Vaccine-Induced Thrombotic Thrombocytopenia (VITT)
(Version 2.0)

Version History:

Version	Date	Updates
Version 1.0	April 22, 2021	New Document
Version 2.0	May 2, 2021	• Added statement in definition of unlikely case. • More clarification on predisposing factors. • Added "Contraindications or caution to receiving AstraZeneca vaccination" section. • Added more statements in "Management of the confirmed/probable case" section. • Added "Frequently asked questions" section

Abbreviations:

VITT: Vaccine-Induced Thrombotic Thrombocytopenia
HITT: Heparin-Induced Thrombotic Thrombocytopenia
DOACs: Direct Oral Anticoagulants
LMWH: Low-Molecular-Weight Heparin

Introduction

Vaccines are essential for managing the COVID-19 pandemic caused by SARS-CoV-2. No major safety warnings were reported in the initial trials, and the risk of serious adverse effects has remained remarkably low after vaccinating more than 400 million people worldwide. Reports have emerged of some vaccine recipients who developed unusual and very severe thrombotic syndrome and thrombocytopenia 4-28 days after receiving the first dose of the AstraZeneca vaccine. Later on, more reports have descried a similar syndrome in recipients of the Johnson & Johnson/Janssen vaccine

The First cases of thrombosis with thrombocytopenia reported in Feb/Mar 2021. This syndrome is now known as vaccine-induced thrombotic thrombocytopenia (VITT). So far, 169 possible cases of cerebral venous sinus thrombosis and 53 possible cases of splanchnic vein thrombosis have been described in the 34 million recipients of the AstraZeneca vaccine.

This syndrome is very rare, and because of the potential severity of COVID-19 infection, the European Medicines Agency (EMA) and the World Health Organization (WHO) concluded that the overall benefits of the vaccine continue to outweigh the risk of developing VITT.

When to suspect a case:

1. The patient should have both thrombosis **AND** thrombocytopenia.
2. Venous thrombosis, especially at an unusual site like cerebral vein thrombosis, splanchnic vein thrombosis, portal vein thrombosis, or hepatic vein thrombosis. DVT and PE can also be seen in addition to arterial thrombosis (least likely).
3. Thrombocytopenia with high D-dimer or low fibrinogen.
4. Type of vaccine: AstraZeneca COVID -19 Vaccine, a new report of a possible association with Johnson & Johnson/Janssen vaccine (less commonly).
5. Onset: the average on 4- 20 days after the vaccine (up to 28 days post-vaccination).
6. Usually after the first dose of the vaccine.

Definition of VITT:

- **Unlikely case:** If there is thrombocytopenia < 150X10 ^{9}/L with **norma**l D-dimer and fibrinogen and **No** thrombosis. Or, if there is thrombosis only without thrombocytopenia, elevated D-dime or low fibrinogen level.

- **Suspected case**: if there is thrombocytopenia with platelet count <150X10^{9}/l or falling platelet more than 50% from baseline **AND** high D dimer or low fibrinogen.

- **Probable case:** if there is thrombosis in a suspected case of VITT.

- **Possible case:** if there is **NO** evidence of thrombosis in a suspected case of VITT.

- **Strongly supported:** if there is a positive HITT ELISA test in a suspected case of VITT.

- **Confirmed case:** if there is a positive HITT ELISA test **AND** positive functional HITT assay (if available) in a suspected case of VITT.

Incidence:

This is an extremely rare complication of the AstraZeneca / Jansen vaccination with an incidence of 1: 1 million according to WHO, 1:250,000 according to EMA, and 1:100,000 according to MAHRA and German literature.

Case fatality:

The case fatality is very high, and it's estimated to be around 40 % according to a different study however, the case fatality is expected to improve with better awareness of the condition by the treating physician and more prompt treatment.

A possible explanation for the condition:

The exact mechanism is not very clear; however, its speculated to be very similar to autoimmune/ spontaneous HITT, where there is a production of autoimmune antibodies against PF4 in the patient who was not previously exposed to any form of heparin. The exact component in the vaccine that triggers the formation of these antibodies is not known, but it could be the adenoviral sequence, spike protein, or other components.

