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Chest 2009;135;1651-1664
DOI 10.1378/chest.08-2830

CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Heparin-Induced Thrombocytopenia*

A Contemporary Clinical Approach to Diagnosis and Management

Eduard Shantsila, MD; Gregory Y. H. Lip, MD; and Beng H. Chong, MD

Thrombocytopenia following heparin administration can be associated with an immune reaction, now referred to as *heparin-induced thrombocytopenia* (HIT). HIT is essentially a prothrombotic disorder mediated by an IgG antiplatelet factor 4/heparin antibody, which induces platelet, endothelial cell, monocyte, and other cellular activation, leading to thrombin generation and thrombotic complications. Indeed, HIT can also be regarded as a serious adverse drug effect. Importantly, HIT can be a life-threatening and limb-threatening condition frequently associated with characteristically severe and extensive thromboembolism (both venous and arterial) rather than with bleeding. This article provides an overview of HIT, with an emphasis on the clinical diagnosis and management. ***(CHEST 2009; 135:1651–1664)***

Abbreviations: aPTT = activated partial thromboplastin time; CPB = cardiopulmonary bypass; DTI = direct thrombin inhibitor; ELISA = enzyme-linked immunosorbent assay; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; LMWH = low-molecular-weight heparin; PCI = percutaneous coronary intervention; PF4 = platelet factor 4; SRA = serotonin release assay; UFH = unfractionated heparin

Heparin-induced thrombocytopenia (HIT) is a prothrombotic disorder initiated by heparin administration and is related to antibody-mediated platelet activation causing thrombin generation and thrombotic complications. Essentially, HIT can be regarded as a very severe adverse drug reaction resulting from multicellular immune activation.[1]

The administration of heparin is often associated with a reduction in platelet count. In the majority of cases, this phenomenon is independent of any immune reaction, and thrombocytopenia is mild (platelet count, $> 100 \times 10^9$ cells/L), not progressive, and is not associated with bleeding or thrombosis.[2] Such nonimmune heparin-associated thrombocytopenia (previously called *HIT type I*) can occur during the first few days of heparin administration (Table 1). Direct platelet membrane binding of heparin has been suggested as a potential mechanism of the condition.[3–5] Other factors unrelated to heparin administration, such as sepsis, platelet-reactive autoantibodies, drug reactions, transfusion reactions, and foreign-body reactions (endograft), can also provoke thrombocytopenia.[6] Nonimmune heparin-associated thrombocytopenia gradually resolves without heparin treatment interruption, and platelets gradually rise to pretreatment levels within a few days with no special treatment required.[7–10] Nonetheless, thrombocytopenia following heparin administration may also be associated with an immune heparin-related response, now referred to as HIT (formerly called *HIT type II*). HIT can be a life-threatening and limb-threatening prothrombotic complication, which can lead to a systemic thrombotic response (both venous and arterial) rather than to bleeding.[3,11] This article provides an overview of HIT, with an emphasis on the clinical diagnosis and management.

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The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Manuscript received December 1, 2008; revision accepted February 26, 2009.

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DOI: 10.1378/chest.08-2830

Table 1—*Heparin-Associated Thrombocytopenia vs Nonimmune Heparin-Associated Thrombocytopenia*

Variables	Immune HIT (Previously Type II HIT)	Nonimmune Heparin-Associated Thrombocytopenia (Previously Type I HIT)
Frequency	2–3%	10–30%
Reduction in platelet count	Moderate or severe	Mild
Time from initiation of heparin therapy	> 5 d (may be less after recent heparin exposure)	<5 d
HIT antibodies	Present	Absent
Risk of thrombosis	High	Low
Management	Heparin therapy discontinuation; administration of alternative anticoagulants	Observation

Search Strategy

A thorough search of the English-language literature was performed using electronic bibliographic databases such as MEDLINE, EMBASE, and the Cochrane Database. For example, we applied the following terms for the search: "heparin"; "thrombocytopenia"; and "heparin-induced thrombocytopenia." Additionally, we reviewed the references contained in the identified articles. A hand search for abstracts from international meetings and supplements of some major journals was also performed.

HIT: The Size and Scope of the Problem

Nonimmune heparin-associated thrombocytopenia occurs in 10 to 30% of patients receiving heparin.[12] In contrast, HIT is less common, developing in 1 to 3% of all patients exposed to unfractionated heparin (UFH) and in 0 to 0.8% of patients receiving low-molecular-weight heparin (LMWH) who are exposed for ≥ 5 days, particularly in postoperative patients receiving antithrombotic prophylaxis.[12,13]

Of note, antibodies against complexes of platelet factor 4 (PF4) with heparins (HIT antibodies) are detected in approximately 20% of patients treated with UFH and approximately 8% of those treated with LMWH.[14] The rate of antibody formation differs by clinical condition, for example, in approximately 20% of patients receiving heparin following orthopedic surgery but in up to 70% of patients following cardiopulmonary bypass (CPB).[14] However, heparin-dependent antibodies form functionally active antibodies that are able to activate platelets and develop HIT in only a subset of patients (approximately 20%).[6] Only in a subset of patients with HIT would these antibodies trigger the thrombotic cascade and result in thrombotic complications. Thus, the appearance of HIT antibodies in circulation alone may not be clinically significant, and most patients expressing them suffer no clinical consequences.[15] In a study[16] of patients undergoing coronary bypass surgery, for example, no cases of thrombosis were registered despite the finding that > 70% of patients formed HIT antibodies.

