Waikato District Health Board

Guideline

Heparin Induced Thrombocytopenia - Diagnosis and Management

Guideline Responsibilities and Authorisation

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Guideline Review History

Version	Updated by	Date Updated	Description of Changes
1.0	Denis O'Keeffe	1 Feb 2016	New document
2.0	Julia Phillips	1 March 2019	Review, minor revisions

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1. Introduction and Definitions

Heparin-induced thrombocytopenia (HIT) is a **pro-thrombotic** disorder caused by platelet-activating antibodies directed at a complex of platelet factor 4 (PF4) and heparin. It affects ~1-2% of patients receiving unfractionated heparin (UFH) for more than a week. Consider HIT if a patient has received unfractionated heparin or low molecular weight heparin in the previous 10 days and has now developed thrombocytopenia and/or thrombosis.

2. Initial assessment

Clinical likelihood of HIT – the 4Ts score

The 4Ts score is a validated tool for considering the clinical likelihood of HIT

Apply 4Ts score –

1. Assess **T**hrombocytopenia
2. Assess **T**iming
3. Assess for **T**hrombosis
4. Is there an alternative (o**T**her) cause for thrombocytopenia

	Score = 2	Score = 1	Score = 0
Thrombocytopenia Compare the highest platelet count within the sequence of declining platelet counts with the lowest count to determine the % of platelet fall. **(Select only 1 option)**	○ > 50% platelet fall AND nadir of ≥ 20 AND no surgery within preceding 3 days	○ > 50% platelet fall BUT surgery within preceding 3 days OR ○ any combination of platelet fall and nadir that does not fit criteria for Score 2 or Score 0 (eg, 30-50% platelet fall or nadir 10-19)	○ < 30% platelet fall ○ any platelet fall with nadir < 10
Timing (of platelet count fall or thrombosis*) Day 0 = first day of most recent heparin exposure **(Select only 1 option)**	○ platelet fall day 5-10 after start of heparin ○ platelet fall within 1 day of start of heparin AND exposure to heparin within past 5-30 days	○ consistent with platelet fall days 5-10 but not clear (eg, missing counts) ○ platelet fall within 1 day of start of heparin AND exposure to heparin in past 31-100 days ○ platelet fall after day 10	○ platelet fall ≤ day 4 without exposure to heparin in past 100 days
Thrombosis (or other clinical sequelae) **(Select only 1 option)**	○ confirmed new thrombosis (venous or arterial) ○ skin necrosis at injection site ○ anaphylactoid reaction to IV heparin bolus ○ adrenal hemorrhage	○ recurrent venous thrombosis in a patient receiving therapeutic anticoagulants ○ suspected thrombosis (awaiting confirmation with imaging) ○ erythematous skin lesions at heparin injection sites	○ thrombosis suspected
oTher cause for Thrombocytopenia** **(Select only 1 option)**	○ no alternative explanation for platelet fall is evident	**Possible other cause is evident:** ○ sepsis without proven microbial source ○ thrombocytopenia associated with initiation of ventilator ○ other	**Probable other cause present:** ○ within 72 h of surgery ○ confirmed bacteremia/ fungemia ○ chemotherapy or radiation within past 20 days ○ DIC due to non-HIT cause ○ posttransfusion purpura (PTP) ○ platelet count < 20 AND given a drug implicated in causing D-ITP (see list) ○ non-necrotizing skin lesions at LMWH injection site (presumes DTH) ○ other

Drugs implicated in drug-induced immune thrombocytopenia (D-ITP)

Relatively Common: glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban); quinine, quinidine, sulfa antibiotics, carbamazepine, vancomycin
Less Common: actinomycin, amitriptyline, amoxicillin/piperacillin/nafcillin, cephalosporins (cefazolin, ceftazidime, ceftriaxone), celecoxib, ciprofloxacin, esomeprazole, fexofenadine, fentanyl, fucidic acid, furosemide, gold salts, levofloxacin, metronidazole, naproxen, oxaliplatin, phenytoin, propranolol, propoxyphene, ranitidine, rifampin, suramin, trimethoprim. Note: This is a partial list.

