Platelet Count Monitoring and Laboratory Testing for Heparin-Induced Thrombocytopenia

Recommendations of the College of American Pathologists

Theodore E. Warkentin, MD

Objective.—Heparin-induced thrombocytopenia (HIT) is an antibody-mediated adverse drug reaction that paradoxically is associated with a brief but dramatically increased risk for thrombosis (transient acquired thrombophilia). The objective of this article is to provide practical recommendations for platelet count monitoring in patients receiving heparin, as well as for selection of laboratory assays to detect pathogenic HIT antibodies.

Study Selection.—Relevant literature that focused on frequency and timing of HIT in various clinical settings and that dealt with laboratory testing for HIT antibodies was critically appraised.

Data Extraction and Synthesis.—The author prepared a preliminary manuscript including recommendations that was presented to participants at the College of American Pathologists Conference XXXVI: Diagnostic Issues in Thrombophilia (November 10, 2001). Support of at least 70% of conference participants was required for recommendations to be adopted.

Heparin-induced thrombocytopenia (HIT) is a paradoxical anticoagulant-induced prothrombotic disorder characterized by thrombocytopenia. It is appropriate to consider HIT as an acquired (immune-mediated) thrombophilia, as it is caused by heparin-dependent, platelet-activating immunoglobulin (Ig) G, and because it is associated with thrombosis (transient acquired thrombophilia). The intensity of platelet count monitoring should be stratified depending on the clinical situation. Platelet count monitoring should focus on the period of highest risk (usually days 5 to 10 after starting heparin) and should use an appropriate platelet count baseline (generally, the highest platelet count beginning 4 days after start of heparin). However, earlier platelet count monitoring is appropriate if the patient received heparin within the past 100 days, as already circulating HIT antibodies can cause rapid-onset HIT with heparin re-exposure. Although both antigen and (washed platelet) activation assays are very sensitive for detecting clinically significant HIT antibodies, activation assays have greater diagnostic specificity for clinical HIT.

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Conclusions.—The risk of immune HIT varies depending on the type of heparin (unfractionated heparin greater than low-molecular-weight heparin) and patient population (surgical greater than medical). Thus, the intensity of platelet count monitoring should be stratified depending on the clinical situation. Platelet count monitoring should focus on the period of highest risk (usually days 5 to 10 after starting heparin) and should use an appropriate platelet count baseline (generally, the highest platelet count beginning 4 days after start of heparin). However, earlier platelet count monitoring is appropriate if the patient received heparin within the past 100 days, as already circulating HIT antibodies can cause rapid-onset HIT with heparin re-exposure. Although both antigen and (washed platelet) activation assays are very sensitive for detecting clinically significant HIT antibodies, activation assays have greater diagnostic specificity for clinical HIT.
to heparin-like glycosaminoglycans located on the endothelial cell surface; endothelium injured by HIT antibodies expresses tissue factor. There is also recent evidence that HIT antibodies can cause monocytes to synthesize tissue factor. Finally, PF4 released from activated platelets binds to heparin and neutralizes its anticoagulant properties. All these events conspire to generate a procoagulant state; these patients appear to have high titer of platelet-activating IgG antibodies, which clinically resembles a transient autoimmune prothrombotic syndrome.

**CLINICAL PICTURE**

**Timing of Thrombocytopenia**

The typical presentation of HIT is a plateau count decrease that begins 5 to 10 days after starting heparin (day heparin starts equals day 0). In about 30% of patients, HIT is recognized when there is a rapid fall in the platelet count, starting within minutes or hours of heparin administration. Recent heparin use, generally within the past 100 days, explains this profile, that is, rapid-onset HIT is caused by heparin administered to a patient with already existing chronic thrombocytosis. Heparin-induced thrombocytopenia antibodies are generally transient and become undetectable at a median of 50 to 85 days following the occurrence of HIT, depending on the assay performed. The rapid formation of pathogenic IgG antibodies as early as 5 days after starting heparin, as well as the transience of these antibodies, appears to explain the temporal profile of HIT. Rarely, thrombocytopenia and thrombosis attributable to HIT can begin several days after discontinuation of heparin (delayed-onset heparin-induced thrombocytopenia and thrombosis); these patients appear to have high titer of platelet-activating IgG antibodies, which clinically resembles a transient autoimmune prothrombotic syndrome.

**Severity of Thrombocytopenia**

In large studies, the median platelet count nadir has been reported as approximately 55–60 × 10⁹/L. Only about 10% of patients have platelet counts less than 20 × 10⁹/L, which is in marked contrast with typical drug-induced immune thrombocytopenia caused by quinine, quinidine, sulfa antibiotics, and others, in which the platelet count nadir almost invariably is less than 20 × 10⁹/L. Also, in about 10% of patients with HIT, the platelet count nadir never falls to less than 150 × 10⁹/L, often because the HIT complicates a postoperative course that would otherwise be characterized by postoperative thrombocytosis, or occasionally because the patient has a pre-existing chronic thrombocytosis. However, in these patients, there usually is a substantial fall in the platelet count attributable to HIT of 50% or more.

**Thrombosis**

Heparin-induced thrombocytopenia is strongly associated with venous and arterial thrombosis (odds ratio, 37;
Venous thrombosis is most common, particularly lower limb deep venous thrombosis and pulmonary embolism. Upper limb deep venous thrombosis is strongly associated with the use of a central line. Arterial thrombosis is also relatively common and occurs most often in lower limb arteries, followed by stroke and myocardial infarction (ie, the opposite of the usual target distribution for arterial disease). The arterial thrombi are often platelet- and leucocyte-rich, and are known as “white clots.” Limb loss can be caused by arterial thromboembolism involving large arteries or by microvascular thrombosis; the latter syndrome usually is characterized by progression of deep venous thrombosis to acral necrosis in a patient who develops a supratherapeutic international normalized ratio during treatment with warfarin or other oral anticoaguants, that is, coumarin-induced venous limb gangrene.

Other Sequelae

Bleeding is uncommon in HIT; even the occasional patient with severe thrombocytopenia typically does not have petechiae. The uncommon, but characteristic, complication of adrenal hemorrhagic necrosis is believed to result from adrenal vein thrombosis that leads to hemorrhagic necrosis of the adrenal glands. Necrotic or erythematous skin lesions at heparin injection sites occur in 10% to 20% of patients who form HIT antibodies during subcutaneous heparin administration. Only a minority of these patients develop thrombocytopenia, however. Acute systemic reactions that begin 5 to 30 minutes after intravenous heparin bolus can be the first clue that a patient has HIT. Although virtually all patients with HIT can be regarded as having disseminated intravascular coagulation based on laboratory markers of in vivo thrombin generation, in only 5% to 10% of patients is the disseminated intravascular coagulation uncomplicated, that is, associated with hypofibrinogenemia or prolongation of the international normalized ratio.

Frequency

An unusual aspect of HIT is its variable frequency, depending on the type of heparin and the type of patient population. Unfractionated heparin (UFH) is more likely to cause both HIT antibody formation and clinical HIT, compared with low-molecular-weight heparin (LMWH). In addition, surgical patients appear to be more likely to develop HIT than medical patients. About 15% of orthopedic surgery patients who receive UFH for 2 weeks develop HIT antibodies; one third of these patients (5% overall) develop clinical HIT (defined as a 50% or greater fall in the platelet count). In contrast, although 50% of cardiac surgery patients form HIT antibodies following heart surgery, only about 5% of these (2%–3% overall) develop clinical HIT. The frequency of both HIT antibody formation and clinical HIT is believed to be lower in medical patients receiving heparin, but this patient group has not been studied as extensively.

Table 2. Sensitivity and Specificity of Selected Activation and Antigen Assays for Detecting Clinically Significant Heparin-Induced Thrombocytopenia Antibodies

<table>
<thead>
<tr>
<th>Diagnostic Assay</th>
<th>Sensitivity, %</th>
<th>Early Platelet fall</th>
<th>Late Platelet fall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet [14C] serotonin release assay</td>
<td>90–98†</td>
<td>&gt;95</td>
<td>80–97§</td>
</tr>
<tr>
<td>Heparin-induced platelet aggregation assay</td>
<td>90–98†</td>
<td>&gt;95§</td>
<td>80–97§</td>
</tr>
<tr>
<td>Platelet aggregation test using citrated platelet-rich plasma</td>
<td>35–85</td>
<td>90§</td>
<td>82§</td>
</tr>
<tr>
<td>Platelet factor 4/heparin enzyme immunoassay</td>
<td>&gt;90</td>
<td>&gt;95</td>
<td>50–93</td>
</tr>
<tr>
<td>Combination of sensitive activation and antigen assay</td>
<td>100§</td>
<td>&gt;95§</td>
<td>80–97§</td>
</tr>
</tbody>
</table>

* “Early” refers to a fall in the platelet count that begins within the first 4 days of starting heparin; “late” refers to a fall that begins on day 5 or later. The data range for the late platelet count fall indicates cardiac patients receiving unfractionated heparin and orthopedic patients receiving low-molecular-weight heparin, respectively."

† Assumes use of certain control maneuvers, including use of weak positive control sera and selected and/or multiple platelet donors. Also, in about 5% of heat-inactivated serum, heparin-independent platelet activation is observed. If a new serum aliquot is heat-inactivated, and the test repeated, an interpretable result is achieved in at least half the cases. However, about 30% to 40% of samples (~2% overall) give a repeated “indeterminate” result and the activation assay is nondiagnostic.

‡ Assumes that the heparin-induced platelet aggregation test and serotonin release assay have similar sensitivity and specificity profiles; other platelet activation endpoints that may also give acceptable results using washed platelets include detection of platelet-derived microparticles by flow cytometry.

§ Assumes a 90% specificity in early thrombocytopenia attributable to non–heparin-induced thrombocytopenia (HIT) disorders (eg, nonspecific platelet activation related to acute inflammatory proteins) declines to an 82% specificity in late thrombocytopenia, which may be attributable to subclinical HIT antibody seroconversion.

∥ Clinopathologic definition assumes that at least 1 sensitive test must be positive for diagnosis of HIT; specificity of the activation assay is indicated.
Figure 1. Comparison of activation and antigen assays for heparin-induced thrombocytopenia—immunoglobulin G (HIT-IgG) antibodies in patients who have undergone cardiac and orthopedic surgery. Quantitative results of activation and antigen tests for HIT-IgG are shown for 3 clinical treatment settings: orthopedic unfractionated heparin (UFH) (A), orthopedic low-molecular-weight heparin (LMWH) (B), and cardiac UFH (C). Results are shown for all 744 patients. All antigen assay data are given quantitatively. For the activation assay results, samples that gave >20% serotonin release are shown without reference to the actual quantitative result (see box designated >20%). Arrows indicate the data points corresponding to the 15 patients with HIT identified in these prospective studies ($\geq 50\%$ fall in the platelet count from the postoperative peak platelet count). The results indicate that whereas the antigen assay is more sensitive for detecting clinically insignificant HIT-IgG, both the antigen and activation assays have equally high sensitivity for detecting clinical HIT. Furthermore, the activation assay has the highest specificity for clinical HIT. Reprinted with permission from Blood.9 Copyright 2000, WB Saunders.

Washed Platelet Activation Assays

Washed platelet activation assays, such as the platelet [$^{14}$C]serotonin release assay and the heparin-induced platelet activation test, are used by a few reference laboratories. A major drawback is their technically demanding nature; for example, Eichler et al reported results of a workshop that showed considerable variability among laboratories in reporting results using the platelet activation (heparin-induced platelet activation) test, compared with the antigen assay. Attention to methodologic detail is crucial; for example, use of apyrase in a wash step is necessary to maintain platelet reactivity to HIT antibodies.

A fundamental problem is that these assays use a non-specific endpoint (platelet activation), and thus care must be taken to ascertain that a given platelet activation response is actually caused by HIT antibodies, rather than residual thrombin or immune complexes. This can be accomplished by requiring the following reaction criteria to detect HIT antibodies: (1) significant platelet activation at a heparin concentration of 0.1 to 0.3 U/mL that is generally greater than that observed at 0 U/mL heparin; (2) absence of significant platelet activation at a high heparin concentration; (3) absence of significant platelet activation in the absence of heparin; (4) absence of significant platelet activation in the presence of an inhibitor of thrombin; (5) absence of significant platelet activation in the presence of an inhibitor of platelet factor 4; (6) absence of significant platelet activation in the presence of an inhibitor of immune complexes; (7) absence of significant platelet activation in the presence of an inhibitor of platelet aggregation; (8) absence of significant platelet activation in the presence of an inhibitor of platelet factor 4-dependent enzyme immunoassay. Reprinted with permission from Warkentin and Greinacher.8Copyright 2001, Marcel Dekker Inc.

