Heparin-induced Thrombocytopenia: Perioperative Diagnosis and Management

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Heparin-induced thrombocytopenia (HIT) is a severe immune-mediated disease in which heparin promotes thrombosis.[1] Approximately 10% of patients who experience HIT die in the hospital.[1] The incidence of HIT varies, depending on the type of heparin used and the patient population.[2,3] In a recent analysis of the United States' Nationwide Inpatient Sample, the incidence of HIT in patients after cardiac surgery with cardiopulmonary bypass (CPB) was 0.63%,[1] consistent with incidences reported in prospective trials.[2,3] In contrast, the incidence of HIT after trauma or injury was only 0.02 to 0.09% in that large retrospective population-based study, but 1 to 4% in prospective trials.[1,3,4] This might indicate that HIT, although intensively studied and discussed over a period of more than 20 yr, often remains undiagnosed.

In this clinical focus review, we are aiming to provide recent information on the mechanisms, diagnostic challenges, and therapy of HIT. This information should help address four important questions: (1) when to consider a diagnosis of HIT, (2) when to perform laboratory testing, (3) when to change heparin to an alternative anticoagulant, and (4) when to request a functional HIT confirmation assay.

New Insights into the Thrombogenic Mechanisms of HIT

HIT is caused by the formation of immunoglobulin G antibodies directed against ultralarge complexes of heparin and platelet factor 4 (PF4).[5–8] PF4 is a 7.8-kd, 70–amino acid highly basic protein stored in the alpha granules of platelets and released with platelet activation. Formation of such large complexes between PF4 and heparin requires stoichiometric ratios associated with charge neutralization, while ratios with significant charge imbalance lead to their disruption.[6]

The large-molecular-weight fragments of unfractionated heparin (hereinafter referred to as heparin) have greater immunogenicity than low-molecular-weight heparins, as at least 12 saccharides are necessary to form ultralarge complexes.[9] For heparin, the concentration most likely to cause HIT ranges from 0.1 to 1 U/ml. These concentrations resemble the plasma levels achieved during prophylactic and therapeutic anticoagulation.[5,9]

Binding of the immunoglobulin G antibodies to the PF4-heparin complex results in the formation of immune complexes which target immunoglobulin G binding to $Fc_{\gamma}RIIa$ receptors on platelets (fig. 1). Decreases in the platelet count result from this platelet activation and consumption, although, in contrast to other immune thrombocytopenic reactions, platelets rarely fall below 20×10^9.[5–8] Binding of the HIT immune complexes to monocyte and neutrophil $Fc_{\gamma}RIIa$ receptors leads to activation, with further acceleration of thrombin generation (fig. 1).[5–8] In addition to this immune immunoglobulin G–mediated cell activation, multiple prothrombotic pathways are activated, which may then additionally promote thrombosis in both venous (approximate incidence, 30%) and arterial (70%) locations.[5]

The Unique Timing of HIT: Implications for Diagnosis/Anticoagulation during Surgery and Intervention

HIT antibodies usually develop 4 to 14 days after the start of heparin therapy, and the subsequent decline in the platelet count usually occurs 2 to 4 days after seroconversion.[5–8] Thrombocytopenia or a decline of more than 30% in the platelet count compared to baseline, ensuing between 5 and 10 days after the start of heparin therapy, is the most characteristic feature of HIT. A special condition is major surgery, particularly cardiac surgery, where thrombocytopenia commonly sets in directly after the operation but usually resolves after 2 to 6 days.[2] In this case, resurgence of thrombocytopenia or a significant decline of the platelet count 5 to 10 days postoperatively is highly predictive for HIT.[2] The HIT immunoglobulin G antibodies are transient and usually persist 40 to 100 days before declining.[5–8] After re-exposure to heparin, it again takes 4 to 10 days until new antibody formation is observed.[10]

The American Society of Hematology (Washington, D.C.) guidelines describe four phases of HIT, depending on the value of the platelet count and antibody status observed in different

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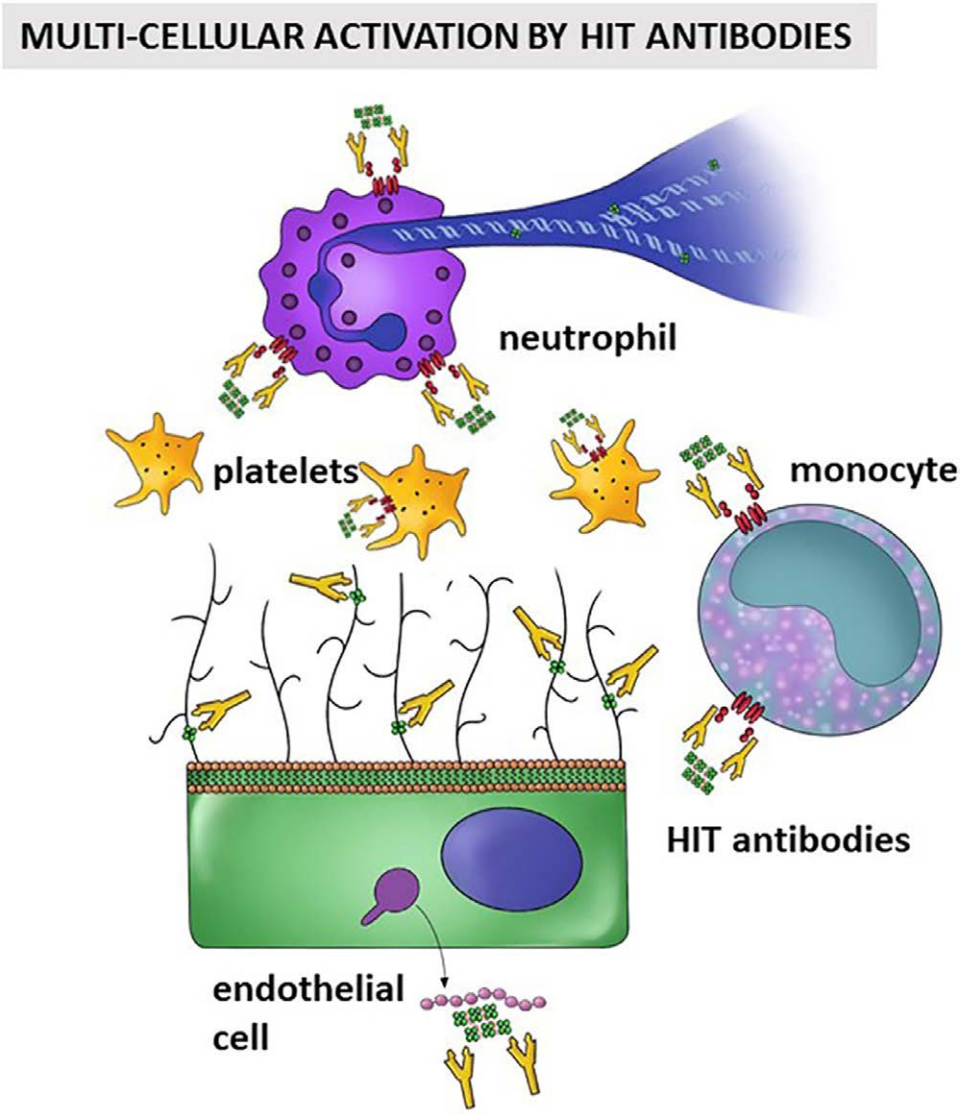

