



COVID-19 RESOURCES

Thrombosis with Thrombocytopenia Syndrome (also termed Vaccine-induced Thrombotic Thrombocytopenia)

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Key Takeaways

Thrombosis with Thrombocytopenia Syndrome (TTS)

- **Diagnosis** (must meet all four criteria):
 1. COVID vaccine (Johnson & Johnson/AstraZeneca only to date) 4 to 30 days previously
 2. Venous or arterial thrombosis (often cerebral or abdominal)
 3. Thrombocytopenia*
 4. Positive PF4 "HIT" (heparin-induced thrombocytopenia) ELISA
- **Incidence is extremely rare.** Risk of death and serious outcome of COVID-19, including thrombosis, far outweigh risk of TTS possibly associated with highly efficacious vaccines.
- **Urgent medical evaluation for TTS** is indicated if any of the following develop 4 to 30 days after vaccination:
 - Severe headache
 - Visual changes
 - Abdominal pain
 - Nausea and vomiting
 - Back pain
 - Shortness of breath
 - Leg pain or swelling
 - Petechiae, easy bruising, or bleeding
- **If TTS is suspected,** perform **immediate CBC with platelet count** and imaging for thrombosis based on symptoms.
- If thrombocytopenia or thrombosis are present, recommend urgent consultation from hematologist with expertise in hemostasis. **Avoid use of heparin until TTS has been ruled out or until an alternative other plausible diagnosis has been made.**
- **Initial work-up (a normal platelet count is less concerning for TTS*):**
 - CBC with **platelet count** and peripheral smear
 - Imaging for thrombosis based on signs/symptoms
 - PF4-ELISA (HIT assay); **draw blood prior to any therapies**
 - Fibrinogen and D-dimers
- **Initiate therapy** with intravenous immune immunoglobulin and nonheparin anticoagulation pending PF4 ELISA results if:
 - Signs/symptoms of serious thrombosis **AND** at least one of the following
 - Positive imaging **OR**
 - Low platelets* **OR**
 - Both

If PF4 ELISA returns negative and there is no thrombocytopenia, TTS is ruled out; treat as standard venous thromboembolism.

OR

- No signs, symptoms or imaging documenting thrombosis **BUT**
 - Low platelets **AND**
 - Very high or rising D-dimer **OR** positive PF4 ELISA
- If thrombocytopenia but no thrombosis and negative PF4 ELISA, likely ITP; see Q4
- Avoid platelet transfusions unless other treatments have been initiated **AND** life-threatening bleeding or imminent surgery
- Consider referral to tertiary care center if TTS is confirmed.

TTS is an evolving disorder, and updates will be made as new data become available.

***A patient who presents with thrombosis and a normal platelet count post-vaccination might be in an early stage of TTS.** Continued assessment for development of thrombocytopenia/TTS required. Use of non-heparin anticoagulant may be indicated if patient is 4 to 30 days post-Johnson & Johnson or AstraZeneca vaccine.

On April 13, the U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) suggested pausing administration of the AD26.COV2.S Johnson & Johnson (JJ) vaccine to allow investigation of several cases of a severe thrombosis with thrombocytopenia occurring post-vaccination. This announcement came on the heels of the initial reports of similar events in individuals receiving the ChAdOx1 nCov-19 AstraZeneca (AZ) vaccine outside the United States. Clinical and laboratory characteristics of TTS have recently been reported.¹⁻⁴ This syndrome has been termed "vaccine-induced prothrombotic immune thrombocytopenia (VIPT)" or "vaccine-induced immune thrombotic thrombocytopenia (VITT)" but is now termed "thrombosis with thrombocytopenia syndrome (TTS)" by the CDC and FDA.

