Host: Welcome to the *ANESTHESIOLOGY* journal podcast, an audio interview of study authors and editorialists.

Dr. BobbieJean Sweitzer: Hello, I'm BobbieJean Sweitzer, an associate editor for *ANESTHESIOLOGY*. And you are listening to an *ANESTHESIOLOGY* podcast designed for physicians and scientists interested in our publications and research.

Today we are speaking with two experts in the field of hemostasis. Today we are discussing the science and clinical challenges of hemostasis and coagulopathy and the management of the myriad disorders that are seen in patients with COVID-19.

With us is Dr. Jerrold Levy. Dr. Levy is the professor at Department of Anesthesiology and Critical Care at Duke University Medical Center in Durham, North Carolina. He's a critical care specialist, anesthesiologist, researcher, and author. Welcome Dr. Levy.

Dr. Jerrold Levy: Thank you.

Dr. BobbieJean Sweitzer: And joining Dr. Levy is Dr. Jean Connors. Dr. Connors is an associate professor in the Department of Hematology at Brigham and Women's Hospital and Harvard Medical School, both in Boston, Massachusetts. She is a practicing hematologist, researcher, and author. Welcome, Dr. Connors.

Dr. Jean M. Connors: Thank you, and thank you for having me participate in this podcast.

Dr. BobbieJean Sweitzer: Dr. Levy, let's start with you. Why do patients with COVID-19 seem to be so hypercoagulable?

Dr. Jerrold Levy: Well, I think it's important to understand that part of the normal host immune response to any kind of acute infection is, in essence, a hypercoagulability response. When the virus basically enters into the body and particularly through the respiratory tract into the lung and the microcirculation, pretty much what happens is – and in any kind of sort of acute infections and especially acute viral process, is there's a hypercoagulability response, the body trying to immobilize the virus and sort of lay clot around and activate all of this complex proinflammatory responses as part of a host immune system again.

This is actually termed thrombin inflammation, a term that Dr. Connors and I were one of the first to actually coin in describing this acute hypercoagulability response. So I think this is just part of a normal host initial response initially. And it's seen in other acute infectious diseases as well. It's just that there's so much of it people have sort of rediscovered what we've known for a long period of time.

Dr. BobbieJean Sweitzer: Yes, I believe you and Dr. Connors co-authored a paper using the term endotheliopathy. Did you guys come up with that term? And can you define that term for our listeners?

Dr. Jerrold Levy: So the term endotheliopathy is basically a term I think that kind of first emerged into our literature from the trauma surgeons and from talking about traumatic coagulopathy. And the whole idea of using kind of fresh frozen plasma and using a – kind of a balanced type of solution was to prevent the diffuse endothelial injury, in particular loss of the glycocalyx, this complex sort of hopanoid-like structure that lines the blood vessels. As part of any kind of acute, systemic, or localized infectious process, the endothelium becomes injured and loses its anticoagulant sort of – and anti kind of inflammatory effect and goes to a procoagulant, proinflammatory effect.

And I think that's specifically what we see. The entry of the virus through the lung and, again, the microcirculation creates that microcirculatory thrombotic sequelae that really is responsible initially for the acute hypoxemia we see and acute lung injury that can actually spread and become more diffuse. So it's an older term, but it has to do with diffuse endothelial injury.

Now, you also see endotheliopathy in systemic sepsis, septic shock, with DIC, disseminated intravascular coagulopathy. But this is, more interestingly, initially in localized response that can progress to be systemic, and we'll talk more about that when we talk about some of the multi-inflammatory response syndrome.

Dr. BobbieJean Sweitzer: Yes, and I want to touch on a little bit more on ARDS and the lung injury as well. But before we go there, can you talk us – kind of walk us through a little bit more around that pathophysiology of this prothrombotic response that the body (inaudible)?

Dr. Jerrold Levy: So sort of briefly summarize is, you know, the body, again, mounts this acute inflammatory, thromboinflammatory, also called immunothrombotic response to an invading organism. The problem we have with COVID-19 and the SARS-CoV-2 virus is we don't have – well, with the increasing immunization, we do probably increasingly but previously really didn't have acute ability to sort of respond to the virus. And the antiviral remdesivir doesn't have acute quick kill in terms of, you know, as we do when we treat acute infections with antibiotics.