Predisposing factor:

The classical risk factors for thrombosis **were not found to be associated** with VITT. These risk factors include the following:

1. Previous VTE (whether on long term anticoagulation or not)
2. Personal or family history of thrombophilia (congenital or acquired)
3. Pregnancy or postpartum period
4. The use of oral contraceptive pills (OCP)
5. Thrombocytopenia
6. Autoimmune diseases

Risk factors for developing VITT from the available studies:

1. Age < 55 years
2. Female gender
3. First dose of the vaccination (AstraZeneca and possible Johnson & Johnson/Janssen vaccine)

Contraindications or caution to receiving AstraZeneca vaccination:

The contraindication to the vaccination with AstraZeneca vaccine includes individuals with a history of rare immune-mediated syndrome that causes both thrombosis and thrombocytopenia, which includes the following:

1. VITT with the first dose of the vaccine with or without antiphospholipid antibody syndrome
2. HITT (Type-2 HITT)

Signs and symptoms of VITT: ***[The patients should seek immediate medical attention if they develop any of the following symptoms within 4-28 day following the first dose of the AstraZeneca vaccination]***

1. Persistent headache lasting > 3-4 days post-vaccination
2. Focal neurological symptoms including blurred vision, seizure, and slurred speech
3. Shortness of breath
4. Abdominal pain
5. Chest pain
6. Lower limb pain. swelling, redness
7. Pallor, cold extremity
8. Skin bruising, petechial rash, or bleeding.

Investigations to be sent for the suspected case and the expected results
(thrombocytopenia **AND** low fibrinogen or high D-dimer/ thrombosis/ thrombosis and thrombocytopenia):

1. D-dimer: can be elevated, usually very high >4000 ng/ml DDu
2. Fibrinogen level: can be low
3. Coagulation profile: Normal pt/Aptt
4. CBC: Low platelet (< 150 $X10^9$/L) or dropping platelet more than 50% from the baseline
5. Blood film: should be normal apart from thrombocytopenia
6. Appropriate imaging according to the initial presentation to rule out thrombosis
7. ELISA HITT assay: will be positive with very high optical density (>2-3)
8. Functional HITT assay (if available): will be positive

Management of the confirmed/probable case:

1. Send HITT ELISA assay
2. if HITT ELISA assay was positive, send functional HITT assay (if available) which includes serotonin release assay (SRA) or Heparin induces platelet activation (HIPA).
3. The patient should be immediately started on treatment before the result of the ELISA test or functional assays are available.
4. Avoid all forms of heparin.
5. Avoid platelet transfusion (unless there is life-threatening bleeding and only after giving IVIG).

6. Start non-heparin anticoagulation: DOACS/ fondaparinux, Argatroban, bivalirudin and danaparoid once platelet > 30 $X10^9$/L and fibrinogen > 1.5 g/L.
7. Give IVIG 1 gm/kg once daily for 2 days.
8. Consider steroid therapy if platelet count was below 50 $X10^9$/L.
9. Consider plasmapheresis if the platelet count was persistently low (< $30x10^9$/L) despite treatment with IVIG and steroid.
10. Fibrinogen replacement if the patient is bleeding or fibrinogen level id < 1.5g/l and the patient is on anticoagulation.
11. Avoid thrombopoietin receptor agonist.
12. Avoid aspirin for treatment or prophylaxis of VITT as it can increase the risk of bleeding without obvious benefit.
13. Avoid warfarin till platelets are > 150 X109/L, and the fibrinogen level is normal
14. Duration of anticoagulation is 3-6 months according to the site of thrombosis and till normalization of platelet count and till the HITT ELISA assay and functional assay are negative.

Management of suspected cases with thrombosis but NO thrombocytopenia after AstraZeneca vaccine:

1. Start immediately on therapeutic dose non-heparin anticoagulation.
2. Frequent monitoring of CBC, fibrinogen, and D-dimer.
3. If platelets count start to drop, manage as a probable case (start IVIG and consider steroid) after sending the appropriate investigations, including ELISA test for HITT and/or functional assay for HITT.

Management of possible case (thrombocytopenia and elevated D-dimer or low fibrinogen level) without thrombosis:

1. Admit to the hospital for monitoring.
2. Frequent monitoring of CBC, D-dimer, and fibrinogen.
3. Send HITT assay if falling platelet.
4. IVIG can be given in case of severe bleeding and profound thrombocytopenia.
5. Extra vigilance for the development of new thrombosis.
6. Start prophylactic dose with non-heparin anticoagulation.
7. Continue the prophylactic anticoagulation for at least 3 months or till normalization of platelet count and D-dimer and HITT assay is negative.

