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Heparin-Induced Thrombocytopenia:

Keys to Recognition and Management

Heparin is one of the oldest drugs that remains in widespread clinical use today. It was discovered in 1916, and it was included in human trials starting in 1935. For more than half a century, heparin has been a mainstay in the treatment and prophylaxis of thrombotic disorders. In a recent single-center study, 20% of inpatients were exposed to unfractionated heparin (UFH), divided nearly equally between medical patients (50.0%) and surgical or procedural patients (47.8%).[1]

Unfortunately, heparin-induced thrombocytopenia (HIT), a serious adverse event from heparin, develops in approximately 3% of patients who receive UFH and approximately 0.2% of patients who receive low-molecular-weight heparin (LMWH).[2] HIT is unusual because although the patients are thrombocytopenic, they are actually at increased risk for the very complications that heparin is supposed to prevent. For HIT patients with isolated thrombocytopenia, the risk of thrombosis over the next 30 days is between 20% and 50% even after heparin has been discontinued.[3] The mortality rate associated with HIT is between ~17% and 30%.[4] Simply discontinuing heparin is not sufficient. If heparin is discontinued and an alternative anticoagulant is not initiated, 50% of patients with HIT will suffer a thrombotic event within 30 days.[5,6]

HIT is a life-threatening, immune-mediated reaction to heparin. It is a prothrombotic disorder caused by antibody-mediated platelet activation and increased thrombin generation. The mechanism of the hypercoagulability state is multifactorial, but a key determinant is the occurrence of neo-epitope complexes of heparin and platelet factor (PF) 4 to which immunoglobulin G (IgG) antibodies form. These HIT antibodies bind to heparin-PF 4 complexes present on the platelet surface and trigger platelet activation. In turn, procoagulant platelet-derived microparticles are released. An associated marked generation of thrombin is largely responsible for the prothrombotic character of HIT.[7]

Patients receiving heparin for at least 5 days, and possibly at least 1 week,[8,9] are at increased risk for HIT, and the risk increases with the duration of therapy.[9] However, HIT may develop earlier or later than this. Two less frequent temporal presentations of HIT are rapid-onset and delayed-onset HIT. Rapid-onset HIT is associated with prior exposure to heparin and manifests as an abrupt decline in the platelet count and severe, life-threatening anaphylactoid reactions or thromboembolic events shortly after the administration of heparin rather than days later.[10] In delayed-onset HIT, thrombocytopenia and thrombotic events can occur days or weeks after heparin has been discontinued.[11,12] Typical-onset HIT is described below in the section, "Diagnosis of HIT."

Table 1. Complications of HIT[5]

Venous thrombosis
Deep-vein thrombosis
Warfarin-induced venous limb gangrene
Pulmonary embolism
Arterial thrombosis
Myocardial infarction
Lower-limb artery thrombosis
Cerebrovascular accident
Skin lesions/necrosis at heparin injection site
Acute systemic reaction*
Disseminated intravascular coagulation
End-organ damage
Death

*May include chills, fever, flushing, tachycardia, hypertension, tachypnea, dyspnea, chest pain, cardiopulmonary arrest, nausea, vomiting, diarrhea, headache, and/or transient global amnesia.

Clinical Consequences

HIT is strongly associated with thrombosis; in fact, thrombosis may be what leads to the initial recognition of HIT.[4] Thromboembolic complications of HIT may be venous, arterial, or both and include deep-vein thrombosis (DVT), pulmonary embolism, myocardial infarction, thrombotic stroke, or limb artery occlusion requiring amputation (Table 1).[4]

Erythematous or necrotizing skin lesions occur at the injection site in 10% to 20% of patients who develop heparin-PF4 antibodies during subcutaneous heparin therapy. These skin lesions may also serve as markers; ~25% go on to develop thrombocytopenia.[13]

Acute systemic reactions have also been associated with HIT. These reactions include fever, chills, hypertension, chest pain, or dyspnea, and they occur 5 to 30 minutes after administration of an I.V. heparin bolus. Thrombocytopenia also occurs in ~25% of patients who experience an acute systemic reaction.[5]

In the landmark 14-year study of 127 patients with serologically confirmed HIT, the ratio of venous to arterial thrombotic events was 4:1.[5] Thrombotic complications developed in 52.8% of patients who were initially recognized with isolated thrombocytopenia in the 30 days after HIT was diagnosed.

