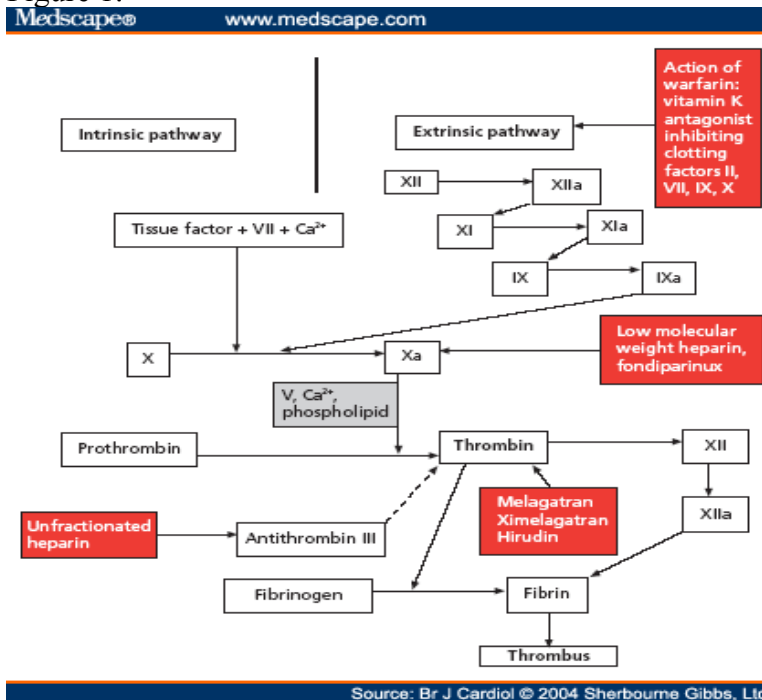


Heparin Induced Thrombocytopenia
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Introduction

Unfractionated heparin is widely used in numerous clinical settings from thromboprophylaxis to treatment of acute coronary syndromes. It has been estimated that 12 million Americans have some exposure to heparin each year. (1) Heparin works by binding to the enzyme inhibitor antithrombin III causing a conformational change which results in its active site being exposed. The activated AT-III then inactivates thrombin and other proteases involved in blood clotting, most notably factor Xa (Fig 1). The rate of inactivation of these proteases by AT-III increases 1000-fold due to the binding of heparin. A well-known adverse event of heparin exposure is thrombocytopenia, which is termed heparin-induced thrombocytopenia (HIT). HIT can be further categorized by type I and type II. Type I is a non immune-mediated syndrome where patients have a transient decrease in platelet count (down to 50% normal) usually without any further symptoms. The syndrome is self-limiting and counts often recover even after heparin is continued. (2) Type II is discussed more commonly as an immune-mediated adverse drug reaction caused by platelet activating IgG antibodies. Activated platelets then release microparticles with prothrombotic activity, potentially leading to fatal thrombotic complications. The clinical understanding of HIT continues to grow in medicine and because of the critical role of hemostasis in surgery, intensive care, and trauma, understanding the event and therapeutic approaches becomes extremely important.

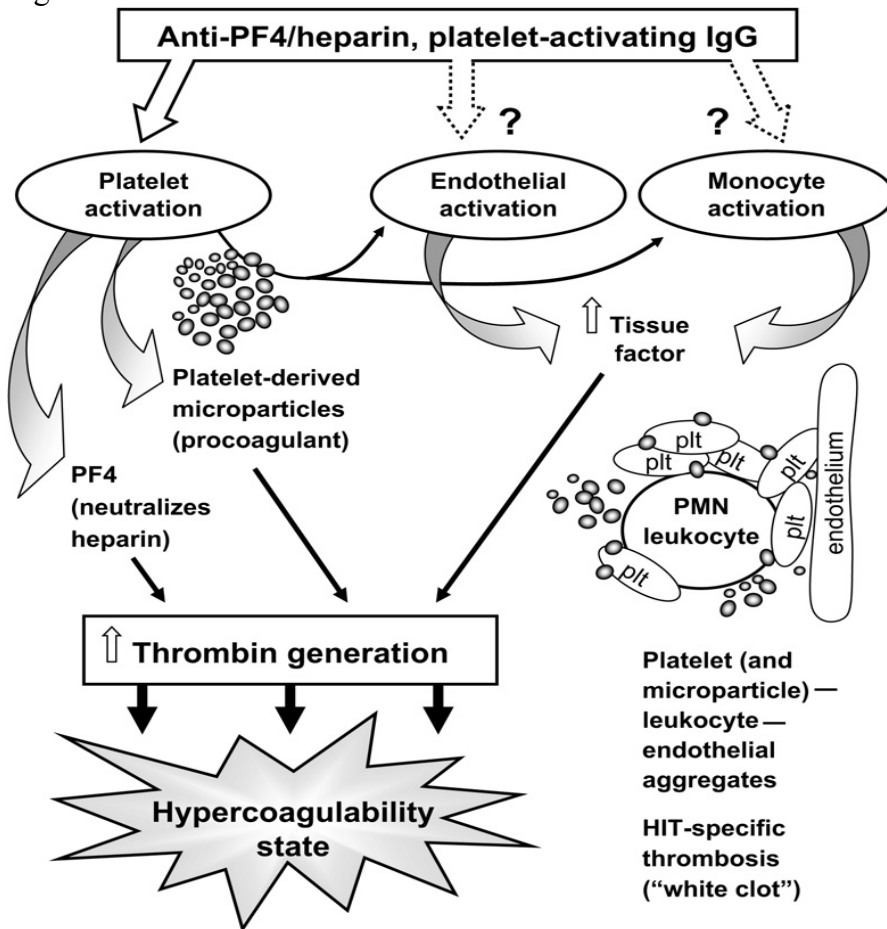
Figure 1:



Pathophysiology

Platelet factor-4 (PF4) is a heparin neutralizing protein contained in the alpha granules of platelet cells. With exposure to heparin, levels of platelet factor-4 increase (3) and the complex of heparin-PF4 may trigger an IgG or IgM antibody response. The heparin-PF4-antibody complex (IgG) then binds to the platelet surface via the Fc portion of the immunoglobulin molecule leading to the activation of the platelet and further releasing PF4 in a positive feedback loop mechanism. (3) Activated platelets also release prothrombotic platelet microparticles (Fig 2) which may lead to potentially fatal thromboses associated with HIT. It is this concept that characterizes the term “white clot syndrome,” as the thromboses in HIT are known to be platelet-rich and occur in arterial locations, rather than fibrin-rich as seen in most venous thromboses. (6) In addition, there is pancellular activation of the endothelium and monocytes which stimulate the release of tissue factor thereby initiating the extrinsic pathway of the coagulation cascade and further worsening thrombosis with thrombin generation. (4) Thrombocytopenia is seen when activated platelets prematurely aggregate and are removed via circulation, which is the most common even described in HIT. (5)

Figure 2:



1) ↑ Venous and/or arterial thrombosis

2) ↑ Risk for warfarin-associated microvascular thrombosis,
e.g., venous limb gangrene

Epidemiology

The reported estimates of the frequency of HIT vary widely with the higher percentages likely representing Type I in addition to Type II HIT. Immune-mediated HIT is suggested to have a frequency of 0.2% to 5% in patients exposed to heparin for more than four days. (7, 8)

The risk of developing HIT is related to many factors, including the type of heparin product administered, route of administration, duration of therapy, patient population, and previous exposure to heparin products. (4) Females carry an odds ratio of 1.5 to 2.0 in their incidence of HIT over male counterparts and surgical patients receiving heparin thromboprophylaxis have an odds ratio of 3.0 to 4.0 over those receiving prophylaxis in a medical setting. (5) A widely discussed risk factor deals with the form of heparin used; naturally occurring unfractionated (UFH) found most commonly in porcine intestine or bovine lung versus the depolymerisation of heparin to create a low molecular weight form (LMWH). Prospective studies have documented an incidence of heparin-induced thrombocytopenia among patients treated with unfractionated heparin was ten times the incidence among those receiving the low molecular weight form. (9) Further, in an analysis from seven prospective studies, the risk of HIT was higher following the use of UFH than LMWH with a relative risk of 5.3 (95% confidence interval of 2.8-9.9). (10) An explanation accounting for such findings may be related to the negative-charge density and length of the heparin compound. Approximately 10-12 saccharide units are required for such compounds to adequately bind to the positively charged platelet factor-4. (4) Although low molecular weight heparins are approximately 15 saccharide units, there is a lower potential (as compared to 40-45 saccharide units on heparin) for interaction with PF4 and subsequent antibody generation. Interestingly, a synthetic pentasaccharide fondaparinux has never been reported with an association to HIT. (4) Although similarly immunogenic as LMWH, fondaparinux does not form well with the antigens on PF4 suggesting a perhaps negligible risk of causing HIT (5).

To better evaluate risk of HIT from UFH and LMWH, a randomized double-blind clinical trial was performed by Warkentin et al and reported in *The New England Journal of Medicine* in 1995. Daily platelet counts were obtained in 665 surgical patients receiving prophylaxis against venous thrombosis with either UFH (porcine intestinal mucosal derivative) or LMWH (Lovenox in mentioned study). Heparin-dependent IgG antibodies were used to confirm the diagnosis of HIT in those who had thrombocytopenia after receiving heparin for at least five days. 387 additional patients were tested for IgG antibodies regardless of their platelet count. Clinical outcomes of deep vein thrombosis, pulmonary embolism, hemorrhage, and incidence of thrombocytopenia with and without IgG antibodies were recorded and interpreted. 12 out of 665 total patients had evidence of late (six days or greater after receiving study drug) thrombocytopenia after receiving either UFH or LMWH. All 12 had tests for heparin-dependent IgG antibodies, nine of whom had tested positive. All nine of these patients had received unfractionated heparin thereby accounting for 2.7% of the 332 patients in one arm of the study (95% confidence interval 1.3 to 5.1). By contrast, none of the 333 patients receiving LMWH had HIT (95% confidence interval 0 to 1.1) with a P value =0.0018 suggesting statistical significance. Figure 3 illustrates another endpoint in calculating the incidence of thrombosis in the nine patients diagnosed with HIT. Eight of the nine patients with HIT

went on to receive thrombotic complications. Seven had deep-venous thrombosis, five of which were proximal in nature. One patient had an arterial thrombosis in the mesenteric artery. Platelet counts varied at the time of diagnosis of thrombosis from 20,000 per cubic millimeter to 355,000 per cubic millimeter; however, in all patients the platelet count had begun to fall before the onset of thrombosis or at the same time.

