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Heparin-Induced Thrombocytopenia

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Abstract

Heparin-induced thrombocytopenia (HIT) is an immune-mediated hypercoagulable disorder caused by antibodies to platelet factor 4 (PF4) and heparin. HIT develops in temporal association with heparin therapy and manifests either as an unexplained thrombocytopenia or thrombocytopenia complicated by thrombosis. The propensity for thrombosis distinguishes HIT from other common drug-induced thrombocytopenias. Diagnosing HIT in hospitalized patients is often challenging because of the frequency of heparin use, occurrence of thrombocytopenia from other causes, and development of asymptomatic PF4/heparin antibodies in patients treated with heparin. This review summarizes our current understanding of the pathogenesis, clinical features, diagnostic criteria, and management approaches in HIT.

Keywords

platelet factor 4; heparin; thrombosis; immunoassays; direct thrombin inhibitors; immune thrombocytopenia; immune-mediated thrombosis

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is one of the most clinically important drug-induced complications encountered in hospitalized patients. HIT is a prothrombotic, immune-mediated disorder caused by unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) therapy. HIT is mediated by antibodies that bind macromolecular complexes formed by a self-platelet protein, platelet factor 4 (PF4), and heparin. The diagnosis of HIT is based on clinical features (thrombocytopenia with or without thrombosis in temporal relation to heparin therapy) and laboratory demonstration of PF4/heparin antibodies using immunologic or functional assays. This article provides a current perspective on the pathogenesis, clinical manifestations, diagnosis, and management of HIT.

DISCLOSURE STATEMENT

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PATHOGENESIS

HIT is an idiosyncratic immune reaction typically initiated by treatment with UFH or LMWH (hereafter collectively referred to as heparin) and caused by antibodies that recognize complexes of PF4 and heparin. HIT is etiologically and clinically distinct from a recent outbreak associated with contaminated lots of UFH, which was limited in scope [affecting 113 patients over a 10-week period (1)] and involved the deliberate introduction of synthetic oversulfated chondroitin sulfates (OSCS) (2) into the UFH manufacturing supply. Unlike HIT, which occurs 5–14 days after heparin exposure, OSCS hypersensitivity results in immediate, anaphylactic-type reactions due to bradykinin generation and/or complement activation (3).

The immune response initiated by heparin is unusual in that it recognizes two components that are normally found in circulation: PF4, an abundant platelet protein, and glycosaminoglycans (GAGs), to which the heparin family of carbohydrate compounds belongs. PF4 is a positively charged protein belonging to the CXC family of chemokines, a chemoattractant class of proteins. PF4 is synthesized by megakaryocytes and stored in platelet alpha-granules (4). When platelets are activated at sites of vascular injury, PF4 is released locally and binds to negatively charged heparin-like GAGs, such as heparan sulfate, on the endothelial cell surface. Binding of PF4 to endothelial heparan sulfate results in displacement of antithrombin from heparan sulfate and converts the normal anticoagulant surface of resting endothelium to a more prothrombotic environment. Because of the higher affinity of PF4 for heparin relative to cell-surface GAGs [heparin > heparan sulfate > chondroitin sulfate (4)], exogenous administration of heparin leads to displacement of endothelial cell-bound PF4 into circulation (see Figure 1), resulting in the formation of immunogenic multimolecular complexes (5, 6). Differences in chain length and/or patterns of sulfation of various commercial heparin preparations (UFH, LMWH, heparinoids, and fondaparinux) significantly influence PF4 affinity (UFH > LMWH > heparinoids >> fondaparinux) and affect multimolecular complex assembly (6, 7). The immunogenicity of LMWH and fondaparinux compared to UFH correlates with the formation of smaller complexes of these compounds with PF4 (6).

Recent studies indicate that charge-dependent interactions of PF4 and GAGs govern much of the observable disease biology in HIT (5, 7). Optimal PF4/heparin complex assembly occurs at near-equimolar concentrations of PF4 and GAGs, which approximate the amounts needed for charge neutralization (5, 8). Higher or lower concentrations of either reactant (positively charged PF4 or negatively charged GAG) result in reduced size of complexes and/or complex disassembly due to increased repulsive interactions (5, 8). These charge-based interactions explain the unique heparin dependency of HIT antibodies, wherein antibody binding to antigen or cells occurs optimally in the presence of low-dose heparin but not in the presence of excess heparin. Indeed, demonstration of loss of HIT antibody binding in the presence of excess heparin is a critical feature of laboratory testing, which eliminates antibodies with nonspecific cross-reactivity, such as antiphospholipid antibodies (9).

Once an immune response is initiated, HIT antibodies of IgG isotype effect cellular activation by engaging cellular Fc receptors. The principal cellular targets for HIT

antibodies are platelets, which express FcγRIIa receptors (10). Antibody binding leads to increased platelet clearance and platelet activation as well as release of procoagulant microparticles (11). Cellular activation of monocytes, neutrophils, and endothelial cells (12–14) additionally contributes to the significant thrombin generation seen in HIT (15). Because PF4/heparin antibodies from patients with and without thrombosis and even from some asymptomatic patients exhibit broadly overlapping effects with respect to cellular activation (16, 17), it has not been possible to identify a pathogenic class of antibodies solely based on biologic properties of cellular activation.

EPIDEMIOLOGY

The frequency of HIT is influenced by heparin formulation and the clinical context in which heparin is administered. The incidence of HIT is approximately tenfold higher with UFH (~3%) than with LMWH (0.2%) in surgical patients (18) treated with thromboprophylactic doses. Whether similar striking differences exist for medical populations given therapeutic dosing of UFH or LMWH is currently not known. Although rates of seroconversion appear to be similar for fondaparinux and LMWH (19), there appears to be a far lower incidence of HIT associated with fondaparinux as compared to LMWH (20).

HIT is more likely to occur in certain adult clinical populations (general medical, cardiologic, surgical, and orthopedic) but less likely in others (patients on chronic hemodialysis; obstetric or pediatric populations) (21, 22). The reasons for this variable risk are not known, but are presumed to arise from differences in basal levels of platelet activation and circulating PF4 levels. Other minor influences on HIT epidemiology have been noted, including tissue derivation of heparin [bovine > porcine (23)], route [intravenous > subcutaneous (24)], and gender [females > males] (25). Increased duration of LMWH therapy may confer an increased risk for HIT [28 days > 7 days (26)]. The reader is referred to recent American College of Chest Physicians guidelines for detailed recommendations on platelet-count monitoring for various clinical populations at risk of HIT (22).

CLINICAL FEATURES

Thrombocytopenia occurs in ~95% of HIT patients sometime during the course of illness and manifests either as an absolute drop in platelet count below the normal range or a relative decrease of 30%–50% from baseline counts (27). Absolute thrombocytopenia is usually mild-moderate ($50\text{--}70 \times 10^9/\text{L}$), rarely associated with bleeding complications, and, when severe ($<20 \times 10^9/\text{L}$), usually accompanied by fulminant disease (27). Relative thrombocytopenia can be overlooked in surgical patients who develop postoperative thrombocytosis prior to a HIT-induced platelet-count fall (28). When thrombocytopenia is the only manifestation of HIT (isolated HIT), a high rate of subsequent thrombosis (20%–50%) has been noted in several retrospective and prospective studies (29, 30). A high incidence of subclinical thromboses (~50%) has been noted in one small case series of patients with isolated HIT (31). Very rarely, thrombotic complications can occur in the absence of thrombocytopenia, particularly in patients with atypical manifestations, such as skin necrosis (32).

Thrombosis complicates thrombocytopenia in ~30%–60% of patients at disease presentation (27). Thrombosis can arise in any vascular bed, although venous complications and line-related thrombotic complications (33) tend to predominate. Arterial thrombosis is also common in vessels traumatized by catheterization or surgery (34). Atypical sites of presentation, including bilateral adrenal hemorrhage (35), venous limb gangrene, and skin necrosis should prompt diagnostic consideration of HIT (32). Thrombotic complications contribute to the significant morbidity associated with HIT. Although recent therapeutic advances have reduced the overall rate of thrombosis, risks of amputation and death remain high (20%–30%) in HIT (24, 30).

Traditional risk factors for hypercoagulability, such as protein C, protein S, antithrombin, clotting factor mutations (Factor V Leiden or prothrombin gene mutation), and/or platelet polymorphisms are not increased in patients with thrombotic HIT (34, 36). However, certain serologic features appear to be present in patients with disease compared to those without, including IgG isotype (17), antibodies capable of platelet activation (37), and high antibody levels as gauged by optical density (OD) and/or titer (37–40). Whether IgA or IgM antibodies can elicit disease in the absence of IgG antibodies is unresolved at this time (41, 42). In most studies, high OD values (>1.0) are predictive for both the presence of platelet-activating antibodies [OR = 17.9,(43)] and increased risk (3.4–6-fold) of thrombosis compared to patients with lower levels (38, 40). Early cessation of heparin therapy does not appear to lower risk of subsequent thrombosis (44). Magnitude of thrombocytopenia appears to be a surrogate marker for antibody burden; patients with severe thrombocytopenia (defined as >90% decline from baseline counts) are eightfold more likely to develop thrombotic complications than are patients with a <30% platelet-count decline (27). However, high-titer platelet-activating IgG antibodies are present in some patients with asymptomatic PF4/heparin antibodies (16), and lower-titer antibodies are seen in some patients with a clinically confirmed diagnosis of thrombotic HIT (38), so OD is not reliable for absolute risk stratification.

HIT appears to be an acute, self-limited illness. Complete platelet-count recovery is seen in ~65% of patients within one week of heparin discontinuation (44). A prolonged duration of thrombocytopenia (>7 days) is usually indicative of severe disease (44). Despite platelet-count recovery, thrombotic risk in HIT remains high for 4–6 weeks after diagnosis (29), a period associated with the presence of functionally active PF4/heparin antibodies (45). The median time to antibody clearance is 85–90 days (40, 45), although 35% of patients may remain seropositive for up to one year (40). Whether isolated PF4/heparin antibodies, in the absence of thrombocytopenia and/or thrombosis, predispose patients to thrombotic complications remains controversial; some studies have documented increased rates of adverse events [thromboses and/or death (40)] whereas others have shown no effect (46). Data are also lacking on the risk of recurrence of HIT with subsequent heparin re-exposure; most retrospective analyses suggest that the risk is likely to be low in patients who become seronegative (47).

DIAGNOSIS

The diagnosis of HIT is challenging in most medical settings, given the frequency of heparin administration (48), common occurrence of thrombocytopenia from other causes (49), and convergence of these two clinical phenomena in hospitalized patients (50). This difficulty in establishing a diagnosis is increased by the high incidence of “asymptomatic” PF4/heparin antibodies in heparin-exposed patients without clinical features of disease (26, 51) and by the lack of a “gold-standard” laboratory test for diagnosis. In a recent study, only 12% of 1650 samples submitted for HIT testing had evidence of circulating PF4/heparin antibodies; only half of seropositive samples came from patients who had a clinical course consistent with HIT (42).

Clinical Diagnosis

Presently, HIT is diagnosed using a combination of clinical and laboratory criteria. Two principal criteria are essential for establishing a clinical diagnosis: (a) development of thrombocytopenia and/or thrombosis in temporal association with heparin therapy and (b) exclusion of other causes of thrombocytopenia. The timing of clinical complications (thrombocytopenia and/or thrombosis) is predicated on the history of heparin exposure. For heparin-naïve individuals, thrombocytopenia and/or thrombosis develop 5–14 days after drug exposure and occur several days after an immune response is established (39). If circulating PF4/heparin antibodies (45) are present owing to recent heparin exposure (<120 days), then a more abrupt clinical presentation, termed rapid-onset HIT, occurs within 24 h of re-exposure. Another clinical variant, termed delayed-onset HIT, occurs in a small subset of patients days to weeks after heparin exposure (52). The epidemiology of this latter variant is unknown, but it is presumed to be underdiagnosed. Inadvertent heparin exposure in patients with a diagnosis of delayed-onset HIT is associated with high morbidity and mortality (52).

