Guidance from the Expert Haematology Panel (EHP) on Covid-19 Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT)

Updated Guidance on Management. Version 2.2 **31 August 2021**

Note this is a live document and is updated frequently as further information comes to light.

Please also refer to the NICE guidelines on management of VITT (NG200) August 2021
https://www.nice.org.uk/guidance/ng200/resources/fully-accessible-version-of-the-guideline-pdf-pdf-51036811744

VITT is a rare life-threatening immunological reaction to covid-19 vaccination.
In this condition in the UK, primarily the Oxford-AstraZeneca vaccine triggers the production of anti-platelet factor 4 (PF4) antibodies, which cause platelet activation with thrombocytopenia and thrombosis. Thrombosis is often widespread and involves the cerebral veins in 50% of cases (half of which have secondary intracranial haemorrhage), the splanchnic veins in a third of cases, arterial stroke, heart attack or ischaemic limbs and unusual sites such as adrenal thrombosis.
Suspected cases have also been reported to us after Pfizer COVID-19 vaccination although this is much more unusual and they may have a different phenotype; we will update on this in future living guidance.

There is no clear signal of risk factors other than young age. Patients with prior thrombosis or prothrombotic disorders including antiphospholipid syndrome are no more at risk than the general population.

Clinicians need to be on alert for this syndrome, to understand how to make the diagnosis and to note the specifics of how to treat it. The Expert Haematology Panel (EHP) offers MDT support for management of cases. Since AZ was stopped for the under 40s, there have been very few new cases and the daily 2pm meetings have now been reduced to Mondays only. However immediate help and support is offered by the EHP authors of this guidance.

Suspected cases must be reported to the EHP and Public Health England via this link https://cutt.ly/haem_AE.
Additionally, all cases of thrombosis or thrombocytopenia occurring within 30 days of COVID-19 vaccine must be reported to the MHRA via the online yellow card system https://coronavirus-yellowcard.mhra.gov.uk/

Please also note that new or relapsed post-vaccine ITP cases can also be reported to Public Health England
https://snapsurvey.phe.org.uk/snapwebhost/s.asp?k=162574113593

Clinical and laboratory findings

Cases usually present 5-30 days after vaccination and are characterised by thrombocytopenia, very raised D Dimers, low Clauss fibrinogen levels and thrombosis, which is often rapidly progressive.
We now recognise that deep vein thromboses (DVT) and pulmonary emboli can present up to 42 days after vaccination; we presume the DVT develops subclinically between days 5-30.

Antibodies to platelet factor 4 (PF4) have been identified and so this has similarities to heparin-induced thrombocytopenia (HIT), but in the absence of exposure to heparin treatment. PF4 antibodies are detected by ELISA HIT assay but not usually by other HIT assay methods.

We now recognise that up to 5% of patients have NORMAL platelet counts at presentation. Most of these patients develop thrombocytopenia in the next few days.

The case definition criteria should be applied to classify the case into Definite, Probable, Possible or Unlikely.

Expert Haematology Panel VITT Case definition criteria	**Onset of symptoms 5-30 post COVID-19 vaccine (or up to 42 days if isolated DVT/PE)** **Presence of thrombosis** **Thrombocytopenia (platelet count <150 x10^9/L)** **D dimer >4000 mcg/L (FEU)** **Positive anti-PF4 Abs ELISA assay**
Definite VITT (D)	**Meets all five criteria**
Probable (P)	**D dimer >4000 FEU but one criterion not fulfilled (Timing, Thrombosis, Thrombocytopenia, anti-PF4 Abs) or D dimer unknown or 2000-4000 FEU with all other criteria present**
Possible (S)	**D dimer unknown or 2000-4000 FEU with one other criterion not fulfilled, or two other criteria not fulfilled (Timing, Thrombosis, Thrombocytopenia, anti- PF4 Abs)**
Unlikely (U)	**Platelet count < 150 x 10^9/l without thrombosis with D dimer <2000 FEU, Or thrombosis with platelet count > 150 x 10^9/L and D dimer <2000 FEU,** **regardless of anti-PF4 Ab result,** **and/or alternative diagnosis more likely**

Table: VITT Case definition criteria. Ref: Pavord et al, Clinical features of vaccine-induced thrombocytopenia and thrombosis, NEJM 2021 DOI: 10.1056/NEJMoa2109908

Management of a Probable Case – Treat first while Awaiting Confirmatory Diagnosis:

1. GIVE intravenous immunoglobulin urgently as this is the treatment most likely to influence the disease process. Give 1g/kg (divided into two days if needed), irrespective of the degree of thrombocytopenia, and review clinical course. Repeated IvIg may be required.

2. Steroids may also be helpful and although this is unknown, the benefit is likely to outweigh risks of harm.

3. Anticoagulate with non-heparin-based therapies such as DOACs, fondaparinux, danaparoid or argatraban* depending on the clinical picture. Bleeding and thrombotic risk needs to be carefully balanced and low dose fondaparinux or critical illness dose argatroban may be appropriate whilst platelet count is <30 x10^9/L .

