

Current Concepts Review: Heparin-Induced Thrombocytopenia

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INTRODUCTION

Immune-type (Type II) heparin-induced thrombocytopenia (HIT) is a rare but potentially fatal complication that can result from the use of heparin or its derivatives employed to reduce the risk of venous thromboembolic disease (VTED) after surgery. As such, the onset of HIT creates a therapeutic paradox: VTED prophylaxis that induces systemic thrombosis. Orthopaedic patients often necessitate chemoprophylaxis after surgery because of their particularly high risk for developing VTED, but concomitantly they represent a population at high risk for developing HIT. Although HIT is known to occur after exposure to unfractionated (UFH) or low molecular weight (LMWH) heparin, it can develop with the use of any heparin-derived product. Unfortunately, the orthopaedic patient who develops this incompletely understood disease also ranks amongst the highest in development of its most devastating manifestation, HIT-mediated arterial thrombosis, which can result in amputation or death.^{29,74a,108,114}

Since it remains unclear exactly how much treatment can alter the natural course of HIT, preventing its onset is paramount. This current concepts review is intended to increase the awareness and highlight the potential severity of HIT, and familiarize the orthopaedic surgeon with the many challenges associated with its diagnosis and treatment.

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BACKGROUND AND INCIDENCE

A heightened vigilance regarding VTED has increased the use of chemoprophylaxis after orthopaedic procedures in this country.^{11,12,23,40,49,88,51,93,94,119} While this practice has reduced the prevalence of thromboembolic events after surgery, the unintended morbidity associated with a more widespread use of heparin and heparin derived anticoagulants represents a mounting challenge.^{21,67,93,94,106} Although HIT and its associated risk for paradoxical thrombotic disease, limb amputation, and death, represents an example of one of the most severe complications of VTED chemoprophylaxis, only 15 papers have been published in the English orthopedic literature focusing on this disease. These case reports discuss less than a total of 30 cases, and do not differentiate between Type I and Type II disease.^{4,6,7,9,17,20–22,31,40,42,47,56,57,63–68,70,74a,75,76,93,94,106,108,111,114} Collectively, these clinical accounts provide at best for only Level IV evidence on this issue. A meta-analysis of these scattered orthopaedic publications identified an estimated 22% amputation rate, 11% mortality rate, and 33% major complication rate with HIT.^{6,7,9,17,42,47,56,64,65,68,70,74a,75,76,93,94} Although there are no known published reports of immune-mediated HIT in an orthopedic patient after a singular exposure to heparin or its derivatives, this author has observed a patient die of systemic complications related to HIT approximately one month after a single perioperative injection with a LMWH as prophylaxis for a foot and ankle procedure.^{50,67,106,109}

The current literature suggests that HIT is an important pathological entity which must be better understood by the medical and surgical community.^{42,56,82} The reported incidence of HIT ranges from 10–20% for Type I and 0.2% to 5.0% for Type II^{27,66,87,104,111} (Level I, II evidence). Based on results reported by Warkentin et al. and a meta-analysis of 15 studies including more than 7,000 patients, it appears that the clinically significant form of HIT (Type II) occurs in 1% to 3% of all patients receiving unfractionated heparin (UFH) and in only 0.3% to 0.8% of patients receiving low-molecular weight heparin (LMWH)^{19,23,29,50,67,77,106,109,111,113} (Level I, II evidence). Therefore, the odds ratio for developing

HIT in patients treated with UFH as compared to those treated with LMWH is 5.29.¹⁰² Four factors appear to be closely associated with the risk of developing HIT: 1) longer duration of medication exposure (more than 4 days), 2) use of UFH (versus LMWH by an order of magnitude), 3) surgical patients (versus medical), and 4) females (versus males)^{18,31,42,66,102,104,111,113,115} (Level I, II evidence). Taken together, the combined relative risk for these factors approaches 17 (95% CI 4.2–72).^{104,115} Although the overall incidence of HIT Ab and positive HIT assays is highest in cardiac surgical patients (up to 15% to 50%), orthopaedic patients are the ones most prone (0 to 5 fold higher) to developing HIT when these antibodies are present^{8,21,29,87,114} (Level I, I, III evidence). Interestingly, there is no increased risk for developing HIT in patients with hypercoagulable conditions such as Factor V Leiden, protein C/antithrombin deficiency, and antiphospholipid antibody syndrome.⁵⁷

ETIOLOGY AND PATHOGENESIS

Type I versus Type II

HIT is a complication of receiving heparin or heparin-derived products. It can result from even minute exposures to these agents, such as flushing an intravenous line with a 250-U heparin solution or the use of a heparin-coated catheter.^{51,71} Knowledge of this disease began in the late 1970s to early 1980s, and it has come to be characterized into two forms. HIT Type I is not immune-mediated, not associated with thromboembolic or hemorrhagic events, and usually presents as a mild, transient decrease in platelets occurring one to two days after exposure to heparin or its derivatives. The platelet count usually does not drop below 100,000 /ul with this form, and generally recovers spontaneously even in the face of continued exposure to these medications.⁶⁷ The pathophysiology of HIT Type I is not fully understood, although it is thought to be related to a direct effect on platelet activation.²² Because this form is typically self-limiting and clinically inconsequential, most articles discussing HIT and its effects refer solely to the Type II form. HIT Type II represents the effect of a systemic autoimmune response prompted not by exogenous heparin alone but rather by the formation of complexes between heparin and endogenous platelet factor 4 (PF4), a protein naturally secreted by the alpha granules of platelets.^{3,22,81,106} The manifestations of this form usually occur after at least four days of exposure to a heparin product, and are frequently (estimated 30% to 80%) accompanied by serious or life-threatening complications.^{4,20,21,22,31,40,57,63,66,67,106,108,111,114} Based on its clinical relevance and magnitude, the remainder of this review regarding HIT will pertain exclusively to the Type II form.

Pathophysiology (Type II disease)

In this disease, antibodies typically develop between 5 to 8 days after exposure to heparin or its derivatives.¹¹¹ They are usually polyclonal IgG immunoglobulins which bind platelets via receptors that recognize the heparin/PF4 complexes. Binding with the antibodies augments platelet activation which further provokes the release of PF4 and thereby creates a positive feedback loop.⁷³ These complexes are also capable of binding with and activating endothelial cells and monocytes to release other procoagulants such as Interleukin-6 (IL-6), tissue factor (TF), and Von Willebrand factor (VWF). Such events promote the activation of a cascade that triggers the release of platelet-derived microparticles and increases serum thrombin levels to produce a hypercoagulable state.^{10,43,77} Perpetuation of this cascade propagates the progressive aggregation of platelets, which leads to their consumption and elimination from the circulation, and systemic thrombosis.¹⁰⁸ This paradoxical thrombotic state in the face of thrombocytopenia remains a distinguishing feature of HIT, and is considered a result of the unique process of platelet activation associated with this disease. In the Type II order, there is an increased risk of thrombotic events for up to 30 days after the onset of HIT. This phenomenon is most likely caused by immunoglobulins that continue to circulate in the patient. It is important to note, however, that most patients who produce these antibodies do not progress to actual HIT.^{50,67,99,106,109,110} Several theories exist to explain why some patients with circulating antibodies acquire the disease, yet others do not. Possible explanations include 1) an increased overall antigenicity of PF4-heparin complexes in patients, 2) an increased endogenous concentration of PF4 in patients or an increased expression of the PF4 on the platelet surface, or 3) the independent binding of PF4 to other glycosaminoglycans (GAG) in the absence of heparin.^{16,81,91} A genetic predisposition may also account for the variability in development of HIT Type II. Further study in this area will ideally enable the preoperative identification of patients at risk for this disease. Unfortunately, some data suggest that the risk of developing HIT as well as the severity of its manifestations may be independent of the onset or nature of treatment and the timing of heparin cessation.^{50,67,96,106,109,110} (Level III and IV evidence).

