Suspected Vaccine induced immune thrombotic thrombocytopenia (VITT)

THANZ Advisory Statement for Haematologists (check for weekly updates):

December 18, 2021

Purpose of this document:

- **Aid clinicians in recognition, diagnosis and management of suspected vaccine associated thrombosis (VITT)**

Background

A thrombocytopenic thrombotic syndrome has been described in a proportion of patients exposed to COVID-19 ChAdOx1-nCov-19 AstraZeneca vaccination. There are reports of cases with the Janssen (J and J) COVID-19 vaccine which is not currently being used in Australia or New Zealand. The thrombosis can be severe and rapidly progressive, but not in every case.

Antibodies against platelet antigens (PF4) post vaccination have been detected, with some *similarity to heparin induced thrombocytopenia (HIT)* but with a distinct profile on immuno- and functional testing. This immune thrombosis syndrome is currently being called several names: "VIPIT": vaccine induced prothrombotic immune thrombocytopenia; "VATT": vaccine associated thrombosis and thrombocytopenia; "TTS": thrombosis with thrombocytopenia syndrome and "VITT" vaccine induced immune thrombotic thrombocytopenia.

Antibodies against PF4 or PF4/polyanion complexes have been detected using ELISA methods, but not other platforms used for HIT testing. Platelet activating antibodies on functional testing are considered pathological, and requisite for *confirming* the diagnosis of VITT. Within Australia, these assays are currently centralised through Concord Hospital in NSW.

Our accepted understanding of this syndrome is rapidly evolving, and we plan to update this advisory statement regularly, accordingly.

Patients with any site of new thrombosis who have recently received vaccination against COVID (day 4-42), should be further investigated for VITT as per algorithm on Page 2.

Suspected adverse events following immunisation (AEFI) are notifiable conditions reportable to the TGA in Australia (link provided below).
https://www.tga.gov.au/reporting-suspected-side-effects-associated-covid-19-vaccine
https://www.health.gov.au/health-topics/immunisation/health-professionals/reporting-and-managing-adverse-vaccination-events

VITT is a distinct syndrome that is separate to HIT. Standard HIT diagnostic pathways are NOT appropriate for the diagnostic work-up.

Link to request form for specialised investigations: REQUEST FORM

When should I suspect VITT?

1. **Onset days 4-42 after vaccination**
2. **Thrombosis: predominant sites: cerebral venous sinus or splanchnic thrombosis. Other VTE and arterial ischaemia also reported**
3. **Thrombocytopenia* or falling platelet count (platelets can be normal on presentation but drop within 4-6 hours)**
4. **High D-Dimer (typically very high)**
5. **Some patients are refractory to standard anti-coagulation**
6. **Response to IVIG**

Although most reported cases involve presentation with cerebral venous sinus thrombosis, other sites have also been involved (splanchnic, DVT, pulmonary embolism, arterial ischaemia), so any patients presenting with symptoms of thrombosis shortly after vaccination should be considered carefully for VITT, and testing initiated in the appropriate clinical context, even though we currently anticipate most cases of common site venous thrombosis (DVT in the lower leg) *will be unrelated to VITT.* In the absence of thrombocytopenia, we advise management as per usual VTE pathway in consultation with a sub-specialist thrombosis haematologist (see list of authors at end of statement).

We suspect the timing of greatest risk is between days 4-42 based on case reports to date. Common side effects from immunization can also present with overlapping symptoms within the same timeframe.

Patients presenting with organ specific symptoms of thrombosis (eg. Persisting or severe headaches unresponsive to simple analgesia, abdominal pain or respiratory symptoms) 4-42 days after vaccination should be reviewed carefully for signs of thrombosis or bleeding. Other neurological symptoms of cerebral vein thrombosis can include visual changes, seizures, focal neurological deficits, and general symptoms of encephalopathy. All age groups and genders have been affected. In some cases, progression of thrombosis whilst on therapeutic anticoagulation occurs.

Not all thrombocytopenia post vaccine is VITT. Immune thrombocytopenia post COVID-19 vaccine is also reported and SHOULD NOT be treated in the same manner. Clinical judgement, as always, should guide management.

