New Approaches to the Diagnosis of Heparin-Induced Thrombocytopenia*

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Heparin-induced thrombocytopenia (HIT) is a clinicopathologic syndrome that is most reliably diagnosed when a patient with a clinical scenario that is consistent with heparin-induced immunization is shown to have antiplatelet factor 4/heparin, platelet-activating IgG antibodies. A Bayesian diagnostic approach is discussed, wherein the physician estimates the pretest probability of HIT (*eg*, the timing and severity of thrombocytopenia in relation to heparin treatment and associated thrombosis) and determines the posttest probability using the results of HIT antibody testing. By this approach, the magnitude of a positive test result determines its likelihood ratio in influencing the posttest probability of HIT. ***(CHEST 2005; 127:35S–45S)***

Abbreviations: DVT = deep-vein thrombosis; EIA = enzyme immunoassay; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; LR = likelihood ratio; PE = pulmonary embolism; PF4 = platelet factor 4; SRA = serotonin release assay; UFH = unfractionated heparin

Heparin-induced thrombocytopenia (HIT) is an immune-mediated disorder caused by IgG antibodies that bind to platelet factor 4 (PF4). The PF4 becomes immunogenic when it binds to heparin.[1–3] Multimolecular complexes of heparin, PF4, and IgG form on platelet surfaces, and the occupancy of the platelet Fc receptors by HIT-IgG results in platelet activation. Heparin binds PF4 in relation to the chain length and degree of sulfation, perhaps explaining why unfractionated heparin (UFH) is more likely to cause HIT than low-molecular-weight heparin (LMWH).[4–6] Platelet activation in HIT is associated with the activation of coagulation, as shown by increased levels of markers of *in vivo* thrombin generation (*eg*, thrombin-antithrombin complexes).[7,8] Once these events are triggered, the prothrombotic risk remains for days to weeks, even after stopping heparin therapy.[9,10]

HIT Myths

Certain myths exist regarding HIT. One is that this complication can be diagnosed on clinical grounds alone. While it is true that HIT can be diagnosed in some patients with near certainty based on their characteristic presentation, exclusive reliance on clinical features alone can result in erroneous conclusions. For example, Figure 1 compares two similar clinical scenarios, namely, thrombocytopenia and pulmonary embolism (PE) occurring during UFH prophylaxis following major surgery.[11] However, only one patient (Fig 1, *bottom*, *B*) tested positive for HIT antibodies. The other patient (Fig 1, *top*, *A*), who tested negative for HIT antibodies using two different assays for HIT antibodies, demonstrated clinical and platelet count recovery when the heparin dose was increased to overcome heparin resistance. This patient's thrombocytopenia was explained by PE, which can be associated with thrombocytopenia,[12,13] perhaps because clot-bound thrombin within the thromboemboli activate platelets directly within the high-flow pulmonary circulation.[11] Thus, PE is one of the causes of *pseudo-HIT*, a term that is used to describe a clinical situation that strongly mimics HIT on clinical grounds, but in which HIT antibodies are not detected.[11]

A second myth is that a positive test result for HIT antibodies automatically means that a thrombocytopenic patient has a diagnosis of HIT. However, this is not necessarily the case. Nonpathogenic PF4/heparin-reactive antibodies are a relatively common occurrence in patients who have received heparin within the past days or weeks.[14,15] Thus, if a patient treated with heparin develops bacteremia and clinical sepsis, this patient could test positive for HIT antibodies, but the sepsis would have caused the platelet count to fall.[16] Figure 2 illustrates such a clinical dilemma. The patient has features that

