REVIEW ARTICLE

Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) Following Vaccination Against COVID-19: An Overview

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Abstract

Considering the global context, vaccine-induced immune thrombotic thrombocytopenia (VITT) is an extremely rare (likely <1 in 100,000) yet a serious condition that has been reported following certain vaccinations against COVID-19. The risk of life-threatening thrombosis from COVID-19 itself exceeds the risk of VITT from vaccination by over 100-fold. It appears to be associated more with AstraZeneca/Johnson and Johnson adenoviral vaccines than Moderna/Pfizer mRNA vaccines applied to combat the pandemic. The syndrome likely begins typically between 5 to 30 days post-vaccination. VITT shares some similarities with heparin induced thrombocytopenia (HIT) in the pathogenesis. Venous thrombosis is more commonly found. Thrombocytopenia must be present to fulfil the diagnostic criteria of VITT. There is usually positive platelet factor 4 antibody (PF4 antibody) testing and raised level of D-Dimer. Investigations are done according to the site of involvement as well as to exclude the differentials. Treatment should not be delayed if VITT is suspected. This condition warrants appropriate management soon after the diagnosis is made. Non-heparin anticoagulants and intravenous immunoglobulin (IVIg) are the mainstay of treatment. Timely taken measures bear good outcome. There is no role of doing investigation related to VITT prior to an event. Prophylaxis is not advised to avoid such occurrences. Proper monitoring is required for good prognosis in the hospitalized patients. As the benefits of vaccination against COVID-19 far outweigh the chance of developing VITT, continuing the vaccination programme running worldwide is highly recommended to limit this pandemic situation.

Keywords: VITT, Thrombosis with thrombocytopenia, Vaccination against COVID-19, Platelet Factor 4 antibody (PF4 Antibody), Cerebral Venous Sinus Thrombosis (CVST)

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Introduction:

Vaccination is considered the most promising approach for containing the coronavirus disease 2019 (COVID-19) pandemic. Available vaccines are safe, effective and with minimal adverse effects. Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a novel entity that emerged in March 2021 following reports of unusual thrombosis after ChAdOx1 nCoV-19, (AstraZeneca) vaccination.[1] Following recognition of this syndrome, multiple consensus guidelines have been released for risk stratification of the patients presenting with possible post-vaccination symptoms. All guidelines rapidly identify VITT in patients with the complete triad of thrombocytopenia, thrombosis and elevated D-dimer after this adenovirus vector-based vaccination against COVID-19. Recently, VITT is recognized as a rare but serious condition that has raised public alarm with concerns regarding the development of thrombotic events which appear similar to heparin-induced thrombocytopenia (HIT), both clinically and pathologically.[2] The COVID-19 pandemic has resulted in significant morbidity and mortality worldwide.[3,4] Clinically, critically ill COVID-19 patients develop coagulation abnormalities, leading to significant thrombosis and death.[5-8] Recent studies indicate that platelet activation by immunoglobulin G-immune complexes can activate platelets in critically ill COVID-19 patients via platelet FcγRIIa.[9,10] Whereas in VITT, thrombosis and thrombocytopenia occur 5 to 28 days after

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administration of the vaccine. These include rare thrombotic events such as cerebral sinus vein and splanchnic vein thrombosis.[11,12] Although data on VITT is limited, the devastating effects of COVID-19 have been found more serious than the detrimental effect of VITT.[2]

This clinical review focuses on the epidemiology, pathogenesis, clinical features, evaluation, investigations, management and prognosis of VITT.

Methods:

This review article is based on the evidences obtained from multiple sources such as PubMed, Science Direct, UpToDate, Wiley Online Library, MEDLINE, Cochrane databases, Google Scholar using the terms VITT, Vaccination against COVID-19, Thrombosis with thrombocytopenia, HIT, CVST, SARS-CoV-2 infection, PF4 antibody. However, searching articles focusing on the so far details of VITT following vaccination against COVID-19 was supported by the literatures, guidelines/consensus related to this topic available from January 2021 to December 2021.

