BBGuy Essentials 056CE:
Transfusion in Liver Disease with Jeannie Callum
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Joe Chaffin: Hi everyone. It's my privilege to welcome you to Blood Bank Guy Essentials, the podcast designed to help you learn the essentials of Transfusion Medicine. This is Episode 056CE and I am Joe Chaffin. On today's episode, I'm interviewing one of my favorite previous guests, Dr. Jeannie Callum, about one of her favorite topics, which is transfusion in liver disease. More on that in just a second.

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If you practice transfusion medicine in a hospital setting, there is just no doubt that patients with liver failure have occupied a decent amount of your time. These are patients who just look BAD in so many ways, and they often have lab values, quite frankly, that cause many clinicians to just react with, "Oh my gosh, we've gotta transfuse this patient." Unfortunately, it's not quite that easy. And liver failure patients in general are complicated. And their care is not easy in general, so why should their transfusion care be easy?

Well, my guest today is Dr. Jeannie Callum. She's director of Transfusion Medicine and Tissue Banks at Sunnybrook Health Science Center in Toronto. Jeannie just loves talking about this particular topic. And she's published on it as well. Jeannie's just the best to talk to. I know you're going to learn a ton from her. So let's get right straight to it, ok? Here's my interview with Dr. Jeannie Callum on transfusion in liver disease.

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Joe: Jeannie, welcome back to the Blood Bank Guy Essentials Podcast!

Jeannie: Hey, thanks for having me. I love your podcast! You actually save me a lot of time with my residents because I can send them off saying, "Oh, go listen to this podcast." And they come back in an hour.

Joe: Well, I very much appreciate that! And you have been gracious enough to be a part of that. Everyone, Jeannie was with us back in 2016, where she talked about the use of plasma in kind of settings where it's not completely obvious. I think that's how I titled it, "Plasma Transfusion When It's Not Obvious." And that's BBGuy.org/016. I would highly recommend that you listen to that. Jeannie, I'm actually kind of interested in this because I've noticed for you, over the years, you've a little bit become kind of a go-to expert, not just a little bit, a lot. I know

that some of the stuff that you published in the past with Sunny Dzik. And I know you worked with Sunny on a book chapter and the like, in terms of transfusing when transfusion isn't obvious, things like pre-procedural indications and plasma transfusion, as we talked about before when maybe it is/maybe it isn't indicated. I'm curious, how did you get interested in that, Jeannie? How did that kind of fall into your niche?

Jeannie: Well, I have to say from a clinical point of view, it's so common. I would say every day the blood bank calls me and says, "Somebody's ordered plasma for some procedure." And then you start digging deeper into every procedure. And then you realize, one, there's no data, good quality data to tell you what you're supposed to be doing. And there's essentially few randomized trials. But then at the same time, people come up with these pretty solid guidelines that say, "You MUST transfuse plasma if the INR's above 1.5," despite there would be no evidence for that. So that really kind of got me interested, and then, that book chapter with Sunny Dzik. And he's such a great mentor to guide you through how you think about this, that I started to think more about it. Sunny and I have also just written a recent book chapter for ICU docs on liver disease and plasma.

Joe: Nice. Oh wow. I'm looking forward to seeing that. Can you tell us what the book is and when it's coming out?

Jeannie: The book is a book on hematologic challenges for the ICU patient. And I think it comes out early 2019. And Aryeh Shander is the lead editor on the book.

Joe: Excellent. Well, that's awesome. We'll be definitely looking forward to that, for sure. Well Jeannie, as I said, you and I have obviously spoken before, and I was eager to get you to appear again on the podcast. And when we were talking about what to discuss, I think what we ended up deciding (and it really wasn't that long a discussion because you mentioned this and I was like, "Yes!"), we decided that we were going to talk about liver disease and transfusion. And again, with your background ... and those of you that don't know, Jeannie is both a clinician and a Transfusion Medicine expert. I guess we should just start with this. And here it is: Liver disease and figuring out how to transfuse patients with liver disease seems to be something that comes up often. But as you kind of mentioned before, it kind of seems to be something that maybe we either don't have enough data, or maybe we don't fully understand. Is that your perception, and I guess how would you summarize the issues in general that come up with liver disease and transfusion?

Jeannie: So, the first thing is I would say it's super-common that we deal with patients with liver disease. It's a really common entity in the hospitalized patient. **Somewhere around 15% of the red cells, 20% of the plasma, and 15% of the platelets are transfused to patients with liver disease**, so this is a really common area that we face all the time. What's a little shocking is the fact that we haven't done large randomized trials in it. And I'm not sure whether or not this was just a blind spot, or we've made a ethical judgment that patients with liver disease, because much of it is self-inflicted, we're not going to do research in that area. Lots of it is alcohol-related liver disease. I'm not sure where that came from.

And historically, it was pretty easy. We just said, "Oh, if the INR is above 1.5, you're going to do some procedure, or the patient's bleeding, transfuse plasma;

platelet count under 50, transfuse platelets." But then somewhere over the last 15 years, people have done more and more studies and realized that a patient with an elevated INR with liver disease actually is "rebalanced." They have quite a nice balance between "procoagulant" and "anticoagulant." Even though the laboratory test result is abnormal, it doesn't actually mean anything to the patient. But we haven't gone beyond that and said, "Okay, now that we know the patients are probably in balance despite an INR of 3, what do we do now? How do we operationalize that into clinical care?"

Joe: And we're going to spend a decent amount of time talking about all of that. So as we get started, Jeannie, I wonder if ... Can you just kind of give us an example or maybe just a very quick patient sketch of something that might come up as a question in the setting of liver failure, where someone might be deciding whether or not they should transfuse, and something that we can kind of come back to at the end, and circle around and see what the answers might be?

Jeannie: Okay. So I think probably one of the most common things is a patient with liver disease. They have an elevated INR somewhere between that 1.8 and 3, and they're going to have a liver biopsy done. Common tests that we do, it might be transcutaneous or transvenous, but they're going to have a liver biopsy. Even though we have lots of non-invasive assessment of the liver, still many patients have a liver biopsy. Other common procedures in a patient with liver disease is probably the paracentesis. So those are the two situations that are faced every day in a large academic or non academic hospital. And the other place is a variceal bleed with an elevated INR. And what do you do about that patient?

