### Heparin-Induced Thrombocytopenia

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#### Feature

<table>
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<th>Synonyms</th>
<th>White thrombosis syndrome.</th>
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<td><strong>Epidemiology</strong></td>
<td>Common, occurs in 10-15% of patients receiving therapeutic heparin, and has been reported in patients receiving “mini-dose heparin,” low molecular weight heparin, and even heparin line flushes.</td>
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<td><strong>Etiology and Pathogenesis</strong></td>
<td>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).</td>
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<td><strong>Clinical Presentation</strong></td>
<td>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.</td>
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#### Disease Facts

**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:

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

**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.
Heparin-Induced Thrombocytopenia

**Feature**

**Clinical Presentation (Cont’d)**

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 10⁹/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.

**Pattern of Inheritance**

HIT is not inherited. However, the presence of His-His at codon 131 of the CD32 molecule increases the susceptibility of an individual to HIT over individuals with Arg-Arg at this codon.

**Laboratory Features**

The diagnosis of HIT requires thrombocytopenia with a history of heparin therapy within the past five days, the exclusion of other causes of thrombocytopenia, recovery of the platelet count after the cessation of heparin therapy, and characteristic laboratory findings.

HIT Type I. Mild to moderate thrombocytopenia is found. However, there are no laboratory tests specific for Type I HIT.

HIT Type II. The PT, aPTT, and bleeding time are prolonged, and the platelet count is decreased < 150,000 x 10⁹/L. Peripheral blood smear examination demonstrates frequent fragmented red blood cells. However, the definitive diagnosis of HIT, type II requires demonstration of heparin-dependent antibodies in the absence of other causes of thrombocytopenia.

Heparin-dependent antibodies are detected by platelet activation tests (platelet aggregation studies, serotonin release assay), or more specific assays for antibodies to the heparin-PF4 complex (ELISA, fluid-phase assay, or flow cytometry). Although more than 90% of patients with HIT have anti-heparin/PF4 antibodies, these antibodies are not specific for HIT, and have been demonstrated in about one-fourth of patients following cardiopulmonary bypass surgery in the absence of HIT.

**Heparin-induced platelet aggregation assay.** A platelet aggregation assay is performed using donor platelets, patient serum, and unfractionated heparin. The sensitivity of this assay for anti-heparin-PF4 antibodies is low (~40%) due to variable antibody reaction with donor platelets.
Serotonin release assay (SRA). The SRA utilizes donor platelets labeled with $^{14}$C-labeled serotonin. The labeled platelets are reacted with heat-treated patient serum and therapeutic concentrations of heparin (0.1 U/mL), and the release of $^{14}$C-serotonin is measured. The sensitivity of the SRA is dependent upon the control platelets. Control platelets with His-His at FcyRII-131 increases the sensitivity of the assay to 81%, from 47% with Arg-Arg and 74% with His-Arg.

ELISA assay for anti-PF4-heparin Abs. Plastic ELISA trays coated with PF4-heparin complexes are utilized. Patient serum is incubated in the trays, and antibodies bound to the PF4-heparin complexes are detected by a chromogenic reaction. The sensitivity of ELISA is ~90%.

The Asserachrom HPIA assay (Diagnostica Stago, Asnieres-Sur-Seine, France) is used in the VCU Coagulation Laboratory and representative of ELISA HIT assays. This assay utilizes plastic microwells precoated with heparin-PF4 complexes. A summary of the assay is as follows:

Patient plasma samples are incubated in the microwells, resulting in capture of any anti-heparin-PF4 antibodies by the heparin-PF4 complexes. Peroxidase-labeled anti-human IgG, IgA, and IgM antibodies are added to the microwells. They bind to available antigenic determinants of the immobilized antibodies. 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). A strong acid is added to stop the reaction, and the color is measured with a spectrophotometer.

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).

Flow cytometry. The efficacy of flow cytometry in the diagnosis of HIT has been demonstrated in the research laboratory, although flow cytometry is presently not utilized in the clinical laboratory for this purpose. Flow cytometric detection of activated platelets induced by heparin/PF4 immune complexes has been demonstrated to show 100% specificity and 95% sensitivity in some studies. Flow cytometric detection of the platelet activation marker P-selectin (CD62P) has been documented to differentiate between HIT and HIT.

In view of the relatively low specificity of these assays for HIT, utilization of a platelet activation assay and anti-heparin/PF4 antibody assay is recommended for definitive diagnosis. HIT is very likely if both types of assays are positive, and very unlikely if both are negative. A positive platelet activation assay and a negative heparin/PF4 antibody assay usually indicates the presence of antiplatelet antibodies of non-HIT origin, while a negative platelet activation assay and positive heparin/PF4 antibody assay indicates probable HIT.
### Clinical Course and Prognosis

HIT, type I is a benign, self-limited condition without clinical consequences. HIT, type II is a very serious medical problem with a high incidence of morbidity and mortality.

**HIT Type I.** The risk of bleeding or thrombosis is not increased from this condition alone. The platelet count returns to normal if heparin therapy is discontinued, but progressively worsens in the continued presence of heparin.

**HIT Type II.** Platelet levels return to normal within several days (4-10) after the discontinuation of heparin infusion. Progressive thrombocytopenia can occur if the diagnosis is not made and heparin infusion is continued.

### Treatment

The immediate discontinuation of heparin therapy in any form is required at the earliest suspicion of HIT. This includes subcutaneous or intravenous unfractionated heparin, low molecular weight heparin flushes, heparin-coated catheters, etc. A laboratory evaluation for HIT and other causes of thrombocytopenia is initiated.

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

Oral anticoagulant therapy should not be used alone, since several days is required for the full anticoagulant effect, and decreases in protein C and protein S can exacerbate HIT-induced thrombosis. Antiplatelet drugs alone are not indicated and platelet transfusions should be avoided. Surgical placement of an inferior vena caval filter can be considered if deep venous thrombosis is present.

### Web Sites

- [http://www.refludan.com/](http://www.refludan.com/)
- [http://www.argatroban.com/aboutheparin_01.htm](http://www.argatroban.com/aboutheparin_01.htm)
- [http://www.thedoctorsdoctor.com/diseases/heparin_induced_thrombocytopenia.htm#pathogenesis](http://www.thedoctorsdoctor.com/diseases/heparin_induced_thrombocytopenia.htm#pathogenesis)
- [http://www.tigc.org/eguidelines/hit02.htm](http://www.tigc.org/eguidelines/hit02.htm)
- [http://www.unc.edu/~rvp/RP_Anesthesia/Basics/HIT.html](http://www.unc.edu/~rvp/RP_Anesthesia/Basics/HIT.html)

### References

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References


Breddin HK: Platelet count monitoring and laboratory testing for heparin-induced thrombocytopenia. Arch Pathol Lab Med 127:782-783; author reply 783, 2003


Horner BM, Myers SR: Don't miss HIT (heparin induced thrombocytopenia). Burns 30:88-90, 2004


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References


