

Management of Immunogenic Heparin-induced Thrombocytopenia

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ABSTRACT

Immunogenic heparin-induced thrombocytopenia (HIT) is an immune response to heparin associated with significant morbidity and mortality in hospitalized patients if unidentified as soon as possible, due to thromboembolic complications involving both arterial and venous systems. Early diagnoses based on a comprehensive interpretation of clinical and laboratory information improve clinical outcomes. Management principles of strongly suspected HIT should not be delayed for laboratory result confirmation. Treatment strategies have been introduced including new, safe, and effective agents. This review summarizes the clinical therapeutic options for HIT addressing the use of parenteral direct thrombin inhibitors and indirect factor Xa inhibitors as well as the potential non-Vitamin K antagonist oral anticoagulants.

Key words: Heparin-induced thrombocytopenia, heparin, low molecular weight heparin

INTRODUCTION

Unfractionated heparin (UFH) or related molecules such as low-molecular-weight heparin (LMWH) are widely used in both outpatient and inpatient settings for many thromboembolic events. Paradoxically, patients exposed to UFH or LMWH are at risk for thrombotic complications that may include deep vein thrombosis, pulmonary embolism, myocardial infarction, thrombotic stroke, cerebral vein thrombosis, and disseminated intravascular coagulation. These thrombotic complications are due to a serious adverse reaction called immunogenic heparin-induced thrombocytopenia (HIT).^[1-5]

HIT is defined as a drop in platelet count during or after heparin administration.^[4-6] The non-immune heparin-associated thrombocytopenia, traditionally called type I HIT, is mediated by direct interaction between heparin and circulating platelets, causing platelet clumping or sequestration. Heparin-associated thrombocytopenia is a

self-limiting thrombocytopenia that affects 10% of patients receiving heparin formulations, usually develops within the first 72 h after heparin administration, and platelet counts do not drop below 100,000/mm³; it often normalizes once the heparin is ceased.^[7,8] The immune-mediated HIT, known as HIT Type II,^[8-10] is a prothrombotic and potentially lethal disorder caused by platelet, endothelial, and monocyte-activating antibodies that target multimolecular complexes of platelet factor 4 (PF4) and heparin.^[11] The immune-mediated HIT is reported count begins to fall between 5 and 10 days after the initiation heparin formulation.^[4,5,12-14]

The devastating clinical consequences of the immune-mediated HIT, which may include amputation and death, should alert clinicians to identify patients with HIT and those with increased risk of the development of immune-mediated HIT as soon as possible to initiate early management and prevent serious complications. For the purpose of this review, the term HIT refers to the immune-mediated Type II that causes paradoxical thromboemboli.

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RISK FACTORS

Exposure to heparin is the main risk factor and a critical step in the development of HIT [Table 1]. A heparin source such as bovine lung is more immunogenic than those produced from porcine intestine,^[15] and the risk of HIT rises with the length and volume of exposure to heparin as well as the route of administration^[16] and more likely with intravenous heparin than subcutaneous administration.^[17-19] Nevertheless, HIT can develop from any heparin exposure, including incidental amounts from heparin flushes or heparin-coated devices.^[20,21] Although HIT is more common in patients receiving UFH than in those treated with LMWH.

LABORATORY AND CLINICAL ASSESSMENT

HIT may occur rapidly or with a delayed onset, depending on the presence of heparin-PF4 antibodies from a previous administration and sensitization of heparin and related molecules may induce rapid-onset HIT.^[22] In patients exposed to heparin for the 1st time, the onset of HIT may occur 5–10 days after receiving heparin.^[4,5,12,23] The thrombocytopenia in HIT is usually moderate in severity, with a median platelet count being between 50 and 80 $10^9/L$, although the nadir platelet count can remain at a level considered normal (i.e., $>150 \times 10^9/L$) but having dropped by 50%. The immunoassays (enzyme-linked immunosorbent assay) are very sensitive to detect the HIT antibody that binds to the PF4/heparin complex. However, not all antibodies detected (immunoglobulin [Ig] G, IgM, and IgA) are capable to induce clinical HIT. Immunoassays are both technically easier to perform and more sensitive than functional assays. On the other hand, functional assays are more specific and better in the diagnosis of clinical HIT.^[1,24]

PLATELET MONITORING

Platelet count monitoring should be started as baseline measurement before heparin administration, whereas routine

monitoring is recommended for most patients receiving heparin formulation based on stratified incidence of HIT according to patient's population and type of heparin exposure [Table 2].^[3,4]

MANAGEMENT OF IMMUNOGENIC HIT

Initially, a clinician should apply the 4Ts (thrombocytopenia, timing of platelet count fall, thrombosis, and other cause of thrombocytopenia) scoring system to identify patients who are at high, intermediate, or low risk of developing HIT [Table 3].

NON-HEPARIN ANTICOAGULANT

Direct thrombin inhibitors and indirect factor Xa inhibitors are two anticoagulant classes that were used in the treatment of HIT with or without thrombosis [Table 4]. The clinical presentation of the patient, availability of the drugs, and clinician experience should dictate the choice of therapy.

CONCLUSION AND RELEVANCE

The diagnosis of HIT requires clinical evaluation and laboratory confirmation. Platelet count monitoring should perform every 2 or 3 days in patient population with a risk of HIT $>1\%$. When HIT is strongly suspected, management should include immediate discontinuation of all heparin formulations and the start of alternative, non-heparin anticoagulants. Vitamin K antagonist (VKA) should not be given. Instead, if VKA was given, reverse elevated international normalized ratio by administering Vitamin K and avoid platelet transfusions. A serotonin release assay may be performed for HIT antibody detection; however, if such a test was not available, enzyme-linked immunosorbent assay would be sufficient to confirm the diagnosis. Doppler ultrasonography of the upper and lower limbs and computed tomography of the chest should be performed when clinically

Table 1: Factors contributing to the development of heparin-induced thrombocytopenia

Risk category	Immunogenicity value (immunogenic effects)
Heparin source	Bovine higher than porcine
Heparin type	UFH more than LMWH
Volume of heparin dose	Therapeutic dose > prophylactic > flush or heparin-coated devices
Heparin exposure	
First exposure	Platelet fall day 5–10 after heparin initiation
Previous exposure (within 90 days)	Platelet fall within 1 day after heparin initiation
Patient population	Post-operative more than medical more than obstetric
Patient gender	Female more than male

LMWH: Low-molecular-weight heparin, UFH: Unfractionated heparin

Table 2: Platelet count monitoring guideline for HIT

Population	Scenario	Monitoring of platelet count
Recent heparin exposure	Patient starting UFH and LMWH and who received UFH within the previous 100 days; patients whose heparin exposure history is unknown	Obtain baseline platelet count and repeat platelet count within 24 h of starting heparin
Acute, systematic reactions after intravenous UFH bolus	Patients with acute inflammatory, cardiorespiratory, neurologic, or other unusual symptoms and signs within 30 min after an intravenous UFH bolus.	Obtain platelet count immediately to compare with recent prior platelet counts
Risk* of HIT >1%	Patients receiving UFH and LMWH at therapeutic doses Post-operative patient receiving UFH/LMWH antithrombotic prophylaxis	Obtain baseline then at least every 2 or 3 days until day 14 of treatment or until heparin is stopped, whichever occurs first Baseline then at least every 2 or 3 days between post-operative days 4 and 14 or until heparin is stopped, whichever occurs first
Risk of HIT <1%	Medical/obstetric patients receiving prophylactic dose UFH, or LMWH after receiving UFH, post-operative patients receiving prophylactic dose LMWH, or intravascular catheter UFH flushes	As clinically indicated (no routine monitoring)

LMWH: Low-molecular -weight heparin, UFH: Unfractionated heparin, *Risk stratification is based on the overall incidence of HIT in different patient population

