Title	**Guideline for the management of suspected Vaccine associated thrombosis with thrombocytopenia (VATT)**
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Background

A rare syndrome of thrombosis, often cerebral venous sinus thrombosis, associated with thrombocytopenia is being noted within 28 days of coronavirus vaccination. Other types of thrombosis (both arterial and venous) have also been reported. The mechanism is thought to involve platelet-activating antibodies in a similar way to heparin-induced thrombocytopenia.

While the risk of developing this condition is low overall, there are relevant management implications. Cases to date have been associated with significant morbidity and mortality, therefore it is important this condition is recognised early and treated appropriately by Haematology experts.

This is interim guidance and will be updated as new national guidance becomes available.

The latest version of national guidance can be found on the British Society for Haematology website https://b-s-h.org.uk/about-us/news/covid-19-updates/. It is important that you review this as the most up to date guidance may have changed since this guideline was written.

Who is affected?

This is affecting all ages and both genders. At present there is no clear signal of risk factors. Patients in the UK have presented after their first dose of the Oxford/Astra Zeneca vaccine.

How common is this?

This is a rare event. The estimated incidence of this phenomenon is < 1 in 100,000.

Clinical Features

- Cases are characterised by thrombocytopenia, raised D-Dimer and progressive thrombosis, with a high preponderance of cerebral venous sinus thrombosis.
- Cerebral venous thrombosis may present as persistent headache+/- focal neurology +/- seizures
- Pulmonary embolism and arterial ischaemia are also common.
- Hyperfibrinolysis and bleeding can occur.

Suspect VATT in any patient presenting with acute thrombosis, or new onset thrombocytopenia, within 28 days of receiving COVID-19 vaccination.

Laboratory Features

Typical laboratory features include the following combination

- platelet count <150 x10^9/L
- very raised D Dimer levels above the level expected for VTE (ranging from 4,000-60,000)
- inappropriately low fibrinogen.

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

Investigations

Suspected case

- Full blood count to confirm thrombocytopenia<150x 10^9/L
- Coagulation screen, including Clauss fibrinogen
- D-Dimer
- Blood film to confirm true thrombocytopenia and identify alternative causes

Probable case

If initial investigations suggest a probable case (see Figure 1)

- **Contact the on call haematologist** for further advice. Patients may require transfer to NHS Lothian for ongoing investigation and management.
    - Monday to Friday 9-5 contact the consultant haematologist at the BGH (bleep 6246).
    - Out of hours and weekends call NHS Lothian switchboard and ask for the haematology registrar covering the BGH.

- Send serum sample for PF4 antibody assay (HIT assay) by ELISA based technique – **discuss with Haematologist first**
    - Anti PF4 assays by ELISA based technique will be carried out in Aberdeen
    - HIT assay using Accustar have generally shown negative results and so cannot be relied upon.

- Additional investigations required will be undertaken by the Haematology team (Appendix 1)

