AGA Clinical Practice Guideline on the Management of Coagulation Disorders in Patients with Cirrhosis

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All members were required to complete a disclosure statement. These statements are maintained at the American Gastroenterological Association Institute (AGA) headquarters in Bethesda, Maryland. Panel members disclosed all potential conflicts of interest according to the AGA Institute policy. No guideline panel member was excused from participation in the process owing to disqualifying conflict.

Abbreviations and acronyms:

AGA: American Gastroenterological Association Institute; Child's-Turcotte-Pugh: CTP; DVT: deep venous thrombosis; EGD: esophagogastroduodenoscopy; ERCP: endoscopic retrograde cholangiopancreatography; FFP: fresh frozen plasma; GRADE: Grading of Recommendations Assessment, Development and Evaluation; INR: international normalized ratio; PE: pulmonary embolism, PICO: patient, intervention, comparator, outcome; PLT: platelet; PT: prothrombin time; RAM: risk assessment model; RCT: randomized controlled trial; ROTEM: rotational thromboelastometry; SOC: standard of care; TEG: thromboelastogram; TPO-RA: thrombopoietin receptor agonist; TR: technical review; VET: visco-elastic testing; VKA: vitamin K antagonist;

Introduction

Cirrhosis is a disease state that is accompanied by significant alterations in laboratory parameters such as platelet count (PLT) and prothrombin time/international normalized ratio (PT/INR), routinely used to estimate clotting. Based on this measured thrombocytopenia and coagulopathy, it has traditionally been assumed these results convey a high risk of bleeding and therefore, significantly increased risk for patients undergoing invasive procedures. In addition, there is an assumption that treatment for conditions usually requiring anticoagulation may not be warranted in these patients.

However, it has become clear that this understanding underestimates the balanced nature of alterations in hemostasis associated with end stage liver disease, and that neither thrombocytopenia nor an elevated PT/INR necessarily predicts bleeding outcomes in most of these patients.[1] Moreover, the severity of coagulopathy estimated by these parameters is not predictive of bleeding complications in patients with cirrhosis, including major complications such as variceal hemorrhage.[2] Although these patients are at risk for thrombosis – including deep vein thrombosis (DVT), pulmonary embolism (PE), splanchnic vein thrombosis, or stroke – there has been some trepidation on the part of clinicians to treat them with conventional anticoagulants, such as vitamin K antagonists (VKA).

Furthermore, testing strategies using PT/INR to estimate the likelihood of bleeding and monitor treatment endpoints in patients taking VKAs may not be relevant in patients with cirrhosis who have an equilibrium in the derangements of both procoagulant and anticoagulant factors. More recently, investigators have tested the utility of a more integrative approach, using measurements of fibrin clot formation and lysis to try and capture the full spectrum of abnormalities seen in cirrhosis.

It is important to recognize that this literature is largely derived from observational studies, often including patients whose lab values fall within a specific range of abnormality – and thus it may not be reasonable to extrapolate study results beyond the usual parameters seen in patients with cirrhosis.

Methods

This document presents the official recommendations of the American Gastroenterological Association Institute (AGA) on the management of coagulation disorders in patients with cirrhosis. The guideline was developed by the AGA Institute's Clinical Guideline Committee and approved by the AGA Governing Board. It is accompanied by a technical review (TR) that provides a detailed synthesis of the evidence

from which these recommendations were formulated. Development of this guideline and the accompanying TR was fully funded by the AGA Institute without additional outside funding.

Optimal understanding of this guideline will be enhanced by reading applicable portions of the TR.[3] The guideline was developed using a process outlined elsewhere.[4] Briefly, the AGA process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [5] and best practices as outlined by the Institute of Medicine.[6] GRADE methodology was used to prepare the background information for the guideline and TR that accompanies it (Table 1), including the focused population, intervention, comparison, and outcome (PICO) questions. The strength of a recommendation reflects an understanding of the balance of the quality of the evidence, the likelihood of desirable and undesirable effects, values and preferences, as well as resource allocation (Table 2).[7]

Guideline panel composition, funding, and conflicts of interest

Members of the Guideline Panel and Technical Review Panel were selected by the AGA Governing Board and Chair of the Clinical Guidelines Committee with careful consideration of conflict of interest. The guideline panel included the chair, gastroenterologists and hepatologists, technical review GRADE methodology chairs, and GRADE experts.

