BBGuy Essentials 092:
When Platelet Transfusion Might Not be Wise with Ruchika Goel
Released October 6, 2021

Ruchika: Hi, I'm Dr. Ruchika Goel, and this is the Blood Bank Guy Essentials Podcast.

Joe: Hi everybody. This is Joe Chaffin, welcome back to the Blood Bank Guy Essentials Podcast. This is episode 092. Thank you so much for your patience. It's been a while since I've put out a new episode, but I'm very much looking forward to having more frequent episodes coming out in the coming months. Today I have a really great interview for you that I did a number of months ago with my friend, Dr. Ruchika Goel, where she and I are discussing platelet use in ITP and TTP and heparin-induced thrombocytopenia (or "HIT").

But before we get to that, you should be aware that this particular episode is not a continuing education episode. You can find those episodes where you can get free continuing education hours at BBGuy.org/podcast. They're cleverly labeled with the letters "CE". You can also find those episodes at wileyhealthlearning.com/transfusionnews, as well as, of course, any podcast outlet, such as Apple Podcasts, Google Podcasts, Spotify, etc. The CE episodes are courtesy of transfusionnews.com, and Transfusion News is brought to you by Bio-Rad, who has no editorial input into this podcast.

Okay. I really, really like today's interview and it's not just because Ruchika Goel is so brilliant and fun to talk to. The decision on whether to transfuse platelets when you're not sure the platelets are actually going to help or that they might even hurt is really one that blood bankers struggle with a lot. And honestly, those who are ordering transfusions should be struggling with it, too. Ruchika is going to discuss two papers that she and her colleagues published regarding platelet use in ITP or Immune Thrombocytopenic Purpura, as well as the possible dangers of platelets in TTP (Thrombotic Thrombocytopenic Purpura) as well as HIT (as I mentioned before, Heparin-Induced Thrombocytopenia). I think you're going to find a lot of information here, and in fact, some of it that you may not have known before. I'm excited for you to hear it.

Let me tell you a little bit about Ruchika. She has been a guest on this podcast before. Dr. Ruchika Goel is an Assistant [**CORRECTION: Associate**] Professor of Internal Medicine and Pediatrics in the division of Hematology/Oncology at the Simmons Cancer Institute at Southern Illinois University School of Medicine. She's also an Adjunct Assistant Professor of Pathology in the Division of Transfusion Medicine at Johns Hopkins. In addition (because that's not enough), she serves as the Medical Director of ImpactLife, which is the blood center formerly known as the Mississippi Valley Regional Blood Center. Ruchika is not only a transfusion medicine

physician, she's also a practicing hematologist/oncologist, and she's actively engaged in a lot of different research, especially focusing on big data applications in transfusion medicine, as well as in pediatric and neonatal transfusion medicine. She's the current chair of the pediatric subgroup of the ISBT, the International Society of Blood Transfusion, and she also participates in the AABB's standards committee. Dr. Goel has numerous accolades and awards. There's just too many to mention. You can look at them at the show page on this episode at BBGuy.org/092. She also has over 70 peer reviewed publications to her name, and she's been invited to lecture nationally and internationally on numerous topics.

I'm very, very excited for you to hear Ruchika's thoughts, and I'm ready to go if you are. Let's roll! Here's my interview with Ruchika Goel that I'm calling, "When Platelet Transfusion Might Not Be Wise."

****

Joe: Hi, Ruchika, welcome back to the Blood Bank Guy Essentials Podcast.

Ruchika: Hi Joe. It's an honor to be here.

Joe: Well, the honor is mine. I have been really looking forward to getting a chance to talk to you today about transfusion in some varying forms of thrombocytopenia. I think we're going to spend the majority of our time talking about transfusion in ITP, because that's something that you've published on as well as some of the other forms of thrombocytopenia that we'll get into. But let's talk a little bit about ITP first, and I think it's really important for people to make sure that they understand the background and make sure that they just understand the basics. If we can, can we just start with the name? I mean, I'm old enough that I've been around to hear the name of "ITP" standing for, it feels like about a million different things. But what technically is the most appropriate name for the entity we abbreviate as ITP nowadays?

Ruchika: I think, Joe, you're spot on with starting with actually the nomenclature. It is a disease that has gone a lot of change, its name itself being defined. ITP traditionally used to be called as "Immune Thrombocytopenic Purpura" or "Idiopathic Thrombocytopenic Purpura." And there's been a lot of discussion and debate about the name and currently, it has been renamed to simply being called as "Immune Thrombocytopenia". And the term "purpura" has actually been dropped because it's a bleeding symptom, but it's not present in all of the cases so it's not a defining feature. And so it's basically the International Working Group on ITP has renamed it simply as Immune Thrombocytopenia, although the word ITP still sticks around.

Joe: I got you. I know that does confuse people because people try to remember what that "P" stands for. "What is it? Purpura, yes." I think that it's important that we get that cleared up right away. But I think more importantly is for people to understand a little bit about the disease and we're going to get into the specific details about the pathophysiology of ITP in just a second. But again, big picture, Ruchika, is ITP common? Does this happen often?

