Heparin-induced thrombocytopenia in the critical care setting: Diagnosis and management^

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Identify patients at high risk of heparin-induced thrombocytopenia (HIT).
2. Identify effective treatment regimens for HIT.
3. Use this information in the clinical setting.

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Background: **Thrombocytopenia is a common occurrence in critical illness, reported in up to 41% of patients. Systematic evaluation of thrombocytopenia in critical care is essential to accurate identification and management of the cause. Although sepsis and hemodilution are more common etiologies of thrombocytopenia in critical illness, heparin-induced thrombocytopenia (HIT) is one potential etiology that warrants consideration.**

Objective: **This review will summarize the pathogenesis and clinical consequences of HIT, describe the diagnostic process, and review currently available treatment options.**

Data Source: **MEDLINE/PubMed search of all relevant primary and review articles.**

Data Synthesis and Conclusions: **HIT is a clinicopathologic syndrome characterized by thrombocytopenia (≥50% from baseline) that typically occurs between days 5 and 14 after initiation of heparin. This temporal profile suggests a possible diagnosis of HIT, which can be supported (or refuted) with a strong positive (or negative) laboratory test for HIT antibodies. When considering the diagnosis of HIT, critical care professionals should monitor platelet counts in patients who are at risk for HIT and carefully evaluate for, a) temporal features of the thrombocytopenia in relation to heparin exposure; b) severity of thrombocytopenia; c) clinical evidence for thrombosis; and d) alternative etiologies of thrombocytopenia. Due to its prothrombotic nature, early recognition of HIT and prompt substitution of heparin with a direct thrombin inhibitor (e.g., argatroban or lepirudin) or the heparinoid danaparoid (where available) reduces the risk of thromboembolic events, some of which may be life-threatening. (Crit Care Med 2006; 34:2898–2911)**

KEY WORDS: thrombocytopenia; heparin; heparin-induced thrombocytopenia; critical care; intensive care unit

Thrombocytopenia is a common laboratory abnormality in critically ill patients that has been associated with adverse outcomes. The incidence of thrombocytopenia in the critical care setting has been reported to vary from 23% to 41% with mortality rates between 38% and 54% in retrospective studies (1–5). Although the incidence of severe thrombocytopenia (platelet counts $<50 \times 10^9$/L) is lower (10%–17%), adverse outcomes are even greater (1–5).

Data from a prospective observational cohort study of 329 surgical intensive

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Table 1. Potential etiologies of thrombocytopenia

- Sepsis and healthcare-associated infections
- Perioperative and postresuscitation hemodilution
- Drug-induced thrombocytopenias, including HIT
- Liver disease/hypersplenism
- Platelet consumption or destruction
- Disseminated intravascular coagulation
- Massive transfusion
- Primary marrow disorder
- Antiphospholipid antibody syndrome/lupus anticoagulant
- Immune thrombocytopenias (ITP, TTP, PTP)
- Intravascular devices (IABP, LVAD, ECMO, pulmonary artery catheter)

HIT, heparin-induced thrombocytopenia; ITP, idiopathic thrombocytopenic purpura; PTP, posttransfusion purpura; TTP, thrombotic thrombocytopenic purpura; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; ECMO, extracorporeal membrane oxygenation.

care unit (ICU) adult patients documented that thrombocytopenia (defined as a platelet count $<150 \times 10^9$/L) was present in 41.3% (n = 136) of patients and independently predicted mortality (6). A drop in platelet count to ≤50% of levels at admission was associated with higher death rates (ICU mortality odds ratio [OR], 6.0; 95% confidence interval [CI], 3.0–12.0; $p < .0001$) than admission variables of severity of illness, including Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II, and multiple organ dysfunction syndrome (MODS) scores (adjusted OR, 4.2; 95% CI, 1.8–10.2).

Most recently, the relationship between the time course of platelet counts and mortality in critically ill patients (n = 1,449) was examined in a cohort analysis of a prospective, multiple-center, observational study in 40 ICUs from 16 countries in Europe, America, and Australia (7). Data were collected from all ICU admissions in a 1-month period, excluding patients <12 yrs old and those with an ICU stay of <48 hrs after uncomplicated surgery. Platelet counts were collected daily throughout the ICU stay, and thrombocytopenia was defined as a platelet count of $<150 \times 10^9$/L. The platelet count decreased significantly in the first days after admission to reach a nadir on day 4 in all patients and was lower in the nonsurvivors (n = 313) than in survivors (n = 1,131) throughout the ICU course. A total of 138 (54%) patients had thrombocytopenia on day 4, and the mortality rate in these patients was increased by two-fold (33% vs. 16%; $p < .05$). Among subjects who stayed in the ICU for >2 wks, thrombocytopenia was present in 20% of these patients by day 14 and was associated with greater mortality rate (66% vs. 16%; $p < .05$). This study documented that late thrombocytopenia is more predictive of death than early thrombocytopenia in critically ill patients but did not address the specific etiology of thrombocytopenia.

Systematic evaluation of thrombocytopenia in critical care is essential to accurate identification and management of the cause. There are numerous potential etiologies of thrombocytopenia in critically ill patients (Table 1). Sepsis is the most common etiology of thrombocytopenia in critical illness, accounting for 48% of cases of thrombocytopenia, but >25% of ICU patients have more than one cause of thrombocytopenia (8). Drug-induced thrombocytopenias present diagnostic challenges, because many medications can cause thrombocytopenia and critically ill patients often receive multiple medications (9). One such drug is heparin—the most common cause of drug-induced thrombocytopenia due to immune mechanisms—and one of the most common drugs administered to critically ill patients.

Heparin-induced thrombocytopenia (HIT) is an anticoagulant-induced *prothrombotic* disorder caused by platelet-activating heparin-dependent antibodies of immunoglobulin G class. The diagnosis of HIT should be considered when the platelet count falls to $<150 \times 10^9$/L (or by >50% from baseline) between days 5 and 14 of exposure to any heparinoid product (10). The thrombocytopenia is usually moderate (mean platelet count is 60×10^9/L) and recovers within a few days of discontinuing heparin. Since heparin use in hospitalized patients is nearly ubiquitous (including those that have occurred recently in other hospitals, or in areas outside the ICU), a high index of suspicion on the clinician's part is necessary for proper recognition. The reported mortality rate associated with HIT ranges between 10% and 20% (11–14). The term "isolated HIT" refers to the development of HIT without any apparent HIT-associated thrombosis, whereas the "HIT thrombotic syndrome" (HITTS) denotes the clinical picture of acute thrombosis complicating HIT.

Once HIT is strongly suspected in a critically ill patient, prompt discontinuation of all heparin sources, including low molecular weight heparins (LMWHs), and substitution of an alternative anticoagulant with a direct thrombin inhibitor should be accomplished without awaiting laboratory confirmation of the presence of HIT antibodies. A clinicopathologic diagnostic approach that integrates clinical findings and results of HIT antibody testing is recommended.

PATHOPHYSIOLOGY OF HIT

HIT is an immune-mediated hypersensitivity reaction to the platelet factor 4 (PF4)/heparin complex. PF4 is a heparin-binding tetrameric protein found naturally in platelet α granules and bound to heparin sulfate on endothelial surfaces. Binding of PF4 with heparin results in conformational changes in PF4 that produces an immune response (i.e., the production of immunoglobulin G antibodies). Anti-PF4/heparin antibodies are produced by a relatively high percentage of heparin-treated patients; however, only a minority of patients with antibodies will develop thrombocytopenia.

