# Beaumont

# Assessment of Thrombosis Symptoms Post Vaccination with J&J COVID Vaccine, Vaccine Induced Thrombotic Thrombocytopenia (VITT) April 21st, 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 cerebral vein sinus thrombosis (CVST) with thrombocytopenia 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. No cases of CVST with thrombocytopenia have been reported with the Moderna or Pfizer COVID-19 vaccines which use messenger RNA technology.
- 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. This mechanism is referred to as Vaccine Induced Thrombotic Thrombocytopenia (VITT) or as Vaccine Induced Prothrombotic Immune Thrombocytopenia (VIPIT). The term VITT will be used for Beaumont guidance.
- Cases with J&J vaccine as of April 13$^{th}$, 2021:
    - Six CVST cases with thrombocytopenia were reported through VAERS (vaccine adverse event reporting system) during 6-week period involving ~7 million doses. Rate appears ~ 3 times higher than baseline CVST rate. Four patients with concurrent intracerebral hemorrhage, one fatality reported.
    - In 3 of 6 cases, additional sites of thrombosis included portal vein, internal jugular vein & pulmonary artery
    - Events occurred 6-13 days (median 8 days) post vaccination in female patients aged 18 to 48 years, mean age 33 years
    - Platelet counts nadirs ranged from $10x10^9$/L to $127x10^9$/L
    - 5 patients positive for HIT antibodies, 1 not tested. All patients were negative for SARS-CoV-2 viral test
    - Non-CVST thrombosis with thrombocytopenia case(s) currently under investigation
- Cases with AstraZeneca vaccine as of April 4$^{th}$, 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 VITT 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

**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
- Positive HPF4 IgG antibody results with OD < 2 will automatically be sent out for serotonin release assay (SRA) testing by Beaumont laboratory.
- A negative SRA is possible with VITT
- 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, consult hematology for all suspected cases, consult neurology for CVST
- Symptom based imaging is recommended
- Send 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 VITT or confirmed VITT
- **Anticoagulation with heparin or enoxaparin 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
- Consider high dose immune globulin (IVIG) 1 gram/kg for 2 days; consider for cases of life-threatening or progressive thrombosis, high risk for deterioration, slow response to anticoagulation or the need to raise platelet count to allow for anticoagulation
- Duration of thrombosis treatment: Consider 3-6 months for venous thrombosis
- All cases of VITT should be reported to VARES @vares.hhs.org

**VITT ASSESSMENT**

Multidisciplinary approach is encouraged (consult hematology in all patients and neurology if CVST)

Thrombotic symptoms 4 – 30 days post vaccination: severe headache, focal neurologic deficit, seizures, blurred vision, abdominal, back pain, chest pain, shortness of breath, redness or swelling in leg, limb coldness, petechiae or bruising

Yes

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

No → VIPIT unlikely
No HIT testing

Yes

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

HPF4 Negative (OD < 0.4) → Treatment with heparins possible

HPF4 Positive (OD > 0.4)

Beaumont Lab automatically sends SRA for all HPF4 IgG antibody positive results with OD between 0.4-2

- Hematology to confirm diagnosis in patients with a positive HPF4 IgG antibody result in context of the appropriate clinical picture/imaging*
- A negative SRA result with VITT is possible

Patient Management Considerations – Shared Decision Making Encouraged

- Consider anticoagulation with non-heparin anticoagulant
- Consider high-dose IVIG
- Avoid platelet transfusions unless bleeding present
- Avoid warfarin until platelet count recovery

<u>Considerations for Anticoagulation (with non-heparin anticoagulant)</u>

- 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
- Consider thrombosis treatment duration of 3-6 months

<u>Considerations for IVIG 1g/kg x 2 days</u>

- Increase platelet count to allow for anticoagulation
- Life threatening/progressive thrombosis
- High risk for deterioration
- Slow response to anticoagulation

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

^HPF4 should be performed prior to initiation of IVIG as false negative results are possible
*VITT confirmation requires hematology input, HIT testing must have preceded any heparin exposure
Guidance developed by medical hematology/oncology, pharmacy and clinical pathology. Approved by Vaccine Medication Review Committee April 21, 2021

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