Ruchika: It is an autoimmune disorder and it is actually a relatively common cause of thrombocytopenia in both adults, as well as children. And we say the estimated prevalence is somewhere from 2 to 10 cases per 100,000 and the incidence is about the same range, 1 to 2 cases per 100,000 patient years. It is more common in children, especially so the less than five year old age group. And then at the other end of the spectrum, the incidence of and prevalence in the adults actually is greatest in the elderly population. We do see some form of female preponderance as with other autoimmune disorders. As the nomenclature has been revised, also the classification of ITP has recently been revised, and now, "newly diagnosed" or "acute ITP" is ITP within the first 3 months, and 3 to 12 months, we call this "persistent ITP," and after 12 months it's called as "chronic ITP."

The presentation is variable. The children, most commonly having acute ITP, a single episode preceded by a viral infection, and then it typically resolves without needing a lot of intervention. In contrast, it's in the adult population, more so in the elderly that we see the chronic manifestation of ITP, and it's persistent and keeps recurring. There is quite a difference as far as the definition goes and manifestation clinically is very different.

Joe: We have this relatively common form of thrombocytopenia. Let's talk a little bit about why it happens and what the deal is behind it. What's the pathophysiology? What do we know about why this occurs? You mentioned it's autoimmune. Do we have more details than that?

Ruchika: Yeah, certainly. There are a range of pathophysiologic mechanisms which have been proposed, but the most common is that there are nonspecific anti-platelet antibodies. And what happens is that these are more recognizing the glycoproteins on the platelet surface, especially the GPIb/IX and the GPIIb/IIIa glycoproteins. The antibodies tend to coat the platelets and these antibody coated platelets are cleared from the circulation by the phagocytes in the reticuloendothelial system so primarily the spleen.

And so what we are seeing truly is a shortened platelet survival as a primary pathophysiology of ITP. However, it's important to note that while this is proposed as a primary mechanism, ITP antibodies, the platelet specific antibodies, are not always detected in ITP patients. Other mechanisms have been proposed, for example, dysregulated T-cell function so the T regulatory cells function may be decreased. And some of the mechanisms like antigen mimicry, for example, if we have it in context of other diseases like Hepatitis C, they may be mimicking antigen. But predominantly, it's the anti-platelet coating antibodies, which are the main mechanism.

Joe: You mentioned something there when you were talking about Hepatitis C. And I know that there's been abundant discussion in the literature about primary versus secondary forms of ITP. And I don't want to go too far down that rabbit hole because that's not the point of our time together today, but can you talk just very briefly about primary versus secondary ITP?

Ruchika: Primary ITP or "idiopathic ITP," as it used to be called previously is basically when it's a diagnosis of exclusion when no underlying cause has been identified. It is seen more commonly, as I said, in the pediatric population. In contrast,

secondary ITP can have a range of underlying disorders. For example, lymphoproliferative disorders, SLE, Antiphospholipid Syndrome, infections like Hepatitis C, HIV, and some also immune deficiency syndromes, like Common Variable Immunodeficiency. In the routine setting, the commonest ones that we tend to see are Hepatitis C, HIV and the lymphoproliferative disorders.

Joe: There's a whole lot more that we could go to there, but this is not meant to be an in-depth discussion of the pathophysiology of ITP. But I do think it's important for those of us in transfusion medicine world to understand a little bit of the background that those like you, who cross both the clinical world and the transfusion medicine world deal with. Let's talk a little bit about when you see, in your practice, for example, when you see a patient that you suspect has ITP, what are the steps that you take to establish the diagnosis?

Ruchika: Like I said, Joe, it is a diagnosis of exclusion and that's important to remember primarily, especially so for primary ITP. We may have a clinical history like a preceding viral infection, especially so in the case of children and the youngest children present with it. For ITP specifically, as far as the diagnostic criteria goes, the cutoff is platelets less than 100K. But it's important to remember that they can present with a range of platelet counts and sometimes very low counts in single digits or teens. And we first and foremost rule out, is there any other secondary cause responsible for the thrombocytopenia? For example, is there any new medications the patient is on?

Typically, in primary ITP, you will find a history of preceding viral infection, or if it's secondary ITP, we start going down through our list of the "other" mechanisms I pointed out, like infections or lymphoproliferative diseases. We have to rule out obvious causes like Chemotherapy-induced Thrombocytopenia. If it's a transplant patient, post-transplant thrombocytopenia. All of those mechanisms once ruled out, it is a diagnosis of exclusion. It does not require a bone marrow testing for its diagnosis. And importantly, it does not require diagnosing antiplatelet antibodies for its diagnosis. It is essentially a clinical diagnosis.

Joe: That's huge. I well remember days when I would look at bone marrows to evaluate a patient with ITP, and I have had many discussions with people about antiplatelet antibody testing being necessary in the past. That's really interesting to know that neither of those is required necessarily to make the diagnosis. With that being said, Ruchika, let's talk a little bit about what we're here to discuss today, which is how do you treat ITP? Let's just talk through, again, just as an overview, what are the various treatment options that a clinician might have? What are the tools in your arsenal when you're considering how to treat someone with ITP?

