This guidance is based primarily on expert opinion from the Organ and Tissue Donation and Transplantation (OTDT) Clinical Team and UK experts in haematology and thrombosis. We will update this guidance regularly and therefore ask that you access this information electronically as opposed to printing to ensure you always refer to the most recent version.

1.0: Introduction

Vaccine induced thrombosis and thrombocytopenia (VITT), also termed vaccine induced prothrombotic thrombocytopenia (VIPIT) is a rare syndrome of:

- thrombosis (most frequently cerebral venous sinus thrombosis but venous or arterial thrombosis may occur at any site), and/or intracranial haemorrhage
- thrombocytopenia (platelet count of < 150 x 10^9/l)
- high levels of D-dimer (usually >4000 µg/L), often with low fibrinogen levels
- with positive testing for antibodies to Platelet Factor 4 (PF4) (heparin induced thrombocytopenia; HIT test) by ELISA, despite the absence of prior exposure to heparin treatment.

A link to current guidance on the diagnosis and care of patients with VITT derived by the Expert Haematology Panel (EHP) can be found here: https://b-s-h.org.uk/about-us/news/covid-19-updates/

The guidance below relates to deceased organ donors who meet the EHP criteria for definite (meets all clinical criteria and PF4 antibody confirmed positive) or probable (meets all clinical criteria and PF4 antibody result awaited) diagnosis of VITT.

2.0 Safety of organ donation from deceased donors with VITT:

- VITT is thought to be driven by an auto-antibody that leads to platelet activation. In conditions with an auto-immune patho-physiological basis, current NHSBT guidance recommends caution when utilising organs with high passenger leucocyte burden (e.g. liver, lung, small bowel and pancreas) due to the potential of transmitting immune cells that could trigger a similar auto-immune phenomenon in the naive recipient (passenger lymphocyte syndrome; PLS).
- To date other than the UK experience of organ donation following possible VITT diagnosis there are no other published case reports or case series describing such outcomes.
- As of 31st May 2021, 45 UK patients have received kidney (30), simultaneous pancreas & kidney (1), liver (9), lung (1), islet (1), or heart (3) transplants from 18 deceased donors with proven or probable VITT. Recipient outcomes are being carefully monitored and are due to be published imminently.

3.0 Guidance

3.1 Donor organ selection

- Although all organs can be used after evaluation of risks vs benefits to individually matched recipients, there is potential for VITT to develop in the organ recipient. This risk is likely to be higher in liver, lung, pancreas, and small bowel transplants. Risk might also be associated with a recipient developing VITT themselves after exposure to coronavirus vaccination in the preceding 28 days prior to transplantation. Hence a careful review and MDT decision on risks vs benefits and detailed informed patient consent is recommended before utilisation of these organs. At the present time it is felt that accepting liver, lung, pancreas or small bowel transplantation should only happen in the most urgent situations

and with clear documentation of the MDT discussion and the consent processes. Islet transplantation is deemed to be low risk of passenger leucocyte syndrome and could proceed after careful discussion and documentation of risk versus benefits with the patient.

- Organs may bear petechiae in many donors who have very low platelet counts. This should not deter use of the organ unless there is evidence of poor parenchymal flush with cold perfusate.
- VITT in the donor or treatment of the donor with IVIg following diagnosis of VITT is not a contraindication to tissue donation (pulmonary & aortic grafts, arteries, bone, tendons meniscus, skin and cornea /sclera). These tissues are not considered to be at risk for passenger lymphocyte syndrome.

3.2 Organ retrieval

- Care of the donor in the immediate pre-retrieval phase and during retrieval including the use of systemic anticoagulants and platelet transfusions
    - Although it is unknown whether platelet transfusion could exacerbate VITT, platelet transfusion should be avoided where possible before or during retrieval. During transplantation to the recipient, caution is appropriate. Necessary peri-operative platelet transfusion is not contra-indicated
    - At this stage it is not known if use of Unfractionated Heparin (UFH) in the donor at time of retrieval or NRP could contribute to intravascular thrombosis in the organ. Therefore, alternative regimens using argatroban are described below (Appendix A & B).

