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Diagnosis and Management of Heparin-Induced Thrombocytopenia

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Definition and History

Unfractionated heparin (UFH) and its derivatives, the low-molecular weight heparins (LMWHs; henceforth, collectively referred to as heparin), remain the most commonly prescribed anticoagulants for the prophylaxis and treatment of venous thromboembolism (VTE) in hospitalized patients.[1] In a subset of treated patients (< 5%), heparin elicits a life-threatening immune complication, heparin-induced thrombocytopenia (HIT). HIT is a self-limited hypercoagulable disorder occurring predominantly in hospitalized patients. The cardinal manifestations of HIT are declining platelet counts within 5-14 days after heparin exposure and a predilection for arterial and venous thrombosis.[2]

The clinical syndrome of HIT was first described in the 1950's by Weissman & Tobin.[3] Subsequent studies revealed the immune origins of this syndrome[4] with the identification of antibodies directed to antigenic complexes of platelet factor 4 (PF4) and heparin (H).[5] With the advent of immunoassays for detection of PF4/H antibodies, it is now recognized that an asymptomatic immune response to PF4/H occurs far more commonly than clinical complications of disease (thrombocytopenia and/or thrombosis). This chapter reviews our current understanding of the pathogenesis, clinical features, laboratory testing and therapeutic options for patients with HIT.

Etiology and Pathogenesis

PF4/H complexes and the immune response in HIT

The primary physiologic role of PF4 is to neutralize the antithrombotic effect of heparin and heparin-like molecules (heparan sulfate, chondroitin sulfate) on cell-surfaces. Upon platelet

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activation, PF4, a positively charged protein residing in platelet α-granules, is released in large amounts, binds to endothelial heparin sulfate and displaces antithrombin (AT) from the cell-surface. When patients are administered pharmacologic doses of heparin for thromboprophylaxis or for treatment, cell-bound PF4 dissociates from endothelial sites to form ultra-large complexes with circulating heparin through electrostatic interactions. Recent murine studies have shown that these circulating and/or cell bound PF4/H complexes are highly immunogenic in vivo.[6] Once formed, immune complexes containing IgG antibody and antigen are capable of engaging cellular Fc receptors on platelets,[7] monocytes,[8,9] and neutrophils[10] to promote cellular activation and thrombin generation.[11]

Epidemiology of HIT

In recent prospective investigations employing UFH and/or LMWH, the overall incidence of HIT is estimated at 0.5-0.8% of treated patients.[12,13] Drug and host characteristics contribute to the risk of developing HIT. Of the various drug dependent characteristics influencing immunogenicity: chain-length (UFH > LMWH ≥ fondaparinux), animal source of heparin (bovine > porcine)[14] and route (intravenous > subcutaneous),[15] heparin chain length appears to be the most clinically significant. The incidence of HIT is approximately ten fold higher with UFH (~3%) as compared to LMWH (0.2%)[16] in patients receiving thromboprophylactic doses. These differences in UFH and LMWH subside, however, when treatment doses are administered. In a meta-analysis involving 13 studies and > 5,000 patients, the rates of HIT were comparable in patients receiving UFH or LMWH (LMWH 1.2% vs UFH 1.5%).[13] Surprisingly, no increase in HIT incidence has been reported[17,18] despite the increased utilization of LMWHs in recent years for the prevention of hospital-acquired VTE. Although rates of seroconversion are similar for fondaparinux and LMWH,[19] the occurrence of HIT appears to be infrequent with fondaparinux.[20]

Host risk factors include clinical context of heparin exposure and patient characteristics (age, gender and race). Patients on the general medical, cardiology and surgical services (orthopedic and trauma) are at higher risk than patients on obstetric, pediatric or renal (chronic hemodialysis) services.[2,21] The reasons for this variable risk are presently unknown, but are thought to arise from differences in basal levels of platelet activation and circulating PF4 levels. Consistent with observations of a low incidence of HIT in pediatric and obstetric patients, a recent large analysis of hospital discharges of ~ 270,000 inpatient records showed that HIT was exceedingly rare in patients less than 40 years of age.[13] In this same study, among patients with VTE, the incidence of secondary thrombocytopenia, presumably due to HIT, was higher among blacks (relative risk or RR 1.3) as compared to whites. Although one recent study showed a higher incidence of HIT among females (odds ratio or OR of 2.4[22]), other studies have found a slightly higher risk among males (RR 1.1).[13] Several genetic polymorphisms, including homozygozity of the FcγRIIIa-158V allele,[23] the protein tyrosine phosphatase CD148[24] and the interleukin-10 promoter[25] have been described in single center studies of patients with and without HIT. The clinical significance of these findings remains to be established in larger studies.

Clinical Elements of Diagnosis

Because of the high incidence of asymptomatic PF4/H conversion (see section on Laboratory Elements of Diagnosis) in patients exposed to heparin, it is essential to understand the clinical features associated with disease presentation. Three essential elements comprise the clinical evaluation of patients suspected of HIT: 1) Documenting the presence of thrombocytopenia and/or thrombosis 2) Establishing the temporal course of thrombocytopenia relative to heparin exposure and 3) Excluding other causes of thrombocytopenia. A detailed discussion of these clinical diagnostic elements and

commonly used diagnostic algorithms is provided below. Table 1 summarizes the clinical features commonly or infrequently seen in HIT.

