Intensive Care guidance for the management of vaccine induced immune-thrombocytopenia and thrombosis (VITT)

(Guidance agreed with Expert Haematology Panel (EHP) April 30, 2021, as per the attached guideline).

Version 1 Published: 10 May, 2021

Supersedes Intensive Care guidance for the management of vaccine associated thrombocytopenia and thrombosis (VATT) Version 1 Published: 9 April 2021[i].

This guidance has been endorsed by the Intensive Care Society (ICS), the Neuro Anaesthesia and Critical Care Society (NACCS), and the British Society of Neurological Surgeons (BSNS).

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.

The guidance will be regularly updated as new information emerges

Please read guidance in full before utilising.

1. Background

1.1. Rare syndrome after first dose of the COVID-19 vaccine, most typically with the AstraZeneca nCOV-19 Vaccine[ii] [iii].
1.2. Characterised by thrombocytopenia, elevated D-dimer and progressive thrombosis, with a high incidence of cerebral venous sinus thrombosis (CVST).
1.3. Similar to heparin-induced thrombocytopenia (HIT) but without heparin exposure[iv].
1.4. No additional risk factors identified yet [v].

2. Clinical features

Note: The spectrum of severity and presentation of VITT is not yet fully known.

2.1. Affects all ages, as well as male and female equally.
2.2. Flu-like symptoms after the vaccine do not appear to be relevant.
2.3. Usually presents 5-28 days after vaccine (median 12 days) [vi].
2.4. May present with venous or arterial thrombosis or thromboembolic disease [vii].
2.5. CVST may present with:
2.5.1. Headache: consider all cases of new or worsening headache >4 days after COVID-19 vaccine, in particular, headaches that are both severe and have a sudden onset ('thunderclap') or are rapidly progressive over an hour to day ('persistent and/ or diffuse severe headache').
2.5.2. Features of raised intracranial pressure including: visual obscuration on coughing, sneezing or bending; pulsatile tinnitus; or papilledema.
2.5.3. Focal neurological symptoms or signs including visual disturbance, focal neurological deficit (including focal weakness).
2.5.4. Speech disturbances.
2.5.5. Altered conscious level or confusion.
2.5.6. Seizures.
2.6. Alternative cause of ICH less likely with:
2.6.1. Age <60 years.
2.6.2. No history of coagulopathy or hypertension.

Note: a number of cases with intracerebral haemorrhage secondary to CVST have also been reported in the absence of thrombocytopenia, and it is unclear whether these are a less severe form of VITT.

3. Laboratory investigations

3.1. Full blood count to identify thrombocytopenia with platelet count < $150x10^9$/ L.

3.2. Coagulation screen including PT, APTT, fibrinogen (including Clauss) and D-dimer to identify low fibrinogen and D-dimer >4000 µg/ L[1], or 2000-4000 µg/ L[2] with high clinical probability.

3.3. Blood film to confirm true thrombocytopenia.

3.4. PF4 antibody assay (ELISA HIT assay) [viii].

Note: If PF4 assays by an ELISA based technique should be performed locally or sent to the Filton NHSBT. HIT assay by Accustar and Diamend has generally shown negative results and so cannot be relied upon [ix].

