HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

Thrombosis Canada
Thrombose Canada

OBJECTIVE:

To assist clinicians with the investigation and management of suspected and documented heparin-induced thrombocytopenia (HIT).

BACKGROUND:

HIT is a transient, immune-mediated adverse drug reaction in patients recently exposed to heparin that causes thrombocytopenia and often results in venous and/or arterial thrombosis. HIT occurs in up to 5% of patients receiving unfractionated heparin (UFH) for longer than 4 days and in <1% who receive low molecular weight heparin (LMWH). HIT is characterised by immunoglobulin G (IgG) antibodies that recognize an antigen complex of platelet factor 4 (PF4) bound to heparin. These antibodies trigger a highly prothrombotic state by causing intravascular platelet aggregation, intense platelet, monocyte and endothelial cell activation, and excessive thrombin generation.

CLINICAL FEATURES:

HIT typically presents with a fall in platelet count with or without venous and/or arterial thrombosis.

- Thrombocytopenia: A platelet count fall >30% beginning 5-10 days after UFH or LMWH exposure, in the absence of other causes of thrombocytopenia, should be considered to be HIT, unless proven otherwise. A more rapid onset of platelet count fall (often within 24 hours of heparin exposure) can occur when there is a history of heparin exposure within the preceding 3 months. Bleeding is very infrequent.
- Thrombosis: HIT is associated with a high risk (30-50%) of new venous or arterial thromboembolism. **Thrombosis may be the presenting clinical manifestation of HIT** or can occur during or shortly after the thrombocytopenia.
- Other clinical manifestations of HIT: Less frequent manifestations include heparin-induced skin lesions, adrenal hemorrhagic infarction (secondary to adrenal vein thrombosis), transient global amnesia, and acute systemic reactions (e.g. chills, dyspnea, cardiac or respiratory arrest following IV heparin bolus).

DIAGNOSIS:

The diagnosis of HIT is based on three criteria:

1) The patient is receiving or has had recent exposure to UFH or LMWH.
2) At least one clinical feature of the syndrome is present (significant fall in platelet count, new venous and/or arterial thrombosis).
3) There is laboratory evidence of HIT antibodies.

Figure 1 and **Table 1** provide a rational approach to suspected HIT.

HIT ASSAYS:

Therapeutic decisions, including the cessation of UFH or LMWH and the administration of a HIT-safe, alternative anticoagulant (see below), should not be delayed pending the results of laboratory testing if the clinical suspicion of HIT is not low. There are two main types of tests for HIT:

1) **immunologic assays** which detect antibodies to PF4/heparin complexes ("HIT antibodies"; e.g. enzyme-linked immunosorbent assay [ELISA], particle gel immunoassay, latex particle agglutination assay), and;
2) **functional assays** (e.g. serotonin release assay [SRA], heparin-induced platelet aggregation [HIPA]).

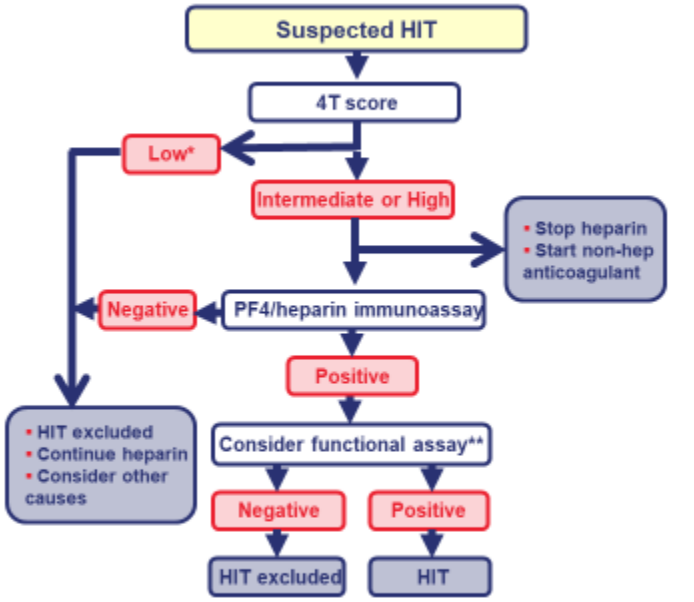
In most centres, only the immunologic assay results are available on an urgent basis. Although both assay types are sensitive for HIT (≥90%), false positives are common with the immunologic assays.

4TS SCORE:

Criteria for the 4Ts score, which is used to determine the likelihood that a patient has HIT, are outlined in **Table 1**. Given the high negative predictive value of the 4Ts score, laboratory testing for HIT is not always required for patients with low pre-test probability according to the 4Ts score, as long as all the elements of the score are known. Occasionally, there may be uncertainty about the score due to multiple missing platelet counts, unclear history of recent heparin exposure or concurrent potential causes of thrombocytopenia; in this case, testing for HIT should be done.

Since the majority of patients with a positive immunologic assay do not have HIT, and because of the long-term implications of a HIT diagnosis, obtaining a confirmatory functional assay should be considered in patients with an intermediate 4Ts score and/or ELISA optical density <2.0.

Figure 1. Approach to suspected HIT



*Laboratory testing is not always required for low 4Ts score as long as all elements of the score are known (i.e. no missing counts/unknown exposure during recent admissions)
**Consider functional assay in patients with intermediate 4Ts score (4 or 5) or ELISA OD <2.0

Table 1. "4 T's" clinical probability score

	2 points	1 point	0 points
Thrombocytopenia (platelet count)	>50% decrease to nadir ≥ 20 x 10^9/L	30-50% decrease, or nadir 10-19 x 10^9/L	< 30% decrease or nadir < 10 x 10^9/L
Timing of onset of platelet count fall or other sequelae of HIT. (Day 0 = first day of heparin exposure)	Days 5-10, or ≤ day 1 with history of heparin exposure within past 30 days	> Day 10 or timing unclear; or < day 1 with heparin exposure in past 31 – 100 days	< Day 4 (no recent heparin prior to current exposure)
Thrombosis or other sequelae	Proven new thrombosis; skin necrosis; or acute systemic reaction after IV UFH bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis	None
o**T**her cause(s) of thrombocytopenia	None evident	Possible	Definite

Total points	Clinical probability of HIT
6-8	High
4-5	Intermediate
0-3	Low

MANAGEMENT:

Patients with HIT are best managed by, or in consultation with, a specialist experienced in managing HIT.

Each of the following points is important in the management of HIT:

- Stop all heparin exposure, including LMWH, prophylactic heparin, heparin locks or flushes, and remove heparin-coated catheters.
- Start anticoagulation with a non-heparin, HIT-safe anticoagulant such as fondaparinux, argatroban, a direct oral anticoagulant (DOAC), bivalirudin, or danaparoid (see **Table 2 for** dosing). If a new thrombotic event is present (HIT with thrombosis, or "HITT"), then the acute VTE treatment regimen for the DOAC is preferred, rather than the maintenance dosing regimen. For example, rivaroxaban should be initiated at 15 mg BID x 3 weeks followed by 20 mg daily.
- Consider if the patient may already have had a thromboembolic event. Patients with suspected venous or arterial thrombosis should have objective confirmation since this will affect the duration of HIT-safe anticoagulant use. Even without a clinical suspicion of deep vein thrombosis (DVT), bilateral leg ultrasonography to screen for asymptomatic DVT are recommended, especially if the patient has additional risk factors for VTE.
- Avoid platelet transfusions unless the patient is bleeding or requires a procedure associated with a high risk of bleeding.
- Early use of warfarin should be avoided in acute HIT since it may make the prothrombotic state worse. If warfarin has already been started when HIT is diagnosed, it should be

stopped, and vitamin K administered to reverse the warfarin effect. Warfarin alone is insufficient to protect against thrombosis secondary to HIT as long as HIT is considered active (i.e. platelets less than 150 x 10^9/L).

- Warfarin or a DOAC are appropriate for longer-term anticoagulation, if indicated, after thrombocytopenia has resolved. If transitioning to warfarin from a HIT-safe anticoagulant, such as fondaparinux, bivalirudin, or danaparoid:
  - Do not initiate warfarin until platelet count is ≥150 x 10^9/L.
  - Overlap warfarin with therapeutic doses of the HIT-safe anticoagulant for ≥5 days and until the international normalized ratio (INR) is therapeutic. Caution should be used when transitioning to warfarin from argatroban because it also increases the INR.
- Duration of anticoagulation for HIT with thrombosis: at least 3 months.
- Duration of anticoagulation for HIT without thrombosis: at least 4 weeks.
- Heparin or LMWH should not be given to a patient with previous HIT without consultation with a specialist.

TABLE 2. NON-HEPARIN ANTICOAGULANTS FOR THE TREATMENT OF ACUTE HIT*

Anticoagulant	Pharmacology	Initial Dosing	Monitoring
Argatroban	**Mechanism:** Direct thrombin inhibitor **Clearance:** Hepatic **Half-life:** 40-50 min Prolongs aPTT, PT/INR	**Bolus:** None **Continuous Infusion:** 0.5 – 1.5 ug/kg/min IV Reduce dose to 0.5 mcg/kg/min or avoid in patients with: • hepatic insufficiency • heart failure • multiple organ failure • severe anasarca • post-cardiac surgery	aPTT 2h after initiation or dosage change, then at least daily once therapeutic **Target:** 1.5-2.5 x patient baseline (or mean laboratory) aPTT, not to exceed 100 sec
Bivalirudin (not approved for treatment of HIT)	**Mechanism:** Direct thrombin inhibitor **Clearance:** Plasma proteases and renal **Half-life:** 25 min Prolongs aPTT, PT/INR	**Bolus:** None **Continuous Infusion:** 0.1-0.2 mg/kg/h IV **Reduce dose in renal failure:** Creatinine Clearance (mL/min) / Initial Infusion Rate (mg/kg/h IV) > 60 / 0.10 30-60 / 0.08-0.10 < 30 or renal replacement therapy / 0.03-0.05	aPTT **Target:** 1.5-2.5 x patient baseline (or mean laboratory) aPTT
Fondaparinux (not approved for treatment of HIT and rare cases of	**Mechanism:** Factor Xa-inhibitor **Clearance:** Renal **Half-life:** 17-20 hours	**Bolus:** None **SC Injection:** Weight (kg) / Dosage < 50 / 5 mg SC daily 50-100 / 7.5 mg SC daily	Not routinely required

fondaparinux-induced HIT have been reported)	No effect on aPTT, PT/INR		> 100	10 mg SC daily	
Danaparoid	**Mechanism:** Factor Xa-inhibitor **Clearance:** Renal **Half-life:** 25 hours No effect on aPTT, PT/INR Clinical cross-reactivity with HIT antibodies in 3%	**Bolus:**	Weight (kg) < 60 60-75 75-90 > 90	IV Bolus (units) 1,500 2,250 3,000 3,750	Anti-Xa levels **Target:** 0.5-0.8 anti-Xa U/mL (using danaparoid standards)
		Continuous Infusion: 400 units/h IV x 4h, then 300 units/h IV x 4h, then 200 units/h IV			
Rivaroxaban** (not approved for treatment of HIT)	**Mechanism:** Factor Xa-inhibitor **Clearance:** Renal **Half-life:** 9 hours No effect on aPTT, Transient effect on PT/INR	**HIT with thrombosis:** 15 mg bid x 3 weeks (longer if platelets not recovered) then 20 mg daily **HIT:** 15 mg bid until platelet recovery then 20 mg daily			

* This table does not address special populations and circumstances such as children, pregnancy, percutaneous coronary interventions, cardiac surgery, vascular surgery, and renal replacement therapy.

**Apixaban and dabigatran have also been used to treat patients with HIT; however, there is very limited trial data

SPECIAL CONSIDERATIONS:

Pediatrics:

The incidence of HIT is less than in adults, but the approach to investigation and management is similar. Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with HIT. When this is not possible, a combination of a neonatologist/pediatrician and an adult hematologist, supported by consultation with an experienced pediatric hematologist, is recommended.

Pregnancy:

HIT is infrequent in pregnancy. The approach to investigation is as outlined above. Danaparoid does not cross the placenta and has been used to treat HIT in pregnancy. The use of fondaparinux (with the cautions noted above) is an option where danaparoid is not available; however, this drug has been reported to cross the placenta in small amounts and experience with fondaparinux in pregnancy is very limited (especially during the first trimester). DOACs should not be prescribed during pregnancy.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES

- Rivaroxaban (Xarelto®)
- Unfractionated Heparin, Low Molecular Weight Heparin and Fondaparinux

- Warfarin

REFERENCES

Cuker A, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;22(2):3360-3392.

Davis KA, et al. Direct acting oral anticoagulants for the treatment of suspected heparin-induced thrombocytopenia. Eur J Haematol. 2017;99(4):332-335.

Greinacher A. Heparin-induced thrombocytopenia. N Engl J Med. 2015;373(3):252-261.

Kelton JG, et al. Nonheparin anticoagulants for heparin-induced thrombocytopenia. N Engl J Med. 2013;368(8):737-744.

Linkins LA, et al. 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. Chest 2012;141(2 Suppl):e495S-530S.

Linkins LA, et al. Combination of 4Ts score and PF4/H-PaGIA for diagnosis and management of heparin-induced thrombocytopenia: prospective cohort study. Blood 2015;126(5):597-603.

Linkins LA. Heparin induced thrombocytopenia. BMJ. 2015;350:g7566

Linkins LA, et al. Systematic review of fondaparinux for heparin-induced thrombocytopenia: When there are no randomized controlled trials. Res Pract Thromb Haemost. 2018 Aug 9;2(4):678-683.

McGowan KE, et al. Reducing the hospital burden of heparin-induced thrombocytopenia: impact of an avoid-heparin program. Blood 2016;127(16):1954-1959.

Warkentin TE, et al. Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review. Blood 2017;130:1104-1113.

Date of Version: 23October2021

Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.