ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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COVID-19 and Hypercoagulability

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H&O What are the manifestations of COVID-19 that relate to coagulation?

MS The manifestations of coronavirus disease 2019 (COVID-19) that relate to coagulation appear to be thromboembolic in nature; hemorrhage has not been reported as a consistent finding. These thromboembolic manifestations predominantly involve the venous and microvascular systems, especially the pulmonary vasculature. We are also seeing cases of arterial thromboses, even in young patients without pre-existing risk factors. Before the pandemic, physicians were accustomed to seeing pulmonary emboli in hospitalized patients. But we are now more suspicious that in situ pulmonary thromboses are occurring in patients hospitalized for COVID-19. Our best hypothesis at this time is that the strong thromboinflammatory signal is stemming from the pulmonary vascular endothelium. Our knowledge surrounding COVID-19 and the resultant coagulopathy is evolving rapidly, so it is important to keep an open mind and wait for prospective data.

H&O What is the death rate associated with these thromboembolic manifestations of COVID-19?

MS A variety of death rates associated with COVID-19 thromboembolism have been described. The truth is that we do not yet have an accurate estimate of the death rate, but we have a sense of the overall risk associated with coagulopathy, as detected by an elevation in the D-dimer level. We know that having a D-dimer level of greater than 2 times the upper limit of normal is an independent risk factor for in-hospital mortality in patients with COVID-19. In fact, the odds ratio for in-hospital mortality with this D-dimer level is greater than 18, according to a recent study by Zhou and colleagues. Also, a D-dimer level that is even higher than that—above 3 times the upper limit of normal—is able to predict mortality with a sensitivity of more than 90% and a specificity of more than 80%, according to a study by Cui and colleagues. The fact that the D-dimer level correlates with the risk of dying is something that researchers were able to identify very early on in this pandemic based on data from Wuhan, China.

H&O Do researchers understand the way in which this virus causes thrombotic events?

MS We do not yet know specifically what is happening, but we think that it likely involves the endothelium of the pulmonary blood vessels. The pulmonary endothelium has very high expression of the angiotensin-converting enzyme 2 (ACE2) receptor, which seems to be the portal of entry for the virus. Importantly, the vascular endothelium of many organs appears to express the ACE2 receptor. The virus may trigger a hyperinflammatory sequence of events by irritating the endothelium of the pulmonary vasculature. The hyperinflammatory response also seems to lead to the release of multiple clotting factors, including fibrinogen, factor VIII, and von Willebrand factor. It is possible that the profound increase in von Willebrand factor explains some of the microvascular thromboses that we are seeing in the pulmonary vessels.

H&O Does anything similar happen with other coronaviruses, or with influenza?

MS It is hard for us to know definitively because we have not been met with a viral pandemic of this proportion in

the modern era. This pandemic is providing us with a lot of opportunity to make observations. Physicians are also communicating with each other more than ever because of the Internet and social media. Having said that, we do think there was evidence of hypercoagulability in the thromboinflammatory picture present with severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1). Hyperinflammatory responses with influenza also have been described. Published studies have also noted an increased risk of thromboses and elevated D-dimer levels in non-COVID patients with viral pneumonia.

H&O What else should physicians know about the use of D-dimer levels as predictive biomarkers?

MS The D-dimer level is one of the most important prognostic biomarkers for patients with COVID-19. Initially, we were not sure whether an elevated D-dimer level simply reflected inflammation, or whether it reflected clot formation and clot lysis. I think that as time has passed, we have become more confident that this measurement really does reflect clot burden. COVID-19 is associated with abnormally elevated levels of other markers in the blood, such as C-reactive protein, lactate dehydrogenase, and ferritin, but the D-dimer level appears to be one of the most important biomarkers from a prognostic perspective. Other proinflammatory cytokines that are associated with COVID-19 include interleukin 6 (IL-6), granulocyte colony–stimulating factor, and tumor necrosis factor α. These associations have been described in a few studies, including one from Wuhan by Huang and colleagues.

H&O Is everyone who is hospitalized for COVID-19 getting a D-dimer test?

MS The answer probably varies according to the institution, but I would say—based on conversations with numerous physicians around the world who are treating patients with COVID-19—that many patients are automatically getting D-dimer testing when they are being evaluated in the hospital for COVID-19. Here at St. Michael's Hospital, we include this test in our initial order set to help us get a better understanding of their overall risk for poor outcomes. The D-dimer test is often repeated when patients are admitted to our critical care unit, and may even be repeated multiple times over the course of their admission. Again, the reason is to help frontline clinicians better understand the clinical course of the disease. D-dimer testing in hospitalized patients is a new approach because this test used to be restricted to ruling out venous thromboembolism in patients presenting to the emergency department or outpatient setting with a low probability of this condition. So this is all very new for us, and we are all still learning.

H&O How should anticoagulants be used to mitigate thrombotic events in these patients?

MS We do not yet know precisely how they should be used. We have some preliminary observational data suggesting that individuals who receive heparin-based thromboprophylaxis have lower mortality rates than those who do not receive pharmacologic thromboprophylaxis. That said, as expected, low-dose heparin does not appear to be entirely protective from a venous thromboembolic risk perspective.

> Trials usually take at least a year to go from inception to launch, but we, and other colleagues around the world, have developed clinical trials in record time, which is what the pandemic requires.

