

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

Updated Guidance on Management. Version 2.0

28 May 2021

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

There are currently no robust data to inform management of this condition. In the absence of published evidence, these are pragmatic guidelines based on experience of managing the initial cases, alternative similar conditions and the theoretical risks and benefits of interventions. As evidence emerges, recommendations are expected to change. Patient management should be individualised according to specific circumstances.

A rare syndrome of immune-driven thrombosis, often cerebral venous sinus thrombosis, and thrombocytopenia has been reported after Astra-Zeneca COVID-19 vaccination and possible cases have more recently been reported to us after Pfizer COVID-19 vaccination although they may have a different phenotype and we will update on this in future living guidance. It is affecting patients of all ages and both genders; at present there is no clear signal of risk factors.

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.

Probable 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 through the same initial link which diverts down a different line of questioning (https://cutt.ly/haem_AE)

DEFINITE CASE:

Cases usually present 5-30 days after vaccination and are characterised by thrombocytopenia, raised D Dimers 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.

There is a high preponderance of cerebral venous sinus thrombosis. Portal vein and splanchnic vein thrombosis, pulmonary embolism and arterial ischaemia are also common, as well as adrenal infarction and haemorrhage. Intracranial haemorrhage can be significant and unexpected.

- Typical laboratory features include a platelet count $<150 \times 10^9/L$, very raised D Dimer levels above the level expected for VTE and many develop low fibrinogen levels.
- 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

Suggested actions to be taken for the identification and management of suspected cases:

POSSIBLE CASE:

Any patient presenting with acute thrombosis and new onset thrombocytopenia within 30 days of receiving COVID 19 vaccination

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Investigations

1. FBC- specifically to confirm thrombocytopenia $<150 \times 10^9/L$
2. Coagulation screen, including Clauss fibrinogen and D Dimers
3. Blood film to confirm true thrombocytopenia and identify alternative causes

UNLIKELY CASE:

- Reduced platelet count without thrombosis with D dimer at or near normal and normal fibrinogen.
- Thrombosis with normal platelet count and D dimer <2000 and normal fibrinogen

PROBABLE CASE:

- D Dimers > 4000 mcg/L (or D Dimers > 2000 with strong clinical suspicion)
 1. Send serum sample for PF4 antibody assay (ELISA HIT assay). Please see below *
 2. Ultrasound abdomen for portal and splanchnic vein thrombosis (even if no symptoms)
 3. Look carefully for CVST, initial imaging may be negative but may be seen on subsequent imaging

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 argatroban 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 $<30 \times 10^9/L$.
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 $< 30 \times 10^9/L$; 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, if platelet recovery is slow.
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) Platelet 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 $>100 \times 10^9/L$ and cryoprecipitate to maintain fibrinogen $>1.5g/L$.

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6. Platelet transfusion. It is unclear whether platelet transfusions will exacerbate the condition; the risk/benefit in supporting patients with platelets $<50 \times 10^9/L$ 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. It is unknown whether heparin exacerbates the condition but until further evidence is available, as the syndrome mimics HIT, heparin is best avoided, including heparin flushes.
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, rituximab 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.

DEFINITE CASE

If PF4 antibodies positive by ELISA:

1. Continue ongoing treatment as above
2. Send serum sample to Colindale for Covid-19 antibody testing and storage*
3. Send EDTA sample for whole genome sequencing – please email gel@liverpoolft.nhs.uk with the patient details

If there is a high index of clinical suspicion but PF4 antibodies are negative, please send serum and EDTA anyway and discuss before changing treatment.

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** should also be sent to Colindale for Covid antibody test and storage:

* For the attention of Kevin Brown
Virus Reference Department
National Infection Service
Public Health England
61 Colindale Avenue
London, NW9 5EQ

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950573/E59m_lab_request_form_vw_2289_01.pdf

Please use the code VITT for easy identification.

3. **EDTA** for whole genome sequencing - email gel@liverpoolft.nhs.uk

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with 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 from patients suggests that most of the patients we have followed up over the last two months have continued to have anti-PF4 antibodies, so are therefore at potential risk of relapse. Close monitoring and contact with the patient is imperative. A fall in platelet count or rising D-dimers should be treated considered for treatment with steroids, rituximab or Ivlg.

It is advisable to continue anticoagulation long term for now, until more is known about the long term course of the condition. If anticoagulation needs to be discontinued, ensure 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, the patient can be switched to an antiplatelet agent. Monitor platelet count closely to observe for relapse and consider repeating PF4 ELISA at day 28 from presentation.

