Joe Chaffin: Alright everyone, as promised, I am super-honored to welcome Dr. Jeannie Callum to the Blood Bank Guy Essentials Podcast! Jeannie, welcome!

Jeannie Callum: Thanks very much! I'm very happy to be here today.

Joe: I really, really appreciate it. I want to tell everyone just a little bit about you. Quite honestly, everyone, Dr. Callum is, well let's just be frank: She's a star! She's got so much going on, and is doing so much, it's incredible! I'll just give you the highlights. Dr. Jeannie Callum is the Director of Transfusion Medicine and Tissue Banks at Sunnybrook Health Sciences Center in beautiful Toronto. She's an associate professor in the Department of Laboratory Medicine and Pathobiology, also at the University of Toronto. She trained in both her medical degree and a fellowship in internal medicine, again, at the University of Toronto and did her transfusion medicine fellowship training with Canadian Blood Services in Ottawa. Just to kind of change things up, right Jeannie, to get out of Toronto for a short time?

Jeannie: Actually, it's officially in Ottawa because the company's in Ottawa, but I'm still based in Toronto.

Joe: Clearly, Toronto has a hold on you. That's a good thing, right?

Jeannie: Absolutely!

Joe: (laughs) It's a beautiful place! That's for sure! Everyone, you can hardly turn around without seeing work that Dr. Callum has done. It really is incredible. She's published over 100 peer-reviewed articles, she's authored numerous book chapters, and in fact, just several episodes ago of the Blood Bank Guy Essentials Podcast an episode 013, we discussed, if you recall, a paper on Transfusion-associated Graft vs. Host Disease and Dr. Callum was the senior author on that paper. So again, incredible.

What we are going to talk about today with Dr. Callum is—well, we initially discussed talking about bedside procedures and plasma use, but we've expanded it to really be more of a look at plasma transfusion in general. Where we get it right, where we get maybe not so right and really an extensive discussion, including some cases on where we're going with all of this. So, I've talked too much in terms of the intro, but Jeannie, again, there's just so much that you do and are doing. I want to ask you like I ask basically every guest that I have on the podcast. What is it about transfusion medicine that got you started? I mentioned you trained in internal medicine so that's a little bit different than most of the folks I have on the podcast What is it about transfusion medicine that kind of got to you and made you want to do it?

Jeannie: So in Canada almost all of our transfusion medicine fellowships go through intro medicine and hematology and then a two year fellowship in transfusion medicine.

During my hematology training, I was really training to be a lymphoma doctor. I've been doing longitudinal clinics and lymphoma management for almost three years at that point, and then I did my standard 2 month block in blood bank, that's required for your training to graduate from the hematology program and I loved transfusion medicine! So, I did a basically 360 and looked at what I was doing and then completely switched tracks and that's when I decided to do a fellowship. Part of it was just like the antibody ID, doing the antibody panels, I just thought it was so fascinating! It was very much interactive with everybody within the hospitals. You were talking to surgeons and intensivists; it was a very social kind of subspecialty. It was just perfect for me!

Joe: It's really interesting to hear that. In the U.S., as you know, most transfusion medicine docs start out in pathology and obviously that's different for you up there in Canada. But I think in both cases what you see with people that really like transfusion medicine, they enjoy the interaction and the "give and take" more than perhaps, some of the stereo typical pathology personality types. Don't you think?

Jeannie: Absolutely!

Joe: I would like to move into our topic for today, which is a big topic. I don't want to spend anymore time on the introduction. I have to tell you, one of the things that people should be aware of is that, I mentioned, you've written a ton of different things, including multiple book chapters. Those of you out there, if you ever want to get a life changing look at the use of blood components prior to bedside procedures, I strongly recommend that you pick up the AABB's "Transfusion Therapy Clinical Principles and Practice" book. You can get it online from AABB. Jeannie and Dr. Sunny Dzik wrote the first chapter again, titled that, " Use of Blood Components Prior to Bedside Procedures." It is SO GREAT! Jeannie, I know that you and Sunny worked hard on that and man, that is such a spectacular chapter! So great job on that!

Jeannie: The thing that was so crazy when I was reading paper after paper to slot them in, for each procedure. Just paper after paper showing that plasma before bedside procedures, really has no evidence to support it. So after paper after paper I was like, "Wow! We're all doing the wrong thing!"

Joe: (laughs) Well, and you guys put that in such a gentle and….well, it's just so well-put and so well-researched. Honestly, I think that anyone that deals with hospital transfusion medicine, because that issue comes up all the time. You gotta read that chapter, folks! The residents out there and even the techs out there, really something important to check out.

So Jeannie, let's start talking about plasma. One thing I did want to do, because again, some of my audience are learners, I wanted to point out a couple of things about plasma first. We're going to say "plasma" throughout this podcast. But plasma in Canada, for example, is a little bit different on how it's defined than plasma in the United States. I don't want to just spring this on you, but correct me if I'm wrong, but my understanding is that in Canada, you guys don't do a distinction between what we call

“fresh frozen plasma” and “plasma frozen within 24 hrs” in the United States. Is that correct?

Jeannie: Well we actually try and keep that distinction sort of hidden from trainees and physicians because we’re sort of afraid it might confuse them!

Joe: (laughs) Right.

Jeannie: Bags that we’re actually supplying the patients, some of them will be FFP (fresh frozen plasma - frozen within 8 hours of collections). The rest of it is FP, and of course, some of it is thawed plasma because we thawed it for one patient, they didn’t use it so we’re crossing it over to another patient. Essentially, we have three different products, but we don’t let the clinicians at the bedside know which one they are getting because we consider them equivalent. The slight difference in amount of Factor VIII, every hospitalized patient has a Factor VIII level that’s through the roof, because it’s an acute phase reactant. So, essentially, we use them interchangeably.

Joe: Got it. The only reason I point that out is that I just want to make sure that whatever country you’re in, whatever terminology you are using, we’re just going to say “plasma” today, but generally speaking, we are referring to, in most cases, a previously frozen plasma product—whatever it’s called in your particular locale!

So Jeannie, plasma is not new! We’ve been transfusing plasma for decades around the world. You would think that after all this time, we’d be doing it right. Don’t you think? Wouldn’t you think we would have figured it out by now? You’ve already given us a hint that maybe we’re not. But do we have any idea of how frequently or what percentage of the time plasma is being used appropriately?

Jeannie: Yes. There’s multiple studies that have been published from multiple different countries, including multiple publications from the UK, from Canada, and from Finland, showing that about half of the plasma transfused on the planet is unnecessary. Always makes me wonder, “Are people just flipping coins when they decide that they are about to give plasma?” Or, are we really all completely confused about when we’re supposed to be giving this?

Joe: Man! That’s a staggering number, really! Why do you think that is? Is it a training issue? Clearly it’s not malicious intent! Why do you think that happens?

Jeannie: Well, I think some of it’s training. Dr. Yulia Lin and Dr. Rich Haspel from Boston have tested internal medicine residents and hematology residents and their knowledge about plasma is pretty abysmal. For sure, the education is not getting out there. And then I think there’s a lot of historic practice, you know we used to have this rule, it’s pretty simple: If your INR is over 1.5 or your PTT is more than 1.5 x normal, patient’s bleeding or they’re about to bleed because they are going to the OR, then we transfuse plasma. It’s a very simple rule. We used to, I think when I was in training, everybody got 4 units and then somewhere along the line, it got switched to be where we were just getting like 1 or 2 units of plasma. So at the bedside, I think more senior

physicians are teaching this old practice. And then we have obviously, data coming out that that's wrong. But it's very hard to turn clinical medicine on it's head and turn it around. Everything moves very slowly in medicine, in terms of changing practice.

