# HEPARIN-INDUCED THROMBOYTOPENIA: A MISDIAGNOSED CLINICAL SYNDROME.

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## ABSTRACT

Heparin-induced thrombocytopenia (HIT) is an immune adverse drug-induced reaction characterized by thrombocytopenia and an increased incidence of thrombosis following subsequent exposure to heparin. Clinical pictures included thrombocytopenia followed by venous thrombosis or arterial thrombosis, the most frequent clinical presentations are deep venous thrombosis and pulmonary embolism. The pathophysiology of HIT is complex, involving the activation of coagulation, endothelial dysfunction, and platelet activation. HIT is induced by heparin dependent IgG antibodies that activate platelets. Clinical suspicion f HIT can be confirm by using two different types of laboratory assay: a platelet activation assays and immunoassays for detection of PF4--heparin antibodies.

Recent 2012 practice guidelines from the ACCP recommended discontinuation of heparin and administration of direct thrombin inhibitors and factor Xa inhibitors.

## INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is an immune-mediated adverse drug reaction that occurs following exposure to unfractionated heparin (UFH) or low-molecular--weight heparin (LMWH) (1,2). Heparin is among the most frequently prescribed medications in cardiovascular disease and in surgery as prevention of deep vein thrombosis, with million patients treated annually. HIT is an important adverse drug reaction to heparin. HIT occurs in approximately 0.5–5% of patients treated with heparin and up to 24% in cardiac surgery patients (3,4).

Patients with cardiovascular disease are at particular risk for the development of HIT antibodies. As many as 25% to 50% of patients who undergo cardiac surgery develop positive levels of anti heparin/PF4 antibodies postoperatively (5).

It has been reported to HIT is an immuno-mediated syndrome due to IgG antibodies against platelets factor-4/heparin complex that activates platelets by way of their FccIIa receptors (6). During UFH infusion,

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PF4 levels increase 15- to 30-fold for several hours, by displacing PF4 from endothelial cell surfaces. PF4/heparin complexes bind to platelet surfaces. IgG antibodies recognize neoepitope sites on PF4, leading to formation of PF4/heparin/IgG complexes on the platelet surface. This phenomenon leads to platelet activation. Activated platelets release additional PF4 that induces a cycle of progressive platelet and coagulation activation. Binding of HIT-inducing antibodies to a complex of heparin and platelet factor 4 (PF4) produces platelet activation and aggregation, including formation of procoagulant, platelet-derived microparticles as well as endothelium activation leading to thrombus formation in either the venous or arterial system. (7,8).

## CLINICAL FEATURES

Heparin-induced thrombocytopenia type II (HIT) is clinically considered when the platelet count falls by 50% or more of the baseline value (thrombocytopenia), occurring temporally between day 5 and 14 of therapy, and usually followed by fatal paradoxical thrombotic events.

The timing of thrombocytopenia is influenced by the presence or absence of prior exposure to UFH. In patients who have been exposed to UFH within the previous 3 weeks, the thrombocytopenia begins at a median time of 10.5 hours after the initiation of UFH therapy. These patients already have circulating heparin-dependent antibodies that developed during the prior treatment with UFH.

In rare circumstances, HIT may begin several days after heparin has already been stopped (***delayed-onset heparin-induced thrombocytopenia***) and this is associated with strongly positive tests for HIT antibodies. Delay onset HIT is very dangerous because it is always undiagnosed due to the delay in clinical manifestation. Delay onset HIT can cause devastating venous thromboembolism or arterial clots, prolongs hospitalization, and increases costs. (9)

At least four factors influence the frequency of HIT: type of heparin, duration of heparin treatment, patient population, and gender. The risk of HIT is higher in patients treated with unfractionated heparin compared with patients treated with low molecular weight heparin and to patients treated with fondaparinux. Female are more likely to develop HIT antibodies during prophylaxis with heparin. Highest reported frequencies of HIT are in postsurgical thromboprophylaxis compared to medical treatment. (10,11) Patients at highest risk for HIT/thrombosis are critically ill patients and post cardiovascular surgery patients. A high number of cardiac surgery patients (19%) has already develop antibodies before surgery. Most of these patients has a history of prior exposure to UFH, and the prevalence of antibodies detected after cardiac surgery in this heavily treated population is higher compared with patients who have no prior exposure to unfractionated heparin (83% on the fifth day of treatment). These results suggest a mechanism of anamnestic response (2).

