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Expert Perspectives on Immune Thrombocytopenia

Narrator: You're listening to ReachMD. This medical industry feature, titled "Immune Thrombocytopenia: Expert Perspectives" is sponsored by Amgen.

Immune thrombocytopenia, or ITP, is a heterogenous disease characterized by unpredictable rates and severities of bleeding events, which can complicate both its diagnosis and management. On today's program, we'll hear from two ITP experts discussing how we can overcome common challenges in the diagnosis and treatment of this disease.

Your host is Dr. Matt Birnholz.

Dr. Birnholz:
This is ReachMD, and I'm Dr. Matt Birnholz. With me today are Doctors James Bussel and Ralph Boccia. Dr. Bussel is Professor Emeritus of Pediatrics and Medicine at Weill Cornell Medicine in New York City. Dr. Boccia is Medical Director of the Center for Cancer and Blood Disorders in Bethesda, Maryland, and Clinical Associate Professor of Medicine at Georgetown University in Washington.

Dr. Bussel and Dr. Boccia join us to provide an overview of ITP, the diagnostic steps they recommend, and important treatment considerations through the care continuum.

So, Dr. Boccia, let me turn to you first. Can you just start us off with a general overview of ITP?

Dr. Boccia:
Sure. We know ITP to be an uncommon bleeding disorder caused by increased platelet destruction, as well as decrease platelet production. This is a, disease that results in increased risk of bleeding. By definition, patients must have a platelet count of less than 100,000.

Unfortunately, we don't have a direct test to diagnose ITP, so it's a diagnosis of exclusion.

Today, we consider three different phases of ITP: the newly diagnosed phase in the first three months, the persistent phase for the next nine months, and then the chronic phase after a year. We see about 20,000 new cases a year, and that is from about six per 100,000-person years. Unfortunately, females tend to have more autoimmune disorders, and we see that this has two peaks, one in the child-bearing age, and another one after age 65. And actually, after age 65, we see the highest incidence of autoimmune thrombocytopenia develop. This is a bleeding disorder of mucocutaneous sites. So, we see petechiae, we see purpura, we see gingival bleeding with brushing of teeth. We see wet purpura, what people call blood blisters and, unfortunately, rarely, we can see catastrophic intracranial hemorrhage. Patients may have GI bleeding and GU bleeding. Of course, that's mucosal as mentioned before, epistaxis, and although patients may have thrombocytopenia, this is really a disorder of thrombosis as well, especially during therapeutic periods. It can and often does affect quality of life, and you may not know it, but there is some evidence that patients with ITP in the untreated state have increased fatigue.

Dr. Birnholz:
Thanks, Dr. Boccia. So Dr. Bussel, can you tell us a bit more about the risks of bleeding and the platelet counts that are generally associated with bleeding.

Dr. Bussel:
Severe bleeding occurs in about 10% of adults with ITP, and especially, we worry about intracranial hemorrhage, which occurs not very frequently in younger people, but more commonly in people over the age of 60 or 65 when comorbidities, blood vessel disease, medications, et cetera, creep in. They're all great majority less than a platelet count of 10,000 and maybe 90% less than 20,000. So, I

do think that platelet count is important, and bleeding is important.

Some patients come in to see the physician because they feel tired, and that's their clue that their platelets are low even though they're not bleeding, exactly as you said. Looking at this from another viewpoint, Altomare and colleagues summarized bleeding in a large series of patients and showed that bleeding was substantially more frequent in the newly diagnosed patients. We believe that this is because, typically, they come to attention because of bleeding, and they have not initiated treatment.

Dr. Birnholz:
Dr. Boccia, earlier you referenced ITP as a diagnosis of exclusion. Can you tell us how you walk through the diagnostic considerations to rule out other underlying conditions?

Dr. Boccia:
When we approach a patient with thrombocytopenia, it's important to take a good history and physical. When did the bleeding start? What type of bleeding is it? Is there any family history of bleeding? Then we move into the laboratory. We want to know what the platelet count is, so we do a complete blood count. It's important to look at the peripheral blood smear because there are congenital thrombocytopenia's that you might pick up by looking and finding giant platelets.

Also, there is this entity called pseudo-thrombocytopenia, where because of the chemicals in the tube, there may be some platelet clumping and give you an artificial count if it's just run through the machine.

Reticulocyte count and direct antiglobulin test or Coombs test are probably most important in patients who have anemia at the same time to make sure they don't have both immune thrombocytopenia, as well as autoimmune hemolytic anemia or the so-called Evans syndrome.