Joe: So Jeannie, let's start off with just simply talking about ... We've danced around this a little bit and you've mentioned some of this. But let's talk a little bit about the fundamentals of the hemostatic derangement in liver disease. Why are people with liver disease messed up in terms of both their laboratory values and potentially what's going on actually in their veins?

Jeannie: Okay. So I think that that there are really several parts to this. The first is that they have a vascular disturbance. Because of their portosystemic venous shunting, they've got engorged gastric and esophageal varices, these things are big. And just because of the hemodynamics in that area, they tend to bleed. So you've got that vascular disturbance. The second disturbance that you have is their coagulation system ends up with this kind of tenuous balance between pro- and anti-coagulant factors.

So we all know that most of your procoagulant factors are synthesized in your liver, other than your von Willebrand Factor and your Factor VIII. So they're all down, so that when you do your INR, you find that it's elevated. One of the reasons that your PTT is usually not as elevated as your INR is that your Factor VIII in liver disease is actually really high. And the worse your liver disease gets, the higher your Factor VIII gets. And so it kind of offsets that PTT. So most types of liver disease, you're looking at the INR to try and judge is there coagulopathy going on. But what you fail to remember with your INR is that your ... The system actually doesn't include thrombomodulin in the system. And so it doesn't actually measure the balance between your procoagulant and your anticoagulant. So your protein C and your protein S proportionately decrease just as your other

clotting factors go down. **So at the end of the day, you're essentially balanced**, so that when clinicians do studies on elevated INR liver disease patients, their thrombin generation is normal. They can still make a clot.

The other thing that happens obviously is patients become thrombocytopenic. And thrombocytopenia is exceptionally common, including even platelet counts below 50. And that's thought to be related to primarily sequestration and that engorged spleen, as well as suppression of your "TPO" production because the liver is not functioning at 100 percent, very analogous to a patient that has renal disease and doesn't have enough EPO, and so the hemoglobin's low. So you gotta give exogenous EPO to hit your target of your hemoglobin to avoid transfusion.

Joe: And Jeannie, just to interrupt you for a second, just for the beginners that are listening, when you say "TPO," I just want to make sure everyone understands what you mean.

Jeannie: So TPO is thrombopoietin. It's the hormone that's made by your liver to generate ... force the bone marrow to make platelets. Because your liver isn't synthesizing at 100%, the TPO's low, so your platelet count's low.

Joe: So it's more than just the old traditional thought that, "Hey, you got a big honking spleen because of the portal hypertension, and all the platelets are sitting in the spleen." It's multifactorial, right?

Jeannie: Absolutely. And I think we've overstated the hypersplenism part of that explanation and understated the TPO. And that's because the relationship between your platelet count and the spleen size is very poor, really just calling into question whether or not this splenic sequestration is the dominant feature of the thrombocytopenia.

Joe: Got it. Okay. So you've mentioned the rebalancing. And I want to pop back to rebalancing in just a second. And you've also mentioned the thrombocytopenia. Is there anything else that is going on in liver disease that we should talk about?

Jeannie: The only other major dominant part is the fibrinolysis. Just like you have your balance in your procoagulant and anticoagulant, you have that same balance going on in your fibrinolytic pathway. And if you look at all of the studies that have been published over the last decade in liver disease and what's happening on the fibrinolysis side, it looks like it's tipped in the most in patients slightly in favor of thrombolysis. And the dominant thing going on is that tPA is not being adequately cleared in liver disease. It's made by your endothelial cells. But then the clearance is reduced, so it starts to accumulate. And that's really tipping in favor of hyperfibrinolysis.

But every patient is very variable. Some patients will be hypofibrinolytic, normal, or hyperfibrinolytic. You can see all patterns. So we're using a strategy of one size fits all for patients with liver disease, even though underneath all this, each individual patient ... Some might be bleeders. Some might be clotters. But we're treating them all exactly the same without really understanding physiologically that individual patient. In terms of precision care for that patient, we are so far from that in liver disease.

Joe: You are preaching to the choir there because I am in total agreement. And coming back to where we started there, with the rebalancing, I want to explore that just a little bit more if you don't mind, Jeannie. And specifically, I will tell you I've had that very conversation that you described about how ... I kind of describe it to people as a "teeter-totter" or "seesaw" kind of thing. Not only we have the impression that the patient doesn't have enough coagulation factors, which is true, and so we think that things are tipped towards bleeding. But we often don't recognize that the other side is decreased too. So you end up, as you said, in balance. But I will tell you that I have had clinicians push back on that and really say, "Well Joe, how can you say that? Look at this lab value. Look at this INR. It's SO bad! How can you tell me that this patient isn't going to bleed?" So I guess my question is, do we have any data, do we have any evidence, has anything been studied to kind of show that these patients really are in balance?

Jeannie: So my favorite study that I quote when people ask me that question is there was a study done of a bunch of patients who had acute liver failure, had a median INR of 3 [NOTE: See Lisman T et al, J Thromb Haem 2012;20:1312-1319]. And they did a whole bunch of tests on them including their thrombin generation, as well as looking at their fibrinolytic pathway. And those patients were hypercoagulable. And the authors of that study said, "Wait, stop. What are we doing transfusing plasma to these patients before a procedure, when the vast majority of them are actually HYPERcoagulable?" And I think the other thing is, clinically, if you look at the patients, they only bleed from their varices. It's exceptionally uncommon for one of them to have an intracranial bleed or bleed spontaneously from some other site.

The bleed rate at both a liver biopsy or a paracentesis, is well less than 1%. So they're not even bleeding when we do procedures on them. And they still got clots. We all know, they get a lot of portal tract clots. So they're actually hypercoagulable. So **there's lots of evidence suggesting that the INR is really garbage**. And I think we have to really openly say that, and say, "Okay. Well, we have to move on from this." And say, "Well, what are we going to do now?"