Diagnostic evaluation for HIT requires excluding other causes of thrombocytopenia. In hospitalized patients, other causes of thrombocytopenia include infection, medications (e.g., GPIIb/IIIa inhibitors, antibiotics), mechanical devices (balloon pumps), and/or end-stage multiorgan failure. Distinguishing HIT is particularly difficult in patients undergoing cardiac bypass surgery, where the prevalence of heparin-dependent antibodies is high (~20%–50%) (53) and multiple causes of thrombocytopenia (e.g., dilutional, infection, cardiogenic shock, mechanical devices) often coexist in the same patient. In these patients, a characteristic triphasic pattern of platelet-count recovery has been observed in association with HIT. Platelet counts initially decline for 2–4 days after surgery, rebound into the normal range or beyond, and then fall once again (54) in association with antibody development.

Algorithms have been developed in recent years to codify the clinical diagnostic criteria of HIT. The most widely used and tested of these algorithms is the “4Ts,” developed by T.E. Warkentin at McMaster University (see Table 1), which assigns scores (0, 1, or 2) based on the presence of pertinent clinical features (a) timing of platelet count fall or thrombosis, (b) severity of thrombocytopenia, (c) presence of thrombosis, and (d) exclusion of other causes of thrombocytopenia. Cumulative scores are then used to assign pretest probability scores of high (6–8 points), intermediate (4–5 points), or low (<3 points) likelihood of disease. The

utility of the 4Ts clinical scoring system has been prospectively evaluated in a number of studies (55–57). These studies show that as a stand-alone test, the 4Ts scoring system is not effective for HIT diagnosis owing to the variability in the clinical experiences of physicians applying it (55). However, most studies agree that the 4Ts scoring system is reliable for excluding disease.

Laboratory Diagnosis

Laboratory studies for HIT diagnosis are based on immunologic or functional assays of platelet activation. Immunoassays detect PF4/heparin antibodies in circulation using an immobilized antigen on a microtiter plate (enzyme-linked immunoassays, EIAs) or agglutination assays of antigen-coated particles (particle gel immunoassay, PaGIA). Functional assays measure platelet-activating effects of HIT antibodies and vary with regard to the endpoint used to measure platelet activation: light transmission (via platelet aggregometry), platelet-activation markers detected by flow cytometry, or platelet granule release of ATP or radio-labeled ^{14}C -serotonin.

Most medical centers offer immunoassays because of their ease of performance, rapid turnaround time, and high sensitivity (58). Serologic assays for PF4/heparin antibody detection are highly sensitive [$>99\%$ (42)] but lack specificity [40%–70% (17, 59)] owing to the frequent occurrence of asymptomatic seroconversions. The sensitivities and specificities of the PaGIAs appear comparable to those of commercial EIAs [PaGIA versus EIA: sensitivity of 94% versus 100%, specificity of 87% versus 80% (60)]. Asymptomatic PF4/heparin antibodies can be detected in ~8%–17% of general medical and surgical patients treated with UFH, 2%–8% of those treated with LMWH, and 1%–2% of those treated with fondaparinux (19, 21). The highest rates of asymptomatic seroconversions occur in patients undergoing cardiac surgery (~27%–61%) (46, 53, 61). Specificity of immunoassays can be improved by detecting antibodies of IgG isotype (17), using a heparin confirmatory procedure (62), using a higher OD cutoff (57), and/or concomitant use of a clinical scoring system (56).