Bone marrow aspirate and biopsy can be very helpful. We don't do that many bone marrow aspirates and biopsies in younger patients, but it's recommended to do them in patients over age 60 or 65 in order to rule out myelodysplastic syndrome. And then there are things that you may or may not need based on other things, glycoprotein-specific antibodies, antithyroid antibodies, and thyroid function. Of course, antiphospholipid antibodies, especially if you have somebody with thrombosis because of the increased incidence of a terrible antiphospholipid antibody syndrome that can include thrombocytopenia. Antinuclear antibodies to make sure it's not an autoimmune disorder that results in secondary thrombocytopenia such as systemic lupus or rheumatoid arthritis, and then depending on the clinical situation, you may be looking at Epstein- Barr and CMV, so you may be looking at PCR to identify whether there's an active disease burden going on there.

Dr. Birnholz:
Dr. Bussel, turning to you, is there a single test that everyone agrees on that is important to measure?

Dr. Bussel:
There's a big debate. So, very few people completely agree on what to look at, and I think it's fair to say that the only thing everybody would agree on would be a blood count and looking at the smear in addition to the physical. I think you've provided great rationales for looking at the other things, but whether you should measure those in everybody, some people, I don't think we have a clue.

Dr. Birnholz:

Those are great insights into the rationales and challenges behind making the diagnosis of ITP, so why don't we carry that line of thinking toward therapeutic strategies. Dr. Boccia, how do you approach treatment.

Dr. Boccia:
So, we know that ITP in general results in increased platelet destruction either from T-cells or auto-antibodies. We also know that we can take advantage of that by blocking some of this process. We also know that instead of blocking platelet destruction, sometimes we can outstrip that by increasing platelet production with the agents that stimulate the cMpl and the megakaryocyte for proliferation, maturation, and platelet production. The frontline therapies that we use include the corticosteroids anti-D as well as immunoglobulin in very high doses. So, cornerstone of corticosteroid is suppress B and T cell-mediated auto-antibody production.

Dr. Bussel:
When we talk about second line therapies, we're talking about anti-CD20 and the thrombopoietin receptor agonists. Recently, SYK inhibition has come into play, so that's another possibility.

Anti-CD20s can knock out the B cells that are making the antiplatelet antibodies. TPO agents stimulate platelets, so they can outweigh the rate of destruction by increasing the rate of production. SYK inhibitors can block phagocytosis of antibody-coated platelets. So, in that way, we can take advantage of some of our knowledge of the pathophysiology. And finally, splenectomy use in the US and

worldwide is way down, very few people do it anymore.

Dr. Boccia:
So how do we formulate a plan in our mind? Well, it has to take into account many different factors. The patient's age, and we've already talked a little bit about that patients that are older have other comorbidities, have other medications that they're on. They may be on anticoagulant, maybe on antiplatelet agents. Is the patient going to need surgery? Has the patient had any traumatic episodes? What is their lifestyle? Do they like to hike? Do they like to bicycle ride? Do they like to ski? That will come in to play because when platelets are very low, those are lifestyles that we recommend patients avoid at all cost. And then what's the access to care? That has to be taken into account, especially for people who like to travel or live in remote areas.

Dr. Birnholz:
So let's circle back to the subject of corticosteroids as a cornerstone of therapy. Now I understand there are some factors and issues to consider with this treatment approach. Dr. Boccia, what can you tell us about that?

Dr. Boccia:
We certainly know that multiple cycles of high-dose corticosteroid pulses are over-utilized right now. And there are times when we see patients in second opinions who have never responded to steroids and yet they're still on steroids. Fortunately, we now have updated ASH guidelines, they made changes in first frontline use of corticosteroids administered for a short, fixed period of time now rapidly tapered for those patients who don't achieve a response.

Dr. Birnholz:
And Dr. Bussel, how do you define this issue of insufficient response to corticosteroids?

Dr. Bussel:
You could use two different definitions for that. One would be somebody responds but you can't take them off steroids, they're dependent on it, they're counts fall to less than 30, and even if you give it for more than six to eight weeks, you still don't have a treatment-free response. And another is if the platelet count just doesn't go up at all in the beginning, where you've given steroids for a couple of weeks, and there's not been a platelet response should be rapidly tapered off as opposed to continuing on. I think it's very exciting that the ASH guidelines and the consensus document both focus on not going with steroids for beyond six to eight weeks.

Dr. Birnholz:
So, if we focus on newly diagnosed patients for a moment, how do the treatment goals differ from acute bleeding settings to post-acute settings?