1) Documenting the presence of thrombocytopenia and/or thrombosis

Thrombocytopenia in HIT

Thrombocytopenia is an essential diagnostic feature of HIT and is reported to occur in ~95% of HIT patients during the course of illness.[26-28] Patients who develop skin necrosis are a notable exception to this diagnostic rule, as thrombocytopenia frequently does not accompany this atypical manifestation.[29,30] Thrombocytopenia in HIT can present as an absolute drop in platelet count below the normal range (platelet count $< 150 \times 10^9$/L) or as a relative decrease of 30-50% from baseline counts. Absolute thrombocytopenia results in a moderate thrombocytopenia, with mean platelet counts of $50\text{-}70 \times 10^9$/L. In the postoperative period, where platelet counts typically rebound to a higher number than the pre-operative count, the immediate post-operative platelet count should be considered as the baseline platelet count for determining the change in platelet count. This revised definition of thrombocytopenia has been shown to be sensitive and specific for diagnosing HIT.[31]

Less than 5% of patients with HIT will have a platelet count $< 20 \times 10^9$/L.[29] The presence of petechiae or extensive ecchymoses in the absence of disseminated intravascular coagulation (DIC) should prompt a search for an alternative diagnoses (see Table 1).[29] Severe thrombocytopenia as a manifestation of HIT is associated with a high risk of thrombotic complications, likely due to platelet consumption.[28] In a retrospective series of 408 patients, patients with severe thrombocytopenia (defined as > 90% decline from baseline counts) were noted to have an 8-fold higher risk for thrombotic complications as compared to patients with a < 30% platelet count decline.[28]

Several retrospective and prospective studies have shown that isolated thrombocytopenia is a harbinger of subsequent thromboses in patients (20-50%).[28,32-34] In one-third of patients, the thromboembolic complication (TEC) can occur concurrently or precede the development of thrombocytopenia.[28,35,36] Because of the therapeutic implications of finding a VTE in HIT patients with isolated thrombocytopenia, patients diagnosed with isolated HIT should undergo routine screening for subclinical TEC (such as lower extremity ultrasound).[34]

Thrombosis in HIT

Thrombosis is the most feared complication of HIT. In prospective and retrospective series, thrombotic complications have been reported to occur in 29%-57%[28,37] of HIT patients. In one registry, 25% of patients developed 3 or more thromboembolic complications.[28] Prior to the availability of current therapies, 16% of all thrombotic complications were fatal and 9% of all thrombotic events resulted in limb amputation.[37] In relation to thrombocytopenia, a large retrospective study of patients with HIT found that in 34% of patients, thrombotic complications will precede or occur concurrently with a major decrease in platelets.[28]

Thrombotic events involving the venous circulation occur far more commonly than arterial thrombotic events, with reported frequencies of 2.4:1-4:1.[28,33] Lower limb deep venous thrombosis (DVT) and pulmonary embolism comprise the vast majority of venous thrombotic events.[28] Upper limb DVTs are also common but are reported to occur almost exclusively at central venous catheter sites.[38] The postoperative period has also been strongly associated with venous thrombosis in HIT.[33,37,39]

Arterial thromboses occur in 7-14%[33,37] of patients affected with HIT. In one series of patients with HIT, a history of cardiovascular events, including myocardial infarction, and a history of cardiovascular surgery were associated with a significantly increased incidence of

arterial thrombosis.[39] In order of decreasing frequency, common sites of arterial thrombosis include: limb artery thrombosis, thrombotic stroke and myocardial infarction.[28] Atypical sites of presentation including bilateral adrenal hemorrhage,[40] venous limb gangrene, cerebral venous thrombosis,[41] spinal ischemia,[41] and skin necrosis should warrant consideration of HIT in the differential diagnosis.[42]

Presently, there are no definitive means for predicting the risk of thrombosis in patients who develop isolated thrombocytopenia in HIT. Studies have shown that established risk factors for hypercoagulability, such as protein C, protein S, antithrombin clotting factor mutations and/or platelet polymorphisms do not contribute significantly to thrombotic tendency.[39,43] Certain common serologic features occur at a higher frequency among patients with thrombotic HIT as compared to those with isolated thrombocytopenia in HIT, including IgG isotype,[44] antibodies capable of platelet activation[44-46] and high antibody levels (as gauged by optical density (OD) and/or titer).[47-49] Risk factors for thrombosis development are outlined in Table 2.

Despite these serologic features, the presence of platelet activating IgG antibodies in some patients with asymptomatic PF4/heparin antibodies[50] or the occurrence of low titer antibodies in other patients with a clinically confirmed diagnosis of thrombotic HIT[47] does not permit unambiguous segregation of these risk factors. Discontinuing heparin therapy after early recognition of HIT does not appear to lower the risk of subsequent thrombosis.[51]

2) Establishing the temporal course of thrombocytopenia relative to heparin exposure

In heparin-naïve patients, platelet counts classically decline within 5-10 days of heparin initiation. As shown in a recent study of the evolution of the HIT immune response, 12 patients with HIT were examined serially for PF4/H antibody levels and platelet counts. As shown in Figure 1, seroconversions occurred at a median of 4 days from start of heparin therapy, with a fall in platelet count occurring 2 days after seroconversion (~ 6 days from start of heparin therapy). The interval time to when the platelet count decline met diagnostic criteria for HIT in this study (> 50% platelet count fall) occurred 4 days after seroconversion (median time interval of 8 days from the start of heparin). Thrombosis also occurred after seroconversion, but often was coincident with changes in platelet counts.[36] These observations, coupled with studies of murine models,[52] suggest that patients' PF4/H seroconversions must precede thrombocytopenia and or thrombosis, and clinical events predating seroconversion are unlikely to be related to HIT.[36] In 30% of patients with HIT, an atypical, rapid fall in the platelet count, occurring at a median of 10 hours after beginning heparin therapy can occur from pre-existing PF4/H antibodies caused by recent heparin exposure (within 3 months).[26] A small-subset of patients develops thrombocytopenia days to weeks after heparin exposure,[53] a clinical variant called "Delayed-Onset HIT." Delayed onset HIT is frequently associated with complications of DIC and/or extensive thrombosis[54] and should be considered in patients presenting with new onset thrombocytopenia within 2-4 weeks of a recent hospitalization.