DIAGNOSIS AND CLINICAL PRESENTATION

The platelet count

HIT Type II is characterized by a precipitous drop in platelets, often greater than 50% from baseline.^{99,108,113} However, recent studies suggest that defining the thrombocytopenia as a percentage decrease of 30% to 50% rather than as a drop below an absolute value of $150 \times 10^9/L$ may result in higher diagnostic specificity.^{20,102,108,113} It must be noted that, under normal postoperative circumstances, the platelet count should rise between 4 and 14 days after surgery. Given the normal expectation of a transient thrombocytosis,

a “normal” platelet count does not preclude the presence of HIT. Furthermore, compared to idiopathic, post-transfusion, or other drug-induced thrombocytopenias, the absolute drop in the platelet count in HIT is rarely as severe (median nadir of $60 \times 10^9/L$). An absolute value below $20 \times 10^9/L$ is very uncommon with HIT, and therefore the risk of spontaneous bleeding with this condition is minor.^{46,98}

Disease onset

HIT has three temporally related profiles. ‘Classic’ HIT characteristically presents between 5 to 10 days after onset of heparin derivative exposure, usually occurring while the patient is still on the medication. Historically, presentation outside of this time frame has been considered relatively rare.^{106,110,111} There are matching publications and case reports, however, which report that that exceptions to this rule are not uncommon, and may actually be increasing in frequency.^{4,18,99,101} (Level IV evidence). Indeed, HIT can have a rapid or ‘early’ onset (mean, 10 to 12 hours post-exposure; range, 0 to 4 days). In this case, the effectively re-exposed patient has a primed immune system from prior heparin exposure within the preceding 100 days, and has persistent HIT antibodies (which in all cases an average of 85 days to completely clear).^{4,18,50,61,99,100–106,110} Finally, patients can also have a ‘delayed’ onset (mean, 14 days; range, 9 to 40 days), which begins well after heparin has been withdrawn.^{4,18,82,97,101,106,109} Patients with delayed onset HIT often re-present after a fairly benign postoperative or post-hospital course (during which they encountered some form of heparin), and are finally diagnosed on the basis of overt thrombosis and thrombocytopenia.^{82,109} Data suggest that these patients, upon re-presentation, frequently receive further exposure to heparin products before the diagnosis of HIT is made, which can often worsen their clinical condition (Level III evidence). In one recent study by Rice et al. over a 3-year period at three major centers, this occurred in almost 80% of cases (11 of 14 patients), and three of these patients eventually died.⁸² In another study by Warkentin et al. in 2001, this re-exposure approached 75% (9 of 12 patients), with similarly potentially severe consequences.¹⁰⁹

HIT can vary greatly in presentation, and as such timely diagnosis requires a high index of suspicion. Unfortunately there is no sine qua non test for this disease, and the diagnosis remains foremost a clinical one.^{101,106,108,113} It is therefore imperative to remember that this is not just a disease relegated to the hospitalized patient; rather, it is being reported with increasing frequency in the outpatient setting.⁵⁰ Serious consideration of HIT should be entertained for any patient who develops a new thrombosis, arterial or venous, while actively on or having been recently treated with heparin or one of its derivatives, particularly in the face of unexplained thrombocytopenia or a platelet count fall of greater than or equal to 30% to 50%.^{34,35,113} When patients present in this manner (with known lab abnormalities and VTE), one recent study found that their VTED was

more likely the result of HIT as opposed to any failure of anticoagulation.⁵² This holds particularly true for any patient with VTED who, in the past 30 days, was either in a health facility setting and/or could be suspected of having had heparin derivative exposure by some other means. On a more generic level, a recent meta-analysis of 10 studies identified that 8.2% (32/386 patients, 1 in 12) of all (6,219) chemoprophylaxed patients who presented with VTE (386/6,219 patients) also had HIT.⁵² The frequency of HIT associated VTE was 12.8% (1 in 8) for the UFH recipients and 0.7% (1 in 144) for the LMWH recipients.

Clinical manifestations

There is no ‘typical’ presentation for patients who have developed HIT. HIT may not be easily differentiated in post surgical patients who often exhibit fluctuations in platelet counts due to fluid shifts, intravenous hydration, or blood loss. The underlying cause of any thrombocytopenia can also be confounded by medications taken postoperatively. HIT rarely causes bleeding complications, however, and alternative diagnoses must be considered when the platelet count drops below $25 \times 10^9/L$. These include sepsis, pharmacologic agents other than heparin, and post-transfusion purpura.^{18,100,110} A myriad of non-specific symptoms and signs have been described for HIT, including fevers, chills, sweats, hypertension, tachycardia, dyspnea, chest pain, rash, transient global amnesia, adrenal hemorrhage, and cardiopulmonary arrest.^{67,99,102,107,109} These become more suspect when they occur within minutes to hours after the administration of any heparin product. Two of the more common and perhaps specific clinical scenarios include thrombosis and skin necrosis at the site of heparin injection or bolus.^{102,118}

There is a high overall morbidity and mortality rate associated with HIT. Recent reports estimate a mortality rate which can approach 50%, as well as a 20% major limb amputation and 30% organ failure rate.^{92,99,102} The primary clinical problem in these patients appears to be their thrombotic risk, with an odds ratio of 20 to 40 and an absolute risk approaching 30% to 75% (30-day risk 53%).^{4,57,67,108} This may correlate with the severity of platelet drop¹⁰⁸ (Level III evidence). Venous clotting is the most common sequela, especially DVT (even in the upper extremity, at the site of central line placement) and pulmonary embolus, although cerebral sinus thrombosis and skin necrosis have also been described.^{31,41,57,67,105,108} Thrombosis of deep tissue venules can also cause limb gangrene or acute adrenal failure, although the former is more commonly implicated with warfarin administration in the setting of acute HIT.^{5,99,102} Arterial thrombosis is much less common but much more serious, and represents a complication capable of occluding aortic, coronary, spinal, mesenteric, cerebral, renal, and distal extremity arteries. This can result in any constellation of problems, including limb or end-organ ischemia/infarction, graft occlusion, myocardial infarction, stroke, multisystem organ failure, amputation, or even death.^{31,48,57,67,92,99,102,108}

The incidence of thrombosis associated with HIT in one retrospective review of 127 patients was 61% and 14% for venous and arterial clots, respectively. Half of these patients were identified as having HIT as a result of the thrombotic event¹⁰⁸ (Level III evidence).

