Heparin-induced thrombocytopenia (HIT) is an adverse drug reaction characterized by thrombocytopenia and a high risk for venous or arterial thrombosis. It is caused by heparin-dependent, platelet-activating antibodies that recognize a “self” protein, platelet factor 4 (PF4), bound to heparin. The resulting platelet activation is associated with increased thrombin generation (Figure). Typically, the platelet count fall begins 5 to 10 days after starting heparin, although a rapid platelet count fall can occur in a patient who has antibodies from recent heparin use. Remarkably, transience of HIT antibodies permits safe heparin reexposure in selected patients (for example, heart surgery patients) despite a history of HIT.

Case Summary
A 61-year-old woman with Raynaud’s phenomenon underwent mechanical aortic valve replacement for aortic insufficiency. She developed persistent vasospasm of fingers and toes after surgery that responded to warming measures. Unfractionated heparin (UFH) prophylaxis was given until postoperative day 4, and warfarin (5, 5, and 2.5 mg) was given from days 2 to 4. On day 8, the patient developed ischemic necrosis of multiple fingers and toes. The platelet count had fallen by 44% from 221 x 10^3/L (day 4) to 124 x 10^3/L (day 8), and the international normalized ratio (INR) rose to 4.3. The diagnosis of delayed-onset HIT complicated by warfarin-induced digital necrosis was supported by strong positive tests for HIT antibodies, including a positive platelet serotonin release assay (100% serotonin release; normal <20%).

When Should HIT Be Suspected?
Thrombocytopenia is common in hospitalized patients receiving UFH, yet only a minority have HIT. A clinical scoring system may be useful for identifying those with HIT.

Pretest Probability of HIT: The “4 T’s”
Table 1 summarizes a clinical scoring system (“4 T’s”) for estimating the pretest probability of HIT based on its characteristic features (Thrombocytopenia, Timing, Thrombosis) and the absence of other explanation(s). Preliminary evaluation suggests that HIT antibodies are unlikely (<5%) when a low score (≤3) is obtained but are likely (>80%) with a high score (≥6). An intermediate score (4 or 5) indicates a clinical profile compatible with HIT but with another plausible explanation. Laboratory testing for HIT antibodies is especially useful in this last group of patients.

HIT After Cardiac Surgery
HIT often begins 5 to 10 days after cardiac surgery, especially if UFH is given after postoperative day 4. It is recommended that the platelet count be monitored at least every other day in these patients. In contrast, HIT within the first 4 days after cardiac surgery is uncommon even in patients who received heparin before surgery. This is because heparin-induced immunization in preoperative medical settings is relatively uncommon and because thrombocytopenia soon after cardiac surgery invariably can be explained by hemodilution and platelet consumption.

Delayed-Onset HIT
Sometimes, the platelet count begins to fall in HIT only after heparin has been stopped. Such patients with delayed-onset HIT can present as inpatients or outpatients and typically have strong positive HIT antibody tests caused by high titer of antibodies with autoimmune features, such as platelet activation in the absence of heparin.
HIT and Invasive Cardiology

Thrombocytopenia is relatively common after percutaneous coronary intervention (PCI). However, abrupt onset of severe thrombocytopenia within hours of PCI utilizing UFH and a platelet glycoprotein (GP) IIb/IIIa (fibrinogen receptor) antagonist (abciximab, eptifibatide, tirofiban) almost always is caused by the GP IIb/IIIa antagonist because of naturally occurring antibodies that react against GP IIb/IIIa in the presence of the drug.8 If HIT is wrongly diagnosed in such a patient and the patient is anticoagulated, severe bleeding could result.

HIT and Clinical Cardiology

Cardiologists prescribe UFH for many clinical situations, including acute coronary syndrome, congestive heart failure, and atrial fibrillation, which creates the potential for HIT. Even low-dose subcutaneous UFH has been reported to cause HIT in about 1% of such patients.9 Low-molecular-weight heparin (LMWH) probably reduces risk of HIT in these patients (although this remains un-

