Heparin Induced Thrombocytopenia and Thrombosis@

By: Rajath Bappanad, Samarth Mishra, and Vaishanvi Bavadekar, the GTF Group

Introduction:

Georgia Thrombosis Forum (GTF, www.gtfonline.net) is an affiliate of North American Thrombosis Forum (NATF, www.natfonline.org). GTF is dedicated to the advocacy of thrombosis in the community and conducting research in the area of various aspects of management of thrombosis. GTF is also focused on training the next generation of leaders, and encourages youth volunteers as a medium for action in the community. This research project is on HITT, a dangerous complication of the use of heparin in treatment for VTE. In October 2016, one of the GTF members, Rohil Badkundri, presented his research on 100 years of Heparin, including a serious complication of heparin therapy, Heparin Induced Thrombocytopenia and Thrombosis (HITT). In this research article, the authors plan to shed some light on the types of HITT, mechanism, diagnosis, the different risk factors, and possible treatment options.

What is HITT?

HITT is a rare complication of heparin therapy. It is triggered by the immune system and results in thrombocytopenia (decrease in blood platelets). Unlike other forms of thrombocytopenia, HIT is generally not marked by bleeding; instead, venous thromboembolism.

There are two types of HITT

There are 2 types of HITT: HITT 1 and HITT 2.

HITT type 1 is not a serious condition and occurs within 2 days of heparin therapy.

HITT type 2 is a serious condition that occurs within 4-10 days of heparin therapy. This type of HITT can result in the loss of limbs and even death.

Mechanism for HIT Type 1

The mechanism for type 1 HIT is relatively unknown, is likely to be non-immune, probably related to its platelet pro-aggregating effect. It affects up to 10% of patients under treatment with heparin, and is characterized by a mild and transient asymptomatic thrombocytopenia (rarely less than 100,000 platelets/μL) that develops early (usually within the first two days of starting heparin) and disappears equally quickly once heparin is withdrawn.

Mechanism for HIT Type 2

The mechanism of HIT Type 2 is more complicated than HIT Type 1. It starts when the immune system forms antibodies (of the IgG class, IgG anti-PF4–heparin antibodies), when Heparin binds to platelet factor-4 (PF4). The IgG antibodies form a complex with Heparin and PF4. The tail of the antibody binds with the Low affinity immunoglobulin gamma Fc region receptor II-a, resulting in platelet activation, which initiates the formation of blood clots. Immune complexes interact with monocytes and endothelial cells inducing tissue factor expression and damage to the endothelial cells. Platelet counts fall, causing thrombocytopenia. The following figure is a representation of this description of the mechanism.