Pathophysiology:

VITT is caused by immunoglobulin G (IgG) antibodies which recognize platelet factor 4 (PF4, also called CXCL4) bound to platelets and activate them which result in marked stimulation of the coagulation system and clinically significant thromboembolic consequences.

Characteristics of VITT antibodies-[11-13]

- IgG class.
- Recognize PF4 bound to platelets and detectable in PF4/polyanion and PF4 enzyme-linked immunosorbent assay (ELISA).
- Cause platelet activation which is not heparin dependent.

VITT antibodies bind to platelets via an eight amino acid region of PF4 on the platelet surface, located within the heparin binding site.[13] VITT antibody binding is blocked by heparin and VITT antibody binding to platelets is stronger than that of HIT. A series of 35 individuals with serologically confirmed VITT had repeated functional assay results over an 11-week period found that the assay became negative in 23 (66%) and 5 individuals also subsequently received their 2nd dose of vaccine while continuing anticoagulation for VITT without any further complication.[14] These data support the safety of giving an mRNA vaccine if needed as a second dose or booster dose.

Mechanisms/triggers of antibody formation- Preliminary theories include the possibility that components of the vaccine bind to PF4 and generate a neoantigen.[11] PF4 is a positively-charged tetrameric protein that repels each other, but in the presence of negatively charged molecule, PF4 may form higher order structures that act as neoantigens.[15,16] DNA and RNA also have polyanionic properties and may create a neoantigen when bound to PF4.[17,18]

The SARS-CoV-2 spike protein antigens in the vaccine do not seem to be a source of molecular mimicry. There is no antibody cross-reactivity with the SARS-CoV-2 spike protein.[19]

Mechanisms of thrombosis- Anti-PF4 antibodies cause "pancellular" activation, that means, besides activating platelets and coagulation reactions, the antibodies activate monocytes, neutrophils and endothelial cells. Activation of these other cell types further contributes to high thrombosis risk. Thrombosis in VITT can occur in typical sites of venous thromboembolism such as pulmonary embolism (PE) or deep vein thrombosis (DVT) in the leg; however, a distinctive feature of the syndrome is thrombosis in unusual sites involving multiple large and small vessels including the splanchnic veins, adrenal veins (risk for adrenal failure), cerebral and ophthalmic veins.[20,21] Arterial thrombosis including ischemic stroke (often, middle cerebral artery) and peripheral arterial occlusion can occur in same individual with venous thrombosis.

Similarity to HIT- VITT most strongly resembles spontaneous HIT, triggered by an adenoviral vectored COVID-19 vaccine. The key feature that distinguishes VITT from other thrombocytopenic disorders is that anti-platelet antibodies in the non-VITT/non-HIT disorders are unable to activate platelets to cause thrombosis.

Epidemiology:

Implicated vaccines in causing VITT-

- ChAdOx1 nCoV-19 (AstraZeneca, University of Oxford, and Serum Institute of India)
- Ad26.COV2.S (Janssen; Johnson & Johnson)

Confirmed case of VITT has not been reported after the mRNA-based vaccines.

Incidence and risk factors- The incidence of VITT appears to be exceedingly rare. Most reports have described a small number of cases among tens of millions of vaccinated individuals.[11,22] The highest incidence was reported from Norway, suggesting an incidence of 1 in 26,000, with ChAdOx1 nCoV-19.[12] An initial report from the Centers for Disease Control (CDC) in the United States identified an incidence of 1 in 533,333, with Ad26.COV2.S.[23]

Risk factors for VITT are unknown.

