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Transcript – Coag Conversation

Alternate Warfarin Monitoring When the Prothrombin Time is Unreliable

Conversation # 2 Anticoagulation in Antiphospholipid Syndrome

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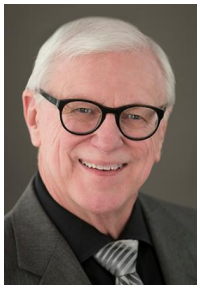

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Transcript of Conversation 2

Mr. Fritsma: Hello, and welcome to Coag Conversations. an educational series sponsored by BioMedica Diagnostics of Windsor, Nova Scotia, Canada. Our topic for this three-part series is **Alternate Warfarin Monitoring When the Prothrombin Time is Unreliable**. We will focus on anticoagulation management in the antiphospholipid syndrome.

And we begin the second conversation with a discussion entitled Anticoagulation in Antiphospholipid Syndrome. I'm George Fritsma, faculty for the University of Alabama at Birmingham School of Medicine, Division of Laboratory Medicine and proprietor of The Fritsma Factor, your Interactive Hemostasis Resource.

We welcome Nicole Zantek, MD, PhD, Professor, Department of Laboratory Medicine and Pathology, University of Minnesota Medical School. Dr. Zantek is a pathologist with expertise in transfusion medicine and blood banking. She is the Medical Director of the Special Coagulation Laboratory and conducts research in the areas of hemostasis, transfusion medicine, and blood utilization.

She is interested in general issues surrounding hemostasis test performance, utilization, and interpretation. In particular, she is exploring how medical circuits, such as ventricular assist devices and apheresis cell separators, influence hemostasis in adult and pediatric patients. Dr. Zantek is also interested in advancing transfusion medicine and blood utilization practices.

Mr. Fritsma: Dr. Zantek, what are some of the clinical indications in antiphospholipid syndrome? What are the symptoms and what are the risks for the patients?

Dr. Zantek: Antiphospholipid syndrome is characterized primarily by thrombotic issues, so arterial, venous, or microvascular thrombotic events and / or a pregnancy-related morbidity, in association with having an

antiphospholipid antibody. And the main criteria are antiphospholipid antibodies, again, are the lupus anticoagulant, and then anticardiolipin, IgG and IgM, and then anti-beta 2 glycoprotein 1, IgG and IgM. And those need to be persistent. It's a syndrome of having a persistent antibody. The testing is usually done at least 12 weeks apart to confirm the presence of that. And the patients with antiphospholipid syndrome, as I said, are at risk for thrombosis.

And most commonly it's deep venous thrombosis in the legs and pulmonary embolism, but they are also at risk for stroke and ischemic attacks. And actually, in younger individuals, about 14% of patients with ischemic stroke have antiphospholipid antibodies.

And you can also see other kinds of non-criteria, classically findings with antiphospholipid syndrome. These are things like heart disease, livedo reticularis, which causes sort of like a mottling pattern on the skin, thrombocytopenia, problems with the kidneys, neurologic conditions and visual complications all can be seen with antiphospholipid syndrome.

Mr. Fritsma: And there are also some problems with pregnancies as well?

Dr. Zantek: Pregnancy. Yes. That's one of the classic main findings have been thrombotic events and then pregnancy, morbidity or mortality related to that. Complications like **HELLP [H**emolysis, **E**levated **L**iver enzymes and **L**ow **P**latelets**]** Syndrome as well, and other pregnancy related complications.

Mr. Fritsma: Is it important, besides testing for lupus anticoagulant, to also test for the beta 2 glycoprotein 1 antibody and the anticardiolipin antibody?

Dr. Zantek: It's really important if you are, it's important to test for all of those three things. So, because you want to determine one, dissipation of any antiphospholipid antibodies, but it's also important to determine if they are what we call triple positive.