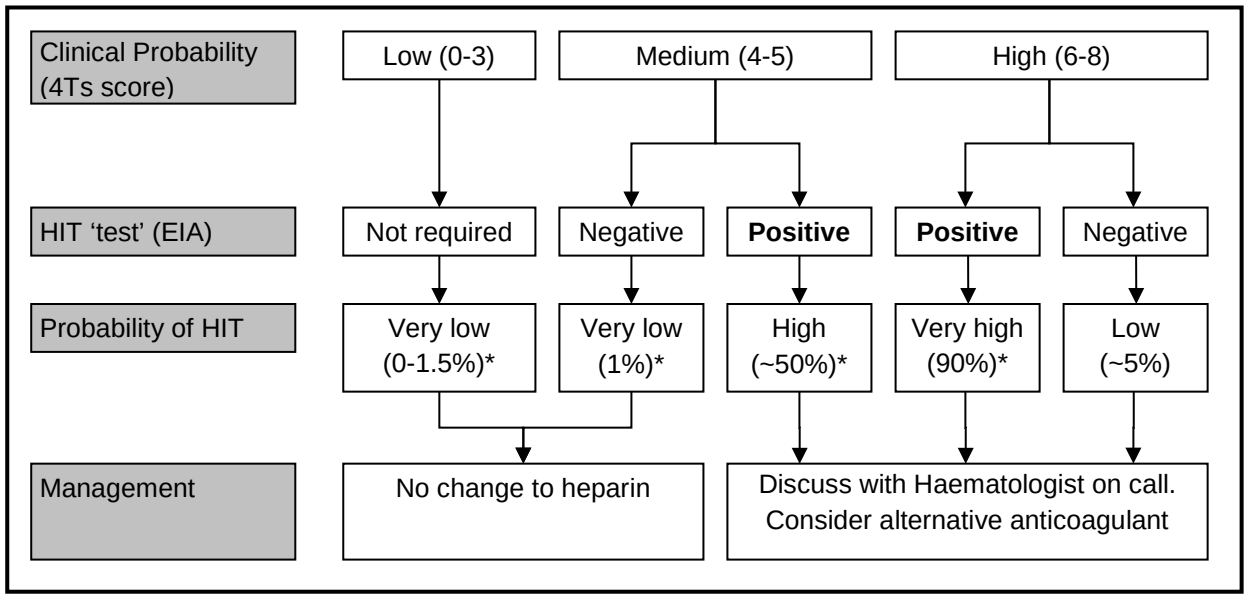
FIGURE 1. 4Ts score. *Timing of clinical sequelae, such as thrombocytopenia, thrombosis, or skin lesions. **Two points if necrotizing heparin-induced skin lesions even if thrombocytopenia not present. (Modified with permission from Warkentin and Linkins.[59])

4Ts score from ACCP guidelines (see references)

Low score 0-3, intermediate score 4-5, high score 6-8.

3. Diagnosis

Apply the 4Ts score to the algorithm below.
Low score 0-3, intermediate score 4-5, high score 6-8.



- Data are from Cuker (see refs)

3.1 Laboratory testing for HIT

- An EIA (enzyme immunoassay) looks for anti-PF4/heparin antibodies. Fast (60min), simple. Highly sensitive (HIT pts are positive; therefore, good negative predictive value) but not very specific (i.e. can have false positives). This test should be requested if the 4Ts score is intermediate (4-5) or high.
- Other tests in the literature (e.g. HIPA & serotonin release assays) are not available.

4. Management

- Immediately **STOP all heparin** (unfractionated and low molecular weight) including that used to flush lines etc.
- **STOP warfarin** if it has already been started and administer Vitamin K (10mg orally, or 5-10mg IV)
- **Do not transfuse platelets** as this can precipitate further thrombosis (only use if significant bleeding)
- **Prevent** (further) **thrombosis by initiation of alternative anticoagulation** (section 4.1). The choice of treatment will depend on the patient and should be discussed with the Haematologist. The two agents available in this hospital are bivalirudin and fondaparinux.
- **Transition to ongoing oral anticoagulation**

4.1 Alternative Anticoagulation

There are no medicines in NZ currently licensed for HIT. Danaparoid is no longer available.
Options include

- Bivalirudin (IV, direct thrombin inhibitor)
- Fondaparinux (subcutaneous, factor Xa inhibitor)
- Rivaroxaban (oral, factor Xa inhibitor)

4.1.1 Bivalirudin

Is an IV direct thrombin inhibitor. It is dialyzable and therefore able to be used in renal failure. It is the usual first choice for unstable patients including those on the ICU. Dosing is by continuous IV infusion. See Bivalirudin Drug Guideline (#2749) for detailed information.

