

April 23, 2021

HEALTH ADVISORY: Vaccine-induced Immune Thrombotic Thrombocytopenia

On April 13, 2021, the U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) suggested pausing administration of the COVID-19 Johnson & Johnson (J&J) vaccine to allow investigation of several post-vaccination cases of a new severe clotting and thrombocytopenia syndrome named **vaccine-induced immune thrombotic thrombocytopenia (VITT)**.

According to the American Society of Hematology, VITT is a syndrome characterized by 1) thrombosis, particularly at unusual sites including cerebral sinus venous thrombosis (CSVT)/splanchnic thrombosis; 2) mild to severe thrombocytopenia; and 3) positive PF4-heparin ELISA and platelet activation assays.

The April 13th announcement came on the heels of the initial reports of VITT in individuals receiving the COVID-19 AstraZeneca (AZ) vaccine outside the United States. Based on current information, **the risks of COVID-19 disease and COVID-19-associated thrombosis far outweigh the extremely rare risk of VITT**. Additionally, there is no information to date to suggest an increased risk for VITT in patients with blood diseases and/or pre-existing risk factors for thrombosis or autoimmunity.

VITT was originally described in patients vaccinated five to 16 days previously with the COVID-19 Astra Zeneca vaccine, which has been used extensively in the United Kingdom, Europe, and Canada, but is not available in the United States. Patients in these reports were primarily younger than 55 years, and more than 80 percent were female. None had received recent heparin, and few had other known risk factors for thrombosis. Many of the patients were critically ill by the time thrombosis and thrombocytopenia were discovered, and up to one-third of the initially reported patients died.

More recently, VITT has been reported in at least six patients [receiving the COVID-19 J&J vaccine](#). AZ and J&J vaccines consist of recombinant adenoviral vectors based on a chimpanzee adenovirus or a human adenovirus, respectively, both encoding the SARS-CoV-2 spike protein immunogen. As of April 14, 2021, according to the FDA, while a few individuals receiving the Moderna lipid nanoparticle encapsulated mRNA vaccine have been diagnosed with CSVT, no patients receiving the Moderna or the similar mRNA Pfizer-BioNTech vaccine have been known to develop VITT.

The striking clinical similarities of VITT to heparin-induced thrombocytopenia (HIT) and the uniformly positive PF4-heparin ELISAs in these index cases led investigators to identify circulating PF4-reactive antibodies that are able to directly activate platelets in the absence of heparin.

It is common for vaccinated individuals to experience mild-to-moderate constitutional symptoms following vaccination. These can include fever, fatigue, headache, or muscle aches, are usually limited to the 24 to 36 hours following vaccination and are not suggestive of VITT. **However, patients with severe, recurrent, or persistent symptoms, particularly intense headache, back pain, abdominal pain, nausea and vomiting, vision changes, shortness of breath, petechiae or easy bruising and/or leg pain and swelling, either persisting or beginning four to 20 days following vaccination, should be evaluated urgently by a medical provider and consideration should be given to underlying VITT.** While current information links VITT to AZ and J&J vaccines, patients with suggestive timing and symptoms following any COVID-19 vaccine should be evaluated for VITT.

The **initial VITT work-up** should include the following:

1. **CBC with platelet count and peripheral smear** (the mean platelet count in published reports was 20,000 with a range of 9,000-107,000)
2. **Imaging for thrombosis** based on symptoms, focused on detection of cerebral sinus venous thrombosis (CSVT) with **contrast** CT or MRI venogram, splanchnic thrombosis, and/or pulmonary emboli
3. **D-dimer** (the majority of VITT patients have markedly elevated values)
4. **Fibrinogen** (some VITT patients have low values)
5. **PF4/heparin ELISA**: almost all cases reported had positive assays, with optical density > 2.0 -3.0 in the majority. Non-ELISA HIT assays have not been validated as sensitive or specific for VITT and should not be used.
6. **Blood drawn for a confirmatory PF4 platelet activation assay** (serotonin release assay, P-selectin expression assay, or HIPA). These assays can be obtained if locally available and if the PF4 ELISA is low positive or if there is uncertainty regarding the diagnosis.
7. Blood should be drawn *prior* to any therapeutic interventions such as IVIG, given the potential interference with both the ELISA and platelet activation assays.
8. An hematology consult should be considered early on.

Patients with worrisome symptoms and/or positive imaging in addition to low platelet counts and high D-dimers should be considered to have VITT and should be started on treatment while awaiting ELISA results.

Patients who present with thrombosis and a normal platelet count post-vaccination might be in an early stage of VITT and should be carefully monitored for the development of thrombocytopenia/VITT.

VITT is a newly described syndrome, and all treatment recommendations are based on extrapolations from similarities to HIT and to non-heparin-dependent autoimmune thrombotic thrombocytopenia, analysis of the clinical features in reported cases, and predictions based on laboratory investigations to date of possible pathophysiology. Several national and international societies ([Guidance Statement from the GTH](#); [Guidance produced by the Expert Haematology Panel \[EHP\] focused on Vaccine induced Thrombosis and Thrombocytopenia \[VITT\]](#)) have published detailed position papers on VITT that include expert consensus recommendations and algorithms, with planned frequent updates.

In patients presenting with thrombocytopenia, documented or suspected thrombosis, and a positive or pending ELISA 4-20 days post-vaccination, **the recommended treatment is similar to that of severe HIT** and includes:

1. **IVIG** 1 gram/kg daily X 2 days
2. **Non-heparin anti-coagulation**, chosen based on the clinical status and organ function of the patient:
 - a. Parenteral direct thrombin inhibitors (argatroban or bivalirudin provided the baseline aPTT is normal)
 - b. Direct oral anticoagulants without lead-in heparin phase
 - c. Fondaparinux, or
 - d. Danaparoid
3. Low fibrinogen or bleeding are associated with VITT, and should not absolutely preclude anticoagulation, particularly if platelets are $>20,000/\mu\text{L}$ or rising following IVIG initiation.
4. Based on similarities to HIT, **platelet transfusions should be avoided**. However, risk/benefit assessment in individual patients with serious bleeding and/or need for surgical intervention may favor platelet transfusion, following initiation of IVIG, non-heparin anti-coagulation, and fibrinogen replacement (if deficient).

At this time, the duration of risk of thrombosis in patients with VITT is not known. Pending more data, those with documented thrombosis should receive a **minimum of three months anticoagulation**, as for any provoked venous thrombo-embolism (VTE).