Joe: This is why I love talking to you, Jeannie, because you don't pull any punches. That's awesome. That's going to be the quote for this episode: "The INR is garbage." Okay, I probably won't publicize that too much, but that's awesome. That's hilarious. But I think that's hugely important because we do hang our hat so much on that one number. And you mentioned before that there's an issue with how the test is performed. I'm wondering can you ... just again, since so many beginners listen to this and we kind of whipped past it quickly when we were talking about thrombomodulin, can you delve into that just a little bit more? Why is the INR only sensitive to the factor-deficient, the bleeding side of that teeter-totter that I described?

Jeannie: So I think there is a couple things about this. So the first is there's no thrombomodulin in the test system. And thrombomodulin is a transmembrane protein on your endothelial cells, that downward regulates the thrombin generation. So if there's no thrombomodulin in your assay, protein C is not actually activated and so you don't measure that inhibitory side that's actually naturally happening. And since, in liver disease, protein C levels are down, just

like your factors are down, they're back in balance, but you're only measuring one side of that equation.

The other really big thing is that the INR is based on the international sensitivity index, or the ISI, for patients on warfarin. It was never done for liver disease patients. And if you try to go hospital to hospital comparing the INRs on liver disease patients, it's very variable hospital to hospital. So you couldn't compare an INR for a liver disease patient at your hospital, and if you airlifted them to me, and an hour later I did an INR, I'd get a different value, so big, big limitations to this test in liver disease.

Joe: Unfortunately, we're often relying on a test that is leading us down the wrong pathway in these patients. So that obviously brings me to the next question, and that is, we certainly know that there are other tests out there, some of which are being used fairly widely, things like ROTEM and TEG for example. But what do we know about those kind of tests and any others that are available, either in the clinical world or the research world, that tells us how these patients with liver failure are doing?

Jeannie: Yes. So the bottom line is, as far as we know, there is no other test that we could use as a gold standard that is really hard locked in to very valuable. So what's believed to be the gold standard test is something called the "Thrombin Generation Test." It's thought to be a superior measure of being able to pick up that balance in the assay, because there is thrombomodulin in this test. But this test is very finicky. It's not widely available so it's not been standardized. And it hasn't been ... A lot of testing hasn't been done except in research settings.

And when people compare the Thrombin Generation Test to the ROTEM and the TEG, there's not great correlation. So either the ROTEM's wrong and the Thrombin Generation Test is right, or the other way around. It hasn't stopped people though from doing studies of looking at TEG before procedures. And one really great study randomized patients to the standard preprocedure investigations with your INR and your platelet count, compared to the other group got TEG. And the only people they included in this study had to have an INR above 1.8 and a platelet count below 50. So 100% of patients in this standard of care group, by definition, got transfused, compared to only 17%. Only one patient bled in the standard of care arm. So whether those other 17% that were transfused based on their TEG results needed any blood products at all, we don't know. But all it tells us is using INR is vastly overexposing patients to blood products.

Joe: For sure. Okay. So unfortunately, no great tests that give us a very specific answer. And that kind of leaves us, I guess, in somewhat of an awkward position. So tell you what, why don't you, if you would, we're going to talk about some non-transfusion options that are potentially available out there. But if you could, just summarize where we are right now. What are the problems that are facing us based on the things that you've already talked to us about?

Jeannie: What we've got is a very unique coagulation disturbance that's wholly different from your patient that's on an anticoagulant, on warfarin, is on rivaroxaban. It's a completely different thing. So when you approach the coagulation in a liver disease patient, you cannot apply anything else that you know about other

patients with coagulation disturbances. We know that the INR, the PTT, or any other standard lab test that's available in your regular hospital lab, it can't help you make any decisions. We know that pretty clearly. There's no research test that's en route to fix this knowledge gap. So it means when you're making a decision about whether to give plasma to a patient, you certainly are just really eyeballing the patient, and it's an "end-of-the-bed" decision. "This patient looks like a bleeder, here's why: They're bleeding from multiple sites, they have bruises everywhere, they're 'oozy.' I think this is a bleeder. We're going to do a liver biopsy. This one we're going to give plasma. This other one? They're not bleeding from everywhere, anywhere, and last week they had a clot somewhere. This patient, we're going to do the liver biopsy. We're only going to transfuse plasma if the patient bleeds." And that risk is 0.5%.

Joe: Okay. So we're in a situation where we know that we've got issues. We know that these patients are not simple necessarily to evaluate and that the laboratory testing that we have doesn't necessarily tell us the whole story. Before we get to the how we make decisions on whether or not to transfuse these patients, if you don't mind, can we just kind of run through some of the non-transfusion options? And what's been studied with any of those and any thoughts that you have? Something like for example Vitamin K, obviously a lot of times patients with liver failure are thought to have Vitamin K issues. Why don't you talk to us about that and then just go from there.

Jeannie: That's a great idea. And it's the right order too, because we want to promote that we use patient blood management. We try and use non-transfusion options whenever we can, just like when you would try to prevent a red cell transfusion, we're giving IV iron and other therapies. So for Vitamin K, there's essentially minimal data to suggest that Vitamin K might be helpful for patients with liver disease. But I have to tell you, I see it as a, in my center at least, a routine thing that happens to everyone that has an elevated INR, including in the middle of a trauma, which obviously makes absolutely no sense, because it would take a week for them to become Vitamin K deficient. So I think we just somehow it went from, "Well, we've reversed warfarinized patients with 10 mg of IV Vitamin K, we're going to do that for everybody that has an elevated INR."

Joe: I'm sorry to laugh, but that's just kind of funny, isn't it?

Jeannie: I know. So one study, it looked at about 90 patients that had some sort of liver disfunction, whether it was cirrhosis or chronic viral hepatitis, and measured INR, PTT, clotting factor levels, as well as what's called "PIVKA" proteins. So these are "Proteins Induced by Vitamin K Absence," or P-I-V-K-A. And when you get Vitamin K in this study and another study that was published, there's no increase in your clotting factors. So it doesn't change the INR. It doesn't ramp up your Factor VII or your Factor II or your Factor X. Those factors don't change. There is a drop in your PIVKA levels. So there is some accumulation, but it doesn't correspond to if you drop that, the other ones go up. So there's absolutely no evidence for the use of Vitamin K. That being said, you might have a patient who's been on a binge for two weeks, has not eaten any food, there INR is way above where it normally is. And you think, "Oh. Maybe this person is actually Vitamin K deficient," because of the history.

