

## Lower Extremity Manifestations and Treatment of Heparin-Induced Thrombocytopenia Syndromes: A Cohort Study

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### ABSTRACT

Heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia with thrombosis (HITT) syndromes are the result of an adverse reaction to heparin that results in a spectrum of laboratory and end-organ manifestations secondary to thrombosis of both arterial and venous small and large vessels. HITT most often manifests in the extremities as acral ischemia and necrosis, with a spectrum of severity. The lower extremity surgical patient is at risk for deep venous thrombosis, and when exposed to heparin products, is also at risk for the development of a heparin-induced thrombocytopenic syndrome. This article reports on a cohort of patients from a tertiary referral lower extremity reconstruction practice with the HIT/HITT syndromes, with an analysis of the frequency, medical characteristics, clinical settings, lower extremity manifestations, management, and outcomes of patients with HIT/HITT.)

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Prophylaxis of deep venous thrombosis (DVT) and the major sequelae of venous thromboembolism (VTE) has become a standard of care for patients who are at risk for lower extremity DVTs. The patient populations considered to be at risk for DVT include trauma patients, patients who have undergone elective lower extremity musculoskeletal surgery, and those who are otherwise bedridden. A special subset of patients prone to the development of DVT includes patients who have inherited procoagulant states and acquired hypercoagulable states (Table 1). In these patients, methods for DVT prophylaxis generally fall into 2 classes: pharmacologic and mechanical. Mechanical prophylaxis is considered a baseline measure, most suitable as a stand-alone for those patients who have considerable mobility (ambulatory) and have not had an injury or surgical procedure that places them at risk for a DVT (eg, major joint arthroplasty or trauma). Those patients who have incurred trauma, have undergone major musculoskeletal surgery, are bedridden, or have undergone minor procedure but are at high risk because of an inherited or acquired procoagulant state, pharmacologic prophylaxis is added to mechanical measures. In certain settings, such as musculoskeletal oncology patients with pathologic lower extremity fractures who are unable to receive pharmacologic prophylaxis, mechanical prophylaxis

may not suffice to prevent DVT and VTE. In these patients, vena cava filters should be implemented (1). In the setting of an acute DVT or DVT with VTE, the initial clinical management begins with anticoagulation via the administration of either unfractionated heparin (UFH) or a low molecular weight heparin (LMWH) product. By the nature of the work of the lower extremity surgeon (trauma and large reconstructions that may require periods of immobility and bed rest, provision of amputation services, and so forth) we often participate in both primary surgical or consultative care of patients who are at risk for the development of a DVT/VTE event. As such, these at-risk patients often require the administration of heparin products. Exposure to heparin products, whether for prophylaxis or treatment, carries the inherent risk of an adverse reaction to heparin products, termed the heparin-induced thrombocytopenia syndromes. These syndromes stem from a complex pathophysiologic process resulting in a derangement of platelet (PLT) function and hemostasis. The clinical manifestations of these syndromes range from a simple drop in platelet counts (HIT), to the development of systemic thrombosis (HITT), with resultant organ system dysfunction, and even death. This article analyzes a cohort of patients with HIT/HITT syndrome, their demographics, clinical manifestations and settings, and treatments, as well as ultimate clinical outcomes.

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### Materials and Methods

Institutional review board approval was obtained for this study. A patient database retrieval of the medical records from patients treated by the lead author (C.B.) at a tertiary medical center over a 10-year period was searched for thrombocytopenia via ICD-9 codes. Subsequently, the medical histories, laboratory data, and consultation and

**Table 1**  
Acquired and inherited hypercoagulable states

Factor V Leiden mutation
Hyperhomocysteinemia
Prothrombin G 20210-A mutation
Protein S deficiency
Protein C deficiency and resistance to activated form
Antiphospholipid antibody syndrome
Antithrombin III deficiency (inherited and acquired)
Metastatic cancer
Chronic congestive heart failure
Disorders affecting endothelial cell function (eg, Behcets, Kawasaki's)
Dysfibrinogemias with rapid release of fibrinopeptides
Pharmacologic agents (eg, oral contraceptives, Tamoxifen)
Trauma
Immobilization, prolonged bed rest

operative reports were further reviewed in detail to determine the cause of thrombocytopenia and for confirmation of the diagnosis of HIT/HITT. Patient demographics, medical comorbidities, the clinical settings in which the diagnosis of HIT occurred, lower extremity manifestations, along with the medical/surgical treatments and outcomes were analyzed.

## Results

Over a 10-year period in the lead author's practice, among 5486 documented hospital patient encounters, 48 patients were identified with thrombocytopenia. Of these 48 patients, a detailed analysis of the medical record revealed that in 32 patients (67%), thrombocytopenia was attributable to causes other than exposure to heparin (Table 2). The remaining 16 patients (33%) were identified as having exposure to heparin with the subsequent development of thrombocytopenia (HIT). HIT was diagnosed by a drop in PLT by 20% from baseline values, and confirmed by PF4 immunoassay (ELISA), or a surrogate functional test (14C-serotonin release assay) (vide infra). Among these 16 patients with heparin exposure and thrombocytopenia, 6 patients were exposed to LMWH, 9 patients were exposed to UFH, and 1 patient to both (treatment overlap). The mean patient age of thrombocytopenia after heparin exposure was 57 years (range = 36–84 years), with a gender distribution of 7 females and 9 males (56% male). The reasons for heparin exposure included both routine DVT prophylaxis, as well as the treatment of acute DVT, occurring in a variety of clinical settings (Table 3).

Of the patients with thrombocytopenia after exposure to heparin products, 4 patients (25%) developed systemic thrombotic complications associated with the HIT syndrome (HITT) (Table 4). The mean age of the patients who developed HITT was 67 years; all were men. Heparin was used as little as 5 days before the development of HITT, and in all instances the heparin product was UFH.

In all patients with thrombocytopenia after exposure to heparin, the medical management of HIT and HITT consisted of immediate discontinuation of the heparin product. In 8 patients with HIT, warfarin was initiated. All patients with HIT normalized their platelet count within a week, and no further sequelae ensued. Of the 4 patients who developed HITT, argatroban was immediately initiated in 3 patients, and when medically stable long-term warfarin therapy was initiated (target NR 2–3).

In all but one of the HITT patients, operative intervention was required. Emergent operative interventions included compartment

**Table 2**  
Other causes of thrombocytopenia other than heparin exposure in study population

- Hematologic malignancy
- Sepsis
- Acute, severe anemia
- Drug exposure (other than heparins)

release and VAC therapy (KCI, San Antonio, TX). However, in general, definitive surgery was undertaken only when patients were medically maximized and after the tissue had “declared itself” to a level of definitive demarcation. Demarcation generally occurred over 2 to 3 weeks, during which time nonadherent silver sulfadiazine cream dressings were performed every 8 hours.

Among the HITT patients, 1 patient developed HITT after total knee replacement with the development of deep venous thrombosis (DVT) of the foot and leg which extended proximally to the level of the iliac vein. This extensive DVT resulted in an early compartment syndrome of both the foot and leg. In an attempt to salvage the limb, this patient required an emergent foot compartment release along with 4 compartment fasciotomies of the leg with the application of a VAC. Despite aggressive anticoagulation with argatroban, progression of vessel thrombosis and tissue necrosis ensued. Ultimately, after a final level of tissue demarcation occurred, a delayed below-knee amputation with skin grafting of leg fasciotomy incisions was required (Table 4, Figure 1A and B).

A second patient developed HITT after emergency repair of an ascending thoracic aortic dissection. In this case, the development of HITT resulted in bilateral pan-tissue necrosis (skin, subcutaneous tissue, muscle, and bone) of both feet and distal leg (just above the ankles), requiring bilateral below knee amputation. This patient also developed fingertip skin necrosis on his nondominant left hand, treated successfully with conservative measures, and severe necrosis of his dominant right hand necessitating subtotal hand amputation (Table 4, Figure 2A–F).

The third HITT patient developed bilateral cutaneous vessel thrombosis of the feet after having peripheral bypass and on low-dose UFH. In this patient, for unknown reasons, argatroban was not initiated, but rather UFH withdrawn and warfarin initiated. This patient, because of the foot manifestations of HITT and underlying peripheral vascular disease (PVD), underwent a below-knee amputation (Table 4, Figure 3A and B).

The fourth patient developed HITT after an endovascular intervention for peripheral arterial disease (PAD). In this instance, only the skin of the foot (and toes) developed ischemic changes. This patient was treated with argatroban followed by warfarin. The cutaneous foot lesions were treated with silver sulfadiazine dressings and observation. All cutaneous changes resolved by 12 weeks. The patient developed no further sequelae of HITT (Table 4, Figure 4A and B).

## Discussion

Commercially available heparin is a mixture of various sized (5000–50,000 MW) negatively charged acidic mucopolysaccharides, and is termed “unfractionated.” In large doses, this admixture of various-sized mucopolysaccharides has broad effect as an anticoagulant, but is dependant upon the availability of sufficient supply of nascent antithrombin-III (AT-III). Simply, unfractionated heparin acts as a catalyst that accelerates the stoichiometric 1:1 interaction between AT-III and the coagulation cascade protease thrombin (factor IIa), as well as factors VIIa, XIa, Xa, and XIIa. To a lesser extent, heparin also inhibits heparin cofactor II from blocking the action of thrombin. At lower doses (eg, administration of 5000 IU), heparin assumes the role of blocking the conversion of prothrombin (factor II) to the active protease thrombin (IIa). The side effect of such a broad effect on the coagulation cascade (anticoagulation) is the risk of bleeding. The risk of significant bleeding (eg, gastrointestinal, surgical site) from unfractionated full-dose heparin therapy has led to the adoption of “low-dose heparin” administration for DVT prophylaxis. However, even in low-dose prophylaxis, the broad anticoagulant effect of unfractionated heparin may still lead to undesired surgical site bleeding. After major joint arthroplasty,

**Table 3**  
Thrombocytopenia patients: patient clinical setting, heparin product /use, HIT/HITT extremity manifestations, medical and surgical treatments

Clinical Setting	Heparin Product	Heparin Use	Diagnostic Method	Dx	LE S/S from HIT/HITT	Medical Tx
Ankle fusion	UFH	Prophylaxis	PLT count	HIT	none	d/c heparin
DVT	UFH	Therapeutic	PLT count	HIT	none	d/c heparin
LE bypass surgery	UFH	Low dose therapeutic	PLT count, PF4 ELISA	HITT	Forefoot thrombosis	d/c heparin
DVT, foot ulcers	UFH	Prophylaxis		HIT	none	d/c heparin, warfarin
DVT after total knee	UFH	Therapeutic	PLT count, PF4 ELISA	HITT	Foot necrosis, leg compartment syndrome	d/c heparin, Argatroban, warfarin
Forefoot surgery	UFH	Prophylactic bridge to warfarin	PLT count	HIT	none	d/c heparin, warfarin
Emergency ascending aortic Sx	UFH	Therapeutic	PLT count, PF4 ELISA, (C-14)-5HT	HITT	Hand necrosis, bilateral LE pan-tissue necrosis	d/c heparin, Argatroban, warfarin
Endovascular procedure	UFH	Low dose therapeutic	PLT count	HITT	Skin changes feet/ankles	d/c heparin, warfarin
LE bypass surgery	UFH	Low dose therapeutic	PLT count	HIT	none	d/c heparin, warfarin
Poly-trauma	LMWH	Prophylaxis	PLT count	HIT	none	d/c heparin, warfarin
ORIF Fx, AML	LMWH	Prophylaxis	PLT count	HIT	none	d/c heparin
ORIF Fx	LMWH	Prophylaxis	PLT count	HIT	none	d/c heparin, warfarin
ORIF Fx	LMWH	Prophylaxis	PLT count	HIT	none	d/c heparin, warfarin
ORIF Fx, a-fib	LMWH	Prophylactic bridge	PLT count	HIT	none	d/c heparin, warfarin
DVT, PVD, CLL, toe ulcers	LMWH	Low dose therapeutic	PLT count	HIT	none	d/c heparin, warfarin
Poly-trauma	Both	Overlapping prophylaxis	PLT count	HIT	none	d/c heparin

Abbreviations: a-fib, atrial fibrillation; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; (C14)-5HT, platelet serotonin release assay; d/c, discontinue; DVT, deep vein thrombosis; Dx, diagnosis; HIT, heparin-induced thrombocytopenia (HIT-1); HITT, HIT with thrombosis (HIT-2); LE, lower extremity; LMWH, low molecular weight heparin; ORIF Fx, open reduction & internal fixation of fracture; PF4, platelet factor-4 ELISA; PLT, platelet count; PVD, peripheral vascular disease; S/S, signs/symptoms; Sx, surgery; Tx, treatment; UFH, unfractionated heparin.

persistent hemarthrosis from pharmacologic anticoagulation has been shown to be a risk for postoperative infection (2–4). The development of fractionated heparin products (3000 MW) has been promoted as beneficial in reducing the risk of bleeding by the effect of the lower molecular weight products being more selective against Factor Xa. The use of these products (eg, enoxeparin) has become commonplace in the setting of trauma, and after

musculoskeletal surgery. Despite the risk of bleeding on heparin products, this risk outweighs the risk of developing a potentially fatal DVT/VTE event. However, a second risk during the administration of heparin products is the development of the HIT syndromes, which may result in altered PLT counts, and hypercoagulability with arterial and venous thrombosis manifesting in a spectrum of end organ damage.

**Table 4**  
Detailed clinical profile of HITT patients: all patients with HITT were males in their sixth and seventh decades, and received unfractionated heparin

Clinical Setting	HITT Manifestations	Treatments	Outcome
Popliteal DVT after TKR	Thrombosis of entire left leg venous system to iliacs; Left foot compartment syndrome; Left leg compartment syndrome; Necrosis of left foot and leg; Acute renal failure	Emergent left foot and leg fasciotomies and VAC; Silver sulfadiazine dressings; Argatroban → warfarin; Delayed left BKA; STSG to leg fasciotomies	Ambulates with BKA prosthesis, with successful retention of TKR
Emergency repair of dissecting thoracic aorta	Right hand thrombosis; Left finger-tip necrosis; Bilateral foot and ankle thrombosis with pan-tissue necrosis [skin →, bone]; Acute renal failure; Mental status changes	Argatroban → warfarin; Silver sulfadiazine dressings; Right hand amputation; Bilateral BKAs	Ambulates with bilateral BKA prostheses; Hand assistive device
Peripheral vascular bypass	Foot thrombosis, compounded by PVD resulting in foot necrosis to level of midfoot	BKA	Limited ambulation with BKA prosthesis
Peripheral endovascular procedure	Ischemic changes of bilateral toes and feet above ankles; Left side worse than right	Argatroban → warfarin; Silver sulfadiazine dressings; observation	Feet salvaged

Abbreviations: BKA, below knee amputation; B/L, bilateral; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia (HIT-1); HITT, HIT with thrombosis (HIT-2); Lt, left; PVD, peripheral vascular disease; Rt, right; STSG, split thickness skin graft; TKR, total knee replacement; UFH, unfractionated heparin; VAC, vacuum-assisted closure.



**Fig. 1.** (A) Left limb of patient #1 demonstrating ischemic changes of the foot and ankle, which progressed despite fasciotomies of the foot and leg from compartment syndromes. Note purpura extending to the level of the knee replacement incision. (B) Left BKA at 1 year with well-healed skin and successful retention of total knee implant. Patient walks with a BKA prosthesis.

#### Heparin-Induced Thrombocytopenia Syndromes

A transient drop in PLT count during heparin therapy is still generally referenced as “HIT” or “HIT-I”: “nonimmune heparin-associated thrombocytopenia.” This drop in the PLT count, usually occurs within 4 days of heparin administration, and is not an uncommon event, occurring in 1% to 5% of patients receiving UFH. This event has been reported to occur less commonly in patients receiving LMWH (5).

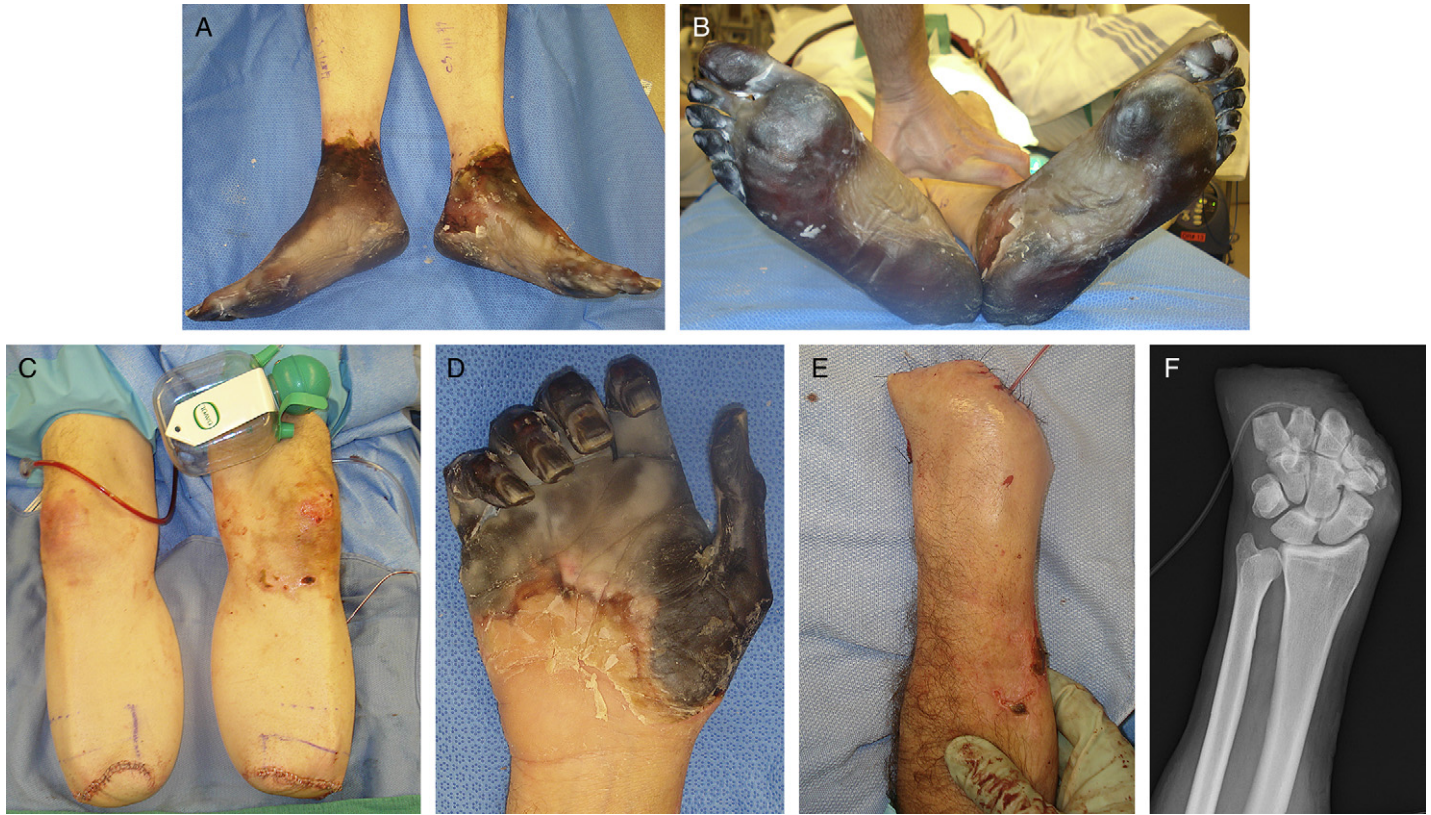
The exception to this time frame for the PLT drop is in those patients who have been exposed to heparin within 30 days before reexposure; these patients may manifest HIT earlier than 5 days after reexposure to heparin (6). Additionally, it has been reported that patients receiving bovine-derived heparin are exposed to a greater risk of developing HIT than that for porcine-derived heparin (5).

The drop in PLT count is believed to be the result of a heparin agglutination of PLTs, and is usually limited in magnitude, approximately 20% of baseline to 60,000 to 100,000/ $\mu$ L, and typically resolves spontaneously within several days. Within this clinical setting (“HIT-I”), many clinicians will withdraw heparin and use alternate methods of anticoagulation. Thus, upon initiation of heparin therapy, many clinicians monitor PLT counts. A decrease in PLT count by 20% from baseline should prompt cessation of heparin and serial monitoring of PLT counts to verify normalization of the PLT count. Musculoskeletal and cardiovascular surgery appear to be risk factors for HIT/HITT (6). Heparin-induced thrombocytopenia with thrombosis (commonly referred to as “HIT-II”) is a far more serious and potentially life-threatening disorder. As such, it has been suggested that any reference to HIT be reserved for this major adverse event (7). However, the designations HIT-I and HIT-II are entrenched in the literature and will likely continue to be used in clinical practice. An alternate and more descriptive designation that the authors prefer (used throughout this article to describe our study population cohort) is HIT (ie, HIT-I) and HITT (HIT with systemic thrombosis, ie, HIT-II). True HITT (HIT-II) typically occurs 5 to 14 days after the initiation of heparin therapy,

often heralded by a drop in PLT count by more than 40% (8, 9). In our series of patients, all patients with HIT and HITT (with one exception) were either musculoskeletal (elective and trauma), cardiovascular, or peripheral vascular surgery patients. Excluding a single patient who had exposure to both forms of heparin, our study cohort of patients who developed a heparin-induced thrombocytopenic syndrome exhibited a 1.5:1 (UFH:LMWH) exposure ratio (Table 3). All cases of HIT resolved without sequelae upon withdrawal of the heparin product and the initiation of warfarin, as clinically indicated. All our observed cases of HITT were after exposure to UFH, diagnosed at approximately the fifth day of UFH exposure.

#### Pathogenesis of HIT: Molecular Mechanisms and Systemic Pathophysiology

Previous investigators believed the pathogenesis of HIT was strictly attributable to an antigenic response to heparin. This mechanism was theorized based on the presence of antiheparin antibodies in the serum of patients with HIT syndrome. The evolution of HIT is now unified around the concept of immunoglobulin G (IgG) antibodies that bind to epitopes on platelet factor 4 (PF4). PF4 is released from PLTs and activated when the PLTs complex with heparin. PF4 and UFH ultimately form ultralarge (>670 kD) complexes that bind multiple IgG molecules, rendering a highly antigenic complex, which promotes further platelet activation. LMWH, which is less antigenic, forms ultralarge complexes less efficiently, stoichiometrically requiring supratherapeutic concentrations. In vivo, the binding of HIT associated IgG to platelets, and the subsequent induction of thrombocytopenia, is directly proportional to degree of PF4 expression (10) (Figure 5). Only heparin fractions larger than 5 kD interact with HIT antibodies, explaining why LMWH usually does not generate antibodies. HIT antibodies are heterogeneous in structure, affinity, and specificity (11). Heparin is not required for HIT antibody binding, but rather shifts the concentration of PF4 needed for optimal surface antigenicity to a higher level (12). When the Fab region of HIT IgG



**Fig. 2.** (A) HIT patient #2 demonstrating mummification of feet and above ankles. (B) Plantar surface of feet of HIT patient #2. (C) Immediate appearance of bilateral BKAs in HIT patient #2. (D) Palmar view of right hand involvement of HIT patient #2. (E) Posterior view of right subtotal hand amputation for HIT patient #2. (F) Radiograph of right hand amputation; this patient experienced 4-limb involvement with HIT; 3 limbs required amputation.

binds to PF4-heparin on the surface of activated platelets, only the Fc portion of the bound IgG further activates the same or adjacent platelets through the Fc receptor (13). In a minority of HIT cases, antibodies to H-PF4 are not present, but antibodies to other cytokines have been found. These cross-reactive antibodies frequently react either with interleukin-8 (IL-8) or with neutrophil-activating peptide 2 (NAP-2) (14). Although less common, LMWH may be associated with HIT syndromes. In contrast to UFH, the antibodies generated by LMWH treatment are more often IgA and IgM, as opposed to IgG antibodies, which are associated with symptomatic clinical HIT generated by exposure to UFH. However, platelet activation/aggregation can occur from LMWH in the presence of most preexisting HIT antibodies that had previously been generated from UFH exposure, although the response is less than that caused by UFH plus HIT antibody (15). The pathophysiologic cascade involved in the HIT syndromes cascade can be summarized as follows: (1) Infused heparin neutralizes a portion of excess surface PF4, directly enhancing local thrombosis. (2) The excess PF4 is mobilized into PF4/heparin complexes that stimulate HIT antibody production. (3) The remaining PF4 complexed to heparanoids and heparin on the vascular surfaces now binds to these HIT antibodies and through surface Fc gammaRII receptors leads to more platelet activation and removal, thrombus formation, and vessel inflammation (8) (Table 1). Other procoagulant effects of the HIT antibody include endothelial cell damage, stimulation of platelet-leukocyte aggregates, and release of tissue factor from monocytes (16). Vascular endothelial cell injury arises from anti-heparin antibodies binding to and directly activating microvascular endothelial cells, whereas macrovascular endothelial cell injury involves the priming of macrovascular endothelium by platelets or tumor necrosis factor alpha (TNF-alpha). The subsequent

inflammatory milieu involves both neutrophils and monocytes (but not lymphocytes) binding to and forming complexes with platelets in the presence of HIT antibodies. Activated monocytes may bind directly to endothelial cells, also producing a local procoagulant state. Once again it should be noted for HIT antibodies: Only heparin fractions larger than 5 kD interacted with HIT antibodies, explaining why LMWH usually does not generate antibodies. HIT antibodies are heterogeneous in structure, affinity, and specificity (11).

#### Diagnosis of HIT

Heparin-induced thrombocytopenia (HIT) is a potentially serious drug adverse effect. Unlike other drug-induced thrombocytopenias, HIT does not usually cause bleeding, but instead causes thrombosis (17). The manifestation among organ systems is widespread, heralded by end-organ-specific characteristics. The hallmark of all organ systems damaged by the HIT syndromes is characterized by the unifying feature of vessel thrombosis in the setting of PLT consumption. In 2 of our study patients, acute renal failure was observed, and in 1 patient, mental status changes also occurred. In the extremities, thrombosis associated with HIT may present as a spectrum of changes from mild cutaneous changes to frank limb necrosis requiring limb amputation. The diagnosis of HIT should be made based on laboratory and clinical criteria. Routine PLT monitoring is required during the administration of heparin products. If the PLT counts drop by 20% from baseline values, HIT should be suspected. If HIT is suspected, confirmation is typically made by laboratory tests. However, a common practice observed in our study population is patients who develop a drop in the PLT count within the first few days of heparin therapy are discontinued from the heparin product without further



**Fig. 3.** (A) Right foot dorsal view in HIT patient #3 who also had peripheral vascular disease. (B) Plantar view of foot of HIT patient #3, who required a BKA. Note asymmetric changes compared with the dorsum of the foot, which can challenge tissue-sparing surgery.

laboratory workup. This signifies the more common (and more benign) simple HIT syndrome. Conversely, when patients develop a large drop in the PLT count or a decrease in PLTs after 5 days (especially with organ system manifestations), a confirmatory laboratory diagnosis of HIT is sought. The tests for HIT antibodies are either through a PF4 immunoassay (ELISA), or a surrogate functional test (14C-serotonin release assay) (17).