Discontinuation of heparin should allow prompt resolution of thrombocytopenia. In clinical practice, platelet counts typically increase within 48 hours of heparin discontinuation and thrombocytopenia usually resolves within 4-14 days.[29] A prolonged duration of thrombocytopenia (>7 days) after heparin discontinuation has been linked with disease severity.[51] Despite platelet count recovery, thrombotic risk remains high for 4-6 weeks, due to the presence of circulating PF4/H antibodies[33] and these antibodies likely contribute to the development of delayed onset HIT.[54] The median time to antibody clearance is 85-90 days,[26,49] although in one series, ~35% of patients were noted to be seropositive for up to

one year.[49] To what extent PF4/H seropositivity, in the absence of thrombocytopenia and/or thrombosis, predisposes patients to thrombotic complications remains controversial.[49,55-57] Unlike other drug-induced thrombocytopenias, the risk of recurrent HIT with subsequent heparin re-exposure appears to be low, but these findings have not been prospectively investigated. Although several retrospective analyses and case reports suggest that the risk of recurrence may be low in patients who become seronegative for PF4/H antibodies,[58] current guidelines recommend avoiding routine heparin re-exposure in these patients.[59]

3) Excluding other causes of thrombocytopenia

The majority of patients suspected of HIT are not likely to have disease.[60,61] With the routine implementation of heparin thromboprophylaxis in most hospitals as well as the frequent occurrence of thrombocytopenia in hospitalized patients,[62] the statistical likelihood that these two clinical scenarios will converge is far more likely than the occurrence of HIT. Illustrating this point was a recent study by Oliveira and colleagues of 2420 patients treated with heparin[63] who were assessed for development of thrombocytopenia (defined as a platelet count less than 150×10^9/L, reduction in platelet count of 50% or more from the admission level, or both). In this study, 881 patients or 36.4% (95% confidence interval [CI], 34.5%-38.3%) met the definition for thrombocytopenia while receiving heparin therapy; 13% of patients met both criteria of a decreased absolute platelet count as well as a reduction in platelet count of > 50%. In this study, ~ 0.7% of patients were diagnosed with HIT.[63]

The differential diagnosis of acute thrombocytopenia in a hospitalized patient is extensive as shown in Table 1 **(HIT Unlikely column)**. Thrombocytopenia is common in the intensive care units (ICU) occurring in 38-46% of patients.[64] Thrombocytopenia is particularly problematic in the cardiac surgery setting, where patients have a number of risk factors for HIT, including recent heparin exposure, the inflammatory milieu of surgery and high rates of PF4/H seroconversion.[50,55,65,66] In one recent study of cardiac surgery patients requiring > 7 days in the cardiac ICU, 21% of patients (70/329) developed thrombocytopenia, with 67/70 patients (95%) having alternative or non-HIT related causes for thrombocytopenia.[67] Adding to the complexity of evaluation of cardiac surgery patients is the relatively frequent use of mechanical devices, such as intra-aortic balloon pumps (IABP). Thrombocytopenia is frequently encountered in patients with IABP, occurring at a frequency of 30-50% of cases.[68]

Clinical Algorithms in assessing likelihood of HIT

Given the broad differential diagnosis and frequency of thrombocytopenia in hospitalized patients, clinical algorithms have been developed to assist clinicians in tabulating the risk of HIT in a given patient.

4T's Scoring System

The most widely-used clinical scoring system is the 4T's, developed by Dr. Warkentin at McMaster University. The 4T scoring system assesses the clinical diagnostic elements discussed above and assigns a score (0, 1, or 2; maximum total score of 8) for the following features: the magnitude of **T**hrombocytopenia, **T**iming of platelet count fall or complication in relation to heparin use, **T**hrombosis or other HIT-associated sequelae, and absence of ano**T**her explanation for thrombocytopenia.[29] A 4T score of 6-8 is consistent with a high pretest probability of HIT, a score of 4-5 is consistent with an intermediate probability of HIT, and a score of 0-3 is consistent with a low probability of HIT.[29] The diagnostic utility of the 4T score has been examined in numerous prospective and retrospective studies.[46,69-73] In all studies to date, the 4T's has consistently demonstrated excellent

negative predictive value (NPV), with a 4T score < 3 reliably translating into a low likelihood of serologically confirmed HIT.[46,69-74] On the other hand, the positive predictive value (PPV) of the 4T scoring system is variable and highly dependent on the practitioner's background.[69] To demonstrate the effect of a practitioner's experience in utilizing the 4T's scoring system, Lo and colleagues tested this algorithm at two medical centers, in Hamilton, Canada and Greifswald, Germany (GW). The practitioner applying the 4T's at the Hamilton General Hospital (HGH) was Dr. Warkentin, the developer of the 4T's scoring system. In Greifswald, general practitioners utilized the 4T's for diagnosing HIT. When the clinical scores were correlated with laboratory testing, the NPV was high at both medical centers (98% at HGH and 100% at GW). However, the predictive value of intermediate scores [HGH: 8/28 (28.6%), GW: 11/139 (7.9%)] and high scores [HGH: 8/8 (100%), GW: 9/42 (21.4%)] markedly differed by institution. The clinical utility of the 4T's in predicting the likelihood of HIT was low in Germany, where primary care providers were using the algorithm, but much higher in Canada in the hands of an experienced HIT diagnostician. This study, as well as others, [70-73] confirms that the PPV of intermediate and high scores is far less reliable than the NPV.

HIT Expert Probability (HEP) Score

In an effort to improve on the specificity and the PPV of the 4T's, the HIT Expert Probability (HEP) score was developed using expert opinion to refine the clinical scoring system. In this model, 26 experts were asked to assign points to 8 clinical features of HIT based on diagnostic relevance (magnitude of fall in platelet count, timing of fall in platelet count, nadir platelet count, thrombosis, skin necrosis, acute systemic reaction, bleeding, and other causes of thrombocytopenia).[75] Based on the median score, each clinical feature was then assigned a point ranging from −3 to +3 and the HEP score, a pretest probability model, was created. In a validation study at a single institution, the HEP score demonstrated improved interobserver agreement and improved correlation with serologic HIT testing when compared to the 4T's score. In this study, the HEP score was 100% sensitive and 60% specific for diagnosing HIT.[75] However, unlike the 4T's which is fairly simple to perform, the HEP score is more complex and cumbersome to use. Additional prospective studies are needed to validate the HEP Scoring system.

Cardiac Surgery (Lillo-Le Louet) Scoring System

Nowhere is the challenge of distinguishing HIT from other causes of thrombocytopenia more difficult than in the clinical setting of cardiac surgery. Cardiac surgery is associated with a number of comorbidities that confound the diagnosis of HIT, including several risk factors for thrombocytopenia (dilutional effect, infection/DIC, cardiogenic shock, mechanical devices, multiple medications), increased rates of thrombosis (20% in one recent retrospective study of non-HIT patients)[76] and a high prevalence of PF4/H seroconversion (see Laboratory Elements of Diagnosis). Despite the high-risk features of this clinical setting, retrospective and prospective series have demonstrated that the post-operative risk of HIT after cardiac surgery is low (0.6-2%).[77,78] Due to the difficulty in recognizing HIT post-cardiac surgery, Lillo-Le Louet and colleagues identified three independent clinical variables (platelet count pattern, time from cardiopulmonary bypass (CPB) to suspicion of HIT and CPB duration) based on a clinical cohort suspected of HIT.[79] In patients with HIT, a characteristic biphasic pattern of platelet count recovery was observed. Platelet counts initially decline for 2-4 days after surgery, then rebound into the normal range or beyond, and then fall once again[79] due to antibody development and HIT. Based on these observations, scores were assigned for platelet count time course or pattern (biphasic = 2, persistent thrombocytopenia = 1), time from CPB to date of HIT suspicion (≥ 5 days = 2, < 5 days = 0) and CPB duration (≤ 118 min = 1, > 118 min = 0). In their retrospective study, a score of ≥ 2 was associated with a high probability of HIT (PPV of 62%), whereas a score ≥

5 was associated with a markedly higher PPV of 95%.[79] In a recent prospective study of 1,722 patients undergoing cardiac surgery, the Lillo-Le Louet scoring system was compared to that of the 4T's in predicting the likelihood of HIT.[78] In this study, both scoring systems were found to have a low PPV (56% for the 4T's and 41% for Lillo-Le Louet) and low concordance (kappa coefficient = 0.39). The Lillo-Le Louet scoring system also had a lower NPV (78%) than the 4T's (91%). The authors concluded that the diagnostic performance of both scoring systems were low. However, the authors found that the biphasic pattern of platelet count recovery in the post-cardiac surgery setting remained a strong predictor for HIT.[78]

Laboratory Elements of Diagnosis

In clinical practice, the majority of patients suspected of HIT are likely to have an intermediate clinical probability for HIT. In these patients, establishing the presence or absence of PF4/H antibodies by laboratory methods comprises an essential element of the diagnostic evaluation. This section will discuss the types of immunologic and functional assays for diagnosing HIT.

Immunoassays

Immunoassays for the detection of PF4/H antibodies are widely available. These assays detect binding of antibodies from plasma or serum to immobilized PF4/H complexes. Bound antibody is then detected by secondary labeled antibodies using a colorimetric endpoint. Detailed descriptions or comparisons of the strengths and limitations of the various assays are beyond the scope of this chapter. The reader is referred to Table 3 with test-specific information and references.

Commercial immunoassays are routinely used at most medical centers due to technical ease, rapid turnaround time and high sensitivity of the assays (> 99%[44,72,80,81]). However, the main shortcoming of these assays is their lack of specificity (40-70%[44,65]) due to the frequency of asymptomatic seroconversions. Seropositivity, without HIT, can be seen in ~8-17% of general medical and surgical patients treated with UFH,[82-85] 2-8% of those treated with LMWH[19,82] and 1-2% of patients treated with fondaparinux.[19,21] Heparin exposure during cardiac surgery remains the highest risk factor for asymptomatic seroconversions. Depending on the immunoassay, asymptomatic seroconversions can be demonstrated in 27% to 61% of patients after cardiac surgery.[55,83,86]

Because of these constraints in specificity, several test modifications have been introduced to improve on the diagnostic performance of immunoassays. These include the use of IgG specific assays, quantitative measurement of optical density (OD), and utilization of high heparin concentration to demonstrate heparin-dependent binding. Several studies have shown that the IgG-specific ELISAs improve diagnostic specificity.[87-89] In a pooled analysis of studies examining the sensitivity and specificity of the polyclonal v. IgG specific ELISAs, Cuker et.al showed that the specificity of the IgG ELISA was increased compared to the polyspecific ELISA (94% for IgG specific v. 89% for the polyclonal ELISA), but occurred at a small expense to the sensitivity of the assay (96% for IgG specific v. 98% for the polyclonal ELISA).[87] This translates into a small number of patients who truly have HIT but who will have a false negative result on the IgG-specific ELISA. Studies have also shown that the quantitative assessment of ODs or expression of titers in particle-based ELISAs also improves the diagnostic accuracy of the ELISAs. These studies confirm a strong correlation of the OD/titers with platelet activating properties[48,90] and thrombotic risk.[47,56] Several investigators have examined the utility of using higher OD cut-offs in ELISA's for determining the likelihood of HIT.[72,91] In these studies, based on the type of immunoassay and the cut-off values, a change in the cut-off value was uniformly associated

with a loss in sensitivity (17%-91% sensitivity reported using an IgG-specific ELISA with cut-off OD > 1).[72,91]

