

CLINICAL PRACTICE

Heparin-Induced Thrombocytopenia

Gowthami M. Arepally, M.D., and Thomas L. Ortel, M.D., Ph.D.

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,^{1,2} 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.²⁻⁴

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^{5,6} 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.^{1,7-9} 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, whereas 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.¹⁰ 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,⁴ 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.¹¹ The risk of thrombosis remains high for days to weeks after discontinuation of heparin, even after the platelet count normalizes.³ Atypical manifestations include heparin-induced skin necrosis, venous gangrene of the limbs, and anaphylactic-type reactions after receipt of an intravenous bolus of heparin.¹²

Among 209 patients for whom platelet counts were available before a diagnosis of thrombosis related to heparin-induced thrombocytopenia was made,² 40 per-

From the Department of Medicine, Division of Hematology (G.M.A., T.L.O.), and the Department of Pathology (T.L.O.), Duke University Medical Center, Durham, N.C. Address reprint requests to Dr. Ortel at the Hemostasis and Thrombosis Center, Duke University Health System, Box 3422, Stead Bldg., Rm. 0563, Durham, NC 27710, or at thomas.ortel@duke.edu.

N Engl J Med 2006;355:809-17.
Copyright © 2006 Massachusetts Medical Society.

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.¹³ 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.² Limb ischemia may result in amputation in 5 to 10 percent of patients with heparin-induced thrombocytopenia.^{14,15} 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.^{14,15}

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,¹⁶ 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)¹⁷ or with a drop in platelet counts of more than 70 percent, or both.^{2,17}

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.²⁷ 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.⁹ 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.²⁸

The incidence of heparin-induced thrombocytopenia appears particularly high after orthopedic surgery⁷ (Table 1) and is higher among surgical patients than medical patients.⁸ Heparin-induced thrombocytopenia is uncommon among pediatric patients²⁰ and obstetrical patients²⁴ and patients receiving long-term hemodialysis.²⁵

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.²⁹

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

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

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

* Rates of seropositivity were determined by antigen or serologic enzyme-linked immunosorbent assays.

† Recommendations for monitoring platelets are those of the American College of Chest Physicians.¹⁸

‡ Recommendations for monitoring platelets are those of the British Committee for Standards in Haematology.¹⁹

limited by the fact that they also detect PF4–heparin antibodies in patients who do not have heparin-induced thrombocytopenia (Table 1).^{6,7,30} Thus, the positive predictive value of the immunoassay can be low (range, 10 to 93 percent, depending on the population),^{30,31} but the negative predictive value is high (greater than 95 percent).^{30,32} The specificity of serologic testing for clinical disease can be improved if only IgG antibodies are measured,⁶ 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.¹⁸ Its specificity ranges from 77 to 100 percent, depending on the clinical context of the heparin exposure.^{18,30} 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.^{6,18,30} 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) than the negative predictive value (81 percent).³⁰

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.^{6,32} Laboratory testing is not advised when there is a low clinical suspicion of heparin-induced thrombocytopenia.^{6,30} 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.³⁰

MANAGEMENT

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.¹⁸ 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.³⁴ Aspirin, the placement of an inferior vena caval 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.¹⁸ 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^{36,40,41} examined lepirudin in 403 patients and 120 historical controls. In a summary analysis of these studies,¹⁵ 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.¹⁵ 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.^{15,35,36}

Antibodies to lepirudin develop in approximately 30 percent of patients after initial exposure and in about 70 percent of patients after repeated exposure.¹⁵ Because fatal anaphylaxis has been reported after sensitization to lepirudin,⁴² 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.^{14,43} 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).^{14,43} 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-

