1. Introduction

This guideline is to guide investigation and management of heparin induced thrombocytopenia.

2. Scope

This guideline applies to all patients managed within UHL who are exposed to heparin and its derivatives. Further expert guidance may be required for certain groups of patients (eg pregnant women, children <18 years)

3. Recommendations, Standards and Procedural Statements

3.1 Background

Heparin-induced thrombocytopenia is a rare immunological side effect of heparin that carries a significant risk of thrombosis.
The diagnosis is made on the basis of clinical criteria and confirmed by the detection of 'HIT' antibodies.
All patients who receive heparin should have a baseline platelet count performed.

Those patients more at risk of HIT (such as any patients on unfractionated heparin or post cardio-pulmonary bypass patients) should have a repeat platelet count checked every 2-3 days from day 4 onwards until heparin is stopped.

In this guidance, "HIT" refers to type 2 HIT rather than type 1; type 1 is a benign early fall of platelets following heparin exposure and is not associated with morbidity.

3.2 The Clinical Manifestations of HIT

HIT should be suspected in any patient on heparin who:

- Has a platelet count fall by 30% or more

- and/or develops a new thrombosis or skin allergy (even if the platelet count remains >150x10^9/L)

However, a platelet count of <10x10^9/L is **unlikely** to be due to HIT and other causes (such as ITP/quinine/drugs etc) should be considered.
The manifestations of HIT include thrombocytopenia in the context of:

- **Venous thrombosis** including deep vein thrombosis (DVT), coumarin-induced venous limb gangrene, pulmonary embolism (PE), cerebral venous thrombosis, acute adrenal haemorrhagic infarction
- **Arterial thrombosis** including lower limb artery thrombosis, CVA, myocardial infarction
- **Skin lesions** at heparin injection sites
- **Acute systemic reaction** post heparin bolus (chills, rigors)
- **DIC** with hypofribrinogenaemia

3.3 Timing of HIT

The platelet count typically falls (or symptoms develop) at least **5 days** after the onset of heparin (indicating the time required to develop the immunological response). HIT is more unlikely if the fall occurs after day 10 of exposure, and in these cases another cause should be considered. The exceptions to this include:
Rapid onset HIT – Associated with rapid fall in platelets soon after exposure to heparin. Generally occurs in patients with heparin exposure in the previous 3 months (due to pre-existing antibodies).
Delayed onset HIT – HIT may develop after heparin administration has been stopped or persist for several weeks. It has been shown that substantial platelet acvitvation *in vitro* can be caused by some patient sera even in the absence of added heparin.

3.4 Diagnosis of HIT: (see appendix 1.)

Pre-test Probability – '4Ts' scoring system

The probability of HIT should be initially judged on clinical grounds and can be assessed using a pre-test probability score known as the '4Ts' scoring system originally described by Warkentin *et al* and later validated by Lo *et al* 2006
Re-printed from Lo et al 2006

- Patients can be excluded from a diagnosis of HIT by a **low pre-test probability score** (0-3) without the need for laboratory investigations and other causes for thrombocytopenia should be considered
- If the pre-test probability of HIT is not low, all heparin (including bolus flushes, heparin infiltration) should be stopped and an alternative anticoagulant started at treatment dose whilst laboratory tests are performed

3.5 Laboratory Investigations (see appendix 4)

HIT occurs due to the development of antibodies directed towards the complex formed by heparin and PF4 (platelet factor 4) which is released from platelets due to the effect of heparin. The detection of these antibodies confirms the diagnosis of HIT in those patients with an intermediate or high pre test probability. This is done in Leicester using the AcuStar HIT-IgG assay
The test is performed at the Special Haematology Lab, Level 2 Sandringham Building, Leicester Royal Infirmary. Please inform the lab on extension 6619 prior to sampling and

all cases should be discussed with the haematological medical team prior to testing. Samples from the LGH and GH need to be sent to their local haematology lab and transported to the LRI for testing.
Testing requires 1 x 4.9ml brown top serum gel sample. This must be processed within 4 hours of being taken as delayed testing can lead to erroneous results.
Urgent results can be available within 2 hours of being received within the Special Haematology lab. All other results should be available within 24 hours of receipt. Routine testing is not available out of hours, but can be arranged if required. **All** test requests should be discussed with the haematology medical team.