So what happens is it generates a very hypercoagulable response again, as I mentioned, to try to immobilize the acute infection. And this is characterized by hyperfibrinogenemia. And what happens is the laying down of clot with endothelial injury also kind of creates a fibrinolytic shutdown scenario, where not only are you generating clot, but the inability to lyse it due to multitude of issues sort of ensue. And you create this, again, very interesting hypercoagulable response with other cells sort of being activated neutrophils. Mononuclear cells are releasing a whole series of proinflammatory constituents that cause further vascular injury. And, again, in the ARDS, you see the microcirculatory or diffuse edema, so – and that's something we'll talk about later.

Dr. BobbieJean Sweitzer: So, Dr. Connors, Dr. Levy has mentioned that, you know, all infectious diseases are associated to some degree with a coagulopathy. But isn't it true that COVID-19 is much more thrombotic than most other infectious diseases that we're familiar with?

Dr. Jean M. Connors: Well, that's an excellent question. And I think we have to sort of step back and look at the spectrum of COVID-19 disease that we see in patients. So as Dr. Levy mentioned, there is this innate crosstalk activity between the immune system and the immune response to an invading infectious pathogen and the coagulation system. And so with any infection, there is always a bit of increased coagulation state or hypercoagulability.

But what we see in COVID is that, you know, some people get mild symptoms and mild presentation of the disease, and they rapidly clear the virus, and they do well. We have other people who end up with very severe COVID-19. And in part, that is due to the fact that they have never encountered the SARS-CoV-2 virus, and they end up with an unchecked inflammatory and immune response to this virus with skyrocketing levels of inflammatory markers and inflammatory cytokines, such as IL-6 and IL-10 and others. And this drives up the procoagulant factors, as Dr. Levy mentioned, hyperfibrinogenemia, increased factor VIII, increased von Willebrand factor. These coagulation procoagulant factors are also released in some ways by the endotheliopathy with VWF that's stored in the vascular endothelial cells.

And the natural protective mechanisms of the vascular endothelial cells, the natural protein C and protein S inhibition of coagulation, is damaged when the vascular endothelial are damaged. And so it may not be that it's more prothrombotic per se, but that in many people, they have a severe COVID disease. And that, in association with that severe COVID disease, and its severe inflammatory response drives up the procoagulant pathway.

The other thing to mention is that we are seeing infected patients in unprecedented numbers in this global pandemic compared to, say, isolated outbreaks of MERS or Ebola or similar very prothrombotic or hemorrhagic disorders that are usually isolated to small geographic areas or small numbers of people. And so the combination of unchecked inflammatory reaction in some patients as well as the sheer numbers of patients make it seem that it is a highly prothrombotic state. The virus itself does not appear to be prothrombotic, but it's the response. And it's the inflammatory response that's driving the coagulopathy.

Dr. BobbieJean Sweitzer: That's an excellent explanation. Dr. Levy, as the intensivist, are the findings in these COVID-19 patients with ARDS and acute lung injuries really new or different than that seen with other patients with ARDS, especially related to other infections?

Dr. Jerrold Levy: So that's a great question. Interestingly, remember that patients present with acute hypoxemia, which is due to that, again, microcirculatory clot formation that occurs, creating major ventilation perfusion abnormalities. Patients aren't often acutely dyspneic because they're not hypercarbic, but they're basically hypoxemic. And a lot of clinicians always say hypoxic, but it's really hypoxemic, the low PO2, and the sat falls, et cetera.

So what's, I think, really important is that – Dr. Warren Zapol, who I trained with many years ago in 1983, reported in the pathology literature a post mortem of 22 patients who died of infectious pneumonia, mostly influenza and other infection. And they found the exact same microvascular thrombotic sequelae.

The more recent studies that have looked at COVID-19 versus influenza or looked at MERS, which is, again, a SARS-CoV-2 type virus, basically the incidence is higher, and the number of sort of vascular injury pattern is greater compared to influenza from more recent data. But, again, you know, we have ways to treat influenza, which we don't with the SARS-CoV-2 issue and with COVID-19.