Joe: Oh for sure, that's absolutely true! Are there consequences to that? Obviously, if it's being used unnecessarily, does that have the potential to harm anyone?

Jeannie: Yes, for sure. Probably the most notable concerning side effect of plasma transfusion is transfusion-associated circulatory overload or what we colloquially call "TACO."

Joe: Yuck! (laughs) Don't you hate—forgive me for interrupting! I hate that acronym! (laughs)

Jeannie: Well, you know, I'm actually starting to really like this acronym because during a clinical trial called "TACO best eliminated with Lasix" or otherwise known as "TACOBEL!"

Joe: Nice!!!! (laughs)

Jeannie: So, sort of like an acronym! About 4-6% of plasma recipients, and if you put that into metrics 1 in 17 times you transfuse plasma, somebody is going to get a TACO. Maybe 2% of those patients will actually get very sick and have a fatality associated with that. There are other rarer concerns; you can get an anaphylaxis, transfusion-related acute lung injury or TRALI, but those are much less common. The other thing that has been fascinating, there's an article published this year in one of the Lancet series that looked at patients who were going to the operating room and divided patients into (and all of these patients had INRs > 1.5). One group got plasma because that's what the physician decided to do compared to another group where either they didn't see the result or they decided they didn't need to correct the abnormal laboratory test result. They showed that patients who got plasma had higher rates of peri-operative bleeding, longer ICU stays, longer times on the vent, higher mortality. Really concerning flag that may be this preoperative plasma just to reverse slightly abnormal laboratory test results is doing harm.

Joe: Wow. That's scary, quite frankly. I think I did see that study. I believe it was from Mayo, if I recall correctly. The only thing that made me wonder if people could raise objections to how well-matched the groups were? Am I misinterpreting that?

Jeannie: No, it was interesting. The patients who got the plasma were more likely to be general surgery type patients compared to the patients that didn't get plasma were ortho/urology. I wonder whether or not maybe the orthopedic surgeons, they just never saw that result and maybe the general surgeons were just more thorough? I wasn't really sure. Obviously, because it's non-randomized there's bias in there and whatever they found might have been associated with some other bad factor association, nothing to do with the plasma. But, should make us all sit up and say, "Whoa! What are we doing?"

Joe: Right. That's the take-home message, right? I mean even if there is some bias and confounding factors in there, that's still not the result that you would expect to see. It's the opposite.

Jeannie: Absolutely.

Joe: Okay, so you mentioned a little bit about the dose thing. I think we'll come back to that as we discuss things further down the line. Is there any evidence, I mean, you had mentioned the looks that have been done in Finland, the UK and Canada, etc., and those were done, some of them done ten years ago or so. Is the word getting out? Are people starting to get better?

Jeannie: No. So we do (in the province of Ontario and Canada) "audit week" every year, and every year it's a different product that we audit, so we've done plasma twice. Actually, the inappropriate use of plasma actually got worse between 2008 and when we repeated it in 2013.

Joe: Oh no!

Jeannie: So we didn't get better! Partially it's because we changed the adjudication criteria. On all of our audits we do dual blood adjudication, two different transfusion medicine specialists. The second time period, we finally decided it was completely inappropriate to use plasma to reverse warfarin. Whereas, in the earlier one, because the warfarin antidote the prothrombin complex concentrates, it was a bit new. So we weren't going to fault physicians if they haven't heard about it yet. But five years later, we said, "No, no, no! That's wrong." So part of that getting worse was because we got more strict on how they had to behave.

Joe: That makes sense. Were there any other common things that you saw in terms of noncompliances?

Jeannie: Yes. Probably the biggest noncompliances were that **non-massively bleeding patients with normal coags were getting plasma**. These were patients in the OR, ER with some bleeding. I laugh sometimes because someone will pull out the Iraqi 1:1:1 plasma resuscitation for a rectal bleed for hemorrhoids. They get two units of blood, so they must get two units of plasma?! So yeah. So don't push that button, unless it's really a gunshot or a postpartum hemorrhage or a really significant bleed. Using plasma to reverse warfarin, that was 14% of the noncompliance and that's in a place for our national guidelines say, "Don't do that." Using plasma to reverse you know, the novel other anticoagulants, including heparin. Heparin, when you give plasma to a heparinized patient, you're giving antithrombin, you actually actually anticoagulate them *further*, so you actually make them bleed and have antidotes, and that's a whole other frightening thing happening there.

Joe: That's my favorite when people give it for heparin. I love that. I say, "I love that," meaning the opposite, of course! Argh! Frustrating!

Jeannie: Yeah! You and I need a twitter account, where we can send these things back and forth!

Joe: We do! For sure! Absolutely! Okay, you also mentioned….well, let's do "dose" real quickly! You had mentioned that when you were training, that the people tended to use above roughly 4 units or so. I remember those days, as well. And more recently, maybe in response to the way red cell transfusion went, where they said….well, honestly, we in transfusion medicine were saying, "If you're transfusing red cells, by God, you gotta use two." Maybe to keep it simple, people fell into that with plasma, as well. But I think what you're telling me is that, that may not be or what you were implying before, is that may not be *enough* in a lot of patients. Is that what you were saying?

Jeannie: Yes. So the recommended dose that is in guidelines, not based on any high quality evidence, is 15 mL/Kg. We're talking about a small adult - 3 units. Average size adult - 4 units and a big guy - 5 units. That's a lot! At 15 mL/Kg, increases your clotting factor levels only by about 20%. So, just really like a slight increase in the clotting factor levels. If you have a patient where you're transfusing only 1 unit and you measure clotting factors before and after, and I gave you those clotting factors, you wouldn't be able to tell which was before or after because it wouldn't have changed the levels. So if it can't change the levels, how can it affect hemostasis and stop somebody from bleeding? In our last audit in Ontario, half of the orders were for 1 or 2 units and these were all adults. That's the appropriate dose I always say for about a 10 year old. We kind of have to think about what we're doing. Sometimes I understand maybe the first dose is 4 units and maybe, the second dose, (you didn't quite get where you wanted to go in a massively bleeding patient) you ask now, for two more. But your first dose when you're actually trying to stop somebody from bleeding or correct a significant defect, you would really need to go after that 15 mL/Kg. And obviously, with a big risk for TACO because of the high volume. 15 mL/Kg, 4 units, that's a liter of colloid. That's a lot for an older patient and hard to tolerate.

Joe: Absolutely. For sure. Really, what I guess what I'm hearing you say, and let's talk just a little bit about the—we don't have time obviously to beat this to death in terms of great detail, but you mentioned that 15 mL/Kg might bump you up 20-25% or so, in terms of your coag factors. What do you *need* in order to bleed? Is there a critical threshold?

Jeannie: We generally believe that if your, obviously when you're giving plasma you're generally giving it to a patient with liver disease, and all of their factors are low except for Factor VIII, which isn't made in the liver. So you're really trying to take them, all their levels to about 30%. Once you get to that, we think that you got good hemostasis. And that 30% is about an INR of about 1.8. Once you get to about 1.8, you're in the zone of adequate hemostasis and it's okay to stop. So that's where you get the liver disease. All the other coagulopathies from say, rivaroxaban or apixaban, completely different cutoffs.

Joe: Okay and why is that? Why do they have different cutoffs, Jeannie?