Formulation of clinical questions

The authors of the TR and this guideline, with input from the AGA governing board, identified critical areas of clinical need. Specific questions were developed within PICO framework for defined populations and were broadly divided into issues related to bleeding risk, particularly around procedures, and issues related to risk of clotting and anticoagulation in patients with cirrhosis. The absence of clear guidance from this literature prompted this practice guideline to address the specific questions summarized in Table 3.

Development of recommendations

Members of the guideline panel, along with AGA support staff, met with the authors of the technical review on January 8, 2021. The information in the technical review was discussed in a systematic manner, facilitating subsequent creation of the guideline recommendations for or against each intervention. The strength of each recommendation was also rated as either strong or weak (conditional).

External review

The guideline and the accompanying TR underwent independent peer review and a 30 day open public comment period. All comments were collected by AGA staff. The comments were reviewed and addressed by the guideline panel and TR panel. Changes were incorporated in a revised document and if comments were not accepted, a response document was created for each comment.

Plans for updating this guideline

In accordance with the Clinical Guidelines Committee policies, all guidelines are reviewed annually by the AGA clinical guideline committee for new information. The need for an update will be determined no later than 3 years from publication (2024).

Recommendations

PICO Question 1: What testing strategy for bleeding risk assessment is most beneficial for patients with cirrhosis?

This question is aimed at the estimation of bleeding related procedural risk (either bleeding or mortality) in patients with cirrhosis undergoing non-surgical procedures. The authors broke this question into two components:

<u>Question 1A:</u> Should visco-elastic testing (VET) be performed in patients with cirrhosis prior to procedures?

<u>Question 1B:</u> Should platelet (PLT) and PT/INR testing be done prior to procedures to prevent procedure-related bleeding?

The role of PT/INR and PLT testing prior to invasive procedures is not well-defined, and accumulating evidence suggests that these are not relevant markers for assessment of bleeding risk. Thromboelastography (TEG) has received growing attention as an alternative marker for bleeding risk. TEG has been used in clinical practice in surgery for upwards of three decades[8], and reviewed in multiple studies as a predictor of procedure-related bleeding risk. The authors of the TR identified a total of five randomized controlled trials (RCTs) which studied the effect of using VET, using either TEG or rotational thromboelastometry (ROTEM), versus standard of care (SOC) before procedures (three RCTs) or during bleeding events (two RCTs) in patients with cirrhosis and coagulopathy. Coagulopathy was typically defined as INR>1.8 and/or PLT<50,000/mL. Outcomes that were studied included bleeding after procedures, transfusion requirements, and mortality.

There was no direct comparative evidence from RCT or cohort studies with regard to pre-procedural laboratory testing with PLT and PT/INR or pre-procedural prophylaxis with PLT and fresh frozen plasma (FFP) transfusion and the risk of procedural bleeding. Indirect evidence was examined from case series of consecutive patients and single arm cohort studies that examined bleeding outcomes during or after the procedure in cirrhosis patients with elevated PT/INR and low PLT in whom no prophylactic administration of PLT or fresh frozen plasma (FFP) was given.

The use of VET did not impact post-procedural bleeding compared to SOC in three studies (RR=0.33; 95%CI 0.01, 7.87) and similarly, was not helpful in prediction of failure to control or prevent rebleeding or long-term mortality (RR = 1.05; 95% CI 0.45 – 2.44). There was a clear trend toward lower use of blood products in patients who were managed with VET, but these studies used variable thresholds for blood product transfusions, making comparisons difficult. No other impact was seen on clinically relevant outcomes.

Two studies examined the role of VET in management of bleeding events in patients with cirrhosis; there was no clear benefit in ability to control bleeding or prevent rebleeding.

RECOMMENDATION

<u>Question 1A.</u> In patients with stable cirrhosis undergoing common gastrointestinal procedures, the AGA makes no recommendation for the use of visco-elastic testing prior to procedures to predict bleeding risk (no recommendation, knowledge gap).