To put things in perspective, the risk of thrombosis in untreated HIT patients managed by heparin discontinuation alone is estimated at 20 to 50%.[17,18] Venous thrombotic complications are fourfold more common than arterial thrombotic events, but the latter are associated with significant morbidity.[19,20] Because UFH has now been largely replaced in clinical practice by LMWH, HIT is less frequently reported. However, as demonstrated by Gruel et al,[21] HIT is at least as severe as UFH-induced HIT should it occur in LMWH-treated patients. UFH is still used for anticoagulation during CPB surgery because it is most appropriate drug for this indication, providing it is not contraindicated (*eg*, because of acute HIT). Patients who have undergone CPB are at a high risk for HIT (*ie*, 2 to 3% of these patients).[22] In patients with acute coronary syndromes treated with heparin, the incidence of HIT with or without thrombosis was reported as 0.8% and 1.6%, respectively.[23]

Thrombocytopenia develops in approximately 100,000 cardiovascular patients annually in the United States alone, with 25,000 to 50,000 of these patients experiencing associated thrombotic complications.[24] Although the majority of cases of thrombocytopenia are not associated with HIT antibodies, the risk of HIT should always be considered in those receiving heparins. HIT occurs in patients of different ages (although rarely in small children and probably does not occur in neonates) with any type of heparin, at any dose, and by any route of administration. However, HIT is more often seen with the use of bovine heparin when compared with porcine heparin, in women, postsurgical patients, and those patients who have a longer duration of therapy.[25,26] A lower incidence of HIT is observed in medical patients and general surgery patients receiving prophylactic doses of UFH or LMWH. Medical and obstetric patients treated with prophylactic doses of LMWH represent the lowest risk groups.[27]

Nonetheless, the risk of HIT may be underestimated and unrecognized in everyday clinical prac-

tice. In the Complications After Thrombocytopenia Cause by Heparin registry,[28] HIT was suspected in 20% of patients with thrombocytopenia, and heparin therapy was discontinued within 24 h in only 30% of patients with suspected HIT. Death or thrombotic complications occurred in 30% of patients in the registry while they were receiving heparin therapy. Of note, data from the Complications After Thrombocytopenia Cause by Heparin registry[28] suggest that < 10% of patients with thrombocytopenia receive diagnostic evaluation of HIT. However, HIT also results in additional spending for health services. On average, HIT results in a financial loss of > $14,000 per patient and an increase in length of stay of 14.5 days,[29] although lower costs have been reported in France (3,230 € per patient).[30]

Pathogenesis of HIT

Free heparin is not immunogenic, but its conjugates with PF4 are very immunogenic. PF4 is a chemokine, a member of the CXC subfamily, produced by megakaryocytes. PF4 is stored in platelet α granules and released into circulation following weak platelet activation; it binds cell-surface glycosaminoglycans (*eg*, heparan sulfate on endothelial surfaces) and heparin.[31] Plasma PF4 concentrations are normally very low but may be high in specific clinical circumstances, such as prosthetic hip or cardiac surgery, due to the associated platelet activation, thus increasing the risk of HIT antibody formation.[31] An infusion of heparin can increase plasma PF4 from trace levels by 15- to 30-fold in several hours by displacing endothelial PF4.[32] PF4 may form the complex of heparin that triggers a conformational change of the protein, exposing cryptic epitopes, and stimulates production of specific anti-heparin-PF4 complex antibodies.[33,34]

HIT antibodies react with PF4/heparin complexes to form macromolecular structures that bind platelet and monocytes via the FcγRIIA receptors and induce subsequent strong platelet activation and degranulation with release of procoagulant substances (*eg*, serotonin, histamine, and adenosine diphosphate), thromboxane biosynthesis, Ca2+ influx, and a generation of highly prothrombotic phospholipid microparticles.[35–37] Furthermore, released PF4 tetramers bind to glucosaminoglycans on platelet surface, allowing more HIT antibody molecules to bind via their Fab domains, promoting additional platelet FcγRIIA cross-linking, aggregation, and activation. HIT antibodies also can activate monocytes and endothelial cells tissue factor on the monocyte and endothelial cell surface and further accelerates the generation of thrombin.[32,38–41] Additional activation of platelets by thrombin and other released agonists results in a further increase of the numbers of FcγRIIA receptors on the platelet surface, which contributes to more platelet activation.[42,43] These interrelated thrombotic processes lead ultimately to a hypercoagulable state, and in many patients, severe and extensive thromboembolic complications.

Most HIT patients have an HIT antibody of IgG class, although IgA, and IgM HIT antibodies can also be detected, and in a few cases (< 10%) only IgA or IgM antibodies to PF4/heprin are detectable.[44] At least *in vitro*, IgA or IgM HIT antibodies do not activate platelets in the presence of heparin, indicating that their presence in the circulation could simply be coincidental to other non-HIT explanations for the patient's thrombocytopenia.[45]

The reticuloendothelial system clears antibody-coated platelets from circulation and prevents the clinical manifestation of HIT in most patients. After interruption of heparin administration, the HIT antibody gradually disappears, and tests for HIT antibodies are usually "negative" or "weakly positive" at 100 days. When these patients are reexposed to heparin after disappearance of the antibody, HIT will not develop in most of the patients. The redeveloping of HIT would require formation of the HIT antibody again, which will again take a minimum of 5 days.[35,46]

The influence of FcγRIIA polymorphism on platelet activation induced by HIT antibodies and the development of the disease has been investigated and tested, with discordant results obtained.[47] An association between the PlA_2 polymorphism of glycoprotein IIIa and the risk of thrombosis in patients with HIT antibodies has been suggested in one study[48] but needs to be further confirmed. Additionally, because heparins are a mixture of various mucopolysaccharides with a very high molecular mass, they can stick to platelets, thus affecting platelet function.

