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Clinical Cirrhosis Dilemmas: Survey of Practice from the 7th International Coagulation in Liver Disease Conference

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Abstract

Introduction and Aim Hemostatic disorders in chronic liver disease and cirrhosis show continued expansion of research efforts. However, clinical decision making is often practiced on an individual patient level as consensus guidelines are lacking. We aimed to better assess individual day-to-day clinical practice through gauging clinicians' responses to common clinical scenarios.

Materials and Methods A series of ten clinical scenarios (seven procedural coagulation and three thrombosis management) were posed to conference attendees utilizing real-time polling software (Poll Everywhere). Responses were binomial and were submitted as "Agree" or "Disagree." Results were displayed real time following a standardized response period and an open-forum discussion ensued between conference faculty and attendees following response submission.

Results Twenty conference attendees participated in the clinical scenario plenary session. In general, agreement rates were high. All but one of the ten clinical scenarios had $\geq 70\%$ agreement. Agreement was based both on procedural risk, with greatest agreement seen for low-risk procedures (80–93%), and on peri-procedural coagulation parameters of platelet count and fibrinogen level where $> 50,000\mu\text{L}$ and 120 mg/dL were the most agreed upon thresholds, respectively. 75–95% agreement was reached when surveying the need for anticoagulation for mesenteric vein thrombosis in liver transplant candidates; slightly less (71%) agreement was found when deciding to proceed with anticoagulation in non-liver transplant candidates with mesenteric vein thrombosis.

Conclusions While large-scale, methodologically rigorous randomized controlled trials are lacking to guide clinical decision making in patients with coagulation disorders and chronic liver disease, consensus expert opinion regarding mitigating peri-procedural bleeding risk and treatment of thrombosis appears consistent and strong.

Keywords Hepatology · Liver transplantation · Venous thromboembolism · Procedures · Bleeding risk

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Introduction

Historically, patients with cirrhosis were thought to be “auto-anticoagulated” based on elevations in the prothrombin time–international normalized ratio (PT–INR) and that this “auto-anticoagulation” was protective against local and systemic thrombotic disease; the counterpoint is that elevations in these tests predisposed patients with cirrhosis to bleeding events [1, 2]. Recent work in the discipline of hemostatic disorders in chronic liver disease and cirrhosis has largely dispelled this dogma and additionally demonstrated that there is appreciable thrombotic risk in patients with cirrhosis, as abnormalities in the hemostatic system in proportions of these patients may predispose to venous thromboembolism (deep vein thrombosis and pulmonary embolus) and/or portal vein thrombosis [3–9]. Current research has pointed to hemostasis in cirrhosis as a precarious struggle to maintain equilibrium between pro- and anti-hemostatic drivers. Clinicians are faced with dilemmas due to this unstable balance where cirrhosis patients may have bleeding, clotting, or simultaneous bleeding and clotting events given the scenario of underproduction of many hemostatic factors on both sides of the hemostatic equation.

Bleeding in cirrhosis patients is common whether spontaneous or procedure related and leaves a lasting impression on clinicians and caregivers alike. Clinical guidelines regarding optimal treatment regimens for venous thromboembolism are also lacking in cirrhosis patients, and many treatment decisions are often made on a case-by-case basis factoring in the risks and benefits of anticoagulation or mechanical thromboprophylaxis unique to each patient and clinical scenario. For this reason, the 7th International Coagulation in Liver Disease Conference was convened in Rome, Italy, in October, 2017, to discuss and debate the most pressing issues in the field of coagulation and chronic liver disease. We would direct the interested reader to the paper by Intagliata et al. [10] for an in-depth summary of this meeting including twenty-five summary statements to guide the clinician in day-to-day practice. A unique element to this edition of the international proceedings was the incorporation of real-time technology-based interactive polling of conference attendees to assess current day-to-day clinical practice more objectively and with less bias and to stimulate international discussion and collaboration through common clinical scenarios.