Figure 2. Diagnostic algorithm if using an antigen assay to screen for heparin-induced thrombocytopenia (HIT). For patients with “typical onset” of thrombocytopenia, the pretest probability of HIT is usually judged to be moderate or high, depending primarily on whether another plausible explanation for thrombocytopenia is apparent, and whether new thrombosis has occurred. For patients with rapid onset of thrombocytopenia, the pretest probability of HIT is usually judged to be low or high, depending primarily on whether there has been recent exposure to heparin, and whether another plausible explanation for thrombocytopenia is apparent. The asterisk indicates that a platelet activation assay could be useful in a patient with only a moderate pretest probability for HIT and a positive platelet factor 4 (PF4)-dependent enzyme immunoassay, as a positive activation assay has a higher specificity for clinical HIT. NEG indicates negative test result; IND, indeterminate test result (e.g., result for PF4-dependent enzyme immunoassay weakly positive, e.g., <1.0 optical density [OD] units); POS, clear positive test result (>1.0 OD units); SRA, serotonin release assay (activation test); HIPA, heparin-induced platelet activation assay. Reprinted with permission from Warkentin and Greinacher.8Copyright 2001, Marcel Dekker Inc.
concentration (100 U/mL); and (3) platelet activation inhibited by a monoclonal antibody that blocks the platelet Fc receptor.

Prior to performing the assay, residual thrombin in the serum or plasma sample must be heat-inactivated (56°C for 30 minutes). In about 5% of samples tested, the heat-inactivated serum gives an “indeterminate” result, that is, the serum causes platelet activation at all heparin concentrations tested. By obtaining another untreated serum aliquot and performing heat-inactivation, the second aliquot may then give a clear positive or negative result (suggesting that heat-aggregated IgG immune complexes may have been formed using the first serum sample). Unfortunately, almost half of these samples (about 2% overall) give persistent indeterminate results, perhaps because of circulating immune complexes; in these cases, an antigen assay must be used for investigation of HIT antibodies.45

There is considerable variability among HIT sera in their ability to effect platelet activation, as well as in platelets obtained from various normal donors to be activated by HIT sera.40 Fortunately, these differences in reactivity are hierarchical, that is, HIT sera and platelet donors can be ranked from most to least reactive, with individual serum/platelet reactions following a predictable pattern. This hierarchy has important quality control implications, for example, optimally reactive platelet donors should be used whenever possible, and both weak and strong positive control sera should be used to ensure that the platelets used in any activation assay are capable of responding even to a weak HIT serum.40 Some laboratories test against a panel of 4 different platelet donors, which may increase diagnostic sensitivity.41

**Platelet Aggregation Test**

The platelet aggregation test (PAT) using citrated platelet-rich plasma and standard platelet aggregometry was among the first assays used to detect HIT antibodies.43 One method42 found the sensitivity and specificity to each to be about 80% (using the most reactive platelets and in comparison with nonthrombocytopenic patients receiving heparin). Two studies that directly compared the PAT with either the serotonin release assay46 or the heparin-induced platelet activation assay42 found the sensitivity of the PAT to be only 33% to 46% of that of the washed platelet assays. A major problem with the PAT is that only a limited number of test conditions and patient/control samples can be tested at any one time. This restriction limits the number of maneuvers that can be used to ensure high test sensitivity and specificity. It is also possible that platelets suspended in citrated platelet-rich plasma will react nonspecifically to heparin in the presence of fibrinogen and other acute phase reactants that may be present in the plasma of an ill patient, suggesting the potential for false-positive diagnosis and lower test specificity.47 For these reasons, platelet aggregation assays have been superseded in recent years by other assays, particularly the antigen assays. If the PAT is used as an initial test for HIT, a positive test generally supports the diagnosis of HIT, and further testing is usually not required. However, given the lower sensitivity of the PAT (Table 2), a negative test does not exclude HIT in a patient with a moderate or high pretest probability for HIT. In these situations, further testing with the antigen assay or washed platelet activation assay (or both) should be performed. Some laboratories perform the PAT when there is a weak positive antigen assay result so as to help determine the clinical significance of the positive antigen assay.

