Enforcing the "4T": An In-Line Calculator for HIT Antibody Ordering in the Electronic Medical Record

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ABSTRACT

Heparin-induced thrombocytopenia (HIT) remains a difficult clinical diagnosis, even with the under-utilized standardized scoring systems, like the '4T' score, to aid in clinical decision-making. Our quality improvement study sought to assess the use of '4T' score, improve the use of HIT antibody (HITA) testing and improvement management of possible HIT by implementing an in-line calculator with guidance within our electronic medical record (EMR) at our institution.

We retrospectively reviewed patient charts between October 2017 and October 2018, assessing practices before and after implementation of the '4T' in-line calculator in April 2018. HITA were ordered inappropriately (for 4T <4) in 141 (67%) of 210 instances (75 before and 66 after). We found no statistically significant difference in positive predictive value (PPV) or 4T documentation in provider notes after its implementation.

We were able to identify problematic areas in HIT management, such as the ordering of non-heparin anticoagulants, and implement additional changes addressing these problems.

KEYWORDS: Heparin-Induced Thrombocytopenia, 4T score, Epic, Quality Improvement, EMR

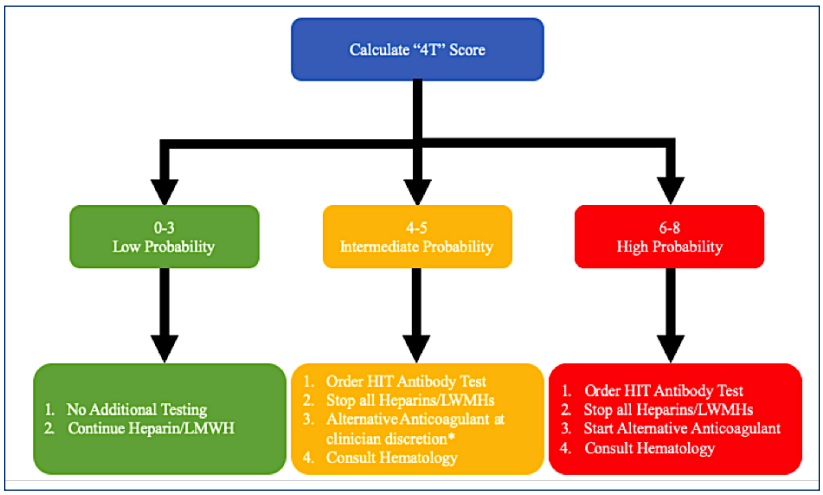
INTRODUCTION

Immune-mediated (formerly Type II) heparin-induced thrombocytopenia (HIT) is one of the most concerning etiologies of thrombocytopenia in the hospitalized patient. Immune HIT occurs when an antibody is formed against the complex of heparin and platelet factor-4 (PF4), ultimately leading to platelet activation and potential arterial or venous thrombosis.[1,2] Given its catchy acronym and paradoxical thrombosis formation despite falling platelets counts, it often vaults to the top of differential diagnoses of medical students and seasoned medical practitioners alike. However, it remains a rare entity compared to other etiologies of thrombocytopenia, namely infection, liver disease, bone marrow suppression, and other drug-mediated forms of thrombocytopenia. The incidence of thrombocytopenia in hospitalized patients is quite variable depending on the patient population, ranging from 1 to 9%, while rates in the critical care setting are even more variable, ranging from 8 to 68% upon ICU admission and 13–44% of patients during their ICU course.[3,4] Although thrombocytopenia can occur frequently after heparin exposure [the frequency of non-immune HIT (formerly Type I) is estimated to be between 10-30%], the estimated frequency of clinically significant immune HIT for hospitalized patients is in the range of 1 in 2500 to 1 in 5000.[5,6] The incidence rates of immune HIT vary greatly based on the patient population, duration and type of heparin exposure: estimated at 0.2% for low-molecular weight heparin (LMWH), 0.8% for subcutaneous heparin, and up to 2.6% overall for unfractionated heparin (UFH).[7,8] HIT is ultimately a clinical diagnosis as many patients who develop antibodies do not have clinical HIT.[6,9]

