Heparin-Induced Thrombocytopenia

Stephen Lanzarotti, MD,*, John A. Weigelt, MD, DVM

INTRODUCTION

Anticoagulation therapy in the hospital is widespread and many patients will be exposed to heparin at some time during their hospitalization. Proper medication use requires an understanding of the medication’s indications and side effects. The purpose of this article is to review heparin-induced thrombocytopenia (HIT), which is a commonly misunderstood complication from heparin-therapy.

Thrombosis related to heparin administration has been described for almost as long as heparin has been used in the clinical setting. Heparin was discovered in the 1930s at Johns Hopkins Hospital and found widespread clinical use as an anticoagulant in the early 1950s. In 1959, Dr Rodger E. Weismann described a series of 10 patients who developed thromboses after heparin administration. An immunologic cause for the thrombosis was suggested as early as 1964 by Dr Brooke Roberts at the University of Wisconsin.

KEYWORDS

- Heparin-induced thrombocytopenia
- Thrombosis
- Platelets
- PF-4
- Direct thrombin inhibitor

KEY POINTS

- Heparin-induced thrombocytopenia is an immune process, triggered by the administration of a heparin molecule, which binds to a platelet-specific protein—platelet factor 4.
- The antigenic complex of heparin–PF4 induces an immunoglobulin response, which binds the antigen as well as platelets, contributing to both thrombocytopenia and thrombosis.
- Diagnosing the condition requires clinical suspicion, platelet count monitoring, and identification of the causative antibody.
- Treatment involves stopping all heparin administration and starting alternative anticoagulation therapy.

http://dx.doi.org/10.1016/j.suc.2012.08.015
0039-6109/12/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
of Pennsylvania. Once platelet counts became available in the 1970s, the association between the thrombosis and thrombocytopenia became evident. Dr Glen R. Rhodes described HIT as a distinct clinical entity and identified the associated antibody. HIT is still prevalent today, but misdiagnosis of the syndrome, as well as misunderstanding of the disease process contributes to its continuing morbidity for the hospitalized patient.

The purpose of this article is to review HIT, especially its pathophysiology, diagnostic challenges, and therapeutic options. This article also discusses the current recommendations for surveillance of HIT, as well as special clinical circumstances relating to the disease. At the end of this article, three patient scenarios are presented to allow the reader to evaluate their understanding of the disease in regard to clinical situations.

PATHOPHYSIOLOGY

There are two described entities relating to HIT. HIT type I is a nonimmunogenic phenomenon, in which a self-limited thrombocytopenia occurs and spontaneously normalizes. There are no thrombotic complications and there is no need to stop heparin. It is also referred to as heparin-associated thrombocytopenia. There are no long-term effects from this form.

HIT type II is an immune process, triggered by the administration of a heparin molecule that binds to a platelet-specific protein called platelet factor 4 (PF-4). The antigenic complex of heparin–PF-4 induces an IgG response that can bind both the antigen and platelets, contributing to thrombocytopenia and thrombosis. When there is an associated thrombosis, the disease may be called heparin-induced thrombocytopenia with thrombosis (HITT). Diagnosing the condition requires clinical suspicion, platelet count monitoring, and identification of the causative antibody. Treatment involves stopping all heparin-administration and starting alternative anticoagulation therapy as necessary. HIT Type II is the entity discussed in this article.

The Antigen

One portion of the antigen is the heparin molecule itself. Unfractionated heparin (UFH) is a large, heavily sulfated glycosaminoglycan with a strong negative charge. It exists as a polymer with a molecular weight ranging from 3 kDa to 30 kDa, with a median range of 15 kDa. Heparin acts as a cofactor with antithrombin III to inhibit several coagulation factors, but has its strongest effect against thrombin (activated factor II) and somewhat less activity against activated factor X. There are several factors that effect heparin’s metabolism, specifically its route of administration, dose concentration, and its ability to bind nonselectively to endothelium. Heparin is broken down in the circulation, as well as being excreted by the kidney. UFH is produced in two forms: one from bovine lung tissue and the other from porcine gut tissue. The bovine form has been shown to produce a higher incidence of HIT. UFH is given subcutaneously or intravenously for either prophylaxis or therapeutic reasons.