Patients with VITT are at risk of post traumatic stress disorder. Please consider early psychological support using local services

Further Vaccination:

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

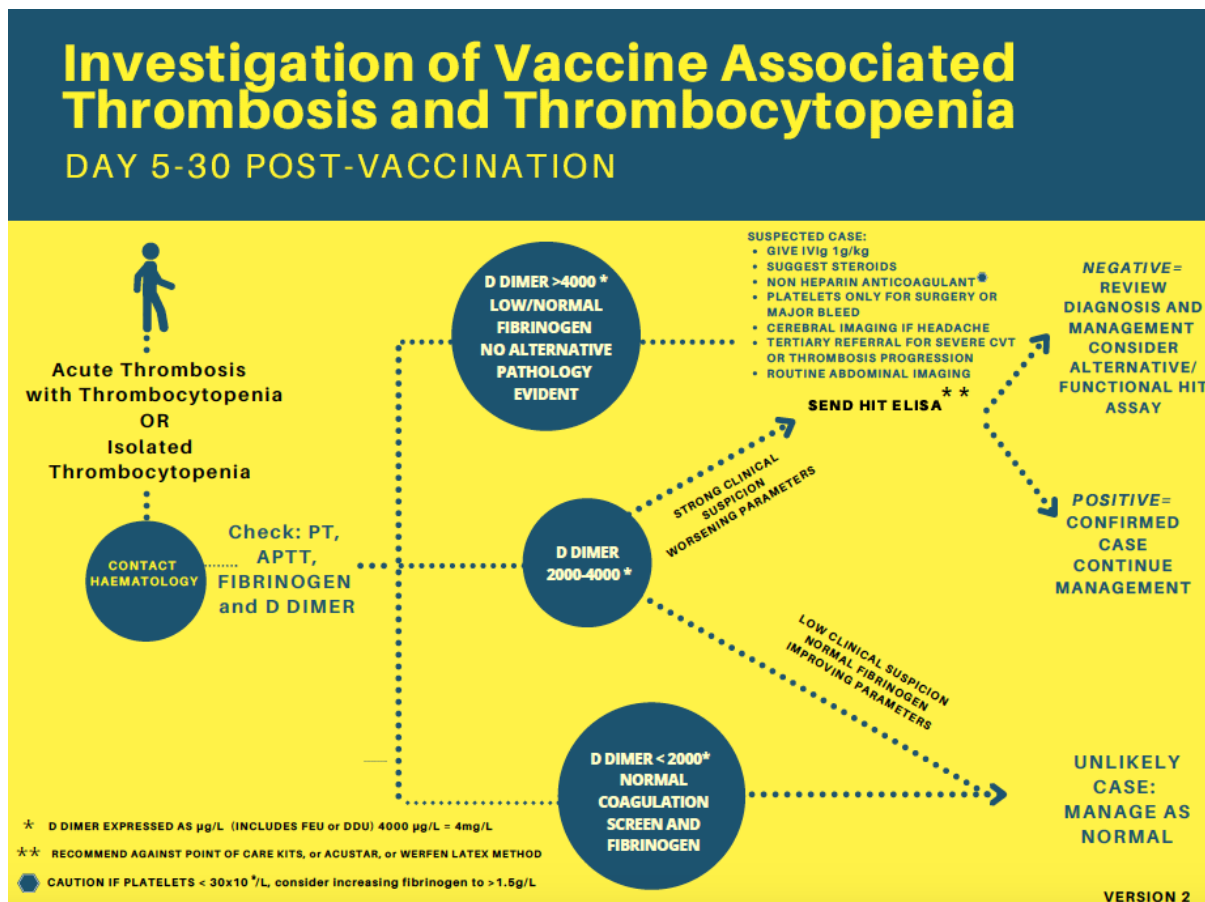
Advice re First Vaccination is given in the Government Greenbook
(see <https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a>)

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Additional themes/learning points from the daily meetings:

1. If coronary artery thrombosis or other arterial thrombosis occurs in healthy (not atherosclerosed) vessels, anticoagulation is required (potentially in addition to antiplatelet agents) for at least a month and the fibrinogen, D Dimers and platelet count must have remained normal after initial therapy. Thereafter it may be appropriate to switch to antiplatelet agents however consideration must be given to the lack of evidence, the potential risk of relapse and the individual characteristics of the patient.
2. 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.
3. 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.
4. 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.

Management algorithm:



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