**HEPARI N INDUCED THROMBOCYTOPENIA**

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**BACKGROUND**

Heparin-induced thrombocytopenia (HIT) occurs in two major forms — Type I, which is non-immunologic and associated with mild transient thrombocytopenia, and Type II, caused by an immunologic reaction that induces a declining platelet count and an intense prothrombotic state. Type II HIT, the focus of the reminder of this review, will henceforth be referred to as simply “HIT.”

HIT more commonly occurs in association with unfractionated heparin (UFH; 1-5% incidence) than with low molecular weight heparin (LMWH; 0.1-1% incidence), and is more frequent among surgical patients (1-5%) than medical patients (0.8-3%).

**PATHOPHYSIOLOGY**

Released during platelet activation, Platelet Factor 4 (PF4) forms complexes with UFH or LMWH on the surface of platelets. In some individuals the resultant neoantigen becomes the target of a pathologic IgG antibody (HIT-Ab). This induces the formation of a Heparin-PF4-HIT-Ab immune complex that attaches to Fc IIa receptors on the platelet membrane, resulting in platelet activation and elaboration of platelet microparticles. In such instances the presence of warfarin, which leads to decreased production of Protein C, can exacerbate the HIT-hypercoagulable state.

**CLINICAL FEATURES AND DIAGNOSIS**

Thromboembolic complications occur in 50-75% of affected individuals and involve the venous more commonly than the arterial vasculature. Events may include deep venous thrombosis (DVT), pulmonary embolism (PE), catheter-related thrombosis, limb ischemia, stroke, myocardial infarction, cerebral venous sinus thrombosis, adrenal vein thrombosis, warfarin-induced limb gangrene plus skin necrosis, and necrotic skin lesions at sites of heparin injection. Such complications can be accentuated by continued administration of heparin.

The diagnosis of HIT should be considered when platelet counts decline in proximity to UFH/LMWH exposure. Variations of HIT include: (1) "rapid onset HIT" (platelet decline less than 4 days after initiation of heparin; median of 10.5 hours – up to 30% of cases), (2) “classic HIT” (platelet decline 4 to 14 days after initiation of heparin – at least 65% of cases), and (3) “delayed onset HIT” (platelet decline 9-14 days after discontinuation of heparin – 2-3% of cases). Of key utility to clinicians is what is referred to as the “4T’s” scoring system – see Table – in which a score ≤ 3 denotes a high negative predictive value for HIT (0.998; 95% CI, 0.97-1.00), whereas a score of 6-8 indicates a high probability that HIT is present. Interestingly, despite the reduced platelet counts associated with HIT, bleeding manifestations are rare, and some experts suggest the presence of bleeding supports a non-HIT etiology for the thrombocytopenia.

Testing for HIT involves selection of either a serologic (i.e., PF4-dependent EIA) or functional platelet assay (i.e., C Serotonin Release Assay, SRA, believed to be the “gold standard”). For most facilities, the SRA is a send-out test. The degree of PF4-dependent EIA (i.e., PF4/heparin or PF4/polyvinyl sulfonate) reactivity — reported in optical density (OD) units — is predictive for SRA reactivity. With weakly positive EIA results (e.g., 0.40-1.40 OD units) there is a low probability (≤ 5%) for a strong-positive SRA result. At OD values of > 1.40 and ≥ 2.00, the probability for a positive SRA increases to 50% and 90%, respectively. A negative PF4-dependent EIA virtually excludes the diagnosis of HIT.

**TREATMENT AND MANAGEMENT DECISIONS**

Treatment is initiated when the clinical likelihood is intermediate to high (i.e., a 4T’s score of ≥ 4 – see Table) and should not be delayed while awaiting test results. All sources of UFH/LMWH exposure (including line flushes, dialysis

(continued on next page)
Heparin Induced Thrombocytopenia 2

Anticoagulant due to the high residual risk for stopped and treatment must be initiated with a non-heparin catheter lock solutions, and DVT prophylaxis) must be to 2.5 the patient’s baseline level.11 Other treatment options include danaparoid (where available), bivalirudin (particularly in cardiac surgery), and fondaparinux. Treatment is continued until the platelet count has reached a stable plateau, ideally ≥ 150,000/μL. Most patients will be transitioned to warfarin at this time with a period of five days of overlapping therapy being recommended. A hematology consultation should be considered during this transition phase.

Two case series have failed to demonstrate a link between platelet transfusions and thromboembolic complications in patients with HIT, though data are insufficient to conclude absolute safety.15,16 Lastly, the reader is encouraged to review other excellent references with regard to the management of patients who have recovered from HIT and who once again require anticoagulation.11,14

CONCLUSION

HIT represents a drug-induced thrombocytopenia marked by reductions in the platelet count and initiation of an intense thrombophilic state. Patients may be diagnosed clinically using the 4T’s scoring system; HIT EIA and SRA testing provide additional diagnostic support. Treatment is initiated using an appropriate, alternative anticoagulant and maintained until the platelet count has normalized.

References

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Table: The 4 T’s Method for Estimating – Prior to Immunologic Testing – the Probability for HIT: Up to two points are assigned to each of the four categories listed below and these scores are then totaled. Low, Intermediate, and High probabilities for HIT correspond to scores of 1-3, 4-5, and 6-8, respectively.10

<table>
<thead>
<tr>
<th>Category</th>
<th>Score = 2 Points</th>
<th>Score = 1 Point</th>
<th>Score = 0 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of thrombocytopenia</td>
<td>≥ 50% decrease in platelet count to nadir ≥ 20,000/μL</td>
<td>30-50% decrease in platelet count OR nadir of 10,000-19,000/μL</td>
<td>&lt; 30% in platelet count OR nadir &lt; 10,000/μL</td>
</tr>
<tr>
<td>Timing of thrombocytopenia following first heparin dose</td>
<td>Clear onset during Days 5-10 OR within 1 day in patient given heparin during past 30 days</td>
<td>Possible onset during Days 5-10 but not certain (e.g., missing platelet count data) OR onset after Day 10 OR onset within 1 day in patient given heparin 31-100 days ago</td>
<td>Onset prior to Day 5 and no heparin exposure within past 100 days</td>
</tr>
<tr>
<td>Evidence of thrombosis or other problems</td>
<td>New confirmed thrombosis, skin necrosis, AND/OR systemic reaction associated with IV bolus of UFH</td>
<td>Progressive or recurrent thrombosis, non-necrotic skin lesions, AND/OR suspected (but unproven) thrombosis</td>
<td>None</td>
</tr>
<tr>
<td>Existence of other possible causes for thrombocytopenia</td>
<td>No other apparent cause</td>
<td>Possible alternate cause</td>
<td>Definite alternate cause</td>
</tr>
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</table>

* Determined from peak platelet count following initiation of heparin therapy.