

Heparin-induced thrombocytopenia: A complex clinical and laboratory paradox requiring multidisciplinary management

BY ISMAIL ELALAMY, MD, PHD

For over fifty years, heparins, the true standard in antithrombotic prophylaxis and treatment, have been widely used in clinical practice. However, heparin therapy is associated with 2 types of thrombocytopenia that are described as: heparin-associated thrombocytopenia types I and II. Heparin-induced thrombocytopenia (HIT) refers to type II. This immune thrombocytopenia, paradoxically, causes thrombosis and constitutes the most severe adverse event associated with heparin treatment.¹ In the absence of any absolute criteria, the diagnosis of HIT is established on the basis of a wide spectrum of clinical and laboratory markers combining a careful analysis of the patient's history and specialized tests. Nevertheless, patient management remains urgent and should not be postponed because of pending test results. This issue of *Anesthesiology Rounds* reviews the epidemiology, pathology, clinical features, and diagnosis of HIT. The applicable tests that may help in diagnosing HIT are also examined and the treatment modalities outlined.

THE DRAMATIC CLINICAL EXPRESSION OF HIT

HIT is generally characterized by a precipitous diminution in platelet count with a relative fall of >50% of the initial value.¹ HIT is actually a state of acquired immune mediated hypercoagulability, which is associated with disseminated cell activation involving platelets, monocytes, and the vascular endothelium. As an acronym, from a clinical standpoint, HIT usually indicates Heparin-Induced Thrombosis.

This state of acquired hypercoagulation persists even if heparin is discontinued. Therefore, the rate of thrombotic events is 5% to 10% per day during the first week, and reaches a cumulative incidence of >50% at 1 month.²

The clinical setting and patient factors influence the incidence of such thrombotic events. Venous thromboembolic events occur particularly in surgical settings, and arterial events are more often described in patients with atherosclerosis. Intravascular devices such as stents, arterial lines, cardiac filters, or prosthetic cardiac valves are prone to thrombus formation and should be explored first.

Venous thromboembolic adverse events (AEs) are usually distinct from the thrombotic event that originally required the initiation of heparin treatment. In >60% of patients, these thrombotic events exist at the time thrombocytopenia is discovered,² and their presence must be sought systematically.³ Various locations for thromboembolic events have been described: proximal deep veins in the lower limbs (50%), pulmonary embolism (25% of cases), mesenteric or portal veins, cerebral venous sinuses, and even the upper limbs, especially if a central venous catheter is in place (5%). The presence of thrombotic AEs is a negative outcome factor that quadruples the risk of mortality.

Venous gangrene of the limbs with distal necrosis can occur in a limb with venous thrombosis. Most often, it is associated with oral anticoagulant therapy and a supratherapeutic International Normalized Ratio or INR >4, while heparin is discontinued and therapy is switched to a vitamin K antagonist (VKA).

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Arterial thrombosis has been observed in most vascular beds. During HIT, thrombosis of the posterior wall of the abdominal aorta, which has a strong potential for emboli, as well as damage to right cardiac chambers, can result in negative outcomes and death. In fact, the areas involved are specific to the course of HIT, with an inverted frequency order (lower limbs > stroke > myocardial infarction [MI]) compared with that of atherosclerosis (MI > stroke > lower limbs). Typically, these thrombi are rich in platelets and fibrin, two anatomical characteristics of the white clot syndrome.⁴

Various **skin lesions** at injection sites (erythema induratum, localized or diffuse urticaria, diffuse exanthema) can be suggestive of HIT in 20% of cases. Livedo (*livedo reticularis*) is observed in some patients and is associated with microangiopathy and microvascular thromboses of the dermis. Lesions are painful, spread centrifugally, and may appear like necrotic purpura with a hemorrhagic bullous course, and central necrosis. These necrotic lesions affect various parts of the body (thorax, breast, abdomen, thighs). In fact, 75% of patients showing cutaneous symptoms do not have any notable thrombocytopenia.⁵