HIT antibodies show heparin-dependent binding over a range of physiologic heparin concentrations (0.1-1U/mL). The presence of excess heparin (10-100 U/mL) significantly attenuates the binding of HIT antibodies to antigen. This principle is the basis of using high heparin concentrations in serologic and functional assays to confirm the presence of heparin-dependent antibodies. Studies have shown that the use of a high heparin step improves the specificity from 72% to 89%.[91,92] The high heparin step, however, can fail to show inhibition in instances where the OD is extremely high.[91,92] Recent studies have also shown that combined use of two[91,92] or all three maneuvers (IgG, ODs and high heparin step) can be used to improve the diagnostic utility of the ELISAs. While such an approach, theoretically, should markedly improve the assay's specificity, there are many examples/ reports of HIT patients whose serologic profiles do not conform to these criteria.[47,87,91] Until prospective evaluation and validation of these laboratory modifications occurs, it should be stressed that laboratory testing must accompany a clinical evaluation to avoid serious adverse outcomes from under- or over-diagnosis of HIT.

Functional assays

Functional assays such as the serotonin release assay (SRA; in North America) and the heparin induced platelet activation test (HIPA; in Europe) utilize washed platelets to measure HIT antibody induced platelet activation.[93] A positive result is established when heparin-dependent platelet activation is demonstrated along with inhibition of platelet activation in the presence of excess heparin (100 units/mL) and in the presence of an antibody which blocks platelet Fc receptors.[29]

Functional assays are more specific for HIT [44] and more predictive for thrombocytopenia when compared to ELISA based testing. Whereas functional assays, in particular the SRA, have high specificity (> 95%)[44] and are associated with a high positive predictive values (89-100%),[21] the sensitivity of functional assays are less robust (62-100%)[44,65,94,95] due to a number of technical variables affecting platelet reactivity.[96] Other important drawbacks to these assays include lack of standardization,[97] complexity of the assays and the use of radioactive isotopes with the SRA. For these reasons, many medical centers do not offer this test on-site, and testing is often referred to specialized commercial laboratories. Consequently, functional assays are rarely available to clinicians at the time of initial evaluation and are often used to confirm the diagnosis of HIT post-hoc.

Normalization of laboratory testing

After discontinuing heparin, the median time to platelet recovery is approximately 4 days, although it can take up to 4 weeks for platelets to fully recover to > 150×10^9/L.[29] However, both ELISA testing for HIT antibodies and functional assays, such as the SRA, require longer to normalize. In a retrospective study of 243 patients with serologically confirmed HIT, the median time for the antigen assay to normalize was 85 days and the median time for the activation assay to normalize was 50 days.[26]

Therapeutic Options and Prognosis

General principles

Management of HIT requires that the clinician navigate between the Scylla of overdiagnosis/overtreatment and Charybdis of withholding therapy in patients with true HIT. With the widespread use of ELISAs and the false-positive detection rate of PF4/H antibodies in many clinical settings, current clinical practices have leaned towards the

overdiagnosis of HIT.[60] Overtreatment with potent non-heparin anticoagulants, such as the direct thrombin inhibitors, is associated with a high risk of bleeding (1% risk for major bleeding per treatment day).[98] Similarly, disastrous consequences can be expected if the clinical manifestations of HIT are not promptly recognized (5-10% daily risk of thrombosis).[11] To avoid these extremes, physicians need to apply clinical algorithms (described above) and initiate treatment based on the strength of the clinical suspicion of HIT, even prior to availability of laboratory results.

Patients with a low-clinical suspicion of HIT should not undergo laboratory testing, nor have their heparin discontinued, as the NPV of clinical scoring systems approaches 100% in numerous studies.[46,69-74] Patients who are deemed to have an intermediate or high clinical suspicion for HIT should have all heparin products (including heparin flushes) discontinued and an alternative anticoagulant, ideally a parenteral direct thrombin inhibitor (DTI), started. Simply discontinuing heparin alone or starting a vitamin K antagonist alone is not adequate to prevent the development or progression of thrombotic complications. In a retrospective review of patients with serologically confirmed HIT, 47.6% of patients who had heparin substituted for warfarin suffered a subsequent thrombosis.[33]

Of the three agents available in the United States for the treatment of HIT, two belong to the DTI family (argatroban and bivalirudin; lepirudin production has been discontinued by the manufacturer as of May 2013) and the other, fondaparinux, a synthetic pentasaccharide belongs to the heparin family but has minimal cross-reactivity with heparin. Refer to Table 4 for recommendations on dosing and monitoring of the alternative anticoagulants.

Argatroban

Argatroban is the only DTI approved by the US FDA for the prevention and treatment of thrombosis in patients with HIT as well as for patients undergoing percutaneous coronary intervention with, or at risk for, HIT. Argatroban was approved based on two prospective, open-label multicenter studies enrolling a total of 373 patients with HIT.[32,99] In these trials, patients treated with argatroban were compared to historical controls and were found to have a reduced incidence of new thrombosis, the need for amputation, and death (34% to 35%) as compared to controls (43%).[32,99] More rapid platelet recovery was also seen in the argatroban arm and major bleeding rates were not different between the two study arms.[99]

In patients with normal hepatic function, argatroban should be infused at an initial rate of 1.5-2 mcg/kg/min without an initial bolus. Initial infusion rates should be reduced to 0.5-1.2 mcg/kg/min for patients with heart failure, anasarca, or other conditions resulting in hepatic dysfunction.[100] An activated partial thromboplastin time (aPTT) should be obtained 2 hours after starting the infusion, and the infusion should be adjusted by 0.25-0.5 mcg/kg/min to achieve a goal aPTT 1.5-3 times the baseline aPTT value, with a maximum goal aPTT of 100 seconds. The infusion rate should not exceed 10 mcg/kg/min.[100] Argatroban is hepatically cleared, and, therefore is the agent of choice for patients with HIT and renal insufficiency.[59]

Once a patient is stably anticoagulated on argatroban and the platelet count has fully recovered ($> 150 \times 10^9$/L), warfarin can be initiated at a low dose (≤ 5 mg) and overlapped with argatroban for at least 5 days.[59] Because argatroban prolongs the International Normalized Ratio (INR),[101] the transition to warfarin requires close monitoring of factor X levels, as measured by chromogenic assays. A chromogenic factor X level ≤ 45% at the time of argatroban discontinuation has been shown to be predictive of a therapeutic INR.[102]

Reported major bleeding rates with argatroban range from 0%-10%.[103,104] _ENREF_76 Identified risk factors for major bleeding on argatroban include: the presence of a HIT

associated TEC, pulmonary impairment, and an aPTT > 100 seconds.[105] If bleeding occurs, the infusion rate should be decreased or the infusion should be entirely discontinued. Once argatroban is discontinued, the aPTT will typically normalize within 2-4 hours.[106] No specific antidote for argatroban is available at this time. The reported wholesale acquisition cost of one vial of argatroban (100 mg/mL; 2.5 mL vial) required for one day's treatment is $1313.[107]

Bivalirudin

Bivalirudin is a DTI approved for use by the FDA only in patients who have or are at risk of developing HIT during percutaneous coronary intervention (PCI), a setting where its safety and efficacy have been demonstrated.[108] Bivalirudin has not been approved by the FDA for other clinical settings of HIT, but several case series have reported the safety of this agent for HIT in non-PCI settings.[109,110]

If used for treatment of HIT, bivalirudin should be given without a bolus and infused at an initial rate of 0.15-0.2 mg/kg/h for a goal aPTT which is 1.5-2.5 times the patient's baseline aPTT.[59] Bivalirudin has a short half-life of 25 minutes and is cleared by both renal (20%) and plasma enzymatic (80%) mechanisms.[109] For patients with renal insufficiency, bivalirudin should be dose reduced (0.08-0.1 mg/kg/h for creatinine clearance 30-60 mL/minute; 0.03-0.05 mg/kg/h for creatinine clearance < 30 mL/minute or for patients receiving renal replacement therapy).[109] The reported wholesale acquisition cost of one vial bivalirudin (250 mg vial) required for one day's treatment is $742.[107]

Fondaparinux

Fondaparinux belongs to the heparin family and is a long-acting (half-life = 17 hours), selective inhibitor of factor Xa.[93] This drug has not received FDA approval for use in HIT. However, emerging data suggests a role for fondaparinux in HIT, as HIT antibodies show minimal cross-reactivity with this agent in vitro < 5%.[111] In several small series of HIT patients treated with fondaparinux (n=55), no recurrent TEC were reported.[112-115] Therapy with fondaparinux was well tolerated and only one patient, who had developed renal dysfunction, developed a major bleed.[115] These studies demonstrated that fondaparinux may be an effective anticoagulant for the treatment of HIT.

If used for the treatment of HIT, guidelines for therapeutic dosing should be followed (see Table 4). 5 mg subcutaneously (SC) daily should be given for patients who weigh < 50 kg, 7.5 mg SC daily for patients who weigh 50-100 kg, and 10 mg SC daily for patients who weigh > 100 kg.[59] Fondaparinux is primarily eliminated in the urine as unchanged drug (77%).[116] Therefore, the use of fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) due to the increased risk of bleeding in patients when renal clearance is reduced.[116] The reported wholesale acquisition cost of one vial of generic fondaparinux (7.5 mg vial) required for one day's treatment is $103.[107]

Warfarin therapy

Once the patient is stably anticoagulated on an alternative, non-heparin anticoagulant and the platelet count has fully recovered (> 150×10^9/L), warfarin can be initiated at a low dose (≤ 5 mg).[59] Administration of the alternative anticoagulant and warfarin should overlap for at least 5 days, as premature discontinuation of the alternative anticoagulant may lead to thrombotic events.[117] Up to 4 weeks of anticoagulation with warfarin have been recommended for patients with isolated HIT who do not suffer a TEC.[21,59] For patients with HIT who develop a thrombotic complication, extending anticoagulation with warfarin for a total of 3-6 months is recommended.[59]

Platelet transfusions

Despite the frequency of thrombocytopenia in patients with HIT, bleeding complications remain very rare[29] and historically, routine platelet transfusions were not advised due to concern for an increased risk of thrombosis.[118] Although recent reports indicate that platelet transfusions may be safe and are not associated with TEC,[119] there is considerable theoretical concern that platelet transfusions may heighten the prothrombotic state in HIT due to the high concentrations of the antigen PF4 in platelets.[120] Thus, at this time, platelet transfusions are only recommended for patients with HIT who have active bleeding or for those patients who need to undergo procedures associated with a high risk of bleeding.[59]

