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Heparin-Induced Thrombocytopenia in the Critically Ill Patient

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Heparin-induced thrombocytopenia (HIT) is associated with clinically significant morbidity and mortality. Patients who are critically ill are commonly thrombocytopenic and exposed to heparin. Although HIT should be considered, it is not usually the cause of thrombocytopenia in the medical-surgical ICU population. A systematic approach to the patient who is critically ill who has thrombocytopenia according to clinical features, complemented by appropriate laboratory confirmation, should lead to a reduction in inappropriate laboratory testing and reduce the use of more expensive and less reliable anticoagulants. If the patient is deemed as being at intermediate or high risk for HIT or if HIT is confirmed by means of the serotonin-release assay, heparin should be stopped, heparin-bonded catheters should be removed, and a direct antithrombin or fondaparinux should be initiated to reduce the risk of thrombosis. Warfarin is absolutely contraindicated in the acute phase of HIT; if administered, its effects must be reversed by using vitamin K. CHEST 2017; ■(■):■-■

KEY WORDS: critically ill; heparin; heparin-induced thrombocytopenia; thrombocytopenia; thrombosis

Heparin-induced thrombocytopenia (HIT) was described first in 1977,[1,2] 20 years after the first report of heparin-associated thrombosis.[3] Early recognition is important because of the high morbidity and mortality from arterial and venous thrombosis. It is caused by platelet-activating IgG antibodies binding the neoepitopes of platelet factor 4 (PF4)-heparin complexes, which originally were elucidated in 1992.[4,5] The diagnosis and treatment are particularly challenging in patients who are critically ill, owing to a high baseline prevalence of thrombocytopenia, risks for thrombosis from interruption in anticoagulation, or bleeding from the use of alternative anticoagulants in suspected or proven HIT. In this article, we provide an overview of HIT and an approach to diagnosis and treatment in patients who are critically ill, and we complement earlier reviews on this topic.[6-9]

Incidence

The incidence of HIT varies based on the patient population and type of heparin exposure, and it ranges from 1% to 5%[10] (Table 1).[11-19] Risk factors associated with HIT include undergoing surgery (OR,

ABBREVIATIONS: APTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; DOAC = direct oral anticoagulant; ECMO = extracorporeal membrane oxygenation; ELISA = enzyme-linked immunosorbent assay; FcγRIIA = Fc γ receptor IIA; HIT = heparin-induced thrombocytopenia; IVIg = IV immunoglobulin; LMWH = low-molecular-weight heparin; OD = optical density; PF4 = platelet factor 4; PROTECT = PROphylaxis for ThromboEmbolism in Critical Care Trial; SRA = serotonin-release assay; UFH = unfractionated heparin

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TABLE 1] Incidence of HIT as Reported in Registries, Clinical Trials, and Cohort Studies

Study/Year	No. of Patients	Incidence (%)	Population at Risk
Warkentin et al[11]/2000	100	1.00	Cardiac
Cook et al[21]/2011	3,746	0.45	Medical-surgical ICU
Selleng et al[24]/2007	12,528	0.02	Medical-surgical ICU
Pouplard et al[12]/1999	263	3.42	Cardiac surgery for bypass
Walls et al[13]/1992	4,261	1.92	Cardiac surgery
Walls et al[14]/1992	764	4.58	Intraaortic balloon pump
Singer et al[15]/1993	1,500	0.75	CABG, valve and combined
Ganzer et al[16]/1997	307	4.89	Orthopedic
Warkentin et al[17]/1995	332	2.41	Orthopedic elective hip
Leyvraz et al[18]/1991	204 205	2 with UFH 0 with LMWH	Orthopedic elective hip
Louridas[19]/1991	114	4.39	Vascular surgery

CABG = coronary artery bypass graft; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

3.25),[20] being female (OR, 2.37),[20] exposure to unfractionated heparin (UFH; 0.6%-2.6%) vs low-molecular-weight heparin (LMWH; 0.2%-0.3%)[21,22] (OR, 5.29),[20] and an elevated BMI. A BMI of 30 to 39 kg/m^2 with an OR of 2.94 (95% CI, 1.2-7.5) and a BMI > 40 kg/m^2 with an OR of 6.98 (95% CI, 1.6-28.2)[23] are associated with the development of HIT. Thrombocytopenia in patients who are critically ill is common and often leads physicians to consider HIT as a cause. However, HIT is not usually the culprit, and the incidence has been reported only at 0.02% to 0.45%.[24] A single-center German study of 12,528 patients reported an incidence of HIT of 0.21% in a medical-surgical ICU.[24] One of the largest prospective studies of the incidence of HIT was the HIT evaluation in critical care study embedded within the PROphylaxis for ThromboEmbolism in Critical Care Trial (PROTECT)[2,25]—a prospective evaluation of UFH vs LMWH (dalteparin) in 3,764 patients who were critically ill.[20] With use of the serotonin-release assay (SRA) to confirm the diagnosis, the overall incidence of HIT was 0.40%, or 0.53% with UFH and 0.26% with dalteparin. Within cardiac ICUs using UFH, this rate is substantially higher at 1% to 3%.[26,27]

