Heparin-Induced Thrombocytopenia

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors’ clinical recommendations.

A 63-year-old man with coronary artery disease who has recently undergone bypass surgery presents with dyspnea. Findings on physical examination are unremarkable. Laboratory testing reveals a platelet count of 86,000 per cubic millimeter, as compared with 225,000 per cubic millimeter at the time of discharge nine days earlier. The results of chest radiography are unremarkable; spiral computed tomography of the chest shows a pulmonary embolism. Heparin-induced thrombocytopenia is suspected. What diagnostic studies are warranted, and how should this patient be treated?

THE CLINICAL PROBLEM

Heparin-induced thrombocytopenia is a life-threatening disorder that follows exposure to unfractionated or (less commonly) low-molecular-weight heparin. Patients classically present with a low platelet count (<150,000 per cubic millimeter) or a relative decrease of 50 percent or more from baseline, although the fall may be less (e.g., 30 to 40 percent) in some patients. Thrombotic complications develop in approximately 20 to 50 percent of patients.

Heparin-induced thrombocytopenia is caused by antibodies against complexes of platelet factor 4 (PF4) and heparin. These antibodies are present in nearly all patients who receive a clinical diagnosis of the disorder and cause disease in animals. However, they are also present in many patients who have been exposed to heparin in various clinical settings but in whom clinical manifestations do not develop. It is uncertain why complications occur in some patients but not in others.

The time to the onset of thrombocytopenia after the initiation of heparin varies according to the history of exposure. A delay of 5 to 10 days is typical in patients who have had no exposure or who have a remote (more than 100 days) history of exposure. The precipitous declines in platelet counts (within hours) occur in patients with a history of recent exposure to heparin and detectable levels of circulating PF4–heparin antibodies. Platelet counts seldom drop below 10,000 per cubic millimeter, are rarely associated with bleeding, and typically recover within 4 to 14 days after heparin is discontinued, although recovery may take longer in some patients.

In patients with heparin-induced thrombocytopenia, the thrombotic risk is more than 30 times that in control populations. The risk of thrombosis remains high for days to weeks after discontinuation of heparin, even after the platelet count normalizes. Atypical manifestations include heparin-induced skin necrosis, venous gangrene of the limbs, and anaphylactic-type reactions after receipt of an intravenous bolus of heparin.

Among 209 patients for whom platelet counts were available before a diagnosis of thrombosis related to heparin-induced thrombocytopenia was made, 40 per-
cent of the patients had a decrease in the platelet count (greater than 50 percent) before thrombosis occurred, 26 percent presented with concurrent thrombocytopenia and thrombosis, and thrombosis developed in 33 percent one to seven days before an apparent fall in the platelet count. Although in this last group of patients some thrombotic complications developed that might have been related to suboptimal heparin therapy, these data underscore the need to consider heparin-induced thrombocytopenia whenever a new or progressive thrombosis occurs during heparin therapy, regardless of whether the platelet count is reduced.

Thrombotic complications may affect any vascular bed and frequently occur at sites of vascular injury. Venous thromboses predominate in medical and orthopedic patients, whereas arterial and venous thromboses occur at a similar frequency in patients who have undergone cardiac or vascular surgery. Limb ischemia may result in amputation in 5 to 10 percent of patients with heparin-induced thrombocytopenia. Rarely, thromboses occur at unusual sites, such as the adrenal veins or cerebral venous sinuses. The mortality rate is high (8 to 20 percent), regardless of therapy.

It is not clear why thromboses develop in some patients with heparin-induced thrombocytopenia and not in others. In cross-sectional studies in humans, thrombotic manifestations correlate with biochemical markers of platelet activation and increased thrombin generation, and PF4–heparin antibodies have been shown to have platelet-activating effects in studies in animals. Retrospective studies in humans suggest that the thrombotic risk is greater among patients with higher levels of PF4–heparin antibody (an optical density of more than 1.5 on commercial immunoassays) or with a drop in platelet counts of more than 70 percent, or both.