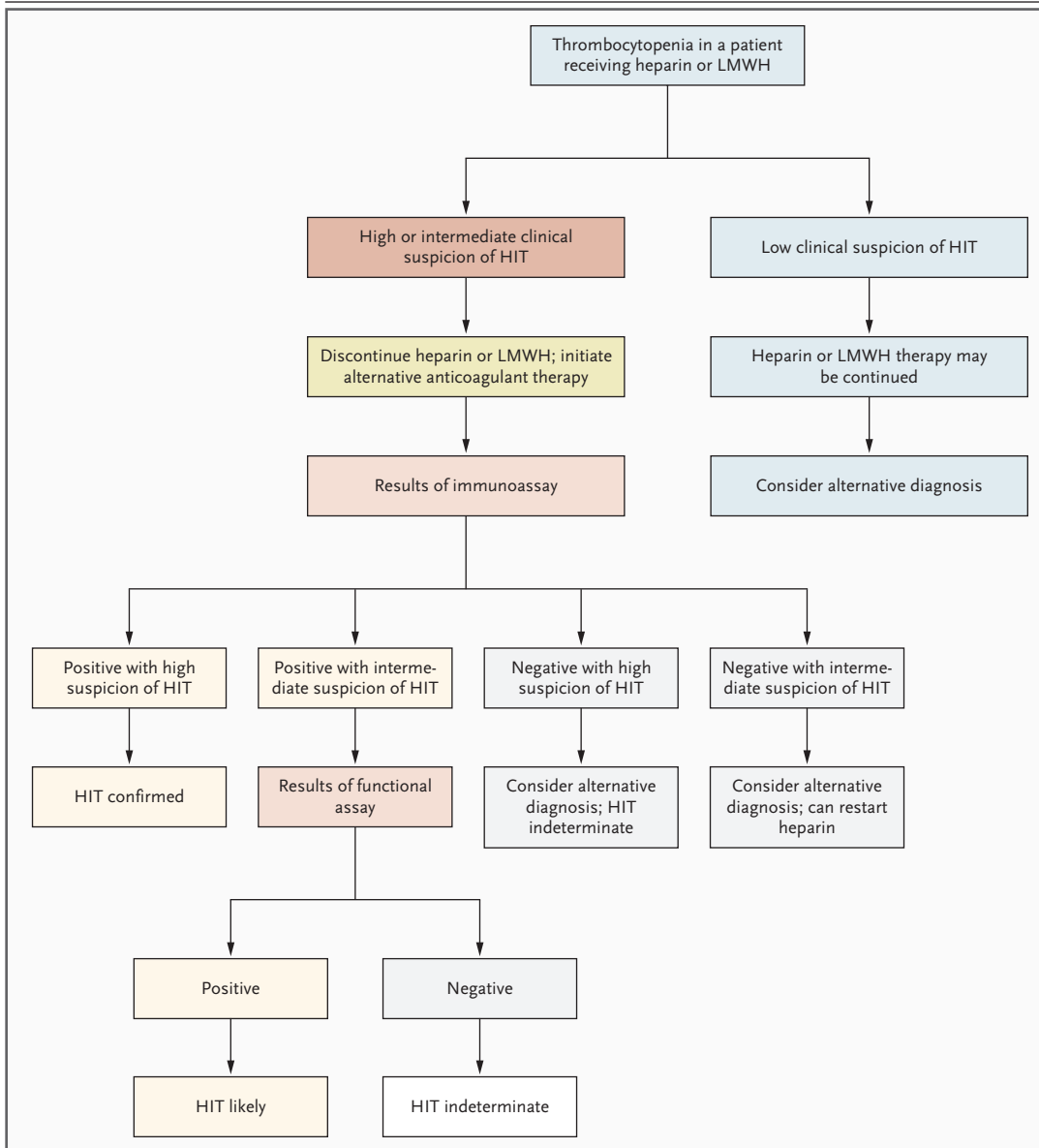


Figure 1. Diagnostic Algorithm to Confirm or Rule Out Heparin-Induced Thrombocytopenia (HIT) in Patients Who Have Not Undergone Bypass Surgery.

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.

