Heparin-Induced Thrombocytopenia (HIT)

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Introduction

Heparin remains the anticoagulant of choice for many clinical needs. Because heparin is used ubiquitously in the hospital setting, millions of patients are exposed each year. In some patients, heparin therapy elicits formation of antibodies which cause heparin-induced thrombocytopenia (HIT) a severe adverse effect characterized by low platelet count and high risk of thrombotic complications. Healthcare providers must be aware of and understand the clinical diagnosis, laboratory testing, and treatment of HIT because of the devastating clinical consequences of stroke, acute myocardial infarction, pulmonary embolism, limb amputation, and death due to thrombosis with which it is associated.

While much of the work in understanding the pathophysiology, clinical presentation, and treatment of HIT has centered on cardiovascular and orthopedic surgery populations, neurology/neurosurgery patients also have a high frequency of developing HIT (up to 15 % has been reported) [1]. In addition, neurological symptoms are characteristic of HIT making all HIT patients potential neurovascular patients [2, 3]. This chapter summarizes the current practice for the management of patients with HIT (Table 14.1).

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Development of HIT

Antibodies elicited by heparin therapy are not specifically anti-heparin antibodies. HIT antibodies recognize particular complexes of heparin and the platelet release protein, platelet factor 4 (PF4) [4, 5]. The presence of PF4 is critical to the development (immunogenesis) of HIT antibodies and to their pathogenic function.

PF4 is a positively charged protein that binds to negatively charged heparin and heparin-like molecules. Upon release from activated platelets, PF4 rapidly associates with heparan sulfate on endothelial cells, promoting a procoagulant surface for vascular repair. In the presence of therapeutic heparin, this binding results in large, highly immunogenic PF4-heparin complexes in circulation. In addition to its hemostatic role, PF4 (a member of a highly conserved family of host defense peptides) has both antimicrobial and immune functions. The similarity of PF4 bound to certain pathogens and the conformation of PF4 bound to heparin may explain the immunogenicity of PF4/heparin complexes [6] resulting in the generation of HIT antibodies.

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Table 14.1 Clinical management of heparin-induced thrombocytopenia

• HIT is an immune response to PF4, an activated platelet release protein, bound to heparin
• HIT is a complex syndrome that requires immediate and knowledgeable clinical management
• Patient-dependent variables are associated with a higher risk of developing HIT and poorer outcomes
• Patients with HIT can develop neurological symptoms (thrombosis, but also bleeding from anticoagulant treatment); also the cause of cerebral thrombosis in a neurology patient can be traced back to HIT
• HIT is largely a clinical diagnosis; scoring systems are available to aid in determining the probability that a patient has HIT
• Laboratory tests for HIT help in the diagnosis but they are not optimal and require knowledgeable interpretation of results
• Using a scoring system also helps with lab test ordering (to reduce false positive results)
• An immunoassay is used to screen for HIT antibodies (many false positives); a platelet function assay is the standard to confirm HIT (but sensitivity is low)
• The titer (optical density reading) of the immunoassay for HIT antibodies can be used to follow the clinical progress of a patient
• The first step in managing a patient with HIT is to remove heparin, but until HIT is confirmed consideration for the risk of thrombosis from other causes that dictates anticoagulant protection must be given
• Use intravenous argatroban or bivalirudin, with monitoring, for treatment of acute, severe HIT and HIT thrombosis
• Use bivalirudin for interventional or surgical procedures in patients with HIT; optimal dosing and monitoring protocols are in development
• Be aware of the potential for intracranial bleeding with argatroban and bivalirudin treatment
• Use of fondaparinux for prevention of thrombosis in patients with suspected HIT with no indication for full anticoagulation is gaining favor but not yet approved
• Prevent the occurrence of HIT by limiting exposure to heparin; use LMW heparin, fondaparinux, or other non-heparin anticoagulants in place of heparin where possible; reduce platelet activation

The risk of developing HIT increases with heparin dose and longer treatment duration and is more likely with intravenous than subcutaneous heparin. Still, HIT antibodies can develop from any heparin exposure including incidental amounts from heparin flushes or heparin-coated devices. Due to their smaller molecular size compared to therapeutic heparin, low molecular weight (LMW) heparin and fondaparinux have less ability to bind PF4, alter its configuration, and cause the generation of antibodies.