#### Medical Management of HIT Syndromes

Once a clinical diagnosis of HIT is made, heparin administration is immediately ceased. This includes all forms of heparin administration from therapeutic parenteral infusions, prophylactic administrations, and even the flushing of intravenous catheters and ports with heparin. Treatment with an alternative anticoagulant (argatroban, bivalirudin, and lepirudin) is immediately commenced. These treatment agents are known as direct thrombin inhibitors (DTIs). This should continue for at least 5 days unless the diagnosis of HIT is subsequently proven to be incorrect via laboratory testing. Warfarin should also be started when the patient is clinically stable and thrombosis is under control. The treatment with warfarin and the alternative anticoagulant should overlap several days (17). The transition from DTI therapy to oral anticoagulation in patients with DVT complicating HIT has been identified as a risk period for warfarin-induced venous limb gangrene. The DTI should be given alone during acute HIT with oral anticoagulants deferred until substantial resolution of the thrombocytopenia has occurred (18). During the treatment of the HIT syndromes, the patient PLT count, coagulation profile, and any specific end-organ serum chemistry is monitored daily.

Among the alternative anticoagulants agents used to treat HIT syndrome, argatroban is the most commonly used DTI agent in the United States. Argatroban is a synthetic direct thrombin inhibitor derived from L-arginine, indicated for parenteral use in the prevention and treatment of thrombotic phenomenon in patients

with HIT. Argatroban is eliminated hepatically, with a half-life of 45 to 50 minutes. Patients with HIT syndrome treated with argatroban have been shown to experience lower rates of the composite end point of death, amputation, and new thrombosis. Dosing is initiated at 2  $\mu\text{g}/\text{kg}/\text{min}$  and adjusted to maintain the activated partial thromboplastin (aPTT) time at 1.5 to 3.0 times the patient's baseline; dosing adjustments must be made in patients with hepatic involvement of HIT (19). Argatroban has been shown to significantly reduce new thrombosis and death attributable to thrombosis (20), and has also been shown efficacious in the treatment of patients receiving renal dialysis and renal replacement therapy (21). An additional benefit of argatroban therapy is that it significantly reduces the likelihood of new stroke and stroke-associated mortality in heparin-induced thrombocytopenia without increasing intracranial hemorrhage (22). Patients receiving concomitant therapy with warfarin and argatroban may often have an INR greater than 4, and although the risk for bleeding is increased during cotherapy, it has been suggested that the benefits of thrombus inhibition outweigh the potential bleeding complications (23). Other alternative anticoagulants used to treat HIT (bivalirudin and lepirudin) have also been shown to be effective. Bivalirudin has shown to be the most cost-effective agent, with patients receiving bivalirudin also reaching therapeutic aPTT sooner than argatroban and lepirudin. Unfortunately this treatment has yet to be approved by the Food and Drug Administration (24). Upon the initiation of warfarin, the DTI is continued until the therapeutic effect of warfarin is evident, with a target INR of 2 to 3.

#### Surgical Management of HIT-Associated Extremity Complications

Supportive care is provided to assist in the recovery of both pre-existing medical comorbidities as well as organ system dysfunction incurred by the HIT syndromes. The treatments of the altered coagulation and thrombotic phenomenon in HIT (vide supra) greatly

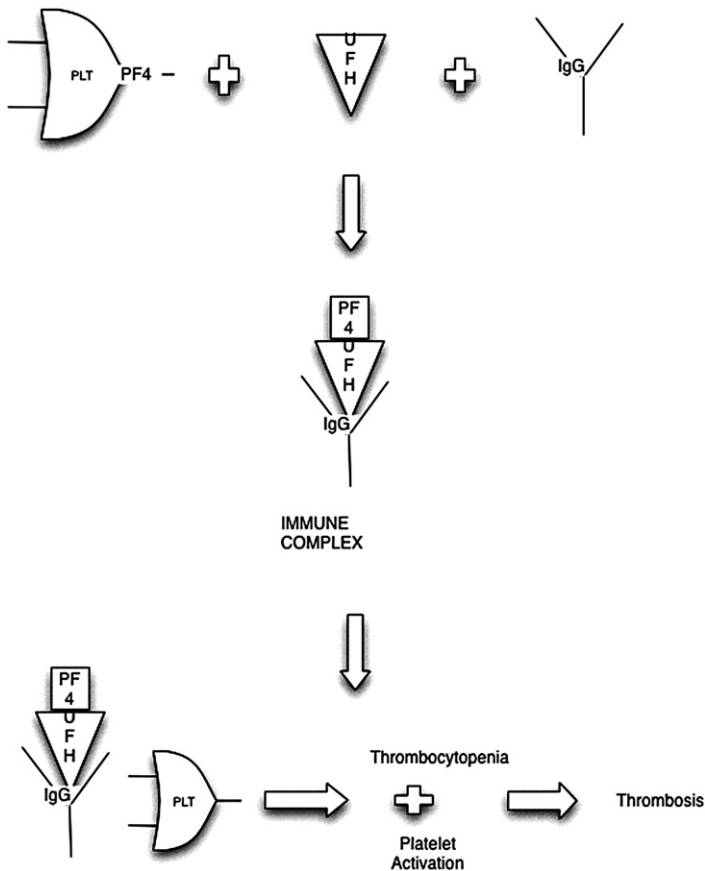


**Fig. 4.** (A) Right foot of HIT patient #4, with restively mild cutaneous thrombosis. (B) Left foot of HIT patient #4. Note asymmetry in degree of involvement between feet. Careful observation accompanied by conservative measures allowed salvage of feet.

