

# Heparin-Induced Thrombocytopenia: A Review

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## ABSTRACT

Immune heparin-induced thrombocytopenia (HIT) is a relevant adverse drug reaction consisting in a hypercoagulable state caused by an anticoagulant agent. The incidence is ~6.5% in patients receiving unfractionated heparin after orthopedic surgery, and is equal to or lower than 1% in other settings. HIT occurrence is a function of heparin type, duration of heparin administration, patient population, and gender. The pathogenesis is due to an antibody response to the complex heparin/platelet factor 4 in most cases, with secondary activation of platelets and coagulation, and finally increased thrombin generation. Thrombocytopenia, venous or arterial thrombosis, heparin-induced skin necrosis, adrenal hemorrhage, and transient amnesia can characterize the clinical course of HIT. Platelet monitoring in patients receiving heparin is indicated to early detect HIT. A thrombotic event can be the first manifestation of HIT. Laboratory demonstration of heparin-dependent platelet activation confirms the clinical diagnosis; antigenic or functional assays are available. Once HIT is highly likely or confirmed serologically, immediate heparin cessation is mandatory and an alternative therapeutic anticoagulant is needed due to the high risk (or the presence) of thrombotic events. The available nonheparin anticoagulants aim to reduce thrombin generation. Lepirudin, argatroban, and bivalirudin (direct thrombin inhibitors) and danaparoid and fondaparinux (factor Xa inhibitors) represent the current treatment options for HIT. Vitamin K antagonists can be used safely only after a stable platelet count has been obtained.

**KEYWORDS:** Heparin-induced thrombocytopenia, heparin therapy, review

Of the two identified forms of heparin-induced thrombocytopenia (HIT; Table 1), the immune type (HIT type 2) represents a relevant adverse drug reaction. Although HIT type 1 has a benign course, with platelet counts recovering without heparin withdrawal and no clinical consequences, HIT type 2 constitutes a clinical-pathological syndrome with a strong association with thrombotic events. Immediate heparin withdrawal is required, and in most cases, an alternative anticoagulant must be administered.<sup>1,2</sup>

HIT type 2, the object of this review, can be defined as an unexplained thrombocytopenia of 50% or more

compared with any previous value during exposure to unfractionated heparin (UFH) or low molecular weight heparin (LMWH),<sup>3</sup> confirmed by the demonstration of specific antibodies against the heparin-platelet factor 4 (PF4) complex by means of a functional and/or antigenic assay.<sup>4,5</sup> In this article, we will refer to HIT type 2 simply as HIT.

## EPIDEMIOLOGY

The reported frequencies of HIT vary widely. In a review of prospective trials, the reported estimates ranged from

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**Table 1 Main Features of the Two Different Forms of Heparin-Induced Thrombocytopenia (HIT)**

Feature	Type 1	Type 2
<b>Frequency</b>	Up to 20%	Up to 5%
<b>Onset</b>	1–4 d	5–14 d
<b>Pathogenesis</b>	Heparin-induced aggregation	Antibody to PF4–heparin complex
<b>Thrombosis</b>	No	Yes
<b>Management</b>	No heparin withdrawal required	Heparin withdrawal mandatory + alternative anticoagulation

PF4, platelet factor 4.

1 to 30% among patients receiving UFH and 2% in patients receiving LMWH.<sup>6</sup> In a more rigorous review, the estimated incidence was lower than 3% with UFH, and 0% with LMWH.<sup>6a</sup> Considering only prospective studies in which an appropriate definition of HIT is present (50% platelet count decrease or thrombotic event with a positive antibody assay or satisfactory clinical criteria for HIT), the frequency of HIT results as reported in Table 2, according to different patient populations and different heparin compounds. HIT is more frequent in patients who have had orthopedic surgery<sup>3,7–10</sup> (up to 6.5% when receiving UFH), and is equal to or lower than 1% in other settings.<sup>11–18</sup> Notably, LMWHs are not free of risk in terms of HIT compared