TABLE 1. Estimating the Pretest Probability of HIT: The “Four T’s”

| Points (0, 1, or 2 for Each of 4 Categories: Maximum Possible Score = 8) |
|---|---|---|
| **Thrombocytopenia** | >50% Platelet fall to nadir ≥20 | 30–50% Platelet fall, or nadir 10–19 | ≤30% Platelet fall, or nadir <10 |
| Timing* of onset of platelet fall (or other sequelae of HIT) | Days 5–10, or ≥day 1 with recent heparin (past 30 days) | >Day 10 or timing unclear; or <day 1 with recent heparin (past 31–100 days) | <Day 4 (no recent heparin) |
| Thrombosis or other sequelae | Proven new thrombosis; skin necrosis; or acute systemic reaction after intravenous UFH bolus | Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis (not proven) | None |
| Other cause(s) of platelet fall | None evident | Possible | Definite |

Pretest probability score: 6–8 indicates high; 4–5, intermediate; and 0–3, low.

*First day of immunizing heparin exposure considered day 0.
Laboratory Testing for HIT Antibodies

Two types of assays for HIT, washed platelet activation assays and commercial PF4/polyanion enzyme immunoassays (EIAs), are sensitive for detecting clinically relevant HIT antibodies; thus, a negative test generally rules out HIT. However, because weak (nonpathogenic) antibodies can also be detected (especially by EIA), a positive test does not necessarily confirm HIT, especially if the test is only weakly positive and an alternative explanation for thrombocytopenia exists. It is important to interpret the test in the appropriate clinical context. For example, HIT antibodies are detectable by EIA in about 50% of patients one week after cardiac surgery, so diagnostic specificity is low.

At our center, where we use the platelet serotonin release assay (a washed platelet activation assay), we have observed that most patients with HIT have a strong positive test result (>80% serotonin release), which yields good diagnostic specificity. Delays in obtaining test results mean that physicians must make appropriate decisions on the basis of their assessment of the pretest probability of HIT.

In general, the greater the magnitude of a positive test result, the greater the likelihood that the patient has HIT, eg, most patients with HIT have serotonin release >80% and optical density >1.0 absorbance unit, ie, values well above the cutoffs defining a positive test.

**Assay from GTI (Brookfield, Wis) uses PF4/polyvinyl sulfonate, whereas assay from Stago (Asnieres, France) uses PF4/heparin.**

**High sensitivity for clinical HIT (similar to EIAs) but with greater diagnostic specificity than the EIAs.**

### TABLE 2. Comparison of Laboratory Assays to Detect HIT Antibodies

<table>
<thead>
<tr>
<th>Assay</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial PF4/polyanion-EIA*</td>
<td>Widely available; high sensitivity</td>
<td>Detects many nonpathogenic anti-PF4/polyanion IgA, IgM, and IgG antibodies (moderate specificity)</td>
</tr>
<tr>
<td>PF4/heparin-EIA that only detects IgG</td>
<td>Detecting only IgG improves specificity</td>
<td>Limited availability (research labs)</td>
</tr>
<tr>
<td>Platelet aggregation test (citrated platelet-rich plasma)</td>
<td>Many labs have conventional platelet aggregometers</td>
<td>Poor sensitivity and specificity; limited number of tests can be done; platelet donors required</td>
</tr>
<tr>
<td>Washed platelet activation assay (eg, serotonin release assay)</td>
<td>Highest sensitivity–specificity tradeoff†</td>
<td>Technically demanding; limited availability (research labs); platelet donors required</td>
</tr>
</tbody>
</table>

*High sensitivity for clinical HIT (similar to EIAs) but with greater diagnostic specificity than the EIAs.

**TREATMENT PRINCIPLES WHEN HIT IS STRONGLY SUSPECTED (OR CONFIRMED)**

1. Discontinue and avoid all heparin.
2. Give a nonheparin alternative anticoagulant.
3. Postpone warfarin pending substantial platelet count recovery (give vitamin K if warfarin has already been started).
4. Test for HIT antibodies.
5. Investigate for lower-limb deep-vein thrombosis.
6. Avoid prophylactic platelet transfusions.

If HIT is strongly suspected, all heparin should be stopped and further heparin avoided. UFH is commonly used to “flush” intravascular catheters, and an order simply to “discontinue heparin” may not necessarily prevent such incidental heparin exposure.