Methods

Prior to the conference, ten common clinical scenarios (Table 1) were developed by a working group consisting of four experts (CA, SC, NI, JS) selected from the conference scientific committee (CA, SC, NI, TL, JS, FV) following

individual systematic reviews completed independently by each member of the group. Seven procedural, bleeding risk scenarios with differing procedural and laboratory bleeding risk parameters were developed. Table 2 presents a definition of low, moderate, and high-risk procedures. Three hemostatic scenarios with different extent of mesenteric vein thrombosis and patient liver transplantation candidacy were also developed. Subsequent group review and approval of each individual clinical scenario were completed prior to the conference.

The series of ten clinical scenarios were posed to the conference attendees attending this specific scientific session at the start of the second day of the conference. There were no inclusion or exclusion criteria for survey participation beyond conference registration. The clinical scenarios were showcased utilizing polling software Poll Everywhere (San Francisco, CA), a cloud computing web-based software previously validated as an accurate, effective real-time, interactive audience response survey instrument and educational resource [11]. Through a secure server, conference faculty presented the ten common clinical scenarios in multiple-choice format and responses were submitted by personal cell phone (text messages and Twitter), tablet computers, and/or laptop computers (<http://www.pollev.com>). Responses were binomial and were submitted as “Agree” or “Disagree.” Results were displayed real time following a standardized 1-min response period and an open-forum discussion ensued between conference faculty and attendees.

Results

Twenty conference attendees participated in the clinical scenario plenary session under the direction of two faculty moderators. The majority (70%) had been in clinical practice for > 10 years and were considered experts in their respective fields as determined by scientific contribution, while 10% were in practice 5–10 years and 20% < 5 years. 75% of respondents were hepatologists, 10% anesthesiologists, 10% hematologists, and 5% basic scientists (Table 3). Response rates were variable by question and ranged from 60 to 100%. In scenarios where 100% response was not observed, respondents either experienced technical issues or abstained from responding.

Procedural Bleeding Risk

The largest agreement was seen with Scenario #4 where 93% (14/15) of respondents agreed that a low-risk procedure (endoscopy with variceal band ligation) should be performed without pre-procedure use of blood products given

