

# Overdiagnosis of Heparin-Induced Thrombocytopenia in Surgical ICU Patients

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- BACKGROUND:** Heparin use in surgical patients places them at increased risk for developing heparin-induced thrombocytopenia (HIT). The false positive rate of HIT using the current standard criteria is unknown in surgical ICU patients, who often have confounding factors that cause thrombocytopenia.
- STUDY DESIGN:** Surgical ICU patients, admitted over a 2-year period with a positive screening test for HIT (platelet factor [PF] 4  $\geq$  0.4 optical density [OD]), were reviewed retrospectively at a single institution. Correlation of the Warkentin 4-T score and commercial heparin PF4 ELISA with serotonin releasing assay (SRA) was performed. Logistic regression was used to determine independent risk factors associated with the development of HIT.
- RESULTS:** PF4 tests were requested in 643 patients based on a clinical suspicion of HIT. Of these, 104 patients had a PF4 result, an SRA value (%), and a 4-T score available. Twenty patients (19%) had true positive HIT, defined as a positive PF4 and positive SRA (SRA  $\geq$  20%). Eighty-four patients (81%) were false positive, defined as a positive PF4 and negative SRA. Five of 58 patients with Warkentin score of 0 to 3, and 6 of 14 patients with Warkentin score of 6 to 8 were HIT positive by SRA.
- CONCLUSIONS:** In surgical ICU patients, clinical suspicion for HIT necessitates PF4 and SRA analysis. Testing for HIT or treatment with a direct thrombin inhibitor should not depend on the Warkentin 4-T score alone. Although a PF4  $\geq$  0.4 OD is considered a positive screening test for HIT, a PF4  $\geq$  2.0 OD is preferable in surgical ICU patients. (J Am Coll Surg 2011;213:10–18. © 2011 by the American College of Surgeons)
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Venous thromboembolism is a common complication for patients undergoing operations, and pulmonary embolism is the most common cause of preventable death in patients hospitalized for surgical procedures.<sup>1,2</sup> In patients undergoing general surgery without prophylaxis, the rates of deep vein thrombosis and fatal pulmonary embolism range from 15% to 30% and from 0.2% to 0.9%, respectively.<sup>1-3</sup> Prophylaxis with either low-dose unfractionated heparin or low-molecular-weight heparin has been shown to reduce the risk of venous thromboembolism in surgical patients by

at least 60%.<sup>2-4</sup> The American College of Chest Physicians (ACCP) 2008 guidelines<sup>5</sup> state that for moderate-risk general surgery patients who are undergoing a major procedure for benign disease, thromboprophylaxis with low-molecular-weight heparin, low-dose unfractionated heparin twice daily (3 times daily in high-risk patients), or fondaparinux is recommended.

Heparin use in surgical patients places them at increased risk for developing heparin-induced thrombocytopenia (HIT). HIT is an acquired, transient, antibody-mediated thrombocytopenia occurring in a subset of patients exposed to heparin, that confers a high risk of venous and arterial thrombosis. Once the diagnosis of HIT is suspected, the American Society of Hematology recommends<sup>6</sup> discontinuation of heparin, administration of a nonheparin anticoagulant (lepirudin, argatroban, or bivalirudin), and HIT confirmation with a serologic assay (Fig. 1). Two groups of serologic assays are available: immunologic tests used as screening assays and functional tests used as confirmatory assays. Immunologic tests such as the platelet factor

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### Abbreviations and Acronyms

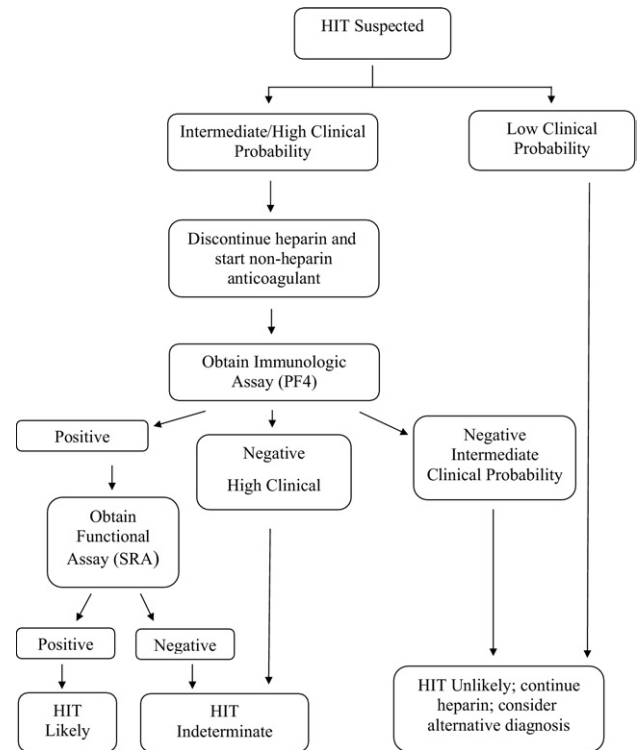
ACCP	= American College of Chest Physicians
HIT	= heparin-induced thrombocytopenia
OD	= optical density
OR	= odds ratio
PF	= platelet factor
SAPS	= Simplified Acute Physiology Score
SRA	= serotonin releasing assay