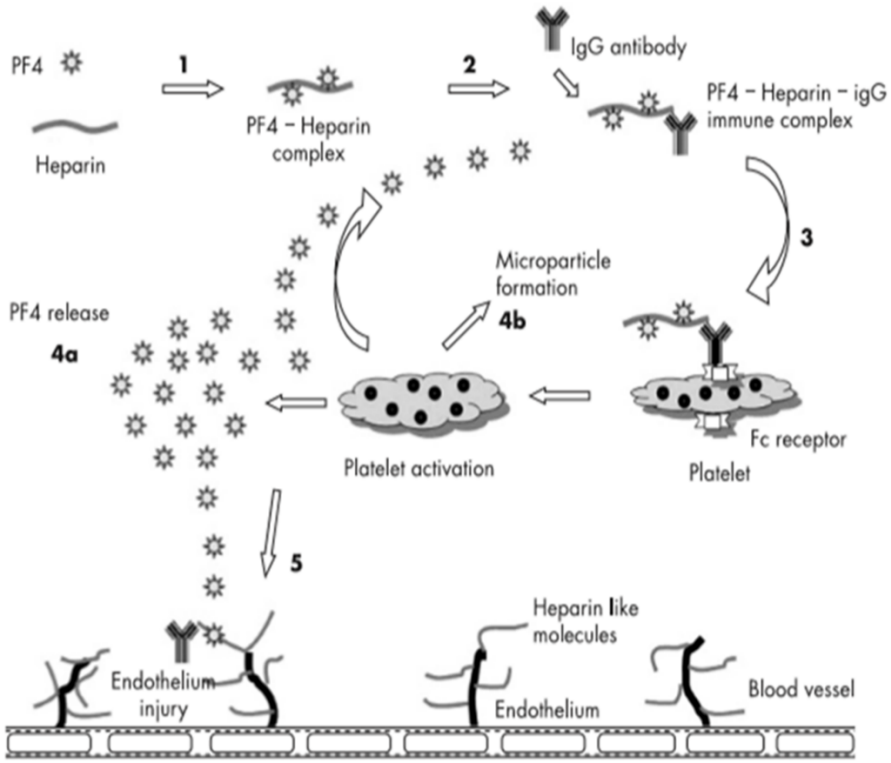


Figure 1 Pathophysiology of HIT. (1) Heparin binds with PF4 and act as immunogens. (2) IgG antibody thus produced forms PF4–heparin–IgG multimolecular complex. (3) The complex then binds via Fc receptor to platelets and activates them (4a) activated platelet releases additional PF4 and (4b) prothrombotic microparticles. (5) Immune complex interacts with endothelial cells and promotes immune mediated endothelial damage.

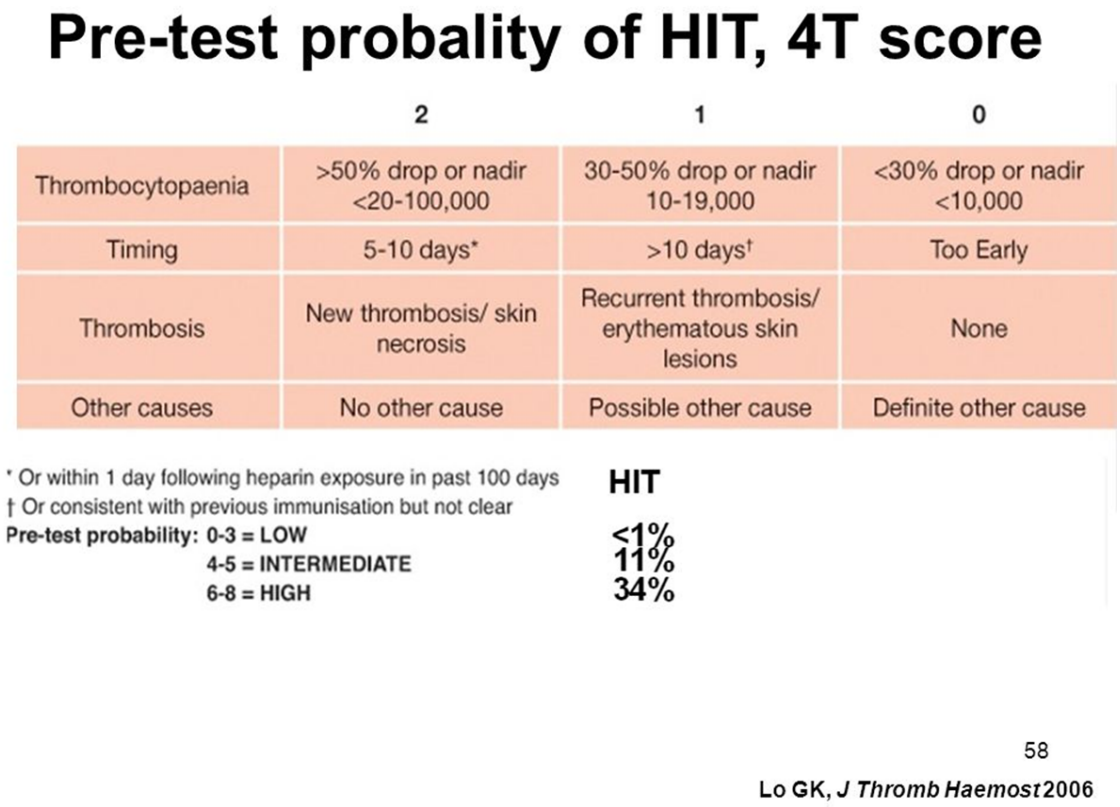
The Incidence of HIT

12 million hospitalized Americans receive some form of Heparin each year and the incidence of thromboembolic complications after major traumatic injures is high (<50%). The overall risk of developing Type 2 HITT is about 0.2% in all heparin-exposed

patients, the mortality rate is approximately 20%. Approximately 10% of type 2 cases require amputation. HITT is more common after use of UFH compared to LMWH, and more common in post-surgical patients, when compared to medical and obstetric patients.