Data from the CATCH study shows a higher incidence of throm-

bocytopenia among patients being treated with UFH or LMWH than previously reported (12). Patients who develop thrombocytopenia has a lower baseline platelet count and a lower body mass index, and also are more likely to be admitted because of cardiovascular diseases: i.e. acute coronary syndrome or cardiovascular surgery. The CATCH investigators also find a direct and consistent relationship between the type, route, and duration of heparin therapy and the likelihood of thrombocytopenia.

Patients that receive UFH intravenously are at higher risk than those who receive UFH or LMWH subcutaneously.

The risk increases with longer heparin exposure, 4% per 1-day increment beyond 4 days of heparin therapy. This observation has important implications for routine clinical practice.

The median platelet count nadir in HIT is about 60 x $10^9$/L. Most patients show a 50% or greater decrease in the platelet count. In postoperative patients, the appropriate ‘‘baseline’’ platelet count is not the preoperative platelet count, but rather the highest postoperative platelet count preceding the HIT-associated platelet count decrease (13,14).

After adjustment for important covariates, the CATCH study found that thrombocytopenia, in particular, a greater than 70% reduction in platelet count from baseline, remained independently associated with adverse short-term clinical outcomes.

Clinically, the majority of patients who develop HIT antibodies do not develop thrombocytopenia and thrombosis. In addition, there are several potential explanations for thrombocytopenia in patients receiving heparin. Although there are sensitive assays available to detect HIT antibodies, in clinical practice, test results are not always available in a timely fashion. Moreover, the tests often detect non-pathogenic antibodies inducing diagnostic doubt. For these reasons, in evaluating a patient for possible HIT, a clinical scoring system can help (15). The most frequently used is the 4 Ts Score, evaluates Thrombocytopenia, its Timing, the presence of Thrombosis (or other sequelae of HIT), and whether oTher plausible. The 4Ts Score has a high--negative predictive value; a low score (<3 points) makes HIT unlikely (< 2%). However the positive predictive value varies in different clinical settings. In some settings, a high score predicts a high likelihood of HIT.

Thrombosis is the main contributor to morbidity and mortality associated with HIT, and HIT is fatal in 5–10 % of patients, due to thrombotic events. Thrombosis can occur in any vascular bed, however venous thrombosis is more common than arterial thrombosis and the most frequent clinical presentations are deep venous thrombosis and pulmonary embolism.

## LABORATORY TESTS

Two general types of laboratory assay are used to confirm the diagnosis: platelet activation assays such as the serotonin release assay (SRA) and immunoassays such as the enzyme-linked immunosorbent assay

(ELISA) for detection of PF4-heparin antibodies.

Activation assays, such as the platelet serotonin release assay, detect HIT-IgG on the basis of their ability to activate platelets. The SRA is considered to be the gold standard for a laboratory diagnosis of HIT. The SRA measures the platelet-activation response to the anti–PF4- heparin complex as opposed to solely determining the presence of antibody (16,17)

Commercial antigen assays, the enzyme-linked immunosorbent assay (ELISA) for detection of PF4-heparin antibodies is easier to find in clinical practice (18,19).

Commercially available ELISAs are highly sensitive in the detection of PF4-heparin–Ig G antibodies; however, nonpathologic, non– platelet--activating antibodies are also detected by these assays. As such, available polyspecific ELISAs have low specificity for PF4-heparin platelet--activating antibodies.

However, because HIT antibodies can be transient, it is important the timing for serum or plasma tests (20,21). Anti heparin/PF4 antibodies persist for a relatively long period, and this persistence is

associated with a high risk of HIT and HIT-thrombosis (20). Patients in whom heparin/PF4 antibodies are already detectable before surgery as a result of previous exposure to heparin has an even greater increase of titer after surgery and a more prolonged persistence of positivity during follow-up. These patients are also more likely to have thrombotic events during follow-up (22).

