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Heparin induced thrombocytopenia

Lori-Ann Linkins

Heparin induced thrombocytopenia (HIT) is a clinicopathological syndrome that occurs when heparin dependent IgG antibodies bind to heparin/platelet factor 4 complexes to activate platelets and produce a hypercoagulable state. This results in thrombocytopenia or thrombosis in temporal relation to a preceding heparin exposure.¹ HIT typically develops 5-10 days (range 4-15 days) after heparin is started and can occur with unfractionated heparin, low molecular weight heparin, or, rarely, fondaparinux.

Who gets heparin induced thrombocytopenia?

The prevalence of HIT ranges from 0.1% to 5.0% and varies considerably according to several host and drug related risk factors. The highest incidence is in patients who receive heparin after surgery or trauma (1-5%), although the condition is uncommon in medical patients who receive prophylactic doses of heparin (<1%) and rare in pregnant women (<0.1%).³⁻⁷ The risk of HIT is considerably higher with unfractionated heparin than with low molecular weight heparin.⁸ Women seem to have a 1.5-fold to twofold increased risk of HIT compared with men.⁹

What causes it?

The cause of HIT is unknown. The rapid production of IgG antibodies (median four days) without initial IgM antibody production suggests a secondary immune response, despite the absence of previous heparin use in most patients who develop HIT.¹⁰⁻¹¹ Based on these observations it is hypothesised that sensitisation of the antiheparin/platelet factor 4 antibody occurs as the result of exposures to other environmental factors (for example, bacterial infection) that produce the same antigen as that produced by the heparin/platelet 4 complexes.¹²⁻¹³

Can it be prevented?

Primary prevention

The best way to prevent HIT is to minimise or avoid the use of heparin. New oral anticoagulants such as dabigatran, rivaroxaban, and apixaban may be used as alternatives for thromboprophylaxis for some indications, such as after elective hip or knee arthroplasty.

Screening

Screening for HIT usually entails obtaining serial platelet counts in patients who are receiving unfractionated heparin or low molecular weight heparin, or, rarely, fondaparinux for at least four days, or in patients who present with thrombosis and have used these drugs within the past 100 days. Owing to the large number of alternative causes of thrombocytopenia, routine monitoring of platelet count also has the potential to cause harm because of the unnecessary withdrawal of heparin and institution of non-heparin anticoagulants in patients without HIT.

How is it diagnosed?

HIT should be suspected when patients present with new thrombocytopenia or thrombosis in the context of confirmed or suspected use of heparin (unfractionated heparin, low molecular weight heparin, or, rarely, fondaparinux) within the past 100 days, particularly in the context of recent cardiac or orthopaedic surgery. HIT should also be considered when patients present 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 low molecular weight heparin within the past 100 days (box 1, see thebmj.com).

Diagnosis requires the combination of 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 patient's likelihood of HIT based on clinical criteria. This includes a careful review of the patient's history of heparin use (unfractionated heparin, low molecular weight heparin, or fondaparinux). According to heparin type, the risk of HIT in order from highest to lowest is unfractionated heparin, then low molecular weight heparin, then fondaparinux. Despite its structural similarity to heparin, fondaparinux does not usually promote antibody binding to platelet factor 4, owing to absent or weak cross reactivity. Therefore it has a low but not zero risk of inducing HIT. Despite rare reports of fondaparinux induced HIT, this drug has been used successfully to treat HIT in case series and is considered to be a non-heparin anticoagulant.²

The likelihood of HIT is increased by an absence of conditions or drugs that cause thrombocytopenia (table 1). A history of recent surgery (especially orthopaedic or cardiovascular) or trauma increases the likelihood of HIT in patients using heparin. Patients with a history of HIT who reuse heparin for at least four days are at risk of recurrence.

Features consistent with a recent venous or arterial thromboembolic event (for example, deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction) are common. These include new unilateral leg oedema,

THE BOTTOM LINE

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

Table 1 | Differential diagnoses of heparin induced thrombocytopenia (HIT)

| Differentiating signs/symptoms by condition | Differentiating tests |
|---|---|
| Postoperative state | |
| It is not uncommon for the platelet count to initially decrease after surgery and then increase 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 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 variables |
| Drug induced thrombocytopenic purpura | |
| A thorough medical history is needed to identify potential drugs (for example, antineoplastic agents, sulfa drugs, quinine/quinidine, vancomycin, carbamazepine, and glycoprotein IIb/IIIa antagonists). Platelet nadir may be $<20 \times 10^9/L$ ($<20 \times 10^3/\mu L$). This is rare in HIT. Petechiae may be present | No differentiating tests |
| Sepsis/severe infection | |
| Patients with sepsis tend to have hypotension, fever, and other signs of organ dysfunction | HIT assay test negative for HIT antibodies |
| Evidence of disseminated intravascular coagulation may also be present in patients with severe HIT | Positive blood culture results |