Low-molecular-weight heparin (LMWH) is derived from UFH, and consists of shorter chains with a molecular weight between 2 and 9 kDa, with an average of 5 kDa. It has greater therapeutic activity against activated factor X than thrombin. It is only given by the subcutaneous route and can be used either prophylactically or therapeutically. Renal excretion is linear and not dose dependent.

UFH’s size and sulfation to saccharide ratio makes it an ideal antigen. Heparin itself is not antigenic because it shares a similar biochemical makeup to that of heparan sulfate, a proteoglycan that is normally found throughout the body. Heparin is one determinant in the antigenic complex that initiates the disease process. In order for
heparin to initiate the immunologic response, it must bind to PF-4, a protein that is stored and secreted by the α-granule of the platelet. Owing to heparin’s highly negative charge, it binds well to most structures within the bloodstream, including the PF-4 molecule that normally exists in the bloodstream.

The PF-4 molecule is an α-granule particle that is stored and released by the platelet. It is a highly positively charged particle and a member of the C-X-C cytokine family. Other members of the C-X-C cytokine family, including but not limited to IL-8 and platelet basic protein, can also react with the heparin molecule and produce the HIT antibody.6

Once the heparin–PF-4 complex exists, it can generate an immune response. In a naïve individual, the response can happen no sooner than 4 to 14 days. Once the antigen is cleared, the antibody production stops, but antibody activity can be present for up to 100 days. If the antigen has not initiated an immune response by at least 2 weeks after initial exposure, the risk of an immunologic response is minimal.

The Antibody

Once the antigen is recognized, antibody formation begins through the humoral arm of the immune system. IgM, IgA, and IgG antibodies are all formed, but it is the IgG antibodies that have clinical significance. They take approximately 5 days from initial exposure to develop. Antibody formation is stimulated as long as the antigen exists, and production stops once the antigen is cleared from the system. LMWH has less ability to produce the antibody because of its smaller size and lower sulfation to saccharide ratio. However, if LMWH does generate an antibody response, it has the same effect as UFH, and the antibody produced by UFH will cross-react with the antigen produced by LMWH–PF-4 antigen. Once the antigen is cleared, the antibody is undetectable in serum after about 100 days. This antigenic response is not anamnestic. Thus, a subsequent heparin exposure once the antibody is cleared does not initiate a stronger response. It is unclear why this occurs. The implication of no anamnestic response is that a person’s risk for a second occurrence of HIT does not seem to be higher once the antibody is cleared.

As many as 20% to 60% of people exposed to heparin will develop the heparin–PF-4 antibody, but only a small percentage of individuals will actually progress to the clinical syndrome.7,8 This phenomenon has been described as the iceberg model of HIT antibody detection (see later discussion).

The Effects

The IgG antibody binding to the heparin–PF-4 epitope initiates the disease process. The very long heparin molecule can bind many PF-4 molecules, creating a long chain of epitopes, each which can react with a separate antibody. Once the immune complex forms, the Fc portion of the anti-heparin or PF-4 IgG antibody binds to the platelet membrane or the endothelial cell through an Fc receptor located on the surface membrane. The IgG–Fc portion binds to the Fc receptor on the target activating it. If the platelet becomes activated, it releases its granules, propagating platelet aggregation and further activation. If bound to the endothelium, procoagulant factors will be released, which initiates the coagulation cascade. The long complex of heparin–PF-4, with its multiple antibodies attached can activate multiple platelets and/or endothelial cells. Activated platelets induce other platelets to aggregate and initiate the coagulation cascade, including direct activation of thrombin. Thrombin is a procoagulant, which significantly increases the risk for spontaneous thrombosis.9

The immune complex–platelet groups not included in thrombosis are cleared from the circulation by the reticuloendothelial system. Thrombocytopenia occurs as
platelets are consumed in thrombosis or as the immune complex-platelet groups are removed from the circulation.10

The Disease

Thrombocytopenia is seen in 80% to 90% of patients, and thrombosis occurs in up to 75% of the patients diagnosed with HIT.11 Thrombosis most frequently occurs in the venous system, but can also present in the arterial system, with a ratio of 4 to 1. Pulmonary embolism is the most common presentation of HIT.12 It seems that arterial thromboses occur at places with endothelial damage or atherosclerosis, and usually form a white clot which was originally thought to be a hallmark of this disease. Skin thromboses at sites of subcutaneous heparin injections are nearly pathognomonic of the disease.13

The diagnosis of a new or propagating thrombosis while on therapeutic or prophylactic anticoagulation should generate significant concern for this disease process. Nontraditional types of thrombosis should also raise suspicion of HIT. These include dural venous sinus thrombosis, adrenal vein thrombosis with or without subsequent adrenal hemorrhage and adrenal insufficiency, recurrent clotting of a continuous venovenous dialysis circuit, or acute myocardial infarction or stroke. The more severe a thrombosis, the more the clinician should entertain the thought that the patient could have HIT. Significant thrombosis can occur even when the platelet count is greater than 100,000/μL, and in 15% of patients, a thrombotic event can precede thrombocytopenia.14

The presence of the HIT antibody places the patient at the highest risk for spontaneous thrombosis compared with any other congenital or acquired thrombotic disease. For patients who are not anticoagulated and do not already have a thrombosis at the time of diagnosis, the cumulative 30-day risk of thrombosis is just over 52%.12 HIT thrombocytopenia is usually not as severe as other drug-induced thrombocytopenias. The platelet count begins to drop once the antibody is active (average is 5 days postexposure).10 The nadir range is between 20,000 to 100,000/μL, with a median value around 60,000/μL. This is in contrast to other types of drug-induced thrombocytopenia in which the initial decrease is more immediately related to exposure, and the nadir is usually less than 20,000/μL.15 The thrombocytopenia does not seem to predispose the patient to spontaneous bleeding, unless there is another, underlying bleeding diathesis. There is no indication to give platelets based on the thrombocytopenia alone, unless there is concomitant bleeding. Once the heparin is stopped, the platelet count returns to normal levels in about 4 days. Suspicion of the disease should be highest when platelet counts drop to less than 50% below baseline.16 Using platelet counts below 150,000/μL as an indicator for HIT is no longer part of the clinical suspicion for the diagnosis.

HIT can occur with any type of heparin exposure, but UFH carries a higher risk than LMWH.17 Higher dosages and long-term use carry higher risks, and intravenous administration seems to have a stronger causative effect. Heparin flushes and heparin-bonded devices also have been implicated in the disease.18 Cardiac and orthopedic surgical procedures have been associated with the highest rates of the disease.

DIAGNOSIS

One common misconception is that HIT can be diagnosed with clinical evidence alone, or independently, with the documented presence of the PF-4 antibody. In truth, it takes both, along with good clinical judgment to appropriately diagnose this condition.
**Clinical Evaluation**

The evaluation of the patient suspected of HIT comprises understanding of the four Ts: the Timing of onset, the severity of Thrombocytopenia, the presence of Thrombosis, and oTher causes for thrombocytopenia. A pretest scoring system, which is detailed below, can assist the clinician in considering which patients should be further evaluated for HIT.

The timing of the platelet count decline relative to heparin exposure is important to understand. If a person is naïve to heparin exposure, it takes a minimum 4 to 5 days for the clinically significant IgG antibody to be produced. However, because the antibody can exist for up to 100 days, the onset of signs and symptoms will be immediate after another heparin exposure when the antibody is already present. Patients with circulating antibody can develop an acute inflammatory reaction to injected heparin, consisting of tachycardia, diaphoresis, dyspnea, chest pain, and fever, which can mimic an acute pulmonary embolus. If a patient has this type of reaction after heparin injection, the clinician must immediately consider the patient as having HIT, obtain a platelet count, and discontinue the heparin.19 An acute drop with rapid recovery in the platelet count can occur and identification of thrombocytopenia in this clinical scenario is highly suggestive of HIT. This syndrome is called rapid-onset HIT.

Another atypical presentation is the delayed onset of HIT. These patients are in the hospital and exposed to heparin. They are then discharged within the next few days before any clinical indication they may be developing the disease and are discharged without additional heparin. They return to the hospital within the next few days with a new thrombosis. These patients have developed a very high titer of the antibody and have a delayed presentation, even though the heparin stimulus has been discontinued. Patients who present with a thrombotic episode within 2 weeks of being discharged from the hospital after receiving heparin should generate a significant concern for the diagnosis of HIT and should be screened before starting heparin.20

To evaluate a patient suspected of HIT, begin with the scoring system shown in Table 1. Evaluate each row and assign its numerical value (0–2 points) per patient criteria. If the total for all four columns is less than or equal to 3, the patient is very unlikely to have HIT and does not need to be tested for the antibody. If the score is between 4 and 5, there is a reasonable possibility that the patient has HIT, and the serologic evaluation should be sent. Depending on the clinical suspicion, the heparin should be stopped and alternative anticoagulation therapy should be started if necessary. If the score is greater than or equal to 6, there is a high probability for HIT and heparin should be stopped, alternative anticoagulation should be initiated, and the antibody test should be sent.21

This tool has been validated in clinical studies, specifically showing a high negative predictive value for those with low (<3) scores. However, in patients with intermediate (score 4–5) or high (>6) scores, there seems to be a high positive predictive value, but not as significant as the negative predictive value for the low score.8 There are also good correlations with serologic studies to prove or disprove the presence of the antibody.22,23

**Laboratory Evaluation**

Confirmation of the disease process entails proving the antibody is present. However, the presence of the antibody alone does not inherently diagnose HIT. The clinical and laboratory evaluation of HIT is described as an iceberg model. The number of patients developing the antibody far exceeds the number of patients with clinical manifestations of HIT. The patient with the clinical signs and symptoms along with a confirmatory
Table 1
The 4T pretest scoring system for HIT

<table>
<thead>
<tr>
<th></th>
<th>2 Points</th>
<th>1 Point</th>
<th>0 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Platelet count decrease &gt;50% and platelet nadir ≥20</td>
<td>Platelet count decrease 30%–50% or platelet nadir 10–19</td>
<td>Platelet count decrease &lt;30% or platelet nadir &lt;10</td>
</tr>
<tr>
<td>Timing of platelet count decrease</td>
<td>Clear onset between days 5–10 or platelet decrease ≤1 d (prior heparin exposure within 100 d)</td>
<td>Consistent with days 5–10 decrease, but not clear (eg, missing platelet counts; onset after day 10; or decrease ≤1 d (prior heparin exposure 30–100 d ago)</td>
<td>Platelet count decrease &lt;4 d without recent exposure</td>
</tr>
<tr>
<td>Thrombosis or other sequelae</td>
<td>New thrombosis (confirmed); skin necrosis; acute systemic reaction postintravenous UFH (UFH) bolus</td>
<td>Progressive or recurrent thrombosis; nonnecrotizing (erythematous) skin lesions; suspected thrombosis (not proven)</td>
<td>None</td>
</tr>
<tr>
<td>Other causes for thrombocytopenia</td>
<td>None apparent</td>
<td>Possible</td>
<td>Definite</td>
</tr>
</tbody>
</table>

The functional antibody assay represents the tip of the iceberg of the percentage of patients with positive antibody and clinical disease.

The newest and most rapid screening test is the PIFA Heparin/PF-4 Rapid Assay (Akers Biosciences, Inc, Thorofare, New Jersey, USA), a microparticle, immunofiltration, single-use system. It can detect the presence of HIT antibodies in fresh serum within minutes by the presence or absence of color change on the test strip (http://www.akersbiosciences.com/products/us/heparin/index.php).

The standard assay is the ELISA test, the commonly known PF-4 antibody assay. This assay is rapid, readily available, and detects the presence of all antibodies that can react with the heparin–PF-4 epitope, including the IgM, the IgA, and IgG antibodies. It has a reasonably high sensitivity, but a low specificity for the disease because it cannot separate which antibodies are significant. It is performed and read out as an optic density (OD) and the lower limit is usually set at 0.4 OD. If the reading is greater than 0.4 OD, the test is read as positive. If the reading is greater than 1.0 OD, there is enough concentration of clinically significant antibody to consider the patient as positive for the disease and a confirmatory test is not necessary unless the clinical presentation is questionable. If the reading is greater than 2.0 OD, no further testing is indicated and HIT can be confirmed solely with this test.

Once antibody presence is proven, a confirmatory evaluation can be used in clinically unclear patients to identify if a clinically significant antibody exists. The next step in testing is to prove the antibody can activate platelets. Functional platelet assays are time-consuming, difficult to set up, and done in fewer centers than the ELISA assay. A common type of functional assay is the serotonin release assay, which uses serotonin radiolabeled platelets as the substrate. The patient’s serum is mixed with the platelets, heparin is added, and, if there is a significant antibody present, the platelets will release the serotonin. The supernatant is evaluated for presence of the radiolabeled serotonin and reported as percent activity. The lower limit of normal is 20%, so any number higher is considered positive.

The sensitivity of the ELISA is greater than 90%, whereas the specificity is 50% to 70%. The specificity of many functional assays is greater than 95%, but the sensitivity is less than 90%. Together, the two assays are near 100% sensitive and specific.\(^\text{16}\)

The usual scenario to generate a HIT diagnosis includes thrombocytopenia 4 to 14 days after initiation of heparin, with a nadir around 60,000/μL, and at least a 50% drop from baseline. All other causes of thrombocytopenia are excluded. Thrombosis might be present, but is not necessary for diagnosis. The patient has a positive serologic test, confirmed by a positive functional assay.

Once the diagnosis of HIT is confirmed, or even highly suspected, all heparin must be immediately stopped. Because the rate of spontaneous thrombosis remains high, simply stopping heparin is not enough, the patient needs to be treated because they are now in an extremely prothrombotic state with a thrombosis incidence of greater than 50% within 30 days of diagnosis.\(^\text{12}\) Treatment consists of using an alternate anti-coagulation strategy.

**INCIDENCE AND SCREENING**

The incidence of HIT varies in the hospitalized population, and depends on whether the patient has a medical or surgical illness, type of heparin, and duration of heparin exposure. The highest risk for HIT belongs to orthopedic patients undergoing hip fracture repair, hip, or knee replacement, receiving UFH. That risk has been reported as high as 4.5%. The same patient population receiving LMWH has a risk of around 0.5%. Cardiac surgery patients also are high risk with a reported incidence of up to
3%. Cardiac transplant patients have the highest risk at 11%. It is interesting that cardiac surgical patients form the antibody more frequently, but orthopedic patients represent the highest risk patient population for HIT. General surgical patients receiving UFH have a risk of about 3%, whereas the same patient population receiving LMWH has a risk of about 0.3%. Critical care patients have a risk of 0.5% and HIT is the least common cause of thrombocytopenia in this patient population. The general medical population receiving UFH has a risk of 0.3% to 2.0%, but cardiac patients receiving UFH for coronary interventions have a frequency of 1.5% or higher. Obstetric patients have the lowest risk for HIT at less than 0.1%. For all patients receiving either UFH or LMWH, the overall risk for HIT is around 1.2%. The chronic hemodialysis patient population has an ELISA antibody prevalence of 12%, but the rate of HIT in the dialysis population is very low. HIT in the chronic hemodialysis patient is usually related to an additional exposure of heparin for some type of procedure and not to the usual heparin exposure of chronic hemodialysis. However, patients who are on chronic hemodialysis and possess the HIT antibody seem to have a higher mortality than hemodialysis patients without the antibody do.

Because thrombocytopenia is the heralding event of this disease, screening the patient population at risk is considered prudent, but the level of evidence supporting the frequency of testing for screening is not strong. Both the American College of Chest Physicians (ACCP) and the College of American Pathologists have published recommendations regarding platelet count monitoring on patients receiving heparin. Both recommendations are essentially the same. Here are the recommendations from the ACCP clinical practice guidelines from the 9th edition of Antithrombotic therapy and prevention of thrombosis:

- For patients receiving heparin in whom clinicians consider the risk of heparin-induced thrombocytopenia (HIT) to be greater than 1% (based on 4T score), we suggest that platelet count monitoring be performed every 2 or 3 days from day 4 to 14 (or until heparin is stopped, whichever occurs first) (Grade 2C)
- For patients receiving heparin in whom clinicians consider the risk of HIT to be less than 1%, we suggest that platelet counts not be monitored. (Grade 2C)

TREATMENT AND THERAPEUTIC MODALITIES

Once the diagnosis of HIT is confirmed or strongly suggested, therapy to prevent or treat the thrombotic complications must be initiated. Simply stopping the heparin is not sufficient because the patient has a very high risk of spontaneous thrombosis if they do not already have a thrombotic complication. Whether or not a thrombotic complication has already occurred, alternative anticoagulation treatments must be started to prevent either initiation, or propagation and worsening of the thrombosis.

The approved initial therapy for HIT includes several classes of medications, including the direct thrombin inhibitors (DTI), Factor Xa inhibitors (heparinoids and pentasaccharides), and vitamin K antagonists (VKA). The medications must be given in therapeutic dosages because a severely prothrombotic state is being treated, even if no thrombotic complications have yet occurred. The length of treatment depends on the presence of thrombosis.

LMWH is absolutely contraindicated as an alternative anticoagulation strategy for HIT, even if HIT was caused by UFH, because the antibody will cross-react with the LMWH and propagates the thrombosis.

Ancrod (Viprinex), a medication derived from pit viper venom, as well as the glycoprotein (Gp) IIb/IIIa inhibitors have been trialed for use in HIT, and have either shown no
efficacy, or worsened the thrombotic complications or bleeding tendencies. They have no role in the treatment of HIT or HITT.

**DTIs**

The DTIs are recombinant or synthetic molecules derived from hirudin, the anticoagulant found in the salivary gland of the leech *Hirudo medicinalis*. They act directly on thrombin, and can bind to both free and bound thrombin. In contrast, anti-thrombin III/heparin can only act on unbound thrombin. The two medications currently approved for HIT therapy are lepirudin and argatroban. A third DTI, bivalirudin, is indicated for percutaneous coronary intervention (PCI) in patients with HIT.

DTIs include

- **Lepirudin** (Refludan) was the first recombinant therapy developed. It exists as a bivalent inhibitor which acts on thrombin’s two exosites, which are both active in many of thrombin’s biologic activities. Lepirudin is provided as a continuous intravenous infusion. It is mostly excreted by the kidneys, so it is not useful in patients with renal failure. However, there are renal adjustments available in dosing. Therapeutic levels are monitored by the activated partial thromboplastin time (APTT), and the therapeutic goal is a clotting time 1.5 to 2.0 times the normal APTT clotting time. The main side effect from lepirudin administration is an anaphylactic reaction when bolus injections are given.

- **Argatroban** is a synthetic molecule that is also provided as a continuous infusion. It is a monovalent molecule, acting only on thrombin’s exosite responsible for propagation of coagulation. It is metabolized by the liver and is monitored with the APTT. Argatroban affects the prothrombin time-international normalized ratio (PT/INR), which can make the transition to VKA difficult. Goal APTT is 1.5 to 3.0 times normal clotting time for the APTT. Argatroban is indicated as therapy for HIT, and also for PCI in patients with documented HIT or HITT.

- **Bivalirudin** (Angiomax) is a synthetic, bivalent molecule that does not have Food and Drug Administration (FDA) approval for treatment of HIT or HITT, but there are some ongoing studies to detect its efficacy in the treatment of this disease. It has a unique method of metabolism, in which 80% of the molecule is cleaved to an inactive state by thrombin itself, and 20% is renally cleared, contributing to its extremely rapid plasma clearance. Its only indication at this time is for PCI in patients with HIT or HITT. Its efficacy is monitored with the APTT or activated clotting time.

- **Oral DTIs**, including dabigatran (Pradaxa) and ximelagatran (Exanta), are not currently approved for use in patients with HIT.

- **Desirudin** (Iprivask), a newer DTI given by the subcutaneous route, has not been approved for treatment in HIT.

**FACTOR XA INHIBITORS**

The only factor Xa inhibitor-approved therapy for HIT is danaparoid (Orgaran), but it is not available in the United States. The pentasaccharides are not approved for HIT therapy, but have shown efficacy in the management of both treatment as a bridge to VKA, as well as for deep venous thrombosis (DVT) prophylaxis in patients with a documented HIT antibody.

Factor Xa inhibitors include

- **Danaparoid** (Orgaran) is a heparinoid derived from porcine gut mucosa. Its active components are heparan, dermatan, and chondroitin sulfate. There is no heparin
or heparin fragments. It is administered subcutaneously, and has no intravenous component. It can be administered both in prophylactic and therapeutic doses. Factor Xa levels are used to follow its effects.

- Pentasaccharides are small molecules that act on Factor Xa. They are dosed only subcutaneously, and can be given in prophylactic or therapeutic dosages. The FDA has not approved any pentasaccharide for use in treatment of HIT or HITT, but there are some small studies that have shown efficacy in patients with documented HIT.\textsuperscript{31} Pentasaccharides might have efficacy for DVT prophylaxis in the patient with a moderate clinical suspicion of HIT who is awaiting confirmation of an antibody test but the clinician does not wish to convert to a DTI for treatment while awaiting results. There is some concern that the HIT antibody will cross-react with the pentasaccharides. However, the molecule seems to be too small to generate a significant thrombotic potential. There is one documented instance of fondaparinux (Arixtra) as the causative agent for HIT.\textsuperscript{26}

**VKAs**

VKAs are the group of agents that act against vitamin K-dependent factors (factor II, VII, IX, X, and proteins C and S) by inhibiting the enzyme vitamin K epoxide reductase, which acts to reduce Vitamin K after it carboxylates the coagulation factors mentioned above. It is used only in the chronic management of HIT and is absolutely contraindicated during the acute phase of HIT or HITT. VKAs are monitored by the INR. The goal is to maintain the INR at two to three times normal.

During the acute phase of HIT, thrombin is activated, which shifts the coagulation cascade toward a procoagulant state. Protein C and its cofactor, protein S, act to inhibit thrombin. The half-life of protein C is significantly shorter than the other vitamin K-dependent factors. Using the VKA in the acute phase will deplete protein C faster than thrombin. Once protein C is inhibited, thrombin activity is enhanced. This can result in systemic thrombosis, which may lead to the condition called venous limb gangrene, coumarin-induced skin necrosis, or other significant life-threatening or limb-threatening thromboses. It is imperative that if HIT is diagnosed in the acute phase and a VKA has been initiated before resolution of the thrombocytopenia (return of platelet count to at least 150,000/μL), vitamin K should be given to reverse the effects of the VKA and limit the chance of venous limb gangrene.\textsuperscript{30}

VKAs can be started once the platelet count returns to normal on the alternative anticoagulation therapy and there have been at least 5 days of concurrent treatment with non-heparin anticoagulation and VKA therapy. The non-heparin therapy can be discontinued after at least 5 days of overlap and a stable, therapeutic INR.\textsuperscript{30}

**LENGTH OF THERAPY**

There is no consensus statement regarding length of therapy for HIT with or without thrombosis. What is clear is that once HIT is diagnosed, full anticoagulation therapy must be undertaken using a non-heparin anticoagulant at therapeutic doses and then transitioned to VKA. Many experts suggest that if there are no thrombotic events, treatment be continued for the duration the antibody exists or 100 days maximum. If a thrombotic event occurs, the judgment of duration must be made by the clinician, based on current evidence regarding length of therapy for treatment of thromboses.
SPECIAL CIRCUMSTANCES

There are several special circumstances involving patients with documented HIT requiring anticoagulation therapy, as well as special patient populations who may have difficult therapeutic management options.\textsuperscript{32,33}

These patient populations include

- Patients with current or historical evidence of HIT who require cardiopulmonary bypass (CPB)
  
  The first step is to check for the presence of the antibody by ELISA. Three scenarios exist:
  
  1. The antibody is undetectable. If there is no antibody present, it is likely safe for the patient to undergo CPB with the normal heparin doses. Because there does not seem to be an anamnestic response to heparin in patients with a history of HIT, it would seem that the patient is at the same risk as the general population regarding production of HIT antibodies. This patient should be monitored for thrombocytopenia in the postoperative period.
  
  2. There is detectable antibody and normal platelet counts (subacute HIT). Re-exposure to heparin must be avoided and the patient should either be delayed until the antibody is, at best, weakly detectable by ELISA. Or, alternate anticoagulation may be used for the procedure and postoperative period.
  
  3. For acute HIT (antibody plus thrombocytopenia), no heparin should be used. The same principles apply as for the subacute patient and, unfortunately, there are few data to support the ideal agent or therapeutic levels of DTI for CPB. However, the current ACCP guidelines suggest a regimen for alternative anticoagulation in the patient population requiring CPB, but the levels of recommendation are not very strong. For patients requiring PCI, argatroban and bivalirudin have been approved for antithrombotic adjuncts in the patient with HIT.

