

GUIDELINE

Recommendations for the diagnosis and management of vaccine-induced immune thrombotic thrombocytopenia

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There have recently been safety concerns regarding an increased risk of vaccine-induced immune thrombotic thrombocytopenia (VITT) following administration of SARS-CoV-2 adenoviral vector vaccines. The Southern African Society of Thrombosis and Haemostasis reviewed the emerging literature on this idiosyncratic complication. A draft document was produced and revised by consensus agreement by a panel of professionals from various specialties. The recommendations were adjudicated by independent international experts to avoid local bias. We present concise, practical guidelines for the clinical management of VITT.

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Several vaccines against SARS-CoV-2 have been licensed and are currently being used in the global pandemic. These include messenger RNA-based vaccines (viz, Pfizer-BioNTech and Moderna) and recombinant adenoviral vector vaccines (viz, AstraZeneca and Johnson & Johnson/Janssen). There have recently been safety concerns regarding an increased risk of vaccine-induced immune thrombotic thrombocytopenia (VITT) following administration of the two adenoviral vector vaccines.^[1]

The clinical picture of VITT, also referred to as vaccine-induced prothrombotic immune thrombocytopenia (VIPIT), is that of a moderate to severe thrombocytopenia with thrombotic complications, particularly at unusual sites, including cerebral sinus vein thrombosis and splanchnic vein thrombosis.^[2] The onset is usually 4 - 16 days after vaccination. The proposed mechanism, which forms the basis for the following recommendations, is similar to that of heparin-induced thrombocytopenia with thrombosis (HITT). The immune response is triggered by the culprit vaccine and not heparin (heparin independent).^[2,3]

This is a newly described syndrome. It should be differentiated from thrombosis associated with established venous risk factors.

Recommendations in this guideline are extrapolated from the management of HITT, and reflect current best practice (Table 1).^[1,4,5]

The guidance statements provided here will be updated on availability of new evidence.

Clinical presentation of VITT

The following side-effects that persist or recur >4 days after vaccination should raise clinical suspicion of VITT:

- new and unusual neurological symptoms, such as severe and/or persistent headache, blurred vision, seizures and/or focal neurological symptoms
- symptoms or signs of thrombosis, such as persistent severe abdominal pain, shortness of breath, chest pain, leg pain or swelling.

Diagnosis of VITT

The initial recommended investigation is a full blood count with determination of platelet count and a peripheral blood smear for review of pseudo-thrombocytopenia and other causes of thrombocytopenia.

A diagnosis of VITT should only be considered in a patient with a platelet count <150 × 10⁹/L, or a decrease in the platelet count of 50%, in the presence of symptoms 4 - 16 days after COVID-19 vaccination with adenoviral vector vaccines, namely AstraZeneca and Johnson & Johnson/Janssen.

The '4 Ts' score of HITT has been adapted to establish the pretest probability (Table 2).^[5,6] An intermediate or high 4 Ts score is indicative of the diagnosis of VITT. If the 4 Ts score is low, treatment for VITT is not indicated, as the associated risk of VITT is low. Any change in clinical or laboratory findings warrants re-evaluation.

Further suggested laboratory investigations include D-dimers and fibrinogen. Raised D-dimers (>0.25 mg/L) and low fibrinogen (<2 g/L) are suggestive of the diagnosis of VITT.^[4] Diagnostic assays can be performed if immediately available in patients with an intermediate or high 4 Ts score.

These assays include antibodies to platelet factor 4 (PF4), as detected by commercial PF4/heparin enzyme-linked immunoassays or functional heparin-induced platelet activation assays. A presumptive diagnosis of VITT should not be delayed while awaiting results of HITT antibody testing. Furthermore, at this time it is unknown whether a positive result correlates with thrombotic risk.

Radiology imaging may be appropriate depending on the site of the suspected thrombosis: cerebral magnetic resonance venography,

computed tomography angiography of the chest/abdomen, and compression ultrasound of the limbs.

Other important causes of thrombocytopenia that should be considered include malaria, HIV or immune thrombocytopenia.

In patients with thrombocytopenia and thrombosis, the following differential diagnoses should be considered:

- disseminated intravascular coagulation
- sepsis
- malignancy
- thrombotic microangiopathy
- systemic lupus erythematosus and/or antiphospholipid syndrome
- paroxysmal nocturnal haemoglobinuria
- sickle cell anaemia.

Management principles of VITT

The treatment principles are similar to severe HITT.^[5]

Treatment of suspected or confirmed VITT requires urgent consultation with a clinical haematologist or facility with expertise in thrombosis.