In true cases of HIT, rates of thrombosis can reach 6% daily and have an overall risk of 20–50% without timely recognition and implementation of alternative anticoagulation.[10,11] Fortunately, clinical scoring systems to assess the risk of HIT and guide management exist. The 4T score (4T) is based four clinical factors: degree of thrombocytopenia, timing of platelet count drop, other explanations for thrombocytopenia, and thrombotic events (new or worsening).[12] Each of these factors are scored from 0–2 and a cumulative score is calculated, ranging from 0–8. A result of 3 or less is consistent with low risk, 4–5 with intermediate risk, and 6 or more with high risk of HITT.[12-15] It has been well validated as a means to predict the likelihood of true HIT. A large meta-analysis has demonstrated the negative predictive value (NPV) of a low-probability 4T score (3 or less) to be 99.8%, while the PPV for high (6-8) and intermediate (4-5) scores were 14% and 64%, respectively.[13] Traditionally, for high suspicion of HIT, our institutional practice has been to start alternative anticoagulation while confirmatory testing commences and to begin alternative anticoagulation with an intermediate score at clinicians' discretion (**Figure 1**). Alternative anticoagulation has traditionally consisted of argatroban, although fondaparinux, while not FDA-approved, appears safe and is approved in Canada, resulting in its increasing use.[11,16] Finally, there is evidence to suggest that direct oral anticoagulants (DOACs), including rivaroxaban and apixaban, can be used as well, although their use remains off-label.[17]

With an intermediate or high score, guidelines suggest

Figure 1. Initial Management Recommendations for Suspected HIT at our institution



*Recommendation to start alternative anti-coagulation in this setting with no active thrombosis at clinician discretion differs from ASH HIT Guidelines

laboratory assays (**Figure 1**). The two primary classes of laboratory assays available to aid in making the diagnosis of HIT are: enzyme immunoassays (EIAs) that measure antibodies immunochemically and functional assays – such as serotonin release assay (SRA) – that measure antibody activation of platelets. Functional testing, namely SRA, remains the "gold standard" for HIT diagnosis in the US; however, its use is limited by cumbersome lab technique requiring a send-out to reference laboratories, leading to delayed results and yielding it ineffective in rapid clinical decision-making.[18] As a result, many institutions rely on EIA testing to assist in bedside management of patients with suspected HIT. EIA testing measures either polyspecific antibodies (IgA, IgM, and/or IgG), or only the pathogenic IgG class alone.[19] The limitation to EIA testing is that it cannot assess the functionality of the antibody (Ab) present. Both the polyspecific and IgG class EIA tests have robust sensitivity (98.1% and 95.8%, respectively), and negative predictive values (99.9% and 99.7%, respectively).[14] However, the IgG-specific test has better specificity (93.5% vs. 89.4%) and PPV (49.6% vs. 38.7%), although a positive result via either method does little to confirm true HIT.[14] The implementation of IgG-specific EIA has resulted in a decreased duration of exposure to parenteral direct-thrombin inhibitors (DTIs) without change in significant WHO Grade III and IV bleeding rates.[20]

The introduction of electronic medical record (EMR) systems into healthcare systems has provided opportunities to embed clinical tools and critical information for decision-making, and alerts to assist providers in diagnosis and management of complicated and critical diagnoses. While studies across the United States have about the impact on healthcare outcomes had mixed results, these studies have been limited by small sample sizes. No studies have been published to date discussing the use of EMR tools in the diagnosis of HIT.

While performing inpatient hematology consults, we found that the 4T score was seldom calculated, or even considered, prior to ordering of HIT antibody (HITA). Hence, there was the risk of false-positive results and either cessation of appropriate anticoagulation, or initiation of expensive and not indicated alternative anticoagulation. Our objectives were to use the electronic medical record to provide succinct education regarding the diagnosis of HITT, improve diagnostic stewardship through more appropriate ordering of HITA and improve the management of thrombocytopenia when HIT is considered.