So it's a previous finding. But again, I think, as Dr. Connors thoughtfully mentioned, you know, the unprecedented numbers that we see, everybody started measuring fibrinogen hypercoagulability biomarkers. And seeing this and the tremendous number of acute lung injury, ARDS, prompted not only multiple methods of invasive and noninvasive ventilation, but also driving large numbers of patients with refractory hypoxemia to ECMO and other potential therapeutic maneuvers. So, again, this is, again, a typical sort of hypercoagulability response. But, again, the unprecedented numbers really has sort of changed our perception of the incidence in evaluating these patients.

Dr. BobbieJean Sweitzer: Dr. Connors, you know, I think sort of most of the routine coagulation tests that we're used to sort of seeing in patients, even acutely ill patients, often are normal or relatively normal in these COVID-19 patients. Can you talk more about that and about the tests that we perhaps should be utilizing?

Dr. Jean M. Connors: Well, that's a great observation. And we know from data that, you know, originally came out of China, and then were validated in Europe and then even here in the United States is that when patients present newly symptomatic, the PT and the PTT are often normal. And as we've discussed with the inflammatory response and the sort of acute-phase reactant procoagulant proteins—again, fibrinogen, factor VIII—that these elevated levels, you know, aren't reflected in the PT, PTT, you know, because they stop, and so they're normal. So you have normal PT, normal PTT. We also see a normal platelet count.

What we do see in some patients—and this is where the coagulation tests start to diverge—is an elevated D-dimer in many patients. And the elevation in D-dimer tracks with the severity of illness so that the more inflamed someone is or the more sick they are with SARS-CoV-2 infection, the higher the D-dimer will be. And so very early on in the pandemic, although we measured PT, PTT, and platelet count, as well as fibrinogen levels, or factor VII less frequently – but, you know, fibrinogen levels that we see in these patients are maybe one and a half times to, at most, two times greater than we normally see. But we see those levels of elevated fibrinogen in infected patients all the time.

What we don't see is the dramatic increase in D-dimer in patients with other types of infections. And so there are a number of excellent studies that demonstrate very early on that the D-dimer level tracks with morbidity and mortality. And so that when people present and their D-dimer is elevated and then you sort of measure it over ensuing days, those that start to develop marked increase in D-dimer levels, you know, three times the upper limit of normal, five times the upper limit of normal, are the ones that are having significant problems with COVID-19.

And as Jerry mentioned, the pulmonary microvascular thrombosis, which results in the hypoxemia, is likely reflected in this elevated D-dimer. So the more severe your microvascular thrombosis, the more likely it is that your D-dimer is elevated, the more likely it is that you need mechanical ventilation.

So we suggested here at Brigham and Women's Hospital very early on in the pandemic that patients who were admitted have the routine PT, PTT, CBC, but that we also measured D-dimer and more as a prognostic biomarker to get a sense of how ill patients were on presentation.

Dr. BobbieJean Sweitzer: Dr. Levy, I think you mentioned earlier that COVID coagulopathy is often described as thromboinflammatory or immunothrombosis state. Can you elaborate on those a bit more?

Dr. Jerrold Levy: Absolutely. I think this is really important to understand that, again, the body's acute immune response is all about generating various ways to sort of immobilize and actually kill the invading organism. What's very interesting is that the role – you know, we always think of thrombin and thrombin generation as part of the whole clot formation, but it plays a critical role in orchestrating the sort of inflammatory immune response.

Again, Dr. Connors mentioned thromboinflammation or immunothrombosis. Many cells, when they get activated, they release a whole series of sort of toxic factors that basically are to kill or immobilize the invading organism from free DNA to things that are involved with neutrophils called NETosis and a whole series of very impressive, proinflammatory response, again to try to kill the organism.

The problem we see clinically is that in addition to immobilizing or trying to destroy the organism, it also ends up causing host's defense, host's inflammatory responses. And thus you see acute lung injury, ARDS. Subsequently, you can see multiorgan, you know, dysfunction. The heart can be involved, kidneys, and a variety of other scenarios. That sort of exuberant response may also occur elsewhere.