Pathogenesis

HIT is a condition that results from the host production of platelet-activating IgG antibodies directed against heparin-platelet glycosaminoglycan and PF4 complexes that form following the exposure to heparin.[4,28] PF4 is a positively charged chemokine released from the alpha granules of activated platelets.[4] PF4 binds the negatively charged heparin anion in patients receiving either therapeutic or prophylactic doses of heparin.[28] Once ligated, these IgG antibodies cause cross-linkage of the platelet Fc γ receptor IIA (FcγRIIA).[29] This process in turn activates platelets,[29] leading to the release of platelet-derived microparticles that accelerate the thrombin formation and thrombotic complications of HIT.[30] The gene coding for FcγRIIA has two allotypes that differ in their ability to bind IgG immune complexes.[31] The RR131 allotype was shown to confer a higher risk of thrombosis.[32] The authors of that study implicated the increased thrombotic risk to be related to an increase in cell activation by antibodies to PF4-heparin and a lower inhibitory effect of endogenous IgG (presumably owing to lower IgG2 binding of the RR131 allotype). Typically, in a patient who is heparin naive, HIT-related thrombocytopenia occurs at least 5 days after heparin exposure because of the time required for primary antibody formation.[33,34] The risk for thrombosis may continue after platelet count recovery, and the binding of monocytes to PF4 to form antigenic complexes also has been implicated in thrombotic complications.[35,36]

Diagnosis

There are many clinical mimics of HIT, and the development of anti-PF4 antibodies does not always lead to HIT. Therefore, there are two requisites for the clinical diagnosis of HIT. First the patient must exhibit a clinical picture consistent with HIT, and second the patient's heparin-dependent antibodies must be platelet activating.

Clinical Features

The accurate diagnosis of HIT first requires recognition and understanding of its clinical manifestation. HIT's

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clinical manifestation is based on the severity of the thrombocytopenia, the timing of its occurrence, the presence of alternative explanations, and thrombotic complications.

Thrombocytopenia

HIT-related thrombocytopenia usually manifests as a $>$ 50% reduction in platelet count (10% will have 30%-50% reduction).[37] The platelet count nadir is usually $\geq 20 \times 10^9$/L ($\sim$90% of patients with HIT).[8] However, thrombocytopenia alone does not differentiate HIT from other, possibly equally concerning, causes of thrombocytopenia in patients in the ICU. Twenty percent to 25% of medical patients who are critically ill and 35% to 41% of patients who have undergone surgery or trauma will have thrombocytopenia (platelet counts $< 100 \times 10^9$/L).[38-40] In PROTECT, the incidences of mild (100×10^9/L to 149×10^9/L), moderate (50×10^9/L to 99×10^9/L), and severe ($< 50 \times 10^9$/L) thrombocytopenia were 15.3%, 5.1%, and 1.6%, respectively.[41] The severity of the thrombocytopenia, however, may help the physician differentiate HIT from autoimmune, drug-dependent, or marrow-suppressive (eg, sepsis) causes because these entities often have platelet count nadirs $< 20 \times 10^9$/L.

Timing

The timing of HIT-related thrombocytopenia can vary. The typical course is between 5 and 10 days after heparin exposure (day 0).[33] A more rapid onset occurs in patients previously exposed to heparin. In these patients, platelet counts decrease on day 1 of exposure.[8,33] HIT antibodies can remain detectable, on average, 50 to 85 days after heparin exposure,[33] with the anamnestic (booster or immune reactivation) principle also applying to the faster secondary response in the latter scenario. These two predominant patterns of onset are reflected in the 4Ts (thrombocytopenia, timing, thrombosis, other) score[42] described in more detail later.

Other less common presentations of HIT have been described. A more delayed onset of HIT may begin or worsen up to 3 weeks after discontinuation of heparin, owing to higher levels of circulating HIT antibodies at the time, with strong serum-induced platelet activation despite the absence of heparin.[43,44] A spontaneous or naturally occurring seroconversion to heparin may occur (perhaps by means of endogenous heparan targeting), such that the patient develops the HIT syndrome, albeit without heparin exposure.[45] Finally, protamine-heparin antibodies can produce a similar clinical picture or potentiate the severity of concomitant HIT.[46] This change tends to occur earlier than HIT ($<$ 5 days) and in patients after cardiac surgery exposed to both heparin and protamine.[46]