4 (PF4) ELISA detect antibodies against PF4/heparin complexes. Functional tests such as the serotonin releasing assay (SRA) detect IgG antibodies that induce heparin-dependent platelet activation. Controversy exists in accurately diagnosing HIT in complex severely ill surgical ICU patients. In ICU patients, the diagnosis and treatment of HIT is especially problematic because HIT affects less than 1% of ICU patients, even though 30% to 50% develop thrombocytopenia.<sup>7</sup>

Treatment of HIT often begins once the screening assay is positive (PF4  $\geq$  0.4 optical density [OD], as defined by the manufacturers) which involves significant changes in management, places postoperative surgical patients at increased risk of bleeding compared with medical patients by using alternative anticoagulants recommended by the current clinical guidelines, and increases costs. Therefore, accurate diagnosis of HIT is critical. Because the current guidelines are based primarily on general medicine patients, the false positive rate of HIT using traditional criteria is unknown in surgical ICU patients, who often have confounding factors such as sepsis, resuscitative hemodilution, or liver disease, which place them at increased risk for the development of thrombocytopenia and thrombosis. The purpose of this study was to determine the value of PF4 and Warkentin 4-T score when there is suspicion of HIT in surgical ICU patients.

## METHODS

This is a retrospective study of patients admitted to the surgical ICU of an urban, academic medical center. All patients presumed to have HIT by clinical suspicion and who had a positive PF4 ELISA screening test between January 2008 and February 2010 were included in the study. Clinical suspicion for HIT was initiated by the treating physician based on the Warkentin 4-T score,<sup>8</sup> a drop in platelet count, or evidence of new thrombosis while receiving heparin. At the time the PF4 test was ordered, a Warkentin 4-T score was documented in the electronic medical record and, in general, confirmatory SRA was ordered by pathology consultation. No post-hoc Warkentin 4-T score analysis was conducted. The Warkentin 4-T scor-



**Figure 1.** American Society of Hematology diagnostic and initial treatment algorithm. (From: Cuker A, Crowther A. 2009 Clinical practice guideline on the evaluation and management of heparin-induced thrombocytopenia (HIT). American Society of Hematology 2009;1-8., with permission.) HIT, heparin-induced thrombocytopenia.

ing system<sup>8</sup> (Table 1) is based on 4 features: thrombocytopenia; timing of thrombocytopenia; thrombosis; and an alternative cause for thrombocytopenia. Each feature is allotted 0 to 2 points, and a subsequent score of 0 to 8 points is generated. Previous reports suggest that if the score is 0 to 3, HIT is unlikely. A score of 4 to 5 indicates an intermediate suspicion of HIT, and a score of 6 to 8 makes HIT highly likely.<sup>8-10</sup> A PF4 test was considered positive for HIT for values  $\geq$  0.4 OD, as recommended by GTI Diagnostics' PF4 Enhanced Solid Phase ELISA Manufacturers. Confirmation of HIT was made with a <sup>14</sup>C serotonin releasing assay (SRA), run by Quest Diagnostics and the Blood Center of Wisconsin (after 2008). Values  $\geq$  20% (for Quest Diagnostics) or  $\geq$  20% with low dose heparin and  $<$  20% with high dose heparin (Blood Center of Wisconsin) were considered positive for HIT.