Frequently asked questions:

1. **Can patients who had received the first dose of the AstraZeneca vaccine and developed probable/confirmed VITT take the second dose of the vaccine?**

   Anyone who had developed any form of thrombosis (arterial or venous) in association with thrombocytopenia after the first dose of AstraZeneca vaccination **should not** take the second dose of the AstraZeneca vaccine.

2. **Can a patient who had received the first dose of vaccine and developed isolated thrombosis without thrombocytopenia take the second dose of the AstraZeneca vaccine?**

   This is not considered to be a contraindication for the second dose of the AstraZeneca vaccine. Anyone who had developed thrombosis only without thrombocytopenia with the first dose of AstraZeneca vaccine **can take** the second dose of the vaccine.

3. **Can a patient who had received the first dose of vaccine and developed isolated thrombocytopenia without thrombosis take the second dose of the AstraZeneca vaccine?**

   Anyone who had developed thrombocytopenia only without thrombosis with the first dose of AstraZeneca vaccine **can take** the second dose of the vaccine.

4. **Can a patient who had received the first dose of vaccine and did not develop any complication (neither thrombosis nor thrombocytopenia) take the second dose of the AstraZeneca vaccine if they belong to a high-risk group (female, below the age of 55 years)?**

   Anyone who had d received the first dose of AstraZeneca vaccine and did not develop thrombosis nor thrombocytopenia **can take** the second dose of the vaccine since this condition is mainly described with the first dose of the vaccine.

5. **Can a patient with a past history of thrombosis only (without thrombocytopenia) unrelated to vaccination receive the first or second dose of the AstraZeneca vaccine?**

   Anyone who had a past medical history of thrombosis only without thrombocytopenia **can take** the first or second dose of the AstraZeneca vaccine.

6. **Can a patient with thrombophilia (with or without a history of prior thrombosis) receive the first or second dose of the AstraZeneca vaccine?**

   Anyone with thrombophilia (with or without thrombosis) **can take** the first or second dose of the AstraZeneca vaccine.

7. **Can aspirin reduce the risk of VITT, and is there any benefit of giving it before the AstraZeneca vaccine?**

   It is **NOT recommended** to take aspirin before vaccination unless this is already part of your patient's regular medications.

8. **Can DOACS be given in a prophylactic dose before the AstraZeneca vaccine to prevent VITT?**

   It is **NOT recommended** to take DOACS thromboprophylaxis before vaccination unless this is already part of your patient's regular medications. LMWH and fondaparinux are advised against because of the pathophysiology of the condition

Reference:

1. Cines Douglas B., Bussel James B.. (2021) SARS-CoV-2 Vaccine–Induced Immune Thrombotic Thrombocytopenia. *N Engl J Med* DOI: 10.1056/NEJMe2106315.
2. cully Marie, Singh Deepak, Lown Robert, Poles Anthony, Solomon Thomas, Levi Marcel, Goldblatt David, Kotoucek Pavel, Thomas William, Lester William. (2021) Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. *N Engl J Med* DOI: 10.1056/NEJMoa2105385.
3. Muir Kate-Lynn, Kallam Avyakta, Koepsell Scott A., Gundabolu Krishna. (2021) Thrombotic Thrombocytopenia after Ad26.COV2. S Vaccination. *N Engl J Med* DOI: 10.1056/NEJMc2105869
4. Schultz NH, Sørvoll IH, Michelsen AE. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med. DOI: 10.1056/NEJMoa2104882.
5. Greinacher A, Selleng K, Mayerle J, et al. Anti-SARS-CoV-2 spike protein and anti-platelet factor 4 antibody responses induced by COVID-19 disease and ChAdOx1 nCov-19 vaccination. April 09, 2021 (https://www.researchsquare.com/article/rs-404769/v1. opens in new tab). preprint.
6. European Medicines Agency. COVID-19 vaccine AstraZeneca: benefits still outweigh the risks despite possible link to rare blood clots with low blood platelets. March 18, 2021 (https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots. opens in new tab).
7. Warkentin TE. High-dose intravenous immunoglobulin for the treatment and prevention of heparin-induced thrombocytopenia: a review. Expert Rev Hematol 2019;12:685-698.
8. Paul-Ehrlich-Institut (PEI). Federal Institute for Vaccines and Biomedicine. Sus-pen-sion vac-ci-na-tion AstraZeneca [Internet]. Langen, Hesse (Germany): Paul-Ehrlich-Institut; 2021 Mar 16 [cited 2021 Mar 29]. Available from: https://www.pei.de/EN/service/faq/coronavirus/faq-coronavirus-node.html?cms_tabcounter=3.