Table 3: The pretest probability of HIT: 4Ts scoring system*

Clinical feature	Score=2	Score=1	Score=0
Thrombocytopenia: Compare the highest platelet count within the sequence of (declining platelet counts with the lowest count to determine the percentage of platelet fall (select only one option)	>50% platelet fall and nadir of ≥ 20 and no surgery within preceding 3 days	>50% platelet fall but surgery within preceding 3 days; any combination of platelet fall and nadir that does not fit criteria for score of 2 or 0 (e.g., 30%–50% platelet fall or nadir 10–19)	<30% platelet fall; Any platelet fall with nadir <10
Timing (of platelet count fall or thrombosis*): Day 0=first day of most recent heparin exposure (select only one option)	Platelet fall 5–10 days after start of heparin Platelet fall within 1 day of start of heparin and exposure of heparin with the past 5–30 days	Consistent with platelet fall days 5–10 but not clear (e.g., missing counts) Platelet fall within 1 day of start of heparin and exposure to heparin in the past 31–100 days platelet fall after day 10	Platelet fall \geq day 4 without exposure to heparin in the past 100 days
Thrombosis (or other clinical sequelae; Select only one option)	Confirmed new thrombosis (venous or arterial) Skin necrosis at injection site Anaphylactoid reaction to IV heparin bolus Adrenal hemorrhage	Recurrent venous Thrombosis in a patient receiving therapeutic anticoagulants Suspected thrombosis (awaiting confirmation with imaging) Erythematous skin lesions at heparin injection sites	Thrombosis suspected
Other causes of thrombocytopenia (select only one option)	No alternative explanation for platelet fall is evident	Possible another cause is evident: Sepsis without proven microbial source Thrombocytopenia associated with initiation of ventilator Other	Probable another cause present: Within 72 h of surgery Confirmed bacteremia/ fungemia Chemotherapy or radiation within the past 20 days DIC due to non-HIT cause other

DIC: Disseminated intravascular coagulation, HIT: Heparin-induced thrombocytopenia, IV: Intravenous, *Upon adding the score, the patient is stratified into low (0–3 points), intermediate (4–5 points), or high (6–8 points) risk for having HIT. Table adapted with permission from Linkins *et al.*^[4]

Table 4: Dosing and monitoring guidelines for the parenteral treatment options of HIT

Agent	Mode of action	Normal dose	Dose adjustment	Monitoring	FDA/ACCP Approval/ Recommendation for HIF
Argatroban	Direct thrombin inhibition	2 µg/kg/min IV	CKD: No change HF: 0.5 µg/kg/min	aPTT 1.5–3xbaseline (not to exceed 100 s)	DA: Yes ACCP: 2C
Desirudin	Direct thrombin inhibitor	15–30 mg SC every 12 h	CKD: CL _{CR} <60 mL/min: Adjustment needed HF: No change	None needed	FDA: No ACCP: 2C
Bivalirudin	Direct thrombin inhibitor	0.15–0.20 mg/kg/h IV	CKD: CL _{CR} 10–29 mL/min: 0.06 mL/kg/h IV; CL _{CR} <10 mL/min: 0.015 mg/kg/h IV	aPTT 1.5–2.5xbaseline	FDA: Yes ACCP: C
Danaparoid	Indirect factor Xa inhibitor	400 U/h IV xh then 300 U/h IV x4 h then 200 U/h IV	Not studied in patients with severe renal failure	Antifactor Xa level 0.5–0.8 U/mL	FDA: Yes ACCP: 2C
Fondaparinux	Indirect factor Xa inhibitor	<50 kg: 5mg SQ: 50–100 kg: 7.5 mg SQ: >100 kg: 10 mg SQ	CKD: CL _{CR} 30–50 mg/min: Use caution: CL _{CR} <30 mL min: contraindicated	None needed	FDA: Yes ACCP: 2C

ACCP: American college of chest physician, aPTT: Activated partial thromboplastin time, CKD: Chronic kidney disease, CL_{CR}: Creatinine clearance, FDA: Food and drug administration, HIT: Heparin-induced thrombocytopenia, HF: Hepatic failure

indicated. At present, two parenteral therapeutic approaches are available to treat HIT with or without thrombosis: (a) Direct thrombin inhibitors or (b) indirect Xa inhibitors. The third potential option for the treatment of HIT is using NOACs. Unfortunately, all of the available anticoagulation agents used to treat HIT are associated with hemorrhage and none of these drugs has an antidote for rapid reversal. Adequate hydration and early mobilization are supportive measures may utilized in the prevention of thrombotic complication. It is our recommendation and conviction that research should continue to identify new therapeutic agents offering effective and safe non-heparin alternatives for the management of patients with HIT.

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