Patient characteristics (age, sex, race, Acute Physiology and Chronic Health Evaluation [APACHE] II Score, Simplified Acute Physiology Score [SAPS], type of surgery, and type of heparin exposure) and outcomes (ICU length of stay, hospital length of stay, mortality, and thrombosis)

**Table 1.** Warkentin 4-T Score<sup>8,9</sup>

4Ts Category	2 Points	1 Point	0 Point
Thrombocytopenia	Platelet count falls >50% from baseline AND platelet nadir $\geq 20 \times 10^9/L$ .	Platelet count falls 30% to 50% from baseline OR platelet nadir $10-19 \times 10^9/L$ .	Platelet count falls < 30% from baseline OR platelet nadir < $10 \times 10^9/L$ . Platelet count falls < 4 d without recent heparin exposure.
Timing of platelet count fall.	Clear onset between days 5 and 10 OR platelet count falls $\leq 1$ d with heparin exposure within 30 prior d.	Fall in platelet counts consistent with onset between days 5 and 10, but timing is not clear due to missing platelet counts OR onset after day 10 of heparin exposure OR fall in platelet counts $\leq 1$ d with prior heparin exposure between 30 and 100 d previously.	Platelet count falls < 4 d without recent heparin exposure.
Thrombosis or other sequelae	New thrombosis, skin necrosis, or acute systemic reaction after unfractionated heparin exposure.	Progressive/recurrent thrombosis or unconfirmed but clinically suspected thrombosis.	No thrombosis or thrombosis preceding heparin exposure.
Other causes of 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 clinical suspicion; 4 or 5 is considered intermediate clinical suspicion; and 6, 7, or 8 is considered high clinical suspicion.

(From: Crowther MA, Cook DJ, Albert M, et al. The 4Ts scoring system for heparin-induced thrombocytopenia in medical-surgical intensive care unit patients. *J Crit Care* 2010;25:287–293, with permission).

were recorded and evaluated. Data regarding the PF4 values, Warkentin 4-T score, and SRA were also documented. Patients with SRA  $\geq 20\%$  were classified as true positive for HIT; patients with SRA < 20% were classified as HIT false positive. Only patients with PF4  $\geq 0.4$  OD were included in this study, therefore, no true negatives or false negatives were included for analysis. Comparisons of patient characteristics and outcomes were made between the true positive group and the false positive group.

Categorical variables were compared by the Fisher exact test. Numerical variables were compared by the *t*-test (normal distribution) or the Wilcoxon rank sum test (non-normal distribution). Logistic regression was used to determine the relationship between independent risk factors and the development of HIT. Odds ratios (OR), as well as their 95% confidence intervals, were calculated. Values of  $p < 0.05$  determined significance. All statistical analysis was performed using SAS, version 9.1 (SAS Institute). This study received institutional review board approval.

## RESULTS

Based on a clinical suspicion of HIT, PF4 ELISA tests were requested for 643 surgical ICU patients; 137 of those patients were positive (PF4  $\geq 0.4$  OD). In the excluded 506 PF4 negative patients (PF4 < 0.4 OD), 97 SRA tests were ordered and all were negative for HIT. Of the 137 patients with a positive PF4 test and calculated Warkentin 4-T score, 104 patients had an available SRA test. Twenty pa-

tients (19%) were true positive HIT and 84 patients (81%) were false positive HIT. Forty-two percent of the sample population had undergone cardiac surgery; 49% of patients were postoperative general surgery, trauma surgery, neurosurgery, vascular surgery, kidney transplant, and urology patients. Thirteen surgical ICU patients had undergone central line placement (Table 2).

Within 24 hours of sending the PF4 test, the SRA test was sent in 95 of 104 (91%) patients. In 2 of 104 (1.9%) patients, the SRA test was sent within 48 hours and within 3 to 6 days the SRA test was sent in 7 of 104 (6.7%) patients. There were multiple SRA tests sent on 35 patients.

There were 17 patients with initial SRA values < 20% who were initially categorized as “indeterminate” HIT due to either a high 4-T score or elevated PF4 values. These patients underwent further analysis for potentially confounding factors. In one patient labeled as true positive, the SRA increased from 10% to 75% within 4 days of repeating the test. In another patient labeled as true positive, the SRA rose from 0% to 31% to 86% within 3 days of the initial test. A third patient had an initial SRA value of 0. On repeat testing in 14 days, the SRA value had increased to 52%. However, the SRA test was evaluated again 3 days later and the value decreased to 19%, so this patient was classified as false positive. The fourth patient had an initial SRA value of 17%; however, when the same specimen was sent to a different laboratory, the SRA value was 97% so the patient was classified as true positive. The next 2 patients