Following FDA/CDC review of all sources of vaccine event reporting in the United States following JJ vaccine administration, and a detailed risk/benefit analysis, the CDC Advisory Committee on Immunization Practices met on April 23, 2021, and voted to recommend that the JJ vaccine again be available for persons aged 18 years and older under the FDA's Emergency Use Authorization. The 10-day pause in administration of the JJ vaccine was believed to be sufficient to educate health care providers regarding TTS diagnosis and treatment. The overall safety, efficacy, and need for the JJ vaccine was thought to far outweigh the very low risk of TTS. The updated incidence of this constellation of findings was extremely rare at two per million for the JJ vaccine, based on a total of 15 cases reported following 798 million doses administered. The rate was seven per million in the highest risk group of women younger than 50 years; however, even in this group, the risk/benefit strongly favored vaccination, based on a predicted 116 deaths from COVID-19 disease per million at current infection and mortality rates. Educational materials being provided by the CDC and FDA will inform the public regarding the option of mRNA vaccines with lower risk of TSS, particularly women younger than 50 years who have developed TTS at the highest rate to date following the JJ vaccine.

Based on current information, we strongly agree with the CDC panel that the risk of COVID-19 disease, including thrombosis, far outweighs the extremely rare risk of TTS associated with highly efficacious vaccines.⁵ Of note, there is no information to date on any increased risk for TTS in patients with blood diseases and/or pre-existing risk factors for thrombosis or autoimmunity. The single-dose JJ vaccine may be particularly attractive for administration to patients before initiation of chemotherapy or other immunosuppressive interventions.

This FAQ is designed to provide an overview of considerations around the diagnosis and treatment of TTS and will be updated as more information becomes available. Hematologists with expertise in hemostasis should be consulted as soon as TTS is diagnosed or under consideration, and many institutions will devise algorithms based on local laboratory testing availability and practices.

Q1. What is thrombocytopenia with thrombosis syndrome (TTS)?

A syndrome characterized by 1) venous or arterial thrombosis, particularly at unusual sites including cerebral sinus venous thrombosis (CSVT)/splanchnic thrombosis; 2) mild to severe thrombocytopenia; and 3) positive PF4-heparin ELISA ("HIT" ELISA) was first described in patients vaccinated five to 16 days previously with the ChAdOx1 nCov-19 AZ vaccine, utilized extensively in the United Kingdom, Europe, and Canada, but not yet available in the United States.^{1,2,4} Patients in European and UK reports were primarily younger than 50 years (with a range up to 77 years), and more than two thirds 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 initial reported patients died.

More recently, TTS was reported in patients receiving the Ad26.COV2.S JJ vaccine.³ The clinical syndrome, time post-vaccination, and age and gender trends were very similar to cases following the AZ vaccine. Both vaccines utilize recombinant adenoviral vectors (chimpanzee for AZ and human for JJ) encoding the SARS-CoV-2 spike protein immunogen. To date, no patients receiving the Moderna or Pfizer-BioNTech mRNA vaccines have been known to develop TTS, as of April 23, 2021.

The striking clinical similarities of TTS to heparin-induced thrombocytopenia (HIT) and the uniformly positive PF4-heparin ELISAs in these index cases led investigators to identify circulating PF4-reactive antibodies able to activate platelets in the absence of heparin. Intravenous immune globulin (IVIg) or a monoclonal antibody blocking the Fc receptor were able to prevent platelet activation by these antibodies in vitro. These clinical and laboratory features are similar to rare cases of HIT-like autoimmune thrombosis with thrombocytopenia previously described following surgery, certain medications, or infections in patients not receiving heparin.

Q2. What clinical presentation should trigger consideration of TTS, and what is an appropriate initial work-up?

Mild-to-moderate constitutional symptoms such as fever, fatigue, headache, or muscle aches are common in the first 24 to 48 hours following vaccination and are not suggestive of TTS. Patients with severe, recurrent, or persistent symptoms four to 30 days following AZ or JJ vaccination, including intense headache, abdominal pain, back pain, nausea and vomiting, vision changes, change in mental status, shortness of breath, leg pain and swelling, and/or bleeding/petechiae, should be evaluated urgently by a medical provider, and consideration given to underlying TTS. The peak time period for initial symptoms is days 6 to 14.

