Heparin-Induced Thrombocytopenia: A Practical Review

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Heparin-induced thrombocytopenia (HIT) remains under-recognized despite its potentially devastating outcomes. It begins when heparin exposure stimulates the formation of heparin-platelet factor 4 antibodies, which in turn triggers the release of procoagulant platelet particles. Thrombosis and thrombocytopenia that follow comprise the 2 hallmark traits of HIT, with the former largely responsible for significant vascular complications. The prevalence of HIT varies among several subgroups, with greater incidence in surgical as compared with medical populations. HIT must be acknowledged for its intense predilection for thrombosis and suspected whenever thrombosis occurs after heparin exposure. Early recognition that incorporates the clinical and serologic clues is paramount to timely institution of treatment, as its delay may result in catastrophic outcomes. The treatment of HIT mandates an immediate cessation of all heparin exposure and the institution of an antithrombotic therapy, most commonly using a direct thrombin inhibitor. Current "diagnostic" tests, which primarily include functional and antigenic assays, have more of a confirmatory than diagnostic role in the management of HIT. Special attention must be paid to cardiac patients who are often exposed to heparin multiple times during their course of treatment. Direct thrombin inhibitors are appropriate, evidence-based alternatives to heparin in patients with a history of HIT, who need to undergo percutaneous coronary intervention. As heparin remains one of the most frequently used medications today with potential for HIT with every heparin exposure, a close vigilance of platelet counts must be practiced whenever heparin is initiated.

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Whenever a medication has the potential to result in the very adverse outcome that it is intended to treat, serious ramifications will inevitably occur. Such is the predicament continually facing the use of heparin. Its use is undoubtedly far more pervasive today than it was 13 years ago when over 1 trillion units were estimated to treat nearly 12 million patients.[1] With its long-heralded ability to effectively prevent and treat thromboembolic events, as well as its relative inexpensive cost compared with its

newer and more expensive counterparts, heparin is often preferentially used to manage thromboembolic vascular complications, especially during current economic times when cost-effective medical care is emphatically encouraged.

The use of heparin is especially intertwined with the various management strategies in the field of cardiology, where its use is bolstered by a robust body of evidence. From the management of acute coronary syndromes (ACS) to adjunctive therapy in interventional and ablative procedures, one simply cannot discount heparin's proven efficacy in antithrombotic management in improving outcomes.[2-5] The extent of its use has only been tempered by its inherent risk of bleeding, which has always been heparin's Achilles heel. Indeed, as newer antiplatelet agents are beginning to shape the foundation of ACS management, finding ways to limit the risk of significant hemorrhagic complications has certainly garnered greater attention.

Perhaps because it makes less intuitive sense, heparin-induced thrombocytopenia (HIT), or heparin's paradoxical ability to promote thrombosis, continues to remain under the radar. Such is the finding of the recent Complications After Thrombocytopenia Caused by Heparin (CATCH) registry trial, which illustrates a persistent and nagging gap in our medical community to recognize what is often a devastating complication.[6] In this prospective analysis involving over 2400 patients, the development of thrombocytopenia on heparin, arguably the most obvious feature of HIT, not only infrequently prompted a timely diagnostic evaluation, but even when the diagnosis of HIT was considered, management strategies were delayed and rarely followed published guidelines. Indeed, it is quite puzzling how the phenomenon of HIT continues to escape our diagnostic acumen despite repeated attempts over the past decade to raise our awareness.

This review refreshes our minds with regard to what is now substantially established in literature: HIT and its catastrophic outcomes. With the US Surgeon General's recent "call to action" to reduce the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE), there will inevitably be a rise in patient exposure to the heparin products and concomitantly, the incidence of heparin-induced thrombocytopenia.[7] With this in mind, the salient features of HIT, from pathogenesis to diagnosis to updated treatment options, are discussed.

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Pathogenesis of HIT

The term *heparin-induced thrombocytopenia* (traditionally known as HIT type II), is now primarily reserved to denote the immune system–mediated complication of heparin with the potential for devastating thrombotic outcomes. Historically, it was differentiated from the nonimmune type, or HIT type I, now an outdated term used to describe an asymptomatic, benign transient drop in platelet count in some patients receiving heparin therapy. It was specifically characterized by the absence of heparin-dependent antibodies.[8] In contrast, the immune response plays a paramount role in the pathogenesis of HIT.[9,10]

HIT begins when the exposure to heparin stimulates the release of platelet factor 4 (PF4) from the α granules of platelets (Figure 1). PF4, a positively charged glycoprotein (GP), is then exteriorized on the surface of platelets creating a binding site for heparin, a negatively charged polyanion. This highly immunogenic PF4/heparin complex soon triggers the binding of IgG antibody (PF4/heparin or HIT antibody), resulting in the activation of the Fc receptor on the platelet and subsequent release of platelet-derived microparticles into the blood.[9] It is hypothesized that these microparticles accelerate the generation of thrombin and the formation of new thromboses.[10] Ultimately, thrombin generation is uncontrollably upregulated, creating a vastly hypercoagulable milieu. Thrombocytopenia itself results from removal of these abnormal platelets from circulation by the spleen. It is this combination of thrombocytopenia and thrombosis that forms the hallmark trait of HIT.

The Differential Activation of HIT Antibodies

There remain persistent questions as to why HIT selectively occurs in some but not all patients who are exposed to heparin. One possible explanation stems from the observation that heparin does not always seem to induce the formation of PF4/heparin complex. As HIT antibody is unable to recognize PF4 or heparin molecule alone, the previously described cascade of immune response simply cannot be sustained without the actual formation of PF4/heparin complex. Furthermore, it has also been observed that even when HIT antibodies do develop, this does not necessarily progress to clinical HIT.[11] In fact, there are

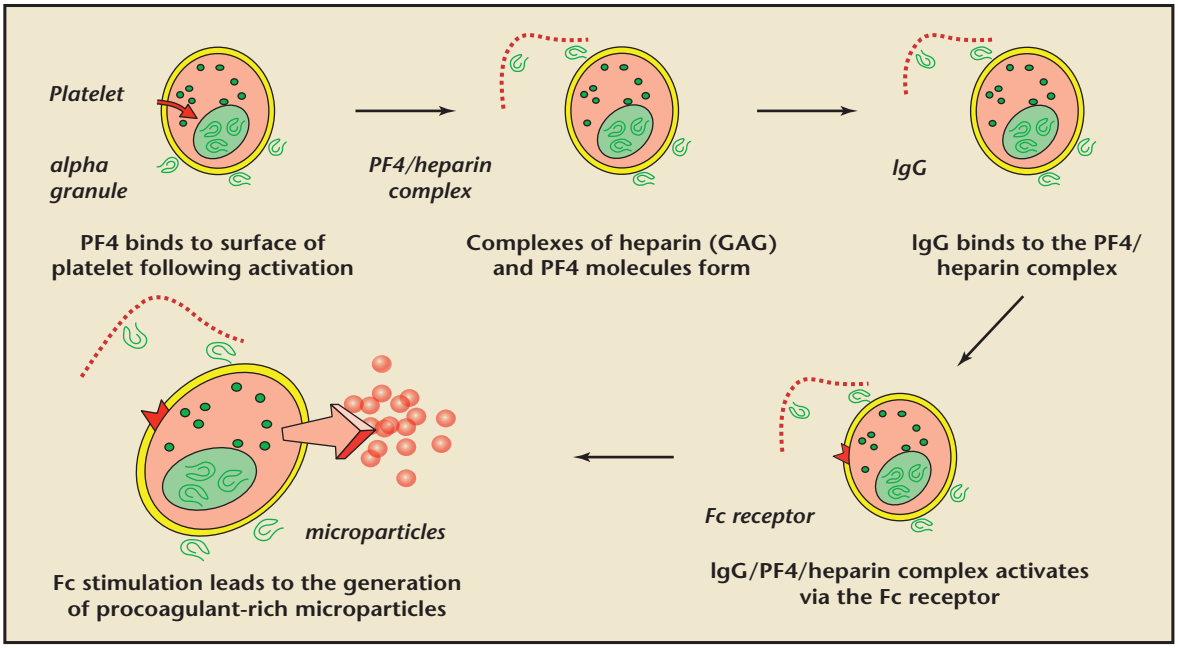

Figure 1. *The pathogenesis of heparin-induced thrombocytopenia. GAG, glycosaminoglycans; PF4, platelet factor 4. Adapted with permission from Hirsch et al.*[44]

reports in the literature in which patients with a high titer of HIT antibodies fail to progress to HIT. The underlying reason for the differing responses to heparin exposure by various subsets of the population is not yet clear, but may be explained by differential platelet-activating abilities by a given antibody type and titer.[11,12]

The Iceberg Model of HIT

The iceberg model has often been used as an analogy to illustrate the observation that only a relatively few of those who are exposed to heparin actually progress to a full clinical manifestation of thrombosis and thrombocytopenia that characterize HIT (Figure 2).[11,12] In this paradigm, the population that stays "above the water" represents those who exhibit the complete clinical features of the syndrome. Those who stay hidden or "under the water" comprise a significantly greater number of patients, who have seroconverted when detected by highly sensitive assays, but remain clinically silent. The tapering feature of the iceberg or pyramid is analogous to the different extents the immune response progresses in different populations.

It needs to be emphasized, nonetheless, that even the presence of heparin-PF4 antibodies that fail to induce HIT may still be clinically relevant. In patients presenting with ACS and normal platelet counts, the sole presence of heparin-PF4 antibodies has been independently associated with significantly higher rates of myocardial infarction (MI) at 30 days.[13] These data are concerning as there are currently no recommendations on how to treat or identify the patients who appear to develop HIT antibodies without actually progressing to the clinical syndrome. Indeed, we may be greatly underestimating those who are exposed to heparin and thus develop increased risk for adverse cardiovascular outcomes.

Frequency of HIT

In general, HIT occurs in 3% to 5% of patients receiving intravenous (IV) unfractionated heparin (UFH). The incidence is lower (0.5%) with the use of other types of heparins (eg, subcutaneous [SQ], low molecular weight).[11] The propensity of HIT to develop depends on various factors, including the patient population, the dose and the type of heparin used, and the duration of heparin therapy. The overall incidence of HIT is more prevalent in the surgical rather than the medical population.[11,14] Within the surgical population, orthopedic patients tend to have a greater predilection toward development of HIT than those undergoing cardiothoracic procedures

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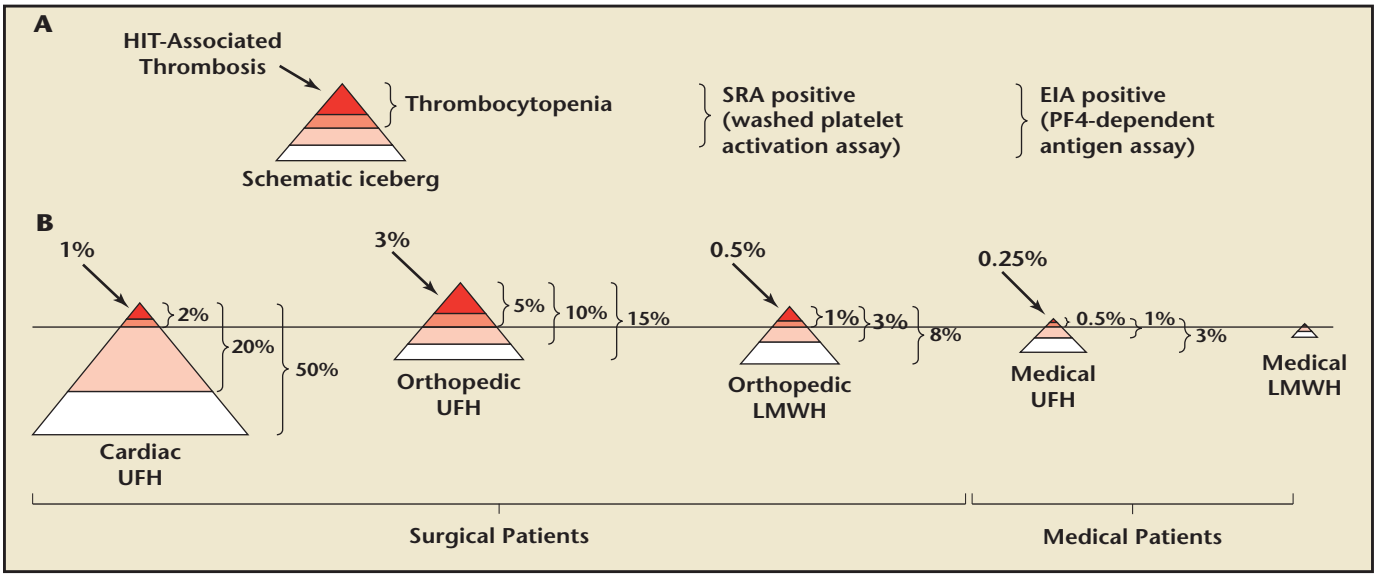

Figure 2. *The iceberg model of heparin-induced thrombocytopenia (HIT). Note the different "sizes" and "shapes" of the icebergs depending on the exposed population and the type of heparin used. EIA, enzyme immunosorbent assay; LMWH, low molecular weight heparin; PF4, platelet factor 4; SRA, serotonin release assay; UFH, unfractionated heparin. Adapted with permission from Warkentin TE.*[12]

(Figure 2). The type of heparin also matters; bovine source is more immunogenic than porcine, as is UFH over low molecular weight heparin (LMWH).[11,15,16] Duration and the extent of heparin exposure are the other key factors, with the general rule that the longer and the higher the dose of heparin, the more likely HIT is to develop.[11] It should be acknowledged that a patient of any age receiving any type of heparin at any dose by any route of administration has the potential to develop HIT (Table 1).

Serologic Manifestation of HIT

The timely recognition of HIT is paramount to optimal management, yet the diagnosis of HIT is sometimes difficult to ascertain. To put it simply, HIT should always be suspected if the thrombocytopenia develops after a patient is exposed to heparin. Specifically, there should be a platelet count drop of at least 50% of the initial count, often to less than 150,000/μL, which typically starts 5 to 14 days after the initiation of heparin.[17] The actual platelet counts in patients with HIT, however, rarely fall below 15,000/μL; more important is the occurrence of a sudden drop in platelet count of at least 50% from the patient's baseline. In a series of 142 HIT patients evaluated by Warkentin and Kelton,[18] 10% to 15% of patients had platelet counts that fell within the normal range. This emphasizes that relative reduction in overall platelet count rather than an absolute cutoff may be a more useful marker in the diagnosis of HIT.

Early and Delayed Onset and the Role of Enduring HIT Antibodies

Although the window of 5 to 14 days after exposure to heparin has been identified as the usual time period for thrombocytopenia in HIT to develop, the onset may be much earlier (within 24 hours) or even delayed (weeks to months after heparin

Table 1
Individuals at Risk for HIT

Risk for Developing HIT	Risk Factor
High (> 1%)	Postoperative or trauma patients, especially cardiac, vascular, or orthopedic surgery receiving UFH
Intermediate (0.1%-1%)	Postoperative patients receiving UFH flushes Postoperative patients receiving LMWH Medical or obstetrical patients treated with therapeutic or prophylactic doses of UFH
Low (< 0.1%)	Medical or obstetrical patients treated with LMWH

HIT, heparin-induced thrombocytopenia; LMWH, low molecular weight heparin; UFH, unfractionated heparin.
Adapted with permission from Napolitano LM et al.[45]

discontinuation).[19-21] Although the difference in their timing may suggest 2 separate phenomena, their mechanisms share the same pathologic basis: the enduring presence of HIT antibodies.

It has been recognized that circulating HIT antibodies remain detectable for up to 4 months. Unless actively treated, the potential for thrombosis persists as long as the antibodies remain. Consequently, HIT must be considered if a recently hospitalized patient returns with thromboembolism.[20] Furthermore, if heparin is reintroduced in the time period when these antibodies are still present, the onset of thrombocytopenia (and thrombosis) may be much more rapid than expected.[21] This explains why heparin cessation alone is not enough and an alternative form of anticoagulation is often necessary to prevent future thrombosis. In short, it is not necessarily the timing, but just the mere development of thrombocytopenia on heparin that should precipitate an initial suspicion of HIT. If the timing of thrombocytopenia falls outside the norm, a careful evaluation of most recent heparin exposure must be performed to rule out the early or delayed onset subtypes.

Other Causes of Thrombocytopenia

One of the major reasons the diagnosis of HIT remains complicated and often cumbersome is that thrombocytopenia encompasses a wide differential. Concurrently during the diagnostic work-up of HIT, it is recommended to systematically consider and rule out other known causes of thrombocytopenia such as sepsis, disseminated intravascular coagulation, and drug therapy (eg, GP IIb/IIIa inhibitors and antibiotics) (Table 2).[22] Although it may be regarded as a "diagnosis of exclusion," HIT should nonetheless be considered with priority among the causes of thrombocytopenia in a heparin-treated patient.

Clinical Manifestations of HIT

Counterintuitively, clinical manifestation of HIT is not bleeding, but serious thromboembolic events. In fact, HIT is intensely associated with thrombosis, with an approximately 35-fold increase in thrombotic risk compared with that of the general population. Contextually, this risk is much higher than any known hypercoagulable disorders, such as protein C deficiency (14.4 × risk) and even antithrombin deficiency (24.1 × risk).[23,24] Needless to say, the thrombotic risk of HIT should never be underestimated.

Thrombosis may involve either venous or arterial circulation, occurring at a nearly 4:1 ratio, with complications ranging from DVT (50%), PE (25%), MI and stroke (3%-5%), to limb artery occlusion leading to amputation (5%-10%) (Table 3).[11] It may also complicate procedural outcomes, as the occlusion rate for saphenous vein grafts has been found to be significantly increased in HIT patients compared with non-HIT control subjects undergoing coronary artery bypass graft.[25-27] Without appropriate therapy, mortality of HIT may reach up to 30%.

Table 2
Potential Etiology of Thrombocytopenia

Sepsis and health care–associated infections
Perioperative and postresuscitation hemodilution
Drug-induced thrombocytopenias, including HIT, GP IIb/IIIa
Liver disease/hypersplenism
Platelet consumption or destruction
Disseminated intravascular coagulation
Massive transfusion
Primary marrow disorder
Antiphospholipid antibody syndrome/lupus anticoagulant
Immune thrombocytopenias (ITP, TTP, PTP)
Intravascular devices (IABP, LVAD, ECMO), pulmonary artery catheter

ECMO, extracorporeal membrane oxygenation; GP, glycoprotein; HIT, heparin-induced thrombocytopenia; IABP, intra-aortic balloon pump; ITP, idiopathic thrombocytopenic purpura; LVAD, left ventricular assist device; PTP, post-transfusion purpura; TTP, thrombotic thrombocytopenic purpura.

Table 3
Types of Thrombosis that Occur in Patients with HIT

Deep venous thrombosis (50%)
Pulmonary embolism (25%)
Skin lesions at injection site (10%-20%)
Acute limb ischemia (5%-10%)
Warfarin-associated venous limb gangrene (5%-10%)
Acute thrombotic stroke or myocardial infarction (3%-5%)
Acute systemic reactions following IV bolus (~ 25%)

HIT, heparin-induced thrombocytopenia; IV, intravenous.

Table 4
Laboratory Testing for HIT

Functional (Platelet Activation) Assays	Antigenic Assays
Serotonin-release assay (uses "washed" platelets)	PF4/heparin immunoassay (ELISA immunoassay)
Heparin-induced platelet activation assay (uses "washed" platelets)	Particle gel immunoassay
Platelet aggregation test (uses citrate-anticoagulated platelet-rich plasma)	

ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia.

Confirmation of HIT: Assays

Although the timing of treatment is crucial in the management of HIT, there is currently no "point of care" or timely efficient tests with adequate sensitivity and specificity that can aid in the initial diagnosis for HIT.[28-32] As such, serologic tests in HIT are used mainly to aid in the confirmation of the diagnosis. There are currently 2 major groups of serologic tests that are used in this manner: antigenic assays and functional assays (Table 4).

Antigenic Assays

As the name implies, antigenic assays identify the presence of HIT antibodies that are bound to PF4/heparin complexes (Figure 3). This test has a high sensitivity, but predictably a poor specificity, as it also measures the presence of HIT antibodies that may not necessarily elicit a HIT response (eg, false-positive).[29] Although it cannot be used as a single test without other clinical suspicion to "rule in" HIT, its high sensitivity translates to a

Figure 3. *Laboratory assay for heparin-induced thrombocytopenia (HIT) antibodies. Top, the SRA. Washed platelets loaded with radiolabeled 14C-serotonin are incubated with patient serum and pharmacologic concentrations of heparin. The presence of HIT-IgG antibodies can be detected by the measurement of serotonin release. Bottom, PF4/heparin EIA. The assay shown utilizes PF4 and heparin bound in optimal stoichiometric concentrations to detect HIT antibodies. EIA, enzyme-linked immunosorbent assay; PF4, platelet factor 4; SRA, serotonin release assay. Adapted with permission from Warkentin TE.*[12]

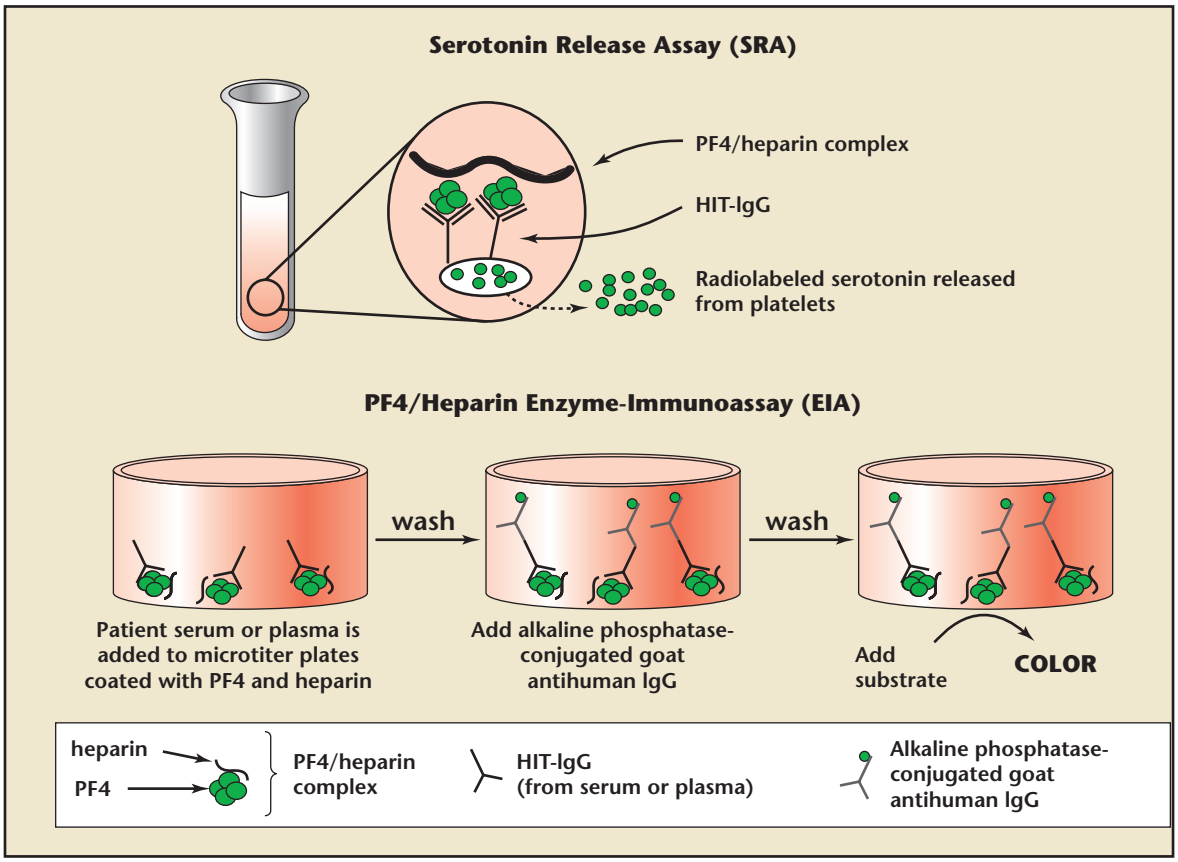

Table 5
Comparison of Common Laboratory Testing for HIT

Test	Advantages	Disadvantages
Serotonin-release assay	High sensitivity and specificity (false positives rare)	Technically demanding, not readily available, long turnaround time
Platelet aggregation assay	High specificity	Low sensitivity, technique-dependent
PF4/heparin immunoassay (ELISA)	High sensitivity (high negative predictive value), relatively rapid turnaround time	Low specificity (higher rates of false positives)

ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia.

