

Heparin-Induced Thrombocytopenia: Controversies and Updates

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50% of patients exposed to UFH develop HIT antibodies



1-5% develop symptomatic HIT

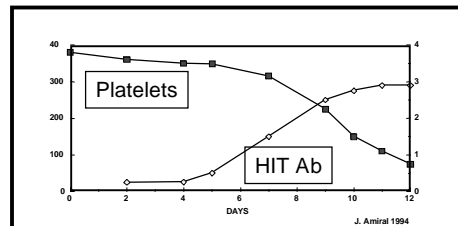


30-40% develop thrombosis



30% mortality and a 20% limb amputation rate

Patients with co-morbidities (sepsis, vascular pathology, renal impairment)
have a higher risk of a poorer outcome.



Update on Issues Related to HIT

- It is important to continue to better understand HIT
 - Associated with a high risk of life-threatening thrombosis
 - It is a difficult diagnosis
- Awareness/education are key; physicians, all health care providers and patients need to keep in mind the potential for the development of HIT
- From translational research studies, the incidence of death/amputation due to HIT has been reduced:
 - improved understanding of the disease process
 - development of diagnostic testing
 - new anticoagulant drugs

Update on Issues Related to HIT

Clinical Diagnosis Issues

- Recommend platelet count monitoring in patients receiving heparin if risk of HIT is >1.0% *
- See *Chest* for detailed platelet count monitoring guidelines

*** 8th Edition ACCP Guidelines**

Chest 2008;133(6):340S-380S

Update on Issues Related to HIT Clinical Diagnosis Issues

- For patients having received heparin within the previous 2 weeks, HIT should be suspected if * :
 - the platelet count falls by $\geq 50\%$,
 - and/or a thrombotic event occurs between 5 and 14 days (inclusive) following initiation of heparin, *even if the patient is no longer receiving heparin therapy* when thrombosis or thrombocytopenia has occurred.

* 8th Edition ACCP Guidelines: Chest 2008;133(6):340S-380S

Update on Issues Related to HIT Clinical Diagnosis Issues

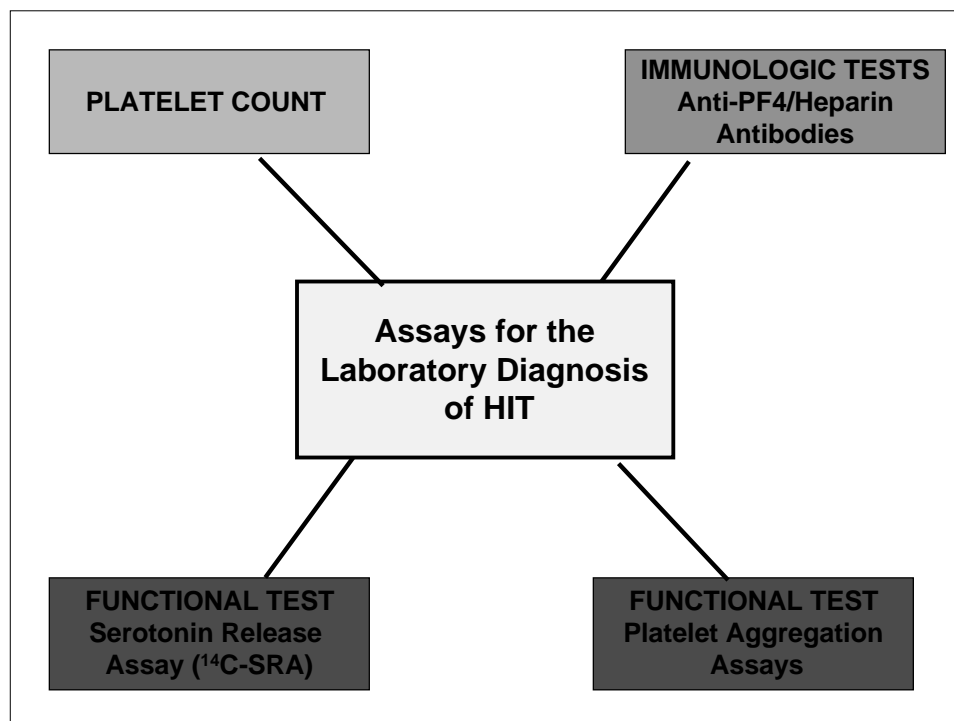
- For patients after cardiac surgery # :
 - Symptomatic HIT occurs exclusively in cardiac surgery patients who receive UFH post-op (2.8%; 2 studies) but not in patients receiving LMWH (Greinacher; Gruel)
 - Japan has lower incidence of post-cardiac/vascular surgery HIT than in Western countries (Miyata)
 - Clinical practice: shorter use of UFH post-op (max 2 days)
 - Genetic variability (?)

