

Toward better utilization of laboratory resources: The impact of a mandatory 4Ts pretest clinical assessment form on the diagnosis of heparin-induced thrombocytopenia

Physicians ordered tests for a greater proportion of patients with a high rather than a low probability of HIT after a pretest form was introduced at Vancouver General Hospital.

ABSTRACT:

Background: Frequency rates for heparin-induced thrombocytopenia range from 0.5% to 5.0% of all heparin-treated patients. The most readily available laboratory tests are very sensitive for heparin-dependent platelet factor 4 antibodies, but are not specific for heparin-induced thrombocytopenia. Tests with greater specificity are more technically demanding and less readily available. In addition to laboratory testing, four clinical features—known as the 4Ts—are used when diagnosing this immune-mediated process: Thrombocytopenia, Timing of thrombocytopenia, Thrombosis, and exclusion of other causes of Thrombocytopenia.

Methods: A study was conducted to assess the impact of a mandatory 4Ts pretest form on the appropriateness of test ordering for heparin-induced thrombocytopenia. Data were collected and analyzed before and after the form was introduced at Vancouver General Hospital.

Results: During the 2.5-year study period, 145 laboratory tests for heparin-induced thrombocytopenia were ordered; 65 of these were ordered before and 80 after the mandatory 4Ts pretest clinical assessment form was introduced. After the form was introduced, more tests were ordered for patients with high (6–8) 4Ts scores (8% vs 23%, $P = .015$) and with intermediate (4–5) 4Ts

scores (40% vs 55%, NS). As well, fewer tests were ordered for patients with low (1–3) 4Ts scores (24% vs 54%, $P < .001$) after the mandatory 4Ts pretest form was introduced. None of 53 patients with low 4Ts scores had laboratory-confirmed heparin-induced thrombocytopenia. **Conclusions:** The mandatory use of a 4Ts pretest clinical assessment form for diagnosis of heparin-induced thrombocytopenia resulted in more appropriate utilization of laboratory testing, standardization of patient assessment, and better physician understanding of heparin-induced thrombocytopenia. Testing may not be indicated for patients with low 4Ts pretest scores.

Dr Hudoba is a hematopathologist in the Department of Pathology and Laboratory Medicine at Vancouver General Hospital and clinical associate professor at the University of British Columbia. Dr Dalal is a hematopathologist in the Department of Pathology and Laboratory Medicine at VGH and clinical professor at UBC. Dr Warkentin is a professor in the Department of Pathol-

ogy and Molecular Medicine at McMaster University, Hamilton, Ontario. Mr Pal is a data analyst in the Department of Pathology and Laboratory Medicine at VGH. Dr Chipperfield is a hematopathologist in the Department of Pathology and Laboratory Medicine at VGH and clinical associate professor at UBC. Dr Pi is a hematopathologist in the Department of Pathology and Laboratory Medicine at VGH and clinical associate professor at UBC. Dr Tsang is a hema-

tologist in the Department of Medicine, VGH and clinical associate professor at UBC. Dr Coupland is a hematopathologist and department head of the Department of Pathology and Laboratory Medicine at VGH and clinical professor at UBC. Dr Carter is a hematopathologist, coagulation director in the Department of Pathology and Laboratory Medicine at St. Paul's Hospital and associate professor at UBC.

This article has been peer reviewed.

Background

Heparin-induced thrombocytopenia (HIT) is an immune-mediated process that presents with a drop in platelet count related to proximate exposure to unfractionated or low molecular weight heparin. It results from the activation of platelets by heparin-dependent platelet factor 4 (PF4) antibodies, which become detectable 5 days or more after initiation of heparin therapy. There is associated increased generation of thrombin *in vivo*, and thus patients are hypercoagulable even though their platelet counts are low.^{1,2} This means HIT often results in major venous and arterial thrombosis.