Fig. 1. Key elements of heparin-induced thrombocytopenia (HIT)–induced severe prothrombotic state. Antibodies bind to ultralarge complexes formed by platelet factor 4 and heparin. Binding of these immunocomplexes to the platelet Fc_{γ}RIIa immunoreceptor leads to platelet activation, with platelet degranulation, further release of platelet factor 4 and platelet aggregation, with release of microparticles that enhance thrombin generation and further platelet activation. This self-amplifying cascade of platelet activation, platelet consumption, and sequestration finally results in an acute decrease of the platelet count and thrombocytopenia. Thrombin generation is further accelerated *via* binding of the immunocomplexes to neutrophil Fc_{γ}RIIa immunoreceptors, which induces the formation of neutrophil extracellular traps (NEtosis). Binding to the monocyte Fc_{γ}RIIa immunoreceptor leads to cell surface tissue factor expression and its release *via* microparticles. In addition to this immune immunoglobulin G–mediated cell activation, immunoglobulin G binds to endothelial cell–bound platelet factor 4, which further promotes tissue factor expression, thrombin generation, and thrombus formation. From Arepally GM, Padmanabhan A: Heparin-induced thrombocytopenia: A focus on thrombosis. Arterioscler Thromb Vasc Biol 2021; 41:141–52, https://www.ahajournals.org/doi/10.1161/ATVBAHA.120.315445, with permission. © 2020 American Heart Association, Inc.

assays, as shown in table 1.[10] This classification has important implications for the intraoperative management of patients with HIT, as it defines situations in which heparin can be safely given and the conditions for which the use of an alternative anticoagulation strategy is recommended in guidelines.

Diagnosis of HIT

Diagnosis of HIT is based on clinical assessment and laboratory assays. Clinical scoring systems that calculate a pretest probability for HIT are used first. Immune assays are performed

Table 1. Phases of Heparin-induced Thrombocytopenia and American Society of Hematologists Recommendations for Perioperative/Peripocedural Anticoagulation Strategy[10]

Phase	Platelet Count	Functional Assay (Showing Heparin-induced Thrombocytopenia–induced Platelet Activation)	Immunoassay (Measuring Heparin-induced Thrombocytopenia Antibody Burden)	Anticoagulation Strategy
Acute heparin-induced thrombocytopenia	Decreased	+	++	➢ Bivalirudin ➢ Heparin +
Subacute heparin-induced thrombocytopenia A	Normal	+	++	• perioperative plasmapheresis *or* • antiplatelet agent
Subacute heparin-induced thrombocytopenia B	Normal	–	+	Heparin
Remote heparin-induced thrombocytopenia	Normal	–	–	Heparin

The acute phase of heparin-induced thrombocytopenia is characterized by a sudden decrease in the platelet count and detection of platelet-activating antibodies in the functional assay. After stopping heparin and starting alternative anticoagulation, the platelet count recovers within days. However, the antibody burden is still high, so that the functional assay remains positive (subacute heparin-induced thrombocytopenia A). Over time, the antibody burden decreases, so that the functional assay becomes negative, but the more sensitive immunoassay remains positive (subacute heparin-induced thrombocytopenia B). Usually, after 40 to 100 days, the antibody levels have decreased, and as a result, the immunoassay becomes negative (remote heparin-induced thrombocytopenia). It is believed that once the antibodies have decreased, the short-term use of heparin is safe, as it again takes days until antibodies can potentially respond to heparin administration.

to rule out HIT or to confirm the presence of antibodies. A definitive diagnosis is usually based on functional HIT assays, which show HIT-induced platelet activation.

Pretest Probability: Clinical Scoring Systems

The two main characteristic patterns of the HIT response, which form the basis for all scoring systems, are timing and decrease of platelet count. The platelet count falls 5 to 10 days after the start of heparin (or 1 day or less in case of heparin exposure within the past 100 days). Decrease of platelet count is characterized by a change of more than 30% and/or more than 20×10^9/l.[11] The 4Ts score is the most widely used HIT score (table 2).[11]