From ISTH-SSC, Vienna 2008

Update on Issues Related to HIT

Clinical Diagnosis Issues

- 4 T's (Thrombocytopenia, Timing, Thrombosis, oTher) to aid in the clinical diagnosis of HIT (negative predictive value)
 - Algorithms are being developed
- The potential to develop HIT after the patient is discharged home has increased
 - Patients are sent home earlier than in the past; HIT can develop even after heparin has been discontinued
 - Patients need to be informed of the signs for a new thrombosis or skin lesions [Included in *Chest* guidelines *]



Update on Issues Related to HIT Laboratory Diagnosis Issues

- HIT antibodies are heterogeneous
- Still working to develop an optimized lab test
- New antigen-based assays
 - PF4/heparin ELISAs
 - ELISA that incorporates 'platelet-leukocyte lysate' (Zymutest; Hyphen)
 - ELISA tests for IgG only
 - 'Rapid' Particle Gel Immunoassay (PaGIA; Diamed)
 - 'Rapid' Particle ImmunoFiltration assay (PIFA; Akers)
- Lack of standardization for all HIT assays
 - Demand for reference material, but many issues to be clarified

Update on Issues Related to HIT Laboratory Diagnosis Issues

- Quantitative ELISA optical density (OD) reporting (Warkentin) # :
 - Weak + (low OD; 0.40-1.00) associated with low frequency (<5%) of ¹⁴C-SRA +
 - Strong + (high OD; >2.00) associated with high frequency (~90%) of ¹⁴C-SRA +
 - Needs to be confirmed
 - C/B more useful for improving diagnostic specificity than use of IgG-specific ELISA (!)

From ISTH-SSC, Vienna 2008

Update on Issues Related to HIT Laboratory Diagnosis Issues

- Different results from different ELISA kits
- Recent study (Elalamy) # :
 - Stago vs Hyphen Zymutest showed good correlation between 2 tests
 - Zymutest has less positive results in patients with low probability of HIT, while it was positive in all patients with a high probability of HIT
- Recent study (Gruel) # :
 - Zymutest has higher specificity (90%) than other ELISA (51% GTI) with high sensitivity (98%)
 - Caution: comparisons are made to ¹⁴C-SRA which only tests for IgG

From ISTH-SSC, Vienna 2008

Update on Issues Related to HIT Laboratory Diagnosis Issues

- Recent study (Ortel) # :
 - Improve specificity by using high heparin in the ELISA (GTI)
 - Inhibition with high heparin improves the specificity for clinically relevant antibodies
 - Interpretation of OD >1.00 requires caution as all HIT patients do not show inhibition

From ISTH-SSC, Vienna 2008

Update on Issues Related to HIT Laboratory Diagnosis Issues

- To maintain specificity of clinically relevant HIT antibodies (to reduce sensitivity for non-relevant antibodies) (Amiral) # :
 - Affinity purify antibodies using a column coated with PF4/heparin
 - Peak 1 low affinity; Peak 2 high affinity to PF4/heparin and showed stronger activation of platelets
 - Using special buffers the avidity of the antibodies can be included in the test: stronger chaotropic buffers reduce the binding of low affinity antibodies

