Heparin-induced thrombocytopenia (HIT) in 2011: An epidemic of overdiagnosis

Adam Cuker

Department of Medicine and Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Heparin-induced thrombocytopenia (HIT) is a prothrombotic and potentially fatal iatrogenic disorder mediated by IgG antibodies that target multimolecular complexes of platelet factor 4 (PF4) and heparin (1). Although the first description of the disorder dates back more than 50 years (2), it was not until the 1990s that the target antigen in HIT was identified and the now widely used anti-PF4/heparin ELISA was developed (1), a detailed clinical characterisation of the disorder emerged, and the first effective therapies for HIT gained regulatory approval. Little wonder, then, that a major thrust of medical training, and the literature of the day was to raise clinicians' awareness of this nascent disorder. Papers entitled "*Think of HIT*" and "*Don't miss HIT*" exhorted physicians to recognise the disease early in its course and initiate therapy promptly (3–4).

Perhaps owing to the success of this educational campaign, the last several years have witnessed a sea change in the diagnostic landscape. The major clinical problem in 2011 is no longer *under*-recognition of HIT, but *over*-diagnosis and *over*-treatment. Among a recently reported cohort of patients managed with a direct thrombin inhibitor (DTI) for HIT at the University of Pennsylvania, 41% received treatment despite a very low clinical probability of disease as judged *post hoc* by a panel of expert adjudicators (5). Over a recent 12-month interval at the same institution, 91 of 100 DTI-treated patients were ultimately determined to have a negative result by serotonin release assay (SRA), the gold standard laboratory test for HIT (unpublished data). Over-diagnosis is particularly rampant in the intensive care units and the post-cardiac surgery setting, where the frequency of alternative anticoagulant use outstrips the incidence of HIT by an order of magnitude or more (6–8). With exposure of large numbers of thrombocytopenic patients to costly alternative anticoagulants and their attendant 10–20% risk of major bleeding, the clinical and economic impact of such over-diagnosis and over-treatment is likely to be substantial. Thrombotic complications may also arise in this population as a result of inappropriate withholding of heparin (9).

Why is over-diagnosis of HIT so pervasive? The answer likely lies in the poor specificity of clinical diagnosis and the anti-PF4/heparin ELISA, the diagnostic tools most readily available to clinicians. The cardinal clinical manifestation of HIT, a fall in the platelet count in the setting of a proximate heparin exposure, is an exceedingly common finding among hospitalised patients for which alternative explanations often exist. In a multicenter registry of 2,420 hospitalised patients receiving heparin for four or more consecutive days, fully 36.4% developed thrombocytopenia during their hospital course, though the incidence of HIT in this largely medical population was likely on the order of only 1–2% (10). Scoring models lend a degree of standardisation to clinical diagnosis, but also suffer from limited specificity (5, 11).

The anti-PF4/heparin ELISA fares little better than clinical diagnosis in this regard. False-positive results are common and may result from detection of non-pathogenic antibodies or antiphospholipid antibodies directed against PF4 (12, 13). A review of one institution's experience suggested that the ELISA was associated with the potential to over-diagnose HIT by as much as 100% (12). Use of an IgG-specific ELISA, a higher optical density cut-off, or the high heparin confirmatory procedure improves specificity, but false-positive results remain common and false-negative results may also occur (14–16). Moreover, many institutions perform the ELISA in batch once or twice a week, often leaving clinicians to make initial management decisions without the benefit of laboratory results. Turnaround time is an even greater problem for more specific functional assays such as the SRA, which are performed at a small number of reference laboratories around the world and are only available as send-out tests to the vast majority of providers.

In light of the limitations of available diagnostic tools, the novel anti-PF4/polyanion IgG-specific lateral-flow immunoassay (LFI) reported by Sachs et al. in this issue of *Thrombosis and Haemostasis* offers a ray of hope (17). The authors compared the LFI to two IgG-specific ELISAs and a particle gel immunoassay (PGIA) using samples from 452 patients consecutively referred to a reference laboratory for HIT testing. Clinical information was supplied by the referring providers and scored using the 4Ts system (11) by two investigators, who were blinded to the results of laboratory testing. HIT was defined as an intermediate or high clinical probability 4Ts score in conjunction with a positive heparin-induced platelet activation (HIPA) assay, a functional test with favourable operating characteristics similar to those of the SRA.

Of the 34 patients that met the protocol definition for HIT, all tested positive by LFI using a visual inspection endpoint as well as by the two IgG-specific ELISAs. Three HIT-positive patients were missed by the PGIA. In addition, the LFI was associated with a significantly smaller number of false-positive results than the ELISAs and PGIA (29 vs. 45–55). While these observa-

Correspondence to:
Adam Cuker, MD, MS
Penn Comprehensive Hemophilia and Thrombosis Program
3 Dulles, Hospital of the University of Pennsylvania
3400 Spruce Street, Philadelphia, PA 19104, USA
Tel.: +1 215 615 8015, Fax: +1 215 615 6599
E-mail: adam.cuker@uphs.upenn.edu

Received: September 26, 2011
Accepted: September 29, 2011
Prepublished online: October 20, 2011
doi:10.1160/TH11-09-0677
Thromb Haemost 2011; 106: 993–994

tions require confirmation in other laboratories and patient populations, their clinical implications are clear: if the decision to begin an alternative anticoagulant in the current study had been made solely on the basis of immunoassay results, use of the LFI, relative to the comparator assays, would have reduced unnecessary DTI use by approximately 35–45%.