Diagnosis and Clinical Presentation

HIT is often difficult to diagnose because of a wide range of background disorders, usually the very indications for heparin treatment, and also as a result of the coadministration of other drugs that can also potentially cause thrombocytopenia.[49,50] The diagnosis of HIT should be based both on clinical criteria (*eg*, thrombocytopenia and thrombosis) and laboratory data (*eg*, platelet count dynamics and detection of HIT antibodies).

Thrombocytopenia and Platelet Count Monitoring

Thrombocytopenia or a substantial decrease in the platelet count is a primary manifestation of HIT. In one study[51] of 809 patients with clinically diagnosed HIT, the severity of the baseline thrombocytopenia was the best predictor of death, amputation, or thrombotic progression. According to recent guidelines[52] published by the American College of Chest Physicians (ACCP), platelet count monitoring is recommended for heparin-treated patients with a high risk (*eg*, postoperative patients) or intermediate risk (*eg*, medical or obstetrical patients receiving a prophylactic dose of heparin or postoperative patients receiving LMWH prophylactic agents) of HIT.

In those patients who received heparin within the past 100 days, platelet counts should be performed before the initiation of heparin therapy and 24 h after. Subsequently, platelet counts should be performed every other day in high-risk patients and every 2 to 3 days in patients with intermediate risk from day 4 to day 14 (unless heparin therapy is discontinued earlier). In patients with systemic, cardiorespiratory, or neurologic symptoms that occur within 30 min following an IV heparin bolus, platelet counts should be performed immediately. HIT should be suspected when thrombocytopenia (*ie*, a platelet count of $< 150 \times 10^9$ cells/L or a fall in the number of platelets of $> 50\%$) occurs during heparin administration, typically 5 to 14 days following heparin therapy initiation.[35] Of note, very severe thrombocytopenia (*eg*, platelet count of < 15 to 20×10^9 cells/L) is usually not due to HIT. For example, in patients who have undergone angioplasty and were treated with a combination of heparin and glycoprotein IIb/IIIa antagonist, an abrupt decrease in platelet count to $\leq 10 \times 10^9$ cells/L is almost always a result of the administration of a glycoprotein IIb/IIIa antagonist rather than to HIT.

Analysis of the time profile of the platelet count changes may be difficult in postoperative patients because of the commonly seen operation-related decrease in the platelet count of approximately 30% from the initial level.[53] A biphasic pattern of the platelet count with initial thrombocytopenia immediately after surgery, followed by the restoration of platelet numbers during the next 6 days is expected. A repeated fall in platelet count is suggestive of HIT and would require screening for HIT antibodies.

It is worth emphasizing that when unexplained thromboses occur after recent heparin administration, the absence of thrombocytopenia does not exclude the diagnosis of HIT. Furthermore, so-called *delayed-onset HIT* has even been described[54] when HIT develops up to 3 weeks after the exposure to heparin.

When HIT is suspected, the differential diagnosis should include disseminated intravascular coagulation due to non-HIT disorders, sepsis, multiorgan failure, and other causes of thrombocytopenia. The potential side effect of drugs such as glycoprotein IIb/IIIa inhibitors, antimicrobial agents, nonsteroidal antiinflammatory drugs, and so on, should be considered as the cause of the thrombocytopenia.

Thrombosis

Thrombotic complications are the main contributors to the severity of HIT.[55] The development of thrombosis is unpredictable and can occur throughout the period from the drop of the platelet count to the time of the initial platelet recovery stage, and even after discontinuation of heparin therapy. HIT-associated thrombosis may develop at almost any vascular location, although venous thrombosis, in the form of deep venous thrombosis (often extensive or bilateral), pulmonary embolism, upper limb thrombosis at the site of a central venous catheter, and thrombosis of the adrenal veins with hemorrhagic infarction accounts for about half of all thrombotic events.[18,55] Background clinical settings are significant determinants of thrombi localization. Venous thromboses typically occur in patients after surgery, and arterial thrombosis (*eg*, thrombosis of the distal aorta or the large arteries of the lower limbs) in occurs in cardiovascular patients.[21] Development of a new thrombus or an extension of existing thrombus while the patient is receiving prophylactic or therapeutic UFH or LMWH should always raise a suspicion of HIT.

Skin lesions (erythema with or without a central necrosis) at sites of heparin injection or acute systemic reactions following the IV bolus of heparin as well as disseminated intravascular coagulation can also be manifestations of HIT.[56] However, HIT itself can be associated with disseminated intravascular coagulation.[57] Of note, skin lesions have been observed in patients without thrombocytopenia but with circulating HIT antibodies.[58] When abdominal pain, hypotension, and fever occur during heparin therapy, and are associated with a fall in platelet count, HIT-associated acute adrenal insufficiency should be considered. Venous limb gangrene may occur in HIT patients treated with oral anticoagulants.[59] A thorough clinical and duplex evaluation for any venous and arterial thromboses should be carried out in all patients with HIT, especially in those with multiple pathologies.

Laboratory Diagnosis of HIT

The following two main types of assays are commonly used in the diagnostic testing for HIT: platelet activation tests (*eg*, the serotonin release assay [SRA]); and antigen assays (*eg*, enzyme-linked immunosorbent assay [ELISA]). Platelet activation tests are based on the detection of donor platelet activation in the presence of the patient's plasma or serum and heparin. Platelet aggregometry performed with citrated platelet-rich plasma, is commonly used to detect platelet-activating HIT antibodies. However, to increase its sensitivity and specificity, test conditions need to be optimized including using washed platelets.[60–62] The heparin-induced platelet aggregation test uses washed platelets stirred by micro-steel balls in microtiter wells, and visual inspection of the platelet aggregation serves as the test end point.

HIT antibody-induced platelet activation can also be assessed by other methods, but the SRA is currently considered the "gold standard."[63] The test involves exposure of washed donor platelets loaded with ^{14}C-serotonin to the serum or plasma of patients suspected of HIT in the presence of a low concentration (0.1 or 0.2 μm/mL) and a high concentration (100 units/mL) of heparin. Anti-PF4 antibodies present in the patient's serum/plasma would activate platelets *in vitro* inducing ^{14}C- serotonin release from platelet granules in the presence of the low heparin concentration, and the reaction is suppressed by the high heparin concentration.[64] The two-point approach gives the test high specificity.[59] A "positive" result would support the diagnosis of HIT. In general, tests using washed platelets (*eg*, SRA and heparin-induced platelet aggregation test) are more sensitive than tests using platelet-rich plasma (*eg*, platelet aggregometry) because of the presence of inhibitory materials in plasma and the priming of washed platelets for activation by the HIT antibody. Platelets from donors known to be highly reactive to the HIT antibodies should be used to further increase test sensitivity.[60]

Antigen assays (*eg*, ELISA) detect HIT antibodies by incubating patient serum or plasma in wells coated with PF4 and heparin or polyvinyl sulfonate (heparin surrogate).[65] This test is available in the form of two commercial kits. The limitation of the ELISA is that it detects both clinically irrelevant (nonpathogenic) and clinically relevant (pathogenic) antibodies. The nonpathogenic antibodies are present in patients who do not clinically have HIT, such as those frequently detected in cardiac surgery patients. However, it is highly sensitive (up to 99%) with an excellent negative predictive value for HIT.[44,66–69] Thus, the detection of HIT antibodies by ELISA does not confirm HIT but, a negative ELISA result makes HIT highly unlikely.

Either a platelet activation assay (*eg*, SRA) or an ELISA alone may not be adequate for clinical decision making in all cases of HIT; their use in combination is usually recommended. However, the clinical presentation should always be taken into consideration in making the diagnosis of HIT.[70] If the results of both tests are negative, the diagnosis of HIT can generally be ruled out (with a negative predictive value close to 100%) and should lead to further investigations into other causes of thrombocytopenia. If both activation and antigen assays are positive, the diagnosis of HIT is very likely. When discordant results of the antigenic assay and platelet activation test are obtained, the latter should be considered as a more reliable approach to justify a HIT diagnosis.

Blood sampling for the detection of HIT antibodies should be performed in patients with clinically suspected HIT on days 5 to 14 following the initiation of heparin therapy.[52] Although HIT antibodies are detectable in the circulation for several weeks after heparin administration, discontinuation samples should be collected as soon as possible because the antibodies levels can decrease quite rapidly.

Warkentin and Heddle[70] have proposed a pretest score (using the "4Ts") [Table 2] for HIT based on the following four criteria: (1) thrombocytopenia; (2) timing of the fall in platelet count; (3) thrombosis or other sequelae; and (4) other potential causes of thrombocytopenia. A diagnostic score for HIT after cardiac surgery was also proposed.[71] Other studies[71–73] have demonstrated the usefulness of combining the 4Ts score and laboratory testing in the diagnosis of HIT. An online survey[74] of 44 laboratories performed by the North American Specialized Coagulation Laboratory Association revealed a high variation in the protocols of laboratory tests for HIT diagnosis, indicating the need for some consensus guidelines on HIT laboratory testing.

Management of HIT

When HIT is suspected, heparin administration from all sources should be discontinued. Given that HIT is an immunologic reaction, it may develop following exposure to any dose of heparin. It has been reported[75] that even exposure to very low amounts of heparin through heparin-coated catheters or heparin flushes to maintain IV lines may trigger HIT.

The discontinuation of heparin alone is not adequate treatment for HIT patients with or without thrombosis.[47] In fact, thromboembolic events subse-

Table 2—*The 4Ts Assessment Point System for Patients With Suspected HIT

Category	2 Points	1 Point	0 Points
Thrombocytopenia	> 50% fall or nadir of 20–100 × 10^9 cells/L	30–50% fall or nadir of 10–19 × 10^9 cells/L	< 30% fall or nadir < 10 × 10^9 cells/L
Timing of platelet count fall	Days 5–10 or ≤ 1 d if heparin exposure within past 30 d	Beyond day 10 or unclear (but fits with HIT) or ≤ 1 d if heparin exposure within past 30–100 d	No recent heparin use
Thrombosis or other sequelae	Proven thrombosis, skin necrosis, or, after heparin bolus, acute systemic reaction	Progressive, recurrent, or silent thrombosis; erythematous skin lesions	None
Other cause for thrombocytopenia	None evident	Possible	Definite

*Points assigned in each of four categories are totaled, and the pretest probability of HIT determined by the total points is as follows: high, 6 to 8 points; intermediate, 4 to 5 points; and low, 0 to 3 points. Adapted from Warkentin and Heddle.[70]

quently developed in 30 to 50% of HIT patients who had no HIT-associated thrombosis at diagnosis within a month after stopping heparin therapy if they did not receive an alternative anticoagulant therapy.[76]