**Table 2 Prospective Studies Evaluating the Incidence of Immune HIT in Different Patient Populations, Receiving UFH or LMWH**

Reference	Incidence (%)
After orthopedic surgery, UFH	
Ganzer et al <sup>7</sup>	6.5
Mahlfeld et al <sup>8</sup>	2
Warkentin et al <sup>9</sup>	4.8
After orthopedic surgery, LMWH	
Ganzer et al <sup>9</sup>	0
Marx et al <sup>10</sup>	0
Mahlfeld et al <sup>8</sup>	0.4
Warkentin et al <sup>11</sup>	0.6
After heart surgery, UFH	
Warkentin et al <sup>4</sup>	1
After general or vascular surgery, UFH and LMWH	
Calaitges et al <sup>12</sup>	0
Lindhoff-Last et al <sup>13</sup>	0
Medical patients, UFH	
Kappers-Klunne et al <sup>14</sup>	0.3
Lozano et al <sup>15</sup>	0.9
Lindhoff-Last et al <sup>16</sup>	0.5
Girolami et al <sup>17</sup>	0.8
Medical patients, LMWH	
Lindhoff-Last et al <sup>16</sup>	0.5
Prandoni et al <sup>18</sup>	0.8

Study inclusion criteria: prospective (randomized studies, single- or double-cohort studies), declared adequate definition of HIT, laboratory demonstration of antibodies, or presence of stringent clinical criteria.

HIT, heparin-induced thrombocytopenia; UFH, unfractionated heparin; LMWH, low molecular weight heparin.

with UFH. HIT occurrence is a function of heparin type (bovine UFH > porcine UFH > LMWH), duration of heparin administration (higher risk from days 5 to 14), gender (female > male),<sup>2</sup> HIT definition, and type of test used for detecting heparin-dependent antibodies.<sup>11</sup> In general, antibodies are more likely to form in patients undergoing cardiac surgery than orthopedic surgery, as well as in orthopedic surgery patients who receive UFH instead of LMWH. However, among patients in whom antibodies do form, orthopedic patients are much more likely to develop HIT.<sup>11</sup>

## PATHOGENESIS

Heparin administration can trigger an antibody response, given that antibodies are produced against the heparin–PF4 complex<sup>19–22</sup> in some patients,<sup>11</sup> depending on heparin molecular weight.<sup>23</sup> PF4 is the most important antigen,<sup>14</sup> but the neutrophil-activating peptide 2 and interleukin 8 may also be involved.<sup>24</sup> After heparin binds to PF4, a conformational change within PF4 determines the exposition of epitopes,<sup>25,26</sup> and immunoglobulin M (IgM), IgA, or IgG antibodies are produced consequently. Clinically, only the IgG class antibodies are pathogenic<sup>27</sup> and associated with thrombosis. The heparin–PF4–antibody complex binds to the platelet surface FcγRIIIa receptor.<sup>19,28</sup> Cross-linking of FcγRIIIa results in activation of platelets and the coagulation cascade with thrombin generation (a potent platelet activator). Because additional PF4 is released, a positive–feedback loop enhances the process.<sup>29</sup> Activated platelets aggregate and are removed prematurely from the circulation, leading to thrombocytopenia and, in some patients, to venous or arterial thrombosis. In summary, HIT pathogenesis can be described as a three-step process: first, the antibodies are generated (immune response); second, platelets are activated and thrombin generation is increased (hypercoagulable state); third, in some unpredictable patients, thrombosis occurs (clinical–pathological syndrome).

## CLINICAL MANIFESTATIONS

Thrombocytopenia typically occurs 5 to 10 days after initiation of heparin.<sup>1</sup> However, in the particular case of an early re-exposure to heparin in patients who developed

anti-PF4-heparin antibodies in the previous 100 days, onset may be earlier and rapid.<sup>30</sup> In general, an onset of thrombocytopenia after 2 weeks is unusual. However, a delayed onset of HIT also has been described<sup>31</sup> in which thrombocytopenia developed after heparin withdrawal. In general, thrombocytopenia rarely is severe, with median nadir platelet counts of  $\sim 60 \times 10^9/L$ <sup>32</sup> and it is rarely associated with bleeding.

