Heparin-induced thrombocytopenia: An Update

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Abstract:

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Heparin-induced thrombocytopenia (HIT) is the most important and most frequent drug-induced, immune-mediated type of thrombocytopenia. It is associated with significant morbidity and mortality if unrecognized. In this review, we briefly discuss the main features of heparin-induced thrombocytopenia, particularly analyzing the most recent advances in the pathophysiology, diagnosis and treatment of this syndrome.

Introduction

Heparin is an important and widely used anticoagulant. Heparin-induced thrombocytopenia (HIT) is a serious, life and limb threatening complication of heparin. It was first identified in the 1970s and emerged in the 1990s as one of the most difficult immunohematologic issues. Unfortunately, because thrombocytopenia is common in hospitalized patients and can be caused by a variety of factors,[1] HIT often remains unrecognized.

Heparin-induced thrombocytopenia is defined as a decrease in platelet count during or shortly following exposure to heparin.[2] While it is mainly associated with unfractionated heparin (UFH), it can also occur with exposure to low-molecular weight heparin_(LMWH), but at significantly lower rates.[3,4] Despite the low platelet count, it is a thrombotic disorder, with very high rates of thrombosis,in both arterial and venous vascular bed. Of note, the rate of DVT (deep vein thrombosis) is roughly 4 times that of arterial thrombosis,[5] and while thrombocytopenia is the most common "event" in HIT, DVT is in fact the most common complication.[6]

The diagnosis of HIT is based on three criteria: 1. The patient is currently receiving or has had recent exposure to heparin, 2. the presence of at least one clinical feature of the syndrome (usually thrombocytopenia with or without thrombosis), and 3. laboratory evidence of HIT antibodies.[7]

There are two forms of HIT. *Type I HIT (also called heparin associated thrombocytopenia) occur in* 10-20% of patients receiving heparin, emerges within 1-2 days of heparin therapy is mediated by a direct interaction between heparin and circulating platelets causing platelet clumping or sequestration.[8] Here platelet count remains greater than 100,000 . Patient remains asymptomatic and no intervention is necessary.[9,10] Whereas *Type II HIT* is caused by auto-antibodies and emerges within 4-14 days of initiation of heparin therapy,[11] earlier if patient received heparin within last 100 days. However, because HIT has been reported up to 3 weeks after exposure to heparin, there also exists a phenomenon known as delayed-onset HIT. It causes severe thrombocytopenia and platelet count falls to levels less than 100,000.

Incidence

- 0.5% of patients with occult exposure to heparin e.g., catheter flushes, heparin-coated catheters

- 0.1%–1% of patients treated with low-molecular-weight heparin

- 3%–5% of patients receiving unfractionated heparin (bovine UFH > porcine UFH > LMWH)

- HIT occurs more commonly in surgical settings rather than non-surgical settings (after surgery > medical > pregnancy).

Pathogenesis of HIT

- HIT is caused by autoantibodies to a complex of heparin and platelet factor 4 (PF4).[12,13]

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Platelet factor 4 is a small positively charged molecule of uncertain biological function normally found in á-granules of platelets. When platelets are activated, PF4 is released into the circulation and some of it binds to the platelet surface. Because of opposite charges, heparin and other glycosaminoglycans bind to the PF4 molecules, exposing neoepitopes that act as immunogens leading to antibody production. Although PF4 is the most important protein involved in the immune response of HIT, neutrophil activating factor (NAP-2) and Interleukin 8 (IL8) also play role. Binding with PF4 depends on molecular weight of heparin. Longer and highly sulphated heparins are more immunogenic than low molecular heparins. In clinically symptomatic patients HIT antibodies are mostly of IgG subclass with or without IgA or IgM HIT antibodies. IgG antibodies binds to the complex on platelet surface through the Fab region.[14] The Fc portion of the HIT antibody can then bind to the platelet Fc receptor and this interaction triggers activation and aggregation of the platelets. Activated platelets release PF4, thus perpetuating the cycle of heparin-induced platelet activation. Thrombosis is induced by four mechanisms; first the platelet activation leads to the production of prothrombotic platelet micro particles, which promote coagulation. Second, as a result of the presence of heparin-like molecules (heparan sulfate) on the surface of endothelial cells, the HIT antibody-PF4-heparan sulfate complexes formed on the endothelial surface may induce tissue factor expression with further activation of the coagulation cascade and thrombin generation.[15,16] Third, Expression of tissue factor by monocytes activated by HIT antibodies. Fourth is Neutralization of the anticoagulant effects of heparin by PF4 released from activated platelets. Thrombocytopenia in HIT is largely due to the clearance of activated platelets and antibody-coated platelets by the reticulo-endothelial system.[17] Figure 1 illustrates the pathophysiology of HIT.
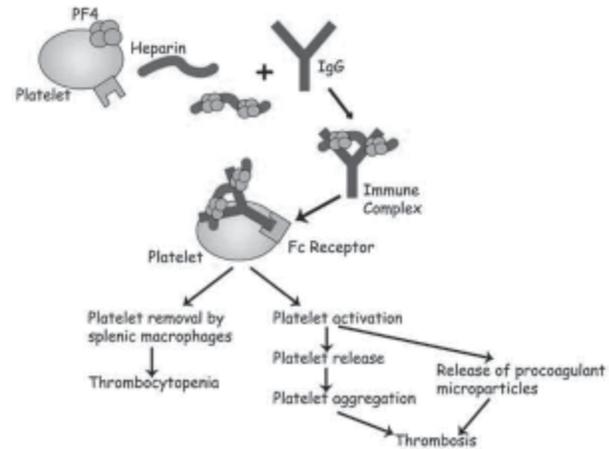

Fig.-1: *Pathophysiology of heparin-induced thrombocytopenia.*

Clinical Features of HIT

In HIT, the relative decrease in platelet counts is key to diagnosis.[18] The thrombocytopenia in HIT is usually moderate in severity, with a median platelet count being between 50 and 80×10^9/L, although the nadir platelet count can remain at a level considered normal (i.e. $> 150 \times 10^9$/L) but having dropped by 50% or more with respect to the pre-heparin value. The platelet count starts to rise 2 to 3 days after discontinuing heparin and usually returns to normal within 4 to 10 days. The antibody disappears within 2 to 3 months after cessation of heparin therapy.[19] Although HIT does not invariably recur during subsequent re-exposure to heparin, future use of heparin is contraindicated.[20] Despite thrombocytopenia, bleeding is rare.[21] Contrariwise, HIT is strongly associated with thrombosis, which frequently leads to the recognition of HIT.[22] The overall risk for thrombosis in patients with HIT managed by heparin cessation is 38% to 76% [23-26]. In HIT patients without thrombosis at diagnosis, the risk for thrombosis in the days to weeks after heparin cessation is 19% to 52%.[23-26] This risk persists well after platelet counts return to normal, which typically occurs within a week of stopping heparin.[25-27] Thrombosis in HIT is associated with a mortality of approximately 20–30%, with an equal percentage of patients becoming permanently disabled by amputation, stroke or other causes.[28] The most common complications of HIT are presented in Table 1.

Table-I

Thrombotic complications of heparin-induced thrombocytopenia

- Venous thrombosis
  Deep vein thrombosis
  Pulmonary embolism
  Cerebral venous thrombosis
  Adrenal heamorrhagic infarction
  Coumarin induced venous limb gangrene

- Arterial thrombosis
  Lower limb artery thrombosis
  Cerebrovascular accident
  Myocardial Infarction
  Aortic occlution
  Cardiac intraventricular thrombosis
  Thrombosis in upper limb,lower limb,
  mesenteric,renal, and spinal arteries

- Skin lesion (at heparin injection site) skin
  necrosis erythematous plagues

A few risk factors for progression to adverse outcomes in HIT have been identified. The severity of the thrombocytopenia is a significant independent predictor of the composite of death, amputation, or new thrombosis.[29] Patients with the lowest platelet counts experience the poorest outcomes. Comorbid malignancy increases the thrombotic risk (odds ratio, 13.6; 95% CI, 2.9 to 63.8).[30] Females are more likely than males to suffer ischemic stroke as an outcome of their HIT (odds ratio, 2.5; 95% CI, 1.1 to 5.5).[31]

Other complications of HIT include skin lesions and acute systemic reactions. Erythematous or necrotizing skin lesions occur at the heparin injection site in 10% to 20% of patients who develop heparin-PF4 antibodies during subcutaneous heparin therapy. Thrombocytopenia develops in 25% of these patients.[32] Acute systemic reactions, including fever, chills, hypertension, tachycardia, chest pain, dyspnea, or other symptoms, occur 5 to 30 minutes after administration of an intravenous heparin bolus in up to 25% of patients with circulating HIT antibodies. The platelet count usually falls suddenly, and prompt suspicion of HIT is critical, as cardiopulmonary fatalities have occurred.[33] Recent reports also suggest that HIT could explain approximately 5% of cases of acute

adrenal failure caused by bilateral adrenal hemorrhagic infarction and end-organ damage eg. bowel, spleen, gallbladder or hepatic infarction; renal failure.[34,35]

Circulating heparin-PF4 antibodies remain detectable for 4 months after the diagnosis of HIT in 10% to 40% of patients, depending on the assay used.[34] The antibody longevity thereafter remains unclear. Data suggest that enduring antibodies, rather than an anamnestic immune response to heparin, precipitate the rapid thrombocytopenia that can occur when patients with recent, previous heparin exposure are reexposed to heparin.[36,37]

Fig.-2: *Baseline view of HIT*

Investigations
- Platelet count
- Antigen assay (ELISA)
      PF4/Heparin-EIA
- Activation assay
Washed platelet assay
      Serotonin release assay (SRA)
      Heparin induced platelet activation test (HIPA)
Using citrated platelet rich plasma
      Platelet aggregation assay (PAA)

Fig.-3: *Gangrene in a patient with HIT.*

Table-II
Advantage and disadvantage of different tests for diagnosis of HIT

Test	Advantages	Disadvantages
ELISA	High sensitivity, detects IgA and IgM	High cost, lower specificity for clinically significant HIT
PAA	Rapid and simple	Washed platelet (technically demanding), needs radiolabeled material 14C
SRA	Sensitivity >90%	Washed platelet (technically demanding), needs radiolabeled material 14C
HIPA	Rapid, sensitivity >90%	Washed platelets

The College of American Pathologists recommends heparin-PF4 antibody testing for patients in whom there is suspicion of HIT based on the temporal features of the thrombocytopenia or on the occurrence of new thrombosis during or soon after heparin treatment.[38] Results from laboratory tests for HIT antibodies may not be obtained for hours to days after being ordered. Because of the increased thrombotic risk early in the progression of HIT.[39,40] appropriate therapy in a patient with suspected HIT must not be delayed pending laboratory results.

Antigenic and functional tests for heparin-PF4 antibodies are available yet often are labor intensive and time intensive.[38] Antigenic assays, such as the ELISA, measure antibodies to PF4 complexed with heparin or other polyanions. The ELISA has a sensitivity of >90%; however, it also detects antibodies that do not elicit HIT (false-positives) and has decreased specificity in certain populations such as cardiac surgery patients.

Functional tests, including platelet aggregometry and the [^{14}C] Serotonin release assay, measure platelet activity in the presence of patient sera and heparin. Platelet aggregometry has a sensitivity of 35% to 85%, and acute-phase reactants can cause false-positives; its sensitivity and specificity can be improved by using washed platelets from normal donors.[41] The serotonin-release assay is sensitive and specific (>95%) yet is technically demanding, involves radioactivity, and is generally used as a confirmation test only. Flow cytometric assays,

including methods to detect platelet microparticle release[11] and annexin V binding.[42] are described that are strongly correlated with the serotonin-release assay yet do not use radioactivity. No single assay, however, has 100% sensitivity and specificity. Although testing becomes most effective when functional and antigen tests are done in combination and multiple samples are taken.[43] this approach is often impractical, and results are unlikely to be available in a timely manner.

Diagnosis
- Normal platelet count before the commencement of heparin
- Develop thrombocytopenia 5–10 days after initiation of heparin treatment, which can occur earlier with previous heparin exposure (within 100 days)
- Acute thrombotic event
- The exclusion of other causes of thrombocytopenia
- The resolution of thrombocytopenia after cessation of heparin
- HIT antibody seroconversion

Preliminary evaluation suggests that HIT antibodies are unlikely (<5%) when a low score (3) is obtained but are likely (>80%) with a high score (6). An intermediate score (4 or 5) indicates a clinical profile compatible with HIT but with another plausible explanation. Laboratory testing for HIT antibodies is especially useful in this last group of patients.[44]

Monitoring
According to guideline drafted by a working party of the Haemostasis and Thrombosis Task Force of the BritishCommittee for Standards in Haematology recommendations for management of HIT are as follows -

- All patients who are to receive heparin of any sort should have a platelet count performed on the day of starting treatment. Grade C Level IV.
- For patients who have been exposed to heparin in the last 100 d a baseline platelet count and a platelet count 24 h after starting heparin should be obtained. Grade C Level IV.
- For all patients receiving UFH, alternate day platelet counts should be performed from days 4 to 14. Grade C Level IV.

Table-III

Estimating the Pretest Probability of HIT: The "Four T's"

| Points	2	1	0
Thrombocytopenia	>50% Platelet fall or nadir e" 20	30–50% Platelet fallor nadir 10–19	<30% Platelet fallor nadir <10
Timing of onset of platelet fall	Days 5–10, or day 1 with recent heparin (past 30 days) <Day 4 (no recent heparin)	>Day 10 or timing unclear; or <day 1 with recent heparin	
Thrombosis or other sequelae	Proven new thrombosis; skin necrosis; or acute systemic reaction after intravenous UFH bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis (not proven)	None
Other cause(s) of platelet fall	None evident	Possible	Definite
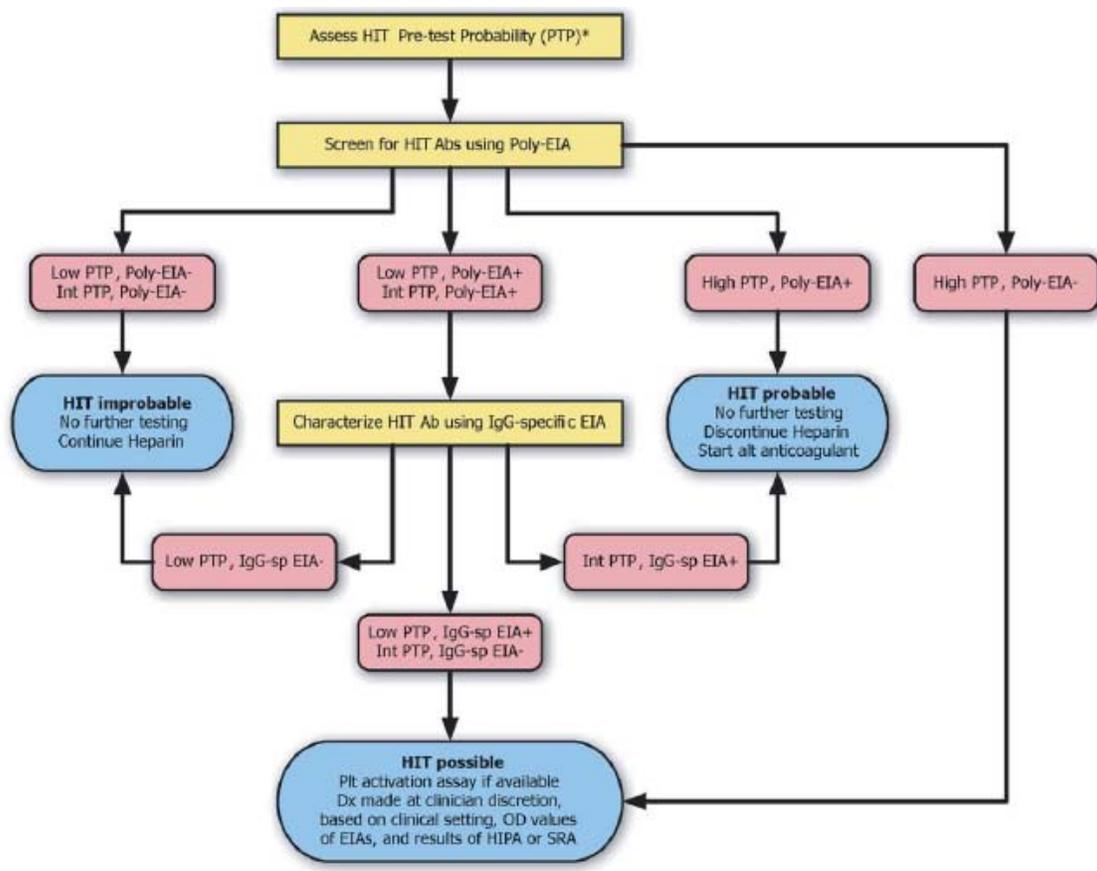
Fig.-4 : *Algorithm for diagnosis and management of HIT. PTP, pretest probability; Poly-EIA, Polyspecific EIA (IgM, IgG, IgA); HIT Ab, HIT Antibody; IgG-sp EIA, IgG-specific EIA; Alt, Alternative; Int, Intermediate. *Recommend using 4T's score.[45]*

- For surgical and medical patients receiving LMWH, platelet counts should be performed every 2–4 d from days 4 to 14. Grade C Level IV.

- Obstetric patients receiving treatment doses of LMWH should have platelet counts performed every 2–4 d from days 4 to 14. Obstetric patients receiving prophylactic LMWH are at low risk and do not need routine platelet monitoring. Grade C Level IV.

- If the platelet count falls by 50% or more and/or the patient develops new thrombosis or skin allergy between days 4 and 14 of heparin administration, HIT should be considered and a clinical assessment made. Grade C Level IV.

- If the pretest probability of HIT is high, heparin should be stopped and an alternative anticoagulant started in full dosage whilst laboratory tests are performed unless there are significant contraindications. Grade C Level IV.

Treatment
General Principal

- Immediate cessation of all formulations of heparin

- Initiate alternative anticoagulation for at least 2–3 months to prevent recurrence of thrombosis

- Send blood samples for laboratory confirmation

- Monitor carefully for thrombotic event

- Monitor platelet count till recovery

- Warfarin should not be used until the platelet count has recovered

- Avoid prophylactic platelet transfusion

Table-IV
Differential Diagnosis of HIT

Pseudo HIT disorders	Comment
Adenocarcinoma	Thrombocytopenia may complicate cancer associated DIC/ thrombosis, especially after stopping heparin; warfarin- associated venous limb gangrene has been reported in these patients.
Pulmonary embolism	Platelet activation may be secondary to clot-bound thrombin
Diabetic ketoacidosis	Hyperaggregable platelets predispose to thrombocytopenia and thrombosis
Antiphospholipid antibody syndrome	Pathogenesis of thrombocytopenia is obscure, but could invole platelet- activating antibodies in some instances
Thrombolytic therapy	Platelet activation by thrombin bound to fibrin degradation products
Septicaemia associated DIC/ Purpura fulminans	Symmetric peripheral gangrene secondary to DIC with depletion of protein C has been reported
Infective endocarditis	Infection associated thrombocytopenia, ischaemic events secondary to septic emboli.
Paroxysmal nocturnal haemoglobinuria	Platelets susceptible to complement mediated damage
Post transfusion purpura	Although timing of thrombocytopenia resembles HIT, patients develop bleeding rather than thrombosis

Pseudo HIT disorders are the conditios that resemble HIT, but with negative testing for HIT antibodies using both activation and antigen assays.

AlternativeAnticoagulants-

Alternative anticoagulants are:

1.**Direct thrombin inhibitors (DTI)**

· Lepirudin

· Argatroban

· Bivalirudin

2.Factor Xa inhibitors

Direct thrombin inhibitors, including argatroban, lepirudin, and bivalirudin, are non-heparin anticoagulants that inhibit thrombin without need of a cofactor and that do not generate or interact with HIT antibodies.[46] In prospective, historical controlled studies, argatroban[38,43] and lepirudin[47,48,49] significantly improved outcomes in HIT, particularly reducing new thrombosis. Major bleeding rates assessed by similar criteria were 6% to 7% with argatroban (7% with control)[38,43] and 13% to 19% with lepirudin (control not reported).[47,48,49] These agents are routinely monitored with the activated partial thromboplastin time (aPTT) or, at higher levels of anticoagulation, the activated clotting time (ACT) for argatroban or ecarin clotting time (ECT) for lepirudin. No controlled studies have evaluated any other direct thrombin inhibitor in patients with HIT, although there are limited prospective data on the use of bivalirudin in HIT patients.[4,50-52]

Whereas direct thrombin inhibition reduces thrombin activity, factor Xa inhibition reduces thrombin generation. Danaparoid, which is a mixture of heparan, dermatan, and chondroitin sulfates, exerts its anticoagulant effects predominantly by inhibiting factor Xa (anti–factor Xa to anti–factor IIa activity of roughly 22:1) with anti-thrombin or heparin cofactor II as a cofactor. In vitro cross-reactivity of danaparoid with HIT sera is 10% to 50%, depending on the assay.[53]

The choice of the alternative anticoagulant should consider its demonstrated efficacy and safety in the intended use, availability of the drug and methods for monitoring, and the patient's clinical status, including renal and hepatic function.