The published HIT frequency rates range from 0.5% to 5.0% of all heparin-treated patients. HIT is much more commonly associated with unfractionated heparin than with low molecular weight heparin (1% to 5% vs <1%). Other risk factors for HIT include recent surgery and female gender.^{3,4}

If the diagnosis of HIT cannot be confirmed, then the treatment consists of immediate substitution of unfractionated or low molecular weight heparin with an alternative rapid-acting anticoagulant (e.g., argatroban), a direct thrombin inhibitor, or a factor Xa inhibitor (e.g., fondaparinux).⁵

Diagnosis of HIT is based on two criteria: appropriate clinical features (**Table 1**) and a positive laboratory test for platelet-activating HIT antibodies.⁶ Clinical features include the following 4Ts:

- Thrombocytopenia or a greater than 50% fall in platelet count.
- Appropriate Timing of the onset of thrombocytopenia after initiation of heparin.
- Thrombosis, skin necrosis, or systemic reaction with exposure to heparin.
- Exclusion of other causes of Thrombocytopenia.⁷

Table 1. 4Ts system for assessing heparin-induced thrombocytopenia.

Parameter	Score		
	2	1	0
Thrombocytopenia: Extent of fall in platelet count	> 50% fall or nadir $\geq 20 \times 10^9/L$	30%–50% fall or nadir $10\text{--}19 \times 10^9/L$	< 30% fall or nadir $< 10 \times 10^9/L$
Timing: Onset of fall in platelet count or thrombosis in relation to initiation of heparin	After day 5–10; or ≤ 1 day with recent heparin exposure (< 30 days)	> day 10 or timing unclear; or < day 1 with recent heparin exposure (31–100 days)	< day 4 without recent heparin exposure
Thrombosis or other sequelae	Proven new thrombosis; skin necrosis; acute systemic reaction after intravenous unfractionated heparin bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis (not proven)	None
Other cause(s) of Thrombocytopenia	None evident	Possible	Definite

The published HIT frequency rates range from 0.5% to 5.0% of all heparin-treated patients. HIT is much more commonly associated with unfractionated heparin than with low molecular weight heparin.

Laboratory diagnosis requires demonstration of platelet-activating HIT antibodies in the sera of patients. Tests such as the enzyme-linked immunosorbent assay (ELISA) and a commercially available rapid particle gel immunoassay (PaGIA) are very sensitive for heparin-PF4 antibodies, but are not specific for HIT. These tests—particularly the ELISA—have a high negative predictive value and thus a negative test is very good at excluding HIT. In contrast, functional tests using

washed platelets, such as the platelet 14C-serotonin release assay (SRA) and the heparin-induced platelet activation (HIPA) test, detect heparin-dependent platelet-activating antibodies. These assays have the highest diagnostic specificity for HIT, but are technically demanding and are offered only by reference centres. Consequently, both these tests have a long turnaround-time. To help determine when such testing is warranted, we designed a 4Ts pretest clinical assess-

Table 2. Comparison of 4Ts scores and results of rapid PaGIA test before and after mandatory pretest form was introduced.

4Ts scores	Results before pretest form introduced (positive/total)	Results after pretest form introduced (positive/total)	All results (positive/total)
Low (1–3)	1/34	1/19	2/53
Intermediate (4–5)	4/26	8/43	12/69
High (6–8)	5/5	8/18	13/23

ment form and proceeded to study the impact of this form on ordering patterns and the frequency of positive results when testing for heparin-induced thrombocytopenia.

Methods

A study to determine whether a pretest clinical assessment form could improve the utilization of laboratory resources was conducted at Vancouver General Hospital over 2.5 years. In the first 15-month retrospective phase of the study (December 2006 to February 2008), all requests for HIT testing were accepted without screening; patient characteristics and the results of HIT testing during this phase were reviewed by two of the coauthors (CJC and MH). The patients' 4Ts scores were recorded retrospectively and cor-

related with test results. In the second 15-month prospective phase (October 2008 to December 2009), the 4Ts form was introduced as a mandatory requirement for HIT testing. The changes in the testing pattern were then analyzed.

HIT testing in both study phases was performed using a rapid gel immunoassay (PaGIA, ID-HPF4 from DiaMed, Cressier sur Morat, Switzerland) followed by verification of all samples by the 14C-serotonin release assay, performed at the McMaster University Reference Coagulation Laboratory (Hamilton, ON, Canada).

Data were analyzed using Minitab release 14.2 (Minitab Inc.), employing the chi-square test, Fisher exact test, and unpaired *t*-tests, as appropriate.

Indiscriminate use of laboratory tests with high sensitivity but low specificity can result in confusion, misdiagnosis, inappropriate treatment, and additional expense.

Results

A total of 145 tests were ordered during the study period, 65 before the mandatory 4Ts pretest form was introduced, and the remaining 80 after the mandatory 4Ts pretest form was introduced.