9. Pai M, Grill A, Maltsev A, Miller KJ, Razak F, Schull M, et al. Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT) following AstraZeneca COVID-19 vaccination. Version 1.0. Ontario COVID-19 Science Advisory Table. 2021 Mar 26. doi: https://doi.org/10.47326/ocsat.2021.02.17.1.0.
10. NACI rapid response: Recommended use of AstraZeneca COVID-19 vaccine in younger adults
11. https://b-s-h.org.uk/media/19530/guidance-version-13-on-mngmt-of-thrombosis-with-thrombocytopenia-occurring-after-c-19-vaccine_20210407.pdf
12. https://covid19-sciencetable.ca/sciencebrief/vaccine-induced-prothrombotic-immune-thrombocytopenia-vipit-following-astrazeneca-covid-19-vaccination/
13. https://www.who.int/news/item/07-04-2021-interim-statement-of-the-covid-19-subcommittee-of-the-who-global-advisory-committee-on-vaccine-safety
14. https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood
15. Interim Guidelines: Diagnosis and Management of Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT) following AstraZeneca COVID-19 Vaccinations12April 2021
16. https://www.health.gov.au/news/atagi-statement-on-astrazeneca-vaccine-in-response-to-new-vaccine-safety-concerns
17. https://covid19-sciencetable.ca/sciencebrief/vaccine-induced-prothrombotic-immune-thrombocytopenia-vipit-following-astrazeneca-covid-19-vaccination/
18. Guidance produced from the Expert Haematology Panel (EHP) focussed on syndrome of Thrombosis and Thrombocytopenia occurring after coronavirus Vaccination Guidance produced from the Expert Haematology Panel (EHP) focussed on syndrome of Thrombosis and Thrombocytopenia occurring after coronavirus Vaccination | British Society for Haematology (b-s-h.org.uk).

2 May 2021

Version 2.0

Flow diagram for Vaccine-Induced Thrombotic Thrombocytopenia (VITT)

Patient present **with severe persistent organ-specific** symptoms suggestive of thrombosis **on day 4-28 post 1st dose** of the AstraZeneca vaccine

To do basic VITT investigations

- CBC
- D-dimer level
- Fibrinogen level

"ALL" results are NORMAL

- **Normal** platelet count
- **Normal** D-dimer
- **Normal** fibrinogen level

To do appropriate imaging

Negative for thrombosis

Discharge home

Positive for thrombosis

- To start therapeutic anticoagulation with **non-heparin** agent.
- Frequent monitoring of CBC, D-dimer and fibrinogen level
  - ❖ if platelets count falls **AND** D-dimer increased or fibrinogen become low, manage as confirmed/probable VITT case

ABNORMAL result

- Platelets count < 150 $X10^9$/L **OR** a drop of >50% from baseline

AND

- Elevated D-dimer > 4000 **OR** Low fibrinogen level

To do appropriate imaging

Negative for thrombosis

- Send ELISA test for HITT.
- Consider thrombo-prophylaxis with **non-heparin** anticoagulant for 3 months or till platelet recovery.
- Consider IVIG if severe thrombocytopenia and bleeding.

Positive for thrombosis (Confirmed VITT

- Send ELISA test for HITT to confirm the diagnosis.
- Consult hematology.
- Start therapeutic dose of **non-heparin anticoagulant** for 3-6 months.
- Avoid platelets transfusion
- Consider IVIG
- Consider steroid/ plasmapheresis

Last Update: 2 May 2021 (Clinical protocols are suspect to change, always check the updated version) **Kuwait Adult COVID-19 Task Force Tea**