Table 1 Ten common clinical coagulation dilemmas in cirrhosis

Procedural bleeding risk		
1.	54-year-old woman presents acutely with a history of moderate alcohol intake (1–2 drinks/day) and ALT 400 U/L, IgG 3200 U/L, total bilirubin 8.4 mg/dL, ASMA titer 1:80, and nodular liver on ultrasound. You are concerned about evaluation of alcoholic versus autoimmune hepatitis and presence of cirrhosis. I would perform a percutaneous liver biopsy without transfusion of blood products (fibrinogen = 120 mg/dL) if platelets > 30 K	
2.	62-year-old man with known cryptogenic cirrhosis and portal hypertension presents with his third episode of acute dyspnea secondary to hepatic hydrothorax in the last 4 weeks. I would perform a therapeutic thoracentesis without transfusion of blood products for symptomatic hepatic hydrothorax (fibrinogen = 120 mg/dL) if platelets ≥ 30 K?	
3.	48-year-old man with known alcoholic cirrhosis and portal hypertension presents acutely to the Emergency Department due to abdominal pain and dyspnea related to symptomatic ascites. I would perform a therapeutic paracentesis with ultrasound guidance without transfusion of blood products (fibrinogen = 120 mg/dL) if platelets ≥ 20 K?	
4.	61-year-old woman with cirrhosis from primary biliary cholangitis and portal hypertension presents as an outpatient for esophageal variceal surveillance and prophylactic band ligation if indicated by endoscopic findings. I would perform prophylactic band ligation of esophageal varices without transfusion of blood products (fibrinogen = 120 mg/dL) if platelets ≥ 30 K?	
5.	46-year-old man who is immunosuppressed status post-liver transplant with recurrent hepatitis C-related cirrhosis in the graft and portal hypertension presents with new onset altered mental status and fever to 38.9°C with no improvement with three doses of lactulose and no focal neurologic deficits. I would perform fluoroscopy-guided lumbar puncture without transfusion of blood products (fibrinogen = 120 mg/dL) if platelets ≥ 50 K?	
6.	49-year-old man with newly diagnosed hepatitis B infection presents to your clinic with ALT 96 U/L, albumin 3.5 mg/dL, total bilirubin 1.7 mg/dL, and INR 1.4. Hepatitis B viral load is 120,000 IU/mL. On ultrasound, liver contour appears mildly nodular, spleen size is 14 cm, and there is no ascites. I would perform a percutaneous liver biopsy without transfusion of blood products (platelets = 90 K) if fibrinogen ≥ 120 mg/dL?	
7.	74-year-old woman with known NASH cirrhosis with past history of ascites and edema presents with acute dyspnea secondary to new onset hepatic hydrothorax with large right pleural effusion. I would perform a therapeutic thoracentesis without transfusion of blood products for symptomatic hepatic hydrothorax (platelets = 65 K) if fibrinogen ≥ 100 mg/dL?	
Venous thromboembolism treatment		
8.	49-year-old man with alcoholic cirrhosis, currently listed for liver transplantation, presents with new onset ascites, diarrhea, and nausea with vomiting. MELD-Na is 23, platelets 55 K, Cr 1.3 g/dL. Cross-sectional imaging with triphasic CT abdomen/pelvis shows occlusive acute left portal vein branch thrombosis with no evidence of cavernous transformation of the thrombosis and with no concerning liver masses. I would administer a chronic anticoagulant agent for portal vein thrombosis.	
9.	49-year-old man with alcoholic cirrhosis, listed for transplantation, presents with new onset ascites, diarrhea, and nausea and vomiting. MELD-Na is 23, platelets 55 K, Cr 1.3 g/dL. Cross-sectional imaging with triphasic CT abdomen/pelvis shows non-occlusive main PVT with non-occlusive extension to the confluence with the SMV, with no evidence of cavernous transformation and no concerning liver masses. I would administer a chronic anticoagulant agent for portal vein thrombosis.	
10.	49-year-old man with alcoholic cirrhosis, not listed for transplantation, presents with generalized abdominal pain and bloating. MELD-Na is 23, platelets 55 K, Cr 1.3 g/dL. Cross-sectional imaging with triphasic CT abdomen/pelvis shows non-occlusive extrahepatic main trunk portal vein thrombosis without extension, with no evidence of cavernous transformation of the thrombosis and with no concerning liver masses. I would administer a chronic anticoagulant agent for portal vein thrombosis.	

Table 2 Classification of procedure risk

Higher risk procedures	Intermediate-risk procedures	Lower risk procedures
Brain or spinal surgery	Lumbar puncture	Paracentesis
All major surgery (cardiac, intraabdominal and orthopedic)	Percutaneous or transjugular liver biopsy	Thoracentesis
Intracranial pressure catheter insertion	Transjugular intrahepatic portosystemic shunt	Dental extraction
Endoscopy (large polypectomy with endoscopic mucosal or submucosal resection, NOTES)	Endoscopy (percutaneous gastrostomy placement, cystgastrostomy, biliary sphincterotomy)	Endoscopy (diagnostic, variceal band ligation, uncomplicated polypectomy)
	Percutaneous biopsy of extrahepatic organ or lesions	Cardiac catheterization
	Transarterial or percutaneous HCC therapies	Central line placement

Risk is estimated here based on relative vascularity, degree of expected vascular breach, and potential clinical consequences but risk should always be defined by clinician performing the procedure

