SESLHD GUIDELINE COVER SHEET

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KEY TERMS	Heparin induced thrombocytopenia (HIT); anticoagulants, laboratory testing.
SUMMARY	A guideline to provide information on diagnosis of HIT including laboratory testing, management, anticoagulation availability and choices. Includes information on requirements for requesting laboratory testing.

SESLHD GUIDELINE COVER SHEET

Heparin Induced Thrombocytopenia – Diagnosis and Management

Section 1 - Background

HEPARIN INDUCED THROMBOCYTOPENIA (HIT)

Thrombocytopenia is a well-recognised complication of heparin therapy. The most important type, called Heparin-induced thrombocytopenia Type 2 or HIT, is an immune-mediated disorder characterised by the formation of IgG antibodies to heparin-platelet factor 4 complex. This results in immune thrombocytopenia, activation of platelets and coagulation, and thrombosis. The prothrombotic state of HIT is associated with an increased risk or arterial and venous thrombosis (odds ratio 20-40 fold).

HIT is a serious complication of heparin therapy with 30% mortality. Recognition of this problem and rapid treatment is essential. All patients on heparin therapy should undertake routine platelet counts every other day (3 per week) in order to detect HIT early. Important risk factors for HIT include the use of heparin sodium rather than LWMHs, recent surgery (especially orthopaedic or cardiothoracic surgery), being female, and older age.

The diagnosis of HIT is not straight-forward, being based on clinical features supplemented by laboratory testing. The 4T score assesses key clinical features and provides an estimate of whether HIT is unlikely, possible or likely based on the cumulative score. Haematology consultation is recommended if HIT is possible or likely.

Patients diagnosed with possible or likely HIT should cease all heparin–based anticoagulant therapy immediately (including thromboprophylaxis and line flushes) and undertake anticoagulation with non-heparin alternatives. The mortality of HIT is high, and treatment decisions should be made in consultation with a haematologist.

Section 2 – Diagnosis and 4T Score

2.1 - Diagnosis

The diagnosis of HIT is a clinical diagnosis based on clinical features supplemented by laboratory testing. The pretest clinical probability is measured using the 4T score (see Table below). The 4T score rates key clinical features and provides an estimate of whether HIT is unlikely (4T score of 0-3), possible (4T score of 4-5) or likely (4T score of 6-8) based on the cumulative score. Haematology consultation is recommended if HIT is possible or likely.

Patients with an **unlikely** clinical likelihood of HIT (4T score of 0-3) require no change in management initially. Patients with **possible** HIT (4T score of 4-5) or **likely** HIT (4T score of 6-8) should cease heparin-based anticoagulant therapy immediately, including thromboprophylaxis and line flushes. Haematology consultation should be initiated. Alternative non-heparin anticoagulation may be required. The outcome of laboratory testing will determine subsequent management. Patients with high likelihood or confirmed HIT should undertake imaging to search for asymptomatic pulmonary embolism (V/Q or CT-PA) and leg vein thrombosis (bilateral compression ultrasonography).

The key characteristic clinical features of HIT are as follows:

- Thrombocytopenia occurring 5-10 days after commencing heparin therapy. Early onset (<5 days) or late onset (>10 days) thrombocytopenia are less common.
- The nadir platelet count is usually between 20-100 x 10^9/l, with at least a 50% reduction from baseline. Severe thrombocytopenia (< 20 x 10^9/l) is unusual.
- Occurrence of thrombosis. The manifestations of thrombosis are protean and include vein thrombosis (deep vein thrombosis and/or pulmonary embolism), macrovascular arterial thrombosis especially in arteriopathic patients (stroke, MI, limb ischaemia), catheter-related thrombosis, and microvascular thrombosis with skin necrosis and digital gangrene. Patients with high likelihood or confirmed HIT should undertake imaging to search for asymptomatic pulmonary embolism (V/Q or CT-PA) and leg vein thrombosis (bilateral compression ultrasonography).
- Resolution of thrombocytopenia after cessation of heparin

2.2 - 4T Score

Points	2	1	0
Thrombocytopenia	Platelet count fall > 50% **and** nadir ≥ 20 x 10^9/L	Platelet count fall 30 – 50% **or** nadir 10-19 x 10^9/L	Platelet count fall < 30% **or** nadir ≤ 10 x 10^9/L
Timing of fall in platelet count or other sequelae	Onset day 5 – 10 or < 1 day (if heparin exposure within 30 days)	Beyond Day 10, or timing unclear, or < day 1 with recent heparin 31 – 100 days	Platelet count fall ≤ day 4 (without recent heparin exposure)
Thrombosis or other sequelae	New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis – not confirmed	None
Other cause of thrombocytopenia	No other cause for platelet count fall is evident	Possible other cause is evident	Definite other cause is present
Total Score			
0 – 3	HIT Unlikely		
4 – 5	HIT Possible		
6 – 8	HIT Likely		

(Source: Lo et al. 2006 - Journal Thrombosis and Haemostasis)

Section 3 – Laboratory Testing

Laboratory testing is recommended in patients with suspected HIT when 4T score suggests HIT is Possible or Likely. Laboratory testing in "Unlikely HIT" cohort is not recommended.

