Anticoagulation in the COVID-19 Era: What We Know So Far

Dr. Raghu Kolluri talks with Dr. Geoffrey Barnes about the Anticoagulation Forum, the evidence base for venous thromboembolism related to COVID-19, what we know about COVID-related coagulopathy, his current approach to anticoagulation in the COVID-positive patient, and more.

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Dr. Kolluri: Congratulations on the publication of the Anticoagulation Forum guidelines.[1] The recommendations seem very balanced. Can you give us some background on what the Anticoagulation Forum is?

Dr. Barnes: The Anticoagulation Forum is a large North America–based organization focused on operationalizing evidence-based care for patients on anticoagulants, with an emphasis on frontline anticoagulation providers. Although there are physician and nurse practitioner/physician assistant members, the majority of members are nurses and pharmacists. These clinicians do most of the frontline pharmacy and anticoagulation care, both in the inpatient and outpatient settings, including the historical "Coumadin clinic." They also lead hospital-based anticoagulation stewardship efforts.

The Anticoagulation Forum is very multidisciplinary and tries to understand how anticoagulation care can be optimized by supporting anticoagulation providers. When the COVID-19 pandemic started to hit the United States, we saw that there were issues specific to the operation of anticoagulation care that our nursing and pharmacy colleagues were having to address. We wanted to provide resources, not just about COVID-19 itself and associated thrombotic issues, but things such as: How do you get an international normalized ratio checked if patients are afraid to come to the lab? How do you set up a drive-through testing option? Should

patients be switched from warfarin to a direct oral anticoagulant (DOAC) to avoid the need for lab testing?

These are very practical issues that our nursing and pharmacist colleagues are faced with all the time as the primary managers of anticoagulation. After doing a series of webinars addressing outpatient and inpatient issues, the group determined that there was an opportunity to provide some very concrete guidance on how to manage different thrombotic- and anticoagulation-related issues in the setting of COVID-19. Although there were other evidence-based guidelines, our pharmacists and nurses needed something to take to their pharmacy and therapeutics committees and anticoagulant clinic leadership so that they could figure out how to operationalize the recommendations.

Dr. Kolluri: Evidence-based guidance is challenging to develop even with years of evidence gathering via methodically planned trials. Given the relatively brief history of COVID-19, its sudden onset, and controversies surrounding discrepant early data, how would you describe the evidence bases for venous thromboembolism (VTE) treatment and prophylaxis to date and the ability to draw conclusions and create guidance from it?

Dr. Barnes: We're in a very interesting scientific time. COVID-19 has captured the attention of the world, and the disease itself did not exist 9 months ago. Hence, it's understandable that there is a lot of enthusiasm around trying to learn how best to care for patients experiencing complications from COVID-19. In the Anticoagulation Forum guidance document, we tried to encourage clinicians to carefully review where the evidence comes from, assess the quality of the evidence, and not forget the foundational evidence on which our existing therapies and preexisting guidelines are based.

If there is evidence from a randomized controlled trial, there is a high degree of certainty that we can rely on and extrapolate from that trial evidence to help make decisions in patients with COVID-19. For instance, we have a wealth of high-quality data for VTE prophylaxis that tell us that using appropriate prophylactic doses of either low-molecular-weight heparin (LMWH) or unfractionated heparin is beneficial in high-risk patients. This really needs to be the foundation on which we start managing these patients.

Then there is the question: What information is new that may be specific to COVID-19? The challenge is that we haven't necessarily built the skills for all of our physicians and health care providers to be able to appraise a paper critically. It can be easy to read an abstract, jump straight to the conclusion of a paper, or just look at a figure and not spend time with the methods to really critique them. I think there are a couple of rules that you can always lean on. One of the most important rules is that retrospective data should always be used to either help generate a new hypothesis, ask a new question, or confirm something seen in a prospective trial.

We should really be careful about taking observational data and using them to make treatment decisions. When I look at an observational study, I wonder about selection bias—considering why each patient received a particular treatment. When there is higher mortality in a group of patients who did not receive anticoagulation treatment, I wonder whether that group of patients was too sick to receive the treatment in the first place, had ongoing bleeding as a potential contraindication, or had other comorbidities and contraindications to anticoagulation. Those unmeasured confounders and selection biases are really important pieces. Second, I look at how the analysis was done. If a patient is enrolled in the study at a time point that's different than the time at which treatment is started, there's potential for immortal time bias. For instance, when a patient is admitted to the hospital, they had to live long enough to get the anticoagulation (which may not start for a few days). If that patient dies in those first couple of hours or days before a decision to give anticoagulation could be made, he/she never had the opportunity to be placed into the treatment group. That's a major limitation of observational study designs if not specifically addressed.

However, what I do see from observational studies are some really robust data raising the question that therapeutic anticoagulation might have some benefit. Therefore, there is very good clinical equipoise and justification to conduct a prospective head-to-head trial.