Formation of immune complexes comprised of immunoglobulin G/PF4/heparin on the platelet surface leads to clustering of the platelet FcγIIa receptors and thereby strong platelet activation. The release of PF4 from platelet activation leads to further formation of PF4/heparin complexes resulting in progressive platelet activation. Neutralization of the anticoagulant activity of heparin by PF4 is another possible prothrombotic effect. Platelet activation also causes profound platelet membrane changes, including the formation of procoagulant platelet-derived microparticles, leading to accelerated thrombin generation, and the hypercoagulability state that characterizes HIT (Fig. 1) (15–17). These antibody complexes also bind to heparin (or heparin-like molecules) on endothelial cells and monocytes, leading to tissue factor expression by these cells (18, 19). Anti-PF4/heparin antibodies are transient: They usually become undetectable a median of 50–85 days following the occurrence of HIT, depending on the assay used (20). In some patients, antibodies remain detectable for several months, usually at low levels. If heparin is readministered to a patient who has high levels of HIT antibodies, abrupt onset of thrombocytopenia can occur. However, this event is unlikely >100 days following any heparin exposure (20).

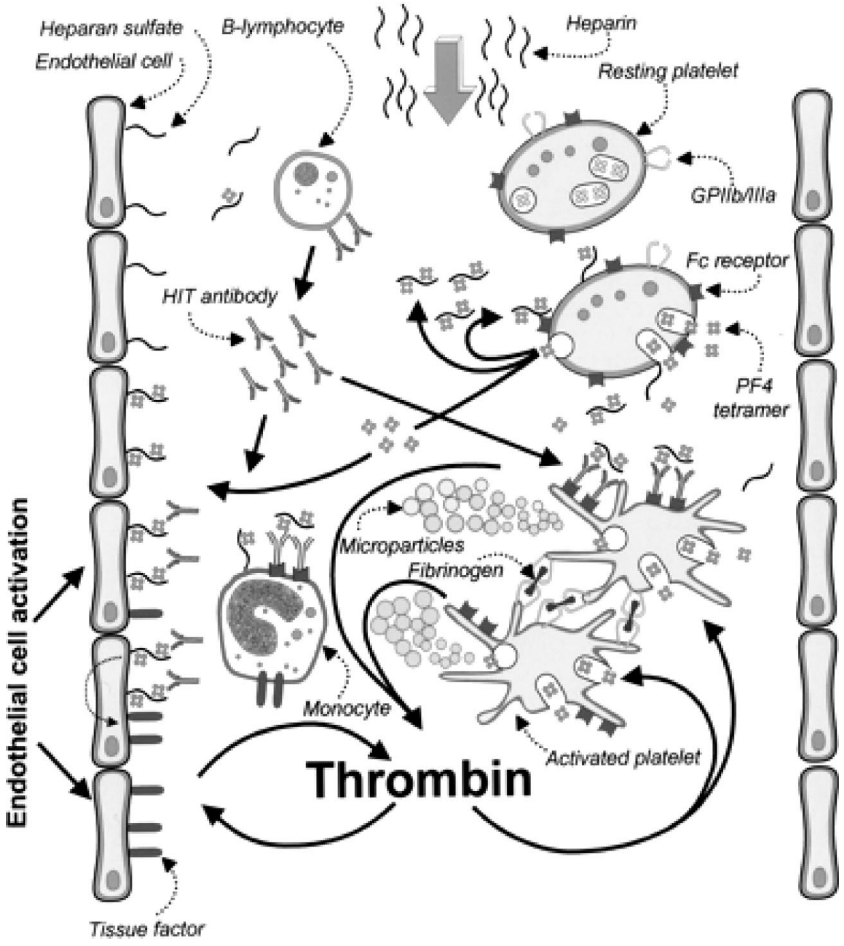


Figure 1. Pathogenesis of heparin induced thrombocytopenia (*HIT*). HIT antibodies of immunoglobulin (Ig) G class bind to multimolecular complexes of platelet factor 4 (*PF4*) and heparin on platelet surfaces, resulting in platelet activation when the IgG molecules interact with the platelet Fc receptors. Platelet-derived microparticles are generated, which enhance coagulation reactions. In addition, HIT antibodies can activate endothelium and monocytes, exacerbating the procoagulant response. Activation of platelets and increased production of thrombin could explain the high risk of arterial and venous thrombosis in HIT. Reproduced with permission from Warkentin TE: Heparin-induced thrombocytopenia: Diagnosis and management. *Circulation* 2004; 110:e454–e458.

FREQUENCY AND THROMBOTIC SEQUELAE OF HIT

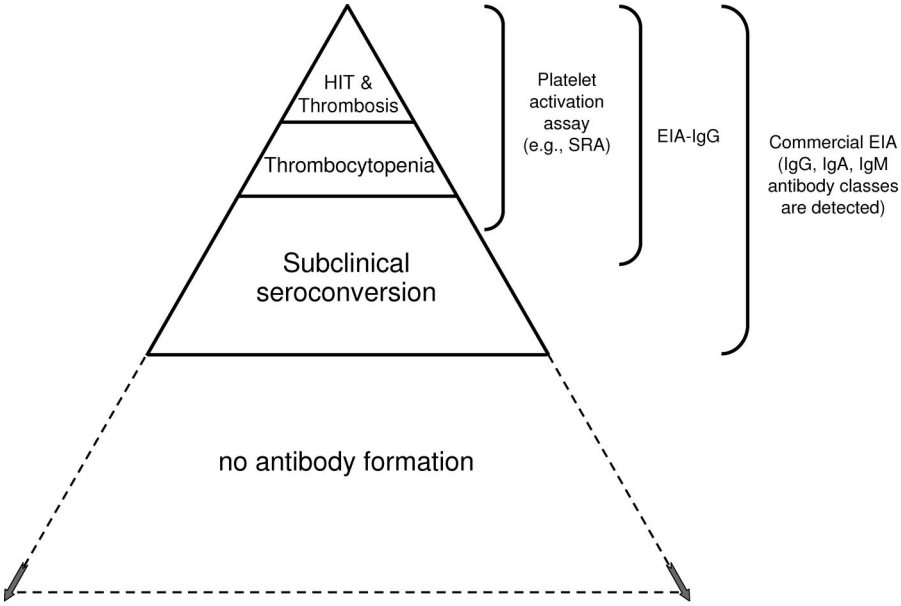
Frequency. The frequency of HIT varies based on the type of heparin used and the patient population. Although HIT has been described for every heparin preparation given at any dose, unfractionated heparin (UFH) is far more likely than LMWH to cause both HIT antibody formation and clinical HIT (21–23). Bovine lung-derived UFH has been reported to cause HIT more often than porcine intestine-derived UFH (24).

Surgical patients appear to be at a higher risk for HIT than medical patients, and individuals exposed to larger doses of UFH for a longer duration appear to be at higher risk for HIT. It is important to note that seroconversion does not necessarily constitute a diagnosis of HIT. For example, although up to 15% of patients may test positive for the HIT antibody by the PF4/heparin enzyme-linked immunosorbent assay (ELISA), the incidence of HIT in this population is only 3–5%.

Figure 2 illustrates this "iceberg" phenomenon of HIT, which is useful for understanding the interrelationship between various HIT antibody assays and clinical manifestations (thrombocytopenia and thrombosis) of HIT. The highest frequency of HIT (about 3–5%) has been reported in postoperative orthopedic patients who received prophylactic doses of UFH for 10–14 days (21–23, 25). The incidence of HIT among cardiac surgical patients receiving postoperative UFH for a week or more is 1–3%. The incidence of HIT among medical patients who were given prophylactic or therapeutic doses of UFH is lower (≤1%) (22, 23, 25, 26). Patient groups at lowest risk of developing HIT are medical or obstetric patients being treated with prophylactic doses of LMWH. However, the risk of LMWH-induced HIT may be as high as 0.5% in orthopedic patients receiving treatment for 10–14 days (Table 2) (22, 23, 25–28).

