Heparin-Induced Thrombocytopenia in a Pediatric Population: Implications for Clinical Probability Scores and Testing

Laura Avila, MD, PhD[1,2], Nour Amiri, MD, MScCH[1], Paul Yenson, MD[1], Shirin Khan, MD[1,3], Zahra Tofighi Zavareh, MD[1,3], Anthony K. C. Chan, MD[4], Suzan Williams, MD[1], and Leonardo R. Brandão, MD, MSc[1]

Objectives To determine the applicability of the 4Ts score and the Heparin-Induced Thrombocytopenia (HIT) Expert Probability (HEP) score in children with suspected HIT and to estimate the number of children potentially at risk of HIT.

Study design We retrospectively estimated 4Ts and HEP scores in a cohort of 50 children referred for laboratory screening with enzyme immunoassay. In addition, minor modifications were introduced to the 4Ts score (modified 4Ts score) to adapt it for use in the pediatric setting. All patients with positive enzyme immunoassays were tested with serotonin release assay. We also extracted the number of patients started on heparins in a similar period of time.

Results The median age at the time of testing was 4 years (25th-75th percentile, 8.7 months to 13.5 years); 78% of patients had low and 22% had intermediate risk pretest probability scores using the original 4Ts score; 86% had low risk and 14% had intermediate risk scores using the modified 4Ts score; 54% of children had a HEP score of ≥2. Six patients (12%) had a positive (≥0.40 optical density units) enzyme immunoassay, but none had a positive serotonin release assay. Based on anticoagulation dose, there were 1-2 new daily potentially high-risk exposures to heparinoids at our institution.

Conclusions The modified 4Ts and original 4Ts scores may be more adequate than the HEP score to determine HIT pretest probability in children. Despite the number of patients potentially at risk, HIT is rare in pediatrics. *(J Pediatr 2020;226:167-72)*.

Heparin-induced thrombocytopenia (HIT) is an immune-mediated side effect of heparin therapy clinically characterized by a platelet count decrease typically beginning between 5 and 10 days from the immunizing exposure to heparin and associated with a paradoxical increase in the risk for arterial and venous thrombosis.

The frequency of HIT in adult patients ranges between 0.2% and 5.0%, depending on heparin- and host-related factors; the incidence of HIT seems to be lower in children.[1] A systematic review including only pediatric studies with adequate study design to allow estimation of HIT incidence and in which adequate laboratory testing was used for HIT diagnosis, found no cases of HIT among neonates. The same review found only 1 case of HIT without thrombosis reported among non-neonates undergoing cardiopulmonary bypass, with an incidence of 0.33%.[2]

HIT presents a complex clinical scenario. Untreated HIT is associated with high morbidity and mortality in adults, thus requiring heparin discontinuation and the use of alternative anticoagulation to prevent thrombotic events.[3,4] However, incorrectly identified patients may be exposed to unnecessary therapeutic interventions and their associated side effects.

Several pretest scoring systems, such as the 4Ts, have been developed to facilitate and standardize the diagnosis of HIT in adult patients.[5-8] A systematic review concluded that a low probability 4Ts score had high negative predictive value.[9] A second scoring system, the HIT Expert Probability (HEP) score performs similarly to the 4Ts score in adults.[10]

Given the potentially severe consequences of a HIT misdiagnosis, our main goal was to investigate the applicability of the 4Ts score and HEP score in children with clinically suspected HIT. As a secondary outcome, we sought to estimate the number of children potentially at risk of HIT in our institution.

EIA	Enzyme immunoassay
HEP	HIT Expert Probability
HIT	Heparin-induced thrombocytopenia
LMWH	Low-molecular-weight heparin
OD	Optical density
SRA	Serotonin release assay
UFH	Unfractionated heparin

From the [1]Division of Hematology/Oncology, Department of Pediatrics; [2]Child Health Evaluative Sciences, The Hospital for Sick Children; [3]G. Raymond Chang School of Continuing Education, Ryerson University, Toronto; and the [4]Division of Hematology/Oncology, Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada

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Methods

This retrospective review included all pediatric patients screened for HIT between May 1, 2006, and August 31, 2008, at The Hospital for Sick Children using enzyme immunoassay (EIA) testing. The study was approved by the local Ethics Review Board. Informed consent was waived.