Dr. Kolluri: Tell me how you're approaching VTE prophylaxis and treatment in hospitalized patients with COVID-19.

Dr. Barnes: We now have enough data to tell us that all patients who are admitted to the hospital with COVID-19 are at increased risk of VTE. Per our recent guidance, those patients should receive prophylactic anticoagulation. That's the baseline. We don't have great data beyond that in the setting of COVID-19. Personally, I think it is reasonable to consider weight-based dosing for an obese patient (eg, twice-daily enoxaparin) instead of fixed-dose prophylaxis for all patients regardless of weight. There are some data in the pre-COVID era to support this.

Once a patient ends up in the intensive care unit (ICU), there is a fairly high risk of thrombosis, especially pulmonary embolism (PE) and proximal deep vein thrombosis (DVT). It is reasonable, but probably not

mandatory, to increase to intermediate-dose anticoagulation in the ICU patient. At our institution, we often use a low-dose unfractionated heparin infusion based on experience with the H1N1 influenza pandemic.

With confirmed VTE (proximal DVT, PE) regardless of critical status, the treatment dose should be given as long as there are no contraindications. However, we found at our center that it's not always easy to objectively confirm VTE either because the patient is too sick to go down to the CT scanner or because the vascular ultrasound technologist cannot come in due to limited resources in the setting of the pandemic. So, for patients in whom there was a high suspicion for DVT or PE, we proceed to empirically treat them as long as their bleeding risk is manageable.

Decision-making for continued anticoagulation after patients improve and leave the ICU is also a challenge. At our institution, if VTE was not objectively confirmed, we still recommend treating the patient as if they had provoked VTE or a hospital-associated VTE event with a 3-month course of anticoagulation. As far as imaging upon ICU discharge, the clot may have resolved by that time, and a CT or DVT scan may not be reliable.

Next, what do you do on hospital discharge? We don't have any data about how often patients with COVID-19 come back to the hospital for VTE events. We have to suspect it's at least the same rate it would have been in the pre-COVID era, potentially higher. Our institution has been recommending that we follow the evidence from our clinical trials, such as MAGELLAN and MARINER (using rivaroxaban, which is now FDA approved for posthospital prophylaxis) and the APEX trial (using betrixaban, which is also FDA approved). I also assess which patients would get the most benefit—those who are severely immobilized in the ICU, prone, intubated, and will probably go to a rehab facility. I'm concerned about immobility and that raises a flag. Other factors that I consider are ongoing infection or ongoing inflammation (elevated D-dimer or C-reactive protein throughout their course), if the patient still requires oxygen at the time of hospital discharge, and history of a VTE event, even 3 or 4 years ago.

Dr. Kolluri: What do we know about COVID-induced coagulopathy, and where are the most reliable data coming from?

Dr. Barnes: This is where I always give the caveat that I'm not a hematologist. Early on, there was talk about a coagulation disorder resembling disseminated intravascular coagulopathy based on the reports from China. With more recent data, including those from Italy and the United States, we learned that the lab values weren't really matching up with a true disseminated intravascular coagulopathy picture. They didn't meet the International Society of Thrombosis and Hemostasis criteria. Nonetheless, we are certainly seeing a lot of thrombosis, in both the venous and arterial systems. Plus, we were seeing both macrothrombosis and microthrombosis. The largest burden has been in the venous system, whether in the legs or pulmonary arterial vasculature; but with reports of reasonably young patients experiencing stroke, it's difficult to determine if that would have happened in the absence of COVID-19. Therefore, there's certainly a lot of concern about COVID-associated coagulopathy.

The inflammatory response to COVID-19 is likely a major driving factor, and my basic science colleagues are seeing elevated inflammatory markers across the board. We see elevations in not just D-dimer and C-reactive protein, but also in other markers such as interleukin-6. So, I have to believe that the intersection between inflammation and thrombosis is really being exploited in this particular infection, and the manifestations can be largely venous but are also arterial in nature.

This raises questions about what preventive action we should be taking, particularly in patients who test positive for COVID-19 but are healthy enough to stay home. Should they be on some type of anticoagulation therapy like baby aspirin? Although I'm not sure I would go all the way to therapeutically anticoagulate all of my outpatients with COVID-19, I do think that I would reassess this possibility in COVID-positive patients with a history of VTE or other prothrombotic disorder. Similarly, for any patient who presents to the hospital with some sort of thrombotic event, I think we will have to consider COVID-19 as a potential contributor. However, this would not likely change my anticoagulation protocol. We need more data to inform these decisions.

Dr. Kolluri: What is the role of nonpharmacologic compression for thromboprophylaxis, specifically in COVID-19 patients?