Thrombosis and Systemic Events

Thrombotic events can occur in 25% to 68% of patients with HIT and may occur before the onset of thrombocytopenia.[12,34,47-50] The frequency of thrombotic events reported may vary because of differences in the patients studied (medical vs surgical vs critically ill) and initial methods of case finding and diagnosis of thrombosis (clinical vs subclinical). In the initial PROTECT, 17 patients (12 in the UFH group, five in the dalteparin group) became SRA positive a mean of 8 days (range, 1 to 20 days) after study enrollment. Among these patients, there were two cases of prevalent VTE and seven cases of incident VTE (two pulmonary embolism, six DVT [one patient had both pulmonary embolism and DVT]) and two cases of incident arterial thrombosis (one patient also had VTE) during the course of the study. Six of the 17 patients died in the ICU (Deborah Cook, MD, written communication, July 2017).[2] The thromboses in HIT are often extensive, with venous thrombosis occurring more frequently than arterial, and lower limb thrombosis occurring more frequently than upper limb.[8,51] Thromboses can occur in atypical locations, including adrenal veins,[52] central circulation,[44] and mesenteric veins.[8] In PROTECT, patients treated with dalteparin not only had lower rates of seroconversion but also had less thrombocytopenia and thrombosis.[20] Furthermore, in two patients, the platelet counts recovered despite the ongoing use of dalteparin.

Warfarin use is absolutely contraindicated in HIT because it enhances the prothrombotic state by acutely producing an acquired protein C deficiency, which may not be counterbalanced sufficiently by bridging antithrombotic agents. The acute protein C deficiency may promote macro- and microvascular thrombosis with preserved arterial flow and cause skin necrosis and venous gangrene.[53] For this reason, vitamin K must be administered immediately in patients with HIT who received warfarin. Finally, acute anaphylactic reactions can occur immediately after heparin administration in patients with circulating HIT antibodies.[52]

Does the Patient Have HIT?

Several scores have been developed to assess quantitatively the likelihood of a patient having HIT and

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to help inform the next course of action (Fig 1). Depending on the pretest probability of HIT, this course of action could involve initiating immediate heparin-free antithrombotic treatment plus serologic testing or could involve serologic testing alone to confirm the diagnosis. These scores include the 4Ts,[42] modified 4Ts,[54] and HIT Expert Probability[55] scores. All attempts to quantify the pretest probability of having HIT by delineating low, intermediate, and high clinical suspicion of HIT ultimately guide the decision to treat and/or proceed with serologic testing. None of these HIT risk scores have been validated extensively in patients who are critically ill. Therefore, caution needs to be taken in using them to rule out HIT in this population. On the basis of the small number of studies evaluating the utility and performance characteristics of the HIT scores in patients who are critically ill, it is our practice to use the 4Ts score in this population.[2,54,56,57] A 4Ts score less than 4 represents a low probability of HIT (Table 2). A 4Ts score ≥ 4 can be subdivided into intermediate (4-5)