Heparin re-exposure

HIT is thought to be a self-limited disorder, based on the transience of circulating PF4/H antibodies,[26] and isolated case series of inadvertent exposure demonstrate lack of disease recurrence. In a small case series, seven patients with a history of HIT who were now serologically negative did not experience recurrent thrombocytopenia or thrombotic events after subsequent courses of heparin.[26] Likewise, patients with a history of HIT who become seronegative for PF4/H antibodies have been successfully and safely anticoagulated with heparin during hemodialysis[121] and during cardiopulmonary bypass surgery.[58,122]

In the absence of prospective studies examining the safety of heparin re-exposure in HIT patients, current guidelines recommend avoidance of heparin in patients with recent HIT who still have detectable PF4/H antibodies, as they are at risk for developing rapid-onset HIT and thrombosis.[59] However, once HIT antibodies become undetectable by serologic assays, short-term re-exposure to heparin can be considered.[59] In this scenario, administration of heparin should be restricted to the procedure itself and unnecessary heparin exposure should be avoided._ENREF_47[59]

Summary

Heparin-induced thrombocytopenia is a prothrombotic disorder caused by antibodies to PF4/H complexes. It classically presents with declining platelet counts 5-14 days after heparin administration and results in a predisposition to arterial and venous thrombosis. Establishing the diagnosis of HIT can be extremely challenging, especially in patients with multiple medical comorbidities. Therefore, it is essential to conduct a thorough clinical evaluation in addition to laboratory testing to confirm the presence of PF4/H antibodies. Multiple clinical algorithms have been developed to aid the clinician in predicting the likelihood of HIT. Once HIT is recognized, an alternative anticoagulant (DTI or fondaparinux) should be initiated to prevent further complications.

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- Heparin-induced thrombocytopenia is a prothrombotic disorder caused by antibodies to PF4/H complexes. It classically presents with declining platelet counts 5-14 days after heparin administration and results in a predisposition to arterial and venous thrombosis.
- Establishing the diagnosis of HIT can be extremely challenging, especially in patients with multiple medical comorbidities.
- Once HIT is recognized, an alternative anticoagulant (DTI or fondaparinux) should be initiated to prevent further complications.

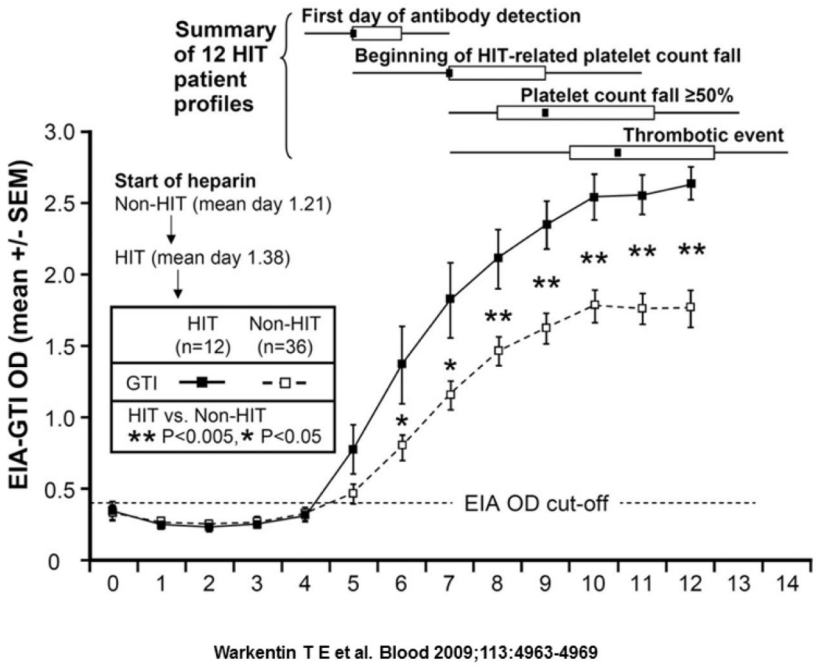

Figure 1. Evolution of the immune response relative to clinical manifestations of HIT

12 patients with HIT and 36 seropositive non-HIT control patients were monitored for PF4/heparin antibodies, thrombocytopenia and thrombosis after orthopedic surgery. HIT patients are indicated by ■, and seropositive non-HIT controls by □. Time course of seroconversions are shown on the x-axis and OD levels between the patients with HIT and the seropositive non-HIT controls ($P < 0.05$ by nonpaired t test) are shown on the y-axis. At the top of the figure, summary data for 12 HIT patient profiles are shown for 4 key events (first day of antibody detection, beginning of HIT-related platelet count fall, platelet count fall ≥ 50%, and thrombotic event), summarized as median (small black squares within rectangles), interquartile range (open rectangles), and range (ends of thin black lines). Adapted from Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. The New England journal of medicine 1995;332:1330-5.with permission.

Table 1
Clinical Features Consistent/Not Consistent with HIT

Consider HIT	HIT Unlikely
Following clinical symptoms within 4-14 days of new heparin therapy ***or*** within 24 hours of heparin re-exposure * ➢ absolute thrombocytopenia (<150K/μL) ➢ relative thrombocytopenia (30-50% drop from baseline platelet count) ➢ new or progressive arterial or venous thrombosis on heparin therapy ➢ new thrombocytopenia and/or thrombosis presenting 14-30 days after recent hospitalization and heparin exposure ➢ thrombosis at catheter sites ➢ thrombosis at unusual sites (venous limb gangrene, skin necrosis, spinal ischemia, cerebral venous thrombosis) ➢ bilateral adrenal hemorrhage (secondary to adrenal thrombosis) ➢ skin necrosis at subcutaneous injection sites ➢ severe thrombocytopenia (< 20K/μL) in association with DIC or extensive thrombosis	➢ pancytopenia or chronic thrombocytopenia ➢ petechiae or hemorrhage in the absence of DIC ➢ thrombocytopenia: • within 24-72 hours in patients without prior heparin exposure • in association with intra-aortic balloon pump, ventricular assist device or extracorporeal membrane oxygenation • in patients with documented severe bacterial, fungal or viral infection • after recent chemotherapy or pelvic radiation • with microangiopathic changes on blood film in absence of DIC • within 72-96 hours of cardiopulmonary bypass • within 24-96 hours after cardiogenic shock • from splenic sequestration

