



# Heparin-induced thrombocytopenia: Principles for early recognition and management

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## ■ ABSTRACT

Heparin-induced thrombocytopenia (HIT) is a potentially devastating complication of therapy with either unfractionated or low-molecular-weight heparin. Thrombocytopenia is no longer essential for the diagnosis of HIT, since a 50% drop in the platelet count may be a more specific indicator. Once HIT is clinically suspected, heparin should be stopped immediately and direct thrombin inhibitor therapy started; waiting for laboratory confirmation may be catastrophic.

**H**eparin-induced thrombocytopenia (HIT) is one of the most important and potentially catastrophic drug complications known. Although first reported in 1958, it remains a diagnosis not frequently considered or even recognized by many physicians. This review briefly surveys the key issues surrounding HIT for clinicians: when to suspect it, how to approach its diagnosis, and strategies for its effective management.

## ■ HIT: WHAT IT IS AND WHY IT MATTERS

HIT is a serious complication of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) therapy that affects both the venous and arterial circulation. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are its most frequent sequelae, although arterial events—including loss of limb, myocardial infarction, and stroke—can also occur.

The incidence of HIT may be as high as 5% in patients receiving UFH but is lower (1% or less) with LMWH therapy.<sup>1</sup> Any route of administration (subcutaneous or intravenous) or amount of heparin (prophylactic doses, heparin flushes, small amounts on

heparin-coated catheters) can cause HIT.

Historically, two types of HIT have been described.

**Type I HIT**, a non-immune-mediated form, results in a transient drop in the platelet count between days 1 and 4 of treatment. In this type, the platelet count seldom drops below 100,000 per  $\mu\text{L}$ , thrombocytopenia resolves without heparin discontinuation, and no thromboembolic events occur.

**Type II HIT** is an immune-mediated process that can result in devastating thromboembolic complications, including death. It develops within 5 to 14 days of heparin exposure, though it may occur within hours if the patient has had recent treatment, or days to weeks after heparin has been discontinued. In Type II HIT, administration of heparin stimulates the release of platelet factor 4 (PF4), a heparin-neutralizing protein found in the alpha granules of platelets. Heparin and PF4 form a complex that leads to development of HIT antibodies (immunoglobulin G [IgG]). These IgG-PF4-heparin immune complexes bind to the Fc receptors on platelet surfaces, resulting in platelet activation, aggregation, release of prothrombotic platelet-derived microparticles, and, eventually, the development of thrombocytopenia and thrombosis. These complexes also stimulate monocytes, resulting in tissue factor production, and activation of the extrinsic coagulation pathway system, increased thrombin generation, and thrombosis (**Figure 1**).<sup>2</sup>

## ■ WHEN TO SUSPECT HIT

HIT should be suspected in any patient who develops thrombocytopenia (defined as a platelet count  $< 150,000$  per  $\mu\text{L}$ ) while receiving UFH or LMWH therapy. Although most patients do not develop the severe thrombocytopenia (or bleeding complications) often seen with other immune-mediated drug reactions, the median platelet count in one large series was 59,000 per  $\mu\text{L}$ , and counts under 15,000 were reported.<sup>3</sup> The thrombocytopenia is not always associated with thrombosis; when it is not, it is referred to as isolated HIT.

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## ■ The pathogenesis of heparin-induced thrombocytopenia