Initial work-up (note: draw blood *prior* to any therapeutic interventions such as IVIG, given potential interference with diagnostic assays):

1. CBC with platelet count and peripheral smear (mean platelet count in published reports, 20,000; with a range from profound to mild, current TTS definition <150,000/ μ L)
2. Imaging for thrombosis based on symptoms, focused on detection of cerebral sinus venous thrombosis (CSVT) with CT or MRI venogram, splanchnic thrombosis, pulmonary emboli, and/or DVT.
3. D-dimers: the majority of TTS patients have markedly elevated values
4. Fibrinogen: some TTS patients are reported to have low values
5. PF4-heparin ELISA: almost 100 percent of cases reported had positive assays, with optical density greater than 2.0 to 3.0 in the majority. **Non-ELISA rapid immunoassays for HIT are not sensitive or specific for TTS and should not be used.**

Patients with worrisome symptoms and/or positive imaging in addition to low platelet counts and high D-dimers, can be considered to have TTS and be started on treatment (see Q3) while awaiting PF4 ELISA results. Whether the degree of PF4 ELISA positivity correlates with risk of TTS is unknown. Patients with low fibrinogen and extremely high D-dimers, suggesting disseminated intravascular coagulation, fall within the TTS syndrome. Microangiopathy with red cell fragmentation and hemolysis has not been a common feature of reported cases; however, at least one case with both TTS and TTP/HUS features has been reported.⁷ Thus, review of a blood smear and attention to signs of intravascular hemolysis would be appropriate.

Patients with isolated thrombocytopenia and continued absence of thrombosis may have post-vaccine ITP and not TTS (see Q4), as confirmed by a negative PF4 ELISA.

Q3. How should TTS be treated?

This is a newly described syndrome, and all recommendations are based on extrapolation from similarities to HIT and to non-heparin-dependent autoimmune thrombotic thrombocytopenias; analysis of the clinical features in reported cases, and predictions based on laboratory investigations of pathophysiology.¹⁻⁴ 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 TTS that include expert consensus recommendations and algorithms, with planned frequent updates. Note that the response rate to any of these interventions has not been established.

In patients presenting with thrombocytopenia, documented or suspected thrombosis, and a positive or pending PF4 ELISA 4-30 days post-vaccination, we recommend rapid initiation of treatment similar to treatment of severe HIT, including:

1. IVIG 1 g/kg daily for two days. Note that at least two patients with new clots arising post-IVIg have been reported²; thus, patients should be carefully monitored even once treatment has begun, and initiation of anticoagulation coincident with IVIG is recommended.
2. Non-heparin anticoagulation, 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), OR
 - b. Direct oral anticoagulants without lead-in heparin phase, OR
 - c. Fondaparinux, OR
 - d. Danaparoid
3. Low fibrinogen or bleeding are associated with TTS and should not absolutely preclude anticoagulation, particularly if platelets are >20,000/ μ L or rising following IVIG initiation. Concurrent replacement of fibrinogen in patients with bleeding and/or very low values should be considered.
4. Based on similarities to HIT, avoid platelet transfusions. 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 anticoagulation, and fibrinogen replacement (if deficient).
5. Corticosteroids have been administered along with IVIG in some cases, with no consensus or data yet available on the need for this additional therapy.
6. Avoid aspirin as either treatment or prophylaxis for TTS. Aspirin is not efficacious in preventing HIT antibodies from activating platelets and could increase the risk of bleeding in TTS.
7. Additional therapies: At present, we do not recommend utilization of plasma exchange unless the patient shows continued thrombosis despite IVIG and non-heparin anticoagulation. The large extravascular volume of distribution of IgG antibodies, causative in both HIT and TTS, prevents rapid or complete removal via PE, and the concurrent bleeding complications in TTS may make catheter placement and prolonged apheresis challenging. Complement inhibition with eculizumab has been utilized in several patients progressing despite other therapies, with evidence for improvement.⁷

While there is no direct evidence that heparin products worsen TTS, the similarities of the syndrome to HIT suggest avoidance of unfractionated or low-molecular-weight heparin in patients with a positive PF4 ELISA, or while awaiting test results. It should be pointed out that patients with TTS reported to date generally had prolonged symptoms before thrombocytopenia or thrombosis were detected. Many received heparin and/or platelet transfusions. It is hoped that earlier recognition of TSS and treatment with IVIG and non-heparin anticoagulants will result in improved outcomes.