Ruchika: We have primarily guidelines from American Society of Hematology, as well as there is an International Working Group dedicated to ITP treatment modalities. And we've actually had guidelines that came up very recently. This is a good time to discuss ASH, which is the American Society of Hematology, released guidelines in 2019. And same year the International Working Group released its ITP treatment guidelines. And we classify them as primary treatment, which is a first line treatment, typically, is using steroids with, or without combination with IVIG. And that happens to be the first line suggested treatment for most cases, whether it's primary or are you thinking secondary ITP in children as well as

adults. Once we have in most of the cases, in children especially, with just a single treatment, the disease actually doesn't come back. And it's only in less than 20% of cases that a recurrent disease or what we would call as "chronic disease" comes up. In contrast in adults, up to 70 to 80% of the cases can take a chronic form. You will see a disease would come back, either as you go in remission and the disease comes back, or there is some chronic low level thrombocytopenia with, or without bleeding symptoms that we have to deal with.

The second line treatment options, we have mostly immunomodulator therapy, which includes Rituxan. We also actually could have Thrombopoietin Receptor Agonists. These are drugs that directly are working on the thrombopoietin receptor, the c-MPL receptor, to increase the platelet production at the marrow level. And then we have a novel treatment that got FDA approved in 2018, called as "Tavalisse" or fostamatinib, which is an oral SYK inhibitor. It's trying to target the pathophysiology of platelet destruction and trying to decrease the actual destruction process. The tools in our armamentarium range from immunosuppressive therapy like Rituxan, which is basically, this Anti-CD20 agent, which will work with suppressing the lymphocytes from producing the antibodies against the platelets. Two, working on the thrombopoietin receptor and to try to produce more platelets or the other end to try to decrease the platelet destruction using a SYK inhibitor like Tavalisse, as I mentioned. If none of these therapies work, we have surgical interventions like splenectomy, which depending on the clinician preference, some people use that like a second line therapy as well. And then further, it comes down to third or fourth line therapy where we could have a range of immunosuppressions. For example, Vinca Alkaloids, Dapsone. The list is like very extensive. But at that point you're really talking about refractory disease.

Joe: One thing that I just want to clear up a little bit, because we in blood bank world hear about this and that's intravenous form of Rh Immune Globulin, of anti-D, in some patients with ITP. Is that still something that's considered? How commonly is that use nowadays?

Ruchika: Yeah. I actually should have mentioned that, Joe. You're spot on. Anti-D therapy, intravenous form is definitely still one of the frontline therapies recommended as a treatment option for ITP. It has to be used in patients who are Rh positive for effectivity. Importantly, FDA issued a black box warning a few years ago about the possibility of hemolytic anemia or hemolysis, a major episode after anti-D administration. The use of anti-D has decreased in the past decade or so. It definitely remains a treatment option, but we always monitor significant drop in hemoglobin after anti-D administration. In pediatric use, it is decreasing because we have just the range of options in our armamentarium are really increasing. If there is something which has a potential for a significant side effect, it is something that's less preferred.

Joe: Makes sense. Okay. Well just again, before we move on to talk about specifically platelets and I promise everybody I'm coming to that using platelets, from your perspective, again, with your clinicians hat on for just a moment, you talked about using glucocorticoids, IVIG, et cetera, in the population of patients that you see with ITP, do those generally work? And if so, how quickly do they work?

Ruchika: Joe, glucocorticoids and IVIG are definitely the most effective therapy. And they also are typically the quickest to take effect. Usually, we can start seeing an increase in platelet counts within two to three days, although the complete response may require one to two weeks. But they are still among the fastest responses that we see. As early as one day, we can start seeing a response, more typically, within two to three days after administration, platelets count start rising.

Joe: Okay. Ruchika, if those first line things don't work, what are your thoughts on the second line things like the Thrombopoietin Receptor Agonists, how long did those take to work and how effective are they?

Ruchika: Most of the data, Joe, about the Thrombopoietin Receptor Agonists have evolved in the past couple decades. They are highly effective medications, both Eltrombopag and Romiplostim. Those are the top two Thrombopoietin Receptor Agonists therapies that are used and in patients, they use second line therapy after steroids or IVIG are not effective typically. And they would have an effectiveness with showing median increase in platelet counts above 50,000, within two to three weeks of administration. Likewise, for the oral SYK inhibitor, Tavalisse, which I mentioned, that also shows effectiveness within two weeks of administration.

The point which I do want to highlight, which is important that you bring about is that some of these medications because they're trying to target the basic pathophysiology of an autoimmune disease, they may be effective, but they can take time. Their platelet counts will rise. The rise can be sustained and it can actually in long term be effective in preventing bleeding, which is our primary goal of therapy. But they may take time anywhere from three to seven days or even longer.