Jeannie: Yeah, so say a patient is on apixaban instead of warfarin for their atrial fibrillation. Their INR might be 1.3, but they are fully anticoagulated with apixaban. That 1.3 doesn't relate to any sort of clotting factor numbers. So you have to really, when you're looking at the coags on a patient you're thinking, "Okay. Why are they high? What's the point where that would cause a hemostatic derangement?" So for apixaban, 1.3, fully anti-coagulated, high risk for bleeding. INR1.3 in a liver disease patient that patient's factor levels are at 60% of normal, no chance of bleeding. Same number, totally different outcome.

Joe: That's so key. It's all context, right? You can't just look at one number (Wow, this seems like something that we talk about with red cell transfusion, as well, but whatever) and understand everything about the patient. It's all in what the clinical, historical, and pharmacological context of what's happening with the patient.

Jeannie: Yes. I think that this is partly why we don't get plasma right because now we're talking about every surgeon, anesthetist, internist, interventional radiologist, understanding why the INR, the PTT are high, and then deciding what to do. Understanding the coagulation cascade and how to interpret those numbers, that's really hard unless you do it all the time, like you do as a hematologist or as a laboratory pathologist.

Joe: Well, that's for sure! True confession time for me, Jeannie. Okay, this is Joe bearing his soul on his own podcast. I don't know why I am doing this, but I'm going to do it. I swear to you, I can learn the coagulation cascade and five seconds later it feels like I've forgotten it! I can call it back up to my head but it's unbelievable! (laughs) I have mnemonics and acronyms and everything running through my brain and I still have to sit down and go, "Wait a minute. It's 12, 11, what?" It's incredible! I can't imagine how a clinician who doesn't do this can keep that straight!

Jeannie: Absolutely! Somebody wrote an article in about 1985 that I can no longer find but it was entitled, "How to memorize the coagulation cascade." It was beautiful! And one of the key things you had to do was that you had to convert from Roman numerals to Arabic numbers. Is it called Arabic? Because your brain can't remember Roman numerals! So try that first and go and see if you can memorize it!

Joe: I may have been overstating it slightly! But it is true that I do have to think about it if I'm not doing it every minute. So let's go back to something that you mentioned before. You've mentioned a couple of things that I want to explore really briefly before we get to our cases, which we will—I promise! You had kind of alluded to the fact that we talk about plasma and we talk about how plasma is something that can be used to reverse anticoagulation in some circumstances, but it also sounds like there are some options, as well, right? Again, it's not just as simple as it used to be where somebody has a high INR, slam them with plasma. We have options now. I wonder if you could take a moment to explore that?

Jeannie: Yes. So, probably one of the most common reasons that we're reversing a high INR is because the patient's on warfarin. We now have prothrombin complex

concentrate, it's a warfarin antidote, just has Factors II, VII, IX, and X. It's safer, easier, faster for the patient and so we use that universally in Canada to reverse warfarin. For dabigitran, we have a new reversal agent that's licensed for use in both Canada and the United States, called "idarucizimab." It's a monoclonal antibody that once infused, you got 12 -24 hrs coverage. We've got specific factor concentrates, so you identify if a patient's got a high PTT and then you figure out if the patient's Factor XI deficient, well, we have a specific Factor XI concentrate. Or, if the Factor VIII is low and you figure out oh, they've got von Willebrand disease and that's why the VIII is low, von Willebrand concentrate. So, for lots of different situations, plasma is actually not the correct choice.

Joe: Right. That's so important. I do want to mention one thing, actually, a question first. In Canada, are all of your PCCs four-factor PCCs?

Jeannie: Yes, correct. We have two four-factor PCCs, licensed under different names, but in the United States, the Kcentra it's licensed differently. So we have two products in Canada called Octaplex and Beriplex.

Joe: Got it. So folks that are listening to this in the U.S., it's important to understand that not all PCC is created equal in the United States. Up until Kcentra was licensed, the versions of PCC that were licensed in the U.S. were primarily three-factor PCCs and let's be clear, Jeannie mentioned, Factor II, VII, IX, and X, those are the four vitamin K-dependent coagulation factors that we discuss, anyway. But Factor VII is hardly present at all in the U.S. PCCs aside from Kcentra. It's not a commercial for Kcentra, it's just something that you need to consider. So anyway, sorry for that, Jeannie.

Jeannie: Oh no…and also, because Kcentra was only recently licensed for use in the United States compared to other countries…Canada, we were 2008, but when we started, both Australia, the U.K., France, they've been using it for a decade before us! We were so far behind! Now you guys are just sort of, on that wave of conversion, as well.

Joe: Yes, indeed. Is there anything else? One thing I did want to ask you about was, when people think about prothrombin complex concentrates, I think there is still among clinicians, at least, confusion and sometimes, transfusion medicine docs between forms of prothrombin complex concentrates that are not activated vs. activated. Do you have any thoughts on that?

Jeannie: Yes. The one that we use in Canada is called "FEIBA." Is that the same one you guys use?

Joe: It is.

Jeannie: Yes, so that's Factor VIII inhibitor bypassing activity and it was classically developed for patients with congenital or acquired Factor VIII inhibitors or Factor IX inhibitors. But, we don't ever use that just for warfarin reversal because we're concerned about the increased risk of thromboembolic complications so we stick to

PCCs. The only time that we were using FEIBA was to reverse dabigatran before idarucizimab was licensed. So we essentially now just reserve that for inhibitor patients.

Joe: Okay. Well, one last thing before we do the cases, Jeannie. I can't let us escape without doing this. You had mentioned before that when you have someone who has a quantitative issue across the board with coag factors and you get them to about an INR of 1.8, and we could talk another day about the INR and what it's original use was for and how it's not intended to be a bleeding predictor, whatever. We can do that another time. What I really want to make sure that I give you the chance to talk about is: Why, at 1.8 it's not only not necessary to give more, but why in many cases, it doesn't *do anything* to give more? What's the deal with that?

Jeannie: Yes. So, Sunny Dzik from Boston, his group did this classic study where they looked at intensive care patients who were not bleeding, not planned for procedure, whatever insane reason, their physician ordered plasma. Sometimes, they ordered one or two or three or four or even more than four. And then they looked before and after plasma transfusion, and lo and behold, there was no change if the INR was below 1.8. And so, essentially, you can get no more gain once you get below that level. Part of it is because the INR of plasma isn't perfect. It's gone through a "freeze-thaw cycle," sat in the blood bank up to five days before it gets infused. Also, it doesn't last that long. So by the time your last bag of plasma goes in, your first one probably is mostly worn off. Right? So you just essentially, you never can get below that. So I think once you get below that 1.8 for a person with liver disease, at that point, stop. You're not going to get any more gain. So actually the Canadian Society for Transfusion Medicine in their "Choosing Wisely," actually, put out a statement, "Don't try to correct INR's below 1.8."

Joe: Nice! But yet, people still obviously do it! If you're a clinician, and you're looking at a lab value and you see, well, even an INR of what—1.2 or 1.3 is going to be listed as "abnormal," right? And it's getting that across to them that they don't have to correct that, can be challenging.

Jeannie: Absolutely. But on the other side, too, we can see INR's below 1.8, say, because of apixaban. You cannot ignore those ones! So it's really kind of a mixed message that we're sending to surgery and anesthesia. Some of them we can ignore, other ones we must pay attention!

Joe: (laughs) Goes back to that context thing that we were talking about?

Jeannie: Absolutely!

Joe: Okay, we need to get to these cases, Jeannie, because you've prepared some cases for us to talk about and I really appreciate you doing this, because I think our listeners will really benefit from this. So let's do Case One. Are you ready?

Jeannie: I'm ready.