Figure 3: Clinical and Laboratory Findings in Nine Patients with Heparin-Induced Thrombocytopenia after Hip Surgery

LOWEST PLATELET COUNT	FIRST HEPARIN-DEPENDENT IgG ANTIBODIES	FIRST DECREASE IN PLATELET COUNT	FIRST PLATELET COUNT BELOW 150,000/mm ³	OCCURRENCE OF THROMBOSIS	PLATELET COUNT ON DAY OF THROMBOSIS	LOCATION AND TYPE OF THROMBOSIS
<i>per mm³</i>		<i>postoperative day</i>			<i>per mm³</i>	
18,000	≤9†	6	6	10	20,000	Proximal lower-limb deep venous thrombosis
22,000	7	7	9	7	228,000‡	Bilateral proximal lower-limb deep venous thrombosis
				9	36,000	Pulmonary embolism
28,000	5	5	6	—	—	No thrombosis
34,000	7	7	8	11	34,000	Distal lower-limb deep venous thrombosis
				17	77,000	Pulmonary embolism
75,000	6	7	9	8	172,000§	Bowel infarction due to pathologically confirmed mesenteric-artery thrombosis
79,000	≤13†	6	8	8	140,000	Bilateral proximal lower-limb deep venous thrombosis
90,000	≤12†	7	9	13	106,000	Proximal lower-limb deep venous thrombosis
102,000	7	8	13	9	355,000¶	Distal lower-limb deep venous thrombosis
133,000	7	9	10	12	133,000	Bilateral lower-limb deep venous thrombosis (one proximal, one distal)

*All nine patients had received unfractionated heparin. Deep venous thrombi were confirmed by contrast venography, and pulmonary emboli were confirmed by high-probability ventilation-perfusion lung scans.

†Serial plasma samples were not available with which to determine the day of seroconversion, because this patient was not part of the 387-patient subgroup from which serial samples were obtained.

‡The first thrombosis in this patient occurred after seroconversion to heparin-dependent IgG antibodies and was associated with a decrease in the platelet count from 319,000 per cubic millimeter (on day 6) to 228,000 per cubic millimeter (on day 7); the second thrombosis (the pulmonary embolism) occurred when the platelet count was 36,000 per cubic millimeter.

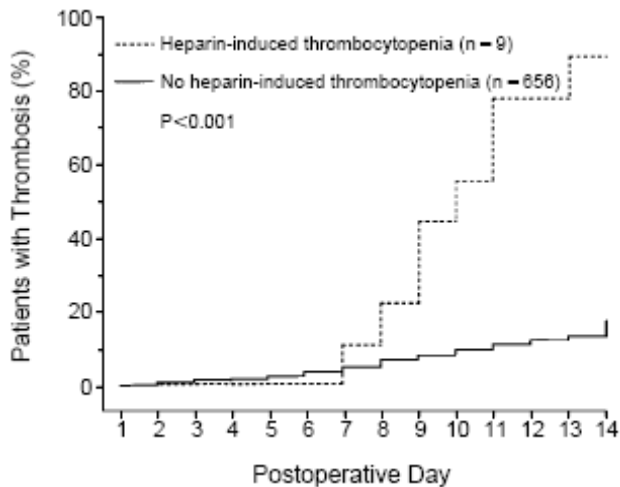
§The mesenteric-artery thrombosis is presumed to have occurred on postoperative day 8 (the day of onset of abdominal pain) but was confirmed at laparotomy on day 10. The thrombosis occurred after seroconversion to heparin-dependent IgG antibodies and was associated with a decrease in the platelet count from 401,000 per cubic millimeter (on day 6) to 172,000 per cubic millimeter (on day 8).

¶The thrombosis occurred after seroconversion to heparin-dependent IgG antibodies and was associated with a decrease in the platelet count from 570,000 per cubic millimeter (on day 7) to 355,000 per cubic millimeter (on day 9).

Other comparisons were done to evaluate the incidence of thrombosis in those with HIT (n=9) to those without (n=656) as seen in Figure 4. Heparin-induced thrombocytopenia was found to be strongly associated with thrombotic events, particularly DVT and PE, with an odds ratio of 36.9 (95% CI 4.8 to 1638, P=<0.001).

Other endpoints involved the detection of IgG antibodies by testing 387 control patients regardless of platelet count. 20 patients were found to be positive for heparin-dependent antibodies. Not all 20 patients went on to receive late thrombocytopenia (HIT) though there was a strong association with its development with an odds ratio of 78.2 (95% CI 12.0 to 818.8, P=<0.001). Interestingly, there was also a higher frequency of IgG antibody development in those who received unfractionated heparin than in those who received low molecular weight heparin; 16/205 in UFH and 4/182 in LMWH respectively (P=0.02). Further subgroup analysis showed the incidence of thrombosis was higher in patients who were IgG positive with normal platelet counts when compared to those who did not seroconvert however the results were not statistically significant with P=0.72. Conclusions from this study found that patients treated with unfractionated heparin had a higher frequency of HIT and formation of heparin-dependent IgG antibodies than those who were treated with LMWH. HIT was also found to be a risk factor for thrombotic complications, including venous thrombosis.

Figure 4: Cumulative Frequency of Thrombosis in Patients with HIT and Patients without HIT



Clinicopathologic Syndrome

HIT is termed a clinicopathologic syndrome because its diagnosis requires clinical signs and symptoms with pathologic confirmation using established laboratory tests. Patients with isolated HIT usually present with thrombocytopenia typically defined as a 50% decrease in the platelet count with a median platelet count of $40-60 \times 10^3/\text{mm}^3$. (4) Three patterns for the onset of thrombocytopenia in relation to heparin exposure are described. The most common pattern, termed typical onset HIT, is a decrease in the platelet count occurring 4-10 days after initial exposure. The second pattern, termed delayed-onset HIT, occurs a mean of nine days after heparin is stopped but may occur up to 40 days afterwards. For this reason patients who experience an acute thrombotic event within 40 days of heparin based products should have a platelet count checked to determine if delayed-onset HIT may be present. The third pattern is rapid-onset HIT, occurring in patients with a recent history of heparin exposure (with retained IgG antibodies) who are then re-exposed. Symptoms may be severe and result in tachycardia, fever, hypertension and cardiac arrest. (4) Antibodies due to heparin exposure may continue to persist to explain this phenomenon for up to three months. (11)

