

HIT range

A photograph of a wooden pier extending into a vibrant blue ocean under a clear sky. On the pier, a person stands holding a large blue umbrella, and a dog stands holding a large magenta umbrella. The scene is bright and sunny, with the water's surface shimmering with light.

Diagnosis of
Heparin Induced Thrombocytopenia

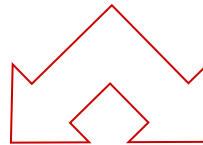
What is HIT ?

- **Heparin Induced Thrombocytopenia**
- Adverse effect of heparin
- Antibody-mediated
- Main symptom: **thrombocytopenia**
 - platelet count drop > 50% from the baseline
 - generally occurs 5-14 days after the start of heparin treatment
- May affect up to 5% of patients on UFH and 0.5 - 1% of patients on LMWH therapy
- Strong association with venous and arterial thrombosis
 - high morbidity risks

➔ HIT suspicion: huge stress for clinician/lab

Diagnosis

- **Combination of clinical and biological criteria**
 - pre-test scoring (4T's)
 - biological assays



Functional assays

(SRA, HIPA)

= detect platelets activating antibodies



highest sensitivity/specificity



complex, expensive,
time consuming



not standardised



not widespread use

Immunoassays

= detect antibodies against [Heparin/PF4]



better standardisation



easier to use



lower specificity

➔ No perfect test, room for improvement

Treatment of HIT

HIT: **Severe** clinical impacts

Suspicion of HIT = stress for clinician/lab



Clinician does not wait for lab results

**→ switch to alternative
anticoagulant**



Alternative anticoagulants

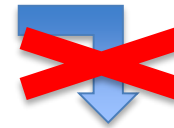
→ high risk of bleeding (no antidote)

→ much more expensive

HIT Facts

HIT: **Severe** clinical impacts

Suspicion of HIT = stress for clinician/lab



Clinician does not wait for lab results

→ **switch to alternative anticoagulant**



Alternative anticoagulants

→ **high risk of bleeding (no antidote)**

→ **much more expensive**

Real frequency of HIT

→ **6~12% of patients investigated for HIT really have HIT***

→ **88~94% of patients suspected of HIT don't have HIT**

OFFICIAL COMMUNICATION OF THE SSC

Laboratory testing for heparin-induced thrombocytopenia: a conceptual framework and implications for diagnosis

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Heparin-induced thrombocytopenia (HIT) is a 'clincopathologic' syndrome (i.e. diagnosis depends on both clinical and pathologic criteria being present) [1]. The 'clinical' criteria include the presence of thrombocytopenia and/or thrombosis bearing a temporal relationship to an immunizing exposure to heparin. The 'pathological' criterion is the detectability of 'HIT antibodies' in acute patient serum or plasma. HIT is caused by heparin-dependent platelet-activating antibodies that in almost all patients recognize complexes of platelet factor 4 (PF4) bound to heparin [2]. Sensitivity of solid-phase enzyme-immunoassays (EIAs) for anti-PF4/heparin antibodies is very high (approximately 99%), due to certain unique properties of HIT antigens; they are expressed on large, stable multimolecular complexes comprised of PF4 and polyanions [3]. This differs from other drug-induced, immune-mediated thrombocytopenic disorders, where laboratory tests for drug-dependent antibodies often lack high diagnostic sensitivity. The antigens in these other disorders are labile complexes of drug (or drug metabolites) and platelet glycoproteins [4].

The high diagnostic sensitivity of the PF4/heparin EIAs is accompanied by a parallel problem in diagnostic specificity for HIT. This arises because EIAs also have high sensitivity for detecting clinically insignificant anti-PF4/heparin antibodies, which can be present coincidentally in patients with thrombocytopenia caused by non-HIT factors. This leads to the

potential for HIT 'over-diagnosis,' especially in critically-ill patients. Systematic serosurveillance studies show that only a minority (2-15%) of heparin-treated patients who form anti-PF4/heparin antibodies develop clinically evident HIT [5,6]. Even among those who form platelet-activating antibodies, no more than half develop HIT. This Subcommittee statement provides a framework on when to perform and how to interpret laboratory tests for HIT diagnosis.

Patients should not be routinely screened for anti-PF4/heparin antibodies (other than for research studies). Patients should only undergo testing if clinical features reasonably suggest a diagnosis of HIT. Scoring systems can be helpful to estimate the pretest probability of HIT [7-9]. HIT antibodies are transient, however [10], and thus testing should be performed using acute serum or plasma.