Joe: Alright, here we go! So **case one** is that of a 52 y/o man with end-stage liver disease. He has that because he's been a heavy drinker his whole life. He's had multiple admissions for spontaneous bacterial peritonitis. Also, hepatic encephalopathy, and also, bleeding esophageal varices. He comes to the emergency department. He's confused, he is tachycardic, he's hypotensive, and his abdomen is very, very tense. He has tense ascites and he's febrile, as well. So you think, reasonably, that he probably once again has spontaneous bacterial peritonitis. So the obvious choice is, "let's do a paracentesis," an abdominal tap, if you will, to confirm your suspicion. But when the labs come back, he has a platelet count that is 52,000 and his INR is 2.7. Uh oh! So the clinician is sitting there going, "Well, what do I do? Do I need to correct this person's INR, before I stick a needle in his belly?" Why don't we talk about that? In fact, why don't we start, Jeannie, with talking about just coagulopathy and liver disease. Because man, that's common! I think it's important to get a clear perspective on what it means.

Jeannie: I think there's been a lot of papers recently published on this. I don't think we really realized this since until the last, maybe 5-10 years. When you're measuring the INR, you're measuring just the clotting factors. You're not measuring the natural inhibitors, your protein C and S, and your antithrombin. And with liver disease, you stop making your protein C, protein S and your antithrombin. They did a really classic study where they took about 50 patients with acute hepatic failure. The median INR was about 3. They measured their thrombin potential, how well they clotted, and it was completely normal with the INR of 3, with this rebalance of the hemostasis. And actually they did a second test where they measured how fast the clot lysed. And lo and behold, it took *longer than normal* for the clot to lyse. So they concluded that these patients with an INR of 3 were *hypercoagulable*.

Joe: Wow! Just to be clear, what you're talking about is a balance…yes, you're losing factors that make you clot, but you're also losing factors that keep you from clotting, right?

Jeannie: Absolutely!

Joe: Got it. Sorry, I didn't mean to interrupt you and throw you off there, Jeannie. I apologize. So in fact, these patients may be more risk of thrombosis than of bleeding?

Jeannie: Yes, and even in that study, half of the patients had actually experienced a thrombotic complication. I think most of us know this, you know. Now in our liver transplant programs, patients go to the OR, sometimes their INR's are 6 or higher. And really, at the time of the OR, we don't transfuse a lot of plasma. The patients do fine. So we can do whole liver transplants without plasma, I think we can do things like paracentesis without plasma!

Joe: (laughs) So is it fair to say then that, well you tell me? What's the correlation between the INR and bleeding in patients like that?

Jeannie: There's a classic study done in 1980, so we've had the data for more than thirty years, where, at this century, they knew it was wrong to transfuse plasma before a

liver biopsy. But just to prove the point, they put a laparoscope into the abdomen at the same time they did the liver biopsy. And then, some poor guy who was blinded to the results of the INR had to record the time how long it took that spot to bleed and they recorded the liver bleeding time. And they plotted on a graph the INR, the PT in this case, with the liver bleeding time, and it was a scatter plot. There was no relationship between those two numbers! Obviously, it's a bit disconcerting, because it means that the test that we're using, you CAN'T use that to make any decisions before a liver biopsy. But that means we don't actually have *another* test! So, then it leaves, people sort of *ignoring* that evidence because they have no better test.

Joe: Right. Trying to hang their hat on something, but unfortunately, it's not a strong hook! Do we have any…What you're saying makes total logical sense. Has it been looked at? Do we have any studies to suggest that there isn't any benefit to giving plasma in these patients?

Jeannie: So, a recent randomized trial randomized patients to one of two strategies. The classic old strategy, if the platelet count was below 50, or the INR was above 1.5, patients were randomized to the classic…you got platelets if you were below 50 for the platelets, or plasma if the INR was above 1.5. The other group got randomized to TEG-based decision making. TEG (Note: Thromboelastography) is a whole blood clotting time, so it's a cellular based assay, it's a bit different. But they use two metrics on there to decide whether or not you got plasma or platelets. By definition, 100% of the patients in the "standard" group got either plasma or platelets. In the other group, about 17%. So, 100% vs. 17%, and there was absolutely no difference in bleeding! There was a single bleed, and it was in the plasma group. And so, they concluded that definitely the old way is wrong, they give way too much plasma, but even with the TEG, nobody bled at the cutoffs that they used, so possibly you could go lower. Possibly you didn't need *anything*.

Joe: And it seems to me, from reading the chapter that you and Sunny wrote, I think it's fairly clear as well, while we do happen to have one RCT there, for the most part, with most of this, not just with paracentesis, but also with thoracentesis etc, we don't have a lot of randomized studies to hang our hats on. Is that a fair assessment?

Jeannie: Yes, so let's take liver biopsy. So, your bleed risk with liver biopsy is maybe 1 in 6000. Your bleed risk with a central line is, I don't know, 1 in 2000, or it's in those realms. So if you were to design a randomized control trial, you'd have to take in, you know, 100,000 patients that were hemostatically deranged, going for a liver biopsy, randomizing to plasma or no plasma. Of course, that trial will *never* be done, because it's too large, because you're looking at a difference between less than one percent to half of less than one percent. So, the trials will never happen, so we have to stop waiting for them. We have to change the practice now. The only thing that you can kind of look at are studies where "Center A" changed their guidelines and compared bleeding from time period A to time period B, showing that they don't change. And there are studies like that for, as you can tell from the book chapter that we wrote, really *hundreds* or more of these studies, just showing that the INR doesn't correlate with the risk of bleeding at the time of procedure.

Joe: Well, so maybe could we just whip through a few procedures here, and you can give me your thoughts quickly on what you think about them?

Jeannie: So I divide procedures into three categories. You got your minor things, which I include the classic are the paracentesis, the thoracentesis, and the central line placement. And maybe, art line, PICC line, and all those certain things fall into that category? For those things, I'd like a platelet count above 20. *I don't care what the INR is*; go ahead, do the procedure. And only treat bleeding, because in a series on paracentesis and thoracentesis, and there were multiple ones, not a single patient bled in any of the large cohort studies. For paracentesis and thoracentesis, the American Society for Liver Disease a decade ago, came out with a guideline saying it's not necessary. So the guideline's say you don't need to do it, the studies don't support doing it, so don't do it.

Joe: Does central line fall into that category, as well, Jeannie?

Jeannie: Yes. Probably the best study, I think it was done by the Pennsylvania Group. They looked at the Society for Radiology Guidelines which said that you had to have an INR below 1.5, a platelet count above 50 to have a tunneled catheter. Ok, they said, "That's crazy! We would never do that." They just pulled out of the hat their own guidelines. So they said, "INR of 2 and a platelet count of 25." And they showed in their study that dropping at least to those levels, made absolutely no difference. So there's no bleeding. So you can at least go to 2 for your INR, and you can at least go to a platelet count of 25. You could probably go lower, we just don't know how much lower you can go.

Joe: Okay. That's the minor group, the one's that you say that the INR doesn't matter! And you'd like to have a count of 20 or so for platelets. What's the next group?

Jeannie: So the next group I put into that category, kind of like non-compressible procedure like a liver biopsy. And for those, there's a recent just observational study that showed that the bleeding risk is slightly higher if your platelet count is below 50. So probably you need a platelet count of 50. But for the INR, there's really no correlation between patients with abnormal laboratory test results vs. normal laboratory test results and their risk of bleeding and the risk of bleeding, as I said before is about 1 in 6,000. I'm not sure how high you can go, but definitely you can go to 2. And of course, we're talking about just INR's that relate to liver disease which usually patients going for a biopsy, is liver disease. So, it's usually pretty straight forward. I would put into that liver biopsy category, the appendectomy, those liver resections, those sort of procedures.