### Strategies and Evidence

#### Incidence

The incidence of heparin-induced thrombocytopenia is variable and is influenced by the heparin formulation and the clinical context in which heparin is administered (Table 1). Prospective studies have documented an incidence of heparin-induced thrombocytopenia among patients treated with unfractionated heparin that was 10 times the incidence among those receiving low-molecular-weight heparin. Heparin-induced thrombocytopenia develops more frequently in patients being treated with low-molecular-weight heparin who have had a recent exposure to unfractionated heparin (within 100 days) than in those who have not had a recent exposure to unfractionated heparin. Although experience is limited, heparin-induced thrombocytopenia has not been reported in association with the pentasaccharide fondaparinux; however, PF4–heparin antibodies have been detected after treatment with this drug.

The incidence of heparin-induced thrombocytopenia appears particularly high after orthopedic surgery (Table 1) and is higher among surgical patients than medical patients. Heparin-induced thrombocytopenia is uncommon among pediatric patients and obstetrical patients and patients receiving long-term hemodialysis.

### Clinical Diagnosis

Establishing a diagnosis of heparin-induced thrombocytopenia in patients with complicated medical conditions can be challenging. Other causes of thrombocytopenia, such as bacterial infection, drugs other than heparin, and bone marrow disease, should be excluded, and platelet counts should recover after the discontinuation of heparin.

Diagnosing heparin-induced thrombocytopenia in patients who have undergone recent cardiac surgery is particularly difficult, since in such patients the prevalence of heparin-dependent antibodies is high (up to 25 to 50 percent), thrombocytopenia is common, and other medications may be administered that could cause thrombocytopenia. Studies suggest that in patients with heparin-induced thrombocytopenia after cardiopulmonary bypass surgery there is a biphasic pattern of platelet recovery, similar to that in other surgical patients, in which a postoperative rise in the platelet count is followed by a new decline.

### Laboratory Diagnosis

When heparin-induced thrombocytopenia is suspected, testing is indicated for heparin-dependent antibodies with the use of serologic or functional assays, or both. Serologic assays are available at most clinical laboratories, and they detect circulating IgG, IgA, and IgM antibodies. Although immunoassays have high sensitivity (greater than 97 percent), their specificity (74 to 86 percent) is
limited by the fact that they also detect PF4–heparin antibodies in patients who do not have heparin-induced thrombocytopenia (Table 1). Thus, the positive predictive value of the immunoassay can be low (range, 10 to 93 percent, depending on the population), but the negative predictive value is high (greater than 95 percent).

The specificity of serologic testing for clinical disease can be improved if only IgG antibodies are measured, but IgG-specific assays are not commercially available.

Functional assays measure platelet activation and detect heparin-dependent antibodies capable of binding to and activating the Fc receptors on platelets. The sensitivity of platelet-aggregation testing is greater than 90 percent at experienced laboratories. Its specificity ranges from 77 to 100 percent, depending on the clinical context of the heparin exposure. An assay measuring the 14C-serotonin release from activated platelets has high sensitivity (88 to 100 percent) and specificity (89 to 100 percent) but is not widely available. Because of the variability in responsiveness among platelet donors to PF4–heparin antibodies, the positive predictive value of functional assays tends to be higher (89 to 100 percent).