Extracted data from health records included the patient's age at the time of EIA testing, sex, underlying condition, clinical features of HIT, and type and dose of heparin exposure.

4Ts Score and HEP Score

The 4Ts score and HEP scores (**Tables I-III**; available at www.jpeds.com) were retrospectively estimated using the information related to the clinical components of each score that was recorded in the patients' charts at the time of EIA testing.

Owing to the retrospective nature of the data, 2 assessors adjudicated this outcome and a third assessor resolved disagreements. In a first round of data extraction and score estimation, items of the 4Ts score were applied strictly as indicated in the adult scoring system. After this first round of data extraction, the following 4Ts score modifications were deemed relevant to avoid overcalling HIT risk in a pediatric setting: timing and thrombosis.

Timing. Pediatric patients in whom HIT diagnosis was suspected had lengthy hospitalizations and heparin exposures. Therefore, we deemed appropriate to specify the upper limit of timing for thrombocytopenia. Thrombocytopenia that started ≥20 days after starting heparin exposure was scored 0 points unless a surgical intervention was reported or low-molecular-weight heparin (LMWH) was switched to unfractionated heparin (UFH). In these 2 cases, timing was counted from the day of surgery or the day of the heparin formulation switch. Onset of platelet decrease between days 11 and 19 of heparin exposure was scored 1 point.

Thrombosis. In view of the lengthy heparin exposures in our institution, thrombotic events many times occurred several days or weeks before the onset of thrombocytopenia or time of HIT suspicion. Hence, new thrombosis was defined as an event occurring within 2 days before or after the clinical suspicion of HIT or, if the clinical suspicion was delayed, from the onset of thrombocytopenia.

These modifications were carried out by consulting the original 4Ts developers, who are known experts in HIT in adult patients. In addition, information regarding bleeding events occurring during the time of HIT suspicion were classified as per the HEP score and according to international definitions, the latter to further characterize our patient population.[11]

Laboratory Testing

EIA laboratory screening was performed using a commercial PF4-dependent EIA from GTI Diagnostics (Waukesha, Wisconsin). This EIA detects PF4-dependent antibodies of 3 immunoglobulin classes (IgG, IgA, IgM) against PF4/polyvinyl sulfonate. Samples with a test result ≥0.40 optical density [OD_{405}] units, considered positive per the manufacturer, were referred to the McMaster Platelet Immunology Laboratory, Hamilton, Ontario, for confirmatory laboratory testing by platelet-activating antibodies by serotonin release assay (SRA).[12] Only patients with a positive SRA result and clinical findings compatible with HIT were diagnosed as true HIT cases.

Outcomes

We collected information on new or progressive objectively confirmed thrombosis and mortality on the month after the time of clinical suspicion of HIT.

Repeated EIAs

The reason for, OD, and timing of repeated EIA testing were extracted.

Patients at Risk of HIT

To estimate the population that was potentially at risk of developing HIT, we collected information on the number of patients that were started in a new course of continuous UFH infusion or LMWH in a similar period of time, between May 1, 2009, and August 31, 2011. We chose to collect data from 2009 because a new electronic system started that year, allowing to more accurately determine anticoagulant orders and doses throughout the hospital. High-risk exposures were defined as those related to therapeutic doses of UFH or LMWH.

Statistical Analyses

Categorical data were summarized with percentages and ratios; for continuous data, measures of central tendency and dispersion according to data distribution were estimated. Agreement on the 4Ts score and HEP score between the assessors was estimated using the absolute agreement 2-way random effects intraclass correlation coefficient. Because some studies reported EIA positivity to be associated with adverse events in adult patients, we compared the characteristics and outcomes of patients with positive and negative EIA at the OD ≥0.40-unit cut-off value.[13,14] Only the first EIA testing was considered for this part of the analysis. The Wilcoxon rank-sum test and Fisher exact test were used for these comparisons, as appropriate.

