UKHealthCare

UK HealthCare Antithrombosis Stewardship Committee
Guidance on COVID-19 Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT)
Version 04.16.2021 v6

OBJECTIVE

To assist UK HealthCare professionals in the diagnosis and management of Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT). *NOTE this is living document with evolving information and will be updated as new information is available.*

BACKGROUND

Cases of unusual thrombotic events and thrombocytopenia have been reported after COVID-19 vaccination using adenoviral vectors encoding the for SARS-CoV-2 spike glycoprotein manufactured by Johnson & Johnson/Janssen (JnJ) and the vaccine manufactured by AstraZeneca. Thrombotic events that have been reported include cerebral venous thrombosis (CSVT), portal, hepatic or splanchnic-vein thrombosis, pulmonary embolism, deep venous thrombosis and arterial thrombosis. Platelet counts have ranged from 10,000 – 110,000 /μl. The syndrome has features that suggest that it may be immune mediated, including elevated anti-PF4 antibodies. Thus, it has been named Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT). Cases of VITT have occurred within 4 – 28 days of vaccination.

Immune-mediated thrombocytopenia has also been reported after the two mRNA-based vaccines from Pfizer and Moderna.

It is important to note that while VITT can be lethal, its prevalence is remarkably low relative to the vaccine benefits of preventing COVID-19 complications and mortality.

DIAGNOSIS OF VACCINE-INDUCED IMMUNE THROMBOTIC THROMBOCYTOPENIA (VITT)

Patients presenting with the following symptoms should be asked about their COVID-19 vaccine history with focus on time period of 4-30 days following administration of the vaccine:

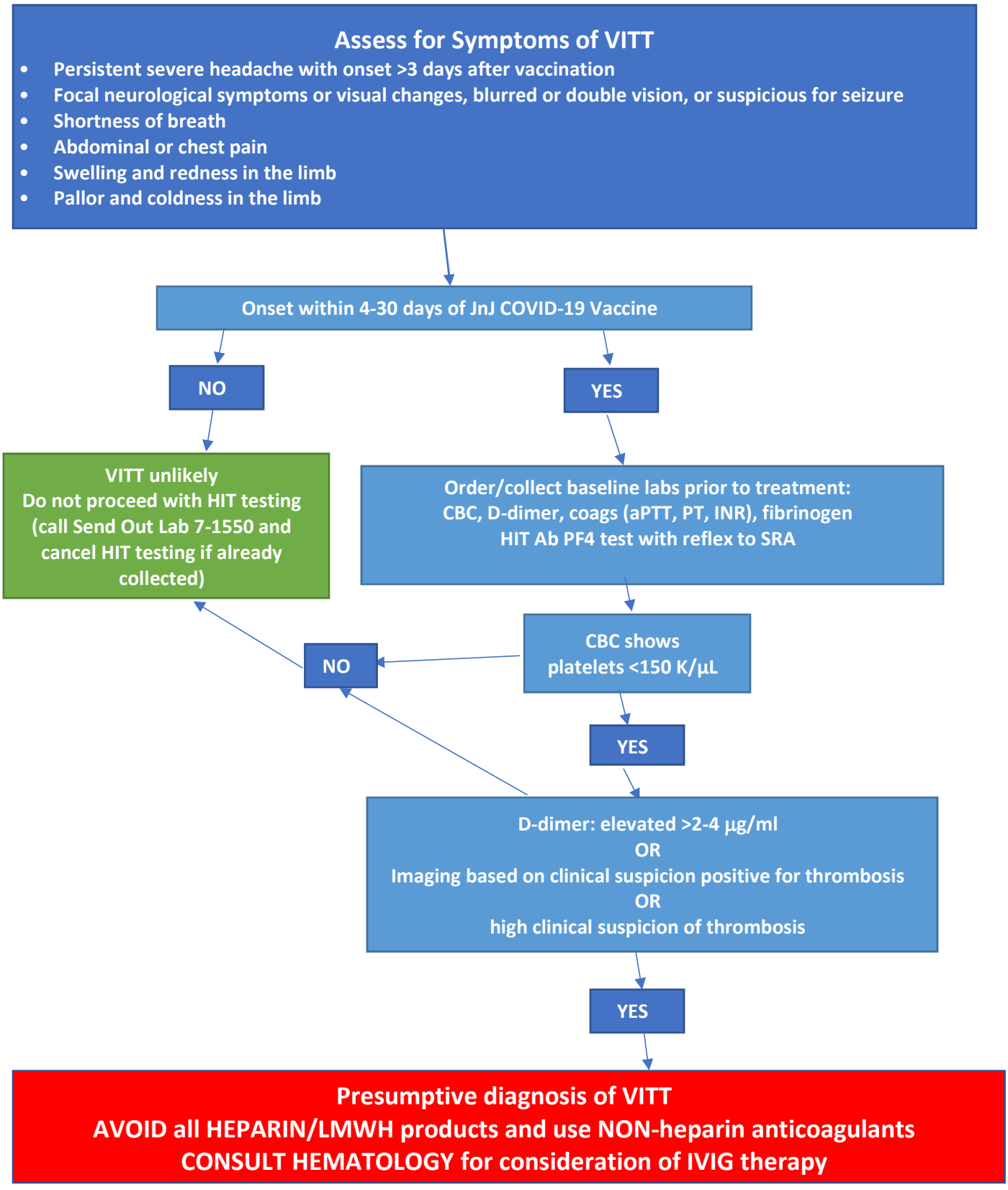
- Persistent severe headache with nausea, vomiting and neurological deficits
- Focal neurological symptoms or visual changes, blurred or double vision, or episodes suspicious for seizure
- Shortness of breath
- Abdominal or chest pain
- Swelling and redness in a limb
- Pallor and coldness in a limb