Alternative nonheparin, immediate-acting, anticoagulant therapy should be initiated promptly once a diagnosis of HIT has been suspected or confirmed, whether or not it is complicated by thrombosis.[51] When treatment was delayed while awaiting laboratory confirmation of the diagnosis, the incidence of new thrombosis was about 10-fold higher (*ie*, 6.1% vs 0.6%, respectively) compared to those treated promptly with a direct thrombin inhibitor (DTI).[77]

To make a choice between replacement drugs, their availability (which varies by country) must be considered, along with the clinical features of HIT (venous or arterial thrombosis; prophylactic or therapeutic regimen) and the patient's clinical status (*eg*, renal and hepatic function) [Tables 3, 4]. LMWHs can also induce severe HIT, although they do so less frequently than UFH.[22,53,78] Because of the high

Table 3—*Clinical Trials on Nonheparin Anticoagulant Treatment of HIT

Anticoagulants	Patients, No.	Control Group (No. of Patients)	Background Disorder	Composite End Point, %		Major Bleeding, %	
				Treatment Group	Control Subjects	Treatment Group	Control Subjects
Argatroban[84]	418	Historic control subjects (185)	Mixed	28.0†‡ (41.5)‡§	38.8‡ (56.5)‖	5.3‡ (6.1)‖	8.6 (2.2)‖
Argatroban[85]	304	Historic control subjects (193)	Mixed	25.6†	38.8	3.1‡ (11.1)‖	8.2‡ (2.2)‖
Argatroban[87]	390	Historic control subjects (98)	Acutely ill patients	38.8	34.1	8.2	7.7
Argatroban[88]	121	Historic control subjects (26)	CAD	30†	50	4§	15
Lepirudin[92]	112	Historic control subjects (120)	Mixed	30.9§	52.1	12.9	9.1
Lepirudin[93]	71	Historic control subjects (120)	Mixed	25.4‡	52.1	9.9	9.1
Lepirudin[94]	25		PCIs	8		4	
Lepirudin[78] (prophylactic doses)	91	Phenprocoumon or acetylsalicylic acid or no anticoagulants (47)	Mixed	19.8§	29.8‡	14.3	8.5
Danaparoid[103]	42	Dextran (70)	HIT	88‖	47‖	0	0
Danaparoid[105]	1,478		Mixed	16.4		8.1	
Danaparoid (with or without coumarin)[114]	62	Historic control subjects: treated with ancrod and/or coumarin (56)	Mixed	19.4†	42.9	11.3§	28.6
Lepirudin/danaparoid[106]	175	Danaparoid (26)	Mixed	12.4	8.1	10.4‖	2.5
Bivalirudin[99]	52		PCI	4		2	
Fondaparinux (followed by warfarin)[107]	7	Historic control subjects: DTI treated (100)	Mixed	14.3	40 (limb gangrene)	0	0

*CAD = coronary artery disease; Mixed = mixed population treated.
†The difference between the treatment and control groups is statistically significant ($p < 0.05$).
‡HIT patients without thrombotic complications.
§HIT patients with thrombotic complications.
‖End point in this prospective randomized controlled study is recovery of HIT-associated thromboembolic complications and not composite end point of new thrombosis, limb amputation, and deaths.

Table 4—*Alternative Anticoagulants for HIT Management

Variables	Argatroban	Lepirudin	Bivalirudin	Danaparoid	Fondaparinux
Structure	Synthetic, l-arginine derivative	Recombinant form of hirudin	Synthetic peptide	Mixture of glycosaminoglycans	Synthetic pentasaccharide
Activity	Direct thrombin inhibitor	Antithrombin	Antithrombin	Anti-factor Xa	Anti-factor Xa
Elimination	Hepatobiliary	Renal	Enzymatic (80%), renal	Renal	Renal
Half-life	40–50 min	80 min	25 min	18–24 h	17–20 h
Monitoring	aPTT, ACT	aPTT, ACT, ECT	aPTT, ACT, ECT	Anti-Xa level	Anti-Xa level†
Dosing in HIT	Initial infusion rate, 2 μg/kg/min IV (no initial bolus); a reduced initial infusion rate (0.5–1.2 μg/kg/min)	Bolus 0.2–0.4 mg/kg IV (only in case of life- or limb-threatening thrombosis); maximum initial infusion rate, 0.10 mg/kg/h IV (target, 1.5–2.0 × patient's baseline or mean of laboratory normal range)	Initial infusion rate, 0.15–0.20 mg/kg/h IV (target, 1.5–2.5 × patient's baseline or mean of laboratory normal range [no initial bolus])	Bolus: 2,250 units IV; infusion, 400 units/h × 4 h, then 300 units/h × 4 h, then 200 units/h IV, subsequently adjusted by anti-Xa levels (target, 0.5–0.8 anti-Xa units/mL)	Doses for HIT treatment need to be established. Because of limited data available on the drug in HIT, fondaparinux could be tried only when other medicines in this table are not available or contraindicated
Dose adjustment	Hepatic insufficiency	Renal dysfunction	Renal dysfunction	Renal dysfunction, body weight	Renal dysfunction

*ACT = activated clotting time; ECT = ecarin clotting time.
†The therapeutic range of anti-Xa levels for fondaparinux in HIT is still to be established.

cross-reactivity rate between heparin and LMWH (approaching 100%), LMWH is not recommended for the treatment of HIT patients.[2,52]