Sex – Initial reports suggested a female predominance.[11,12] However, in a series of 220 definite and probable cases from the United Kingdom, there was no sex preponderance.[24]

Age – Initial reports suggested that individuals with VITT were younger (<55 or 60 years). However, cases in individuals >60 years are emerging.[24,25]

Clinical Features:

Overview of clinical presentation- VITT likely begins in a narrow window 5 to 10 days after vaccination, but most cases are identified leading typically between 5 to 30 days following vaccination. It may begin as a flu-like syndrome which suggests an enhanced inflammatory response.[11,26,27]

In a series of 220 patients with definite or probable VITT, the following features were noted:[24]

- Age – Median 48 years, range 18 to 79 years.
- Sex – 55 percent female, 45 percent male.
- Time since vaccination – Median 14 days; range 5 to 48 days.
- Sites of thrombosis – Cerebral veins (including intracranial haemorrhage), deep veins of the leg, pulmonary arteries, and splanchnic vessels. More than 50% cases had thrombosis in multiple sites.
- Platelet count – Median 47,000/microL, range 6000 to 344,000/microL.
- Fibrinogen – Median 2.2 g/L (220 mg/dL), range 0.3 to 4.4 mg/dL.
- D-dimer – Median 24,000 fibrin equivalent units, range 5000 to 80,000 FEU.

Thrombocytopenia- It may be suspected based on the presence of petechiae or mucosal bleeding, or as an incidental finding. The typical platelet count range of patients with definite VITT is between 10,000 and 100,000/microL, with a median platelet count of 20,000 to 25,000/microL.[12]

Thrombosis- It has been the presenting feature in most of the initial reported cases of VITT.[11,12,22,28] Both venous and arterial thromboses have been described. Cerebral venous sinus thrombosis and dural sinus thrombosis, which may present as intracerebral haemorrhage, appears to be the most common site of thrombosis in some series.[22,29,30] An individual with strongly suspected VITT requires immediate treatment and continued evaluation, even if initial imaging fails to document thrombosis.[31]

Table I

Symptoms of thrombosis and their diagnostic evaluation in VITT

Site of thrombosis	Typical presenting symptoms	Diagnostic imaging
Cerebral veins and dural venous sinuses	• New, persistent headache • Vomiting • Visual impairment • Focal neurologic deficits or seizures • Encephalopathy	• Magnetic resonance venography • Conventional angiography • MRI of Brain (CT is often normal here)
Splanchnic veins (splenic, hepatic, portal, mesenteric)	• Severe abdominal pain • Back pain	• CT with contrast • Doppler ultrasound
DVT of the leg	• Leg pain • Leg swelling/oedema	• Compression USG with Doppler
Pulmonary embolism	• Acute chest pain • Dyspnoea	• CT pulmonary angiography • Ventilation/perfusion scan
Ophthalmic vein thrombosis	• Orbital pain • Diplopia or vision loss	• MRI • MRV
Ischemic stroke	• Sudden onset focal neurologic deficit • Encephalopathy	• Brain MRI and/or head CT • CT / magnetic resonance angiography of head and neck
Acute limb ischemia	• Pain • Pulseless pallor • Neurologic deficits	• CT angiography • Catheter-based angiography

MRI: magnetic resonance imaging; CT: computed tomography; MRV: Magnetic resonance venography; CBC: complete blood count; PT: prothrombin time; aPTT: activated partial thromboplastin time.

Coagulation abnormalities- Disseminated intravascular coagulation (DIC).

Bleeding- Severity varies in individuals in the form of minor bleeding to severe haemorrhage.

Evaluation:

When to suspect- The mnemonic VITT can be used to codify these key features:

- **V**accine given
- **I**nterval (5 to 30 days post-vaccine)
- **T**hrombosis (usually the event that draws attention to VITT)
- **T**hrombocytopenia

Due to the rarity of the syndrome, routine testing of platelet counts following COVID-19 vaccination is not recommended. D-dimer testing should not be considered as a screening test because of low specificity. In preliminary reports of VITT, testing for SARS-CoV-2 infection was performed and was uniformly found to be negative.[11,12,22] Testing for infection is reasonable. However, treatment of VITT should not be delayed for the investigation results.

Urgent medical evaluation for is indicated if any of the following develop 4 to 42 days after vaccination:[32]

- Severe headache
- Visual changes
- Abdominal pain
- Nausea and vomiting
- Back pain
- Shortness of breath
- Leg pain or swelling
- Petechiae, easy bruising, or bleeding

Laboratory testing- Diagnosis of VITT requires consideration of clinical and laboratory features.