NOTE: These symptoms are distinct from the commonly reported side effects that people may experience in the first few days following vaccination, which can include headache, fatigue, muscle aches and nausea that generally mild to moderate in severity and last 1-2 days post-vaccine.

If the patient received JnJ or AstraZeneca COVID-19 Vaccine within the period of 4-30 days prior to presentation, a complete blood count (CBC) should be drawn. The same algorithm should be considered for other vaccines.

- If the platelet count is < 150 K/μL and vaccination within 4-30 days, the patient should be evaluated for VITT.
- Patients whose vaccine administration was > 1 month period or whose platelet count is > 150 K/μL are unlikely to have VITT.
- Patients with suspected VITT should have a D-dimer level, PT, INR, PTT, fibrinogen and anti-PF4 antibodies ordered.
- Diagnostic imaging should be performed based on clinical symptoms to evaluate for venous and arterial thrombosis.
- If the patient presents with a persistent and severe headache, nausea/vomiting, visual changes, focal neurological deficits or episodes suspicious for seizures, imaging for CSVT should be performed.

FIGURE 1. DECISION TREE FOR DIAGNOSING AND RULING OUT VITT



Management of Probable VITT Case – Treat first while awaiting confirmatory diagnosis:

1. **AVOID all forms of heparin products including low-molecular heparin (enoxaparin) and heparin flushes.**
    a. It is unknown whether heparin exacerbates the condition but until further data is clear, this is best avoided.
2. **CONSULT HEMATOLOGY.**
    a. **To determine if IVIG warranted** for immediate administration and to distinguish VITT from ITP.
        i. IVIG dose: 1 gram/kg daily X 2 days [use UKHC IVIG Order Set], irrespective of the degree of thrombocytopenia, and review clinical course.
        ii. Further IVIG may be required balancing bleeding and thrombotic risk.
        iii. Steroids should be considered and in particular if there is a delay giving IVIG.
        iv. Plasma exchange may also be considered.
3. **When platelets >30 K/μl or rising following IVIG initiation consider starting anticoagulation.**
    a. Bleeding and thrombotic risk needs to be carefully balanced and lower doses may be appropriate while platelet count is still low. *Low fibrinogen or bleeding are associated with VITT, and should not absolutely preclude anticoagulation, particularly if platelets are >30 K/μl or rising following IVIG initiation.*
    b. AVOID all forms of heparin products including low-molecular heparin (enoxaparin) and heparin flushes.
    c. **ANTICOAGULATE with non-heparin-based therapies such as bivalirudin (preferred; Pharmacist to Dose order)** or argatroban, fondaparinux or DOACs (apixaban, rivaroxaban or dabigatran), depending on the clinical picture.
    d. If anticoagulation is needed before platelets >30 K/μl, suggest NON-heparin anticoagulant with critical illness dose bivalirudin (Pharmacist to Dose order) be considered, initially without dose escalation and maintained at low dose.
    e. Refer to UK HealthCare Guidelines on HIT for non-heparin anticoagulant options and dosing: 1. Adult Heparin Induced Thrombocytopenia Guidelines
    f. Antiplatelet agents are not recommended as initial therapy based on current experience
4. **AVOID platelet transfusions and discuss if any potential interventions.**
    a. If procedures or surgery is required, platelet transfusion may be warranted in severe thrombocytopenia to minimize procedural bleeding risk.
5. **If no overt thrombosis, but thrombocytopenia persists with elevated D Dimer, thromboprophylaxis with non-heparin-based anticoagulants should be considered** – balancing bleeding and thrombotic risk.
    a. **Non-heparin VTE prophylaxis options:** DOAC (rivaroxaban or apixaban) or subcutaneous fondaparinux can be considered.
6. **Diagnosis**
    a. **If HIT Ab PF4 antibodies POSITIVE** – POTENTIAL CONFIRMED CASE and continue ongoing treatment as above and await SRA test
    b. **If HIT Ab PF4 antibodies NEGATIVE** – UNCLEAR as some cases have been HIT Ab PF4 antibody negative - review diagnosis and management, consider ITP
7. **Discharge:**
    a. For VITT with thrombosis, treat as provoked VTE and continue anticoagulation for at least 3 months.
    b. If thrombosis was only arterial, once D Dimer, platelets and fibrinogen have returned to normal, the patient can be switched to an antiplatelet agent and continued for 3 months.
    c. Monitor platelet count closely to observe for relapse and consider repeating PF4 ELISA at day 28 from presentation.
    d. Follow-up appointment with UK Hematology Clinic within 1 month
8. **Providers should follow the UKHC COVID-19 Vaccine Adverse Event Reporting Process posted on the COVID-19 Vaccine Information website: https://covid-19.ukhc.org/wp-content/uploads/sites/121/2021/01/COVID-19-Vaccine-Adverse-Event-Reporting-Process.pdf.** This process ensures we have the event on file at UKHC through an SI report and are reporting all necessary info the VAERS.