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Previous articles in this series

- ▶ The management of chronic breathlessness in patients with advanced and terminal illness (*BMJ* 2015;350:g7617)
- ▶ Ebola virus disease (*BMJ* 2014;349:g7348)
- ▶ Managing perineal trauma after childbirth (*BMJ* 2014;349:g6829)
- ▶ Crohn's disease (*BMJ* 2014;349:g6670)
- ▶ Meniere's disease (*BMJ* 2014;349: g6544)

tenderness, or discoloration (deep vein thrombosis); chest pain, tachypnoea, hypotension, or tachycardia (pulmonary embolism or myocardial infarction); and focal neurological deficits (stroke).

An acute systemic reaction consisting of fever, chills, tachycardia, hypertension, dyspnoea, or cardiopulmonary arrest may occur within 30 minutes of a dose of heparin being administered and is usually accompanied by an abrupt decrease in platelet count.

Clinical prediction tools

Several clinical prediction tools have been developed to help doctors determine the clinical probability of HIT—for example, the Warkentin (4Ts) probability scale (box 2) and HIT expert probability score.

Although the clinical prediction rules differ on specific details, they all focus on several key features: the magnitude of decrease in platelet count, the timing of decrease in platelet count (or other HIT related event) in relation to start of heparin, and the presence or absence of alternative explanations for thrombocytopenia.

Laboratory confirmation of heparin induced thrombocytopenia

A full blood count should be ordered for all patients with suspected HIT. The platelet count is typically decreased in patients with HIT (table 2, see thebmj.com). The timing of the decrease in platelet count (beginning from the first day (day 0) of heparin use) is key. A classic example would be a patient who experiences a 50% decrease in platelet count with a nadir $>20 \times 10^9/L$ ($>20 \times 10^3/\mu L$) between days 5 and 10 of heparin use. The platelet count does not have to decrease $<150 \times 10^9/L$ ($150 \times 10^3/\mu L$) for HIT to be considered—for example, $\geq 50\%$ decrease from baseline during the correct time frame is still suspicious for HIT, even if the absolute platelet nadir is $>150 \times 10^9/L$ ($>150 \times 10^3/\mu L$).

It is not uncommon for the platelet count to initially decrease after surgery and then increase 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 when determining the clinical probability of HIT in these patients. Thrombocytopenia in the context of pancytopenia reduces the likelihood of HIT.

Coagulation studies (international normalised ratio, activated partial thromboplastin time) should be ordered in patients with suspected HIT to exclude coagulopathy. HIT may induce disseminated intravascular coagulation in 10–20% of patients with HIT; therefore, coagulopathy and low fibrinogen levels do not exclude HIT if the clinical scenario is otherwise consistent.³³

Patients with at least an intermediate clinical suspicion for HIT (4Ts score ≥ 4) should undergo testing for HIT antibodies. Emerging evidence shows that a low 4Ts score (≤ 3) alone has a high negative predictive value, suggesting that laboratory testing for HIT antibodies may not be necessary in this group of patients.³⁰ However, some doctors order an antigen assay to exclude the diagnosis and avoid the small risk of missing a true case of HIT.

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

Antigen assays

Antigen assays (for example, antiplatelet factor 4/heparin enzyme linked immunosorbent assay (ELISA), heparin/platelet factor 4 particle gel immunoassay) are available at most clinical centres, but they have a high false positive rate, depending on the patient population.

Functional assays

Functional assays (for example, serotonin release assay, heparin induced platelet activation) are limited to a small number of clinical centres but they 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.^{3 32}

In patients with indeterminate laboratory assay results despite repeat testing, use of an additional laboratory test is recommended, and preferably from a different category of assays (for example, if the first assay was an antigen assay, a functional assay would be an appropriate confirmatory test). 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 (table 3).