Diagnostic algorithm

Lo and colleagues have popularized a validated algorithm for facilitating early identification of HIT (Level II evidence). Termed the '4 T's Test', this formula calculates an HIT Score based on four parameters: 1) % decrease or absolute nadir of thrombocytopenia, 2) timing of platelet count decline, 3) presence of thrombotic event, and 4) presence of viable alternative explanations for thrombocytopenia. Each category is given 0, 1, or 2 points, and the numeric total results in determination of an overall low, intermediate, or high probability of HIT and concomitant need (or lack thereof) for any further confirmatory serologic testing. This assessment tool is easy to understand and has been prospectively validated by an increasing number centers, although its utility in patients exhibiting higher scores as well as its true sensitivity, specificity, and reliability are still somewhat unclear.^{18,20a,58,80a,90} When HIT is suspected, performing immediate confirmatory serological assays is paramount. Because of the many complexities involved in managing these patients, consultation with both the vascular and hematology services should also be obtained.

Serologic assays

Confirmatory assays can be either functional or antigenic. The functional tests, such as the serotonin release assay, the heparin induced platelet aggregation (HIPA) assay, and the ATP release, are both specific and sensitive. However, they are also generally the slowest, costliest, and most difficult to perform.²⁸ By virtue of its greater than or equal to 95% sensitivity and specificity and the fact that it has been clinically validated in a prospectively randomized trial, the 14C-Serotonin release assay remains the diagnostic gold standard^{100,111} (Level I evidence). However, in many labs such tests are not readily available. In these frequent instances, a good alternative is a highly sensitive (91% to 97%) but less specific (74% to 86%) antigenic test such as the solid phase ELISA immunoassay for anti-PF4-heparin.^{4,79,84,85} This is due to its high negative predictive value (greater than or equal to 95%) in ruling out HIT.^{4,78,95,106} While it has been suggested that two confirmatory immunologic assays be considered to prevent false negative or false positive results, a version of the antigenic immunoassay has become increasingly acknowledged as perhaps the best initial serologic test because of the potential discord in trying to interpret multiple assay results.^{20a, 80a} Technological advancements in the complex arena are rapid and forthcoming, however, which will hopefully simplify the testing algorithm in the near future. When performance of the ELISA is supplemented by the serotonin

release assay, sensitivity and specificity approach 100% and 97%, respectively.^{20,37,99,106}

TREATMENT

Mainstream management strategies

The cornerstone of initial management for suspected HIT in all patients, with or without the presence of thrombosis, is immediate cessation of heparin or heparin derived products, including catheters and heparin flushes^{40,72,106} (Level I,II evidence). This treatment alone, however, is not sufficient. Nor is isolated use of a vena cava filter, since the thrombosis can occur anywhere and its subsequent risk after identification of thrombocytopenia in HIT approaches 10% at 2 days, 40% at 1 week, and exceeds 50% at 1 month^{30,38,59,106,108} (Level II, III evidence). 'Heparin allergy' should be noted on the chart, at the bedside, and on all intravenous devices, so that it is easily identified. Both lower extremities must be scanned via ultrasound to rule out DVT. Despite a lack of randomized, prospective trials to dictate optimal pharmacologic management, one must also carefully choose and administer an alternative form of parenteral anticoagulation which lacks cross-reactivity to heparin—as a means of both treating active thrombosis and preventing further or initial thrombosis while the platelet count normalizes^{59,108} (Level I,II,III evidence). There are two priorities to such management: (1) reduction of thrombin generation, and (2) prevention of platelet activation. Current alternatives include direct thrombin inhibitors (DTIs) (lepirudin, argatroban, and bivalirudin) and the factor Xa inhibitor danaparoid. The latter is not currently available in the U.S. due to a shortage, and only two of the former are approved by the Food and Drug Administration (FDA) for HIT treatment in orthopaedics (Level I,II,III evidence).^{14,15,32,33,39,44,53,55,59,60,62,63,101}

There is a comparative 10-fold increase in thrombosis risk and an elevated mortality rate when a DTI is not begun upon recognition of HIT via a low platelet count and positive antibody screen.^{30,38} The direct thrombin inhibitors are unique in their ability to bind circulating and bound (fibrin clot) thrombin, although great care must be exercised in both choosing and titrating these medications because of their 10% to 20% bleeding risk, divergent half lives, lack of adequate antidotes, potential immunogenicity/anaphylaxis, and variable dependence on hepatic or renal clearance.^{13,30,32,44,54,59,60,92} It remains unclear for how long HIT-affected patients should be treated with these drugs, although most agree that they should be administered at least until the platelets recover, and thereafter supplanted by oral anticoagulant therapy for another 3 to 6 months, depending upon thrombotic severity^{4,106} (Level III,IV evidence). Evidence is also lacking in determining to what level these medications improve outcome, since even with appropriate administration their utility in preventing

hemorrhage, new thrombosis, amputation, and death is incomplete^{45,54,55} (Level II,III,IV evidence).

Potential alternative treatments

A number of other alternative therapies also exist for treatment consideration in HIT, although they are not advocated as mainstays of management. Although warfarin as a sole or first-line therapeutic agent is contraindicated in acute HIT because it increases microvascular thrombosis and can lead to skin or venous limb gangrene, warfarin is considered effective when employed after initial treatment with a direct thrombin inhibitor as a means of transition towards long term oral anticoagulation.^{40,86,105,116} Warfarin can safely be used once platelet counts reach 150,000 per cubic millimeter, as long as the direct thrombin inhibitors have been used for at least 5 days prior and there are at least 48 hours of overlap between the two agents^{25,96,106,117} (Level I,II evidence). Although many other agents have been mentioned as potential therapeutic options, little data support their use and they remain unproven (Level IV,V evidence). These include antiplatelet agents such as aspirin, Arvin, dextran, plasmapheresis, thrombolytic therapy, thromboembolectomy, and intravenous IgG.^{47,50} Platelet transfusions are contraindicated because they may augment the consumptive process and propagate thrombosis.

There are still other potentially promising agents on the horizon. These include the synthetic heparin pentasaccharide analogue, fondaparinux, which activates antithrombin III^{43,74,102} (Level IV,V evidence). Although neither the FDA nor the American College of Chest Physicians (ACCP) advocate its use for preventing or treating HIT, there are anecdotal reports of its successful employment in this capacity⁸⁵ (Level III evidence). Unlike heparin, fondaparinux has been purported not to interact with platelets, PF4, other plasma proteins, or cellular elements, and hence not to produce HIT. However, within this past year the first known case report of documented fondaparinux-provoked HIT has been published by Warkentin et al.¹¹² (Level IV evidence).

Future trends

The issue as to whether or not patients who develop and recover from HIT can receive a heparin product again has yet to be answered definitively. While this has been shown possible for cardiac patients, there are a number of other patient populations in which this remains unclear. These include orthopedic patients, patients on dialysis or in the ICU, and patients undergoing interventional cardiology.^{1,79} Heparin-dependent antibodies do not invariably reappear with subsequent heparin use,¹¹⁰ and this may have promise for future prevention of this problem in affected patients who require heparin. Unfortunately, aside from complete abstinence from any heparin or heparin-derived product, there to date remains no agreed upon preventive measure against the development of HIT. The

ACCP has yet to provide any recommendation on this question.

There are currently a number of newer antithrombotic drugs touted to be potential solutions to avoiding HIT because they lack any clear association with the disease. These include heparinoids such as danaparoid, synthetic heparin pentasaccharides such as idraparinux, oral direct thrombin inhibitors such as ximelagatran, and oral anti-factorXa drugs such as razaxaban, rivaroxaban, efegatran, and dabigatran. However, none are backed by any validated evidence to support such a role.

RECOMMENDATIONS FOR MONITORING

The most recent ACCP guidelines, published in 2008, list a number of specific recommendations for screening patients potentially at risk for HIT²⁵. The grading of these recommendations, however, unfortunately denotes marginal scientific evidence to support these findings, and the recommendations are frequently vague and ill defined, underscoring the need for further research. They are as follows: 1) Patients with heparin exposure who are felt to be at greater than 1.0% risk of HIT are recommended to receive platelet count monitoring (Grade 1C); 2) Patients either actively receiving heparin or having received it within the past 2 weeks whose platelet counts drop greater than or equal to 50% and/or who develop a thrombosis between 5 to 14 days following initial exposure should be assessed for possible HIT even if they are no longer on the heparin agent when these occur (Grade 1C); 3) Patients who are strongly suspected of having or confirmed to have HIT, regardless of the presence or absence of thrombosis, should be placed on an alternative, non-heparin anticoagulant such as danaparoid (Grade 1B), lepirudin (Grade 1C), argatroban (Grade 1C), fondaparinux (Grade 2C), or bivalirudin (Grade 2C) in lieu of further management with UFH, LMWH, or vitamin K antagonists (Grade 1B); 4) Coumadin therapy for patients with suspected or confirmed HIT should only be used after normalization of the platelet count to at least $150 \times 10^9/L$, and begun only at low (less than or equal to 5 mg) initiating doses (Grade 1B); 5) The three aforementioned Grade 1 non-heparin anticoagulants, once begun, should be continued until the platelet count has reached a stable plateau, the INR has reached the desired target range, and there has been at least a 5-day overlap between non-heparin and vitamin K antagonist anticoagulation (Grade 1B); 6) For patients receiving vitamin K antagonists at the time of diagnosis of HIT, use of vitamin K (10 mg po or 5 to 10 mg iv) is recommended (Grade 1C).

For patients receiving heparin who have a perceived risk of HIT between 0.1–1.0%, platelet count monitoring is recommended (Grade 2C). For patients beginning UFH or LMWH treatment and who have received UFH within the past 100 days, or in those with unknown exposure, a baseline platelet count followed by a repeat platelet count within 24 hours of

heparin exposure is recommended (Grade 1C). For patients who develop acute inflammatory, cardiorespiratory, neurologic, or alternative unusual symptoms and signs within 30 minutes of an intravenous UFH bolus, an immediate platelet count is recommended for comparison to previous platelet levels (Grade 1C). For patients who are receiving therapeutic dose UFH, platelet counts are recommended at least every 2 to 3 days from day 4 to 14 or until heparin is discontinued, whichever occurs first (Grade 2C). For patients who are receiving post-operative anti-thrombotic prophylaxis with UFH and hence those with an HIT greater than 1.0%, every other day platelet count monitoring between post-operative day 4 to 14 or until UFH is stopped, whichever occurs first (Grade 2C). For post-operative patients receiving prophylactic dose LMWH or intravascular catheter UFH flushes, who have an estimated HIT risk of 0.1% to 1.0%, platelet count monitoring is suggested at least every 2 to 3 days from day 4 to 14 or until heparin is stopped, whichever occurs first (Grade 2C). For patients receiving fondaparinux thromboprophylaxis or treatment (Grade 1C), and in others who are also perceived to have an HIT risk greater than 0.1% (Grade 2C), no platelet count monitoring is recommended. In outpatients who will receive heparin prophylaxis or treatment, informed consent should include HIT and its typical sequelae, and the patient should be advised to seek medical advice if these events occur (Grade 2C). In patients who receive heparin or in whom heparin treatment is anticipated, routine HIT antibody testing is not recommended in the absence of thrombocytopenia, thrombosis, heparin induced skin lesions, or other signs suggestive of HIT (Grade 1C).²⁵

Interestingly, it is very important to note that, to date, neither the ACCP nor any other expert panel has provided any formal recommendations for monitoring patients once they are discontinued from active heparin derivative treatment, nor has any appropriate timeline for post-treatment screening ever been provided, despite the various case reports of HIT which have been reported in these settings.^{25,26,74}

Based on the current review of the literature, and in consideration of the timeline in which patients can present with HIT, one might consider other steps to monitor for HIT. These include: 1) obtaining a preoperative baseline platelet count in any orthopaedic surgical patient in whom exposure to heparin or a heparin derived product is anticipated, 2) obtaining followup platelet counts in any patient while on the agent, on day 1 (24 hours after exposure) and once a week thereafter, and 3) obtaining weekly platelet counts for 4 weeks after discontinuing the agent for any patient having been exposed to heparin derived products perioperatively, regardless of dosage, agent type, or length of use. One should watch for a fall in platelet count greater than 30% to 50% or an absolute count below 100, and any sign or symptom suggesting arterial or venous thrombosis at any site. Lastly, one should be wary of all patients who present with VTED, particularly if the patient has a known or suspected history of

recent heparin exposure, hospitalization, nursing home care, or VNA care. In these patients, screening platelet counts should be obtained.

SUMMARY

Diagnosis of HIT requires a very high index of suspicion due to lack of a sine qua non test, an often delayed onset and varied nature of presentation, and a very low incidence. As a general rule, any recently hospitalized or postoperative patient with a documented or potential history of heparin/derivative exposure who exhibits an acute drop in platelet count of 50% or more from baseline should be ruled out for HIT, and, in the presence of thrombosis of any kind, assumed to have the disease until proven otherwise. Initial treatment includes immediate cessation of all heparin-derived products, followed by administration of a rapidly acting non-heparin derived anticoagulant and supportive care. Immediate involvement of the hematology and vascular surgery services are strongly recommended.