Thrombin generation plays a prominent role in HIT pathogenesis, which provides the rationale for the use of DTIs and anti-factor Xa agents (*eg*, danaparoid) that inhibit thrombin generation in the treatment of HIT. DTIs act by inhibiting free and clot-bound thrombin. Three DTIs currently approved by the US Food and Drug Administration are lepirudin, argatroban (both are primarily used for HIT), and bivalirudin (mainly used for angioplasty in non-HIT settings). They possess different pharmacologic properties. An addition to DTI, danaparoid, the LMW heparinoid, is also widely used for HIT management.[52]

Argatroban

Argatroban is a synthetic l-arginine-derived DTI that reversibly binds to the thrombin active site. It has a rapid onset of action with a plasma half-life of approximately 45 min and is excreted mainly by the hepatobiliary system with minimal renal clearance; thus, it has two major advantages in critically ill patients.[79] Argatroban is currently approved in the United States for the treatment of HIT and for anticoagulation during percutaneous coronary intervention (PCI) when heparin is contraindicated. Argatroban is administered IV as a continuous infusion, with dose adjustment to maintain activated partial thromboplastin time (aPTT) at 1.5 to 3.0 times the baseline value.[80]

The efficacy of argatroban therapy in HIT patients was assessed in two nonrandomized, multicenter studies (the ARG 911 study[81] and the ARG 915 study[82]). In both trials,[81,82] treatment with argatroban was associated with a significant reduction in the composite end point of all-cause death, all-cause limb amputation, or new thrombosis (25.6 to 28%) compared with historical control subjects (38.8% in both studies). The decrease in the relative risk for the composite end point ranged from 27.8 to 34.0%. The number of new thromboses was lower in those receiving argatroban therapy, whereas no significant difference was observed in mortality, limb amputation rate, and the number of major bleeding episodes.

In a pooled analysis[83] of prospective randomized trials on argatroban in HIT patients requiring PCI, the number of unfavorable events was comparable to those treated with heparin. In two multicenter, historically controlled studies,[84,85] argatroban significantly reduced the frequency of the primary thrombosis-related composite end point in patients with peripheral artery disease who required intervention (17.7% vs 30.6%, respectively) and in patients with coronary artery disease (30% vs 50%, respectively). In HIT patients undergoing lower extremity revascularization, the composite end point of deaths, urgent revascularization, or limb amputations developed in 25% of patients treated with argatroban, and 6% of patients had major bleeding episodes.[86] Recent case reports[87,88] have suggested that argatroban might

also be efficacious and safe treatment in HIT patients on dialysis and in those with a percutaneously implanted left ventricular assist device.

Restoration of platelet counts is usually observed within 6 to 7 days of the initiation of argatroban therapy.[89] Some precautions are required when argatroban infusion is overlapped by warfarin anticoagulation therapy because argatroban causes a further substantial increase in the international normalized ratio (INR). Premature cessation of DTI infusion before sufficient warfarin anticoagulation may increase the risk for new thrombotic complications. The initiation of warfarin anticoagulation should be postponed until the platelet count has recovered (to at least 150×10^9 cells/L), and vitamin K should be given in case argatroban therapy is to be started for a patient recognized as having HIT only after warfarin therapy has already begun. Consideration should be given to the contribution of DTI to the patient's INR when assessing whether the warfarin effect is therapeutic. Because other DTIs (lepirudin and bivalirudin) also affect INR, although to a lesser extent (especially lepirudin), these comments are also generally true for overlapping treatment of other DTIs and warfarin. When argatroban is used in patients with heart failure, multiple organ system failure, and severe anasarca, or in post-cardiac surgery patients, it should be started from minimal doses with subsequent dose adjustment under aPTT control.[52]

Lepirudin

Lepirudin, a recombinant form of hirudin, is a direct, specific, and irreversible inhibitor of thrombin for IV administration with a plasma half-life of 60 to 80 min (but it is greatly increased in the presence of even mild renal failure).[90] Its biggest drawbacks are the need for strict laboratory monitoring, whereby aPTT monitoring should be performed at 4-h intervals until a steady state within the therapeutic range is achieved, and the risk of bleeding.[52] Moreover, patients should be informed that they have received lepirudin because fatal anaphylactic reactions have been reported[91] in patients treated with IV lepirudin and reexposed to this drug. Lepirudin elimination is impaired in patients with renal dysfunction, even when renal impairment is moderate.

In two prospective, multicenter, historically controlled Heparin-Associated Thrombocytopenia-1[92] and -2[93] trials, lepirudin significantly reduced the combined end point of death, limb amputation, or new thromboembolic complications in patients with HIT-associated thrombosis compared with historical control subjects but demonstrated similar bleeding rates. Cochran et al[94] performed PCI in 25 HIT patients treated with lepirudin alone, and 21 patients were given adjuvant glycoprotein IIb/IIIa inhibitors. Angiographic success was obtained in 100% of patients with isolated HIT (*ie*, HIT without thrombosis), and clinical success (freedom from death, myocardial infarction, stroke, or target vessel revascularization) was achieved in 92% of patients.[76] In a metaanalysis[76] of three prospective trials of patients with serology-confirmed acute HIT, lepirudin was superior to control group in the prevention of adverse events.