Comprehensive data on the frequency of HIT in critical care are sparse, with only five published studies (Table 3), two studies in general critical care patients and three studies in specialty populations (subarachnoid hemorrhage, heart transplant, pediatric critical care). One prospective study documented the frequency of HIT in a large cohort (n = 748) of critically ill patients using a positive 14C-serotonin release assay (SRA) as the reference standard (29). Of 267 critical care patients in a combined intensive and coronary care unit who were exposed to heparin for a sufficient length of time to be considered at risk for HIT, 40 patients (15%) met the clinical criteria for suspicion of HIT. Serum samples were available for 32 of these patients, but only one patient tested positive by the predefined serologic criteria, yielding a HIT frequency of 0.39%. Of the 31 patients testing negative in the SRA, nine tested positive in the PF4/heparin ELISA, suggesting the potential for a false diagnosis of HIT in this patient population. This inference is based on prospective studies of postorthopedic and postcardiac surgery patients indicating that clinical HIT generally yields strong positive testing in both the SRA and ELISA, whereas subclinical seroconversion often manifests as a positive ELISA alone (17).

In a prospective cohort study investigating the prevalence, incidence, and risk factors for lower extremity deep vein thrombosis (DVT) among 261 critically ill medical-surgical patients (most receiving UFH) over a 1-yr period, the investigators also provided information on results of testing for HIT antibodies (by 14C-serotonin release assay) among patients (n = 33, 12.6%) clinically suspected as having HIT (30, 31). None of the 33 patients who underwent serological testing was found to have HIT antibodies; 32 patients tested negative by the more specific SRA test. The investigators also reported (30) that 46% of patients had thrombocytopenia (62 on ICU admission and 59 acquired during their ICU stay). Patients who developed thrombocytopenia were more likely to die, required longer duration of mechanical ventila-



Patient population	ELISA Antibody Detected	Positive Platelet Activation / Functional Assay (SRA)	Thrombocytopenia	HIT and thrombosis
Post Open Heart Surgery	50%	20%	2%	1%
Post Orthopedic Surgery – unfractionated heparin (UFH)	15%	10%	5%	3%
Post Orthopedic Surgery – low molecular weight heparin (LMWH)	8%	3%	1%	0.5%
ICU Patients	< 1%	< 1%	41 – 54%	--

Figure 2. Iceberg model of heparin-induced thrombocytopenia (*HIT*). This model depicts several features of HIT, including the hierarchy of sensitivity and specificity of three types of assays: a) a platelet activation assay that uses washed platelets (e.g., platelet serotonin release assay [*SRA*]); b) a platelet factor 4 /heparin enzyme immunoassay (*EIA*) that detects immunoglobulin (*Ig*) G class antibodies; c) and a commercial EIA that detects antibodies of IgG, IgM, or IgA class. Clinical HIT indicates either of the top two levels of the iceberg (HIT and thrombosis; thrombocytopenia). Subclinical seroconversion indicates formation of antibodies in the absence of developing clinical HIT. The relative proportion of patients who form antibodies vs. those who do not form antibodies differs in various clinical situations.

Table 2. Individuals at risk for heparin-induced thrombocytopenia (HIT)

Risk for Developing HIT	Risk Factor
High (>1%)	• Postoperative or trauma patients, especially cardiac, vascular, or orthopedic surgery receiving UFH
Intermediate (0.1–1%)	• Postoperative patients receiving UFH flushes • Postoperative patients receiving LMWH • Medical or obstetrical patients treated with therapeutic or prophylactic doses of UFH
Low (<0.1%)	• Medical or obstetrical patients treated with LMWH

UFH, unfractionated heparin; LMWH, low molecular weight heparin.

tion, and were more likely to require blood product transfusion. HIT was frequently suspected, but confirmatory diagnostic testing was performed in very few patients (n = 33).

These two studies (29, 30) of HIT in ICU patients suggest the following. First, only a small minority of ICU patients with thrombocytopenia receiving UFH have HIT. Second, testing with the PF4/heparin ELISA assay is more likely to detect PF4/heparin-reactive antibodies than the SRA, suggesting the potential for significant overdiagnosis of HIT in this patient population. Furthermore, the PF4/heparin ELISA antibody response is polyclonal, and only a subset of these antibodies cause clinical HIT. There is a possibility, however, that these two studies may have underestimated the prevalence of HIT in the ICU setting, since not all patients underwent careful diagnostic laboratory testing for confirmation of a presumptive clinical diagnosis.

Investigators have also reported the development of HITTS in 22% of patients awaiting cardiac transplant by ELISA testing and in 2.3% of pediatric intensive care patients (32, 33). A recent single-center retrospective 3.5-yr review of subarachnoid hemorrhage patients documented that 59 (15%) of 389 patients met the clinical diagnostic criteria for HIT (34). The authors used clinical criteria to diagnose HIT rather than confirmatory laboratory tests, and this should be taken into account when interpreting the results. The clinical criteria were a) thrombocytopenia that occurs 4–14 days after beginning heparin therapy; b) platelet reduction to <100,000/μL or <50% baseline; c) exclusion of other causes of thrombocytopenia such as infection, drug-associated, and autoimmune; and d) resolution of thrombocytopenia after cessation of heparin therapy. The subarachnoid patients with HIT had significantly higher rates of thrombotic complications (37 vs. 7%, $p < .001$), new hypodensities on head computed tomographic scans (66 vs. 40%, $p < .001$), more deaths (29 vs. 12%, $p < .001$), and more unfavorable outcomes (62 vs. 48%, $p < .05$).

Additional studies are warranted to clarify the true incidence of HIT in specific critically ill patient populations, including medical, surgical, cardiac, trauma, and burn ICU patients. The Complications After Thrombocytopenia Caused by Heparin (CATCH) Registry is a recent attempt to achieve a better understanding of the prevalence, consequences, and temporal relationship of HIT and thrombocytopenia among patients treated with anticoagulants (35). The CATCH Registry is an open-label prospective observational study that will explore the incidence of HIT by examining three groups of patients. The first group will be patients with thrombocytopenia in acute coronary syndromes. The second group of patients will be those who receive prolonged anticoagulation (>4 days) of either unfractionated or LMWH. In addition, a third group of patients in whom serological laboratory HIT assays

Table 3. Studies regarding frequency of heparin-induced thrombocytopenia (HIT) in critical care

Study Type and Reference	Study Population	HIT Criteria	No. (%) Thrombocytopenia	No. (%) Suspected HIT	No. (%) Positive HIT Serology	Remarks About Study
Prospective Crowther et al. (30)	261 critically ill medical-surgical patients	Platelet count $<50 \times 10^9$/L or decreased by >50% of their value at the ICU admission	121/261(46) (95% CI 40–53%)	33/261 (12.6)	0/33 (0) 1 patient had indeterminate SRA result but tested negative in the ELISA	Excluded HIT prone patients such as those admitted to the ICU after orthopedic and cardiac surgery
Prospective Verma et al. (29)	748 consecutive UFH-treated patients admitted to a combined intensive and coronary care unit evaluated over a 2-yr period 267 had sufficient heparin exposure to be considered for HIT	Two or more consecutive platelet counts $<150 \times 10^9$/L or decreased by >33% within ≥5 days after starting UFH or sooner if UFH exposure within the preceding 8 wks	Not stated	40/267 (15)	Serum available for 32/40 "at-risk" patients 1/32 (0.39) (95% CI, 0.01–2.1%) had positive SRA and ELISA 9/31 (29) had positive ELISA but negative SRA	Serology missing from 8/40 patients clinically suspected of HIT Median platelet counts in patients suspected of HIT 63×10^9/L
Retrospective Hoh et al. (34)	389 SAH patients over 3.5-yr period	Platelet count $<100 \times 10^9$/L or <50% between days 4 and 14 of heparin exposure		59/389 (15)	N/A	No serologic data available Mean platelet count nadir in HIT patients 68.6×10^9/L
Retrospective Hourigan et al. (32)	46 patients over a 3-yr period (1998–2000)		26/46 (46)		11/26 had positive ELISA; 10/11 developed clinical HIT	Mean platelet count in HIT patients at diagnosis 88×10^9/L
Retrospective Schmugge et al. (33)	612 pediatric ICU patients exposed to heparin for <5 days over 2.5 yrs	HITT; identified radiologically confirmed thrombosis in 57 patients (9.3%)	Not stated	Not stated	14/38 samples had positive ELISA calculated incidence rate for HIT-associated thrombosis was 2.3%	No information regarding prevalence of thrombocytopenia on heparin therapy; plasma samples only available in 38 of 57 patients with thrombosis

