Article:
Selena Wong, Jenna Slingerland, Jane A Dickerson, Jennifer Pak, Gavin D Roach, and Nabiha H Saifee.
Development of a Rapid Qualitative Screen for Anticoagulant Presence.
J Appl Lab Med 2024; 9(2): 305–15. https://doi.org/10.1093/jalm/jfad081

Guest: Dr. Nabiha Saifee from Seattle Children's and the Department of Laboratory Medicine and Pathology at the University of Washington.

Randye Kaye: Hello, and welcome to this edition of *JALM* Talk from *The Journal of Applied Laboratory Medicine,* a publication of the Association for Diagnostics & Laboratory Medicine. I'm your host, Randye Kaye.

For several decades, vitamin K antagonists such as warfarin were the primary anticoagulants used for the long-term treatment and prevention of thrombosis. In recent years, however, a newer class of drugs known as direct oral anticoagulants, or DOACs, has become the standard. Unlike warfarin, which is affected by vitamin K intake, DOACs are not affected by diet and are considered to have more favorable efficacy and safety profiles. While DOAC drug levels are not routinely monitored, they can be useful in some select situations. Liquid chromatography tandem mass spectrometry is considered the gold standard for measuring DOAC levels, but it's expensive and technically challenging. Therefore, a DOAC activity test that uses routine coagulation assays already found in clinical laboratories would be useful.

The March 2024 issue of *JALM* features an article that describes the development of a rapid qualitative screen for anticoagulant presence using commonly available heparin and anti-Xa activity and thrombin time assays. Today we're joined by the article's corresponding author, Dr. Nabiha Saifee. Dr. Saifee is the Transfusion Service Medical Director at Seattle Children's and an Assistant Professor in the Department of Laboratory Medicine and Pathology at the University of Washington. Dr. Saifee's professional passion is centered around merging her expertise in pediatric transfusion medicine and coagulation with practical insights to lead impactful quality improvement projects at the institutional level. Welcome, Dr. Saifee.

First, what prompted your group to develop this rapid anticoagulant screen?

Nabiha Saifee: Yeah, so we're a pediatric hospital and direct oral anticoagulants have been used more in adults, and there's a lot more data there, they're very easy to use because they're given via an oral route, very stable pharmacokinetics, a fast on and offset for the drug. But now there is more pediatric

trial data. There's been more recent approvals of these new oral anticoagulants in pediatrics. So our hospital, we've seen more use of it, and our clinicians are using more, and so we have come across some urgent situations where patients who are needing surgery and they want to know like is that DOAC present or not, or there's another drug called fondaparinux we're using here that has a longer half-life that we don't have an assay for in house.

And we also have, there's reversal agents also available. So if patients are bleeding, and then we want to quickly reverse it to help stop the bleeding, you want to know if you're detecting the drug or not. And so we did feel like this is something that's being used more by our clinicians, and we need to have something available to help them care for our patients.

Randye Kaye: Can you tell us a little bit more about how the screen works? What tests does it include? What anticoagulants can it detect?

Nabiha Saifee: Yeah, so our screen includes two tests that we have included in our anticoagulant screen, so the anti-Xa activity assay and the thrombin time assay. The anti-Xa activity assay is one that we keep available 24/7 for our patients because patients who are on IV kind of unfractionated heparin, we need to frequently monitor them. So we have that test available, and the anti-Xa activity just so happens that there's direct oral anticoagulants that are factor Xa inhibitors, and so that will actually found to linearly correlate with the anti-Xa activity level, so we knew that we could use that for a certain group of our oral anticoagulants.

And then for the other direct oral anticoagulants, there's ones called dabigatran, and that's a direct thrombin inhibitor. So our thrombin time assay is one that is affected by that direct thrombin inhibitor. So we have both of those for sure that we knew that we could use our assay and those we could detect. The other one that we sort of included in our testing, as I mentioned before, is there's this fondaparinux, which is kind of like heparin. It also inhibits factor X. And so we also went ahead and validated that in our [interp] as well, because that's not an assay that we have, requires routine monitoring and we didn't have that level available at our hospital either, so we also looked at that, too.

Randye Kaye: What would you say are some of the unique aspects of your approach?