Diagnosis of HIT

The diagnosis of HIT is primarily a clinical diagnosis. It can also be diagnosed through confirmatory laboratory testing. Other visible indicators include skin changes, lesions, bruising or blackening around heparin injection site, fingers, toes and nipples and may progress to gangrene. The 4T chart (pictured below) is used to give an accurate percentage of the probability of someone having HIT.



Pre-test probality of HIT, 4T score

	2	1	0
Thrombocytopaenia	>50% drop or nadir <20-100,000	30-50% drop or nadir 10-19,000	<30% drop or nadir <10,000
Timing	5-10 days*	>10 days†	Too Early
Thrombosis	New thrombosis/ skin necrosis	Recurrent thrombosis/ erythematous skin lesions	None
Other causes	No other cause	Possible other cause	Definite other cause

* Or within 1 day following heparin exposure in past 100 days
† Or consistent with previous immunisation but not clear
Pre-test probability: 0-3 = LOW
4-5 = INTERMEDIATE
6-8 = HIGH

HIT
<1%
11%
34%

58

Lo GK, *J Thromb Haemost* 2006

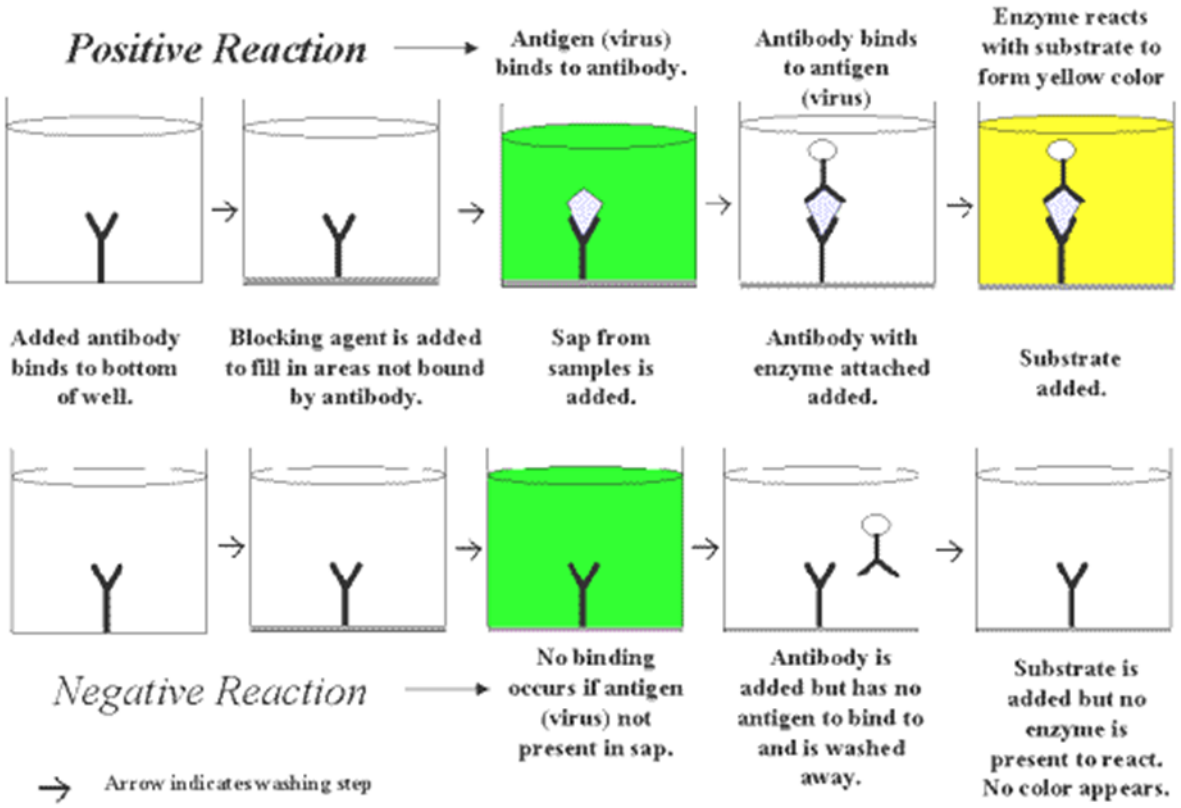
Types of Laboratory Testing

Laboratory testing (PF4 Antibody testing)

PF4 antibody testing is performed to detect antibodies that develop in some people who have been treated with heparin. Its used to help establish HITT type II in someone who has thrombocytopenia and thrombosis. Its most useful in those with a moderate to high likelihood of having HIT II, based upon the timing of heparin use, significant thrombocytopenia, and thrombosis. Its typically ordered along with or following a platelet count and may be followed by additional tests such as functional assays to confirm a finding.