The incidence of thrombosis in HIT is reported as high as 30-50% of patients. (9, 12) Retrospective analysis in humans indicates that thrombosis associated with HIT is usually inversely related to the platelet count. That is, the lower the platelet count, the higher the risk of thrombosis. (4, 9) Thrombosis may present in the venous or arterial circulation with venous thrombosis (deep vein thrombosis, pulmonary embolism) being the most common sequela. (5) A review of sites of thrombosis in 127 serologically confirmed HIT patients was published in the *American Journal of Medicine* in 1996 by Warkentin et al. An incidence ratio of venous to arterial sites of 4:1 was seen with pulmonary embolism being the most common life-threatening event and occurring in 25% of patients. (12) Arterial thrombosis associated with HIT most likely occurs at sites of vascular damage, thus explaining a higher incidence in post cardiac surgery patients. (1)

Diagnosis

Establishing a diagnosis of HIT in patients with complicated medical conditions can be very challenging as there are many etiologies of thrombocytopenia from infections to bone marrow diseases. Furthermore, the discontinuation of heparin based therapy can be quite detrimental in many clinical situations.

In evaluating a patient for possible HIT, a clinical scoring system may be of help. One system often referred to as 4 Ts is used for estimating the pretest probability of HIT. Points are assigned for severity of **T**hrombocytopenia, its **T**iming, the presence of **T**hrombosis (or other sequela of HIT), and whether **O**ther explanations could account for the thrombocytopenia or thrombosis so termed pseudo-HIT. (5,4) Pseudo-HIT may include sepsis, cancer, and effects of chemotherapy. Clinical scoring may be seen in Figure 5. A low score (≤ 3 points) makes HIT unlikely ($< 2\%$) whereas a high score (≥ 6 points) suggests the patient is likely to test positive for heparin antibodies. (5, 1) An intermediate score of 4-5 suggests a 10-30% incidence of HIT and further laboratory testing would be required.

Figure 5: Estimating the pretest probability of heparin-induced thrombocytopenia: the “4 T’s” scoring system

Date:	Points (0, 1, or 2 for each of 4 categories: maximum possible score = 8)		
	2	1	0
Thrombocytopenia score = _____	>50% platelet decrease to nadir $\geq 20 \times 10^9/L$	30%–50% platelet count decrease (or >50% directly resulting from surgery) or nadir $10\text{--}19 \times 10^9/L$	<30% platelet decrease or nadir $<10 \times 10^9/L$
Timing ^a of platelet count decrease, thrombosis, or other sequelae (first day of heparin course = day 0) Score = _____	Day 5–10 onset ^a or ≤ 1 day (with recent heparin exposure within past 5–30 days)	Consistent with day 5–10 decrease, but not clear (eg, missing platelet counts), or ≤ 1 day (heparin exposure within past 31–100 days), or platelet decrease after day 10	Platelet count decrease ≤ 4 days without recent heparin exposure
Thrombosis (including adrenal infarction) or other sequelae (eg, skin lesions) Score = _____	Proven new thrombosis, or skin necrosis (at injection site), or post-IV heparin bolus anaphylactoid reaction	Progressive or recurrent thrombosis, or erythematous skin lesions (at injection sites), or suspected thrombosis (not proven)	None
Other cause for thrombocytopenia Score = _____	No explanation for platelet count decrease is evident	Possible other cause is evident	Definite other cause is present
Total score = _____	Pretest probability score: 6–8 = high; 4–5 = intermediate; 0–3 = low		
Changes to score can occur, based upon new information (eg, further decrease in platelets, new thrombosis, other causes for platelet decrease). The scoring system shown has undergone minor modifications from previous publications. Abbreviation: IV, intravenous. ^a First day of immunizing heparin exposure considered day 0; the day the platelet count begins to decrease is considered the day of onset of thrombocytopenia (it generally takes 1 to 3 more days until an arbitrary threshold that defines thrombocytopenia is passed. Usually, heparin administered at or near surgery is the most immunizing situation).			

Clinical suspicion of HIT must be confirmed with laboratory testing, though a gold standard test does not currently exist. Two complimentary ways to detect HIT antibodies are platelet activation assays and PF4-dependent immunoassays. (5) Platelet activation assays, or functional assays, include the serotonin-release assay (SRA) where 14-C serotonin is radiolabeled on normal platelet donors and later mixed with patient serum and differing doses of heparin concentration. If HIT antibodies are present, platelet activation will later ensue thus causing the release of serotonin and platelet aggregation. This mechanism can be technically demanding and relies on experienced laboratories. Results are reported as positive or negative, positive indicating the release of serotonin at therapeutic concentrations of heparin rather than high concentrations. Sensitivity approaches 88-100% with specificity of 89-100% and is often used in conjunction with immunoassays. (9) Immunoassays are able to detect IgG, IgM, and IgA antibodies thus accounting for their lower specificity of 74-86%. (9) In addition, enzyme-linked

immunosorbent assays (ELISA) detect PF4-heparin antibodies in patients who do not have heparin-induced thrombocytopenia thereby lowering the positive predictive value. PF4-dependent enzyme immunoassays approach a sensitivity of near 99% and thereby compliment functional assays in clinical practice. (5) Results of serologic and functional assays must be interpreted in the appropriate clinical context of pretest probability. A negative ELISA essentially rules out the diagnosis of HIT however when a positive ELISA is obtained especially in a low probability setting, referral to a laboratory that performs a high-quality platelet activation assay can be useful. (5) A proposed diagnostic algorithm taken from *The New England Journal of Medicine* in 2006 for patients in whom HIT is suspected is illustrated in Figure 6. (9) Other methods, such as flow cytometry, particle agglutination, rapid antigen assays, and monoclonal ELISA designed to detect immunoglobulin G antibodies are currently under development. (4)

