Heparin-Induced Thrombocytopenia

Indications for Ordering

Aids in diagnosis of heparin-induced thrombocytopenia (HIT) in patients at risk for the syndrome who develop thrombocytopenia 5-10 days after heparin exposure

Test Description

Test methodology
HIT platelet factor 4 (PF4) IgG antibodies
- Semiquantitative enzyme-linked immunosorbent assay (ELISA)
Serotonin release assay (SRA)
- High-performance liquid chromatography (HPLC) quantification of serotonin
- Results expressed as percent release

Clinical validation
- The IgG ELISA was compared to a polyvalent ELISA (IgG/M/A) and to the SRA
- For the SRA, serotonin measured by HPLC methodology is as sensitive and specific as serotonin measured using radiolabelled carbon 14

Tests to Consider

Typical testing strategy
- CBC screening while patient is on heparin to monitor for the development of thrombocytopenia
- Initial screening for HIT may include ELISA for PF4 IgG antibodies if thrombocytopenia develops 5-10 days after initiation of heparin exposure
- Gold standard test for HIT is SRA

Primary tests
Heparin-Induced Thrombocytopenia (HIT) PF4 Antibody, IgG with Reflex to Serotonin Release Assay (Heparin Dependent Platelet Antibody), Unfractionated Heparin 2012181
- Gold standard reflex test for confirming diagnosis of HIT
- Reflexes to SRA if ELISA test is positive
Serotonin Release Assay (Heparin Dependent Platelet Antibody), Unfractionated Heparin 2005631
- Gold standard test for diagnosis of HIT

Related test
Heparin-Induced Thrombocytopenia (HIT) PF4 Antibody, IgG 2012179
- Recommended initial screening test for heparin-PF4 antibodies that cause HIT
- Confirmation with SRA may be necessary based on clinical presentation

Disease Overview

Prevalence — 1-5% of patients receiving heparin
- Prevalence is population dependent
  - Lower rate of occurrence with low-molecular-weight heparins
  - Higher rate of occurrence in surgical and transplant patients

Signs/symptoms
Thrombocytopenia
- Occurs 5-10 days after heparin exposure
  - May be more rapid if patient has recently developed HIT antibodies and is reexposed to heparin
Thrombosis
- Venous — common sites (eg, lower-extremity deep vein thrombosis) as well as uncommon sites (eg, cerebral vein thrombosis)
- Arterial — cerebral (stroke), myocardial (infarction), limbs (ischemia)

Physiology
- HIT is caused by the development of heparin-PF4 IgG antibodies
- PF4 is released from platelets in circulation
- Heparin binds to PF4 to form a complex
  - In some patients, this complex causes development of heparin-PF4 IgG antibodies and immune complex formation
  - May cause platelet activation in some patients
- Leads to a cycle of additional platelet activation, thrombocytopenia, and clot formation (HIT)
Consensus/diagnostic criteria
• Clinical risk scoring system most commonly used is “4 Ts” to predict pretest probability
  o Thrombocytopenia
  o Timing of platelet decrease
  o Thrombosis
  o Other causes for thrombocytopenia
• Good negative predictive value, poor positive predictive value

Diagnostic issues
• Two different test types – sensitivity and specificity vary
  o ELISA
    ▪ Sensitive for heparin-PF4 IgG antibody detection
    ▪ Only significant antibody for HIT is IgG
    ▪ Use of IgG ELISA rather than IgG/M/A ELISA improves test specificity by avoiding detection of nonclinically significant antibodies
  ▪ Not completely specific
    ▪ Detection of antibodies does not necessarily correlate with the ability of these antibodies to activate platelets
      o Platelet activation induces HIT
    ▪ Use of optical density (OD) values improves specificity
      o Higher OD increases likelihood that pathogenic antibodies are present
  ▪ High negative predictive value – patients lacking antibodies do not have HIT
  ▪ Note – some laboratories perform ELISA heparin neutralization procedure (confirmatory step)
    o Not performed at ARUP as it does not appear to be of additional diagnostic value and, in some cases, can lead to specimen misclassification
  o SRA
    ▪ Functional assay and gold standard for HIT diagnosis due to high sensitivity and specificity
    ▪ Platelet activation in HIT/SRA causes the release of serotonin
      ▪ Serotonin is the surrogate marker for platelet activation
      ▪ Quantity of serotonin released from activated platelets is determined
    ▪ Test uses 2 concentrations of unfractionated heparin (low/therapeutic and high/supra-therapeutic doses) to demonstrate heparin-dependent activation in HIT
      ▪ Platelet-activating HIT immune complexes are disrupted by excess heparin
        o In patients with HIT, only a low dose of heparin will cause platelet activation
      ▪ Non-HIT antibodies that demonstrate platelet activation (such as human leukocyte antigen [HLA] antibodies) are not disrupted by excess heparin
        o In these patients, both low and high doses of heparin will cause platelet activation

Test Interpretation

Clinical sensitivity/specificity – >90% for SRA

Results
PF4 IgG antibodies ELISA
• Positive – OD >0.399
• Negative – OD <0.399

Serotonin release assay
• Positive – ≥20% release with low but not supra-therapeutic concentrations of heparin
• Negative – <20% release with both low and supra-therapeutic concentrations of heparin
• Indeterminate – ≥20% release with both low and supra-therapeutic concentrations of heparin

Limitations
• Occasional false negatives occur with HIT testing
  o Does not exclude HIT if clinical suspicion is high
• Results should always be correlated with clinical findings