

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Thrombosis With Thrombocytopenia Syndrome After COVID-19 Vaccination



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H&O What types of blood clotting issues are being seen in people after COVID vaccination?

AC We are seeing both venous and arterial thromboembolic events. A particularly notable finding is venous thrombosis in unusual locations, including the cerebral venous sinuses and the splanchnic veins. Lower-extremity deep vein thrombosis and pulmonary embolism are occurring, and some patients have been reported to present with arterial events such as stroke and acute limb ischemia.

H&O Could you describe the unusual combination of a low platelet count and blood clotting that is being seen?

AC This appears to be a very rare complication of certain COVID-19 vaccines, in which patients are presenting with blood clots, as we just discussed, in addition to thrombocytopenia. Patients tend to present within 5 to 42 days after vaccination.

The most commonly used term for this syndrome is *thrombosis with thrombocytopenia syndrome*, or TTS. I am not a big fan of the name TTS in the context of COVID-19 vaccines, however, because it is nonspecific. Multiple other conditions are associated with both thrombosis and thrombocytopenia, including heparin-induced thrombocytopenia (HIT), antiphospholipid syndrome, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulation (DIC).

H&O What term do you prefer?

AC The term I like best is *vaccine-induced thrombosis and thrombocytopenia*, or VITT. The advantage of this term is that it differentiates the syndrome from other thrombotic/thrombocytopenic conditions by noting that it is induced by vaccination. However, this term has fallen out of favor because it draws attention to the link between the syndrome and certain vaccines, so I am willing to go along with the rest of the world in calling the syndrome TTS.

H&O How common is TTS after each specific vaccine?

AC We are still learning about the incidence. First, it is important to say that TTS has not been reported with the mRNA-based vaccines from Pfizer-BioNTech and Moderna. It appears to be a very rare complication of the Johnson & Johnson and AstraZeneca vaccines, both of which are adenovirus-based. The incidence of TTS has been highest with the AstraZeneca vaccine, known as Covishield. This vaccine is not yet authorized in the United States, but in Norway, 5 cases were reported among approximately 130,000 vaccinated individuals, for an incidence of approximately 1 in 26,000. Regarding the Johnson & Johnson vaccine, the Centers for Disease Control and Prevention has reported 17 cases among more than 8 million vaccinated individuals in the United States, for an incidence of roughly 1 in 500,000.

Immune thrombocytopenia has been reported with

other vaccines, including the one for measles, mumps, and rubella, but immune thrombocytopenia is primarily a bleeding disorder. We have not seen TTS with any vaccines other than the AstraZeneca and Johnson & Johnson COVID-19 vaccines.

H&O What are the demographics of the persons affected?

AC In the United States and in some other countries, most of the cases have been reported in women younger than 50 years. It is possible that this demographic is predisposed to the development of TTS, but when you analyze the data more closely, it is not yet clear whether younger women are more susceptible to TTS or simply overrepresented among the individuals who have received adenovirus-based vaccines. It is important to note that TTS has been reported in both women and men, and in adults of all ages around the world.

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H&O What is the mortality rate for TTS?

AC The mortality rate in early case series is substantial, in the neighborhood of 50%, according to studies by Greinacher and colleagues and by Schultz and colleagues. This is a serious and potentially lethal condition. The mortality rate may decline as the recognition and treatment of TTS improve.

H&O Can we identify a subgroup of patients in whom the risk for TTS might outweigh the benefit of the vaccine?

AC We do not have enough information at this point to identify what sort of factors might increase the chance of TTS after COVID-19 vaccination, but the overall risk is very low. In contrast, the mortality rate of COVID-19 is estimated to be 0.5% to 1%, and higher than that in older individuals and in men. The risk for a blood clot

is 8% among people who are hospitalized for COVID-19, and 23% among those who are sick enough to need intensive care. A recent report by Bikdeli and colleagues found that cerebral vein thrombosis, a cardinal manifestation of TTS, occurred in 3.6 per million people after the AstraZeneca COVID-19 vaccine, 0.9 per million people after the Johnson & Johnson vaccine, and 207 per million people hospitalized with COVID-19. In other words, the risks of nonvaccination are orders of magnitude greater than the risk of vaccination, which is what I emphasize to my patients and people who ask me about whether they should receive the vaccine. Vaccination is by far the most effective measure for preventing COVID-19 and for getting us out of this pandemic.

H&O What causes this combination of blood clots and a low platelet count?

AC All signs point to TTS arising from an autoimmune reaction in which antibodies against a chemokine called platelet factor 4 (PF4) are produced. The antibodies bind to PF4 on the surface of platelets and cause the platelets to become activated, resulting in thrombosis and thrombocytopenia. We still have more work to do, however, in understanding the underlying pathophysiology.

H&O What are the symptoms of TTS?

AC The most prominent symptoms are those caused by thrombosis and depend on the location of the blood clot. For example, a patient presenting with cerebral venous thrombosis will often have severe headache, whereas a patient with splanchnic vein thrombosis may experience severe abdominal or back pain. In addition to symptoms referable to thrombosis, some patients may have easy bleeding or bruising, and a flulike prodrome beginning 5 to 10 days after vaccination and preceding the onset of TTS has been reported.

H&O How is the condition diagnosed?

AC We are still learning about the best way to diagnose the condition, but laboratory testing will typically demonstrate a low platelet count. Some patients will have overt DIC, with a low fibrinogen level and a markedly elevated D-dimer level. High levels of PF4 antibodies can be used to confirm this disease, but most centers do not have access to PF4 antibody tests that are specific for TTS. In that case, the recommendation is to use a standard enzyme-linked immunosorbent assay (ELISA) for HIT to test the patients. A functional assay for HIT, such as a serotonin-release assay, may also be helpful, although the result is not always positive in patients

with TTS. It is important to bear in mind that although rapid immunoassays for HIT are available, they are not reliable for diagnosing TTS and should not be used for this purpose.

When we see patients with thrombosis, particularly thrombosis in unusual locations, we should ask them whether they have received the Johnson & Johnson or AstraZeneca vaccine in the last 5 to 42 days.

H&O What is the treatment?

AC The treatment involves anticoagulation of therapeutic intensity. Because of some similarities between TTS and HIT, and the theoretical concern that heparin could worsen TTS, treatment with a nonheparin anticoagulant is recommended. In addition, many experts recommend giving high-dose intravenous immunoglobulin to block autoantibody-mediated platelet activation. Finally, there is a theoretical risk that platelet transfusion could worsen TTS. As a result, platelet transfusion should be reserved for patients who have critical bleeding or who need urgent surgery and have severe thrombocytopenia.

H&O What is the best anticoagulation regimen to use?

AC The optimal regimen has not been defined, but fondaparinux or a direct oral anticoagulant are reasonable options for anticoagulation in stable patients who have good organ function. Shorter-acting intravenous agents such as argatroban or bivalirudin are preferred in patients who have critical illness or organ dysfunction.

H&O What other special concerns arise in the management of these patients?

AC The management of patients who have overt DIC and bleeding can be especially challenging. Giving anticoagulation to a bleeding patient can be risky, and

these patients may require blood product replacement in addition to anticoagulation to manage their bleeding.

H&O How should physicians adjust their evaluation of patients with thrombosis, given this newly discovered link?

AC When we see patients with thrombosis, particularly thrombosis in unusual locations, we should ask them whether they have received the Johnson & Johnson or AstraZeneca vaccine in the last 5 to 42 days. If they have, that raises a concern for possible TTS, and we should order a complete blood cell count and a DIC panel. If patients are found to be thrombocytopenic, which would point to possible TTS, they should undergo PF4 antibody testing.

H&O Should individuals with a personal history of venous thromboembolism (VTE) or a family history of confirmed thrombophilia be directed toward or steered away from certain vaccines?

AC The short answer is no. We have no evidence that a personal or family history of VTE or thrombophilia increases an individual's risk for TTS. Furthermore, such individuals might be at increased risk for thrombosis if they were to contract COVID-19. Therefore, all individuals should be encouraged to receive vaccination as soon as they have the opportunity.

H&O Should special close surveillance for the development of VTE be initiated in these patients, such as with platelet counts or duplex Doppler ultrasound?

AC We are not recommending surveillance in asymptomatic individuals. However, people who receive the Johnson & Johnson or AstraZeneca vaccine should be educated about the signs and symptoms of TTS and instructed to seek medical attention immediately if such manifestations arise. Because of the rarity of TTS, surveillance in asymptomatic patients is not warranted.

H&O If a patient experiences TTS after the Johnson & Johnson vaccine, should that vaccine be avoided in the future if a booster shot is required?

AC We do not know the answer to this question yet, but unless and until such evidence is available, my instinct would be to avoid further administration of an adenovirus-based vaccine to a patient in whom TTS developed after vaccination with the Johnson & Johnson or AstraZeneca

vaccine. If such a patient needed a booster, my personal recommendation would be to use an mRNA-based vaccine rather than an adenovirus-based one.

H&O What other adenovirus-based vaccines are used worldwide?

AC At least 2 other adenovirus-based vaccines against COVID-19 are available: the Convidecia vaccine from CanSino Biologics, which is used primarily in China, and the Sputnik V vaccine, which was developed by the Gamaleya Research Institute of Epidemiology and Microbiology and is used primarily in Russia. In addition, Janssen's adenovirus-based Ad26.ZEBOV-GP Ebola vaccine is being used around the world. I am not aware that cases of TTS have been ascribed to any of these other adenovirus-based vaccines. Whether that may be because of differences in the vaccine constituents or differences in the reporting of adverse events is unknown at this time.

H&O Do we have any system beyond the Vaccine Adverse Events Reporting System (VAERS) for tracking thrombotic complications?

AC We are relying on VAERS in the United States, and other countries have similar systems. The International Society on Thrombosis and Haemostasis has established an international registry for VITT.

Disclosures

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Suggested Readings

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