- Patients requiring vascular procedures with current or historical evidence of HIT
  
  This patient population can be treated the same as the cardiac patient. If there is no or even weak antibody detected by ELISA, it should be safe to use heparin. There are no good data to suggest which DTI is preferred and what therapeutic level must be achieved in the patient with a HIT antibody requiring surgical intervention. There is no approved indication for the use of DTI in noncoronary vascular interventions, whether open or endovascular. The safest route is to wait until the antibody clears, if possible.

- Patients with remote history of HIT requiring DVT prophylaxis
  
  If no antibody exists, UFH or LMWH are safe, ensuring that routine monitoring for thrombocytopenia is undertaken. If the patient also has a history of thrombosis, he or she may be at increased risk of developing another thrombosis whether or not the original thrombosis was related to HIT. Pentasaccharides, danaparoid, and even warfarin (in the subacute phase) have all shown good efficacy for chemical prophylaxis in this patient population.

- Patients who are pregnant patient and have HIT
  
  Pentasaccharides do not cross the placenta and are likely safe. VKAs are contraindicated in pregnancy, and lepirudin and argatroban may cross the placenta.

- The patient is a child
  
  There are no current trials of DTI with children.
SUMMARY

HIT is an immune process, triggered by the administration of a heparin molecule, which binds to a platelet-specific protein—PF-4. The antigenic complex of heparin–PF-4 induces an IgG response that binds the antigen as well as platelets, contributing to thrombocytopenia and thrombosis. Diagnosing the condition requires clinical suspicion, platelet count monitoring, and identification of the causative antibody. Treatment involves stopping all heparin administration and starting alternative anticoagulation therapy.

Here are some patient situations that allow the reader to think about this disease from a clinical standpoint.

- Patient 1 is a 27-year-old man involved in a high-speed motor vehicle crash with polytrauma, including an open femur fracture, crushed spleen requiring damage control laparotomy, and a flail chest requiring a chest tube and prolonged invasive ventilation. UFH is started for DVT prophylaxis on hospital day 2. On hospital day 4, his platelet count is 40,000/μL. A PF-4 antibody is sent and returns weakly positive. Does this patient have HIT?
  - Discussion: This patient has multiple reasons for thrombocytopenia, and has a very low probability of HIT as a diagnosis. His weakly positive ELISA test is of no significance. No further workup or therapy is warranted.

- Patient 2 is a 74-year-old woman who undergoes elective sigmoid resection for diverticulitis. She has a history of coronary artery disease, peripheral vascular disease, and hypertension. Preoperative platelet count is normal at 160,000/μL. LMWH is started for DVT prophylaxis in the preoperative area, and continued for her hospital stay. On hospital day 6, she develops unilateral leg edema. Duplex ultrasound reveals a deep vein thrombosis. Therapeutic heparin intravenous infusion is initiated. On hospital day 7, her platelet count is noted to be 60,000/μL. She subsequently develops shortness of breath and a chest CT scan reveals a pulmonary embolus. The PF-4 antibody is drawn and sent, but will take two days to return a result. What is the appropriate next step?
  - Discussion: This patient is an older woman with a DVT and PE on heparin therapy after elective sigmoid resection. She has a high enough concern for HITT that all heparin should be stopped and alternative anticoagulation started. She should be transitioned to VKA after her platelet count returns to normal and she has been covered with both DTI and VKA for at least 5 days, provided her antibody assay returns positive. The length of therapy should be based on current guidelines for thrombotic therapy.

- Patient 3 is a 62-year-old dialysis-dependent man, who is admitted to the hospital with a lower extremity arterial thrombus. A therapeutic heparin drip is started. On hospital day 4, his platelet count is noted to be 85,000/μL, and his baseline is 110,000/μL. PF-4 antibody is sent and the result returns as positive. Does this patient have HIT?
  - Discussion: This patient is a chronic hemodialysis patient with a new arterial thrombus, mild thrombocytopenia, and positive ELISA assay. This patient has a low probability for HIT in that he receives chronic heparin, and has not been exposed to a separate source of heparin before his thrombosis. Arterial thrombosis is fairly common in this patient population and the thrombocytopenia is likely reflective of the consumption from the clot. However, this assay should be confirmed by a functional platelet assay and, if positive, he has confirmed HIT and will need alternative anticoagulation. The presence of the HIT antibody may put him at higher risk of mortality compared with other hemodialysis patients without the antibody.
REFERENCES