So I think what's important is that this whole immunothrombotic response is, again, to try to immobilize and try to sort of limit the spread and the effects of the SARS-CoV-2 virus, but unfortunately, as in any acute inflammatory response, it ends up causing injury in the host. So this is, I think, particularly important. And a lot of the therapies that have been sort of designed, cytokine antagonists and other therapies, have all been sort of in response to try to limit this exuberant, hyperinflammatory response.

The problem is that the response is so complex and so varied that any inhibiting (inaudible) seems to not have been incredibly effective. But what is effective? Obviously is immunization and limiting any kind of ability for the immune response to respond.

Dr. BobbieJean Sweitzer: So, Dr. Connors, most of us are familiar with hospitalized or acutely ill patients, you know, being at risk for venous thromboembolism, but it seems like these COVID-19 patients have a lot of arterial thrombosis going on. Is that true? Or is it just, again, one of those things that is perception because we're talking about this new disease that is so widespread, as you guys have mentioned?

Dr. Jean M. Connors: That's a great question. And if you recall very early in the pandemic in the United States, there were a lot of young people who were getting a lot of lay press coverage with arterial thrombotic events like stroke and limb-threatening arterial lower extremity thrombosis. This is also a huge area of active investigation because historically we certainly have divided venous and arterial thromboses and sort of conceptually think that they occur through different mechanisms based on, you know, blood flow patterns and shear stress and plaque and platelets and arterial perhaps and more stasis in venous.

The rate overall of arterial thrombosis is around 4%. And if you take all the studies that have been done in single centers, sort of retrospective data from around the world – and last I knew there was a meta-analysis performed based on studies from January through August 2020 in which 66 studies qualified, looking at hospitalized patients for rate of venous thrombosis. And the average rate from that meta-analysis in ICU patients

was 18%. So we know that arterial events do occur, but they occur much less frequently. But they have gotten a lot of press.

Now, what's very unique – and as a hematologist, we would love to sort of, you know, explore some of the factors that we see occurring in arterial thrombosis, including the fact that we see megakaryocytes. They've been noted in the pulmonary circulation in the past, but now we're seeing megakaryocytes in the heart. And whether that means that platelet activation plays a bigger role in arterial thrombosis with COVID-19, which is something we haven't seen, although I can't say we've looked for it, with other types of infections.

So I think the patients that we see having arterial thrombosis also have venous thrombosis. And, again, as Dr. Levy and I have both mentioned, it's really the response to the unchecked inflammation. Again, many people have never been exposed to anything resembling the SARS-CoV-2 virus and have no prior, you know, either humoral or cellular defense against COVID-19.

Dr. BobbieJean Sweitzer: Yes. That's quite the challenge. Dr. Levy, why are some patients often relatively asymptomatic early in the course of disease? What do we know about that? There's just – there's different set of patterns that we…

Dr. Jerrold Levy: So with acute infection and sort of the VQ, ventilation perfusion, abnormalities that occur, the microcirculatory thrombotic issues in the lung, again, with the viral sort of entering in through the respiratory tract into the lungs and into the microcirculation of the lung, you get that sort of ventilation perfusion, hypoxemia. But we are dyspneic. Under, you know, relatively reasonable levels of hypoxemia, we're not dyspneic. What makes you dyspneic is the hypercarbia.

And since patients are not hypercarbic, I think that's really an important finding and why a lot of clinicians have gotten for their own home use the pulse oximeter, so they indeed get sick, they know exactly when they dropped their sat below maybe 90%, 88% or some other, you know, arbitrary level like that. They – clearly it's time to go in and explore additional therapeutic modalities in things such as anticoagulation that I know Dr. Connors will talk in more detail.

So that in particular – the other, I think, issue is interesting as part of this inflammatory response. We're going to talk about it, about multi-inflammatory syndrome later, but it's the way this sort of inflammatory response rages on to produce a more sort of later phase response with the – with any kind of multi-organ injury.