Resource Links/References:

1. American Society of Hematology. Vaccine-induced Immune Thrombotic Thrombocytopenia: Frequently Asked Questions (Version 1.0; last updated April 15, 2021)
2. Advisory Committee on Immunization Practices (ACIP) Presentation Slides. April 14, 2021 Meeting. https://www.cdc.gov/vaccines/acip/meetings/slides-2021-04.html
3. Guidance produced by the Expert Haematology Panel (EHP) focussed on Vaccine induced Thrombosis and Thrombocytopenia (VITT). April 10, 2021.
4. Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT) Following AstraZeneca COVID-19 Vaccination. Menaka Pai, Allan Grill, Noah Ivers, Antonina Maltsev, Katherine J. Miller, Fahad Razak, Michael Schull, Brian Schwartz, Nathan M. Stall, Robert Steiner, Sarah Wilson, Ullanda Niel, Peter Jüni, Andrew M. Morris on behalf of the Drugs & Biologics Clinical Practice Guidelines Working Group and the Ontario COVID-19 Science Advisory. Published March 26, 2021. Version 1.0.
5. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. N Engl J Med. 2021 Apr 9. doi: 10.1056/NEJMoa2104840. Online ahead of print. PMID: 33835769
6. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, Wiedmann M, Aamodt AH, Skattør TH, Tjønnfjord GE, Holme PA. N Engl J Med. 2021 Apr 9. doi: 10.1056/NEJMoa2104882. Online ahead of print. PMID: 33835768
7. Scully M, Singh D, Lown R, Poles A. Solomon T, Levi M, Goldblatt D, Kotoucek P, Thomas W, Lester W. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. published on April 16, 2021, at NEJM.org. DOI: 10.1056/NEJMoa2105385.

Additional BACKGROUND:

Recently, after widespread vaccination with the AstraZeneca vaccine in Europe and Johnson & Johnson's Ad26.COV2.S vaccine (JnJ Vaccine) in the US, there have been reports of some vaccine recipients developing unusual thrombotic events and thrombocytopenia referred to VITT. VITT is associated with development of a prothrombotic disorder that clinically resembles heparin-induced thrombocytopenia (HIT).

- On 4/13/2021, the FDA and CDC recommended a pause in the use of JnJ Vaccine after six cases of cerebral venous sinus thrombosis (CVST) in combination with low blood platelets were reported among recipients in the US, all involving women between the ages of 18 and 48 years, with onset occurring within two weeks of receiving it.
- The agencies noted that since the single-dose vaccine was authorized by the FDA for emergency use in late February, more than 6.8 million doses had been administered as of 4/12/21.
- On 4/14/2021, Advisory Committee on Immunization Practices (ACIP) reviewed the available data in order to make recommendations on how to respond to reports of CVST in some people administered JnJ Vaccine.
- At the ACIP meeting, panel members reviewed data from the six cases, and also heard about a possible seventh, as well as details of one instance involving a volunteer during clinical trials of Ad26.COV2.S – a case where Johnson & Johnson had said that "no clear cause" could be identified. In addition, ACIP panel members looked at data on similar incidents linked to AstraZeneca's COVID-19 vaccine Vaxzevria that have emerged in Europe.
- The striking clinical similarities of VITT to 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.
- Intravenous immune globulin (IVIG) and a monoclonal antibody to the Fc receptor were able to block platelet activation by these antibodies in vitro. These clinical and laboratory features are similar to rare cases of a HIT-like syndrome previously described following certain medications or infections in patients not receiving heparin.
- An Emergency ACIP meeting will be held to discuss Janssen (Johnson & Johnson) COVID-19 vaccine on April 23, 2021, 11:00 a.m. to 5:00 p.m. ET.

- FDA-agreed Warning and Precaution Regarding Thrombosis with Thrombocytopenia presented by Janssen during Emergency ACIP meeting on 4/23/2021: