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1. DEFINITION

Heparin-induced thrombocytopenia (HIT) is a drug-induced immune-mediated syndrome characterized by thrombocytopenia and thrombotic events that may be life- or limb threatening. HIT occurs in up to 5% of certain types of patients receiving unfractionated heparin (e.g., postoperative orthopedic patients), and less than 1% of patients receiving low-molecular weight heparin.

The diagnosis of HIT is based on three criteria: 1. The patient is currently receiving or has had recent exposure to heparin, 2. the presence of at least one clinical feature of the syndrome (usually thrombocytopenia with or without thrombosis), and 3. laboratory evidence of HIT antibodies.

HIT must be distinguished from other causes of thrombocytopenia.

2. PATHOGENESIS OF HIT

HIT is caused by antibodies (HIT-Ig) that generally recognize a target antigen complex of platelet factor 4 (PF4) and heparin. The resulting antibody/antigen complexes activate platelets, generating procoagulant platelet-derived microparticles, and activate endothelial cells and monocytes. These diverse effects likely explain the thrombocytopenia and thrombotic events observed in HIT.

3. CLINICAL FEATURES OF HIT

HIT typically presents with a fall in platelet count with or without thrombosis.

a. Thrombocytopenia. A platelet count fall of greater than 50%, or an absolute thrombocytopenia, beginning 5 to 10 days after heparin exposure in the absence of other causes of thrombocytopenia should be considered to be HIT, unless proven otherwise. HIT can also present with a more rapid fall of the platelet count soon after starting heparin in patients who have had previous exposure to heparin, usually within the preceding 100 days. The severity of thrombocytopenia in HIT is usually moderate: most patients have a platelet count between 30-100 x 10⁹/L, with only 20% having a platelet count of 30 x 10⁹/L or less. In about 20% of patients, the platelet count never falls below 100 x 10⁹/L.

Despite thrombocytopenia that can occasionally be severe, bleeding complications are infrequent in HIT.

b. Thrombosis. Paradoxically, patients with HIT are at higher risk of thrombosis than bleeding, even when thrombocytopenia is severe. HIT is associated with a high risk (30 to 50%) of new thrombosis or extension of existing thrombosis. Thrombosis may be the presenting clinical manifestation of HIT and can occur during the period of thrombocytopenia or several days after platelet count recovery, even despite discontinuation of heparin. Most thrombotic events are venous, although both venous and arterial thrombotic events can occur. Thrombotic events typically include deep vein thrombosis, pulmonary embolism, limb arterial thrombosis, venous limb gangrene, thrombotic stroke, and myocardial infarction; however, thromboses in unusual locations can also occur.

HIT should be considered in the differential diagnosis of patients with new or recurrent venous or arterial thromboembolism that develops during or shortly after exposure to heparin.

c. Other clinical manifestations of HIT. Less frequently observed manifestations of HIT include heparin-induced skin lesions, adrenal hemorrhagic infarction, and acute systemic reactions (e.g., chills, dyspnea, cardiac or respiratory arrest following intravenous heparin bolus therapy).

4. LABORATORY TESTING

Therapeutic decisions should not be delayed for the results of laboratory testing if the clinical suspicion of HIT is strong. Serum should be sent for HIT-Ig testing using a sensitive and specific functional assay (e.g., the platelet serotonin release assay), or antigen assay (e.g., PF4/heparin ELISA).

5. MANAGEMENT OF PATIENTS WITH HIT

There are few prospective randomized studies on which to base recommendations regarding the management of HIT. Patients with HIT are best managed by, or in consultation with, a specialist experienced in managing HIT.

a. All heparin should be discontinued in patients with HIT or suspected HIT. This includes unfractionated and low-molecular weight heparins by any route, heparin flushes, and vascular catheters that are heparin-coated.

b. In patients with HIT or suspected HIT, with or without thrombosis, anticoagulation with an alternative non-heparin anticoagulant (danaparoid, lepirudin, or argatroban, listed in historical order of availability) is recommended (see #6. Anticoagulants for HIT).

c. Warfarin should be avoided in acute HIT unless it is used in combination with therapeutic-dose danaparoid, lepirudin, or argatroban. Warfarin has been associated with worsening venous thrombosis, venous limb gangrene, and/or skin necrosis when used alone or in combination with ancrod in acute HIT. However, warfarin is appropriate for longer term anticoagulation in patients with HIT and thrombosis. Warfarin should be delayed until therapeutic anticoagulation with danaparoid, lepirudin or danaparoid is achieved, and ideally, until there is substantial resolution of the thrombocytopenia. Warfarin-associated thrombotic complications have been described in patients in whom the alternative anticoagulant was stopped prior to resolution of thrombocytopenia. The optimal duration of anticoagulation in patients with HIT with or without thrombosis is not known.

d. Surgical thromboembolectomy, or systemic/local thrombolysis may be appropriate for selected patients with large vessel arterial thromboembolism or severe pulmonary embolism, respectively.

e. Low-molecular-weight heparin (LMWH) should not be used in patients with HIT. LMWH is associated with treatment failure in several reports, and on occasion, has been associated with disastrous complications in patients with HIT.

f. Prophylactic platelet transfusions are not recommended in HIT. This is because petechiae and other clinical evidence for thrombocytopenic bleeding is uncommon in HIT. In addition, thrombotic events occurring soon after the transfusion of platelets have been reported. However, platelet transfusion can be justified in thrombocytopenic patients who develop serious hemorrhagic complications.

g. Unfractionated and LMWH should be avoided in patients with a previous history of HIT. Under special circumstances, exceptions to this recommendation may be considered. For example, use of unfractionated heparin for cardiac surgery is an appropriate option for a patient with previous HIT in whom HIT antibodies are no longer detectable by sensitive and specific laboratory assay(s).

h. Although there are promising reports describing the use of fondaparinux and bivalirudin for the treatment of HIT, the safety and efficacy of these agents in patients with HIT has not yet been established.

6. ANTICOAGULANTS FOR HIT

a. Danaparoid. Danaparoid is a heparinoid that inhibits factor Xa, and to a lesser extent, inhibits thrombin. It is renally excreted and there is no specific antidote. The anti-Xa half-life in plasma is approximately 25 hours. In patients with significant renal failure, the half-life is prolonged and dosage reduction is recommended. Clinically significant cross-reactivity with the HIT antibodies has been reported, but appears to be uncommon. Patients should be monitored for unexplained platelet count fall, and new, progressive or recurrent thromboembolism. Dosing regimens for therapeutic anticoagulation and prophylaxis in adult patients with normal renal function are shown below. There is evidence that therapeutic-dose danaparoid may be more appropriate for treating most patients with HIT than prophylactic-dose danaparoid, even when the indication for anticoagulation is prevention of thrombosis in a patient with isolated HIT.

Clinical Guide - Heparin-Induced Thrombocytopenia

Clinical indication	Danaparoid dosing schedule
Treatment of thromboembolism in patients with acute HIT or a prior history of HIT	IV route: 2250 units IV bolus*, then 400 units/h x 4 h, then 300 units/h x 4 h, then 150 to 200 units/h by continuous IV infusion for at least 5 days. Aim for a plasma danaparoid level of 0.5-0.8 anti-Xa units/mL (using danaparoid standards). SC route: 2250 units IV bolus*, then 1500 to 2250 units SC every 12 h.
Prophylaxis of thromboembolism in patients with acute HIT and isolated thrombocytopenia	Strongly consider treatment doses (as described above).¶
Prophylaxis for venous thromboembolism in patients with prior HIT	750 units SC every 8-12 h.
*Adjust danaparoid bolus for body weight: < 60 kg, 1500 units; 60-75 kg, 2250 units; 75-90 kg, 3000 units; > 90 kg, 3750 units. ¶There is evidence suggesting that 750 units SC every 8-12 h may be suboptimal for prophylaxis of thromboembolism in patients with acute HIT and isolated thrombocytopenia.	

b. Lepirudin (recombinant hirudin). Hirudin is a direct thrombin inhibitor that is produced by the salivary glands of the medicinal leech. Lepirudin is a recombinant hirudin that has a structure that is almost identical to the natural leech-derived protein. Lepirudin is eliminated renally, and has a half-life of approximately 1.3 hours. In patients with renal failure, the half-life is greatly prolonged and substantial dosage reduction is recommended. There is no known antidote. Rare cases of anaphylaxis have been associated with IV bolus infusion of lepirudin, occurring in patients with and without previous exposure to lepirudin. Monitoring of therapeutic-dose lepirudin by activated partial thromboplastin time (aPTT) is required. Dosages for adult patients (up to 100 kg) with normal renal function are shown below.

Clinical indication	Lepirudin dosing schedule
Treatment of thromboembolism in patients with acute HIT or a prior history of HIT	0.4 mg/kg IV bolus, then 0.15 mg/kg/hr by continuous IV infusion. Target aPTT ratio: 1.5 to 2.5.*
Prophylaxis of thromboembolism in patients with acute HIT and isolated thrombocytopenia	0.10 mg/kg/hr by continuous IV infusion. Target aPTT ratio for continuous IV infusion: 1.5. to 2.0.*
Prophylaxis of venous thromboembolism in patients with prior history of HIT	15 mg SC twice daily.
*The aPTT should be measured 4-6 h after initiation of IV infusion or any dose adjustment, and at least daily if the aPTT is within the therapeutic range.	

c. Argatroban. Argatroban is a synthetic, small-molecule direct thrombin inhibitor with an even shorter half-life (40-50 min.) than lepirudin. In further contrast to lepirudin, argatroban is excreted normally in patients with renal insufficiency; however, the dose of argatroban must be reduced in patients with hepatic failure. Like lepirudin, argatroban is usually monitored using the aPTT. Concurrent use of argatroban and warfarin increases the INR beyond that produced by warfarin alone. A guideline for the transition to warfarin monotherapy can be found in the product monograph. Dosages for adult patients with normal hepatic function are shown below.

Clinical indication	Argatroban dosing schedule
Treatment of thromboembolism in patients with acute HIT or a prior history of HIT	2 µg/kg/min by continuous IV infusion (not to exceed 10 µg/kg/min). Target aPTT ratio: 1.5 to 3.0 (not to exceed 100 seconds).*
Prophylaxis of thromboembolism in patients with acute HIT and isolated thrombocytopenia	2 µg/kg/min by continuous IV infusion (not to exceed 10 µg/kg/min). Target aPTT ratio: 1.5 to 3.0 (not to exceed 100 seconds).*
*The aPTT should be measured 2 h after initiation of argatroban or any dose adjustment, and at least daily if aPTT is within therapeutic range.	

7. REFERENCES

1. Warkentin TE, Greinacher A, eds. Heparin-Induced Thrombocytopenia, Third Edition. New York: Marcel Dekker Inc., 2004.
2. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:311S-337S.