In a more recent review of 408 patients with HIT, those who had undergone cardiovascular surgery were at higher risk for arterial thrombosis (ratio of 8.5:1), but venous thrombosis predominated overall (ratio of 2.4:1).[8]

Life-threatening thrombosis from HIT results in amputation in 20% of patients and death in 30% of patients.[5,14] Less frequent consequences of HIT include disseminated intravascular coagulation, adrenal hemorrhage, and end-organ damage.[5]

Table 2. Risk for HIT[16]

Patient Risk	Heparin Preparation	Dose	Patient Population	HIT Incidence, %
High	UFH	Prophylactic	Orthopedic surgery/trauma	3-5
	UFH	Prophylactic	Cardiac surgery	1-3
	UFH	Therapeutic	Thrombosis treatment	1
Intermediate	LMWH	Prophylactic	Medical, postoperative	0-0.9
	LMWH	Therapeutic	Thrombosis treatment	<1
	UFH	Prophylactic	Medical, obstetric	0.8-1.0
	UFH	Catheter flushes	Postoperative	0.1-1.0
	UFH or LMWH following UFH ≤100 d	Prophylactic	Medical, obstetric, postoperative	0.1-1.0
Low to very low	UFH or LMWH	Prophylactic	General pediatric, long-term hemodialysis	<0.1
	LMWH	Prophylactic	Medical, obstetric	<0.1
	UFH	Catheter flushes	Medical	<0.1

LMWH, low-molecular-weight heparin; **UFH,** unfractionated heparin

Who Is at Risk?

The risk for HIT has been observed to vary depending on the type and duration of heparin, as well as the type of patient receiving it. These observations should be interpreted with caution, given the differences in studies as well as the time over which these observations have been noted.

These observations are listed in Table 2. However, it is important to remember that any patient receiving or who has received heparin products is at risk for developing HIT.[4,7] The mechanisms responsible for the development of HIT with various heparin products for patient types are still under investigation and require further research.

The risk for HIT is approximately 10 times greater after exposure to UFH than after exposure to LMWH.[2] In addition, the risk for HIT is higher with bovine than with porcine UFH.[15] HIT can occur earlier after heparin administration if the patient has previously been exposed to heparin. HIT should be differentiated from the mild and occasional thrombocytopenia that may develop in the day or two after initial exposure to heparin. This latter form of thrombocytopenia is not immune-mediated and is distinct from HIT.

Patients receiving heparin who have undergone orthopedic or trauma surgery are at highest risk for HIT postoperatively,[5,15,16] followed by patients who have undergone cardiac surgery (see Case Study 1).[17] Any patient receiving thromboprophylaxis or treatment with UFH or LMWH may be at risk for HIT.[4,7]

Women may be at greater risk for HIT (see Case Study 2) than men.[18] In a review of data extracted from randomized, controlled trials of UFH versus LMWH, HIT was twice as likely to develop in female patients as in male patients. In addition, interactions were noted between gender, type of heparin, and type of patient that affected risk for HIT. Female patients were almost 5 times more likely to develop HIT than male patients, and surgical patients of both genders were almost 7 times more likely to develop HIT than medical patients.

The timing of the occurrence of HIT in relation to previous heparin therapy is variable.[10] Patients who have been exposed to heparin previously may develop rapid-onset thrombotic or acute events.[4] In addition, patients may have a delayed onset, with either thrombocytopenia or a thrombotic event developing days to weeks after heparin therapy has ended.[11,12]

Diagnosis of HIT

Multidisciplinary evidence-based guidelines for the diagnosis, treatment, and prevention of HIT have been established by the American College of Chest Physicians (ACCP) and were recently updated in 2008.[19]