Figure 6: Diagnostic Algorithm to Confirm or Rule Out HIT

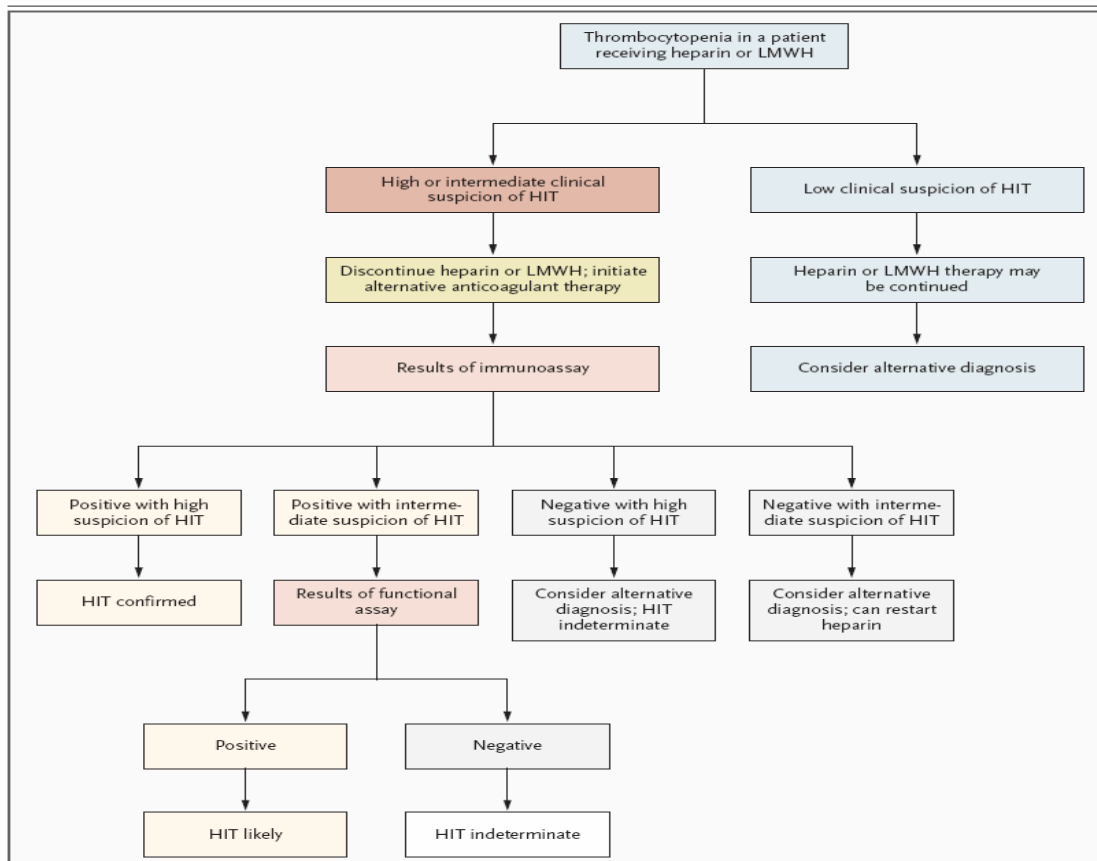


Figure 1. Diagnostic Algorithm to Confirm or Rule Out Heparin-Induced Thrombocytopenia (HIT) in Patients Who Have Not Undergone Bypass Surgery.

Thrombocytopenia can be absolute (platelet count, <150,000 per cubic millimeter) or relative (defined as a decrease in the platelet count of >50 percent from the highest level before the initiation of heparin therapy). The clinical index of suspicion should be based on a temporal association between the start of heparin therapy and the development of thrombocytopenia (typically beginning 5 to 10 days after the start of heparin) or a new thrombosis; the exclusion of other causes of thrombocytopenia (e.g., drugs other than heparin, disseminated intravascular coagulopathy or other consumptive processes, post-transfusion purpura); rebound in the platelet count on discontinuation of heparin; or some combination of these criteria. On the basis of the criteria, the suspicion could be assessed as high when all three criteria are met, intermediate when one or two are met, and low when none are met. Alternatively, the clinical risk can be assessed according to scores based on other criteria.^{30,32} The decision to initiate alternative anticoagulant therapy should be guided by assessment of the patient's bleeding risk and coexisting conditions. The decision to continue unfractionated heparin or low-molecular-weight heparin (LMWH) should be tailored to the patient. A functional assay is recommended, where clinically available. Antibodies not specific to PF4-heparin may cause HIT.³³ The decision to continue alternative anticoagulant therapy should be individualized.

Treatment

Strong clinical suspicion warrants the discontinuation of all forms heparin including low molecular weight forms, given the cross-reactivity with circulating PF4-heparin antibodies. (9) Although a review of the medication profile is generally preformed, two often over-looked sources for continued exposure are through heparinized catheters and heparin lock flushes. (1) The discontinuation of heparin is not sufficient in the overall management of HIT. Given the strong association of thrombosis with HIT, attempts should be taken to reduce the risk by reducing platelet activation and thrombin generation. (9) A retrospective analysis conducted by Warkentin *et al* and published in 1996 reviewed documented thrombotic events that complicated the course of 127 patients with serologically confirmed heparin-induced thrombocytopenia in one medical community over a 14-year period. (12) Two cohorts were made based on incidence of thrombosis. The cohort designated isolated HIT (without evidence of thrombosis upon diagnosis) consisted of 62 patients. This group was studied for its subsequent 30-day risk of thrombosis and found to be 52.8%. It is this concern that encourages anticoagulation in the population with isolated HIT in addition to those who have HITT (thrombosis upon diagnosis of HIT). Anticoagulation can be accomplished with one of two classes of non-heparin anticoagulants, direct thrombin inhibitors and anti-factor Xa agents. (9) Three direct thrombin inhibitors (DTIs) are currently available for patients diagnosed with heparin-induced thrombocytopenia: lepirudin (Refludan®), argatroban, and bivalirudin (Angiomax). (9) These agents bind directly to and inactivate thrombin but unlike heparin, do not require the presence of antithrombin (Fig 1). Efficacy of lepirudin and argatroban have not been studied in large randomized trials due to the heterogeneity of patients with HIT and the relatively low incidence of the syndrome, however prospective cohort studies using historical controls have been conducted. (1)