In one case report,[95] lepirudin anticoagulation was successful in a child with HIT undergoing cardiac surgery. In a retrospective comparative study of lepirudin vs danaparoid,[96] similar outcomes were observed in HIT patients treated with the therapeutic regimen, but, with the prophylactic regimen, patients receiving danaparoid had a higher risk of thromboembolic events. This comparison is inappropriate because the "prophylactic" dose of danaparoid used in this study was grossly inadequate for HIT treatment. However, the inferiority of danaparoid was not confirmed in another study[97] of critically ill patients with HIT, probably implying the role of background comorbidities. Initial doses of lepirudin should be low (0.05 to 0.10 mg/kg/h), particularly when there is renal dysfunction. The initial IV bolus should be omitted unless there is a perceived life-threatening or limb- threatening thrombosis.

Bivalirudin

Bivalirudin is a synthetic peptide composed of two short hirudin peptide fragments, with a short plasma half-life (25 min), and it is primarily metabolized via proteolytic degradation. Campbell et al[98] reported a series of 17 patients with HIT undergoing PCI with 94% procedural success. In the Anticoagulant Therapy with Bivalirudin to Assist in the Performance of Percutaneous Coronary Intervention in Patients with HIT (or ATBAT) multicenter open-label trial,[99] clinical PCI success, defined as the absence of death, emergency bypass surgery, or Q-wave infarction, was achieved in 96% of the patients treated with bivalirudin with a low rate of bleeding, attesting to the safety and efficacy of bivalirudin therapy during PCI. In recent small trials, bivalirudin was successfully used to replace heparin in the treatment of patients with HIT undergoing cardiovascular surgery. However, varying bivalirudin dosing regimens were used for treatment in the reported studies and different clotting times were employed for monitoring treatment.[100] For the treatment of HIT, a reasonable dosage regimen is 0.15 mg/kg/h, with subsequent adjustments made to keep the aPTT between 1.5-fold and 2.5-fold higher than the baseline. Given

recent data on the role of bivalirudin in patients with acute coronary syndromes, including primary PCI, the use of bivalirudin in clinical practice is likely to increase. Of note, bivalirudin is approved in the United States for use during PCIs in patients with acute or previous HIT but not for other HIT indications, which constitute the vast majority of HIT cases.

Danaparoid

Danaparoid, a heparinoid with predominantly anti-Xa activity and some anti-IIa activity, is a mixture of three glycosaminoglycans (heparin sulfate, dermatan sulfate, and chondroitin sulfate) that exerts its anticoagulant effect by catalyzing the inactivation of factor Xa in the presence of antithrombin. It has a unique property of specific suppression of HIT antibody-induced platelet activation that is not observed with other drugs used for HIT treatment.[101] Danaparoid has a low cross-reactivity rate with HIT antibodies *in vitro* but very rarely *in vivo*. It was withdrawn from US markets in 2002, but use of the drug to treat HIT has been approved in many European countries and some countries outside Europe (*eg*, Canada, Australia, New Zealand, and South Africa). For the treatment of HIT, danaparoid is given IV according to the following dosing regimen: a bolus of 2,250 units, followed by an infusion of 400 units/h for 4 h, 300 units/h for 4 h, and then 200 units/h for at least 5 days, or longer if clinically appropriate. After the initial period, the danaparoid infusion rate is adjusted to maintain a plasma anti-Xa level between 0.5 and 0.8 anti-Xa units/mL (performed with a danaparoid standard curve).[102] However, significantly fewer major bleeding episodes were recorded[97] in those patients treated with danaparoid compared with those treated with lepirudin.

Among the drugs used for the treatment of HIT, danaparoid is the only drug whose efficacy and safety have been confirmed by a prospective randomized controlled study.[103] Additionally, danaparoid efficacy in preventing new, progressive, or recurrent thrombosis (including thrombotic death) or limb amputation was also found in comparison with a control group of ancrod (defibrinogenating snake venom) and/or coumarin (historically controlled study).[104] The clinical usefulness of danaparoid in HIT treatment is also evident from the large published clinical experience of 1,478 danaparoid-treated patients reported by Magnani and Gallus.[105]

Fondaparinux

Fondaparinux is a synthetic pentasaccharide with potent indirect anti-Xa inhibitor properties. It has the same structure as the five sugar moieties in UFH and LMWH, but it has no significant cross-reactivity with the HIT antibody. The risk of the development of HIT in patients receiving fondaparinux is very low.[106] However, a case of fondaparinux-related thrombocytopenia in a previous LMWH-induced HIT patient has recently been reported. Fondaparinux does not require platelet count monitoring. To date, only a limited number of patients with HIT have been treated with fondaparinux.[107,108] Even though the cost of fondaparinux is relatively low, and thus it is financially attractive to use this drug, its use for the treatment of HIT cannot be recommended until there are more data demonstrating its efficacy and safety.[107,108]

Other Treatments

Unlike the treatment of patients with non-HIT thrombosis, in which warfarin therapy is often started within 24 h of commencing UFH, LMWH, or fondaparinux therapy, in HIT patients it is important to postpone warfarin therapy until the platelet count has recovered to at least 150×10^9 cells/L. Platelet recovery is an indication that the HIT-associated acute platelet-consuming thrombotic process is under control. Commencing warfarin therapy before the thrombosis is well-controlled and while the patient remains thrombocytopenic and hypercoagulable poses the risk of precipitating venous limb gangrene due to sharp reductions in protein C and protein S levels. Warfarin therapy, if required (*eg*, for the longer term management of deep vein thrombosis), should only be started while the patient is receiving alternative anticoagulant therapy (DTI or danaparoid), and for at least a 4- to 5-day overlap period. Furthermore, the alternative anticoagulant should not be stopped until two INRs (24 h apart) are within the target range and the platelet count has reached a stable plateau within the normal range. Given the short half-lives of DTIs (vis-à-vis danaparoid), it is especially important not to stop DTI therapy prematurely. DTI, particularly argatroban, significantly prolongs the INR at > 2.0 even when the warfarin effect is still subtherapeutic. The cessation of DTI would drop the INR below the therapeutic range, and the patient would be at risk of thrombosis recurrence or progression. After the cessation of DTI or danaparoid therapy, warfarin therapy is continued for 3 to 6 months or longer if clinically appropriate. If there is no thrombosis (HIT with isolated thrombocytopenia) that needs long-term warfarin treatment, the alternative anticoagulant therapy can be stopped after platelet recovery.