What's really important to consider is that any acute inflammatory response, infectious process, I think the clinical manifestations can all be so different among patients because of the variability of their response and pre-existing immunity, pre-existing hemostasis issues, and other perspective. So I think it's a really interesting phenomenon. And, again, with the unprecedented numbers, as Dr. Connors mentioned, we really have this incredible number of patients to sort through with things that perhaps we've never seen before.

What I think particularly interesting is that with the long-standing interest in infectious coagulopathy and DIC, disseminate intravascular, coagulopathy – in all critically ill acute infected patients, I tend to DIC screen, look at D-dimers, look at fibrinogen levels, and, you know, coagulation test, platelet count. But that concept really has evolved now, I think, for all clinicians, understanding the importance, as Dr. Connors mentioned, the critical role of D-dimer in understanding the disease severity, as well as many clinicians have used to understand the clot burden that may be part of the sort of prothrombotic milieu.

Dr. BobbieJean Sweitzer: We've talked a lot about the sort of pathophysiology and disease states. Dr. Connors, can we talk a little bit about therapy, particularly anticoagulant therapy? Like, what is being used, and is there an optimal protocol for that?

Dr. Jean M. Connors: Well, as a coagulation hematologist, this for me is the question of the pandemic. This is the one question that many around the world very early on recognized, no matter what the specialty, that thrombosis was a significant problem. But how to anticoagulate patients? What does, what timing are the questions that need to be answered.

And so very early on, many centers, including my own, empirically used increased doses of anticoagulants in patients admitted to the ICU because of the marked D-dimer elevations and the marked increase rate of venous thromboembolism that was seen. You know, as I mentioned, a meta-analysis showed that on average 18% of patients admitted to the ICU will develop venous thrombosis. We did this, of course, without data. And a number of randomized control trials were launched last spring and over the summer to try to identify the optimal dose of anticoagulant therapy, usually in comparison to standard of care, dosing, heparins for inpatients that we use to prevent or prophylax against venous thromboembolism.

We've also launched trials to address is there a role for antithrombotic therapy in those who are acutely infected but in the outpatient setting and not yet sick enough to be admitted to the hospital, as well as for patients who are discharged from the hospital? Again, these are all randomized control trials that were launched to try to address this question across the whole spectrum of, you know, timing of COVID-19 from onset to recuperation, post-discharge if patients were discharged.

And as you can see, I'm not directly answering your question because we don't have a definitive answer. We do have trial data that are starting to emerge, and I can discuss in general the – that there have been data released from three trials involving hospitalized patients, three randomized controlled trials, two which have been published, and one set of studies that we are eagerly awaiting the publications for but which press release and Data Safety Monitoring Board interim analyses and preprint server data are available.

So we have the multi-platform trials that were launched. Last summer, three global trials started, one primarily in Canada, ATTACC, A-T-T-A-C-C; one primarily in the US, ACTIV-4a; and one in Europe called REMAP-CAP. And very early on, they decided to harmonize their endpoints and pool their data. And so in December 2020, there was a press release about one of the arms of their trial in which they were taking severely ill patients, those admitted to the ICU meeting certain requirements for oxygen support and other criteria to deem them as severely ill, and randomize those patients to prophylactic dose heparin versus therapeutic dose.

And in the severely ill, we were all very surprised to find that the Data Safety Monitoring Board recommended that the trial be halted because of futility for therapeutic dose anticoagulation in these ICU level of care patients with COVID-19 in that it did not afford any greater benefit than prophylactic dose anticoagulation. We were all surprised around the world. We're still waiting for the peer-reviewed manuscript to be published. The data are out on a preprint server.

But interestingly, that data, in combination what the multi-platform group found for the moderately ill – so in the other arm or component of their trial, they took patients who were admitted to the hospital but not requiring ICU care. That trial was halted a month later in January 2021 because of superiority for therapeutic dose heparin to prevent progression of COVID-19 disease and to decrease mortality.

So both arms of these multi-platform trials had a composite endpoint of organ support-free days, out for 21 days, and mortality. And in that composite, the moderately ill benefited from getting therapeutic dose heparin, whereas those in the ICU derive no benefit. There was no difference in need for organ support or in mortality. And so this was surprising, and we are still grappling with that information and how to apply it to our patients.