Joe: Okay. That makes sense. In patients that have serious liver disease, maybe you can think about it as it's a factory problem. You can have all the supplies that you want, but if the factory isn't working, you're not going to do much. Is that a fair way? The way my simple mind looks at it Jeannie. That's how I roll.

Jeannie: We're both in the simple mind category, for sure.

Joe: All right. So that's Vitamin K. What about one of the hot, and I use that in quotation marks, the "hot" medication that people are talking about in non transfusion options is tranexamic acid, do we know anything about that, about TXA?

Jeannie: Well, not very much actually. Studies have been done in gastrointestinal bleeding from all causes. And of course, you lump in there the variceal bleeds and the liver disease patients. And they account for about a quarter of the patients that get into those kind of trials. And in a single meta-analysis of all the published trials, the relative risk of death, now we're not even talking just stopping red cell transfusions, death, is reduced by an odds ratio of 0.6, so quite substantial. A very large trial called the HALT-IT trial, is being done. And it is going to be 12,000 patients with GI bleeding randomized to tranexamic acid versus placebo.

Obviously, if a quarter of those patients have variceal bleeding, then there'll be a subgroup analysis comparing people that had upper GI bleeds, variceal bleeds versus lower GI bleeds. Where is the benefit? And I think almost more importantly, is there a thromboembolic complication risk? Because many of these patients are hypercoagulable. But throw TXA at them, are they going to have a portal vein clot? And so we're not just looking for efficacy, but we're also looking in liver disease patients, is it also safe?

Joe: I should be fair to our beginners that are listening Jeannie, and I skipped over this. But is ... Could you give us the super brief thumbnail on what TXA actually does?

Jeannie: So tranexamic acid inhibits your pathway of your fibrin clots and fibrinogen degradation by your plasminogen pathway. So it's really shutting down the clot breakdown, and also shutting down degradation of fibrinogen. It not only eats up your fibrin, it eats up your fibrinogen.

Joe: Okay. Okay. Got it. Forgive me Jeannie. I didn't mean to interrupt you there, but I'd figured we'd better say that for our folks that are listening. Anything else on TXA before we move on?

Jeannie: The only other thing where it's been tested in patients that have liver disease is patients undergoing liver transplantation and liver resection. And there's no question that it reduces blood loss and transfusion rates in those studies, without increasing the thromboembolic complications. Now, the studies aren't huge. But even in meta analysis of those populations, it appears to be effective and safe. So we're really hoping that when the HALT-IT trial comes out, it's going to find the same thing. That will be a huge advance if it reduces mortality and transfusion rates in patients with liver disease and variceal bleeding, 'cause currently when you look at retrospective reviews and find out, well, how often are patients with liver disease, with bleeding, getting antifibrinolytics? It's about 5%. So we would

go from never using it to always using it. So it's really going to be, if it's a positive trial, it will change really how we manage the GI bleed in this population.

Joe: So Jeannie, we've talked about things that are kind of leaning towards the coagulation factor and the whole coagulation cascade side of things. Do we have any information on some of the new “fancy-shmancy” platelet drugs, the ones with names that are impossible to pronounce? So I'm not even going to try. I'm going to let you do it.

Jeannie: Have you ever wondered about why they always make those drug names so long that we can't even prescribe them? So this looks like it is a potential to reduce a need for platelet transfusions around the time of the procedure. So people have done placebo-controlled trials of eltrombopag, of romiplostim which is “Nplate,” as well as the "new kid on the block," which is avatrombopag, if I say that right. I could have completely butchered that drug name. All of those trials compared to placebos showed that you could increase the platelet count in the vast majority of patients. You would avoid a platelet transfusion if you're using a platelet count of 50 to make your platelet decisions. And of course, we don't know what the right threshold is, but if you were doing that, it would avoid those platelet transfusions. The largest study that was done with eltrombopag raised a flag for a concern of an increase in the thromboembolic complications three-fold. And this is without driving the platelet count to 1,000, This is just driving the platelet count into the normal range. And so, obviously, before this hits outside of the clinical trial setting, we're going to need more space on the safety. We know it works. But actually, is it safe? And I guess it's bouncing between the risk of the platelet transfusion versus the risks of these TPO drugs. Platelet transfusions have side effects too. They cause thrombosis. They cause bacterial contamination, TRALI, TACO. There's lots of stuff that might happen from a platelet transfusion. And where's the balance between those two different agents? And that's not been completely clarified. But no question efficacy is there, it's the safety we're worried about.

Joe: Got it. Okay. Well, there's two others that I want to just very briefly mention, Jeannie. I don't know that we'll have a lot to say about them, maybe I'm wrong. But the first one, I think I might know the answer to this, because of what you've said before about Factor VIII and von WIllebrand's Factor and liver disease. But what about DDAVP?

Jeannie: So DDAVP, despite liver disease being so common and DDAVP so available, very few studies have been done. We do know that the Factor VIII level doesn't go up when you give DDAVP to these patients. So that's obviously ... you can't even ... even a surrogate marker of some potential that's how it works, and that doesn't even change. People have done studies of people going for dental extraction, giving them DDAVP and nobody bleeds, but there's no control group. So what do you make about that? So essentially, there's nothing in the setting of variceal bleeding, liver transplantation from the published studies that suggests there's any efficacy to DDAVP. Probably similar to Vitamin K. I bet you if you did a retrospective review, you would find lots of these patients are getting DDAVP, and it's probably not beneficial.

Joe: I gotcha. Okay, well what about Recombinant Factor VIIa.

Jeannie: Yeah, so obviously, that's a very expensive treatment. So obviously, you would have to show that it's effective, not just for transfusion end points, but mortality end points. And people have looked at this in hepatectomy, liver transplantation, variceal bleeding, some to treat bleeding, some to prevent bleeding, and it doesn't have any significant impact on clinically important outcomes such as mortality, with extreme cost and clear increased risk of thromboembolic complications. So as far as we can tell, harm, no benefit. We don't use it.