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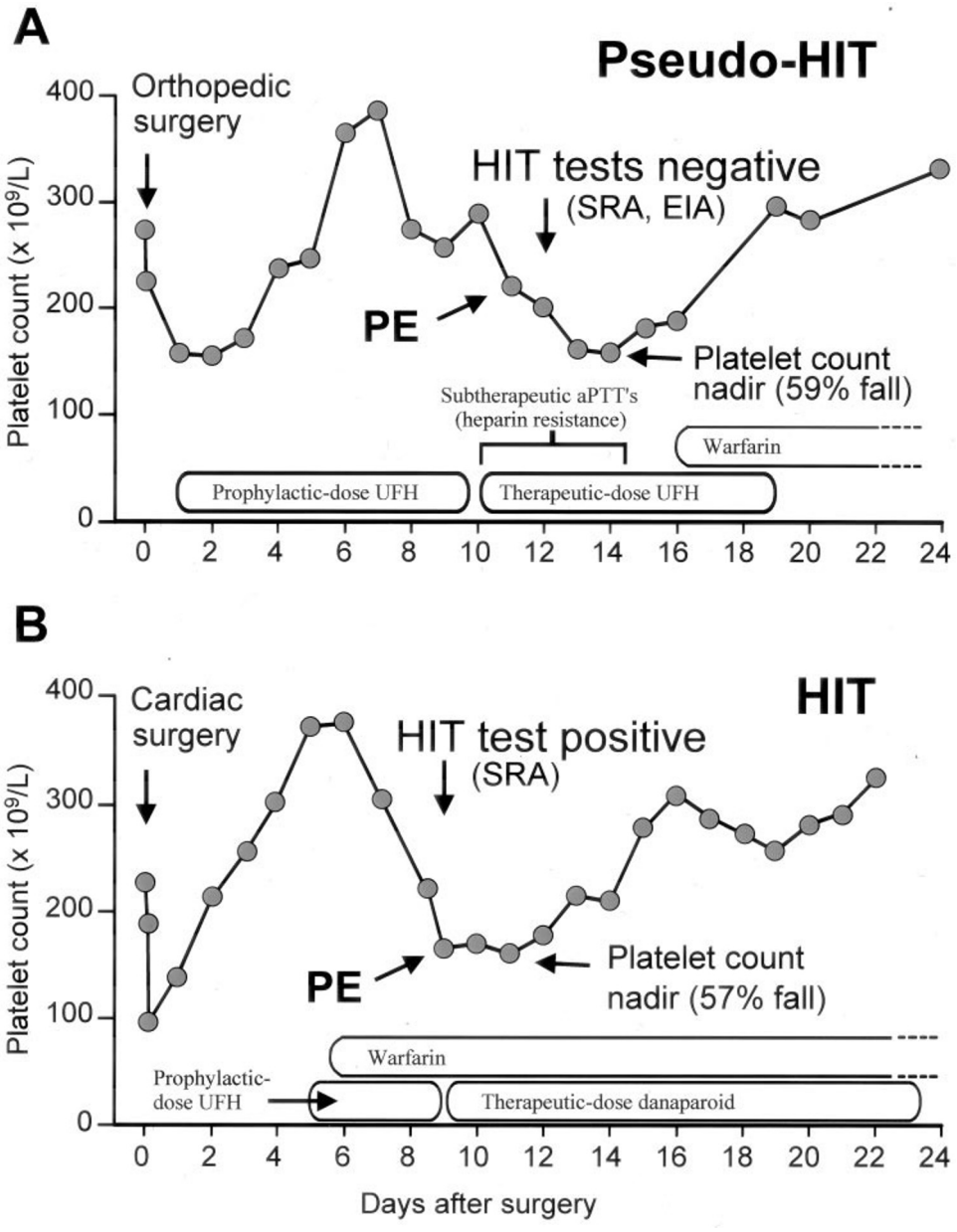

FIGURE 1. Two patients with thrombocytopenia and PE. *Top*, *A*: pseudo-HIT. This patient developed thrombocytopenia and PE during the second week following orthopedic surgery. HIT was excluded by negative results for the platelet SRA and a PF4-dependent EIA. The explanation for thrombocytopenia was PE (see text). The platelet levels recovered with increasing doses of UFH that were used to overcome heparin "resistance." *Bottom*, *B*: HIT. This patient developed thrombocytopenia and PE during the second week following cardiac surgery. HIT was diagnosed based on a strongly positive SRA result. The platelet count recovered after therapy with the nonheparin anticoagulant danaparoid. Reprinted (with modifications) from Warkentin,[11] with permission.

strongly support the presence of sepsis (*eg*, fever, hypotension, and positive blood culture results) but also has features suggesting HIT (*eg*, thrombocytopenia and proximal deep-vein thrombosis [DVT]). This patient tested positive for HIT antibodies by two different assays. However, the patient's subsequent clinical course revealed platelet count recovery while receiving UFH in a therapeutic dose (arguing against the presence of HIT) but also PE on postoperative day 16 (which is consistent with the presence of HIT).

The importance of both clinical and laboratory features in the diagnosis of HIT means that HIT should be considered a "clinicopathologic syndrome" (Table 1), whereby the diagnosis is made most confidently when the patient has an episode of