**Table 2.** Characteristics of Study Population

Characteristic	Total sample (n = 104)	True positives (n = 20)	False positives (n = 84)	p Value
Age, y, mean $\pm$ SD	60.4 $\pm$ 16.9	61.0 $\pm$ 18.7	60.2 $\pm$ 16.6	0.68
Male, n (%)	67 (64.4)	13 (65.0)	54 (64.3)	>0.95
Race, n (%)				0.51
Asian	6 (5.8)	0 (0)	6 (7.1)	
African American	16 (15.4)	4 (20.0)	12 (14.3)	
Caucasian	78 (75.0)	15 (75.0)	63 (75.0)	
Hispanic	2 (1.9)	0 (0)	2 (2.4)	
Other	2 (1.9)	1 (5)	1 (1.2)	
APACHE II, mean $\pm$ SD	22.0 $\pm$ 10.5	17.7 $\pm$ 10.4	23.1 $\pm$ 10.4	0.016
SAPS, mean $\pm$ SD	15.4 $\pm$ 6.4	12.9 $\pm$ 7.4	16.0 $\pm$ 6.1	0.043
Type of surgery, n (%)				0.019
Cardiac	44 (42.3)	6 (30.0)	38 (45.2)	
General surgery	11 (10.6)	2 (10.0)	9 (10.7)	
Kidney transplant	1 (1.0)	1 (5.0)	0 (0)	
Neurosurgery	17 (16.4)	3 (15.0)	14 (16.7)	
None	9 (8.6)	0 (0)	9 (10.7)	
Other procedure				
Central line placement	13 (12.5)	5 (25.0)	8 (9.5)	
Trauma	4 (3.8)	3 (15.0)	1 (1.2)	
Urology	1 (1.0)	0 (0)	1 (1.2)	
Vascular	4 (3.8)	0 (0)	4 (4.8)	
Heparin exposure, n (%)				0.35
Drip	19 (18.3)	4 (20.0)	15 (17.9)	
Flush	18 (17.3)	3 (15.0)	15 (17.9)	
Prophylactic	57 (54.8)	9 (45.0)	48 (57.1)	
Unknown	10 (9.6)	4 (20.0)	6 (7.1)	
PF4 [OD], mean $\pm$ SD	1.22 $\pm$ 0.87	2.23 $\pm$ 0.96	0.98 $\pm$ 0.65	<0.0001
SRA, %, mean $\pm$ SD	14.0 $\pm$ 27.4	65.2 $\pm$ 24.0	1.9 $\pm$ 4.2	<0.0001
Warkentin 4-T score, median [interquartile ranges]	3 [2–5]	5 [3.5–6]	3 [1.5–4]	0.0008

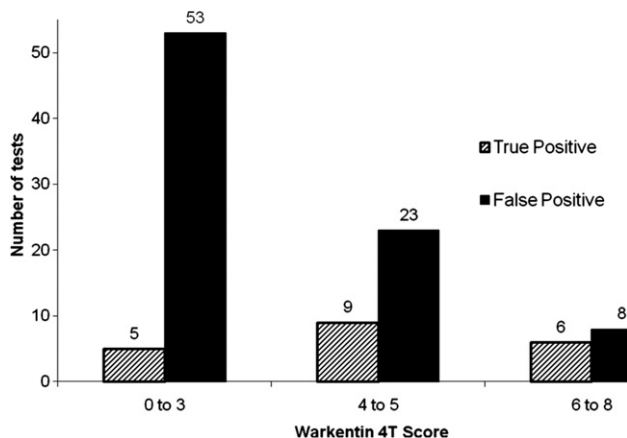
OD, optical density; PF, platelet factor; SAPS, Simplified Acute Physiology Score; SRA, serotonin releasing assay.

had an intermediate clinical suspicion of HIT based on the Warkentin 4-T score, PF4 > 0.8 OD, and deep vein thrombosis; they were classified as false positive because their initial and confirmatory SRA values were <20%. The 11 remaining patients who were initially categorized as “indeterminate” were called false positive per study protocol because their SRA values were <20%.

In comparing true positive with false positive, false positive patients were more critically ill, with significantly higher APACHE II and SAP scores. The PF4 value for the true positive group was significantly higher than that for the false positive group (2.23  $\pm$  0.96 OD vs 0.98  $\pm$  0.65 OD,  $p$  < 0.0001) (Table 2). As expected, the SRA value and the Warkentin 4-T scores for true positives were significantly higher when compared with false positives. Figure 2 shows HIT results for increasing Warkentin score. With low suspicion for HIT (Warkentin score 0 to 3), 5

patients were true positive and 53 patients were false positive. With an intermediate suspicion for HIT (Warkentin score 4 to 5), 23 patients were false positive and 9 patients were true positive. A Warkentin score of 6 to 8 (high suspicion for HIT) resulted in 8 false positive patients and 6 true positive patients. Low suspicion for HIT by Warkentin score could not rule out HIT because 5 of 58 (8.6%) were true positive. High clinical suspicion for HIT by Warkentin score could not rule in HIT because 8 of 14 (57%) were false positive.

Similar trends were noted when cardiac patients were analyzed separately. Twenty-six patients had Warkentin scores that were low (24 false positive and 2 true positive), 13 had intermediate scores (11 false positive and 2 true positive), and 5 had high clinical suspicion scores (3 false positive and 2 true positive). In cardiac patients, low suspicion for HIT by Warkentin score could not rule out HIT



**Figure 2.** Heparin-induced thrombocytopenia (HIT) results, grouped by Warkentin score (0 to 3, HIT unlikely; 4 to 5, intermediate suspicion; 6 to 8, high suspicion) (x-axis), from 104 Warkentin tests ordered (y-axis) based on a clinical suspicion of HIT. True positive, lined bar, patients with SRA  $\geq$  20%. False positive, black bar, patients with a serotonin releasing assay  $<$  20%.

because 2 of 26 (7.7 %) were true positive. High clinical suspicion for HIT by Warkentin score could not rule in HIT because 3 of 5 (60%) were false positive.

Figure 3 shows HIT results for increasing PF4 ELISA OD. Of the 104 patients included in the analysis, 84 patients were false positive for HIT. Values ranging from 0.4 to 1.99 OD were noted in 84 patients, with only 7 true positives (8.3%). For PF4 values above 2.0 OD, 13 were true positive out of 20 patients (65%). Similar trends were noted when cardiac patients were analyzed separately. PF4 values ranging 0.4 to 1.99 OD resulted in 3 true positives in 38 patients (7.9%). For PF4 values above 2.0 OD, 3 of 6 patients were true positive (50%).

There were no significant differences in ICU length of stay, hospital length of stay, and mortality between the true positive and false positive groups, respectively (Table 3). Thrombosis was noted in all true positive patients, with deep vein thrombosis representing the most common type. Table 4 demonstrates the odds ratios for developing HIT in patients with a PF4  $\geq$  0.4 OD. When compared with patients with a Warkentin 4-T score of 0 to 3, the group of patients with a Warkentin 4-T score of 4 to 5 had 4.15 times the odds of developing HIT and those with a Warkentin 4-T score of 6 to 8 had 7.95 times the odds of developing HIT.

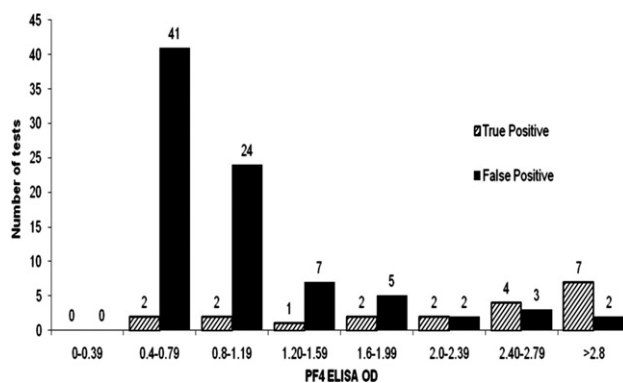
In evaluating the total sample population, heparin was discontinued in 59.6% of patients with no further treatment; 31.7% were further treated with argatroban or lepirudin (23% of the false positive group and 65% of the true positive group). Heparin was discontinued in all true positive patients, although 8.7% of the patients, all false positive, were continued on heparin therapy.

## DISCUSSION

HIT is an acquired, transient, anticoagulant-induced, antibody-mediated thrombocytopenia caused by heparin exposure, which confers a high risk of venous (causing deep vein thrombosis, pulmonary embolism, and adrenal hemorrhagic infarction) and arterial thrombosis (causing myocardial infarction and/or stroke, skin necrosis, and limb ischemia).<sup>11-15</sup> Heparin binds to a protein known as PF4, causing the immune system to develop antibodies (usually IgG) against this complex usually within 5 to 10 days of the heparin exposure. The antibody then binds to the Fc receptor, found on the surface of platelets, causing their activation. Activation of platelets results in platelet consumption and thrombocytopenia in addition to the formation of platelet-derived procoagulant microparticles, resulting in thrombosis.<sup>16</sup>