Joe: Got it. Before we leave this Jeannie, I think we would be doing a disservice to our listeners if we didn't cover something that, quite frankly ... Well, I'll put it to you this way. You're a clinician so you have the credibility of being a clinician. I'm a pathologist. Sometimes, when I say to a GI doc, for example or a hepatologist, "Well gee, we're throwing all this product at the patient. What's been done in terms of actually looking at what's going on?" Let's talk about that, about actually doing endoscopic procedures to try and help with these situations. How do you feel about that?

Jeannie: Well, I think actually it's kind of a global thing that we're going to be doing in transfusion medicine. So whether you're faced with a trauma patient that's bleeding, it's like, "Guys, how are we going to stop the bleeding? Are we getting them into surgery or IR? How are we going to stop them from bleeding?" If it's a pregnant woman with a severe postpartum hemorrhage, "Guys, are we taking the uterus out? How are we stopping the hemorrhage?" And the same thing is very true with endoscopic ligation. It's very effective both in terms of treatment, it's the core treatment. So, if somebody's activated your massive transfusional protocol, you go down there to your emerge and it's a variceal bleed, the first question you should be is, "Guys, is GI coming? 'Cause somebody needs to band this patient."

And the second thing is if patients are on a, as the recommended guideline, structure for prevention, you can reduce the risk of bleeding from varices by half. And essentially, patients should have a baseline screening endoscopy. And if they have small varices, every two years they should be scoped to make sure they're still small. But if they're medium or large, they should be banded, and then they should be followed recurrently to make sure they don't regrow back. And that strategy, whether it's using ligation or even pharmacological agents, such as a beta blockade, they reduce the chance of bleeding. And we shouldn't forget that that's the most important thing to prevention of variceal bleeding.

Joe: I couldn't agree more. And Jeannie, what you just said, I think, is hugely important. To my listeners who are beginning in Transfusion Medicine, what Jeannie just said is so huge. And that's, we are practicing “Transfusion MEDICINE.” We are not just practicing "transfusion." We're a part of the team. And we need to get away from, in my opinion ... I think you'll agree with this Jeannie, but please tell me if not, in my opinion, we need to absolutely get away from the whole, "This is our lane, this is everyone else's lanes". We're practicing medicine here, and we need to consider the entire patient and make appropriate recommendations. So Jeannie, I love what you just said. I absolutely agree with that.

Jeannie: And I think we have to be on that advocate side of, "Okay, how are we going to help?" Right? Rather than we're just supplying blood products, how can I help make the right decisions for this patient?

Joe: So, I think it's fair to say from ... And again, correct me if I'm wrong, but I think it's fair to say from what we've talked about so far, that in terms of the non-transfusion therapies, other than doing appropriate endoscopy both for prevention and when something happens, am I correct in assuming there's not a lot of data that suggests that anything is super helpful there?

Jeannie: So, I think the only thing is the TPO agonists might be coming, but they're not ready for prime time. They look promising. And I think the HALT-IT trial is going to change the face of how we manage variceal bleeding, but right now essentially ... so we don't have the right ... a test. We don't have any non transfusion therapies readily available to you, so ...

Joe: I guess that means we need to move into talking about transfusion. I mean, the podcast name is "Liver Disease and Transfusion," so I suppose we should talk about that. And I just want to prepare everyone. The reality is that in a lot of what Jeannie and I are going to talk about in the rest of this podcast, you're going to feel a little bit unsettled and a little bit unhappy at the end. I'm just warning you. It's just kind of how it is. It's where we are with these discussions, but I think what Jeannie is going to do for us is give us a way to approach this that I think is more reasonable than has been done traditionally. So no pressure on you Jeannie, but you gotta come through for me. Okay? Well let's start with platelets. I want to close it out with plasma. So let's start with platelets.

So, what do we have in terms ... You mentioned before that there are ... at the beginning in fact, that there are some very specific guidelines that have come out in terms of how to handle patients that can be somewhat frustrating. So what, if anything, do we have out there for guidelines for platelet transfusions in liver disease?

Jeannie: So, the American Association of the Study of Liver Disease, put a position paper on a whole bunch of things related to liver disease and came out with, just like all guidelines, a series of recommendations. One of the recommendations is really good and it's really valid, and it really reflects where we are right now. And they basically say in quotes, "No specific PT/INR and/or platelet count cutoff at or above which potentially adverse bleeding can be reliably predicted." So they're basically saying, "We can't use those, it's no question." That's true. And it was great that they made that statement to let people know that we're in an area of "I don't know". But then they go on to say, "The platelet transfusion should be considered..." They don't say you have to give them, but "...should be considered when levels are less than 50 to 60." Not just 50, but 50 to 60, to give some range about where it is. So our coulter counters are so accurate that we can have such a range….

Joe: Yeah. Oh no.

Jeannie: Yeah, so that puts us-

Joe: That's not helpful.

Jeannie: And then we have, also, we have obviously the AABB guidelines that were put up for platelets to say that if you're going for a major procedure, they don't specifically say in liver disease. We have the Society for International Radiology guidelines that also say 50, which is a bit of a problem because that's saying a platelet count that's for an acute leukemic is the same as a platelet count for a patient with liver disease. For example, a patient with liver disease has an elevated von Willebrand's level. They have elevated fibrinogen. And so, even though they might have a slight handicap on the platelet side, some of that is combated by elevations in their platelet binders. And so a platelet count, say, of 30, might be the same as a platelet count of 50 in an acute leukemic.

So just even having one platelet threshold for all diseases, that cannot possibly be true. So there are some quite obvious problems with guidelines, because you're putting out very general guidelines that really don't involve the intricacies in how complicated our patient populations really are.

Joe: So I think what you just said, I want to expand on it for just a moment, Jeannie, 'cause I think that's a hugely important point that, again, learners in our field might not appreciate. So, you mentioned that because the von Willebrand's Factor and Factor VIII are increased, that that might make the platelets work better. What's the rationale for that? Why would we think that?