1. The success of heparin-derivative chemoprophylaxis in avoiding the potentially fatal complications of VTED in at-risk orthopaedic surgical patients has made it one of the gold standards in the United States today, but this efficacy has not come without a price.
2. The more severe immune-mediated form of HIT (HIT Type II) is a complication that has been documented to occur after exposure to even minute quantities of these heparin-related products, including singular doses of LMWH or introduction of a heparin coated catheter or flush.
3. HIT can be a limb- and life-threatening problem, and orthopaedic surgical patients appear to be among the highest risk populations to acquire the most catastrophic form of this potentially devastating disorder. Despite this fact, however, there is little in the orthopaedic literature regarding this disease.
4. A high index of suspicion is paramount in diagnosing HIT, which must be considered in any orthopaedic patient who exhibits an abrupt, significant platelet decline (greater than or equal to 30% to 50%), or presents with a diagnosis of VTED, especially in the setting of any recent hospitalization or suspected heparin exposure.
5. HIT has no sine qua non diagnostic test, and can present in myriad ways as a rapid (0 to 4 days), classic (5 to 10 days), or delayed (9 to 40 days) onset disease after initial heparin-derivative exposure. Any suspicion should be followed up immediately with at least a platelet count, and possibly also a venous ultrasound. Confirmation is by serologic testing.

6. Although the natural history of HIT is unpredictable and its optimal management strategy and impact on outcome unclear, early recognition is imperative because early intervention appears to help. Immediate cessation of all heparin-derivative products is the cornerstone of initial management, followed by careful pharmacologic and supportive care guided by hematology and vascular consultation.
7. HIT may represent another autoimmune disorder, with perhaps the greatest risk in patients who are genetically predisposed to such problems or who have innately high PF4 levels. In the future, hopefully genetic pre-testing and non-cross reactive pharmaceutical agents capable of replacing heparin will eradicate HIT.

REFERENCES

1. **Alving, BM:** A. How I treat heparin-induced thrombocytopenia and thrombosis. *Blood*. 2003 **101**(1):31–7, 2003.
2. **Anderson, FA Jr.; Hirsh, J; White, K; Fitzgerald, RH Jr.** Temporal trends in prevention of venous thromboembolism following primary total hip or knee arthroplasty 1996–2001: findings from the Hip and Knee Registry. *Chest*. **124**:349S–356S, 2003.
3. **Arepally, G; Cines, DB:** Pathogenesis of heparin-induced thrombocytopenia and thrombosis. *Autoimmun. Rev.* **1**:125–132, 2002.
4. **Arepally, GM; Ortel, TL:** Clinical practice. Heparin-induced thrombocytopenia. *N Engl. J. Med.* **355**:809–817, 2006.
5. **Arthur, CK; Grant, SJB; Murray, WK; et al.:** Heparin-associated acute adrenal insufficiency. *Aust. N Z J Med.* **15**:454–5, 1985.
6. **Baird, RA; Convery, R:** Arterial thromboembolism in patients receiving systemic heparin therapy: a complication associated with heparin-induced thrombocytopenia. *J Bone Joint Surg. Am.* **59**:1061–1064, 1977.
7. **Barber, FA; Burton, WC; Guyer, R:** The heparin-induced thrombocytopenia and thrombosis syndrome. Report of a case. *J Bone Joint Surg. Am.* **69**:935–937, 1987.
8. **Bauer, TL; Arepally, G; Konkle, BA; et al.:** Prevalence of heparin-associated antibodies without thrombosis in patients undergoing cardiopulmonary bypass surgery. *Circulation*. **95**:1242–6, 1997.
9. **Bicalho, PS; Hozack, WJ; Rothman, RH; Eng, K:** Treatment of early symptomatic pulmonary embolism after total joint arthroplasty. *J. Arthroplasty*. **11**:522–524, 1996.
10. **Blank, M; Shoenfeld, Y; Tavor, S; et al.:** Anti-platelet factor 4/heparin antibodies from patients with heparin-induced thrombocytopenia provoke direct activation of microvascular endothelial cells. *Int. Immunol.* **14**:121–9, 2002.
11. **Caprini, JA:** Thrombosis risk assessment as a guide to quality patient care. *Dis. Mon.* **51**:70–78, 2005.
12. **Caprini, JA; Tapson, VF; Hyers, TM; et al.:** Treatment of venous thromboembolism: adherence to guidelines and impact of physician knowledge, attitudes, and beliefs. *J. Vasc. Surg.* **42**:726–733, 2005.
13. **Cardenas, GA; Deitcher, SR:** Risk of anaphylaxis after reexposure to intravenous lepirudin in patients with current or past heparin-induced thrombocytopenia. *Mayo Clin. Proc.* **80**:491–3, 2005.
14. **Chong, BH; Gallus, AS; Cade, JF; et al.:** Prospective randomized open-label comparison of danaparoid with dextran 70 in the treatment of heparin-induced thrombocytopenia with thrombosis: a clinical outcome study. *Thromb. Haemost.* **86**:1170–1175, 2001.
15. **Chong, BH; Ismail, F; Cade, J; et al.:** Heparin-induced thrombocytopenia: studies with a new low molecular weight heparinoid, Org 10172. *Blood*. May **1**:73(6):1592–6, 1989.
16. **Cines, DB; Rauova, L; Arepally, G; et al.:** Heparin-induced thrombocytopenia: an autoimmune disorder regulated through dynamic autoantigen assembly/disassembly. *J. Clin. Apher.* **22**:31–6, 2007.
17. **Colwell, CW Jr.; Spiro, TE; Trowbridge, AA; et al.:** Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. A clinical trial comparing efficacy and safety. Enoxaparin Clinical Trial Group. *J Bone Joint Surg. Am.* **76**:3–14, 1994.
18. **Davoren, A; Aster, RH:** Heparin-induced thrombocytopenia and thrombosis. *Am. J Hematol.* **81**:36–44, 2006.
19. **Dahl, OE; Caprini, JA; Colwell CW, Jr.; et al.:** Fatal vascular outcomes following major orthopedic surgery. *Thromb. Haemost.* **93**(5):860–6, 2005.
20. **Deitcher, SR; Carman, TL:** Heparin-induced thrombocytopenia: natural history, diagnosis, and management. *Vasc Med.* **6**:113–119, 2001.
- 20a. **Denys, B; Stove, V; Phillippe, J; Devreese, K:** A clinical-laboratory approach contributing to a rapid and reliable diagnosis of heparin induced thrombocytopenia. *Thromb Res.* DOI:10.1016/j.thrombres.2008.04.020. In press, June 2008.
21. **Fabris, F; Luzzatto, G; Soini, B; et al.:** Risk factors for thrombosis in patients with immune mediated heparin-induced thrombocytopenia. *J Intern. Med.* **252**:149–154, 2002.
22. **Fabris, F; Luzzatto, G; Stefani, PM; et al.:** Heparin-induced thrombocytopenia. *Haematologica.* **85**:72–81, 2000.
23. **Freedman, KB; Brookenthal, KR; Fitzgerald RH, Jr.; Williams, S; Lonner, JH:** A meta-analysis of thromboembolic prophylaxis following elective total hip arthroplasty. *J Bone Joint Surg.* **82-A**(7):929–38, 2000.
24. **Friedman, RJ; Gallus, AS; Cushner, FD; Fitzgerald, G; Anderson, FA, Jr.:** Physician compliance with guidelines for deep-vein thrombosis prevention in total hip and knee arthroplasty. *Current medical research and opinion.* **24**:87–97, 2008.
25. **Warkentin, TE; Greinacher, A; Koster, A; Lincoff, AM:** Treatment and prevention of heparin induced thrombocytopenia: American College of Chest Physicians evidence based clinical practice guidelines (8th Edition). *Chest*. **133**(6 Suppl):340–380, 2008.
26. **Geerts, WH; Pineo, GF; Heit, JA; et al.:** Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. **126**:338S–400S, 2004.
27. **Girolami, B; Prandoni, P; Stefani, PM; et al.:** The incidence of heparin-induced thrombocytopenia in hospitalized medical patients treated with subcutaneous unfractionated heparin: a prospective cohort study. *Blood*. **101**:2955–9, 2003.
28. **Greinacher, A; Amiral, J; Dummel, V; et al.:** Laboratory diagnosis of heparin-associated thrombocytopenia and comparison of platelet aggregation test, heparin-induced platelet activation test, and platelet factor 4/heparin enzyme-linked immunosorbent assay. *Transfusion.* **34**(5):381–5, 1994.
29. **Greinacher, A; Eichler, P; Lietz, T; Warkentin, TE:** Replacement of unfractionated heparin by low-molecular-weight heparin for postorthopedic surgery antithrombotic prophylaxis lowers the overall risk of symptomatic thrombosis because of a lower frequency of heparin-induced thrombocytopenia. *Blood*. **106**:2921–2, 2005.
30. **Greinacher, A; Eichler, P; Lubenow, N; Kwasny, H; Luz, M:** Heparin-induced thrombocytopenia with thromboembolic complications: meta-analysis of 2 prospective trials to assess the value of parenteral treatment with lepirudin and its therapeutic aPTT range. *Blood*. **96**(3):846–51, 2000.
31. **Greinacher, A; Farnar, B; Kroll, H; et al.:** Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408 patients. *Thromb Haemost.* **94**:132–135, 2005.