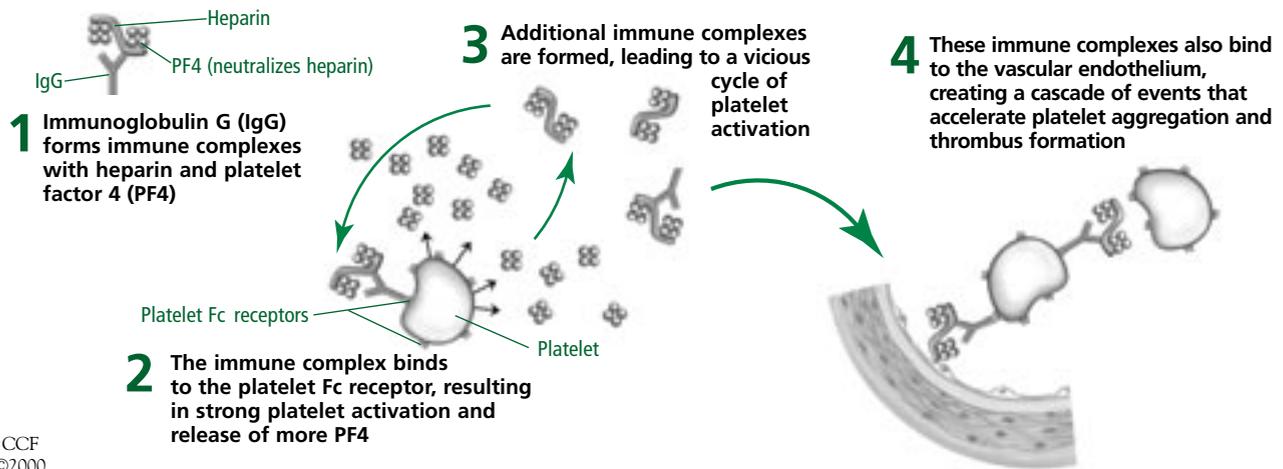


FIGURE 1. Adapted, with permission, from reference 2.

HIT can also occur in patients who have normal or even elevated platelet counts. These patients demonstrate a 50% or greater decline in their platelet count from their pretreatment level. Recent evidence-based guidelines suggest that the degree of this drop in platelet count may be a more sensitive predictor of HIT in post-operative patients than is absolute thrombocytopenia.<sup>4</sup>

HIT must also be considered in patients who develop new thrombosis or an extension of existing thrombosis despite adequate treatment with UFH or LMWH. It should also be considered when there is a resistance to UFH, defined as an inability to maintain therapeutic activated partial thromboplastin time (aPTT) levels despite increasing dosage.<sup>5,6</sup>

### Three patterns of HIT presentation

In a heparin-naïve patient, HIT usually develops within the first 5 to 14 days after exposure. This classic presentation is referred to as **typical-onset HIT** and represents approximately 65% of all reported cases.<sup>4</sup>

Two other temporal patterns have recently been described. **Rapid-onset HIT**, which represents up to 30% of all cases, occurs within hours to days of heparin administration (median, 10.5 hours) in patients who have received prior heparin therapy within the previous 100 days.<sup>7</sup> It is attributable to the continued presence of circulating heparin-dependent antibodies following recent exposure. **Delayed-onset HIT** develops 9 to 40 days after UFH or LMWH has been withdrawn and is seen in 2% to 3% of all HIT patients.<sup>7-9</sup> These patients are often sent home off anticoagulants without complications, only to return later with a new thrombotic event. High antibody titers and low or borderline platelet counts are often identified on presentation.<sup>9</sup> Delayed-onset HIT must be differentiated from a delayed recognition of HIT in patients for whom the platelet count was not closely followed or the diagnosis not considered.

### Thrombotic complications of HIT

More than half of all patients who develop HIT will experience a thrombotic complication.<sup>10</sup>

Venous thromboembolism (VTE) occurs four times more often than arterial events. DVT of the leg (often bilateral) is the most frequent clinical sequela, followed by upper extremity involvement, which often occurs at the site of a central venous catheter.<sup>1,11</sup> PE is more common than all of the arterial events combined and is reported to occur in up to 25% of all cases.<sup>1</sup> Additional reported VTE events include cerebral sinus thrombosis and adrenal vein thrombosis resulting in hemorrhagic necrosis of the adrenal gland.<sup>1</sup>

The most common arterial thrombosis is acute limb occlusion, which may occur at the site of an endovascular procedure or intravascular catheter insertion, or in areas of previous vascular trauma or surgery.<sup>1,11</sup> The iliac arteries and distal aorta are most often involved. HIT may also result in acute thrombotic stroke, myocardial infarction, an intracardiac thrombus, or thrombosis of a prosthetic graft or extracorporeal circuit.