There is no diagnostic test for HIT. Screening assays are generally immunoassays (e.g. ELISA) and detect antibodies to PF4. Functional assays (which include serotonin release assay and MEA), demonstrate heparin-dependent platelet activation and maybe done as confirmatory assays.

Not all patients require both laboratory investigations. In general patients with a score ≤ 5 and negative screening assay for HIT do not have HIT and functional assays are not generally performed. In general patients with a score ≥ 6 may occasionally have HIT despite negative screening assay.

The final diagnosis of HIT however remains a clinical diagnosis as laboratory testing is not 100% sensitive or specific.

HIT testing can be requested with NSW Health Pathology (NSWHP) on eMR with the completion of the required clinical information on APPENDIX A: NSWHP – Heparin-Induced Thrombocytopenia/Thrombosis (HITT) Request form. This is the clinical data sheet for requests for Serotonin Release Assay (HITT antibodies) and APPENDIX B – 4 T Score.

Both forms should be completed and faxed back to either the Prince of Wales Hospital (POWH) - Randwick NSWHP (02) 9382 3504 or the St. George Hospital (SGH) - Kogarah NSWHP (02) 9113 3942. The results of this will help determine the likelihood of HIT and whether further investigations are required.

No testing will be performed in the absence of a completed request form.

Enquiries can be made to the Coagulation Laboratories at:

- POWH Coagulation Laboratory on (02) 9382 3250 or
- SGH Coagulation Laboratory on (02) 9113 3423.

Section 4 – Management of HIT

Management of HIT patients requires experience and specialist Haematology advice is recommended.

All suspected (at least moderate probability score ≥ 4) and confirmed HIT patients require immediate cessation of their heparin therapy. Low molecular weight heparins (such as enoxaparin, dalteparin) are to be avoided because of the high cross reactivity of the HIT antibody with these heparin derivatives.

All patients with suspected or confirmed HIT require therapeutic anticoagulation unless absolute contraindications are present. Heparin cessation alone is inadequate therapy due to the high risk of thrombotic complications.

In general, these patients are initially anticoagulated with non-heparin parenteral anticoagulation and subsequent oral anticoagulation with warfarin or DOACs.

The choice of non-heparin anticoagulation depends on

(1) urgency of anticoagulation - rapid therapeutic anticoagulation achieved with danaparoid, fondaparinux, argatroban and bivalirudin,

(2) possible need for reversal of anticoagulation – argatroban and bivalirudin have short elimination half-lives,

(3) renal and or liver impairment – argatroban and bivalirudin can be dose adjusted to manage patients with significant renal and/or liver impairment,

(4) and local experience with/availability of non-heparin anticoagulants.

4.1 - Availability of anticoagulants for treatment of HIT

Oral agents are only used after a period of IV therapy and normalization of the platelet count.