- CBC- A complete blood count is needed to document thrombocytopenia and platelet counts over time should be compared too. No specific abnormalities are seen on the peripheral blood film.

The presence of severe thrombocytopenia (<30,000/uL) and/or intracranial haemorrhage was associated with the highest mortality.[32]

- Coagulation testing- 1. PT and aPTT 2. Fibrinogen and D-dimer
- PF4 antibody testing – Positive testing is confirmatory. However, a positive anti-PF4 antibody test alone (without thrombocytopenia or thrombosis) is not sufficient to make the diagnosis.

ELISA – It is the recommended test in VITT.[33]

SRA – Functional assays like serotonin release assay (SRA) are often positive here.

Rapid HIT assays – Mostly negative in VITT and should not be used.[22,27,33,34]

VITT is unlikely in people with:[29]

- No thrombocytopenia
- Thrombocytopenia without thrombosis, but normal level of D-dimer and fibrinogen, or

  Thrombosis without thrombocytopenia, with raised D-dimer and normal fibrinogen.

  However, if a high clinical suspicion of VITT remains, following is to be considered:
- Repeating the complete blood count after 2 to 3 days or if there is any worsening of symptom or discussing the need for further investigations with a clinical haematologist.

Imaging to diagnose thrombosis- It depends on the site of involvement.

Differential diagnosis:

In a series of nearly 300 individuals evaluated for possible VITT, alternative diagnoses included metastatic cancer and chronic DIC from an aortic aneurysm.[24] However, other causes of thrombocytopenia and/or thrombosis should be considered as well, especially when PF4 antibody testing negative.

- COVID-19- The disease itself carries a high risk of thrombosis and coagulation abnormalities in hospitalized individuals, including severe thrombocytopenia. Unlike VITT, it usually shows a negative PF4 assay result.
- Other causes of thrombocytopenia with thrombosis- Heparin Induced Thrombocytopenia (HIT), Disseminated Intravascular Coagulation (DIC), Thrombotic Thrombocytopenia Purpura (TTP).

Management:

VITT is a potentially life-threatening disorder. Management recommendations including those listed below are rapidly evolving.

Hospitalization- Patients of VITT need to be hospitalized due to the potentially serious nature of thrombotic complications and severity of the clinical condition.

Anticoagulation- Anticoagulants in order of preference are:

- A direct oral anticoagulant (DOAC) such as a factor Xa inhibitor (apixaban, edoxaban, or rivaroxaban).
- Fondaparinux or Danaparoid.
- A parenteral direct thrombin inhibitor (argatroban or bivalirudin).

For VITT with very low platelet count (under 30 x10^9 / litre), one of the following alternative anticoagulation strategies that may reduce the risk of bleeding:[29]

A critical illness dose of argatroban, or a therapeutic dose of argatroban along with platelet transfusion.

Dose – Standard full-therapeutic dosing is appropriate, provided there is no active bleeding, with appropriate adjustments for body weight and renal function.

Duration – A reasonable approach for-

- VITT with thrombosis, anticoagulation for three months after normalization of the platelet count, as long as no further thrombosis occurs.
- VITT without thrombosis, anticoagulation until platelet count recovery and perhaps longer if tolerated (four to six weeks after platelet count recovery).

IVIG- High-dose intravenous immunoglobulin (IVIG) is recommended along with anticoagulation to interrupt VITT antibody-induced platelet activation. Unless there is a contraindication, IVIG should be used in all individuals with VITT.

A typical dose is 1 gm/kg intravenously once per day for 2 to 3 days initially, based on actual body weight. After that, if there is inadequate response to immediate treatment, a second dose of intravenous immunoglobulin (dose may be split over 2 days) is required.[29]

Following IVIG administration, thrombocytopenia can recur (within a few days after IVIG is completed). Hence, it is important to continue to monitor the platelet count during hospitalization and following discharge from the hospital.