A number of unusual complications have also been recognized with HIT, including warfarin-induced venous limb gangrene, warfarin-induced skin necrosis, heparin-induced skin necrosis, and an acute systemic reaction following an intravenous bolus of UFH.

Warfarin-induced venous limb gangrene or skin necrosis develop when patients receive unopposed warfarin or when this oral anticoagulant is initiated too early during active HIT.<sup>12,13</sup> Patients with warfarin-induced venous limb gangrene develop acral necrosis with DVT in an ipsilateral arm or leg, often accompanied by a supratherapeutic international normalized ratio (INR), whereas warfarin-induced skin necrosis affects fatty tissue areas, including the breast, buttocks, and thigh.<sup>12</sup>

Patients who develop heparin-induced skin lesions

**TABLE 1**  
Using “the four T’s” to estimate the pretest probability of HIT\*

	<b>2 Points</b>	<b>1 Point</b>	<b>0 Points</b>
<b>Thrombocytopenia</b>	> 50% fall or platelet nadir of 20,000–100,000 per $\mu$ L	30%–50% fall or platelet nadir of 10,000–19,000 per $\mu$ L	Fall < 30% or platelet nadir < 10,000 per $\mu$ L
<b>Timing of platelet count fall or other sequelae</b>	Clear onset between days 5 and 10; or less than 1 day if exposed to heparin within past 100 days	Consistent with immunization but not clear (eg, missing platelet counts); or onset after day 10	Fall in platelet count is too early (without recent heparin exposure)
<b>Thrombosis or other sequelae (eg, skin lesions)</b>	New thrombosis; skin necrosis; acute systemic reaction following heparin bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
<b>Other cause of thrombocytopenia</b>	No other cause for fall in platelet count is evident	Possible other cause is evident	Definite other cause is present

\* A patient’s pretest probability equals the total points in all four categories: 0–3 points = low; 4–5 points = intermediate; 6–8 points = high.

Adapted, with permission, from reference 16.

present with erythematous plaques, nodules, or skin necrosis in areas where subcutaneous injections of UFH or LMWH were given. These lesions are usually painful and pruritic, and although as many as 75% of these patients will not develop thrombocytopenia, these skin changes should be considered a marker for HIT.<sup>14</sup>

An acute systemic reaction may occur within 5 to 30 minutes following an intravenous bolus of UFH. An abrupt fall in the platelet count is generally identified if the platelet count is assessed, while the most common signs include fever, chills, tachycardia, and hypertension. Flushing, headaches, nausea, vomiting, diarrhea, chest pain, and transient global amnesia have also been reported. Development of this reaction in association with HIT may result in sudden cardiorespiratory collapse and, rarely, death.<sup>15</sup>

Disseminated intravascular coagulation may also develop in patients with HIT. It is characterized by hypofibrinogenemia and a transient acquired natural anticoagulant deficiency including low levels of antithrombin and protein C. Patients may have a prolonged INR and aPTT. Schistocytes are often seen on the peripheral blood smear, and livedo reticularis, renal failure, and other signs of microvascular thrombosis may be present.<sup>1</sup>

### ■ DIAGNOSIS: COMBINE CLINICAL ASSESSMENT WITH LABORATORY TESTING

HIT is commonly referred to as a clinicopathologic syndrome and requires both clinical and laboratory findings to confirm the diagnosis.<sup>14</sup> Patients present with clinical evidence of thrombocytopenia or thrombosis, while the laboratory diagnosis relies on detection of HIT antibodies to UFH or LMWH.

Because thrombocytopenia is a common finding in the hospital setting, other possibilities must be considered in the differential diagnosis of HIT. These include pseudothrombocytopenia, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, infections, effects of other medications or alcohol, bone marrow failure, and dilution.