Jeannie: With the von Willebrand Factor and the fibrinogen are both elevated ... so these are your proteins that bind to your platelets to help them bind to both the endothelial cells and other platelets. And so those are elevated. So if the plate count's a little bit lower, the platelets are actually going to function better because those other proteins are elevated because of the other derangements that are happening with liver disease. For example, von Willebrand's accumulates because your ADAMTS13 is downgraded and so you get more high molecular weight von Willebrand factor. Your fibrinogen is elevated because it's an acute phase reactant. And these patients have a lot of bacteria coming in from their gut.

Joe: Got it. I think that's something that is not as well-appreciated as it should be. So Jeannie, I'm going to take a wild guess here and say that we don't have a ton of studies, randomized studies, in platelet transfusion and liver disease. Is that a true statement?

Jeannie: And that's a true statement. And we will NEVER have studies, although you may prove me wrong. Because the incidence of a hemorrhagic complication, let's say, at the time of a liver biopsy, is 0.5%. And that's been documented in one study that had 6600 liver biopsies and another one that had over 2700, so 0.5%. So if you're going to do a randomized controlled trial, trying to take it from 0.5 to 0.25, you're talking about 100,000 patients randomized into two trials. And if you look at it, that means we're going to transfuse 99 patients with platelets for one potential benefit. So there's no way that we could just so liberally transfuse platelet transfusions without having complications from the platelet transfusions.

Joe: Okay. Well let's bottom line this then, Jeannie. How do you feel? What do you conclude about the use of platelets, at least prophylactically, and we'll talk about bleeding patients in a sec, but when patients just have a low platelet count and you're trying to decide whether or not they should get a platelet transfusion, how do you approach it?

Jeannie: So, I still look at the platelet count. But I, in my head now, try and make a correction for the etiology, so that if it's liver disease, I say, "Oh, it's 40." I know it's higher than 40. And if my guidelines are saying, okay, I gotta have 50, that patient with the liver disease at 40 really is at a higher platelet threshold. And that's the kind of patient I say ... No history of bleeding. Last time they had a procedure or dental extraction, no bleeding. And the patient's otherwise systemically well, that's the kind of patient I say, "Let's hold off. Let's do the liver biopsy. If they're the 0.5% that bleeds, then they should get the platelet transfusion." And we have to be starting to think about, when we do say a retrospective review of practice, probably 90% of the platelet transfusions given to liver disease patients should be therapeutic. They should be given at the time of bleeding rather than prevention. But currently right now, we're sitting at a 60/40 split. 60% are being given for bleeding, 40% for prophylaxis. And that, we need to shift that number. We need to be transfusing more when we're bleeding, less as a prophylaxis. And because there's no data to suggest that the platelet transfusions are helpful, this is where you kind of have to sit down with the patient and have to say, "Look it. We don't know. Your platelet count is very low. Here are our two options. We can do platelets, and here's what would most likely happen, and here are the risks. Or we don't give you platelets, and we only give them to you if you bleed."

What a lot of people don't realize is when you give a platelet transfusion to a patient with liver disease, their average increment is about 13 points in their platelet count. It doesn't go up by 25 that you might see in another platelet population. And in one in five patients, it won't budge at all, no matter how many platelet transfusions you give to that patient, it's not budging, something to do with the hypersplenism. So they're very ineffectual. They have adverse side effects. They probably increase the risk of thrombosis. They have the risk of bacterial contamination. There's lot of bad things that happen to them. And if the risk of bleeding is around 0.5%, then why not just do the procedure, and in the rare patient that bleeds, give them their platelet transfusion at that point?

Joe: Okay, so Jeannie, that's awesome information. So what about the patients who already are bleeding? How do you make that evaluation?

Jeannie: So, for platelet transfusion in a patient that is bleeding from liver disease, we have to remember that at least 95% of this bleeding will be from their varices. And so it just needs to remind us again that we must use our local measures, and is it possible that GI is standing there at the bedside and they can quickly band that [varix] and it will immediately stop bleeding? Or it's going to be some delay? Sometimes, they're bleeding so much that they actually can't see what they're doing, and you need to somehow figure out how to slow the bleeding. So there are essentially very few published studies on platelet thresholds in a bleeding patient, whether it's a leukemic or liver disease or some other surgical patient population.

So most experts currently recommend a platelet count of 50, but they uniformly say based on very low quality evidence. Most of us use that. As I said before, if you have a bleeding patient, most of our platelet and plasma transfusion decisions should be in a bleeding patient. That's when it's going to be ... the risk/benefit ratio is probably tipping to the side of getting the platelet transfusion

rather than holding back. But the most important message is get GI in there, get them to band, because the vast majority of time, this is going to be a variceal bleed.

Joe: Got it. Okay. So we need to finish this with a discussion about plasma. And again everyone, Jeannie has been on the podcast before. And she talked a lot about plasma transfusion in many different clinical situations. We talked a little about liver disease back then. So again, I would refer you to BBGuy.org/016 for that discussion. But let's start here Jeannie, and just ask again, do we have evidence, has there been any evaluation of whether or not we're transfusing plasma wisely in patients with liver disease?

Jeannie: People have actually done some pretty amazing retrospective studies looking at this. So there was a study done in the UK that looked at 1300 cirrhosis patients admitted to 85 hospitals in the UK. And the transfusion practice was pretty inexplicable. 11% of the plasma use was with an INR below 1.5, where you can say there can't possibly be any benefit from that. We know that there's probably no benefit at least up to 1.8 to 2, so if you're 1.4, 1.3, 1.2, it's definitely not going to do you any benefit, and that's a big chunk of the plasma use. We do know from several large studies looking before and after a plasma transfusion, looking at the delta in your INR, and if your INR goes up to 1.8 to 2, almost no drop in the INR. And that's because the difference between your patient and the plasma is now getting very close. And so the benefit is much less. And the plasma only lasts for about six hours, so generally, between when you start infusing it, finish the last bag of plasma, and go to measure it, the first couple of bags have already worn off.