Lepirudin is a recombinant analogue of hirudin, a leech protein, that binds irreversibly to thrombin and is cleared renally. It has been studied in three prospective cohort studies for therapy of HIT. (9, 1) These studies are referred to as the HAT 1, 2, and 3 trials. Lepirudin was examined in a total 403 patients against 120 historical controls. Enrolled patients had positive HIT-IgG antibodies with a diagnostic decrease in platelet count. Bolus and infusional lepirudin was adjusted to the diagnosis of HIT or HITT and various other clinical criteria including need for thrombolysis. The aPTT was maintained 1.5 to 3.0 times the baseline value. Endpoints included death, limb amputation, new thromboembolic complications, and bleeding rates. A summary analysis of the three HAT trials is found in Figure 7. (1) The rates of death, amputation, and thrombosis were lower among those receiving lepirudin than among the historical controls. A statistical significance was seen only for prevention of new thromboembolic complications (TEC) and only when patients were combined from all three studies with a P-value of <0.001. Though statistical significance was seen only in the TEC subgroup, it has been suggested that the prevention of new TEC represents the true efficacy of DTIs. (1) Grouping death, amputation, and TEC into one composite endpoint (from all 3 studies) did reveal a significant reduction in patients treated with lepirudin, 27% compared to 44.2% with a P-value of <0.001. The results comparing major bleeding in treated patients to historical controls is seen in Figure 8. (1) Major bleeding was defined as fatal or life-threatening, intracranial, permanently or significantly disabling, requiring surgical intervention, or

overt bleeding requiring transfusion of >2 units of red blood cells. (1) Not surprisingly, these rates were significantly higher in the population treated with lepirudin with a P-value of 0.0015. This highlights the difficulty of maintaining anticoagulation in a patient population with thrombocytopenia and a hypercoagulable state. Antibodies to lepirudin develop in approximately 30% of patients after initial exposure and in about 70% of patients after re-exposure. Because fatal anaphylaxis has been reported after sensitization in addition to its renal clearance and bleeding complications in those with renal insufficiency, lepirudin is not considered an ideal agent for treatment. If given, patients should not be treated with this agent more than once. (9)

Figure 7: Individual Endpoints from Studies Evaluating Lepirudin and Argatroban for the Treatment of HIT and HITT

Study	Death (%)			Amputation (%)			New TEC (%)		
	Treated Patients	Historical Controls	P Value	Treated Patients	Historical Controls	P Value	Treated Patients	Historical Controls	P Value
<i>Lepirudin</i>									
HAT-1 ⁵⁴	8.6	22.3	0.071	5.7	8.2	0.783	18.4	32.1	0.27
HAT-2 ⁵⁵	10.5	22.3	0.21	10	8.2	0.43	17.4	32.1	0.26
HAT-3 ⁵⁶	14.6	17.5	—	5.9	8.2	—	5.4	32.1	—
HAT 1-3 ⁵⁶	11.7	17.5	0.095	6.5	6.7	0.933	13.9	30.8	<0.0001
<i>Argatroban</i>									
Argatroban-911 (HIT) ⁵⁸	16.9	21.8	0.31	1.9	2	1	8.1	22.4	<0.001
Argatroban-911 (HITT) ⁵⁸	18.1	28.3	0.15	11.1	8.7	0.79	19.4	34.8	0.044
Argatroban-915 (HIT) ⁵⁷	19	20.9	0.78	4.2	2.9	0.57	5.8	23	<0.001
Argatroban-915 (HITT) ⁵⁷	23.1	28.3	0.45	14.8	10.9	0.664	13.1	34.8	<0.001

TEC, thromboembolic complications; HIT, heparin-induced thrombocytopenia; HITT, heparin-induced thrombocytopenia with thrombosis.

Figure 8: Summary of Composite Endpoints from Studies Evaluating Lepirudin and Argatroban for the Treatment of HIT and HITT

Study	Composite Endpoint (%)			RRR	Major Bleeding (%)		
	Treated Patients	Historical Controls	P Value		Treated Patients	Historical Controls	P Value
Lepirudin, HAT 1-3 ⁵⁶	27	44.2	0.0001	0.39	17.6	5.8	0.0015
Argatroban-911 (HIT) ⁵⁸	25.6	38.8	0.014	0.34	3.1	8.2	0.078
Argatroban-911 (HITT) ⁵⁸	43.8	56.5	0.131	0.23	11.1	2.2	0.077
Argatroban-915 (HIT) ⁵⁷	28	38.8	0.04	0.28	5.3	8.6	0.27
Argatroban-915 (HITT) ⁵⁷	41.5	56.5	0.07	0.27	6.1	2.2	0.48

RRR, relative risk reduction; HIT, heparin-induced thrombocytopenia; HITT, heparin-induced thrombocytopenia with thrombosis.