ICU, intensive care unit; CI, confidence interval; SRA, serotonin release assay; ELISA, enzyme-linked immunosorbent assay; UFH, unfractionated heparin; SAH, subarachnoid hemorrhage.

have been undertaken will ensure completeness of concurrent data. The unblended registry will record approximately 5,000 patients at 60–80 U.S. hospitals. Enrollment began in the first quarter of 2003 and was completed at the end of 2004. This registry may provide additional valuable information regarding the incidence and consequences of HIT.

Thrombotic Sequelae. HIT is a strong risk factor for symptomatic thrombosis. Hirsh et al. (36) conducted a literature review to determine the risk for thrombosis in patients with HIT when heparin therapy was discontinued. The available evidence from one prospective and three retrospective studies indicates that the risk for venous and arterial thrombotic complications after stopping heparin therapy is ≥20% and as high as 50% in patients with HIT. Venous thromboses are four times more common than arterial thromboses. These studies are, however, limited by lack of laboratory confirmation of HIT, lack of appropriate controls, and other study weaknesses. Clinical sequelae of HIT include DVT, pulmonary embolism, skin necrosis, limb ischemia, thrombotic stroke, and myocardial infarction, which may result in amputation and death (Table 4) (37). Venous thrombosis is the most common thrombotic manifestation in HIT, and lower extremity DVT predominates. Upper limb DVT is strongly associated with current or recent central venous catheter use (38).

The prothrombotic nature of HIT can result in a high frequency of limb ischemia (39, 40). Limb ischemia can be caused by large artery thrombosis (classic "white clot" syndrome) but also by venous limb gangrene, which classically is large-vein thrombosis complicated by ipsilateral small vessel thrombosis. This latter syndrome has been associated with warfarin use in the treatment of HIT-associated DVT (41). Very rarely, severe disseminated intravascular coagulation and natural anticoagulant depletion could account for microvascular thrombosis and limb ischemia in a patient with palpable pulses but limb ischemia who has not received warfarin.

Stroke, particularly ischemic stroke, can also occur as a complication of HIT and significantly increases mortality risk. A retrospective analysis of two prospective studies of argatroban therapy in patients with HIT (n = 960, 767 argatro-

Table 4. Clinical complications of heparin-induced thrombocytopenia

Venous thrombosis
• Deep venous thrombosis (50%)
• Coumarin-induced venous limb gangrene or "classic" skin necrosis
• Pulmonary embolism (25%)
• Cerebral venous thrombosis
• Adrenal hemorrhagic infarction
Arterial thrombosis
• Lower limb artery thrombosis (amputation: 20% risk)
• Cerebrovascular accident (transient global amnesia)
• Myocardial infarction (3–5%)
• Miscellaneous artery thrombosis (e.g., brachial, mesenteric, spinal)
Skin lesions (at heparin injection sites)
• Skin necrosis
• Erythematous plaques
Acute systemic reaction after intravenous heparin bolus
Hypofibrinogenemia secondary to decompensated DIC
Death: 10–30% risk

DIC, disseminated intravascular coagulation.

Adapted with permission from Warkentin TE: Platelet count monitoring and laboratory testing for heparin-induced thrombocytopenia. *Arch Pathol Lab Med* 2002; 126:1415–1423.

ban-treated patients, 193 historical controls) documented that stroke occurred in 30 (3.1%) patients (42). Of 35 stroke events, 33 (94%) were ischemic and two (6%) were hemorrhagic (one per group, none during argatroban infusion); 30 (86%) were present at or within 13 days of entry. Stroke in HIT patients occurred most often in females (odds ratio, 2.48, 95% CI, 1.11–5.53; $p = .026$), in patients with more severe thrombocytopenia, and within 2 wks of HIT presentation. Stroke (OR, 3.66; 95% CI, 1.73–7.73; $p < .001$) was a significant predictor of all-cause mortality.

Important risk factors for thrombotic complications were examined in a retrospective analysis of patients (n = 408) with clinical suspicion of HIT who tested positive using a sensitive functional assay. In the 408 HIT patients, a predominance of venous thrombosis was observed (214:1) with 40% of patients developing a pulmonary embolism. However, in the subgroup of postcardiovascular surgery patients there was a predominance of arterial thrombosis (1:8.5). The most important risk factors for thrombosis were orthopedic/trauma surgery and the magnitude of platelet count decrease (43).

The incidence of thromboembolic and hemorrhagic complications in critically ill patients with HIT and with multiple organ dysfunction syndrome is high, as reported in a recent case-control study (44). HIT was confirmed by a positive platelet aggregation test in 20 ICU patients, and UFH or LMWH was replaced by danaparoid sodium in these patients. Arterial and venous thromboembolic complications occurred more frequently in HIT patients than in control patients (10 of 20 [50%] vs. 0 of 20 [0%]; chi-square $p < .001$). Hemorrhagic complications also occurred more frequently in HIT patients than in control patients (17/20 [85%] vs. 7/20 [35%]; chi-square $p = .001$). However the specific etiology of the hemorrhagic complications in this study is unclear.

A CLINICOPATHOLOGIC APPROACH TO HIT

Because only a few patients in whom HIT antibodies develop actually become thrombocytopenic during heparin therapy, integration of both clinical and laboratory findings (a clinicopathologic approach) is crucial for an accurate diagnosis (16–18).

Diagnosis Based on Clinical Features and Onset Relative to Recent Heparin Exposure. With regard to clinical findings, an accurate diagnosis must consider the degree and timing of thrombocytopenia in relation to the previous heparin exposure and must include a thorough physical evaluation for the presence of alternative explanations for thrombocytopenia, as well as the presence of thrombotic events, the last feature pointing more strongly to a possible diagnosis of HIT.

A recent clinical scoring system has been proposed to identify patients with HIT, called the "4 T's" (Table 5) (45). This clinical scoring system is based on the characteristic features of HIT, including *T*hrombocytopenia, *T*iming, *T*hrombosis, and the absence of o*T*her explanations. Preliminary evaluation of this scoring system in estimating the pretest probability of HIT suggests that HIT antibodies are unlikely (<5%) when a low score (≤3) is obtained but are likely (>80%) with a high score (≥6). An intermediate score of 4 or 5 indicates a clinical profile compatible with HIT but with another possible explanation, and laboratory testing for HIT antibodies is especially useful in this group of patients.