Nabiha Saifee: Yeah, so we're a pediatric hospital, and these direct oral anticoagulants, they're not requiring routine monitoring. So we don't have a lot of samples, actually, for patients who are taking these direct oral anticoagulants, and so it's hard to validate a test without a lot of samples, and then even when

we get samples, as our pediatric patients are small and we get very small sample sizes as well, we thought this would be something that we still wanted to validate and be something very useful. So we took kind of a practical approach to it by buying commercial calibrators and controls that have a known amount of each of these direct oral anticoagulants, or fondaparinux, and then just seeing on our two assays, the anti-Xa activity and thrombin time, what results do we get, and where can we tell: Is this drug present, or is it kind of present at a low level, or is it not detectable at all?

And so I think it is something that is practical in other hospitals and labs could use, even a small hospital that doesn't have a lot of samples or patients with it could potentially bring it online.

Randye Kaye: So now that you've developed this anticoagulant screen, can you tell me some of the practical applications and where could it have the most impact?

Nabiha Saifee: So I think for us, the most impact we see is in our patients who are getting kind of urgent procedures, and the team might have stopped the drug, but then they want to kind of assess. Is there still anything detectable or not, so they could see is there an increased risk of bleeding, and the more urgent the procedure, and the more high risk of a procedure, the more likely that they're going to want to know, is this drug present or not? So that's where I see kind of the biggest impact for us.

Another scenario is kind of more urgent bleeding situations, especially if a patient comes into the ED and there's unknown timing of the last time a dose was taken. It's good to know a level, especially if before they're going to administer a reversal agent or something, or to know is that presence of anticoagulant contributing to the bleeding? Do I need to give something to counteract that anticoagulant if it's present? So those are what I see at our hospital.

Another kind of use could be in some kind of a stroke screen or something. So patients coming to the ED with a stroke, sometimes if they need a specific therapy, like a thrombolytic therapy. Again, they might want to know for the urgent procedure if there's anticoagulant on board, and then maybe sometimes in drug overdose or something too, just to detect like okay what's going on now with this patient? Is this something, again, that's contributing to the scenario? So there is like a few kind of these urgent scenarios where I see it could be useful, but always, if they want to get the specific drug level, we might need to send that out, because that's not something we have, but definitely something that can help in the moment.

Randye Kaye: All right, thank you. So we have a sense of the applications and the impact and a little bit about a limitation. Let's go further with that. Are there any limitations of the anticoagulant screen and how can they be mitigated?

Nabiha Saifee: Yeah, so our screen is really just trying to say, is it present or not present and we are trying to give a little bit of a sense of is it like a clinically significant amount present, or a low level present, or not present at all? That clinically significant one is a little bit difficult with the direct oral anticoagulant, the dabigatran, because the thrombin time is very sensitive to any amount being present. So if we detect any present, it's hard to know, is that still a clinically significant amount just because that test is so sensitive. So we can say it's present, but I can't really gauge how much is really there. So that's one limitation of ours -- it's very qualitative, it's not quantitative. We're not giving you a specific level, and especially with that thrombin time and the dabigatran.

With the anti-Xa activity assay, that one can, you know, we're trying to detect if there's a direct oral anticoagulant of edoxaban or apixaban, but we still have to take in the clinical context into all of this as well. And so that is a chromogenic assay, so it's affected by color. So if there's a patient that has like a high level of bilirubin or a high plasma free hemoglobin, they're hemolyzing a lot, there could be some interference in our assay because of that. So you could get kind of falsely low levels. So we just have to keep that clinical context in mind.

And again, kind of keeping the clinical context in mind, we have to think about is there other things other than an anticoagulant that might be leading to these other results, like with the thrombin time, is there some other kind of fibrinogen deficiency or something else going on that could also give you a prolonged time besides just taking an anticoagulant? And then I guess the final limitation that you can talk about is that our assay wasn't -- if a patient got a reversal agent like andexanet alfa, then our anti-Xa assay is not validated for that situation. So we've kind of validated some limited situations, and our comments kind of include what some of these limitations are so we have to take into account some of these other clinical factors when we're interpreting these results.

Randye Kaye: All right, that's a very full picture. Thank you so much for joining the podcast.

Nabiha Saifee: Thank you.

Randye Kaye: That was Dr. Nabiha Saifee from Seattle Children's discussing the *JALM* article, "Development of a Rapid Qualitative Screen for Anticoagulant Presence." Thanks for tuning in to this

episode of *JALM* Talk. See you next time. And don't forget to submit something for us to talk about.