Some institutions around the world are now giving their moderately ill patients admitted to the ward therapeutic dose heparin, but many have not moved forward with that. Many institutions have now pulled back on the intensity of anticoagulation given to those patients in the ICU.

We have a trial, a randomized controlled trial, that looked at intermediate dose anticoagulation versus the standard prophylaxis, the INSPIRATION trial. And, again, these were in critically ill or ICU level of care patients. And there was no difference in outcome in that population either between what we would call intermediate dose versus standard of care, although you need to look carefully because there was a wide range of what was considered intermediate dose.

And then we have – from Brazil we have the ACTION trial recently published that took moderately ill or stable patients. Over 90% were stable. They received in-hospital therapeutic dose rivaroxaban and then were discharged for 30 days on rivaroxaban. And there was no benefit with regard to progression of disease or survival in that group compared to in-hospital 14 days of low molecular weight heparin.

So we're still waiting for more randomized controlled trial data to emerge. What we can surmise from these different datasets is that by the time patients get to the ICU, it may be too late to interfere or intervene with anticoagulation and that, as Dr. Levy, you know, has elegantly described with the ARDS and the pulmonary microvascular circulation thrombosis, that the thrombosis has already occurred. And giving anticoagulation at that time might prevent a DVT or a PE, a secondary outcome, which therapeutic dose definitely did better than standard prophylactic dose, but it didn't change the course of disease.

And so potentially intervening earlier with anticoagulants may be of benefit, but I think we still need to continue to process this data. And we have many randomized controlled trials out there that are still running that will be informative and help us to care for these patients.

Dr. BobbieJean Sweitzer: Lot to figure out still. So, Dr. Levy…

Dr. Jean M. Connors: Absolutely.

Dr. BobbieJean Sweitzer: Yes, yes. Well, good luck with all of that. No. Dr. Levy, is COVID-19 just a clotting, thrombotic, problem, or do these patients sometimes bleed? Is there some component of DIC?

Dr. Jerrold Levy: If you read this growing literature for COVID coagulopathy - the problem is when in the course of the disease are we describing what's going on? So early on, it's profoundly hypercoagulable. But it's like any disease process progresses. And actually, Anne Godier out of Paris published a very interesting paper showing that, you know, after, you know, 10 days, 12 days, you start developing potential bleeding. As Dr. Connors mentioned, maybe due to anticoagulation or a variety of other scenarios.

The timestamp on when the disease occurs in the acute versus sort of midterm and chronic is really different. The other problem is when they've described patients having sort of a full-blown sort of consumptive coagulopathy with everything being consumed, low platelets, INR prothrombin time going up. Many of these patients, if you have a prolonged hospitalization, at least half developed secondary things like nosocomial pneumonia, hospital-acquired infections, and then develop a bacteremia on top of it because, obviously, they've got multiple lines. They're maybe on ECMO.

So I think this is really part of the issue. Critically ill patients can manifest (sounds like: any one combination). But as Dr. Connors mentioned, early on in the course of disease, clearly it's a hypercoagulable that can evolve due to secondary infections, other scenarios. But, again, you have to define the time sequence and the link to the hospitalization. That really helps you understand what the actual disease processes.

But it is not a classic DIC because, as Dr. Connors mentioned, early on the prothrombin and partial thromboplastin times are normal. Platelet counts are reasonably normal, and it's a real focus on elevated D-dimers and hyperfibrinogenemia. Von Willebrand factor, which she described as VWF, is increased a very potent age, and that really contributes to the hypercoagulability. So it's a very complex evolving coagulopathy.

Dr. BobbieJean Sweitzer: Dr. Connors, I know for other patients, you know, once they've had clots, they often are deemed at risk for, you know, recurrent hospitalizations or even have, you know, longer term anticoagulation. What is the status now with those kinds of recommendations for these patients if they've, you know, technically recovered, I guess, and now they're, you know, discharged?