When using this scoring system, it is important to evaluate the time that the platelet count *begins* to fall during any given thrombocytopenic episode. Thus, a patient who is admitted with sepsis and whose platelet count is falling progressively from admission would receive a low score (0 points) for onset of thrombocytopenia, even if the platelet count remains low during the subsequent day 5–10 period. If, however, a patient with an early platelet count fall (due to sepsis or postoperative hemodilution) then has stabilization or the platelet count has recovered, followed by another platelet count fall that begins during the day 5–10 "window," that patient would score high (2 points) for that temporal pattern of platelet count fall. This clinical scoring system (the 4 T's) has not yet been fully validated. A recent study (46) examined this pretest clinical scoring system, the 4 T's, in 100 consecutive patients referred for possible HIT in one hospital and in 236 patients by clinicians in Germany referring blood for diagnostic testing for HIT. The clinical scores were correlated with results of laboratory testing for HIT antibodies using serologic criteria for HIT with high diagnostic specificity. Patients with low pretest scores (0–3) were unlikely to test positive for HIT antibodies (1 of 64 [1.6%] and 0 of 55 [0%]). Patients with intermediate (4–5) scores (8 of 28 [28.6%] and 11 of 139 [7.9%]) or high (6–8) scores (8 of 8 [100%] and 9 of 42 [21.4%]) were more likely to test positive for clinically significant HIT antibodies.

These authors concluded that a low pretest clinical score for HIT seems to be suitable for ruling out HIT in most situations (high negative predictive value). The implications of an intermediate or high score varied in different clinical settings. Furthermore, it remains to be seen whether this (or any other) scoring system is helpful in evaluating critically ill patients for a diagnosis of HIT. Although the 4 T's score needs further validation in the ICU setting, its potential value is in providing a mnemonic that helps to iden-

Table 5. Estimating the pretest probability of heparin-induced thrombocytopenia (HIT): The "4 T's"

	Points (0, 1, or 2 for Each of 4 Categories: Maximum Score = 8)		
	2	1	0
*T*hrombocytopenia	>50% platelet decrease to nadir ≥20	30–50% platelet decrease, or nadir 10–19, or >50% decrease secondary to surgery	<30% platelet decrease, or nadir <10
*T*iming[a] of onset of platelet decrease (or other sequelae of HIT)	Days 5–10 or ≤day 1 with recent heparin (past 30 days)	>Day 10 or timing unclear; or <day 1 with recent heparin (past 31–100 days)	<Day 4 (no recent heparin)
*T*hrombosis or other sequelae	Proven new thrombosis, skin necrosis, or acute systemic reaction after intravenous unfractionated heparin bolus	Progressive or recurrent thrombosis, erythematous skin lesions, suspected thrombosis (not proven)	None
O*t*her cause(s) of platelet decrease	None evident	Possible	Definite

[a]First day of immunizing heparin exposure considered day 0. Pretest probability score: 6–8 indicates high; 4–5, intermediate; and 0–3, low. Reproduced with permission from Warkentin TE: Heparin-induced thrombocytopenia: Diagnosis and management. *Circulation* 2004; 110:e454–e458.

tify patients who are less likely to have HIT as a cause for their thrombocytopenia.

Thrombosis that begins on or after day 5 of a course of heparin treatment is a feature that should trigger consideration of the diagnosis of HIT, that is, prompt evaluation of platelet counts including temporal features of onset of thrombosis and platelet count fall in relation to heparin treatment. The development of extension or recurrence of clot in a patient receiving heparin should also prompt consideration of the diagnosis of HIT. Other concomitant prothrombotic factors such as perioperative state, diabetes, neoplasm, cardiac insufficiency, systemic lupus erythematosus, antiphospholipid syndrome, infection, and trauma exist in >60% of patients with HIT and must be considered (32, 47). In all, 36–50% of patients with HIT have been noted to develop life- or limb-threatening thromboses as a result of HITTS (10). The thrombotic tendency associated with HIT can last for ≥30 days, and HITT can develop well after the discontinuation of heparin and platelet count recovery. The fact that the thrombocytopenia seen in HIT usually resolves within 3–7 days of heparin withdrawal is a useful aid to making the diagnosis of HIT.

Symptoms of acute platelet activation, which occurs 5–30 mins after the administration of an intravenous heparin bolus to a patient with circulating HIT antibodies, is an uncommon but specific clinical feature of HIT (48). Reported symptoms and signs may include fever, chills, tachycardia, hypertension, flushing, chest pain, dyspnea, nausea, vomiting, diarrhea, transient global amnesia, or even cardiac or respiratory arrest within a few minutes following intravenous bolus administration of heparin (49).

Skin lesions (ranging from erythematous plaques to frank necrosis) at heparin injection sites are another possible clinical feature of HIT that should prompt platelet count assessment and HIT antibody testing. Not all of these patients develop thrombocytopenia, despite the presence of skin lesions and strong positive testing for HIT antibodies (50, 51).

Temporal Pattern and Onset of Thrombocytopenia. The most common clinical presentation, known as "typical HIT," occurs in about 70% of patients and is characterized by thrombocytopenia (defined as a large proportional drop in platelet count, e.g., ≥50%) that occurs between 5 and 14 days after initiation of heparin (52, 53). Therefore, although physicians should obtain baseline platelet counts when heparin therapy is initiated, it is notable that often the postoperative platelet count increase that typically begins about 3 days after surgery means that the "baseline" platelet count before onset of HIT could be a platelet count value even greater than the preheparin platelet count. This typical temporal profile of HIT parallels the rapid formation of anti-PF4/heparin antibodies, which usually begins about 5 days after starting an immunizing heparin exposure, such as unfractionated heparin given during, or started soon after, surgery.

Twenty percent of HIT patients have platelet count nadirs $>100 \times 10^9$/L. The majority of patients (60%) have moderate thrombocytopenia (platelet count nadir, $30–100 \times 10^9$/L), and only 20% of patients have platelet counts $<30 \times 10^9$/L (52, 54–56). The platelet count is rarely $<10 \times 10^9$/L, which is in marked contrast to other drug-induced immune thrombocytopenia (e.g., caused by quinine or sulfa antibiotics), which typically have platelet counts $<20 \times 10^9$/L (56). Although platelet count recovery after stopping heparin is regarded as a feature consistent with HIT, this is not specific for HIT, as most acute thrombocytopenic episodes will recover.

Clinicians should be aware of certain atypical presentations of HIT. For example, onset of thrombocytopenia can occur rapidly (within hours to a few days) in a patient with a history of recent heparin exposure (usually, within the past 3 wks, but occasionally up to about 3 months earlier). Such "rapid-onset" HIT is related to the presence of circulating HIT antibodies that resulted from the recent heparin exposure and that have not yet declined to negligible levels (20). This information can be a "clinical pearl" to critical care physicians: Any platelet count decrease that occurs within 4 days of a patient receiving heparin *cannot* be HIT, if the physician is confident the patient could not have been exposed to heparin in the preceding 3 months (54).

Another atypical presentation is "delayed onset" of HIT. This refers to a patient who has a fall in the platelet count that begins *after* the heparin has been stopped, and thus pharmacologic heparin is no longer present. There are documented cases in which the platelet count begins to fall as much as a week after the patient's last exposure to heparin (16, 57, 58). Some patients with "delayed-onset" HIT may even present up to 3 wks after heparin exposure, when complicating thrombosis causes the patient to return

to hospital. Although the pathogenesis of this syndrome remains poorly understood, it could be caused by transient formation of anti-PF4 autoantibodies that do not require heparin or that recognize PF4 bound to endogenous glycosaminoglycans. In one report, delayed-onset HIT with thrombosis began 1 wk after a single 5000-unit administration of UFH (59).

Many case reports have described delayed onset of HIT that may be better termed "delayed recognition" of HIT because of a lack of platelet monitoring in earlier weeks. Early platelet count monitoring may be appropriate in high-risk patients who have had known or suspected heparin exposure within the previous 100 days and may prevent the morbidity and mortality associated with the development of thromboses (57). Lubenow et al. (54) reported that platelet count monitoring after day 5 of heparin therapy was too late for early recognition in up to 63% of patients. These investigators suggest that monitoring of platelet counts carefully from day 1 of treatment in patients exposed to heparin within the previous 100 days would detect HIT early in these high-risk patients. Recommendations from the College of American Pathologists and the American College of Chest Physicians state that the intensity of platelet count monitoring should be stratified depending on the clinical situation (37, 60). For high-risk patients (e.g., postoperative patients, especially cardiac or orthopedic surgery; Table 2), platelet count monitoring should focus on the period of highest risk (5–14 days after starting heparin) with testing at (minimum) 2-day intervals.

