Evidence-Based Guidelines on the Diagnosis and Treatment of Acquired Thrombotic Thrombocytopenic Purpura
Speaker(s): David Kuter, MD, DPhil and Spero Cataland, MD

Dr. Kuter:
Hello, my name is David Kuter. I'm a Professor of Medicine at Harvard Medical School and Chief of the Program in Hematology at Massachusetts General Hospital in Boston. And I'm pleased to welcome you to this activity entitled, The Latest Insights into Rare Blood Disorders: Diagnosis and Treatment Strategies. We're going to be discussing three different topics today: acquired thrombotic thrombocytopenia, cold agglutinin disease, and ITP.

Our first chapter is entitled, Evidence-Based Guidelines on the Diagnosis and Treatment of Acquired Thrombotic Thrombocytopenic Purpura. And we're going to be, as our learning objective here, describing the recent ISTH evidence-based recommendations for the diagnosis and treatment of acquired ITP.

And I'm pleased to introduce Dr. Spero Cataland. Professor Cataland is Professor of Internal Medicine in the Division of Hematology at Wexner Medical Center at The Ohio State University in Columbus, Ohio. And I'll begin with my first question to him, which is: What is acquired TTP? And how is it different from ITP?

Dr. Cataland:
Well, thank you, David. Really a pleasure to be here and talk with you about this interesting topic. I think simply put, acquired TTP is a disorder of widespread microthrombi that occur throughout the body, injuring multiple organs in the microvasculature. It really arises from either a congenital, or in this case we're talking about the acquired form, an acquired antibody-mediated clearance of the ADAMTS13 protease. So, without that ADAMTS13 protease, you don't get cleavage of these ultra-large vWF multimers into the physiologic sizes. Without that clearance, you can get ultra-large multimers in spontaneous platelet aggregation and microthrombus formation.

Dr. Kuter:
So, in this situation, it's different from ITP in that it's got a thrombotic component to it, which is probably less so than an ITP, is that correct?

Dr. Cataland:
I think you're correct. If I could take the liberty of overly simplifying ITP as a disorder of just platelet destruction, both will be characterized by a significant and severe thrombocytopenia. I think the difference is in how they get there. The ITP is the clearance or destruction of platelets, and in TTP it's the consumption of platelets, so forming the microthrombotic disease that leads to that acquired thrombocytopenia.

Dr. Kuter:
So, thrombocytopenia is a common clinical question to us hematologists that affects about 10% of hospitalized patients, for example. When do you think about TTP in terms of just the platelet count number? How low does it got to be to think about this disease?

Dr. Cataland:
Yes, I remember being taught many years ago that a platelet count of less than 10,000, you should be thinking about TTP, ITP, or a drug-induced thrombocytopenia. And I think we'd like to think about it in that context to start with. Then we start thinking about end-organ injury which might steer you closer to TTP, meaning abdominal pain, nausea, headaches, other findings such as elevations of the LDH and cardiac injury with the troponin. And also keeping in mind the more common things, drug-induced causes; when a patient comes to the hospital with a normal platelet count, and 6 days later they have a thrombocytopenia, we're thinking more of a hospital-acquired thrombocytopenia, or a drug-induced cause rather than something more rare like TTP.

Dr. Kuter:
So, patients with TTP should think about if they've got a thrombotic component, and is the bleeding component equally important? Or is that of a lower priority?

Dr. Cataland:
Yeah, that's an excellent point. I mean, they can certainly have bleeding issues. But I think you want to think about TTP more as a thrombotic disorder. And you're looking more for the thrombotic component of the disease. So, the abdominal pain, the nausea, the confusion, the end-organ injury that goes along with that thrombocytopenia.

Dr. Kuter:
So, some ITP patients, since I take care of a lot, can have ITP for weeks, months, or have no troubles with it. But is there an urgency of distinguishing acquired TTP from ITP?

Dr. Cataland:
Yeah, I think so. I mean, we certainly worry about both in terms of bleeding and clotting disorders. But there's certainly an urgency to diagnose and start treatment very quickly for TTP to avoid sort of catastrophic complications of a delay in the diagnosis and treatment. Certainly, very important to identify quickly and treat it.

Dr. Kuter:
So, if I'm trying to find out if my patient with thrombocytopenia has got TTP, what are the important aspects of the diagnosis? What are the – what's the ISTH evidence-based recommendations for diagnosing this condition? How do I prove that someone's got it?

Dr. Cataland:
So, that's a good question. And a lot of the guidelines, scoring systems we see really try to distill down how an experienced clinician who sees a lot of patients with these TMAs will look at these patients. And I remember Dr. George telling me many years ago, he spent the first half of his career teaching the pentad of TTP, and he spent the last half telling people to forget the pentad of TTP. The idea being, you don't want to wait for the pentad to be fulfilled, you don't need all those criteria. And we now use thrombocytopenia, fragmented cells without another explanation, and clear end-organ injury as a result of that to really hone in on the diagnosis.