Dr. Jean M. Connors: Yeah, no, so it's a great question. And we don't have data on that per se, but we do have recommendations so that patients who are admitted to the hospital who develop a thrombotic event, a venous thrombotic event, or even those who develop thrombosis in the outpatient setting – we view that as, if you will, a provoked event. So, you know, in the coag world, we like to – you know, when we're talking about VTE treatment, if we can identify sort of a provoking factor, such as, you know, major surgery, like cholecystectomy or abdominal pelvic surgery, and someone gets a clot in the next few days, clearly the surgery was a provoking factor, and we know that their risk for recurrence is very low.

We look at COVID-19 as a similar, strong provoking factor so that most patients only need a limited duration of anticoagulation of, say, three months for maybe a leg vein DVT or maybe six months if they've had a PE, unless there are other sort of extenuating circumstances. So every patient has to be individually approached once three or six months of anticoagulation have passed.

You know, there's this whole concern about the long COVID patients and what's going on with those patients, and why are they so symptomatic? We have not seen in those patients increased risks of thrombosis, although again, you know, somewhat of a moving target. So I think anybody who develops a thrombosis early in the course of COVID-19 can get limited duration of anticoagulation.

Dr. BobbieJean Sweitzer: So, Dr. Levy, there's been some well publicized and covered cases of some patients who developed clots after getting the vaccine. Can you tell us more about this? Is there a vaccine-induced hypercoagulability much like with the virus, even though, obviously, the vaccines do not have any virus? And maybe also touch on the vaccine-induced thrombotic thrombocytopenic.

Dr. Jerrold Levy: Interestingly, there's always going to be in any pharmaco or any kind of vaccine therapy a very low incidence of rare, super rare events. And this is unusual scenario. The vaccine-induced hypercoagulability, what's termed vaccine-induced thrombotic thrombocytopenia is a scenario that is similar to this heparin-induced thrombocytopenia that you don't have previous exposure to heparin, what's called autoimmune heparin-induced thrombocytopenia, where there is some mechanism by which you start creating antibodies to the molecular configuration called platelet factor IV. It's a very small basic protein stored in platelets that allows you to sort of create an autoimmune response. It's the basis of HIT.

When you're exposed to heparin for – you know, after four or five days where you get this thrombotic sequelae because antibodies bind to platelets. And when they bind, they activate and create a very hypercoagulable milieu. It's exceedingly rare. It's associated with the adenovector virus, which is an interesting perspective because remember that the mRNA virus is just simple mRNA without having that particular antigenic component.

So it – the body's inflammatory response to viruses and other scenarios induces this incredibly rare event, which is, I think, you know, certainly – as was mentioned in one of the articles, the chance of being hit by lightning is greater than actually having this thrombotic sequelae. But as all pharmacotherapies, it's all risk-benefit ratio, but the incidence is exceedingly low. And I think it's an interesting phenomenon. And there's been a lot of recent publications. These patients all have antiplatelet factor IV antibodies with very certain tests that are used for HIT.

But the other point is that people who do indeed have COVID-19 develop a multitude of autoantibodies, the phospholipids, and other scenarios due to the tremendous tissue injury that occurs. So a very rare event. And I think that it seems to be in patients 30 or less. Some of the early reports suggest that they may have been at slightly increased risk. But the bottom line is that the safety of the vaccines to me are pretty clear with the important profound benefit versus very low risk.

Dr. BobbieJean Sweitzer: Dr. Connors, should patients who do have this unfortunate reaction to the vaccine also be considered contraindicated to receiving heparin in the future?

Dr. Jean M. Connors: Well, that is a great question. Seriously. And you've come up with a lot of good questions for today, because we just don't know the answer to that. As Dr. Levy noted, that these patients have a very positive heparin-PF4 IgG ELISA assay result. The results are

often higher optical densities, which is the readout than we see in true heparin-induced thrombocytopenia in the hospital.

What we don't know is how long the duration of those antibodies last or how long that test remains positive. Very early cases of the VITT that were described in Europe, patients who were treated with heparin did get worse. So that – it's felt that if you suspect you have a case of VITT, you should, you know, do a full diagnosis that includes symptom-directed imaging, such as cerebral sinus thrombosis imaging if it's a young woman with a headache or looking for a DVT or a PE but that you also send the heparin-PF4 ELISA.