Table 1. Incidence of Heparin-Induced Thrombocytopenia (HIT), According to Population at Risk, and Recommendations for Monitoring of Platelet Count.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Risk</th>
<th>Clinical Population at Risk</th>
<th>Incidence of PF4–Heparin Antibodies&lt;sup&gt;a&lt;/sup&gt; percentage</th>
<th>Incidence of HIT</th>
<th>Platelet-Count Monitoring</th>
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| Heparin (new or remote [>100 days] exposure) | High | Patients undergoing orthopedic surgery<sup>1,7</sup> | 14 | 3–5 | At baseline and at least every other day from days 4 to 14 of heparin therapy or until hep 
| | | | | |arin discontinued†‡ |
| | Intermediate | Adults undergoing cardiac surgery<sup>7</sup> Children undergoing cardiac surgery<sup>20</sup> | 25–50 | 1–2 |
| | Intermediate | General medical patients<sup>6,11</sup> Patients with neurologic conditions<sup>23</sup> Patients undergoing percutaneous coronary intervention for acute coronary syndrome<sup>22</sup> Patients undergoing acute hemodialysis<sup>23</sup> | 8–20 | 0.8–3.0 |
| | Low to rare | General pediatric patients<sup>20</sup> Pregnant women<sup>24</sup> Patients undergoing chronic hemodialysis<sup>34</sup> | 0–2.3 | 0–0.1 | Not essential† |
| Low-molecular-weight heparin (new or remote [>100 days] exposure) | Intermediate | Medical patients<sup>6,9</sup> Patients with neurologic conditions<sup>21</sup> Patients undergoing surgical or orthopedic procedures<sup>7</sup> | 2–8 | 0–0.9 | At baseline and every 2 to 4 days after days 4 through 14 of low-molecular weight heparin therapy or until therapy discontinued‡ |
| | Rare | Pregnant women<sup>26</sup> General pediatric patients<sup>20</sup> Unknown | Unknown | 0–0.1 | Routine monitoring not recommended† |
| Heparin or low-molecular-weight heparin (exposure within 100 days) | Unknown | All clinical populations<sup>10</sup> | Unknown | Unknown | At baseline, within 24 hr, and every other day from days 4 through 14 until hep 
| | | | | |arin is discontinued†‡ |

<sup>a</sup> Rates of seropositivity were determined by antigen or serologic enzyme-linked immunosorbent assays.

<sup>†</sup> Recommendations for monitoring platelets are those of the American College of Chest Physicians.<sup>18</sup>

<sup>‡</sup> Recommendations for monitoring platelets are those of the British Committee for Standards in Haematology.<sup>19</sup>
A proposed diagnostic algorithm for patients in whom heparin-induced thrombocytopenia is suspected, based on our clinical experience, is shown in Figure 1. Serologic testing for PF4–heparin antibodies is recommended in patients when the clinical suspicion of heparin-induced thrombocytopenia is high or intermediate, because in such patients, negative results on serologic testing have a high negative predictive value and suggest an alternative diagnosis. Laboratory testing is not advised when there is a low clinical suspicion of heparin-induced thrombocytopenia. A difficult scenario occurs when the patient with an intermediate probability of heparin-induced thrombocytopenia has a positive result on serologic testing. In this setting, a functional assay may be helpful, because a positive result would increase the probability of heparin-induced thrombocytopenia.

MALAGEMENT

The goals of management of heparin-induced thrombocytopenia are to reduce the thrombotic risk by reducing platelet activation and thrombin generation. All sources of heparin, including the heparin solutions that maintain the patency of intravenous lines that are temporarily not in use, should be discontinued when the clinical suspicion of heparin-induced thrombocytopenia is intermediate or high, and alternative anticoagulant therapy should be initiated (Fig. 1). When the clinical suspicion of heparin-induced thrombocytopenia is low, the decision to stop heparin and pursue alternative anticoagulant therapy should be tailored to the patient's condition.

Patients who have heparin-induced thrombocytopenia should not be treated with low-molecular-weight heparins, since these have high cross-reactivity with circulating PF4–heparin antibodies. Warfarin monotherapy in active heparin-induced thrombocytopenia is also contraindicated, on the basis of reports of warfarin-induced skin necrosis and venous gangrene in the limbs. Aspirin, the placement of an inferior venacaval filter, or both are not considered adequate therapies.

Treatment of heparin-induced thrombocytopenia requires anticoagulation with one of two classes of anticoagulant agents (Table 2), direct-thrombin inhibitors or heparinoids. Three direct-thrombin inhibitors are currently available for patients with heparin-induced thrombocytopenia: lepirudin, argatroban, and bivalirudin. These agents directly bind and inactivate thrombin and, unlike heparin, do not require antithrombin. Direct thrombin inhibitors have short half-lives and show no cross-reactivity to heparin. Therapeutic dosing is recommended for patients who have isolated thrombocytopenia or heparin-induced thrombocytopenia with thrombosis.