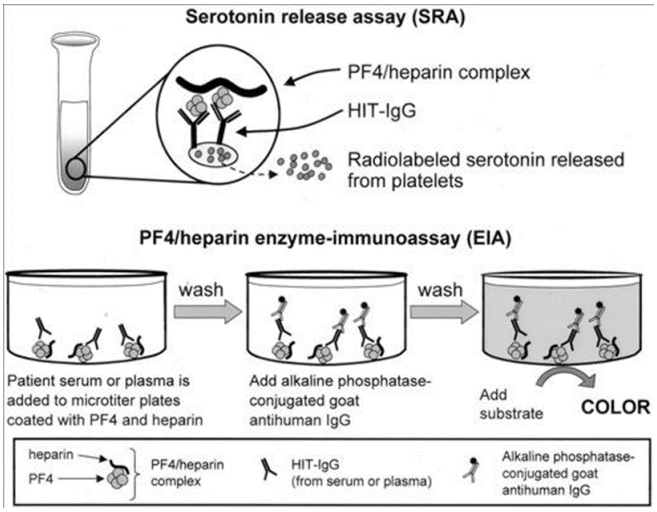
Laboratory testing (***Enzyme Linked Immunosorbent Assay)***

Enzyme Linked Immunosorbent Assay (ELISA) detects the presence (vs activity) of HIT antibody. It is based on the discovery that antibodies are directed toward PF4:H, not heparin alone. A pro of this laboratory testing is that no platelet donor is required. It is more sensitive than the activation assays to antibodies in HIT patients. Most laboratories have the necessary equipment to perform this assay. The assay can be completed within a few hours.



Laboratory testing Serotonin Release Assay

The Serotonin Release Assay (SRA) is a functional assay that measures heparin-dependent platelet activation. The patient serum is incubated with donor platelets containing radioactive Carbon-14 serotonin and different concentrations of heparin. The antibody present in the patient serum will bind and activate donor platelets, releasing radiolabeled serotonin from the platelet granules. A positive SRA is expected to show >20% release of the carbon-14 serotonin when mixed with patient serum and low-dose heparin. A sample is considered negative if there is <20% release.

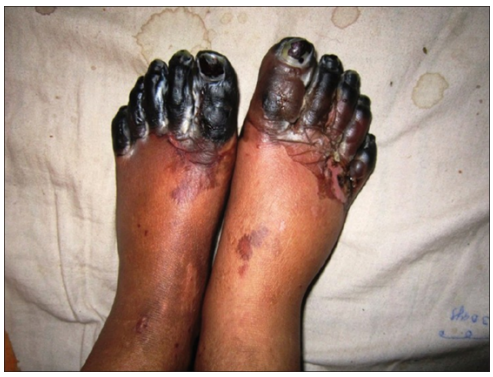


Laboratory testing (Platelet Aggregation Assay)

The platelet aggregation assay is a bio assay. It requires fresh, donor platelets. These donors must be aspirin-free. It tests for platelet activation by HIT-antibody immune complexes. It is detected by aggregation of platelets, and is less sensitive than SRA and is available from referral labs - authorized to do high complexity testing (CLIA).