Table 2. Alternatives to Heparin for the Treatment of Heparin-Induced Thrombocytopenia.*

Agent	Clearance	Therapeutic Dose	Monitoring	Adverse Effects
Direct thrombin inhibitors				
Lepirudin (Refludan, Berlex)†	Renal	IV, 0.4 mg/kg of body weight (up to 110 kg); IV bolus‡ followed by 0.15 mg/kg/hr (up to 110 kg) (maximal initial bolus, 44 mg; maximal initial infusion, 16.5 mg/hr)	Measure aPTT 2 hr after therapy started and after each dose adjustment; therapeutic range, 1.5 to 2.5 times the baseline value (optimal aPTT, <65 sec§); check baseline PT before switching therapy to warfarin¶	Bleeding with therapeutic dose in 17.6% of patients; antilepirudin antibodies develop in 30% of patients
Argatroban (Novastan, GlaxoSmithKline)†	Hepatic	2 µg/kg/min continuous infusion (maximal infusion, 10 µg/kg/min)	Measure aPTT 2 hr after initiation of therapy and after each dose adjustment; therapeutic range, 1.5 to 3 times the baseline value (not to exceed 100 sec); switching to warfarin complicated by baseline prolongation of the PT	Bleeding with therapeutic dose in 6 to 7% of patients
Bivalirudin (Angiomax, The Medicines Company)**	Enzymatic (80%) and renal (20%)	For PCI, 0.75 mg/kg IV bolus followed by 1.75 mg/kg/hr for remainder of procedure; infusion may be continued for 4 hr after the procedure or administered as low-dose infusion (0.2 mg/kg/hr) for an additional 20 hr	Measure ACT 5 min after completing IV bolus	Bleeding with dose used in PCI in 2.4% of patients
Anti-factor Xa therapy				
Danaparoid (Orgaran, Diosynth)††	Renal	IV, 2250 U bolus followed by 400 U/hr for 4 hr, then 300 U/hr for 4 hr, then 150 to 200 U/hr	Not required, but if needed, maintain anti-factor Xa level, 0.5 to 0.8 U/ml	Bleeding with therapeutic dose in 8.1% of patients; cross-reactivity with PF4-heparin antibodies in 3.2% of patients

* Except where indicated, the guidelines for dosing and monitoring are from the manufacturers of the drugs. Guidelines for therapeutic dosing are for intravenous (IV) infusion, except for bivalirudin, which is used in patients undergoing percutaneous coronary intervention (PCI). The guidelines of the American College of Chest Physicians recommend overlap use of direct thrombin-inhibitor therapy and warfarin therapy for more than 5 days,¹⁸ whereas the Hemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology recommends overlap use of direct thrombin-inhibitor therapy and warfarin therapy until the international normalized ratio (INR) is at a therapeutic level for at least 48 hours.¹⁹ PT denotes prothrombin time, aPTT activated partial-thromboplastin time, and ACT activated clotting time.

† These drugs have been approved in the United States for the treatment of heparin-induced thrombocytopenia.

‡ Bolus therapy is not advised in older patients or patients with renal insufficiency.³⁵

§ This value is the maximal aPTT recommended by Lubenow et al.³⁶

¶ Therapeutic lepirudin may prolong the baseline PT slightly, but it generally does not interfere with conversion from lepirudin to warfarin therapy. If the PT is prolonged by more than a few seconds, further evaluation should be undertaken before initiating warfarin.

|| Combined anticoagulant therapy with argatroban and warfarin produces an INR response that is significantly greater than that obtained with warfarin alone. To change therapy from argatroban to warfarin for outpatient anticoagulant therapy, the INR should be monitored daily and, when the INR is greater than 4, the argatroban infusion should be withheld and the INR rechecked to determine whether it is therapeutic.³⁷ An alternative strategy would be to use a chromogenic factor X assay to monitor warfarin therapy while the patient is also receiving argatroban.

** This drug has been approved in the United States for the treatment of patients undergoing percutaneous coronary intervention who have heparin-induced thrombocytopenia or a history of heparin-induced thrombocytopenia.³⁸

†† This drug is not available in the United States.³⁹

trols, $P < 0.05$), but was not seen regarding death or amputation.^{14,43} Rates of serious bleeding did not differ significantly between the two groups.^{14,43} Antibodies to argatroban have not been reported.

Bivalirudin is another synthetic thrombin in-

hibitor 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

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).⁴⁴ 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.⁴⁴ 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.⁴⁵ 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.³⁹ 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).³⁹

Clinical trials are lacking comparing these agents with one another, and meaningful comparisons of clinical trials of individual agents are not possible because of differences in study design and patient populations. Consequently, the choice of alternative anticoagulant therapy should

be tailored to the patient, taking into account the availability of the drug, the patient's hepatic function and renal function, the need for a surgical procedure, and drug-specific features, such as prior exposure to lepirudin.

Duration of Therapy and Use of Oral Anticoagulants

The duration of alternative anticoagulant therapy and the subsequent use of oral anticoagulants depend on whether the patient has had a thrombotic event. For patients with isolated thrombocytopenia, therapeutic doses of alternative anticoagulants are recommended until the platelet counts recover to a stable plateau, if not to baseline values.¹⁸ Because the risk of thrombosis remains high for two to four weeks after treatment is initiated,^{3,46,47} consideration should be given to continuing anticoagulant therapy with an alternative agent or warfarin for up to four weeks. Further study is needed to determine the optimal duration of therapy.

For patients who have heparin-induced thrombocytopenia and thrombosis, therapy with an alternative anticoagulant should be followed by a transition to warfarin, but only after platelet counts have recovered to above 150,000 per cubic millimeter. Oral anticoagulants should be initiated at low doses and overlap with a direct thrombin inhibitor for at least 5 days and until the international normalized ratio (INR) is therapeutic for at least 48 hours; these recommendations are based on case reports of warfarin-induced venous gangrene in the limbs, skin necrosis occurring during shorter periods of overlap therapy, or both.¹⁸ Because direct thrombin inhibitors variably prolong the prothrombin time,⁴⁸ clinicians should follow the manufacturer's guidelines for monitoring warfarin overlap therapy and repeat measurement of the INR after discontinuing the thrombin inhibitor (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,⁷ 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.¹⁰ Although there are reports of limited repeated exposure to heparin in patients in whom the antibodies cleared,⁴⁹ 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.^{18,19}

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^{18,19} 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.

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.

Supported by the Louise and Gustavus Pfeiffer Foundation and a Beginning Grant-in-Aid from the American Heart Association (to Dr. Arepally); a cooperative agreement (U18DD00014) with the Hematologic Diseases Branch, Centers for Disease Control and Prevention (to Dr. Ortel); and grants (HL077878, HL072289, HL081395) from the National Institutes of Health (to Drs. Ortel and Arepally).

Dr. Ortel reports having received lecture fees from GlaxoSmithKline and holding equity in Zycare. Dr. Arepally reports having received lecture fees from GlaxoSmithKline. No other potential conflict of interest relevant to this article was reported.

