Suspected Vaccine Induced Prothrombotic Immune Thrombocytopenia (VIPIT)/Vaccine induced immune thrombotic thrombocytopenia VITT):

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

April 17th, 2021

Purpose of this document:

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

Background

A severe thrombocytopenic thrombotic syndrome has been described in a small proportion of patients exposed to COVID-19 AstraZeneca vaccination. There are reports of possible cases with the J and J COVID-19 vaccine which is not currently being used in Australia or New Zealand.

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: "VITT": 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 for HIT testing. Platelet activating antibodies on functional testing are considered pathological, and requisite for *confirming* the diagnosis of VIPIT/VITT. Within Australia, these assays are currently being validated.

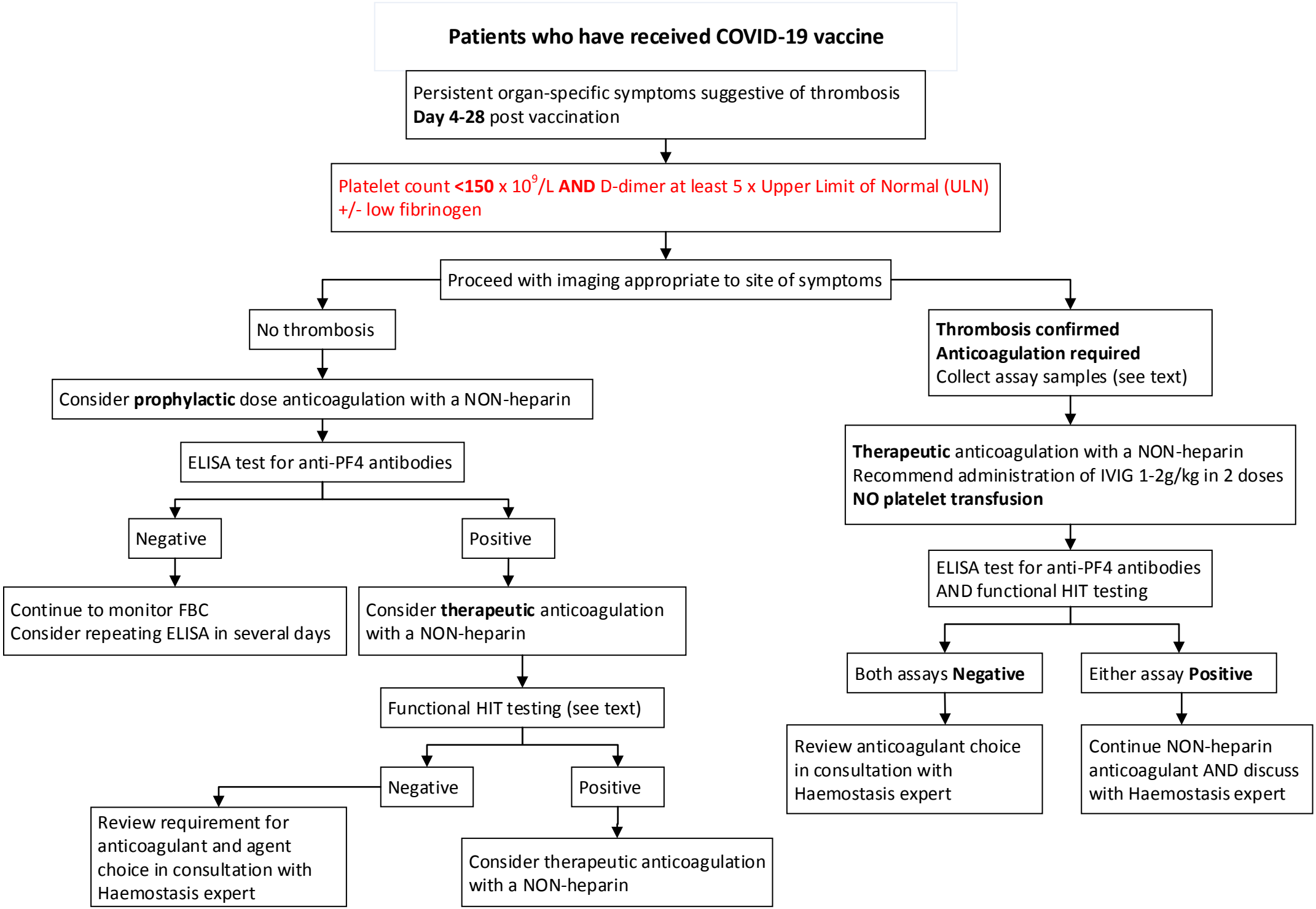
Our accepted understanding of this syndrome is rapidly evolving, and we plan to update this advisory statement regularly, accordingly. Information is emerging in peer-reviewed publication and being shared pre-publication.

Patients with any site of new thrombosis who have recently received vaccination against COVID (day 4-20), should be further investigated for VIPIT/VITT as per algorithm on Page 2.