Single or bilateral hemorrhagic infarct of the adrenal glands remains an unusual complication of HIT.⁶

Other signs and symptoms associated with an **acute systemic response** during heparin treatment are alarm signals in themselves: fever, respiratory distress (pseudo pulmonary embolism), transient global amnesia (acute anterograde amnesia), flushing, hypertension, tachycardia, headaches, or digestive symptoms such as nausea or diarrhea. These symptoms develop a few minutes after heparin injection (especially with an intravenous bolus).⁷

Thromboses originating from a **cardio-pulmonary bypass circuit** and vascular or cardiac prostheses have been reported. Thus, it is important to ensure there are no clots or obstructions in the filter (hemodialysis or other) or the bypass circuit. An unusually short life span of a filter is a sign that should not be overlooked. In practice, the risk of thrombosis is ubiquitous in cases of HIT and warrants the earliest and most efficient therapeutic management.⁸

EPIDEMIOLOGY AND COMPLEX PATHOGENIC MECHANISMS

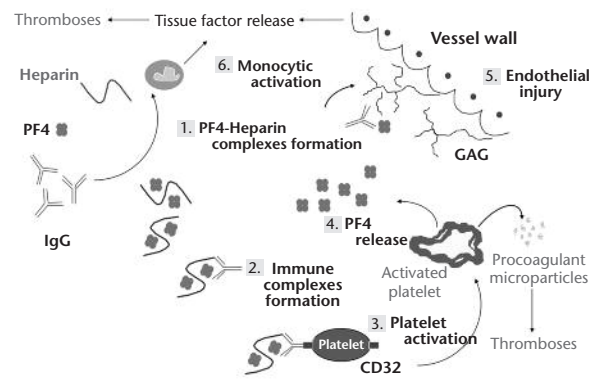
Type I heparin-induced thrombocytopenia

Type I thrombocytopenia often goes undetected because it occurs at the onset of anticoagulation with a moderate reduction (<20%) in platelet count. It is nonimmune, asymptomatic, and often corrects spontaneously despite a continuation of therapy.

Type II heparin-induced thrombocytopenia = HIT

Type II heparin-induced thrombocytopenia is immune-mediated and occurs later; in >80% of

FIGURE 1: Multifactorial pathophysiology of HIT



HIT = Heparin-induced thrombocytopenia; PF4 = Platelet factor 4; IgG = Immunoglobulin G; GAG = Glycosaminoglycan.

cases, it appears between the 5th and 15th day, but is rare after the 3rd week of treatment. It occurs in 1% to 5% of prolonged treatments (7 to 14 days) with unfractionated heparin (UFH).⁷ This incidence is probably 10 times less (0.1% to 0.5%) with low molecular weight heparins (LMWHs).²

It is well established that HIT is a peripheral thrombocytopenia due to the appearance of antibodies directed against a heparin/platelet factor 4 (PF4) macromolecular complex.¹ Initially, inflammation and/or platelet activation associated with the various medical or surgical settings increase PF4 release, favouring the formation of heparin/PF4 complexes. These complexes alter PF4 conformation and induce antibody synthesis. Immune-complex formation triggers direct platelet activation by the interaction of the Fc fragment of immunoglobulin G (IgG) with membrane FcγRII receptors (CD32). Other Ig (A or M) can activate other cells (endothelium, lymphocytes, monocytes, neutrophils). As a result, HIT is associated with disseminated cell activation of the vascular compartment that can lead to global coagulation (Figure 1). Rarely, some patients present with antibodies directed against different chemokines, such as the neutrophil-activating peptide (NAP-2) and interleukin-8 (IL-8).² The wide heterogeneity of the antibodies generated and their “atypical” genetic profiles could explain, in part, the discrepancies between a clear HIT clinical presentation and laboratory tests.