Argatroban-
In the United States, the only approved anticoagulants for use in adult patients with HIT are the direct thrombin inhibitors argatroban, which is a synthetic molecule derived from L-arginine, and lepirudin, which is a recombinant protein derived from leech hirudin. In addition to its use in prophylaxis or treatment of thrombosis in HIT, argatroban is also approved for use in patients with or at risk for HIT who is undergoing percutaneous coronary intervention (PCI).

The recommended initial dose is 2 μg/kg per minute adjusted to achieve aPTTs 1.5 to 3 times the baseline value. Reduced doses are required in patients with hepatic impairment. There is no evidence of antibody generation to argatroban on prolonged or repeated administration,[54] Argatroban is routinely monitored with the aPTT.

The clinical efficacy and safety of argatroban therapy in HIT patients have been demonstrated in the multicenter, prospective studies known as Argatroban-911[38] and Argatroban-915.[43] In each study, patients having clinically diagnosed HIT received intravenous argatroban starting at 2 μg/kg per minute (or lower, in the presence of hepatic impairment), adjusted to maintain aPTTs 1.5 to 3.0 times the baseline value. Mean doses of 1.7 to 2.0 μg/kg per minute were infused for 5 to 7 days, on average, to 304 patients in Argatroban-911 and to 418 patients in Argatroban-915. In both studies, argatroban therapy significantly reduced the composite end point (all-cause death, all-cause amputation, or new thrombosis at 37 days) in HIT patients without thrombosis (25.6% and 28.0%, respectively, versus 38.8% in controls, *P*<0.04).

Lepirudin
Lepirudin is indicated in the United States as anticoagulation for patients having HIT with associated thromboembolic disease to prevent further thromboembolic complications.[47,48] The recommended dose is a 0.4-mg/kg initial bolus followed by a 0.15-mg/kg per hour infusion, adjusted to aPTT ratios of 1.5 to 2.5. Relative overdose can occur with lepirudin at standard doses in patients with renal impairment. Hence, lepirudin requires reduced doses, with careful monitoring, in patients with serum creatinine values >1.6 mg/dL and must be avoided in patients on hemodialysis or with acute renal failure.[55] Approximately 50% of patients exposed to lepirudin form anti-hirudin antibodies that can alter the drug's pharmacokinetics, leading to increased plasma

lepirudin concentrations and the need for close monitoring to reduce bleeding risk.[56,57] Anaphylaxis, including anaphylactic death, occurs in an estimated 0.2% of patients reexposed to lepirudin.[58] The severity of anaphylaxis may be reduced by omitting the bolus during lepirudin administration. Because of the severity of this adverse reaction, nonhirudin anticoagulants should be considered for use in patients with previous lepirudin exposure.[6,58]

Three multicenter, prospective, similarly designed studies, known respectively as Heparin-Associated Thrombocytopenia (HAT)-1,[47] HAT-2,[48] and HAT-3,[49] evaluated the safety and efficacy of lepirudin in patients with serologically confirmed HIT. Lepirudin therapy significantly decreased the combined end point of death, new thromboembolic complications, and amputation at 35 days in 2 studies (25.4% in HAT-1 and 26.2% in HAT-3 versus 52.1% in control, $P<0.014$). In HAT-2, the combined end point was 30.9% ($P=0.12$ versus control). There were no significant between-group differences in the individual components of the combined end point, with the exception that lepirudin therapy significantly reduced new thromboembolic complications in HAT-3 (9.9% versus 32.1%, $P<0.001$). aPTTs increased rapidly to target values and generally remained there during lepirudin therapy. Platelet counts were $>100 \times 10^9$/L within 10 days in 89% to 93% of the lepirudin-treated patients. There was an excess of bleeding in the lepirudin group, compared with control, in HAT-2 (45% versus 27%, $P<0.001$). Major bleeding rates in the respective studies were 13.4%, 17.0%, and 19.5% (not reported for controls). In combined-study analyses for HIT patients with or without thrombosis, lepirudin therapy, compared with historical controls, significantly reduced the time to event for the combined end point ($P<0.03$) irrespective of the HIT presentation, primarily due to reductions in new thromboembolic complications.[59,60] In HIT patients with thrombosis, lepirudin significantly increased bleeding that required transfusion (18.8% versus 7.1% in controls, $P=0.02$.