Immune complexes of HIT IgG bound to PF4-heparin complexes cross-link platelet FcγIIa receptors, resulting in platelet activation with release of additional PF4 and platelet-platelet aggregation. In the presence of heparin, there is continued formation of antigenic complexes, platelet activation and aggregation, and generation of highly procoagulant platelet microparticles. Sustained platelet activation contributes to platelet clearance and thrombin generation that can lead to both thrombocytopenia and HIT-associated thrombosis.

HIT antibodies, once formed, become involved in various hemostatic activation processes beyond platelet activation [7]. These antibodies also recognize PF4 bound to cell membranes via heparan sulfate, which contributes to an inflammatory state whereby macrophages, monocytes, and neutrophils are activated. Antibody and leukocyte binding to activated endothelial cells cause release of tissue factor, plasminogen activator inhibitor-1 (PAI-1), and cytokines, as well as an upregulation of adhesion molecule expression, promoting localized platelet and monocyte binding. The interrelationships of platelets, leukocytes, the endothelium, and the inflammatory state determine the clinical expression of HIT.

The presence of HIT antibodies does not cause thrombocytopenia or thrombosis in the majority of patients. It is when certain HIT antibodies bind PF4, forming immune complexes, that subsequent FcγIIa receptor-mediated platelet activation ensues which can lead to thrombocytopenia and/or thrombosis. Thus, the HIT syndrome depends not only on the presence of HIT antibodies of sufficient *titer* and *specificity* but also on the *presence of PF4* [8].

The availability of PF4 is influenced both by acute and chronic platelet activation and logically plays a role in the risk for generation of PF4-heparin antibodies in the context of anticoagulant therapy. Increased platelet activation and

circulating PF4 levels are observed in inflammatory and infectious diseases, diabetes, cardiovascular disease, atherosclerosis, conditions affecting vascular health, and in response to traumatic medical procedures or cardiopulmonary bypass. This suggests an explanation for the common observation that specific patient populations (type of surgery, severity of trauma, age, comorbidities such as renal impairment, low cardiac output, malignancy, critical illness, vascular disease) are known to be at an increased risk of developing HIT antibodies.

Clinical Presentation of HIT

In up to 30 % of patients, administration of heparin is followed by a benign, transient, and self-limited fall in platelet count which occurs through a non-immunological mechanism and resolves within 24–48 h (referred to as HIT Type I). The clinically relevant HIT syndrome discussed herein is immune-mediated HIT (known as HIT Type II) that is associated with thrombocytopenia and an extreme hypercoagulable state.

Immune-mediated HIT is defined as thrombocytopenia or new thrombosis starting 5–10 days after exposure to heparin, in the absence of other explanations for the symptoms [9]. HIT should be suspected on the basis of an unexplained 30–50 % drop in platelet count from baseline in patients being treated or having been recently treated with heparin. No single definition of thrombocytopenia based on platelet count is appropriate in all clinical situations. For example, an abrupt decrease in platelet count that does not result in thrombocytopenia (e.g., platelet count may fall from 450,000 to 225,000/μL) can be HIT. Not all patients with thrombocytopenia experience thrombosis, and thrombotic complications can occur before or in the absence of thrombocytopenia. There can also be variability in the timing of onset of clinical symptoms. Patients with HIT antibodies resulting from heparin exposure within the prior 100–120 days may have an immediate, rapid onset of HIT when restarting heparin [10]. Delayed-onset HIT has been observed with symptoms appearing days to weeks after discontinuation of heparin [11].