Determination of the likelihood of heparin exposure within the previous days or weeks is a critical piece of information to gather while taking a history in a patient with thrombocytopenia or thrombosis. Physicians should consider likely scenarios for heparin exposure such as recent hospitalization for surgery or illness, outpatient procedures (e.g., orthopedic surgery), rehabilitation (e.g., posttrauma), or use of heparin-coated devices during prolonged hospitalization. All forms of heparin should be considered as a potential source of exposure, including heparin catheter flushes and heparin-coated catheters (61). If heparin exposure is unknown or unclear, the possibility of a HIT diagnosis cannot be ruled out until serologic testing for antibodies is performed.

Diagnosis of HIT based on Laboratory Testing. The second part of the clinicopathologic approach to confirming (or refuting) the diagnosis of HIT is determining the presence of platelet-activating, anti-PF4/heparin antibodies. Issues of test sensitivity and specificity are important, as in the ICU, the origin of thrombocytopenia may be multifactorial (e.g., sepsis, hemodilution). Laboratory testing for HIT should ideally be performed with the patient off heparin.

Supportive Antibody Tests. There is no single laboratory test that perfectly correlates with a clinical diagnosis of HIT, because there is currently no test with 100% sensitivity and specificity for the detection of pathogenic HIT antibodies (Table 6) (17). Furthermore, HIT antibodies are transient, and so testing should be performed using blood samples obtained during (or soon after) the thrombocytopenic episode (20). Two types of complementary assays are useful in the detection of HIT antibodies: activation/functional assays (SRA, platelet aggregation assay) that detect antibodies based on their ability to activate platelets in the presence of heparin, and antigen assays that detect antibodies reactive against the PF4/heparin complex using ELISA (62) Table 6).

The SRA has a sensitivity of >95% when performed by experienced laboratories (63–65). The ELISA can be performed relatively quickly and has high sensitivity (90–98%) and high negative predictive value (95%); however, it has a low specificity with a moderately high false-positive rate in patients who have received heparin between 5 days to a few weeks earlier. The presence of HIT antibodies does not necessarily predict the development of clinical HIT (66). A positive ELISA test for HIT antibodies occurs in approximately 3–20% of patients treated with heparin (37), and this percentage is even higher (40–60%) after open heart surgery, yet relatively few of these patients develop HIT (67–69). Because of the high sensitivity of these two assays, these tests are better at refuting the tentative diagnosis of HIT (i.e., high negative predictive value) than confirming a suspected diagnosis (moderate positive predictive value). However, the magnitude of a positive HIT result can be diagnostically useful, as the greater the "strength" of the reaction (higher serotonin release, higher optical density reading by ELISA), the greater the likelihood that the patient has HIT (70–72). When used together, the results of SRA and ELISA are complementary. Negative results yield highly negative predictive values thus ruling out HIT, even when the clinical picture was highly suggestive of HIT. Strong positive results are associated with high likelihood ratios (62).

As discussed earlier, there is only one published study that has examined the sensitivity and specificity of these two assays in the diagnosis of HIT in critically ill patients (29). The specificity of the anti-PF4/heparin ELISA among thrombocytopenic patients with negative SRA results was 71% and the positive and negative predictive values of this test were estimated to be 10% and 100%, respectively. The low positive predictive value and high negative predictive value of the heparin-PF4 ELISA suggest that it can be used to exclude HIT as a cause of thrombocytopenia in the critically ill patient population. It is likely that greater magnitude of a positive ELISA is associated with a greater likelihood of the patient having clinical HIT (71, 72).

TREATMENT OF HIT

Historically, anticoagulant treatment of HIT included warfarin, dextran, and LMWH. Because placebo-controlled studies were judged to be unethical during evaluation of new treatments for HIT, historical controls were used as the comparator arm for evaluation of the direct thrombin inhibitors (DTIs), argatroban and lepirudin.

Historical Treatments. Warfarin is an anticoagulant that acts by reducing the synthesis of the vitamin-K dependent clotting factors, including factors II, VII, IX, and X and proteins C and S. The significant reduction of synthesis of protein C by warfarin may on occasion have deleterious clinical effects, including worsening of thrombosis, venous limb gangrene resulting in limb amputation, and/or skin necrosis, especially when used as single therapy for acute HIT. Therefore, warfarin should never be used alone in the initial treatment of active HIT (60), and its use should be postponed until substantial platelet count recovery has occurred during treatment with alternative, rapidly acting anticoagulants (discussed subsequently).

Dextran 40, a low molecular weight polymer, is a weak antithrombotic agent in the setting of acute venous or arterial thrombosis. It is not widely used in clinical practice due to its high cost, difficulty of administration, long half-life, and likely lack of significant therapeutic ben-

Table 6. Comparison of laboratory assays to detect heparin-induced thrombocytopenia antibodies

Classification of Laboratory Test	Assay	Assay Methodology	Advantages	Disadvantages
Activation (functional) assays: 1. Washed platelet assays				
	Serotonin release assay	Quantitation of C-radiolabeled serotonin released from dense granules of activated platelets, or chemical detection of serotonin	Highest sensitivity (>95% in experienced laboratories)—specificity tradeoff[a]	Technically demanding radioactive method; limited availability (research labs); platelet donors required
	Heparin-induced platelet activation test	Visual assessment of platelet aggregation		
	ATP release	Detected by luminography		
	Platelet microparticle assay	Quantitation of platelet-derived microparticles by flow cytometry		Research assay
Activation (functional) assays: 2. Platelets in citrated platelet-rich plasma				
	Platelet aggregation test	Assessment of platelet aggregation using conventional aggregometry	Many labs have conventional platelet aggregometers	Poor sensitivity and specificity; limited number of tests can be done; platelet donors required
	Annexin V binding assay	Quantitation by flow cytometry of annexin V binding to anionic phospholipids expressed by activated platelets		
Antigen assays				
	Commercial PF4/polyanion-EIA[b]	Target antigen: platelet factor 4/polyvinyl sulfonate	Widely available; high sensitivity (90–98%), high negative predictive value (95%); low specificity	Detects many nonpathogenic anti-PF4/polyanion IgA, IgM, and IgG antibodies (moderate specificity)
	PF4/heparin-EIA that only detects IgG	Target antigen: PF4/heparin complexes	Detecting only IgG improves specificity	Limited availability (research labs)

ATP, adenosine triphosphate; PF4, platelet factor 4; EIA, electroimmunoassay; Ig, immunoglobulin.

[a]High sensitivity for clinical HIT (similar to EIAs) but with greater diagnostic specificity than the EIAs. [b]Assay from GTI (Brookfield, WI) uses PF4/polyvinyl sulfonate, whereas assay from Stago (Asnieres, France) uses PF4/heparin. In general, the greater the magnitude of a positive test result, the greater the likelihood that the patient has heparin-induced thrombocytopenia (HIT); for example, most patients with HIT have serotonin release >80% and optical density >1.0 absorbance unit, values well above the cutoffs defining a positive test. Adapted from Warkentin TE: Heparin-induced thrombocytopenia: Diagnosis and management. *Circulation* 2004; 110:e454–e458 and Ohman, Granger CB, Rice L, et al: Identification, diagnosis and treatment of heparin-induced thrombocytopenia and thrombosis. *J Thromb Thrombolysis* 2005; 19:11–19.

efit in HIT. Low molecular weight heparins should not be used in patients with suspected HIT because they have a high likelihood of cross-reactivity with the antibodies that cause HIT (up to 80%), potentially worsening the syndrome.

