International Consensus Statement 2013
Guidelines According to Scientific Evidence

Developed under the auspices of the:

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Heparin-Induced Thrombocytopenia

Chapter 19
General Considerations

- Heparin-induced thrombocytopenia (HIT) is an important adverse effect of heparin
- HIT is a life-threatening, prothrombotic, immune-mediated coagulopathy caused by antibodies that bind to the complex of platelet factor 4 (PF4) and heparin
- HIT occurs most frequently in cardiac surgery, orthopedic surgery, and medical patients, but can be found in other patient populations and clinical settings

General Considerations

- Progression to overt thrombosis is the most serious complication of patients with HIT as it often leads to amputation or death\(^1-4\)
- Spontaneous bleeding and petechiae have been reported only rarely
- HIT Type I is a transient but self-limited fall in platelet count in up to 30% of treated patients
- This occurs through a non-immunological mechanism in the first 24 hours of receiving heparin and resolves within 24-48 hours\(^5\)

General Considerations

Frequency of HIT

- The frequency of HIT is influenced by several factors
- The risk of developing HIT is higher from exposure to UFH (bovine > porcine) than LMWH and is more duration- than dose-dependent\(^1\)\(^-\)\(^10\)
- HIT can occur with a higher frequency in LMWH treated patients who were previously exposed to UFH\(^11\)
- HIT due to LMWH is as severe as UFH induced HIT\(^4\)

General Considerations
Frequency of HIT

• HIT can occur with prophylactic doses of heparin and heparin from exogenous sources\(^1,2\)

• Preventive measures include:
  
  ‣ The use of LMWH, fondaparinux, and non-heparin anticoagulants rather than UFH for post-surgical prophylaxis
  
  ‣ The use of porcine rather than bovine UFH
  
  ‣ Avoiding unnecessary and prolonged exposure to UFH

General Considerations

Diagnosis of HIT

- Diagnosis of HIT is based on clinical findings and platelet count
- If recently treated with heparin, HIT should be suspected on the basis of a 30% decrease in platelet count from baseline in the absence of other reasons for thrombocytopenia\(^1\)\(^-\)\(^3\)
- The diagnosis can be made if the platelet count reduction is 50% of baseline, assuming no other reasons for thrombocytopenia\(^1\)\(^-\)\(^3\)

General Considerations
Diagnosis of HIT

- An abrupt decrease in platelet count in the absence of other etiologies, that does not result in thrombocytopenia, and unexplained thrombosis are also characteristics of HIT\(^1-3\)

- Symptoms typically appear 4 to 14 days after exposure to UFH or 8 to 14 days after exposure to LMWH\(^4-6\)

- Patients who received heparin within the prior 100 days can have an immediate, rapid-onset HIT when restarting UFH or LMWH\(^5,6\)

General Considerations

Diagnosis of HIT

- Delayed-onset HIT has been observed with symptoms appearing several days after discontinuation of UFH\(^1,2\)
- The diagnosis of HIT is difficult in patients after surgery, particularly after cardiac surgery\(^3-5\)
  - HIT should be suspected if the platelet count recovery in the immediate post-operative period is interrupted by a sudden and marked platelet count decrease 5-10 days post-operation
  - HIT cannot be definitely excluded in patients with a monophasic pattern of persistent post-operative thrombocytopenia

General Considerations

Diagnosis of HIT

- A clinical presentation of HIT that can be challenging is the patient with only mild thrombocytopenia receiving heparin or LMWH
- These patients are to be individually assessed for their risk of having HIT
- The level of risk will determine whether or not to continue heparin/LMWH treatment while laboratory testing is sent to confirm the diagnosis
- Clinical scoring systems are available and continue to be developed to assist in the diagnosis of HIT\textsuperscript{1-4}

General Considerations

Diagnosis of HIT

- Clinical diagnosis of HIT should be confirmed by a laboratory assay that detects heparin-dependent antibodies
- Pathologic HIT immune complexes are composed of the PF4-heparin complex bound to an immunoglobulin G (IgG)
- These complexes bind to platelet FcγIIa receptors (CD32), inducing platelet activation, aggregation, and generation of platelet microparticles

General Considerations

Diagnosis of HIT

- IgA and IgM have also been identified in HIT patients\(^{49}\)
- HIT antibodies provoke leukocyte and endothelial cell activation that augment both the hypercoagulable and inflammatory states\(^{1-7}\)
- The combined cellular activation leads to a burst of thrombin generation\(^{8}\)
- Of all patients at risk of thrombosis, those with HIT are at highest risk (>30%)\(^{9}\)

General Considerations
Diagnosis of HIT

- Non-drug factors also influence the risk of developing HIT and related clinical outcomes\(^1-4\)
  - Type of surgery, severity of trauma, severity of thrombocytopenia, renal impairment, low cardiac output, and timing of first anticoagulant dose