Apart from the characteristics mentioned, any new thrombosis and other reasons for thrombocytopenia are also considered when using the 4Ts score. The negative predictive value of a low test result in the 4Ts score is high (0.99) and therefore essentially excludes HIT, while the positive predictive value of a high test result is only 0.64 and thus requires confirmation with laboratory tests.[11]

Apart from perioperative platelet consumption, there are multiple reasons for postoperative thrombocytopenia in patients after major surgery, such as transfusion-related or other rare immune reactions, sepsis, shock with or without temporal mechanical circulatory support, and disseminated intravascular coagulation.[12–15] Furthermore, heparin may directly activate platelets, leading to a decrease in the platelet count. However, the decrease is mostly only moderate (less than 100×10^9/l) in this case.

After cardiac and other types of major surgery, dilutional changes may frequently occur. In addition, drugs routinely used in this setting, such as cephalosporins and other antibiotics or amiodarone, may cause drug-induced immune thrombocytopenia, a condition often consistent with the onset of HIT.[14] Although the typical platelet nadir in immune thrombocytopenia is lower than in HIT (less than 20^9/l), it is likely that a critically ill patient after major trauma will be transfused with platelet concentrates before this very low nadir is reached.[16] Therefore, the fourth T—"another reason for thrombocytopenia"—often confuses the diagnosis.[17]

The HIT expert probability score is more complex than the 4Ts score,[18] and particularly weights selected different causes of thrombocytopenia such as disseminated intravascular coagulation, temporal mechanical support, and CPB procedure in the last 96 h. In the intensive care setting, one group reported that the HIT expert probability score provides favorable results compared to the 4Ts score.[19] In the receiver operating characteristic analysis, the areas under the receiver operating characteristic curves (AUCs) were significantly higher for the HIT expert probability score when compared to the 4Ts score (0.86 *vs.* 0.79; $P = 0.03$). Among trainee scorers, the HIT expert probability score performed significantly better than the 4Ts score (AUC 0.80 *vs.* 0.73; $P = 0.03$). In a single-center study in cardiac surgery patients, both scores revealed almost comparable results and fair accuracy, with an AUC of 0.77 for the HIT expert probability score and 0.80 for the 4Ts score.[16] However, the specificity (49 *vs.* 71%) and sensitivity (94 *vs.* 69%) varied substantially between the systems tested. The "computerized risk score" and the "Groupe Français Hémostase et Thrombose HIT score" have been developed recently, but additional validation is needed.[20,21]

Laboratory Assays

Screening Test for HIT: Direct Detection of HIT Antibodies

HIT antibodies can be directly measured using immunoglobulin G–specific immunoassays.[22] The classical test system

Table 2. The 4Ts Scoring System

4Ts Category	2 Points	1 Point	0 Points
Thrombocytopenia/ platelet count decrease:	➢ Nadir ≥ 20^9/l ➢ > 50%	➢ Nadir 10–19^9/l ➢ 30–50%	➢ Nadir < 10^9/l ➢ < 30%
Timing of platelet count decrease	➢ Clear onset days 5–10 ➢ ≤ 1 d if previous heparin exposure within 30 d	➢ Consistent with days 5–10 decrease, but not clear ➢ Onset after day 10 or ➢ Decrease ≤ 1 d if previous heparin exposure in past 30–100 d	➢ ≤ 4 d without recent exposure
Thrombosis or other sequelae	➢ New thrombosis confirmed ➢ Skin necrosis ➢ Acute systemic reaction after intravenous heparin bolus	➢ Progressive thrombosis ➢ Nonnecrotizing skin lesions ➢ Suspected thrombosis (not proven)	➢ None
OTher causes of thrombocytopenia	➢ Bone apparent	➢ Possible	➢ Definite

Score according to the sum of points: score 6 to 8, high probability; score 4 to 5, intermediate probability; score 1 to 3, low probability.

is an enzyme-linked immunosorbent assay (ELISA), which is usually performed in batches, rather than daily, and as a result is not suitable to be used as an "on-demand" assay.[22]

More user-friendly rapid immunoassay test systems have been developed, such as the polyspecific (immunoglobulin A, immunoglobulin M, and immunoglobulin G antibodies measured) particle gel immune assay, and the chemiluminescent immunoassay, which are available in the form of a polyspecific or an immunoglobulin G–specific assay. These test systems provide results within 1 h, and the immunoglobulin G–specific rapid immunoassays, in particular, can be considered to be a revolution in the contemporary diagnosis of HIT.[22] However, the diagnostic accuracy depends on the thresholds of the assay. The immunoglobulin G–specific ELISA achieves a sensitivity of 99.6% with the low threshold of an optical density of 0.7 or less. However, a high specificity (greater than 90%) is only achieved with an intermediate (optical density of 0.8 to 1.4) threshold.[22] The immunoglobulin G–specific chemiluminescent immunoassay achieves a high sensitivity (greater than 95%) and a high specificity (greater than 90) only with a low threshold of 1.0 U/ml while the polyspecific chemiluminescent immunoassay archives these excellent results only with a high threshold of greater than 3.85 U/ml.[22]

Pretest Probability and Results of Immunoassays

A low to intermediate pretest probability and a negative result in the immunoglobulin G–specific or unspecific immunoassay rules out HIT.[23–25] A new strategy is to combine the pretest probability of the 4T score with a stratified interpretation of the strength of the test result of the immunoassay. Using both values, a posttest probability for HIT is calculated.[22] However, such Bayesian algorithms are complex and currently not implemented in clinical routine.

The Accepted Standard: Functional Washed Platelet Assays

The accepted standards for diagnosis of HIT are the functional washed platelet assays (the serotonin release assay and the heparin-induced platelet aggregation assay), which evaluate platelet activation in the presence of defined concentrations of heparin, patient serum, and donor platelets.[22] Test systems are not commercially available, so that "in-house" assays must be used. These often require preanalytic washing of platelets, which may cause activation and/or lack of sensitivity.

The reaction of donor platelets to immune activation varies among individuals, with polymorphisms of the platelet Fc_γRIIa receptor possibly playing a pivotal role.[7,22] Usually, only platelets of donors validated as being HIT-sensitive are employed when performing these assays.[7,22] The complex performance characteristics of the assays might explain the variation observed in results between different institutions.[26,27]

Recently the term "serotonin release assay negative HIT" was established. It describes the condition when the patient has HIT, but the definitive assay is negative.[28–30] The proposed mechanism is a loss of PF4 during the demanding preanalytical procedure, especially during the washing of the platelets. Modification of the assay by adding exogenous PF4 to the reaction mixture increases the sensitivity.[30] In this regard, the term "serotonin release assay negative HIT" indicates that even this "accepted standard" for laboratory diagnostics must be carefully evaluated.[22] Further functional HIT assays using platelet aggregometry or techniques measuring HIT antibody-induced platelet activation *via* flow cytometry have been developed, but are not widely available or validated.[22]

Correlation of Results of Immunoassays and Functional Assays

A highly positive result in the immunoassay (particularly the immunoglobulin G–specific assays) closely correlates with a positive reaction in the functional assay.[22] However, such thresholds in the immunoassay vary considerably. For example, for the chemiluminescent immunoassay, values of 3 U/ml or greater to 10 U/ml or greater (normal value, less than 1 U/ml) have been proposed, and for the ELISA,

an optical density of 1.4 or greater to 2 or greater (normal value, 0.3 to 0.5).[10,31–36] However, variability in the institutional "in-house" functional confirmation assay rather than the result of the commercially available ELISA or the rapid immunoassay can be considered significant.