Danaparoid is a mixture of anticoagulant glycosaminoglycans that was superior to dextran in the only randomized clinical trial performed for management of HIT (73). It was also more effective than treatment with ancrod and/or coumarin in a historical comparative study (74). This heparinoid has predominant anti-factor Xa activity and some antithrombin effect. It exhibits cross-reactivity with HIT antibodies in about 10–20% of patients, although this usually does not result in adverse clinical effect. However, we have listed this agent as "historical" given its withdrawal from the U.S. market in 2001 (75). It was approved for treatment of HIT in other countries (e.g., Canada, European Union) and remains in active use in those jurisdictions.

Direct Thrombin Inhibitors. The initial goal for treatment of HIT is halting the uncontrolled thrombin generation and arresting the thrombotic storm. This can be achieved by the prompt initiation of a DTI (76). The currently approved and available DTIs are argatroban (Argatroban; GlaxoSmithKline, Philadelphia, PA) and lepirudin (Refludan; Berlex Laboratories, Montville, NJ). DTIs neutralize clot-bound and soluble thrombin and directly inhibit the ability of thrombin to catalyze the conversion of fibrinogen to fibrin. They block the ability of thrombin to activate platelets as well as coagulation factors V, VIII, and XIII. DTIs have no cross-reactivity with HIT antibodies. However, neither argatroban nor lepirudin has an antidote, and thus careful patient selection, dosing, and monitoring are required to reduce risk of major bleeding. In normal individuals, their half-lives are relatively short (lepirudin, 80 mins; argatroban, 45 mins) but can be prolonged in critically ill patients. These agents have not been compared directly in clinical trials. Furthermore, important differences in study design limit drawing conclusions regarding comparative efficacy or risk of bleeding from indirect comparison (Table 7) (65).

Argatroban. Argatroban, a small synthetic L-arginine-based molecule, binds reversibly to thrombin and inhibits thrombin-catalyzed reactions. The shorter, reversible period of thrombin inhibition of argatroban, compared with lepirudin, may be an advantage in some situations, such as a need for rapid reversal of anticoagulation because of bleeding or need for invasive procedure. Argatro-

Table 7. Direct thrombin inhibitors reduce relative risk of thrombosis-related outcomes in heparin-induced thrombocytopenia

Trial	HIT Type	All Outcomes Combined (%)	Death (%)	New Thromboembolic Event (%)	Amputation (%)	Reference
Lepirudin studies						
HAT-1	HIT					84
	HITTS					
	HIT/HITTS[a]	18.3	7.3	9.8	3.7	
	HIT/HITTS	25.4	8.6	18.4	5.7	
Control⇒	HIT/HITTS	52.1	22.3	32.1	8.2	
HAT-2	HIT	33.8				11
	HITTS	20.9				
	HIT/HITTS	30.0		27.2		
Control⇒	HIT/HITTS	52.1		51.8		
Meta 1–2	HITTS		8.9	10.1	6.5	89
Control⇒	HITTS		17.6	27.2	10.4	
HAT-3	HIT	11.9	2.4	4.8	7.1	92
	HITTS		6.1	6.1	5.1	
Meta 1–3	HIT	9.0	4.5	2.7	2.7	93
Registry	HIT	15.7	12.3	2.1	1.3	94
	HITTS		10.9	5.2	5.8	
Argatroban studies						
ARG-911	HIT	—	16.9	6.9	1.9	78
Control⇒	HIT	—	21.8	15.0	2.0	
	HITTS	—	18.1	14.6	11.1	
Control⇒	HITTS	—	28.3	19.6	8.7	
Post-911	HIT	—	19	5.8	4.2	
Control⇒	HIT	—	20.9	23	2.9	79
	HITTS	—	23.1	13.1	14.8	
Control⇒	HITTS	—	28.3	34.8	10.9	

HIT, isolated heparin-induced thrombocytopenia; HAT, heparin-associated thrombocytopenia; HITTS, heparin-induced thrombocytopenia and thrombosis syndrome; ARG, argatroban.

[a]Combined HIT and HITTS arms of HAT-1 study. Important differences in study design of the individual studies limit any conclusions regarding efficacy drawn from indirect comparison. Adapted with permission from Dager WE, White RH: Pharmacotherapy of heparin-induced thrombocytopenia. *Expert Opin Pharmacother* 2003; 4:919–940

ban is hepatically metabolized and requires dose adjustments in patients with hepatic dysfunction. Although in theory dose reduction is not required in renal insufficiency, data indicate that lower doses may achieve therapeutic activated partial thromboplastin time (aPTT) levels in critically ill patients (77). Further studies are needed to fully elucidate argatroban elimination and dosage adjustments for intensive care patients. Drug-specific antibodies have not been developed to argatroban. Argatroban is indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT and in patients with or at risk for HIT undergoing percutaneous coronary interventions.

Two prospective clinical trials evaluated the efficacy and safety of argatroban in patients with HIT and HITTS (78, 79). These clinical study data showed significant risk reductions in clinical outcomes (all-cause death, all-cause amputation, and new thrombosis within 37 days of baseline) relative to historical controls (Table 7) (66). Rates of death in argatroban-treated patients ranged from 16.9% to 23.1% compared with 20.9% to 28.3% in the historical control groups. Rates of new thromboembolic events ranged from 5.8% to 14.6% compared with 15% to 34.8% in the historical control group. Also, platelet counts recovered more rapidly in patients treated with argatroban than in patients in the historical control group. These results were achieved without an increased risk of bleeding.

The efficacy of argatroban in HIT patients who developed stroke was recently examined in a retrospective analysis of two prospective studies of argatroban therapy (argatroban 2 μg/kg/min, adjusted to achieve activated partial thromboplastin times 1.5–3 times baseline) for treatment of HIT (42). Stroke occurred in 30 (3.1%) patients (stroke at entry, n = 9; new stroke during follow-up, n = 24; more than one stroke, n = 4). By logistic regression with treatment, protocol, age, and gender as covariates, argatroban-treated patients had significantly reduced odds vs. control of new stroke (OR, 0.31; 95% CI, 0.10–0.96; $p = .041$) and stroke-associated mortality (OR, 0.18; 95% CI, 0.03–0.92; $p = .039$). This study documented that argatroban therapy significantly reduced the likelihood of new stroke and stroke-associated mortality in HIT without increasing intracranial hemorrhage.

Lepirudin. Lepirudin, a desulfated recombinant hirudin-like protein, produces *irreversible* thrombin binding but less potent inhibition of clot-bound thrombin, compared with argatroban. Lepirudin is renally eliminated, and substantial dose reduction is required in renal insufficiency. Up to 74% of patients treated with lepirudin develop antihirudin antibodies, which in a few patients increase the anticoagulant response (due to reduced renal excretion of anticoagulant-active hirudin-antibody complexes). Frequent monitoring of the aPTT is required: At initiation of therapy, the aPTT should be measured every 4 hrs until it is clear that the aPTT is stably within the therapeutic range (1.5–2.5 times the mean of the laboratory aPTT range, or the patient's baseline aPTT level) (80, 81). (Because the half-life can be prolonged even with mild renal dysfunction, one should not assume that a single "therapeutic" aPTT obtained 4 hrs after initiation means that the infusion rate is appropriate.)