How do I investigate for VITT?

Clinical assessment with appropriate investigations should always be initiated based on the patient context. Do not delay the commencement of life-saving management while awaiting investigations. However, while suspicion of VITT is explored:

1. Do not administer platelet transfusions
2. Do not begin heparin-based anticoagulation (IV unfractionated heparin infusions, LMWH).

Testing for VITT in Australia/New Zealand will occur in at least two stages – A. SCREEN and B. CONFIRM.

A. SCREEN

Blood tests – FBC, D-dimers, fibrinogen levels

1. VITT is *suspected* if (1) the platelet count is <150x10^9/L or falling AND either (2) D-dimers are elevated (5x upper limit of normal; ULN) OR (3) fibrinogen is reduced. Further serum and plasma samples must be taken (at least 4x blue top citrate tubes and 4 serum clot tubes), specialist haematology consultation is obtained, and locally available radiology must be performed and reported urgently to investigate for relevant organ-specific thrombosis (e.g. CT brain +/- venogram for CSVT, abdominal CT for splanchnic vein thrombosis).
    a. If thrombosis is found, VITT is *probable*, and treatment must be urgently initiated with non-heparin anticoagulation and IVIG. Haematology may consider addition of high dose methylprednisone and/or plasma exchange in the appropriate context (e.g. signs of new/progressive thrombosis).
    b. If no thrombosis is found, VITT is *possible*, and treatment initiated with non-heparin anticoagulation. Haematology may consider the addition of IVIg in the appropriate context (e.g. rapidly falling platelet count with/without bleeding).
2. VITT is *less likely* if the platelet count is >150x10^9/L, but D-dimers are elevated or fibrinogen is reduced. Re-evaluation and repeat testing (within 24-hours or sooner if clinical deterioration) may be required in the appropriate context (e.g. ongoing symptoms of severe headaches).
3. VITT is *much less likely* if repeated platelet counts are >150x10^9/L, D-dimers are not elevated AND fibrinogen is normal. If thrombosis is subsequently found, close monitoring of these parameters may remain relevant while treatment is initiated.

If persistent or escalating symptoms or other concern about thrombosis: rescan and repeat lab tests.

VITT is a distinct syndrome that is separate to HIT. Standard HIT diagnostic pathways are NOT appropriate for the diagnostic work-up.

B. CONFIRM

Patients with *suspected* VITT either have 1.a) thrombosis (*probable*) or 1.b) no thrombosis (*possible*) and should be further investigated as follows:

1. Antigen-based “VITT” immune assay

- consult your local hemostasis haematologist re: local testing
    a. PF4/polyanion ELISA normally used for “HIT” appears to detect the VITT antibody
    b. AcuStar, STiC and Particle gel immunoassay (PaGIA) DO NOT reliably detect antibody and are NOT appropriate for use in this setting.

2. Functional antibody testing:

- Functional testing for platelet activating antibodies are triaged centrally. They should be performed in all samples of suspected VITT– consult local haemostasis haematologist.

Please fill out request form, contact local haemostasis expert and send samples to appropriate location as indicated on the request form. **REQUEST FORM**

SAMPLES REQUIRED:

For all suspected cases, please collect the following samples at diagnosis prior to treatment:

1. 4 citrate (blue top tubes)
2. 4 serum clot tubes

Diagnostic lab to aliquot double spun plasma and serum into 500uL aliquots, store at -80 degrees or -20 degrees and contact local expert for samples to be directed urgently to sites with testing.

How do I treat suspected VITT?

Most cases of suspected VITT will require the treatment before results of ELISA testing for PF4 or PF4/polyanion antibodies are available. Specialist consultation with haematology will be required.