3.6 Management of HIT (See appendix 2)

General Treatment

Once a diagnosis of HIT is suspected, all heparin and low molecular weight heparin or derivatives **must** be stopped.

1. As there is a high frequency of thrombosis despite stopping heparin (up to 50%), an alternative rapidly acting anticoagulant at therapeutic dose should be commenced.

2. Therapeutic anticoagulation should continue even after the platelet count has recovered

3. Platelet transfusions should not be given for prophylaxis due to an increased risk of thrombosis, but may be used in the event of significant bleeding. Prothrombin complex concentrates in the context of bleeding in HIT is contraindicated.

Specific treatments

In Leicester, options for alternative anticoagulation are Fondaparinux and “DOACs” (Direct oral anticoagulants); or Argatroban (for use in the presence of renal failure, acutely unwell patients).

3.6.1 Fondaparinux (Please see UHL policy for unlicenced drug use B29/2004)
Fondaparinux is not licensed for use in HIT but is accepted as a safe alternative anticoagulant for managing the condition. Fondaparinux is a synthetic factor Xa inhibitor given by subcutaneous injection. Therapeutic doses should be given in the context of HIT and these are weight dependent.
Dosing schedule:

- <50kg: 5mg OD
- 50-100kg: 7.5mg OD
- >100kg: 10mg OD

Monitoring is with anti-Xa levels (“fondaparinux assay”) taken 4 hours post dose. These may be required in those with extremes of weight (<50kg or >90kg), age or renal impairment.
There is no known antidote for fondaparinux. Protamine has no effect.
The use of fondaparinux in UHL has been audited by the pharmacy team and shown to be a safe alternative for use in HIT.

3.6.2 Argatroban
Argatroban is a direct thrombin inhibitor given by intravenous infusion. It undergoes hepatic metabolism and is therefore the anticoagulation of choice in HIT in the context of renal impairment. Dose adjustment will be required in patients with liver failure, the critically ill or post cardiac surgery. Argatroban causes a prolonged APTT and this is used for monitoring purposes and dose adjustment, with a target APTT ratio of 1.5-3.0.

Argatroban also causes prolongation of the PT. This is not used for monitoring purposes but needs to be considered when warfarin is commenced.

Dosing schedule

- No IV bolus required
- IV infusion starting dose of 2microgram/kg/min for patients with no evidence of liver failure
- IV infusion starting dose of 0.5microgram/kg/min in those critically ill patients, post cardiac surgery or with liver failure
- IV infusion starting dose of 1microgram/kg/min as an alternative if required
- MAXIUMUM DOSE 10micrograms/kg/min

	Initial Infusion Rate **2 microg/kg/min**		Critically Ill/Hepatically impaired patients Initial infusion rate **0.5 microg/kg/min**		Initial infusion rate **1 microg/kg/min**	
APTT (s)	**Infusion Rate change**	**Next APTT**	**Infusion Rate change**	**Next APTT**	**Infusion Rate change**	**Next APTT**
< 1.5 times baseline	Increase by 0.5 microg/kg/min. (*i.e*. increase by one-quarter of initial rate)	2 hours	Increase by 0.1 microg/kg/min. (*i.e*. increase by one-fifth of initial rate)	4 hours	0.25 microg/kg/min (*i.e*. increase by one-quarter of initial rate)	2 hours
1.5-3.0 times baseline (not exceeding 100 s)	No change	2 hours; after 2 consecutive APTT's within target range, Check at least once per day	No change	4 hours; after 2 consecutive APTT's within target range Check at least once per day	No change	4 hours; after 2 consecutive APTT's within target range Check at least once per day
> 3.0 times baseline or > 100 s	Stop infusion until the APTT is 1.5-3.0 times baseline; Resume at half of the previous infusion rate	2 hours	Stop infusion until the APTT is 1.5-3.0 times baseline; Resume at half of the previous infusion rate	4 hours	Stop infusion until the APTT is 1.5-3.0 times baseline; Resume at half of the previous infusion rate	2 hours

3.6.3 Direct oral anticoagulants (DOACs).(Please see UHL policy for Unlicenced drug use B29/2004)

These anticoagulants are not licenced for the management of acute HIT but there are numerous case reports/series of their use, and in vitro studies have failed to show heparin cross reactivity. They are not appropriate for patients with significant renal impairment (CrCl<30ml/min) or patients who are acutely unwell.