Bivalirudin

Bivalirudin, which is not approved for HIT, is a 20–amino acid polypeptide with sequence homology to hirudin. Preliminary data are available on bivalirudin use in a limited number of HIT patients.[50,51] One study described 45 patients who received bivalirudin at an average infusion dose of 0.17 mg/kg per hour, adjusted to aPTTs of 1.5 to 2.5 times the baseline value; 6 patients died, 1 patient had new thrombosis, and no patient experienced major bleeding.[50] Another study described 15 patients treated with a mean initial dose of 0.16 mg/kg per hour; 6 patients died, and bivalirudin was stopped in 1 patient because of bleeding.[51] Approximately 51% of anti-hirudin antibodies occurring in lepirudin-treated patients cross-react with bivalirudin in vitro,[61] raising the theoretical concern that anaphylactic reactions may occur in patients treated with bivalirudin who have been previously exposed to lepirudin.

Danaparoid

Danaparoid is approved as an alternative anticoagulant for HIT in many countries (unavailable in the United States). It is contraindicated in patients with a history of thrombocytopenia with danaparoid or in whom an in vitro platelet aggregation test is positive in the presence of danaparoid. Danaparoid cross-reacts with 10% to 50% of HIT sera, depending on the assay.[53] Although used in many patients, including >750 patients treated in a compassionate-use program, and often with success,[53,62] danaparoid has also been associated with unfortunate treatment failures from clinically significant cross-reactivity.[53,63] Danaparoid is renally cleared, and doses should be reduced in patients with renal impairment. When monitoring is needed, plasma anti–factor Xa levels are typically used because the aPTT and activated ACT are not significantly prolonged at clinically relevant doses.

In the compassionate-use program, the recommended danaparoid dose for thromboprophylaxis in HIT patients without thrombosis was 750 U administered subcutaneously twice or thrice daily. The recommended treatment of HIT patients with thrombosis was a 1500- to 3750-U bolus (depending on body weight) followed by a 400-U/h infusion for 4 hours, then a 300-U/h infusion for 4 hours, then a 150- to 200-U/h infusion for at least 5 days, with a target of 0.5 to 0.8 anti–factor Xa U/mL in plasma. In one report,[62] 15 (6.5%) of 230 patients in the

program experienced the appearance or persistence of thrombocytopenia (9 patients), new thromboembolism (4 patients), or bleeding (2 patients) during or within 2 days after treatment, and 59 (25.7%) patients died within 3 months.

A retrospective study of 175 lepirudin-treated HIT patients from HAT-1 and -2 and 126 danaparoid-treated HIT patients from the same time period[64] found no significant between-group difference in the 42-day combined end point of death, new thromboembolic complications, or amputation (21.5% versus 18.5%, P=0.53). Danaparoid therapy caused less bleeding requiring transfusion (2.5% versus 10.4%, P=0.02). In a subgroup analysis of HIT patients without thrombosis, the cumulative risk of the combined end point was significantly higher with danaparoid than with lepirudin therapy (P=0.02), suggesting that the recommended prophylaxis dose for danaparoid in HIT may be suboptimal.

Fondaparinux

Fondaparinux is also an indirect, yet more selective, factor Xa inhibitor. It is a synthetic pentasaccharide that is structurally related to the anti-thrombin–binding site of heparin, is not approved for patients with HIT. The generation of HIT-related antigen depends on the polysaccharide chain length, with an optimum of 14 to 16 saccharides.[8] In theory, because fondaparinux has 5 saccharides and is smaller than LMWH, it is expected to be less likely to induce HIT.[65] In the single case series reported in full on fondaparinux use in HIT, 6 patients with a history of HIT and 2 patients with LMWH-induced HIT received fondaparinux 2.5 mg subcutaneously daily for 14 days, without bleeding or thromboembolic complications.[66] Preliminary data are available for HIT patients administered fondaparinux 2.5 mg for at least 5 days as an initial treatment (n=10) or after direct thrombin inhibition therapy (n=10); no continued or recurrent thrombocytopenia and no thrombotic complications occurred.[67] Fondaparinux is not approved for treating HIT and is contraindicated in patients with thrombocytopenia associated with a positive in vitro test for HIT antibody in the presence of fondaparinux. Limited data exist on its use in HIT.[66,67]