Thrombosis, venous and/or arterial, is the major clinical problem associated with HIT. The prothrombotic state associated with HIT is due to thrombin generation, platelet activation, and endothelial cell activation.<sup>33</sup> The frequency of venous thrombosis in HIT patients reaches 90% in patients after orthopedic surgery, whereas arterial thrombosis occurs less frequently. Approximately one half of patients with HIT are recognized only after the occurrence of a complicating thrombotic event. The risk of thrombosis after HIT is higher than 50% in the first 30 days.<sup>34</sup> Deep vein thrombosis and (fatal) pulmonary embolism are the most relevant thrombotic events in HIT patients. Other thrombotic manifestations include venous limb gangrene, cerebral sinus thrombosis, and upper extremity deep vein thrombosis. Arterial thrombosis can lead to stroke, myocardial infarction, limb ischemia from peripheral arterial occlusion, and bowel or kidney infarction. Heparin-induced skin necrosis may occur in fat-rich areas or in distal extremities and the nose; erythema is followed by purpura and hemorrhage, leading to necrosis. Other unusual complications of HIT include adrenal hemorrhage and transient global amnesia.<sup>35,36</sup>

## DIAGNOSIS

The diagnosis of HIT initially is clinical. An awareness of the syndrome is necessary to suggest HIT in cases of

unexplained thrombocytopenia during heparin exposure, in the case of (new or worsening) thrombosis during heparin prophylaxis or treatment, or even in the case of thrombocytopenia or thrombosis after heparin withdrawal. Furthermore, the assays with the highest sensitivity and specificity are not available in many centers, and are time consuming and expensive. Clinical scores have been developed in the past to support the clinical diagnosis of HIT.<sup>4,5</sup> These scoring systems are able to stratify patients as unlikely, likely, or highly likely to have HIT, on the basis of several parameters (platelet decrease, temporal aspects of platelet decrease, platelet recovery after heparin withdrawal, presence of cutaneous reactions, or thrombosis or other causes of thrombocytopenia). Recently, a pretest probability score has been developed<sup>2</sup> to suggest HIT and it is listed briefly in Table 3. Early diagnosis is also dependent on the frequency of platelet monitoring. It is recommended to perform platelet counts every other day in patients receiving therapeutic dose of UFH or in postoperative patients receiving UFH prophylaxis, whereas in medical patients receiving prophylactic UFH or LMWH, or postoperative patients receiving LMWH prophylaxis, platelet counts can be performed every 2 or 3 days.<sup>1,18</sup>

Once a high suspicion of HIT has been formulated, the diagnosis should be confirmed with the demonstration of heparin-dependent platelet activation. The most specific diagnostic tests for HIT include platelet aggregation tests, serotonin release assays, heparin-induced platelet aggregation assays, and solid-phase immunoassays (enzyme-linked immunosorbent assay [ELISA]). The main features of the available assays are listed in Table 4. The serotonin release assay represents the gold standard of the diagnostic tests for HIT<sup>4</sup> and has been validated with a prospective study<sup>37</sup>; however, it is costly and requires technical expertise. The

**Table 3 Pretest Probability of HIT According to Thrombocytopenia, Timing of Platelet Decrease, Presence of Thrombosis, and Other Causes of Platelet Count Decrease**

Parameter	Points for Each of the Four Parameters		
	2	1	0
Thrombocytopenia	> 50% decrease or nadir $20\text{--}100 \times 10^9/L$	30–50% decrease or nadir $10\text{--}19 \times 10^9/L$	< 30% decrease or nadir $< 10 \times 10^9/L$
Timing of platelet decrease	Onset between days 5 and 10 (or less than 1 d if heparin exposure within previous 100 d)	Consistent with immunization but not clear, or onset after day 10	Platelet decrease too early (without recent heparin exposure)
Thrombosis or other sequelae	New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspicion of thrombosis	None
Other causes of thrombocytopenia	No evidence	Possible	Definite

Pretest probability score: 6–8, high; 4–5, intermediate; 0–3, low.