Warkentin and Heddle<sup>16</sup> recently recommended a clinical decision-making model to establish a pretest probability for HIT in patients who receive UFH or LMWH. This model is based on what they term the “four T’s” (see **Table 1**). Points are given for each of these four categories, and point totals are summed to classify the likelihood of HIT as either low, intermediate, or high, as detailed in **Table 1**.

Two types of laboratory tests are readily available for the diagnosis of HIT: **functional tests**, which detect heparin-dependent platelet activation in the presence of the patient’s sera and UFH or LMWH; and **antigen assays** (immunoassays), which measure IgG, IgM, or IgA antibodies that bind PF4 to UFH. It is important to recognize that these laboratory tests should be ordered only when there is a clinical suspicion of HIT.

Several functional assays are available, as detailed in **Table 2**. Of these, the washed-platelet assays have a higher sensitivity and specificity relative to the platelet aggregation test, and the serotonin release assay (SRA) is considered the gold standard among the washed-platelet tests.<sup>17</sup> Its major disadvantage, however, is that it is technically demanding, requires the use of radioisotopes and fresh donor platelets, and is not readily available in all laboratories. Most clinical laboratories do not perform the SRA, preferring the less demanding platelet aggregation test or

**TABLE 2**

Assays for use in laboratory testing for HIT

Functional assays	Antigen assays
<p><i>Washed-platelet assays</i></p> <ul style="list-style-type: none"> <li>• Serotonin release assay</li> <li>• Heparin-induced platelet aggregation assay</li> </ul> <p><i>Citrated plasma assays</i></p> <ul style="list-style-type: none"> <li>• Platelet aggregation test</li> </ul>	<ul style="list-style-type: none"> <li>• Solid-phase enzyme immunoassay               <ul style="list-style-type: none"> <li>—GTI-PF4 immunoassay</li> <li>—Asserachrom®</li> </ul> </li> <li>• PF4-polyvinylsulfonate antigen assay</li> <li>• Fluid-phase immunoassay</li> <li>• Particle gel immunoassay</li> </ul>
Characteristics	Characteristics
<ul style="list-style-type: none"> <li>• Less sensitive</li> <li>• More specific</li> <li>• Technically demanding</li> <li>• Not standardized</li> <li>• Expensive, not readily available</li> </ul>	<ul style="list-style-type: none"> <li>• More sensitive</li> <li>• Less specific</li> <li>• Technically simple</li> <li>• Standardized</li> </ul>

heparin-induced platelet aggregation assay.

Four types of antigen assays are available, as detailed in **Table 2**. The two solid-phase enzyme immunoassays can detect clinically unimportant amounts of IgG, IgM, and IgA antibodies in patients exposed to UFH or LMWH, leading to high false-positive results and low specificity. More recently, a rapid antigen assay (particle gel immunoassay) has been developed.<sup>18</sup> It has a specificity similar to that of the functional assays with improved sensitivity, producing fewer false-positive results than the solid-phase immunoassays. This rapid antigen assay has the potential to fulfill a longstanding need for a quick (< 30 minutes) and reliable HIT assay.

Washed-platelet assays are recognized as more reliable than antigen assays because they have a better combined sensitivity and specificity, though no single test has 100% sensitivity and specificity.<sup>16</sup> Most reports recommend a combination of assays (a washed-platelet functional assay and an antigen assay) to help confirm the diagnosis of HIT.

## ■ HOW TO MANAGE ANTICOAGULATION IN HIT

Although the treatment of HIT has evolved over the past decade, the mainstay of therapy remains immediate discontinuation of UFH or LMWH once the diagnosis is suspected, followed by substitution of an alternative anticoagulant. Treatment should not be delayed while waiting for laboratory test results, as this only increases the risk of thrombosis. It is important that all sources of UFH or LMWH be removed, including any found in heparin flushes or total parenteral nutrition solutions, any that is bound to catheters, or any used intermittently during dialysis or angiography.

