Heparin Induced Thrombocytopenia (HIT): A Review.

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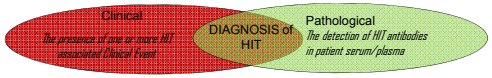
General Information

HIT is a life threatening immune mediated condition caused by heparin that presents with contradictory features such as thrombosis despite being caused by an anticoagulant and being associated with thrombocytopenia.[2,5,14]

Thrombocytopenia is common in hospital patients on heparin but only 1-5% will develop HIT. [3-4,9]

The production of heparin-dependent antibodies in patients on heparin is not uncommon but only a small subset of these patients develop HIT.[11]

HIT is considered to be a clinico-pathological condition.[2]



- Distinguishing HIT from non-HIT thrombocytopenia is essential to treatment since heparin is contraindicated in HIT but it is the best anticoagulant in non HIT thrombocytopenia.[14]
- Misdiagnosis is common due to the poor specificity of clinical diagnosis (4T's) and the poor turnaround time and low positive predictive value of anti-PF4/Heparin ELISA test – the most common test for HIT.[1,7-8]
- The Serotonin Release Assay is considered the gold standard for HIT testing[16] because of its high specificity and sensitivity [7] but it is preformed at reference laboratories and thus is only available as a send out test in most facilities.[8]
- Having faster turnaround times or introducing on demand tests for HIT can aid in the diagnosis and treatment of HIT and has the potential to cut down costs associated with misdiagnoses or delayed treatment of HIT. [12,16]

Pathophysiology

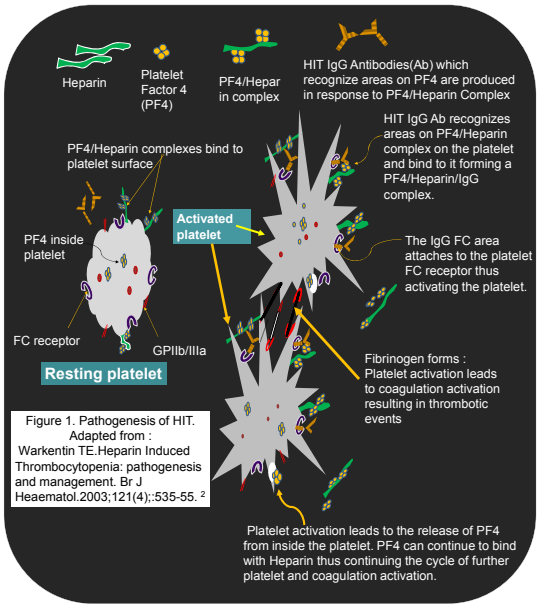


Figure 1. Pathogenesis of HIT. Adapted from : Warkentin TE.Heparin Induced Thrombocytopenia: pathogenesis and management. Br J Heaematol.2003;121(4);:535-55. [2]

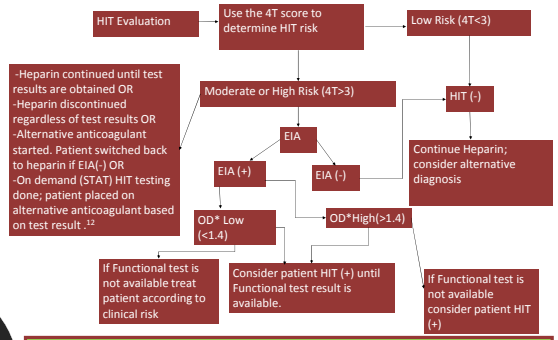
Diagnosis

HIT classically shows a >50 % drop in platelet count 5-10 days after exposure to Heparin or **a >50% drop in ≤ 1 day** when patient had been currently exposed to heparin within 30 days. A new *thrombosis and/or other suspected heparin related sequelae* is presented and there is *no other apparent cause for thrombocytopenia*. In many patients this classic picture is muddled by other factors.[13] The 4T's pretest is used to classify suspected HIT cases into low, moderate or high risk. [10,13]

The 4T's is a pretest clinical scoring system that is used to screen out patients a low probability of having HIT. The 4T's have a high NEGATIVE predictive value: thus patients with a low score are unlikely to have HIT.[13]

4T's

- Thrombocytopenia
- Timing of platelet fall (after Heparin)
- Thrombosis and/or other sequelae
- Other causes of Thrombocytopenia



Algorithm showing the management of a patient with suspected HIT.[6-7,12,16]

*Optical Density (OD) thresholds will vary by institution: in a study by Lu, Kudlowitz and Gardner published in the Journal of Blood medicine low positives were defined as 0.7≥ OD ≤1.4 and high positives had an optical density of ≥ 1.4. Patients with high positives were more likely to have HIT.[7]

