Heparin-induced thrombocytopenia: when a low platelet count is a mandate for anticoagulation

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Heparin-induced thrombocytopenia (HIT) is an immune-mediated disorder caused by the development of antibodies to platelet factor 4 (PF4) and heparin. The thrombocytopenia is typically moderate, with a median platelet count nadir of ~50 to 60 × 10^9 platelets/L. Severe thrombocytopenia has been described in patients with HIT, and in these patients antibody levels are high and severe clinical outcomes have been reported (eg, disseminated intravascular coagulation with microvascular thrombosis). The timing of the thrombocytopenia in relation to the initiation of heparin therapy is critically important, with the platelet count beginning to drop within 5 to 10 days of starting heparin. A more rapid drop in the platelet count can occur in patients who have been recently exposed to heparin (within the preceding 3 months), due to preformed anti-heparin/PF4 antibodies. A delayed form of HIT has also been described that develops within days or weeks after the heparin has been discontinued. In contrast to other drug-induced thrombocytopenias, HIT is characterized by an increased risk for thromboembolic complications, primarily venous thromboembolism. Heparin and all heparin-containing products should be discontinued and an alternative, non-heparin anticoagulant initiated. Alternative agents that have been used effectively in patients with HIT include lepirudin, argatroban, bivalirudin, and danaparoid, although the last agent is not available in North America. Fondaparinux has been used in a small number of patients with HIT and generally appears to be safe. Warfarin therapy should not be initiated until the platelet count has recovered and the patient is systemically anticoagulated, and vitamin K should be administered to patients receiving warfarin at the time of diagnosis of HIT.

The development of thrombocytopenia or a new thrombus in a patient receiving heparin or a low-molecular weight heparin (LMWH) necessitates careful assessment for heparin-induced thrombocytopenia (HIT), an antibody-mediated complication of heparin therapy.[1] It is essential that HIT is accurately identified, since it is associated with a substantially increased thrombotic risk, and treatment includes stopping the heparin and initiating a therapy with a non-heparin anticoagulant such as a direct thrombin inhibitor. Incorrect diagnoses can lead to patients who need to be treated with an alternative anticoagulant not receiving appropriate therapy, while patients who do not have HIT potentially may receive inappropriate anticoagulation, contributing to an increased hemorrhagic risk.

Thrombocytopenia and Heparin

Thrombocytopenia occurs quite frequently in hospitalized patients receiving heparin, but not all patients receiving heparin who are thrombocytopenic will have HIT. Each patient needs to be carefully evaluated for other causes of thrombocytopenia, regardless of whether they clearly meet appropriate diagnostic criteria for HIT or not (**Table 1**). Common clinical settings in which thrombocytopenia and heparin therapy converge in the same patient include the intensive care unit, particularly those with devices such as an intra-aortic balloon pump or left-ventricular assist device; the post-operative setting, particularly individuals after cardiac bypass procedures; and in patients receiving hemodialysis or similar procedures. These patients are also frequently receiving multiple other medications that can cause thrombocytopenia, such as antibiotics and immunosuppressive agents. Furthermore, HIT can occur concomitantly with other potential causes of thrombocytopenia, including antiphospholipid syndrome and disseminated intravascular coagulation (DIC), which can further complicate the picture (**Table 1**).

A subset of patients will develop a transient, non-immune–mediated mild thrombocytopenia early in the course of

Table 1. Comparison of selected thrombocytopenic disorders that should be considered when evaluating a patient for heparin-induced thrombocytopenia (HIT). Common clinical manifestations focus on thrombotic versus hemorrhagic symptoms. Comments include relationships to other disorders and/or drugs that need to be considered. HIT has also been reported to occur concomitantly in patients with antiphospholipid syndrome or disseminated intravascular coagulation.

Disorder	Common clinical manifestations	Useful clinical laboratory analyses	Comments
Heparin-induced thrombocytopenia (HIT)	>50% present with thrombosis; venous thrombosis > arterial.	Anti-heparin/PF4 antibody testing (ELISA, functional assays).	Temporal relationship with heparin or LMWH therapy.
Antiphospholipid syndrome (APS)	Recurrent venous and/or arterial thromboembolic complications; recurrent fetal loss.	Anticardiolipin antibody and anti-β_2-glycoprotein I antibody testing (ELISA); lupus anticoagulant testing.	Autoimmune disorder, either primary or associated with other rheumatologic conditions (eg, lupus); in some cases, may be drug-induced (eg, procainamide).
Disseminated intravascular coagulation (DIC)	Hemorrhagic or thromboembolic events predominate, depending on underlying cause and clinical course.	PT, PTT, thrombin time, fibrinogen, D-dimer.	May be acute (eg, associated with sepsis, obstetric complications, severe trauma) or chronic (eg, associated with cancer, aortic aneurysm). DIC can complicate severe HIT.
Thrombotic thrombocytopenic purpura (TTP)	Neurologic manifestations may include stroke, TIA, altered mental status, seizures; other symptoms include fever, renal insufficiency.	Microangiopathic hemolytic changes on blood film, elevated LDH, decreased ADAMTS13 levels.	Associated with severe ADAMTS13 deficiency due to inhibitors in most patients; may be seen in patients taking ticlopidine or clopidogrel, or with other drugs, (eg, cyclosporine, tacrolimus, mitomycin). Microangiopathy can also be seen in severe HIT with associated DIC.
Drug-induced thrombocytopenia (non-heparin)	Petechiae, purpura, and other hemorrhagic symptoms with severe thrombocytopenia.	Isolated thrombocytopenia, may be severe.	Associated with multiple drugs (eg, abciximab, quinine, multiple antibiotics).
Post-transfusion purpura (PTP)	Hematoma, ecchymoses, purpura.	Severe thrombocytopenia that begins approximately five days after blood product use.	Temporal relationship to transfusion therapy; most common in multiparous females. The timing of PTP approximately one week after surgery can mimic HIT.

LMWH indicates low molecular weight heparin; DIC, disseminated intravascular coagulation; ELISA, enzyme-linked immunosorbent assay; TIA, transient ischemic attack; PT, prothrombin time; PTT, partial thromboplastin time; LDH, lactate dehydrogenase; ADAMTS13, a disintegrin and metalloproteinase with thrombospondin components-13.

heparin therapy, which will subsequently resolve as heparin is continued. This benign process, sometimes referred to as heparin-associated thrombocytopenia, is not associated with an increased risk for thromboembolic events and needs to be clinically distinguished from HIT. It is not a reason to stop heparin. A recent meta-analysis of thirteen randomized trials comparing unfractionated heparin to LMWH for the treatment of venous thromboembolism reported that the incidence of non-immune–mediated thrombocytopenia was similar for both treatments (LMWH, 1.2%; unfractionated heparin, 1.5%; $P = .246$).[2]

Pathophysiology of the Thrombocytopenia and the Hypercoagulable State in HIT

HIT is an idiosyncratic immune reaction characterized by the formation of antibodies that recognize complexes of platelet factor 4 (PF4) and heparin (unfractionated or low-molecular weight). PF4 is a CXC chemokine that binds to heparin and other negatively charged glycosaminoglycans with high affinity, in part because PF4 forms tetramers that have a circumferential belt of positively charged amino acids.[3] PF4 is synthesized during megakaryopoiesis and stored in platelet α-granules, and large amounts of PF4 are released during platelet activation.[4] Normally, PF4 released into the circulation will bind to negatively charged glycosaminoglycans on the surfaces of endothelial cells. In the presence of circulating heparin, however, PF4 appears to bind preferentially to heparin due to a higher affinity for heparin compared with cell surface glycosaminoglycans.[5]

Formation of complexes of PF4 and heparin leads to the exposure of neoepitopes, which results in the formation of the anti-heparin/PF4 antibodies that are identified in patients with the syndrome. Anti-heparin/PF4 IgG antibod-

ies bind to heparin/PF4 complexes in solution, and the resultant ternary complexes bind to platelets through FcγRIIa receptors expressed on the platelet surface.[6] Binding of antibody-antigen complexes to this receptor leads to increased platelet clearance, platelet activation, and release of procoagulant microparticles and additional PF4.[7] Anti-heparin/PF4 antibodies can also bind to platelet surface–bound PF4 in the absence of heparin and activate the platelets.[8] These complexes can also bind to Fc receptors on the surfaces of monocytes, neutrophils, and endothelial cells, which can further contribute to the profound thrombin generation seen in patients with HIT.[6,9] The development of a prothombotic state in the setting of a dropping platelet count is a relatively unique aspect of HIT that distinguishes it from other drug-induced thrombocytopenias.

Although the presence of these antibodies is essential for confirming the diagnosis of HIT, many patients who test positive for anti-heparin/PF4 antibodies do not develop thrombocytopenia or thrombosis. For example, as many as 50% of patients undergoing cardiac bypass surgery will develop anti-heparin/PF4 antibodies in the postoperative setting, but only a small number of these patients will develop clinical manifestations of HIT.[10,11] The clinical significance of these "non-pathogenic" anti-heparin/PF4 antibodies remains unclear, and the molecular basis that distinguishes them from "pathogenic" anti-heparin/PF4 antibodies is unknown.

In addition to the frequent development of non-pathogenic anti-heparin/PF4 antibodies, approximately half of the patients who meet criteria for HIT do not (at least initially, at the time of diagnosis) develop thromboembolic complications, referred to as "isolated HIT." Differences in the clinical phenotype of HIT may partially reflect the biophysical properties of the heparin/PF4 complexes formed in the presence of different circulating concentrations of PF4 occurring in different clinical settings.[12] Additional hypercoagulable factors, such as a central venous catheter or atherosclerotic disease, may also modulate the risk for vascular thrombosis. Anti-heparin/PF4 antibodies of IgM and IgA subclass have been described in patients with HIT, but it is unclear whether these antibody classes cause HIT in the absence of anti-heparin/PF4 IgG antibodies.

Diagnosis of HIT

The diagnosis of HIT can be challenging, given the frequency of administration of unfractionated heparin/LMWH,[13] the common occurrence of thrombocytopenia from other causes,[14] and the frequent convergence of these two phenomena in hospitalized patients.[15] This difficulty in establishing a diagnosis is further exacerbated by the lack of a readily accessible "gold-standard" laboratory test for the disease and the frequent detection of elevated anti-heparin/PF4 antibody levels in patients exposed to heparin who do not have clinical features of the disease.[1] Consequently, testing for anti-heparin/PF4 antibodies should be primarily reserved for evaluation of patients in whom there is reasonable suspicion of the syndrome based on clinical criteria.

Currently, HIT is diagnosed by a combination of clinical observations and laboratory results. Clinical criteria for the syndrome include the development of thrombocytopenia and/or thrombosis in temporal association with heparin therapy and the exclusion of other causes of thrombocytopenia. Thrombocytopenia is defined as an otherwise unexplained drop in the platelet count by 50% or more while on heparin, which occurs in the great majority of patients with HIT.[16] Typically, the thrombocytopenia is of moderate severity, with median platelet count nadirs of approximately 50 to 60×10^9 platelets/L.[7] It is atypical for a patient with HIT to have a platelet count less than 20×10^9 platelets/L, and alternative causes of thrombocytopenia should be considered in this situation. For those patients with HIT who do have profound thrombocytopenia, however, the clinical presentation can be rapidly progressive, including the development of DIC and microvascular thrombotic complications. HIT may also be recognized in patients with drops in the platelet count of less than 50% who present with thrombosis or skin lesions at heparin injection sites.[7]

Timing of the thrombocytopenia in relation to the initiation of heparin therapy is also critical for the diagnosis of HIT. Typically, the drop in the platelet count (or thrombotic event) begins 5 to 10 days after the initiation of heparin therapy in heparin-naïve individuals, although thrombocytopenic levels may not be reached until several days later.[17] For patients in the postoperative setting, the expected pattern would be for an initial rise in the platelet count after surgery, followed by an unexpected drop.[7] Persistent thrombocytopenia following cardiac bypass surgery is usually due to causes other than HIT (eg, postoperative complications); however, postoperative thrombocytopenia lasting for 5 days or longer, without an apparent alternative cause, is also suggestive of HIT.[18]

Thrombocytopenia can develop more quickly in patients who have been recently exposed to heparin (within the preceding 3 months, and especially within the past 30 days), referred to as "rapid-onset" HIT.[17,19] This presentation, which may occur in some 15% to 20% of patients diagnosed with HIT, represents the abrupt onset of platelet activation in a patient who has residual circulating anti-

heparin/PF4 antibodies related to recent prior exposure.[17] Conversely, some patients have been described who develop HIT days to weeks after heparin exposure, referred to as "delayed-onset" HIT.[20] Delayed-onset HIT may occur in patients exposed to minimal amounts of heparin (eg, heparin flushes to maintain intravascular catheter patency), but also occurs in patients exposed to large amounts of heparin during coronary artery bypass grafting.[21,22] These patients may present with a new thromboembolic event, and treatment with heparin results in a rapid fall in platelet count and either a new thromboembolic event or exacerbation of an existing clot. Heparin-dependent and -independent platelet activation has been demonstrated for these patients in laboratory analyses, suggesting that the anti-heparin/PF4 antibodies may be able to react with endogenous glycosaminoglycans on platelets or other cells, in these patients.[20]

About half of all patients with HIT present with a new thromboembolic complication related to the syndrome.[23,24] Of those patients presenting with thrombocytopenia only, referred to as "isolated HIT," almost half will subsequently develop a thromboembolic event.[23] Venous thromboembolism complicates HIT more often than arterial thromboembolic events, and pulmonary embolism is particularly common.[25] Arterial thrombosis most commonly involves the arteries of the lower limbs, with thrombotic strokes and myocardial infarction seen less frequently.[25] Rare but well-described thromboembolic events include cerebral sinus venous thrombosis and adrenal vein thrombosis, resulting in hemorrhagic infarction of the adrenal gland.[7]

Several diagnostic algorithms have been developed to provide a more systematic approach to the diagnosis of HIT. The "4Ts" score provides an estimate of pre-test probability for HIT by assigning scores based on the degree of Thrombocytopenia, the Timing of the fall in the platelet count or other sequelae, the presence of Thrombosis, and the exclusion of oTher causes of thrombocytopenia (**Table 2**).[7,26] This scoring system has been evaluated in two studies, both of which determined that a low score (ie, a score of 0-3) appeared to be a reliable strategy to rule out HIT.[27,28] A scoring system has also been reported for the diagnosis of HIT after cardiopulmonary bypass, which includes the pattern of the platelet count after surgery, the time from surgery, and the duration of time on cardiopulmonary bypass.[18] As with the "4Ts" method, the negative predictive value for this scoring system appeared to be most useful (97%).[18]

Laboratory testing is necessary to confirm or refute the diagnosis of HIT and is most appropriately used in patients assessed to be at intermediate or high clinical suspicion for HIT.[1] Because of the high frequency of elevated anti-heparin/PF4 antibody levels in certain patient populations (eg, after cardiopulmonary bypass surgery), testing should not be used to "screen" patients for HIT or evaluate patients assessed to have a low pre-test probability for HIT (ie, a low score in one of the diagnostic algorithms described above).[16] Laboratory studies for HIT include immunoassays and functional assays that detect platelet activation or aggregation. Most clinical laboratories offer an immunoassay due to the ease of performance, the rapid turnaround time, and the high sensitivity of the assays.[29] The primary limitation of the immunoassays, however, is their limited specificity (74% to 86%), due to the fact that they also detect anti-heparin/PF4 antibodies in patients who do not have clinical HIT.[30] Higher immunoassay results have been shown to correlate with strong-positive platelet serotonin-release assay results[31] and an increased risk for thrombosis

Table 2. Criteria for estimating pre-test probability of HIT using the "4 T'" score (from Warkentin[7] and Bryant et al[26]). The pre-test probability score would be high for a score of 6-8, intermediate for a score of 4-5, and low for a score of 0-3.

	Points (0, 1, or 2 for each of 4 categories; maximal possible score = 8)		
Findings	**2**	**1**	**0**
Thrombocytopenia	>50% fall or platelet nadir 20-100 $\times 10^9$/L	30%-50% fall or platelet nadir 10-19 $\times 10^9$/L	Fall <30% or platelet nadir < 10 $\times 10^9$/L
Timing of platelet count fall or other sequelae	Clear onset between day 5-10; or less than 1 day (if heparin exposure within past 30 days).	Consistent with immunization but not clear, or onset of thrombocytopenia after day 10, or within 1 day and prior heparin exposure within past 31-100 days.	Platelet count falls too early, without recent heparin exposure.
Thrombosis of other sequelae (eg, skin lesions)	New thrombosis; skin necrosis post heparin bolus acute systemic reaction.	Progressive or recurrent thrombosis; erythematous skin lesions; clinically suspected thrombosis not yet proven.	None.
Other cause for thrombocytopenia not evident	No other cause for platelet count fall is evident.	Possible other cause is evident.	Definite other cause is present.

in patients with HIT.[32] Not all patients with HIT have immunoassay results above 1.00 optical density units, however, and the immunoassay results are most useful when combined with a clinical scoring system.[33] Other strategies that have been used to improve the specificity of the immunoassays include restricting the assay to detecting IgG antibodies only[34] and adding a heparin confirmatory procedure.[24]

Functional assays detect heparin-dependent antibodies capable of binding to Fc receptors on platelets and measure platelet activation. The serotonin release assay measures the release of ^{14}C-serotonin from activated platelets and has high sensitivity (88% to 100%) and specificity (89% to 100%) for HIT; this test may be obtained through referral to a specialized coagulation laboratory. Alternative functional assays include platelet aggregation using either washed platelets or platelet rich plasma, or detection of platelet activation by flow cytometry (eg, platelet-derived microparticles, annexin V binding). Limitations of the functional assays include lack of standardization of the assays,[29] technical complexity, and variability in the reactivity of platelet donors, which can lower the sensitivity of the assays.[35]

Additional laboratory studies can also be useful in the assessment of patients developing thrombocytopenia while on heparin (**Table 1**). Laboratory evidence for DIC, characterized by a prolonged PT or aPTT, or hypofibrinogenemia, can be detected in a small subset of patients with HIT.[7] Severe DIC is not seen in most patients with HIT, although it has been described in patients with "delayed-onset" HIT.[7] The peripheral blood film should be reviewed for evidence of microangiopathic hemolysis, which may suggest an alternative diagnosis. Bleeding is an uncommon clinical manifestation in patients with HIT, and the presence of clinically significant bleeding should lead the clinician to thoroughly assess for other causes of thrombocytopenia.

Treatment of HIT

The initial management of patients with HIT is dependent on the degree of clinical suspicion that the physician has for the diagnosis of the syndrome. When clinical suspicion for HIT is low, the decision to stop heparin and initiate an alternative anticoagulant needs to be tailored to the individual patient's condition, that is, it may well be appropriate to maintain heparin therapy. Conversely, if clinical suspicion for HIT is intermediate or high, all sources of heparin, including the heparin solutions used to maintain patency of intravenous lines that are temporarily not in use, should be discontinued and an alternative anticoagulant therapy initiated.[1] In addition, for patients suspected of having HIT, substitution of an LMWH for unfractionated heparin is contraindicated. Although LMWHs are less likely to cause HIT,[36] they can cross-react with antibodies that have developed in response to unfractionated heparin and consequently exacerbate the syndrome.

Although patients with HIT can have markedly decreased platelet counts, they require anticoagulation with an effective antithrombotic agent that does not cross-react in vivo with the circulating anti-heparin/PF4 antibodies. Three direct thrombin inhibitors that directly bind and inactivate thrombin are currently available for patients with HIT: lepirudin, argatroban, and bivalirudin. Danaparoid is a mixture of non-heparin glycosaminoglycans that has been used extensively in patients with HIT, but this agent has not been available for use in the United States since 2002. Fondaparinux, a synthetic pentasaccharide that binds to antithrombin and inhibits factor Xa, has been used effectively in some patients with HIT,[37] although apparent "fondaparinux-induced" thrombocytopenia has been reported in two patients.[38,39]