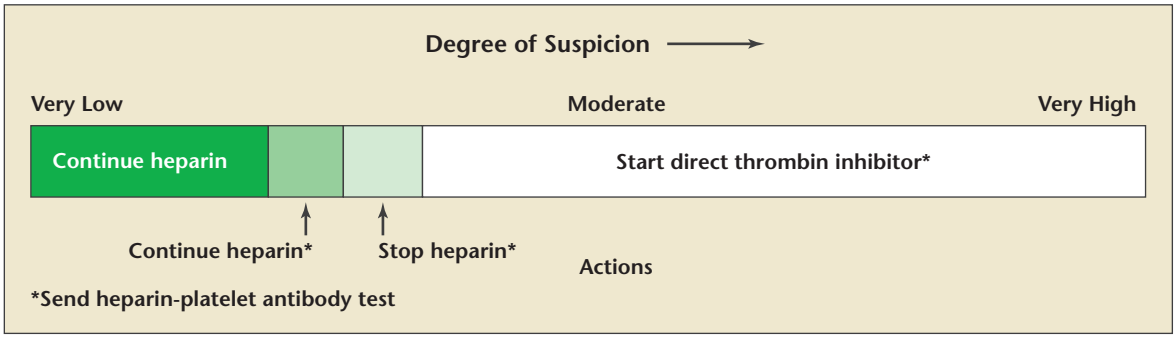

Figure 4. *Decision making when confronting possible heparin-induced thrombocytopenia. Adapted with permission from Rice L et al.*[20]

high negative predictive value in ruling out HIT (ie, HIT is unlikely to be the diagnosis if the assay is negative). For this reason, the College of American Pathologists currently recommends heparin-PF4 antibody testing for patients in whom there is a suspicion of HIT based on the temporal features of the thrombocytopenia or on the occurrence of new thrombosis during or soon after heparin treatment.[30]

Functional Assays

The functional tests, on the other hand, directly assess the level of platelet activity in the presence of patient sera and heparin.[31,32] As it is actually measuring the activity of platelets in producing thrombosis, it has a much higher specificity than antigenic assays. Serotonin release assay, perhaps the most accurate functional test currently available, has the highest sensitivity and specificity, with both parameters reaching above 95%. However, it is significantly hindered by its technical limitations essentially negating its use as a cost-effective initial diagnostic test (Table 5).[32]

As current tests are often labor and time intensive with a typical turnaround time of days to weeks, serologic tests in HIT are largely ineffective as diagnostic tests and are hence used primarily as confirmatory tests. At this time, there is no single effective test. In fact, it would be more accurate if antigenic and functional tests are done in combination and multiple samples are taken. Needless to say, this would be an impractical and unnecessarily time consuming manner to achieve a diagnosis. Consequently, it is currently recommended not to delay treatment if clinical suspicion of HIT is moderate to high, while awaiting the result of the confirmatory test (Figure 4). However, a highly sensitive test may be helpful in confirming HIT, which by and large remains a clinical diagnosis.

Diagnosis of HIT

Reaching a clinical diagnosis often hinges on a careful assessment of the pretest likelihood of disease. To help achieve this process, a user friendly scoring system has been proposed to predict the pretest likelihood of HIT in heparin-exposed patients (Table 6). This point-based system takes into account the salient features of HIT: (1) the degree of Thrombocytopenia, (2) Timing of thrombocytopenia, (3) evidence of Thrombotic events, and (4) oTher causes for thrombocytopenia (aptly

Table 6
The 4Ts Assessment Point System for Patients with Suspected HIT

Category[a]	2 Points	1 Point	0 points
Thrombocytopenia	> 50% fall, or Nadir of 20-100 × 10^9/L	30% to 50% fall, or Nadir of 10-19 × 10^9/L	< 30% fall or Nadir of < 10 × 10^9/L
Timing of platelet count fall	Days 5 to 10, or ≤ 1 day if heparin exposure within past 30 days	> Day 10 or unclear (but fits with HIT), or ≤ 1 day if heparin exposure within past 30-100 days	≤ 1 Day (No recent heparin)
Thrombosis or other sequlae	Proven thrombosis, skin necrosis, or other heparin bolus, acute systemic reaction	Progressive, recurrent, or silent thrombosis; erythematous skin lesions	None
Other causes for thrombocytopenia	None evident	Possible	Definite

HIT, heparin-induced thrombocytopenia.
[a]Points assigned in each of 4 categories are totaled, and the pretest probability of HIT by total points is as follows: 6-8 = high; 4-5 = intermediate; 0-3 = low.
Adapted with permission from Warkentin TE et al.[24]

named the 4Ts) to formulate the pretest likelihood of having HIT. Those with high pretest likelihood of having HIT based on this scoring formula should be treated while awaiting the results of confirmatory study.

Monitoring Platelet Counts

Because the drop in platelet count is the very first step in recognizing HIT, routine monitoring of platelet count is strongly recommended for most patients receiving heparin therapy whose risk of HIT is at least 0.1%.[30,33] A baseline platelet count before initiating heparin treatment is crucial to allow estimation of relative changes. In higher-risk patients, such as individuals receiving UFH at therapeutic doses, the platelet count should be checked at least every other day until day 14 of therapy (or until heparin is stopped, whichever is sooner). In lower-risk patients, monitoring should be at least every 2 to 3 days between days 4 and 14 while on heparin therapy (Table 7).

Treatment of HIT

Direct Thrombin Inhibitors

The treatment strategy in HIT encompasses the following goals: (1) interrupting the immune response, (2) inhibiting uncontrolled thrombin generation, and (3) minimizing the complications of HIT.[34] The clearest way to halt the self-perpetuating immune cycle of HIT is obviously to disrupt its driving force. As such, it should be emphasized that all types of heparin should be discontinued, however minimal the exposure, when HIT is suspected, including IV flushes, SQ injection, and heparin-coated lines. Appropriate nursing measures should be implemented to prevent inadvertent heparin exposure in this regard. Next, proper steps should be acutely undertaken to identify and treat active and potential thrombosis. This evokes the judicious use of direct thrombin inhibitors (DTIs) (Table 8).

DTIs have multiple characteristics that confer on them a distinct edge over other agents in the management of HIT.[35] First, they have no potential for cross-reactivity with HIT antibodies, and thus cannot trigger a similar antibody response. More importantly, they are physiologically a powerful thrombin inhibitor as they can inhibit both clot-bound and circulating thrombin while blocking both prothrombotic and procoagulant effects.

DTIs have multiple characteristics that confer them a distinct edge over other agents in the management of HIT.