Joe: We are here to talk about using platelets in these situations, Ruchika, because you've done a lot of work on this and you've published on this. And everyone there, I want to make sure that you're aware that you can go to the show page for this episode and find a bunch of links to articles that Ruchika, and her colleagues have published on the use of platelets in some of these disorders that we're talking about today. Let's talk about platelet transfusions in ITP. You didn't mention platelet transfusions in any of your discussion previously about things that we would do for ITP. Let's talk about it. Do platelet transfusions even work in ITP? Is there a role for them?

Ruchika: I think Joe, with your question about the timing for the effectiveness of the other therapeutic options, it's a perfect segue to bring in a potentially very important role for role of platelet transfusions in ITP. As we discussed that the primary pathophysiological mechanism is destruction of the antibody-coated platelets. Theoretically, the transfused platelets also tend to get coated with these antibodies, which are targeting primarily the glycoproteins. Just as the native platelets are susceptible, the transfused platelets are all also susceptible by the phagocytic action of the reticuloendothelial system cells or the macrophages. However, what that can lead to is a shortened survival and a rapid clearance of the transfused platelets as well. Irrespective of this, there is a role potentially important role for emergency treatments of ITP.

If a patient has severe thrombocytopenia and life-threatening bleeding, the treatment options that I mentioned previously can work, but they will take time. And that brings in the role that if there is an emergency bleeding which can be life-threatening, then there's a role for platelet transfusions at that time. I would like to preface it by saying that majority of the bleeding in ITP is actually non-serious. However, it presents mostly with mucocutaneous bleeding, epistaxis, nose bleeds, purpura as we said, but rare bleeding, for example, internal bleeding, including GI hemorrhage, genitourinary hemorrhage, and very critically intracranial hemorrhage can happen as well. And what the epidemiological numbers tell us is that the intracranial hemorrhage, which is the most serious and the most concerning, can happen in 0.5 to 1.5% of the ITP cases.

It can happen in children as well as in elderly, more tendency to happen in the elderly. If there is major life threatening bleeding, we have to bring in an emergency therapy, which will be platelet transfusions.

Joe: What I'm hearing is that things that you would consider minor bleeding, such as nose bleeds, because I've had this phone call, Ruchika, as I'm sure you have, probably in both your roles as a hematologist as well as transfusion medicine expert. I've had the phone call that this patient has ITP and they have epistaxis. I've got to start transfusing. What you're saying is that at least according to current evidence and current guideline, that something like that would not be considered an urgent enough bleed, that it would necessarily warrant a platelet transfusion. Is that accurate? Or am I overstating it?

Ruchika: Joe, you're right with stating that, typically, an epistaxis would not be a major bleeding. However, this is something that is at the time left of the clinical judgment of treating physician. An epistaxis can evolve into a major bleeding. What's truly recommended is that follow a standardized bleeding assessment tool, for example, there's WHO grading criteria for severity of bleeding. Follow one of the bleeding assessment tools and something which may be not at a very critical site like intracranial hemorrhage could also evolve into a major bleeding if there is significant drop in hemoglobin, if it is something that's significant enough to be requiring blood transfusions, and otherwise not, harmless bleed can evolve into a critical bleed for the given patient. And the risk for actually fatal bleeding, particularly it's greatest in the elderly patients and with severe thrombocytopenia.

Another thing I want to highlight here is that I do say “severe thrombocytopenia,” however, there's actually no specific platelet count or a number in ITP, which is considered to be safe. As an example, in pediatric population, we actually ordinarily deal with extremely low platelet counts like in single digits and where the patient may be completely stable. Or in other case, we may have patients who have higher counts, even above 30,000 and may experience a life threatening bleed. The bleeding phenotype can be very patient-specific. There's a very important role for individualized therapy for taking into account what is actually happening at the patient level in your decision making for the treatment.

Joe: That is so huge. And I want to make sure that we don't leave that point, Ruchika, because I think that is a point that is really commonly missed in patients with ITP. Let's make sure that we hammer that home clearly. What I'm hearing you say is that there is no specific platelet count that is considered safe versus unsafe in someone with ITP. Is that how you would put it?

Ruchika: Yep. You stated that right. I agree.

Joe: Okay. Well, excellent. And that's hugely important. We're going to get a little bit more in a little while, on some of the data that you and your group have helped develop in terms of how patients with ITP are actually getting transfused. But before we get there, there have been different opinions given about how platelets transfusions should be given in patients with ITP when they are given. Could you talk a little bit about some of the options, in other words, some of the ways that platelets could be given or strategies that platelets could be given in a patient with ITP?

Ruchika: Yeah, that's important. Before I give that answer about the range of modalities or by which we could actually transfuse platelets, I want to say that the data, the level of evidence supporting any of these is very little. We have either retrospective case studies or small case series or case reports largely that are showing what the effectiveness of platelets can be or not. There's no large studies. There are no randomized control data or studies that have evaluated the question. Our level of evidence when we talk about using platelets as a therapeutic option, as well as the grade of evidence as I'd like to say, they're both low.