	PBS	SESLHD Formulary Status relevant to treatment of acute HIT
Rivaroxaban (Xarelto®) 10mg	Not listed for treatment of HIT	Venous Thromboembolism (VTE) prophylaxis for inpatients previously diagnosed with HIT. Not listed on the SESLHD Formulary – will require a formulary submission or an IPU.
Rivaroxaban (Xarelto®) 15mg, 20mg	Not listed for treatment of HIT	For use as an alternative anticoagulant therapy for management of HIT in patients with a calculated GFR greater than 15 mL/min. **Note:** patients must be under the care of a Consultant Physician with consideration for an additional Haematology consultation Not listed on the SESLHD Formulary – will require a formulary submission or an IPU for inpatient use. If patients have VTE no IPU is required. For outpatients, this will be obtained from a community pharmacy on a private script.
Bivalirudin (Angiomax®)	Non-PBS	For use as an alternative anticoagulant therapy for management of HIT in patients where rivaroxaban or fondaparinux is inappropriate. **Note:** patients must be under the care of a Consultant Physician with consideration for an additional Haematology consultation. No IPU required. On formulary for HIT as outlined in SESLHDPR/711 - Prescribing Protocol - Bivalirudin for Heparin Induced Thrombocytopenia.
Fondaparinux (Arixtra®)	Non-PBS	For use as VTE prophylaxis in patients with a history of HIT where rivaroxaban is inappropriate. For use as an alternative anticoagulant therapy for management of HIT in patients with a calculated GFR greater than 30 mL/min where rivaroxaban is inappropriate. Note: fondaparinux 7.5mg injections (treatment dose for HIT in patients weighing 51kg to 100kg) are SAS and require a SAS Category A form and approved IPU prior to supply. **Note:** patients must be under the care of a Consultant Physician with consideration for an additional Haematology consultation SESLHD Medicine Guidelines - Fondaparinux for Heparin Induced Thrombocytopenia (HIT). Further information about fondaparinux sodium (Arixtra®) can be found on the TGA Website.
Argatroban (Acova®)	SAS Category A	For use as an alternative anticoagulant therapy for management of HIT in patients where rivaroxaban or fondaparinux is inappropriate or where bivalirudin is unavailable or inappropriate **Note:** patients must be under the care of a Consultant Physician with consideration for an additional Haematology consultation

	PBS	SESLHD Formulary Status relevant to treatment of acute HIT
		SAS Category A form required prior to supply. No IPU required. On SESLHD Formulary for HIT as outlined in SESLHDPR/719 - Prescribing Protocol - Argatroban for Heparin Induced Thrombocytopenia.
Danaparoid (Orgaran®)	Non-PBS	For use as VTE prophylaxis in patients with a history of HIT where rivaroxaban is inappropriate. For use as an alternative anticoagulant therapy for management of HIT in patients where rivaroxaban or fondaparinux is inappropriate. **Note:** patients must be under the care of a Consultant Physician with consideration for an additional Haematology consultation Anticoagulation for intermittent haemodialysis in patients with a history of HIT TGA approved for the treatment of HITs or a history of HITs and on formulary. No IPU required, but must be on the advice of a Haematologist SESLHD Medicine Guideline - Danaparoid

4.2 - Clinical Factors Influencing Anticoagulant Choice for HIT Treatment

Clinical Factor	Preferred anticoagulant	Qualifying remarks
Oral administration **Only used after a period of IV therapy and normalization of the platelet count**	Rivaroxaban	Rivaroxaban is absorbed orally and reaches maximum concentrations within 2 to 4 hours when taken with food.
	Apixaban	Apixaban is rapidly absorbed, with maximum concentrations occurring 3-4 hours after oral administration.
	Warfarin	Warfarin is rapidly absorbed, reaching a maximum plasma concentration between 2 – 6 hours.
Parenteral administration	Bivalirudin Fondaparinux Argatroban Danaparoid ***Choice of anticoagulant is based on case-by-case assessment by a Haematologist***	If the patient is unable to take oral medications, a parenteral preparation is required. For patients able to take oral medications, parenteral administration is required until the platelet count has recovered.
Kidney impairment (less than 30 mL/min) [Note: refer to section 6 for anticoagulation during intermittent dialysis}	Bivalirudin Argatroban	Rivaroxaban contraindicated if estimated kidney function is less than 15 mL/min. Fondaparinux and danaparoid are contraindicate if estimated kidney function is less than 30 mL/min. Bivalirudin and argatroban are options for patients with end-stage kidney disease (i.e. estimated kidney function less than 15 mL/min).
Liver disease and coagulopathy	Bivalirudin	Argatroban requires a dose reduction if liver dysfunction and should be avoided if Child-Pugh score greater than 6.

Clinical Factor	Preferred anticoagulant	Qualifying remarks
Monitoring requirements	Rivaroxaban Fondaparinux	Rivaroxaban and fondaparinux - monitoring is not routinely required unless signs of kidney impairment. Danaparoid requires monitoring of anti-Xa levels. Bivalirudin requires monitoring of APTT levels 4 hourly. Argatroban requires monitoring of APTT levels 2 hourly.
Reversibility	All Drugs (other than warfarin where immediate and effective reversal can be achieved)	No reversal agent. Half-life of medication equates to duration of action.
Duration of Action: Plasma elimination half-lives	Argatroban Bivalirudin Danaparoid Fondaparinux ivaroxaban Apixaban	~60 minutes ~30 minutes, or longer 24 hours 17-24 hours 5-10 hours 8-15 hours

4.3 - Oral Anticoagulation

Most patients with HIT require oral anticoagulation following initial non-heparin anticoagulation. Oral anticoagulation is initiated once the platelet count has recovered to normal levels.