A DIFFICULT LABORATORY DIAGNOSIS

HIT can be asymptomatic and only discovered fortuitously on a routine platelet count. The natural evolution of the platelet count in a given setting is important because HIT causes a massive reduction in platelet count of over 50% of the baseline value.² The typical profile of platelet kinetics is an important starting point to “track” an unusual drop or “suspicious deviation,” allowing for the early detection of HIT. Tracking platelet count is the real diagnostic “hook” for HIT; the test offers the

simplest and most relevant tool for suspecting HIT when a break in the platelet curve is observed.

In the case of AEs occurring with heparin, but without actual thrombocytopenia, a diagnosis of clinical resistance to heparin could be contemplated, but the condition must be considered HIT until proven otherwise. The laboratory diagnosis of HIT remains difficult and involves several steps: first, ensure that the thrombocytopenia is real by excluding the possibility of a pseudo-thrombocytopenia by thromboagglutination on ethylenediamine tetraacetic acid (EDTA); check this on a new sample; and observe the smear on a slide with an optical microscope to look for platelet clusters, etc. Two types of tests are available to pinpoint this diagnostic likelihood: functional and immunologic tests.

Functional tests

These tests use various methods to detect the existence of a strictly heparin-dependent plasma platelet activator.

- The aggregation test most widely used by specialized laboratories was developed based on the Fratantoni method, the Platelet Aggregation Test or PAT, described in 1975.¹ This test reveals good specificity, > 90%, and its sensitivity depends on the performance conditions and the choice of control platelets.² In the case of a strong clinical suspicion of HIT, a negative test could be associated with a plasma level of free antibodies that is too low; in that case, the test should be repeated a few days later.
- The radioactively labelled serotonin release assay (SRA), considered the gold standard, measures the secretion of ¹⁴C-serotonin by washed control platelets when in presence of heparin and plasma from the HIT patient. This test is lengthy to perform and is constrained by the requirements for available radioactive isotopes and washed platelets; for these reasons, it is only used in a few specialized centres.
- Other functional tests have been described, such as bioluminescence (adenosine diphosphate [ADP] or A-triphosphate [ATP] release) and flow cytometry (P-selectin [CD62] expression at the platelet surface or procoagulant microparticle expression); however, these techniques await validation.

Immunologic tests

ELISAs (enzyme-linked immunosorbent assays) are used to detect and quantify the three IgG, IgA and IgM isotypes of the PF4/heparin antibodies. The Heparin Platelet Induced Antibodies[®] test or PF4 Enhanced[®] identify antibodies directed against PF4-polyvinyl sulfate complexes.⁸ These tests are simple, standardized, and readily available for all laboratories.

A novel agar gel diffusion diagnostic test, the particle gel immunoassay (ID-PaGIA[®]), has recently

TABLE 1: The 4T score

Relative Thrombocytopenia	
>50% or nadir \geq 20 G/L	2
relative 30%–50% or nadir 10–19 G/L	1
relative < 30% or nadir < 10 G/L	0
Time of occurrence of thrombocytopenia	
D5-D10 or \leq D1 if exposure \leq 30 days	2
> D10 or \leq D1 if exposure 31-100 days or uncertain timing (missing CBC) but HIT compatible	1
< D4 without recent exposure	0
Thrombosis or other clinical manifestation	
New documented thrombosis; cutaneous necrosis or acute systemic reaction after UFH IV bolus	2
Thrombosis extension or recurrence or suspected but undocumented thrombosis; erythematous plaques	1
none	0
Other cause for thrombocytopenia	
None obvious	2
Possible	1
Definite	0

Pre-test probability: high 6-8; intermediate: 4-5; low 0-3; D = day

been made available in France.⁹ This test is strictly qualitative. The sensitivity of the ID-PaGIA test reaches 86%, its specificity 97%, its positive predictive value 93%, and its negative predictive value nearly reaches 100%.⁹ The test is convenient in that it only takes 15 minutes to perform, does not require any special handling, and is readily available as unit test at all times. Therefore, this method could be very helpful to diagnose HIT. In case of a pretest score <6 (see Table 1), a negative ID-PaGIA test could then justify a continuation of heparin treatment. On the other hand, its specificity is similar to that of the ELISA and is equally limited in the context of cardiopulmonary bypass (CPB).¹⁰