Functional assays of HIT are much more specific for the diagnosis of HIT. In experienced coagulation laboratories, the sensitivity and specificity of functional assays is $>95\%$ (17), yielding high positive predictive values [89%–100% (21)]. Drawbacks to the functional assays include lack of assay standardization (58), the technical complexity of the assays, and variable reactivity of platelet donors, which can lower the sensitivity of assays to $<50\%$ (63).

Because functional assays are not routinely available at most medical centers, we recommend a diagnostic approach combining a clinical algorithm, such as the 4Ts, with EIA testing for suspected HIT. Patients with a low clinical probability of HIT have an extremely low likelihood of disease and are uniformly negative on EIA (55, 56), and therefore do not require additional testing (see Figure 2). For patients with an intermediate or high clinical suspicion for HIT, testing is advised. Negative serologies in this latter population would exclude HIT due to the high negative predictive value of immunoassays (false-negative rate of $<0.5\%$, NPV 99%) (42, 56). For patients with a high risk score (4Ts score = 6–8) and a confirmatory positive EIA, no further testing is required, as the post-test probability of EIAs is sufficiently high in this setting [$>98\%$ (56)]. The majority of patients suspected of HIT

fall, however, into the intermediate clinical risk category (4Ts score = 4–5) with a positive EIA. In this group, evaluation of the OD level (57) and/or additional functional testing (42, 56) would identify patients at increased risk of clinical HIT.

MANAGEMENT

The initial management of patients with HIT depends on the degree of clinical suspicion (Table 1). When clinical suspicion for HIT is intermediate or high, all sources of heparin, including the heparin solutions that maintain patency of intravenous lines that are temporarily not in use, should be discontinued, and alternative anticoagulant therapy should be initiated (Figure 2). Substitution of LMWH is contraindicated in these patients owing to the risk of antibody cross-reactivity and potential exacerbation of symptoms. When clinical suspicion for HIT is low, the decision to stop heparin and initiate alternative anticoagulant therapy needs to be tailored to the patient's condition.

Direct Thrombin Inhibitors

Patients with HIT require anticoagulation with an effective antithrombotic agent that does not cross-react in vivo with the circulating anti-PF4/heparin antibodies. Three direct thrombin inhibitors that directly bind and inactivate thrombin are currently available for patients with HIT. Unique characteristics of the individual therapeutic agents contribute to their role in treating certain subsets of patients. For detailed dosing guidelines, the reader is referred to recent American College of Chest Physicians guidelines (22).

Lepirudin—Lepirudin is a recombinant analogue of hirudin, an anticoagulant protein from leeches, which irreversibly inhibits thrombin by binding to the catalytic site and the anion binding exosite of the molecule. In a summary analysis of three prospective observational studies of patients with HIT, the rate of the combined outcome of death, amputation, and thrombosis at 35 days was lower among 403 patients receiving lepirudin than among 120 historical controls (20.3% versus 43%, $p < 0.001$) (64). However, bleeding rates were significantly higher for those receiving lepirudin (17.6%) than for controls (5.8%), and bleeding was the cause of death in 5 of the treated patients (1.2%) (64). Because of the higher risk for bleeding events at higher doses, without evidence of superior antithrombotic efficacy, current guidelines recommend lower doses of lepirudin than those used in these studies (22). In addition, lepirudin is primarily cleared by the kidney, and the dose needs to be further decreased in patients with renal insufficiency.

Antibodies to lepirudin may develop in ~30% of patients after initial exposure and in up to 70% after repeated exposure. Because fatal anaphylaxis has been reported after sensitization to lepirudin, patients should not be treated with this agent more than once (65).

Paradoxically, a small subset of patients who develop antilepirudin antibodies manifest an increased anticoagulant effect due to an increased half-life of the circulating drug-antibody complex (66).