assist with maximizing the recovery potential of the lower extremity skin, subcutaneous tissue, and muscle. Improvements in renal, hepatic, and central nervous system parameters may be seen upon the initiation of argatroban and simultaneous efforts at organ system support. The lower extremity manifestations of HIT may be transient or acutely fulminant, as seen in 2 of our study patients. The latter presentation is often observed in the more critically ill patients. As such, once lower extremity manifestations of HIT become present, the surgeon must judiciously allow the disease process to “declare itself” over a period of time. In this manner, transient problems such as minor skin ischemia are allowed time to clear, while more critically ill patients are given the opportunity to be resuscitated enough to undergo major invasive procedures such as debridements and amputations. During this observation period, limbs are cared for by providing adequate warmth, padding, hydration, and barriers to infection. Simple measures such as soft boot padding (“Rook boots”) and a 3 to 4 times per day application of silver sulfadiazine cream covered with a nonadherent dressing are implemented. Although it may appear ideal to observe the affected areas daily, because changes occur slowly, every other or every third day inspections and assessments by the surgeon are acceptable. This may allow better objective comparative inspections. Once a plateau in both overall medical and local tissue improvement is achieved, definitive operative intervention is planned. Nonetheless, in certain instances in an effort to maximize limb preservation, emergent surgery may need to be performed, such as compartment release. This was a necessity in one of our study patients. A second setting indicating emergent surgery is the HIT patient in sepsis, where the septic source is thrombotic and

necrotic tissue. In this instance, expedient debridements may greatly assist with normalization of organ system function, or may prove to be life-saving. If possible, anticoagulation should be carefully monitored just before any operative intervention. Unless circumstances would mitigate against drug withdrawal, anticoagulation may be temporarily stopped in the immediate perioperative period. An example is a critically ill patient with multisystem organ failure secondary to vessel thrombosis but who requires an urgent limb amputation to assist with controlling sepsis. Argatroban is easily regulated, as the half-life is less than 1 hour. Warfarin is more difficult to regulate. In the lead author’s experience, patients on warfarin may undergo emergent surgery unless the INR is higher than 3.5. In emergency surgery situations in patients with HIT, typed and screened blood should be available in a quantity of at least 2 units of packed red blood cells.

The surgical management strategy for HIT also includes debridements and the liberal use of VAC dressings. The goal is to preserve as much tissue as possible, all the while planning a surgical margin that is suitable for function. In our patients, the severity of vessel thrombosis resulted in extensive ischemic changes that required both below-knee amputations, as well as a hand amputation (a relatively uncommon procedure). Often tourniquet use is not optional, as surgical bleeding while fully anticoagulated may be significant. Thus, in addition to meticulous hemostatic techniques, closed suction drains are used liberally (2–3 drains or more). The use of the “incisional VAC” should be considered. The lead author has used this technique for 8 years, whereby the VAC foam is placed only over a “leaky” incision and set at a lower negative pressure (typically



**Fig. 5.** Schematic diagram of mechanism involved with HIT (HIT-II) leading to platelet consumption, arterial and venous thrombosis, and subsequent tissue necrosis. PLT, platelet; PF4, PLT factor 4; IgG, immunoglobulin-G; UFH, unfractionated heparin.

75 mm Hg pressure) and at either a constant or intermittent setting. The peri-incision skin is protected with either DuoDERM extrathin dressing (ConvaTec USA, Princeton, NJ), or pretreated with Cavilon (3M, St. Paul, MN) with or without an adherent drape material. When using this technique, to avoid skin damage, the incision must be checked every 2 to 3 days.

Often these patients require extensive medical support and may be critically ill. Additionally, it is the lead author's observation that the tissues proximal to the level of demarcation are often of less than optimal quality—perhaps a subclinical involvement. Furthermore, despite early enteral and parenteral feeding, these patients may exhibit nutritional deficit; the monitoring of nutritional parameters such as total protein, albumin, and prealbumin are warranted. After a major limb amputation in these patients, sutures are retained well beyond 2 weeks and the judicious use of protection (padded splints, immobilization) assist with the healing of the amputated appendage. If skin grafting has been performed, the authors find great utility in the VAC system to assist with skin graft incorporation. This is vitally important considering the continued use of anticoagulants in these patients with the inherent risk of hematoma formation that may result in infection or skin graft slough. Skin graft donor site morbidity is a consideration in anticoagulated patients, and as such, alternate harvest methods may be used. For example, a split thickness graft may be harvested but may be converted to a full thickness donor site that may be closed primarily with or without a closed suction drain.

Physical and occupational therapy are initiated when tissues demonstrate good healing. Physical therapy is a vital component in the rehabilitation of these patients and is begun in the hospital setting

continuing for months in the outpatient setting. A multidisciplinary team approach to the overall medical care, rehabilitation, and return to the community for these patients is essential.

In summary, the development of HIT/HITT is an inherent risk to the use of heparin products, especially in musculoskeletal and cardiovascular patients. Large studies document an incidence of 1% to 2% of patients exposed to heparin. Our study, which documents a lower rate of heparin-induced thrombocytopenia, is limited by (1) the unknown number of patient encounters in which subjects were exposed to heparin; (2) sampling error extending from a single surgeon's experience; and (3) flaws inherent to documentation of databases associated with data warehousing. This study does, however, provide insight to the clinical settings, the spectrum of clinical manifestations, and management strategies of the HIT/HITT syndromes. When using heparin products, the authors recommend that the PLT count be monitored frequently (at least every third day), and any heparin product be discontinued at the first laboratory indication of an adverse event interfering with the PLT/coagulation system. Further laboratory investigation is warranted to evaluate for HIT versus HITT. Appropriate alternate anticoagulation with a DTI, such as argatroban, is indicated in the appropriate clinical setting of HITT. Patients developing the HITT syndrome must be assessed carefully for multiple organ system dysfunction. The lower extremity surgeon should be versed in the risks associated with the use of heparin products, as well as the pathophysiology, clinical manifestations, and management principles of patients with both HIT and HITT syndromes.