Joe: Okay. The last one, I'm guessing.

Jeannie: The last one, I would say, is kind of that neurosurgery, critical space, epidural, those sort of things. I think that's where I think we need to try to get that INR, I say below 1.8 for liver disease because of course, we're giving plasma, we can't get much below than 1.8. So you have to be happy with that 1.8 because you can't do better. For patients that are on warfarin, I aim for an INR of 1.5 or less, mainly because we can

because we can give prothrombin complex concentrates. There were some cohort studies out of tracking patients with ICH, suggesting that better reversal with a brain bleed was associated with better outcomes, so it makes me a little bit nervous with neurosurgery until we have future data. But for those warfarin-related bleeds, I try to get below 1.5. For liver disease? 1.8 is as good as it's gonna get.

Joe: Got it. Okay, so going back to the case, we had a 52 y/o guy with suspected, spontaneous bacterial peritonitis. Heavy end-stage liver disease, with an INR of 2.7 and a platelet count of 52, and the question is, do I need to correct that before I do a paracentesis? And I'm guessing I know your answer.

Jeannie: No!

Joe: (laughs) That's about as simple as it gets! There we go!

Jeannie: I probably get a call once a week from a resident because our blood bank, someone tries to order plasma for a paracentesis, the tech just walks out of my office and hands me the piece of paper and says, "tell them no." So, I call these residents, I always say, "You know, if they bleed, I want you to call me." So it's been, whatever, 17 years on the job and not one person's ever called me back for a paracentesis or thoracentesis, and I'm sure they would!

Joe: I'm *sure* they would! Absolutely, no question! Alright, let's move on to case 2. It's important, I think, to have that discussion because it is such a big issue, and you guys devoted a whole chapter to it, obviously, so the rest of the cases will move a little faster. But I really wanted to make sure we spent enough time on there. Jeannie, did we miss anything in that?

Jeannie: No, I think we've covered it all.

Joe: You know what, I actually just thought of one question I did want to ask. Something that I see from time to time…well, I'm in blood center world now, so I don't see it as much, but when I was in hospital world, is the clinician calling and saying, for example, "I'm going to do a liver biopsy, and I want the platelet count over 50," and I know, it's not a platelet podcast! But I look and I say, "Well, the platelet count's 49!" and they say, "But it's GOTTA be over 50!" Do you have any thoughts on that?

Jeannie: Yeah, you know, the standard error on that measurement, I'm sure, is more than one, so I say, "You know, look, 49 is fine." I always try and reassure them, for platelets, "Platelets are ready to go all the time. You know, you don't need a crossmatch, they're on the shelf, you just gotta slap a sticker on them and out they go." So, I always say, "You know, if you get bleeding, they are ready! We've got lots on the shaker!"

Joe: Absolutely, good deal. I just wanted to cover that, because I know residents hear that from time to time.

Alright, **case number 2**: A 72 y/o man who is on warfarin, for an aortic mechanical valve and he comes to the emergency department. He's not doing well. He's got leg weakness, he's got right leg myoclonic jerks, and he's got a shuffling gait. His INR is 2.5 and they do imaging; an urgent head CT shows that he has an acute on chronic subdural hematoma with a midline shift, and he needs surgery. He needs an emergency evacuation by neurosurgery. So, this is kind of a classic case of where we've got someone who's bleeding and we need to reverse the warfarin. Jeannie, what's your general approach to a case like this?

Jeannie: Even this one, it's like really hard for clinicians to do it right. So we do audits and we still have failures on this. But in my mind, there's one right answer for this. This patient needs immediately prothrombin complex, that's your short-term intervention. And they need intravenous vitamin K, that's your long term plan that will start working around 6 hours, so you won't get a rebound of the INR. So we use prothrombin complex concentrates. That's your antidote for warfarin. It's got II, VII, IX, and X. It also has protein C and protein S, so it's balanced. It's not going to cause a clot. It also has a trace of heparin that you need to remember, because one of the contraindications to PCCs is heparin-induced thrombocytopenia.

Joe: Good. Good call, yes.

Jeannie: So, when we talk about the difference should we use plasma vs. PCC, there have been a couple of randomized controlled trials. PCCs is clearly faster. As soon as it's in the patient, the INR is corrected. It's associated with less TACO. The first RCT showed a difference of 6% risk of TACO compared to 0%, because the PCC volume for an average reversal is somewhere between 40-80 ml. It's obviously logistically simpler. You don't need a blood group, you don't have to thaw a product, you don't have to label it up, you don't have a liter of fluid to infuse into an older person with cardiac disease, and then it's safer from a transfusion-transmitted infection risk. And you know I would say, you know, we go to extreme effort to make sure our hemophilia population receives only virally inactivated or recombinant products. I think we need to stretch and make that same commitment to all of our patients.

Joe: Hm. Um hm. So it's a simpler, smaller product to give. Now, the push-back I hear from time to time from clinicians, goodness knows, they don't care about this most of the time, but I hear this all the time, "Man! It's so expensive! Man!"

Jeannie: Yeah, so for Canada, we don't have that as a deferral because Canadian Blood Services purchases all the PCCs for the whole country. So, they are probably the biggest buyer of prothrombin complex concentrate. We have two different vendors to help drive that price down. So, our cost for PCCs vs. plasma in Canada is the same. So price doesn't get into our decision making.

Joe: Really? Wow! I see. Well, for us in the U.S. that's very different, especially since our one four-factor PCC in the U.S. has a corner on the market. It's substantially more expensive to do Kcentra to a patient than it is vitamin K, in terms of raw costs. You

know, we're not counting the cost of treating a TACO, I fully admit that. But just in terms of raw cost, it's definitely more expensive.

Jeannie: Yeah, and remember, you got to do a blood group, you got to employ technologists 24/7 to work in your blood bank. There's lots of other stuff that cost money for that TACO. Actually, Aryeh Shander's group just published a paper on the activity-based cost of plasma, and it's substantially more expensive than you'd think.

Joe: Yep. I absolutely believe that. We're talking about a product that is targeted specifically to what you're trying to do. It's lower volume, it's logistically simpler as you said, so why wouldn't everyone just do that? Why are we seeing such lousy compliance with that?

Jeannie: So, in Canada, so as I said in our last audit, 14% of our plasma use is used for warfarin. And so, there are two problems that we're seeing. So we have one, the physician trained elsewhere, so they don't know that prothrombin complex concentrates exist. And, so we put in a strategy within our blood banks that when they get an order for plasma, they have to ask the nurse, "Has this patient received warfarin in the last 4 days? Is the INR high because of warfarin?" If the answer is "Yes," they offer them prothrombin complex and get them on the straight and narrow. Occasionally, they have to get the transfusion medicine physician involved. We got on the phone, and occasionally, I've had the funniest conversations with physicians that have been in practice for a long time. But my favorite one was recently, this physician said to me, "Darling, if there were such a thing as warfarin antidote, I'd know about it."

Joe: (laughs)

Jeannie: So we have doctors out there that haven't heard about it.

Joe: (laughs) I'm trying to get over the "darling!"

Jeannie: I know!

Joe: Were you tempted to just crawl through the phone and slap him?

Jeannie: Nooo! I was just so happy that he agreed with my advice, and we switched the patient to PCCs. I chose the educated physician route. We also have some physicians who are thinking, "Okay, PCCs is way too expensive. So what I'm going to do is when it really matters, like an intracranial hemorrhage, then we'll use PCCs. But if it's just I got to reverse it before liver biopsy, oh, I'll just use plasma for that." Because of the cost, not recognizing that there are also things to consider other than cost like the TACO risk.