[*notes for Argatroban

levels ideally should be monitored by a Direct Thrombin inhibitor assay, if available, e.g. HEMOCLOT as APTT correlates poorly with the argatroban effect due to the high levels of Factor VIII.

Switch to fondaparinux or a direct oral anticoagulant, as soon as the bleeding risk is considered to have reduced, given that these patients are highly prothrombotic and argatroban monitoring results may not reflect therapeutic anticoagulation.

Some Clauss fibrinogen assays may give falsely low fibrinogen results during concurrent use of argatroban. Assays that use high concentrations of thrombin e.g. 100 UNIH/ml may be more accurate.]

4. Plasma exchange may be considered, if very severe or resistant disease. We recommend early use of plasma exchange in those with extensive thrombosis, platelets < 30 x 10^9/L; these patients often have high levels of anti-PF4 and IVIg may not be enough. This may be required daily for up to 5 days, or longer, until platelet count is normal.

5. Cerebral venous sinus thrombosis. This group of patients have a high mortality, even with conventional treatment. It is not possible to give evidence based advice on improving outcomes, however, we currently recommend:
   A) Very early use of PEX rather than waiting for IVIg response
   B) High dose steroids
   C) Transfer to neurosurgical unit and consider early recourse to neuroradiology and/or neurosurgery if deterioration/progressive bleed.
   D)Platlelet transfusion is an option to support therapeutic anticoagulation [however there is insufficient evidence to state that this is superior to critical care (low dose) argatroban without platelet transfusion]
   E) If urgent neurosurgery is required transfuse platelets to >100 x10^9/L and cryoprecipitate to maintain fibrinogen >1.5g/L.

6. Platelet transfusion. It is unclear whether platelet transfusions will exacerbate the condition; the risk/benefit in supporting patients with platelets <50 x10^9/L on anticoagulation who have a secondary cerebral bleed and not requiring procedures is unknown and therefore clear advice cannot be given at present.

7. Heparin. Laboratory data suggests platelet activation is not exacerbated by heparin. However, as VITT is associated with anti PF4 antibodies, heparin based anticoagulation has been avoided to date.

8. Fibrinogen. Replace fibrinogen supplementation if needed, to ensure level does not drop below 1.5 g/L, using fibrinogen concentrate or cryoprecipitate

9. VIT without thrombosis. If no overt thrombosis, but thrombocytopenia with markedly raised D Dimer is present, thromboprophylaxis with non-heparin-based anticoagulants should be considered – balancing bleeding and thrombotic risks. DOAC, fondaparinux or danaparoid can be used.

10. Rituximab. For patients who are refractory to repeat doses of IVIg and plasma exchange, rituxmab can be considered although there is no evidence of its efficacy in VITT at present.

11. Please inform the Expert Haematology Panel (uclh.vatt@nhs.net) and please discuss your cases at the 2pm daily MDT meeting.

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Samples:

1. **Anti PF4** assays by an ELISA based technique should be performed locally or sent to Filton NHSBT. HIT assay using Accustar and Diamed have generally shown negative results and so cannot be relied upon.

2. **Serum** and plasma should be stored onsite if possible, for future use as new information comes to light.

3. Send EDTA sample for whole genome sequencing – please email gel@liverpoolft.nhs.uk with the patient name, dob, gender, NHS number and location, to receive a barcode for the EDTA tube and a document pack with patient information and consent form

Consent is obtained using 100K approved PILs and CFs and there are options for deceased and patients lacking capacity. The Research Ethics Opinion for this study is in line with a Research Tissue Bank approval therefore individual Trust approval is not required. However if needed, GEL will liaise with the referring Trust's Research & Development and provide the Genomics England Research Library letter to notify the department of the recruitment activity. This ethics covers England, Wales & Northern Ireland. Separate arrangements are made for Scotland.

Report the case!

1. Please enter case details on this link which is quick and easy to use https://cutt.ly/haem_AE

2. It is also **crucial** that the MHRA **online yellow card** is completed https://coronavirus-yellowcard.mhra.gov.uk/

Discharge:

Close followup is required, with regular platelet counts and assessment of symptoms. Patients should be given written information and a number to contact if symptoms become worse. See appendix for patient information leaflet and example triage SOP.

Current information suggests that many patients have persistent anti-PF4 antibodies, so are therefore at potential risk of relapse. Close monitoring and contact wth the patient is imperative. A fall in platelet count or rising D-dimers should be treated considered for treatment with steroids, rituximab or IvIg.

Anticoagulation should be continued for at least 3 months after discharge and providing platelet count, D-dimer and fibrinogen are normal and PF4 antibodies are negative.

If thrombosis was only arterial, once D Dimers, platelets and fibrinogen have returned to normal, and at least 1 month has passed, the patient can be switched to an antiplatelet agent. Monitor platelet count closely to observe for relapse and repeat PF4 ELISA weekly for 4 weeks and then monthly for 6 months.