Platelet transfusions should be avoided in the management of HIT. Although it has recently been shown[109] to be "safe" in four patients with clinically

suspected HIT and a positive SRA, stronger evidence and more convincing data are needed before we can be confident that platelet transfusion is indeed safe. HIT is a hypercoagulable state driven by intense platelet activation. Infusing platelets into a patient with HIT is akin to adding fuel to a raging fire. Besides, many HIT patients have experienced serious adverse consequences after platelet transfusion (B.H. Chong, MD; unpublished data).

Glycoprotein IIb/IIIa inhibitors do not have direct anticoagulant effects and do not inhibit Fc receptor-mediated platelet activation. The addition of a glycoprotein IIb/IIIa inhibitor to argatroban in HIT patients with acute coronary syndromes undergoing coronary PCI did not provide additional clinical benefits but was associated with a tendency toward an increase in major bleeding episodes (5.8% patients in the glycoprotein IIa/IIIb inhibitor group vs 0 patients in the argatroban-alone group).[110] For these reasons, glycoprotein IIb/IIIa inhibitors should not be used as a sole therapy for HIT and may be cautiously used in combination with other anticoagulants.

Oral direct factor Xa inhibitors, such as rivaroxaban or apixaban, are novel oral anticoagulants in advanced clinical development for the prevention and treatment of thromboembolic disorders. These medicines have no cross-reactivity with the HIT antibody and may potentially be useful in the treatment of HIT, but to date there are no data regarding their use in the treatment of patients with HIT.

Drotrecogin α (activated) is the recombinant form of human activated protein C, a naturally occurring protein C, which affects the inhibition of factors Va and VIIIa (cofactors of factor IXa and Xa) and possesses antithrombotic, antiinflammatory, and profibrinolytic activities. Drotrecogin is approved in North America for severe sepsis. Rubeiz et al[111] have reported the successful use of this agent in a patient with HIT and thrombotic complications with severe sepsis and shock. Following the discontinuation of heparin therapy, drotrecogin α (activated) was used as the sole antithrombotic agent with a successful outcome (the patient survived with limbs preserved). However, the use of these novel drugs in HIT management is not recommended until there are data supporting their efficacy and safety.

Subsequent Management

Reexposure to Heparin

The HIT antibodies usually disappear approximately 100 days after the onset of HIT, and brief reexposure to heparin thereafter is unlikely to result in a recurrence of HIT. Nonetheless, it is usually recommended that heparin use be avoided in such patients. If heparin therapy is indicated, absence of the antibody should be documented by a sensitive test, and heparin should be used only for a short period. Recent data have suggested that heparin reexposure might also be effective in patients with subacute HIT with an enzyme immunoassay test that is positive for HIT antibodies but a washed platelet activation assay that is negative for HIT antibodies.

Thus, UFH therapy is recommended for patients with a history of HIT who undergo cardiac or vascular surgery. However, if prolonged anticoagulant treatment is required, they should receive an alternative nonheparin anticoagulant (*eg*, a DTI).

HIT Patients Requiring Cardiac Surgery or Coronary Interventions

If possible, cardiac surgery or coronary intervention should be postponed until platelet count restoration and the elimination of HIT antibodies from circulation.[112] However, UFH is currently the anticoagulant of choice for cardiac bypass surgery in patients without HIT. Given these reasons, in patients with a history of HIT without circulating HIT antibodies or with HIT antibodies detected by ELISA and not detected by a washed platelet activation assay, UFH should be used during cardiac surgery.[52]

When patients require cardiac surgery while still having acute HIT with the antibody still detectable by washed platelet activation assay, ACCP guidelines[52] recommend the following approaches, in descending order of preference: (1) delaying surgery if clinically possible until platelet recovery and the antibody is undetectable, and then using UFH; (2) using bivalirudin during CPB or (3) during off-pump cardiac surgery using lepirudin; or (4) using UFH plus the antiplatelet agent epoprostenol, UFH plus the antiplatelet agent tirofiban, or danaparoid. If UFH is used, it should be used only during surgery, and an alternative anticoagulant should be used preoperatively and postoperatively if it is required.[52]

Bivalirudin, argatroban, lepirudin, or danaparoid are recommended for use in patients with previous HIT who require PCI.[52] Nonheparin anticoagulants were also effective for treating HIT in patients using ventricular assist devices, in whom HIT not infrequently develops (approximately 4.5%).[113]

Conclusion

HIT is a well-recognized serious adverse drug reaction that is associated with heparin use. Nonheparin anticoagulants that do not cause HIT are gradually replacing heparin in clinical practice. If

this trend continues, the incidence of HIT will decrease with time and may ultimately disappear. Until then, HIT still occurs and remains a potentially life-threatening condition that requires prompt diagnosis and treatment management.

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