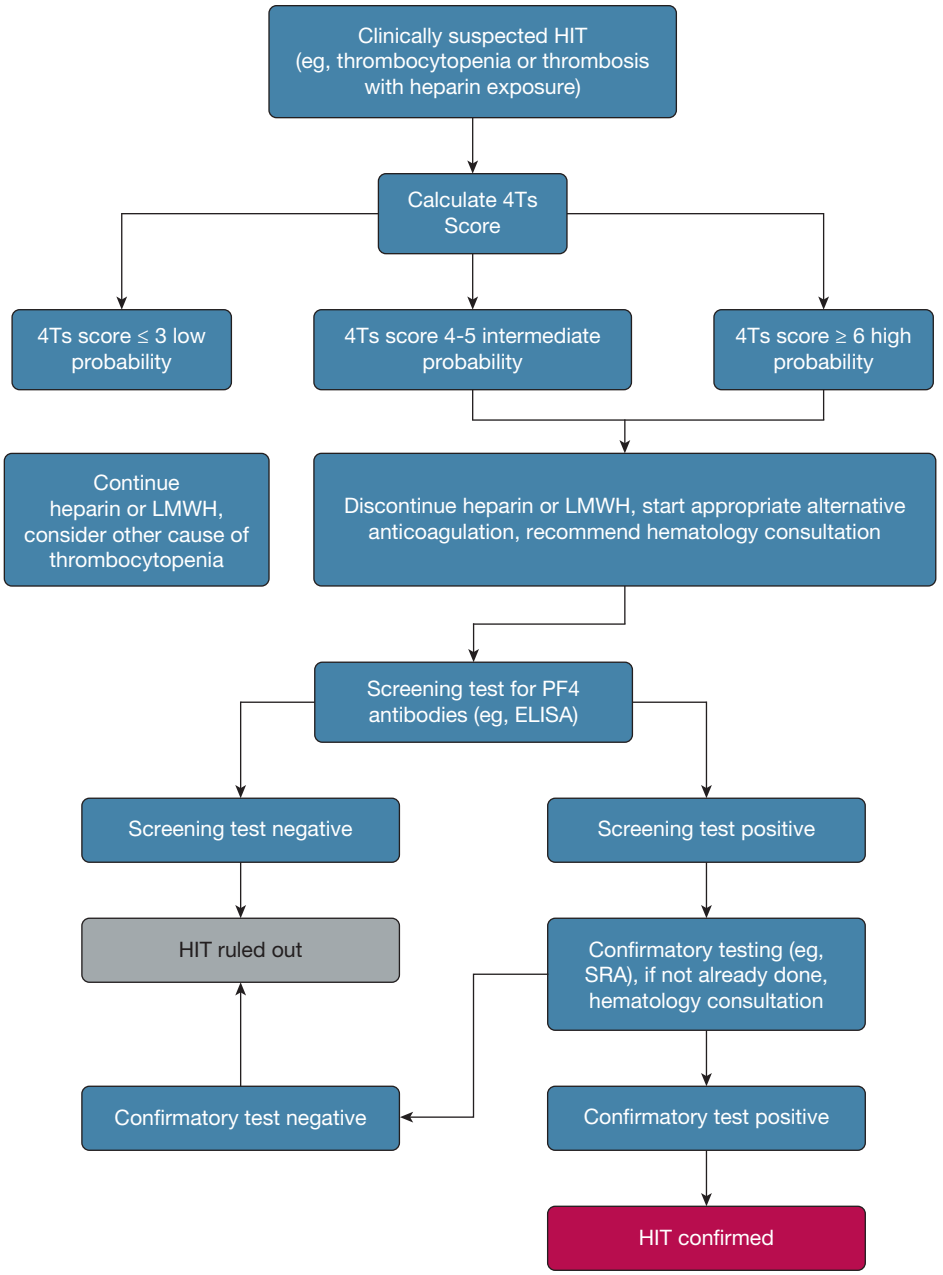

Figure 1 – *Algorithm for the diagnosis and treatment of heparin-induced thrombocytopenia (HIT). ELISA = enzyme-linked immunosorbent assay; LMWH = low-molecular-weight heparin; PF4 = platelet factor 4; SRA = serotonin-release assay.*

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TABLE 2] 4Ts and Modified 4Ts Score

Variable	Score		
	2	1	0
Thrombocytopenia	> 50% platelet count decrease to nadir ≥ 20	30%-50% platelet count decrease; or nadir 10-19	< 30% platelet count decrease; or nadir < 10
Timing of platelet count decrease	Decrease in days 5-10 or decrease ≤ 1 d (with heparin exposure in past 30 d)	Consistent with days 5-10 decrease but not clear; decrease ≤ 1 d (heparin exposure within past 31-100 d)	Decrease ≤ 4 d (with no recent exposure to heparin)
Thrombosis or other sequelae	Proven new thrombosis or skin necrosis or anaphylactoid reaction after heparin bolus	Progressive or recurrent thrombosis, erythematous skin lesions, suspected thrombosis or hemofilter thrombosis	None
Other causes of thrombocytopenia[a]	No explanation for platelet count decrease	Possible other cause is evident	Definite other cause is present

See Table 1 legend for expansion of abbreviation. (Adapted with permission from Lo et al.[42])
[a]Excluded from the modified 4Ts score.

and high (6-8) risk for HIT. These correlate with positive predictive values ranging from 0.14 to 0.21 and 0.64 to 0.78, respectively. The modest positive predictive value of this cutoff illustrates the need for confirmatory testing in HIT.[56,58]

It is also important to consider the dynamic nature of HIT and the practical limitations of the HIT risk scores. For example, omissions of previous exposures to heparin, occurrences of thrombosis prior to the onset of HIT-related thrombocytopenia, and imprecise calculation of the timing component of the 4Ts score may yield erroneously low 4Ts scores.[2] Therefore, the 4Ts scores should be reevaluated in patients with an initial low probability HIT risk score if the diagnosis of HIT remains a concern. Crowther et al[2] in a follow-up substudy of the original PROTECT demonstrated that the agreement in the 4Ts scores determined by study coordinators and scores determined by adjudication was not ideal with agreement on the 4Ts category in 71% of the patients ($\kappa = 0.23$). One of the main pitfalls they found related to knowledge about prior heparin exposure. This gap affected the ability to time the onset of either thrombocytopenia or thrombosis accurately with first exposure to heparin, which led to the finding of a positive SRA in six patients with an initially low 4Ts score. Knowledge of heparin exposure prior to ICU admission would have modified the score to a higher probability value, reducing the number of false-negative results.[2] This finding emphasizes the need to evaluate the domains of the 4Ts score carefully and ensure that research and clinical personnel are well trained in its application. Their results also illustrate the pitfalls in interrupting heparin or resorting to the use of alternate, more complex agents with a narrower therapeutic window on the basis of a clinical HIT score alone.