**Platelet Factor 4–Dependent Antigen Assays**

Two PF4-dependent antigen assays have been developed that are commercially available for detecting HIT antibodies.8,38,48,49 One assay, known as the Asserachrom (Stago, Asnières, France), detects antibodies reactive with PF4-heparin complexes. A more recent test, known as the GTI-PF4 (GTI, Brookfield, Wis), detects antibodies reactive with PF4 bound to polyvinylsulfonate. Both tests use goat anti-IgG/IgA/IgM to detect HIT antibodies. However, although there is anecdotal evidence that IgM and IgA HIT antibodies might occasionally cause HIT,50 prospective studies have shown that assays that detect only HIT-IgG antibodies have very high sensitivity for diagnosing clinical HIT.9,10 Thus, a drawback of the antigen assays is that they are more likely to detect clinically insignificant HIT antibodies, compared with sensitive washed platelet activation assays. This finding was indeed true even when an activation assay (serotonin release assay) was compared with an in-house antigen assay that detected only IgG antibodies reactive with PF4-heparin (Figure 1).9

Newman and colleagues51 developed a fluid-phase antigen assay that avoids problems of protein (antigen) denaturation inherent in solid-phase assays. This assay may give a lower rate of false-positive reactions and also is useful for assessing in vitro cross-reactivity of HIT-IgG against LMWH and heparinoids. Van and colleagues52 found that binding of HIT-IgG to PF4-heparin adsorbed onto positively charged nylon membranes could also permit an antigen assay that avoided using PF4-heparin bound to plastic. There is emerging consensus8,36,53,52 that antigen assays that detect only HIT antibodies of the IgG class are suitable to confirm a clinical diagnosis of HIT; at present, however, these assays are not commercially available.

**Particle Gel Immunoassay (ID-H/PF4 Test)**

The particle gel immunoassay (ID-H/PF4 test) has adopted the ID microcolumn system used for red cell serology by using special red-dyed, high-density polystyrene particles coated with PF4-heparin complexes that serve as a solid phase. Patient serum and PF4-heparin-coated microbeads are added to the incubation chamber of the microcolumn card, and after a 5-minute incubation, the card is centrifuged. A strong positive result is indicated by the agglutinated microbeads remaining at the top of the column.53 The assay is technically easy, rapid, and can be automated. A preliminary study44 suggested that this assay may have sensitivity intermediate between activation and commercial antigen assays, with specificity resembling that of the activation assays. This assay therefore offers promise as a rapid, routine assay for HIT.

**TEST APPLICATIONS**

Heparin-induced thrombocytopenia assays are performed most often to investigate patients who develop thrombocytopenia, with or without thrombosis, that begins during, or soon after, heparin treatment. For such patients, both the washed platelet activation assays and antigen assays have similar high sensitivity for detecting clinically significant HIT antibodies (Table 2). Diagnostic specificity is greater for washed platelet activation assays, however, particularly in patients following cardiac sur-
Heparin-induced thrombocytopenia assays are also performed for research purposes, such as to determine the frequency of HIT antibody seroconversion in various clinical settings during treatment with various preparations of heparin. In these situations, the antigen assay is more sensitive for detecting antibodies, and thus for determining differences in frequency of HIT antibodies in different clinical settings. Serologic studies have also shown that many patients develop PF4–heparin-reactive antibodies of the IgA and/or IgM classes that do not cause clinical HIT (generally, thrombocytopenia and thrombosis), but with negative testing for HIT antibodies using both activation and antigen assays. For some pseudo-HIT disorders, heparin treatment can result in platelet count recovery (eg, cancer-associated and pulmonary embolism–associated disseminated intravascular coagulation [DIC]).

Figure 2 suggests an algorithm for diagnostic testing that assumes an antigen assay is used as a screening test for HIT. In a patient with low or moderate pretest probability for HIT, the sensitivity of an antigen assay is sufficient high that a negative test essentially rules out the diagnosis of HIT. However, this practice often will require the serum to be referred to a reference laboratory.

**CRITERIA FOR DIAGNOSIS**

Heparin-induced thrombocytopenia should be viewed as a clinicopathologic syndrome, that is, the diagnosis should be made only if clinical abnormalities are seen and HIT antibodies are detected (see Table 1). A corollary is that negative testing for HIT antibodies using 2 sensitive assays (preferably, 1 activation and 1 antigen assay) essentially rules out HIT, even if the clinical picture otherwise is suggestive of HIT. Indeed, there are a number of “pseudo-HIT” disorders that can resemble HIT clinically, but in which HIT antibodies are not detectable and another explanation for thrombocytopenia and thrombosis is apparent (Table 3).