3.5. Repeat above laboratory investigations daily in the first instance, and then regularly thereafter.

4. Imaging

4.1. CT cerebral venography is recommended for diagnosis of suspected CVST (see above for presentation).

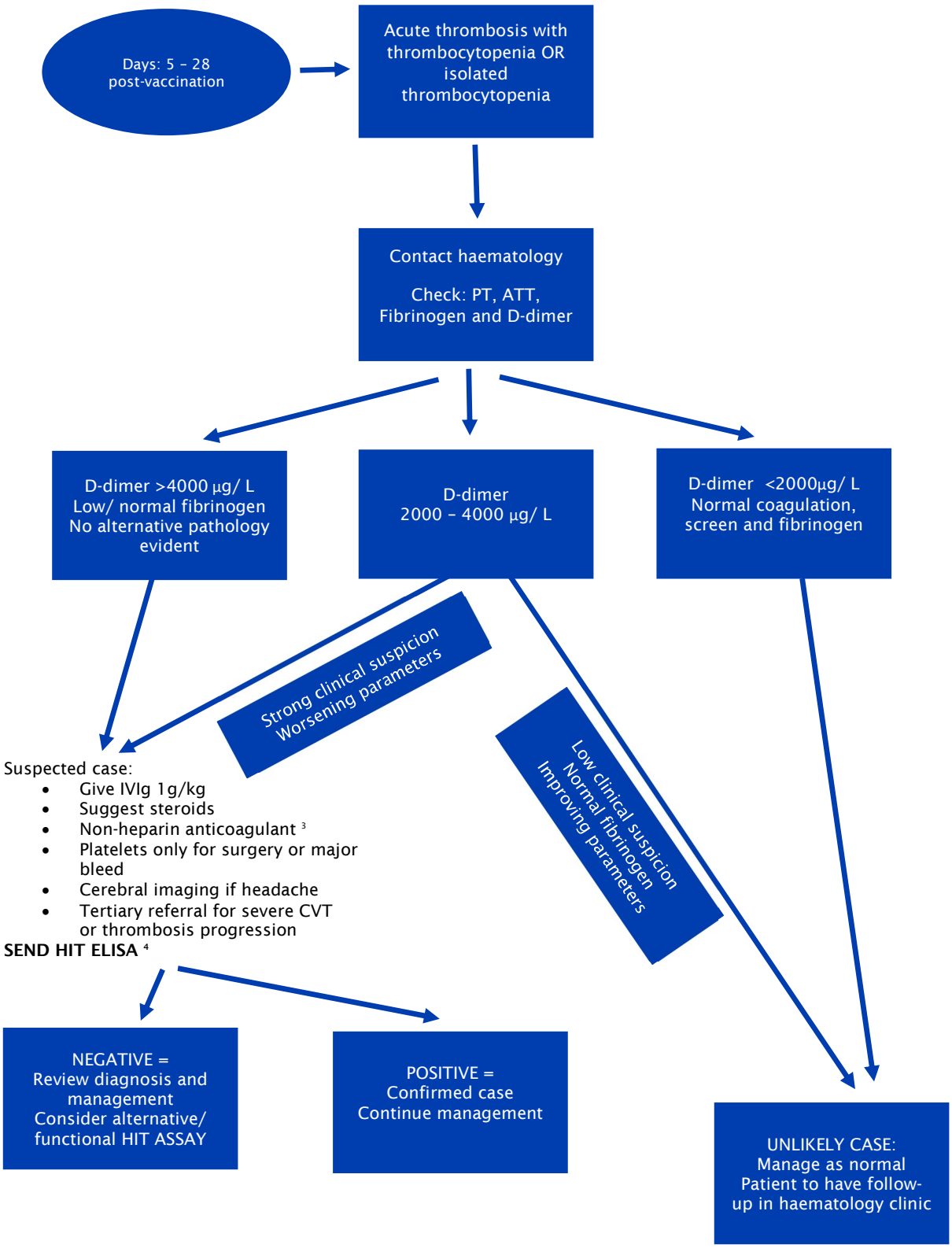
4.2. CT cerebral venography should be performed to exclude CVST in any VITT patient with extracranial thrombosis or embolic complications within critical care admission.

4.3. Conversely, in patients where the primary diagnosis is CVST, clinicians should consider CT imaging of thorax, abdomen, pelvis and limbs: other arterial or venous thrombosis are also possible, including pulmonary embolism, portal vein thrombosis, and peripheral arterial thrombosis.

[1] >4000 mcg/ L

[2] 2000 – 4000 mcg/ L

Diagram: Suggested algorithm for investigation of vaccine induced immune thrombocytopenia and thrombosis (VITT).



[3] **Caution**: if platelets < 30 x 10^9/ L, consider increasing fibrinogen to > 1.5g/ L.
[4] Do **not** use point of care kits, or Acustar or Werfen latex method.

5. Management: general considerations

5.1. Early diagnosis and treatment are crucial.

5.2. Urgent Haematology advice for all suspected cases to guide laboratory testing and management.

5.3. **Immediate administration of intravenous immunoglobulin 1g/kg** (divided into 2 days if necessary) irrespective of degree of thrombocytopenia and review clinical course. Repeated IVIg may be required. Intravenous steroids may also be required if immunoglobulin administration is delayed.

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

5.4. Platelet transfusions should be avoided if possible due to concerns of worsening the underlying pathological process and exacerbating the prothrombotic state. However in situations where the risks of bleeding are high, a platelet transfusion may be necessary to increase the platelet count as appropriate. Consider on a case-by-case basis, in consultation with expert haematology panel.