Current guidelines recommend investigating for a diagnosis of HIT if a patient is receiving or has received heparin within the last 14 days and the platelet count decreases by ≥ 50% and/or a thrombotic event occurs between days 5 and 14 following the initiation of heparin, even if heparin has been discontinued at the time of thrombosis or thrombocytopenia onset.[59,60] If there is a clinical suspicion of HIT, a confirmatory diagnostic test is required to make the diagnosis. The current recommendations regard a 4Ts score ≥ 4 (intermediate probability of HIT) as grounds for performing a serologic test for the presence of HIT IgG antibodies.[56]

A staged laboratory diagnostic approach is recommended. The first stage is an immunologic assay such as the PF4-heparin enzyme-linked immunosorbent assay (ELISA) followed by a second stage washed platelet functional assay such as an SRA or heparin-induced platelet activation. Functional assays such as the SRA are considered the gold standard for the diagnosis of HIT. However, SRAs are technically difficult and expensive and performed only at select laboratories. In addition, these samples are usually batched, resulting in turnaround times of up to 4 days.[61] As a result, the SRA typically is reserved as a confirmatory test after a positive ELISA in patients with intermediate- to high-risk 4Ts scores.[62]

ELISA commonly is used as the initial test for HIT because of low cost and rapid turnaround time.[63] It has a high sensitivity but low specificity for HIT, helping to rule out the condition if negative. The low specificity

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relates to the frequent development of nonpathologic antibodies to PF4-heparin complexes.[63] Immunologic assays were originally only polyspecific ELISAs. However, they have expanded to include five different classes of assay including ELISA: particle gel immunoassay, particle immunofiltration assay, lateral flow immunoassay, chemiluminescence immunoassay, and latex agglutination assay.[64] The immunologic assay used in any given center is highly variable, usually driven by cost and turnaround time (eg, batched samples vs real-time results).

Most immunologic assays are expressed as both positive and negative and (ideally) quantitatively by using optical density (OD). OD thresholds for positive results vary by the ELISA manufacturer and by institution. The most common cutoff of a positive result is $>$ 0.4 OD units (sensitivity, 99.99).[65] However, the higher the OD units used as the threshold, the higher the positive predictive value of the assay.[63] Every 0.5 increase in OD results in an increase in the likelihood of positive SRA by an OR of 6.39, and every 1.0 increase in OD causes an increased likelihood of a positive SRA by an OR of 40.81.[63] Patients with ELISA OD $>$ 2.0 have a 91% to 100% chance of positive SRA, with a 90% chance of thrombosis.[62]

Morbidity of Suspected Diagnosis

Given the high false-positive rate of screening tests (eg, ELISA), a clinically significant proportion of patients with 4Ts scores $\geq$ 4 will receive nonheparin anticoagulation until confirmatory testing excludes or establishes the diagnosis HIT. This period of diagnostic uncertainty exposes patients to a series of potential harms at an additional cost to the health-care system. Costs include ordering of additional testing and the antithrombotic agents. Risks include those relating to the misdiagnosis of the thrombocytopenia itself (which may be prohemorrhagic rather than prothrombotic) and the risks associated with the use of nonreversible antithrombotic agents. Some studies report major bleeding rates of 6% to 30%, illustrating the perils associated with the overdiagnosis of HIT.[50,66] This discussion is not to dissuade from both the consideration and empiric treatment of HIT, but it is important to consider the increased morbidity and mortality of patients who have 4Ts scores $\geq$ 4.[66,67]

Pitfalls

In ICU populations, up to 41.3% of patients develop thrombocytopenia from any cause.[68] This potential source of confusion is compounded by the fact that patients with positive HIT assay results tend to have other more common causes of thrombocytopenia than do patients with negative HIT assay results.[54] With an OD threshold of $>$ 0.4, up to 60% of patients will test positive for PF4-heparin antibodies with no clinical signs of HIT and no increased rate of death or thromboembolism.[69] Thus, without a clinical context suggestive of HIT (4Ts scores $\geq$ 4), routine screening for HIT antibodies is not recommended. The other causes of thrombocytopenia form an important component of the 4Ts score and should be considered (Table 3).

One particularly difficult overlap is disseminated intravascular coagulation (DIC). DIC and HIT are not different by median platelet counts, prothrombin time, activated partial thromboplastin time (APTT), fibrinogen, DIC score, or overt DIC.[70] Mixed evidence exists for the ability of quantitative D-dimers to separate the two entities.[70,71] One study demonstrated

TABLE 3] Differential Diagnoses of HIT and Their Potential Distinguishing Clinical Features

Condition	Diagnostic Clues
Sepsis	SIRS criteria, positive blood cultures
DIC	Increased PT and APTT, decreased fibrinogen
Massive blood loss	Source of bleeding, large-volume transfusions, increased PT and APTT, hypocalcemia, hypothermia
Thrombotic microangiopathy	Schistocytes on blood film, acute kidney injury, stroke or neurologic deficits, hemolysis
Immune thrombocytopenia	Diagnosis of exclusion, no universally accepted antibody test
Drug-induced thrombocytopenia	Decreased megakaryocytes in bone marrow, rebound of platelets after discontinuation of drug
Cardiopulmonary bypass and extracorporeal membrane oxygenation	...
Intraaortic balloon pump	...

APTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; PT = prothrombin time; SIRS = systemic inflammatory response syndrome. See Table 1 legend for expansion of other abbreviation.

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that among limited-availability tests, such as thrombin-antithrombin complex and plasmin-α2-plasmin inhibitor complex, levels were higher in DIC compared with those in HIT, although further evaluation is required before incorporation into clinical decision-making.[71] Fibrinogen levels were decreased in only 5.4% of patients with DIC, illustrating its weakness as a screening test for DIC.[72] The international Society on Thrombosis and Haemostasis, harmonized the available diagnostic DIC scores in 2013.[73] The International Society on Thrombosis and Haemostasis score has a sensitivity of 91% and a specificity of 97%.[72] In addition, with the exception of the setting of DIC during hematologic malignancy, the scores show concordance of 93%.[74] Finally, the concurrent presentation of HIT with DIC is also well described, further complicating the ability to diagnose these conditions in a patient who is critically ill.[71] If suspecting either HIT or DIC, physicians should take steps to ensure they have the correct diagnosis so they can treat appropriately for both conditions until one or both are ruled out appropriately, so as to avoid the morbidity and mortality associated with missing either.

Drug-induced thrombocytopenia is common and can be confused with HIT. In general, the platelet counts decrease 7 to 20 days after commencing the offending agent. The challenge in patients who are critically ill is finding the culprit agent because many medications can cause thrombocytopenia and often are administered concurrently. Drug-induced thrombocytopenia tends to lead to extremely low platelet counts ($< 20 \times 10^9$/L) and, by extension, more bleeding complications as opposed to thrombosis.[24]

Intravascular devices may cause platelet destruction and produce thrombocytopenia that is related temporally to either the initiation or senescence of a device (eg, extracorporeal membrane oxygenation [ECMO], continuous venovenous hemodialysis, intraaortic balloon pump, and so forth).[24] The caveat is that repeat filter or device clotting should raise concerns equally for HIT-associated thrombosis because most devices depend for their patency on the use of UFH as the first-line anticoagulant and/or have heparin impregnated in the circuit materials themselves (http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm135347.htm). Patients using ECMO are screened far more frequently than most other patients in the ICU, despite extremely low incidence of confirmed HIT.[67]

The onset of immune thrombocytopenia or antiphospholipid antibody syndrome would not be linked temporally to heparin dosing, whereas the immunopathogenesis of either is also distinct. However, there is no accepted antibody test for immune thrombocytopenia, and 20% to 25% of immune thrombocytopenia is not even B-cell (antibody) mediated (eg, there is a T-cell-mediated immunopathologic condition). However, there are many direct immune detection tests (eg, anticardiolipin antibodies, ELISA) and functional assays (eg, lupus anticoagulant titres, hexagonal phase phospholipid confirmation, or platelet neutralization procedure) for antiphospholipid antibody syndrome.

Acute liver failure causes both thrombocytopenia and rebalanced hemostasis despite an increase in international normalized ratio.[75] Rather than being prone to bleeding, a mismatched decrease in the production of various coagulant and anticoagulant factors may associate instead with a hypercoagulable state in some patients. As a result, as with the examples presented, Budd-Chiari syndrome should cue physicians to suspect the possibility of HIT; thus, these patients also should have 4Ts scores calculated to assess the appropriateness for further screening if at high risk for HIT.

Treatment

Given the high mortality and morbidity associated with ongoing heparin use in patients with HIT, immediate treatment changes must occur in cases of suspected or confirmed HIT. If a patient has confirmed HIT or moderate to high clinical suspicion of having HIT (4Ts scores ≥ 4), then all heparin products should be discontinued, and all heparin-containing devices (eg, heparin-bonded central venous catheters) should be removed.

In addition to stopping heparin, a nonheparin, nonvitamin K antagonist anticoagulant should be started immediately.[59,60] Currently, the only guideline-supported alternatives include IV direct thrombin inhibitors (lepirudin, argatroban, and bivalirudin) or indirect factor Xa inhibitors (danaparoid and fondaparinux).[59,60] Although there is emerging evidence that novel or direct oral anticoagulants (DOACs; rivaroxaban, dabigatran, and apixaban) may be a safe alternative to treat HIT,[76-79] they are not incorporated into current HIT guidelines[59] and do not yet have regulatory approval for this indication.[59,60]

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Transfusion thresholds for states of thrombotic thrombocytopenia are not established, and studies in some conditions (such as thrombotic thrombocytopenic purpura or antiphospholipid antibody syndrome) may not be generalizable to HIT.[80,81] Platelet needs or hazards in the patient suspected of having HIT may not be different from those with other forms of platelet insufficiency. Given the high bleeding risk of patients in the ICU, and perioperative patients in particular, the bleeding risk (by deferring platelet transfusion) may outweigh that of theoretical thrombosis (with platelet transfusion). If HIT is confirmed, then consultation from hematology or thrombosis services should help guide platelet thresholds in a patient with HIT confirmed on an individualized basis.