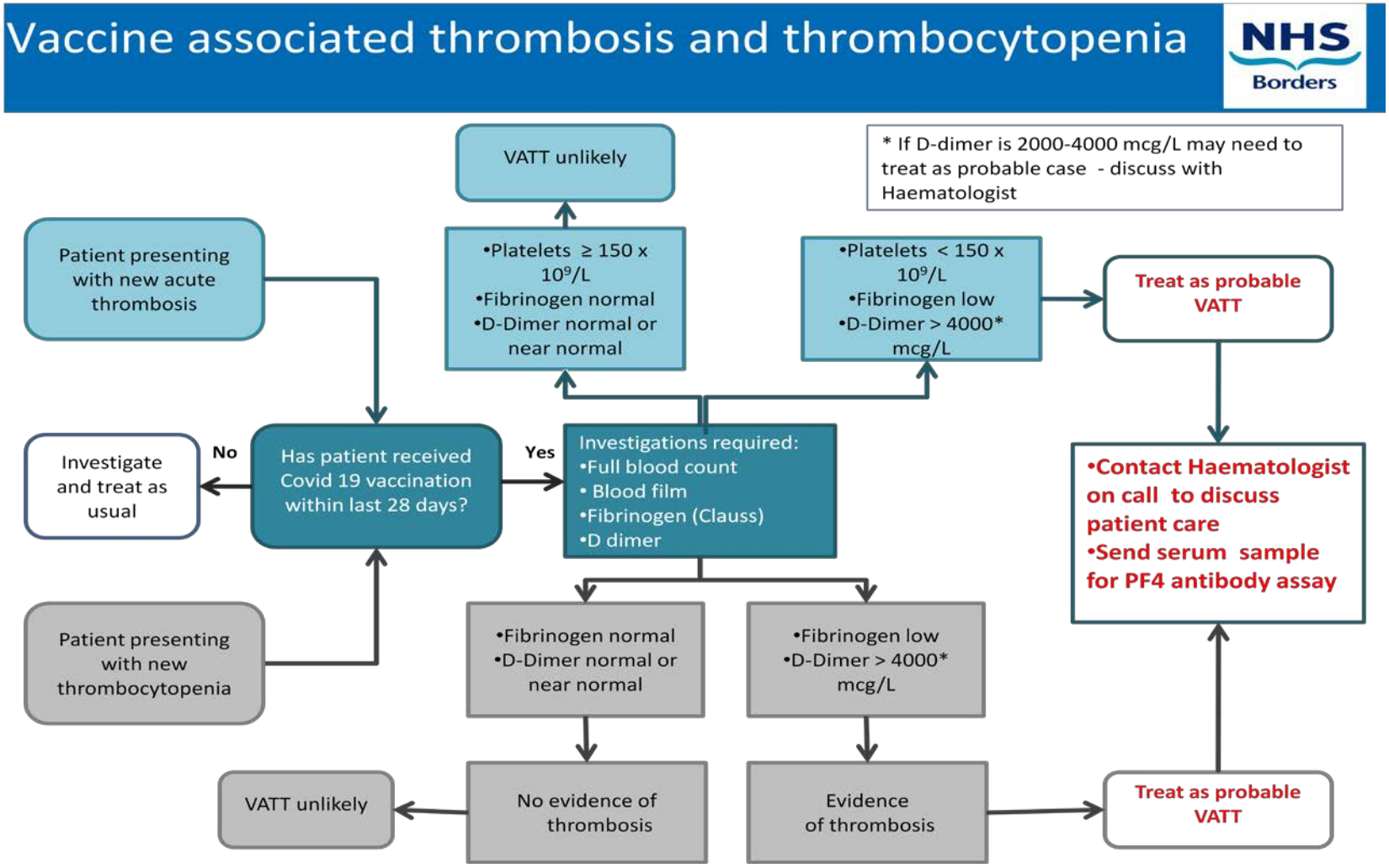

Figure 1: Investigation of suspected vaccine associated thrombosis and thrombocytopenia

Clinical Management of Suspected Cases

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. Further IV immunoglobulin may be required balancing bleeding and thrombotic risk

2. Avoid platelet transfusions. Discuss any required interventions with the Haematologist on call as a matter of URGENCY

3. Avoid all forms of heparin including heparin-based flushes. (It is unknown whether heparin exacerbates the condition but until further data is clear, this is best avoided)

4. Correct fibrinogen if needed to ensure a level above 1.5 g/L with fibrinogen concentrate or cryoprecipitate

5. Anticoagulate when Fibrinogen is >1.5 g/L and platelets >30 x109 /L. If anticoagulation is needed before then critical illness dose argatroban should be considered

6. Anticoagulate with non-heparin-based anticoagulation, such as DOACs, argatroban, fondaparinux or danaparoid depending on the clinical picture.

7. Steroids may be required usually dexamethasone orally 40 mg daily or IV methyl prednisolone.

8. Plasma exchange may also be considered.

9. Avoid thrombopoietin receptor agonists (romiplostim, eltrombopag)

10. Antiplatelet agents are not recommended based on current experience

11. If no overt thrombosis, but thrombocytopenia with raised D-Dimer, thromboprophylaxis with non-heparin-based anticoagulants should be considered – balancing bleeding and thrombotic risk. DOAC, fondaparinux or danaparoid can be used.

Case Reporting

- Probable cases must be reported to the Expert Haematology Panel and Public Health England via this link https://cutt.ly/haem_AE

- **Complete yellow card.** All cases of thrombosis or thrombocytopenia occurring within 28 days of coronavirus vaccine must be reported to the MHRA via the online yellow card system https://coronavirus-yellowcard.mhra.gov.uk/

Discharge

- Continue anticoagulation for at least 3 months.
- If thrombosis was only arterial continue antiplatelet agent for 3 months.
- Monitor platelet count to observe for relapse.

Further Vaccination

Those either affected by, or under investigation for this complication **should not** receive their second vaccine until the stimulant for this condition is clear.

Appendix 1

If PF4 antibodies positive by ELISA:

- Send serum sample to Colindale for Covid-19 antibody testing and storage

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

  Use the code VATTS for easy identification.

- Collect EDTA sample for whole genome sequencing– to be stored locally until location of central lab is confirmed. Email Anita.Hanson@liverpoolft.nhs.uk with the patient details so you can be sent bar-coded sample tubes, an information pack and consent form

- Inform the Expert Haematology Panel (uclh.vatt@nhs.uk)