Dr. Barnes: I always struggle with the compression approach to VTE prophylaxis in the hospitalized patient. While it is likely effective, I'm not sure that it is as effective (or more effective) than pharmacologic prophylaxis. One thing that is stressed at our hospital is that the enoxaparin or unfractionated heparin dose must not be skipped if the patient has COVID-19. In the ICU setting, it's reasonable to put compression stockings on when the patient is intubated and immobilized. Again, this is probably the highest-risk group because of the inflammation. For patients on the general hospital floor, I worry about the potential hazards associated with compression stockings; patients may get confused and trip and fall, so I am not recommending them routinely. Certainly, if the patient has a contraindication to anticoagulation, then that's our best option.

Dr. Kolluri: Can you summarize why the relationship between physicians, pharmacists, and nurses is essential in the anticoagulation world, apart from what you're doing nationally with the Anticoagulation Forum?

Dr. Barnes: The collaboration between these specialists is critical. We are fortunate to have a group of pharmacists and nurse experts in anticoagulation care who can help augment what a physician provides. First, the nurses and pharmacists manage outpatient anticoagulation and warfarin, and they know the nuances of how to deal with minor bleeding issues better than any physician could hope to. We should be relying on their expertise to help us figure out how best to manage patients when COVID-19 throws us a curveball, including for patients who can't get into the lab. When you flip to the inpatient setting, I rely on my pharmacist colleagues to help me flesh out the evidence behind different doses of enoxaparin for patients with impaired renal function or obesity and how to use results of anti-Xa labs to ensure my patients are getting safe therapeutic doses.

In my patients with COVID-19 who are receiving newer or experimental treatments or new antiviral drugs, I look to my pharmacist colleagues regarding any potential drug-drug interactions or to help work through transitions between different drugs, whether it's unfractionated heparin, LMWH, or a DOAC. Pharmacist and nurse colleagues also help collect data from a quality assurance standpoint. At my institution, there are two pharmacists who lead data collection for all our COVID patients. They are informing that decision process in a way that's invaluable. They are absolutely critical members of the health care team, and the COVID-19 pandemic has only further spotlighted the important role that pharmacists and nursing colleagues play in ensuring that all patients receive high-quality anticoagulation care.

Dr. Kolluri: What data do you want to see before the next set of guidance comes out? If you could put together a trial setting in this very unpredictable field, what does that look like?

Dr. Barnes: There are pieces of data that are going to be very high yield. The first and most obvious one is comparing different doses of anticoagulation in a hospitalized patient with COVID-19. I know of at least three different ongoing trials comparing a treatment dose with some sort of a prophylactic dose. I think the results of those clinical trials are going to be potentially practice-changing for us and are really critical.

Second, I would love to see data on the risk of VTE in the posthospital COVID-positive patient. We have that data in the pre-COVID era, and we need to determine if these patients should get extended prophylactic anticoagulation or not. Does the COVID coagulopathy persist beyond the hospital period, and does it raise the risk high enough that we should be giving more patients prophylactic anticoagulation? These data will be critical and do not have to come from a randomized trial. A good observational study could really inform that piece of the puzzle.

Finally, what happens to patients who had a COVID-related VTE event? Do they continue to be at that higher risk for VTE, much like a patient who we used to call unprovoked, or does this risk decrease after 3 months, more like what we would consider provoked? Good-quality retrospective data will be able to shed some important light here.

Dr. Kolluri: How would you summarize the key take-home points about COVID-19 and anticoagulation for the vascular medicine and interventional community?

Dr. Barnes: It's really important that health systems develop a protocol to stick to. Then, they need to follow their own data collection to understand whether that protocol is being implemented effectively. That protocol is going to look a little bit different from hospital to hospital. In my opinion, that's fine in the absence of high-quality randomized controlled trial data. It's really important to have a VTE committee, anticoagulation stewardship committee, or a pharmacy and therapeutics committee evaluating and then reevaluating processes to ensure protocols are being followed, ensure the best evidence is being systematically applied, and adapt as needed. This is a good time for pharmacists, nurses, and physicians to all collaborate together and bring their unique expertise to make sure that protocols are safe and effective.

Because hospital functions have largely been shut down aside from what is critically necessary to care for COVID-19, another key point might be related to managing anticoagulation for a patient who had a COVID-related VTE event and might need an intervention. How do you do this? In the absence of data, my advice would be to treat the patient like one who has had a provoked VTE event; try to avoid elective procedures in the first 3 months because we do not want to stop anticoagulation, and beyond that 3-month point, it's very reasonable to think about doing the procedure. Any patient who has had a VTE event really needs prophylaxis whenever they're having a future procedure. That is particularly true if you're doing endovascular procedures. Thus, being diligent about anticoagulation care is critical. ■

1. Barnes GD, Burnett A, Allen A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticogulation forum. J Thromb Thrombolysis. 2020;50:72-81. https://doi.org/10.1007/s11239-020-02138-z