Conversely, there are also significant disadvantages. Perhaps most notably, the actions of DTIs cannot be reversed. Needless to say, this would become seriously problematic if significant bleeding complications

Table 7
Consensus Guidelines for Platelet Count Monitoring for HIT

Population	Examples	Monitoring Guideline[a]
Recent heparin exposure	Patients starting UFH or LMWH and who received UFH within the previous 100 days; patients whose heparin exposure history is unknown	Obtain baseline platelet count and repeat platelet count within 24 hours of starting heparin
Acute, systemic reactions after intravenous UFH bolus	Patients with acute inflammatory, cardiorespiratory, neurological, or other unusual symptoms and signs within 30 minutes after an intravenous UFH bolus	Obtain platelet count immediately to compare with recent prior platelet counts
Risk of HIT > 1%	Patients receiving UFH at therapeutic doses	Monitor at least every 2 days until day 14 of therapy or until UFH is stopped, whichever comes first
	Postoperative patients receiving UFH antithrombotic prophylaxis	Monitor at least every 2 days between postoperative days 4 and 14[b] or until UFH is stopped, whichever comes first
Risk of HIT 0.1% to 1%	Medical/obstetric patients receiving prophylactic-dose UFH, or LMWH after first receiving UFH; postoperative patients receiving prophylactic-dose LMWH, or intravascular catheter UFH flushes	Monitor every 2 or 3 days from days 4 to 14[b] or until UFH is stopped, whichever comes first, when practical
Risk of HIT <0.1%	Medical/obstetric patients receiving only LMWH; medical patients receiving catheter UFH flushes	As clinically indicated (no routine monitoring)

HIT, heparin-induced thrombocytopenia; LMWH, low molecular weight heparin; UFH, unfractionated heparin.
[a]As recommended by the College of American Pathologists (data from Warkentin TE[30] and Warkentin TE et al.[33]).
[b]Days 4-10, with additional monitoring if platelet count falls in that time window, according to the College of American Pathologists Guidelines.

Table 8
Summary of DTIs

	Argatroban	Lepirudin	Bivalirudin
Structure	Synthetic L-arginine derivative	Recombinant hirudin	Semisynthetic hirulog
Half-life in healthy subjects	39-51 min	80 min	25 min
Elimination	Hepatic	Renal	80% enzymatic 20% renal
Monitoring needed	aPTT, ACT	aPTT	aPTT, ACT
Thrombin binding	Reversible	Irreversible	Partially reversible
Antidote	None	None	None

ACT, activated clotting time; aPTT, activated partial thromboplastin time; DIT, direct thrombin inhibitors.

were to arise. This poses a special bleeding risk in patients with HIT who are undergoing cardiovascular surgery, where heparin is pervasively used. Additionally, the use of DTI is somewhat cumbersome, requiring a careful patient selection, dosing, and monitoring that are quite different from what general clinicians have been used to. DTIs prolong the International Normalized Ratio and hence the currently established parameters for risk of bleeding and the level of anticoagulation do not apply.[36] Monitoring algorithms specific to each DTI have been established and need to be followed when transitioning to oral anticoagulation. Indeed, this may be a daunting task and help may be needed from a vascular medicine specialist.

Lepirudin (Refludan®; Bayer HealthCare Pharmaceuticals, Montville, NJ) and argatroban (GlaxoSmithKline, Philadelphia, PA) are the 2 current US Food and Drug Administration (FDA)–approved DTIs for the management

of HIT.[33-35] Lepirudin is a recombinant hirudin analog, with irreversible thrombin binding, and a half-life of 90 minutes. Argatroban is a synthetic L-arginine derivative that binds reversibly to thrombin and has a half-life of approximately 50 minutes. The use of argatroban is preferred in patients with renal insufficiency because it is eliminated by the hepatobiliary system of which the opposite is true for lepirudin. Lepirudin is the oldest of the commercially used DTIs and has been associated with anaphylaxis.[35]

Bivalirudin (Angiomax®; The Medicines Company, Parsippany, NJ), the newest DTI, may be the safest of its kind to treat HIT given its short half-life of only 20 to 25 minutes. As there is no proven reversal agent in DTI, the duration of half-life becomes especially crucial in limiting the extent of bleeding complications that may arise. Bivalirudin has the shortest half-life of all DTIs and is arguably the safest.[35]

The safety and efficacy of bivalirudin has been studied in a prospective, multicenter trial involving 52 patients with serologically proven HIT.[37] Although a rather small study, bivalirudin was found to be both safe and effective, with minimal bleeding and cardiac complications. Bivalirudin may be the most preferred anticoagulant agent of choice in patients at risk of HIT undergoing percutaneous coronary intervention (PCI).

Of note, the use of bivalirudin has also extensively been studied in patients without HIT presenting with the entire spectrum of ACS (stable angina, non-ST-elevation MI [NSTEMI], ST-elevation MI) undergoing PCI, in 3 separate, randomized, noninferiority trials.[38-40] In all 3 studies, bivalirudin was found to be noninferior to heparin and GP IIb/IIIa inhibitors in limiting ischemic outcomes, while significantly decreasing the incidence of hemorrhagic complications. In this regard, bivalirudin may be the most preferred anticoagulant agent of choice in patients at risk of HIT undergoing PCI.

The Timing of Treatment

It needs to be stressed again that the treatment of HIT with an alternative antithrombotic regimen (eg, DTIs) must begin immediately if the suspicion is high, regardless of whether active thrombosis is present (Figure 4). In the treatment of HIT, the cessation of heparin simply is not enough.[33,34,41] As noted previously, HIT is a strong independent risk factor for venous and arterial thrombosis as a substantial number of HIT patients will develop a thrombotic event some time after the cessation of heparin therapy. Furthermore, the accumulating evidence of delayed-onset HIT presenting days to weeks after heparin cessation makes a compelling case to treat HIT with an alternative anticoagulation for a full recommended duration regardless of the presence of active thrombosis. Oral anticoagulation will eventually need to be maintained for a minimum of 3 to 6 months regardless of whether HIT-associated thrombosis is present.[33]

Oral Anticoagulation

There is a common misconception that a bridging therapy prior to starting vitamin K antagonist is unnecessary. Directly starting warfarin is not only ineffective, but may even precipitate venous gangrene due to a precipitous fall in the levels of protein C.[42,43] Vitamin K antagonists should not be started until the platelet count has recovered to at least 150×10^9/L and should always be bridged by a DTI.[33,34] Warfarin should always be started at the expected maintenance (not loading) dose and be overlapped with an alternative anticoagulant for at least 5 days.[33,34]

Common Misconceptions About Treatment Options

Although it can be used as a preventive measure to reduce the risk of HIT in the general population, LMWH should never be substituted as a treatment once HIT has developed due to the high risk of in vivo cross-reactivity.[33,34] Platelet transfusions are generally not recommended unless absolutely required to manage life-threatening bleeding.[33,34] It has the potential to exacerbate the hypercoagulable state leading to additional thrombosis.

Although it can be used as a preventive measure to reduce the risk of HIT in the general population, LMWH should never be substituted as a treatment once HIT has developed.