Argatroban—Argatroban is a small, synthetic compound that binds reversibly to the catalytic site of thrombin. Two prospective multicenter studies investigated the use of argatroban in a total of 373 patients with HIT (30, 67). The combined outcome of death,

amputation, and thrombosis at 37 days was significantly lower among patients receiving argatroban (34%–35%) than among controls (43%) (30, 67). The apparently poorer efficacy of argatroban compared to lepirudin reflects several variables, including different trial design, shorter duration of anticoagulant therapy with the direct thrombin inhibitor in the argatroban studies, and the greater likelihood of transition to a vitamin K antagonist for continued anticoagulant therapy (22). Rates of serious bleeding do not differ between the two groups, however.

Argatroban is primarily cleared by the liver, and its half-life is significantly prolonged in patients with hepatic insufficiency. Consequently, dose reduction is necessary in patients with liver failure, or an alternative direct thrombin inhibitor should be used. Argatroban also results in a significant prolongation of the prothrombin time at therapeutic doses, which can complicate conversion of a patient from argatroban to warfarin therapy.

Bivalirudin—Bivalirudin is a synthetic thrombin inhibitor that binds reversibly to the catalytic site and the anion binding exosite of thrombin. Currently, bivalirudin is only approved for patients who are undergoing percutaneous cardiac intervention and who either have HIT or are at risk for developing HIT. Limited information is available concerning dosing of this agent in other clinical settings, although a recent study indicated that dose reduction was necessary in patients with renal insufficiency (68).

Other Agents

In addition to the direct thrombin inhibitors, two antithrombin-dependent anticoagulant agents have been used in patients with HIT.

Danaparoid is a mixture of heparan sulfate and dermatan sulfate that has been used extensively in patients with HIT. Although it is the only agent that has been investigated in a prospective randomized trial in patients with HIT (compared with dextran sulfate, an agent used before direct thrombin inhibitors became available), danaparoid has not been available for use in the United States since 2002. A recent study demonstrated that danaparoid appears to disrupt formation of the antibody-PF4/heparin complex, which does not occur with the direct thrombin inhibitors or fondaparinux (69).

Fondaparinux is a synthetic pentasaccharide that has also been reported to be effective in patients with HIT (70). However, at least two cases of apparent fondaparinux-induced thrombocytopenia have been reported (20, 71), raising concerns about the safety of fondaparinux in these patients.

Duration of Therapy

For patients with HIT who have not sustained a thromboembolic event, current practice is to administer therapeutic doses of an alternative anticoagulant until the platelet count has returned to a stable plateau. Because the risk of thrombosis remains high for 4–6 weeks after treatment is initiated (29), consideration should be given to continuing anticoagulant therapy with an alternative agent or warfarin for up to 4 weeks. Patients with HIT who have sustained a thromboembolic complication should receive a standard course of therapeutic anticoagulation for the specific clinical event.

Use of Oral Anticoagulants

Patients who are taking warfarin therapy at the time of diagnosis with HIT are at risk for an uncommon thrombotic complication known as warfarin-induced limb gangrene (72). The small-vessel thrombotic occlusions are felt to be caused by decreased protein C levels that develop with vitamin K antagonist therapy in the setting of a profound hypercoagulable state associated with anti-PF4/heparin antibodies (72). Because of the added prothrombotic risk, it is recommended that these patients receive vitamin K supplementation to normalize their international normalized ratio (INR) during the acute phase of HIT (22). Warfarin can subsequently be used in patients with HIT after their platelet counts have returned to baseline levels, although therapy should be initiated with low maintenance doses (i.e., no bolus dosing) and overlapped with one of the nonheparin anticoagulants listed above.