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## References

- Benevenia J, Bibbo C, Patel DV, Grossman MG, Bahramipour PF, Pappas P. Inferior vena cava filters prevent fatal pulmonary emboli in orthopaedic cancer patients. *Clin Orthop Relat Res* 426:88–92, 2004.
- Minnema B, Vearncombe M, Augustin A, Gollish J, Simor AE. Risk factors for surgical-site infection following primary total knee arthroplasty. *Infect Control Hosp Epidemiol* 25(6):477–480, 2004.
- Patel VP, Walsh M, Sehgal B, Preston C, DeWal H, Di Cesare PE. Factors associated with prolonged wound drainage after primary total hip and knee arthroplasty. *J Bone Joint Surg Am* 89(1):33–38, 2007.
- Della Valle CJ, Jazrawi LM, Idjadi J, Hiebert RN, Stuchin SA, Steiger DJ, Di Cesare PE. Anticoagulant treatment of thromboembolism with intravenous heparin therapy in the early postoperative period following total joint arthroplasty. *J Bone Joint Surg Am* 82(2):207–212, 2000.
- Bell WR, Royall RM. Heparin-associated thrombocytopenia: a comparison of three heparin preparations. *N Engl J Med* 303:902–907, 1980.
- Fabris F, Luzzatto G, Stefani PM, Girolami B, Cella G, Girolami A. Heparin-induced thrombocytopenia. *Haematologica* 85(1):72–81, 2000.
- Rice L. Heparin-induced thrombocytopenia: myths and misconceptions (that will cause trouble for you and your patient). *Arch Intern Med* 164:1961–1964, 2004.
- Poncz M. Mechanistic basis of heparin-induced thrombocytopenia. *Semin Thorac Cardiovasc Surg* 17:73–79, 2005.
- Deichter SR, Carman TL. Heparin-induced thrombocytopenia: natural history, diagnosis, and management. *Vasc Med* 6:113–119, 2001.
- Cines DB, Rauova L, Arepally G, Reilly MP, McKenzie SE, Sachais BS, Poncz M. Heparin-induced thrombocytopenia: an autoimmune disorder regulated through dynamic autoantigen assembly/disassembly. *J Clin Apher* 22(1):31–36, 2007.
- Walenga JM, Jeske WP, Prechel MM, Bakhos M. Newer insights on the mechanism of heparin-induced thrombocytopenia. *Semin Thromb Hemost* 30(Suppl 1):57–67, 2004.
- Rauova L, Zhai L, Kowalska MA, Arepally GM, Cines DB, Poncz M. Role of platelet surface PF4 antigenic complexes in heparin-induced thrombocytopenia pathogenesis: diagnostic and therapeutic implications. *Blood* 107(6):2346–2353, 2006.
- Newman PM, Chong BH. Heparin-induced thrombocytopenia: new evidence for the dynamic binding of purified anti-PF4-heparin antibodies to platelets and the resultant platelet activation. *96(1):182–187, 2000.*
- Amiral J. Antigens involved in heparin-induced thrombocytopenia. *Semin Hematol* 36(1 Suppl 1):7–11, 1999.
- Walenga JM, Jeske WP, Prechel MM, Bacher P, Bakhos M. Decreased prevalence of heparin-induced thrombocytopenia with low-molecular-weight heparin and related drugs. *Semin Thromb Hemost* 30(Suppl 1):69–80, 2004.

16. Reilly RF. The pathophysiology of immune-mediated heparin-induced thrombocytopenia. *Semin Dial* 16(1):54–60, 2003.
17. Chong BH. Heparin-induced thrombocytopenia. *J Thromb Haemost* 1(7):1471–1478, 2003.
18. Warkentin TE. Management of heparin-induced thrombocytopenia: a critical comparison of lepirudin and argatroban. *Thromb Res* 110(2–3):73–82, 2003.
19. Kondo LM, Wittkowsky AK, Wiggins BS. Argatroban for prevention and treatment of thromboembolism in heparin-induced thrombocytopenia. *Ann Pharmacother* 35(4):440–451, 2001.
20. Lewis BE, Wallis DE, Hursting MJ, Levine RL, Leya F. Effects of argatroban therapy, demographic variables, and platelet count on thrombotic risks in heparin-induced thrombocytopenia. *Chest* 129(6):1407–1416, 2006.
21. Reddy BV, Grossman EJ, Trevino SA, Hursting MJ, Murray PT. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia requiring renal replacement therapy. *Ann Pharmacother* 39(10):1601–1605, 2005.
22. LaMonte MP, Brown PM, Hursting MJ. Stroke in patients with heparin-induced thrombocytopenia and the effect of argatroban therapy. *Crit Care Med* 32(4):976–980, 2004.
23. Bartholomew JR, Hursting MJ. Transitioning from argatroban to warfarin in heparin-induced thrombocytopenia: an analysis of outcomes in patients with elevated international normalized ratio (INR). *J Thromb Thrombolysis* 19(3):183–188, 2005.
24. Dang CH, Durkalski VL, Nappi JM. Evaluation of treatment with direct thrombin inhibitors in patients with heparin-induced thrombocytopenia. *Pharmacotherapy* 26(4):461–468, 2006.