If anti-Xa levels are required, 2 citrate blood tubes (green top) are needed. These are processed at LRI only and therefore, if required please discuss with the Special Haematology lab (extension 6619) or Haematology SpR on call. These are not routinely available out of hours but can be arranged if required urgently.

Conversion to Warfarin (see appendix 3)
Patients with confirmed HIT should be converted on to warfarin once the platelet count has recovered and remains stable.
Warfarin should be initiated by slow induction; i.e. avoid doses >5mg on initiation.
If fondaparinux is used, it must be continued at the same time overlapping with warfarin until 2 consecutive INRs, > 24 hours apart are within the therapeutic range (INR 2-3).
If argatroban is used, it must be overlapped with warfarin for at least 5 days and continued until patients have an INR ≥ 4 on 2 occasions, > 24 hours apart.
A DOAC can be continued without conversion to warfarin.

3.7 Duration of anticoagulation (see appendix 3)

1. In patients with isolated HIT, without thrombosis, therapeutic anticoagulation should continue for 4 weeks to cover the period of highest risk. These patients should be monitored for signs of thrombosis.

2. In patients with HIT associated with a thrombotic complication, therapeutic anticoagulation should be continued for at least 3 months.

3.8 Follow up

All patients with confirmed HIT should be referred to the haemostasis and thrombosis team for routine follow up and post event counselling. This will enable plans for future management to be made.
Recurrence of HIT is rare, but all patients with previously confirmed HIT should ideally avoid any future use of heparin (therapeutic and prophylaxis). In these cases, fondaparinux/argatroban may be used. An exception to this can be made for urgent situations, such as cardiothoracic surgery where the established use of UFH and need for rapid reversal should be considered. All such cases may be discussed with the haemostasis and thrombosis team.

4. Education and Training

There are no specific educational requirements pertaining to this guideline.

5. Monitoring and Audit Criteria

All guidelines should include key performance indicators or audit criteria for auditing compliance,

if this template is being used for associated documents (such as procedures or processes) that support a Policy then this section is not required as all audit and monitoring arrangements will be documented in section 8 of the Policy.

Key Performance Indicator	Method of Assessment	Frequency	Lead
Satisfactory completion of HIT test request form (100%)	Laboratory audit	24m	R Gooding
All patients referred to H&T MDT	MDT audit	24m	R Gooding
All patients with confirmed HIT commenced on alternative therapeutic anticoagulant within 6 hours of diagnosis	Clinical audit	24m	R Gooding

6. Legal Liability Guideline Statement

See section 6.4 of the UHL Policy for Policies for details of the Trust Legal Liability statement for Guidance documents

7. Supporting Documents and Key References

Appendix 1: Flowchart for diagnosis of acute HIT

Appendix 2: Management options for acute HIT

Appendix 3: Anticoagulation schedule for HIT

Appendix 4: HIT assay request/MDT referral form (1 document)

References:

American Society of Haematology 2011 Clinical practice guide on anticoagulant dosing and management of anticoagulant-associated bleeding complications in adults..