3.3 Care of recipient

Post-transplant care of recipient of an organ from a donor with definite or probable VITT

- In most respects, care will be as per standard protocols. Thromboprophylaxis can be given in the normal way unless VITT is suspected. It is safe to use Heparin as part of cardio-pulmonary bypass when using hearts from donors with suspected/confirmed VITT.
- The risk for emergence of VITT is likely to be highest in the first 10-20 days post-transplant. If VITT is suspected, it is recommended to stop any form of UFH or Low Molecular Weight Heparin (LMWH) and using intermittent pneumatic compression or fondaparinux.
- Recommended additional monitoring: pre-transplant platelet count, daily FBC and D-dimer on POD 0-7, three/week POD 7-21 and then on POD 28 (or as clinically indicated). Test for PF4 antibodies at baseline and weekly for a minimum of 4 weeks (testing beyond 4 weeks as clinically indicated). Low threshold for investigating for venous or arterial thrombosis (including graft vasculature) by appropriate imaging

- When to suspect VITT in a recipient post-transplant
    - On serial monitoring, a rise in D-dimer levels of >20% or fall in platelet counts of >20% should trigger closer surveillance, including testing for PF4 antibodies.
    - Consider with any new thrombosis POD 0-21 associated with thrombocytopenia and a high D-dimer. It should also be considered if no thrombosis but a thrombocytopenia with a platelet count lower than expected (it is accepted that thrombocytopenia is

common after some organ transplants) with a raised D-dimer (usually >4000 µg/L) and a low Claus fibrinogen.

- What to do if VITT is suspected
    - Consider other causes of thrombocytopenia (e.g. immunosuppression, sepsis)
    - Avoid platelet transfusions and all forms of heparin including heparin-based flushes
    - Test for PF4 antibodies
    - Seek prompt expert haematology advice. Urgent treatment such as intravenous immunoglobulins may be required. Contact the regional haemostasis and thrombosis team on-call out of hours, and an expert haematology panel can also be contacted via the regional ODT manager on-call for case discussion and support.
    - Under the Quality and Safety of Organs Intended for Transplantation Regulations, any incident that has any undesired, unintended consequences for any recipient must be reported as per the usual channels: https://safe.nhsbt.nhs.uk/IncidentSubmission/Pages/IncidentSubmissionForm.aspx
    - Establish local systems to complete and return to NHSBT the recipient VITT monitoring form including all relevant data up to POD 28. If such follow up data is not received by POD 35, NHSBT will make contact with the lead clinician and recipient coordinator to expedite this data submission. Timely, accurate and national data collection are critical to advance understanding and update guidance on safe care of organ transplant recipients who may develop post transplantation VITT. The current version of recipient VITT monitoring form is available at **https://www.odt.nhs.uk/covid-19-advice-for-clinicians/**

This guidance will be updated with emerging evidence in consultation with relevant specialist societies and experts.

Appendix A: Protocol for the use of Argatroban in organ retrieval – DBD and DCD.
V2. 16.04.21

Background

Donor surgery may require organ retrieval without the use of heparin in cases where there is a suspicion of anti-platelet factor 4 antibody activity (e.g. VITT, HIT). However, full anticoagulation is still required, using a non-heparin alternative.
Few data are available regarding the use of argatroban in organ donors, an unlicenced indication. In a recent UK DBD donor, a dose of 350 microgram/kg (0.35mg/kg) was given intravenously over 3-5 minutes instead of the usual heparin bolus of 300U/kg. Cross clamp proceeded directly thereafter, with no evidence of intravascular coagulation. There were no bleeding complications in the recipients.
The product insert directs 'when there is no alternative, (anticoagulant) therapy could be initiated with a bolus dose of 350 microgram/kg over 3 to 5 minutes. Therefore, the use described here corresponds with the manufacturer's instructions.