- Platelet transfusions must be avoided.
- Anticoagulation with heparins (including heparin flushes) should be avoided.
- Warfarin should be avoided in the acute period.
- Treatment with high-dose intravenous immunoglobulin (1 g/kg daily for 2 days) has been recommended.^[7] However, its limited availability together with limited data preclude its routine recommended use.
- The platelet count should be closely monitored. Platelet recovery is defined as a platelet count $>150 \times 10^9/L$.
- In the setting of vaccines requiring a second dose, the culprit vaccine should not be re-administered.^[4]

First-line anticoagulants according to the clinical picture include direct oral anticoagulants (e.g. rivaroxaban, apixaban, dabigatran) or fondaparinux. Most experience in HITT is with rivaroxaban.^[8]

Monitoring of peak anti-Xa activity is advised. Samples must be drawn 3 hours after the last anticoagulant dose and repeated until a therapeutic anti-Xa level is achieved. Once therapeutic levels are achieved, continued regular monitoring and dose adjustments are recommended.

- Recommended rivaroxaban dose: 15 mg twice per day for 3 weeks followed by 20 mg once per day (reported target anti-Xa activity 189 - 419 ng/mL)
- Recommended fondaparinux dose: <50 kg: 5 mg sc once per day; 50 - 100 kg: 7.5 mg sc once per day; >100 kg: 10 mg sc once per day (reported target anti-Xa activity 1.20 - 1.26 mg/L).

Initial and periodic assessment of renal function is recommended. The dose of these anticoagulants should be adjusted in individuals with renal dysfunction (creatinine clearance 30 - 50 mL/min).

Anticoagulation should be continued for at least 3 months.^[9]

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Table 1. Key recommendations

- VITT is an extremely rare but potentially fatal complication of vaccination with adenoviral vector vaccines
- It is important to consider this complication, because management differs from other thrombotic events and standard treatment may worsen outcome
- Thrombosis with thrombocytopenia 4 - 16 days post vaccination should prompt clinicians to consider the entity
- Thrombocytopenia post vaccination may be due to many other reasons in the absence of thrombosis, such as malaria, HIV or immune thrombocytopenia
- Patients with VITT should not be given heparin, platelet transfusions or warfarin (acutely)

VITT = vaccine-induced immune thrombotic thrombocytopenia.

Table 2. 4 Ts score evaluating the pretest probability of VITT

Variable	Score
Thrombocytopenia	
Platelet count fall $>50\%$	2
Platelet count fall 30 - 50%	1
Platelet count fall $<30\%$	0
Timing of onset	
Within 4 - 16 days of vaccination	2
>2 weeks of vaccination or unclear exposure	1
No history of vaccination	0
Thrombosis	
New thrombosis post vaccination	2
Progressive or recurrent thrombosis	1
No thrombosis	0
Other causes of thrombocytopenia	
None	2
Possible	1
Definite	0
Total score	
0 - 3 indicates low probability	
4 - 5 indicates intermediate probability	
6 - 8 indicates high probability	

VITT = vaccine-induced immune thrombotic thrombocytopenia.

Conflicts of interest. BFJ has received honoraria from Bayer HealthCare, Boehringer, Aspen, Daichi-Sankyo, Portola and Sanofi-Aventis. ES has received honoraria from Bayer HealthCare, Roche Diagnostics and Sanofi-Aventis. MM has received honoraria from Sanofi-Aventis, Pfizer, Astellas, Aspen and MSD, and reports that he has served as a scientific advisory board member for Acino. SL has received honoraria from Reckitt Benckiser, KAT Medical, STAGO and Roche. SH has received honoraria from Sanofi-Aventis, Bayer HealthCare, Daichi-Sankyo, Pfizer, Portola and Boehringer. HRB reports that he has served as a scientific advisory board member for Sanofi-Aventis, Bayer HealthCare, Bristol-Myers Squibb, Daichi-Sankyo, GlaxoSmithKline, Pfizer, Roche, Isis and Thrombogenics, and received honoraria from Sanofi-Aventis, Bayer HealthCare, Bristol-Myers Squibb, Daichi-Sankyo, GlaxoSmithKline, Pfizer, Roche, Isis and Thrombogenics. DJ has received honoraria from Boehringer and Sanofi-Aventis. PR has received honoraria from Boehringer. DvdJ has received honoraria from Sanofi-Aventis and Smith & Nephew. PFW has received honoraria from Bayer HealthCare, Boehringer, Aspen and Sanofi-Aventis. PGW has received honoraria from AstraZeneca, and reports that he has served as a scientific advisory board member for AstraZeneca and Actelion. BB, ATOA-C, PdJ, PH, ML, BL, HR, LR and MS have declared no conflicts of interest with regard to publication of this article.

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