Box 2 | The Warkentin (4Ts) probability scale

This scale can be used to estimate the probability of a patient having HIT. Points 0, 1, or 2 are scored for each of four categories (maximum possible score 8)^{28, 29}:

Thrombocytopenia

- 2 points if >50% decrease in platelet count to a platelet count nadir of $\geq 20 \times 10^9/L$ ($\geq 20 \times 10^3/\mu L$)
- 1 point if 30-50% decrease in platelet count, or if the nadir is $10-19 \times 10^9/L$ ($10-19 \times 10^3/\mu L$)
- 0 points if <30% decrease in the platelet count, or if the nadir is $<10 \times 10^9/L$ ($<10 \times 10^3/\mu L$).

Timing* of onset of decrease in platelet count (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 use (within past 30 days)
- 1 point if onset is >10 days after starting heparin or if timing is unclear; or if <1 day after starting heparin with recent heparin use (past 31-100 days)
- 0 points if onset is within four days of first time heparin use (no recent heparin)

Thrombosis or other sequelae

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

Other causes of decrease in platelet count

- 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 use is considered day 0. If the patient undergoes surgery, the day that heparin is restarted after the procedure is considered day 0 of heparin use, 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 intraoperatively, 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 HIT³⁰

A classic example of a high score would be a patient who experiences a 50% decrease in platelet count with a nadir $>20 \times 10^9/L$ ($>20 \times 10^3/\mu L$) between days 5 and 10 of heparin use, and who is found to have new thrombosis and no alternative explanation for the decrease in platelet count. The 4Ts score is more commonly used as it is the most evaluated tool to date

tomography pulmonary angiography or ventilation-perfusion scanning (V/Q scan) should be performed in patients with suspected pulmonary embolism, and computed tomography venography or magnetic resonance imaging in patients with suspected cerebral venous thrombosis.

Thrombosis has been reported in up to 50% of patients with untreated HIT.³⁷ In the context of confirmed HIT, the presence of a deep vein thrombosis may prolong treatment.

How is heparin induced thrombocytopenia managed?

Treatment options for HIT are based on the patient's score on the Warkentin (4Ts) probability scale (see box 2). For patients with a 4Ts score of ≤ 3 , the treatment options will depend on the doctor's preference (figure).

Confirmed or suspected heparin induced thrombocytopenia (4Ts score ≥ 4)

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

If a vitamin K antagonist (for example, 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 in whom platelet recovery has not been achieved.

To reduce the high risk of HIT induced 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 few case reports of fondaparinux induced HIT appear 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. Fondaparinux is classified as a non-heparin anticoagulant, despite having structural similarities to heparin. Low molecular weight heparin 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 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.

Suspected heparin induced thrombocytopenia (4Ts score ≤ 3)

Evidence is emerging to show that a low 4Ts score (≤ 3) alone has a high negative predictive value for HIT, suggesting that laboratory testing for HIT antibodies may not be necessary in this group of patients.³⁰ However, some doctors still order an antigen assay to exclude the diagnosis and avoid the small risk of missing a true case of HIT.

Platelet recovery

Platelet recovery is generally said to have occurred when platelet levels have returned to $>150 \times 10^9/L$ ($>150 \times 10^3/\mu L$).

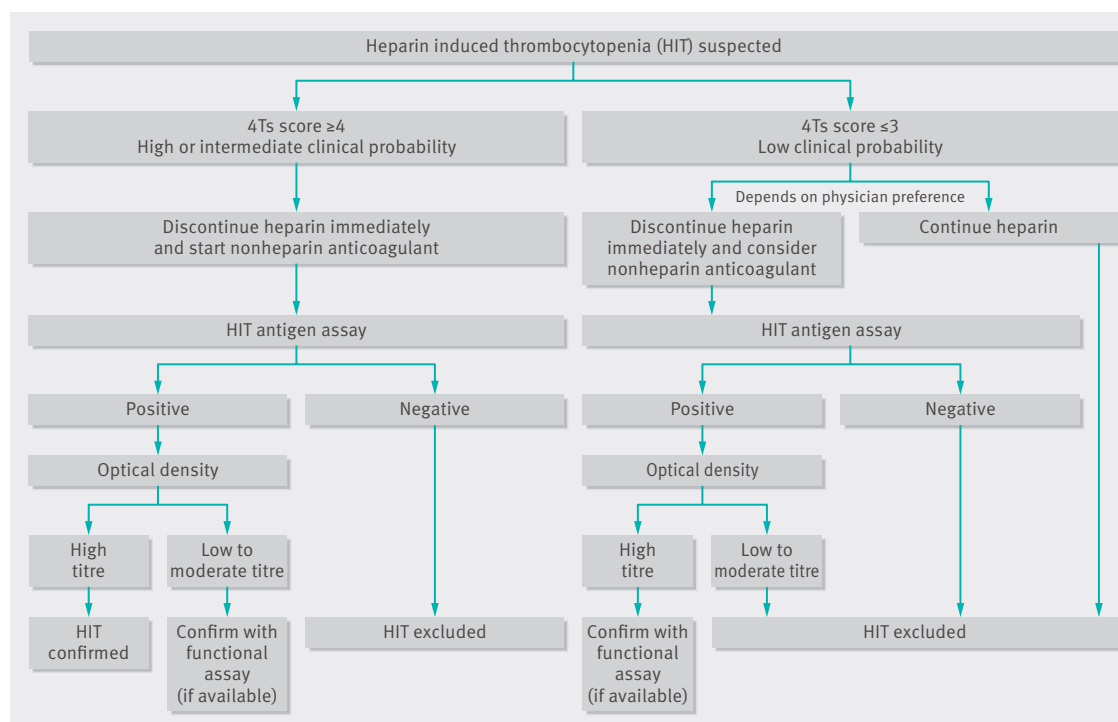
Table 3 | Combination of clinical picture and laboratory evidence of heparin induced thrombocytopenia (HIT) antibodies. Adapted from Raschke et al³⁶

