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COVID-19 Challenges: Vascular Clotting & Catheter Clogging

Dr. Birnholz:

Coming to you from the ReachMD studios, this is *COVID-19: On the Frontlines*. I'm Dr. Matt Birnholz. Joining me to explore new understandings on the complications of blood clotting and related catheter clogging witnessed in COVID-19 patients is Dr. Anil Agarwal, Professor of Medicine and Chief of the Section of Nephrology at The Ohio State University Wexner Medical Center East.

Dr. Agarwal, welcome to you.

Dr. Agarwal:

Thank you. Pleased to be here.

Dr. Birnholz:

Great to have you with us. So, Dr. Agarwal, clearly clinicians on the front lines are facing many challenges in the fight against COVID-19, and that, of course, is a big understatement, but the emergence of blood clotting and clogged equipment for vascular procedures is a more recent phenomenon that's gained a lot of recognition. So, can you tell us about this emerging issue, what we think is going on and how prevalent it seems to be?

Dr. Agarwal:

We are certainly going through unprecedented times with the COVID-19 pandemic, and as you know, the COVID-19 patients are very hypercoagulable. There are high levels of fibrinogen. There are high levels of factor VIII and Von Willebrand factor. If you check the patients, they have high D-dimers and elevated prothrombin time. That indicates that they are indeed very hypercoagulable. And we also know that there are high rates of thromboembolism in severe COVID-19 and a lot of pulmonary emboli and deep vein thrombosis, so with that you can imagine that the vascular accesses do tend to clot.

Dr. Birnholz:

And I'm interested in how this understanding came up. Months ago when the pandemic first became known, there was a pickup of high D-dimers and some of these other measures that were indicative of hypercoagulopathies, but tying that back to understanding which patients are at higher risk for this complication has been a more difficult ordeal to sort through. What do we know about that?

Dr. Agarwal:

Yes, so our understanding has evolved over the last 3 months or so, and we know that renal replacement therapy is really commonly needed in patients who are admitted to ICU, anywhere between 30–50% of patients need some type of dialysis. If you look in general on the process of renal replacement therapy, especially the continuous one, it's very common to see clotting and clogging of the filter, and this is on a steroid in patients with COVID-19 due to the factors that I described earlier. The dialysis filter is a semipermeable membrane. The pores are somewhere around 35 kDa in size for diffusion and convection to occur. Diffusion occurs according to the concentration gradient and is really the ideal way to remove a small molecule, such as creatinine, and convection follows a hydrostatic pressure gradient and is the best method to remove middle to large size molecules, including beta 2 microglobulin. And generally we use these 2 processes in combination, both diffusion and convection, and when we do that together continuously, it's called continuous venovenous hemodiafiltration, or CVVHDF to be short.

Now, what we started seeing, as the patients came to ICU and started getting dialyzed with COVID-19, there were frequent episodes of clotting, so we would get called that the filter is clogging frequently and this is probably the line that is not functioning versus some other factors. We have always seen a little higher degree of clotting in patients with sepsis, but with COVID-19, this is just out of the proportion. I remember the patients where we had 1 femoral catheter, for example, we changed it to a second femoral catheter, used

alteplase to de-clog the catheter; we changed the catheter to one of the internal jugular site and still had more clotting. Almost all the patients who are on continuous dialysis need some type of anticoagulation to prevent that, so the scope is pretty wide in answer to your question.

Dr. Birnholz:

From your experience thus far over at the Ohio State University, is the prevalence rate or incidence rate of these hypercoagulable states in ICUs much, much higher, on a very great magnitude, or is it an incremental adjustment that's needed to be made in ICUs?

Dr. Agarwal:

So, really, we saw that most of the patients with COVID actually required anticoagulation, so it definitely is a much higher magnitude than the usual sepsis patient and to the extent that now we know that we are going to need to systemically anticoagulate patients before they start clotting because we know that they are going to clot their circuit and access.

The other thing is it's important to understand a little bit of the pathogenesis there too. I would say that there are 2 processes that occur in almost all the patients but much more so in the COVID-19 patients. You get the membrane clotting, which is the thrombosis on the intra-arterial side of the membrane, and it starts occurring relatively early during continuous renal replacement therapy, and you can monitor that by taking a look at the pressure drop, which is the pressure reduction as the blood flow passes through the filter. So you look at the trends of the pressure, and if the pressure starts increasing, that tells you that there is a chance of membrane clotting and the processes occurring, and you can start taking measures at that point to reduce the process of clotting, or, if the pressure goes up, you have to change the filter.

The other process that I did want to mention here is that of the membrane clogging. Clogging essentially occurs on the arterial side at the level of the pores of the semipermeable membrane due to the protein absorption. When the protein absorbs there, it starts making a layer over those pores, and now you need a very high level of transmembrane pressure, or the TMP, and a high TMP really tells you that there is membrane clogging. Eventually it becomes almost impossible to filter, and when the TMP levels go to 300, 350, you know that the filter is not going to work and you have to change it. At that point you have to take measures to prevent the circuit failure.

Dr. Birnholz:

Let's talk about those measures in greater detail because you bring up the natural question of whether we can keep up with the demands to take those measures, and there have been questions and concerns about the level of supplies that could be accessed and would be available across different health institutions across the country. Can you speak to that question of supply and whether catheters, filters, even blood thinners are going to be able to meet the demand based on what you're seeing?