REFERENCES

- Warkentin TE, Roberts RS, Hirsh J, Kelton JG. An improved definition of immune heparin-induced thrombocytopenia in postoperative orthopedic patients. *Arch Intern Med* 2003;163:2518-24.
- Greinacher A, Farner B, Kroll H, Kohlmann T, Warkentin TE, Eichler P. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis: a retrospective analysis of 408 patients. *Thromb Haemost* 2005;94:132-5.
- Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. *Am J Med* 1996;101:502-7.
- Wallis DE, Workman DL, Lewis BE, Steen L, Pifarre R, Moran JF. Failure of early heparin cessation as treatment for heparin-induced thrombocytopenia. *Am J Med* 1999;106:629-35.
- Amiral J, Bridey F, Dreyfus M, et al. Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. *Thromb Haemost* 1992;68:95-6.
- Warkentin TE, Sheppard J-AI, Moore JC, Moore KM, Sigouin CS, Kelton JG. Laboratory testing for the antibodies that cause heparin-induced thrombocytopenia: how much class do we need? *J Lab Clin Med* 2005;146:341-6.
- Warkentin TE, Sheppard JA, Horsewood P, Simpson PJ, Moore JC, Kelton JG. Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood* 2000;96:1703-8.
- Lindhoff-Last E, Nakov R, Misselwitz F, Breddin HK, Bauersachs R. Incidence and clinical relevance of heparin-induced antibodies in patients with deep vein thrombosis treated with unfractionated or low-molecular-weight heparin. *Br J Haematol* 2002;118:1137-42.
- Prandoni P, Siragusa S, Girolami B, Fabris F. The incidence of heparin-induced thrombocytopenia in medical patients treated with low-molecular-weight heparin: a prospective cohort study. *Blood* 2005;106:3049-54.
- Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med* 2001;344:1286-92.
- Girolami B, Prandoni P, Stefani PM, et al. The incidence of heparin-induced throm-