32. **Greinacher, A; Janssens, U; Berg, G; et al.:** Lepirudin (recombinant hirudin) for parenteral anticoagulation in patients with heparin-induced thrombocytopenia. Heparin-Associated Thrombocytopenia Study (HAT) investigators. *Circulation*. **100**:587–593, 1999.
33. **Greinacher, A; Volpel, H; Janssens, U; et al.:** Recombinant hirudin (lepirudin) provides safe and effective anticoagulation in patients with heparin-induced thrombocytopenia: a prospective study. *Circulation*. **99**:73–80, 1999.
34. **Greinacher, A; Warkentin, TE:** Recognition, treatment, and prevention of heparin-induced thrombocytopenia: review and update. *Thromb Res*. **118**(2):165–76, 2006.
35. **Gruel, Y; Pouplard, C; Nguyen, P; et al.:** Biological and clinical features of low-molecular-weight heparin-induced thrombocytopenia. *Br. J Haematol*. **121**(5):786–92, 2003.
36. **Hanslow, SS; Grujic, L; Slater, HK; Chen, D:** Thromboembolic disease after foot and ankle surgery. *Foot Ankle Int*. **27**:693–695, 2006.
37. **Harenberg, J; Huhle, G; Giese, C; et al.:** Determination of serotonin release from platelets by enzyme immunoassay in the diagnosis of heparin-induced thrombocytopenia. *Br. J Haematol*. **109**:182–6, 2000.
38. **Hirsh, J; Heddle, N; Kelton, JG:** Treatment of heparin-induced thrombocytopenia: a critical review. *Arch. Intern Med*. **164**(4):361–9, 2004.
39. **Hirsh, J; Raschke, R:** Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. **126**:188S–203S, 2004.
40. **Hirsh, J; Warkentin, TE; Shaughnessy, SG; et al.:** Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest*. **119**:64S–94S, 2001.
41. **Hong, AP; Cook, DJ; Sigouin, CS; Warkentin, TE:** Central venous catheters and upper-extremity deep-vein thrombosis complicating immune heparin-induced thrombocytopenia. *Blood*. **101**(8):3049–51, 2003.
42. **Kejariwal, D:** Heparin-induced thrombocytopenia: a complication of thromboprophylaxis. *J Bone Joint Surg. Br*. **88**:392–393, 2006.
43. **Kelton, JG:** The pathophysiology of heparin-induced thrombocytopenia: biological basis for treatment. *Chest*. **127**:9S–20S, 2005.
44. **Kiser, TH; Fish, DN:** Evaluation of bivalirudin treatment for heparin-induced thrombocytopenia in critically ill patients with hepatic and/or renal dysfunction. *Pharmacotherapy*. **26**(4):452–60, 2006.
45. **Kodityal, S; Nguyen, PH; Kodityal, A:** Argatroban for suspected heparin-induced thrombocytopenia: contemporary experience at a large teaching hospital. *J Intensive Care Med*. **21**:86, 2006.
46. **Lacey, JV; Penner, JA:** Management of idiopathic thrombocytopenic purpura in the adult. *Semin Thromb Hemost*. **3**:160–74, 1977.
47. **Lam, F; Hussain, S; Li, P:** Limb loss following the use of heparin. A lesson to be remembered. *J Bone Joint Surg. Br*. **84**:588–589, 2002.
48. **LaMonte, MP; Brown, PM; Hursting, MJ:** Stroke in patients with heparin-induced thrombocytopenia and the effect of argatroban therapy. *Crit. Care Med*. **2004**; **32**:976–80, 2004.
49. **Lapidus, LJ; Rosfors, S; Ponzer, S; et al.:** Prolonged thromboprophylaxis with dalteparin after surgical treatment of achilles tendon rupture: a randomized, placebo-controlled study. *J Orthop. Trauma*. **21**:52–57, 2007.
50. **Laster, JL; Nichols, WK; Silver, D:** Thrombocytopenia associated with heparin-coated catheters in patients with heparin-associated antiplatelet antibodies. *Arch Intern. Med*. **149**:2285–2287, 1989.
51. **Laster, J; Silver, D:** Heparin-coated catheters and heparin-induced thrombocytopenia. *J Vasc. Surg*. **7**:667, 1988.
52. **Levine, RL; McCollum, D; Hursting, MJ:** How frequently is venous thromboembolism in heparin-treated patients associated with heparin-induced thrombocytopenia? *Chest*. **130**(3):681–7, 2006.
53. **Lewis, BE; Wallis, DE; Berkowitz, SD; et al.:** Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. *Circulation*. **103**:1838–1843, 2001.
54. **Lewis, BE; Wallis, DE; Leya, F; Hursting, MJ; Kelton, JG:** Argatroban-915 Investigators. Effects of argatroban therapy, demographic variables, and platelet count on thrombotic risks in heparin-induced thrombocytopenia. *Chest*. **129**:1407–56, 2006.
55. **Lewis, BE; Wallis, DE; Leya, F; Hursting, MJ; Kelton, JG:** Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. *Arch Intern. Med*. **163**:1849–1856, 2003.
56. **Lilikakis, AK; Papapolychroniou, T; Macheras, G; Michelinakis, E:** Thrombocytopenia and intra-cerebral complications associated with low-molecular-weight heparin treatment in patients undergoing total hip replacement. A report of two cases. *J Bone Joint Surg. Am*. **88**:634–638, 2006.
57. **Lindhoff-Last, E; Wenning, B; Stein, M; et al.:** Risk factors and long-term follow-up of patients with the immune type of heparin-induced thrombocytopenia. *Clin. Appl. Thromb Hemost*. **8**:347–352, 2002.
58. **Lo, GK; Juhl, D; Warkentin, TE; et al.:** Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost*. **4**:759–765, 2006.
59. **Lubenow, N; Eichler, P; Lietz, T; Farner, B; Greinacher, A:** Lepirudin for prophylaxis of thrombosis in patients with acute isolated heparin-induced thrombocytopenia: an analysis of 3 prospective studies. *Blood*. **104**:3072–3077, 2004.