Lepirudin is a recombinant analogue of hirudin, a leech protein (Table 2). Three prospective, observational studies examined lepirudin in 403 patients and 120 historical controls. In a summary analysis of these studies, the rate of the combined outcome of death, amputation, and thrombosis at 35 days was lower among those receiving lepirudin than among controls (20.3 percent vs. 43 percent, P<0.001). Separate analyses of these outcomes revealed significant differences in the rate of new thrombotic events but not in rates of death or amputation; however, the studies were underpowered for these end points. Bleeding rates were significantly higher among those receiving lepirudin (17.6 percent) than among controls (5.8 percent), and bleeding was the cause of death in 1.2 percent of the treated patients. These observations have led to the reconsideration of the manufacturer’s recommended dosing guidelines, particularly in older patients in whom subclinical renal insufficiency may impair drug clearance.

Antibodies to lepirudin develop in approximately 30 percent of patients after initial exposure and in about 70 percent of patients after repeated exposure. Because fatal anaphylaxis has been reported after sensitization to lepirudin, patients should not be treated with this agent more than once.

Argatroban is a small synthetic compound that binds reversibly to the catalytic site of thrombin. Argatroban was investigated in two prospective, multicenter studies involving a total of 722 patients who have heparin-induced thrombocytopenia. The combined outcome of death, amputation, and thrombosis at 37 days was significantly lower among those receiving argatroban (34 to 35 percent) than among controls (43 percent). As with lepirudin, the benefit was seen largely in the reduction of new thromboembolic complications (10 to 14 percent among those receiving argatroban vs. 25 percent among con-
Thrombocytopenia in a patient receiving heparin or LMWH

High or intermediate clinical suspicion of HIT

Discontinue heparin or LMWH; initiate alternative anticoagulant therapy

Low clinical suspicion of HIT

Heparin or LMWH therapy may be continued

Results of immunoassay

Positive with high suspicion of HIT

HIT confirmed

Positive with intermediate suspicion of HIT

Results of functional assay

Negative with high suspicion of HIT

Consider alternative diagnosis; HIT indeterminate

Negative with intermediate suspicion of HIT

Consider alternative diagnosis; can restart heparin

Consider alternative diagnosis

Positive

HIT likely

Negative

HIT indeterminate

Figure 1. Diagnostic Algorithm to Confirm or Rule Out Heparin-Induced Thrombocytopenia (HIT) in Patients Who Have Not Undergone Bypass Surgery.

Thrombocytopenia can be absolute (platelet count, <150,000 per cubic millimeter) or relative (defined as a decrease in the platelet count of >50 percent from the highest level before the initiation of heparin therapy). The clinical index of suspicion should be based on a temporal association between the start of heparin therapy and the development of thrombocytopenia (typically beginning 5 to 10 days after the start of heparin) or a new thrombosis; the exclusion of other causes of thrombocytopenia (e.g., drugs other than heparin, disseminated intravascular coagulopathy or other consumptive processes, post-transfusion purpura); rebound in the platelet count on discontinuation of heparin; or some combination of these criteria. On the basis of the criteria, the suspicion could be assessed as high when all three criteria are met, intermediate when one or two are met, and low when none are met. Alternatively, the clinical risk can be assessed according to scores based on other criteria.30,32 The decision to initiate alternative anticoagulant therapy should be guided by assessment of the patient’s bleeding risk and coexisting conditions. The decision to continue unfractionated heparin or low-molecular-weight heparin (LMWH) should be tailored to the patient. A functional assay is recommended, where clinically available. Antibodies not specific to PF4-heparin may cause HIT.33 The decision to continue alternative anticoagulant therapy should be individualized.
Rates of serious bleeding did not differ significantly between the two groups. Antibodies to argatroban have not been reported.

Bivalirudin is another synthetic thrombin inhibitor that has been approved by the Food and Drug Administration for percutaneous coronary intervention in patients who have or are at risk for heparin-induced thrombocytopenia (Table 2). Because of its short half-life, bivalirudin is being used more frequently in percutaneous coronary intervention procedures.
investigated as an alternative to heparin for patients with heparin-induced thrombocytopenia who are undergoing cardiopulmonary bypass. Its use in the treatment of heparin-induced thrombocytopenia has not been investigated in clinical trials.

