ASH evidence-based guidelines: is the IgG-specific anti-PF4/heparin ELISA superior to the polyspecific ELISA in the laboratory diagnosis of HIT?

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You are asked to consult on a 76-year-old man admitted to the hospital with pneumonia and thrombocytopenia. Ten days before the current admission, he had undergone surgery to repair a small bowel obstruction. A preoperative platelet count had been normal. Following surgery, he received subcutaneous unfractionated heparin thromboprophylaxis until his discharge on post-operative day 5. In your differential diagnosis for the patient’s thrombocytopenia, you consider heparin-induced thrombocytopenia (HIT) and wish to order laboratory testing. In addition to a polyspecific anti-PF4/heparin ELISA for the diagnosis of HIT, your laboratory has recently begun to offer an IgG-specific ELISA. You wonder which of these assays performs better in the diagnosis of HIT.

HIT is mediated by antibodies that target multimeric complexes of platelet factor 4 (PF4) and heparin.1 Conventional ELISAs for the diagnosis of HIT detect anti-PF4/heparin IgG, IgA, and IgM. These polyspecific ELISAs are highly sensitive, but suffer from limited specificity and a high false-positive rate.2 A growing body of evidence suggests that antibodies of the IgG class have the primary, if not sole, potential to cause HIT.3-5 Recently, ELISAs that detect only anti-PF4/heparin IgG have become commercially available. It is hoped that these IgG-specific ELISAs will offer equally high sensitivity and superior specificity as compared with the polyspecific assay. To evaluate the operating characteristics of the polyspecific and IgG-specific ELISAs, we performed a comprehensive literature review of all studies in which these two assays were compared.

A literature search of the PubMed database was performed by combining the MeSH term “heparin,” subheadings “adverse effects” or “toxicity,” with the keyword “heparin-induced thrombocytopenia” (no restrictions, 6720 hits); the MeSH term “immunoassay” with the keyword “immunoassay” (no restrictions, 351,102 hits); and the MeSH term “research” with the keywords “research” and “study” (no restrictions, 8,110,184 hits) between 1950 and 21 May 2009. This strategy yielded 110 citations. Excluded were 91 studies in which one or both of the assays of interest was not performed, 4 case reports, 6 reviews, and 1 editorial. Of the remaining 8 references, 4 did not include the data necessary for determination of test operating characteristics, leaving 4 eligible studies. A review of these studies’ bibliographies identified a fifth eligible study (n = 3366). In a pooled analysis of these studies (Table 1), the IgG-specific ELISA was associated with greater specificity (93.5% vs 89.4%), but lower sensitivity (95.8% vs 98.1%) than the polyspecific ELISA. Table 2 shows the operating characteristics of the two assays.

The validity of these results is limited by differences in the study populations, gold standard definitions of HIT, and immunoassays utilized in the 5 studies. Nonetheless, we conclude that the IgG-specific ELISA yields fewer false-positive results than the polyspecific ELISA, but at the expense of lower sensitivity.

### Table 2. Operating characteristics of the polyspecific ELISA and IgG-specific ELISA.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>LR+</th>
<th>LR−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyspecific ELISA</td>
<td>98.1</td>
<td>89.4</td>
<td>38.7</td>
<td>99.9</td>
<td>9.29</td>
<td>0.021</td>
</tr>
<tr>
<td>IgG-specific ELISA</td>
<td>95.8</td>
<td>93.5</td>
<td>49.6</td>
<td>99.7</td>
<td>14.64</td>
<td>0.045</td>
</tr>
</tbody>
</table>

PPV indicates positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; and LR−, negative likelihood ratio.
Table 1. Studies comparing the polyspecific ELISA and IgG-specific ELISA in the diagnosis of heparin-induced thrombocytopenia (HIT).

<table>
<thead>
<tr>
<th>Ref</th>
<th>Study population (n)</th>
<th>Definition of HIT</th>
<th>Polyspecific ELISA</th>
<th>IgG-specific ELISA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Assay</td>
<td>TP</td>
</tr>
<tr>
<td>6</td>
<td>Patients with suspected HIT (500)</td>
<td>Positive HIPA and intermediate to high clinical pre-test probability*</td>
<td>GT†</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>Patients with suspected HIT (100)</td>
<td>Positive SRA and intermediate to high clinical pre-test probability*</td>
<td>GT†</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>Patients with suspected HIT (1582)#</td>
<td>Positive HIPA</td>
<td>In-house</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>Patients with suspected HIT (736)#</td>
<td>Positive HIPA</td>
<td>In-house</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>Patients receiving thromboprophylaxis after total hip arthroplasty (448)</td>
<td>Clinical¶</td>
<td>GT†</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Pooled total 3366</td>
<td></td>
<td>210</td>
<td>2819</td>
</tr>
</tbody>
</table>

*Clinical probability estimated using the 4Ts scoring system.
†Genetics Testing Institute (Waukesha, WI, USA)
#Patients with an indeterminate HIPA result in the original study were excluded from the current analysis
§Patients with a negative polyspecific ELISA were not tested with the IgG-specific ELISA and are assumed to be negative with respect to this assay for the current analysis
¶Fall of ≥50% in platelet count beginning on day ≥5 of heparin therapy without other apparent cause and platelet count recovery upon cessation of heparin
TP indicates true positive; TN, true negative; FP, false positive; FN, false negative; HIPA, heparin-induced platelet activation assay; and SRA, carbon-14 labeled serotonin release assay.

possible expense of missing a small proportion of patients with true HIT who are captured by the polyspecific assay. Clinical economic analyses that define the costs of false-positive and false-negative results are required to determine whether this is an acceptable trade-off. Until such analyses are available, we recommend use of the more sensitive polyspecific ELISA as a screening test for HIT (Grade 2C).

Disclosures
Conflict-of-interest disclosure: The authors declare no competing financial interests.
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References