- The association of HIT antibodies, in the absence of thrombocytopenia and thrombosis, with future cardiovascular and other thrombotic events has been reported and remains under investigation\(^5\)

General Considerations
Diagnosis of HIT

- Two types of laboratory assays that detect heparin-dependent antibodies:\(^1-4\)
  - Platelet function tests (serotonin release and platelet aggregation assays)
  - Immunoassays that detect antibodies to the PF4-heparin complex

- Each test has particular performance characteristics, and provides unique information\(^5-7\)

General Considerations

Diagnosis of HIT

- Platelet function assays that use washed platelets have a better sensitivity than plasma-based assays, but false negative results can still be obtained.
- Immunoassays have a high rate of positive results that are not always associated with clinical HIT\(^1\)\(^-\)\(^4\)
- For immunoassays:\(^5\)\(^-\)\(^10\)
  - The option to report the titre results and utilizing the high heparin concentration confirmatory step are gaining favor as these provide a closer correlation to the risk of thrombosis and mortality in patients with HIT

General Considerations
Direct Thrombin Inhibitors

- Clinical trials and experience have shown that argatroban and lepirudin to be safe and effective for reducing the risk of thrombosis and associated morbidity/mortality in patients with HIT\(^1-9\)
- These drugs do not cross-react with HIT antibodies
- Development of antibodies to lepirudin has been observed in approximately 50% of patients after 10 days of treatment\(^10,11\)

General Considerations
Direct Thrombin Inhibitors

- Dose adjustments for argatroban in specific populations and for lepirudin in general have been recently recommended\(^1\)-\(^6\)
- Desirudin, with the advantage of SQ dosing, has been successfully used in a limited number of patients with HIT\(^7,8\)

General Considerations

Direct Thrombin Inhibitors

• Bivalirudin, with a short half-life and enzymatic degradation, has been used for anticoagulation of HIT patients during cardiac surgery\(^1\)\(^-\)\(^3\)

• DTIs have also been used successfully in HIT patients requiring invasive cardiac procedures\(^4\)\(^-\)\(^6\)

• DTIs should be treated as individual drugs as each has its own pharmacologic characteristics

General Considerations

- Danaparoid, a heparinoid, has been used to treat HIT patients with success (Grade B) but there are reports that danaparoid cross-reacts with some HIT antibodies leading to treatment failures\(^1-^7\).
- Fondaparinux, a pentasaccharide, has shown to be useful for the management of patients with HIT through several small published case series\(^8-^11\).
- LMWH can cross-react with most HIT antibodies and is contraindicated for use in patients with HIT\(^12-^14\).

General Considerations

- Vitamin K antagonists (VKAs) are recommended for long-term treatment of HIT associated thrombosis\(^1\)
- VKAs are not recommended for use in the acute phase of HIT due to their potential to intensify the prothrombotic state from a transient protein C deficiency\(^2,3\)
- VKAs should be initiated when platelet counts have normalized to a steady state then brought on under bridging with a DTI\(^4-6\)

There is emerging evidence that the newly developed small molecule anticoagulants including apixaban, dabigatran, edoxaban, otamixaban, and rivaroxaban may become new immediate and long-term treatment options for thrombosis in patients with HIT.

Recommendations
Heparin-Induced Thrombocytopenia

- For the first 14 days of treatment, platelet counts should be performed every 2-3 days in patients treated with LMWH and daily if treated with UFH, if the patient’s risk of developing HIT is high
  - Level of evidence: Moderate

- Laboratory testing should be performed when there is a strong suspicion of HIT
  - Level of evidence: Moderate

- UFH and LMWH should be stopped when the diagnosis of HIT is strongly suspected or confirmed
  - Level of evidence: High
Recommendations
Heparin-Induced Thrombocytopenia

- Due to the strong hypercoagulable state and high risk of thrombosis associated with HIT, it is recommended that all HIT patients be treated with a non-heparin anticoagulant such as argatroban, lepirudin, or danaparoid
  - Level of evidence: Moderate

- Fondaparinux may be considered as a second-line agent in the management of patients with suspected HIT
  - Level of evidence: Low

- LMWH is contraindicated in patients with HIT
  - Level of evidence: Moderate
Recommendations
Heparin-Induced Thrombocytopenia

- For long-term anticoagulation, a VKA can be used. To avoid warfarin-induced limb gangrene/skin necrosis in patients with HIT, the VKA should only be administered after rise of platelet counts with substantial recovery to >100 x 10^9/L or to pre-HIT values
  - Level of evidence: Low

- For HIT patients undergoing coronary artery interventional procedures, bivalirudin or argatroban anticoagulation is recommended
  - Level of evidence: Moderate