**Table 3. Pseudo–Heparin-Induced thrombocytopenia (HIT) Disorders**

<table>
<thead>
<tr>
<th>Pseudo-HIT Disorder</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>Thrombocytopenia may complicate cancer-associated DIC/thrombosis, especially after stopping heparin; warfarin-associated venous limb gangrene has been reported in these patients.</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Platelet activation may be secondary to clot-bound thrombin</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>Hyperaggregable platelets predispose to thrombocytopenia and thrombosis</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>Pathogenesis of thrombocytopenia is obscure, but could involve platelet-activating antibodies in some instances</td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td>Platelet activation by thrombin bound to fibrin degradation products</td>
</tr>
<tr>
<td>Septicemia-associated DIC/purpura fulminans</td>
<td>Symmetric peripheral gangrene secondary to DIC with depletion of protein C has been reported</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>Infection-associated thrombocytopenia; ischemic events secondary to septic emboli</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>Platelets susceptible to complement-mediated damage</td>
</tr>
<tr>
<td>Posttransfusion purpura</td>
<td>Although timing of thrombocytopenia resembles HIT (ie, 5–10 d after surgery requiring blood products), patients with posttransfusion purpura develop bleeding rather than thrombosis</td>
</tr>
</tbody>
</table>

* Pseudo–heparin-induced thrombocytopenia (HIT) disorders are defined as those that clinically resemble HIT (generally, thrombocytopenia complicated by thrombosis), but with negative testing for HIT antibodies using both activation and antigen assays. For some pseudo-HIT disorders, heparin treatment can result in platelet count recovery (eg, cancer-associated and pulmonary embolism–associated disseminated intravascular coagulation [DIC]).
helpful to suggest a diagnosis of HIT if the assay was only weakly positive (0.45 < OD < 1.0).

A blood sample obtained during thrombocytopenia is recommended for use in diagnostic testing. Although some investigators have reported that the sensitivity of certain assays may be somewhat higher using a blood sample obtained 1 or 2 days after discontinuation of heparin, this does not appear to be the situation for sensitive washed platelet activation or antigen assays. However, it is important to test ‘acute’ sera, since HIT antibodies are transient and usually become undetectable within just a few weeks following an episode of HIT.

**Table 4.** Recommendations: Platelet Count Monitoring for Early Detection of Heparin-Induced Thrombocytopenia (HIT)*

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients at highest risk for HIT (postoperative patients receiving prophylactic or therapeutic-dose unfractionated heparin): minimum monitoring during heparin therapy, every second day from day 4 to day 10.†4,9,14,15,58 Level 1</td>
</tr>
<tr>
<td>2. The crucial time period for monitoring “typical-onset” HIT is between days 4 and 10† after starting heparin, where the highest platelet count from day 4 (inclusive) onward represents the “baseline.”3,5,25 Level 1</td>
</tr>
<tr>
<td>3. For a patient recently exposed to heparin (within the past 100 d), a repeat platelet count obtained within 24 h following resumption of heparin is recommended to identify patients with rapid-onset HIT due to already circulating HIT antibodies.2,5,26 Level 1</td>
</tr>
<tr>
<td>4. A platelet count should be measured promptly and compared with recent values in a patient who develops thrombosis during or soon after heparin therapy, or in a patient who develops an unusual clinical event in association with heparin therapy (eg, heparin-induced skin lesions, acute systemic reaction post–intravenous heparin bolus).5,25,26 Level 1</td>
</tr>
<tr>
<td>5. A platelet count fall of 50% or greater from baseline can indicate HIT, even if the platelet count nadir remains above 150 × 10⁹/L; occasionally, platelet count declines of even lesser magnitude attributable to HIT can be associated with thrombotic events.5,31 Level 1</td>
</tr>
</tbody>
</table>

* Definition of levels of evidence: Level 1, 1 or more well-designed prospective studies or 2 or more well-designed retrospective studies; Level 2, retrospective studies or multiple anecdotal studies that reach consensus; and Level 3, isolated anecdotal studies and/or the consensus of expert practitioners.

† First day of heparin use is day 0; platelet count monitoring should be extended beyond day 10 if the platelet count begins to fall unexpectedly during the day 4 to day 10 period, or if heparin therapy is interrupted and restarted because of an intervening surgical or procedural intervention.

‡ Platelet count monitoring may not be practical when low-molecular-weight heparin is given to outpatients.