Mixed models were used to determine the average change in OD over time with repeated testing. Significance level was set at an alpha of 0.05. Analysis was performed in R (R Foundation for Statistical Computing, Vienna, Austria) and SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina).

Results

Fifty patients were tested for HIT using EIA during the study period. Median patient age at the time of first EIA testing was 48 months (25th-75th percentile, 8.7 months to 13.5 years); 21 patients (42%) were adolescents (aged 11-18 years), 17 patients (34%) were <1 year of age, and 1 patient was a neonate (18 days old); 29 (58%) were males. The most common underlying conditions included cardiac disease (11/50 [22%]), autoimmune/inflammatory diseases (10/50 [20%]), cancer (7/50 [14%]), organ transplant recipient (5/50 [10%]), organ failure (5/50 [10%]), and infections (3/50 [6%]). Only 1 patient did not have any concurrent health condition. Thirty-one patients (62%) were admitted in an intensive care setting (pediatric, cardiac, or neonatal).

At the time of testing, 22 patients (44%) were exposed to UFH flushes only, 14 (28%) were on hemodialysis, 9 (18%) were exposed to UFH or LMWH at prophylactic (n = 3) or treatment (n = 6) doses, 3 (6%) were on extracorporeal membrane oxygenation, and 2 (4%) were post cardiopulmonary bypass.

4Ts Score and HEP Score

The median original 4Ts score at the time of testing was 3 (range, 0-5); 11 of 50 patients (22%) had an intermediate pretest probability of having HIT (**Figure**). The median modified 4Ts score was 2 (range, 0-4) and 7 patients (14%) had an intermediate pretest probability of having HIT; the rest of the cohort had low probability. Overall, 27 patients (54%) had a lower score when applying the modified 4Ts score, as compared with the original 4Ts score. Twenty-one patients had a lower modified 4Ts score owing to reclassification of timing of thrombocytopenia, 1 owing to reclassification of thrombosis, and 5 owing to reclassification of both components. The median HEP score was 1 (range, −7 to 7); 27 patients (54%) had a HEP score of ≥2.

The intraclass correlation coefficient between assessors was 0.97 (95% CI, 0.95-0.99) for 4Ts original scores and 0.96 (95% CI, 0.92-0.97) for HEP scores. The main source of discrepancy for all 3 scores was seen with the adjudication of other causes of thrombocytopenia.

In terms of the components of the scoring systems, the nadir in platelet count was 33 × 10^9/L (25th-75th percentile, 15-47 × 10^9/L), with a median drop of 59% (25th-75th percentile, 47%-78%) from the peak platelet count. The median time of onset of thrombocytopenia after initial heparin exposure was 12 days (25th-75th percentile, 3-48 days). Most patients (47/50 [94%]) had other definite causes for thrombocytopenia. No patient sustained acute systemic reaction or skin necrosis. Eighteen of 50 patients (36%) had signs of bleeding as per the HEP score; 9 of these patients had a major bleeding (50%) and 3 patients had a clinically relevant nonmajor bleeding.[11] Nine thrombotic events (9/50 [18%]) occurred before testing. Six patients had their thrombi ≤2 days before the date of EIA testing and 3 were diagnosed with thrombi ±2 days from the date of onset of platelet decrease. Six events (6/9 [66%]) were in the lower extremities and the remaining occurred in the upper extremities (n = 1), in a Rex shunt (n = 1), and in the portal and mesenteric vein (n = 1). Of note, all 7 thrombotic events within the extremities were central venous catheter related.

Laboratory Test Results

The median EIA OD was 0.09 (25th-75th percentile, 0.06-0.17). Six of the first 50 EIA tests (12%) were ≥0.40 OD units and only 1 test was ≥1.40 OD units (**Table IV**). All the remaining EIAs were <0.40 OD units. Only the patient with ≥1.40 OD units (1.59 OD units) had an indeterminate SRA, the remaining 5 patients had a negative SRA. There was no statistically significant difference in age at the time of testing (P = .71), sex (P = .99), thrombosis (either before or after testing; P = 0.99), or 30-day mortality (P = .76), when comparing patients positive and negative for EIA at a ≥0.40 OD unit cut-off value.