Joe: Right, right. Okay. So, in the interest of time, let me ask this one next question before we leave PCC. The one question that I get a lot from docs is, because in their mind, as we talked about it in the beginning, "Plasma is easy. You just say 2 units, 4 units, whatever." Dosing of PCC is not as intuitive or obvious at least, to docs, at least that's how they perceive it. What could you say about dosing?

Jeannie: Yeah, the dosing strategy that we use…well we've gone through over ten years multiple different dosing strategies. So originally we used a weight-based dosing strategy. And then, every time the tech called to the emergency to find out the weight of the patient, who's bleeding to their head, they were always told 70 Kg. Because of course, you can't weigh a patient that's having a brain bleed.

Joe: Right, right.

Jeannie: So to get an accurate weight in kilograms is very difficult in an emergency, lots of our patients are traumas, and so, we had to get rid of the weight for our adults. Obviously, for kids we use a weight. And so, we base it just solely on the INR. So if the INR is below 3, we use 1,000. If it's between 3-5, 2,000; and above 5 we use 3,000. And if we don't know? So the patient comes in, they've got a medical alert, wife says their on warfarin, they got a bleed in their head, we give just 2,000. And then, when we get the INR that was pre-transfusion, we kind of back track and say, "Okay, do we need to give any more?" But we don't wait.

Joe: Yeah. That makes sense.

Jeannie: But if you look in the package insert of PCCs, you know, some of them say 50 IU/Kg, that's to correct them to 100%. But remember, we just need to get to about 30%. So don't go looking just in the package insert for your dosing strategy. Most hospitals actually have a recommended dose.

Joe: Yeah, okay. And I"m assuming you were, because it's obviously lower volume, you would be able to get the PCC into the patient a whole heck of a lot faster than you would plasma?

Jeannie: Oh for sure. Every 1,000, you can give over five minutes. Really fast!

Joe: (laughs) Absolutely! Okay, you had mentioned that you have a short term strategy and a longer term strategy. The PCC at the start to do the immediate correction, but then the vitamin K. What would you like to say about vitamin K?

Jeannie: So the right strategy in a patient like this, is you're talking about for days until they are going to be re-anti-coagulated, possibly a week. And you want 100% reversal, so in this situation at my hospital we give 10 mg of IV vitamin K. You know, we use, the only other route that we use for vitamin K in adults is some p.o. If you have a patient whose INR just inadvertently hit 10, because somebody put somebody on an antibiotic, but they're not actively bleeding, that's when we give p.o. We tend to give 10 p.o., just to gently nudge it back full below 3. We don't want to send it to 1.0, and that's what IV does. So you restrict the IV. I need to correct it within 24 hours.

Actually, in cases like this, 100% of our ICH warfarin cases the physician writes the IV order for the vitamin K at our hospital. But only 90% of the time does it actually get into the patient. And that's because the nurse checks it off, 'Yeah, I got that order." But then, the patient gets transferred to the OR, she didn't have time to actually do it, and then

what happens is, in the middle of the OR, the INR goes down to 1.1 and then it's back up to 2.0 six hours later, and that's when we realized, "Oh dear, we forgot to give the IV vitamin K." And at that point, post-op in the neurosurgical ICU, we have to start from scratch again. We have to get PCCs again and the IV vitamin K. So, it's just so critical that that doesn't get missed.

Joe: Okay, well we're going to talk a little bit more about vitamin K in the next case, but Jeannie, I think I'd like to move on to case 3 because it's kind of a variation on case 2, if that's okay with you. Are you good with that?

Jeannie: Perfect.

Joe: Okay. So here's **case 3**. It's January in Toronto. You're having a particularly nasty winter and an unfortunate 89 year old lady arrives in the emergency department because she's slipped and fallen on the ice. She's got a traumatic hip fracture, and she's in a lot of pain, but her vitals are stable, so that's good. Her hemoglobin is 11, so not desperate. Her INR is 2.2, and she is on warfarin for atrial fibrillation. So, she needs to go to the OR, but we've got more time than the last case. The last case was an intracranial bleed and they had to go right away. So there are some urgent cases ahead of her. It looks like it's going to be a little while, and they want to do a regional technique, so the anesthesiologist calls you and he says he wants that INR less than 1.5 before they start the case. How do you approach this one, when the need is not quite as emergent as the previous case?

Jeannie: Yeah, we have a lot of conversations about cases like this, and our conclusion is that *we can get by with just IV vitamin K alone*. So, sometimes we've had conversations about, ya know, maybe it's better if we operate on this poor woman right now. Reverse her with PCCs, give her the IV vitamin K, get her to the OR so she can get into the hospital one day faster, or 12 hours faster. But we really don't have a lot of evidence for that because the PCCs cost money, we tend to go within an IV vitamin K strategy alone. And it works really fast. I think people don't realize how fast it works. So remember, all your clotting factors are synthesized when you're on warfarin. They just don't undergo that final clip. So they're not actually functional, until the vitamin K is there. They get their clip, and out go those factors and they're ready to work. And so, that's why it works so fast, and it's cheap. So one of the deterrents to the vitamin K, "getting this right" is, the first thing is there's a lot of physicians that are still teaching that it causes anaphylaxis.

Joe: I hear that all the time, yep.

Jeannie: Yeah. For sure that was true in about 1970's, you use to have castor oil in it, but they fixed that in about 1970! So I'm not sure who is exactly still teaching that!

Joe: (laughs) It's not the young folks! That's for sure!

Jeannie: I know! But to make things worse, there's a black box warning on the vitamin K, and it's still under the current one, at least that we have at our institution, that comes

with the product. It says, “Only give IV vitamin K is it’s a medical emergency. Otherwise, give it subQ.” Which of course, is the WRONG thing to do! Yes. So, really, giving IV vitamin K, and then on the other side, how to give p.o. vitamin K. So essentially, we give IV by mouth with an orange juice chaser. That’s really secrets you learn in training! Not written down in the package insert. That’s something you learn as part of the trade of medicine, which obviously is hard because you have some first-year resident, they have this patient, and the nurse comes to them with the package insert and says, “Oh no, no! I can’t give IV vitamin K because it’s only for emergencies. You have to give it subQ.” And of course, they give it subQ.

Joe: Yeah. Well, and again, for those listening, subQ = lousy way to give vitamin K. Dr. Callum said, “p.o. or IV,” depending on how much time you have. Now Jeannie, let me ask you that. Let’s change this case, and what if the patient wasn’t going to the OR until 2 days from now. Would p.o. be adequate? Or would you still be doing IV?

Jeannie: I think if it’s going to be more than 2 days later, you can give oral. I tend not to do that. Some of these patients have very poor absorption. What you should not do is say, “Oh. I’m just going to hold the warfarin. They don’t have to go to the OR for 2 days.” But when patients come into the hospital and they’re elderly? Their teeth aren’t great, the food in the hospital isn’t really enriched with vitamin K. They just won’t reverse without some supplementation. And there have been 2 studies done in orthopedics. If you give vitamin K IV on arrival to the emerg, you can speed up time to the OR by 2 days. And 2 days in the hospital? That’s a lot of money! PCCs cost a lot of money? Two days in the hospital? Especially when vitamin K is free!

Joe: That’s a huge one! Two days! That’s impressive. Okay, let me see. I think we’ve covered all we wanted to on vitamin K. Did I miss anything? Jeannie, is there anything else we need to before we do case 4?