Dr. Kuter:
So, if I had to order a lab set, it would include a LDH, a smear to look at, and then other specific blood tests?

Dr. Cataland:
I think so. I think right off the bat, you need to CBC, you need to look at the smear. I think an LDH is very helpful, very quickly. And I think your judgment is just as helpful quickly, really thinking about how did we get here? Are there any other explanations? And I've even been fooled a couple of different times, looking at smears when you don't see schistocytes, as you expect. But you don't have any other explanation for a platelet count of 7,000 and elevated LDH in a confused young female or male patient. In those situations, you're still going to go forward with empirical treatment, while you get some additional testing back later.

Dr. Kuter:
Does a negative Coombs test help you make that distinction from Evans syndrome?

Dr. Cataland:
I think so. That's important as well. We talk about, you know, a Coombs test as bringing in autoimmune hemolytic anemia with the ITP. I think that's helpful. I wouldn't necessarily rely on it, but it's certainly helpful in your evaluation then.

Dr. Kuter:
So, what's the role of an ADAMTS13 assay since they sometimes are hard to get or take a while to turn around?

Dr. Cataland:
Yeah, they are sometimes difficult to get. Sometimes are more readily available within 3 to 4 days. I think it has to be remembered that this is still a clinical diagnosis, and ordering this ADAMTS13 activity and waiting for the result is really an accident waiting to happen. If you think enough of the diagnosis being possible to order that ADAMTS13 testing, you really need to ask yourself about your diagnostic or clinical probability of having a case of TTP, as you see reflected in the ISTH guidelines. And if you have a high clinical suspicion, you'll send the ADAMTS13, which will serve to confirm or exclude your clinical diagnosis, but you should start empiric plasma exchange therapy. And then immune suppressive therapy or caplacizumab based upon your clinical suspicion.

Dr. Kuter:
So, it sometimes is hard to read these ADAMTS13 reports because they'll give you an activity level and then they'll tell you whether an antibody is present or not. How important is it to have both components in making the diagnosis or confirming your clinical suspicions of TTP?

Dr. Cataland:
Excellent question. The most important by far is the ADAMTS13 activity, which really will capture all of the inhibitor status, the functional activity you have as measured in vitro. The inhibitor and the antibody titers, the ELISA is looking at antibody on the ADAMTS13, are very important to confirm the acquired form rather than a congenital form. There can be some idiosyncrasies with the testing. But in general, most important is the activity, and the antibody testing is going to help you differentiate acquired versus congenital form to the disease.

Dr. Kuter:
So, if I think someone's got TTP, and the assay comes back 4 days later into my therapy, I've shown that it's 26%, do they still have TTP?

Dr. Cataland:
It's a good question. I mean, we say less than 10%, clearly they have the disease; we'd like to say 20% or higher, probably not. Think about other reasons why it may be low; sepsis, other acute illnesses, liver disease, the rare cases where you may have somebody as a carrier for congenital TTP, but they may have, not normal necessarily, but lower levels of ADAMTS13 activity.

Dr. Kuter:
So, if I've made a clinical diagnosis, and hopefully that ultimately is confirmed by an ADAMTS assay, what's the initial therapy that's recommended for patients with TTP these days?

Dr. Cataland:
Yeah, no, without question, plasma exchange is still the standard of care. It's the initial therapy that you should use with immune suppressive therapy, which typically will entertain corticosteroids and rituximab. The guidelines reflect the early use of rituximab in patients with a higher clinical suspicion. I think if that's, if I'm going to say, what the standard of care is in most institutions, it's going to be corticosteroids and rituximab, both started as soon as possible with plasma exchange therapy.

Dr. Kuter:
So, when it comes to corticosteroids, is dexamethasone acceptable? Or is it only prednisone or prednisolone?

Dr. Cataland:
Yeah, it's interesting that as much as we talk about steroids, the importance of them in TTP, there's really not a ton of data to really guide us. I think many use prednisone as just as a convention, you've used it

over the years. It's easier, if you will, to taper it. There are groups that use dexamethasone pulse up front. I think those questions become less important with the more frequent use of rituximab early on as a good sort of longer-term version of corticosteroid therapy in patients.

Dr. Kuter:
And the rituximab dosing, is it the typical CLL regimen of four doses? Or have we truncated it to a lesser dosage?

Dr. Cataland:
Yeah, there's been some work that's been done looking at lower doses from Washington University and the late Evan Sadler as well as Marie Scully's group in London, I think the standard approach is still four weekly doses 375 mg/m^2.

Dr. Kuter:
And if you put someone on plasma exchange and corticosteroids and you get the rituximab in, how long does it take for a response to be seen with the normalization of a platelet count?

Dr. Cataland:
It's a good question. The plasma exchange is really going to have that more rapid response and it's going to depend on how much antibody you had, the avidity of the antibody, how strong it may be. But within the first 24 to 48 hours, you should start to see a decrease in the LDH, which will then be followed by an improvement and eventually, you hope, a normalization of the platelet count. So, I think when you're looking for a response, it's not just the platelet count, it's the LDH as well. And when you're looking for the plasma exchange therapy to help in your clinical diagnosis to confirm if that's what you're looking for, a drop in the LDH, then followed by rise in that platelet count.