Although 15% of patients (10/65) tested positive using the rapid PaGIA in the “before” phase compared with 21% of patients (17/80) in the “after” phase, the difference in the positive tests was not statistically significant. Significance was found, however, in other comparisons. For instance, only 4% of patients (2/53) with a low 4Ts score (< 3) tested positive for heparin-induced thrombocytopenia using rapid PaGIA (Table 2). By contrast, 17% of patients (12/69) with an intermediate 4Ts score (4–5) and 57% of patients (13/23) with a high 4Ts score (6–8) tested positive using the rapid PaGIA. No patients (0/53) with a low 4Ts score tested positive using SRA, while HIT was confirmed using SRA in 9% of patients (6/69) with an intermediate 4Ts score and in 39% of patients (9/23) with a high 4Ts score ($P < .001$).

The number of patients with a low 4Ts score who were tested for HIT dropped from 52% (34/65) to 24% (19/80) ($P < .001$) after the 4Ts pretest form was introduced. Meanwhile, the number of patients with an intermediate 4Ts score who were tested rose from 40% (26/65) to 54% (43/80) ($P = \text{NS}$), and the number of patients with a high 4Ts score who were tested rose from 8% (5/65) to 23% (18/80) ($P = .015$) after the 4Ts pretest form was introduced.

Conclusions

Indiscriminate use of laboratory tests with high sensitivity but low specificity can result in confusion, misdiagnosis, inappropriate treatment, and additional expense. Introduction of a pretest based on a probability algo-

rithm can prevent inappropriate testing of patients with low probability for heparin-induced thrombocytopenia, thus improving the specificity of test results, more appropriate treatment, and better utilization of laboratory resources. A good example of this is the use of a pretest clinical assessment with a D-dimer test for the exclusion of suspected deep vein thrombosis.⁸

In a large European study of HIT, using a 4Ts score reduced false-positive results, thus enhancing the specificity of a very sensitive screening test.⁹ In our study, the introduction of a 4Ts pretest clinical assessment form indirectly resulted in physician education: tests were ordered for a greater percentage of patients with a high rather than a low probability of HIT.

Since we found no patients with an SRA-confirmed diagnosis of HIT in the low range of 4Ts scores (1–3), we support the recommendation made by Pouplard and colleagues⁹ that HIT testing should be restricted to patients with intermediate and high 4Ts scores (4 and above). Our current version of the 4Ts pretest form incorporates this recommendation.

Acknowledgments

Dr Warkentin's research is supported by the Heart and Stroke Foundation of Ontario (T.E.W.: #T6950).

Competing interests

Dr Warkentin has received honoraria/speaker fees from Pfizer Canada, Canyon Pharmaceuticals, GlaxoSmithKline, Organon Pharmaceuticals, Sanofi Aventis, and GTI Diagnostics; consultancy fees from medico-legal consultations, Canyon Pharmaceuticals, GSK, Organon Pharmaceuticals, GTI Diagnostics, and ParinGenix; research support from the Heart and Stroke Foundation, GSK, GTI Diagnostics, and Diamed Lab Supplies.

We support the recommendation made by Pouplard and colleagues that HIT testing should be restricted to patients with intermediate and high 4Ts scores.

References

1. Kelton JG. The pathophysiology of heparin-induced thrombocytopenia. Biological basis for treatment. *Chest* 2005; 127(2suppl):9S-20S.
2. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: Recognition, treatment, and prevention. *Chest* 2004; 126(3suppl):311S-337S.
3. Warkentin TE, Sheppard JI, Horsewood P, et al. Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood* 2000;96:1703-1708.
4. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: A meta-analysis. *Blood* 2005;106:2710-2715.
5. Warkentin TE. HIT paradigms and paradoxes. *J Thromb Haemost* 2011;9 (suppl1):105-117.
6. Warkentin TE, Greinacher A, Gruel Y, et al, on behalf of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Laboratory testing for heparin-induced thrombocytopenia: A conceptual framework and implications for diagnosis. *J Thromb Haemost* 2011;9:2498-2500.
7. Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost* 2006;4:759-765.
8. Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med* 2003;349:1227-1235.
9. Pouplard C, Gueret P, Fouassier M, et al. Prospective evaluation of the '4Ts' score and particle gel immunoassay specific to heparin/PF4 for the diagnosis of heparin-induced thrombocytopenia. *J Thromb Haemost* 2007;5:1373-1379. **BCMJ**