Patient with isolated thrombocytopenia should receive therapeutic anticoagulation until the platelet levels are >150x109/L. Patients with HIT and thrombosis should receive therapeutic anticoagulation for a minimum of 3 months in line with THANZ HIT Guidelines 2019.

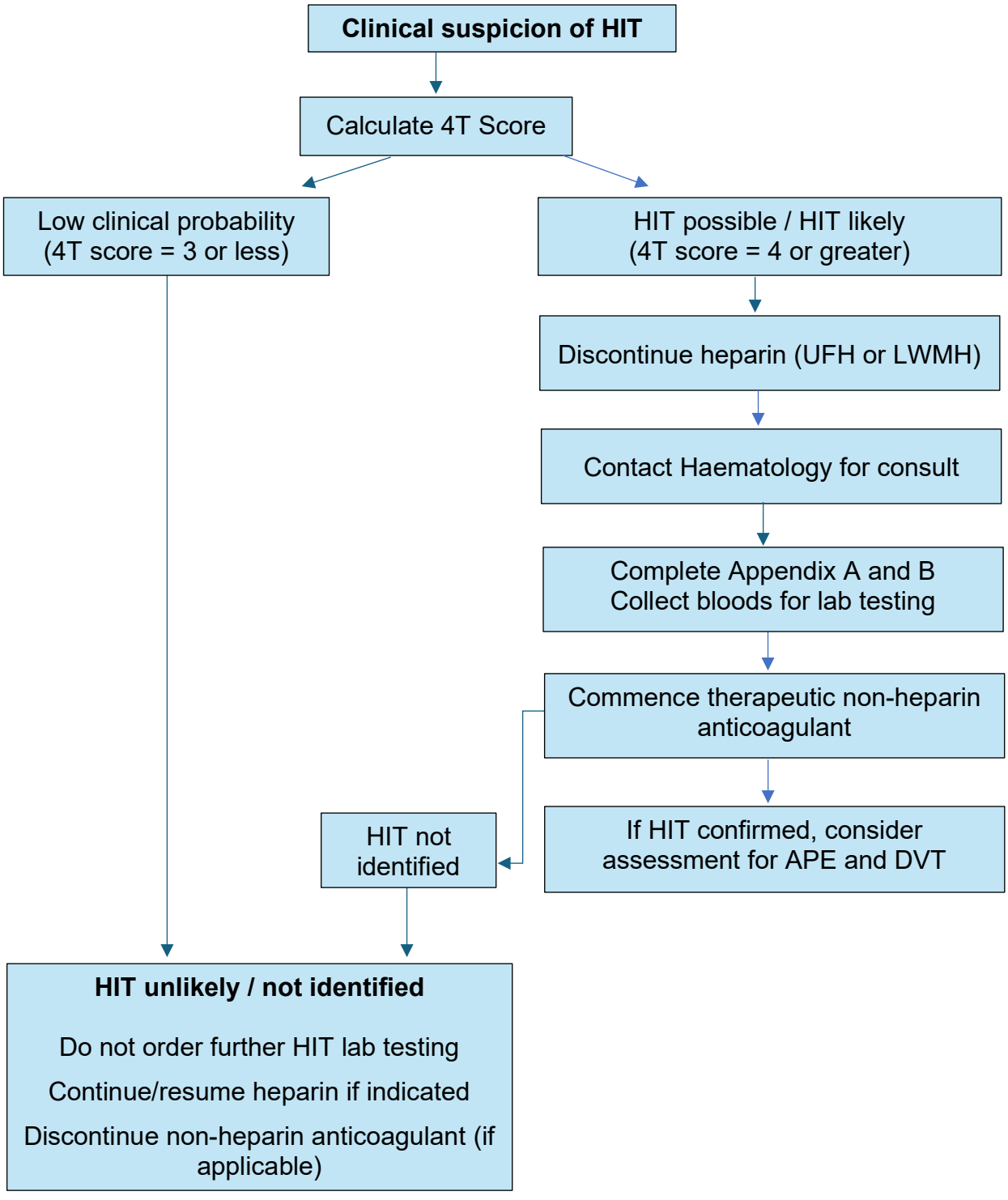
Historically, warfarin has been the drug of choice. If warfarin is being prescribed, local guidelines must be followed:

- St. George Hospital: SGH-TSH BR 568 Warfarin - Initiation, Prescribing, Dispensing, Administration and Documentation
- Prince of Wales Hospital: POWH CLIN061 Warfarin - Guidelines for Prescribing, Administration, Monitoring and Dosage Adjustment
- Royal Hospital for Women: Warfarin - Administration and Dosage Adjustment

Caution is needed when transitioning to warfarin from a direct thrombin inhibitor (bivalirudin and argatroban), APTT and PTT can be affected by both agents. Warfarin should not be introduced until platelet levels are > 150 × 109/L

Evidence is accumulating that direct oral anticoagulants (dabigatran, rivaroxaban, apixaban) may be suitable for subsequent oral anticoagulation in HIT patients when they have suffered an episode of thrombosis. There is insufficient data demonstrating efficacy and safety of DOACs as sole initial anticoagulant treatment of HIT in place of non-heparin parenteral agents - Clinical Excellence Commission DOAC Guidelines October 2023.

Pathway for diagnosing heparin-induced thrombocytopenia



Section 10 –

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Version and Approval History

Date	Version	Version and approval notes
14 October 2024	1.0	New document developed by Haematology teams from SGH and POWH on the request of SESLHD DTC. Approved by SESLHD Drug and Therapeutics Committee and SESLHD Patient Safety and Quality Committee.

Appendix A

Health
Pathology

NSWHP- Heparin-Induced Thrombocytopenia/Thrombosis (HITT) Request form

Clinical data sheet for requests for Serotonin Release Assay (HITT antibodies)

Name: _____ Age:_____

MRN:_____ Hospital/ Ward:_____

1. Indication for heparin:
2. Heparin Treatment Details

   Unfractionated Heparin (UFH) ☐ Enoxaparin ☐ Other ☐ _____

   Dose:- _____

   Date commenced: ____/____/_____ Date ceased: ____/____/_____

   Last Dose (Date and Time) ____:_____ on ____/____/_____

   Other relevant details (e.g recent surgery)_____

_____

3. Platelet count prior to anticoagulation (baseline):

   Platelet count _____ x 10^9/L Date: ____/____/_____

   Nadir platelet count _____ x 10^9/L Date: ____/____/_____

4. Previous exposure to heparin: Nil ☐ < 30 days ☐ 31-100 days ☐
5. Previous History of HITT Yes ☐ No ☐
6. PLEASE COMPLETE THE RESULTS OF ANY LAB INVESTIGATIONS ALREADY PERFORMED:

HITT Screening Test	Result (enter Pos Neg or U/mL)	Platelet Activation Assay	
Diamed (PaGIA)		HIPA	
StagoSTIC		MEA Multiplate	
ELISA		Flow Cytometry	
Acustar		SRA	
		Other	

Appendix B

4T Score Criteria	Points	Patient's Score
Thrombocytopenia		
Platelet count decrease > 50% and platelet nadir ≥ 20 x 10^9/L	**2**	
Platelet count decrease 30% - 50% or platelet nadir 10-19 10^9/L	**1**	
Platelet count decrease < 30% or platelet nadir ≤ 10 x 10^9/L	**0**	
Timing of Thrombocytopenia		
Clear onset between days 5 and 10 **or** platelet decrease ≤ 1 day (prior heparin exposure within 30 days)	**2**	
Consistent with day 5-10 decrease, but not clear (e.g., missing platelet counts) **or** onset after day 10 **or** decrease ≤1 day (prior heparin exposure 30-100 days ago)	**1**	
Platelet count decrease < 4 days without recent heparin exposure	**0**	
Thrombosis or Other Sequelae		
New thrombosis (confirmed) **or** skin necrosis at heparin injection sites **or** acute systemic reaction after IV heparin bolus	**2**	
Progressive or recurrent thrombosis **or** non-necrotizing (erythematous) skin lesions **or** suspected thrombosis (not proven	**1**	
None	**0**	
Other causes for Thrombocytopenia		
None apparent	**2**	
Possible	**1**	
Definite[6]	**0**	
Patient 4 T Score		
Low Probability	**≤ 3 points**	
Intermediate Probability	**4-5 points**	
High Probability	**≥ 6 points**	

Please **fax** both completed pages to **(02) 9382 3504 (POW – Randwick or (02) 9113 3942 (STG – Kogarah) ASAP.** The results of this will help determine the likelihood of heparin induced thrombocytopenia and whether further investigations are required. No testing will be performed in the absence of a completed request form. For enquiries, please phone the laboratory on (02) 9382 3520 (Coagulation laboratory – Prince of Wales Hospital) or (02) 9113 3423 (Coagulation laboratory – St. George Hospital).