Dr. Kuter:
So, in patients like that who then have a successful discontinuation of plasma exchange, they've got their immunosuppressive agents on board, they're still on corticosteroids, you want to send this patient home, is there a need for other therapies to send them home on? For example, the use of caplacizumab – and we'll come to that in a second, is now part of our armamentarium?

Dr. Cataland:
Yeah, I think an interesting question. I think the most important endpoint that we don't talk about enough is this exacerbation, which is the newest definition. It's the recurrence of TTP in the first 30 days after the last plasma exchange or anti-vWF therapy. And this is a very real clinical endpoint, typically occurs in the first 2 weeks after the plasma exchange or anti-vWF therapy is stopped. And it results in a patient's being rehospitalized, the central line typically been placed back in, and another course of plasma exchange therapy. It's quite common. It happens in 30 to 40% of patients. And it's a very large clinical dilemma. The treatments that we've had: steroids, rituximab, have just not impacted that. And as I said earlier, it's most common the first 2 weeks after discharge from the hospital. And rituximab is probably the most effective

immune suppressive agent we know of in TTP, takes 2 to 3 weeks to start to begin to improve that ADAMTS13 activity.

Dr. Kuter:
So, the new drug, caplacizumab, which many of us have not had much experience with, when do you actually use it? Is it only in the refractory patient? Is it in every patient you want to send home? How would you employ it in your practice?

Dr. Cataland:
It's a great question. So, without question, the data really support it in our clinical experience, and I've had extensive experience with it, is very effective and a safe agent in the right hands. Ideally, we'd only use it in the patients who are at risk for exacerbations or at risk for refractory disease; the two most important uses of it or effects of it. Unfortunately, we just can't tell who those patients are up front. We just don't know reliably who it has at risk for exacerbation and who's going to have refractory disease. So, we will typically use it in all patients up front, unless there's concern for bleeding. The mechanism of action, as you know, David, is it binds to A1 domain of vWF and prevents its interaction with platelets. So, it does a great job of blocking the downstream effects of not having protease function to cleave those ultra-large multimers. But again, it does lead to a mild increased risk for bleeding, which is typically manageable, but needs to be considered in patients before we give it.

Dr. Kuter:
And is this a rather costly treatment or not?

Dr. Cataland:
Yeah, unfortunately, it is expensive. And that's I think one of the difficulties that's limited, some of its more widespread use. I don't believe it's the data, or the side effects associated with it. It's quite impressive to use it. And the issue of exacerbations is really more of a non-issue with the regular use of caplacizumab.

Dr. Kuter:
Well, this brings us maybe to our last but brief set of questions here, which is, you know: Where do you see the treatment of acquired TTP going in the next 10 years? I mean, what's going to change how we treat these patients? Is it universal adoption of caplacizumab or other therapies?

Dr. Cataland:
Yeah, I think really, I think we're seeing the really the acceleration of the treatment and the advances in TTP, which is quite impressive, whether it's caplacizumab or the recent FDA approval for recombinant ADAMTS13 for congenital TTP. And I think what we're seeing is the future is right now. I mean, the caplacizumab has to be emphasized, it doesn't alter the disease, the ADAMTS13 activity or improve it. It really can be viewed as temporizing like plasma exchange therapy. And really understanding that tells you why it makes some sense in two ongoing studies now of the use of caplacizumab and recombinant ADAMTS13 alone without plasma exchange in the treatment of acute TTP. So, therapy started with those

individual agents alone, in different studies I should mention, and the use of plasma exchange at the physician's discretion if needed. I think we're going to see some interesting results of the studies that might change how we treat TTP in the future, in the very near future.

Dr. Kuter:
So, it seems like the focus on current research is finding ways to turn off the, or to affect the ADAMTS13 deficiency. How about using more strong immunosuppressive drugs than rituximab, such as a BAF inhibitor or TRAIL inhibitor or neonatal Fc inhibitor to make the antibody just disappear?

Dr. Cataland:
I think that's a great, great, great question and great thought. I think our first cyclosporine study was really taken from an ITP study many years ago. And I think in TTP, there's been a lot of focus on the upfront treatment, the plasma exchange, rituximab. But with plasma exchange, it's hard to reliably do studies to know what effect you're having, there are a lot of confounders. I think one result of having more targeted treatment of TTP, whether it's caplacizumab without plasma exchange or recombinant ADAMTS13 without, is we'll be able to do better at studying immune suppressive therapy. I think that's, along with long-term complications, that's the new area of intense study. What's the best immune suppressive therapy for TTP patients?

Dr. Kuter:
Well, thank you, Dr. Cataland, that was a lovely journey through the new worlds of acquired TTP. Thank you for participating today.

Dr. Cataland:
Thank you, Dr. Kuter, appreciate it.