With that background, platelet transfusions, a life-threatening bleed in ITP can be given by themselves like solo. And that could be given as a single unit. It can be given as another modality where we give a bolus dosing followed by actually running a platelet drip, where it's just transfusing slowly after giving a bolus dose. The other contrast, some of the patients may actually require massive doses, so repeated doses one after another while we are trying to get the hemorrhage under control. Another choice which is proven to be more effective, and actually in 40% of the patients in a retrospective study found out that platelets when given and in a combination with IVIG may have better response in improvement in the platelet count, as well as resolution of bleeding and a more sustained response. The combination of platelet transfusions, if needed being given with IVIG is more common.

Joe: I have also heard people talk about strategies that, I'll be frank, I have had my doubts about in the past, such as constant platelet drips or giving gargantuan doses of platelets. Do you have any thoughts on either of those?

Ruchika: Again, I think, Joe, as a treating hematologist, I would say that, personally, I have transfused platelets in ITP patients or being part of a care team. These are usually patients who are sick enough to be admitted in the Intensive Care Unit. It is very closely monitored, but there are rare cases in which we are not able to get hemorrhage into control, so repeated doses of platelet transfusions are needed. But again, these would stand out as isolated case reports and would not be typically suggested as a standardized therapy. Eventually, we have to remember that even if being given in an emergency setting, there are potential adverse effects of a transfusion and those have all this to be taken into account.

Joe: I think that is hugely important. And we may circle back around to that because what I want to give you the chance to do after we talk about what you and your group found in your excellent paper on this very topic. I want to circle around to something that you guys found in the paper in regards to how we can help be

people that practice at maybe smaller hospitals where there isn't necessarily the level of expertise as in some major hospitals. I'll put a pen in that and we'll come back to it. But Ruchika, let's go right now to your paper, because again, I think it was just such an outstanding look. Put this way, I think it filled a spot in the literature that we really didn't have before. I would love to just give the floor to you to talk a little bit about how you guys came to wanting to do this paper and just the general aspects of what you found?

Ruchika: Sure. I actually circle back to another prior publication we had earlier in 2015, Joe, where we looked at platelet transfusion in some platelet consumptive disorders. Primarily the focus was TTP and HIT, so Thrombotic Thrombocytopenic Purpura, and Heparin-Induced Thrombocytopenia. And we used ITP more as a control disease where we were trying to see, would there be any adverse effects? And once we started digging into the data, we realized that the number of cases in hospitalized patients, we found platelet transfusions as part of like in ad hoc analysis, it was surprising.

And so we decided to look a little bit deeper into it and see, what exactly is happening? Are people following the guidelines and how often are platelets indeed being transfused in ITP patients? For this, we used a nationally representative database called as National Inpatient Sample or NIS. It is the largest all-payer inpatient database in United States. It captures hospitalizations from over 1100 hospitals across the country. And there are 47 of the 50 states are participating in this database. And there's data that is extracted at the time of hospital discharge. It gets a nice snapshot of the entire hospitalization and what were the main comorbidities, main event and the main procedures that happened during the hospitalization. So we captured using at the time of this publication it was data including only the ICD-9 coding. This is prior to 2015, when we had switched to ICD-10 codes. And we identified patients who were primarily admitted with ITP as their primary admission diagnosis. In a span of five years, from 2010 to 2018, we're able to identify about 78,000 admissions. That takes about 15 to 16000 admissions around the country for ITP.

And then we started assessing what the platelet transfusion practices in these were. And what we found is that in patients who are admitted with ITP as a diagnosis, surprisingly about 15% of the patients received a platelet transfusion. That's about one in seven patients. What we found is that about one in seven patients reported receiving a platelet transfusion. We could actually document how many of them, the number of transfusions and in about 2% of the patients, platelets were received twice. And about 1% of these patients receive platelet transfusions three times or more.

And we further went on to see that at least based on the ICD-9 discharge coding, were these patients documented to have a major bleeding? Which we, for the purpose of this study classified as intracranial hemorrhage, GI hemorrhage, or gastrointestinal hemorrhage, or genitourinary bleeding and also included epistaxis. What we found is that in one fourth of the cases, so in about 25% of the subject, at least one bleeding episode was documented. Again, I have to highlight that this is based on the ICD-9 billing codes, okay. And then secondly, we try to see, were these patients undergoing an invasive procedure which could have warranted, offered an explanation for why the platelet transfusions were happening?

Putting both these criterias together, we found that in two thirds of the subjects where a platelet transfusion was reported, which as I said, in majority cases, a single unit was documented. We noticed that neither was a major bleeding episode documented, nor did we identify a major invasive surgical procedure, which was there. The one procedure that was documented in majority of the patients was actually splenectomy. And the patients getting platelet transfusions on the day of the splenectomy.

It was very revealing in the sense that we have the guidelines from, as I mentioned, American Society of Hematology, AABB has commented on it in their guidelines as well as review of data that they put together, as well as International Working Group of platelet of ITP. However, what was surprising is that, first of all, the number of hospitalizations in which platelet transfusions were documented. Secondly, the fact that we did not identify major bleeding episodes or surgery in either of these patients.