Jeannie: I think the only other thing about vitamin K that people are concerned about. They’re concerned that it’s going to cause warfarin resistance. And that, for like two weeks they won’t be able to be anticoagulated with warfarin. So (Denas et al; see reference below) looked at this. They looked at over 1,000 patients looking for warfarin resistance, and they couldn’t find it! It does not exist. So if someone tries to teach that or someone is listening that’s still teaching that, they’ve done the study. They can’t find warfarin resistance.

Joe: Alright! I like it! Let us do case 4 then. **Case 4** is a cool case! It’s a little long, so everybody hang with me and I’ll try to summarize it at the end. A 27 year old male who has acute myelogenous leukemia. He’s 17 days post chemo. Unfortunately, he is admitted to the ICU because he has *Staph aureus* sepsis, mild acute renal failure, and febrile neutropenia; so he’s a sick guy. He has a low platelet count; his platelet count is 8,000. He’s not bleeding, though. His INR is 2.1, his fibrinogen is 1.6 g/L. Coagulopathy is believed to be from sepsis. The resident said, “ok, we’ve got an elevated INR, let’s give him 10 mg IV vitamin K,” but the INR didn’t do anything! Uh-oh! So, since it didn’t correct, the resident ordered a 50:50 mix on the INR study; so a study of 50% plasma, 50% normal plasma, and that did correct to normal. The pre-induction INR, before all

this started, his INR was normal. His liver function, his enzymes are normal. And the resident who is now taking over in the morning says, “well wait a minute. Should I give plasma and cryoprecipitate to correct the INR and fibrinogen levels to normal to keep this patient from bleeding?”

So again, long case, but a patient with AML who’s got an elevated INR that is resistant to IV vitamin K but does correct on a 50:50 coagulation study. And so, the resident is asking you, Jeannie, “What should I do? Should I give plasma and cryoprecipitate?”

Jeannie: So, I think the first thing, I think as we said, like, motherhood principles: “What’s the cause of this coagulopathy?” So, because the patient hasn't responded to the vitamin K, the patient is not on warfarin, dabigatran, rivaroxaban; so, it can’t be any of those. The liver function is normal, it’s not liver disease. So, you’re pretty suspicious that this coagulopathy has got to be from DIC related to sepsis. You’re pretty certain. You know, it corrects with the 50:50 mix, so it’s not an inhibitor, you know, some problem, or heparin contamination of the tube. That’s gotta be what it is. So, it kind of helps you tune in to, ok, well what would be the replacement for someone with DIC? And, what factors are low with DIC?

So this resident did the right thing, orders this 50:50 mix. When they do the 50:50 mix, they just take an equal part of plasma from the patient and an equal part of plasma that’s normal plasma; it’s essentially no different than the plasma you would transfuse to a patient, so instead of transfusing the patient and then repeating the INR, they do it within the laboratory. That saves the patient an unnecessary TACO if it doesn’t correct. And they find that it corrects, so you know that it’s a factor deficiency. So it really kind of narrows down, “OK, I’ve got the right diagnosis.”

In this case, I wouldn’t go further, I’d say, other than check the blood film: Do they have schistocytes that are suspicious for DIC, you know, the fibrinogen’s low, the D-dimer’s high, is everything consistent with DIC? But if it wasn’t consistent, then at that point, we would go on to factor assays to determine, OK, is this liver disease, is this vitamin K deficiency, or is it DIC? And when you do your factor assays, it’s really pretty easy. because with liver disease, all your factors are low except for VIII. If it’s vitamin K deficiency, it’s just the II, VII, IX, and X. And then if it’s DIC, everything’s low. Sometimes those factors are necessary, but most of the time, they’re not.

Joe: So, do you need to correct the INR in this non-bleeding patient? What do you say to that resident?

Jeannie: We don’t have actually, very good studies, but there was a study actually that was done in British Columbia in Canada. In British Columbia, there were two pediatric hospitals. One were believers in replacement, and the other ones didn’t believe in it. The one group, half the kids, with their acute leukemia, ended up getting plasma. And the other hospital, *not a single kid* got plasma to reverse these abnormal numbers! And there was no difference in the bleeding rate, really confirming what’s been reiterated in review article after review article on DIC. The recommendation: In the absence of bleeding, a planned procedure, going to the OR, we don’t correct numbers in the

absence of bleeding. The only exception to that that's been recommended, it's not proven in fact, but many of us do this, is if you have that acute phase of an acute promyelocytic leukemia who start DIC, they have a very high risk of early induction death from bleeding, and we do correct numbers in those patients. We don't know if that's necessary, but I think it's a reasonable thing to do until we have further evidence.

Joe: Ok, so let's throw a little bit of a kicker into this case, and I think I know what your answer is going to be, based on what we've already talked about. But let's just say, so he's had his induction, he's got a tunneled catheter, a central line that's in, a tunneled catheter, and it has to come out, because the docs think that's probably why he's septic: He's got an infected line. So he needs a temporary subclavian line inserted. So here's the question: Does that change your answer? Do you NOW suddenly need to correct? Just to remind everyone: This patient had an INR of 2.1, his platelet count was 8, so his platelet count was substantially low, and his fibrinogen is 1.6 g/L. So does it change it if you are going to take out the tunneled catheter and put in a temporary line?

Jeannie: The best data that we have is that publication from the University of Pennsylvania that looked at over 3000 tunneled catheters. They took the INR up to 2, and found that taking it from 1.5 to 2 did not increase the bleeding risk. We don't know if you go above 2. We believe so, but we don't really have strong evidence. So in this situation, I don't think any of us can have a strong opinion, yes this patient needs plasma or no, they don't. But I generally teach in this situation, when it hits above 2, it's reasonable to give plasma before the procedure.

For the fibrinogen, for a small procedure like this, a fibrinogen above 1 is more than adequate. Then you might ask, "what kind of platelet count do you need for a line placement?," and the American Association of Blood Banks just came out with a recent platelet guideline which is really fantastic, gave very clear recommendations, and they recommended, you need a platelet count of just 20 to put in a tunneled catheter. So definitely this patient's going to need a pool of platelets, and maybe some plasma (other doctors might argue "no, with using imaging at the bedside you don't need it"). I would probably say that 80% of my intensive care physicians would not give plasma in this situation, and maybe 20% would, but they'd all give platelets.

Joe: Got it. Jeannie, just a quick aside, because it just dawned on me that in the U.S., we report fibrinogen in mg/dL, and I think you guys use g/L, so just for everybody out there, when Jeannie said that 1 is ok, that corresponds to 100 mg/dL in the U.S.; just so that no one is confused!

Jeannie: We have to get on the same page between the U.S. and Canada, because you know, hemoglobin, like, a hemoglobin of 10 is 100. It causes a lot of confusion.