Table 3 Demographics of survey respondents

Specialty	
Hepatology	75%
Anesthesiology	10%
Hematology	10%
Basic science	5%
Years in practice	
< 5 years	20%
5–10 years	10%
> 10 years	70%

a fibrinogen level of 120 mg/dL and platelet count $\geq 30,000/\mu\text{L}$. Slightly less agreement (87%, 13/15) was found with Scenario #5 in which an intermediate-risk procedure (fluoroscopic guided lumbar puncture) should be undertaken without pre-procedural blood product administration given a fibrinogen level of 120 mg/dL, and platelet count $\geq 50,000/\mu\text{L}$ was posed. 80% (12/15) of attendees surveyed agreed with Scenario #3 where a low-risk procedure (paracentesis) was recommended with an even lower platelet count of $\geq 20,000/\mu\text{L}$ and fibrinogen of 120 mg/dL and 75% (8/12) of respondents agreed with Scenario #1 and agreed to proceed with an intermediate-risk procedure (percutaneous liver biopsy) without transfusion given a platelet count of $\geq 30,000/\mu\text{L}$ and fibrinogen of 120 mg/dL. A significant level of agreement (87%, 13/15) was seen for Scenario #6 where an intermediate-risk procedure (liver biopsy) was recommended without transfusion for a platelet count of $90,000/\mu\text{L}$ and fibrinogen ≥ 120 mg/dL and also for Scenario #7 (75%, 12/16) which posed an intermediate-risk procedure again (thoracentesis) without transfusion with platelets of $65,000/\mu\text{L}$ and fibrinogen ≥ 100 mg/dL. The most contentious was Clinical Scenario #2 in which 50% (8/16) agreed to recommend a low-risk procedure (thoracentesis) with a platelet count of $\geq 30,000/\mu\text{L}$ and fibrinogen of 120 mg/dL.

Mesenteric Vein Thrombosis Treatment

Much more agreement was seen with the mesenteric vein thrombosis treatment clinical scenarios than the procedural bleeding risk scenarios. 95% (19/20) of respondents agreed with Scenario #9 in which anticoagulation was recommended for a liver transplant candidate with decompensated liver disease and clinically significant portal hypertension with Yerdal Grade 3 [12] (refer to Table 4 for the Yerdal grade) mesenteric vein thrombosis. Slightly less agreement (75%, 12/16) was seen with Scenario #8 in which Yerdal Grade 2 mesenteric vein thrombosis was diagnosed also in a liver transplant candidate with decompensated liver disease and clinically significant portal hypertension. More

Table 4 Grading of portal vein thrombosis (Yerdal classification) [12]

Grade	Description
1	< 50% PV occlusion $\pm$ minimal SMV extension
2	> 50% PV occlusion $\pm$ minimal SMV extension
3	Complete PV occlusion + complete proximal SMV occlusion; distal SMV is non-occluded
4	Complete occlusion of the PV, proximal and distal SMV

controversy surrounded Scenario #10 in which a patient who was not a liver transplant candidate with clinically significant portal hypertension and decompensated liver disease was diagnosed with Yerdal Grade 1 mesenteric vein thrombosis as 73% (11/15) of respondents agreed to proceed with anticoagulated to treat this patient.

Discussion

The 7th International Coagulation in Liver Disease Conference was convened in Rome, Italy, in October, 2017, to discuss and debate the most controversial issues in the field of hemostasis and chronic liver disease. We attempted to better define the day-to-day clinical practice of conference attendees using a real-time, secure web-based interactive polling assessment. The results of this survey indicate that in general, consensus agreement in clinical practice was present as of the ten clinical scenarios presented, all but one had at least 70% agreement and all scenarios carried a majority opinion. This is an acceptable level of agreement statistically speaking [13]. Our findings indicate that there is emerging comfort with the utility of fibrinogen and platelet measures as indicators of bleeding risk prior to invasive procedures in patients with cirrhosis amongst leaders and experts in the field, despite conflicting data surrounding bleeding risk and thrombocytopenia. In vitro evidence demonstrates that platelet-dependent thrombin generation is upheld in cirrhosis with platelet levels $55,000/\mu\text{L}$ or greater [14], although there are several limitations to thrombin generation assays which disregard many key aspects of platelet function including adhesion and aggregation, calling into question the aforementioned threshold [15]. While several in vivo studies have failed to show a correlation between platelet count and procedural bleeding [16, 17], platelet levels below 30–40,000/ μL have independently been shown to predict procedural bleeding in critically ill cirrhosis patients or those undergoing dental extractions [18, 19].