HIT, heparin-induced thrombocytopenia.

(From Warkentin TE. Heparin-induced thrombocytopenia: pathogenesis and management. *Br J Haematol* 2003;121:535–555.)

**Table 4 Assays Available for the Laboratory Diagnosis of HIT**

Assay Type	Components	Measure	Advantages	Limits
Functional assays				
Platelet aggregation tests	Test plasma, donor platelet-rich plasma, heparin	Platelet aggregation	Easy, specific	Variability, low sensitivity
<sup>14</sup> C-serotonin release assay	Test plasma, donor <sup>14</sup> C-serotonin-radiolabeled washed platelets, heparin	<sup>14</sup> C-serotonin release from platelets	Sensitive	Radionuclide, expensive
Heparin-induced platelet aggregation	Test plasma, donor washed platelets or platelet-rich plasma, heparin	Platelet aggregation	Easy, sensitive	Variability
Immunoassays				
PF4/heparin ELISA	Test plasma, PF4-heparin complexes coated on microtiter plates	Presence of heparin-dependent antibodies	Easy, fast, sensitive	Detects only antibodies against the PF4-heparin complex

HIT, heparin-induced thrombocytopenia; ELISA, enzyme-linked immunosorbent assay; PF4, platelet factor 4. (From Fabris F, Luzzatto G, Stefani PM, Girolami B, Cella G. Heparin-induced thrombocytopenia. *Haematologica* 2000;85:72-81.)

ELISA assay, which has a lower sensitivity (it detects only IgG/IgM antibodies), should be used in conjunction with a functional assay. If the two tests are negative, HIT is ruled out.

## TREATMENT

The increased thrombin generation present in HIT is the target of drug therapy. In fact, available agents aim to reduce thrombin generation directly (direct thrombin inhibitors) or by means of factor (F) Xa inhibition (danaparoid and fondaparinux).<sup>1</sup> The evidence supporting the use of these drugs comes mainly from prospective cohort studies (lepirudin and argatroban)<sup>38-42</sup> or retrospective studies (danaparoid).<sup>43-46</sup> Table 5 summarizes the main features of these compounds. Isolated seroconversion without thrombocytopenia or thrombosis does not require any treatment or heparin withdrawal. In contrast, confirmed HIT without thrombosis (isolated HIT) requires heparin cessation and an alternative form of anticoagulation, given that the patients remain at risk for thrombosis in the short term,<sup>34</sup> and heparin withdrawal alone does not protect these patients from thrombotic complications. LMWH should be avoided because of cross-reactivity and risk of induction of heparin-dependent IgG antibodies. Therapy with non-heparin anti-FXa or anti-FIIa inhibitors should be maintained until a stable normal platelet count has been obtained. Patients with HIT complicated with thrombosis require an alternative anticoagulant, as do patients with isolated HIT. Warfarin can be started safely after platelet counts are normalized. The length of treatment with warfarin is not well defined, but in view of the high risk of thrombosis within 30 days of the diagnosis of HIT, warfarin anticoagulation probably

should be continued for at least 2 to 3 months.<sup>1</sup> Table 6 lists the main issues in the management of patients with HIT, with or without thrombosis.

Lepirudin, recombinant hirudin, is approved in the United States for treatment of HIT with thrombosis and is effective in preventing new thromboses in HIT patients without thrombosis, according to prospective studies.<sup>47</sup> In a prospective cohort of 82 patients with confirmed HIT, lepirudin led to a rapid platelet count recovery in 89% of patients and a significant decrease of a combined end point (death, amputation, and new thromboembolic events) compared with historical controls (25 versus 52%), with no differences in terms of bleeding complications.<sup>48</sup> Given that the drug is cleared by the kidneys and no antidote is available, the dosage of lepirudin needs to be decreased in nephropathic patients.