<u>Question 1B</u>. In patients with stable cirrhosis (with known baseline measurements of abnormal coagulation parameters), the AGA suggests against the use of extensive pre-procedural testing,

including repeated measurements of PT/ INR or platelet count (conditional recommendation, very low quality evidence).

PICO Question 2: Does pre-procedure prophylaxis (i.e., using blood product transfusion or thrombopoietin receptor agonists) to correct coagulation parameters and/or platelet level reduce the risk of bleeding in patients with cirrhosis?

This question was addressed in 2 component parts:

<u>Question 2A:</u> Should pre-procedural PLT and/or FFP transfusion be given to cirrhosis patients with thrombocytopenia or prolonged PT/INR to prevent procedure-related bleeding?

<u>Question 2B:</u> Should pre-procedural thrombopoietin receptor agonists (TPO-RA) be given to cirrhosis patients with thrombocytopenia to prevent procedure related bleeding?

The authors of the TR reviewed the literature in reference to six common procedures in patients with cirrhosis, including paracentesis, thoracentesis, esophagogastroduodenoscopy (EGD) with banding, endoscopic retrograde cholangiopancreatography (ERCP), colonoscopy with polypectomy, and liver biopsy. They found no RCTs using traditional coagulation testing such as PT/INR or PLT to either predict procedural bleeding or guide prophylactic blood product administration in patients with cirrhosis. Further, no RCTs were found that used conventional coagulation tests to guide clinical management of post-procedure bleeding events.

The authors of the TR also performed a systematic review of studies that reported on the utility of standard laboratory tests, defined as PT/INR and PLT, for prediction of bleeding risk and found no direct evidence of an abnormal PT/INR or PLT threshold that predicts bleeding risk. The majority of the studies that reported bleeding rates were retrospective cohort studies that chose varying definitions of bleeding and/or thresholds to transfuse patients. As many of the low-risk interventions (e.g., paracentesis or thoracentesis) had reported very low bleeding rates, there was no clear threshold for standard coagulation parameters that defined an unacceptable risk, although one study suggested acute kidney injury might predispose to bleeding. Similarly, in patients undergoing EGD with banding, colonoscopy with polypectomy, or ERCP with sphincterotomy, a specific value of PLT or PT/INR was not defined that identified patients at an increased bleeding risk. Rather, progressive decompensation (as defined by the

Child-Turcotte-Pugh [CTP] score) was a more likely marker for bleeding after variceal banding, colonoscopic polypectomy (especially for larger polyps), or endoscopic sphincterotomy. Lastly, retrospective cohort studies of patients undergoing liver biopsy did not routinely report interventions prior to biopsy, nor complication rates based on severity of liver disease. In the few studies that specifically reported on outcomes in patients with cirrhosis, there was no clear difference in risk of bleeding compared to patients without cirrhosis, nor a specific PT/INR threshold that defined a high-risk group - but a trend of lower PLT counts correlated with higher bleeding risk.

Although procedures are routinely grouped empirically by perceived risk defined by the likelihood of bleeding based on the intervention or on the potential magnitude of bleeding, there are insufficient data to justify cut points of standard coagulation parameters to identify specific risk groups. It is important to acknowledge that this recommendation pertains to patients typically seen in practice; those with profoundly abnormal labs (for example, patients who have concomitant bleeding disorders unrelated to their liver disease) may be at a different level of risk, and they were not typically included in the studies in this literature. The TR authors stratified procedure-related bleeding risk into low or high using a threshold of 1.5%, based on literature review and expert interpretation of indirect evidence.

In patients with severe thrombocytopenia or coagulopathy undergoing high risk procedures, decisions about prophylactic blood transfusions should include shared decisions about potential benefits and risks such as transfusion reactions and alloimmunization. The threshold for severe thrombocytopenia or coagulopathy could not be clearly defined from the literature and remains a matter of clinical judgment. In many cases, clinical care of these patients should be managed in collaboration with an expert hematologist.

