211] Patients with chronic PVT considered potential transplant candidates may also benefit from TIPS as reports are now emerging of the successful use of TIPS in this population to re-vascularize the portal venous system as a bridge to liver transplantation.[209,210,212]

Venous Thromboembolic Disease in Patients with Cirrhosis

22. *Hospitalized medical patients with cirrhosis are at increased risk for VTE.*

Acutely ill medical patients are at risk of developing venous thromboembolism (VTE) with an estimated rate of 4 to 15%.[213] However, large cohort studies examining the incidence of VTE and prophylactic/treatment trials with AC have generally excluded patients with cirrhosis. Recent studies indicate that patients with cirrhosis are at risk to develop VTE.[214–222] Hospitalized patients with cirrhosis are likely at an increased risk to develop VTE and studies indicate that thromboprophylaxis is under-utilized in this group.[223–225]

The Padua Prediction Score (PPS) was developed as a risk assessment model to predict the likelihood of developing VTE in hospitalized medical patients.[226] Current guidelines for prevention of VTE in non-surgical patients rely on the use of the PPS to distinguish between low risk of VTE (score $<$ 4) and high risk of VTE (score $>$ 4).[227] The PPS has been studied in a small retrospective cohort in patients with cirrhosis and was shown to be predictive of development of VTE.[223] The IMPROVE risk assessment model was developed in a large cohort of patients, which included patients with liver disease and can accurately risk stratify patients in terms of thrombosis and bleeding risk.[228]

23. *In high-risk hospitalized cirrhosis patients without contraindication, medical thromboprophylaxis with LMWH or unfractionated heparin (UFH) should be considered, although efficacy remains uncertain.*

Accurate risk assessment and use of VTE medical prophylaxis is sub-optimal in hospitalized medical patients.[229] Patients with cirrhosis are often perceived to be at higher risk of bleeding and likely do not receive appropriate medical VTE thromboprophylaxis.[230] One study examined 75 patients hospitalized with cirrhosis receiving LMWH for VTE prophylaxis and found relatively low rates of bleeding (five patients with reported bleeding events).[231] Two large retrospective studies show that use of UFH and LMWH appears safe with low in-hospital rates of bleeding.[224,225] Bleeding rates were not different between patients with cirrhosis treated with prophylaxis (UFH or LMWH) (8.1%)

compared with patients with cirrhosis not treated with prophylaxis (5.5%).[225] Furthermore, LMWH was safer than UFH, with decreased incidence of procedural-related bleeding.

While no current studies adequately assess efficacy for VTE prophylaxis in the hospitalized cirrhosis population, prophylactic LMWH was safe and prevented development of PVT in a small prospective cohort of cirrhosis patients.[204] Due to the relative infrequency of VTE, properly powered studies in hospitalized patients with cirrhosis will require large cohorts. Consequently, current recommendations are limited to extrapolation from studies in other populations without cirrhosis, small retrospective cohorts and expert opinion.

24. *Cirrhosis patients with peripheral VTE should be treated with medical therapy with AC. LMWH, VKAs or direct oral anticoagulants can be considered.*

The majority of studies examining safety and efficacy in therapeutic AC in patients with cirrhosis have been conducted in patients with PVT (see the "Treatment of Portal Vein Thrombosis in Patients with Cirrhosis" section). Very few retrospective studies have evaluated safety of therapeutic AC in patients with cirrhosis with peripheral VTE. One early, small study examined 17 patients with cirrhosis and VTE treated with LMWH and noted high bleeding rates on AC.[232] Six of the 17 patients had a major haemorrhage (defined as bleeding requiring blood transfusion) on AC. However, from this study the type of bleeding, the particular agent employed or the outcome of each patient was unclear. Numerous studies since have shown the relative safety of AC (LMWH, VKA and DOAC) at therapeutic dosing in patients with cirrhosis treated for PVT, VTE and atrial fibrillation.[126,141,193,195,231,233–236] In a recent study examining patients with cirrhosis treated with DOAC versus traditional AC (LMWH or VKA), 16 of the 39 patients were treated for VTE.[170] There was no difference between cohorts in bleeding events (4/20, 20% in the DOAC group vs. 3/19, 16% in the traditional AC group). A subsequent similar study compared DOAC and traditional AC for VTE in a total of 20 patients (8 in the traditional group and 12 in the DOAC group).[236] Bleeding rates were similar between groups (56% traditional vs. 30% DOAC). Efficacy was not assessed in either study.

The safety of AC and dosing strategy in peripheral VTE can likely be extrapolated from studies in PVT. However, the efficacy of AC therapy in VTE in cirrhosis is not well studied and the indications, timing of therapy and choice of agent are inferred from general guidelines for treatment of VTE.[237]

25. *Prior to starting AC, the bleeding risk should be reassessed with medical history and ideally an upper endoscopy. If high-risk varices are present, consideration of medical or endoscopic therapy is recommended prior to long-term AC.*

See comments in the "Treatment of Portal Vein Thrombosis in Patients with Cirrhosis" section.