Henry Watson, Simon Davidson and David Keeling British Society of Haematology Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition 2012

Treatment and Prevention of Heparin-Induced Thrombocytopenia. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. American College of Chest Physicians2012

Marta A. Miyares, Pharm , and Kyle A. Davis, Pharm Direct-Acting Oral Anticoagulants as Emerging Treatment Options for Heparin-
Induced Thrombocytopenia. Annals of Pharmacotherapy 2015, Vol. 49(6) 735–
739

David A. Garcia , MD ; Trevor P. Baglin, MBChB , PhD ; Jeffrey I. Weitz , MD , FCCP ; and Meyer Michel Samama , MDParenteral Anticoagulants
Antithrombotic Therapy and Prevention of Thrombosis,9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

UHL Trust Policies: Unlicensed Medicines Policy (Trust ref: B29/2004)

8. Key Words

HIT, HITT, Heparin induced thrombocytopenia, Thrombocytopenia, drug-induced thrombocytopenia, fondaparinux, argatroban, DOAC

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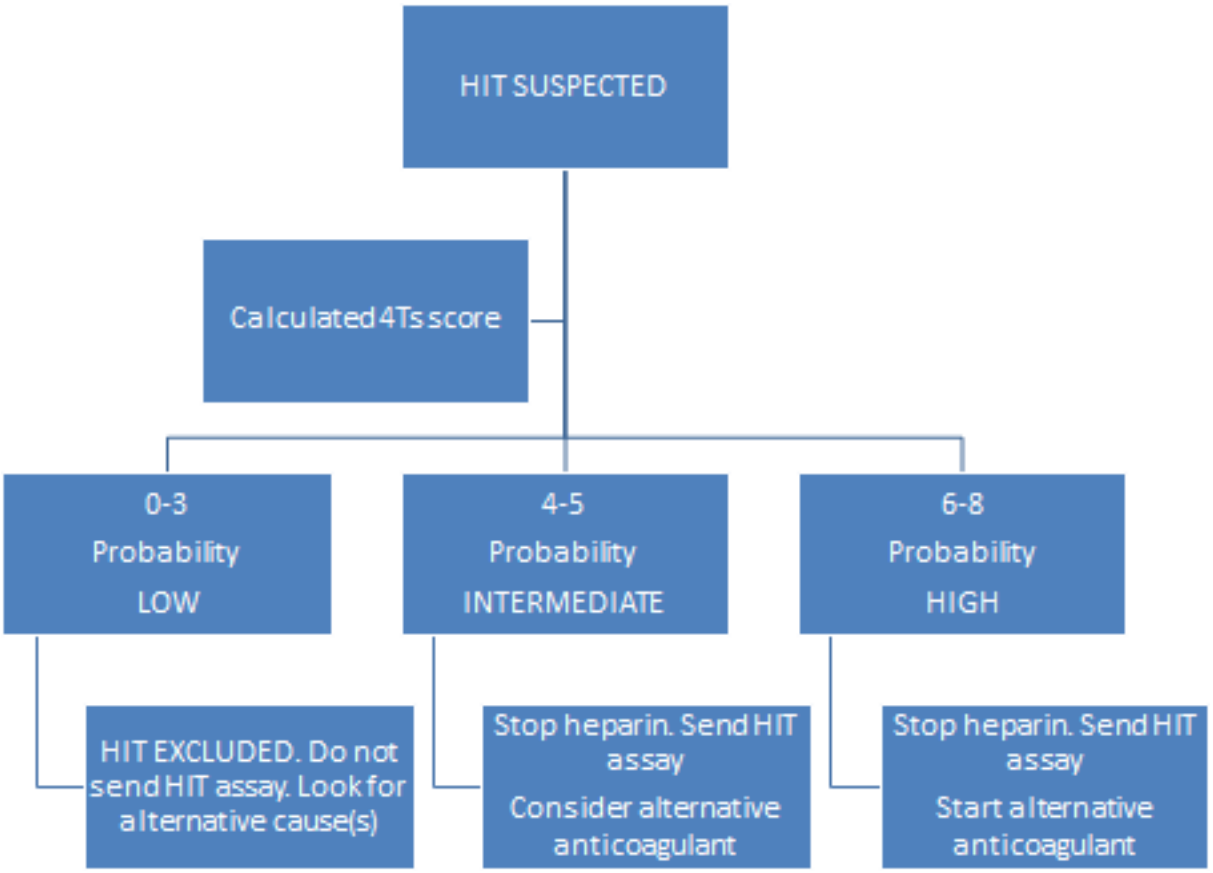
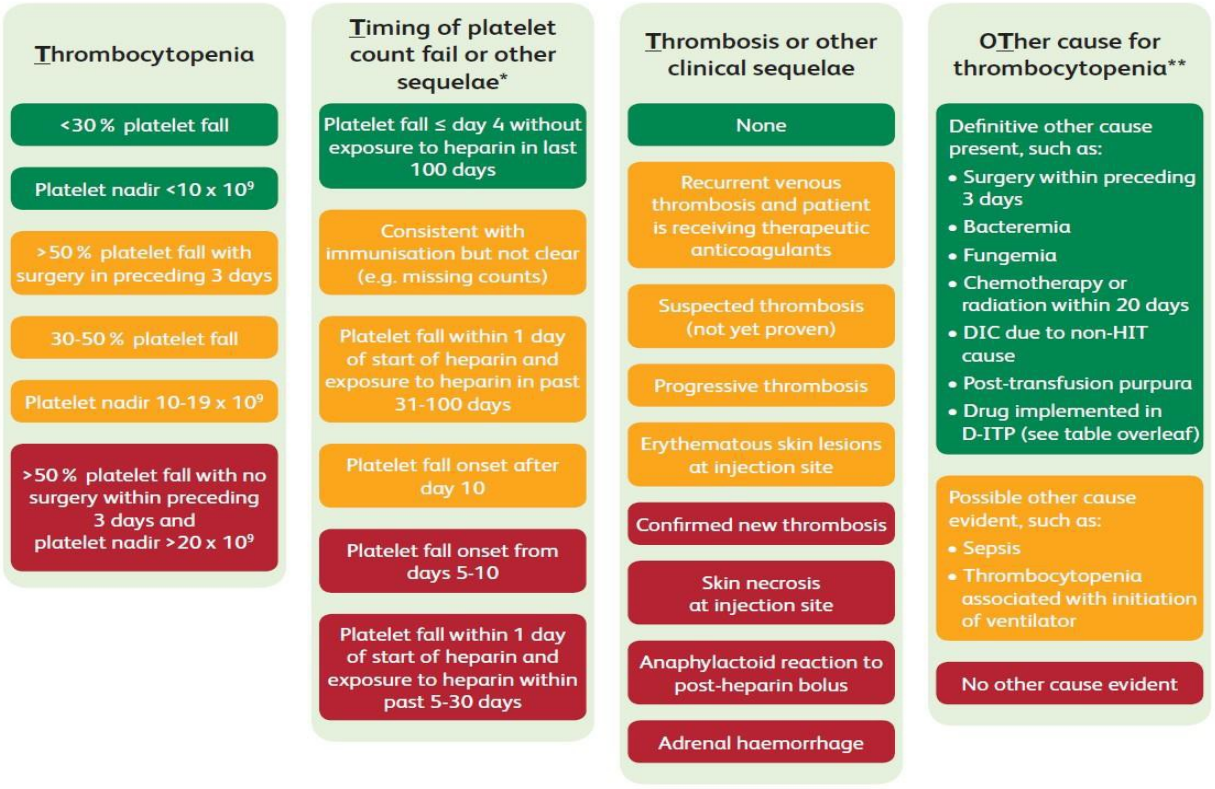
HIT appendix 1.