- The 4 T's assessment has a high negative predictive value thus patients with a low score on the 4Ts are unlikely to have HIT. Testing for HIT antibodies and changing anticoagulants on these patients is not recommended.[10,13]
- Patients with a intermediate or high 4Ts score should undergo HIT immunoassay testing. Any positive immunoassay results should be confirmed by functional testing.[12]
- By limiting treatment and immunoassay testing to patients with a high or intermediate pretest score false positive HIT diagnoses can be avoided.[12]

Treatment & Prognosis

- A diagnosis of HIT requires *an immediate switch from heparin to an alternative replacement anticoagulant* such as argatroban, bivalirudin, danaparoid, fondaparinux and lepirudin.[12]
- Investigate for lower-limb deep-vein thrombosis and avoid prophylactic platelet transfusions.[20]
- False positive HIT results can adversely affect patient. Switching from Heparin to an alternative anticoagulant unnecessarily puts the patient at risk or bleeding or thrombosis.[21]

laboratory Testing

There are two categories of tests for HIT testing : Immunoassay and functional assays

Category	*EIA*	*Functional Assay*
Methodology	Detect PF4/heparin antibodies, regardless of their capacity to activate cells.	Detect PF4/Heparin antibodies that activate cells in a heparin-dependent manner.
Examples	• Poly-specific ELISA • IgG-specific ELISA	• ^{14}C-SRA • HIPA
Pros	High Sensitivity, simple and widely available	High sensitivity and high specificity
Cons	• Limited specificity • Rarely preformed as a stat test	• Need fresh reactive platelet donor • ^{14}C-SRA uses a radio-labelled substance • Typically a send-out test

Table 1. HIT testing.[5,15]

New Developments in EIA HIT Testing

- False positive SRA results caused by non-HIT related platelet activating factors results correlate with lower or negative OD values in EIA testing.[16]
- Lu, Kudlowitz and Gardner report that **higher thresholds** for positive ELA results can be used to reduce false positive HIT diagnoses.[7]

On demand testing

no more waiting hours or days for results!

Fully Automated Chemiluminescent Immunoassay

- One 2012 study showed automated chemiluminescent assays HemosIL AcuStar HIT IgG and HemosIL to be a good alternative to the time consuming ELISA testing.[18] A 2016 study showed that HemosIL AcuStar HIT Ab had comparable to lower sensitivity and a higher specificity in comparison to other immunoassays.[12]
- The most commonly used EIA tests for HIT are usually run in batches once or twice a week thus in many instances clinicians are left to make decisions about suspected HIT cases without the aid of laboratory tests.[8] On demand tests can help resolve this problem.
- These automated tests can replace ELISA testing for HIT.

New Developments in Functional Testing

Alternative methods are being developed to detect HIT dependent platelet activation *without the use of radio-labelled serotonin* including:

- **SRA utilizing High Powered Liquid Chromatography (HPLC)**
  A recent study showed HPLC SRA to be equal in sensitivity and specificity to ^{14}C-SRA. The HPLC SRA method quantifies the serotonin released by donor platelets that have been incubated with patient serum. If patient serum contains HIT antibodies capable of activating platelets serotonin levels will be correspondingly high.[17]
- **Flow Cytometry**
  This is not a new method but it is becoming more popular because flow cytometry is available at most major medical facilities. In a 2013 study published in Blood Coagulation and Fibrinolysis, HitAlert Flow cytometry was compared against SRA and was found to have comparable to sensitivity and specificity to SRA. HitAlert Flow cytometry detects antibodies that are able to activate platelets. It uses a phycoerythrin-labelled antiplatelet antibody and a fluorescein isothiocyanate-labelled platelet activation marker to detect platelet activation.[19]

- HPLC SRA and Flow cytometry testing for HIT share the limitation that all platelet functional assays for HIT have: the need for fresh reactive donor platelets. [17,20]
- ***Nevertheless, these assays are more likely to be implemented at hospital facilities as confirmation tests for HIT than the gold standard(^{14}C-SRA) test because they do not use a radio active substances and because these methods are already widely used for other types of testing.***[17,19]

Conclusion

- A diagnosis of HIT is made in with laboratory tests in conjunction with clinical data.[2]
- Clinical evaluation of patients is done using the 4T's preclinical test.[10]
- Patients with an intermediate to high 4T's score are tested for HIT antibodies using EIA while low 4T's scores are considered HIT negative.[10]
- While weakly positive EIA results should be interpreted with caution, strongly positive EIA results correlate robustly with positive SRA results indicating true HIT.[15]
- Treatment of HIT involves the immediate discontinuation of heparin and the use of an alternative anticoagulant.[20]
- On demand HIT testing will provide lab results a timely manner enabling providers to make better decisions about suspected HIT cases.[12]
- Function Assays utilizing flow cytometry or HPLC have the potential of becoming more popular in hospital laboratories for confirmation HIT testing since many facilities already utilize these methodologies for other testing.[17,19]

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