Complications of HITT

There are many complications from HITT, such as DVT, MI, PE, thrombotic stroke, occlusion of limb artery, gangrene and amputation. DVT and PE appear frequently in postoperative patients. Necrotizing skin lesions at the heparin injection site occur in 10-20% of the patients. There is a Thrombosis induced mortality rate in 20-30% of all patients. Below is a picture of a patient suffering from gangrene due to HITT.



Risk factors of HITT

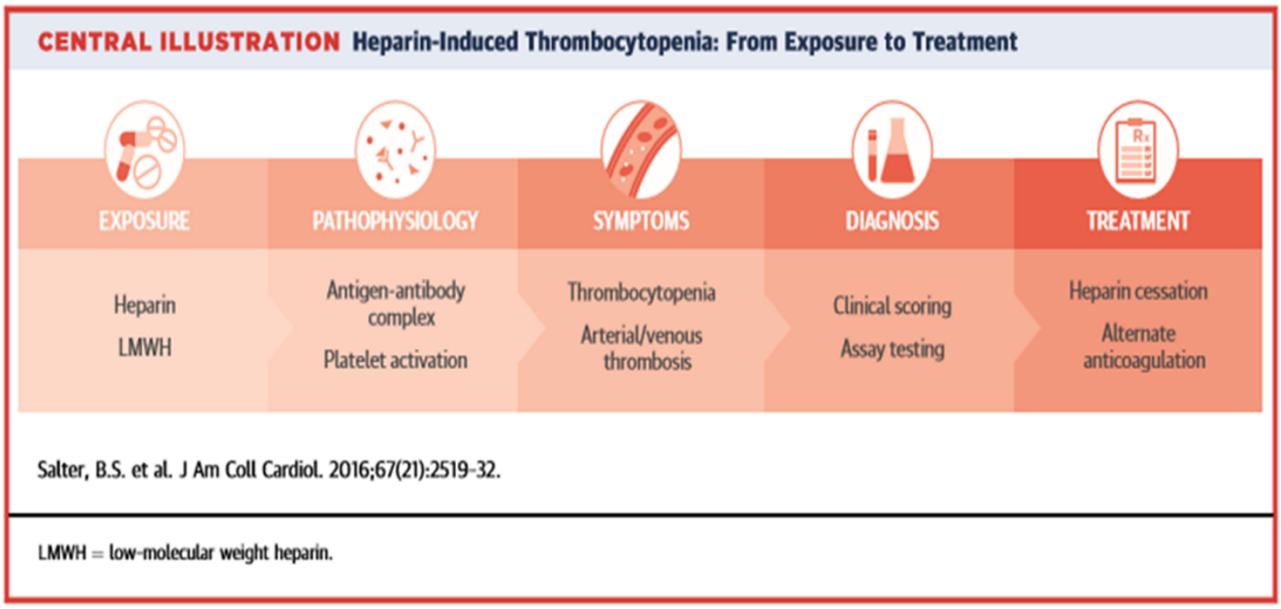
The risk factors for developing HITT include the use of Unfractionated Heparin, lower platelet counts (which can be affected by malignancy or gender), and the duration of heparin therapy.

Treatment for HITT

HITT can be treated by the immediate cessation of treatment from all formulations of heparin. Alternative anticoagulation must be used. Thrombotic events and the platelet count should be monitored closely. Warfarin cannot be used until platelet count has been recovered (WISN). Direct Thrombin Inhibitors, such as Argatroban can also be used as an antidote. Can you use the new oral anticoagulants?

Conclusion and Summary

In conclusion, heparin is a very effective anticoagulant, but in some patients, it could cause the devastating condition of HITT. Careful monitoring of heparin and the proper choice of heparin formulation can reduce the chances of developing HITT.



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