The ACCP Evidence-Based Clinical Practice Guidelines (Eighth Edition)<sup>17</sup> recommend investigating for a diagnosis of HIT if the platelet count drops by 50% and/or a thrombotic event occurs between 5 and 14 days after initiation of heparin, even if the patient was no longer receiving heparin therapy when the thrombosis or thrombocytopenia occurred. One year after the publication of ACCP recommendations, the American Society of Hematology published diagnostic clinical guidelines<sup>6</sup> adapted from the ACCP guidelines, which included the initial treatment algorithm for the management of HIT<sup>18</sup> (Fig. 1). The American Society of Hematology current clinical guidelines<sup>6</sup> recommend treating patients suspected of having HIT with non-heparin anticoagulants (lepirudin, argatroban, or bivalirudin) in place of unfractionated heparin or low molecular weight heparin, before HIT confirmation with the SRA.

The overall incidence of HIT varies from 0.1% to 5%; however, the incidence differs between medical and surgical patients. Girolami and colleagues<sup>19</sup> evaluated 598 hos-



**Figure 3.** Heparin-induced thrombocytopenia (HIT) results, grouped by 0.4 optical density (OD) (x-axis), from 104 PF4 ELISA tests ordered (y-axis) based on a clinical suspicion of HIT. True positive, lined bar, patients with serotonin releasing assay (SRA)  $\geq$  20%. False positive, black bar, patients with a SRA  $<$  20%.

**Table 3.** Outcomes

Outcome	Total sample (n = 104)	True positives (n = 20)	False positives (n = 84)	p Value
ICU LOS, d, mean $\pm$ SD	23.5 $\pm$ 30.9	23.9 $\pm$ 29.8	23.4 $\pm$ 31.3	0.85
Hospital LOS, d, mean $\pm$ SD	38.1 $\pm$ 39.1	36.0 $\pm$ 30.4	38.6 $\pm$ 41.0	0.82
Mortality, n (%)	39 (37.5)	7 (35.0)	32 (38.1)	0.80

LOS, length of stay.

pitalized medical patients treated with subcutaneous unfractionated heparin and determined the incidence to be 0.1% to 1.6%. In contrast, Warkentin and associates<sup>20</sup> evaluated 744 postoperative orthopaedic and cardiac surgery patients treated with heparin and found the frequency of HIT-IgG formation to range from 3.2% in orthopaedic patients receiving low molecular weight heparin to 20% in cardiac surgery patients receiving unfractionated heparin. So, surgical patients are at an increased risk for development of HIT when compared with medical patients.<sup>21</sup>

The diagnosis of HIT in surgical ICU patients can also be challenging due to alternative explanations for the etiology of thrombocytopenia, which could include sepsis, perioperative and postresuscitation hemodilution, drug-induced thrombocytopenia, massive transfusion, liver disease, platelet consumption or destruction, or disseminated intravascular coagulation.<sup>21</sup> In fact, in this study, patients who had a higher severity of illness, as assessed by APACHE II and SAP scores, were more likely to be diagnosed as false positive HIT.

Current guidelines<sup>6</sup> recommend treating patients with an intermediate suspicion of HIT (Warkentin score of at least 4) with nonheparin anticoagulants before HIT confirmation with the SRA. In critically ill patients, the Warkentin 4-T scoring system<sup>8</sup> lacks specificity.<sup>7</sup> It has been suggested that the Warkentin 4-T in the ICU might assist in ruling out HIT for a 4-T score  $<$ 4; an intermediate to high score ( $\geq$ 4) necessitates more specific testing.<sup>7</sup> In our study, 5 of 58 patients with a 4-T score of 0 to 3 were true positive and 31 of 46 patients with Warkentin 4-T score  $\geq$ 4 were false positive.