As expected, turnaround times for the LFI and PGIA were much shorter than for the ELISAs (12–16 minutes vs. approximately 2 hours). More to the point, in contrast to the ELISA, the LFI is designed as a single-sample assay and facilitates testing of individual patient samples upon request, thereby allowing for provision of results to clinicians in the real-time needed to inform initial clinical decision making.

Currently recommended diagnostic algorithms for HIT incorporate an estimate of clinical probability and use of a sensitive immunoassay to guide initial management with subsequent confirmatory testing by a more specific functional assay (18). Although replacement of the ELISA or PGIA with the LFI in this algorithm may have the potential to ameliorate the problem of over-diagnosis and over-treatment, it is unlikely to solve it. In the current study, nearly half of all positive results by LFI were obtained in patients without HIT. Other recently reported immunoassays are likewise limited by modest positive predictive value (19–21). A new generation of sensitive immunoassays with high positive predictive value is sorely needed to curb the current epidemic of over-diagnosis in HIT. The development of such assays will require a greater understanding of the biological properties that distinguish pathogenic anti-PF4/heparin antibodies and antibody-antigen interactions from their non-pathogenic counterparts. Until such assays become available, clinicians should remain wary, not only of missing HIT, but also of misdiagnosing HIT and needlessly exposing patients without the disorder to the potential harms and costs of HIT-directed therapy.

Conflict of interest

Adam Cuker has provided consulting services to Bayer, Biogen-Idec, Canyon Pharmaceuticals, CSL Behring, and Genzyme; he has received research funding from Baxter, Bayer, and Novo Nordisk, and has provided expert witness testimony relating to heparin-induced thrombocytopenia.

This editorial reflects the view of its author(s) and is not representative of the view of the Editorial Board or the Publishers.

References

1. Amiral J, Bridey F, Dreyfus M, et al. Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. Thromb Haemost 1992; 68: 95–96.
2. Weismann RE, Tobin RW. Arterial embolism occurring during systemic heparin therapy. Arch Surg 1958; 76: 219–227.
3. Warkentin TE. Think of HIT. Hematology Am Soc Hematol Educ Program 2006: 408–414.
4. Horner BM, Myers SR. Don't miss HIT (heparin induced thrombocytopenia). Burns 2004; 30: 88–90.
5. Cuker A, Arepally G, Crowther MA, et al. The HIT Expert Probability (HEP) Score: a novel pre-test probability model for heparin-induced thrombocytopenia based on broad expert opinion. J Thromb Haemost 2010; 8: 2642–2650.
6. 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.
7. Berry C, Tcherniantchouk O, Ley EJ, et al. Overdiagnosis of heparin-induced thrombocytopenia in surgical ICU patients. J Am Coll Surg 2011; 213: 10–17.
8. Selleng S, Malowsky B, Strobel U, et al. Early-onset and persisting thrombocytopenia in post-cardiac surgery patients is rarely due to heparin-induced thrombocytopenia, even when antibody tests are positive. J Thromb Haemost 2010; 8: 30–36.
9. Smythe MA, Warkentin TE, Woodhouse AL, Zakalik D. Venous limb gangrene and fatal hemorrhage: adverse consequences of HIT "overdiagnosis" in a patient with antiphospholipid syndrome. Am J Hematol 2011; 86: 188–191.
10. Oliveira GB, Crespo EM, Becker RC, et al. Incidence and prognostic significance of thrombocytopenia in patients treated with prolonged heparin therapy. Arch Intern Med 2008; 168: 94–102.
11. 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.
12. Lo GK, Sigouin CS, Warkentin TE. What is the potential for overdiagnosis of heparin-induced thrombocytopenia? Am J Hematol 2007; 82: 1037–1043.
13. Pauzner R, Greinacher A, Selleng K, et al. False-positive tests for heparin-induced thrombocytopenia in patients with antiphospholipid syndrome and systemic lupus erythematosus. J Thromb Haemost 2009; 7: 1070–1074.
14. Cuker A, Ortel TL. ASH evidence-based guidelines: is the IgG-specific anti-PF4/heparin ELISA superior to the polyspecific ELISA in the laboratory diagnosis of HIT? Hematology Am Soc Hematol Educ Program 2009: 250–252.
15. Ruf KM, Bensadoun ES, Davis GA, et al. A clinical-laboratory algorithm incorporating optical density value to predict heparin-induced thrombocytopenia. Thromb Haemost 2011; 105: 553–559.
16. Whitlatch NL, Perry SL, Ortel TL. Anti-heparin/platelet factor 4 antibody optical density values and the confirmatory procedure in the diagnosis of heparin-induced thrombocytopenia. Thromb Haemost 2008; 100: 678–684.
17. Sachs U, von Hesberg J, Santoso S, et al. Evaluation of a new nanoparticle-based lateral-flow immunoassay for the exclusion of heparin-induced thrombocytopenia (HIT). Thromb Haemost 2011; 106: 1197-1202.
18. Cuker A. Heparin-induced thrombocytopenia: present and future. J Thromb Thrombolysis 2011; 31: 353–366.
19. Legnani C, Cini M, Pili C, et al. Evaluation of a new automated panel of assays for the detection of anti-PF4/heparin antibodies in patients suspected of having heparin-induced thrombocytopenia. Thromb Haemost 2010; 104: 402–409.
20. Pouplard C, Leroux D, Regina S, et al. Effectiveness of a new immunoassay for the diagnosis of heparin-induced thrombocytopenia and improved specificity when detecting IgG antibodies. Thromb Haemost 2010; 103: 145–150.
21. Davidson SJ, Ortel TL, Smith LJ. Performance of a new, rapid, automated immunoassay for the detection of anti-platelet factor 4/heparin complex antibodies. Blood Coagul Fibrinolysis 2011; 22: 340–344.