Prevention of HIT

As with any disease process, the best way to combat its incidence is to focus on its prevention. In HIT, prevention begins with the patient's history. This may range from directly asking the patient about any previous adverse effect from heparin use to identifying any recent hospitalization where heparin may have been used. If chances are high that the patient is being reexposed to heparin in a short amount of time, an earlier monitoring of platelet count would be necessary to identify the early onset subtype.

Prior to the initiation of heparin, one should always note the patient's baseline platelet count as it is the relative drop of 50% that appears to be more reliable than following an

absolute cutoff. In addition, monitoring of platelet count during heparin use is crucial. Different strategies of monitoring platelet count have been advised by the American College of Chest Physicians depending on the risk of HIT for a given patient.[33] Whenever possible, one should try to limit heparin duration to fewer than 5 days. This strategy is reflected in the most recent American College of Cardiology/American Heart Association guidelines for ACS/NSTEMI management, which recommends IV heparin duration of no more than 48 hours for patients undergoing medical management for ACS/NSTEMI.[4] In patients who are undergoing a heparin treatment of a thrombotic event, warfarin should be started early to minimize the length of heparin administration in patients requiring longer-term anticoagulation, except when HIT is diagnosed. In this light, routine initiation of oral anticoagulation is encouraged at the start of heparin therapy in patients who need longer-term oral anticoagulation to minimize the duration of concomitant heparin-bridging therapy. Finally, the use of LMWH, which has much lower immunogenic potential for HIT than heparin, may be more beneficial in prevention.

Special Population: Cardiac Patients

Because heparin plays such an integral role in management strategies in the field of cardiovascular medicine, cardiac patients are often reexposed to heparin at multiple times during the course of their treatment. Consequently, cardiac patients with a history of HIT invariably pose a special management dilemma, particularly those undergoing coronary bypass surgery.[26]

In patients with a history of HIT, all elective cardiovascular surgeries should be delayed until HIT is fully resolved and antibodies become undetectable by a sensitive assay. Taking these measures allows the eventual use of heparin during surgery while minimizing the further risk of propagating the immune response of heparin antibodies. Although logic would opt for the use of alternative forms of anticoagulation, especially in those with active HIT whose surgery cannot be delayed, the paucity of data regarding the efficacy and safety of alternative anticoagulants in this setting makes them less than an optimal choice. First, the effective and safe doses of these anticoagulants have not yet been established in clinical trials. Second, as there is no known antidote to reverse its action, uncontrolled bleeding becomes a much bigger, potentially catastrophic issue. Finally, it is difficult to readily monitor the action/level of these anticoagulants with the available assays (vs activated clotting time/activated partial thromboplastin time for heparin). Hence, the current recommended strategy in managing patients with HIT who are undergoing cardiovascular surgery is not to avoid the use of heparin altogether but to minimize its exposure. This would prompt the use of alternative anticoagulation only before and after

In patients with a history of HIT, all elective cardiovascular surgeries should be delayed until HIT is fully resolved and antibodies become undetectable by a sensitive assay.

Main Points

- Heparin-induced thrombocytopenia (HIT) is an immune-mediated complication of heparin, specifically characterized by the presence of heparin-platelet factor 4 antibodies.
- HIT is a clinicopathologic syndrome requiring both compatible clinical and laboratory features to establish its diagnosis.
- HIT should always be suspected when thrombosis occurs during heparin treatment.
- The treatment of HIT requires an immediate cessation of all heparin exposure and a prompt initiation of nonheparinoid anticoagulant (preferably a direct thrombin inhibitor [DTI]) regardless of whether active thrombosis is present at the time of diagnosis.
- Vitamin K antagonists should not be started until the platelet count has recovered to at least 150×10^9/L and should always be bridged by a nonheparinoid anticoagulant.
- DTIs are appropriate, evidence-based alternatives to heparin in patients with a history of HIT, who need to undergo percutaneous coronary intervention.

surgery, while reducing the amount of heparin exposure as much as feasible during surgery.

Conclusions

HIT is a not uncommon, still underrecognized, but potentially devastating complication of heparin therapy. It is a clinicopathologic syndrome: its diagnosis is based on compatible clinical features in the presence of HIT antibodies. Although antibodies against PF4/heparin form commonly during heparin treatment, HIT only occurs in the subset of patients with strong platelet-activating IgG antibodies.

The diagnosis of HIT centers upon clinical suspicion that incorporates the timing and the extent of thrombocytopenia while ruling out other potential causes for thrombocytopenia. Its treatment should not rely on laboratory confirmation, as high clinical suspicion itself mandates the initiation of non–heparin-based anticoagulation while awaiting the results of the confirmatory test, which often takes a few days to return.

The management of HIT requires the discontinuation of all heparin exposure, a careful assessment of the thrombotic risk, and the initiation of an alternative anticoagulant therapy, usually a DTI. The prevention of HIT begins with the patient's previous history and limiting the duration of heparin as much as possible.

In short, heparin use necessitates a close vigilance to avoid delays in timely diagnosis and treatment of HIT. Perhaps, as the newer, non-heparin-based forms of anticoagulation are introduced and used, the incidence of HIT may decrease in the future. At this time, heparin use remains pervasive and only the increase in its awareness may be the best means to prevent the disastrous outcomes of HIT. ■