So, do they have all three? The risk for thrombotic events, the risk for recurrence of thrombotic events is higher in someone that is triple positive, has all three versus having just one or two of them. And if the other non-lupus anticoagulant antibodies are tested not using clot-based assays, so they're generally tested historically using ELISA-based assays. And the beta-2 glycoprotein 1 and cardiolipin assays are a little bit sort of overlapping.

The cardiolipin antibody testing usually includes cardiolipin bound to beta-2 glycoprotein and the beta-2 glycoprotein assays usually just include beta-2 glycoprotein. Once you can see antibodies that will react in assays, but they may still pick up antibodies individually as well. And the anti-cardiolipin assays can pick up multiple types of antibodies sometimes.

Historically, they've been done by ELISA methods where, you know, you put the target protein into a well and see if a patient has an antibody that binds and then add a secondary antibody to detect it. And that's what the newest EULAR guidelines are continuing to recommend those for like defining how we define patients with antiphospholipid syndrome in like clinical studies. But, those tests are hard to do.

And there's newer methods that still detect antibodies using things like chemiluminescence type assays that are much easier to automate and are more standardized internally with a single assay. And so those are sort of replaced in many labs, the classic ELISA methods. They're helpful for detection of antibodies as well. The main issue between the two is that one assay's level doesn't always match the assay level in another. The range of results is different. Generally, the positive negative side is about the same, but the threshold for like calling something moderate or high differs between assays. And just like lupus anticoagulants, there's difference between assays. So, not all cardiolipin assays are identical, and sometimes a patient's antibodies

are detected differently in one assay versus another. But it is important that you get all three to make sure that you look for that triple positivity.

Mr. Fritsma: Understanding is that for the enzyme immunoassay based tests for beta-2 glycoprotein 1 and for cardiolipin, that they aren't necessarily harmonized across the field.

Dr. Zantek: That's my understanding and appreciation as well. You can get some variation between assays. So, the sort of titer level, the greater than 40, greater than 80, is not perfect between assays. And that greater than, the other way to call it is positive is that it's greater than 99 percentile. Those numbers may not be even between assays as well. It's still a work in progress to try and harmonize these assays. There's no standard calibrator. There's no reference calibrator that's universally applied. I think that adds to some of the dynamic as well.

Mr. Fritsma: We do test for both IgG and IgM. Do you ever test for IgA?

Dr. Zantek: You know, it's one of the non-criteria. The IgG and IgM are part of the criteria for, you know, the five that'll make up the criteria, antibodies for antiphospholipid syndrome. But there are other non-criteria ones. The IgAs, usually by themselves, the IgA, cardiolipin, and beta-2 glycoprotein aren't as predictive of thrombosis and aren't thought to be as strong a risk factor. But there are other non-criteria antibodies that can be helpful, particularly to establish a diagnosis in someone where it's not as clear and maybe they will have a strong non-criteria antibody where other testing has maybe not been positive.

So, while they can be used in sort of that clinical decision making, does someone have antiphospholipid syndrome, we don't use the non-criteria ones in terms of defining it for essentially research-type studies, clinical studies.

Mr. Fritsma: Right. Good. Now, if a patient is shown to be lupus anticoagulant or antiphospholipid antibody positive, does that automatically trigger therapy? And what is the standard therapy?

Dr. Zantek: The antiphospholipid antibodies can be detected in people that don't have antiphospholipid syndrome. It's important to determine, does someone have antiphospholipid syndrome versus you incidentally find, for example, a lupus anticoagulant in someone that has a long PTT? Because you may have a lupus anticoagulant that's not really associated with a thrombotic event.

The main sort of long-term strategy to reduce thrombosis is anticoagulation. You know, largely in patients that have had a thrombotic event. The main anticoagulant used or recommended is vitamin K antagonists. And then in pregnancy, a little molecular weight heparin with or without the combination of aspirin is used due to the warfarin as teratogenic. It needs to be shifted away from that during pregnancy.

Mr. Fritsma: Is warfarin the preferred anticoagulant in someone with antiphospholipid syndrome?