Argatroban is a small synthetic compound that binds reversibly to the catalytic site of the thrombin molecule. (9) It notably differs from lepirudin by its hepatic clearance and increased potency. (9, 4) Its small size is thought to aid in the binding and inhibition of both clot-bound and soluble thrombin. (4) Argatroban has been studied in two prospective multicenter studies involving a total of 722 patients with HIT named Argatroban-911 and Argatroban-915. (1) Patients were enrolled with diagnostic thrombocytopenia without other explanation for HIT. HIT-IgG antibodies, however, were not reported. Arms were created for those with or without evidence of thrombosis at the time of enrollment. Argatroban infusion was titrated to an aPTT of 1.5 to 3.0 times baseline. Endpoints included death, limb amputation, new thromboembolic

complications, and bleeding rates. A summary analysis of the two trials is found in Figure 7. Again, the rates of death, amputation, and thrombosis were lower among those receiving argatroban than among the historical controls. Statistical significance was seen only in incidence of new TEC with P-values of <0.05 in both studies under each arm. (1) Grouping of the three endpoints together into one composite endpoint did not show a statistically significant reduction in those with HIT as compared to historical controls as seen in Figure 8. While there was a trend toward a lower composite endpoint in each arm of both studies, significance was only achieved in the HIT arm of each study. In addition, although not statistically significant, Figure 8 illustrates that the rates of major bleeding were not greater in the population treated with argatroban versus control. Unlike lepirudin, antibodies to argatroban have not been reported. (9) This, along with its hepatic clearance, makes argatroban a more suitable treatment option in clinical practice. Bivalirudin is another synthetic direct thrombin inhibitor and is 20 amino acids in length. (9, 4) Its binding to thrombin is similar to that of lepirudin though its size and half-life are significantly shorter. (4) Proteases in the blood clear bivalirudin drug by 80% and the remaining is cleared renally. (4) Studies with bivalirudin are scant and many have described its use during percutaneous coronary interventions as case studies and retrospective case series. Investigations are underway with the use of this drug in those undergoing cardiopulmonary bypass given its favorable pharmacokinetic profile. (9) Bivalirudin is currently approved by the FDA for percutaneous coronary intervention in patients who have or are at risk for HIT. (9)

Other therapies to direct thrombin inhibitors include those with anti-factor Xa activity. Danaparoid is a mixture of heparan sulfate and dermatan sulfate and in a similar mechanism to heparin, catalyzes the inhibition of factor Xa through antithrombin III. Danaparoid has fewer sulfated groups than unfractionated heparin therefore with reduced negative charge and subsequent decreased binding to other plasma proteins. (4) Danaparoid is the only agent studied in a randomized clinical trial in patients with HIT as compared to Dextran, an agent used widely before DTIs became available. (9) 25 patients were assigned to warfarin plus danaparoid and 17 to warfarin plus dextran sulfate for 72 hours. On the basis of clinical assessments, the resolution of thrombosis (without follow-up imaging) was superior in the danaparoid arm. (9) In another review of danaparoid, 1418 patients were studied retrospectively who received the drug. A recently published summary of these cases revealed new thromboses occurred during 9.7% of the treatment episodes and serious bleeding occurred in 8.1% of the patients, results not unlike those seen with direct thrombin inhibitors. (9, 4) A drawback of danaparoid is its low potential for immunologic cross-reactivity with heparin induced antibodies. (4) When used in HIT patients, the presence of antibodies did not appear to influence recovery of the platelet count. (4) In 2002, danaparoid was removed from the market voluntarily, however it is still available in Canada, Europe, and Australia. The removal of danaparoid corresponded to the 2002 release of fondaparinux and was marketed by the same manufacturer with similar indications as danaparoid. (4)

Fondaparinux is the active pentasaccharide of heparin, demonstrating anti-factor Xa activity. Its absence of additional sulfated chains results in an inability to alter platelet factor-4 for an interaction with IgG antibodies. (4) Published reports of the use of fondaparinux for the treatment of HIT are limited to case reports and abstracts. (4) Although promising for the treatment and management of HIT, this drug has not been

approved by the FDA with this indication. Important considerations for its use are its long half-life, renal elimination, and the lack of an antidote. (13)

Clinical Considerations

Many clinical correlates should be addressed when approaching the care of a patient with HIT including duration of acute therapy, the switch to oral anticoagulation, and the role of re-exposure of heparin in this population. The optimal duration of therapy is unknown, especially for those who have isolated HIT. Some patients receive anticoagulation for up to 30 days out of concern for delayed-onset HIT and continued risk of thrombosis (4). Anticoagulation is generally given and recommended for isolated HIT patients until the platelet counts recover to a stable plateau, if not to baseline values. (9) Consideration for anticoagulation past this mark with an oral anticoagulant should be undertaken by the clinician. For patients with heparin-induced thrombocytopenia and thrombosis, more standard regimens of anticoagulation apply. Patients are generally initiated on warfarin for long-term anticoagulation with a target INR of 2-3 after platelet counts have notably recovered. (4) There is considerable concern initiating warfarin in those with HIT due to its disturbance with the natural anticoagulant protein C.