To the question that really came is that, are platelet guidelines truly being followed? We dug a little bit more into the data to see, are there specific scenarios in which we are seeing more platelet transfusions? And so what we found is that the platelet transfusions in the absence of a documented major bleeding are happening more in smaller hospitals, the non teaching hospitals or the non-urban. So let's say the small hospitals or the rural hospitals. And that brought up the important question that, are people actually following or treating a low platelet count and response to that treating patients prophylactically, or offering platelet transfusion just simply treating a number, rather than an actual indication for a life threatening bleeding?

Joe: What you just said is what I wanted to make sure that we got to, because I think that a lot of the people that listen to this podcast aren't necessarily practicing in the biggest hospitals in the world. Let's just speak for just a second to those who are dealing with this scenario in a non-urban area where a clinician is looking to treat a platelet count specifically. Are there any tools that we can give? Are there any discussion points that we can give to those laboratory folks and those pathologists, perhaps that are covering blood banks that aren't necessarily blood bank experts in those scenarios where your platelets are just being used up the few that you have by scenarios that appear to be someone treating an ITP number rather than bleeding?

Ruchika: Yeah, Joe, that is a very important point you bring up. I think first and foremost to remember is that while transfusions are critical life saving therapies, and there is an inherent risk with every transfusion. Right? Platelet transfusions have their own independent risk of febrile reactions, allergic transfusion reactions. And then most importantly, as we know, bacterial sepsis risk with platelets. There's a very hard discussion about FDA guidance on how to deal with that so much so that it remains a very important topic, which can be a major risk for fatal outcomes in transfusions.

There's also risk for because of the plasma containing platelet products risk for TRALI, Transfusion-Related Acute Lung Injury. And then besides that, any transfusion transmitted infection risk remains. There is a theoretical risk for something which could be as common as a febrile reaction or an allergic

transfusion reaction or something rare as a transmission of a transfusion transmitted infection.

First and foremost to remember that any blood product, any blood component when transfused comes with its inherent risks, that is importantly a very important cost factor to be taken into account. Platelets are amongst the most expensive blood components. Any time where an overuse from a patient-centric perspective, could it actually do harm to the patient than help? And also how it truly affects the overall financial burden on the healthcare. That's something to be important to be taken care of.

The second thing clinically, I want to point out is that, again, no platelet count specifically is outlined as a threshold beyond which someone should be transfused platelets. In general, we say that about 5 to 10,000 K platelet counts, 5 to 10,000 platelet count is required to maintain the baseline endothelial integrity and the risk of spontaneous hemorrhage at platelet count less than 10,000 and specially so at less than 5,000, the risk of spontaneous hemorrhage does go precipitously high. Still regarding the fact, there is not a single cutoff or threshold that has been outlined, whether it's 30,000, 20,000, 10,000, there is no number at which it is said that let's go ahead and transfuse platelets to prevent bleeding. There is no outlined role or recommendation of platelet transfusions as a prophylactic measure in ITP patients. If however, a patient does experienced severe life-threatening bleeding, what the International Working Group and ASH guidelines recommend is that do not delay treatment. If that patient has a major bleeding, you can consider platelet transfusions knowing that, number one, they may not help at all, or if they do help the effect maybe short lasting.

The thing to remember is that taking all of this into account that if you need to reach out and get expert input from a hematologist, do that. But there are times when you have to take spot on decision, that you may not have time for a consultation or an input, that if the patient is bleeding, do go ahead and consider transfusing platelets. But knowing that concurrent therapies, which would reduce like the other treatment modalities I outlined, which will produce a long lasting or a sustained increase in platelet counts is very important. And also knowing that the transfused platelets, they may or may not help. It's not a modality that we can rely on with assurance. If we do need to transfuse, do that knowing that it may not work.

Joe: That's excellent. I love that. Thank you so much. And honestly, even though I prefaced that as saying let's give some tools to those in smaller hospitals, I think you and I both know that sometimes things like this do happen in major hospitals. And while I think it's important to circle back to what you said, we don't have enormous amounts of randomized wonderful data that we can point to, to show that the guidelines are based on huge studies and with wonderful outcomes, et cetera. But at the same time, there's just no signal to show that there is benefit for over transfusing patients like this. Is that an accurate way to put it, Ruchika?

Ruchika: I think you summarized it perfectly, Joe. Yeah, I would agree with that.

Joe: Everyone, there's a whole lot more to that paper that Ruchika, was just talking about. And again, you can find the link to that on the show page for this episode, it's a study from transfusion published in 2019. And it's wonderful. Please, please

be sure to check that out as well as a summary that I will link to on med page today. You guys did a great job on that, Ruchika.

I want to make sure that we spend a few minutes talking about how ITP fits in with the findings that you guys published in the other paper that you mentioned. It published in Blood in 2015, "Platelet transfusions in platelet consumptive disorders are associated with arterial thrombosis and in-hospital mortality." That was a really big and important paper and I want to make sure that you get the chance to talk a little bit about that. As I said, we're spending most of our time today on ITP, but let's talk about what we expect in terms of how platelets can potentially cause problems. In addition to the other stuff that you mentioned, the Transfusion-Related Acute Lung Injury, Transfusion Associated Circulatory Overload, those complications. But there may be an inherent danger that you guys outlined in patients with Thrombotic Thrombocytopenic Purpura and Heparin-Induced Thrombocytopenia. Again, I'm going to open the floor to you a little bit and just have you discuss what you guys found and what your general thoughts and concerns were when you published that blood paper.

