REX HEALTHCARE

# Laboratory Bulletin...

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## HEPARIN INDUCED THROMBOCYTOPENIA

**Case Presentation**: A 52-year old man underwent coronary artery bypass surgery. During bypass he received 30,000 units of heparin and post operatively received 5,000 units twice a day. On post-op day 7, a platelet count of 60,000/ul was noted and his right leg became cold. Heparin induced thrombocytopenia was suspected and the heparin was discontinued. A thrombus was removed by Fogarty catheter from the right superficial femoral artery. Despite the embolectomy, the patient's leg was irreversibly ischemic and required below the knee amputation.

**Definition:** Heparin induced thrombocytopenia (HIT) is defined as a fall in the platelet count of at least 40% from baseline and accompanied by a positive serologic test for the responsible antibody while on heparin therapy. Typically any drop in the platelet count to <100,000/ul while on heparin is presumptive evidence for HIT. *It is important to obtain a baseline platelet count prior to instituting heparin therapy.* If the platelet count drops to 110,000/ul from a baseline platelet count of 220,000/ul, there is sufficient evidence to suspect HIT. *Platelet counts should be repeated daily for all patients on heparin therapy.*

**Incidence:** Heparin induced thrombocytopenia has been known about for over 30 years but only in the last 5 years have we understood the pathophysiology and gained insight into treatment. The incidence is estimated to be between 1% and 30%. Previous heparin exposure, duration of treatment, the dose, and the route of heparin administered all are associated with increased risk. The incidence of HIT associated thrombosis is low in young patients who are less likely to have atherosclerosis. At Rex Hospital and Wake Medical Center, all available heparin is porcine derived. Bovine heparin carries the greatest risk, possibly as high as 10% but porcine heparin carries a risk of 2% to 4%.

The incidence of HIT is also dose-dependent. The frequency is highest in patients who receive full dose heparin, defined as 20,000 to 40,000 units per day. It is lower with low or intermediate doses, defined as 5,000 units two or three times a day. It is even lower with low dose heparin used to keep central line catheters open. Intravenous administration of heparin has a higher incidence of HIT than subcutaneous injections. Low molecular weight heparin carries a risk of about 1%. Nevertheless, heparin induced thrombocytopenia has been identified for every single heparin preparation currently used, by any route and at any dose. It is important to remember that the incidence is highest in cardiopulmonary bypass surgery, high in orthopedic surgery and less on the general medical units. The following table shows the incidence of HIT as it relates to the dose:

***HEPARIN DOSE and HIT***

| Type | Risk | Dose |
|---|---|---|
| Therapeutic | 4+ | >20,000 u/day |
| Prophylactic | 2+ | 10,000 to 15,000 u/day |
| Heparin flush | 1+ | 250 – 500 u/day |
| Heparinized Catheter | 1+ | small amounts |

The risk of HIT-associated thrombosis was once thought to be quite small. However, it is now recognized that thrombosis occurs in about one-third to one-half of patients with HIT. Venous thrombosis is more frequent than arterial thrombosis. Thrombosis can occur at any platelet count, even at a very low count. The older the patient, the more likely there is associated thrombosis.

**Types of HIT:** The benign form of HIT (Type 1) is often seen early in the course of heparin therapy and is not associated with thrombosis. Type 1 HIT is characterized by transient mild decrease in the platelet count, often immediately after initiation of heparin. This form of HIT is often *not* detected clinically. In type 1 HIT the platelet drop is less than 40% from baseline. HIT Type 1 is due to a direct effect of heparin on the platelets resulting in reversible aggregation and sequestration of platelets. There are no deleterious effects and no antibody formation.