4.1.2 Fondaparinux

Is a synthetic pentasaccharide indirect factor Xa inhibitor chemically similar to heparins. It has not been known to cause HIT. It is given by daily subcutaneous injection and is not readily reversed (protamine is ineffective). It is simple to use and may be appropriate for clinically stable patients with good renal function. It should be used cautiously in clinically unstable patients and is not appropriate in renal failure. It is contra-indicated if GFR is < 30, where there is a high risk of bleeding and in children. The recommended dose is 7.5mg if weight is 50-100kg and 10mg if >100kg. This must be discussed with the Haematologist before starting.

4.1.3 Rivaroxaban

Is a direct oral anticoagulant (DOAC) with anti Xa activity. It is given orally and is well tolerated. No specific antidote is available in New Zealand. It should not be given to patients with a creatinine clearance of less than 30 ml/minute or where there is a high risk of gastrointestinal bleeding. The recommended doses are: (i) for HIT with thrombosis, 15mg bd for 3/52, then 20mg daily; or (ii) for HIT (without thrombosis), 15mg po bd until platelet recovery (>150 x 10^9/L) then 20mg po daily. This is a reasonable treatment option in stable patients without a high risk of bleeding. See rivaroxaban guideline (#5983) for further drug information.

Other DOACs have much less evidence for use in HITT.

4.2 Duration of anticoagulation

- If HIT is associated with thrombosis 3-6 months
- HIT without thrombosis assess patient's ongoing risk factors for thrombosis and consider 4-12 weeks anticoagulation. Discuss with Haematologist.

4.3 Transitioning to oral anticoagulation

Patients treated with bivalirudin or fondaparinux will usually need to transition to an oral anticoagulant. Current options are warfarin or rivaroxaban.

4.3.1 Warfarin

Patient with acute HIT are at risk of venous limb gangrene due to diffuse microvascular damage. It is felt that early initiation of warfarin resulting in rapid depletion of protein C and protein S levels can further compound the problem and cause skin necrosis. Warfarin should only start once the platelet count has recovered (>150) and plateaued. In addition no more than 5 mg doses of warfarin should be used whilst loading the patient on warfarin. The initial anticoagulant and warfarin should be overlapped for at least 5 days.

Transitioning from bivalirudin to warfarin can be complicated by the fact than bivalirudin too can prolong the prothrombin ratio. A valid INR reading can be obtained by withholding bivalirudin for 2 hours prior to doing the test (longer if renal impairment).

4.3.2 Rivaroxaban

If transitioning from bivalirudin or fondaparinux to rivaroxaban, suggest following the dose recommendations in section 4.1.3. above. The first rivaroxaban dose should be given 24 hours after the last fondaparinux dose and 4 hours after stopping the bivalirudin infusion.

5. How to deal with a patient with previous HIT?

If a patient with previous HIT requires acute anticoagulation bivalirudin is the treatment of choice. However in selected patients who now test negative on the HIT immunological assay heparin may still be used cautiously. Suggest liaising with the haematology service regarding this.

6. Associated Documents

- Waikato DHB Bivalirudin drug guideline (Ref. 2749)
- Waikato DHB Rivaroxaban drug guideline (Ref. 5983)

7. References

- Cuker A. Does my patient have HITT? Blood 2016;127:522-3
- Cuker A et al. American Society of Hematology 2018 guideines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Advances 2018;2(22):3360-3392
- Linkins LA et al. Treatment and Prevention of Heparin-Induced Thrombocytopenia. Antithrombotic Therapy and Prevention of Thrombosis, 9th Ed: ACCP Guidelines. Chest 2012;141(2)(suppl):e495S-e530S
- Watson H et al. Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: 2nd Ed (2012). BCSH. BJH 2012;159(5):528-40