Ruchika: Thank you, Joe, for bringing that point about. And I think while with ITP, we see one end of the spectrum where we know that platelets may or may not work. And besides the general side effects of any platelet transfusion, there's no disease specific by the physiology, by which platelets should harm. Hopefully, they will help, but if they do not help, that's fine. In contrast, we actually have some other, what I would call as “platelet destructive disorders” or “platelet consumptive disorders.” Hallmark being TTP and HIT where the actual institution of platelet transfusions, also this happens in an emergency setting typically. But it's important to know that because of the underlying disease pathophysiology, the same platelet transfusion can have very contrasting effects. This has been proposed, again, there is biological plausibility for the concept that for TTP there's risk for arterial thrombosis, and which could be fatal thrombotic events, both venous and arterial. But the autopsy analysis was done. The principle histological abnormality found in TTP was that the clot is a platelet microvascular thrombus. It is platelet-rich, it's von Willebrand factor-rich, but it is fibrin poor. It's showing that there's lack of involvement of the traditional clotting cascade and the platelets can have a direct role in causing microvascular thrombosis.

And in the other end, on the similar spectrum, we have Heparin-Induced Thrombocytopenia where we can also have both venous and arterial thrombosis. But in HIT we have these heparin dependent anti-platelet factor immune complexes that are formed, which can cause platelet activation and cause thrombocytopenia and raise risk for thrombosis.

What we did is using the same database, the NIS or National Inpatient Sample, identified cases of TTP and HIT admitted. These are hospitalized patients. And we specifically looked at those patients who were transfused with platelets. Were they associated with any adverse outcomes? And what this paper showed is that among the three disease entities, for both TTP and HIT, where we do have a biological possibility and small case series supporting possibility of arterial thrombosis, we actually did find an increased association with arterial clots in patients who had platelet transfusions. And this effect remained after adjusting for the potential confounders and is also including adjusting for this severity of

illness. For TTP, we also found an association with risk for acute myocardial infarction with platelet transfusions.

And in contrast for ITP, we did not find any increase in venous or arterial thrombosis. I have to point out an important limitation of the study that at the most, this is a statistical association. It is something that there's not enough evidence to draw a temporality or actually propose causality. It is just something that is providing some more evidence using a large database to suggest that, yes, for both TTP and HIT, the platelets could have an adverse effect that's causing arterial thrombosis and higher risk for mortality while not so for ITP. But given the limitations that it is restricted to the coding being ICD-9 and ICD-10 coding and their inherent limitation, as well as lack of exact temporality association. I think it's more a hypothesis generating concept, which if possible, should ideally be studied in a prospective study, or ideally in a randomized controlled trial setting.

Joe: It's very interesting to hear this simply because as you know, Ruchika, I've been around for a long time and I've been teaching learners in pathology and other specialties about transfusion forever. And after I saw this paper, I looked back on materials that I used to discuss with pathology residents back in the 90s. And I said back then, not that I'm brilliant and trying to pat myself on the back. But I think that I said back then that transfusion in ITP, TTP and HIT was contraindicated. And that it probably wouldn't hurt anybody with the ITP, but the possibility of hurting someone with TTP and HIT was there. I think that the supposition, as you said, has been around for a while, but this is to my knowledge and correct me if I'm wrong. This is the first larger scale data that I'm aware of that at least as you said, supports that, doesn't necessarily prove it, but at least supports that.

Ruchika: Joe, this is the first national study and the largest cohort we could put together combining five years of analysis. I don't want to say you're brilliant.

Joe: No, no, no.

Ruchika: And of course, like all the teaching you've been bringing about, which I am one of the huge learners and huge fans who's benefited immensely. I think, you know what you mentioned as a general maxim, it definitely stays true that to avoid prophylactic platelet transfusions when we can in these entities. Unless life-threatening bleeding is present, then take it on a case to case basis. We are just like that, could we be adding fuel to the fire, actually? That part being there and to individualized decision think and follow. We don't go by a general rule that it is highly individualized and closed monitoring is needed.

Joe: Well, I want to put you on the spot for just a second, Ruchika, and this is not fair. I will freely admit that this is not a fair question, but I will tell you that I've seen this scenario in real life multiple times, and it's just this, it's the scenario where a patient presents, they're highly suspected to have TTP. As you know, patients with TTP, clinicians and those who deal in Therapeutic Apheresis tend to have a low threshold for starting Therapeutic Plasma Exchanges in those patients for obvious reasons. The potential bad outcomes are significant. But the patient has extremely low platelet count, just say 5,000 or so and the Therapeutic Apheresis team wants to put in a central line and the Interventional Radiologists don't seem

too terribly happy about putting in a central line with a platelet count of 5,000. I've seen in many cases, blood bankers say, "Okay, fine, give some platelets so that you can put the line in." I've seen in other cases, blood banker saying, "Absolutely, no way. You shouldn't do that. And just do the central line anyway." Like I said, it's not a fair question. And I'm not asking you to give specific advice for everyone in the world. But I guess my question is, how do you deal in general with that, almost a no win situation?