Argatroban, a synthetic direct thrombin inhibitor, is approved in the United States for the treatment of HIT regardless of the presence of thrombosis and during angioplasty when heparin is contraindicated.<sup>1,49</sup> Because argatroban is metabolized mostly by the liver and excreted in the bile, a lower starting dosage is suggested in patients with hepatic dysfunction. A pooled analysis of two prospective cohort studies and a historical control group showed a significant 14% decrease in the primary outcome (all-cause death, all-cause amputation, new thrombosis) in patients with HIT with or without thrombosis and treated with argatroban.<sup>50</sup> The positive result is due mainly to a decrease in new (venous) thrombosis. No differences in terms of bleeding were observed.

Bivalirudin, a recent and promising synthetic hirudin analogue, has been used in patients with HIT, but only uncontrolled case series are available. It is

**Table 5** Drugs for the Treatment of Patients with HIT, with or without Thrombosis

Drug	Principle	Plasma Half-Life	Elimination	Monitoring	Adverse Reactions
Direct thrombin inhibitors					
Lepirudin	Recombinant hirudin	1–2 h	Renal (90%)	aPTT, ecarin clotting time	Bleeding, antihirudin antibodies, anaphylactic reactions
Argatroban	Synthetic thrombin inhibitor	0.8 h	Liver	aPTT	Bleeding
Bivalirudin	Synthetic thrombin inhibitor	0.5 h	Enzymic (80%), renal (20%)	aPTT, ecarin clotting time	Bleeding
Factor Xa inhibitors					
Danaparoid	Heparinoid	24 h	Renal	Anti-F Xa activity	In vitro cross-reaction with HIT antibodies, bleeding
Fondaparinux	Synthetic pentasaccharide	18 h	Renal	Anti-F Xa activity	Bleeding

HIT, heparin-induced thrombocytopenia; aPTT, activated partial thromboplastin time.

**Table 6** Management Issues for Patients with Strongly Suspected or Serologically Confirmed HIT, with or without Thrombosis

Immediate heparin withdrawal
Alternative nonheparin anticoagulant at therapeutic doses
Routine ultrasonography of lower limbs
Avoid vitamin K antagonists (to avoid protein C decline with further hypercoagulable state)
Start (low dose) vitamin K antagonists only when a stable platelet count recovery has been obtained; overlap of at least 5 d with nonheparin anticoagulant
Avoid LMWH (cross-reactivity)
Avoid platelet transfusion in the absence of bleeding

HIT, heparin-induced thrombocytopenia; LMWH, low molecular weight heparin.  
(From Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:311S-337S.)

approved in the United States for anticoagulation during percutaneous coronary interventions.<sup>1</sup>

Danaparoid, a heparinoid (dermatan sulfate and low-sulfated heparan sulfate), is used in Europe, Canada, and New Zealand for HIT with or without thrombosis,<sup>45</sup> and in patients with a history of HIT who require cardiopulmonary bypass surgery.<sup>51</sup> In a non-randomized comparison study, danaparoid was as effective as lepirudin in preventing death, amputation, or new thromboembolic complications with a lower risk of bleeding.<sup>52</sup> Whether the 10% in vitro cross-reactivity between danaparoid and the antibody responsible for HIT is of clinical significance is uncertain. No reversing agent is available.

Fondaparinux has a theoretical role in the treatment and/or prevention of HIT, given that the drug does not appear to interact with platelets or PF4. Only

case reports on its use in patients with HIT are available.

To prevent HIT, the following strategies can be suggested: limit heparin use, avoid bovine UFH, overlap warfarin as soon as possible to limit heparin exposure, and use LMWHs, particularly in the orthopedic setting.<sup>1</sup> Patients with a history of HIT can be re-exposed safely to UFH if assays for antibodies are negative; this generally occurs 100 days after HIT.

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