Although clinical criteria are established for the diagnosis of HIT, the diagnosis often remains difficult. Thrombocytopenia, one of the defining features of HIT, can occur secondary to infection, hemodilution, drugs other than heparin, bone marrow disease, and other hypercoagulability states. The diagnosis is further complicated by recent reports suggesting that thrombotic complications can precede thrombocytopenia in HIT.[8] In surgical patients, the thrombocytopenia of HIT may be superimposed on the rising platelet counts typically seen days after surgery.[17] Thus, serial platelet counts may form an inverted *V* as the platelet count initially rises and then declines, sometimes precipitously.[17]

Other clinical signs of HIT may include skin lesions at heparin injection sites[11] and acute systemic reactions, such as cardiorespiratory distress, chills, or fever after I.V. administration of a heparin bolus.[5,20,21]

A clinical algorithm with a reproducible high positive predictive value would be valuable because it might identify patients at high risk for HIT who should be switched to an alternative anticoagulant while the results of laboratory tests are pending. A clinical scoring system known as the "4 *T*'s" has been proposed to identify patients with HIT. The system is based on the characteristic features of HIT, including *T*hrombocytopenia, *T*iming of platelet count fall, *T*hrombosis or other sequelae, and o*T*her likely cause for thrombocytopenia.[22]

In a recent evaluation, the scoring system had a high negative predictive value, correctly identifying patients who did not have HIT.[22] Only 1 (0.84%) of 119 patients with a low clinical score tested positive for HIT antibodies. However, the positive predictive value of the algorithm varied at the 2 institutions where it was tested. At the first, all 8 (100%) of the patients with a high clinical score tested positive for HIT antibodies, but at the second institution, only 9 (21.4%) of 42 patients with a high clinical score tested positive for HIT antibodies ($P<0.0001$). A similar inconsistent pattern was observed among patients with an intermediate clinical score.

The typical presentation of HIT is a decline in the platelet count beginning 5 to 10 days after heparin therapy is initiated.[10] The ACCP guidelines recommend that a diagnosis of HIT be considered when otherwise unexplained thrombocytopenia, thrombosis, or other potential sequelae of HIT (eg, necrotic skin lesions, anaphylactoid reactions following I.V. heparin boluses) occur in a pattern that is temporally consistent with exposure to heparin.[19] The definition of thrombocytopenia most often used for identifying HIT incorporates a decline in the platelet count of 50% or more, even if the nadir count remains above 150×10^9/L.[23] In other words, the diagnosis may be based on the relative drop in platelet count from baseline, rather than requiring a low absolute platelet count. In most patients with HIT, a 50% or greater decrease in platelet count occurs. However, the decrease may occur on the same day or after the development of a thrombotic event. In a review of 408 cases of serologically confirmed HIT, thrombosis occurred in 26% of the patients on the same day that a decline of 50% or more in the platelet count was documented and in 34% before a decrease in the platelet count was noted.[8]

Levine et al, in a 2006 meta-analysis of 10 studies that evaluated thromboprophylaxis or treatment with UFH or LMWH,[24] suggest that clinicians should maintain a high index of suspicion for HIT if venous thromboembolism occurs during or soon after the use of UFH, particularly in surgical patients. "If thrombocytopenia is present, alternative anticoagulation should be used until HIT is excluded," the authors recommend. Among heparin-treated patients with venous thrombosis from any cause, HIT-associated venous thrombosis occurred in 12.8% who received UFH and in 0.7% of those who received LMWH.

Laboratory Testing

The initial diagnosis of HIT is based on clinical suspicion.[4,7] Laboratory tests are then used to confirm or rule out the diagnosis. Numerous studies have documented that thrombocytopenia or any clinical signs of HIT develop in only a minority of patients with HIT antibodies.[9,25,26] Therefore, HIT antibody seroconversion without clinical sequelae does not constitute HIT. Thus, the ACCP guidelines recommend *against* routine HIT antibody testing in the absence of thrombocytopenia or other clinical manifestations of HIT.[19] The College of American Pathologists recommends HIT antibody testing in patients in whom there is clinical suspicion of HIT, based on thrombocytopenia and/or new thrombosis during or after heparin treatment.[27]