Abbreviations: DIC, disseminated intravascular thrombosis

*Re-exposure within three months of prior heparin therapy

Table 2

Risk Factors for Thrombosis in HIT

Predictors of Thrombosis in HIT	
Correlated with Thrombotic Risk	**No Correlation**
• Sites of previous arterial or venous injury[38,39] • Low platelet nadir28 • High antibody titers[45,47]	• Thrombophilic markers (Protein C, Protein S, Antithrombin III or Factor V Leiden)[39] • FcR H/R 131 and other platelet glycoproteins[43]

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Table 3

Immunoassays available for the detection of PF4/H Abs

Assay	Vendor	Polyclonal v. IgG Specific	Principle	Sensitivity	Specificity
Asserachrom IgGAM	Diagnostica Stago	Polyclonal	ELISA	100%[71,89]	64%-86.46%[71,89]
GTI PF4 IgG	GTI Diagnostics	IgG specific	ELISA	100%[89,123]	42%-95.92%[89,123]
HemosIL AcuStar HIT-Ab(PF4-H)	Instrumentation laboratory	Polyclonal	Latex enhanced immunoturbidimetric assay	100%[124]	81.2%[124]
HemosIL AcuStar HIT-IgG(PF4-H)	Instrumentation laboratory	IgG specific	Latex enhanced immunoturbidimetric assay	100%[124]	96.5%[124]
ID-heparin/PF4 PaGIA	Diamed	Polyclonal	particle gel immunoassay	94%-100%[71,72,125]	61%-95%[71,72,125]
Poly-ELISA	GTI Diagnostics	Polyclonal	ELISA	100%[72]	80.8%[72]
Zymutest HIA IgG	Hyphen Biomed Research	IgG specific	ELISA	100%[89,123]	44%-95.92%[89,123]
Zymutest HIA IgGAM	Hyphen Biomed Research	Polyclonal	ELISA	100%[89]	87.50%[89]

Enzyme linked immunoassay, ELISA

Table 4
Alternative Anticoagulants for Treatment of HIT

	Argatroban	Bivalirudin	Fondaparinux
Approval	HIT or HIT patients undergoing PCI with or at risk for HIT	Patients with or at risk of developing HIT during PCI	Has not received FDA approval for use in HIT
Bolus	None	None	N/A
Initial dose for isolated HIT or HIT with thrombosis	1.5-2 mcg/kg/min[100]	0.15-0.2 mg/kg/h[59]	< 50 kg: 5 mg SC daily 50-100 kg: 7.5 mg SC daily > 100 kg: 10 mg SC daily[59]
Initial dose for renal impairment	No adjustment necessary[126]	0.08-0.1 mg/kg/h (CrCl 30-60 mL/min) 0.03-0.05 mg/kg/h (CrCl < 30 mL/min or for patients receiving renal replacement therapy)[109]	Use with caution if CrCl 30-50 mL/min Contraindicated if CrCl < 30 mL/min[116]
Initial dose for hepatic impairment	0.5-1.2 mcg/kg/min[100]	No adjustment necessary[127]	No adjustment necessary[116]
Monitoring	Obtain baseline aPTT and 2 hours after starting infusion[126]	Obtain baseline aPTT and 2-3 hours after starting infusion	Anti-FXa activity can be monitored in renal insufficiency[115]
Target	aPTT 1.5-3 times the baseline aPTT. Max goal aPTT=100 sec[100]	aPTT 1.5-2.5 times the baseline aPTT59	N/A
Dosage Adjustment (HIT/HITTS only)	Adjust infusion by 0.25-0.5 mg/kg/min to achieve goal aPTT. Recheck aPTT 2-4 hours after each dosage change.[126]	Adjust infusion by 20-25% to achieve goal aPTT. Recheck aPTT 2 hours after each dosage change.	N/A
Maximum dose	10 mcg/kg/min	0.25 mg/kg/h[127]	10 mg daily[116]
Transition to warfarin	Monitor chromogenic FXa level while on combined therapy.[101] Chromogenic FXa:[102] 24-45% (INR 2-3) 15-35% (INR 2.5-3.5) Confirm INR 4-6 hours after infusion is stopped	Monitor INR and/or chromogenic FXa while on combined therapy. Chromogenic FXa: 24-45% (INR 2-3) 15-35% (INR 2.5-3.5)	Monitor INR while on combined therapy. Discontinue therapy when INR ≥ 2 for 2 consecutive days[116]
Cost of daily therapy [107]	$1313	$742	$103
Special considerations	No antidote is available[126]	No antidote is available[127] **HIT in PCI:** 0.75 mg/kg bolus followed by a 1.75 mg/kg/h infusion for the duration of the procedure (all subgroups) After PCI: 1.75 mg/kg/h (CrCl ≥ 30 mL/min) 1 mg/kg/h (CrCl < 30 mL/min) 0.25 mg/kg/h (hemodialysis) Optional infusion after PCI 0.2	No antidote is available[116]

Argatroban	Bivalirudin	Fondaparinux
	mg/kg/h for 20 hours[127]	

Not applicable, N/A; creatinine clearance, CrCl; factor Xa, FX