5.5. Fibrinogen replacement aiming for >1.5g/L by cryoprecipitate transfusion or fibrinogen concentrate administration.

5.6. Start non-heparin based anticoagulation when fibrinogen >1.5 g/ L and platelets $>30x10^9$/ L.

5.7. **Avoid all forms of heparin usage**. Obtain Haematology advice about dosing and monitoring of non-heparin based anticoagulant agents (particular caution required before and after invasive procedures).

5.7.1. As per EHP advisory, **hepsal flushes to be avoided**. Use other flushes (e.g. argatroban flush bag usage).

5.8. **Anticoagulate** with non-heparin-based therapies such as DOACs, Fondaprinux, Danaparoid, or Argatroban depending on clinical picture [x].

Further EHP advisory: argatroban levels to be monitored by Direct Thrombin inhibitor assay, if available, e.g. HEMOCLOT as APP correlates poorly with argatroban effect due to high levels of Factor VIII. Switch to fondaparinux or 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.

Note: 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.

5.9. **Obtain haematological advice about dosing and monitoring of anticoagulant agents, with particular caution required before and after invasive procedures.**

5.10. Patients who are refractory to repeat doses of IVIg and plasma exchange, Rituxmab can be considered although no evidence of efficacy in VITT at present.

5.11. Plasma exchange may be effective if no clinical improvement and if IVIg access is limited. Care should be taken to not allow serum sodium to fall acutely if plasma exchange used. This is particularly an issue in patients who have been treated for intracranial hypertension, where the serum sodium may be above normal because of the use of hyperosmotic agents for raised intracranial pressure. Avoid rapid falls in serum sodium in patients with cerebral oedema and/ or raised intracranial pressure.

6. Management: neurological manifestations of CVST

6.1. Patients with neurological manifestations of VITT should be transferred to and managed in a specialist neurosciences centre as rapid deterioration may occur.

6.2. Management, including anticoagulation, are complex and potentially high risk: a multidisciplinary team (MDT) comprising haematology, stroke medicine/neurology, neurosurgery, interventional neuroradiology and intensive care medicine must be available to guide individual care.

6.3. Consideration to be given to:

6.3.1. Early referral to stroke medicine, neurology, neurosurgery and interventional neuroradiology if cerebral venous sinus thrombosis identified (see Diagram 1).

6.3.2. Early specialist input to consider endovascular and other similar treatments (for example, although not limited to – mechanical thrombectomy, intra-sinus thrombolysis, although not limited to) or cerebral venous thrombectomy. Decompressive craniectomy may be considered for management intracranial hypertension refractory to medical therapy on a case-by-case basis.

Note: with endovascular treatment, the evidence is very poor for the use of venous thrombosis or thrombectomy for CVST [xi].

6.3.3. Early transfer to specialist neurosciences centre for optimal neuromedical/neurocritical care and to facilitate prompt access to all potential adjunctive treatments if proves refractory to standard care. Transfer to be expedited if:

6.3.3.1. Evidence of CVST with associated ICH or mass effect;

6.3.3.2. Extensive venous thrombosis involving dominant side or bilateral occlusion;

6.3.3.3. Deteriorating conscious level (GCS <15) or other clinical features of concern.

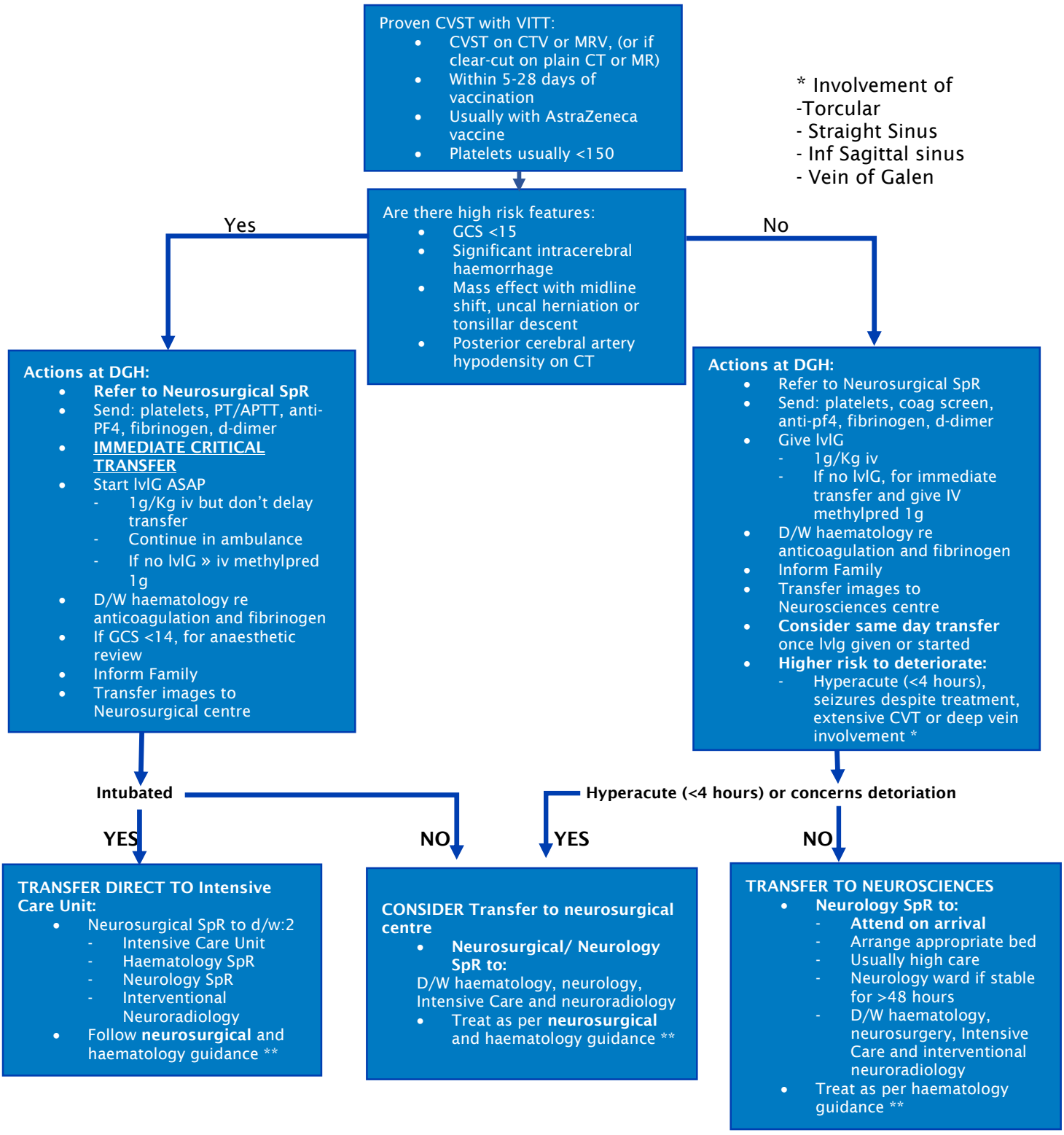
6.4. Decompressive craniectomy may be considered for management of intracranial hypertension refractory to medical therapy, or to prevent acute secondary injury due to mass [xii] effect.

6.5. ICH secondary to extensive CVST is rare, but should be considered as a diagnostic possibility in the context of recent Covid-19 vaccinations, particularly in the absence of other known risk factors.

Note: It is unclear whether platelet transfusions will exacerbate the condition, the risk/ benefit in supporting platelets <50 x 10^9/ Lon anticoagulation who a secondary cerebral bleed and not requiring procedure is unknown and therefore clear advice cannot be offered at the time of writing.

Diagram: Suggested referral flowchart for the management of cerebral venous sinus thrombosis (CVST) associated with vaccine induced immuno-thrombocytopenia and thrombosis

Adapted from OUHFT Pathway Guidance – Lead author Alastair Webb



** https://b-s-h.org.uk/about-us/news/guidance-produced-by-the-expert-haematology-panel-ehp-focussed-on-vaccine-induced-thrombosis-and-thrombocytopenia-vitt/

7. Arterial thromboembolic presentation:

7.1. Consider mechanical arterial thrombectomy as per usual guidelines but **avoiding heparin**.

7.2. Details around periprocedural and post-procedural anticoagulation or antiplatelets in VITT cases should be considered in local SOP.

8. Venous presentation (CVST):

8.1. Venous thrombosis is rapid and progressive (unlike 'conventional' CVST) without anticoagulation.

8.2. Cerebral oedema and ICH may occur due to venous congestion. Urgent/early anticoagulation to be considered in order to prevent progression which may lead to an unsalvageable intracranial haemorrhagic situation.

8.3. Interruptions to anticoagulation should be avoided as far as possible.

8.4. Urgent consideration may be given to neuroradiological intervention thrombectomy to re-establish venous drainage in emergent patients, on a case-by-case basis.

8.5. For significant CVST consider mechanical thrombectomy to restore venous outflow.

Note: see above regarding EVT.