The most widely available serologic tests for HIT are enzyme-linked immunosorbent assays (ELISAs). These commercial assays detect circulating IgG, IgA, and IgM antibodies to complexes of PF 4 with heparin or other polyanions. The antibody primarily involved in HIT is IgG, although IgM and IgA are also implicated infrequently.[27] That these ELISAs detect other classes of antibodies may explain their poor specificity for HIT.[28] The ELISAs are highly sensitive, however, so they are most useful for ruling out a tentative diagnosis of HIT.[21]

The strength of a positive ELISA result, however, may provide useful information.[19] Using an in-house ELISA specific for IgG, Warkentin and Heddle reported that a strongly positive test result was associated with a high likelihood of HIT in both orthopedic surgery patients and cardiac surgery patients.[21]

In a small retrospective chart review, patients with isolated HIT and an optical density measurement of 1.0 or more absorbance units on a commercial ELISA had a risk for thrombosis 6-fold greater than that of patients with weakly positive test results in chart review.[29] Further research is needed to confirm this finding. Some studies suggest that alternative assays (eg, washed platelet activation assay, platelet serotonin release assay, heparin-induced platelet activation assay) may have greater diagnostic specificity for HIT when compared with the PF–4-dependent ELISA.[19,25,28] However, these tests are not widely available outside research institutions, and further research is required to determine the role of these specialized assays in the evidence-based diagnostic algorithm for HIT.

Monitoring of the Platelet Count

Platelet count monitoring will help to ensure prompt recognition of thrombocytopenia in HIT patients. The risk of thrombosis in patients with HIT increases as the severity of thrombocytopenia increases. Sixty percent of HIT patients will have moderate thrombocytopenia with a platelet count nadir of 30 to 10 x 10^9/L. However, it is important to remember that HIT patients can experience a 50% or greater fall in their platelet counts during heparin therapy, even though the platelet nadir may not necessarily reach thrombocytopenic levels, conventionally defined as <150 x 10^9/L. Defining HIT by a 50% drop in platelet count allows for a greater sensitivity for detection.[3]

The ACCP guidelines recommend that the platelet count of patients at high (>1%) or moderate risk (0.1% to 1%) for HIT be monitored.[19] For example, platelet counts should be measured at least every 2 or 3 days from day 4 to day 14 (or until heparin is stopped) in all patients receiving therapeutic-dose UFH; postoperative patients receiving antithrombotic prophylaxis with UFH or LMWH or intravascular catheter UFH "flushes"; or medical/obstetrical patients receiving prophylactic-dose UFH or receiving LMWH after first receiving UFH. By contrast, routine platelet count monitoring is not recommended for patients at low risk (<0.1%) of HIT, including medical/obstetrical patients receiving only LMWH and medical patients receiving only intravascular catheter UFH flushes.[19]

The ACCP guidelines also suggest obtaining a baseline platelet count and a repeat platelet count within 24 hours of starting heparin in patients who have recently received UFH or who have an uncertain history regarding recent heparin exposure.[19] Further, an immediate platelet count with comparison to recent platelet counts is indicated for patients who develop acute anaphylactoid symptoms (eg, inflammatory, cardiorespiratory, neurologic, or other usual symptoms) within 30 minutes following an I.V. UFH bolus.[19] The Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology recommends even more stringent monitoring in patients receiving UFH: platelet counts every other day from days 4 to 14 in *all* patients receiving UFH.[30] The key reason for monitoring the platelet count is to ensure prompt recognition of relative or absolute thrombocytopenia.

Treatment of HIT

Discontinuing heparin is a necessary but insufficient therapy for known or suspected HIT.[3,11] This point may be missed by clinicians, and the lack of appropriate anticoagulation may result in multiple adverse events, including limb- and life-threatening thrombosis. The overall risk for thrombosis in patients with HIT ranges from 38% to 76% in the absence of alternative anticoagulation.[3]

Another factor to consider is isolated HIT, defined as "the initial recognition of HIT because of thrombocytopenia alone." Based on several studies, the ACCP guidelines note that there is substantial risk for symptomatic thrombosis among patients with isolated HIT. In patients with strongly suspected isolated HIT, or when the diagnosis is supported by serological studies, the guidelines recommend (level 1C) continuing alternative anticoagulant therapy until the platelet count has recovered to a stable plateau.[19]