Laboratory diagnosis of HIT differs fundamentally from other antibody-mediated cytopenias, such as autoimmune thrombocytopenia or hemolysis, because free HIT antibodies are readily detectable in patient serum/plasma even during the earliest phase of the platelet count decline indicating HIT [11]. Therefore, a negative result of an HIT antibody test performed because of thrombocytopenia or thrombosis generally rules out HIT. Routine repeat testing a few days later is not indicated (unless a new platelet count decline or thrombosis occurs) because such testing risks detecting clinically irrelevant antibodies (as demonstrated in serosurveillance studies). Over-diagnosis of HIT is potentially dangerous because it may lead to withholding of certain diagnostic and therapeutic interventions during the acute event and in future admissions, and because it usually prompts treatment with alternative anticoagulants, which may increase bleeding risk (approximately 1% risk of major bleeding per treatment day for direct thrombin inhibitors) [12].

Diagnostic accuracy for HIT is optimized by combining the anti-PF4/heparin EIA with a functional (platelet activation)

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➔ Overdiagnosis of HIT is potentially dangerous

bodies (as demonstrated in serosurveillance studies). **Over-diagnosis of HIT is potentially dangerous because it** may lead to withholding of certain diagnostic and therapeutic interventions during the acute event and in future admissions, and because it **usually prompts treatment with alternative anticoagulants, which may increase bleeding risk** (approximately 1%

➔ How to exclude HIT?

Therefore, **a negative result of an HIT antibody test performed because of thrombocytopenia or thrombosis generally rules out HIT**. Routine repeat testing a few days later is not indicated

➔ How to improve specificity?

ity of EIAs. **Patients should be tested for IgG class antibodies, as only this isotype class activates platelets** [2,6,16,17] (rare

Clinicians and labs needs

Clinician

High interest to **quickly rule-out HIT**

Avoid alternative treatment, maintain heparin

- Less bleeding risks
- Cost savings
 - treatment
 - less additional expensive testing, labor cost

From the lab perspective

- Unitary test
- Rapid
- Easy to use
- 24/7, STAT adapted
- Negative Predictive Value 100%
- High specificity

Results

| SERUM | | HIT Rapid test <i>STic Expert®</i> | |
|--------------|---|--|----|
| | | - | + |
| HIT | - | 188 | 38 |
| | + | 0 | 33 |

Ss 100% - NPV 100%
Sp 83.2% - PPV 46.5%

| PLASMA | | HIT Rapid test <i>STic Expert®</i> | |
|---------------|---|--|----|
| | | - | + |
| HIT | - | 245 | 47 |
| | + | 1* | 41 |

Ss 97.6% - NPV 99.6%
Sp 83.9% - PPV 46.6%

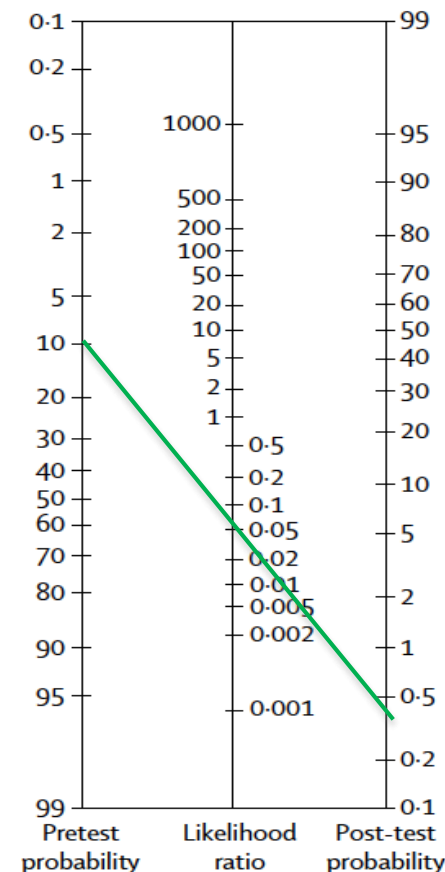
*negative result not confirmed by the centralized center after testing a deformed sample

- **Excellent NPV** : serum 100% and plasma 99.6%
- **High specificity** : serum 83.2% and plasma 46.6%

