Transcript Details
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Understanding Heparin Resistance: Underlying Mechanisms and Alternative Treatment Options

Announcer:
You're listening to *Project Oncology* on ReachMD. On this episode, Dr. Cheryl Maier will discuss alternative strategies for managing heparin resistance, which she shared at the 2024 American Society of Hematology Annual Meeting. Dr. Maier is an Assistant Professor in the Department of Pathology and Laboratory Medicine at Emory University and also serves as the Medical Director of the Emory Special Coagulation Laboratory in Atlanta. Let's hear from Dr. Maier now.

Dr. Maier:
Heparin resistance is this general term that we use to describe patients who aren't hitting an expected level of anticoagulation even when their provider feels like they're giving them an appropriate dose. And unfortunately, even though it's a really common clinical term, we just don't have a consensus on what a precise definition would be for heparin resistance. So, in fact, there is no agreed-upon standard for what the target level should actually be or what constitutes an appropriate dose. And so if we look in the literature from when heparin resistance was first defined, there's a report in 1994 from Levine, et al. in *Archives of Internal Medicine*, and they described heparin resistance as when patients were requiring fixed doses exceeding 35,000 units per day. And a lot of clinicians actually still use this threshold even though a lot of others have now evolved into using more weight-based dosing, which is something I also advocate for.

One of the more common causes of heparin resistance is that the patients don't truly have heparin resistance. This is something that some have argued should be called pseudo heparin resistance. And it really relates to the testing that we're using to monitor our anticoagulation response. So when we think about testing platforms, we have these clot-based assays, which include the aPTT—activated partial thromboplastin time—or for patients who are on very high levels of heparin, like during a cardiac bypass, then we use a different clot-based assay called the aCT—the activated clotting time. And these assays—because they are clot based—are actually just a lot more susceptible to a number of influences beyond just what that heparin level is. We also have a more direct measure. These are chromogenic anti-Xa assays. And some centers only use clot based, others only use chromogenics, and some offer both. But if you have a patient that you're concerned about heparin resistance in, it is important to use an anti-Xa if you can because it's a more direct measure and less susceptible to other influences.

Once you've tried to troubleshoot that, then if you really think you are dealing with heparin resistance, we can think about it mechanistically in two different buckets. And so on the one side, we have to think about whether or not a patient might be deficient in antithrombin, or they might actually have a number of plasma-based proteins in cells that combined heparin and make it less available to bind antithrombin and have its anticoagulant effect. And that's because unfractionated heparin is actually a pretty promiscuous agent. It's not like a lot of drugs with a very specific target, but it sticks to a lot of things. So it can bind to white cells and platelets, certain chemokines like platelet factor 4, different extracellular matrix proteins like laminins, collagens, and even some growth factors and enzymes, and then certainly other coagulation factors, things like factor 8 and von Willebrand factor. So it's important to remember that if you have a patient with increases in these other things that heparin will stick to, less of it will be available to bind antithrombin and have its anticoagulant effect.

Usually, when we're managing a patient who has heparin resistance, one of the things we'll do before we just switch anticoagulant classes is at least consider supplementing with antithrombin, and so there's antithrombin concentrate that's available that many providers will use. And certainly some providers will not go that route at all and just switch to an alternative anticoagulant, and this is the anticoagulant class known as direct thrombin inhibitors. These don't rely at all on antithrombin and only bind to their target—to thrombin.

So these include things like argatroban and bivalirudin, both of which are very efficacious.

One of the bigger concerns with them is that they can be a little more difficult to monitor. Most institutions don't have drug-specific testing available, and so we use the aPTT. And then the other concern is that there is no reversal agent. This generally isn't a problem because of the short half-lives—especially for bivalirudin, it's only about 25 minutes—and so if you need to mitigate an anticoagulant effect, you can basically just stop the infusion. Another consideration is often cost. The antithrombin concentrates are usually more expensive than just switching to a direct thrombin inhibitor, and so that's at least in part why a lot of providers will just go that route as their initial first step.

Probably the most important thing for the future of helping with these patients is that we do develop consensus criteria so that clinicians have some way to know for sure about whether or not a patient has heparin resistance. And we need to have these criteria in place so that our future clinical trials can really be standardized in their approach so that we can make sure we glean as much impactful information from them as possible.

Announcer:
That was Dr. Cheryl Maier talking about alternative management strategies for heparin resistance, which she discussed at the 2024 American Society of Hematology Annual Meeting. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!