Simply discontinuing UFH is inadequate, even if there is no evidence of acute thrombosis (ie, isolated HIT). Three studies have found a cumulative thrombosis rate of 20% to 53% if this approach is followed.<sup>10,19,20</sup>

After many years of having few alternatives for treating HIT, clinicians now have several good options (**Table 3**), owing largely to the development of the direct thrombin inhibitors (DTIs).

## FDA-approved therapies

**Lepirudin**, a recombinant form of the leech-derived anticoagulant hirudin, was the first DTI approved by the US Food and Drug Administration (FDA) for anticoagulation in patients with HIT.<sup>21–24</sup> It has a relatively short half-life (80 minutes) and can be given intravenously or subcutaneously (though the latter route is not FDA-approved) and is monitored via the aPTT or the activated clotting time (ACT). The target aPTT is 1.5 to 2.5 times the baseline level and should be measured 4 to 6 hours after dose adjustments. Lepirudin is metabolized primarily by the kidney and requires significant dose adjustments in patients with renal insufficiency. In three studies comparing lepirudin-treated patients with historical controls, lepirudin was associated with significantly lower rates of the composite end point of mortality, limb amputation, or new thrombotic complications.<sup>21–24</sup>

Lepirudin lacks cross-reactivity with UFH or LMWH antibodies, but anti-hirudin antibodies develop in as many as 60% of patients.<sup>25</sup> These are not associated with increased risk for thrombosis, but anaphylaxis and death have been reported in patients who were reexposed to lepirudin.<sup>26</sup> Antibodies may extend the half-life of lepirudin, which requires closer monitoring of the aPTT.

**Argatroban** is a small synthetic molecule derived from L-arginine. It is FDA-approved for prevention and treatment of thrombosis in patients with HIT and for use in patients with HIT who require percutaneous coronary intervention. It has a short half-life (**Table 3**), lacks cross-reactivity with UFH, and can be monitored via the aPTT or ACT. The target aPTT is 1.5 to 3.0 times the baseline level. Because argatroban prolongs the INR, assessing the anticoagulant effects of warfarin may be challenging in patients receiving argatroban. Therefore, the manufacturer recommends that a target INR greater than 4.0 be used during cotherapy before argatroban is discontinued, and that the INR be checked 4 to 6 hours after discontinuation to ensure that it remains within the therapeutic range.

Argatroban is metabolized in the liver and dose adjustments are recommended in patients with moderate liver disease. No antibody formation has been demonstrated. Similar to the data reported for lep-

**TABLE 3**  
Comparison of available agents used in the treatment of HIT

	Argatroban*	Bivalirudin	Fondaparinux	Lepirudin*
Monitoring	aPTT, ACT	aPTT, ACT	None required	aPTT, ACT
Half-life	39–51 min	25 min	17 hr	80 min
Clearance	Hepatic	Proteolytic and renal	Renal	Renal
Dose adjustment	Moderate hepatic insufficiency	Moderate to severe renal insufficiency	Renal insufficiency	Renal insufficiency
Cross-reaction with HIT antibodies	No	No	Unknown in vivo, none in vitro	No
Antibody development	No	May cross-react with anti-hirudin antibodies	No	Anti-hirudin antibodies in up to 60% of patients

\*FDA-approved for use in patients with HIT.

aPTT = activated partial thromboplastin time; ACT = activated clotting time

irudin, two studies of argatroban-treated patients with active or latent HIT have shown reductions in the risk of new thrombosis and thromboembolic complications compared with historical controls.<sup>20,24,27</sup>

**Comparative considerations.** Comparing the efficacy of lepirudin and argatroban is difficult because patients' baseline factors differed in the respective clinical trials. Neither agent has an antidote. Because of their differing dose adjustment requirements, argatroban may be better suited for patients with renal insufficiency and lepirudin for patients with hepatic dysfunction.<sup>24</sup>

#### 'Off-label' therapies for HIT

Other anticoagulants have been used "off label" for treatment of patients with HIT.