RECOMMENDATION

Question 2A: In patients with stable cirrhosis undergoing common gastrointestinal procedures (paracentesis, thoracentesis, variceal banding, colonic polypectomy, ERCP, liver biopsy), the AGA suggests against the routine use of blood products (e.g., fresh frozen plasma, platelets) for bleeding prophylaxis. (conditional recommendation, very low quality evidence)

Comment: This recommendation applies to the majority of patients with stable cirrhosis who usually do not have severe thrombocytopenia or severe coagulopathy. In patients with severe derangements in coagulation or thrombocytopenia undergoing a procedure with high-risk for bleeding, decisions about

prophylactic blood transfusions should include shared decisions about potential benefits and risks (including transfusion reactions and delay of procedure) and in consultation with a hematologist.

The utility of PLT counts to predict bleeding in patients with cirrhosis is uncertain, and low PLT counts may reflect progression and severity of the underlying liver disease, accompanying portal hypertension, and hypersplenism to a greater extent than bleeding risk at baseline.[9] [10] Despite this, PLT are commonly transfused in patients with cirrhosis and thrombocytopenia prior to invasive procedures. This strategy poses some risk to patients, given the short half-life of the transfusions, cost, and the possibility of alloimmunization and other adverse reactions.

The TR identified 5 RCTs which compared the use of platelet transfusions to TPO-RA (including avatrombopag, eltrombopag and lusutrombopag) which have been FDA-approved for the treatment of thrombocytopenia in cirrhotic patients undergoing a procedure. These studies assessed the impact of the TPO-RAs on PLT counts in patients with cirrhosis and thrombocytopenia prior to planned procedures, which typically were low risk (primarily dental procedures and diagnostic endoscopies). Study endpoints were increases in PLT counts (avoidance of fixed protocol PLT transfusion), rather than clinical bleeding, as well as rates of adverse events, including portal vein thrombosis (PVT).

No studies compared the use of TPO-RA to a restrictive strategy of no TPO-RA. Overall, there was a low rate of bleeding and multiple methodologic concerns exist (use of surrogate markers rather than direct evidence, lack of comparison groups who did not receive transfusion, as well as the low event rate). The risk of thrombotic events at 30 days was approximately 1% for avatrombopag and lusutrombopag.

RECOMMENDATION

Question 2B: In patients with thrombocytopenia and stable cirrhosis undergoing common procedures (and in particular, "low risk" procedures), the AGA suggests against the routine use of thrombopoietin receptor agonists for bleeding prophylaxis. (conditional recommendation, very low quality evidence).

Comment: Patients who place a high value on the uncertain reduction of procedural bleeding events and a low value on the increased risk for portal vein thrombosis may reasonably select a thrombopoietin receptor agonist.

PICO Question 3: Is venous thromboembolism prophylaxis with anticoagulation indicated in hospitalized patients with cirrhosis?

Patients with acute medical illnesses are at high risk of developing venous thromboembolism (VTE); a recent policy statement from the American Heart Association points out that the risk of VTE is 1 to 2 per 1000 adult patients annually, but possibly as high as 1 in 100 annually amongst elderly patients and even higher among subgroups with risk factors. VTE contributes to increasing length of stay and is the leading cause of preventable hospital death in the US and worldwide.[11] Similarly, it has been increasingly recognized that patients with cirrhosis are at significant risk of VTE as well, with typical incidence rates of 0.5 -1.9% - but in some studies, considerably higher.[12]

Despite clear evidence of increased risk for VTE, hospitalized patients with cirrhosis have not been typically included in most studies of thromboprophylaxis with anticoagulation, and no RCTs were found comparing outcomes of prophylactic anticoagulation in patients with cirrhosis. Three retrospective cohort studies did report on bleeding rates in patients with cirrhosis. The VTE risks are best estimated by the use of several risk assessment models (RAM), most recently including the Padua Prediction score[13] and the IMPROVE VTE RAM. These have been developed and widely applied, although review of the literature by the TR identified only 5 retrospective studies that examined the risk of VTE in patients with cirrhosis, and no prospective studies. It is recommended that clinicians should incorporate both VTE and bleeding risk assessments into clinical decision-making. The IMPROVE investigators developed a RAM incorporating liver disease as a risk factor for bleeding (defined as an INR > 1.5), which conveyed an increase in RR of 2.18. [14] [15] [16] The TR analysis pooled data from three retrospective cohort studies and did not detect an increase in the risk of bleeding in patients with cirrhosis treated with anticoagulation in these studies.