The SRA test has high sensitivity ( $>$ 95%) and high specificity ( $>$ 99%). In a prospective clinical trial by Warkentin and coworkers,<sup>22</sup> a strong positive SRA result (defined as  $>$ 50% serotonin release at pharmacologic heparin concentrations) was associated with a high likelihood of clinical HIT (odds ratio [OR] 78.2;  $p <$  0.001). On the other hand, the high sensitivity and low specificity of PF4 ELISA screening tests are known limitations. Warkentin and colleagues<sup>23</sup> commented that many patients exposed to heparin develop anti-PF4/heparin antibodies detectable by the PF4 ELISA test in the absence of clinical HIT, which could lead to a false diagnosis of HIT in a heparin-exposed patient in whom the explanation for thrombocytopenia is

another condition. Warkentin and associates<sup>23</sup> provide 2 reasons for the low diagnostic specificity of the PF4 ELISA test. First, the cutoff values in OD units that define a positive test result are determined using blood obtained from normal individuals who have not been exposed to heparin. In contrast, diagnostic testing is almost always performed in patients who have been exposed to heparin. So, the background OD distribution of heparin-exposed patients without HIT could differ considerably from the distribution of normal individuals. Secondly, not all antibodies detectable by the PF4 ELISA test have the biologic properties needed to effect platelet activation. Lo and colleagues<sup>24</sup> further explain Warkentin's second observation by stating that many patients form nonactivating antibodies of IgM or IgA class, or non- or only weakly platelet-activating antibodies of IgG class, so they do not develop HIT. Warkentin and coauthors<sup>23</sup> propose that the solution to this dilemma is to either raise the diagnostic PF4 cut-off threshold or establish a range of PF4 values that indicate varying probabilities of clinical HIT.

A PF4  $\geq$  0.4 OD is considered a positive screening test by the manufacturers' recommendations. We found that the PF4 value for the true positive group was significantly higher when compared with that of the false positive group. However, when PF4 values ranged from 0.4 to 1.99 OD,

**Table 4.** Odds Ratios for the Development of Heparin-Induced Thrombocytopenia

Variable	Odds ratio	95% CI	p Value
Age, y			
Per 1-y increase	1.00	0.97–1.03	0.86
Per 5-y increase	1.01	0.88–1.17	
Sex, female vs male	0.97	0.35–2.69	0.95
APACHE II			
Per 1-point increase	0.94	0.89–1.00	0.053
Per 5-point increase	0.74	0.55–1.01	
SAPS			
Per 1-point increase	0.92	0.84–1.01	0.065
Per 5-point increase	0.66	0.43–1.03	
Warkentin 4-T score: 0–3	Reference		
Warkentin 4-T score: 4–5	4.15	1.25–13.74	0.020
Warkentin 4-T score: 6–8	7.95	1.96–32.25	0.004

SAPS, Simplified Acute Physiology Score.

only 7 of 84 patients were true positive for HIT. Of the 20 PF<sub>4</sub> tests above 2.0 OD, 13 were true positive. Given the higher observed incidence of HIT above 2.0 OD, if the PF<sub>4</sub> level is  $\geq 2.0$  OD, then a more aggressive HIT management with nonheparin anticoagulants might be considered before SRA availability, although this method was correct only 65% of the time.

Treatment of HIT with nonheparin anticoagulant direct thrombin inhibitors (ie, argatroban, lepirudin, and bivalirudin) places postoperative surgical patients at an increased risk for bleeding when compared with medical patients. In our study, 23% of the false positive patients and 65% of the true positive HIT patients were treated with either argatroban or lepirudin. Extreme caution is necessary in the use of argatroban in patients after major surgery due to the risk of bleeding and the difficulty with reversing this anticoagulant.<sup>25,26</sup> In addition to the increased risk of bleeding, the estimated costs per day are \$533 for bivalirudin, \$884 for argatroban, and \$1,759 for lepirudin.<sup>27</sup> So, accurate diagnosis of HIT in the surgical patient is critical.

Our findings indicate the current algorithm for HIT diagnosis and treatment in critically ill surgical patients should not follow the recommended guidelines (Fig. 1) because 81% of the patients in our study with a clinical suspicion for HIT and a positive PF<sub>4</sub> test by manufacturer guidelines were HIT negative. Additionally, although the Warkentin 4-T score<sup>8</sup> is frequently recommended as the initial step in calculating the clinical probability of HIT, the value of this test was questionable. From our results, neither ordering a PF<sub>4</sub> test nor initiation of treatment with a direct thrombin inhibitor should depend on the Warkentin 4-T score because 8.6% of the patients with 4-T scores of 0 to 3 were HIT positive and 57% of patients with 4-T scores of 6 to 8 were HIT negative.

Based on our results, a PF<sub>4</sub> < 0.4 OD rules out the diagnosis of HIT. If the PF<sub>4</sub> range is 0.4 to 2.0 OD, then the chance of true positive was 8% and if the PF<sub>4</sub> was above 2.0 OD, the true positive rate increased to 65%. As such, if a critically ill patient is at risk for bleeding, acute treatment with a direct thrombin inhibitor may initially be delayed for a PF<sub>4</sub> below 2.0 OD until the SRA results are available. For PF<sub>4</sub>  $\geq 2.0$  OD, a direct thrombin inhibitor may be considered, although 35% of these patients will not require this therapeutic and therefore it might be held in patients at high risk for bleeding.