And there's no evidence from systematic reviews that giving plasma prevents bleeding in patients with liver disease. Now some of the studies have been done just on patients with high INR. And probably the largest one was done looking at 1200 non cardiac surgery patients going to the operating room with high INRs. Obviously, some of them are for liver disease and some of them were from perhaps Vitamin K deficiency. Interestingly, when you would think that probably the bulk of them would get plasma to reverse it. Actually, only 11% of the doctors were actually fixing or attempting to fix that number before the patient went to the OR. And shockingly, the patients that got plasma had no benefit in terms of any bleeding type outcome. And actually, the complete opposite was found. So patients that got plasma bled more, were more likely to go on the ICU, be on the vent for longer, stay in the ICU for longer, and more likely to die. Obviously, because it's not a randomized study, all I can say is "Whoa! That's pretty concerning. Maybe we shouldn't give plasma outside of a clinical trial to such a patient, when we have absolutely no idea where the risk/benefit ratio will fall." We do know that for some procedures where the bleeding risk is pretty close to zero, in the liver disease patient, and that would be a paracentesis, a thoracentesis, and a central line placement, those are the ones where I teach don't even measure the INR.

Perhaps, look at the platelet count and make sure it's above 20. Perhaps we don't even have to go as high as 20 for those procedures. But don't ever look at the INR. Don't ever act on the INR, because the chance of bleeding is infinitesimally small. And I think if we addressed even just those procedures and

not giving plasma to people who have elevated INRs, who aren't bleeding or going for a procedure, and people with normal INRs, if we just stop transfusing those patients plasma, that would probably cut down 50% of the plasma given to liver disease patients, and get us at least well on the road to more appropriate use of plasma.

Joe: All right Jeannie, so that is a magnificent summary. Obviously, the next question is, for patients who are bleeding, how do we make those decisions on whether to transfuse plasma?

Jeannie: Okay. So here's where, just similar to the data for platelet transfusion, there's almost no data. People have not done any prospective randomized trials, even though this is a very common clinical situation. People have, however, done retrospective reviews of intensive care patients who have cirrhosis. And because this is so common, they actually get quite large numbers of patients with cirrhosis admitted to the ICU. And they look at people who developed new major bleeding during their ICU stay some time after their admission. And they found that patients who had more bleeding had lower platelet counts, lower fibrinogen, higher PTT. But those same patients also had a higher history, or a greater history, of larger varices. And they're more likely to be bleeding on admission, and so that was their admitting diagnosis. So whether or not those abnormal laboratory tests were causing the bleeding or just a marker of someone who's got more severe portal hypertension and obviously bigger varices, that's probably, the latter argument is probably the reason why they bleed more.

And so, given the complete lack of clinical studies, really one can't make a recommendation of when to give plasma based on the INR. Certainly, if the INR is below 1.8, because the plasma is not going to change even the laboratory test result, they can't possibly change the outcome for the patient. Probably that's inappropriate. And past that, you really have to individualize the patient decisions. And because you can't use the INR, it's really an end-of-the-bed decision. How fast is this patient bleeding? How soon am I going to get control of the bleeding through some sort of surgical or interventional radiology intervention? Where are they bleeding from? Are they bleeding from multiple sites, suggesting that that coagulopathy actually is tipped in favor of a coagulopathy versus a hypercoagulable state. But you can't possibly transfuse plasma to every single patient who's got an INR above 1.5 that's bleeding in the ICU, because the vast majority of patients, there's going to be minimal benefit expected. And there's certainly risk to transfusing plasma, particularly in a liver disease patient, increasing the portal pressures on that patient and causing that patient to actually bleed more.

Joe: And that's such a big concern. I completely agree with that. And that's one that, unfortunately, I think is often underestimated, the potential risk of it. I mean, obviously, you already said we can't really say exactly how much it contributes to the excess bleeding, but just logically it seems like it could. Right?

Jeannie: Absolutely. And really, we don't know which side of this risk/benefit the plasma's going to fall under, so you should be really thinking twice before you dump platelets and plasma into a liver disease patient.

Joe: Jeannie, before I let you go, there is something that we talked about last time you were on the podcast. And we talked about this primarily in the setting of reversal of warfarin effect, and that's prothrombin complex concentrates. Is there any discussion about using PCCs in patients with liver disease?

Jeannie: So, there have been a couple of studies, small retrospective reviews, under 50 patients in these studies, comparing PCCs to plasma. Obviously, we can't even look at those because they're not powered to give you any answer. So perhaps they can tell you about safety. So on the good side, none of those trials showed an increased risk of thrombosis. But also, number is way too small. It would be nice if PCCs were as good or maybe better than plasma for a patient with liver disease, because the volume is smaller. And this way, you're not increasing the portal pressure. So instead of giving a liter of plasma, you're giving 48 ml of PCCs. So logically, you would like that. It's also less work for your blood bank, might be a little bit more expensive, but it doesn't take quite as much tech time.

There's a trial ongoing. And whether it ever gets done, we don't know. But it's listed and the study protocol actually published, it's called the “PROTON Study.” And this will be randomizing 70 patients who have an INR above 1.5, so there's a problem already there 'cause we're not sure what the INR means in a liver disease patient, but randomizing them to PCCs or placebo immediately before some surgical procedure. So that might tell us whether or not we actually need to do anything. So I'm actually more interested in what happens in the placebo group rather than the PCC group, because my gut feeling is you don't need to do anything.

Joe: Yes. Got it. Got it. Okay. So Jeannie, this has been an amazing tour through liver disease and transfusion. And I wonder if you'd just spend a couple of minutes. You've hit us with a lot of information and a lot of really useful and practical information. Can you just take a few minutes to summarize for us, in your view, the key takeaways for the people listening to the podcast?

Jeannie: Okay. So I think because of the lack of high-quality, randomized control trials in patients with liver disease, or in the absence of randomized control trials, really good epidemiologic studies looking at differences in practice and differences in outcomes, we can really only make recommendations based on low quality of evidence, expert opinion. So my first recommendation is that bleeding from esophageal varices should be prevented with evidence-based screening endoscopy. And that when you do bleed from varices, it should be promptly managed by your GI team, because stopping the bleeding is, just like in all other hemorrhagic situations, that's our primary intervention.