Additional Treatment Considerations

Platelet transfusions should not be used for prophylaxis of bleeding in HIT because they may exacerbate the hypercoagulable state, leading to additional thrombosis.[6] Surgical thromboembolectomy or systemic or local thrombolysis, as adjunctive therapy to alternative parenteral anticoagulation, may be appropriate for selected patients with large-vessel arterial thromboembolism or severe pulmonary embolism, respectively.[68]

Platelet glycoprotein IIb/IIIa inhibitors, which have been used successfully with alternative anticoagulants during PCI,[69,70] reduce thrombin generation indirectly and inhibit platelet aggregation. However, these agents lack direct anticoagulant effects and do not inhibit Fc receptor–mediated activation of platelets by HIT antibody.[68] Hence, glycoprotein IIb/IIIa inhibitors should not be used as a sole therapy for treating HIT.

For patients needing long-term anticoagulation for an underlying medical condition or because of HIT-associated thrombosis, initiation of warfarin must be delayed until adequate alternative parenteral anticoagulation has been provided and platelet counts have recovered substantially (to at least 100×10^9/L or preferably 150×10^9/L).[6] Warfarin should be started at the expected maintenance dose and not at a loading dose. Parenteral anticoagulation should be overlapped with warfarin for minimum of 5 days. When transitioning from a direct thrombin inhibitor, careful monitoring may be needed. Direct thrombin inhibitors prolong the INR,[71] the extent of which depends on the drug and its concentration, the residual vitamin K–dependent protein activity, and the assay reagent.[71,72] Previously established relations with regard to bleeding risk and INRs during warfarin therapy are not fully applicable during direct thrombin inhibition. INRs >5 commonly occur during argatroban therapy and argatroban-warfarin cotherapy in HIT, without bleeding complications. Guidelines for monitoring the transition from lepirudin[47,48] or argatroban[73,74] to oral anticoagulation have been published. The chromogenic factor Xa assay is an alternative means to monitor warfarin during the transition period.[73] Warfarin therapy is appropriate for a

minimum of 3 to 6 months after an episode of HIT-associated thrombosis.[68]

Anticoagulation in patients with a history of HIT

- Cardiovascular surgery
  HIT antibodies negative – use heparin during surgery and administer alternative anticoagulation before and after surgery.

- HIT antibodies positive– if possible surgery should be delayed if not possible administer alternative anticoagulation

- Percutaneous coronary intervention
  Argatroban
  Bivalirudin

Argatroban is the only alternative anticoagulant approved in the United States for use in patients with or at risk for HIT who are undergoing PCI. The safety and efficacy of argatroban in this setting was evaluated in 3 similarly designed, multicenter, prospective studies, and the combined-study data are reported.[75] Overall, 91 patients with HIT or a history of HIT underwent 112 PCIs while receiving intravenous argatroban 25 µg/kg per minute (350-µg/kg initial bolus), adjusted to achieve ACTs of 300 to 450 seconds. Among the 91 patients undergoing their first PCI on argatroban, subjective assessments of the satisfactory outcome of the procedure and adequate anticoagulation during PCI occurred in 94.5% and 97.8%, respectively; 7 (7.7%) patients experienced the composite of death (no patient), myocardial infarction (4 patients), or revascularization (4 patients) within 24 hours of PCI, and 1 (1.1%) patient had periprocedural major bleeding. No unsatisfactory outcomes occurred in 21 patients who underwent repeated PCI on argatroban at a mean of 150 days later. Findings from a multicenter, prospective study evaluating argatroban and glycoprotein IIb/IIIa inhibition therapy in patients undergoing PCI,[69] while not conducted specifically in HIT patients, suggest that a reduced dose of argatroban (perhaps a 300-µg/kg bolus, followed by a 15-µg/kg per minute infusion) provides adequate anticoagulation in combination with glycoprotein IIb/IIIa inhibition during PCI.

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