Discrepancies persist between clinical situations where there is a strong suspicion of HIT, and negative tests. Nevertheless, a number of patients (30% to 50%), including those in cardiac surgery, but also in other clinical situations (eg, pregnancy, diabetes)¹ present with antibodies directed against the PF4/heparin complex with no signs of thrombocytopenia or HIT. As a result, the specificity of a positive test is high only in clinical settings strongly suggestive of HIT.¹¹ Functional and immunologic methods must be considered only as evidence to confirm the diagnosis.⁸

In practice, several criteria must be concurrently met to establish the diagnosis of HIT:

- timing of the occurrence of heparin-induced thrombocytopenia with the caveats related to a prior exposure to heparin
- relative thrombocytopenia or a true (isolated) reduction compared with the initial platelet count
- occurrence of a paradoxical thrombotic event or suspicious clinical symptoms
- exclusion of other possible causes of thrombocytopenia

- after the fact, a rise in and a correction of the platelet count once heparin treatment is discontinued
- positive laboratory tests that support the diagnostic hypothesis.

Warkentin et al¹² proposed a pretest probability score (4T scoring system; Table 1). Comparing the results of laboratory tests with the probability score after a careful analysis of the patient's history should enable a more confident diagnosis of HIT. Diagnostic algorithms are also suggested to assist in the management of these patients.

URGENT TREATMENT

A multidisciplinary (hematologist, anesthesiologist, intensivist, surgeon, vascular specialist) approach and the collaboration with an expert team are two factors that guarantee optimal management of this disorder.

Prevention treatment: The primary prevention of HIT consists of limiting the indications for unfractionated heparin therapy and avoiding prolonged administration through an early transition to oral VKA anticoagulation.

Regular monitoring of platelet count is crucial with an initial determination of baseline at the inception of any heparin treatment. In France, the GEHT (*Groupe d'Études sur l'Hémostase et la Thrombose* – Hemostasis and Thrombosis Study Group) recommends biweekly monitoring of the platelet count from the 5th to the 21st day of heparin treatment. Some authors even recommend daily monitoring in certain acute settings.¹²

Curative treatment: HIT treatment requires a multidisciplinary approach. The 4S rule should be applied: Suspect HIT, Stop heparin, Switch to another antithrombotic, and clinical and laboratory Surveillance.

Immediate discontinuation of heparin

Heparin treatment should be stopped on the basis of suggestive clinical signs without waiting for laboratory confirmation of HIT; administration of even small amounts of heparin must be avoided, such as the “flushing” of catheters or implantable devices.

Switch to another antithrombotic treatment

Substitution is essential because heparin therapy discontinuation does not suppress the high risk of thrombosis.¹² A switch to or use of VKAs must be avoided because it does not guarantee an immediate protection against thrombosis and it can expose the patient to severe thrombotic events or venous gangrene. In France, two therapies are widely used: sodium

danaparoid and recombinant hirudin, also called lepirudin.

Danaparoid (half-life 22 hr) is a natural heparinoid with a mean molecular weight of 5500 daltons; it is formed by a combination of heparan sulfate (84%), dermatan sulfate (12%), and chondroitin sulfate.¹³ With a high anti-Xa activity/anti-IIa activity ratio (>20), this agent fundamentally has the same mechanism of action as heparin (indirect anti-Xa and anti-IIa action). The risk of *in vitro* immune crossover reactivity is low (5%), and the clinical relevance of an *in vitro* crossover reaction is disputed. Some patients have been successfully treated; yet, *a posteriori* it was clear that they had, early on, crossover reactivity objectively documented by immunologic and/or functional tests. Non-correction of platelet count within 72 hours after danaparoid administration or the occurrence of a new thrombotic event are the only situations when immune crossover reactivity or an insufficient dosage to control the prothrombotic process should be considered.¹⁴ Daily platelet count and increased clinical monitoring are therefore essential.

