Scoring systems for heparin-induced thrombocytopenia (HIT): Whither now?

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Heparin-induced thrombocytopenia (HIT) is a "clinical-pathological" syndrome (1, 2). This means that to diagnose HIT a patient must both exhibit a clinical picture compatible with this diagnosis, plus have detectable platelet-activating, heparin-dependent antibodies. (In this context, "clinical" includes the timing and magnitude of the platelet count fall, whereas "pathological" refers to results of serological studies, i.e. does the patient's blood contain HIT antibodies?) If neither the clinical nor pathological profile fits, the patient does not have HIT.

However, heparin exposure and non-HIT thrombocytopenia are common in hospitalised patients. As recently shown in this journal, HIT can manifest in a diverse range of clinical scenarios (3-5), and hence the continued interest in improving its diagnosis and approach to management. Among heparin-exposed, thrombocytopenic patients investigated for HIT, the frequency of a true diagnosis of HIT ranges from 5% to 25% (6-8). Given the high-risk treatment stakes, for example, substituting an alternative, non-heparin anticoagulant (9) (with potentially higher bleeding risk and unknown efficacy for non-HIT diagnoses) versus continuing heparin, some clinicians use pretest scoring systems to help judge the likelihood of HIT.

The most widely used pretest probability scoring system – the 4Ts – was developed by Warkentin in 2003 (10), with outcomes reported in 2006 (11). The 4Ts assesses the patient for four parameters – Thrombocytopenia, Timing, Thrombosis, oTher (diagnoses) – and assigns each either 0, 1, or 2 points, depending on the extent by which the respective clinical information supports (or argues against) a diagnosis of HIT. The points are totalled, leading to three probability estimates: low (0 to 3 points), intermediate (4 or 5 points), or high (6 to 8 points). We observed that a low 4Ts score – obtained in 35% of patients – predicted absence of HIT with high diagnostic accuracy (~99%) (11), a finding confirmed in a meta-analysis (12) of our studies and those of 11 others evaluating the 4Ts. However, the overall positive predictive value (PPV) of intermediate or high 4Ts scores was only 14% and 64%, respectively (12).

In 2010, a new scoring system, the HIT Expert Probability (HEP) score, was developed, based upon broad expert opinion of 26 different experts (13). In contrast to the 4Ts mnemonic, the HEP score is more complex, evaluating eight different parameters, with some individual items scored from -2 to +3 points.

In this issue of Thrombosis and Haemostasis, Joseph et al. (14) from the Department of Cardiovascular Medicine, Cleveland Clinic, report the first prospective comparison of these two scoring systems. Although the study was relatively small (51 patients enrolled over six months, i.e. two patients per week), 14/51 (27.5%) patients had serologically-confirmed HIT, defined as positive testing in both the serotonin-release assay (SRA) and a PF4-dependent enzyme-immunoassay (EIA). Scoring was performed in real time by two thrombosis service fellows, with two consultants judging independently whether the patient was HIT "likely" or "unlikely." All determinations were made independent of the results of lab testing. Although comparisons of the two scoring systems were made for three outcomes (consultant diagnosis, EIA+ status, combined SRA+/EIA+ status), I will discuss their findings primarily in relation to the last outcome, as SRA+/EIA+ status is highly specific for true HIT. Interestingly, 37/51 (72.5%) patients were scored as intermediate or high probability for HIT by the 4Ts, which was higher than the average 44.2% frequency found in other studies (12).

The authors’ main conclusion was that there was no difference between the 4Ts and HEP scores for predicting SRA+/EIA+ status. Analysed per receiver-operating curve (ROC), the areas under the ROC were nearly identical for the 4Ts vs HEP scores (0.74 vs 0.73, respectively; p=0.97). There was higher inter-observer agreement for the 4Ts (kappa score of 0.86 vs 0.50), perhaps reflecting greater ease of use of the 4Ts or simply that fewer different scores are possible. Although both scoring systems were highly sensitive in identifying HIT (based on 4Ts >3 points and HEP score >1 point), their diagnostic specificity (at these cutoffs) was relatively low (35% and 16%, respectively).

This study supports the concept that for the many patients who score intermediate or high probability for HIT, the PPV is sufficiently low that judgment regarding which treatment course to follow will have significant diagnostic uncertainty in the short term. Indeed, Joseph et al. (14) found that alternative anticoagulant was given for a median of almost five days, presumably reflecting in part the time to obtain the SRA result (which required sending blood to an out-of-state reference laboratory).
How can the diagnostic utility of pretest probability scoring be enhanced? In my view, tweaking either scoring system will bring minimal improvement. This is because the main problem – particularly for intermediate probability scenarios – is that one simply cannot judge on clinical grounds alone whether the patient has HIT or not. In fact, I teach trainees that my operational definition for an intermediate probability 4Ts score is a clinical situation where I am not surprised if the SRA result returns strongly positive or completely negative! Here, the SRA truly determines whether or not the patient has HIT.

In my view, the main path forward will be to combine pretest probability scoring systems with rapid PF4-dependent immunoassays, where the lab result can be obtained within an hour of blood sampling. Several rapid assays have now been developed, including the particle gel immunoassay (PaGIA), the particle immunofiltration assay (PIFA), several instrumentation-based immunoassays (utilising the ACL TOPI and ACL AcuStar® analysers), and a lateral flow immunoassay: for review see (15). To date, studies have evaluated combined 4Ts scoring with the PaGIA (16, 17), as well as with the lateral flow immunoassay (18), with promising results. I believe that rapidly-available anti-PF4/heparin assays that provide (semi) quantitative results – rather than a dichotomous positive/ negative readout – will prove most useful when combined with a scoring system, since different likelihood ratios for different positive results – based upon their different magnitudes (strengths of positivity) – will help to fine-tune the post-test probability sufficiently well to help the clinician make an informed and suitably-tailored treatment decision. Here, the instrumentation-based assays, as well as PaGIA testing (when performed with serial sample dilutions), seem most promising. In the end, a functional (platelet activation) test, such as the SRA, will remain the "gold standard" for HIT diagnosis, given that only this type of assay directly detects HIT antibodies based upon their pathophysiological platelet-activating properties. The concept that increasing magnitude of a positive immunoassay result predicts for a higher likelihood of a positive SRA is established (19); however, testing by EIA is usually batched, and so results are not usually available very quickly. A Bayesian approach (20) – which adjusts the pretest probability of HIT (judged by a scoring system) by the likelihood ratio associated with a rapidly available (semi) quantitative laboratory screening test – is a promising strategy.

Perhaps it is fitting for a clinical-pathological syndrome such as HIT, that the way forward will be the combination of an initial clinical assessment (scoring system performed in real time) with a rapid PF4-dependent screening assay, with the ultimate diagnosis depending on the complete clinical picture (as the case evolves over days and various alternate explanations for thrombocytopenia are ruled in or out) together with the results of the more definitive functional assay. And when the initial evaluative strategy yields a working diagnosis that nearly always matches the ultimate diagnosis, then we will know we are combining clinical and laboratory information as effectively as possible.

Conflicts of interests
T.E. Warkentin has received lecture honoraria from Pfizer Canada and Instrumentation Laboratory, royalties from Taylor & Francis (Informa), consulting fees and research funding from W.L. Gore, and has provided expert witness testimony relating to HIT.

References