- We recommend ***probable*** **VITT** (suspected WITH thrombosis) to be treated with non-heparin anticoagulation, similar to patients with HIT.
    - IVIg (1-2g/kg over 2 divisions) is recommended - particularly for cases with severe thrombosis, those that do not respond quickly or are at high risk from deterioration (including presentation platelets < 30 x 10^9/L, fibrinogen <1.5mg/L). Haematologists may consider addition of high dose methylprednisone and/or plasma exchange in the appropriate context (e.g. signs of new/progressive thrombosis).
    - Anticoagulant treatment options are as per local therapeutic practice for HIT: bivalirudin, argatroban, danaparoid, fondaparinux, rivaroxaban, apixaban, dabigatran, and (after initial treatment with another agent) warfarin (see next page for general guidance)
    - Avoid platelet transfusion
    - Anticoagulation duration should probably be time limited (3-6 months), with hospitalisation considered safest until there is a reduction of *in vivo* platelet activation and thrombin generation (increasing platelets, falling D-dimers, normal fibrinogen). Check for resolution of antibodies prior to cessation of anticoagulation.
    - Post-acute phase management: see below

- We recommend **possible VITT** (suspected WITHOUT thrombosis) be:
    - monitored closely with repeat FBC, D-Dimer, fibrinogen approximately every 3 days
    - Anticoagulation with a **non-heparin** anticoagulant should be considered – particularly with very high D-Dimer and positive immunoassay.
    - We currently recommend consideration of fondaparinux or oral DOAC at **prophylactic** dosing (alternatives, IV thrombin inhibitors).
    - Avoid platelet transfusion
    - Hospitalisation may be appropriate, until there is a reduction of *in vivo* platelet activation and thrombin generation (increasing platelets, falling D-dimers, normal fibrinogen).
    - IVIg may be considered if there are any signs to suggest progression of the syndrome despite anticoagulation. Prophylactic administration of IVIg is not yet recommended.
    - Anticoagulation duration should probably be time limited or until HIT ELISA and functional testing is negative.

ITP should be considered in patients with thrombocytopenia with normal D-Dimer and fibrinogen.

Patients with any site of new thrombosis who have recently received vaccination against COVID (day 4-42), should be further investigated for VITT with screening tests. Haematology will determine if confirmatory testing is required.

THANZ refers to ATAGI and TGA for vaccination recommendations

General guidance for anticoagulation choice:

This guidance is offered with the understanding that not all anticoagulants mentioned will be on inventory, particularly outside of the major metropolitan hospitals. Rather than delaying anticoagulation for want of preferred options, it is best to effectively anti-coagulate as soon as a clinical diagnosis of thrombosis has been made, using available anticoagulants.

Early effective anticoagulation is vital.

Avoidance of heparin is advised. A minority of cases have shown enhanced platelet activation in the presence of heparin, which would worsen clotting. Exclusion of this phenomenon will not be available within a clinically relevant time frame.

CVST with intracerebral haemorrhage and platelets <30 x 10^9/L:

- strongly consider immediate plasma exchange (1.5x TPV with FFP, or as per usual local practice with TTP until clinical/platelet count improvement).
- Consider IVIg administration after plasma exchange.
- Anticoagulation with short acting parenteral agents should commence as soon as possible.
- Although evidence is limited, clot retrieval/decompression has been utilised locally and internationally with variable efficacy. Early neurosurgical/ neuroradiological assessment in these cases for discussion of options may be helpful.

Severe thrombosis: CVST/splanchnic/arterial/massive PE/sub-massive PE:

In general, short acting parenteral agents are preferred in severe cases when the risk of haemorrhage is high (eg CVST) or when surgery or invasive procedures may be required (eg splanchnic vein thrombosis with ischaemic bowel). Intravenous bivalirudin (CrCL 30ml/min or above) or argatroban (CrCl < 30ml/min) are preferred agents (see local guidance infusion protocols). Danaparoid and fondaparinux have longer half-lives but can be used if short acting agents are not available. Rivaroxaban and apixaban with full initiation dosing can be used if parenteral agents are not available.

- **CVST/ Splanchnic thrombosis/arterial**: parenteral preferred over oral anticoagulation. Short acting agents bivalirudin or argatroban are definitely preferred if invasive treatment is planned or in presence of concurrent haemorrhage. Otherwise danaparoid and fondaparinux are alternatives.
- For massive PE: bivalirudin or argatroban preferred over danaparoid (in conjunction with thrombolysis)
- For sub-massive PE: bivalirudin or argatroban preferred over danaparoid or fondaparinux.
- Most DVT/PE: treatment upfront with DOACs such as rivaroxaban or apixaban according to local practice. *If dabigatran is used, we recommend a 5 day lead in with a parenteral agent.*

Change to an oral agent is appropriate after stabilisation – recommend change is made after normalisation and plateau of platelet counts in cases of severe thrombosis. DOACs or warfarin are equally acceptable in VITT.