Please ensure you report all suspected adverse effects to the TGA (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

VIPIT/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: https://ww.thanz.org.au/documents/item/579


Patients who have received COVID-19 vaccine
Persistent organ-specific symptoms suggestive of thrombosis
Day 4-28 post vaccination
Platelet count **<150** x 10^9/L **AND** D-dimer at least 5 x Upper Limit of Normal (ULN)
+/- low fibrinogen
Proceed with imaging appropriate to site of symptoms
No thrombosis
Consider **prophylactic** dose anticoagulation with a NON-heparin
ELISA test for anti-PF4 antibodies
Negative
Positive
Continue to monitor FBC
Consider repeating ELISA in several days
Consider **therapeutic** anticoagulation with a NON-heparin
Functional HIT testing (see text)
Negative
Positive
Review requirement for anticoagulant and agent choice in consultation with Haemostasis expert
Consider therapeutic anticoagulation with a NON-heparin
Thrombosis confirmed
Anticoagulation required
Collect assay samples (see text)
Therapeutic anticoagulation with a NON-heparin
Recommend administration of IVIG 1-2g/kg in 2 doses
NO platelet transfusion
ELISA test for anti-PF4 antibodies
AND functional HIT testing
Both assays **Negative**
Either assay **Positive**
Review anticoagulant choice in consultation with Haemostasis expert
Continue NON-heparin anticoagulant AND discuss with Haemostasis expert

When should I suspect VIPIT/VITT?

1. **Onset days 4-28 after vaccination**
2. **Thrombosis: predominant site cerebral venous sinus but splanchnic thrombosis, other VTE and arterial ischaemia have also been reported**
3. **Thrombocytopenia (*severity and trajectory of thrombocytopenia unclear)**
4. **High D-Dimer (typically very high)**
5. **Some patients are refractory to standard anti-coagulation**
6. **Response to IVIG**

*Platelet range 7-149 x 10^9/L in available data

Although most reported cases involve presentation with cerebral venous sinus thrombosis, other sites have also been involved (splanchnic, pulmonary embolism, arterial ischaemia), so any patients presenting with symptoms of thrombosis shortly after vaccination should be considered carefully for VIPIT/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 VIPIT/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 4-20 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) 4-28 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. Most cases of VIPIT described to date have been female and aged between 20–55 years, however males have also been affected. In some cases progression of thrombosis whilst on therapeutic heparin anticoagulation is reported.

Not all thrombocytopenia post vaccine is VIPIT/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.

A link for a national THANZ database will be available next update

How do I investigate for VIPIT/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 VIPIT/VITT is explored,

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

Testing for VIPIT/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. VIPIT/VITT is *suspected* if (1) the platelet count is $<150x10^9$/L 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 2 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, VIPIT/VITT is *probable*, and treatment must be urgently initiated with IVIG and non-heparin anticoagulation. The Haematologist 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, VIPIT/VITT is *possible*, and treatment initiated with **non-heparin** anticoagulation in prophylactic dose. Haematology may consider the addition of IVIg in the appropriate context (e.g. rapidly falling platelet count with/without bleeding).
2. VIPIT/VITT is *much less likely* if the platelet count is $>150x10^9$/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.
3. VIPIT/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 may be required in the appropriate context (e.g. ongoing symptoms of severe headaches).

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

VIPIT/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* VIPIT/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. **HIT ELISA appears to detect the antibody**
    b. AcuStar, STiC and Particle gel immunoassay (PaGIA) DO NOT detect antibody and are NOT appropriate for use in this setting.

2. Functional antibody testing:

- Functional testing for platelet activating antibodies associated for VIPIT/VITT are available and being validated. They should be performed in all samples of suspected VIPIT/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.
https://www.thanz.org.au/documents/item/579

SAMPLES REQUIRED:

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

1. 4 citrate (blue top tubes)
2. 2 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 VIPIT/VITT?

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

- We recommend ***probable*** **VIPIT/VITT** (suspected WITH thrombosis) to be treated with non-heparin anticoagulation, similar to patients with HIT.
    - IVIg (1-2g/kg over at least 2 divisions) is recommended upfront - particularly for cases that do not respond quickly or are at high risk from deterioration (including presentation platelets < 30 x 10^9/L, fibrinogen <1.5mg/L).
    - 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.
    - 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).

- We recommend **possible VIPIT/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 – particular 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 – for patients with thrombocytopenia with normal D-Dimer and fibrinogen.

Patients with any site of new thrombosis who have recently received vaccination against COVID (day 4-28), should be further investigated for VIPIT/VITT.

THANZ refers to ATAGI and TGA for vaccination recommendations

Glossary

All cases of *suspected* (*probable* and *possible*) VIPIT/VITT (symptoms of thrombosis presenting day 4-28 post vaccination) should be managed along the pathway until excluded by further testing.

Suspected	VIPIT/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	VIPIT/VITT is *probable* if there is evidence of thrombosis in *suspected* VIPIT/VITT.
Possible	VIPIT/VITT is *possible* if there is no evidence of thrombosis in *suspected* VIPIT/VITT.
Much less likely	VIPIT/VITT is *much less likely* if the platelet count is $>150x10^9$/L, D-dimers are not elevated AND fibrinogen is normal.
Less likely	VIPIT/VITT is *less likely* if the platelet count is $>150x10^9$/L, but D-dimers are elevated or fibrinogen is reduced.
Strongly supported	VIPIT/VITT is *strongly supported* by positive "HIT" ELISA testing, or by "HIT" functional testing, in cases of *suspected* VIPIT/VITT.
Confirmed	VIPIT/VITT is *confirmed* by positive "HIT" ELISA, AND positive "HIT" functional testing in cases of *suspected* VIPIT/VITT.
Unsupported	VIPIT/VITT is *unsupported* by negative "HIT" ELISA, and/or negative functional "HIT" testing, in cases of *suspected* VIPIT/VITT.
Possible	VIPIT/VITT remains *possible* in suspected VIPIT/VITT whose "HIT" ELISA is strongly positive, but functional "HIT" testing is negative, or "HIT" ELISA negative but function test positive (Alternative conditions may be required for functional testing).

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