ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Update in the Diagnosis and Management of Heparin-Induced Thrombocytopenia

Adam Cuker, MD, MS
Assistant Professor of Medicine and of Pathology & Laboratory Medicine
The Hospital of the University of Pennsylvania
Penn Comprehensive Hemophilia and Thrombosis Program
Philadelphia, Pennsylvania

H&O How common is heparin-induced thrombocytopenia (HIT), and are certain patient groups at higher risk?

AC HIT occurs in 0.2–5% of adults who are treated with heparin, depending on the patient population and the type and duration of heparin exposure. Surgical patients have a higher risk of HIT than medical patients. Unfractionated heparin is associated with roughly a 10-fold greater risk of HIT than low-molecular-weight heparin. Courses of heparin therapy of 5 or more consecutive days carry a higher risk than briefer exposures.

H&O What is the cause of HIT?

AC HIT is caused by antibodies, primarily of the immunoglobulin G class, that target multimolecular complexes of the platelet chemokine, platelet factor 4 (PF4), and heparin. These antibodies induce platelet activation by binding to the FcγRIIa receptor on the platelet surface. Recent evidence suggests that they also bind to the FcγRI receptor on monocytes, inducing tissue factor expression and release of tissue factor-laden microparticles via activation of the MEK1-ERK1/2 signaling pathway. Why only some patients develop antibodies and why only some antibodies are pathogenic is poorly understood and an area of active investigation.

H&O What signs suggest the presence of this condition?

AC The cardinal sign of HIT is a fall in the platelet count in the setting of a proximate heparin exposure. The degree and timing of this fall can help to discriminate HIT from other causes of thrombocytopenia. Moreover, HIT is a profoundly prothrombotic disorder. Thromboembolism is the presenting feature in up to half of cases. It may be venous or arterial and may result in loss of life or limb. Uncommon manifestations of HIT include skin necrosis at subcutaneous injection sites, anaphylactoid reactions after intravenous heparin boluses, and transient global amnesia.

H&O How is HIT diagnosed?

AC HIT is a clinicopathologic disorder, the diagnosis of which rests on both clinical assessment and laboratory testing. Several clinical scoring models have been developed to guide clinical diagnosis. The most extensively studied of these is the 4T score (4Ts). A limitation of the 4Ts is interobserver variability (Table 1). We have developed an alternative scoring model, the Heparin Expert Probability (HEP) score, which includes more detailed and explicit itemization of clinical features in an attempt to clarify their meaning and enhance reproducibility. This model exhibited favorable operating

Table 1. The 4T Score*

Category	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥20 × 10^9 L^{-1}	Platelet count fall 30–50% or platelet count 10–19 × 10^9 L^{-1}	Platelet count fall <30% or platelet nadir <10 × 10^9 L^{-1}
Timing of Platelet Count Fall	Clear onset between days 5 and 10 or platelet fall ≤1 day (prior heparin exposure within 30 days)	Consistent with days 5–10 fall, but not clear (eg, missing platelet counts) or onset after day 10 or fall ≤1 day (prior heparin exposure within 30–100 days ago)	Platelet count fall <4 days without recent heparin exposure
Thrombosis or Other Sequelae	New thrombosis (confirmed) or skin necrosis at heparin injection sites or acute systemic reaction after intravenous heparin bolus	Progressive or recurrent thrombosis or non-necrotizing (erythematous) skin lesions or suspected thrombosis (not proven)	None
Other Causes of Thrombocytopenia	None apparent	Possible	Definite

*Total Score: ≤3=low probability of heparin-induced thrombocytopenia (HIT); 4-5=intermediate probability of HIT; ≥6=high probability of HIT.
Data from Lo GK, 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.

characteristics in a retrospective study and is currently undergoing prospective evaluation. Laboratory tests for HIT fall into 2 categories. Immunoassays detect circulating anti–PF4/heparin antibodies regardless of their pathogenicity. Functional assays detect only the subset of antibodies that are capable of inducing heparin-dependent platelet activation. Immunoassays are highly sensitive, but are limited by frequent false-positive results. Functional assays are much more specific, but are only available through select reference laboratories.