As further data are gathered on patients with possible TTS, "grey zone" situations will arise as the syndrome is considered in patients with any concerning symptoms in the post-vaccine time period.⁸ There are no clear answers, and as data on patients with earlier TTS diagnosis become available, recommendations may change. Examples of challenging situations include:

- Patients followed by hematologists/oncologists who present post-vaccination with potential other reasons for thrombocytopenia and thrombosis. The PF4 ELISA can assist with diagnosis of TTS in these patients if thrombocytopenia is worsened from baseline.
- Patients may present with a typical low extremity venous thromboembolism (VTE) following vaccination in the presence of mild thrombocytopenia or a single low normal value. At present, avoidance of heparin in patients presenting with VTE in the post-vaccine window is reasonable while awaiting PF4 ELISA and following the platelet count.
- Patients four to 30 days following AZ or JJ vaccine with thrombocytopenia and elevated D-dimers without other clear causes, and a pending or positive PF4 ELISA four to 30 days, even in the absence of documented thrombosis or suggestive symptoms, should be treated with IVIG, with close monitoring and a very low threshold for initiating non-heparin anticoagulation, based on very high or rising D-dimers or any symptoms of thrombosis. A recent report documented rapid improvement in laboratory parameters in such a patient treated with both IVIG and a non-heparin anticoagulant, without progression to thrombosis.⁹

More data will be needed to refine the appropriate diagnostic and therapeutic approach in these and other settings that will arise.

At this time, the duration of risk of thrombosis in patients with TTS is not known. Pending more data, those with documented thrombosis should receive a minimum of three months anticoagulation, as for any provoked VTE.

Q4. What if a patient presents with thrombocytopenia or bleeding post-vaccination?

Almost 100 cases of new-onset acute immune thrombocytopenia purpura (ITP), one case being fatal, have been diagnosed in the same timeframe following vaccination as TTS (median, 8 days). These occurrences have been noted following AZ and JJ as well as Moderna and Pfizer vaccines. The platelet count at presentation is often <10,000/ μ L, somewhat lower than in TTS (median, 20,000/ μ L), and thromboses have not been associated with these cases, although very few cases had a PF4 ELISA checked. Most presented with bleeding. Estimates to date suggest that post-COVID vaccine ITP is rare (1 in 100,000 to 1 in 1,000,000) and may be related to vaccination or represent a coincidental event. Most patients respond to the combination of IVIG, and/or steroids, with platelet transfusions if bleeding. Thrombopoietin agents and possibly a single dose of vincristine may be useful if there is not an immediate (2-4 days or cessation of bleeding) response to IVIG and/or steroids. Avoidance of rituximab is important because of slow onset of action (weeks), negation of recent vaccine-induced immunity, and inability to vaccinate again for more than six months. For more details regarding treatment, see the ITP FAQ.

It is important to rule out TTS with a negative ELISA assay in patients presenting with thrombocytopenia four to 30 days post-vaccination, even in the absence of symptoms suggestive of thrombosis. While awaiting PF4 ELISA results, IVIG could be administered to patients with profound thrombocytopenia and bleeding, given the indication for this medication in the treatment of both ITP and TTS.

Patients with pre-existing ITP or other causes of thrombocytopenia may have transient further lowering of platelet count following vaccination. While a PF4 ELISA should be sent in such patients in the absence of signs of thrombosis is unclear, but until more information is available, it would seem prudent to send a screening ELISA in those with a clear significant decrease in platelet count occurring during the relevant timeframe.

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