Given the strength of the data supporting the use of anticoagulation in acutely ill hospitalized medical patients, the evidence of similar VTE risk among patients with cirrhosis, and the lack of evidence of an increased bleeding risk with pharmacologic VTE prophylaxis, it is reasonable to extrapolate estimates of benefit from data derived in general medical populations.

RECOMMENDATION

In hospitalized patients with cirrhosis and who otherwise meet standard guidelines for the use of venous thromboembolism prophylaxis, the AGA suggests standard anticoagulation prophylaxis over no anticoagulation. (conditional recommendation, very low quality of evidence)

PICO Question 4: Should patients with cirrhosis be screened for portal vein thrombosis?

PVT is a common occurrence in patients with cirrhosis; several prospective studies were identified by the TR of patients who underwent serial imaging at varying intervals which described an incidence ranging from 3.5-4.6% at one year, and up to 11% over a 5-year course of follow-up. The clinical impact of non-tumoral PVT however is uncertain and likely reflects the progression of liver disease; whether PVT acts as a precipitant for worsening liver disease is debated. In patients with PVT who undergo liver transplant, outcomes may be worse, and PVT has been characterized as conveying an increased risk of early mortality and graft failure. As a result, some authorities recommend screening for PVT at regular intervals,[17] as well as treating all newly diagnosed PVT. Several studies have demonstrated an increased likelihood of recanalization in patients with PVT treated with anticoagulation.[18] In addition, meta-analyses and systematic reviews of observational studies of anticoagulation do not describe an increased risk of bleeding; in fact, several studies describe a possibly lower rate of portal hypertension related bleeding [19] [20]. However, no comparative efficacy data from RCTs exist to guide therapy in either the transplant or nontransplant populations. Given the lack of data on the clinical significance of non-tumoral PVT and limited data about treatment outcomes, the benefit of routine screening for PVT remains uncertain.

RECOMMENDATION

In patients with cirrhosis, the AGA suggests against routine screening for portal vein thrombosis. (conditional recommendation, very low quality evidence)

Comment: Patients, particularly those considered for liver transplant, who put a high value on the uncertain benefits of portal vein thrombosis screening and a low value on the potential downsides and harms related to treatment would reasonably select screening.

PICO Question 5: What, if any, specific anticoagulation therapies should be offered for treatment of portal vein thrombosis in patients with cirrhosis: low molecular weight heparin (LMWH), direct-acting oral anticoagulants (DOAC), or vitamin K antagonists (VKA)?

The TR identified 12 studies in adult patients with PVT treated with anticoagulation that reported recanalization rates; anticoagulation strategies included LMWH or VKA. No studies of DOACs were identified. There was a substantially increased rate of complete or partial recanalization in patients treated with anticoagulation (RR of 2.27; 95%CI 1.73, 2.98 compared to untreated patients). The studies distinguished patients with tumor-related vs non-tumoral, and acute vs chronic PVT. Higher rates of recanalization were noted in treated patients with acute or sub-acute PVT, defined as recent thrombosis in the absence of signs of chronic PVT, which were mostly asymptomatic. Although the certainty of evidence was low, the overall rates of bleeding in patients treated with anticoagulation did not appear to be elevated compared to controls in these studies.

Moreover, there was a decreased risk of portal hypertensive bleeding in patients who were anticoagulated compared to patients in the control group who were not anticoagulated (RR 0.34, 95%CI 0.16, 0.75). However, there are no data to support the use of one anticoagulant over another as no comparative studies between anticoagulants exist.

RECOMMENDATION

In patients with cirrhosis and acute or sub-acute non-tumoral portal vein thrombosis, the AGA suggests using anticoagulation over no anticoagulation for treatment of portal vein thrombosis. (conditional recommendation, very low quality evidence).

Comment: Patients who put a higher value on the bleeding risk on anticoagulation and a lower value on the uncertain benefits of anticoagulation would reasonably choose no anticoagulation.