FLOWCHART FOR DIAGNOSIS OF HIT



For 4T score, see below.

HIT II:
Suspected diagnosis using the 4T score



* Calculate where day 0 is the first day of most recent heparin exposure.
** 2 points if necrotising heparin-induced skin lesions even if thrombocytopenia not present.

25

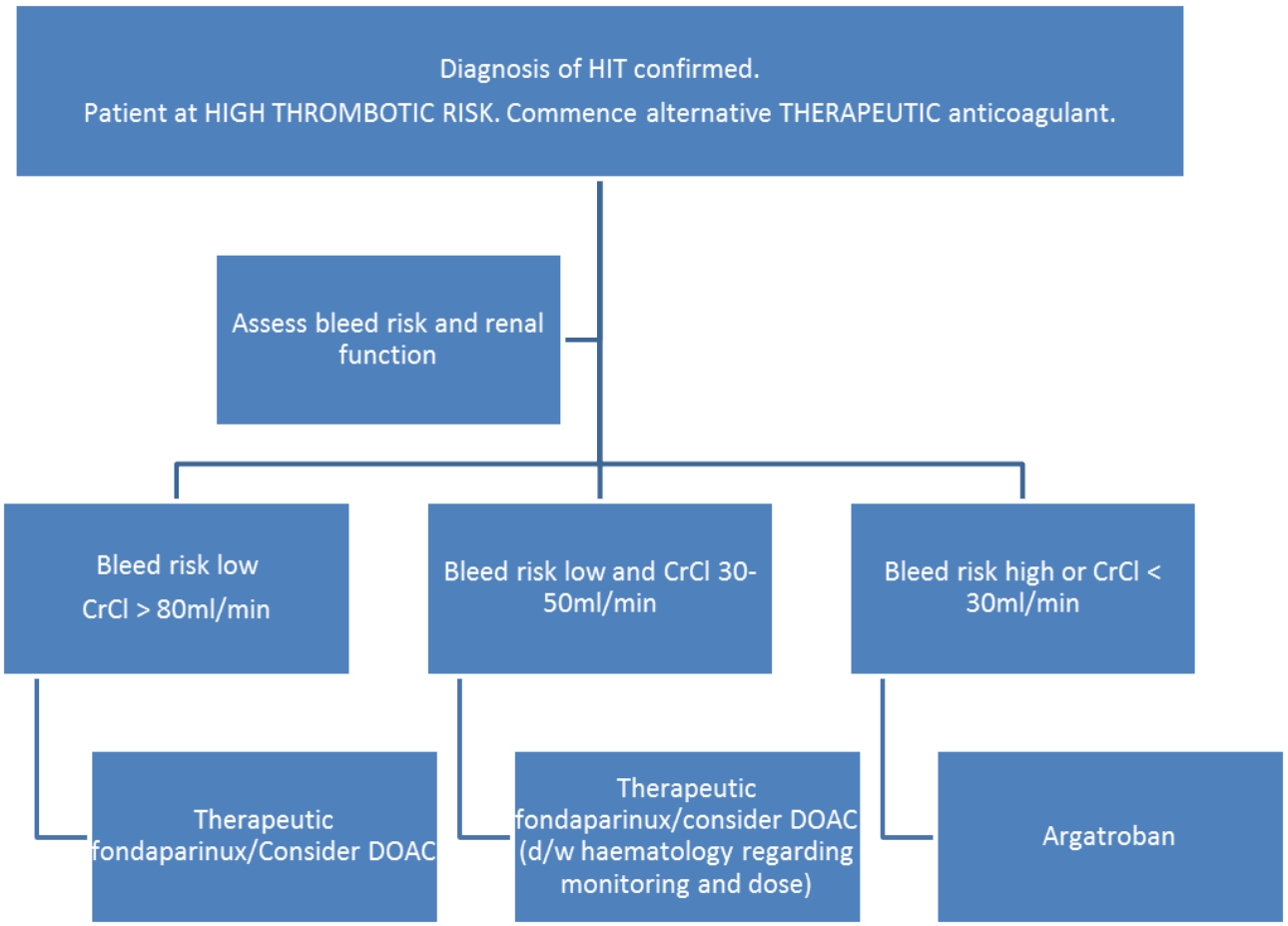
Using the 4Ts score:
Score each column for your patient in whom you suspect HIT.
Green = 0 points Amber = 1 point Red = 2 points

0-3 points	4-5 points	6-8 points
Low probability	Intermediate probability	High probability
HIT EXCLUDED	STOP HEPARIN SEND HIT ASSAY CONSIDER STARTING ALTERNATIVE ANTCOAGULANT	STOP HEPARIN SEND HIT ASSAY START ALTERNATIVE ANTICOAGULANT