METHODS

Our quality improvement study began with a retrospective chart review of patients in the Lifespan hospital network, a three-hospital, 1,095-bed system across Rhode Island between October 2017 and April 2018. Cases were identified in two ways. All HITA orders were retrieved through laboratory records and the reporting workbench function in the Epic® EMR. In addition, the SlicerDicer function of Epic was used to gather data including admission, orders and results. In April 2018, we implemented a 4T calculator directly into the order for HITA within the EMR requiring the following:

- Last five (5) platelet counts within hospital system's EMR
- Heparin/Enoxaparin orders for the last 30 days
- Description of HIT testing and 4T score
- Reference link to online 4T score calculator
- Input for manually calculated 4T score result (Requires numerical input to place order)
- Table of 4T score interpretation and probability of HIT
- Recommendations on acute management based on patient's pre-test probability

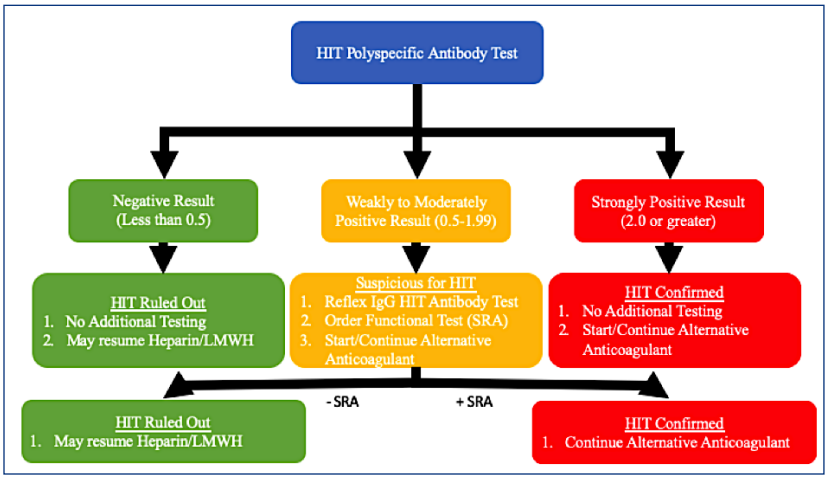
The ordering window required a numerical input into the field for 4T score result, but did not require the ordering provider to follow recommendations for ordering and management outlined within the window. At the time of ordering window creation, it was felt that mandating a specific number could result in appropriate orders not being placed. Since the 4T score is recommended to guide and not replace clinical decision-making, the calculator did not prevent providers from ordering HITA. This score was not required to order SRA which could be ordered separately. Our departmental recommendations for management of possible HIT were to discontinue all heparin products for intermediate and high scores, if not already done, and to start alternative anticoagulation only for high 4T scores. Immediate initiation of alternative anticoagulation for an intermediate score

was left to the treating physician's discretion (**Figure 1**). This recommendation strayed from the consensus guidelines based on our preliminary retrospective review that showed treating physician documented 4T scores were consistently higher than those calculated by reviewing hematologists, which raised concern for overuse of DTIs in patient's potentially at higher risk for bleeding than clotting, given their low probability of HIT. The calculator included a note strongly suggesting hematology consultation at time of consideration of HIT, with further management based on results of polyspecific HITA (**Figure 2**). After 3 and 6 months of the 4T calculator use, from April 2018 to October 2018, we again collected information about patients who underwent HITA testing by the same methods as our initial retrospective analysis.[21] The review was approved by the Lifespan Internal Review Board (IRB), who determined the implementation of the calculator and subsequent review of cases to be exempt from IRB approval.

We retrospectively reviewed measures for management and test utilization, including discontinuation patterns of heparin products by managing service, initiation of alternative anticoagulation, and agent used. It also included review for potential confounding factors, rates of hematology consultation, and independently calculated 4T scores as well as provider-calculated 4T scores (hematology consultants and primary service). The independent reviewers were hematology fellows, consultants and residents with hematology oversight audited for concordance.

Although this quality improvement study was designed to test feasibility of incorporating a calculator into the EMR, we performed exploratory statistical analysis using STATA v15 software to examine rates of ordering, appropriate cessation of heparin and initiation of alternative anticoagulation as indicated. We evaluated for differences between the pre- and post-calculator groups using chi-squared test, and logistic regression with bootstrap standard error. We calculated the PPV and NPV for the HITA using standard 4x4 tables where the polyspecific HITA was the screening test. True positives were defined as a positive screening test with a positive confirmatory test, either IgG HITA (OD >2) or weakly positive IgG HITA (OD=0.5-1.99) with positive SRA, while false positives were defined as an elevated polyspecific with negative confirmatory tests (**Figure 2**).

Figure 2. Further Management Recommendations for Suspected HIT based on polyspecific antibody results at our institution



RESULTS

Based upon our EMR database review, an abnormal platelet count while receiving heparin-based anticoagulants (UFH or LMWH) occurred in 7,562 of 23,119 admitted patients before and 7,397 of 23,288 admitted patients after the 4T calculator implementation. In the 6 months before the 4T calculator implementation, there were 109 HITA orders which reflexed to HIT IgG 21 times. The HIT IgG was then positive in 10 cases. An SRA was ordered 23 times, including 9 in the setting of an abnormal HITA. For the six months after the 4T calculator implementation, there were 101 HITA orders with 22 reflexes to IgG, of which 7 were positive. SRA was ordered a total of 20 times with 6 in the setting of an abnormal HITA.

By review of laboratory records and EPIC reports, we identified 210 patients on whom a HITA was ordered during the study period. Reviewed 4T scores were <4 in 141 (67%) of instances when HITA should not have been ordered. Before implementation of the in-line calculator and ordering window, 88 of the 109 patients with a HITA test ordered did not have a 4T score documented, while 3 patients had a low (<3) 4T score documented and 18 patients had an intermediate (4-5) or high (6-8) 4T score documented. After the implementation of the calculator, all patients tested had a documented 4T score within HITA order. Seventeen of 101 patients had a low score and the remaining 84 patients had either intermediate or high scores. Due to the lack of documentation before calculator implementation, risk scoring was determined by independent reviewer 4T score calculation. Based on these calculations, 75 patients before in-line calculator and 66 patients after in-line calculator who had HITA ordered were low risk by independent reviewer 4T score, and would not have required the test otherwise. No significant difference (p=0.249) was found between calculated 4T scores by independent reviewer and inpatient providers before the implementation of the ordering window, but a significant difference (p<0.001) was seen after it became operational with most independent reviewer scores falling into lower risk category than the documented scores by inpatient providers (**Table 1**). No significant differences were seen between hematology consult provider and

Table 1. 4T Score Comparisons

	Pre-'4T Calculator' HITA (n=109)	Post-'4T Calculator' HITA (n=101)
Uncalculated/Undocumented 4T Score	88	0
Low 4T Score by primary provider (0-3)	3	17
Intermediate/High 4T Score by primary provider (4-8)	18	84
Low 4T Score by independent reviewer (0-3)	75	66
Intermediate/High 4T Score by independent reviewer (4-8)	34	35
No discrepancy between independent reviewer & primary provider	11*	31
Independent reviewer 4T score LOWER than primary provider	10*	62
Independent reviewer 4T score HIGHER than primary provider	1*	7
No discrepancy between independent reviewer & hematology consult	12*	16*
Independent reviewer 4T score LOWER than hematology consult	1*	0*
Independent reviewer 4T score HIGHER than hematology consult	2*	2*

*Undocumented/Uncalculated not included

Table 2. Anticoagulation Management in Patients with Clinical Suspicion of HIT

	Pre-'4T Calculator' HITA (n=109)	Post-'4T Calculator' HITA (n=101)
4T Score <4 (% of HITA tests)	75 (68.8%)	66 (66.3%)
Heparin Discontinuation	19	21
'Inappropriate' Heparin Continuation	6	3
Heparin Already Held	7	11
Initiation of Alternative Anticoagulation for 4T >3	8	8

reviewer 4T scores before or after ordering window. Management of heparin anticoagulants are discussed in **Table 2**. Initiation of alternative anticoagulation at time of order for a 4T >3 was similar before and after the calculator: in 8 of 34 cases before and 8 of 35 cases after. The volume of orders by hospital service remained similar during the time period, with the intensive care unit and cardiothoracic surgery accounting for 45% of orders combined. We also found that HITA testing was ordered in 13 patients with entered 4T scores less than 4 after calculator implementation. PPV for true HIT was initially improved between the three-month intervals before and after implementation, from 9% to 21%.[21] However, when we re-evaluated PPV for the six-month intervals before and after implementation of the calculator, we found that it had worsened from 24% to 22%.

DISCUSSION

Our findings of only 5 cases before and 5 cases after the calculator is consistent with published incidence of HIT. There were fewer orders after the calculator despite an increased number of admissions in this time frame and a consistent number of confirmed cases of HIT, achieving our goal of improving diagnostic stewardship. It also offered potential cost savings as the billed cost of a HITA is about $200, the institutional cost to run the assay is approximately $60 and the cost of an SRA is $572.