PICO Question 6: Should patients with atrial fibrillation and cirrhosis be treated with anticoagulation?

The TR identified six studies that specifically addressed the benefit and risk of bleeding vs. thromboembolic complications in patients with cirrhosis and atrial fibrillation treated with

anticoagulation. Overall mortality and the risk of nonfatal stroke were significantly reduced in patients who were treated with anticoagulation compared to those who were not, with the magnitude of the risk reduction related to the underlying risk estimated by the CHA2DS2-VASC score. The risk of non-fatal stroke seemed to be lower in patients treated with DOACs vs. warfarin. Bleeding risk was evaluated in 7 cohort studies that evaluated outcomes in patients treated with VKA vs untreated controls or patients treated with DOACs; a higher risk of bleeding was seen in patients who were anticoagulated vs. untreated controls (RR 1.91; 95%CI 1.85, 2.26), although the risk was lower among patients treated with DOACs vs. VKAs (with a RR of 0.62).

Similar trends were also seen in estimating risk of intracranial hemorrhage, (RR for bleeding 3.5; 95%CI 3.30, 4.0 comparing incidence in patients treated with VKA to untreated controls), with a lower rate in patients treated with DOACs vs VKA (RR 0.7; 95%CI 0.58, 0.84). The overall benefits of anticoagulation appear to outweigh the risk of bleeding in patients with cirrhosis and atrial fibrillation with a CHA2DS2-VASC score ≥2.

RECOMMENDATION

In patients with cirrhosis and atrial fibrillation with an indication for anticoagulation, the AGA suggests using anticoagulation over no anticoagulation (conditional recommendation, very low quality evidence).

Comment: Patients, particularly those with more advanced cirrhosis (Child-Turcotte-Pugh class C) and or low CHA2DS2-VASC scores who put a higher value on avoiding the bleeding risk on anticoagulation and lower value on the stroke reduction, could reasonably choose no anticoagulation.

Future research needs and evidence gaps

The TR and guideline panels identified multiple knowledge gaps and areas for future research in the management of coagulation and thrombosis in patients with cirrhosis. Although the understanding of the delicate balance between pro-coagulant and anti-coagulant factors in cirrhosis has advanced significantly, this knowledge has yet to translate directly into evidence-based recommendations for clinical care. We have limited knowledge of the best ways to identify patients at risk for thrombosis or hemorrhage and on methods to prevent or treat the clinically relevant events. Future research should focus on the best strategies to identify patients at risk for bleeding or thrombosis, to appropriately

provide prophylaxis using blood product transfusion or TPO-RA in patients at risk for clinically significant bleeding, to screen for and treat portal vein thrombosis, and to prevent clinically significant thromboembolic events. Future prospective cohort studies and randomized controlled trials in these areas are urgently needed given the ongoing large burden of chronic liver disease.

Table 1. GRADE definitions for certainty of the evidence

Quality Grade	Definition
High	We are very confident that the true effect lies close to the estimate of the effect
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low	Our confidence in the estimate is limited. The true effect may be substantially different from the estimate of effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect
Evidence gap	Available evidence is insufficient to determine true effect

Table 2. GRADE definitions on strength of recommendation and guide to interpretation

Strength of recommendation	**Wording in the guideline**	**For the patient**	**For the clinician**
Strong	"The AGA recommends…"	Most individuals in this situation would want the recommended course and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests…"	The majority of individuals in this situation would want the suggested course, but many would not.	Different choices would be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
No recommendation	"The AGA makes no recommendation…"		The confidence in the effect estimate is so low that any effect estimate is speculative at this time.