## DELAYED-ONSET HEPARIN--INDUCED THROMBOCYTOPENIA

Delayed-onset HIT is a rare, often--unrecognized form of HIT. Few case reports describe this syndrome. Delayed-onset HIT was first described by Warkentin and Kelton, and included thrombocytopenia and thrombosis at least 5 days after heparin cessation (9). The 5-day period was arbitrarily chosen to impress that clinical sequelae occur after circulating heparin is eliminated.

The authors describe 12 patients who presented an average of 9.2 days (range 5 to 19 days) after heparin cessation. As a result of lack of disease recognition, 9 patients received additional heparin, resulting in a further decrease in platelet count and thrombosis complications.

Shortly thereafter, Rice et al reported a series of 14 patients with delayed-onset HIT. The criteria, however, for recognition of delayed-onset HIT differed. Rice et al required heparin exposure, discharge after a reasonably benign hospital course during which HIT went unrecognized, objectively proven venous or arterial thromboembolism, and thrombocytopenia at an appropriate time after heparin reexposure.

The different descriptions of delayed-onset heparin-induced thrombocytopenia vary in 2 important areas. The definition by Rice is more consistent with delayed recognition of HIT because heparin--induced thrombocytopenia could have presented clinically during the first heparin exposure but gone unrecognized.

According to Warkentin and Kelton, delayed-onset (as the name suggests) implies that the clinical situation becomes evident days after heparin therapy is complete. Warkentin and Kelton require a platelet count demonstrating thrombocytopenia at presentation, whereas Rice et al. accept thrombocytopenia after heparin reexposure (9).

Both Warkentin and Kelton and Rice et al demonstrate that heparin complications can become evident well after the initial heparin exposure is complete and the heparin is withdrawn (23).

We find that antibodies persist in patients for a long period after cessation of heparin therapy (median time to a negative antigen assay of 90 days); we also observe that in a number of patients antibodies persisted for many months after exposure, similarly to what happen to antibodies induced by other drugs i.e. sulfonamides. Importantly, the number of thrombotic events decreases over time in patients with persisting antibodies, but there remained a higher long-term risk of events. The presence of circulating antibodies is one of the possible mechanisms invoked to explain delay-onset HIT (20).

## THERAPY

Recent 2012 practice guidelines from the ACCP for the treatment of HIT include recommendations for platelet count monitoring for patients with a minimum heparin exposure of at least 4 days (24).

The first step in treatment of HIT is discontinuation of all heparin products, including heparin flushes and heparin-coated catheters. In addition to heparin cessation, appropriate non-heparin anticoagulants should be started immediately, even if in the absence of thrombosis.

Current treatment is focused on reduction of thrombin generation via direct thrombin inhibition (e.g., bivalirudin, argatroban, lepirudin,) or indirect factor Xa inhibition (e.g., fondaparinux or danaparoid) (24). Treatment with direct thrombin inhibitors is strongly recommended in patients with HIT. While both direct thrombin inhibitors (DTIs) and factor Xa inhibitors have been used to treat patients with HIT, few data on randomized trials are available so that guidelines focused on historical control studies.

For patients with HITT, ACCP guidelines recommend use of argatroban, lepirudin and danaparoid (no longer available in the U.S.) over continuation of heparin products or use of vitamin K antagonist therapy (Grade 1C) or other non-heparin anticoagulants (Grade 2C). (24) The ACCP guidelines for treatment of HIT also include recommendations for use of platelet transfusions.

These guidelines are easily applicable to regular HIT but the late diagnosis of delay-onset HIT could cause a prolongation of heparin treatment with life-threatening complications.

With the availability of nonheparin anticoagulants, the potential risk of reexposing previous heparin-induced thrombocytopenia patients to long courses of heparin appears unwarranted.

In conclusion, HIT is a serious adverse drug reaction with potentially fatal consequences. Due to wide varia-

bility in the clinical presentation and limitations of laboratory testing, the diagnosis can be difficult. Treatment of HIT and of thrombosis associated with HIT can also be difficult (25).

Despite the availability of several non-heparin anticoagulant therapeutic options, very little quality data support the use of these agents in patients with HIT (25).

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