Lepirudin is a recombinant analogue of the leech protein hirudin, which irreversibly binds to and neutralizes thrombin. It is cleared by the kidney, and its use in patients with renal insufficiency is relatively contra-indicated. It is an effective antithrombotic agent for patients with HIT, although hemorrhagic complications are not uncommon.[40] Because of the higher risk for bleeding events with increasing doses, without evidence for superior antithrombotic efficacy, current guidelines recommend lower doses of lepirudin than those used in the initial studies leading to approval of the drug for patients with HIT.[16] Argatroban is a synthetic compound that reversibly binds to the catalytic site of thrombin. Two prospective, multicenter studies demonstrated the efficacy of argatroban in a total of 373 patients with HIT.[41,42] In contrast to lepirudin, argatroban is primarily cleared by the liver and should be used with caution in patients with hepatic insufficiency. Bivalirudin is a synthetic thrombin inhibitor that binds reversibly to the catalytic site and the anion-binding exosite of thrombin. Bivalirudin is approved for patients undergoing percutaneous cardiac intervention who either have HIT or are at risk for developing HIT. Bivalirudin has also been studied the most in patients with HIT undergoing cardiac bypass procedures.[43] An issue with the direct thrombin inhibitors is that aPTT monitoring can be problematic in patients with concurrent coagulopathy, including those with severe HIT and associated DIC, thus compromising efficacy of the therapeutic agent.[44]

Patients with HIT and thrombosis should receive a non-heparin anticoagulant until the thrombocytopenia has

resolved, at which time an oral vitamin K antagonist can be introduced. Warfarin should be initiated with a low maintenance dose (specifically, no loading dose) and overlapped with the non-heparin anticoagulant until the target international normalized ratio (INR) has been reached and for a minimum of 5 days.[16] The duration of therapy should be standard for venous thromboembolism, for a minimum of 3 months with consideration for a more extended course depending on clinical circumstances related to the thromboembolic event. For patients with "isolated HIT," anticoagulation with a non-heparin anticoagulant should continue at least until the platelet count has returned to baseline,[16] and some experts would recommend extended anticoagulant therapy for 4 to 6 weeks (eg, with fondaparinux or with conversion from a direct thrombin inhibitor to warfarin after resolution of the thrombocytopenia). Current guidelines also recommend that patients with "isolated HIT" should undergo duplex ultrasonography of their lower limbs as well, given the high likelihood for occult thrombosis.[16]

Patients who are taking warfarin therapy at the time of diagnosis with HIT are predisposed to venous limb gangrene and warfarin-induced central skin necrosis.[45,46] These patients typically have a supratherapeutic INR, but small vessel thrombotic occlusions are felt to be due to acquired protein C deficiency that develops early during the initiation of warfarin therapy and contributes to the hypercoagulable state associated with anti-heparin/PF4 antibodies.[45] In the acute setting of HIT, patients who are taking warfarin should have their elevated INR results normalized with vitamin K.[16] As noted above, warfarin can subsequently be used in patients with HIT after their platelet counts have returned to baseline levels, but it should not be used during the acute phase of HIT.

As with most drug-induced thrombocytopenias, patients with a prior history of HIT should usually not be re-exposed to heparin. However, anti-heparin/PF4 antibodies appear to not persist in the circulation and are frequently not detectable by 3 months after the diagnosis of HIT.[17] This provides an important option for patients with a remote history of HIT who need to undergo cardiopulmonary bypass. Current guidelines recommend re-exposure to heparin during bypass surgery in these patients, given the limited experience with non-heparin anticoagulants during bypass surgery and the inability to rapidly reverse their anticoagulant effect.[16]

In summary, the thrombocytopenia encountered in patients with HIT differs from other drug-induced thrombocytopenias in a number of important areas. First, the thrombocytopenia is typically not as severe as other drug-induced thrombocytopenias and occurs in a well-defined timeframe in relation to the administration of heparin. Second, these patients typically do not bleed, even if the platelet count drops very low. Third, a non-heparin anticoagulant is essential for the treatment of patients with HIT because of the significantly increased thrombotic risk. Finally, the anti-heparin/PF4 antibodies that are responsible for the syndrome appear to disappear over the course of several months, and re-exposure of patients to heparin does not appear to lead to recurrent thrombocytopenia.

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