§ Monitoring as per the “intermediate” risk group is appropriate if 1 or more doses of unfractionated heparin were given prior to initiating therapy with low-molecular-weight heparin.5,25

<table>
<thead>
<tr>
<th>Table 5. Recommendations for Laboratory Testing for Heparin-Induced Thrombocytopenia (HIT) Antibodies*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heparin-Induced Thrombocytopenia antibody testing is recommended for patients in whom there is clinical suspicion of HIT, based on the temporal features of the thrombocytopenia, or based on the occurrence of new thrombosis during, or soon after, heparin treatment.1,3,18,50 Level 1</td>
</tr>
<tr>
<td>2. Acute serum or plasma should be used for testing whenever possible, since HIT antibodies are transient, and may not be detectable even a few weeks after clinical HIT.2,5,25 Level 1</td>
</tr>
<tr>
<td>3. An antigen assay is an appropriate screening test for most laboratories that can perform enzyme immunoassays; however, confirmatory testing using a sensitive washed platelet activation assay (eg, platelet serotonin release assay, heparin-induced platelet activation [HIPA] test) may be appropriate if antigen assay results are weakly positive (indeterminate) or positive testing occurs in a patient with low pretest probability for HIT. In these situations, a negative activation assay suggests the patient likely did not have HIT.1,3,18,42,48,49,57 Level 1</td>
</tr>
<tr>
<td>4. Washed platelet activation assays (eg, platelet serotonin release assay, HIPA test) have high sensitivity and specificity for clinical HIT; however, these assays are technically demanding and are most appropriate for reference laboratories.1,3,18,42,48,49,57 Level 1</td>
</tr>
<tr>
<td>5. If the platelet aggregation test (PAT) using citrated platelet-rich plasma is used as an initial test for HIT, a positive test generally supports the diagnosis of HIT, and further testing is usually not required. However, given the lower sensitivity of the PAT, a negative test does not exclude HIT in a patient with a moderate or high pretest probability for HIT. In these situations, further testing with the antigen assay, the washed platelet activation assay, or both should be performed.1,3,18,48 Level 1</td>
</tr>
</tbody>
</table>

* Levels of evidence are explained in the first footnote to Table 4.

**SPECIFIC RECOMMENDATIONS**

**Platelet Count Monitoring**

The frequency of platelet count monitoring should take into account the risk for HIT, which depends on the type of heparin used and the patient population under consideration (Table 4). The highest risk for HIT (2%–5%) is in postoperative patients receiving prophylactic doses of UFH (10 000–15 000 U/day) for at least 5 days, particularly postoperative orthopedic, cardiac, and vascular surgical patients. Thus, platelet count monitoring should involve a minimum testing at 2-day intervals, beginning on postoperative day 4 and continuing until postoperative day 10, or even later if a suspicious platelet count decline begins within the day 5 to day 10 period. In contrast, medical and obstetrical patients receiving prophylactic or therapeutic doses of LMWH have a low risk of HIT (probably less than 0.2%), and many physicians would not perform routine platelet count monitoring. For patients receiving LMWH following major orthopedic surgery, there is an intermediate risk of HIT, approximately 0.5% in one study. For these patients, it seems reasonable to obtain 1 or 2 platelet counts between days 5 and 10, although such testing may not be practicable if patients are discharged early to home with continued outpatient administration of LMWH. Extended prophylaxis with LMWH is not a reason to perform platelet count monitoring, as the risk of HIT declines after the typical 5- to 10-day at-risk period.
Laboratory Testing

Table 5 lists recommendations for laboratory testing for HIT.

Treatment

Recommendations regarding treatment of HIT are beyond the scope of this article and are described elsewhere.28,29 However, with respect to treatment implications of platelet count monitoring to permit early detection of HIT, it is important to note that there is no evidence that early cessation of heparin because of thrombocytopenia attributable to HIT avoids thrombotic complications.27,29

Indeed, a retrospective study by Wallis and colleagues29 found a trend toward a higher rate of thrombosis among patients in whom heparin was stopped within 48 hours of onset of thrombocytopenia, compared with later cessation of heparin (45% vs 34%; P = .26). Since the 30-day thrombotic event rate may be as high as 40% to 50%,27,29 it is currently recommended that if isolated HIT is suspected based on platelet count monitoring, antiagulation with an alternative antithrombotic agent should be given (danaparoid, lepirudin, argatroban),24,61 usually in therapeutic doses.62 Furthermore, as many of the thrombi occur in the first few days after heparin administration is stopped (approximately 5%–10% per day event rate over the first 1–2 days post–heparin cessation27,60), awaiting results of laboratory testing is not an acceptable reason to withhold antiagulant therapy in a patient with a high pretest probability for HIT.24

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