Type 2 HIT is most frequently seen with prolonged exposure to heparin. Type 2 HIT commonly results in arterial or venous thromboembolic complications or skin necrosis and rarely hemorrhage. There is a marked drop in the platelet count (usually <100,000/ul). The thrombocytopenia will persist if heparin is continued. The mechanism is antibody mediated platelet aggregation but reversible if heparin is discontinued. The mortality of HIT Type 2 is 30% and morbidity (e.g. loss of limbs) 20%. The following table compares features of Type 1 and Type 2 HIT:

| | **HIT** | |
|---|---|---|
| | **Type 1** | **Type 2** |
| Onset | Early (within 2-5 days) | Late (after 6 days)* |
| Platelet count | Mild decrease (>100,000/ul) | Severe decrease (<100,000/ul) |
| IgG Antibody | None | Present |
| Symptoms | Asymptomatic | Thrombosis |
| Duration | Transient | Persistent |
| Incidence | 10 %– 20% | <1% - 30% |

Note: HIT Type 2 may occur early in course of heparin administration if the patient has been previously exposed to heparin (e.g. recent PCTA followed by coronary artery bypass rafts). In cases with previous heparin exposure, HIT may occur within hours after initiation of therapy.

**Pathophysiology:** Although heparin induced thrombocytopenia results from an immune reaction, heparin itself is not immunogenic. Rather, it is a heparin/platelet complex that stimulates antibody production. Exogenous heparin combines with a small platelet alpha granule component called platelet factor 4 (PF-4). Each heparin molecule bundles two to four PF-4 molecules together and this complex then adheres to the platelet membrane. Antibody generated against the heparin/PF-4 complex binds to it and occupies the Fc receptor on the platelet membrane. Once this receptor is occupied, the platelet becomes activated and releases thrombogenic microparticles into the circulation resulting in a hypercoagulable state. The platelet derived microparticles home in on sites of vessel damage where they activate the coagulation cascade and form a thrombus. In addition to the microparticle-induced thrombi, platelet aggregates adhere to diseased arterial walls forming platelet thrombi. PF-4 also binds to heparin like sulfated glycosaminoglycans (e.g. heparan sulfate) on the endothelial cell surface. The cells then become activated, giving rise to thrombosis. Only a minority of patients who form HIT antibodies experience clinical HIT. The induction of HIT antibodies and the development of thrombocytopenia and subsequent thrombosis should be regarded as a continuum. Concomitant thrombotic risk factors probably play a major role in determining the progression and manifestations of HIT. See Figure 1 below.

Unlike the platelet antibodies induced by quinine, quinidine or sulfonamides, which can persist for years, heparin induced antibodies appear to be quite transient. They fall to undetectable levels at a median of 50 to 85 days, depending on the assay performed.

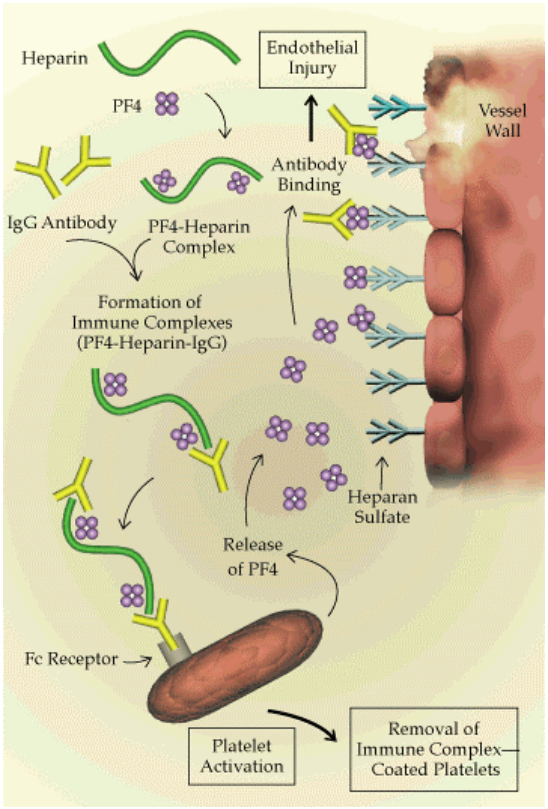


***Figure 1 Pathogenesis of HIT*** [4]

**Clinical Presentation:** Although HIT typically develops 5 to 10 days after the initiation of heparin therapy; patients who have received heparin within the previous 100 days may develop an amnestic response of antibody following a second exposure, resulting in rapid onset of thrombocytopenia within hours of heparin administration. Conversely, onset of HIT may not occur until as long as 19 days after stopping heparin therapy. Venous thrombosis occurs more frequently than arterial thrombosis. Deep vein thrombosis (DVT), with or without pulmonary embolus, is the most common event leading to the diagnosis of HIT. The disorder may be further complicated by limb gangrene, especially in the setting of warfarin treatment. Heparin induced skin lesions may occur at heparin injection sites and range from painful erythematous papules to extensive dermal necrosis.

