1. What is HIT?
Heparin therapy is often complicated by thrombocytopenia. This includes a relatively common, non-immune, clinically innocuous reaction (Type I HIT), and a rare, immune-mediated, potentially serious form of the disease (Type II HIT).

2. What causes HIT?

**HIT Type I**
Type I HIT is caused by direct interaction of heparin with the platelet membrane, resulting in enhanced platelet aggregation. Type I HIT occurs in approximately 10% of patients receiving heparin, usually within the first few days of treatment. The platelet count is not usually decreased below 100,000 x 10^9/L, and gradually rises to normal levels after several days, even if heparin therapy is not discontinued.

**HIT Type II**
Heparin-induced thrombocytopenia, type II, is unusual, occurring in approximately 5% of patients receiving heparin. It is more common with bovine lung heparin than porcine mucosal heparin, and is unusual (but reported) in patients receiving low molecular weight heparin. Type II HIT is immune-mediated, and usually occurs by the following mechanism:

1. Injected heparin reacts with platelet-factor 4 (PF4)
2. IgG antibodies bind to heparin/PF4 complexes to form immune complexes (ICs)
3. The IgG/heparin/PF4 immune complexes bind to the FcγRIIA (CD32) receptor on the platelet membrane, resulting in platelet activation
4. The activated PLTs release more PF4, new ICs formed, and thrombocytopenia occurs from platelet consumption
5. Excess PF4 binds to glycosaminoglycans on endothelial cells forming immune complexes
6. Anti-PF4 antibodies bind to the endothelial cells, causing antibody-mediated endothelial injury
7. Thrombi develop at the sites of vascular injury and disseminated intravascular coagulation (DIC) and other complications can develop.
3. What is the clinical significance of HIT?

The etiology and clinical presentation of Type I and Type II HIT are different. Thrombocytopenia is defined as a platelet count falling below 150,000 x 10^9/L or a decrease in the platelet count of 30-50% after the initiation of heparin therapy.

**Type I HIT**

This form of thrombocytopenia is benign, self-limited, and not associated with bleeding or an increased risk of thrombosis. However, thrombocytopenia originating from HIT type I may exacerbate thrombocytopenia resulting from other causes.

**Type II HIT**

Thrombocytopenia requires several days (4–20) to develop in patients who have never received heparin, but typically appears around day 10. Thrombocytopenia can develop within several hours of heparin infusion in patients with a history of recent heparin therapy, but can occur up to day 20. The platelet count progressively decreases to <100,000 x 10^9/L, thrombi may develop, and hemorrhage, sudden myocardial infarction, peripheral arterial thrombosis, pulmonary embolism, DIC, or skin necrosis can occur. Thrombosis develops in approximately 20% of patients with HIT, with a mortality as high as 30%. The term heparin-induced thrombocytopenia and thrombosis (HITT) is applied to HIT with thrombosis.

The thrombi in Type II HIT principally consist of platelets with few red blood cells (“white thrombi, white thrombosis syndrome”). The thrombi may be arterial or venous. If pre-existing thrombi are present, they may extend with the onset of HIT, resulting in pulmonary embolism. Arterial thrombi may develop in any artery, including the heart, aorta, major aortic branches, or in the cerebral, renal, mesenteric, or other arteries, resulting in stroke, heart attack, organ infarction, limb gangrene, and other serious complications. The disease can be widespread and rapidly catastrophic, particularly in patients with other serious medical problems, and death can occur. HIT is less likely to develop in patients receiving low molecular weight heparin, which interacts less readily with PF4.

4. How is HIT diagnosed?

The diagnosis of HIT requires the following:

1. Thrombocytopenia with a history of heparin therapy within the past five days
2. The exclusion of other causes of thrombocytopenia
3. Recovery of the platelet count after the cessation of heparin therapy
4. Characteristic laboratory findings
5. What are the laboratory features of Type I HIT?
Mild to moderate thrombocytopenia is found. However, there are no laboratory tests specific for Type I HIT.