In one meta-analysis that examined 204 patients (113 patients on a direct thrombin inhibitor [DTI] [lepirudin; Refludan®, Bayer HealthCare Pharmaceuticals] compared with 91 patients who formed a historical control group), untreated HIT was associated with a 6.1% event rate per patient-day; events were defined as new thrombosis, limb amputation, or death.[31] The event rate decreased to 1.3% per patient-day with alternative anticoagulation therapy. Of the 41 clinical outcome events reported during the study period, 14 (34.1%) occurred during the pretreatment period before lepirudin was administered. Therefore, it is strongly recommended that patients with suspected HIT should be removed from heparin therapy and administered a different anticoagulant immediately. Waiting until laboratory tests confirm the diagnosis may result in substantially increasing the patient's risks of further bleeding incidents and/or thromboembolic events and associated costs.[31]

The ACCP guidelines recommend (level 1C) that patients with strongly suspected (or confirmed) HIT, with or without thrombosis, be treated with a non-heparin anticoagulant.[19] Two DTIs are approved by the FDA for the treatment of HIT and are recommended in the ACCP guidelines—lepirudin and argatroban (Argatroban, GlaxoSmithKline). A third DTI, bivalirudin (Angiomax, The Medicines Company), is approved by the FDA for patients undergoing percutaneous coronary intervention (PCI) with or at risk for HIT (Table 3). Argatroban is indicated for prophylaxis and treatment of thrombosis in patients with HIT; argatroban is also indicated in patients with or at risk for HIT undergoing PCI. Lepirudin is indicated for the treatment of HIT.[19]

The dose of the DTIs is titrated according to the activated partial thromboplastin time (aPTT). The target is 1.5 to 2.0 times the aPTT reference value for lepirudin and 1.5 to 3.0 times the aPTT reference value for argatroban.[19,32,33]

Direct Thrombin Inhibitors

When the pivotal studies of lepirudin therapy[34] and argatroban[33,35] therapy in HIT were conducted, there was no FDA-approved drug to use as a comparator and a placebo control was unethical because of the poor outcomes associated with untreated HIT. No prospective clinical trials comparing the 2 DTIs that are FDA-approved for HIT have been conducted.

Table 3. Direct Thrombin Inhibitors Used in the Treatment of HIT[36,41,58]

Criteria	Lepirudin	Argatroban	Bivalirudin*
Mechanism	DTI	DTI	DTI
Approved uses (USA)	HIT	HIT, PCI (if HIT or risk of HIT)	PCI (including if HIT)
Route	I.V. infusion	I.V. infusion	I.V. infusion
Elimination half-life in healthy subjects	80 min	39-51 min	25 min
Primary rate of clearance	Renal	Hepatic	Plasma proteases; renal, 20%
Monitoring	aPTT	aPTT (or ACT at higher levels of anticoagulation)	aPTT (or ACT at higher levels of anticoagulation)
Approved initial dose	0.4-mg/kg bolus, then 0.15 mg/kg/h	For HIT: 2 mcg/kg/min For PCI: 350-mcg/kg bolus, then 25 mcg/kg/min	For PCI: 1-mg/kg bolus, then 2.5 mg/kg/h x 4 h, then 0.2 mg/kg/h

*Bivalirudin is not FDA-approved for use in patients with HIT in the noninterventional setting.

ACT, activated clotting time; **aPTT,** activated partial thromboplastin time; **DTI,** direct thrombin inhibitor; **INR,** international normalized ratio; **I.V.,** intravenous; **PCI,** percutaneous coronary intervention

Argatroban and lepirudin have been tested in prospective open-label studies with historical controls conducted in patients with isolated HIT and HIT complicated by thrombosis. Both the argatroban[35,36] and lepirudin studies[32,34] measured a composite efficacy end point composed of new thrombosis, limb amputation, and all-cause mortality. Both argatroban and lepirudin were effective for the treatment of HIT. Both significantly reduced the incidence of the composite efficacy end point.