Evaluation of the Risk of HIT: Still a Major Task

Despite the existence of algorithms for evaluating the risk of HIT, problems remain, particularly in the perioperative setting. This difficulty is outlined in an expert panel assessment of the HIT expert probability and 4Ts scores.[19] Three HIT experts evaluated whether patients had HIT based on detailed clinical information. This included 30-day follow-up and HIT laboratory testing with a nonspecific ELISA test and a serotonin release assay. Complete consensus among all three experts as to whether patients definitively had HIT or did not was reached in only 43% of patients (36 of 83). In the respective patients finally evaluated as having experienced HIT, 14 had negative serotonin release assays, 10 had a high HIT antibody burden, and 9 had thrombosis. These findings suggest that the serotonin release assay has limitations, including timing of the sample sent, and that HIT-related thrombosis is a multifactorial condition in which other factors may be important for prothrombotic responses.

Therapy and Perioperative Management of HIT Patients

The direct thrombin inhibitor (DTI) argatroban has been approved for prophylaxis and treatment of HIT in the United States and Europe. The DTI bivalirudin is often used "off-label" during cardiovascular surgery and in the intensive care setting, where it has been extensively studied, and it is recommended in guidelines (table 1).[37] Both anticoagulants have previously been reviewed for this indication in this journal.[37] Approximately 20 yr after their approval, both agents are used for suspected or diagnosed HIT but also as a heparin replacement in high-risk settings during extracorporeal membrane oxygenation.[38,39] After platelet count increases, patients are often transitioned from a DTI to warfarin for several months of anticoagulant therapy, due to an increased risk of thrombosis. The non–vitamin K direct oral anticoagulants are also increasingly used in HIT patients for treatment of acute HIT and thrombosis prophylaxis usually lasting at least 3 months.[10,40]

A recent retrospective single-center analysis compared major bleeding events in 310 patients who underwent HIT testing.[41] Four groups of patients were evaluated: (1) HIT-positive and treated with an alternative anticoagulant, (2) HIT-positive and not switched to an alternative anticoagulant, (3) HIT-negative and switched prophylactically to an alternative anticoagulant, or (4) HIT-negative and not treated with an alternative anticoagulant.[41] Evaluation of HIT was performed as described previously in another publication by three experts.[19] Bleeding rates were high but similar (35 to 44%) in all four study groups. However, these data also suggest that in patients with suspected HIT, the choice of anticoagulant is not the predominant factor determining the bleeding risk, but rather the overall critical condition of the patient particularly including those in the intensive care unit and with renal failure and/or thrombocytopenia.[41]

Polyvalent immunoglobulins (intravenous immunoglobulins) have been reintroduced in the treatment of acute HIT refractory to DTI anticoagulant therapy. The mechanism of action is the inhibition of HIT-induced platelet activation and the blocking the multicellular $Fc_{\gamma}RIIa$ receptor-mediated prothrombotic cascades.[42–44] The effects persist for 2 to 3 weeks due to the long half-life of immunoglobulins.[42–44] A specific polymorphism (termed H/R131) in FcγRIIa influences the susceptibility of platelets to intravenous immunoglobulin treatment, so that interindividual variation in the dose/response relationship is observed. However, after a 2 g/kg bolus infusion of immunoglobulins, HIT-induced platelet activation is significantly inhibited.[42] Plasmapheresis is used to reduce the antibody burden, particularly in severe HIT refractory to standard anticoagulant therapy.[44] Experiences with both strategies—high-dose immunoglobulin and plasmapheresis—are basically limited to single cases or small case series.[44] Larger sets of prospective data are needed.

Intraoperative anticoagulation during cardiovascular surgery in patients with active HIT remains a challenge. Bivalirudin, according to current guidelines, is the "alternative" anticoagulant of choice in patients with active HIT who need urgent cardiac surgery.[10,45,46] However, this strategy has important limitations. Bivalirudin is eliminated *via* enzymatic cleavage by thrombin (80%) and the renal pathway.[37] Due to this unique pharmacology, the perfusion technique during CPB must be considerably modified. This requires an experienced team. Despite the short half-life of approximately 30 min, excessive bleeding has been described.[37] This particularly affects patients with severely impaired renal function undergoing complex cardiac surgery.[37] Other approaches have combined heparin with a reversible antiplatelet to inhibit/attenuate the HIT-induced platelet activation, so that heparin can be safely used intraoperatively for CPB.[10,45] Likewise, plasmapheresis has been used perioperatively to reduce the HIT antibody burden, allowing heparin exposure during CPB.[47] Both approaches are consistent with recent HIT guidelines (table 1).[10] However, guidelines clearly point out that this is a conditional recommendation with low certainty regarding the level of evidence.[10]