Other Therapies
Another therapy for heparin-induced thrombocytopenia is danaparoid (a mixture of heparan sulfate and dermatan sulfate), which, like heparin, catalyzes antithrombin-mediated inhibition of activated factor X. Danaparoid is not available in the United States, but it is used in Canada, Europe, and Australia. It is the only agent that has been studied in a randomized trial in patients with heparin-induced thrombocytopenia as an alternative antithrombotic agent (as compared with dextran sulfate, an agent used before direct thrombin inhibitors became available). Twenty-five patients were assigned to warfarin plus danaparoid and 17 were assigned to warfarin plus dextran sulfate for at least 72 hours. On the basis of daily clinical assessments, resolution of thrombosis was considered superior with danaparoid, although follow-up imaging was not reported in the study. In a retrospective comparative study of lepirudin and danaparoid, patients with heparin-induced thrombocytopenia (without thrombosis) who received danaparoid at a prophylactic dose were more likely to have a thromboembolic complication than those receiving lepirudin at a therapeutic dose; however, the use of different therapeutic agents limits the value of this observation. More recently, the experience in 1418 patients who received danaparoid for a variety of indications and with the use of multiple dosing regimens was summarized. New thromboses occurred during 9.7 percent of the treatment episodes, and serious bleeding occurred in 8.1 percent of the patients. The rate of cross-reactivity with heparin (identified on serologic testing and clinical assessment as a new or persistent reduction in the platelet count or new or extended thrombosis, or both) was 3.2 percent (Table 2).

Areas of Uncertainty
The clinical significance of heparin-dependent antibodies in the absence of thrombocytopenia or thrombosis, which is particularly common in patients who have undergone cardiac surgery, is unknown. At present, no treatment is recommended for patients with positive results on antibody testing without other disease manifestations.
Unlike the duration of the response to most drug-dependent antibodies, the immune response to heparin appears to be transient. PF4–heparin antibodies disappear from the circulation within a median of 85 days. Although there are reports of limited repeated exposure to heparin in patients in whom the antibodies cleared, concern remains regarding repeated exposure to heparin in those who have had heparin-induced thrombocytopenia. Although rigorous data are lacking, patients should receive alternative anticoagulant agents for most indications. For certain procedures, such as cardiac bypass surgery, the use of direct thrombin inhibitors poses a considerable bleeding risk, and it is recommended that patients with a remote history of heparin-induced thrombocytopenia who have negative tests for PF4–heparin antibodies receive anticoagulant therapy with heparin during the procedure, with an alternative anticoagulant agent used postoperatively, if required.  

GUIDELINES

The guidelines of the American College of Chest Physicians (ACCP) and the Hemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology for monitoring and management of heparin-induced thrombocytopenia are generally similar, but they differ with respect to monitoring platelet counts in different patient populations receiving heparin and low-molecular-weight heparin (Table 1). The recommendations presented in this article are in general agreement with those of the ACCP.

REFERENCES

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has new thrombocytopenia and had a thromboembolic event several days after heparin exposure during cardiac surgery, a scenario that is highly suggestive of heparin-induced thrombocytopenia. Other causes of thrombocytopenia (medications other than heparin or infection) should be ruled out. Measurement of PF4–heparin antibodies is warranted and is likely to be confirmatory, although it should be recognized that tests for antibodies may be positive in the absence of clinical manifestations of heparin-induced thrombocytopenia. We would treat this patient with a direct thrombin inhibitor until his platelet counts recover, followed by overlap with the initiation of warfarin therapy. Although data are lacking to guide the optimal duration of treatment for thrombosis related to heparin-induced thrombocytopenia, oral anticoagulant therapy should be continued for three to six months. Documentation of heparin-induced thrombocytopenia should be included in the patient’s medical record, and future exposure to heparin should generally be avoided.

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