Dr. Zantek: Currently, that's what the guidelines recommend. Particularly if you have all three; if you have what's called triple positive antiphospholipid syndrome. And the reason is, based on data from randomized controlled trials using the DOACs or rivaroxaban, apixaban, which would be the preferred drug in some other situations, but not in this scenario in antiphospholipid syndrome. And the reason that they're not preferred is that some of the data has been less favorable with DOACs in randomized controlled trials. There's been higher instances of arterial thrombosis with the direct oral anticoagulants, and then also higher incidences of stroke. And in those studies that tested direct oral anticoagulants against vitamin K antagonists. Also, when they looked at triple positives, they saw that they had a higher rate of thrombotic recurrence. Not all things are worse with DOACs between vitamin K antagonists. They didn't see differences in things like heart attacks or bleeding or other thrombotic events.

But the arterial thrombosis and stroke rates are high enough that is pushing the movement towards sticking with the vitamin K antagonist rather than using the direct oral anticoagulants.

If a patient is just starting new, I think they will put them on warfarin. And this is where testing is important to determine, you know, early on, should they be on…what type of anticoagulants could they be on? Because if someone is double or only has one of the three types of antibodies, then there could be some consideration for actually going on a DOAC. Which is in some ways easier for patients because it doesn't have all the testing that is needed for warfarin.

But the testing is problematic because you often need to make decisions. And so, they are starting to test in a center where it's not optimal. So, they've just presented with a thrombotic event. You think they have antiphospholipid syndrome, so it's not a good time to test, but you still need to test because you've got to make some decisions. So, we kind of get caught in this catch-22 scenario with making anticoagulation decisions.

Mr. Fritsma: Just out of curiosity, if you don't mind me asking, in your facility, are you seeing a lot of APS patients who've been placed on DOACs as opposed to warfarin?

Dr. Zantek: I think we see definitely in the triple positive that they're advised to be on warfarin. But always, there's a patient decision factor and patient preferences have to play into it as well. And sometimes patients accept the slightly higher risk because the DOAC is so much easier to take. That you don't have to have all the monitoring, or the INR is unreliable and they would, as we may, we'll talk about that maybe they don't want to have to bother with that extra kind of testing. And so there is always a patient component to the decision-making.

Vitamin K antagonists are recommended. There are scenarios where patients are put on DOACs. I think it's important [to have] informed discussions between clinicians and patients when they make those decisions anytime about anticoagulation. And what their options are and how does it fit in the entire clinical picture for a patient.

Mr. Fritsma: Yes, thank you for that. I have asked people at two or three different facilities, and it sounds as though DOACs are being used fairly regularly, even though the studies, the randomized controlled studies, have shown that warfarin is generally more effective.

I am finding that DOACs are being used quite a bit. Now, if you have somebody who's on a DOAC and you want for some reason to go back and test for an antiphospholipid antibody or lupus anticoagulant, what do you do?

Dr. Zantek: That's the tricky spot. That's right. They're already, I mean, get specimens, they're already on it. So those DOACs in particular are hard to get around. There are, with the lupus anticoagulant testing, the DOAC, there's some absorbing reagents that can be tried. None of them are cleared in the US, but they're used off outside of that clearance, but they are widely used outside of the US.

They can bind up the drug in there. So hopefully you can get a testing in the setting of that drug removal. The other option is also to do the other testing. Lupus anticoagulant is really influenced by anticoagulation, but the other two, the cardiolipin and the beta-2 glycoprotein are insensitive related to the anticoagulation. So, one strategy is to do those two, the IgG and IgM for the beta-2 glycoprotein 1 and cardiolipin.

If both of those are negative, you don't have triple positive lupus antiphospholipid syndrome. If both of them are positive, now you have to worry, they really have it. And so then you can sort of look at what can I test at the right time and make decisions on? If they're both negative, maybe you're not sure they have

antiphospholipid syndrome. Then maybe you test when you take a brief break from anticoagulation, you get good testing so you can make a really good determination if they have it or not.