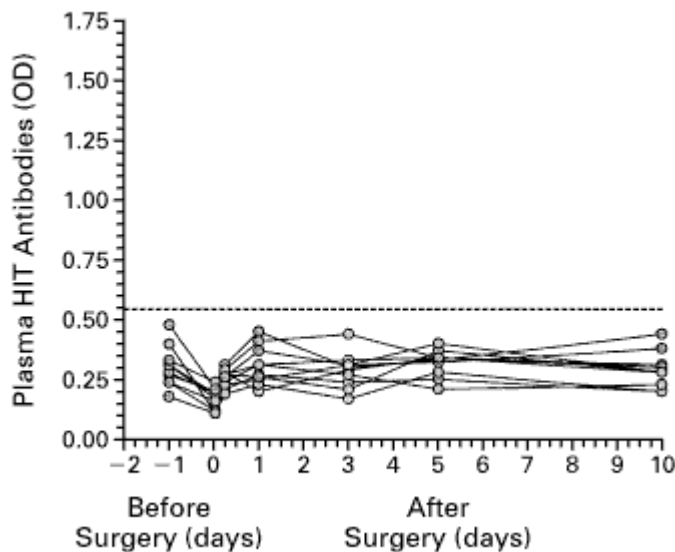
Microthrombosis due to depletion of the vitamin K-dependent protein C, especially in the setting of increased thrombin generation, may lead to warfarin necrosis commonly manifesting as venous limb gangrene. (5) Venous limb gangrene is characterized by an underlying hypercoagulable state, necrosis in a distal extremity affected by a DVT, and a supratherapeutic INR (usually greater than 3.5) representing severe depletion in protein C. (5) The overall risk for warfarin necrosis in the HIT population is 5% to 10% which is significantly greater than the incidence who do not have HIT (0.01%). (5) For this reason, it is advised that if a diagnosis of HIT is made after warfarin has been started, reversal with vitamin K should be given. (5) The overlap of direct thrombin inhibitor therapy with warfarin should also be addressed carefully. In addition to starting a low dose of anticoagulant after a notable rise in platelets (preferably to 150,000 per cubic millimeter), a minimum of five days of overlap is suggested. (9, 4) Management of the overlap may be confusing in a clinical setting because direct thrombin inhibitors variably prolong the prothrombin time and INR. It is best to follow manufacturer's guidelines for monitoring INR during overlap therapy. (9)

Question regarding the use of future heparin in a patient with a history of HIT remains an important issue. Unlike the duration of the response to most drug-dependent antibodies, the immune-response from heparin appears to be transient in nature with antibodies disappearing from the circulation in a median of 85 days. (9) Further, there is no evidence to suggest that a patient who had HIT previously is more likely to form strong levels of HIT antibodies upon re-exposure to heparin. (15) Even yet, until rigorous data are collected, patients with a history of HIT should receive alternative forms of anticoagulation for most indications. (9) For certain important procedures such as cardiac bypass or vascular surgery, direct thrombin inhibitors pose a considerable bleeding risk. For this reason, in this population the use of heparin is recommended during the procedure provided that heparin-dependent antibodies are no longer detectable and sufficient time has passed from the diagnosis of HIT (>2-3 months). (9, 5)

Postoperatively, if required, an alternative anticoagulant is preferred. (9) This approach is based on the theory that a secondary immune response after re-exposure to heparin

should not occur until at least three days after the start of the drug. This concept was tried in ten patients who required cardiopulmonary bypass and published in *The New England Journal of Medicine* in 2000 by Potzsch et al. (14) All patients had a history of acute heparin-induced thrombocytopenia with detectable HIT antibodies at the time of diagnosis. At the time of surgery, all patients were negative according to an antigenic assay. The anticoagulation related to cardiopulmonary bypass used unfractionated heparin at a dose of 400 U per kilogram of body weight. All ten surgeries were performed without adverse complications and none of the patients had prolonged thrombocytopenia afterwards. As shown in Figure 9, there was not an increase in the serum concentrations of HIT antibodies during a follow-up period of ten days. This suggests that a secondary response to heparin was not induced by the heparin given during the surgery itself.

Figure 9: Response of Heparin Induced Thrombocytopenia (HIT) Antibodies to Secondary Heparin Challenge during Cardiopulmonary Bypass



The conclusion from the article showed that patients who are antibody-negative with a history of heparin-induced thrombocytopenia who undergo cardiopulmonary bypass should indeed be treated according to established heparin protocols. Once again, the use of heparin is to be restricted to the operative period and if indicated, alternative agents should be used postoperatively.

As mentioned previously, low molecular weight heparins carry a lower risk of causing heparin-induced thrombocytopenia. This suggests that preferential use of LMWH over UFH would lower the incidence of HIT, however, it is uncertain whether the data obtained from surgical patients receiving heparin can be accurately extrapolated to medicine patients who receive heparin for prophylaxis. Other attempts to prevent HIT include the regular monitoring (every other day) of platelet counts while on heparin therapy beyond four days. (5) In those who carry a lower risk of HIT (medical patients receiving UFH prophylaxis), monitoring of platelet counts may be done twice or thrice weekly and in those whom the risk is considered low (medical patients receiving LMWH) monitoring of the platelet counts is not recommended as routine screening for

HIT. (5) In general, the best way to prevent HIT is the judicious use of unfractionated heparin. Limiting heparin duration to less than five days and starting warfarin earlier for those who require long-term anticoagulation for certain medical conditions are also important strategies to consider.

Conclusion

HIT is a clinicopathologic syndrome that can be associated with severe complications and even death. Patients who present with thrombocytopenia and thrombosis while receiving heparin should be evaluated for HIT with a careful review of the time of heparin exposure in relation to the onset of thrombocytopenia. Once HIT is recognized, all heparin products should be discontinued and alternate anticoagulant therapy usually that of a direct thrombin inhibitor should be initiated to reduce the risk of thromboembolic complications. Laboratory confirmation should not delay treatment when a strong clinical suspicion exists. Patients with isolated HIT require alternate anticoagulant therapy at least until platelet counts recover whereas those with HITT will need to be transitioned to long-term anticoagulant therapy under careful monitoring to avoid complications of venous limb gangrene. There are current limitations in definitive duration of therapy along with the role of a secondary immune response upon re-exposure to heparin. Further studies need to be established to help answer these remaining clinical questions.

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