Preparation

Argatroban is available as a concentrated product in a single use vial containing 50mg in 50 ml. It is widely available from pharmacy stores. You may need to discuss with a haematologist if their approval is required for release.
It is also provided as 250mg in 2.5ml, which requires dilution prior to use. This can be added to 250ml normal saline (1mg/ml), and then used in the same way as the pre-prepared vials described above. **The doses and volumes below are based on a working concentration of 1mg/ml.**

Argatroban has been tested in Edinburgh NORS centre, and can be added to Hartmanns, UW, Soltran or HTK. In these test preparations, 50mg at 1mg/ml was added to a 1 litre bag of each fluid at 4^{o}C, with no cloudiness or precipitation.

Procedure

Dose: The dose depends on the weight of the donor. If in doubt, or if the weight is estimated, it is better to err on the higher side to avoid intravascular coagulation and organ loss after cross clamp. A dosing chart is appended overleaf for ease of calculation. Figures are rounded up to the nearest ml.

DBD

A 70kg DBD donor is given 25 mg (25ml of 1mg/ml solution; 70 x 0.35mg) intravenously over 3-5 minutes, a few minutes prior to cross clamp. Proceed as normal thereafter.

DCD

In a 50 kg DCD donor, 18mg (18 ml of 1mg/ml solution; 50 x 0.35mg) is added to the first bag of intra-aortic flush. The DCD retrieval can then proceed with further preservation solution as usual, according to organs to be retrieved.

Donor Dosing Chart (0.35mg/kg)

40 kg	14mg (14ml)
50 kg	18mg (18ml)
60 kg	21 mg (21ml)
70 kg	25 mg (25ml)
80 kg	28mg (28ml)
90 kg	32 mg (32ml)
100 kg	36mg (36ml)
110 kg	39mg (39ml)
120 kg	42mg (42ml)

Should there be a clotting issue, or perhaps a cross reaction with any drugs or solutions, please communicate urgently with NHSBT (ian.currie@nhsbt.nhs.uk).

If you perform a retrieval using this drug, please report to NHSBT (ian.currie@nhsbt.nhs.uk) as soon as possible to describe handling characteristics or other issues, even if there were no concerns.

Use of Argatroban must be recorded on the 'A' forms, for traceability, in case there are unintended effects.

This protocol may be updated at any time. Please ensure you are accessing the current version of the protocol via OTDT clinical website

References:

Argatroban Anticoagulation for Adult Extracorporeal Membrane Oxygenation: A Systematic Review. Janos Geli et al. J Intensive Care Medicine 2021. DOI: 10.1177/0885066621993739.

Management of coagulation during cardiopulmonary bypass. Britta U. O'Carroll-Kuehn MD FRCA Hanif Meeran MBBS FRCA. Continuing Education in Anaesthesia, Critical Care & Pain | Volume 7 Number 6 2007. Doi:10.1093/bjaceaccp/mkm036

Authors: IS Currie, F Hunt, M Berman, B Hunt

Appendix B: Protocol for the use of argatroban in DCD NRP organ retrieval.
V2. 16.04.21

Background

Donor surgery may require organ retrieval without the use of heparin in cases where there is a suspicion of anti-platelet factor 4 antibody activity (e.g. VITT, HIT). However, full anticoagulation is still required, using a non-heparin alternative.
Few data are available regarding the use of argatroban in organ donors, an unlicenced indication. In a recent UK DBD donor, a dose of 350 microgram/kg (0.35mg/kg) was given intravenously over 3-5 minutes instead of the usual heparin bolus of 300U/kg. Cross clamp proceeded directly thereafter, with no evidence of intravascular coagulation. There were no bleeding complications in the recipients.
The product insert directs 'when there is no alternative, (anticoagulant) therapy could be initiated with a bolus dose of 350 microgram/kg over 3 to 5 minutes'. Therefore, the use described corresponds with the manufacturer's instructions for a loading dose.

