HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

TERM DEFINITION

HIT is an antibody-mediated disorder of coagulation caused by exposure to heparin and associated with significant risk of thromboembolic complications and death

TYPES OF HIT

1. **ISOLATED HIT** *Thrombocytopenia alone*
2. **HIT WITH THROMBOSIS (HITT)** *Thrombocytopenia and venous or arterial thrombosis*

PREVALENCE

Prevalence of HIT Antibodies

8-17%
of patients treated with unfractionated heparin

2-8%
of patients treated with LMWH

~50%
of patients undergoing cardiac surgery

Prevalence of HIT

0.2%
of hospitalized patients with heparin exposure

0.1-1%
of medical inpatients

1-3%
of patients who have undergone cardiac surgery

CLINICAL PRESENTATION

- Thrombocytopenia typically occurs **5-10 days** after heparin exposure.
- Degree of thrombocytopenia is typically moderate (median platelet count **50-60 x 109/L**).
- Thrombosis reported in about **50% of patients** with HIT.
- Clots may occur in any blood vessel, but **venous thrombosis** most common.

Thrombosis may also occur in unusual sites including:

- Microvessels of skin
- Adrenal vein
- Mesenteric vein
- Dural sinus

DIAGNOSIS

Diagnosis of HIT is based on clinical presentation (thrombocytopenia +/- thrombosis in temporal association with heparin therapy without other obvious causes) plus presence of platelet-activating antiplatelet factor 4 (PF4)/heparin antibodies (also called **HIT antibodies**).

Presence of anti-PF4/heparin antibodies can be detected using **immunoassays** (for example, an ELISA; results typically return within 1-3 days) or a **functional assay** called the serotonin release assay (results may not be available for several days). A presumptive diagnosis of HIT should not be delayed while awaiting results of antibody testing. The immunoassay (sensitive but not specific) is ordered first, and if positive is followed by the SRA (gold standard).

CLINICAL PREDICTION RULE - 4T TEST

The 4T Test is used to evaluate pretest probability of HIT. It establishes a presumptive diagnosis of HIT until laboratory data are available.

CATEGORY	2 POINTS	1 POINT	0 POINT
Thrombocytopenia	>50% fall AND nadir >20 x 109/L	Platelet count fall 30%–50% OR platelet nadir 10–19 × 109/L	<30% fall OR nadir < 10 x 109/L
Timing of decrease in platelet count*	Days 5–10 OR < 1 day if recent heparin exposure	> day 10 or timing unclear	≤ day 4 with no recent heparin exposure
Thrombosis or other sequelae	New thrombosis or skin necrosis at injection site	Progressive, recurrent or suspected thrombosis **	None
Other causes of thrombocytopenia	None evident	Possible	Definite

** start of heparin is day 0*
*** awaiting confirmation*

0 - 3 **Low probability (risk of HIT < 1%)**
4 - 5 **Intermediate probability (risk of HIT 10%)**
6 - 8 **High probability (risk of HIT 50%)**

TREATMENT PRINCIPLES

If HIT is suspected (intermediate or high 4T score):

1) **all heparin products must be discontinued** and an appropriate non-heparin anticoagulant started.

2) Order immunoassay for HIT antibodies.

Clinical practice guidelines are available to inform clinicians of an algorithmic approach to diagnosing and treating patients with suspected HIT. **A simplified version is shown on the right**, and a more detailed approach is shown below.

4T SCORE	ACTION
Low	None (continue heparin, do not order immunoassay)
Intermediate or high	Stop heparin, start alternative anticoagulant while waiting for immunoassay result

ALGORITHM

4T TEST

LOW (Score 0-3)

Excludes HIT without need for additional laboratory testing

INTERMEDIATE / HIGH (Score 4-8)

- Stop heparin
- Give alternative anticoagulant in full dose*
- Order HIT antibody test (enzyme immunoassay)

HIT ANTIBODIES

NEGATIVE → HIT ruled out

POSITIVE → Confirmation with SRA

NEGATIVE → HIT ruled out

POSITIVE → Treat as HIT

*** OPTIONS INCLUDE:**

- Argatroban
- Bivalirudin
- Fondaparinux
- Rivaroxaban

The choice depends on the clinical context, physician preferences and institutional policies

PROXIMATE MECHANISMS

HIT results from an ***autoantibody directed against endogenous platelet factor 4 (PF4)*** *in complex with heparin:*

- Platelet factor 4 (PF4) is a cytokine released by activated platelets.
- Once released, PF4 binds to heparin. PF4-heparin complexes expose neo-antigens which are recognized by PF4 antibodies.
- In some patients with PF4/heparin antibodies, the PF4-heparin-antibody complexes bind the Fc gamma RIIA receptor on the platelet surface resulting in platelet activation

Platelet activation leads to:

- **Thrombocytopenia**
- Release of procoagulant microparticles that lead to **thrombosis**

EVOLUTIONARY MECHANISMS

HIT may be considered an example of the **mismatch hypothesis** whereby cultural evolution has outstripped genetic evolution. Our genome is adapted to a far earlier time, perhaps about 10,000 years ago.

At that time, we were not treating sick individuals with heparin. Thus there was no selective pressure to adapt to heparin therapy and evolve mechanisms that would mitigate a deleterious response to the agent.

Heparin is a natural product and it may be argued that the heparin that lines our blood vessels (called 'heparan') should have exerted enough selective pressure, but the doses of therapeutic heparin are overwhelmingly large compared to endogenous stores.

HISTORY OF MEDICINE

Heparin was **discovered 100 years ago** and was widely used as an anticoagulant shortly thereafter. An association between heparin and blood clotting was first described in 1957 and this was followed by several other reports showing the same link. However, platelet count measurements were not routinely performed until the 1970s, and this explains, in part, why the connection between heparin-associated thrombosis and thrombocytopenia was not recognized until **1969, at which time the term heparin-induced thrombocytopenia was first coined**. The immune basis for HIT was reported in 1973. Since then the field has seen enormous advances on the basic science, translational and clinical sides, led most notably by **Ted Warkentin** at McMaster University in Canada.

NOTES

ATTRIBUTIONS
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The Blood Project
ENCYCLOPEDIA OF BLOOD