The immediate use of therapeutic doses with an intravenous (IV) bolus and continuous IV infusion is recommended; various regimens exist depending on the clinical setting. Anti-Xa activity monitoring is necessary together with a daily platelet count. Adjustments must be made in cases of renal failure (RF), wide deviation from ideal body weight, or increased hemorrhagic risk. The excellent ratio of antithrombotic benefit/hemorrhagic risk for danaparoid explains why this agent is the recommended first-line treatment in cases of HIT.¹⁴

Lepirudin (half-life 90 min), originally extracted from leech saliva (hirudin), is now obtained by genetic engineering. Lepirudin is a powerful direct antithrombin with no analogy to heparin and therefore presents no risk of cross-reaction.¹² The cumulative frequency of serious adverse events (death, amputation, new thrombosis) reaches approximately 20%, and is due mainly to delayed management of patients.¹⁵ The hemorrhagic risk is correlated with the existence of renal failure, with doses >0.07 mg/kg/hr and with prolonged treatment.¹⁵ The dosage recommended by the manufacturer is 0.4 mg/kg as a bolus, followed by an infusion of 0.15 mg/kg/hr with monitoring of the activated partial thromboplastin time (aPTT). The aPTT should be assessed 4 hours after treatment onset and must be within 1.5 to 2 times the baseline aPTT. In fact, significantly lower dosages (0.1 mg/kg/hr) with no bolus are currently recom-

mended to limit the risk of hemorrhage without compromising antithrombotic efficacy.¹⁶

The use of lepirudin remains contraindicated for pregnant or breastfeeding women, which is not the case with danaparoid. The appearance of antihirudin antibodies has been reported in 40% of patients, but with no particular clinical incidents or resistance to repeated treatment.

Bivalirudin has shown very promising results when used for angioplasties or during cardiac surgery. Its short half-life, its reversible thrombin inhibiting properties, and its proteolytic degradation could enhance tolerance in patients with hepatic and/or renal failure. The dosage varies depending on the clinical context:¹⁹

- **Coronary angioplasty:** 0.75 mg/kg bolus followed by 1.75 mg/kg/hr continuous IV infusion during the procedure; the aPTT measured 3 hr after the onset of the infusion should be 2 × baseline. Anti-IIa activity should be monitored by chromogenic techniques (Biogenic Kit): 0.5 µg/mL. Doses should be reduced in moderate RF: 0.75 mg/kg bolus followed by 1.4 mg/kg/hr IV infusion; in cases of severe RF: no bolus and 0.15 to 0.2 mg/kg/hr IV infusion.
- **Cardiac surgery with CPB:** Pre-CPB 1.0 mg/kg bolus followed by 2.5 mg/kg/hr continuous IV infusion, and 50 mg in CPB prime, anticoagulation is assessed by prolongation to 2.5 × baseline activated clotting time (ACT) or ecarin clotting time (ECT). If insufficient, add an extra bolus of 0.1 to 0.58 mg/kg.
- **Off-pump cardiac surgery:** 0.75 mg/kg bolus followed by 1.75 mg/kg/hr continuous IV infusion, again adjust anticoagulation assessed by a prolongation of 2.5 × the baseline ACT or ECT. In the case of insufficient prolongation or an ACT <300 sec, add an extra bolus of 0.1 to 0.50 mg/kg or increase the infusion by 0.25 mg/kg/hr.

Argatroban (half-life 45 min), a synthetic arginine derivative, is a reversible direct anti-thrombin proposed for treatment of HIT in the United States, Japan, and several European countries. Because of its hepatic metabolism, this therapeutic option is suitable for patients with renal failure.