Joe: It does, definitely! So, let us move on and let's do the **last case**, because I really think this last case is important (especially in light of, well, in the U.S., virtually every other TV commercial seems like, is for one of the novel oral anticoagulants), so let's talk a little bit about this one:

This is a 72 year old man who comes to the Emergency Department with a traumatic subdural hematoma. He was out biking, which is great for a 72 year old dude (way to go!), but he falls and gets a subdural hematoma. He is on dabigatran for his atrial fibrillation, and he needs to go to the OR right away. So, what are our options, Jeannie? We've got someone on dabigatran who is bleeding…

Jeannie: So, every time I'm faced with someone that's bleeding on dabigatran, there are a whole bunch of "things" we do right away. First, we **stop the drug**. We find out from the patient or the next of kin, **when did the patient last take a tablet**? So, we can calculate how long until this drug is going to be out of him. Dabigatran has a half-life of about 12 hours, so if you're looking at 5 half-lives clearing this out, you're looking at about 2 days for a patient that has normal renal function, 3-4 days if they have abnormal renal function. You want to **hydrate them**; get them peeing the drug out. We **give tranexemic acid** for any traumatic injury, including for ICH (Note: intracranial hemorrhage). And I **check the PTT and the thrombin time** (and I'm expecting it to be high), just to confirm that yes, actually, the patient's been taking the drug. If I did the thrombin time, and it's completely normal, I know the patient's been noncompliant with his medication, and there's no drug on board. You can **use dialysis to remove the drug**, but that's rarely practical. You've got a bleeding patient, very abnormal, high risk for bleeding, nobody wants to put a big dialysis catheter into that patient. They are hemodynamically unstable, have to go to the OR, so essentially we *never* dialyze patients in this situation, but that's on the list of things you could possibly do.

And then, I would **decide, "does this patient need emergency reversal with idarucizimab?**" So, our hospital, for who needs emergency reversal: Life-threatening bleeding, critical site bleeding (like spine, brain), or true emergency surgery (not just because the surgeon has a slot in the OR for elective total hip, it's an emergency! And then the agent that we're currently using at our hospitals is idarucizimab. For whatever reason, it comes as two 2.5 g vials. It's liquid already, so you just have to spike it and run it. Each vial is run over five minutes, so within ten minutes, you can completely reverse this drug. This reversal agent lasts about 12-24 hours, so we recommend checking the PTT at 12 hours and 24 hours, and if you hit bleeding in that first 24 hour period, and that PTT starts to rebound, then we could consider another dose, but so far, we haven't had to do any repeat dosing on any of our patients.

Joe: Jeannie, just real quickly, just to remind everyone that dabigatran is a direct thrombin inhibitor, and does affect the PTT. Does it affect the PT at all?

Jeannie: Yeah, sometimes you can see an elevation in the INR for sure, but there's a pretty good curvilinear relationship between the drug level and the PTT.

Joe: Got it. I have to tell you, I personally, again I admit, I'm not in hospital world anymore, I'm in blood center land right now, so I have not personally seen idarucizimab used. Are you seeing it fairly often?

Jeannie: It got licensed in Canada maybe about six months after the U.S., so we've only used it a handful of times. It's not that common that you run into a situation where you'd need to give this. Probably more data is going to be coming out…

Joe: Of course. Do we know of any risks of that rapid reversal of the dabigatran?

Jeannie: There's only a report of 90 patients that were administered the drug for either bleeding or going for an emergency surgery, and there really were no side effects. They obviously tracked venous thromboembolic (VTE) complications in these patients. There was one patient that had a VTE within the first 72 hours; but you don't know whether or not that's just because they stopped their dabigatran, or whether or not it was related to the drug. It's mechanism of action, it's a monoclonal antibody, it doesn't have any prothrombotic abilities, so you've got to be suspicious that it's just from withdrawal of the dabigatran. You obviously watch for allergic reactions. No one knows what the rate might be, but because it's a monoclonal antibody, for sure, someone's going to have an allergic reaction to it.

Joe: Got it. So, with dabigatran, until we had idarucizimab, it was pretty much dialysis, even though that wasn't great and as you just mentioned, isn't a super-easy thing to do in someone who's crashing, but how would this change if we were talking about someone who is on one of the other novel oral anticoagulants, like rivaroxaban or apixaban?

Jeannie: So, those are Xa inhibitors, so this drug, the idarucizimab, just binds the dabigatran. So, it won't work for these. It's really kind of a designer drug just for one thing. So, with rivaroxaban and apixaban, a little bit better; they have a shorter half-life, of only about 7-11 hours. So they clear out of the patient faster. Dialysis is not effective, so that's off your list. Otherwise, the same list: Tranexemic acid, hydrate them (get them peeing the drug out). There's currently no available antidote. There *is* an antidote that's in clinical studies; it's called "adexanet," and it's a really cool molecule. It's a factor X, but it's missing just part of the molecule, so it has no coagulation ability, but it's able to bind to rivaroxaban and apixaban. So, kind of like a "decoy X." So at our hospital, because we obviously don't have that drug yet, and we're not participating in any trials with it, we're using PCCs like we would use for warfarin. We're using a flat dose of 2000 IU, and we repeat it an hour later if there's ongoing bleeding. We know that from clinical studies, it fixes the INR, it corrects the laboratory test result, but we don't know whether or not that's going to translate into better outcomes. There's a study ongoing, it's an international study called "UPRATE." Hopefully it will come up with some data on how effective is PCCs in reversing the bleeding problems associated with rivaroxaban and apixaban. And this is *really* common. We get called every night on call because somebody's bleeding on one of these three medicines.

Joe: That's really helpful. It think that's important for our audience to understand the differences and the distinctions, and that you *do* have some options, because I think at first when these things were coming out, most of us were kind of throwing up our hands and going, "there's not really anything we can do!" But now we do have some choices, right?

Jeannie: Yeah, I think most hospitals have them all protocolized, so at least everybody's getting kind of "standard management." But for sure, for these drugs, ***never, ever give plasma***! It's not going to help you!

Joe: That's the take-home, for sure. Doesn't help you!

Well, Jeannie, I do want to say one thing before I let you go…well, *two* things. First, thank you so for doing this! This has been super-helpful, and I think people are going to learn a *TON* from it, so thank you very much for that! But the second thing I want to mention, and this is for the audience: I don't know how many people know about this, but I'm going to do a little commercial for something that Jeannie has done that I think is spectacular! Jeannie is the lead author on the Provincial Ontario Transfusion Handbook, with the greatest name in the world! It's called "Blood Easy," and Jeannie, again correct me if I get the web address wrong, but I believe it's **TransfusionOntario.org**, is that correct?

Jeannie: That's correct, and we are working, right now, hopefully for this fall we'll launch the print of "Bloody Easy 4." It's kind of like an iterative process, things are changing so rapidly that every 3-4 years we put out another edition.

Joe: Well, I've got to tell you, I tell my residents this all the time, so those of you that are in training, go to that website now! When Jeannie gets out the 4th version…the "Bloody Easy 3 - Blood Transfusions Blood Alternatives and Transfusion Reactions: Guide to Transfusion Medicine" it will knock your socks off, it is fantastic! There's some things that are a little different between Canada and the U.S., but it's there for the magnificent price of FREE! Jeannie, you've got to work on that price! My gosh!

Jeannie: Well, it's free for Canadians, but I'm suspicious that you guys have to pay for it!

Joe: Well, honestly, I'm not sure that's true, to tell you the truth, I just clicked on it and downloaded it, so…

Jeannie: Oh, yeah, you can download an electronic copy…

Joe: Yeah, that's what I mean. I'm sorry…

Jeannie: Yeah, most people now are using just electronics.

Joe: So, highest recommendation for that, Jeannie. Congratulations on that work. I know it was a TON of work, and I'm sure that version 4 will be even better, so congrats! Way to go!

Jeannie: Thanks very much.

Joe: Well, Jeannie, again, thank you very much for being on the podcast today. Is there anything else you'd like to leave us with before we go, or have we covered it all?

Jeannie: I think you've covered it all, and I'm just so thankful that you're trying to advance, trying to improve that 50/50 getting plasma "right," and maybe with this podcast, we might get to 60%!

Joe: Let's do it! I like it! Thank you very much, Jeannie; you have a great day.

Jeannie: You, too.