Warfarin predisposes to microvascular thrombosis in patients with acute HIT, for example, warfarin-induced venous limb gangrene and skin necrosis syndromes. Affected patients typically have a supratherapeutic INR (typically >4.0) that corresponds to severe protein C depletion. It is recommended that warfarin not be started until substantial resolution of thrombocytopenia has occurred (preferably, platelet count >150×10^9/L). Reversal of warfarin anticoagulation with vitamin K is advised when HIT is diagnosed only after warfarin has already been started; besides reducing risk of coumarin necrosis, it minimizes risk of DTI underdosing (because warfarin prolongs the activated partial thromboplastin time [aPTT] used to monitor the DTI).

**Lepirudin**

Lepirudin is a recombinant hirudin (leech anticoagulant) that forms irreversible 1:1 complexes with thrombin. Its half-life (80 minutes) increases dramatically in renal insufficiency. Because no antidote exists, it must be used cautiously or avoided completely in patients with renal compromise. The approved dose is 0.4 mg/kg (IV bolus) followed by an initial infusion rate at

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0.15 mg/kg per hour, adjusted for target aPTT 1.5× to 2.5× baseline. However, in the absence of severe thrombosis, and to reduce the risk of bleeding, some experts advise omitting the initial bolus, using a lower target aPTT range (1.5× to 2.0× baseline), and monitoring the aPTT every 4 hours until steady state is achieved.

Compared with historical controls, lepirudin was associated with reduced thrombotic events (relative risk reduction, 0.63 to 0.78). Lepirudin also is effective for patients with isolated HIT when a lower-dose protocol is used (0.10 mg/kg per hour adjusted by aPTT without initial bolus).

Because lepirudin is a foreign protein, its use frequently triggers anti-hirudin antibodies that occasionally lead to drug accumulation, presumably from impaired renal clearance of lepirudin–immunoglobulin G (IgG) complexes. Fatal anaphylaxis after intravenous bolus administration has been reported in patients who received lepirudin within the previous few months.

**Argatroban**

Argatroban is approved to treat both HIT complicated by thrombosis and isolated HIT. It is a small-molecule DTI that, unlike lepirudin, is not immunogenic. The usual dose is 2 μg/kg per minute adjusted by aPTT (usual target, 1.5× to 3× baseline aPTT). Compared with historical controls, argatroban was associated with reduced thrombotic events (relative risk reduction, 0.44 to 0.62). The starting dose should be reduced by 75% in a patient with significant liver dysfunction because argatroban undergoes hepatobiliary excretion. Prolongation of the INR by argatroban is considerably greater than that observed with lepirudin, which complicates argatroban-warfarin overlap; this underscores the importance of postponing warfarin pending substantial resolution of HIT (to avoid warfarin-induced microvascular thrombosis).

**Future Anticoagulants**

The patient described at the beginning of this article was treated with danaparoid; no new thrombosis occurred (although severe digital ischemia evolved to acral necrosis). The withdrawal of danaparoid from the US market in April 2001 coincided with the introduction of fondaparinux, a synthetic antithrombin-binding pentasaccharide with exclusive anti-factor Xa activity. Given its lack of in vitro cross-reactivity for HIT antibodies and its favorable early anecdotals results in HIT, fondaparinux may well prove useful in managing HIT, especially in patients with venous thromboembolism—a situation in which its long half-life (17 hours) and lack of INR prolongation facilitate warfarin overlap. However, optimal dosing for the hypercoagulability state of HIT is not established. The oligopeptide hirudin analogue, bivalirudin, is another promising agent, with favorable initial results in HIT. Pharmacological advantages include predominant nonrenal metabolism and lack of immunogenicity (compare with lepirudin) and minor prolongation of the INR (compare with argatroban).

**Acknowledgment**

Some of the studies described in this report were funded by the Heart and Stroke Foundation of Ontario (No. T5207).

**Disclosure**

Dr Warkentin has received grants or research support from Sanofi-Synthelabo and Organon, Inc; has served as a consultant to Medicines Co. and Aventis; and has served on the Speakers’ Bureaus of Aventis, Berlex Laboratories, Calea, GlaxoSmithKline, and Pharmion.

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Heparin-Induced Thrombocytopenia: Diagnosis and Management
Theodore E. Warkentin

Circulation. 2004;110:e454-e458
doi: 10.1161/01.CIR.0000147537.72829.1B
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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