Dr. Boccia:
So, the acute setting is to treat bleeding or at least prevent major bleeding if the patient has really profound thrombocytopenia. In post-acute bleeding setting, we want to reduce the risk of further bleeding. We want to maintain a stable platelet count, so that we could give drugs that will hold the platelet in a certain range without having to adjust therapies very often. Those are the real treatment goals in the newly diagnosed patient, and those moving on from the newly diagnosed to the persistent phase.

Dr. Birnholz:
We know that spontaneous remission occurs in ITP. But is remission feasible in ITP and how would you define remission?

Dr. Bussel:
I think defining remission is a little bit tricky. A number of definitions have been used. I think of something that's been more widely used recently in clinical trials with the thrombopoietic agents has been having a count above 50,000 without ITP therapy for at least six months.

Now, some people could say, but that's not really remission because a platelet count might be less than 150,000 and 150 is lower limit and normal or somebody else could say, "Well, the platelet count is normal, but I could still measure platelet antibodies. So, I think if we put aside the debate about the pathophysiology of remission, you know what does that mean, and just focus on the clinical, I think that makes a lot more sense. I think that's definitely achievable. I think as we talked about maybe half the patients or even a little more will be better within one to three years, and I think that is the goal. You certainly don't want to have major bleeding, but you don't want to keep having to treat somebody either.

Some patients maintain, sustained platelet responses after treatment's discontinued, and we're not always sure how often it's a "spontaneous" remission or natural history, and how often it's due to treatments. With steroids, we think that responses observed in 70% of patients initially, but only 10 to 30% at the most will have a response where they can discontinue steroids, and still maintain an adequate platelet count. Splenectomy, we discussed that it's nice that there's a clear statement about waiting on splenectomy. Maybe

it's around 60 to 65% who have long-term responses, but it may be less if patients currently have their splenectomy delayed.

With anti-CD20, approximately half of the patients will have a good initial response that may last six to 12 months, but approximately half of those will then relapse, so that by one to two years they are not in any kind of remission and require further treatment.

Similarly, treatment-free remission has been shown with the thrombopoietic agents and discontinuation may be feasible in some patients. If it's in early-stage patients who were treated, it may be in up to one-third of patients.

Dr. Birnholz:
Dr. Boccia, turning to you. Does early treatment or intensification of therapy improve chances of remission?

Dr. Boccia:
So, there are some early trials now, and there are certain clinical trials and certain datasets that we have looked back at retrospectively that suggests that those patients that were treated earlier, remember the studies that we've done have had median ITP, durations of anywhere from four to eight years looking at pool datasets, it looks like those patients who were treated with the novel agents in the first year from diagnosis tended to have a longer duration, and had a higher fraction of patients who actually achieved a response and allowed discontinuation of therapy. We don't know what those biologic mechanisms are, but we do know they happen.

Dr. Bussel:
I think the other thing that we've kind of been talking about a little, you said it, I think, exactly right. People have looked at agents in the first year, and they've looked good. I think what we really want now is agents in the first three to six months, and that's been an exciting area of development, and, ideally, if we understood more about which pathophysiology, and which patient, and so on, that would be really good.

Dr. Birnholz:
Excellent. Thank you, Dr. Bussel. Well as we come to the end of our discussion today, I want to open the floor to you both for any additional thoughts or takeaways you'd like to leave with our audience. Dr. Boccia, let me start with you.

Dr. Boccia:
So number one, there is an unmet need that evolves all around ITP. One is we don't understand how to best prognosticate patients today. Number two, we're not great at making a diagnosis at this point in time since we have no test to say, "This is ITP". It's very important to look at using corticosteroids for a shorter duration. Early second-line treatments that may improve long-term disease control has got to be looked at very critically now.

Dr. Birnholz:
Thanks, Dr. Boccia. And Dr. Bussel, you get the last word.

Dr. Bussel:
We are beginning to at least understand the potential mechanisms could be but figuring out which ones are really active and how to exploit them is something that a lot of work is needed on and I hope that our discussion has emphasized that it's really important to have a back and forth exchanges between the academic centers and the community physicians to improve care by focusing on what are the needs, and then how to develop answers or responses to those needs, and make things better.

Dr. Birnholz:
Well with those ITP takeaways in mind, I very much want to thank my guests, Dr. Boccia and Dr. Bussel, for joining me today to walk through the diagnostic and treatment foundations for this disease. Doctors, great to have you both on the program.

Narrator:
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