We identified additional areas for quality improvement. We noted frequent orders for the SRA without knowing the result of screening HITA, often with low 4T scores. We are implementing methods to reduce this. Through consultation and chart review, we identified that treating providers had difficulties with ordering and administration parameters for argatroban, as well as bridging to vitamin K antagonists due to infrequent use. Through the pipeline developed for design and implementation of the 4T calculator, we were able to simplify and structure both ordering and monitoring of argatroban with a dedicated order set.

The in-line calculator and ordering window were intended to provide succinct education within our EMR and decrease inappropriate HITA orders. Our EMR lacks the ability to determine the number of times that the ordering window was opened and order was not placed, which we would expect to occur amongst those with a calculated 'low probability' score, thereby achieving the desired effect of the calculator and educational window. Unfortunately, we failed to meet our goal of improving management of suspected HIT and guide practitioners towards better management. The reasons for this are unclear. Given our initially positive results at three-month analysis, it is possible 'click fatigue' played a critical role in the lack of improvement in PPV at six-months since only inputting of a number is required, while accuracy or adherence to ordering recommendations (4T >3) is required to place order.[21] Several institutions require hematology or similar specialist approval for these tests, which may be a more effective alternative. However, given the national shortage of non-malignant hematologists, developing an effective and reproducible system could help both the hematology workforce and improve patient care. Our decision to only recommend initiation of anticoagulation for a high-probability score at time of order likely played a role in the low number of alternative anticoagulants started at time of HITA order.

Since our independent reviewer 4T scores were consistently lower than those entered by the treating providers even with the calculator in place the decision to leave initiation of alternative anticoagulation in patients with intermediate scores to the ordering provider still seems to be a reasonable choice. We believe that the lack of difference in 4T scores by reviewing and treating providers before the in-line calculator was due a small number of documented 4T scores which likely would only be achieved through a prospective study with enrollment and strict data collection. This would be outside the cost and scope of such a restrospective review and quality improvement project, but is certainly a limitation. Three main possibilities exist for differences in 4T scores after the calculator between our independent reviewers that are not mutually exclusive. Given initially positive findings, 'click fatigue' set in and ordering providers realized that any number entered would allow for ordering. The independent reviewer was more familiar with 4T review especially for categories such as 'other causes of thrombocytopenia. Finally, reviewers were aware of HIT results at the time of review allowing for an element of bias.

Overall, we see that a screening HITA is still frequently ordered with a low 4T score, even if a 4T score needs to be entered. A possible intervention to improve this is to provide focused education to provider groups who most frequently order HITA testing. No outcome measures are worse and no harm seems to have come from this intervention. Furthermore, we also have no way to identify instances when a HITA may have been considered but was ultimately not ordered due to a low 4T. Hence, we may be underestimating the actual benefit.

Although some institutions have reported improvement in HITA test ordering with implementation of an integrated 4T score calculator, no such change was found at our institution.[22-24] The negative results of our study provide an important balance against the small series saying that EMR-based interventions are a solution. Rather than target improvements by including a HIT calculator, other institutions have focused on educational improvements with success in reducing HITA orders. Ultimately, a quick click through screen may be insufficient to improve management and the education provided within the order window may be ignored amidst numerous other alerts in the EMR causing 'alert fatigue'. The addition of education for in-hospital providers could have a more significant impact.

CONCLUSION

Immune-mediated HIT remains a rare entity with significant consequences if diagnosis is delayed or not obtained. While the methods for diagnosis, the importance of clinical suspicion, quantified by probability calculators, like the 4T score, remain paramount in assessing pre-test probability to guide further management decisions. While our study did not result in significant improvement in our system, in part because of the rarity of the condition, it highlights a continued area of needed research in this deadly disease. Additional quality improvement measures need to be made in the management of this potentially devastating clinical diagnosis. Continuing to combine systems-based improvement within the EMR, such as a refined order set, coupled with an increased focus on education to boost provider awareness could offer a long-term, sustainable solution.

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IRB Approval

Our IRB approved the retrospective review and separately deemed the prospective intervention as quality improvement and therefore deemed this IRB exempt.

Disclaimer

The views expressed herein are those of the authors and do not necessarily reflect the views of Lifespan.

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