Dr. Agarwal:

Well, that's a very relevant question in the light of the surge in the cases of COVID-19, and we saw that in some of the northeastern states where people ran out of the PPE and the filters and the dialysate fluid. We got some requests to supply, for example, dialysate fluid because they were running out. It is really, really important to keep this part in mind because you cannot just keep doing the same process that we used to do in normal situations when there were 15 or 20 patients on continuous venovenous hemodiafiltration and you could use as much amount of dialysate as you wanted or the replacement fluid that you wanted. Now, because of so many patients going on dialysis, certainly the same supply that we had at hand was falling short, so we came up with a color-coded system of, if this is the usual stage, we have to monitor how many days of supply we had at hand, and if that went to a yellow range or red situation with the surge, we will have only a few days' worth of supply at hand—similarly for the filters and, of course, the PPEs, which are very, very important, because the healthcare workers are not an indefinite supply either. So you have to save everyone, including the patient. Patient safety is important, and the staff safety is also important.

Dr. Birnholz:

For those just tuning in, this is *COVID-19: On the Frontlines*. I'm Dr. Matt Birnholz, and today I'm speaking with Dr. Anil Agarwal from the Ohio State University about the emerging vascular clotting and catheter clogging issues that are now being seen in COVID-19 patients.

So, Dr. Agarwal, I wanted to spend a moment talking about anticoagulation therapies because there are a number of questions out there. What are your thoughts on anticoagulation?

Dr. Agarwal:

The patients with COVID-19 are very hypercoagulable. Almost everyone, especially the ones who are requiring continuous renal replacement therapy, they have to be anticoagulated in one or the other ways. There are multiple different ways that you can do the anticoagulation. One is you can use unfractionated heparin through the machine, just through the circuit, and the goal PTT, the prothrombin time, is about 60–80 seconds for those. It is sometimes needed to systemically anticoagulate the patient because just

doing the circuit anticoagulation does not work, so in those cases you could use systemic unfractionated heparin with a goal PTT of 60–90 seconds. It is also possible—even though we usually do not use low-molecular-weight heparin because of the renal clearance and need for monitoring factor Xa concentrations—you could certainly use low-molecular-weight heparin also because it is such a peculiar situation at this time with hypercoagulability with COVID-19. Of course, you have to have the antidote protamine available in that case.

A very popular way also of anticoagulating the circuit is the regional citrate anticoagulation. It's very effective, although it might be a little tedious, and one has to be cautious using citrate. You have to give citrate infused prefilter with a goal ionized calcium of less than 0.35 mmol/L, and then you have to counterbalance that by giving postfilter calcium infusion, but then you have to watch for citrate toxicity with metabolic derangements that can also occur. So there has to be a very good protocol and good measurements of ionized calcium periodically and frequently, but regional citrate definitely has potential to prolong filter life. If the patient has heparin-induced thrombocytopenia, it's a good option. You could also use direct thrombin inhibitors like bivalirudin, and also, you can use argatroban for that. Prostacyclin has been used, but it is expensive. It's not really available and causes hypotension.

So there are multiple different protocols. You should definitely have the pharmacy and the staff and the nursing and the physicians on board with every protocol because you have to be very cautious using the anticoagulation, but most patients with COVID-19 we'll use anticoagulation.

Dr. Birnholz:

Dr. Agarwal, before we close, I want to consider some of the upstream impacts possibly relating to the pathogenesis of this clotting and the thrombogenesis in particular. There was an article from the *New England Journal of Medicine* that was exploring whether antiphospholipid antibodies were playing a central role in this clotting phenomenon, and I wonder if there is any new evidence or continuing understandings on that and whether it's worth looking into ways to address that particular aspect of the immune response and whether we need to therapeutically consider the cytokine storms and other immune aspects that might be leading to clotting.

Dr. Agarwal:

Well, viral infection is a state of high immunologic activity, and it is certainly possible to have production of antiphospholipid antibodies, but at the same time there may be false-positive antiphospholipid antibodies as well. So it's not quite clear to me if these antiphospholipid antibodies are actually pathogenic, but, yes, those have been seen with COVID-19 infection as well.

Dr. Birnholz:

Of course. And certainly it would be counterintuitive to say, "Oh, well, maybe we should try immune suppression," and that seems very counter to what is needed in terms of addressing this issue.

Dr. Agarwal:

I totally agree with you. High-dose steroids in this situation may not be the most productive for the patients.

Dr. Birnholz:

Well, Dr. Agarwal, you've given us so many important insights, but before we go, I want to just open up the floor to you. Any other thoughts that you want to share on this developing issue in COVID-19 patients for our healthcare professionals?

Dr. Agarwal:

I would want the audience to take home that most patients with COVID-19, especially with a severe infection, are pro-coagulable, so they all pretty much need anticoagulation, especially if they have severe infection. If they are on renal replacement therapy, they need it. To the extent that patients who have even milder infections, they are considered pro-coagulable, so take the anticoagulation very seriously in these patients. And patients on dialysis will definitely need anticoagulation to prolong filter life, to avoid loss of blood, to avoid nursing exposure to the patients in repeatedly changing the filters and for the patient safety, and to save the PPE and save the precious supply of equipment related to dialysis. I think it is very, very important to anticoagulate these patients.

Dr. Birnholz:

Dr. Agarwal, you've given us so much, not to just think upon but to act upon, regarding this emerging issue of vascular clotting and catheter clogging in our COVID-19 patients. And as our understandings continue to evolve, I'm looking forward to having the opportunity to speak with you again about this and other subjects, but for now I very much want to thank you for taking the time to walk us through this development. It was great speaking with you today, Dr. Agarwal.

Dr. Agarwal:

Thank you very much for having me.

Dr. Birnholz:

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this global pandemic, visit ReachMD.com where you can Be Part of the Knowledge. Thank you for joining us.