Corticosteroids- Adding corticosteroids can be considered if IVIg (which is the 1st line treatment for VITT whether probable or confirmed) treatment is insufficient. Short courses of high-dose steroids, such as methylprednisolone 1 g for 3 days or dexamethasone 20 to 40 mg for 4 days, have been used in more severe cases.[29]

Plasma exchange- Therapeutic plasma exchange (TPE) and immunosuppression have been proposed for refractory disease or disease with concerning features such as cerebral vein thrombosis (CVT) or multiple thromboses with evidence of excessive platelet activation (platelet count <30,000/microL).[24,35,36] TPE was performed daily for 5 to 7 days. Plasma exchange with fresh frozen plasma (1 volume exchange a day) can also be considered as an alternative to a second dose of IVIg.[29]

Rituximab is recommended for refractory VITT that has not responded to a second dose of intravenous immunoglobulin or plasma exchange. Rituximab is not safe for pregnant women. The dosage of rituximab in VITT is 4 infusions of 375 mg/m^2 of body surface area (once a week for 4 weeks).

Minimizing platelet transfusions- Platelet transfusions are generally reserved for critical or life-threatening bleeding or if there is any need for emergency surgery. Haematology and/or transfusion medicine input must be ensured in such cases.

Fibrinogen concentrate or cryoprecipitate- It can be additionally considered in patients of VITT to maintain a level of fibrinogen of at least 1.5 g/litre.

Monitoring:

Clinical monitoring for signs of thrombosis is critical.

- For hospitalized patients, platelet count should be checked daily.
- After discharge from hospital, patient is better to be kept under the care of the haematology department to assess symptoms and monitor as follows:[29]

- Measuring D-dimer, fibrinogen and platelet counts every 2 to 3 days for the first 2 weeks.
- Repeating ELISA for platelet factor 4 antibodies weekly for the first 4 weeks.
- After the initial periods noted above, monitoring tests are to be repeated monthly for the first 6 months and, if no relapses occur, frequency of testing is minimized to every 3 months.