Argatroban

Argatroban is a direct thrombin inhibitor and is currently the only treatment approved by the US Food and Drug Administration for HIT. It is the recommended first-line treatment in patients with renal insufficiency. Given the high prevalence of acute kidney injury and/or chronic renal failure in ICU populations, argatroban has been the mainstay of treatment for the treatment of HIT. Its half-life is 40 to 50 minutes. In patients who have heart failure, liver failure, or severe anasarca, or after cardiac surgery, reduced initial infusions are recommended, with subsequent q2-4h adjustments using the APTT (target APTT, 1.5-3 times patient baseline).[59,60] Careful monitoring is required because comorbidities may affect the APTT and necessitate infusion rate modifications to remain within the therapeutic window. Furthermore, patients requiring ECMO may require modified doses. A nine-patient cohort found that the 2 μg/kg/min dose resulted in clinically significant bleeding and that a lower 0.2 μg/kg/min dose resulted in clinically significant anticoagulation without additional bleeding.[82] Although the average maintenance dose required was 0.15 μg/kg/min, patients with results positive for HIT with active clot formation may require up-titrated doses to achieve clinical anticoagulation beyond these levels.[83]

The risk-benefit profile for anticoagulation should be personalized when selecting the starting dose, followed by close adjustments based on the clinical response. The bleeding rates in patients who are critically ill range from 7.4% to 21.9%, with the only predictive risk factor being major surgery prior to commencing treatment.[50,66,84] Argatroban has been used for perioperative anticoagulation for ventricular assist devices. However, because limited case studies have shown high breakthrough rates of intraventricular thrombus (14.2%), risk of bleeding (57.1%), and mortality (57.1%), it is not used routinely in this setting.[85]

Bivalirudin

A direct thrombin inhibitor, bivalirudin is recommended as first-line treatment for patients requiring emergent cardiopulmonary bypass for cardiac surgery. It is also recommended as one of the first-line agents for percutaneous coronary interventions. The initial dose is 0.15 mg/kg/h and is adjusted to achieve APTT at 1.5 to 2.5 times baseline.[86] Dose adjustments for hepatic dysfunction (0.14 mg/kg/h), renal and hepatic dysfunction (0.03-0.05 mg/kg/h), and continuous renal replacement therapy (0.03-0.04 mg/kg/h) are required.[86] Bivalirudin has been used in ventricular assist devices but with mixed results, and its use in these patients requires some caution.[87,88]

Indirect Factor Xa Inhibitors

Danaparoid and fondaparinux are highly effective in the management of HIT but are of limited clinical usefulness in ICU populations because of their long half-lives and renal clearance. Fondaparinux, a factor Xa-binding heparin-subunit pentasaccharide that does not bind to PF4, is an ideal therapy for patients with HIT with creatinine clearance $>$ 30 mL/min. It is administered subcutaneously and does not routinely require monitoring.[89] However, the guidelines recommend fondaparinux only for HIT in pregnant patients for whom danaparoid is unavailable or in patients with a history of HIT with a new (unrelated) thrombosis until transitioned to warfarin.[59] There have been case reports of HIT complicating fondaparinux use.[90] Despite this finding, up to 50% of HIT was treated with fondaparinux in a multicenter German registry.[91] Retrospective analysis of patients with HIT treated with fondaparinux has found similar thrombosis, bleeding, and mortality rates to those treated with danaparoid and argatroban.[92] Fondaparinux may also be more cost-effective than other recommended agents.[93] However, no prospective evidence is currently available to recommend its routine use for treatment of HIT.[59]

Immunotherapies

There are limited reports on the use of plasmapharesis to treat refractory or severe HIT.[94,95] Plasmapheresis also has been advocated to reduce the risk of thrombosis in patients undergoing cardiac surgery who have a preoperative history of HIT and a current positive

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antiheparin-PF4 antibody titer.[96] Despite these reports, there are limited clinical data to support plasmapheresis as routine practice. IV immunoglobulin (IVIg) administration has been the subject of several case reports to treat HIT.[97-101] Padmanabhan et al[98] reported on three patients with refractory HIT and venous or arterial thrombosis. All three were reported to respond to IVIg administration (two patients had 1 g/kg administered on 2 consecutive days, and the other had the same dose 2 days apart). In vitro data from the patients' sera suggested that immunoglobulin was effective at inhibiting the activation of platelets pretreated with low levels of PF4 in the serum of patients with severe documented HIT (using a PF4-dependent P-selectin expression assay). Two of the patients had the FcγRIIA RR131 allotype and seemed to respond to treatment. It is important to emphasize that IVIg has been associated with thrombosis. In addition, a consensus statement on the clinical use of IVIg advised against its use to treat HIT.[100] Therefore, the use of IVIg to treat HIT must be considered on a case-by-case basis and ideally properly evaluated in the context of a clinical trial.