H&O How can misdiagnosis be avoided?

AC Misdiagnosis, particularly overdiagnosis, is a pervasive problem. There are several strategies that can be used to minimize overdiagnosis. We recently completed a meta-analysis showing that a low-probability 4T score is a robust means of ruling out HIT. Patients with a low-probability 4T score, as judged by the consulting clinician, generally should not undergo HIT laboratory testing or receive HIT-specific therapy. Another approach involves consideration of the antibody titer or optical density (OD) as measured by enzyme immunoassay. The probability of true HIT and a positive functional assay increases with rising OD. In one study, only 1 of 37 patient samples exhibiting a weakly positive OD (0.40-0.99) demonstrated heparin-dependent platelet activation, in contrast to 33 of 37 samples with a strongly positive OD (≥2.00). Therefore, it is important for laboratories to report not only whether the immunoassay is positive or negative, but also the OD. A third approach, whenever possible, is to request a more specific functional assay in patients who have a positive immunoassay. All of these strategies can help to reduce overdiagnosis.

H&O What are the management strategies for HIT?

AC There are 2 initial steps to take. First, all forms of heparin, including heparin-bonded catheters and heparin flushes, should be withdrawn. Second, a non-heparin parenteral anticoagulant, such as argatroban, hirudin, or danaparoid, should be initiated. Argatroban is preferred in patients with renal insufficiency because it is not cleared in the kidneys. Bivalirudin is recommended in patients with acute HIT who require intra-operative anticoagulation for cardiac surgery or other cardiovascular procedures. There is recent evidence that fondaparinux may be an effective and safe treatment strategy for HIT, though this remains controversial. Recently issued guidelines from the American College of Chest Physicians do not recommend fondaparinux for the treatment of HIT, owing to the limited quality of published data and several case reports of fondaparinux inducing or exacerbating HIT.

H&O What are the limitations of these management strategies?

AC Approved agents such as argatroban and hirudin have several important limitations. First, their administration is complex. They require continuous intravenous infu-

sion, serial laboratory monitoring, and frequent dose adjustments. Second, they are associated with incomplete efficacy. These agents reduce thrombosis by approximately 50–65% and do not substantially diminish amputation or mortality rates. Third, these drugs are associated with a daily risk of major hemorrhage of approximately 1%, a risk further compounded by the absence of reversal agents. Fourth, these drugs are expensive and are a prime contributor to the economic burden of HIT.

H&O What are some areas of research in HIT?

AC Ongoing mechanistic studies are examining the underpinnings of HIT susceptibility and pathogenesis—why only some patients who are exposed to heparin develop anti-PF4/heparin antibodies and why only a minority of patients with antibodies develop disease. Studies to develop better clinical scoring models and laboratory assays, with the goal of improving diagnosis and curbing overdiagnosis, are also under way. Finally, the development of novel drugs, particularly agents that affect pathways proximal to coagulation, such as immune complex formation and signaling, is an active area of investigation. Such agents may provide effective therapy without the degree of bleeding risk associated with currently approved agents. New oral inhibitors of thrombin (dabigatran [Pradaxa, Boehringer Ingelheim] and factor Xa (rivaroxaban [Xarelto, Bayer], apixaban) do not cross-react with HIT antibodies or induce platelet activation or PF4 release in vitro, and they may provide effective therapy. There are no published clinical data to support their use in HIT at present, but a prospective study of rivaroxaban in patients with suspected HIT is planned.

Suggested Readings

ClinicalTrials.gov. Rivaroxaban for treatment of patients with suspected or confirmed heparin-induced thrombocytopenia. http://clinicaltrials.gov/ct2/show/NCT01598168?term=NCT01598168&rank=1. Identifier: NCT01598168.

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