Similar to platelet count, guideline-driven targets for optimal fibrinogen level remain controversial. Extrapolating from the trauma surgery literature, fibrinogen levels > 200 mg/dL correlate with effective hemostasis [20], however, in the cirrhosis population variable

recommendations ranging from 100 to 200 mg/dL are often made. Historically, the most agreed upon cutoff in the actively bleeding patient with cirrhosis is > 120 mg/dL, although this is based largely off expert opinion, a concept that is reflected in the findings presented here in our survey of current clinical practice [21]. Our findings support the perception of a fibrinogen cutoff of 120 mg/dL as the minimum acceptable in clinical practice; however, cutoffs below 100 mg/dL were not formally assessed. Considering these limitations, we recognize that the ability of a single test to predict procedure-related bleeding complications is unlikely to have a high positive predictive value given the complicated nature of the hemostatic system.

Several additional salient findings of our survey of clinical practice bear noting, including the fact that more disagreement was seen in clinical decision making regarding peri-procedural bleeding risk and correction of coagulopathy when compared to intervention with anticoagulation for mesenteric vein thrombosis. Inherent procedural risk appears to have the greatest bearing on agreement to proceed with an intervention with blood product administration. This was evidenced by the discrepancy seen between Scenarios #2 and #3, as the type of procedure being performed influenced clinical decision making and the response of conference attendees confirmed that all low-risk procedures are not viewed with the same bleeding risk as respondents were less likely to recommend proceeding with a low-risk thoracentesis versus a upper endoscopy with potential gastroesophageal variceal band ligation with the same level of thrombocytopenia (30,000/mL) and fibrinogen (120 mg/dL). While this may be attributed in part to clinician's familiarity with the procedure as most conference attendees were hepatologists by training (65%) and perform upper endoscopy much more frequently than thoracentesis, the finding is nonetheless intriguing and applying these same clinical scenarios to either radiologists or pulmonologists (<5% of conference attendees) may yield more answers to this important clinical practice question. It is well established that experience with a procedure and clinical volume are correlated to outcomes [22]; however, what remains unknown is whether or not experience correlates with procedural risk, e.g., is the more experienced procedural specialist more likely to take on higher risk procedures? Our survey was underpowered to detect significant findings for this particular outcome of interest; however, this is an attractive question for future study.

Previous studies have found that, not surprisingly, more defensive medicine is practiced as procedural risk escalates with the greatest rates of self-reported defensive medicine practice described with the highest risk procedural interventions [23]. However, this was not necessarily the case amongst conference attendees as clinical scenarios with

intermediate-risk procedures (lumbar puncture, percutaneous liver biopsy) were agreed to proceed with > 75% agreement in the absence of dysfibrinogenemia or significant thrombocytopenia. Nonetheless, defensive medicine including pre-procedural blood product administration is a common occurrence and one that may have unintended consequences where copious volume of factor repletion with fresh frozen plasma or overaggressive transfusion with packed red blood cells may lead to transfusion-associated lung complications or worsen portal hypertension and precipitate gastroesophageal variceal hemorrhage.

Our study has several limitations in that it suffers from selection bias as conference attendees were considered leading experts in the field of hemostatic disorders in liver disease which may also limit the generalizability of our findings to other community and academic medical centers. In addition, the study is relatively underpowered,; however, our survey response rates offset this to some degree.

Conclusions

In conclusion, while large-scale, methodologically rigorous randomized controlled trials are lacking in the area of coagulation disorders and chronic liver disease, consensus expert opinion regarding mitigating peri-procedural bleeding risk and treatment of thrombosis was demonstrated by our interactive, web-based polling instrument which enabled real-time results review and interactive audience response. Future surveys of clinical practice on a larger scale to confirm our findings seem warranted.

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Compliance with Ethical Standards

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