Outcomes

There were 5 deaths (10%) within 30 days after testing in this cohort of patients. The median time to death was 9 days (25th-75th percentile, 4-14 days) after EIA testing.

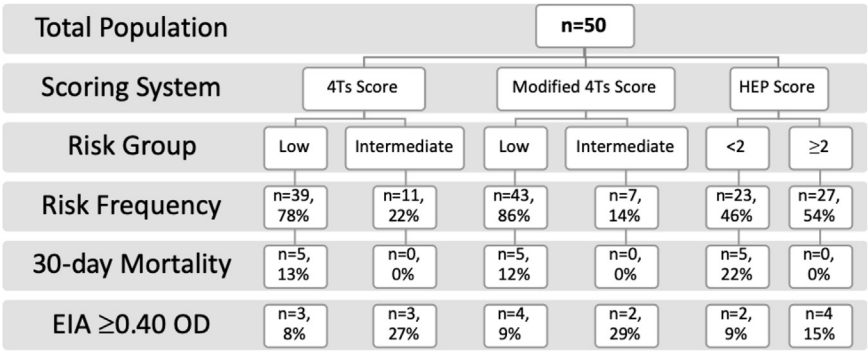

Figure. Score distribution and mortality.

Table IV. Patients with positive EIA results

Case	Age (mo)	4Ts score	Modified 4Ts score	HEP score	EIA result (OD units)	SRA result	Heparin exposure	Heparin cessation	Death	Reason for lower modified 4Ts scoring
1	14	4	1	−1	0.505	Negative	Hemodialysis	No	Yes, 266 days after testing	Onset 61 days after heparin exposure; thrombosis after starting heparin but 48 daus before onset of thrombocytopenia and 60 days before clinical suspicion of HIT
2	26	2	2	2	0.489	Negative	Heparin flushes	Temporary	No	–
3	103	4	4	4	0.405	Negative	Heparin treatment	No	No	–
4	3	5	4	7	0.903	Negative	Hemodialysis	Temporary	Yes, 259 days after testing	Onset 21 days after heparin exposure
5	184	2	2	6	0.561	Negative	Heparin flushes	Temporary	No	–
6	12	3	2	3	1.585	Indeterminate	Heparin treatment	No	Yes, 386 days after testing	Onset 72 days after heparin exposure

Thrombosis was seen in 4 patients (8%) in the first month after EIA testing (range, 1-15 days); all of them had negative EIAs. All of these events were associated with a central venous catheter.

Repeated EIA Testing

Fifteen patients (30%) were retested for EIA at a median of 31 days (25th-75th percentile, 8.5-147 days) after the first test; 29 repeated EIA were requested in these 15 patients, for a median of 1 repeated test per patient (range, 1-6). The median OD of repeated EIA was 0.18 units (range, 0.0225-0.669 units). Reasons for repeated testing were unclear, although a new decrease in platelet count, insufficient blood sample, and a previous positive EIA seemed to be the reason in some cases. Thirteen of 15 retested patients (87%) did not change their status (continued to be either positive or negative upon retesting). One patient was positive and became negative and 1 patient was negative and became positive. Mixed models showed a nonstatistically significant change in OD over time with repeated testing, with an average decrease of 0.0005 OD units per day after the first testing ($P = .61$). One patient was tested for HIT in 2 occasions that were ≥180 days apart. In these 2 occasions, the 4Ts scores were 0 and the HEP scores were −1.

Patients at Risk of HIT

Between May 1, 2009, and August 31, 2011 (852 days), there were 34 305 admissions corresponding with 22 536 unique patients. In total, 1959 of these 22 526 unique patients were exposed to ≥1 heparin courses during the study period. Hence, 8.7% (1959/22 526) of children may have been at risk of developing HIT at least once.

These 1959 unique patients received a total of 2693 new courses of UFH or LMWH (median of 1 course per patient; range, 1-5 courses) during observation period. Of the 2693 new courses, 1140 (1140/2693 [42%]) were UFH doses >10 U/kg/hour, 501 (of 2693 [19%]) were new exposures to a therapeutic dose of enoxaparin, and 95 (of 2693 [4%]) were new exposures to a therapeutic dose of tinzaparin. Therefore, based on the dose of the anticoagulant, 1736 (1736/2693 [64%]) potentially high-HIT risk exposures were recorded in this period, suggesting there were 2 new high-risk exposures every day at our institution. Calculating risk based on drug (UFH) and dose, there was 1 new potentially high-risk exposure at our institution every 1-2 days during the observation period.

Discussion

We found that, as compared with the modified 4Ts score, the application of the original 4Ts score led to a slightly higher number of patients being classified in a higher risk group (22% for the original 4Ts score vs 14% for the modified 4Ts score). Other researchers have reported a higher frequency of children with intermediate or high risk scores than that found in our study, with frequencies of 53% and 75%.[15,16] However, there was only 1 functional assay-proven case of HIT in only 1 of those studies, suggesting a potential overestimation of the risk when using the original 4Ts score. In comparison, the HEP score resulted in a higher frequency of patients classified at high risk for HIT. It is possible that a threshold higher than the ≥2 points we used may be required to classify children as high probability of having HIT when using the HEP score. Of note, the median HEP score in our cohort was lower than the median original 4Ts score.

Using the modified 4Ts score, which was adapted to define an upper cut-off for timing of thrombocytopenia and a timing for thrombotic events, may be warranted particularly for use in pediatric patients with lengthy hospital stays. These modifications resulted in lower overall scores and therefore, could lead to a lower frequency of patients in higher risk groups. This is of relevance, given that adult guidelines suggest the use of alternative anticoagulants in the setting of intermediate or high risk probability for HIT.[17]

Only 1 patient in our cohort had EIA OD units of >1.00, and that patient was the only one who had an indeterminate SRA. This finding is in line with adult studies that suggest that an OD between 0.40 and <1.00 units strongly suggests against a diagnosis of HIT, and that higher cut-offs for OD

units increase specificity without compromising the sensitivity of the test.[18,19] As in our study, no patient with an EIA OD of ≤1.00 units in that cohort had a positive SRA.

We cannot make conclusions about the diagnostic performance of the 4Ts or the HEP score without confirmed cases of HIT in our study. The low prevalence of the disease and the fact children had low scores when using the original or modified 4Ts score indicate these scoring systems are expected to have high negative predictive value in this population. This finding is also in keeping with what has been described in a systematic review of 13 studies involving 3068 adult patients.[9] According to the authors, low 4Ts scores have high negative predictive value (0.99), which obviates the need for testing in this scenario, whereas intermediate or high 4Ts scores have low positive predictive value (0.14).[17]

Prospective validation of the 4Ts score in children would be relevant. Nevertheless, given the low incidence of HIT in this age group, such a study will require a large number of patients. For example, considering an incidence of 0.33% in pediatric patients undergoing cardiopulmonary bypass, 907 children should be enrolled and followed up to observe ≥1 case of HIT.[2]

Although 1-2 new high-risk exposure to anticoagulants occurs at our institution every day, no documented cases of HIT were observed over a period of 28 months. This finding is consistent with other few pediatric studies using SRA for confirmatory testing and supports the concept that the true incidence of HIT in children is extremely low.[20]

Our findings also suggest that laboratory investigation of pediatric patients with suspected HIT should only be initiated in patients with intermediate or high pretest probability scores. We recently observed a case of SRA-positive HIT at our institution in a 4-year-old patient who had an original and a modified 4Ts score of 7, a HEP score of 14 points, and an EIA of 2.89 OD. Similarly, our results equally suggest that a confirmatory functional laboratory test is an essential part of the management of children with suspected HIT.

A pediatric study identified 1 case of SRA proven HIT among 4668 children exposed to therapeutic doses of heparin in 4.25 years of observation, for an incidence of 0.5 HIT cases per 10 000 pediatric patients exposed to therapeutic doses of heparin per year.[16] The reason for the low incidence of HIT in children is not well-understood, but may relate in part to the immaturity of immune system and to age-related differences of coagulation components and in the binding capacity of heparin observed in children.[2] Furthermore, it has been reported that *Staphylococcus aureus* bacteria coated with PF4 can bind anti-PF4/heparin IgG of HIT patient sera and that bacterial sepsis in mice induces the formation of anti-PF4/heparin IgM and IgG.[21] These results suggest that HIT is a secondary immune response from prior bacterial exposure, an exposure that may not yet have occurred in young children.

In contrast, the frequency of HIT seroconversion was relatively higher (12%), which aligns with the 17% and 8% frequency reported in adult hospitalized patients treated with UFH or LMWH.[22] Nationwide registry data have shown a frequency of IgG-specific seroconversion of 24% among 17 pediatric patients with suspected HIT, whereas a retrospective pediatric study found a frequency of 8% of seroconversion by polyspecific EIA.[15,16]

Although a positive EIA has been associated with mortality, prolonged hospitalization, and other adverse events in some adult studies, positivity in our cohort was not associated with either 30-day mortality or thrombosis.[13,14] This finding could be due to the small number of seropositive children included in our cohort. It is also consistent with a study in adults that reported that EIA positivity did not increase the risk of death or thromboembolic events after cardiac surgery in a large cohort of patients.[23]

Our study also shows that repeated EIA testing did not lead to improved diagnosis; on average, patients did not significantly change their OD units or overall classification over time. Repeated HIT testing in the context of an appropriate negative HIT assay and absence of new clinical features of HIT can result in detection of non-HIT seroconversion and lead to HIT overdiagnosis.[24]

There are limitations and strengths to our data. Our cohort of patients was identified by referrals for HIT testing and, therefore, clinically unrecognized HIT with failure to refer the patient for testing may have occurred. However, all patients with thrombosis at our institution are managed by a centralized thrombosis service and at a minimum, cases of HIT with thrombosis were unlikely to be missed. Similarly, the incidence of HIT in similar adult cohorts is low.[25,26] Second, we extracted scores retrospectively from the patient's chart. To overcome issues related to retrospective data collection, scores were extracted in duplicate by independent researchers. Last, in the context of the low incidence of pediatric HIT, the small number of patients enrolled in this study limits our capacity to fully characterize the diagnostic performance of the pretesting scores. This limitation is offset by the fact that SRA was requested in all patients with an EIA of ≥0.40 OD units, which allowed an accurate clinical-laboratory assessment of children with suspected HIT and, therefore, the assessment of the applicability of the scores. The study suggests the importance of using laboratory screening only for patients with at least a moderate suspicion of HIT, as per the 4Ts and modified 4Ts score, as well as the use of a functional test to establish diagnosis. Furthermore, the high number of patients who were in intensive care units or had major or clinically relevant nonmajor bleeding events around the time of HIT suspicion in our cohort suggests high patient acuity and generalizability of our findings regarding the applicability of the scores to other tertiary and quaternary care institutions.

In conclusion, the 4Ts and modified 4Ts score performed better than the HEP score for the pretest risk assessment of pediatric patients. The modified 4Ts score resulted in lower scores in more than half the children included in this cohort and may lead to lower risk score classification among hospitalized children. Our findings also suggest that HIT is rare in children and that testing

is not warranted in children with low pretest probability, as is the case of adult patients.[17] ■

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Reprint requests: Leonardo R. Brandão, MD, MSc, Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada M5G-1X8. E-mail: leonardo.brandao@sickkids.ca

Data Statement

Data sharing statement available at www.jpeds.com.