Outcomes of HIT

Outcomes vary considerably based on the severity of HIT and clinical condition of the patient. Overall, thrombotic events occur in 20% to 68% of patients with HIT.[49-51,86,101] Mortality rates even with treatment vary from 14.5% to 25%,[49,50,102] despite HIT-associated thrombosis directly causing death in only 0% to 1.7% of cases.[49,50] Table 4[102] shows several study outcomes from patients with HIT treated with bivalirudin and argatroban.

Future Directions of Treatment

More research validating the utility and performance of the HIT risk scores is needed to help guide clinical decision-making. On the basis of our interpretation of the literature, we have provided a rather conservative approach to the diagnosis of HIT in the critically ill population (Fig 1). We recognize the inherent limitations of using the 4Ts score and emphasize the dynamic nature of HIT. Therefore, patients with ongoing clinical suspicion of HIT who have an initial low-risk 4Ts score should be reevaluated for changes in their risk score. In addition, we suggest that, in the patient with intermediate risk of HIT, consultation with a hematologist is appropriate to avoid the inherent

TABLE 4] Complications of HIT and HIT Treatment-Related Mortality, Thrombosis, and Bleeding

Study/Year	Drug	No. of Patients	Mortality (%)	HIT-Related Mortality (%)	Thrombosis (%)	Amputation	Any Bleeding (%)	Major Bleeding (%)	Minor Bleeding (%)
Joseph et al[49]/2014	Bivalirudin	124[a]	9.7	0.8	70	0	5.6	4.8	…
		262[b]	17.2		52	0	11	8.4	
Tardy-Poncet et al[50]/2015	Argatroban	20	25	0	68.8	…	…	18.8	…
Vo et al[102]/2015	Argatroban	48	19	…	8	0	31	15	19.00
	Bivalirudin	20	25	…	15	0	30	25	5.00
Kiser and Fish[86]/2006	Bivalirudin	18	22	…	22	…	-0	…	…

Major bleeding in studies was defined variably and usually indicated a reduction in hemoglobin requiring transfusion, bleeding into a critical site, or death. See Table 1 legend for expansion of the abbreviation.
[a]Confirmed HIT indicated the presence of a positive immunogenic assay and a patient suspected of having HIT.
[b]Suspected HIT required only a clinical suspicion in the absence of confirmatory testing.

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complications of interrupting heparin administration with more toxic and less reliable anticoagulants.

With the development of reversal agents for factor Xa inhibitors,[103] the utility of danaparoid and factor Xa-specific DOACs may emerge in ICU populations as useful agents for the management of HIT. Given that these drugs do not interact with PF4, they are theoretically invisible as targets of antibody-mediated HIT.[104] Small case studies already have demonstrated the effectiveness of DOACs in non-ICU populations.[76,79,105] However, the current dearth of precision-monitoring options for DOACs in challenging titration situations remains a concern for patients in the ICU.[106] Prospective trials are necessary to demonstrate DOAC effectiveness and safety in ICU populations, particularly in a fixed-dosing context with assay limitations, prior to their use in HIT.

Furthermore, prospective trials are needed to examine the effectiveness and safety of fondaparinux in patients with preserved renal function. Fondaparinux may be a cost-effective and safer management strategy, and experience in its use is described by several specialist centers throughout the world. Likewise, larger studies are required for patients with HIT who are using ECMO both for the validation of the 4Ts score and the best treatment in this unique population.

The results of PROTECT support the use of LMWH prophylaxis instead of UFH to decrease the incidence and morbidity of suspected and confirmed HIT.[2,107] Therefore, we advocate for the adoption of LMWH thromboprophylaxis in patients in the ICU.

Conclusions

HIT is a complex clinical pathologic condition that threatens patients in both the surgical ICU and the medical ICU with high morbidity and mortality if it is not quickly diagnosed and treated. However, in the critically ill population, HIT is likely overdiagnosed. Overdiagnosis can lead to adverse consequences such as interruption in therapeutic heparin, resulting in unintended thrombosis as well as use of expensive and inappropriate diagnostic testing. The empiric use of direct thrombin inhibitors or indirect factor Xa inhibitors may be associated with increased costs and morbidity relating to bleeding or thrombosis if subtherapeutic doses are used. Monitoring of these agents in the context of renal or hepatic dysfunction is also problematic. To avoid these pitfalls, HIT should be considered only in the context of a high clinical probability quantified by using available prediction scores. Although these scores have not been evaluated fully in the ICU population, used in the proper clinical context they should help inform the decision to proceed with serologic confirmatory testing.

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