Guideline for Investigation and Management Syndrome of Thrombosis and Thrombocytopaenia occurring after Coronavirus Vaccination (VATTS)

There have been reports of an emergent syndrome associated with recent (within 28 days) COVID-19 vaccination resulting in thrombocytopaenia, raised D Dimers and progressive thrombosis, with a high preponderance of cerebral venous sinus thrombosis. Pulmonary embolism and arterial ischaemia are also common. Hyperfibrinolysis and bleeding can also occur.

- Typical laboratory features include a platelet count <150 x109/L, very raised D Dimer levels above the level expected for VTE and 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. PF4 antibodies are detected by ELISA HIT assay but not usually shown by other HIT assay methods (such as AccuStar).

This syndrome appears to effect all ages, men and women in equal proportion and no clear risk factors have yet been identified.

Clinicians need to be on alert for this syndrome, to understand and make diagnosis and to note specifics of how to treat it.

POSSIBLE CASES

All patients presenting with **ANY** of the following within 28 days of COVID vaccination should be screened for the condition without delay:

- Severe headache
- New venous or arterial thromboses including CVA and thrombotic MI
- New thrombocytopaenia (Platelets < $150x10^9$/L)

Screening bloods include:

- FBC (+ blood film if platelets low)
- Coagulation Screen
- Fibrinogen
- D-Dimer

NB: **If VATTS is suspected do not administer Heparins (unfractionated or LMWH) or Platelet transfusion until VATTS is excluded.**

VATTS UNLIKELY

- Reduced platelet count without thrombosis with D dimer at or near normal and normal fibrinogen.
- Thrombosis with normal platelet count and D dimer <2ug/ml FEU (<2000ng/ml) and normal fibrinogen

VATTS PROBABLE

- Platelets < 150 x10^9/L
- If D Dimers >4ug/ml FEU (>4000ng/ml)
- Low or low-normal fibrinogen

NB D- Dimers 2-4 ug/ml FEU (2000-4000 ng/ml) should be treated with a high index of suspicion.

Other tests in probable cases:

Serum (gold) for PF4 antibody assay (HIT assay). Please see below *

EDTA (purple) sample for whole genome sequencing

Serum (gold) sample for COVID antibody testing

U+E, LFT, LDH, Antiphospholipid screening, PNH screen

Management of a VATTS probable case: – treat first while awaiting confirmatory diagnosis

1. Send additional samples as above.
2. Document COVID vaccine- type, date administered and Batch number if possible.
3. Scan urgently for thrombosis as directed by patient symptoms. Note CT Venogram may be negative in early stages and does not exclude cerebral venous sinus thrombosis.
4. Discuss any concerns with on call haematologist.
5. **AVOID** platelet transfusions. Discuss with haematology how to manage any required interventions.
6. **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).
7. **GIVE intravenous immunoglobulin 1g/kg URGENTLY** do not wait until following day irrespective of level of thrombocytopaenia. The IVIg can be divided into two days if needed. Further IvIg may be required balancing bleeding and thrombotic risk.
8. **CORRECT FIBRINOGEN** if needed to ensure a level above 1.5g/l with fibrinogen concentrate or cryoprecipitate.
9. When Fibrinogen is >1.5g/l and Platelets >30x 10^9/L anticoagulate. If anticoagulation is needed before then critically ill protocol argatroban should be considered (see protocol on intranet).
10. ANTICOAGULATE with non-heparin-based therapies such as DOACs, argatroban (as per intranet protocol), fondaparinux depending on the clinical picture, if concerns please discuss with haematologist on call. Advantage of Argatroban is its short half life but requires continuous infusion. DOAC's and Fondaparinux are easier to administer but have longer half lives.

11. Steroids may be required (start 1mg/kg PO prednisolone or 20-40mg PO Dexamethasone).
12. Plasma exchange may also be considered.
13. **AVOID** thrombopoietin receptor agonists (i.e. Romiplostim and Eltrombopag).
14. Antiplatelet agents are not recommended based on current experience.
15. 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 or fondaparinux can be used.
16. Involve haematology team in normal working hours if not discussed as emergency out of hours.
17. Haematology team to seek advice and inform Expert Haematology Panel via email (uclh.vatt@nhs.uk) who will send the link to join the daily meeting to present case.

VATTS CONFIRMED CASE

If PF4 antibodies positive by ELISA

1. Continue ongoing treatment as above
2. Serum sample to Colindale for Covid antibody testing and storage
3. EDTA sample for whole genome sequencing – please email Anita.Hanson@liverpoolft.nhs.uk with the patient details so you can be sent barcoded sample tubes, an information pack and consent form

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

***Lab Samples:**

Anti PF4

Anti PF4 assays by ELISA based technique should be sent to UCLH from BSUH.

HIT assay using Accustar have generally shown negative results and so cannot be relied upon.

Genome sequencing

EDTA for whole genome sequencing- email Anita.Hanson@liverpoolft.nhs.uk with the patient details- name, DOB, gender, NHS number and location for barcoded sample tubes, an information pack 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

COVID Antibody testing:

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 VATTS for easy identification.

Reporting of suspected cases of VATTS

For patients presenting with acute thrombosis or new onset thrombocytopenia within 28 days of receiving COVID 19 vaccination clinicians to ensure that the online **yellow card** (link below) is completed - this will trigger a request from MHRA for further details.

1. Please enter case on this link which is quick and easy to use **https://snapsurvey.phe.org.uk/snapwebhost/s.asp?k=161706705032** (TBC)

2. It is also **crucial** that the **online yellow card** is completed and this will trigger a request from MHRA for further details.
   https://coronavirus-yellowcard.mhra.gov.uk/

Discharge:

Continue anticoagulation for at least 3 months.

If thrombosis was only arterial, once DDimers, platelets and Fibrinogen have returned to normal, the patient can be switched to antiplatelet agent and continue for 3 months.

Monitor platelet count to observe for relapse.

Further Vaccination

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

Further Information on British Society Website

Covid-19 webpage

Summary Flowchart- see below

Please note in BSUH DDimer units expressed in mg/l

4000 ug/l = 4mg/l