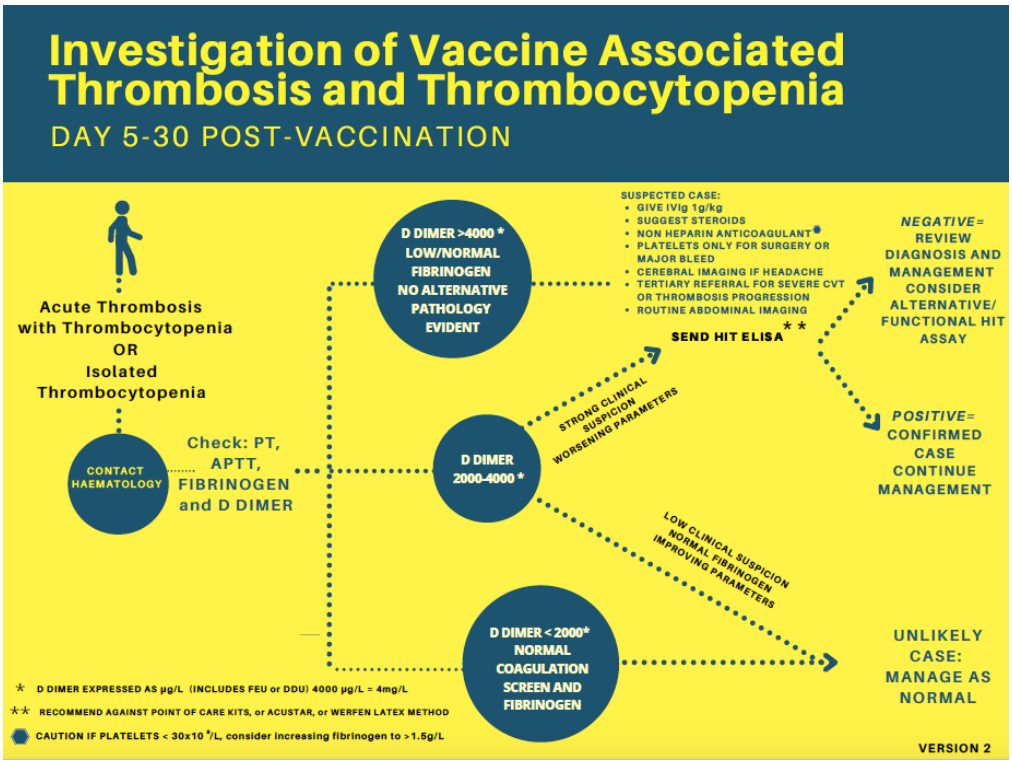
Patients with VITT are at risk of post traumatic stress disorder. Please consider early psychological support using local services and provide them with the EHP/NHSE leaflet giving information where they can also seek outside help. (Appendix)

Further Vaccination:

Those either affected by, or under investigation for this complication should **not** receive a second Astra Zeneca vaccine.

Advice re Vaccination is given in the Government Greenbook
(see https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a)

Investigation algorithm:



Management algorithm:

Management algorithm for patients with suspected VITT

Suspected Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT)

Apply case definition criteria

Definite / Probable

Platelet count <30 x10^9/L
And CVT or extensive thrombosis

Yes: PEX, steroids, IVIg if PEX delayed, Low dose anticoagulation*

No: IVIg, oral/subcut anticoagulation

If no improvement: PEX

Possible

Platelet count <30 x10^9/L
And CVT or extensive thrombosis

Yes: IVIg, low dose Anticoagulation* Consider PEX

No: Oral/subcut anticoagulation Close observation

Anti PF4 antibody positive

Yes: Continue VITT management

No: Consider alternative diagnosis

Unlikely: Consider alternative diagnosis

Platelet transfusion may be required for neurosurgery, and fibrinogen supplementation if concentration <1.5g/L
Current recommendation for anticoagulation is with non-heparin-based therapies; intravenous argatroban, subcutaneous fondaparinux or direct oral anticoagulants (DOACs).
*Low dose anticoagulation is usually with critical illness dose argatroban, initiated at 0.25 to 0.5mg/kg/hr
CVT: Cerebral venous thrombosis. PEX: plasma exchange. PF4: platelet factor 4

Appendix.

Useful links:

Information for patients about VITT
https://b-s-h.org.uk/media/19594/vitt_patient_information_v4-20210420.pdf

Information for patients where they can find psychological and social support
Link TBC

NICE guidelines (NG200) on management of VITT
https://www.nice.org.uk/guidance/ng200/resources/fully-accessible-version-of-the-guideline-pdf-pdf-51036811744

ED Guideline
https://www.rcem.ac.uk/docs/Policy/ED-AM%20%20Vaccine%20pathway%20concerns%20-%20RCP%20-%20SAM%20-%20RCEM.pdf

Multidisciplinary neuro guideline for patients with CVST
https://www.ics.ac.uk/COVID-19/COVID19_PDFs/VITT_Guidance.aspx?WebsiteKey=10967510-ae0c-4d85-8143-a62bf0ca5f3c

Public Health England Advice on vaccines:
https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a)

Description and analysis of UK cases:
https://www.nejm.org/doi/full/10.1056/NEJMoa2109908

MHRA Yellow Card report form
https://coronavirus-yellowcard.mhra.gov.uk/

Expert Haematology Panel / Public Health England VITT report form
https://cutt.ly/haem_AE