There are a number of limitations to our study. As in all retrospective database studies, the design of the database used for data analysis limits the conclusions that can be established. The results are representative of a single institution's experience. Thirty-three patients were excluded because of missing SRA values, introducing a certain level

of bias to the study. In addition, the small sample size weakened the power of the study and the ability to include PF<sub>4</sub> levels in the logistic regression analysis. To address these limitations, a large multicenter, retrospective/observational trial is needed to corroborate our findings and establish specific clinical guidelines for the management of HIT in postoperative surgical patients. For the analysis in this article, some patients were initially categorized as "indeterminate" HIT and required additional analysis. We defined "indeterminate" HIT as a PF<sub>4</sub>  $\geq 0.4$  OD or a Warkentin 4-T score of 4 to 8 (intermediate/high clinical probability of HIT) with an SRA < 20%. Repeat SRA values were >20% in 2 patients, so these patients were subsequently characterized as true positive. In another patient labeled as false positive the SRA value varied from 0 to 52% to 19%. In another true positive patient, the SRA values between laboratories on blood drawn within 48 hours differed remarkably from 17% to 97%. These findings suggest that repeat testing for HIT may be necessary with a high PF<sub>4</sub> or Warkentin 4-T score and an initial SRA < 20%.

## CONCLUSIONS

In conclusion, in surgical ICU patients, clinical suspicion for HIT, as evidenced by a drop in platelet count or new thrombosis with recent heparin therapy, necessitates PF<sub>4</sub> and SRA testing. Ordering PF<sub>4</sub> and SRA tests and treatment with a direct thrombin inhibitor should not depend on the Warkentin 4-T score because 8.6% of the patients with 4-T scores of 0 to 3 were HIT positive and 57% of patients with 4-T scores of 6 to 8 were HIT negative. Although a PF<sub>4</sub>  $\geq 0.4$  OD is considered a positive screening test for HIT, only 19% of the patients in our study with PF<sub>4</sub>  $\geq 0.4$  OD were true positive. We suggest that a PF<sub>4</sub>  $\geq 2.0$  OD is more predictive of HIT, with a true positive rate of 65%. Current guidelines, which are based primarily on medicine patients, overtreat surgical ICU patients.

## Author Contributions

Study conception and design: Ley, Salim, Margulies

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Analysis and interpretation of data: Berry, Tcherniantchouk, Ley, Salim, Mirocha, Martin-Stone, Stolpner, Margulies

Drafting of manuscript: Berry, Tcherniantchouk, Ley, Salim, Margulies

Critical revision: Berry, Tcherniantchouk, Ley, Salim, Margulies

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## Discussion

**INVITED DISCUSSANT: DR. MAGGIE BRANDT** (Ypsilanti, MI): The authors have endeavored to answer the difficult problem of using a guideline in a population that was not included in the initial studies used to create the guideline. That is the diagnosis and treatment of heparin induced thrombocytopenia (HIT) in surgical patients. I share the opinion of the authors that HIT is widely over diagnosed in the SICU at great expense and potential risk to the patient. Guidelines, algorithms, and protocols are excellent tools in the kit of the practicing surgeon. Just like any tool, we need to understand when and how to use the tool and when to deviate from the protocol. The automatic response to stop heparin and start a direct thrombin inhibitor because of a drop in platelets in a critically ill patient may create problems, much less prevent or treat a potential problem.

My questions are these:

Did the true positives have evidence of thrombosis prior to determining there were elevated PF4 and SRA values? Do you know the cost and the turnaround time for the PF4 and the SRA? Does either cost or turnaround time influence therapy? Do all patients on whom an SRA is obtained receive Argatroban or Lepirudin while awaiting results? Do you have an alternate protocol that you currently use or recommend or would like to propose for a large multi-center trial?

**DR. DANIEL MARGULIES** (Los Angeles, CA): Regarding the question of whether the true positives had any evidence of thrombosis prior to the diagnosis; yes, most did. About 95% had some evidence of thrombosis prior to making the diagnosis.

Regarding the cost and the turnaround time for the PF4 and SRA: the PF4 is an ELISA test and is generally much more available and