60. **Lubenow, N; Eichler, P; Lietz, T; Greinacher, A:** Lepirudin in patients with heparin induced thrombocytopenia - results of the third prospective study (HAT-3) and a combined analysis of HAT-1, HAT-2, and HAT-3. *J. Thromb Haemost*. **3**:2428–2436, 2005.
61. **Lubenow, N; Kempf, R; Eichner, A; et al.:** Heparin-induced thrombocytopenia: temporal pattern of thrombocytopenia in relation to initial use or reexposure to heparin. *Chest*. **122**:37–42, 2002.
62. **Magnani, HN:** Heparin-induced thrombocytopenia (HIT): an overview of 230 patients treated with organon (Org 10172). *Thromb Haemost*. **70**(4):554–61, 1993.
63. **Magnani, HN; Gallus, A:** Heparin-induced thrombocytopenia (HIT). A report of 1,478 clinical outcomes of patients treated with danaparoid (Orgaran) from 1982 to mid-2004. *Thromb Haemost*. **95**:967–981, 2006.
64. **Mandt, PR; Robinson, CA; Sarnoff, RB; Colwell, CW Jr:** Heparin-associated thrombocytopenia with venous thrombosis. A case report. *J Bone Joint Surg. Am*. **67**:1123–1124, 1985.
65. **Markovich, GD; Russell, JM; Gagne, P:** Antibody-induced arterial thromboembolism resulting in amputation after total knee arthroplasty. *J. Arthroplasty*. **12**:350–352, 1997.
66. **Martel, N; Lee, J; Wells, PS:** Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood*. **106**:2710–2715, 2005.
67. **Menajovsky, LB:** Heparin-induced thrombocytopenia: clinical manifestations and management strategies. *Am J Med*. **118**Suppl 8A:21S–30S, 2005.
68. **Micheli, LJ:** Thromboembolic complications of cast immobilization for injuries of the lower extremities. *Clin. Orthop. Relat. Res*. **191**–195, 1975.
69. **Mizel, MS; Temple, HT; Michelson, JD; et al.:** Thromboembolism after foot and ankle surgery. A multicenter study. *Clin. Orthop. Relat. Res*. **180**–185, 1998.
70. **Moore, JR; Weiland, AJ:** Heparin-induced thromboembolism: a case report. *J. Hand Surg. [Am]*. **4**:382–385, 1979.
71. **Muslimani, AA; Ricaurte, B; Daw, HA:** Immune heparin-induced thrombocytopenia resulting from preceding exposure to heparin catheter flushes. *Am J Hematol*. **82**:652–5, 2007.
72. **Napolitano, LM; Warkentin, TE; Almahameed, A; Nasraway, SA:** Heparin-induced thrombocytopenia in the critical care setting: diagnosis and management. *Crit. Care Med*. **34**:2898–2911, 2006.
73. **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. *Blood*. **96**:182–7, 2000.
74. **Papadopoulos, S; Flynn, JD; Lewis, DA:** Fondaparinux as a treatment option for heparin induced thrombocytopenia. *Pharmacotherapy*. **27**:921–926, 2007.
 - 74a. **Patel, VP; Bong, M; DiCesare, PE:** Heparin Induced Thrombocytopenia and Thrombosis. *Am J Orthopedics* **36**(5):255–260, 2007.
 75. **Patterson, BM; Marchand, R; Ranawat, C:** Complications of heparin therapy after total joint arthroplasty. *J Bone Joint Surg. Am.* **71**:1130–1134, 1989.
 76. **Pitto, RP; Hamer, H; Heiss-Dunlop, W; Kuehle, J:** Mechanical prophylaxis of deep-vein thrombosis after total hip replacement a randomised clinical trial. *J Bone Joint Surg. Br.* **86**:639–642, 2004.
 77. **Planès, A; Samama, MM; Lensing, AW; et al.:** Prevention of deep vein thrombosis after hip replacement—comparison between two low-molecular heparins, tinzaparin and enoxaparin. *Thromb Haemost.* **81**:22–5, 1999.
 78. **Pötzsch, B; Klövekorn, WP; Madlener, K:** Use of heparin during cardiopulmonary bypass in patients with a history of heparin-induced thrombocytopenia. *N Engl J. Med.* **17343**(7):515, 2000.
 79. **Pouplard, C; Amiral, J; Borg, JY; et al.:** Decision analysis for use of platelet aggregation test, carbon 14-serotonin release assay, and heparin-platelet factor 4 enzyme-linked immunosorbent assay for diagnosis of heparin-induced thrombocytopenia. *Am J Clin Pathol.* **111**(5):700–6, 1999.
 80. **Pouplard, C; Iochmann, S; Renard, B; et al.:** Induction of monocyte tissue factor expression by antibodies to heparin-platelet factor 4 complexes developed in heparin-induced thrombocytopenia. *Blood*. **97**:3300–2, 2001.
 - 80a. **Pouplard, C; Gueret, P; Fourassier, M; Ternisien, C; Regina, S; Gruel, Y:** Prospective evaluation of the '4Ts' scope and particle gel immunoassay specific to heparin/PF4 for the diagnosis of heparin induced thrombocytopenia. *J Thromb. Haemost.* **5**(7):1373–9, 2007.
 81. **Rauova, L; Zhai, L; Kowalska, MA; et al.:** Role of platelet surface PF4 antigenic complexes in heparin-induced thrombocytopenia pathogenesis: diagnostic and therapeutic implications. *Blood*. **107**:2346–53, 2006.
 82. **Rice, L; Attisha, WK; Drexler, A; Francis, JL:** Delayed-onset heparin-induced thrombocytopenia. *Ann. Intern. Med.* **136**:210–215, 2002.
 83. **Schiff, RL; Kahn, SR; Shrier, I; et al.:** Identifying orthopedic patients at high risk for venous thromboembolism despite thromboprophylaxis. *Chest*. **128**:3364–3371, 2005.
 84. **Schenk, S; El-Banayasy, A; Morshuis, M; et al.:** IgG classification of anti-PF4/heparin antibodies to identify patients with heparin-induced thrombocytopenia during mechanical circulatory support. *J Thromb. Haemost.* **5**:235–41, 2007.
 85. **Selleng, K; Warkentin, TE; Greinacher, A:** Heparin-induced thrombocytopenia in intensive care patients. *Crit. Care Med.* **35**(4):1165–76, 2007.