From ISTH-SSC, Vienna 2008

Update on Issues Related to HIT Treatment Issues

- For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, use an alternative, non-heparin anticoagulant * :
 - Danaparoid (Grade 1B)
 - Lepirudin (Grade 1C)
 - Argatroban (Grade 1C)
 - Fondaparinux (Grade 2C)
 - Bivalirudin (Grade 2C)

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Update on Issues Related to HIT Treatment Issues

- Guidelines for non-heparin anticoagulant dosing include specific recommendations that differ from the package inserts.*
 - Lepirudin: lower initial dose (no bolus if possible), lower dose for patients with high serum creatinine, aPTT monitoring every 4 hrs until steady state achieved
 - Argatroban: patients with heart failure, MOSF, severe edema, and post-cardiac surgery lower initial dose with adjustment up using aPTT

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Update on Issues Related to HIT Treatment Issues

- Treatment options in patients (Gruel) # :
 - Clinical probability low or intermediate and EIA negative - continue with heparin
 - Clinical probability low but a clear EIA positive - initiate an alternate anticoagulant and perform a functional test
 - Clinical probability high but a negative EIA - initiate an alternate anticoagulant and perform a functional test

From ISTH-SSC, Vienna 2008

Update on Issues Related to HIT Treatment Issues

- For patients with HIT, vitamin K antagonists (VKA) * :
 - should not be used until after the platelet count has recovered to at least $150 \times 10^9/L$, and
 - should start only with a low maintenance dose (Grade 1B).
 - Non-heparin anticoagulants should be continued until the platelet count has reached a stable plateau, INR has reached the intended target range, and after a minimum overlap of at least 5 days between non-heparin anticoagulation and VKA therapy (Grade 1B).
 - *If patient was receiving VKA therapy at time of diagnosis of HIT, reverse with vitamin K (Grade 1C).*

* 8th Edition ACCP Guidelines: Chest 2008;133(6):340S-380S

Update on Issues Related to HIT Treatment Issues

- Fondaparinux and HIT:
 - 3 known cases of fondaparinux-induced HIT (differing mechanisms? #)
 - ACCP Guidelines * recommend to continue to use fondaparinux for the management of HIT thrombosis and not to monitor platelet counts

From ISTH-SSC, Vienna 2008

* 8th Edition ACCP Guidelines: Chest 2008;133(6):340S-380S

Update on Issues Related to HIT Treatment Issues

- Patients with acute or subacute HIT needing cardiac surgery * :
 - Delay surgery until HIT antibody negative (Grade 1B)
 - Use bivalirudin during surgery (Grade 1B)
 - Other anticoagulant options (Grade 2C)

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Update on Issues Related to HIT Treatment Issues

- Patients needing cardiac catheterization or PCI * :
 - Patients with HIT
 - Bivalirudin (Grade 1B)
 - Argatroban (Grade 1C)
 - Lepirudin (Grade 1C)
 - Danaparoid (Grade 1C)
 - Patients with history of HIT, antibody negative
 - Use a non-heparin anticoagulant

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Summary

1. HIT is an immune response to heparin that remains a difficult diagnosis.
2. HIT presents clinically in 'textbook' as well as atypical ways. Studies continue to develop algorithms to aid in identifying patients with HIT.
3. Lab tests for HIT vary in their correlation to clinical HIT. Each test provides unique information. Studies continue to find optimal test systems.
4. As issues arise studies have provided important information for dosing regimen modifications for specific drugs and specific patient populations. Studies continue to optimize the treatment management of HIT.
5. A high clinical awareness, prevention, early diagnosis and treatment are important to reduce the risk of life- and limb-threatening thrombosis from HIT.

Current Controversial Issues Related to HIT

- HIT diagnosis dependent on positive SRA (IgG)
- Diagnostic validity of different test systems
- Reporting criteria for test results (numerical value or OD for EIAs; % release for SRA)
- Repeat negative lab tests
- HIT with fondaparinux
- Heparin contaminant
- Differential immunogenic profiles of heparin and LMW heparins (FDA)