9. Neurosurgical interventions

9.1. If neurosurgical procedure indicated (e.g. intracranial pressure monitoring, external ventricular drain, haematoma evacuation, or decompressive craniectomy) and thrombocytopenia needs to be corrected, then platelet transfusion may be given if primary treatment has been instituted.

9.2. Invasive intracranial pressure (ICP) monitoring should be considered on a case-by-case basis for guiding management of intubated patients with suspected intracranial hypertension. Ventriculostomy may also be considered together with medical interventions for ICP control. There may be a role for decompressive craniectomy as salvage therapy in patients with uncontrollable intracranial hypertension or mass effect but should be evaluated on an individual basis.

9.3. Consider anticoagulation within 6 hours (provide adequate haemostasis) with FFP and platelet cover perioperatively.

9.4. Post-operative IVIg 1g/kg according to local guidance.

Note: the benefit of surgery, particularly decompressive craniectomy, for refractory raised intracranial pressure secondary to CVST remains uncertain and should be decided on a case-by-case basis.

10. Research samples

10.1. Send samples of serum to Colindale for COVID-19 antibody testing and EDTA for whole genome sequencing (consent required) as per Expert Haematology Panel Guidance.

10.2. For EDTA samples please email gel@liverpoolft.nhs.uk with the patient details.

10.3. Serum for antibody test and storage should be sent to Colindale:

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/E50m_lab_request_form_vw_2289_01.pdf

11. Patient rights

11.1. Shared decision making between patients, family and clinicians is crucial. Active treatment may save lives but leave patients with severe disability.

11.2. Consent should be sought regarding submissions to EDTA.

12. Organ donation

12.1. NHS Blood and Transplant have issued guidance on the organ donation from patients with VITT - current NHSBT guidance recommends caution due to the potential of triggering a similar phenomenon in the recipient. Referral of potential donors to NHSBT should occur as per usual practice and donation potential will be carefully evaluated on a -by-case basis. More information here: https://www.odt.nhs.uk/covid-19-advice-for-clinicians/

and here,
https://nhsbtdbe.blob.core.windowsnet/umbraco-assets-corp/22975/inf1569.pdf

13. Notification and Reporting

13.1. All suspected cases of VITT ('VATT') **must** be referred to the Expert Haematology Panel 2pm daily MDT meeting by email: uclh.vatt@nhs.uk

13.2. All cases of thrombosis with thrombocytopenia after COVID-19 vaccination **must** be reported to Public Health England via this link: https://cutt.ly/haem_AE

13.3. Additionally all cases of thrombosis or thrombocytopenia after COVID-19 vaccination **must** be reported to the MHRA via the Yellow Card system:
https://coronavirusyellowcard.mhra.gov.uk/
https://coronavirus-yellowcard.mhra.gov.uk/

13.4. Please consider reporting all CVST cases to CAIAC_public [xiii]

14. For further specialist information

14.1. This guidance should be read in conjunction with the latest guidance on 'Blood Clotting following COVID-19 Vaccination at:
COVID-19 vaccination and blood clotting - GOV.UK (www.gov.uk)

14.2. Refer to the guidance produced by the Expert Haematology Panel hosted by the British Society for Haematology (BSH): https://b-s-h.org.uk/about-us/news/covid-19-updates/

14.3. Guidance produced from the Expert Haematology Panel (EHP) focussed on syndrome of Thrombosis and Thrombocytopenia occurring after coronavirus vaccination:
https://b-s-h.org.uk/media/19512/guidance-version-10-on-mngmt-of-thrombosis-with-thrombocytopenia-occurring-after-c-19-vaccine_20210401.pdf

14.4. Society of British Neurological Surgeons: Management of cerebral venous sinus thrombosis following Covid-19 vaccination:
https://www.rcseng.ac.uk/-/media/cvstguide_--1942020.pdf

14.5. ABN guidance on vaccination for COVID-19 and neurological conditions updated 26 April 2021 (attached).

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Version Control

Version	Date	Who	Notes
001	17.05.2021	C.Thompson	For publication on 17.05.2021

[i] In previous guidance the term VATT was used to indicate vaccine **associated** thrombosis and thrombocytopenia ('*VATT*'). Based on guidance provided by the BSH, there is a clearer correlation and the term vaccine **induced immune thrombosis and thrombocytopenia** ('**VITT**') is now being used.
[ii] See Public Health England, 'Blood Clotting following COVID-19 Vaccination: Information for Health Professionals', p.7, Apr. 2021.
[iii] Information for healthcare professionals on blood clotting following COVID-19 vaccination - GOV.UK (www.gov.uk):
Information correct up to 28 April, 2021:

- 242 reported cases of thrombosis events with low platelets of which 93 were CVST, out of a total of 22.4 million first doses of the COVID-19 vaccine in the UK.
- Small number of reports by the US Centres for Disease Control and prevention (CDC) and Food and Drug Administration (FDA) of a similar syndrome following receipt of the Johnson & Johnson/ Jansen COVID-19 vaccine. Following a detailed investigation and temporary pause the CDC and FDA announced resumption on the use of these vaccines on 23 April, 2021. **This vaccine is not currently approved for use in the UK.**
- There is currently no evidence to suggest these rare events occur follow administration of either the Pfizer/ BioNTech or Moderna vaccines which are available in the UK.

[iv] Smadja DM, Yue QY, Chocron R, Sanchez O, Lillo-Le Louet A. Vaccination against COVID-19: insights from arterial and venous thrombosis occurrence using data from VigiBase. *Eur Respir J.* 2021.
[v] See Information for healthcare professionals on blood clotting following COVID-19 vaccination - GOV.UK (www.gov.uk), in particular Para. 6 (which only specifies offering an alternative to the AstraZeneca vaccine for unvaccinated patients younger than 39); Para. 9 (suggesting that there is only anecdotal evidence that incidence of occurrence is higher amongst women); Para. 10 does outline that there is an increasing trend of incidence with decreasing age amongst adults, however there is no clear evidence that there is a linkage here yet; Para. 25 indicates that for those on contraception and younger than 40, an alternative to the AstraZeneca vaccine should be offered but does indicate that the BSH (as of 28 April, 2021) indicates that there is currently no evidence that individuals with a prior history of thrombosis or known risk factors for thrombosis are more at risk of developing the immune complication reported after the AstraZenca vaccine (see https://www.fsrh.org/documents/fsrh-ceu-statement-cerebral-venous-sinus-thrombosis-astrazeneca/); Para. 26 only indicates that given that there is more evidence regarding pregnancy and the COVID-19 vaccine amongst administration of the Pfizer and Moderna vaccines that these are preferable to the AstraZeneca vaccine (currently). More information is available at: Use of the AstraZeneca COVID-19 vaccine: JCVI statement - GOV.UK (www.gov.uk)
[vi] This is consistent as per BSH guidance: https://b-s-h.org.uk/media/19539/guidance-version-13-on-mngmt-of-thrombosis-with-thrombocytopenia-occuring-after-c-19-vaccine_20210407.pdf. There is some variation in other guidelines:

- Society of British Neurological Surgeons, 19 April, 2021 'Management of cerebral venous sinus thrombosis following Covid-19 vaccination/ A neurosurgical guide' states 5 to 30 days.
- Association of British Neurologists, 26 April, 2021 'ABN guidance on vaccination for COVID-19 and neurological conditions updated 26 April 2021' uses the following language, "mostly 7 – 14 days".

The range given in the guidelines above are consistent with these ranges.
[vii] Cases present with thrombotic events predominantly affecting the cerebral venous sinuses, as well as pulmonary embolism and arterial ischaemia. See:
Expert Haematology Panel, 'Guidance produced from the Expert Haematology Panel (EHP) focussed on Covid-19 Vaccine induced Thrombosis and Thrombocytopenia (VITT)', Apr. 2021.
[viii] Lee E-J, Cines DB, Gemsheimer T, et al. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. *American Journal of Hematology*. 2021, 96(5): 534 – 537.
[ix] As per BSH guidelines.
[x] As per BSH guidance.
[xi] See the findings of the TO-ACT trials; see:

- Effect of Endovascular Treatment With Medical Management vs Standard Care on Severe Cerebral Venous Thrombosis: The TO-ACT Randomized Clinical Trial | Cerebrovascular Disease | JAMA Neurology | JAMA Network
- Effect of Endovascular Treatment With Medical Management vs Standard Care on Severe Cerebral Venous Thrombosis: The TO-ACT Randomized Clinical Trial - PubMed (nih.gov)
- http://2019.eso-conference.org/2018/Documents/TO-ACT%20Coutinho.pdf

[xii] Indicated due to excessive mass effect causing secondary injuring/ coning.
[xiii] See BASP guidelines in this regard:
BASP-email-COVID-CVST-INFORMATION-AND-ADVICE-v2-For-website.pdf