The ACCP guidelines recommend the use of lepirudin or argatroban in patients with HIT (Table 3). However, because of significant differences in study design, it is not possible to directly compare the efficacy of the 2 agents,[19] and the ACCP guidelines reflect this fact by stating that "selection of a particular anticoagulant agent should be based on patient-specific factors, relevant drug pharmacology and pharmacokinetics, jurisdictional availability/approval, and prior physician experience and confidence in the use of any particular agent."[19]

The most serious side effect of anticoagulants is major bleeding. The incidence of major bleeding was not increased significantly with either lepirudin[32] or argatroban[37] when compared with historical controls. Both agents are contraindicated in patients with active bleeding. Both agents should be used with caution in patients with a high risk of bleeding.

Differences in the pharmacology between the 2 FDA-approved DTIs are shown in Table 3. Lepirudin is renally cleared,[32] whereas argatroban undergoes hepatic clearance and biliary excretion.[38] Based on clinical trials, dosage recommendations for argatroban in patients with hepatic dysfunction are available.[38] Dosage recommendations for lepirudin are available for mild renal impairment, but the drug should not be used in patients with severe renal impairment.[32]

DTIs, including argatroban, cause prolongation of the international normalization ratio (INR) in a dose-dependent manner.[39,40] This prolongation represents a laboratory effect on the INR. The prolongation complicates the monitoring of the effects of early warfarin therapy on the INR during this transition when the DTI is being overlapped with warfarin.

Antihirudin antibodies may develop in up to 30% of patients after initial exposure to lepirudin.[32] Lepirudin is contraindicated in patients with known hypersensitivity to hirudins.[32] In response to reports of severe anaphylaxis after re-exposure to lepirudin, the European Agency for the Evaluation of Medicinal Products recommended that nonhirudin anticoagulants be considered in patients who have previously received lepirudin.[40] Some experts have recommended that patients not receive more than 1 treatment cycle of lepirudin.[41]

The DTIs lack an antidote. If excessive levels of anticoagulation occur, with or without bleeding, the infusion should be stopped, or the dose reduced. Anticoagulant effects typically return to normal within hours of drug cessation in patients with normal organ function but will take longer in lepirudin- or bivalirudin-treated patients with renal impairment and argatroban-treated patients with hepatic impairment.

Ultrasonography

In patients with strongly suspected or confirmed HIT, the ACCP guidelines recommend routine ultrasonography of the lower limbs to exclude clinically silent deep-vein thrombosis DVT.[19]

Vitamin K Antagonists

The ACCP guidelines recommend against beginning a vitamin K antagonist, such as coumarins (eg, warfarin), until after the platelet count has substantially recovered (ie, >150 x 10^9/L).[19] Vitamin K antagonists have been associated with venous limb gangrene in the setting of HIT if the patient has not been given another appropriate anticoagulant before the administration of warfarin.[42,43] If a patient is receiving a vitamin K antagonist at the time HIT is diagnosed, the guidelines recommend reversal with vitamin K (10 mg orally or 5-10 mg I.V.).

Transition to an Oral Anticoagulant

If a patient is transitioned to an oral anticoagulant, the guidelines recommend that initial dosing should be cautious and that therapy should overlap treatment with a DTI. Treatment with the alternative anticoagulant should continue until the INR is in the therapeutic range for at least 48 hours and until the platelet count has reached a stable plateau.[44]

During the transition from argatroban to warfarin, the INR should be monitored daily.[39] The prescribing information for

argatroban provides a formula for converting the INR during the co-administration of argatroban and warfarin to an INR for warfarin alone at the FDA-approved dose of argatroban.[37] Alternatively, when the INR is above 4, the argatroban infusion may be discontinued, and the INR should be measured again to ascertain that it is in the therapeutic range.[39] In a retrospective analysis of one of the argatroban clinical trials, elevated INR values occurred commonly in patients receiving argatroban, and they were not associated with an increased risk of bleeding.[45]

Management of HIT Patients Undergoing Percutaneous Coronary Intervention

For patients with acute or previous HIT who require cardiac catheterization or PCI, the ACCP guidelines recommend the use of an alternative anticoagulant such as argatroban, bivalirudin, lepirudin, or danaparoid (not available in US).[19] Of these, argatroban and bivalirudin are FDA-approved for patients with or at risk of HIT undergoing PCI.[37,46] At the higher levels of anticoagulation required in the interventional setting, anticoagulation is typically monitored using the activated clotting time (ACT).