We need prospective data, and many clinical trials around the world are underway to help identify the optimal approach to anticoagulation for COVID-19 patients. One such trial is RAPID (NCT04362085), which is a randomized controlled pragmatic trial that is evaluating routinely used lower doses of heparin-based thromboprophylaxis vs higher, therapeutic doses. I am one of the principal investigators on this trial, along with Dr Peter Jűni from my institution and Dr Mary Cushman from the University of Vermont in Burlington. We are especially interested in heparin-based therapy because heparin has multiple effects that we would like to take advantage of in patients with COVID-19. For example, heparin has an anti-inflammatory effect in addition to its anticoagulant effect. Low-molecular-weight heparin also has been shown to reduce IL-6 levels in patients with COVID-19, and studies in animal models suggest that acute lung injury responds to heparin. Heparin also seems to bind directly to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein, and interfere with viral attachment and entry. Finally, heparin appears

to improve endothelial function. This diminishes the chance of capillary leak, which is one of the major causes of acute lung injury.

Although we are particularly interested in heparin, other potential antithrombotic therapies include fibrinolytic agents such as tissue plasminogen activator (tPA), antiplatelet agents, and direct oral anticoagulants (DOACs). Agents that are even more selective in their targets, such as those targeting von Willebrand factor, may also be useful. We need to conduct and report clinical trials very quickly to help us define the best standard of care.

H&O What is the status of the RAPID trial?

MS We are now open to recruitment at 2 sites in Canada, and are rapidly opening at another 13 sites in this country. We recruited 6 participants in the first 13 days of being open. We are also quickly moving to numerous centers in the United States and other countries, including Ireland and Saudi Arabia. Trials usually take at least a year to go from inception to launch, but we, and other colleagues around the world, have developed clinical trials in record time, which is what the pandemic requires. We feel very strongly as scientists that this is our responsibility. We cannot leave patients in the lurch, and we cannot leave our medical colleagues without evidence to help define best practice. That is why science is moving at an unprecedented pace right now. Importantly, our trial has specifically chosen sites with excellent minority representation because it is equally our scientific responsibility to understand if therapies work differently among non-white people. Those of African and Hispanic descent appear to fare worse with COVID-19, and we need to understand if biology, along with social determinants of health, contributes to this. The RAPID trial team is committed to acknowledging, studying, and rectifying health inequities among all patients with COVID-19. We also need to understand the basic pathophysiology of COVID-19, which is why we have embedded a translational biorepository into our clinical trial.

Another example of this unprecedented approach is the fact that individual hospitals, recognizing the importance of our trial, have indicated that they want to start recruiting patients prior to the flow of full funding. They are proceeding based on initial funding because we all know that we need answers quickly. This is something that typically does not happen in science. We have seen a tremendous generosity and banding together that is really remarkable, and something that we are very proud of. Everyone needs to pick up the pace to help in real time.

H&O Is there an indication for DOACs in patients with COVID-19?

MS We do not know the answer to that, but clinical trials are looking specifically at that question. In some cases, DOACs are being used in combination with antiplatelet agents. We do not know whether patients with COVID-19 require longer-term prophylactic therapy to decrease their risk of clotting after they have been discharged from the hospital. DOACs might be attractive agents in that setting, but we desperately need prospective data in order to evaluate their usefulness.

H&O How about the role of tPA?

MS Clinical trials are also underway to examine the role of tPA in patients with COVID-19. At this point, we think there might be a role for tPA in critically ill patients, where the risk of death from COVID-19 approaches 50%. Clinical trials are specifically looking at the use of tPA in that patient population, but at this point we do not know if it is efficacious and safe.

H&O Does the use of convalescent plasma infusions alter hypercoagulability in COVID-19?

MS We have no idea, but we certainly hope that it modifies hypercoagulability for the better.

What is particularly distressing right now is that guidance documents have been released that are based on limited retrospective data.

H&O What are the most important knowledge gaps regarding COVID-19 and hypercoagulation?

MS The main problem is that we do not have a defined optimal approach to anticoagulation. What is particularly distressing right now is that guidance documents have been released—institutional protocols from well-respected institutions—that are based on limited retrospective data. Some of these guidance documents are recommending empiric intermediate-dose or even full-dose therapeutic anticoagulation for patients who are hospitalized with COVID-19. This is occurring in the absence of data regarding safety and efficacy, which is very concerning.

We do not know what the optimal approach is. It is possible that a more aggressive approach to anticoagulation helps, but it is also possible that it harms. Although COVID-19 coagulopathy does not appear to manifest with hemorrhage, some cases of intracranial bleeding and pulmonary hemorrhage have been described. The risk of bleeding remains, so we need to learn what the optimal approach is and we need to learn it immediately. Regardless of what our trial finds, those findings will determine the standard of care. If we find that heparin is of benefit, heparin will immediately be adopted as the standard of care. If we find that heparin is of harm, those institutions that have adopted a more aggressive approach will back down. It is rare in science to be in the situation where the results of your trials will have a tremendous impact, whether they are positive or negative. We hope that more aggressive heparinization will mitigate coagulopathy, but we do not know that for certain. So we are dealing with a massive gap in knowledge. Our trial is not the only one in this space, and many commendable efforts are underway, but my belief is that the simplest and most feasible approach is what is required.

H&O Is there anything you would like to add?

MS Our trial also contains a biorepository component that will allow for immediate translational work in order to begin to understand the underlying pathophysiology. The biorepository component is being led by our coprincipal investigator, Dr Mary Cushman, and by our coinvestigators, Drs Paula James and David Lillicrap at Queen's University in Kingston, Ontario. This component is just as important as the main trial.

Disclosure

Dr Sholzberg is a principal investigator of RAPID, a randomized controlled trial that evaluates prophylactic vs therapeutic-dose heparin for patients with COVID-19 coagulopathy.

Suggested Readings

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