Mr. Fritsma: I think facilities handle these things a little differently. I know. I checked with UAB [University of Alabama, at Birmingham] a couple of days ago to find out what they do if they have a request for lupus anticoagulant testing on somebody who's on a DOAC and they simply, just cancel the tests. They will go ahead, as you say, and do anticardiolipin antibody and anti-beta 2 glycoprotein 1, but they will cancel testing altogether for lupus anticoagulant.

And the other question I have about DOACs is, is there ever a time that you need to actually measure or monitor the DOAC level in somebody who is an antiphospholipid antibody syndrome patient?

Dr. Zantek: Just the scenarios for monitoring the DOAC would be similar to patients that didn't have antiphospholipid syndrome. There are times when it would be helpful to determine what the level is, being aware that there's no therapeutic ranges. There's none that have been established for rivaroxaban and apixaban, for example.

But it might be helpful to get a sense of where a level is or detect it before going to surgery. So, things like, are they on a medication that's known to interfere? Is it causing a lot of interference? Are they bleeding? Did they have an event while on that drug? So, do you really want to check to see, are you getting an adequate level on the dose that you were on? And then if you're going to go, as I mentioned, into surgery or some other invasive procedure, you may want to check to see what the drug level is.

So, there are times like spot-checking might be helpful, but like routine monitoring, just like in other patients, isn't really needed. Thankfully, with the rivaroxaban and apixaban, those two are most commonly checked on a clinical side using tests like the anti-FXa test, which are not readily interfered with lupus anticoagulants.

So they're pretty reasonably reliable in the scenario of antiphospholipid syndrome. You can get a result. The dabigatran or the direct thrombin inhibitor, depending on the method used, things like anti-FIIa tests would be potentially used. But sometimes people have antibodies that might cross with some of those kinds of testing. So, but again, it's not typically needed.

Mr. Fritsma: Very good. One last question, and this is a loaded question that is meant to bring us to our conversation number three, which will be next month.

That is, when you are using warfarin, can you just monitor it with the PT / INR as we would in all other circumstances? Can you do that in somebody who has antiphospholipid syndrome?

Dr. Zantek: The question that is going to come as to how reliable is the INR in a patient that's got antiphospholipid syndrome because the INR contains phospholipid--so thromboplastin contains phospholipid. Sometimes antiphospholipid antibodies do prolong and impact the prothrombin time and the INR.

The short answer is sometimes yes, sometimes no. So just like other reagents for lupus anticoagulant testing like PTT and dilute Russell viper venom, there's variable sensitivities to the reagents. And some reagents are more or less sensitive to antiphospholipid antibodies. So, in some patients, it's possible to continue to use it. It's important to check before you start the warfarin or other vitamin K antagonists to make sure that, you know, is the baseline normal? If the baseline isn't normal, then you worry that the antiphospholipid antibodies are interfering and then you would potentially underestimate the amount of effect that you're getting and thus underdose the patient.

And so, it can be done, but you really need to know where you started from and to get a sense of, is this a reagent that looks like their antibody doesn't interfere with? The same is true with point-of-care devices. Those reagents, as well, have some variable sensitivity. So, one would want to determine that.

The one sort of glitch is if the antibody level waxes and wanes. Does it have more effect or less effect? Later on might be hard to tell in the midst of, if you're continuing to monitor with INR. But, it's sometimes why people are rechecked for antiphospholipid antibodies when they've been followed with INR. Because it seems like their levels, INR has been moving different to what they expected from their dosing. So, some patients, yes, but in some patients that isn't going to be a reliable strategy.

Mr. Fritsma: Thank you. And we're going to go into that in even more detail in conversation number three, because that is interesting and it is kind of a limitation.

I want to thank everybody for participating in conversation number two. We will move on to conversation number three. It will be posted on the BioMedica website after about a month or so. So, watch for that. Meantime, thanks for listening.

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