And even if results have not come back from that yet, you feel you need to treat a thrombosis, that you do not use a heparin-based anticoagulant. How long patients with this syndrome need to avoid heparin-based anticoagulants is not at all known right now.

As Dr. Levy mentioned, there's always going to be some unique reactions to vaccines. This is only seen to date with the adenoviral vector vaccines. And it does not appear to be related to any underlying coagulopathic, you know, state, like inherited thrombophilia or oral contraceptives, which was first sort of tossed around when this came out. It's more of an immune reaction phenomena than it is a coagulation phenomena. But the end result is like, as Dr. Levy said, autoimmune heparin-induced thrombocytopenia.

Dr. BobbieJean Sweitzer: Very, very interesting stuff. Dr. Levy, primarily children, I think, have been described as having a multi-inflammatory syndrome. I think it's also been described in adults as well. But how is this different than, I guess, what we think of as traditionally the COVID infection, you know, complex and syndrome that we've been talking about?

Dr. Jerrold Levy: When you think about children, children have actually lower circulating coagulation factor levels, so they're less hypercoagulable. They have pristine vascular endothelium for the most part, so their endothelium is – there's no real pre-existing issues. And they have these – this evolving hyperimmune responses, exuberant responses, if you will, to vaccines or to viral scenarios. And what they do is develop, again, an overexuberant inflammatory response that activates a whole series of cascades that for some unfortunate reason tends to sort of create injury, a multi-organ injury in the host with all sorts of heart, lung, kidneys, and other potential organ dysfunction.

Just think about the people who are at great risk for increased adverse events associated with COVID in the adult world. It's people with pre-existing vascular dysfunction, hypertension, obesity, diabetes, other metabolic sort of syndromes, where the endothelium is pre-existingly dysfunctional. And the added insult really can push them over the edge. And obesity and all these other scenarios increase the mortality.

These children with these, again, hyperinflammatory responses, some of them develop this ongoing, persistent response, which then ends up creating perhaps an autoimmune scenario, as Dr. Connors talked about, where, you know, a multitude of inflammatory processes occur. And this is, unfortunately, part of any acute viral scenario.

Again, I think with the sheer numbers, low incidence events become commonplace in the current era. And we've seen it not only in children but also in adults. Fascinating problem, but an unfortunate scenario too in terms of this sort of exuberant response that starts to create host injury.

Dr. BobbieJean Sweitzer: Um-hum [affirmative]. Dr. Connors, why do children appear to be less likely to catch COVID and then are less likely to have a serious infection when they do get COVID?

Dr. Jean M. Connors: Yeah. I think one of the things by surprise early in the pandemic was lack of testing. And knowing from one of my colleagues who had three (sounds like: elementary) school-aged boys get COVID, the younger ones were less symptomatic. So it seems that children are not as symptomatic as adults when they get it, so there may be kids running around that have no symptoms.

I think, as Dr. Levy mentioned, adults have comorbid disease that sets them up to not only develop more symptoms potentially but also have more severe outcomes, so diabetes, hypertension, obesity, whether or not underlying COPD is a risk factor for more severe disease. Lots of those things are just not seen in children. When we look at the spectrum of disease, kids rarely get infected.

You know, it's interesting. As Dr. Levy was just discussing multi-inflammatory syndrome in children, I think one of the thrusts for scientific research that's coming out of COVID is the unique reaction between people. And it may be that those kids who get severely ill have some sort of, you know, a genetic difference, whether it's in the complement pathways or the inflammatory pathways that make them a little more susceptible. And that may hold true for adults as well, but I think it's more the comorbid disease that we see in adults that already gives them an underlying inflammatory milieu and damaged vascular endothelium that sets them up as opposed to children who have nice, pristine vessels.

Dr. BobbieJean Sweitzer: I hope today's discussion will interest many of our listeners and lead you to read important articles to learn more. Thank you, Drs. Levy and Connors, for discussing this work with us today. I wish you both well as you continue your efforts to enhance the practice of medicine and strive to improve the care of our patients.

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