Ruchika: Yeah, Joe, you are bringing up a very important point, a real life scenario which we end up dealing with, absolutely. How I see is individualized decision making, having a discussion with the clinician about the pros and cons, it's important. At time from a blood bank or a blood center perspective, we eventually have to trust the judgment of the treating clinician. And once from our end, we can't put a hard stop on this. How I always say is that my recommendation would be in this specific case, yes, I understand this is an unusual scenario, to go with it a very low platelet count and try to put in a central line or start an invasive procedure. There is risk for bleeding. Given however, that the potential adverse outcomes can be so critical and we don't want to do an intervention, which is prophylactic, but then adverse effect can be so severe. It can actually, by itself cause mortality or a stroke, or a thrombosis in the patient. What I typically say is that we have a bag ready to go and it's approved if needed. If the patient bleeds, we will transfuse and I would not hold it back. But this exceptional scenario is definitely worth approaching that, could this patient safely have the line put in without bleeding? Usually, that's how I go, and most of the time it's worked fine. And I can tell you that in majority of the cases, Joe, we end up not transfusing. And because it's like they are more reassured that yes, there is a product that's available as an emergent product, if needed immediately, it's approved and ready to go. But a lot of times they just don't need it and the patient does well.

Joe: Right. I'm glad we were able to talk about that, Ruchika, and I didn't mean to surprise you with that. As you said, it's a real world thing. Questions like that and concerns like that happen all the time in hospitals, all across the United States. Ruchika, as we close our time here together, first, I just want to thank you because this has just been a wonderful overview of the challenges that come about, especially with ITP. But as also, obviously, we've talked about TTP and Heparin-Induced Thrombocytopenia a little bit as well. I wonder as we close our time together, if you just summarize what you feel like are the most important learning points that those who are listening to this podcast should take home with them?

Ruchika: Sure. I'd like to state that ITP or Immune Thrombocytopenia can present with extremely low platelets counts. Do not follow a number in taking a decision for an intervention like a platelet transfusion. It is a therapeutic option that is available to us, should the patient have a life threatening bleeding, or hemorrhage. Important to note that platelet transfusions may or may not work. They have shortened survival after transfusion. Institution of a concurrent alternative therapy while we are doing emergency platelet transfusions is important. There is more data supporting concurrent use of platelet transfusions with IVIG as bringing better increment in platelet counts and better resolution of bleeding.

Secondly, also to remember that there are other causes of thrombocytopenia or other platelet consumptive or destructive disorders like TTP or Thrombotic

Thrombocytopenic Purpura and Heparin-Induced Thrombocytopenia, where because of the underlying pathophysiological mechanism, platelet transfusions may not help, but may actually be associated with significant adverse outcomes like arterial thrombosis, and higher risk of mortality. To sum it all, to know that platelets remain an important therapeutic alternative in managing some of these patients, but the decision making should be highly individualized. And if we do transfuse platelets, make sure to have a close monitoring for any adverse effects.

Joe: That's a terrific summary. Ruchika, that's awesome. And I am so deeply appreciative of you spending time with us today. Thank you so much are sharing your amazing expertise with our audience.

Ruchika: Thank you so much, Joe. This is absolutely my pleasure, my honor. Thank you for inviting me. Happy to help in any capacity. And if there's any follow up questions, I'll be happy to take that.

****

Joe: Hey everybody, it's Joe again. Just a couple of quick closing thoughts. Most importantly, don't forget to go to the show page for this episode. That's BBGuy.org/092, where you can find those references to the papers that, Dr Goel, was talking about during this interview. It's really important. Those are papers that you should for your files because there's lots of really good information and really good data in there.

I've mentioned this before, but if you have the opportunity, I would really so much appreciate it if you would go to Apple Podcasts and give this podcast a rating and subscribe. Again, this is not for my ego. In fact, some of the things that people have written on there are "anti-ego," to tell you the truth, which is fine. I'm very excited to get people's feedback because I always want to do this better. In fact, if you write something there, you may find it being read on a future episode of Blood Bank Guy Essentials. At any rate, what it actually does is it allows more people to get exposed to and hear about the podcast. I would really appreciate that if you could manage to do that.

I do have a continuing education episode coming up and it should be out very soon. That will be episode 093. And it's going to be a discussion of the mighty test that we call the “Monocyte Monolayer Assay” or the “MMA.” That's a really fun interview with Sandy Nance, from the American Red Cross. I'm very excited for you to hear that. It is coming up soon, I promise.

But until that time, my friends, I hope that you smile, and have fun, please tell the ones that you love how much you do, and above all never, EVER stop learning. Thanks so much for listening. I'll catch you next time on the Blood Bank Guy Essentials podcast.