Preferred anticoagulants*	Elimination half-life (healthy individuals)
Bivalirudin	25 minutes
Argatroban	45 minutes
Fondaparinux	17-21 hours
Danaparoid	25 hours
Apixaban	12 hours
Rivaroxaban	5-13 hours

*Please consult with your local haematologist and haematology laboratory for dosing and guidance on available monitoring, and if platelet count is ≤50 x 10^9/L.

Glossary

All cases of *suspected* (*probable* and *possible*) VITT (symptoms of thrombosis presenting day 4-42 post vaccination) should be managed along the pathway until excluded by further testing. This glossary is intended to standardise case classification both prior to and following specific VITT testing.

Classification prior to specific VITT testing

Suspected	**VITT is *suspected* if (1) the platelet count is <150x10^9/L AND either (2) D-dimers are elevated (5x ULN) OR (3) fibrinogen is reduced.**
Probable	VITT is *probable* if there is evidence of thrombosis in *suspected* VITT.
Possible	VITT is *possible* if there is no evidence of thrombosis in *suspected* VITT.
Less likely	VITT is *less likely* if the platelet count is >150x10^9/L, but D-dimers are elevated or fibrinogen is reduced
Much less likely	VITT is *much less likely* if repeated platelet counts are >150x10^9/L, D-dimers are not elevated AND fibrinogen is normal.

Classification following specific VITT testing (updated December 17, 2021)

VITT Serologically Confirmed	**VITT specific test positive** (Functional test by any of 3 methods + or – ELISA positive)
VITT – not serologically supported	**VITT specific tests negative** (including 2 functional tests and ELISA). VITT not excluded but not confirmed. Tier 1 thrombosis is highly suggestive of VITT[§]
VITT Not Supported	Does not make clinical criteria**, functional test negative, **regardless of ELISA result**
VITT – without thrombocytopenia	**VITT specific test positive** (ELISA and/or functional test by any of 3 methods) but thrombocytopenia not documented

VIT – without thrombosis	**VITT specific test positive** (ELISA and/or functional test by any of 3 methods) but symptoms of thrombosis present, but thrombosis not documented

§ -"Tier 1" thrombosis (CVST, splanchnic, arterial, mixed venous and arterial) –highly suggestive of VITT

** eg. out of time frame, without raised D-Dimer, alternative diagnosis more likely, thrombocytopenia not acute.

Ongoing management for patients with confirmed and strongly suspected VITT:

We recommend that patients with VITT NOT proceed to second dose AZ ChAdOx1-nCov-19 vaccine.

In the sub-set of VITT patients demonstrating heparin enhancement of the platelet activating antibody on functional assay, we recommend long term avoidance of heparins.

VITT is a new condition and the longitudinal course is not yet clear. In autoimmune HIT, duration of antibody can be prolonged, > 3 months.

Extension of clot and new thrombotic events have occurred in occasional local cases despite treatment with non-heparin anticoagulants and IVIg. Patients have stablised with return to parental anticoagulation. While is this anecdotal, a low threshold for routine review of discharged VITT patients both clinically and with FBC and coagulation parameters is not unreasonable, for example at 2 weeks post presentation.

Use of strategies for HIT like management for severe thrombosis can be considered in VITT. For example:

- continuing a parental anticoagulant until the platelet counts normalise
- if choosing to transition from parental to warfarin, overlap between parental anti-coagulation and warfarin for at least 5 days
- consideration of thrombin inhibition in severe thrombosis (particularly CVST/splanchnic thrombosis)

Duration of VITT antibody persistence is unclear. We recommend repeat ELISA and functional testing at 6 weeks, 3 months and 6 months. We recommend retesting for antibody prior to cessation of anticoagulation.

Useful references:

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