Table 3: Summary of Questions and Recommendations

PICO Question	Recommendations	Strength of Recommendation	Quality of Evidence
1. What testing strategy for bleeding risk assessment is most beneficial for patients with cirrhosis?			
1A. Should visco-elastic testing be performed in patients with cirrhosis prior to procedures?	In patients with stable cirrhosis undergoing common gastrointestinal procedures (paracentesis, thoracentesis, variceal banding, colonic polypectomy, ERCP, liver biopsy), the AGA makes no recommendation for use of visco-elastic testing prior to procedures to predict bleeding risk (knowledge gap).	No recommendation, knowledge gap	Very low quality evidence
1B. Should PLT and PT/INR testing be done prior to procedures to prevent procedure related bleeding?	In patients with stable cirrhosis (with known baseline abnormal coagulation parameters undergoing common gastrointestinal procedures (paracentesis, thoracentesis, variceal banding, colonic polypectomy, ERCP, liver biopsy), the AGA suggests against the use of extensive pre-procedural testing, including repeated measurements of PT/ INR or platelet count for bleeding prophylaxis.	Conditional recommendation	Very low quality evidence
2. Does pre-procedure prophylaxis to correct coagulation parameters and/or platelet level reduce the risk of bleeding in patients with cirrhosis?			
2A. Should platelet and/or fresh frozen plasma (FFP) transfusions be given to patients with cirrhosis prior to procedures to prevent procedure related bleeding?	In patients with stable cirrhosis undergoing common gastrointestinal procedures (paracentesis, thoracentesis, variceal banding, colonic polypectomy, ERCP, liver biopsy), the AGA suggests against the routine use of blood products (e.g., fresh frozen plasma, platelets) for bleeding prophylaxis Comment: This recommendation applies to the majority of patients with stable cirrhosis who usually do not have severe thrombocytopenia or severe coagulopathy. In patients with severe derangements in coagulation or platelet testing undergoing a procedure	Conditional recommendation	Very low quality evidence

	with high-risk for bleeding, decisions about prophylactic blood transfusions should include shared decisions about potential benefits and risks (including transfusion reactions and delay of procedure) and in consultation with a hematologist.		
2B. Should thrombopoietin receptor agonists (TPO-RA) be given to patients with cirrhosis and thrombocytopenia prior to procedures to prevent procedure-related bleeding?	In patients with thrombocytopenia and stable cirrhosis undergoing common procedures (and in particular, "low risk" procedures), the AGA suggests against the routine use of thrombopoietin receptor agonists for bleeding prophylaxis. Comment: Patients who place a high value on the uncertain reduction of procedural bleeding events and a low value on the increased risk for portal vein thrombosis may reasonably select a thrombopoietin receptor agonist.	Conditional recommendation	Very low quality evidence
3. Is venous thromboembolism prophylaxis with anticoagulation indicated in hospitalized patients with cirrhosis?	In hospitalized patients with cirrhosis and who otherwise meet standard guidelines for the use of venous thromboembolism prophylaxis, the AGA suggests standard anticoagulation prophylaxis over no anticoagulation.	Conditional recommendation	Very low quality evidence
4. Should patients with cirrhosis be screened for portal vein thrombosis?	In patients with cirrhosis, the AGA suggests against the routine screening for portal vein thrombosis. Comment: Patients undergoing evaluation or listed for liver transplant who put a high value on the uncertain benefits of portal vein thrombosis screening and a low value on the potential harms related to treatment would reasonably select screening.	Conditional recommendation	Very low quality evidence
5. What, if any, specific therapies should be offered for treatment of portal vein thrombosis in patients	In patients with cirrhosis and acute or subacute non-tumoral portal vein thrombosis, the AGA suggests using	Conditional recommendation	Very low quality evidence

with cirrhosis: low molecular weight heparin, direct-acting oral anticoagulants, or vitamin K antagonists?	anticoagulation over no anticoagulation for treatment of portal vein thrombosis. Comment: Patients who put high value on the bleeding risk on anticoagulation and lower value on uncertain benefits of anticoagulation would reasonably choose no anticoagulation.		
6. In patients with atrial fibrillation and cirrhosis, is anticoagulation safe and effective?	In patients with cirrhosis and atrial fibrillation with an indication for anticoagulation, the AGA suggests using anticoagulation over no anticoagulation. Comment: Patients, particularly those with more advanced cirrhosis (Child-Turcotte-Pugh class C) and or low CHA2DS2-VASC scores who put high value on avoiding the bleeding risk on anticoagulation and lower value on the stroke reduction, would reasonably choose no anticoagulation.	Conditional recommendation	Very low quality evidence

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