References

1. Fahey VA. Heparin-induced thrombocytopenia. *J Vasc Nurs*. 1995;13:112-116.
2. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2008;51:210-247.
3. King SB 3rd, Smith SC, Hirshfeld JW, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *J Am Coll Cardiol*. 2008;51:172-209.
4. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol*. 2007;50:e1-e157.
5. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257-e354.
6. Oliveira GB, Crespo EM, Becker RC, et al. Incidence and prognostic significance of thrombocytopenia in patients treated with prolonged heparin therapy. *Arch Intern Med*. 2008;168:94-102.
7. US Department of Health and Human Services. The surgeon general's call to action to prevent deep vein thrombosis and pulmonary embolism. Available at: http://www.surgeongeneral.gov/topics/deepvein/calltoaction/call-to-action-on-dvt-2008.pdf. Accessed January 12, 2010.
8. Jang IK, Hursting MJ. When heparins promote thrombosis: review of heparin-induced thrombocytopenia. *Circulation*. 2005;111:2671-2683.
9. Visentin GP, Ford SE, Scott JP, Aster RH. Antibodies from patients with heparin-induced thrombocytopenia/thrombosis are specific for platelet factor 4 complexed with heparin or bound to endothelial cells. *J Clin Invest*. 1994;93:81-88.
10. Warkentin TE, Hayward CPM, Boshkov LK, et al. Sera from patients with heparin-induced thrombocytopenia generate platelet-derived microparticles with procoagulant activity: an explanation for the thrombotic complications of heparin-induced thrombocytopenia. *Blood*. 1994;84:3691-3699.
11. Lee DH, Warkentin TE. Frequency of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. *Heparin-Induced Thrombocytopenia*. 3rd ed. New York: Marcel Dekker; 2004:107-148.
12. Warkentin TE. New approaches to the diagnosis of heparin-induced thrombocytopenia. *Chest*. 2005;127:35S-45S.
13. Williams RT, Damaraju LV, Mascelli MA, et al. Anti-platelet factor 4/heparin antibodies: an independent predictor of 30-day myocardial infarction after acute coronary ischemic syndromes. *Circulation*. 2003;107:2307-2312.
14. Warkentin TE, Sheppard JI, Horsewood P, et al. Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood*. 2000;96:1703-1708.
15. Francis JL, Palmer GJ, Moroose R, Drexler A. Comparison of bovine and porcine heparin in heparin antibody formation after cardiac surgery. *Ann Thorac Surg*. 2003;75:17-22.
16. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med*. 1995;332:1330-1335.
17. Warkentin TE. Clinical picture of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. *Heparin-Induced Thrombocytopenia*. 3rd ed. New York, NY: Marcel Dekker; 2004:53-106.
18. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. *Am J Med*. 1996;101:502-507.
19. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med*. 2001;344:1286-1292.
20. Rice L, Attisha WK, Drexler A, Francis JL. Delayed-onset heparin-induced thrombocytopenia. *Ann Intern Med*. 2002;136:210-215.
21. Lubenow N, Kempf R, Echner A, et al. Heparin-induced thrombocytopenia: temporal pattern of thrombocytopenia in relation to initial use or reexposure to heparin. *Chest*. 2002;122:37-42.
22. Kitchens CS. Thrombocytopenia due to acute venous thromboembolism and its role in expanding the differential diagnosis of heparin-induced thrombocytopenia. *Am J Hematol*. 2004;76:69-73.
23. van den Belt AGM, Prins MH, Huisman MV, Hirsh J. Familial thrombophilia: a review analysis. *Clin Appl Thromb Hemost*. 1996; 2:227-236.
24. Warkentin TE, Aird WC, Rand JH. Platelet-endothelial interactions: sepsis, HIT, and antiphospholipid syndrome. *Hematology Am Soc Hematol Educ Program*. 2003:497-519.
25. Visentin GP, Malik M, Cyganiak KA, Aster RH. Patients treated with unfractionated heparin during open heart surgery are at high risk to

form antibodies reactive with heparin:platelet factor 4 complexes. *J Lab Clin Med*. 1996;128: 376-383.
26. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia and cardiac surgery. *Ann Thorac Surg*. 2003;76:638-648.
27. Pouplard C, May MA, Iochmann S, et al. Antibodies to platelet factor 4–heparin after cardiopulmonary bypass in patients anticoagulated with unfractionated heparin or a low-molecular-weight heparin: clinical implications for heparin-induced thrombocytopenia. *Circulation*. 1999;99:2530-2536.
28. Sheridan D, Carter C, Kelton JG. A diagnostic test for heparin-induced thrombocytopenia. *Blood*. 1986;67:27-30.
29. Greinacher A, Michels I, Kiefel V, Mueller-Eckhardt C. A rapid and sensitive test for diagnosing heparin-associated thrombocytopenia. *Thromb Haemost*. 1991;66:734-736.
30. Warkentin TE. Platelet count monitoring and laboratory testing for heparin-induced thrombocytopenia: recommendations of the College of American Pathologists. *Arch Pathol Lab Med*. 2002;126:1415-1423.
31. Greinacher A, Amiral J, Dummel V, et al. Laboratory diagnosis of heparin-associated thrombocytopenia and comparison of platelet aggregation test, heparin-induced platelet activation test, and platelet factor 4/heparin enzyme-linked immunosorbent assay. *Transfusion*. 1994;34:381-385.
32. Favaloro EJ, Bernal-Hoyos E, Exner T, Koutts J. Heparin-induced thrombocytopenia: laboratory investigation and confirmation of diagnosis. *Pathology*. 1992;24:177-183.
33. Warkentin TE, Greinacher A, Koster A, et al. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133:340S-380S.
34. Greinacher A, Warkentin TE. Treatment of heparin-induced thrombocytopenia: an overview. In: Warkentin TE, Greinacher A, eds. *Heparin-Induced Thrombocytopenia*. 3rd ed. New York, NY: Marcel Dekker; 2004:335-370.
35. Di Nisio M, Middeldorp S, Büller HR. Direct thrombin inhibitors. *N Engl J Med*. 2005;353: 1028-1040.
36. Gosselin RC, Dager WE, King JH, et al. Effect of direct thrombin inhibitors, bivalirudin, lepirudin, and argatroban, on prothrombin time and INR values. *Am J Clin Pathol*. 2004;121:593-599.
37. Mahaffey KW, Lewis BE, Wildermann NM, et al., for the ATBAT investigators. The anticoagulant therapy with bivalirudin to assist in the performance of percutaneous coronary intervention in patients with heparin-induced thrombocytopenia (ATBAT) study: main results. *J Invasive Cardiol*. 2003;15:611-616.
38. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA*. 2003;289:853-863.
39. Stone GW, White HD, Ohman EM, et al; for the ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med*. 2006;355:2203-2216.
40. Stone GW, Witzenbichler B, Guagliumi G, et al; for the HORIZONS AMI trial investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008;358:2218-2230.
41. Wallis DE, Workman DL, Lewis BE, et al. Failure of early heparin cessation as treatment for heparin-induced thrombocytopenia. *Am J Med*. 1999;106:629-635.
42. Warkentin TE, Elavathil LJ, Hayward CPM, et al. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. *Ann Intern Med*. 1997;127:804-812.
43. Srinivasan AF, Rice L, Bartholomew JR, et al. Warfarin-induced skin necrosis and venous limb gangrene in the setting of heparin induced thrombocytopenia. *Arch Intern Med*. 2004;164:66-70.
44. Hirsh J, Heddle N, Kelton JG. Treatment of heparin-induced thrombocytopenia: a critical review. *Arch Intern Med*. 2004;164:361-369.
45. Napolitano LM, Warkentin TE, Almahameed A, Nasraway SA. Heparin-induced thrombocytopenia in the critical care setting: diagnosis and management. *Crit Care Med*. 2006;34: 2898-2911.