Potential Re-exposure to Heparin in Patients with a Prior History of HIT

The role of immunologic memory in HIT is unresolved. Although anti-PF4/heparin antibodies disappear over a three-month period following a diagnosis of HIT, patients with a known history of HIT not be re-exposed to heparin. Anticoagulant therapy for cardiac bypass surgery, however, is an area where there is limited experience with alternative anticoagulants and these agents are not reversible, increasing the risk for significant bleeding problems during surgery. For patients who have a history of HIT but no evidence of anti-PF4/heparin antibodies, anticoagulation with heparin during the bypass procedure is recommended, with use of a nonheparin anticoagulant for other indications prior to or after surgery (47). For patients with acute or subacute HIT who need urgent bypass surgery, the most systematic experience is with bivalirudin (73). However, due to increased risk of bleeding, cardiopulmonary bypass with bivalirudin should optimally be performed by a surgeon and perfusionist with experience using this agent.

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SUMMARY POINTS

1. HIT is a life-threatening hypercoagulable disorder caused by PF4/heparin antibodies.
2. Formation of PF4/heparin macromolecular complexes at equimolar ratios of PF4 and heparin account for the “heparin-dependent” binding properties of HIT antibodies.
3. Laboratory testing, in the absence of clinical information, is insufficient for diagnosis owing to the high frequency of “asymptomatic” PF4/heparin antibodies.
4. Clinical algorithms can aid in the clinical diagnosis of HIT and are often used in conjunction with laboratory testing.
5. Direct thrombin inhibitors are the mainstay of therapy for HIT patients with or without thrombosis.

FUTURE ISSUES

1. An improved understanding of the pathogenesis of thrombosis in HIT is needed.
2. The natural history and clinical significance of “asymptomatic” PF4/heparin antibodies need to be defined in prospective studies.
3. The duration and intensity of anticoagulation in HIT patients presenting with isolated thrombocytopenia need to be addressed in future studies.
4. The risk of recurrence in patients with a previous history of HIT needs to be systematically investigated.

Figure 1.

Pathogenesis of heparin-induced thrombocytopenia (HIT). (1) Upon activation, platelets release platelet factor 4 (PF4), which can rebind a glycosaminoglycan (GAG) on the platelet surface; or (2) released PF4 binds to endothelial cells, displacing antithrombin bound to heparan sulfate. (3) Administration of heparin leads to displacement of PF4 into circulation, resulting in circulating large multimolecular complexes of PF4/heparin. (4) In 1%–5% of patients, multimolecular complexes of PF4/heparin elicit antibody formation capable of binding Fc receptors on platelets or other cells. (5) Binding of HIT immune complexes (antibody bound to multimolecular complexes) triggers platelet activation and release of procoagulant microparticles.

Figure 2.

Diagnostic algorithm for heparin-induced thrombocytopenia (HIT). ^aThrombocytopenia can be absolute ($<150,000/\mu\text{l}$) or relative ($>30\%$ decrease in platelet counts from the highest platelet count prior to initiation of heparin therapy). ^bDecision to initiate alternative anticoagulant therapy should be guided by assessment of patient's bleeding risk and comorbidities. ^cDecision to continue unfractionated heparin or low-molecular weight heparin (LMWH) should be individualized. ^dFunctional assay recommended, if clinically available. ^eAntibodies with non-PF4/heparin specificity may be causative of disease. ^fDecision to continue alternative anticoagulant therapy should be individualized.

Table 1Warkentin's (74) 4Ts clinical scoring system^a

	2	1	0
Thrombocytopenia	>50% fall or platelet nadir 20–100 × 10 ⁹ L ⁻¹	30%–50% fall or platelet nadir 10–20 × 10 ⁹ L ⁻¹	Fall < 30% or platelet nadir < 10 × 10 ⁹ L ⁻¹
Timing of fall in platelet count or other sequelae	Clear onset between days 5 and 10; or <1 day (if heparin exposure within past 100 days)	Consistent with immunization but not clear (e.g., missing platelet counts) or onset of thrombocytopenia after day 10	Fall in platelet count too early (without recent heparin exposure)
Thrombosis or other sequelae (e.g., skin lesions)	New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
Other cause for thrombocytopenia not evident	No other cause for fall in platelet count is evident	Possible other cause evident	Definite other cause present

^aPretest probability score: 6–8 = high; 4–5 = intermediate; 0–3 = low.