| Clinical suspicion for HIT by antigen assay result | HIT diagnosis |
|--|--|
| High (4Ts score 6-8): | |
| Positive/high titre | Confirmed |
| Positive/low-moderate titre | Consider functional assay |
| Negative | Excluded, but consider functional assay for confirmation |
| Intermediate (4Ts score 4-5): | |
| Positive/high titre | Confirmed |
| Positive/low-moderate titre | Consider functional assay |
| Negative | Excluded |
| Low (4Ts score 0-3): | |
| Positive/high titre | Consider functional assay |
| Positive/low-moderate titre | Excluded |
| Negative | Excluded |

Imaging

Patients with suspected deep vein thrombosis should undergo venous Doppler ultrasonography. New deep vein thrombosis (incompressible venous segment) or extension of a recent deep vein thrombosis (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, computed



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

The duration of treatment for confirmed HIT is controversial. In patients with HIT induced thrombosis, non-heparin anticoagulant treatment for three months is reasonable. In patients without thrombosis, non-heparin anticoagulant treatment for one month is suggested.²⁵

Once platelet levels have recovered, which suggests that ongoing thrombin generation has been halted, treatment should be switched to an alternative anticoagulant. The primary option for ongoing treatment is a vitamin K antagonist (for example, warfarin).

Fondaparinux is a secondary option; however, it is only available as a subcutaneous injection and is relatively expensive.

What are the complications of heparin induced thrombocytopenia?

New venous or arterial thrombotic event

In patients with untreated HIT the risk of thrombosis during the initial period is 30-50%, including a 5% risk of thrombotic death.²⁶ Treatment with non-heparin anticoagulants seems to reduce the risk of thrombosis by 50-70%.²⁵

Treatment related bleeding

The risk of major bleeding during treatment with non-heparin anticoagulants varies considerably according to the agent used and patient comorbidity (estimated range 3-14%).²⁵

Limb amputation

Limb amputation is required in 6-10% of patients with confirmed HIT.³⁴ To date, none of the non-heparin anticoagulants have been shown to be effective at reducing the risk of amputation in patients with limb ischaemia secondary to HIT induced macrothrombosis and microthrombosis.

Venous gangrene

In the past, when vitamin K antagonists such as warfarin were used to treat HIT without concurrent coverage with a non-heparin anticoagulant, protein C levels decreased faster than prothrombin levels, which induced a prothrombotic state. Such patients are at risk of serious adverse events, such as warfarin induced skin necrosis and venous limb gangrene²⁷ (distal ischaemic limb necrosis in the absence of arterial occlusion).

What is the prognosis?

With appropriate treatment, platelet recovery typically occurs within one week (median four days) in patients with confirmed HIT, although in aggressive cases it can take considerably 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 with prolonged reuse of heparins.

Monitoring

After platelet recovery no monitoring is required, other than routine monitoring of any ongoing anticoagulant treatment.

Patient advice

Patients should be advised to add "heparin allergy" to their list of drug allergies. Affected patients should consider wearing a medical alert bracelet to notify healthcare professionals in an emergency situation of the need to avoid heparin or low molecular weight heparin.

Are there any emerging treatments?

A clinical trial evaluating the use of rivaroxaban in patients with suspected or confirmed HIT is ongoing.⁴⁰

For references, see the version of the review on thebmj.com.