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Table I. The 4Ts Score

4Ts categories	2 points	1 point	0 point
Thrombocytopenia	Platelet count decrease of >50% and platelet nadir ≥20 × 10^9/L	Platelet count decrease of 30%-50% OR platelet nadir 10-19 × 10^9/L	Platelet count decrease of <30% or platelet nadir <10 × 10^9/L
Timing of decrease in platelet count	Clear onset between days 5 and 10 OR platelet decrease of ≤1 day with heparin exposure within 30 prior days	Decrease in platelet count consistent with onset between days 5 and 10, but timing is not clear owing to missing platelet counts OR decrease in platelet after day 10 of heparin exposure OR decrease in platelet counts ≤1 day with prior heparin exposure between 30 and 100 days ago	Platelet count decrease of <4 days without recent heparin exposure
Thrombosis	New thrombosis, skin necrosis, or acute systemic reaction after UFH exposure	Progressive/recurrent thrombosis or unconfirmed but clinically suspected thrombosis	No thrombosis or thrombosis preceding heparin exposure
Other causes for thrombocytopenia	None apparent	Possible other causes present	Probable other causes present

The 4Ts score is assigned by summing the values for each of the 4 categories. A score of 1, 2, or 3 is considered low; 4 or 5 is considered intermediate; and 6, 7, or 8 is considered high. Reproduced with permission from Crowther MA et al. The 4Ts scoring system for heparin-induced thrombocytopenia in medical-surgical intensive care unit patients. Journal of Critical Care 2010;25:287-93.

Table II. The Modified 4Ts Score

4Ts category	2 points	1 point	0 point
Thrombocytopenia	Platelet count decrease of >50% and platelet nadir ≥20 × 10^9/L	Platelet count decrease of 30%-50% OR platelet nadir 10-19 × 10^9/L	Platelet count decrease of <30% or platelet nadir <10 × 10^9/L
Timing of decrease in platelet count	Clear onset between days 5 and 10 OR platelet decrease of ≤1 day with heparin exposure within 30 prior days	Decrease in platelet count consistent with onset between days 5 and 10, but timing is not clear owing to missing platelet counts OR decrease in platelet **between days 11-19** of heparin exposure OR decrease in platelet counts ≤1 day with prior heparin exposure between 30 and 100 days ago	Platelet count decrease of <4 days without recent heparin exposure **OR decrease in platelet count ≥20 days of heparin exposure***
Thrombosis	New thrombosis,† skin necrosis, or acute systemic reaction after UFH exposure	Progressive/recurrent thrombosis or unconfirmed but clinically suspected thrombosis	No thrombosis or thrombosis preceding heparin exposure
Other causes for thrombocytopenia	None apparent	Possible other causes present	Probable other causes present

Modifications are noted in bold.
*Unless a surgical intervention was reported or LMWH was switched to UFH. In these 2 cases, timing is counted from the day of surgery or the day of the heparin formulation switch.
†Thrombosis occurring within 2 days before or after the clinical suspicion of HIT or, if the clinical suspicion was delayed, from onset of thrombocytopenia.

Table III. The HEP Score

Factors	Score assigned
1. Platelet count decrease since heparin initiation	
<30%	−1
30%-50%	1
>50%	3
2a. Decrease in platelet count (typical onset)	
<4 days	−2
4 days	2
5-10 days	3
11-14 days	2
<14 days	−1
2b. Rapid onset after reexposure to heparin in last 100 days	
<48 hours	2
>48 hours	−1
3. Lowest platelet count	
$\leq 20 \times 10^9$/L	−2
$>20 \times 10^9$/L	2
4a. Thrombosis for patients with typical onset (select 1 only)	
New venous/arterial thrombosis at 4 days or more since heparin initiated	3
Progression of venous/arterial thrombosis during heparin therapy	2
4b. Thrombosis for rapid-onset HIT	
New venous/arterial thrombosis after heparin exposure	3
Progression of venous/arterial thrombosis during heparin therapy	2
5. Skin necrosis	
Heparin injection site necrosis	3
6. Acute systemic reaction	
Bolus of heparin with acute systemic reaction	2
7. Bleeding	
Signs of bleeding, petechiae or extensive ecchymosis	−1
8. Other causes of thrombocytopenia (score all that apply)	
Ongoing thrombocytopenic disease	−1
Known medication to cause thrombocytopenia initiated	−2
Severe infection	−2
Severe disseminated intravascular coagulopathy (DIC)	
<mg/dL and D-dimer >5.0 μg/mL	−2
Presence of intra-arterial device	−2
Cardiopulmonary bypass in the last 96 hours	−1
No other apparent cause	3

A total score of ≥2 is likely positive for HIT.
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