Preparation

Argatroban is available as a concentrated product in a single use vial containing 50mg in 50 ml (1mg/ml). It is widely available from pharmacy stores. You may need to discuss with a haematologist if their approval is required for release. You will need a minimum of 2 x 50ml vials per donor and perhaps more for donors > 100kg.
It is also provided as 250mg in 2.5ml, which requires dilution prior to use. This can be added to 250ml normal saline (1mg/ml), and then used in the same way as the pre-prepared vials described above. **The doses and volumes below are based on a working concentration of 1mg/ml.**

Procedure for NRP

Prime Dose: The dose depends on the weight of the donor. If in doubt, or if the weight is estimated, it is better to err on the higher side to avoid intravascular coagulation and organ loss. A loading dose chart is appended overleaf for ease of calculation. Figures are rounded up to the nearest mg. **The loading dose is 0.35mg/kg**, **which should be added to the prime after asystole**, to avoid degradation. The prime dose should be calculated on the donor body weight, irrespective of the perfused weight.

Monitoring: The appropriate interval for repeat argatroban dosing in NRP is unknown. The half-life of Argatroban is 45 minutes. Renal dysfunction does not affect the half-life. In cardiopulmonary bypass (CPB), the ACT is measured routinely every 30 minutes, beginning at time zero. **Initial ACT should be >480 seconds in NRP, as for CPB. ACT is also measured after additional boluses are given,** to ensure a therapeutic effect.
To ensure the donor remains adequately anticoagulated, **ACT is repeated as a routine at 30, 60 and 90 minutes on NRP. ACT less than 400 seconds must be avoided. The ACT target is 480 seconds or greater.**

Repeat dosing: The appropriate repeat bolus dose and interval is unknown. However, the half life of 45 minutes strongly suggests that further boluses will be required on NRP. It is suggested that an ACT between 400-480 seconds prompts a repeat bolus of 1/3 that of the loading dose. An ACT <400 seconds prompts a repeat bolus of 1/2 that of the loading dose. ACT is then measured 5 minutes after administration, to ensure ACT is now therapeutic. Further ACT estimations are carried out as routine (30, 60 and 90 minutes) as described.

NRP teams may wish to consider risks and benefits of the full 2 hour duration of NRP, whilst using this untested anticoagulant. Any concern regarding clot formation should prompt urgent action and early consideration of cold flush.

Donor Dosing Chart (Loading; 0.35mg/kg)

Donor Weight	Loading Dose
40 kg	14mg (14ml)
50 kg	18mg (18ml)
60 kg	21 mg (21ml)
70 kg	25 mg (25ml)
80 kg	28mg (28ml)
90 kg	32 mg (32ml)
100 kg	36mg (36ml)
110 kg	39mg (39ml)
120 kg	42mg (42ml)

Should there be a clotting issue on the circuit, or grossly anomalous (low) ACT values, or perhaps a cross reaction with any drugs or solutions, please communicate urgently with NHSBT (ian.currie@nhsbt.nhs.uk)

If you perform a retrieval using this drug, please report to NHSBT (ian.currie@nhsbt.nhs.uk) as soon as possible to describe handling characteristics or other issues, even if there were no concerns.

Use of Argatroban must be recorded on the 'A' forms, for traceability, in case there are unintended effects.

This protocol may be updated at any time. Please ensure you are accessing the current version of the protocol via OTDT clinical website.

References:

Argatroban Anticoagulation for Adult Extracorporeal Membrane Oxygenation: A Systematic Review. Janos Geli et al. J Intensive Care Medicine 2021. DOI: 10.1177/0885066621993739.

Management of coagulation during cardiopulmonary bypass. Britta U. O'Carroll-Kuehn MD FRCA Hanif Meeran MBBS FRCA. Continuing Education in Anaesthesia, Critical Care & Pain | Volume 7 Number 6 2007. doi:10.1093/bjaceaccp/mkm036

Authors: IS Currie, F Hunt, M Berman, C Watson, B Hunt