There is a wide spectrum of arterial and venous thromboembolic complications associated with HIT, including deep vein thrombosis, pulmonary embolism, ischemic stroke, myocardial infarction, limb ischemia, vein graft occlusion, skin lesions at injection sites, and thrombosis of an extracorporeal circuit. Venous thrombosis predominates 5:1, but arterial thrombosis accounts for the most disturbing symptoms [12]. Mortality among patients with HIT thrombosis that is not effectively treated is 30 %, with 20 % of those who survive requiring a limb amputation [9]. Overall mortality rates of patients with HIT thrombosis approach 10–20 % despite the current practice improvements.

Deep venous thrombosis of the lower limbs and pulmonary embolism commonly occurs; thrombosis in the upper extremities is often associated with a central venous catheter or pacemaker wire. Other less commonly reported events include mesenteric venous thrombosis and adrenal hemorrhagic infarction. Acute limb occlusion is the most common arterial event usually developing in areas of a recent interventional procedure or following trauma.

Stroke was reported in 3 % of all HIT patients and more often in females who tend to experience poorer outcomes [2]. In another study, neurological complications of patients with HIT were reported to be 9 % [3]. Stroke significantly increases the mortality risk [2]. The consideration of HIT in the differential diagnosis when ischemic stroke occurs and of heightened stroke awareness for ≥2 weeks following HIT diagnosis is important.

LMW heparin can also cause HIT but with a tenfold lower rate of occurrence than with heparin. Symptoms are the same but typically appear 8–14 days after exposure to the LMW heparin [13].

Cardiovascular Patients

The cardiovascular patient is at high risk to develop HIT. Patients who undergo percutaneous transluminal angioplasty, percutaneous coronary angioplasty, percutaneous coronary intervention, and coronary artery bypass or vascular surgery

appear particularly vulnerable. This is assumed to be due to the repeated and occasionally prolonged exposure to heparin or LMW heparin. When HIT occurs in a post-procedure patient, the presence of an injured vascular intima provides a unique thrombogenic surface that is at a high risk for thrombosis. The increased level of platelet activation and PF4 release is an added reason for the higher incidence of HIT in this population.

The diagnosis of HIT is difficult in post-surgical patients as postoperative thrombocytopenia is frequently present and always present following cardiac surgery using cardiopulmonary bypass. In these patients, HIT should be suspected if the platelet count recovery in the immediate postoperative period is interrupted by a sudden and marked platelet count decrease 5–10 days post-operation (a biphasic platelet count pattern) [14]. However, HIT cannot be definitely excluded in patients with a monophasic pattern of persistent postoperative thrombocytopenia.

Heart failure patients requiring ventricular assist devices who receive anticoagulation during surgery and for extended postoperative periods often develop HIT antibodies but not necessarily HIT thrombosis [15]. These patients have multiple explanations for low platelet counts. No guidelines are yet established for the diagnosis of HIT in this patient group.

Neurovascular Patients

Although there are limited reports of the true frequency of HIT and rate of thrombotic complications in neurosurgical patients, there is good indication of risk in this patient population. HIT should be part of the differential diagnosis.

Heparin is frequently given to acute ischemic stroke patients. A prevalence of 0.5 % of confirmed HIT in this population based on a clinical scoring system and laboratory assay results (2 % prevalence if based on clinical score alone) has been reported [16]. Other less rigorous studies reported higher frequencies. The clinical severity and outcome of acute stroke patients suspected of having HIT were unfavorable.

Subarachnoid hemorrhage (SAH) patients, among neurosurgical patient populations, are exposed to heparin because they are in critical care units, are at risk of venous thrombosis, and have indwelling vascular catheters. In addition, the increase in neurovascular procedures with associated heparinization increases the exposure of patients to heparin. The incidence of HIT in SAH patients at a single center was reported to be as high as 15 % [1]. Other studies reported rates from 2 % to 6 % [17–19]. The SAH patients with HIT had significantly higher rates of thrombotic complications, new hypodensities on head computed tomographic scans, more deaths, and significantly less favorable outcomes.

Other concerns include the relatively common finding of ischemic stroke in all patients first presenting with other symptoms of HIT (discussed above). In addition, the treatment of choice for patients with HIT thrombosis is a direct thrombin inhibitor anticoagulant, yet intracranial hemorrhage can occur from this treatment.

These issues highlight the fact that HIT can be the cause for cerebral thrombosis in neurovascular patients and also that non-neurovascular patients with HIT can develop neurological symptoms from HIT thrombosis or bleeding from treatment of HIT with anticoagulants.

Patients with Mild Thrombocytopenia

Another challenging clinical presentation of HIT is the patient with mild thrombocytopenia receiving heparin or LMW heparin treatment. These patients are to be individually assessed for their risk of HIT considering past exposure to heparin, competing causes for thrombocytopenia, and new thrombosis. The level of risk will determine whether or not to continue heparin/LMW heparin treatment, while laboratory testing is sent to confirm the diagnosis.

Diagnosis and Early Management

The diagnosis of HIT is complicated because patients often do not fit a simple textbook definition. Clinical judgment remains important for directing patient clinical care. Although the diagnosis of HIT can be difficult, it is critical that

patients with HIT be identified as soon as possible to initiate early treatment to avoid thrombosis. HIT should be considered in the differential diagnosis of any new thrombosis or extension of an existing thrombus in a patient receiving anticoagulation.

Clinical Scoring Systems

The diagnosis of HIT is based on clinical findings, platelet count, and laboratory testing. It is necessary that causes for thrombocytopenia, a common finding in a hospital setting, other than HIT be ruled out.

Scoring systems, such as the 4Ts [20] or the HEP score (an expanded version of the 4Ts score based on the opinions of 26 HIT experts) [21] to estimate pretest probability of HIT, are useful to risk stratify patients facilitating clinicians' management of patients with suspected HIT. Scoring systems are based on the magnitude and nadir of thrombocytopenia, timing of platelet count fall, thrombosis, other heparin-related reactions, and exclusion of other causes of thrombocytopenia. The 4Ts system is summarized in Table 14.2.

Next Steps

Clinical scores should be determined first on patients suspected of HIT. After this is determined, the decision for laboratory testing is to be made. If clinical suspicion for HIT is low and the clinical score is low, no laboratory testing needs to be performed (to avoid false positives). If the score is intermediate or high, an immunoassay should be performed because it is highly sensitive. If the immunoassay result is positive, a functional assay needs to be performed to confirm the presence of HIT and avoid a false positive (see laboratory test section below). Other likely scenarios of clinical scoring, lab test results, and interpretation are given in Table 14.3. Keep in mind that results of the laboratory tests for HIT do not always coincide with the clinical picture.

Clinical management of HIT at the initial stage must take into consideration the risk of thrombosis from other causes that would dictate anticoagulant protection. Cessation of heparin while waiting for lab test confirmation of HIT needs to be weighed against the need for anticoagulant protection. One simple scoring system (Table 14.4) helps with the decision process of whether or not to immediately discontinue heparin in patients suspected, but not confirmed, of HIT [22]. An immediate switch to argatroban or bivalirudin is costly and carries the risk of hemorrhage.

On the other hand, for patients with a high score by any scoring system for HIT, it is not necessary to wait for laboratory test results to initiate non-heparin anticoagulation therapy. It is important, however, to have laboratory confirmation of HIT, because patients with a history of HIT are at risk for recurrence should they be exposed to heparin in the future. Thus, HIT lab tests should be used to confirm a clinical diagnosis of HIT to guide future therapy.

Table 14.2 The 4Ts clinical scoring system to determine patient's risk of HIT [20, 54]

	2 Points	1 Point	0 Points
Thrombocytopenia	>50 % fall or platelet nadir 20,000–100,000/μL	30–50 % fall or platelet nadir 10,000–19,000/μL	<30 % fall or platelet nadir <10,000/μL
Timing of platelet drop or other sequelae	Onset days 5–10 or <1 day if recent heparin exposure	Onset after day 10 or not clear	Onset ≤4 days without recent heparin exposure
Thrombosis or other sequelae	New thrombosis; skin necrosis at heparin injection site; acute systemic reaction after intravenous heparin bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis	None
Other causes of thrombocytopenia	None evident	Possible other causes	Definite other causes

Probability: 6–8 = high; 4–5 = intermediate, 0–3 = low
The HEP SCORE [21] is similar with more detail in each category

Table 14.3 Possible laboratory test results for suspected HIT

Clinical suspicion/score	Immunoassay	Functional assay to confirm HIT	Interpretation
Low	Not done	Not done	HIT unlikely
Intermediate	Positive	Positive	HIT likely
Intermediate	Positive	Negative	Indeterminate; repeat testing over the next days
Intermediate	Negative	Not done	Indeterminate; repeat testing over the next days
High	Positive	Not done	HIT likely
High	Negative	Not done	Indeterminate; repeat testing over the next days

This chart illustrates one example of a diagnostic algorithm
The two types of lab test for HIT provide different but complimentary information, which together aid in an accurate diagnosis of HIT. However, limitations of both assays require knowledgeable interpretation of the assay results. The clinical impression remains important for a diagnosis of HIT

Table 14.4 Scoring system to continue or discontinue heparin in suspected HIT [22]

Score	Clinical criteria	Clinical management
0	Heparin therapy not present for 5 days preceding platelet count drop – or – Platelet count did not fall by 30 % – or – Significant competing cause for thrombocytopenia	Continue heparin therapy if clinically indicated while waiting for HIT lab test results
1	On heparin therapy – and – No significant competing cause for thrombocytopenia – and – Platelet count fall by >30 % – or – New thrombosis	Discontinue heparin therapy while waiting for HIT lab test results

Whenever there is a strong clinical suspicion or confirmed diagnoses of HIT, heparin and LMW heparin have to be immediately discontinued. However, cessation of heparin alone is not sufficient to remove the threat of thrombosis from HIT [23]. A non-heparin alternative anticoagulant should be used to treat existing thrombosis from HIT and/or to prevent thrombosis from occurring (see treatment section below). LMW heparin is contraindicated in patients with HIT because this drug class has a high rate of interaction with established HIT antibodies.

Clinical Laboratory Testing for HIT

Platelet Count

During the initial period of heparin and LMW heparin treatment, platelet counts should be performed [9]. If the patient's risk of developing HIT is high, platelet counts should be done more frequently, daily if necessary.

Assays for HIT

There are two different types of specific clinical laboratory tests for the diagnosis of HIT: (1) immunoassays detect the presence of antibodies that bind to PF4/heparin complexes and (2) platelet-based assays that demonstrate whether the antibodies have the functional capacity to cause heparin-dependent platelet activation. Laboratory testing for HIT should only be performed when there is a strong clinical suspicion of HIT to avoid false positive results.

No test for HIT has optimal sensitivity and specificity, and negative test results do not necessarily exclude the diagnosis of HIT [24]. Furthermore, as antibody titers rise, daily testing can turn from negative to positive with repeat testing.

Immunoassays are increasingly common because of the fast turnaround time to result reporting, and this test can be performed in most laboratories. However, certain limitations of result interpretation must be highlighted. These assays are highly sensitive and have a high rate of false positive results. False negative results can also occur. Studies have shown that the presence

of HIT antibodies alone is not sufficient to cause the clinical symptoms of HIT (thrombocytopenia and thrombosis) [17, 25]. However, a negative immunoassay in patients with low clinical probability for HIT (low clinical score) has a high negative predictive value. A positive immunoassay has to be reflexed to a platelet function assay to confirm HIT. Antibody levels of ≥1.0 optical density by immunoassay are more likely to be associated with HIT thrombosis [26, 27].

While it is known that IgG-type HIT antibodies are important for platelet activation in HIT, IgM and IgA HIT antibodies may also play a pathophysiological role. Non-IgG HIT antibodies are linked to longer hospital stay, poorer clinical outcome, and poorer rate of survival. Immunoassays that test IgG/A/M HIT antibodies are preferable to IgG-only assays.

Platelet activation functional assays have a lower sensitivity than the immunoassay, but they are specific for HIT antibodies that are associated with clinical symptoms. The serotonin release assay (^{14}C-SRA, SRA) that employs radiolabeled serotonin uptake by the platelets is the reference test. Assays based on light transmission platelet aggregation are also used in many centers. These assays require a skilled and experienced lab to assure accurate results. Platelet activation tests are used to confirm an HIT diagnosis in patients who have an intermediate to high clinical risk assessment for HIT with a positive HIT immunoassay. These tests, while important for confirming a diagnosis of HIT, do have limited sensitivity and can produce false negative results.

Treatment of HIT

Despite the hallmark low platelet count, HIT patients rarely have bleeding complications. Platelet transfusions are contraindicated in patients with HIT but may be considered if there is life-threatening bleeding. The major significance of HIT is the paradoxical risk of thrombosis. HIT antibody positive patients without thrombosis initially have up to 50 % risk of developing thrombosis within the next 30 days if not provided prophylaxis with a non-heparin anticoagulant.

Anticoagulant Treatment for HIT Thrombosis

HIT is characterized by a strong hypercoagulable state with a high risk of thrombosis [9]. It is recommended that all patients with HIT thrombosis be anticoagulated with intravenous administration of a strong acting, non-heparin anticoagulant such as argatroban or bivalirudin [9, 28]. These anticoagulants are direct-acting thrombin inhibitors (DTIs). They are potent anticoagulants that inhibit the high level of thrombin generated in patients with HIT. Because their chemical structure differs from that of heparin, DTIs do not bind to PF4, generate HIT antibodies, or interact with preformed HIT antibodies. DTIs reduce the risk of thrombosis and associated morbidity/mortality in patients with HIT. Death, amputation, and new thrombosis are reduced, and platelet counts recover more rapidly in patients receiving treatment than those not receiving treatment.

Argatroban (Novartis) was the first real solution for effective alternative anticoagulation for patients with HIT. Large clinical studies began in the mid-1990s [29, 30], followed by multiple investigations to assess clinical safety and efficacy in pediatrics and other specific populations [2, 31–37].

Argatroban is a small molecule thrombin inhibitor. It is administered by intravenous infusion. Its use is not recommended in patients with liver failure. Based on clinical experience, dose adjustments to reduce the bleeding risk for argatroban in specific populations have been recommended, including reduced dosing for seriously ill patients [34, 38]. Argatroban has the broadest regulatory approval, i.e., for both prophylaxis and treatment of thrombosis in patients with HIT, as well as for anticoagulation in HIT patients requiring cardiovascular interventional procedures. Argatroban is currently the preferred drug for patients with HIT requiring hemodialysis.

Argatroban therapy reduces the likelihood of new stroke and stroke-associated mortality in HIT [2]. A Japanese study showed that argatroban significantly improved global outcome in patients with acute cerebral thrombosis [39]. High-dose argatroban was shown to be an effective treatment

for cerebral infarction including delayed hospitalization after onset [40]. Argatroban in combination with intravenous tissue plasminogen activator in acute stroke was reported to be safe in patients with moderate neurological deficits due to proximal intracranial arterial occlusions [41]. Reports on the use of argatroban, or any DTI, for the treatment of stroke are limited to date. Further studies are needed to better determine safety and efficacy.

Due to an inherent bleeding risk with this potent anticoagulant, argatroban treatment must be monitored. Therapeutic dosages are monitored by the same partial thromboplastin time (PTT) as used for heparin monitoring; higher dosages as used during interventional procedures are monitored by the same activated clotting time (ACT) as used for high-dose heparin monitoring. Argatroban has a substantial effect on the international normalized ratio (INR) [42, 43]; however, monitoring this drug by the INR has not been validated, and it should not be used. Argatroban has an effect on all clot-based assays (e.g., fibrinogen level, coagulation factor assays, protein C assay, etc.) [44]. True values for these coagulation proteins can only be obtained by using a chromogenic-based assay or an immunoassay if testing is to be performed on patients under argatroban treatment.

There is no antidote for argatroban. Given its short half-life of 50 min, the best recourse is to discontinue the infusion to reduce circulating drug levels.

Bivalirudin (Angiomax®; The Medicines Company) is a 20 amino acid synthetic peptide that targets two binding sites within thrombin. It has a very short half-life of 25 min due to enzymatic degradation. Bivalirudin is approved for use as an anticoagulant in cardiovascular interventional procedures in patients with HIT [45, 46]. It is administered intravenously and monitored by the ACT during use. The INR is not to be used for monitoring [42, 43]. As with argatroban, bivalirudin affects all clot-based assays, and it has no antidote.

One of the greatest challenges in the management of patients with HIT is anticoagulation during cardiac surgery where heparin is the drug of choice. Subsequent use of heparin after resolution of HIT can be hazardous, particularly within the first 3 months as rapid onset of the clinical syndrome can erupt. Patients with a previous history of HIT should be tested presurgery for the presence of HIT antibodies. In the absence of antibodies, surgery may be performed using heparin [9, 28]. If HIT antibodies are detectable by immunoassay, it may be reasonable to delay surgery until the antibodies are no longer present. In more urgent situations, surgeries have been successfully performed with heparin in immunoassay positive patients whose antibodies did not cause platelet activation detected by the SRA. In this circumstance standard heparin protocols restricted to the surgery itself can be employed, with a thrombin inhibitor, a factor Xa inhibitor, or warfarin for postoperative care if needed.

Alternative anticoagulation strategies that may be recommended for cardiac surgery use bivalirudin. Anticoagulation with bivalirudin was shown to be feasible in both on-pump (cardiopulmonary bypass pump, CPB) and off-pump (OPCAB) cardiac surgeries [47, 48]. The use of any DTI in cardiac surgery is associated with inherent risks: bleeding can be excessive, standing blood in the pump and devices can clot, and best practice monitoring of the high drug levels is not resolved. Surgical use of bivalirudin remains off-label, yet experience is growing.

Lepirudin had been used for the treatment of HIT thrombosis until recently. This drug has been taken off the market due to hypersensitivity in patients reexposed to the drug. Severe anaphylactic reactions with fatal outcomes have been reported.

Long-Term Anticoagulation

Warfarin is recommended for long-term treatment of HIT-associated thrombosis [9]. Warfarin is not recommended for use in the acute phase of HIT (when platelets are <100,000/μL) due to its potential to intensify the prothrombotic state from a transient protein C deficiency.

Warfarin can be initiated when platelet counts are >100,000/μL or at pre-HIT values starting at a low dose (5 mg warfarin; a loading dose should not be used to avoid possible skin necrosis),

while the patient is fully anticoagulated with a DTI and continued for at least 5 days [9]. The DTI can be tapered off when the INR is therapeutic and stable. Warfarin treatment should continue until platelet counts recover to a stable plateau or longer if clinically warranted. These specific dosing guidelines need to be followed to avoid thrombotic complications.

DTIs prolong the prothrombin time (PT)/INR [42, 44, 49]. INRs >5 commonly occur with argatroban-warfarin co-therapy, but this does not correspond with a decrease in coagulation factor levels and bleeding is not enhanced. There is a predictable linear effect on the INR of argatroban doses up to 2 μg/kg/min during warfarin co-therapy, which allows for reliable prediction of the level of oral anticoagulation [49]. If argatroban dosing is higher, guidelines are available for how to proceed with bridging to warfarin.

Anticoagulation for HIT Without Thrombosis

Not all patients with HIT develop the acute stage of the disorder with thrombosis. Many patients develop HIT antibodies, have a mild thrombocytopenia, and have no thrombosis. For these patients the option to treat prophylactically to avoid thrombosis may be prudent knowing the risk of thrombosis and the medical intensity of acute HIT. There are several potential options for thrombosis prophylaxis that are undergoing evaluation.

Fondaparinux (Arixtra®; Mylan) is a synthetic, small molecule factor Xa inhibitor. It mimics the minimum specific saccharide sequence of heparin that binds to antithrombin and factor Xa. Due to its low molecular weight, fondaparinux does not cross-react with preformed HIT antibodies as heparin does. There have been no clinical trials in HIT. There are case reports, small published case series, and one retrospective analysis of 239 patients that show that fondaparinux provides effective anticoagulation of patients with suspected HIT *who have no indication for full anticoagulation* [50].

Although fondaparinux is considered to be a potential second-line agent for the management of patients with suspected HIT, its use in HIT remains off-label. Caution is warranted as there are reported cases of clinical failures.

Desirudin (Iprivask®; Marathon Pharmaceuticals) is a hirudin-based drug and the only DTI approved in the USA for administration by the subcutaneous route. It exhibits predictable pharmacokinetics when administered at a fixed dose and does not require routine monitoring. Desirudin is currently approved for prevention of DVT after orthopedic surgery. This drug has been successfully used in a limited number of patients with HIT [51], and studies to validate desirudin treatment for patients with or at risk for HIT thrombosis are in progress.

New oral anticoagulants are of interest for thrombosis prophylaxis in HIT patients. These synthetic, small molecules inhibit either thrombin (**dabigatran**) or factor Xa (**rivaroxaban, apixaban, edoxaban**). Laboratory studies show that these drugs do not interact with preformed HIT antibodies [52, 53]. Where warfarin has been used for outpatient anticoagulation or for prophylaxis against the development of HIT thrombosis, the new oral anticoagulants may prove useful. It remains to be determined whether these drugs are potent enough to provide sufficient anticoagulation coverage for all phases of the HIT syndrome. Clinical use in HIT is currently off-label, although case reports are appearing.

Other HIT Thrombosis Treatment Options

Certain patients with HIT develop ischemic limbs or organs in which thrombosis is not alleviated with anticoagulant therapy. Adjunct treatment options include thrombolytic agents or surgical removal of life- or limb-threatening thrombi. Plasmapheresis has been used to hasten reduction of antibody load in severely ill patients. These options should be used under the guidance of a clinician experienced in the procedure.

Future Treatment Options

Even with the success of intravenous DTIs for the management of HIT, amputation and death have not been eliminated in this patient population. Considering the pathophysiology of HIT, inhibition of thrombin, while important, likely cannot provide complete medical management of HIT patients. HIT is associated not only with a hypercoagulable state but also with platelet activation, vascular endothelial dysregulation, and inflammation (leukocyte activation, cytokine upregulation).

Thus, optimization of patient management needs to continue. Optimal medical management for HIT patients requires prophylaxis against thrombosis in patients with a mild form of HIT, treatment during the acute active phase of HIT, treatment of HIT thrombosis, and long-term prevention against new thrombosis development—clinical phases that require different potencies of antithrombotic treatment. The use of antiplatelet drugs, anti-inflammatory drugs, new drugs designed to target the specific mechanism of the HIT pathophysiology (i.e., decrease the available PF4), and drug combinations are all future possibilities.

Prevention of HIT

The expanded use of LMW heparins, fondaparinux, and the new oral anticoagulants for the routine management of thrombosis will naturally reduce the development of HIT because these drugs generate HIT antibodies at a far lower frequency than heparin or not at all.

Duration of exposure to heparin, more than dose, is an important consideration. Thus, avoid unnecessary and prolonged exposure to heparin. Be aware that HIT can occur even with prophylactic doses of heparin and heparin from exogenous sources (e.g., heparin flushes, heparin-coated catheters).

If an alternative to heparin can be used, such as saline in indwelling catheters or citrate in devices, exposure to heparin can be eliminated.

Based on the mechanism of action, efforts to reduce platelet activation and the accompanying increased levels of circulating PF4 should also be considered.

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