Economic Burden of HIT

HIT is a costly condition. In the United States, the estimated total health care cost of HIT complications in cardiac surgery alone is $100 to $300 million.[47] Approaches to minimize the economic burden of HIT and avoid costly thrombotic events are important. Thromboembolic complications occur in up to 60% of patients with HIT[8]; common complications include DVT, pulmonary embolism, stroke, myocardial infarction, and amputation; all of these are expensive to treat.[48-50] A 2002 analysis of an administrative database estimated the 6-month cost of treatment for DVT complicated by drug-induced thrombocytopenia to be $13,469, which is $3,685 higher than the cost of care for uncomplicated DVT.[48] In developing a decision analysis to examine the prevention of DVT in medical patients from use of LMWH prophylaxis in medical patients, one author projected the episodic cost of HIT with thrombosis to be $8,843.[51] This figure includes an estimated 7 additional hospital days, 7 additional physician inpatient visits, additional aPPT monitoring, pharmacotherapy (bolus of lepirudin, I.V. lepirudin therapy, and 6 months of warfarin therapy), as well as additional equipment and monitoring tests (phlebotomy, weekly prothrombin tests). The costs of the drugs were estimated from average wholesale prices, with the amount assumed to be sufficient for a patient weighing 75 kg. Laboratory costs were based on data from the Centers for Medicare & Medicaid Services, and the costs of inpatient and outpatient visits were estimated using the Medicare-Based Relative Value Scale payment rates.

Other costs associated with the management of HIT include longer hospital stays, additional laboratory tests and monitoring, radiology studies, and medication.[52] HIT is likely to be the cause of indirect costs, such as lost work days, but further research is required to determine the extent of these costs.

The medication used for venous thromboembolism (VTE) prophylaxis can reduce the incidence of HIT and therefore avoid some of the economic burden associated with HIT. A 2005 meta-analysis examined 5 studies comparing LMWH with UFH, 4 of which were in orthopedic surgery patients, and found that the rate of HIT was 10-fold higher with UFH.[2] A 2006 meta-analysis of 10 studies evaluating UFH or LMWH for the prophylaxis or treatment of VTE[23] found that the frequency of HIT-associated venous thrombosis was significantly higher among patients receiving UFH than in patients receiving LMWH (approximately 13% vs <1%). Only 2 of the 10 studies were specifically in orthopedic surgery patients. Comparisons of HIT risk with UFH and LMWH in medical patients have yielded inconsistent results.[53,54] However, some recent cost–benefit analyses suggest that LMWH may be more cost-effective than UFH when the prevention of HIT[55] and future thrombotic events[56] are considered.

Several investigators have evaluated the cost-effectiveness of HIT treatment with DTIs using various outcome measures.[57-59] One analysis measured the time to achieve therapeutic aPTT values,[58] while another evaluated the reduction in catastrophic patient outcomes when DTI therapy was initiated early after the diagnosis of HIT rather than after 48 hours (delayed treatment).[59]

Another analysis evaluated the costs associated with various HIT treatment strategies used in clinical practice. This analysis relied heavily on determining a risk stratification model to estimate the prior probability of HIT and the risk of developing a thrombotic event once HIT had been diagnosed.[57] However, while some patient populations have been observed to have a higher risk for developing HIT, the converse cannot be relied on. For example, once suspected, clinicians cannot take the chance that HIT can be ruled out in an individual patient without further testing simply based on whether the patient falls into one of these patient populations. Thus, the optimal treatment strategy for HIT as it relates to cost-effectiveness of DTIs remains unclear.

Further research aimed at assisting clinicians with earlier detection of HIT—confirming the diagnosis and initiation of early treatment for HIT—are needed. Better diagnostic tests that can help confirm the diagnosis and strategies that can help clinicians differentiate HIT from other forms of thrombocytopenia or thrombotic disorders must be identified and validated. This is especially important because when a DTI was not started in HIT patients during the 1 to 3 days while awaiting confirmatory laboratory results, a 6% combined event rate of death, new thrombosis, or limb amputation per patient-day was observed.[31]

At present, the diagnosis of HIT continues to rely on clinical suspicion. Increased vigilance, education, and awareness from all health care providers remain the cornerstone of early initiation of treatment to reduce the potentially devastating consequences of the disease and improve patient outcomes.