Performances of the « 4T's »

combined with HIT Rapid test

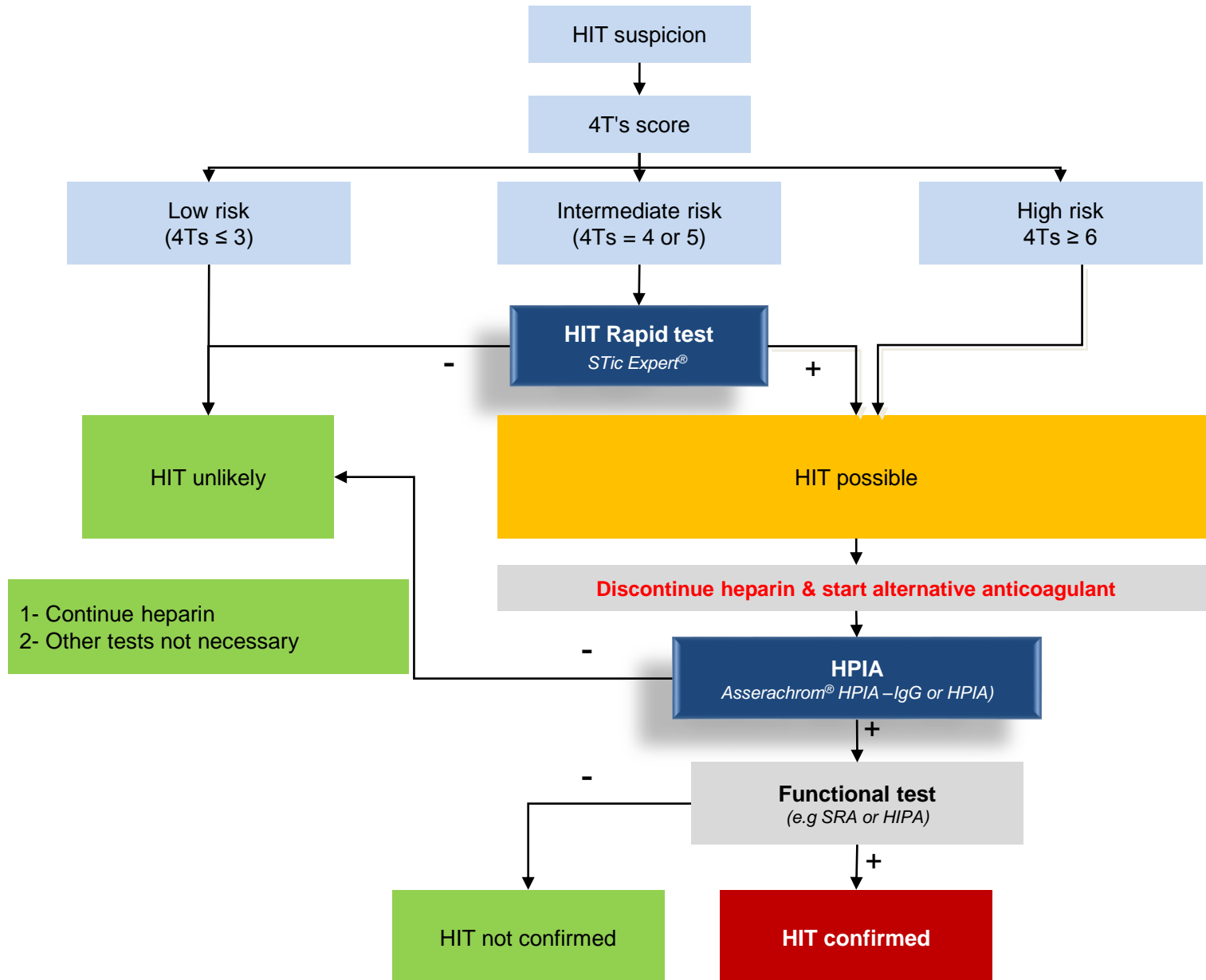
| | | | Post-test probability | |
|------------|-------------------------------|----------------------|--|-------|
| | | Pre-test probability | HIT Rapid test <i>STic Expert®</i> Negative Positive | |
| 4T's score | Low risk (3/95) | 3.1% | 0.1% | 16.4% |
| | Intermediate risk (24/207) | 11.6% | 0.39% | 43.3% |
| | High risk (15/32) | 46.8% | 2.6% | 84.2% |



Low or intermediate risk

- a negative result is able to confidently rule-out HIT
- heparin treatment can be continued

Suggested diagnosis algorithm



Conclusion

- 6~12% of patients investigated for HIT really have HIT
- **Ruling-out HIT** quickly avoids unnecessary changes of heparin
 - ~90% of suspected patients
 - reduce bleedings risks
 - reduce costs
- Stago offers a **comprehensive range** for HIT diagnosis
 - STic Expert® HIT
 - Asserachrom® HPIA-IgG
 - Asserachrom® HPIA