Survey of Concepts and Clinical Practice: Results of Polling of the 2017 7th International Coagulation in Liver Disease Conference Faculty and Participants

In recognition of the limitations of existing data and the variation between evidence-based and actual practice, we conducted both an interactive poll during the conference and a more deliberative on-line poll of specific scenarios related to the above statements. The polls were designed to address actual clinical practices as they related to evidenced-based concepts in this field. Among 150 attendees the overall poll response rate was 80 (53%): among responders, 65% were

Table 2 Research goals: priorities and practicalities

Prophylaxis prior to procedures	Pre-procedural fibrinogen level and platelets have emerged as important markers of bleeding risk. However, prospective trials are now needed to confirm these markers and to establish other potential predictors of bleeding
Global coagulation tests	Future research is needed to better understand how to interpret and use global assays of haemostasis, such as thrombin generation tests (TGA) and VETs (ROTEM and TEG) in compensated and decompensated cirrhosis with a goal to establish standard references within this population
PVT in cirrhosis	In cirrhosis, PVT most clearly affects outcomes after liver transplantation. Studies are now needed to examine the efficacy and risk of anticoagulation for the various grades of PVT in all patients with cirrhosis (not just transplant eligible) with a focus on clinical outcomes. Key aspects to study include incidence, risk factors, natural history, relationships to symptoms and risks of therapy
PVT and disease progression	Intra-hepatic activation of clotting and small vessel thrombosis in parenchymal extinction may contribute to fibrosis and hepatic decompensation, but more robust studies (translational and clinical studies in humans) are necessary
VTE prophylaxis in cirrhosis	Prospective studies are needed to examine the utility of current risk models in cirrhosis patients with a goal of improving knowledge of the incidence and natural history of VTE in cirrhosis
Anticoagulants in cirrhosis	The pharmacokinetics and dosing of all anti-coagulants (low molecular weight heparin, vitamin K antagonists and direct oral anticoagulants) in patients with compensated and decompensated cirrhosis is poorly understood. Prospective studies are now needed to better guide therapy with these medications

Abbreviations: PVT, portal vein thrombosis; ROTEM, rotational thromboelasometry; TEG, thromboelastography; TGA, thrombin generation assay; VETs, viscoelastic tests; VTE, venous thromboembolism.

haepatologists, 10% were anesthesiologists and 7.5% were haematologists.

Regarding all laboratory testing of coagulation indices, agreement was modest for most statements. However, agreement was strongest when surveying perception surrounding the usefulness of traditional parameters of coagulation (PT/aPTT/INR) in poorly predicting haemostasis (77%), the hazard involved in rVIIa use (73%) and the lack of utility of DDAVP in preventing or treating bleeding (69%). One of the most interesting observations involved the necessity of preprocedure plasma fibrinogen and platelet count assessment and correction: 68% of respondents agreed that these tests are useful in high-risk procedures, but 69% felt that these were not needed in low- or moderate-risk procedures.

VTE is a dynamic topic with numerous new developments. Most respondents agreed that hospitalized cirrhosis patients are at increased risk of VTE (84%), but less agreed regarding the use of medical prophylaxis with heparin agents (63%). There was strong agreement (91%) that a peripheral VTE diagnosis warrants therapeutic AC. There was strong agreement that endoscopic control of varices was recommended prior to initiating therapeutic AC (84%).

Regarding the diagnosis and treatment of splanchnic vein thrombosis, agreement was generally very high (greater than 75% for most statements). Most attendees felt that cirrhosis patients should be screened with US every 6 months for PVT (75%), and that patients listed for liver transplant should be assessed every 3 months (79%). Agreement with pursuing confirmation of US results with a cross-sectional imaging method prior to consideration of treatment was nearly unanimous (91%). Results were mixed, however, with regards to the utility of undertaking a hypercoagulability workup (56% agreement), as many felt it would not appreciably alter treatment decision-making in terms of both choice of AC and also duration of therapy. Attendees only had slightly more hesitation about treatment of PVT (76%) with AC compared with peripheral DVT (83%). Use of TIPS as a first-line modality to attempt to achieve re-canalization of PVT was less popular with only 63% agreement.

Compared with the prior 2005 survey of actual practice and opinion,[5] this 2017 survey demonstrated greater agreement on the limitations of conventional measures of bleeding risk assessment using PT/aPTT/INR, but fell well short of a consensus despite existing data. Health care providers are embracing the concept of hypercoagulability in cirrhosis and more willing to utilize therapeutic AC in the setting of peripheral VTE and PVT. Furthermore, there is emerging consensus as to the utility of fibrinogen and platelet measures as indicators of bleeding risk prior to high-risk procedures. However, the utility of more elaborate testing of hypercoagulable states, such as genetic testing remain uncertain in the setting of thrombotic complications in cirrhosis. Notably, in the general population, a hypercoagulable work-up is currently discouraged in the majority of patients with VTE and avoiding these tests in patients with VTE is on the 'Choosing Wisely' list endorsed by multiple specialty societies.[238]

While significant gains in our understanding of the complexities of the coagulation system in liver disease have been made over the last several years, future focused research will be essential to advance the field (►**Table 2**).

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Appendix A Faculty of 7th International Conference on Coagulation in Liver disease

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