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

Updated Guidance on Management. Version 1.3 7 April 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 evidence, these are pragmatic guidelines based on experience of managing 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 thrombosis, often cerebral venous sinus thrombosis, and thrombocytopenia is being noted after COVID-19 vaccination and is highlighted as 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 28 days of COVID-19 vaccine must be reported to the MHRA via the online yellow card system https://coronavirus-yellowcard.mhra.gov.uk/

DEFINITE CASE:

Cases usually present 5-28 days after vaccination and are characterised by thrombocytopenia, raised D Dimers and progressive thrombosis, with a high preponderance of cerebral venous sinus thrombosis. Pulmonary embolism and arterial ischaemia are also common. Bleeding can be significant and unexpected.

- Typical laboratory features include a platelet count <150 x10^9/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 patient exposure to heparin treatment. PF4 antibodies are detected by ELISA HIT assay but not usually shown by other HIT assay methods.

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 28 days of receiving COVID 19 vaccination

Investigations

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

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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 (D Dimers 2000-4000 mcg/L may need to be treated as per probable case)

1. Send serum sample for PF4 antibody assay (ELISA HIT assay). Please see below *

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. Further IvIg may be required balancing bleeding and thrombotic risk.
2. AVOID platelet transfusions. Discuss any required interventions. If neurosurgery is required, this should not be delayed, and if platelet count is <100 $x10^9$/L a platelet transfusion will be appropriate after, or with, ivIg.
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 level does not drop below 1.5 g/L, using fibrinogen concentrate or cryoprecipitate
5. When fibrinogen is >1.5 g/L and platelets >30 $x10^9$/L consider starting anticoagulation. If anticoagulation is needed before then, critical illness dose argatroban can be considered, initially without dose escalation and maintained at low dose.
6. ANTICOAGULATE with non-heparin-based therapies such as DOACs, argatroban, fondaparinux or danaparoid depending on the clinical picture. Bleeding and thrombotic risk needs to be carefully balanced and lower doses may be appropriate while platelet count is still low.
7. Steroids should be considered and in particular if there is a delay giving ivIg.
8. Plasma exchange may also be considered.
9. Avoid thrombopoietin receptor agonists
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.
12. Please inform the Expert Haematology Panel (uclh.vatt@nhs.net) and please discuss your cases at the 2pm daily MDT meeting

CONFIRMED CASE

If PF4 antibodies positive by ELISA:

1. Continue ongoing treatment as above
2. Serum sample to Colindale for Covid-19 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

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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 ELISA based technique should be done locally or can be sent to Filton NHSBT or UCLH. 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 VATTS for easy identification.

3. **EDTA** for whole genome sequencing - email Anita.Hanson@liverpoolft.nhs.uk with patient name, dob, gender, NHS number and location, to receive barcoded blood bottles 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, Anita 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. Conversations are ongoing 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:

Continue anticoagulation for at least 3 months. If thrombosis was only arterial, once D Dimers, platelets and fibrinogen have returned to normal, the patient can be switched to an antiplatelet agent and continued for 3 months. Monitor platelet count closely to observe for relapse and consider repeating PF4 ELISA at day 28 from presentation.

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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.

Themes/learning points from the daily meetings:

1. If neurosurgery is deemed necessary, this should not be delayed. If platelet transfusion is required, give IVIG before/with platelet transfusion.
2. If coronary artery thrombosis was in healthy (not atherosclerosed) vessels (thrombotic myocardial infarction), anticoagulation is preferred over antiplatelet agents, until the fibrinogen, D Dimers and platelet count have normalised. Then it may be appropriate to switch to antiplatelet agents.
3. 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.
4. 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.
5. Most 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:

