BMJ Best Practice

Heparin-induced thrombocytopenia

The right clinical information, right where it's needed

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Summary

- A severe drug reaction to heparin that can lead to life- and limb-threatening venous and/or arterial thromboembolism.
- Diagnosis requires the combination of a compatible clinical picture and laboratory confirmation of the presence of heparin-dependent platelet-activating HIT antibodies.
- Neither discontinuation of heparin alone nor initiation of a vitamin K antagonist alone (e.g., warfarin) is sufficient to stop the development of thrombosis in a patient with acute HIT.
- If clinical suspicion for HIT is at least moderate, all sources of heparin must be discontinued and initiation of treatment with a non-heparin anticoagulant considered.

Definition

Heparin-induced thrombocytopenia (HIT) is a clinicopathological syndrome that occurs when heparin-dependent, IgG antibodies bind to heparin/platelet factor 4 (PF4) complexes to activate platelets and produce a hypercoagulable state. This results in thrombocytopenia and/or thrombosis in temporal relationship to a preceding immunising exposure to heparin.[1] HIT typically develops 5 to 10 days after exposure to heparin (range of 4-15 days) and can occur with unfractionated heparin, low molecular weight heparin, or, more rarely, fondaparinux. The presence of heparin-dependent antibodies alone, without any clinical manifestations, is insufficient for a diagnosis of HIT.

Fondaparinux, a pentasaccharide anticoagulant, does not usually promote antibody binding to PF4, despite its structural similarity to heparin, owing to absent/weak cross-reactivity. Therefore, it has a very low, but not zero, risk of inducing HIT. Despite rare reports of fondaparinux-induced HIT, it has been used to successfully treat HIT in case series, and is considered to be a non-heparin anticoagulant.[2]

Epidemiology

The prevalence of HIT ranges from 0.1% to 5.0% in patients exposed to heparin, and varies significantly according to a number of host- and drug-related risk factors. Postoperative and trauma patients who receive heparin have the highest incidence of HIT (1% to 5%), whereas HIT is very uncommon in medical patients who receive prophylactic doses of heparin (<1%), and is extremely rare in obstetric patients (<0.1%).[7] [8] [9] [10] [11] The risk of HIT is significantly higher with unfractionated heparin compared with low molecular weight heparin (LMWH).[12] Women appear to have a 1.5- to 2-fold increased risk of HIT compared with men.[13]

Aetiology

The aetiology of HIT is unknown. The rapid production of IgG antibodies (median of 4 days) without initial IgM antibody production suggests a secondary immune response, despite the absence of previous exposure to heparin in the majority of cases of patients who develop HIT.[14] [15] These observations have raised the hypothesis that sensitisation of the antiheparin/platelet factor 4 (PF4) antibody occurs as the result of other environmental exposures (e.g., bacterial infection) that produce the same antigen as the one produced by the heparin/PF4 complex.[16] [17]

Pathophysiology

Platelet factor 4 (PF4) molecules bind to heparin on the surface of platelets to form a neo-antigen that is recognised by HIT (IgG) antibodies.[18] [19] Antiheparin/PF4 antibodies bind to the large heparin/PF4 complexes and activate the same or adjacent platelets through their Fc receptors.[20] [21] Activation of platelets leads to production of procoagulant platelet-derived microparticles and thrombin generation with the potential for development of the clinical manifestations that are characteristic of HIT (i.e., thrombocytopenia and venous and/or arterial thrombosis).[22] [23] Activation of monocytes and the endothelium have also been implicated in the pathogenesis of HIT.[24] [25] [26] Typically, HIT antibodies are transient, becoming undetectable within 100 days (depending on the assay performed).[4] [27]

Classification

Clinical classification of HIT

Isolated HIT:

- Patients who have thrombocytopenia secondary to HIT antibodies without evidence of thrombosis or other sequelae of HIT.[3]

Delayed-onset HIT:

- HIT that begins several days after heparin has been discontinued.[4]

Rapid-onset HIT:

- Refers to a platelet count drop occurring within 24 hours of exposure to heparin due to persistence of HIT antibodies from a recent exposure to heparin (i.e., typically <30 days but can be up to 100 days).[4] An appropriate clinical picture and laboratory confirmation of HIT is essential because a rapid drop in platelet count is atypical for most patients with HIT and likely has other causes.

Primary prevention

The best way to prevent HIT is to minimise or avoid heparin exposure. Direct oral anticoagulants such as dabigatran, rivaroxaban, and apixaban may be used as alternatives for thromboprophylaxis for some indications (e.g., following elective hip or knee arthroplasty).

Screening

Screening for HIT usually means obtaining serial platelet counts in patients who are receiving unfractionated heparin/low molecular weight heparin (LMWH), or, more rarely, fondaparinux for at least 4 days, or in patients who have presented with thrombosis in the context of exposure to these drugs within the past 100 days. Due to the large number of alternative causes of thrombocytopenia, routine platelet count monitoring also has the potential to cause harm due to unnecessary withdrawal of heparin and institution of non-heparin anticoagulants in patients who do not have HIT. Lack of evidence to support the efficacy of screening has resulted in a difference of opinion among experts on the value of screening.[43] The potential benefit of screening is likely to be highest in settings where patients have a 1% or greater risk of HIT (e.g., patients receiving heparin or LMWH following surgery or trauma) and a functional test for HIT antibodies is available to reduce the likelihood of false positive results.[43]

HIT antibody assays are not appropriate for screening.

Platelet count monitoring

If screening is performed, platelet counts are typically checked every 2 or 3 days from day 4 to 14 (or until heparin is stopped, whichever comes first). If a platelet count drop is noted during routine screening and the pretest probability of HIT is at least moderate (i.e., 4Ts score ≥4), confirmatory laboratory testing for HIT antibodies is recommended.

It is also worthy of note that, if the patient undergoes surgery, the day that heparin is restarted after the procedure is considered day 0 of heparin exposure, even if the patient received heparin preoperatively. Surgery is a strong immunising risk factor for HIT and can, therefore, potentially reset the clock for the development of HIT. Similarly, if heparin is given intra-operatively, the surgery date becomes day 0.

Secondary prevention

The safety of prolonged re-exposure to unfractionated heparin, low molecular weight heparin (LMWH), or, more rarely, fondaparinux in patients with a previous history of HIT (i.e., currently HIT antibody negative) is unknown. Short-term exposure (<4 days) has been safely used in patients who require cardiac procedures and whose tests are currently negative for HIT antibodies. In general, avoidance of exposure to heparin is recommended in patients with a past history of HIT.

Anticoagulants such as fondaparinux, rivaroxaban, dabigatran, apixaban, argatroban, danaparoid, or bivalirudin may be reasonable alternatives to heparin in a patient with a past history of HIT depending on the clinical situation. Regional citrate anticoagulation may be an option in patients with a past history of HIT who require renal replacement.

Case history

Case history #1

A 55-year-old woman presents with a left-leg deep vein thrombosis 2 days after being discharged from hospital. She had been admitted with acute coronary syndrome and was treated with intravenous heparin for 6 days. Her platelet count has declined to 80 × 10^9/L (80 × 10^3/microlitre) from 250 × 10^9/L (250 × 10^3/microlitre) at the start of her treatment with heparin. Her physical examination is unremarkable except for left-leg oedema and tenderness.

Case history #2

A 65-year-old woman is admitted to a rehabilitation ward 10 days after undergoing elective right total hip arthroplasty. She had received low molecular weight heparin (LMWH) for thromboprophylaxis beginning on postoperative day 1, but intravenous heparin was subsequently started on postoperative day 9 for confirmed pulmonary embolism. Her platelet count was 175 × 10^9/L (175 × 10^3/microlitre) on admission to the rehabilitation ward compared with 350 × 10^9/L (350 × 10^3/microlitre) when intravenous heparin was initiated. Her physical examination is unremarkable except for normal postoperative changes. A venous Doppler ultrasound of her leg is negative for deep vein thrombosis.

Other presentations

HIT less commonly presents as adrenal haemorrhagic necrosis (secondary to adrenal vein thrombosis), necrotising skin lesions at heparin injection sites, cerebral venous thrombosis, or as an acute systemic reaction 30 minutes following an intravenous bolus of unfractionated heparin or subcutaneous LMWH (e.g., fever, chills, tachycardia, hypertension, dyspnoea, cardiopulmonary arrest).[5] Rarely, patients with HIT-provoked deep vein thrombosis will present with venous limb gangrene (as a consequence of inappropriate treatment with a vitamin K antagonist).[6]
[Fig-1]

Step-by-step diagnostic approach

HIT should be suspected when a patient presents with new thrombocytopenia and/or thrombosis in the context of confirmed or suspected exposure to heparin (i.e., unfractionated heparin, low molecular weight heparin [LMWH], or, more rarely, fondaparinux) within the past 100 days, particularly in the context of recent cardiac or orthopaedic surgery. HIT should also be considered when a patient presents with adrenal haemorrhagic necrosis (secondary to adrenal vein thrombosis), necrotising skin lesions at heparin injection sites, or an acute systemic reaction in the context of exposure to heparin or LMWH within the past 100 days.

Diagnosis requires the combination of both a compatible clinical picture and laboratory confirmation of the presence of heparin-dependent platelet-activating HIT antibodies. The presence of HIT antibodies alone, without any clinical manifestations, is not sufficient for a diagnosis of HIT.

Clinical picture

The first step is to determine the likelihood that a patient has HIT based on clinical criteria. This includes a careful review of the patient's history of heparin (i.e., unfractionated heparin, LMWH, or fondaparinux) exposure. The risk of HIT, according to heparin type, in order from highest to lowest is as follows: unfractionated heparin >LMWH >fondaparinux. Fondaparinux, a pentasaccharide anticoagulant, does not usually promote antibody binding to platelet factor 4 (PF4), despite its structural similarity to heparin, owing to absent/weak cross-reactivity. Therefore, it has a very low, but not zero, risk of inducing HIT. Despite rare reports of fondaparinux-induced HIT, it has been used to successfully treat HIT in case series, and is considered to be a non-heparin anticoagulant.[2]

An absence of conditions or medications that cause thrombocytopenia increases the likelihood of HIT. A history of recent surgery (especially orthopaedic or cardiovascular) or trauma increases the likelihood of HIT in patients exposed to heparin. Patients with a history of HIT who are re-exposed to heparin for at least 4 days are at risk of recurrence.

Features consistent with a recent venous or arterial thromboembolic event (e.g., DVT, PE, stroke, MI) are common. These include: new unilateral leg oedema, tenderness, or discoloration (DVT); chest pain, tachypnoea, hypotension, or tachycardia (PE or MI); focal neurological deficits (stroke).

Fever, chills, tachycardia, hypertension, dyspnoea, or cardiopulmonary arrest may occur within 30 minutes of a dose of heparin and is usually accompanied by an abrupt drop in platelet count.

Necrosis may be seen on examination at the heparin injection sites. Bleeding in patients with HIT is rare and there may be no or minimal signs of bleeding (e.g., petechiae, ecchymosis). Patients with adrenal haemorrhagic necrosis may present with abdominal pain, refractory hypotension, and Addisonian crisis. Patients with cerebral venous thrombosis may present with headache, nausea, vomiting, and/or neurological deficits. Rarely, patients with HIT-provoked DVT will present with venous limb gangrene (as a consequence of inappropriate treatment with a vitamin K antagonist).[6]
[Fig-1]

Clinical prediction tools

A number of clinical prediction tools have been developed to help physicians determine clinical probability of HIT (e.g., Warkentin [4Ts] Probability Scale, HIT expert probability [HEP] score).

While the clinical prediction rules differ on specific details, they all focus on several key features:

- Magnitude of the platelet count fall
- Timing of the platelet count fall (or other HIT-related event) in relation to start of heparin
- Presence or absence of alternative explanations for thrombocytopenia.

The 4Ts score is more commonly used as it is the most evaluated tool to date:[30] [31]

- Points from 0-2 are given for 4 categories: magnitude of Thrombocytopenia, Timing of onset of platelet fall (or other sequelae of HIT), Thrombosis, and oTher explanation for the platelet fall.
- A low score (0-3) indicates <1% probability of HIT; intermediate score (4-5) approximately 10% probability of HIT, and a high score (6-8) indicates approximately 50% probability of HIT.[32]
- An example of a classic high score would be a patient who experiences a 50% drop in platelet count with a nadir ≥20 × 10^9/L (>20 × 10^3/microlitre) between days 5 and 10 of heparin

exposure, and is found to have new thrombosis and no alternative explanation for the drop in platelet count.

HEP score:[33]

- Points from -3 to +3 are given for 8 categories: magnitude of fall in platelet count, timing of fall in platelet count, nadir platelet count, thrombosis, skin necrosis, acute systemic reaction, bleeding, other causes of thrombocytopenia.

Laboratory confirmation of HIT

An FBC should be ordered in all patients with suspected HIT and typically shows a falling platelet count. The timing of the fall in platelet count (beginning from the first day of heparin exposure [day 0]) is key. A classic example would be a patient who experiences a 50% drop in platelet count with a nadir ≥20 × 10^9/L (>20 × 10^3/microlitre) between days 5 and 10 of heparin exposure. The platelet count does not have to fall below 150 × 10^9/L (150 × 10^3/microlitre) for HIT to be considered (e.g., 50% or more decrease from baseline during the correct time frame is still suspicious for HIT, even if the absolute platelet nadir is >150 × 10^9/L [>150 × 10^3/microlitre]).

It is not uncommon for the platelet count to initially fall after surgery and then rise to a level higher than the preoperative count (rebound thrombocytosis). In such cases, the postoperative rebound platelet count should be considered the new baseline count in these patients when determining the clinical probability of HIT. Thrombocytopenia in the context of pancytopenia reduces the likelihood of HIT.

Coagulation studies (i.e., INR, aPTT) should be ordered in patients with suspected HIT to exclude coagulopathy. HIT may induce disseminated intravascular coagulation in 10% to 20% of HIT cases; therefore, coagulopathy and low fibrinogen levels do not exclude HIT if the clinical scenario is otherwise consistent.[34]

Patients with at least an intermediate clinical suspicion for HIT (i.e., 4Ts score of ≥4) should undergo testing for HIT antibodies. A low 4Ts score (i.e., ≤3) alone has high negative predictive value, suggesting that laboratory testing for HIT antibodies may not be necessary in this group of patients;[32] however, if there is uncertainty about the score (e.g., multiple missing platelet counts, history of recent heparin exposure is unclear, concurrent potential causes of thrombocytopenia), testing for HIT should be considered.[35]

A wide variety of laboratory assays are used to confirm the presence of HIT antibodies. These assays generally fall into 1 of 2 categories:

- Antigen assays (e.g., anti-PF4/H ELISA, H/PF4-PaGIA) are available at most clinical centres, but they have a high false-positive rate, depending on the patient population. Antigen assays are highly sensitive (>99%) and have a rapid turnover time. False positives result from detection of all types of HIT antibodies, regardless of their ability to activate platelets.[36] For example, up to 50% of cardiovascular surgery patients will develop HIT antibodies, but only 2% of those patients will develop HIT.[8] ELISAs that detect IgG antibodies only are more specific for HIT and the higher the titre of the antigen assay, the higher the likelihood the patient has platelet-activating antibodies (i.e., the greater the likelihood the patient has HIT or improved specificity).[30] Rapid immunoassays that can provide results in less than 30 minutes are becoming more widely available and appear to have similar diagnostic properties to the ELISAs.[35] [37]

- Functional assays (e.g., serotonin release assay, heparin-induced platelet activation) are limited to a small number of clinical centres, but have better specificity than the antigen assays. These assays have high sensitivity (>95%) and specificity (>95%) for HIT; therefore, in the context of a compatible clinical picture, a positive result confirms HIT and a negative result excludes HIT.[7] [38]

In a patient with a high clinical suspicion for HIT (i.e., 4Ts score of 6-8):[39]

- A positive antigen assay (high titre: e.g., IgG anti-PF4/H ELISA ≥1.50 optical density [OD]): HIT is confirmed
- A positive antigen assay (low-to-moderate titre: e.g., IgG anti-PF4/H ELISA 0.60-1.49 OD): confirmation with a functional assay should be considered
- A negative antigen assay (e.g., IgG anti-PF4/H ELISA <0.60): HIT is excluded, although some experts still recommend confirmation with a functional assay with this combination.

In a patient with an intermediate clinical suspicion for HIT (i.e., 4Ts score of 4-5):

- A positive antigen assay (high titre: e.g., IgG anti-PF4/H ELISA ≥2.00 OD): HIT is confirmed
- A positive antigen assay (low-to-moderate titre: e.g., IgG anti-PF4/H ELISA 0.60-1.99 OD): confirmation with a functional assay should be considered
- A negative antigen assay (e.g., IgG anti-PF4/H ELISA <0.60 OD): HIT is excluded.

In a patient with a low clinical suspicion for HIT (i.e., 4Ts score of 0-3):

- A negative antigen assay (e.g., IgG anti-PF4/H ELISA <0.60 OD) or positive antigen assay (low-to-moderate titre: e.g., IgG anti-PF4/H ELISA 0.60-1.49 OD): HIT is excluded
- A positive antigen assay (high titre: e.g., IgG anti-PF4/H ELISA ≥1.50 OD): confirmation with a functional assay should be considered.

In patients with indeterminate laboratory assay results despite repeat testing, use of an additional laboratory test, preferably from a different category of assays (e.g., if the first assay was an antigen assay, a functional assay would be an appropriate confirmatory test), is recommended. However, as many centres do not have access to functional assays, diagnosis is often based on a combination of the clinical picture with the 4Ts score combined with an antigen assay.

Clinical suspicion for HIT	*Antigen assay result*	*HIT diagnosis*
high (4Ts = 6-8)	positive/high titre	confirmed
	positive/low-to-moderate titre	consider functional assay
	negative	excluded, but consider functional assay for confirmation
intermediate (4Ts = 4-5)	positive/high titre	confirmed
	positive/low-to-moderate titre	consider functional assay
	negative	excluded
low (4Ts = 0-3)	positive/high titre	consider functional assay
	positive/low-to-moderate titre	excluded
	negative	excluded

Combination of clinical picture and laboratory evidence of HIT antibodies

Created by the BMJ Evidence Centre based on information taken from: Raschke RA, Curry SC, Warkentin TE, et al. Improving clinical interpretation of the anti-platelet factor 4/heparin enzyme-linked immunosorbent assay for the diagnosis of heparin-induced thrombocytopenia through the use of receiver operating characteristic analysis, stratum-specific likelihood ratios, and Bayes theorem. Chest. 2013;144:1269-1275.

Imaging

Venous Doppler ultrasound should be ordered in patients with suspected DVT. New DVT (incompressible venous segment) or extension of a recent DVT (incompressible venous segment previously fully compressible) increases the likelihood of HIT.

Other tests may be appropriate depending on the site of the suspected thrombosis. For example, a computed tomography pulmonary angiogram (CTPA) or ventilation-perfusion scan (V/Q scan) should be performed in patients with suspected pulmonary embolism, and a computed tomography venogram or MRI in patients with suspected cerebral venous thrombosis.

Thrombosis has been reported in up to 50% of patients with untreated HIT.[40] In the context of confirmed HIT, the presence of a DVT may lengthen the duration of treatment.

Risk factors

Strong

recent heparin exposure (within past 100 days)

- The risk of HIT, according to heparin type, in order from highest to lowest is as follows: unfractionated heparin >low molecular weight heparin (LMWH) >fondaparinux. There is a consensus that differences in the polysaccharide chain length and degree of sulfation of the drugs explains this ranking.[28] [29] Fondaparinux, at one third the length of heparin, still stimulates the formation of antiheparin/platelet factor 4 (PF4) HIT antibodies, but only rarely triggers the platelet activation required to produce the clinical manifestations of HIT.[2]
- HIT typically develops 5 to 10 days after exposure to heparin (range of 4-15 days). It is important to be aware that, even if HIT antibody formation occurs during the typical day 5 to 10 window period, thrombocytopenia can occur later (even after heparin exposure has been discontinued).

recent orthopaedic or cardiovascular surgery

- The risk of HIT is highest in surgical patients, particularly orthopaedic and cardiovascular surgery patients, and is lowest in obstetric patients. Medical, oncology, and critical care patients have a frequency of HIT that falls in between these 2 groups.[7] [8] [9] [10] [11]
- A key link between patient population and risk for HIT is the circulating level of platelet factor 4 (PF4). The higher levels of PF4 produced by surgical and non-surgical trauma favour the stoichometric concentrations of PF4 and heparin required to form the antigen recognised by HIT antibodies.[18]

Weak

female sex

- Women are about twice as likely as their male counterparts to develop HIT.[13] For reasons that are unclear, the difference according to gender is less apparent when LMWH is the cause of HIT.

History & examination factors

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include recent heparin exposure (within past 100 days) and recent orthopaedic or cardiovascular surgery.

hx of recent heparin exposure (common)

- Received unfractionated heparin, low molecular weight heparin (LMWH), or fondaparinux for the past 5 to 10 days (range 4-5 days) or within the past 100 days.
- The risk of HIT, according to heparin type, in order from highest to lowest is as follows: unfractionated heparin >LMWH >fondaparinux.

hx of HIT (common)

- Patients with a remote history of HIT who are re-exposed to unfractionated heparin or LMWH for at least 4 days are at risk of recurrence.

absence of conditions and medications that cause thrombocytopenia (common)

- This increases the likelihood of HIT (e.g., sepsis; absence of drugs such as vancomycin, carbamazepine, sulfa drugs, antineoplastic agents, glycoprotein IIb/IIIa antagonists, quinine/quinidine).

hx of recent surgery or trauma (common)

- Surgery/trauma releases platelet factor 4 (PF4), which increases the likelihood of HIT in patients exposed to heparin.
- The timing of the platelet fall in relationship to surgery/trauma is important because these events are also alternative causes of thrombocytopenia/thrombosis.
- The risk of HIT is highest in surgical patients, particularly orthopaedic and cardiovascular surgery patients, and is lowest in obstetric patients. Medical, oncology, and critical care patients have a frequency of HIT that falls in between these 2 groups.[7] [8] [9] [10] [11]

features consistent with recent venous or arterial thromboembolic event (e.g., PE, DVT, stroke, MI) (common)

- New unilateral leg oedema and/or tenderness and/or discoloration is suggestive of DVT.
- Chest pain, tachypnoea, hypotension, and tachycardia are features of PE and MI.
- New focal neurological deficits are suggestive of stroke.
- Thrombosis precedes thrombocytopenia in approximately 25% of patients with HIT.[40]
- Ratio of venous to arterial thromobotic events in HIT is 2.4 to 4.1.[40]
- Patients with cerebral venous thrombosis may present with headache, nausea, vomiting, and/or neurological deficits.

necrosis at heparin injection site(s) (uncommon)

- May occur without thrombocytopenia.

Other diagnostic factors

absence of bleeding (common)

- No or minimal petechiae/ecchymosis or other signs of bleeding.
- Despite sometimes profound thrombocytopenia, bleeding in patients with HIT is rare.

signs of adrenal haemorrhagic necrosis (uncommon)

- Occurs in 3% to 5% of HIT patients.[41]
- May present with abdominal pain, refractory hypotension, and Addisonian crisis.

acute systemic reaction (uncommon)

- Fever, chills, tachycardia, hypertension, dyspnoea, or cardiopulmonary arrest within 30 minutes of a dose of heparin or LMWH.
- Usually accompanied by an abrupt drop in platelet count.

signs of venous limb gangrene (uncommon)

- Rarely, patients with HIT-provoked DVT will present with venous limb gangrene (as a consequence of inappropriate treatment with a vitamin K antagonist).[6]
  [Fig-1]

Diagnostic tests

1st test to order

Test	Result
FBC • The timing of the fall in platelet count (beginning from the first day of heparin exposure [day 0]) is key. A classic example would be a patient who experiences a 50% drop in platelet count with a nadir ≥20 × 10^9/L (>20 × 10^3/microlitre) between days 5 and 10 of heparin exposure. • The platelet count does not have to fall below 150 × 10^9/L (150 × 10^3/microlitre) for HIT to be considered (e.g., 50% or more decrease from baseline during the correct time frame is still suspicious for HIT, even if the absolute platelet nadir is >150 × 10^9/L [>150 × 10^3/microlitre]). • It is not uncommon for the platelet count to initially fall after surgery and then rise to a level higher than the preoperative count (rebound thrombocytosis). In such cases, the postoperative rebound platelet count should be considered the new baseline count in these patients when determining the clinical probability of HIT. Thrombocytopenia in the context of pancytopenia reduces the likelihood of HIT.	**falling platelet count**

Other tests to consider

Test	Result
Warkentin (4Ts) Probability Scale • A number of clinical prediction tools have been developed to help physicians determine clinical probability of HIT. The 4Ts score is more commonly used as it is the most evaluated tool to date.[30] [31] • Points from 0-2 are given for 4 categories: magnitude of Thrombocytopenia, Timing of onset of platelet fall (or other sequelae of of HIT), Thrombosis, and oTher explanation for the platelet fall. • A low score (0-3) indicates <1% probability of HIT; intermediate score (4-5) approximately 10% probability of HIT, and a high score (6-8) indicates approximately 50% probability of HIT.[32] • The HIT expert probability (HEP) score is an alternative scale.[33]	**score of 6-8 indicates high clinical suspicion for HIT; score of 4-5 indicates intermediate clinical suspicion for HIT; score of 0-3 indicates low clinical suspicion for HIT**

Test	Result
HIT antigen assay • Antigen assays (e.g., anti-platelet factor 4 [PF4]/H ELISA, H/PF4-PaGIA) are available at most clinical centres, but they have a high false-positive rate. ELISA tests that only detect IgG antibodies have better specificity compared with ELISA tests that detect all antibody types. Functional assays (e.g., serotonin release assay, heparin-induced platelet activation) are limited to a small number of clinical centres, but have better specificity than the antigen assays.[7] [38] • In a patient with a high clinical suspicion for HIT (i.e., 4Ts score of 6-8): HIT is confirmed if positive antigen assay with a high titre (e.g., IgG anti-PF4/H ELISA ≥1.50 optical density [OD]), and is excluded if negative antigen assay (e.g., IgG anti-PF4/H ELISA <0.60 OD). In patients with a positive antigen assay with low-to-moderate titre (e.g., IgG anti-PF4/H ELISA 0.60-1.49 OD), confirmation with a functional assay should be considered.[39] • In a patient with an intermediate clinical suspicion for HIT (i.e., 4Ts score of 4-5): HIT is confirmed if positive antigen assay with a high titre (e.g., IgG anti-PF4/H ELISA ≥2.00 OD) and is excluded if negative antigen assay (e.g., IgG anti-PF4/H ELISA <0.60 OD). In patients with a positive antigen assay with a low-to-moderate titre (e.g., IgG anti-PF4/H ELISA 0.60-1.99 OD), confirmation with a functional assay should be considered.[39] • In a patient with a low clinical suspicion for HIT (i.e., 4Ts score of 0-3): HIT is excluded if negative antigen assay (e.g., IgG anti-PF4/H ELISA <0.60 OD) or a positive antigen assay with a low-to-moderate titre (e.g., IgG anti-PF4/H ELISA 0.60-1.49 OD). In patients with a positive antigen assay with a high titre (e.g., IgG anti-PF4/H ELISA ≥1.50 OD), confirmation with a functional assay should be considered.[39] • Patients with at least an intermediate clinical suspicion for HIT (i.e., 4Ts score ≥4) should undergo testing. A low 4Ts score (i.e., ≤3) alone has high negative predictive value, suggesting that laboratory testing for HIT antibodies may not be necessary in this group of patients;[32] however, if there is uncertainty about the score (e.g., multiple missing platelet counts, history of recent heparin exposure is unclear, concurrent potential causes of thrombocytopenia), testing for HIT should be considered.[35] • As many centres do not have access to functional assays, diagnosis is often based on a combination of the clinical picture with the 4Ts score combined with an antigen assay.	**positive for HIT antibodies (with high titre value)**

Clinical suspicion for HIT	*Antigen assay result*	*HIT diagnosis*
high (4Ts = 6-8)	positive/high titre	confirmed
	positive/low-to-moderate titre	consider functional assay
	negative	excluded, but consider functional assay for confirmation
intermediate (4Ts = 4-5)	positive/high titre	confirmed
	positive/low-to-moderate titre	consider functional assay
	negative	excluded
low (4Ts = 0-3)	positive/high titre	consider functional assay
	positive/low-to-moderate titre	excluded
	negative	excluded

Combination of clinical picture and laboratory evidence of HIT antibodies

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DIAGNOSIS

Test	Result
coagulation studies • INR and aPTT should be ordered in patients with suspected HIT to exclude coagulopathy. • HIT may induce disseminated intravascular coagulation in 10% to 20% of HIT cases; therefore, coagulopathy and low fibrinogen levels do not exclude HIT if the clinical scenario is otherwise consistent.[34]	**may be normal or abnormal**
venous Doppler ultrasound • Should be ordered in all patients with suspected DVT. • New DVT (incompressible venous segment) or extension of a recent DVT (incompressible venous segment previously fully compressible) increases the likelihood of HIT. • Thrombosis has been reported in up to 50% of patients with untreated HIT.[42] • In the context of confirmed HIT, the presence of a DVT may lengthen the duration of treatment. • Other tests may be appropriate depending on the thrombosis.	**inability to fully compress lumen of vein using ultrasound transducer**
computed tomography pulmonary angiogram (CTPA) • Should be performed in patients with suspected pulmonary embolism.	**intraluminal filling defect seen on at least 2 views**
ventilation-perfusion scan (V/Q scan) • Should be performed in patients with suspected pulmonary embolism.	**multiple segmental defects seen with normal ventilation (high probability)**
cerebral computed tomography venogram • Should be performed in patients with suspected cerebral venous thrombosis.	**intraluminal filling defect seen on at least 2 views**
MRI head • Should be performed in patients with suspected cerebral venous thrombosis.	**flow defect and/or intense signal within cerebral veins or dural sinuses**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Postoperative state	• It is not uncommon for the platelet count to initially fall after surgery and then rise to a level higher than the preoperative count (rebound thrombocytosis). • The postoperative rebound platelet count should be considered the new baseline count in these patients when determining the clinical probability of HIT. This is particularly noteworthy in patients undergoing cardiovascular surgery who commonly form HIT antibodies (due to exposure to high doses of heparin), but rarely develop clinical evidence of HIT.	• Thrombocytopenia due to surgery usually occurs within the first 24-48 hours and recovers spontaneously. • Thrombocytopenia that begins >4 days after surgery or lasts for >4 days after surgery should raise suspicion of HIT.
Thrombotic thrombocytopenic purpura	• New severe neurological abnormalities, with or without fever and signs of anaemia.	• HIT assay test negative for HIT antibodies. • Microangiopathic haemolytic anaemia with schistocytes on examination of peripheral blood smear. • Normal coagulation parameters.
Drug-induced thrombocytopenic purpura	• A thorough medical history is needed to identify potential drugs (e.g., antineoplastic agents, sulfa drugs, quinine/quinidine, vancomycin, carbamazepine, and glycoprotein IIb/IIIa antagonists). • Platelet nadir may be <20 × 10^9/L (<20 × 10^3/microlitre). This is rare in HIT. • Petechiae may be present.	• No differentiating tests.
Sepsis/severe infection	• Septic patients tend to have hypotension, fever, and other signs of organ dysfunction. • Evidence of DIC may also be present in patients with severe HIT.	• HIT assay test negative for HIT antibodies. • Positive blood cultures.

Diagnostic criteria

Warkentin (4Ts) Probability Scale

Warkentin Probability Scale for HIT can be used to estimate the probability of a patient having HIT. Points are scored (0, 1, or 2) for each of the 4 categories (maximum possible score = 8).[30] [31]

Thrombocytopenia

- 2 points if >50% fall in platelet count to a platelet count nadir of ≥20 × 10^9/L (≥20 × 10^3/microlitre)
- 1 point if 30% to 50% fall in platelet count, or if the nadir is 10-19 × 10^9/L (10-19 × 10^3/microlitre)
- 0 points if <30% fall in the platelet count, or if the nadir is <10 × 10^9/L (<10 × 10^3/microlitre).

Timing* of onset of platelet fall (or other sequelae of HIT)

- 2 points if onset is 5-10 days after starting heparin, or <1 day if there has been recent heparin (within past 30 days)
- 1 point if onset is >10 days after starting heparin or if timing unclear; or if <1 day after starting heparin with recent heparin (past 31-100 days)
- 0 points if onset is within 4 days of first-time heparin exposure (no recent heparin).

Thrombosis or other sequelae

- 2 points if there is a proven new thrombosis, or heparin skin necrosis, or acute systemic reaction after intravenous unfractionated heparin bolus
- 1 point if there is progressive or recurrent thrombosis, or erythematous skin lesions, or suspected thrombosis (not proven)
- 0 points if no thrombosis or other finding.

Other cause(s) of platelet fall

- 2 points if none evident
- 1 point if there is another possible cause
- 0 points if there is another definite cause

Pretest probability score

- High = 6-8 points
- Intermediate = 4-5 points
- Low = 0-3 points.

*First day of immunising heparin exposure is considered day 0. It is also worthy of note that, if the patient undergoes surgery, the day that heparin is restarted after the procedure is considered day 0 of heparin exposure, even if the patient received heparin preoperatively. Surgery is a strong immunising risk factor for HIT and can, therefore, potentially reset the clock for the development of HIT. Similarly, if heparin is given intra-operatively, the surgery date becomes day 0.

A low score (0-3) indicates <1% probability of HIT, intermediate score (4-5) approximately 10% probability of HIT, and a high score (6-8) indicates approximately 50% probability of HIT.[32]

An example of a classic high score would be a patient who experiences a 50% drop in platelet count with a nadir ≥20 × 10^9/L (>20 × 10^3/microlitre) between days 5 and 10 of heparin exposure, and is found to

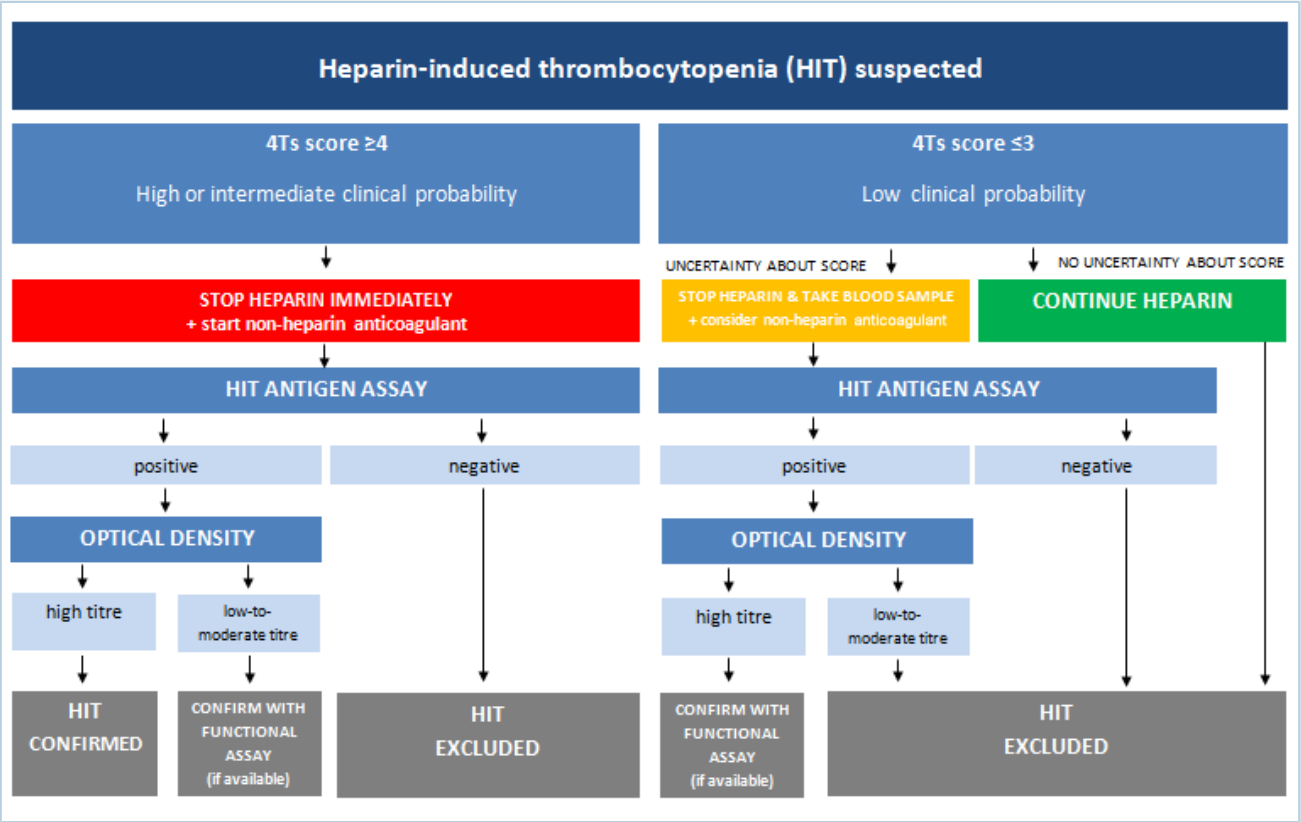
have new thrombosis and no alternative explanation for the drop in platelet count. The 4Ts score is more commonly used as it is the most evaluated tool to date.

HIT expert probability (HEP) score[33]

Points from -3 to +3 are given for 8 categories: magnitude of fall in platelet count, timing of fall in platelet count, nadir platelet count, thrombosis, skin necrosis, acute systemic reaction, bleeding, other causes of thrombocytopenia.

Step-by-step treatment approach

Treatment options are based on the patient's Warkentin (4Ts) Probability Scale score. If the clinical suspicion for HIT is at least moderate (i.e., 4Ts score ≥4), all sources of heparin must be discontinued immediately and a non-heparin anticoagulant considered. For patients with a 4Ts score of ≤3, the treatment options will depend on physician preference.



Diagnostic algorithm for heparin-induced thrombocytopenia showing when to continue or discontinue heparin

Created by the BMJ Evidence Centre

Confirmed HIT or suspected HIT with 4Ts score ≥4

If the clinical suspicion for HIT is at least moderate (i.e., 4Ts score ≥4), all sources of heparin must be discontinued immediately (including heparin used for flushing lines) and a blood sample sent for testing with a HIT assay.

If a vitamin K antagonist (e.g., warfarin) has been started, oral or intravenous vitamin K should be administered. Vitamin K antagonists alone will not prevent the development of HIT-associated thrombosis and they increase the risk of venous gangrene if used without overlap with other non-heparin anticoagulants in patients with confirmed HIT who have not achieved platelet recovery.

To reduce the high risk of HIT-provoked thrombosis, consideration should be given to immediately starting treatment with a non-heparin anticoagulant at therapeutic doses before the result of the HIT assay is available (even if the patient does not currently have thrombosis).

Non-heparin anticoagulant options include argatroban, bivalirudin, and danaparoid. Although there are a few case reports of fondaparinux-induced HIT in the literature, this agent has also been successfully used for the treatment of HIT in case series,[2] and may be used in patients who have never had fondaparinux-

associated HIT. It is classified as a non-heparin anticoagulant, despite it having structural similarities to heparin. Low molecular weight heparin (LMWH) is contraindicated in patients with suspected or confirmed HIT.

The choice of anticoagulant depends on clinical factors such as whether cardiac surgery or percutaneous coronary intervention (PCI) is necessary, the presence of renal impairment, and pregnancy. It may also depend on other factors such as cost, availability, and the ability to monitor the anticoagulant effect.

Cardiac surgery or PCI:

- In patients requiring non-urgent cardiac surgery, argatroban, danaparoid, or fondaparinux should be started with surgery delayed until the HIT antibody assay is negative (i.e., approximately 60-100 days depending on the type of HIT assay used). Heparin can be used during cardiac surgery in patients with a previous history of HIT if HIT antibodies are negative, but exposure to heparin should be limited to the procedure with non-heparin anticoagulants used peri-operatively.
- In those requiring urgent cardiac surgery, bivalirudin is indicated. Use is generally limited to the procedure with other non-heparin alternatives used peri-operatively.
- Patients requiring PCI should be treated with bivalirudin,[44] or, alternatively, argatroban as a second-line option.[45]

Renal impairment:

- Argatroban is the preferred non-heparin anticoagulant in patients with renal insufficiency.
- In patients who require renal replacement therapy, argatroban or danaparoid are used. If platelets have normalised, haemodialysis with regional citrate anticoagulation or use of saline flushes may be used instead of non-heparin anticoagulants.

Pregnant or breastfeeding women:

- None of the non-heparin anticoagulants are approved for use in pregnant or breastfeeding women.
- Danaparoid or fondaparinux are sometimes used in these patients; however, there are limited data available to support this practice.[43]

Suspected HIT with 4Ts score ≤3

If there is no uncertainty about the score, heparin can be continued as needed. If there is uncertainty about the score (e.g., multiple missing platelet counts, history of recent heparin exposure is unclear, concurrent potential causes of thrombocytopenia), testing for HIT should be considered.[35]

A low 4Ts score (i.e., ≤3) alone has high negative predictive value, suggesting that laboratory testing for HIT antibodies may not be necessary in this group of patients;[32] however, if there is uncertainty about the score, testing for HIT should be considered.[35]

If the decision is made to order an assay, heparin should be stopped immediately as it does not make sense to continue heparin if the suspicion for HIT is high enough to warrant a clinician ordering the assay. If the clinician decides that a HIT assay is not necessary, heparin can be continued. While awaiting assay results, an alternative non-heparin anticoagulant can be started in those patients who require it, after weighing the need for continued anticoagulation. However, options such as rivaroxaban and fondaparinux are preferred (depending on the indication) over argatroban or bivalirudin, owing to a lower risk of bleeding and lower cost, until the diagnosis of HIT is confirmed in these low-risk patients.

Platelet recovery

Platelet recovery is generally said to have occurred when platelet levels have returned to >150 × 10^9/L (>150 × 10^3/microlitre), or to the patient's previous baseline platelet count if it was <150 × 10^9/L (<150 × 10^3/microlitre). The duration of treatment for confirmed HIT is controversial. In patients with HIT-provoked thrombosis, 3 months of non-heparin anticoagulant therapy is reasonable. In patients without thrombosis, 1 month of non-heparin anticoagulant therapy is suggested.[43]

Once the patient's platelet levels have recovered, which suggests that ongoing thrombin generation has been halted, the therapy should be switched to an alternative anticoagulant for ongoing treatment. The primary option for ongoing treatment is a vitamin K antagonist (e.g., warfarin). It should be started at low doses and overlapped with the non-heparin anticoagulant the patient has been treated with for a minimum of 5 days until the INR is therapeutic. Warfarin is considered safe to use in breastfeeding women.

Fondaparinux is a secondary option; however, it is only available as a subcutaneous injection and is relatively expensive. It is preferred over warfarin in pregnant women, but data on its safety are limited. A specialist should be consulted for guidance on overlapping fondaparinux with the initial anticoagulant, as the time course will differ depending on the initial anticoagulant.

Rivaroxaban and apixaban have been approved in some countries for the secondary prevention of non-HIT-related deep vein thrombosis and pulmonary embolism. They may be considered for extended anticoagulant therapy in patients with HIT who have achieved platelet recovery.

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Acute (summary)

Patient group	Tx line	Treatment
confirmed HIT, or suspected HIT with 4Ts score of ≥4	**1st**	**stop heparin immediately and take blood sample**
	adjunct	**vitamin K**
non-pregnant normal renal function: not requiring urgent cardiac surgery or PCI	**plus**	**argatroban or danaparoid or fondaparinux + delay non-urgent surgery**
non-pregnant normal renal function: requiring urgent cardiac surgery	**plus**	**bivalirudin**
non-pregnant normal renal function: requiring PCI	**plus**	**bivalirudin or argatroban**
non-pregnant: requiring renal replacement therapy	**plus**	**argatroban or danaparoid**

Acute (summary)

■ non-pregnant: renal insufficiency not requiring renal replacement therapy	plus	argatroban
■ pregnant or breastfeeding	plus	fondaparinux or danaparoid
suspected HIT with 4Ts score ≤3	1st	consider stopping heparin, taking a blood sample, and starting a non-heparin anticoagulant

Ongoing (summary)

Patient group	Tx line	Treatment
platelet recovery	1st	continue initial anticoagulant and transition to warfarin or fondaparinux
■ requiring renal replacement therapy	plus	haemodialysis with regional citrate anticoagulation or saline flushes

Treatment options

Acute

Patient group	Tx line	Treatment
confirmed HIT, or suspected HIT with 4Ts score ≥4	**1st**	**stop heparin immediately and take blood sample** » If the clinical suspicion for HIT is at least moderate (i.e., 4Ts score ≥4), all sources of heparin must be discontinued immediately (including heparin used for flushing lines). A blood sample should be sent for a FBC, INR, aPTT, and HIT antigen assay.
	adjunct	**vitamin K** » If a vitamin K antagonist (e.g., warfarin) has been started, oral or intravenous vitamin K should be administered. » Vitamin K antagonists alone will not prevent the development of HIT-associated thrombosis and they increase the risk of venous gangrene if used without overlap with other non-heparin anticoagulants in patients with confirmed HIT who have not achieved platelet recovery. **Primary options** » phytomenadione: consult specialist for guidance on dose
■ **non-pregnant normal renal function: not requiring urgent cardiac surgery or PCI**	**plus**	**argatroban or danaparoid or fondaparinux + delay non-urgent surgery** » Non-urgent cardiac surgery should be delayed until the patient is HIT antibody negative (i.e., approximately 60-100 days depending on the type of HIT assay used). » Consideration should be given to immediately starting treatment with a non-heparin anticoagulant at therapeutic doses before the result of the HIT assay is available (even if the patient does not currently have thrombosis) to reduce the high risk of HIT-provoked thrombosis. » Options for these patients include argatroban, danaparoid, or fondaparinux. Fondaparinux is usually considered an alternative option as it is off-label for this indication in most countries. » Although there are a few case reports of fondaparinux-induced HIT in the literature, this agent has been successfully used for the treatment of HIT in case series,[2] and

Acute

Patient group	Tx line	Treatment
		may be used in patients who have never had fondaparinux-associated HIT. » Once surgery is scheduled, heparin can be used during cardiac surgery in patients with a previous history of HIT if HIT antibodies are negative, but exposure to heparin should be limited to the procedure with non-heparin anticoagulants used peri-operatively. **Primary options** » argatroban: 2 micrograms/kg/min intravenous infusion initially, adjust dose gradually according to response and target aPTT (1.5 to 3 times baseline, not to exceed 100 seconds), maximum 10 micrograms/kg/min; lower starting doses (0.5 to 1 micrograms/kg/min) are required in patients with heart failure, severe anasarca, multiorgan failure, or following cardiac surgery **OR** **Primary options** » danaparoid sodium: consult specialist for guidance on dose **OR** **Secondary options** » fondaparinux: consult specialist for guidance on dose
non-pregnant normal renal function: requiring urgent cardiac surgery	**plus**	**bivalirudin** » Consideration should be given to immediately starting treatment with a non-heparin anticoagulant at therapeutic doses before the result of the HIT assay is available (even if the patient does not currently have thrombosis) to reduce the high risk of HIT-provoked thrombosis. » Bivalirudin is the non-heparin anticoagulant of choice in patients who require urgent cardiac surgery. Dose varies according to on-pump or off-pump procedures and requires special technical considerations to prevent intra-operative stasis of blood.[44] Use is generally limited to the procedure with other non-heparin alternatives used peri-operatively. **Primary options**

Acute

Patient group	Tx line	Treatment
		» bivalirudin: consult specialist for guidance on dose
non-pregnant normal renal function: requiring PCI	**plus**	**bivalirudin or argatroban** » Consideration should be given to immediately starting treatment with a non-heparin anticoagulant at therapeutic doses before the result of the HIT assay is available (even if the patient does not currently have thrombosis) to reduce the high risk of HIT-provoked thrombosis. » Patients requiring percutaneous coronary intervention (PCI) should be treated with bivalirudin,[44] or, alternatively, argatroban as a second-line option.[45] » High doses of argatroban are not recommended in PCI patients with clinically significant hepatic disease. **Primary options** » bivalirudin: 0.75 mg/kg intravenous bolus initially, followed by 1.75 mg/kg/hour infusion **OR** **Secondary options** » argatroban: consult specialist for guidance on dose; dose depends on activated clotting time
non-pregnant: requiring renal replacement therapy	**plus**	**argatroban or danaparoid** » Consideration should be given to immediately starting treatment with a non-heparin anticoagulant at therapeutic doses before the result of the HIT assay is available (even if the patient does not currently have thrombosis) to reduce the high risk of HIT-provoked thrombosis. » In patients who require renal replacement therapy, argatroban or danaparoid are used. **Primary options** » argatroban: consult specialist for guidance on dose; a dose adjustment may be necessary in dialysis patients **OR** **Primary options** » danaparoid sodium: consult specialist for guidance on dose

TREATMENT

Acute

Patient group	Tx line	Treatment
non-pregnant: renal insufficiency not requiring renal replacement therapy	**plus**	**argatroban** » Consideration should be given to immediately starting treatment with a non-heparin anticoagulant at therapeutic doses before the result of the HIT assay is available (even if the patient does not currently have thrombosis) to reduce the high risk of HIT-provoked thrombosis. » Argatroban is the preferred non-heparin anticoagulant in these patients. **Primary options** » argatroban: 2 micrograms/kg/min intravenous infusion initially, adjust dose gradually according to response and target aPTT (1.5 to 3 times baseline, not to exceed 100 seconds), maximum 10 micrograms/kg/min; lower starting doses (0.5 to 1 micrograms/kg/min) are required in patients with heart failure, severe anasarca, multiorgan failure, or following cardiac surgery
pregnant or breastfeeding	**plus**	**fondaparinux or danaparoid** » Consideration should be given to immediately starting treatment with a non-heparin anticoagulant at therapeutic doses before the result of the HIT assay is available (even if the patient does not currently have thrombosis) to reduce the high risk of HIT-provoked thrombosis. » None of the non-heparin anticoagulants are approved for use in pregnant or breastfeeding women. » Danaparoid or fondaparinux are sometimes used in these patients; however, there are limited data available to support this.[43] » Although there are a few case reports of fondaparinux-induced HIT in the literature, this agent has been successfully used for the treatment of HIT in case series,[2] and may be used in patients who have never had fondaparinux-associated HIT. **Primary options** » fondaparinux: consult specialist for guidance on dose **OR** **Primary options**

Acute

Patient group	Tx line	Treatment
		» danaparoid sodium: consult specialist for guidance on dose
suspected HIT with 4Ts score ≤3	**1st**	**consider stopping heparin, taking a blood sample, and starting a non-heparin anticoagulant** » If there is no uncertainty about the score, heparin can be continued as needed. If there is uncertainty about the score (e.g., multiple missing platelet counts, history of recent heparin exposure is unclear, concurrent potential causes of thrombocytopenia), testing for HIT should be considered.[35] » A low 4Ts score (i.e., ≤3) alone has high negative predictive value, suggesting that laboratory testing for HIT antibodies may not be necessary in this group of patients;[32] however, if there is uncertainty about the score, testing for HIT should be considered.[35] If the decision is made to order an assay, heparin should be stopped immediately as it does not make sense to continue heparin if the suspicion for HIT is high enough to warrant a clinician ordering the assay. If the clinician decides that a HIT assay is not necessary, heparin can be continued. » While awaiting assay results, an alternative non-heparin anticoagulant can be started in those patients who require it, after weighing the need for continued anticoagulation. However, options such as rivaroxaban and fondaparinux are preferred (depending on the indication) over argatroban or bivalirudin, owing to a lower risk of bleeding and lower cost, until the diagnosis of HIT is confirmed in these low-risk patients. » Although there are a few case reports of fondaparinux-induced HIT in the literature, this agent has been successfully used for the treatment of HIT in case series,[2] and may be used in patients who have never had fondaparinux-associated HIT. **Primary options** » fondaparinux: consult specialist for guidance on dose **OR** **Primary options**

Acute

Patient group	Tx line	Treatment
		» rivaroxaban: consult specialist for guidance on dose

Ongoing

Patient group	Tx line	Treatment
platelet recovery	**1st**	**continue initial anticoagulant and transition to warfarin or fondaparinux** » Platelet recovery is generally said to have occurred when platelet levels have returned to >150 × 10^9/L (>150 × 10^3/microlitre), or to the patient's previous baseline platelet count if it was <150 × 10^9/L (<150 × 10^3/microlitre). » The duration of treatment for confirmed HIT is controversial. In patients with HIT-provoked thrombosis, 3 months of anticoagulant therapy is reasonable. In patients without thrombosis, 1 month of anticoagulant therapy is suggested.[43] » Once the patient's platelet levels have recovered, which suggests that ongoing thrombin generation has been halted, the therapy should be switched to an alternative anticoagulant for ongoing treatment. » The primary option for ongoing treatment is warfarin. It should be started at low doses and overlapped with the non-heparin anticoagulant the patient has been treated with for a minimum of 5 days until the INR is therapeutic. Warfarin should be given only after platelet recovery. Warfarin is considered safe to use in breastfeeding women. » Fondaparinux is a secondary option; however, it is only available as a subcutaneous injection and is relatively expensive. It is preferred over warfarin in pregnant women, but data on its safety are limited. Consult a specialist for guidance on overlapping fondaparinux with the initial anticoagulant, as the time course will differ depending on the initial anticoagulant. » Rivaroxaban and apixaban have been approved in some countries for the secondary prevention of non-HIT-related deep vein thrombosis and pulmonary embolism. They may be considered for extended anticoagulant therapy in patients with HIT who have achieved platelet recovery.

Ongoing

Patient group	Tx line	Treatment
		» It should be noted that argatroban prolongs the INR. A specialist should be consulted for guidance on initiating warfarin therapy in these patients. **Primary options** » warfarin: consult specialist for guidance on switching from initial anticoagulant to warfarin; 5 mg orally once daily initially, adjust dose according to INR (higher loading doses are not recommended) **OR** **Secondary options** » fondaparinux: consult specialist for guidance on dose and switching from initial anticoagulant **OR** **Secondary options** » rivaroxaban: consult specialist for guidance on dose and switching from initial anticoagulant **OR** **Secondary options** » apixaban: consult specialist for guidance on dose and switching from initial anticoagulant
requiring renal replacement therapy	**plus**	**haemodialysis with regional citrate anticoagulation or saline flushes** » If platelets have normalised, haemodialysis with regional citrate anticoagulation or use of saline flushes may be used instead of non-heparin anticoagulants.

Emerging

Direct oral anticoagulants

Case reports of the off-label use of direct oral anticoagulants (such as rivaroxaban, apixaban, dabigatran, and edoxaban) for treatment of HIT have been published.[46] The highest level of evidence to date comes from a small prospective cohort study that showed that rivaroxaban was safe and effective for preventing recurrent thrombosis in patients with confirmed HIT.[47]

Plasmapheresis

Proposed as a treatment strategy in patients with a recent history of HIT who require cardiopulmonary bypass surgery, and in patients with active HIT who are not responding to standard therapy. The evidence to date consists of retrospective case reports, therefore this approach remains experimental.[48]

FOLLOW UP

Recommendations

Monitoring

No monitoring after platelet recovery is required, other than routine monitoring of any ongoing anticoagulant therapy.

Patient instructions

Patients should be advised to add 'heparin allergy' to their list of drug allergies. Patients should consider obtaining a medical alert bracelet to notify healthcare professionals in an emergency situation that they should not receive heparin or low molecular weight heparin.

Complications

Complications	Timeframe	Likelihood
new venous or arterial thrombotic event	**short term**	**high**
The risk of thrombosis in a patient with untreated HIT during the initial period is 30% to 50%, including a 5% risk of thrombotic death.[3] Treatment with non-heparin anticoagulants appears to reduce the risk of thrombosis by 50% to 70%.[43]		
treatment-related bleeding	**short term**	**high**
The risk of major bleeding during treatment with non-heparin anticoagulants varies significantly according to the agent used and patient comorbidity (estimated range 3% to 14%).[43]		
limb amputation	**short term**	**low**
Limb amputation is required in 6% to 10% of patients with confirmed HIT.[42] To date, none of the non-heparin anticoagulants have been shown to be effective at reducing the risk of amputation in a patient with limb ischaemia secondary to HIT-provoked macro- and microthrombosis.		
venous gangrene	**short term**	**low**
In the past, when vitamin K antagonists (e.g., warfarin) were used for treatment of HIT without concurrent coverage with a non-heparin anticoagulant, protein C levels fell faster than pro-thrombin levels, which induced a pro-thrombotic state. This can lead to serious adverse events, such as warfarin-induced skin necrosis and venous limb gangrene (distal ischaemic limb necrosis in the absence of arterial occlusion). [Fig-4]		

Prognosis

Platelet recovery in patients with confirmed HIT typically occurs within 1 week (median 4 days) of appropriate treatment, although, in aggressive cases, it can take significantly longer. HIT antibodies are transient and

usually spontaneously resolve within 100 days. In patients who do not experience initial complications, there are no known long-term implications of HIT other than the risk of recurrence on prolonged re-exposure to heparins.

Diagnostic guidelines

Europe

Guidelines on the diagnosis and management of heparin-induced thrombocytopenia (2nd ed)

Published by: British Committee for Standards in Haematology **Last published:** 2012

Summary: Covers the diagnosis of HIT.

North America

Clinical practice guideline on the evaluation and management of adults with suspected heparin-induced thrombocytopenia (HIT)

Published by: American Society of Hematology **Last published:** 2013

Summary: Quick reference guide based on the American College of Chest Physicians' Evidence-based clinical practice guideline on the treatment and prevention of heparin-induced thrombocytopenia (9th ed). Includes recommendations for diagnosis.

Treatment and prevention of heparin-induced thrombocytopenia

Published by: American College of Chest Physicians **Last published:** 2012

Summary: Covers the diagnosis of HIT.

Treatment guidelines

Europe

Guidelines on the diagnosis and management of heparin-induced thrombocytopenia (2nd ed)

Published by: British Committee for Standards in Haematology **Last published:** 2012

Summary: Covers the treatment of HIT.

North America

Clinical practice guideline on the evaluation and management of adults with suspected heparin-induced thrombocytopenia (HIT)

Published by: American Society of Hematology **Last published:** 2013

Summary: Quick reference guide based on the American College of Chest Physicians' Evidence-based clinical practice guideline on the treatment and prevention of heparin-induced thrombocytopenia (9th ed).

North America

Treatment and prevention of heparin-induced thrombocytopenia (9th ed)

Published by: American College of Chest Physicians **Last published:** 2012

Summary: Covers the treatment and prevention of HIT.

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Images

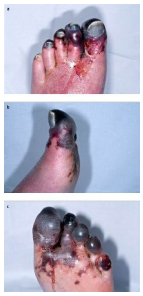

Figure 1: Venous limb gangrene of left foot in HIT: (A) dorsal aspect; (B) medial aspect; and (C) plantar aspect

Rozati H, Shah SP, Peng YY. Lower limb gangrene postcardiac surgery. BMJ Case Reports. 2013; doi:10.1136/bcr-2012-008362

IMAGES

Clinical suspicion for HIT	Antigen assay result	HIT diagnosis
high (4Ts = 6-8)	positive/high titre	confirmed
	positive/low-to-moderate titre	consider functional assay
	negative	excluded, but consider functional assay for confirmation
intermediate (4Ts = 4-5)	positive/high titre	confirmed
	positive/low-to-moderate titre	consider functional assay
	negative	excluded
low (4Ts = 0-3)	positive/high titre	consider functional assay
	positive/low-to-moderate titre	excluded
	negative	excluded

Figure 2: Combination of clinical picture and laboratory evidence of HIT antibodies

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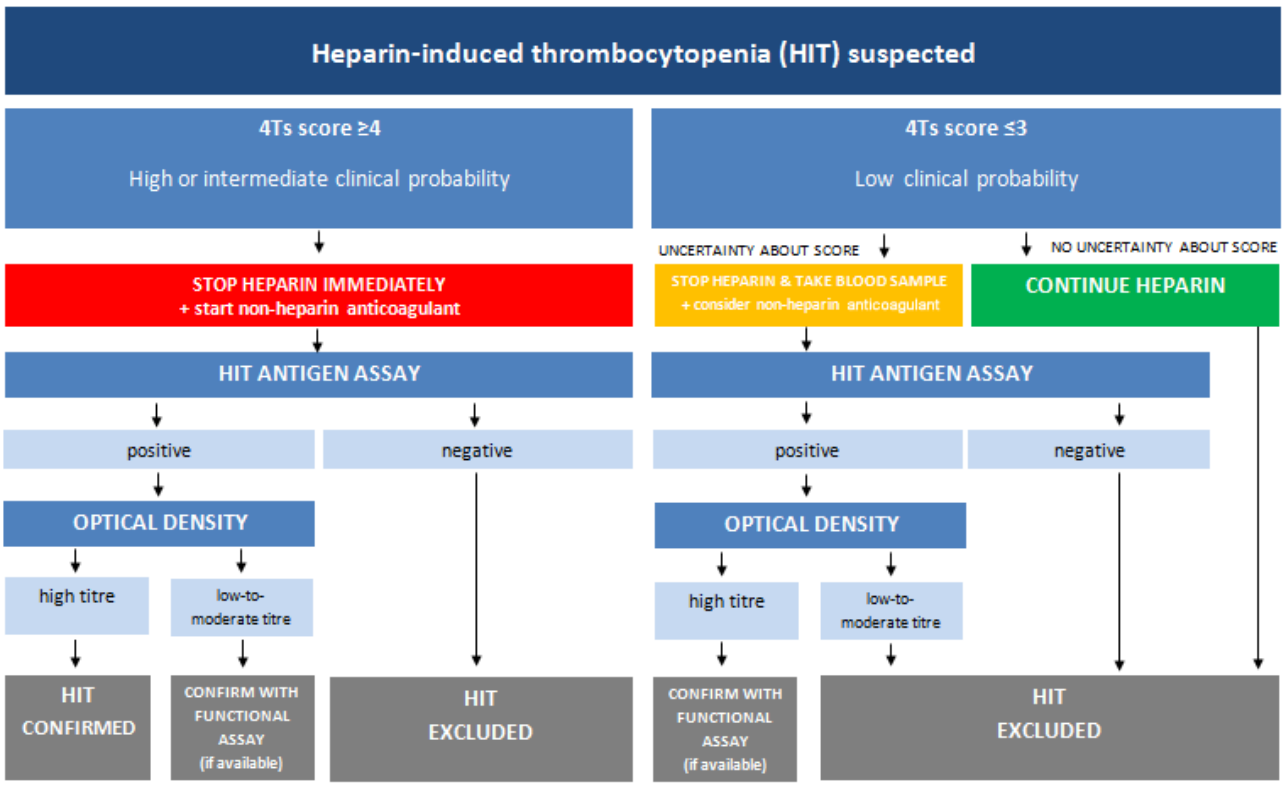

Figure 3: Diagnostic algorithm for heparin-induced thrombocytopenia showing when to continue or discontinue heparin

Created by the BMJ Evidence Centre

Figure 4: Venous limb gangrene of left foot in HIT (dorsal aspect)

Rozati H, Shah SP, Peng YY. Lower limb gangrene postcardiac surgery. BMJ Case Reports. 2013; doi:10.1136/bcr-2012-008362

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