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Diagnosis of Heparin-Induced Thrombocytopenia

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Heparin-induced thrombocytopenia (HIT) is a complication seen in approximately 1%–3% of patients treated with unfractionated heparin therapy. HIT may also be associated with low molecular weight heparin use.[1] Clinical symptoms include moderate thrombocytopenia and, paradoxically, arterial or venous thrombosis in up to 30% of affected patients. Postoperative (specifically orthopedic surgical) patients are at higher risk for HIT than medical patients.[1,2] HIT is considered a disease of adults, although pediatric cases have been reported. HIT usually develops within five to ten days after the onset of heparin therapy in unexposed patients. Patients with a history of heparin use in the past three months may form antibodies much earlier, often within 24 to 48 hours of re-exposure.[3]

HIT is an immunologic disorder resulting from antibodies, most commonly IgG isotype, with specificity for a complex of heparin and platelet factor 4 (PF4).[2] PF4 is contained within platelet alpha granules and is released upon platelet activation. In a subset of reactive patients, immune complexes consisting of heparin, PF4, and antibody activate platelets and ultimately lead to a hypercoagulable state.[4]

Prior to laboratory testing, a clinical scoring system can predict a patient's likelihood of HIT. One validated system is the 4T's score. Four factors (degree of **T**hrombocytopenia, **T**iming of platelet count drop, signs of **T**hrombosis, and presence of other causes of thrombocytopenia) have associated point values. The points for each factor are summed to give a pretest probability of HIT.[5]

Many laboratories use commercial enzyme-linked immunosorbent assay (ELISA) kits to detect antiheparin-PF4 antibodies. ELISA testing measures the optical density (OD) of each patient sample as an indication of the amount of antibody present. The manufacturers provide OD cutoffs based on a reference group not exposed to heparin (typically 0.4–0.5 OD). ELISA is a very sensitive test (95%–99%), but is less specific (74%–86%).[1,6] This may be partly because a subset of patients can form heparin-PF4 antibodies, yet never develop HIT symptoms.[7] Recent literature suggests that OD values higher than the manufacturer's suggested cutoff (OD $\geq$ 1.0) may be more predictive of HIT.[2,8,9,10] Additionally, although many laboratories test for IgG, IgA, and IgM antibodies, several studies have suggested that IgG antibodies may be the most clinically significant.[7,11,12] There is no consensus in the literature about the best way to maximize ELISA specificity, and practice varies between laboratories.[13] Strategies may include using a clinical scoring system along with laboratory testing, increasing the OD cutoff value, and/or using an IgG-only ELISA kit.[8]

Published HIT diagnostic algorithms combine a clinical pretest probability score with the ELISA OD value to determine whether confirmatory testing is warranted. For patients with concordantly low or high pretest probability and OD values, additional testing is probably not necessary. If the patient has an intermediate pretest probability and an OD value near the cutoff, functional testing is recommended for definitive diagnosis.[3,5,6] Functional tests, such as the serotonin release assay, are more specific than ELISAs, but their use is typically limited to specialized hemostasis laboratories due to their technically demanding nature.[3,6]

In summary, HIT is an immune-mediated reaction to heparin therapy that results in decreased platelet counts and hypercoagulability and requires clinicopathologic correlation for accurate diagnosis.

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