**Laboratory Diagnosis:** Currently, there are four laboratory methods available to help in the diagnosis of HIT; the serotonin release assay, platelet aggregation studies, enzyme-linked immunoassay (ELISA) and flow cytometry. (1) The serotonin release assay is the benchmark for all assays but is complicated, time consuming and not readily available. This assay is 100% specific but lacks sensitivity. (2) Platelet aggregation studies are also specific but not very sensitive. Accordingly, an aggregation study may be negative but HIT may be present. Repeat platelet aggregation studies in 3 to 7 days may yield a positive result when previously negative. (3) The flow cytometric method detects activation markers such as P-selectin on the platelet surface. Flow cytometry has a higher sensitivity and higher specificity than platelet aggregation studies but is not but is not as sensitive as the ELISA method. (4) The ELISA method is an antigenic assay as opposed to the functional assays previously described. This method is currently the method of choice and has a higher sensitivity than the platelet aggregation study or flow cytometry. However, this method does have a modest number of false positive results. Although no test is perfect, the ELISA method is preferred for detecting antibodies to heparin-PF4. The test requires centrifugation within 1 hour after being drawn and frozen prior to transport. The test is "Heparin-PF4 Antibody (HIT)" and is sent to the Mayo Medical Laboratories (test code 480033) The turnaround time for results is 2 to 3 days at a cost of $68.00. *The diagnosis of HIT should be based primarily on clinical findings and management started immediately without waiting for laboratory confirmation.*

The test for HIT is different than the one to detect platelet antibodies in idiopathic thrombocytopenic purpura (ITP) or neonates with alloimmune thrombocytopenic purpura. The test for ITP is a serum platelet antibody detected by an ELISA test. This detects antibodies directed against IIb/IIIa glycoprotein platelet membrane antigens and others. The Mayo Medical Laboratory test code is 8538.

**Treatment:** Management of HIT consists of stopping heparin immediately. It is important to discontinue all types of heparin including heparin flushes, heparin coated central lines and low molecular weight heparin. Since there is an underlying hypercoagulable state, starting alternative anticoagulant therapy may prevent thrombosis if not already present. **Patients with acute heparin-induced thrombocytopenia should NOT be given Coumadin.** The administration of Coumadin to patients with HIT results in a precipitous fall in the level of protein C (a natural anticoagulant) which precedes the drop in the clotting factors. Therefore, some of these patients who receive Coumadin will have catastrophic venous limb gangrene. Coumadin should be introduced slowly and only after the acute HIT has resolved (as detected by a rise in the platelet count). Platelet transfusions should also be avoided since additional platelets may form thrombi (adding "fuel to the fire").

Recently introduced anticoagulants, argatroban (Novastan), danaparoid (Orgaran), and lepirudin (Refludan) show promise in the treatment of HIT. The critical aspect in selecting an alternative to heparin is to avoid cross-reactivity with heparin. Argatroban is a direct thrombin inhibitor and does not interact with the antibodies generated in HIT. A multicenter study of patients on argatroban showed favorable outcomes. Danaparoid, a heparinoid, inhibits activated factor X, but recent reports have shown about 10% cross-reactivity with heparin. Although danaparoid was previously recommended in the 1998 Rex Laboratory Bulletin, I believe lepirudin is a better alternative. Lepirudin is currently the only drug approved by the FDA for use as an anticoagulant in patients with HIT. It is recombinantly produced derivative of hirudin, an anticoagulant produced by leeches. Lepirudin binds reversibly and independently of antithrombin III to thrombin and directly inhibits thrombin. There is no cross-reactivity with heparin.

**Beware of Plaintiff's Attorneys:** Drug induced complications that result in injury to a patient is fertile ground for litigation. The first citation on one Internet search engine deals specifically heparin-induced thrombocytopenia for personal injury attorneys. The article provides authoritative medical literature to support a claim, identifies the most notable experts and provides sufficient information to build a solid winning case for attorneys (www.medivillage.com). HIT is a growth industry for lawyers.

References:


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