Lepirudin is indicated for anticoagulation in patients with HIT and associated thromboembolic disease to prevent further complications. Data from several clinical trials have shown that lepirudin

provides a relative risk reduction of death, amputation, and new thrombotic complications in HIT/HITTS (Table 7) (65). In lepirudin-treated patients, relative risks in the composite "all-outcomes combined" measure ranged from 9.0% to 33.8% compared with 52.1% in the historical control groups. Bleeding events were significantly more frequent in patients with lepirudin than in historical control patients.

Lepirudin has also been associated with anaphylaxis, especially after intravenous bolus administration to patients who have previously received this agent (82, 83). For this reason, as well as because of high frequency of renal abnormalities in critically ill patients, most of these patients should not receive an initial lepirudin bolus but rather should begin with a constant infusion, maximum 0.10–0.15 mg/kg/hr (if renal function is judged normal).

The efficacy data of the DTIs presented here emphasize the high morbidity and mortality associated with this serious condition. Even after treatment with rapidly acting DTIs, 9–22% of the patients die, and an additional 6-18% require amputation or experience development of a new thrombotic event (11, 78, 79, 84).

Transition to Warfarin Therapy. Many patients receiving DTI therapy require transition to warfarin. Warfarin treatment should be delayed until therapeutic anticoagulation with a DTI, either argatroban or lepirudin, is achieved and ideally until there is substantial resolution of thrombocytopenia (platelet count recovery to $\geq$100, and preferably 150×10^9/L) (60, 85). The DTI should not be discontinued until there have been $\geq$5 days of DTI/warfarin overlap and the International Normalized Ratio (INR) has been therapeutic for 2 consecutive days. It is also recommended that in patients who are already receiving warfarin when HIT is recognized, vitamin K be given to reverse warfarin anticoagulation. This is based on minimizing the risk of warfarin-induced microvascular thrombosis as well as optimizing DTI therapy (since prolongation of the aPTT by warfarin can lead to underdosing of DTI).

This transition to warfarin therapy may be complicated by DTI-induced elevations in the INR. Argatroban prolongs the INR more than lepirudin (86). However, a recent report has also documented that lepirudin use was associated with an elevated INR in the absence of warfarin (87). This has relevant clinical implications: It makes it more difficult to judge levels of anticoagulation during overlapping warfarin therapy and also might lead to inappropriate plasma therapy in a patient who develops bleeding during DTI therapy. Caution must be used when interpreting coagulation test results in patients receiving these drugs (88).

General Treatment Strategies. The risk of an adverse outcome is highest in the period between diagnosis of HIT and the start of alternative anticoagulant therapy (89). When HIT is suspected in a patient who has had a thrombotic event, standard practice is to discontinue all heparin products, replace heparin with an alternative rapid-acting anticoagulant such as a DTI, and monitor platelet counts. Discontinuation of heparin therapy includes UFH and LMWH by any route, heparin flushes, and vascular catheters that are heparin-coated. However, removal of these sources of heparin does not necessarily stop the activation of platelets and the coagulation cascade (84). To prevent a "thrombotic storm," initiation of alternative rapid-acting anticoagulant therapy is recommended (60, 75, 90). When the diagnosis of HIT is strongly suspected, waiting for laboratory confirmation of HIT before commencing alternative anticoagulation may increase risk for the patient. The treatment principles for HIT can be summarized as the "6 A's" including *A*void and discontinue all heparin (including LMWH), *A*dminister a nonheparin alternative anticoagulant, *A*nti-PF4/heparin antibody test for confirmation, *A*void platelet transfusion, *A*wait platelet recovery before initiation of warfarin anticoagulation, and *A*ssess for lower extremity deep venous thrombosis (Table 8) (17).

In the clinical situation of HIT with no clinically apparent thrombosis, evidence now suggests that alternative rapid-acting anticoagulant therapy should also be initiated in these patients, provided the clinical picture strongly supports the diagnosis of HIT. This recommendation is based on the clinical observations that when patients with HIT are treated by cessation of heparin therapy alone, 50% of patients will progress to a thrombotic event within the ensuing 30 days. Most of these events, however, usually occur within 1 wk (12, 91–94) Therefore, alternative anticoagulation therapy must be started when heparin is discontinued and anticoagulation should be maintained until the platelet count has fully recovered, indicating that the HIT-induced coagulation cascade has been stopped.

However, at present, there remains an important role for physician judgment in the crucial decisions to stop heparin and to initiate alternate anticoagulation, especially in the ICU setting. This is because HIT is a relatively uncommon explanation for thrombocytopenia in this patient population and because DTI-associated bleeding might be even more common in renal- or hepatic-impaired critically ill patients with compromised vascular integrity. Thus, careful consideration of the magnitude and temporal features of the thrombocytopenia, the presence of thrombosis, and the likelihood of alternate explanations for thrombocytopenia is required to formulate a pretest probability of HIT that is required to make a reasonable decision. Consultation with a hematologist or other healthcare professional with expertise in HIT should be considered in all critically ill patients.

In ICU patients who have thrombocytopenia that is judged not likely to be HIT and in which the physician would rather not administer heparin for prevention of venous thrombosis, a number of pharmacologic options are available (60). Options in the United States include low-dose fondaparinux (2.5 mg qD subcutaneously) or low-dose lepirudin (15 mg twice daily subcutaneously if adequate renal function). An additional option in Canada and the European Union is low-dose danaparoid (750 units two or three times daily).

Table 8. Principles of treatment for suspected or confirmed heparin-induced thrombocytopenia: The "Six A's"

1. Avoid and discontinue all heparin (including low molecular weight heparin)
2. Administer nonheparin alternative anticoagulant
3. Anti-PF4/heparin antibody test for confirmation
4. Avoid platelet transfusion
5. Await platelet recovery before initiation of warfarin anticoagulation
6. Assess for lower extremity deep venous thrombosis

These recommendations are based on expert opinion. Adapted with permission from Warkentin TE: Heparin-induced thrombocytopenia: Diagnosis and management. *Circulation* 2004; 110:e454–e458.

PREVENTION OF HIT IN THE ICU

All strategies should be used to prevent HIT in the critical care setting. Heparin flushes should not be used in the routine care of venous and arterial catheters; saline flushes prevent heparin exposure. A recent randomized double-blind study (n = 200) documented no significant difference between heparinized and nonheparinized flush solutions for the maintenance of perioperative radial artery catheter patency (95). In contrast, a randomized study in critical care patients (n = 5,139) documented that arterial pressure monitoring catheters maintained with heparinized flush solutions had a significantly greater probability of remaining patent over 72 hrs than catheters maintained with nonheparinized flush solutions (96).

Heparin "lock" for central venous and hemodialysis catheters is commonly performed in the ICU setting, but it has been documented that heparin can leak into the systemic circulation with this approach (97). In fact, heparin-free hemodialysis has been documented to be as effective as hemodialysis with heparin. Furthermore, in critically ill patients it was documented that the use of heparin locks after heparin-free hemodialysis resulted in prolonged unintentional anticoagulation (98). Similarly, heparin-coated catheters should be avoided whenever possible if all efforts to reduce HIT are undertaken (99–101).

CONCLUSION

Thrombocytopenia is one of the most common laboratory abnormalities in critically ill patients, reported in up to 41% of patients. HIT is an important etiology of thrombocytopenia in critical illness that is associated with high mortality and limb amputation rates if diagnosis is delayed or HIT is untreated or treated inappropriately (e.g., warfarin). The initiation of prompt appropriate treatment of HIT, however, is associated with improved outcomes. HIT must therefore be considered early in the differential diagnosis of thrombocytopenia in critically ill patients. Awareness of the key clinical and laboratory features of HIT by critical care professionals is therefore important in making the presumptive diagnosis of HIT and in making the crucial clinical decisions whether to stop heparin or substitute alternative therapy. Additional clinical studies regarding diagnosis, prevalence, treatment, and outcome of HIT in the ICU setting are warranted.

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