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

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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determined to have a negative result by serotonin release assay (SRA), the gold standard laboratory test for HIT (unpublished data).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-
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.

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References