Summary

HIT is a serious immune-mediated response to heparin therapy that can have di sastrous sequelae, including both venous and arterial thrombosis, limb amputation, and death. Once HIT is suspected, all heparin and LMWHs must be discontinued, and patients should be treated with a DTI, such as lepirudin or argatroban. Both argatroban and lepirudin were effective treatment for HIT and reduced the composite efficacy end point—new thrombosis, limb amputation, and all-cause mortality—in prospective open-label studies. With either medication, this benefit was achieved without increased major bleeding.[32,37] It is associated with significant morbidity and mortality. Vigilant platelet count monitoring, increased awareness and recognition of HIT, and early therapy with an appropriate non-heparin anticoagulant are important to reduce the potentially devastating effects of this immune-mediated disease.

Case Study 1

Based on an actual case. Individual results may vary.

A 65-year-old man recently underwent an uncomplicated 3-vessel coronary artery bypass graft and mitral valve replacement. He was extubated 24 hours postoperatively, and systemic anticoagulation with UFH was administered because of the new mechanical valve. He left the intensive care unit on postoperative day 2 with a platelet count of 250,000/mm^3. Four days later (postoperative day 6), routine laboratory studies revealed a platelet count of 120,000/mm^3. There was no evidence of bleeding and the hematocrit was normal, as was the white blood cell count. The prothrombin time was normal, and the partial thromboplastin time was appropriately elevated. The patient was on no medications known to cause thrombocytopenia. All heparin, including flushed heparin, was discontinued. Because of the need for ongoing anticoagulation in the setting of the new valve coupled with the suspicion of HIT, the patient was started on argatroban. Two days later, the report of HIT antibody testing was returned as positive. A lower-extremity ultrasound revealed a DVT in the leg from which the saphenous vein graft had been harvested. The patient was treated with argatroban intravenously until the platelet count had returned to normal. At this point, warfarin therapy was initiated. Argatroban and warfarin therapy overlapped for several days, at which time argatroban was discontinued. At discharge (postoperative day 12), the platelet count remained normal, and the INR was in the therapeutic range. The patient received chronic anticoagulation therapy for 6 months with warfarin in light of the mechanical heart valve.

Case Study 2

Based on an actual case. Individual results may vary.

A 51-year-old woman had undergone hip replacement surgery 2 weeks before admission. She was receiving extended DVT prophylaxis with enoxaparin. She presented to the emergency department with a 2-day history of a warm, swollen right lower extremity. She had no shortness of breath or chest pain. A lower-extremity ultrasound demonstrated a DVT. Her platelet count was 85,000/mm^3; at discharge, it had been 350,000/mm^3. Because of the combination of ongoing exposure to heparin, new thrombocytopenia, and a venous thrombosis, she was begun on argatroban for presumptive HIT. The result of a subsequent HIT antibody assay was positive. She was continued on argatroban until it was appropriate to transition to warfarin.

Important Safety Information

As with all anticoagulants, bleeding is a serious concern. Argatroban is contraindicated in patients with overt major bleeding or those with hypersensitivity to the product or any of its components. Argatroban should be used with extreme caution in disease states or other circumstances in which there is an increased risk of hemorrhage. Overall major bleeding was reported in 5.3% of patients with HIT treated with Argatroban versus 6.7% of the historical controls. Overall major bleeding was reported in 1.8% of patients undergoing PCI treated with Argatroban versus 3.1% of the historical controls. Intracranial bleeding was not observed in the 568 patients treated with Argatroban for HIT (with or without thrombosis) or in the 91 patients who underwent PCI. The most common nonhemorrhagic side effects in HIT patients, regardless of the relationship to treatment, were dyspnea, hypotension, and fever. In patients undergoing PCI, the nonhemorrhagic side effects, regardless of the relationship to treatment, included chest pain, hypotension, and back pain.

Please see full Prescribing Information for additional safety information on Argatroban.

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