New data suggest that high-dose intravenous immunoglobulins given during CPB, combined with the ultra–short-acting platelet P_2Y_{12} cangrelor, also facilitate heparin use in the setting of acute HIT and subacute HIT A and urgent cardiovascular surgery.[48,49] *In vitro* data showed substantial inhibition of HIT-induced platelet activation not only intraoperatively but, consistent with the long half-life of intravenous immunoglobulin, also during the first postoperative days.[49] Perioperative inhibition/attenuation of

the multicellular HIT reaction with high-dose intravenous immunoglobulins can be considered a new promising option when bivalirudin anticoagulation is evaluated as being associated with an unacceptable bleeding risk. However, the discussed variable effect due to the platelet FcγRIIa receptor polymorphism can be considered to be the Achilles' heel of this concept.[48] Further validation is warranted.

Conclusions

Sophisticated scoring tools form the basis for a rational diagnostic approach to HIT. The 4Ts score has substantial limitations, particularly in the setting of major surgery. The armamentarium available to treat HIT is evolving. It provides better help with balancing the risk of HIT and the risks associated with an alternative perioperative management strategy. In this regard, clear and timely diagnosis rather than perioperative management of the disease remains a key problem.

Therefore, in patients at risk, platelet count assessment should be performed daily based on published guidelines.[10,45] Additionally, scoring tools should be meticulously applied particularly during the critical period of day 4 to 14 of heparin.[10] Until new scoring tools are validated and established, to answer the previously outlined four questions, (1) HIT should be considered when a characteristic decrease of the platelet count and/or thrombosis is observed. This should potentially (2) trigger a laboratory diagnostic approach. (3) If a rapid immunoassay is available, the therapeutic decision can wait for the test result. If the diagnostics take more time, heparin should be discontinued, and anticoagulant therapy changed to a DTI as guidelines recommend.[10,45] The question of (4) when confirmation of the diagnosis with a functional assay is required remains a challenge. Contemporary immunoglobulin G–specific immunoassays provide a high specificity and sensitivity. In line with most recently published guidelines, in a patient with an intermediate or high pretest probability, confirmation may not be necessary,[10] when a "highly positive" test result is achieved. However, threshold values are not clearly defined for all assays or generally accepted. We consider that convincing data support that a high chemiluminescent immunoassay value of 3 U/ml or greater or optical density of 1.4 or greater in the ELISA suggests a substantial antibody burden with a high probability of HIT-induced platelet activation. This probability of severe HIT, respectively the persistence of an antibody burden which is still platelet-activating, has significant implications for the intraoperative anticoagulation management.[10]

Future Perspectives

HIT is associated with high morbidity, and time is of the essence. The improvement of HIT scoring tools and their automated computerization are necessary. Broad availability of rapid immunoglobulin G–specific immunoassays will further help to facilitate timely diagnosis. However, prevention of HIT should be a parallel strategy. In a prospective single-center study, an "avoid heparin" strategy was compared to treatment in a previous period.[50] Heparin was avoided or replaced by low-molecular-weight heparin whenever possible. After the change, a substantial reduction of the incidence of HIT was observed.

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Competing Interests

Dr. Levy is on advisory committees for Instrumentation Labs (Bedford, Massachusetts), Merck (Kenilworth, New Jersey), and Octapharma (Hoboken, New Jersey). The other authors declare no competing interests.

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