The standard laboratory tests; your INR, your PTT, and your other stuff that's available through your standard coagulation lab, really don't reflect what's going on with the coagulation competence of that patient. And you really have to say, "You know, I really can't look at that, the lab value. I see what it is, but I can't make decisions based on it." And we all need to be teaching that, not just within Transfusion Medicine, but we have to get that message out to the critical care physicians, to the GI, interventional radiology, everybody that deals with these patients.

Platelet transfusions are often considered, especially if the platelet count's below 20 for a low-risk bleeding situation like paracentesis or central line placement. And I think that's pretty reasonable situation, or below 50 if someone's going for an operative procedure or a high-risk for bleeding. But the evidence for that is poor. And I still think the vast majority of prophylactic platelet transfusions are probably unnecessary. And I think you have to correct for that platelet count for liver disease, because the von Willebrand Factor and the fibrinogen are bumped up in liver disease because of reduced clearance.

There's no benefit to transfusing plasma if the INR is below 1.8 in liver disease patients. So that's just liver disease. Maybe the patient that's “warfarinized” with an intracranial hemorrhage, 1.8 may not be the right threshold. I don't know what the right threshold is. But you cannot extrapolate what's going on with cutoffs in liver disease compared to some other coagulopathic patient. But certainly, in liver disease, where we know there's that rebalance, definitely below 1.8. It doesn't drop the number. It doesn't make sense based on the basic state on these patients.

There's no benefit for plasma for patients with liver disease with high INR levels, at any level, in that absence of bleeding in your procedure. So if someone just has an INR of 6 and they're in the ICU and they're otherwise stable, don't ever transfuse them plasma, because it's only going to last for a few hours. And it's going to overload them and have transfusion reactions.

It's unknown if you should be transfusing plasma for patients who are undergoing invasive procedures based on an INR above 1.8. My personal opinion is there's no benefit, because the bleeding risk for most procedures is very low, and we can transfuse it for the rare patient that bleeds. And so prophylactically for plasma, I would worry more about the platelet count than I would about the INR.

Vitamin K, it doesn't work.

And the other thing to remember for when you're teaching your medicine colleagues is don't withhold thromboprophylaxis, just don't assume because the INR is 2.5, that that patient has somehow "auto anticoagulated", in quotations, since there is no such thing. That doesn't happen.

And the last thing I would say is all those other adjuvant non-transfusion therapies, such as tranexamic acid, et cetera, none of them are ready for prime time. But there's lots of studies going on with the TPO agonists, and the HALT-IT trial is going to be coming out for tranexamic acid, potentially to really change practice in this area.

Joe: Awesome. Well Jeannie, as I said, this has been incredibly practical and incredibly helpful. Before I let you go, I do want to ask you one other thing. And this is not on this topic, but it is regarding the incredibly wonderful work that you and your team up there in Canada have done on the "Bloody Easy" series. And in particular, I know you guys published Bloody Easy 4 not too terribly long ago. Well, I guess it was a year or so ago. Or am I wrong about that Jeannie? Has it been two years? It's been a little while.

Jeannie: Just about two years. And by the time it comes out, it's already been a year in the completion. It's like you publish a paper and it's a year before you actually see it in print.

Joe: It's a remarkable resource, and you guys offer it obviously on (let me make sure I have it right) at transfusionontario.org. Is that correct? Is that the website to go to find it?

Jeannie: That's correct. And you can download. We now have a little flip book so it's even easier to read it now.

Joe: It's remarkably good, and you guys have done wonderful work with that. There are some things in it that are specific to Canada, but that's what I would expect; it's where you practice. But overall, the information is wonderful and practical and I recommend it all the time. So folks, if you have not gotten a copy of Bloody Easy, the current version is Bloody Easy 4, just go to transfusionontario.org. Jeannie is not paying me to say this. This is a true recommendation from my heart. It's great work Jeannie. Thank you so much for it.

Jeannie: No. There's like a huge team that goes into building that book. The opinions that go into that book are coming from lots of different people. And all of us greatly appreciate the positive reinforcement.

Joe: Outstanding! Well Jeannie, thank you so very much for being my guest on the podcast today. It's always an honor and a pleasure to talk to you. And I just really, really appreciate it.

Jeannie: Thanks for having me. And as I said before, it's such a great resource for all of our residents and trainees because you can send them off, "Okay, well actually, I don't need to spend an hour with you. You can go listen to the podcast and listen to the expert, whether it's Aryeh Shander or one of the other major experts you've had recently on the show."

Joe: Thank you so much, Jeannie. You take care.

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Joe: Well that was really fun. Jeannie has a great way of cutting right to the chase, doesn't she? I have to tell you, my favorite quote from that entire interview, you're probably going to guess this. "The INR is really garbage." That's awesome. That's hilarious. I'm sure that you learned a lot from Jeannie, and I hope that you enjoyed our discussion.

Remember, you can go to www.wileyhealthlearning.com/transfusionnews to get an hour of totally free continuing education credit. That's both for docs and laboratorians. You can also find references and other stuff on the show page for this episode, that's BBGuy.org/056. Also on the Blood Bank Guy site, you can find other episodes including the most recent episode, which was the interview on critical developments in Transfusion Medicine from 2017. That's right there on the website, or wherever you get your podcasts. Speaking of that, if you have a chance, I'd really appreciate it if you'd go to Apple Podcasts and give this podcast a review. It really helps to get the podcast out in front of more people.

So the next episode will be an interview with Dr. Brenda Grossman about those really difficult situations where we have a patient who has a positive antibody screen, but we don't have a definitive answer on what the actual antibody is. Brenda's going to help us work through those frustrating situations. And she has a lot of good stuff to say to us. That's coming very, very soon.

But until that time comes, my friends, as always, I hope that you smile, and have fun, and above all, never, EVER stop learning. Thank you so much for being here. I'll catch you next time on the Blood Bank Guy Essentials Podcast.