- For **continuous veno-venous hemofiltration** (CVVH), a bolus is not recommended. Initiate continuous IV infusion by starting at 1.0 µg/kg/min (if there is no thrombosis) or at 2.0 µg/kg/min (in case of thrombosis) then increase the dosage progressively if necessary. **Monitoring:** aPTT 3 hr after infusion onset; target 1.5 to 2.5 × baseline (before dialysis). Anti-IIa activity should be monitored (Biogenic Kit):

0.4 to 0.8 µg/mL. In the case of hepatic failure (Child-Pugh score >5), initiate continuous IV infusion with 0.5 µg/kg/min and progressively increase dosage if necessary (aPTT 1.5 to 2.5 × baseline).

- **Intermittent hemodialysis:** First dialysis

Administer a 250 µg/kg bolus followed by 2.0 µg/kg/min continuous IV infusion and stop the infusion 1 hr before the end of dialysis (if the filter is “clean”).

Monitoring: aPTT 1 hr after bolus; target 1.5 to 2.5 × baseline (before dialysis). Anti-IIa activity should be monitored (Biogenic Kit): 0.4 to 0.8 µg/mL.

In case of significant thrombotic risk or if the filter is “dirty,” stop the ongoing dialysis early and stop argatroban only 30 min before the end for subsequent dialysis sessions. In case of hepatic failure (Child-Pugh score >5), give an identical bolus of 250 µg/kg then begin continuous infusion, reducing the dosage (0.5 µg/kg/min) for the same target aPTT (1.5 to 2.5 × baseline).

Fondaparinux is a synthetic pentasaccharide that is not recommended during an acute HIT. It could be proposed as a therapeutic alternative in case of a history of HIT, and in situations when prophylactic anticoagulation is needed. The reported association between fondaparinux and HIT is still controversial.^{17,18}

Switching to oral anticoagulation

Transition to oral anticoagulation or therapeutic nonheparin has to be progressive and prolonged in order to obtain a stable INR (2 to 3). There are no recommendations as to the duration of prophylactic treatment in cases of asymptomatic HIT. If there is no thrombosis, prophylactic anticoagulant coverage should be ensured by using VKA for 4 to 6 weeks.¹⁶

HIT during the transition from heparin to VKA: a special situation

If HIT occurs during the transition to VKA, even if the INR is at a satisfactory level (between 2 and 3), the culprit heparin should be substituted with a parenteral antithrombotic agent such as sodium danaparoid. The hemostatic unbalance (protein C/factor II) is worsened by the acquired hypercoagulation caused by HIT; together, they increase the risk of cutaneous necrosis and/or venous gangrene. In these cases, the vitamin K deficit should be corrected (10 to 20 mg slow IV) when the VKA is stopped.¹² Some authors also suggest prescribing protein C concentrates to compensate for this deficit in cases of associated thrombosis.

CONCLUSION

HIT is the most severe AE associated with heparin therapy. HIT is a life-threatening complex disorder; its urgent management must be based on clinical and laboratory data in consultation with specialized services.

A plasma or serum aliquot must always be frozen in order to diagnose HIT, even retrospectively. Confirmation of the diagnosis will impact the future management of anticoagulation in the patient. There have been clear advances in the management of HIT, but better dissemination of these advances is needed.

KEY POINTS

- The diagnosis of heparin-induced thrombocytopenia (HIT) remains uncertain; it is based on a spectrum of clinical and laboratory markers.
- Patient management is urgent and should not be delayed because of pending laboratory results.
- Resulting in an immune-mediated acquired hypercoagulable state, HIT often means Heparin-Induced Thrombosis.
- HIT is characterized by a sudden drop in platelet count with a relative reduction >50% of the baseline value.
- Switching to another antithrombotic treatment is essential, since the discontinuation of heparin does not suppress the high thrombotic risk.
- Several alternatives to heparin are available (danaparoid, lepirudin, bivalirudin, and argatroban) to anticoagulate patients in various settings: continuous or intermittent dialysis, angioplasty, and cardiac surgery with or without CPB.

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