**Bivalirudin** is a DTI designed from the structure of hirudin. It has the shortest half-life of the available DTIs (25 minutes), is metabolized by both proteolytic and renal mechanisms, and is monitored via the aPTT or ACT. Dose adjustments are necessary for patients with moderate to severe renal insufficiency. Bivalirudin has a minimal effect on the INR.

Experience with bivalirudin in patients with HIT is limited, though it has been used extensively to treat acute coronary syndrome in patients without HIT, and recent results from the ATBAT study were favorable for patients with HIT undergoing percutaneous coronary intervention.<sup>28–30</sup> It has also been used successfully in anecdotal cases of HIT patients requiring open-heart surgery,<sup>31</sup> and recent results on its use in patients without HIT who required off-pump coronary artery bypass surgery were encouraging.<sup>32</sup> Bivalirudin is currently under investigation as an alternative anticoagulant in both on-pump and off-pump cardiac surgery.

**Fondaparinux** is a synthetic pentasaccharide that binds to antithrombin. It is given subcutaneously, has 100% bioavailability, is excreted renally, and has only minimal effect on the prothrombin time, INR, aPTT, and bleeding time. It is currently approved for prevention of VTE in orthopedic patients and for treatment of DVT and PE in hospitalized patients. Fondaparinux does not appear to cross-react with HIT antibodies and may be an alternative to the DTIs, although experience with its use in HIT is limited.

#### Discontinued or nonrecommended options

**Danaparoid**, a low-molecular-weight heparinoid with a long half-life (18 to 24 hours), has also been used effectively in HIT patients. It has cross-reactivity with UFH in as many as 30% of cases, and although several studies have demonstrated its efficacy in the management of HIT, it is no longer commercially available in the United States.<sup>17,33,34</sup>

**Warfarin** remains the anticoagulant of choice for the long-term management of HIT, but it is now well recognized that warfarin should be avoided in patients with acute HIT, as it can precipitate warfarin-induced venous limb gangrene or skin necrosis.<sup>12,13</sup> Recent guidelines recommend not using warfarin as monotherapy, waiting until the platelet count has recovered (to  $\approx 150,000$  per  $\mu\text{L}$ ), overlapping with an alternative anticoagulant for at least 5 days, starting with low doses (2.5 to 5 mg), and not discontinuing the alternative anticoagulant until the INR is therapeutic for 2 consecutive days.<sup>4</sup>

**Platelet transfusions** are not recommended even when thrombocytopenia is pronounced, both because bleeding complications are uncommon and because thrombotic events have been reported following such

transfusions. They should, however, be used in the rare patient with bleeding complications.

### What about heparin reexposure?

Reexposure to UFH has generally been thought to be associated with a high risk of thrombocytopenia and thrombosis. In most patients, however, the UFH-dependent antibody will disappear within 100 days from the last dose. In certain clinical circumstances where anticoagulation is essential and the safety and efficacy of UFH is well established, such as cardiopulmonary bypass or vascular surgery, some investigators have advocated reexposure if certain conditions are met.<sup>7</sup> This is dependent upon demonstrating no antibody on sensitive laboratory tests and exposing the patient to UFH for only a short time (eg, during the surgical procedure).

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### SUMMARY

HIT is a serious complication of both UFH and LMWH therapy that occurs more than just rarely. It has recently been recognized to occur more frequently outside of its typical presentation within 5 to 14 days after heparin exposure. Thrombocytopenia is no longer essential for the diagnosis of HIT, as a 50% drop in the platelet count may be a more specific indicator. Once HIT is clinically suspected, heparin should be discontinued immediately and a DTI started; waiting for laboratory confirmation may be catastrophic. Failure to follow these guidelines may lead to VTE, stroke, myocardial infarction, loss of limb, or other devastating complications.