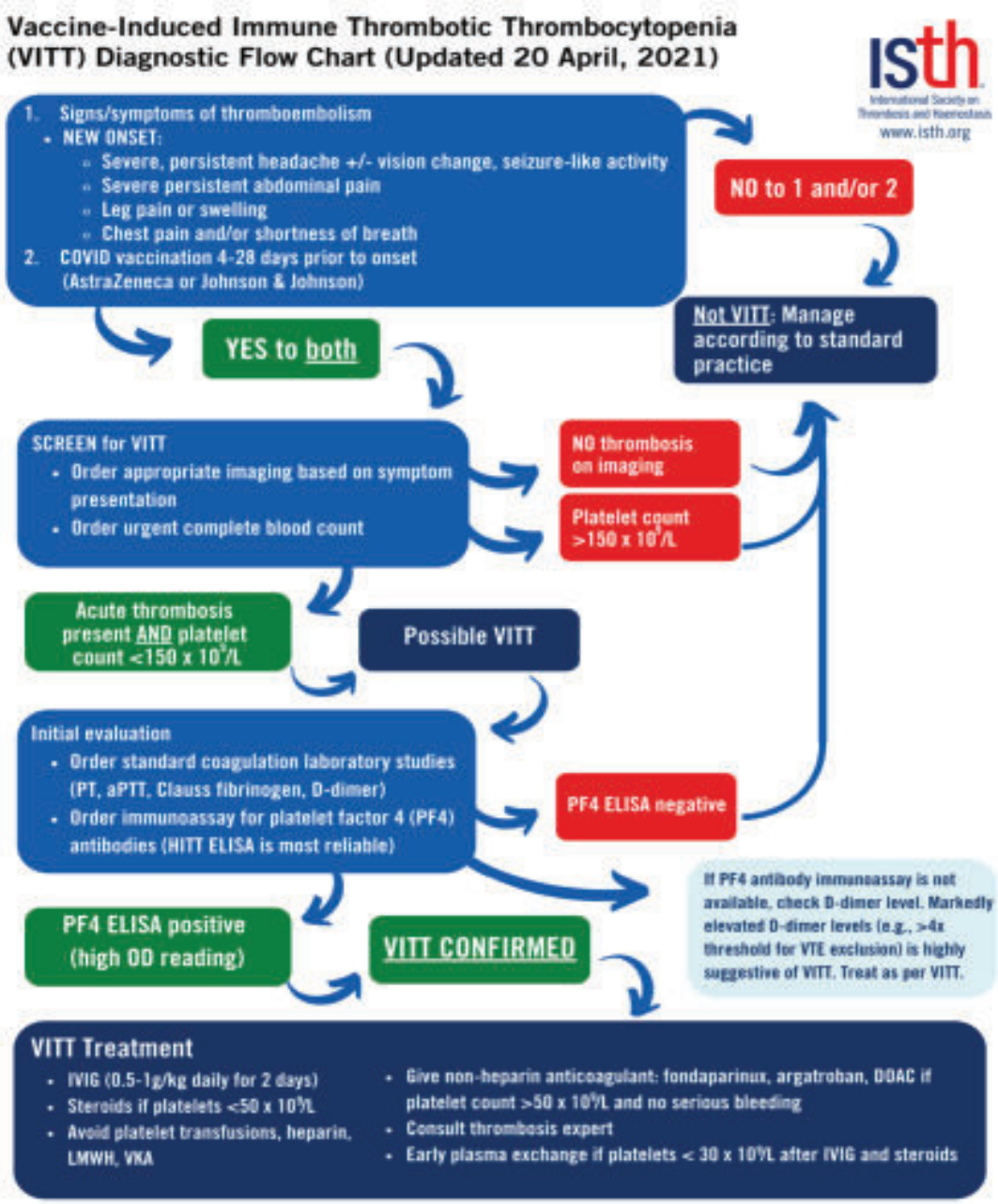

Fig.-1: *Management of VITT in a nutshell.*[37]

Points for safe discharge:

The duration of acute illness in VITT is unknown. Discharge can be allowed when-

- The platelet count is more than >50,000/microL and improving for at least 2-3 days.
- The patient is on stable anticoagulation with no new or progressive thrombosis.
- There is no bleeding for at least 2-3 days.
- Appropriate follow up has been assured.

Prognosis:

It is challenging to establish and may be improving with earlier recognition of the syndrome. In a series of 220 individuals with definite or probable VITT, the mortality rate was 22%.[24]

Risk factors for death include cerebral venous thrombosis (CVT) and more pronounced haemostatic abnormalities (more severe thrombocytopenia, higher D-dimer, and lower fibrinogen). Signs of poor prognosis include any of the following:[29]

- Having CVST

- Having thrombosis at multiple sites
- Developing secondary bleeding
- Having very low platelet levels (less than 30,000/ microL).

An intensive treatment strategy of plasma exchange and high-dose steroids is considered here.

Common questions in general:

Prophylactic role of aspirin- There is no role for aspirin in the prevention of VITT.

Decisions about vaccines-

- Thrombotic risk of COVID-19 vaccination versus COVID-19 illness – The importance of vaccination should be emphasized. The benefits of vaccination greatly outweigh the potential risks of rare vaccine side effects such as VITT.[38,39]
- Choice of vaccine – The primary criterion for selection of a vaccine is availability.
- Individuals with thrombotic risk factors, prior thrombosis, or prior HIT- Studies have not yet demonstrated likelihood of VITT in such cases. But it is suggested that individuals with a history of HIT or thrombosis should avoid adenoviral COVID-19 vaccines and receive a different type of COVID-19 vaccine.
- Evaluation of asymptomatic individuals before or after vaccination – Any screening laboratory or imaging evaluations in asymptomatic individuals is not recommended before or after vaccination without an event of VITT.[40]

Conclusion:

VITT following vaccination against COVID-19 appears to be associated more with the adenoviral vaccines. But the proven benefits of vaccination greatly outweigh the risk of developing this extremely rare side effect. Hence, vaccination should not be compromised to combat COVID-19. Any screening test or prophylaxis for VITT is not recommended prior to vaccination. However, the condition requires early recognition and measures must be taken without any delay whenever VITT is suspected.

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