Beaumont

Assessment of Thrombosis Symptoms Post Vaccination with J&J COVID Vaccine, Thrombosis with Thrombocytopenia Syndrome (TTS) April 27th, 2021

This guidance should not supersede clinical judgment. Should be used in conjunction with latest evidence and patient-specific characteristics

OVERVIEW

- Very rarely, cases of venous or arterial thrombosis with thrombocytopenia (most often cerebral venous sinus thrombosis or splanchnic thrombosis) have been reported with 2 replication-incompetent adenoviral vector COVID-19 vaccines, the Johnson and Johnson (Janssen or J&J) vaccine and the AstraZeneca (AZ) vaccine which is not yet FDA approved. The J&J vaccine uses a recombinant human adenovirus vector while the AZ vaccine uses a recombinant chimpanzee adenovirus vector. Cases with both vaccines demonstrate similar characteristics.
- The proposed mechanism involves formation of antibodies to platelet factor 4 as part of the inflammatory reaction and immune response. The antibodies, even in the absence of heparin, demonstrate massive platelet activation through the Fc receptor analogous to auto-immune heparin induced thrombocytopenia. Cases of unusual site thrombosis with thrombocytopenia are referred to as Thrombosis with Thrombocytopenia Syndrome (TTS). In other countries using the AZ vaccine the term Vaccine Induced Thrombotic Thrombocytopenia (VITT) or Vaccine Induced Prothrombotic Immune Thrombocytopenia (VIPIT) is used.
- Cases of TTS have not been reported with the Moderna or Pfizer COVID-19 vaccines which use messenger RNA technology.
- Cerebral venous sinus thrombosis (CVST) is the most common site of thrombosis in TTS. Other sites include splanchnic vein thrombosis, internal jugular vein, brachial vein, femoral vein and artery, pulmonary artery, iliac artery, superior mesenteric artery, splenic artery and carotid artery. Multiple thrombotic sites are common
- Cases with J&J vaccine as of April 21st, 2021:
    - 15 confirmed cases of TTS (12 with CVST) have been identified among ~8 million doses. Seven CVST patients had concurrent intracerebral hemorrhage. Three fatalities reported.
    - Events occurred 6-15 days (median 8 days) post vaccination in female patients aged 18 to 59 years, mean age 37 years
    - Platelet counts nadirs ranged from $10x10^9$/L to $127x10^9$/L
    - 11 patients positive for HIT antibodies, 4 patients not tested.
    - 10 patients were negative for SARS-CoV-2 viral test, results not available for 5 patients. Two patients with history of COVID-19.
- FDA found that a causal relationship between TTS and the J&J vaccine is plausible
- Cases with AstraZeneca vaccine as of April 4th, 2021:
    - 169 CVST cases and 53 splanchnic vein thrombosis (often with thrombocytopenia) reported through EudraVigilance, more than 30 fatalities
    - Patients may have multiple sites of thrombosis including arterial events
    - Events occurred 4-20 days post vaccination and were more common with women under the age of 55 years.
    - The platelet count nadirs in available data have ranged from 7-100 x 10^9/L with 1 case series reporting a median nadir of $20x10^9$/L
    - Cases associated with positive HPF4 antibodies and positive platelet activation assay results
    - Other relevant laboratory abnormalities: marked elevation in D-dimer, hypofibrinogenemia and evidence of DIC
    - European Medicines Association found a strong association and probable causal link between thrombosis and AZ COVID vaccine
- Risk factors for the development of TTS have not been identified, there is no information to indicate an increased risk in those with blood diseases or those with pre-existing risk factors for thrombosis or autoimmunity
- Alternative causes of thrombosis and alternative causes of thrombocytopenia such as Immune Thrombocytopenia Purpura (ITP) should be excluded
- A patient who presents with thrombosis & normal platelet count post vaccination may be in early stages of TTS, continued assessment for thrombocytopenia/TTS is needed

HIT ANTIBODY TESTING

- In patients with thrombosis, thrombocytopenia or both within 4-30 days post vaccination, a heparin platelet factor 4 (HPF4) IgG antibody should be ordered regardless of heparin exposure. Strongly positive optical density (OD) results with values of above 2 and often above 3 (uncommon in HIT) are reported
- In the US the serotonin release assay (SRA) is the functional HIT assay available at reference centers. In 5 of the initial 6 CVST cases with the J&J vaccine functional assay testing was negative. Cases of thrombosis with thrombocytopenia post AZ vaccine in Europe have been associated with positive platelet activation assays however different assays are available in Europe
- Positive HPF4 IgG antibody results with OD < 2 will automatically be sent out for serotonin release assay (SRA) testing by Beaumont laboratory.
- Hematology to establish the diagnosis

CEREBRAL VENOUS SINUS THROMBOSIS

- Clinical presentation: severe headache, focal neurologic deficit, seizures, blurred vision. **Timing of symptoms from vaccination is important to establish**.
- Neuroimaging with both vascular and parenchymal imaging with a CT head/CT venogram or MRI head/MRI venogram should be performed
- Consult neurology