6. What are the laboratory features of Type II HIT?
The PT and aPTT are prolonged, and the platelet count is decreased to <150,000 x 10⁹/L. Peripheral blood smear examination demonstrates frequent fragmented red blood cells. In addition, heparin-dependent antibodies can be detected by platelet activation tests (platelet aggregation studies, serotonin release assay) or specific assays for antibodies to the heparin-PF4 complex (ELISA, flow cytometry).

7. What assay is used by the VCU Hemostasis Laboratory for the diagnosis of Type II HIT?
The Asserachrom HPIA assay (Diagnostica Stago, Asnieres-Sur-Seine, France). This assay utilizes plastic microwells precoated with heparin-PF4 complexes. A summary of the assay is as follows:

(1) Patient plasma samples are incubated in the microwells, resulting in capture of any anti-heparin-PF4 antibodies by the heparin-PF4 complexes.
(2) Peroxidase-labeled anti-human IgG, IgA, and IgM antibodies are added to the microwells. They bind to available antigenic determinants of the immobilized antibodies.
(3) The peroxidase substrate ortho-phenylenediamine is incubated with the reaction mixture, forming a colored reaction product with an intensity proportional to the amount of peroxidase (and patient anti-PF4 antibody).
(4) A strong acid is added to stop the reaction, and the color is measured with a spectrophotometer.

The VCU Coagulation Laboratory performs an ELISA assay for heparin-PF4 complexes. The assay will be performed at least twice weekly during the day shift. The assay will not be available at nights or on weekends.

8. What are the specimen requirements for the Asserachrom HPIA assay? When will the assay be performed?
One 4.5 mL blue top (3.2% sodium citrate) tube of peripheral blood, delivered to the VCU Coagulation Laboratory within four hours of collection. Immediately invert the tubes gently at least six times after collection, mixing thoroughly. Avoid vigorous mixing. Patients with hematocrits >55% must have the anticoagulant adjusted. Call the Coagulation Laboratory for instructions.

The specimen requirement for the HIT assay is a 4.5 mL blue top tube, delivered to the laboratory within four hours of collection.

The specimen will usually be performed twice weekly during the day shift, depending upon demand. Due to the length and technical complexity of the assay, it cannot be performed during the evening or night hours, or on holidays or weekends. The results will be available immediately following completion of the assay. The results will be reported as positive, negative, or indeterminate.
9. What is the sensitivity and specificity of the Asserachrom HPIA assay?

The assay is positive in approximately 85% of patients with Type II HIT. A positive assay for these antibodies is not completely specific for HIT, since they have been demonstrated in about 25% of patients following cardiopulmonary bypass surgery in the absence of HIT. In addition, very rare patients have naturally-occurring antibodies against PF4 of no known clinical significance.

Antibodies to heparin-PF4 complexes are not detectable in approximately 15% of patients with Type II HIT. Most of these patients have thrombocytopenia induced by autoantibodies specific for other antigens, including interleulin-8 and neutrophil-activating peptide-2 (NAP-2).

10. How is HIT treated?

The clinical suspicion of HIT should intitate the following actions:

(1) IMMEDIATE DISCONTINUATION of heparin administration by any form (i.e., subcutaneous or intravenous unfractionated heparin, low molecular weight heparin (LMWH), heparin flushes, heparin-coated catheters, etc.).

(2) Begin an alternative anticoagulant. Treatment with an alternative anticoagulant is critical, since the thrombotic tendency may continue for as long as 30 days after heparin discontinuation. LMWH should not be used for the treatment of HIT due to a high probability that anti-PF4 antibodies will cross-react with LMWH. FDA-approved drugs for HIT include Lepirudin (REFLUDAN®) and Argatroban.

11. Where can I obtain more information about HIT?

Recent Journal Articles


**Web Sites**

http://www.refludan.com/

http://www.argatroban.com/aboutheparin_01.htm

http://www.thedoctorsdoctor.com/diseases/heparin_induced_thrombocytopenia.htm#pathogenesis

http://www.tigc.org/eguidelines/hit02.htm


http://www.unc.edu/~rvp/RP_Anesthesia/Basics/HIT.html