HIT appendix 2

Acute HIT Management options

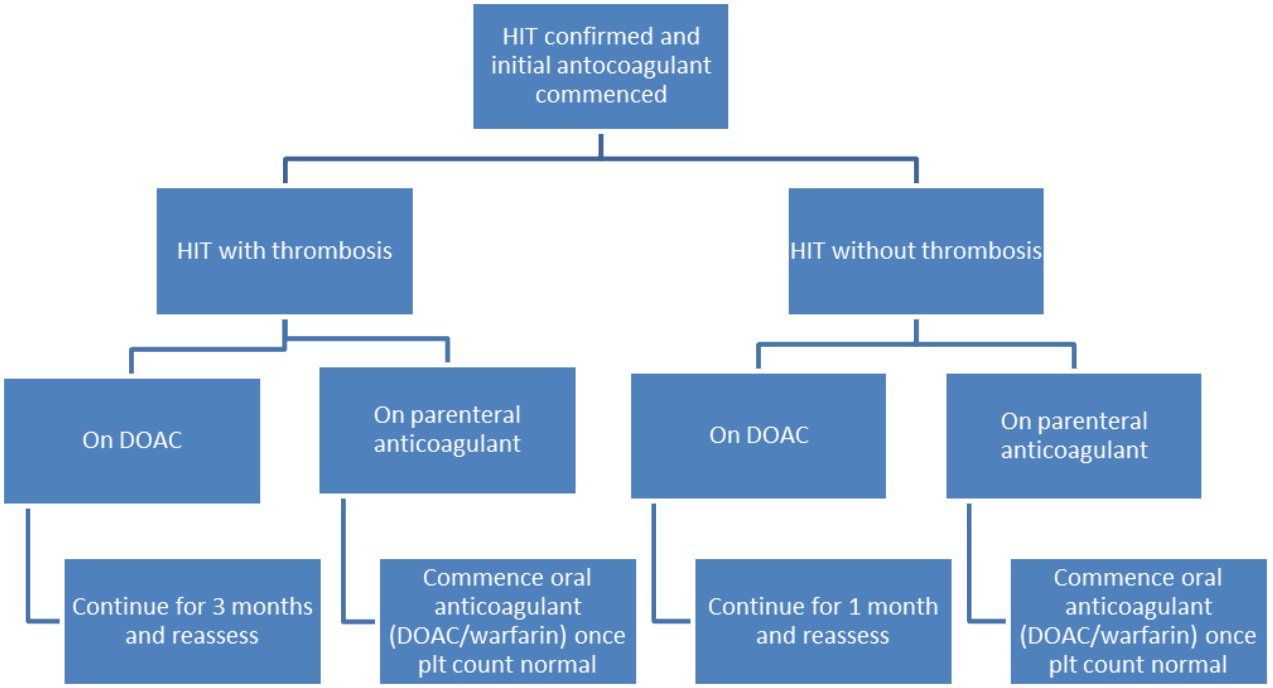
Please discuss with haemostasis team/haematology StR



HIT appendix 3.

Anticoagulation schedule for confirmed HIT

Please discuss with and refer to haemostasis team.



HIT Appendix 4. Laboratory request form/MDT referral (single document)

Demographic details/apply sticker Date:

1. Using “4Ts” score:

Thrombocytopenia	2	1	0
Timing of plt fall	2	1	0
Thrombosis	2	1	0
oTher cause	2	1	0
		Total:	

2. Current indication for heparin:

3. Type of heparin:

4. Most recent renal function: Cr Ur eGFR (date)

IMPORTANT POINTS:

- Send 1 x serum gel sample to Special Haematology – please call lab on ext 6619 prior to sending. Send a copy of this form with the usual request form with the patient’s sample.
- Out of hours (1700-0900) please contact haematology StR or haemostasis on call consultant for advice regarding sampling/treating – via Switchboard
- A positive result may mean your patient is AT INCREASED RISK OF ARTERIAL AND VENOUS THROMBOSIS. IF HIT IS CONFIRMED AN ALTERNATIVE THERAPEUTIC ANTICOAGULANT IS REQUIRED. Please see UHL HIT guidelines for further details on choice of agent and duration of anticoagulation. Please contact haemostasis and thrombosis team to discuss acute management as required.
- Please refer patient to haemostasis clinic