MANAGEMENT

- Multidisciplinary approach is recommended, urgent hematology consult for all suspected TTS cases, consult neurology for TTS with CVST
- STAT symptom- based imaging and CBC
- If thrombosis or thrombocytopenia: Presumptive TTS: obtain HPF4 IgG antibody and a peripheral blood smear, fibrinogen, D-dimer, PT/INR and aPTT
- Draw blood for HPF4 heparin IgG antibody prior to treatment initiation (immune globulin if used can result in false negative results)
- Do not wait for HPF4 IgG antibody test results to initiate treatment; there is no difference in management of presumptive TTS or confirmed TTS
- A negative HPF4 ELISA without thrombocytopenia rules out TTS
- Administer high dose immune globulin (IVIG) 1 gram/kg for 2 days
- Low fibrinogen is associated with TTS and does not absolutely preclude anticoagulation especially if platelet count is > 20 x 10^9/L or rising on IVIG, concurrent replacement of fibrinogen in patients with bleeding and/or very low values should be considered
- **Anticoagulation with heparin, enoxaparin and warfarin should be avoided** until additional information is available unless HPF4 IgG antibody returns negative.
- Alternate non-heparin anticoagulants include argatroban (a direct thrombin inhibitor with a short half- life), apixaban or rivaroxaban (oral direct Xa inhibitors) or fondaparinux (a synthetic long-acting pentasaccharide). Considerations in agent selection:
    - In critically ill or patients with severe thrombocytopenia an argatroban infusion starting at 0.25mcg/kg/min - 0.5mcg/kg/min can be considered, higher argatroban initial doses per hospital protocol can be considered for either non-critically ill or those without severe thrombocytopenia.
    - Apixaban, rivaroxaban or fondaparinux can be considered for stable patients
- Duration of thrombosis treatment: Consider 3-6 months for venous thrombosis
- Administration of corticosteroids have been used, no consensus on role in management
- All cases of TTS should be reported to VARES @vares.hhs.org

TTS Diagnostic Flow Chart;
Urgent hematology consult, consult neuro if CVST suspected

Thrombotic symptoms 4 – 30 days post vaccination: New onset severe headache, focal neurologic deficit, seizures, visual changes, abdominal pain, back pain, chest pain, shortness of breath, redness or swelling in leg, limb coldness, petechiae or easy bruising/bleeding, nausea & vomiting

↓ Yes

STAT imaging based on symptoms and CBC

↓

Imaging confirmed thrombosis AND/OR platelet count < 150 x 10^9/L
Additional lab testing: D-dimer, fibrinogen, PT/INR, aPTT, blood smear

No thrombosis or thrombocytopenia → TTS unlikely
No HIT testing

↓ Yes

Presumptive TTS
1. Order HPF4 IgG antibody regardless of heparin exposure^
2. **Do not wait for test results to initiate treatment**

↓

Patient Management

- Initiate treatment with signs/symptoms of serious thrombosis AND positive imaging OR low platelets† OR both
- Initiate treatment with no signs or symptoms or imaging confirmed thrombosis but low platelets and very high or rising D-dimer or positive HPF4 ELISA
- Administer IVIG 1g/kg x 2 days
- Administer non heparin anticoagulant:
  - Argatroban - Consider initial dose 0.25 mcg/kg/min - 0.5 mcg/kg/min in critically ill or patients with severe thrombocytopenia. Consider higher doses in non-critically ill and patients without severe thrombocytopenia
  - Apixaban, rivaroxaban or fondaparinux - Consider in stable patients
- Avoid platelet transfusions unless other treatments started and life- threatening bleeding or emergent surgery

→ HPF4 Negative (OD < 0.4) without thrombocytopenia~ ↓ TTS ruled out, treatment with heparins possible

↓ HPF4 Positive (OD > 0.4)

- Hematology to confirm diagnosis in patients with a positive HPF4 IgG antibody result in context of the appropriate clinical picture/imaging*
- Beaumont lab automatically sends out positive HPF4 IgG antibody result to external lab for serotonin release assay (SRA)
- A negative SRA result with TTS has been frequently reported in initial US case series

All cases of TTS should be reported to VARES @vares.hhs.org

^HPF4 (heparin platelet factor 4) should be performed prior to initiation of IVIG as false negative results are possible
*HIT antibody testing must have preceded any heparin exposure
~ HPF4 negative with thrombocytopenia evaluate for potential acute immune thrombocytopenia purpura (ITP)
† a patient who presents with thrombosis & normal platelet count post vaccination may be in early stages of TTS, continued assessment for thrombocytopenia/TTS is needed
Guidance developed by medical hematology/oncology, pharmacy and clinical pathology. Approved by Vaccine Medication Review Committee May 3rd 2021

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