 86. **Smythe, MA; Warkentin, TE; Stephens, JL; Zakalik, D; Mattson, JC:** Venous limb gangrene during overlapping therapy with warfarin and a direct thrombin inhibitor for immune heparin-induced thrombocytopenia. *Am J Hematol.* **71**:50–52, 2002.
 87. **Smythe, MA; Koerber, JM; Mattson, JC:** The incidence of recognized heparin-induced thrombocytopenia in a large, tertiary care teaching hospital. *Chest*. **131**:1644–9, 2007.
 88. **Solis, G; Saxby, T:** Incidence of DVT following surgery of the foot and ankle. *Foot Ankle Int.* **23**:411–414, 2002.
 89. **Stanton, PE Jr.; Evans, JR; Lefemine, AA; et al.:** White clot syndrome. *South Med. J.* **81**(5):616–20, 1988.
 90. **Stribling, WK; Slaughter, TF; Houle, TT; Sane, DC:** Beyond the platelet count: heparin antibodies as independent risk predictors. *Am Heart J.* **153**(6):900–6, 2007.
 91. **Suvarna, S; Espinasse, B; Qi, R; et al.:** Determinants of PF4/heparin immunogenicity. *Blood*. **110**:4253–60, 2007.
 92. **Tardy, B; Lecompte, T; Boelhen, F; et al.:** Predictive factors for thrombosis and major bleeding in an observational study in 181 patients with heparin-induced thrombocytopenia treated with lepirudin. *Blood*. **108**:1492–96, 2006.
 93. **Taylor, LM; Smith, KM:** The paradox of heparin-induced thrombocytopenia: future anticoagulation. *Orthopedics*. **28**:651–654, 2005.
 94. **Taylor, LM; Smith, KM:** The paradox of heparin-induced thrombocytopenia: the initial management. *Orthopedics*. **28**:559–562, 2005.
 95. **Verma, AK; Levine, M; Shalansky, SJ; Carter, CJ; Kelton, JG:** Frequency of heparin-induced thrombocytopenia in critical care patients. *Pharmacotherapy*. **23**:745–53, 2003.
 96. **Wallis, DE; Workman, DL; Lewis, BE; et al.:** Failure of early heparin cessation as treatment for heparin-induced thrombocytopenia. *Am J. Med.* **106**:629–35, 1999.
 97. **Wang, F; Wera, G; Knoblich, GO; Chou, LB:** Pulmonary embolism following operative treatment of ankle fractures: a report of three cases and review of the literature. *Foot Ankle Int.* **23**:406–410, 2002.
 98. **Warkentin, TE:** Clinical presentation of heparin-induced thrombocytopenia. *Semin Hematol.* **35**:9–25, 1998.
 99. **Warkentin, TE:** Heparin-induced thrombocytopenia: a ten-year retrospective. *Annu Rev. Med.* **50**:129–147, 1999.
 100. **Warkentin, TE:** Platelet count monitoring and laboratory testing for heparin-induced thrombocytopenia. *Arch. Pathol Lab. Med.* **126**:1415–1423, 2002.
 101. **Warkentin, TE:** Heparin-induced thrombocytopenia: pathogenesis and management. *Br. J. Haematol.* **121**:535–555, 2003.
 102. **Warkentin, TE:** Think of HIT. *Hematology Am Soc Hematol Educ Program.* 408–414, 2006.
 103. **Warkentin, TE; Cook, RJ; Marder, VJ; et al.:** Anti-platelet factor 4/heparin antibodies in orthopedic surgery patients receiving antithrombotic prophylaxis with fondaparinux or enoxaparin. *Blood*. **106**:3791–3796, 2005.
 104. **Warkentin, TE; Eikelboom, JW:** Who Is (still) getting HIT? *Chest*. **131**:1620–2, 2007.
 105. **Warkentin, TE; Elavathil, LJ; Hayward, CP; et al.:** The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. *Ann. Intern. Med.* **127**:804–812, 1997.
 106. **Warkentin, TE; Greinacher, A:** Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. **126**:311S–337S, 2004.
 107. **Warkentin, TE; Hirte, HW; Anderson, DR; et al.:** Transient global amnesia associated with acute heparin-induced thrombocytopenia. *Am J Med.* **97**:489–91, 1994.
 108. **Warkentin, TE; Kelton, JG:** A 14-year study of heparin-induced thrombocytopenia. *Am J Med.* **101**:502–507, 1996.
 109. **Warkentin, TE; Kelton, JG:** Delayed-onset heparin-induced thrombocytopenia and thrombosis. *Ann Intern. Med.* **135**:502–506, 2001.
 110. **Warkentin, TE; Kelton, JG:** Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med.* **344**:1286–1292, 2001.
 111. **Warkentin, TE; Levine, MN; Hirsh, J; et al.:** Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med.* **332**:1330–1335, 1995.
 112. **Warkentin, TE; Maurer, BT; Aster, RH:** Heparin-induced thrombocytopenia associated with fondaparinux. *N Engl J Med.* **356**:2653–2655; discussion 2653–2655, 2007.
 113. **Warkentin, TE; Roberts, RS; Hirsh, J; Kelton, JG:** An improved definition of immune heparin-induced thrombocytopenia in postoperative orthopedic patients. *Arch Intern. Med.* **163**:2518–2524, 2003.
 114. **Warkentin, TE; Sheppard, JA; Horsewood, P; et al.:** Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood*. **96**:1703–1708, 2000.

115. **Warkentin, TE; Sheppard, JA; Sigouin, CS; et al.:** Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. *Blood.* **108**:2937–41, 2006.
116. **Warkentin, TE; Sikov, WM; Lillicrap, DP:** Multicentric warfarin-induced skin necrosis complicating heparin-induced thrombocytopenia. *Am J Hematol.* **62**:44–48, 1999.
117. **Watson, HG; Keeling DM:** BCSH Taskforce in Haemostasis and Thrombosis. The management of heparin-induced thrombocytopenia. *Br J Haematol.* **135**(2):269, 2006.
118. **White, PW; Sadd, JR; Nensel, RE:** Thrombotic complications of heparin therapy: including six cases of heparin–induced skin necrosis. *Ann Surg.* **190**(5):595–608, 1979.
119. **Wolf, JM; DiGiovanni, CW:** A survey of 702 orthopedic surgeons regarding DVT prophylaxis in foot and ankle trauma surgery. *Orthopedics.* **27**:504–508, 2004.