- bocytopenia in hospitalized medical patients treated with subcutaneous unfractionated heparin: a prospective cohort study. *Blood* 2003;101:2955-9.
12. Warkentin TE, Roberts RS, Hirsh J, Kelton JG. Heparin-induced skin lesions and other unusual sequelae of the heparin-induced thrombocytopenia syndrome: a nested cohort study. *Chest* 2005;127:1857-61.
13. Hong AP, Cook DJ, Sigouin CS, Warkentin TE. Central venous catheters and upper-extremity deep-vein thrombosis complicating immune heparin-induced thrombocytopenia. *Blood* 2003;101:3049-51.
14. Lewis BE, Wallis DE, Berkowitz SD, et al. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. *Circulation* 2001;103:1838-43.
15. Lubenow N, Eichler P, Lietz T, Greinacher A. Lepirudin in patients with heparin-induced thrombocytopenia — results of the third prospective study (HAT-3) and a combined analysis of HAT-1, HAT-2, and HAT-3. *J Thromb Haemost* 2005;3:2428-36.
16. Kelton JG. The pathophysiology of heparin-induced thrombocytopenia: biological basis for treatment. *Chest* 2005;127: Suppl:9S-20S.
17. Fabris F, Luzzatto G, Soini B, et al. Risk factors for thrombosis in patients with immune mediated heparin-induced thrombocytopenia. *J Intern Med* 2002;252: 149-54.
18. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126:Suppl:311S-337S. [Erratum, *Chest* 2005; 127:416.]
19. Keeling D, Davidson S, Watson H. The management of heparin-induced thrombocytopenia. *Br J Haematol* 2006;133:259-69.
20. Klenner AF, Lubenow N, Raschke R, Greinacher A. Heparin-induced thrombocytopenia in children: 12 new cases and review of the literature. *Thromb Haemost* 2004;91:719-24.
21. Pohl C, Kredteck A, Bastians B, Hanfland P, Klockgether T, Harbrecht U. Heparin-induced thrombocytopenia in neurologic patients treated with low-molecular-weight heparin. *Neurology* 2005; 64:1285-7.
22. Matsuo T, Tomaru T, Kario K, Hirokawa T. Incidence of heparin-PF4 complex antibody formation and heparin-induced thrombocytopenia in acute coronary syndrome. *Thromb Res* 2005;115:475-81.
23. Yamamoto S, Koide M, Matsuo M, et al. Heparin-induced thrombocytopenia in hemodialysis patients. *Am J Kidney Dis* 1996;28:82-5.
24. Fausett MB, Vogtlander M, Lee RM, et al. Heparin-induced thrombocytopenia is rare in pregnancy. *Am J Obstet Gynecol* 2001;185:148-52.
25. O'Shea SI, Sands JJ, Nudo SA, Ortel TL. Frequency of anti-heparin-platelet factor 4 antibodies in hemodialysis patients and correlation with recurrent vascular access thrombosis. *Am J Hematol* 2002;69:72-3.
26. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood* 2005; 106:401-7.
27. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood* 2005;106:2710-5.
28. Warkentin TE, Cook RJ, Marder VJ, et al. Anti-platelet factor 4/heparin antibodies in orthopedic surgery patients receiving antithrombotic prophylaxis with fondaparinux or enoxaparin. *Blood* 2005;106: 3791-6.
29. Lillo-Le Louet A, Boutouyrie P, Alhenc-Gelas M, et al. Diagnostic score for heparin-induced thrombocytopenia after cardiopulmonary bypass. *J Thromb Haemost* 2004;2:1882-8.
30. Poupard C, Amiral J, Borg JY, Laporte-Simitsidis S, Delahousse B, Gruel Y. Decision analysis for use of platelet aggregation test, carbon 14-serotonin release assay, and heparin-platelet factor 4 enzyme-linked immunosorbent assay for diagnosis of heparin-induced thrombocytopenia. *Am J Clin Pathol* 1999;111:700-6.
31. Verma AK, Levine M, Shalansky SJ, Carter CJ, Kelton JG. Frequency of heparin-induced thrombocytopenia in critical care patients. *Pharmacotherapy* 2003;23: 745-53.
32. Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost* 2006;4:759-65.
33. Amiral J, Marfaing-Koka A, Wolf M, et al. Presence of autoantibodies to interleukin-8 or neutrophil-activating peptide-2 in patients with heparin-associated thrombocytopenia. *Blood* 1996;88:410-6.
34. Warkentin TE, Elavathil LJ, Hayward CP, Johnston MA, Russett JJ, Kelton JG. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. *Ann Intern Med* 1997; 127:804-12.
35. Tardy B. Predictive factors for thrombosis and major bleeding in an observational study in 181 patients with heparin-induced thrombocytopenia treated with lepirudin. *Blood* (in press).
36. Lubenow N, Eichler P, Lietz T, Farner B, Greinacher A. Lepirudin for prophylaxis of thrombosis in patients with acute isolated heparin-induced thrombocytopenia: an analysis of 3 prospective studies. *Blood* 2004;104:3072-7.
37. Sheth SB, DiCicco RA, Hursting MJ, Montague T, Jorkasky DK. Interpreting the International Normalized Ratio (INR) in individuals receiving argatroban and warfarin. *Thromb Haemost* 2001;85:435-40.
38. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003;289:853-63. [Erratum, *JAMA* 2003;289:1638.]
39. Magnani HN, Gallus A. Heparin-induced thrombocytopenia (HIT): a report of 1,478 clinical outcomes of patients treated with danaparoid (Orgaran) from 1982 to mid-2004. *Thromb Haemost* 2006; 95:967-81.
40. Greinacher A, Janssens U, Berg G, et al. Lepirudin (recombinant hirudin) for parenteral anticoagulation in patients with heparin-induced thrombocytopenia. *Circulation* 1999;100:587-93.
41. Greinacher A, Volpel H, Janssens U, et al. Recombinant hirudin (lepirudin) provides safe and effective anticoagulation in patients with heparin-induced thrombocytopenia: a prospective study. *Circulation* 1999;99:73-80.
42. Greinacher A, Lubenow N, Eichler P. Anaphylactic and anaphylactoid reactions associated with lepirudin in patients with heparin-induced thrombocytopenia. *Circulation* 2003;108:2062-5.
43. Lewis BE, Wallis DE, Leya F, Hursting MJ, Kelton JG. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. *Arch Intern Med* 2003; 163:1849-56.
44. Chong BH, Gallus AS, Cade JF, et al. Prospective randomised open-label comparison of danaparoid with dextran 70 in the treatment of heparin-induced thrombocytopenia with thrombosis: a clinical outcome study. *Thromb Haemost* 2001;86: 1170-5.
45. Farner B, Eichler P, Kroll H, Greinacher A. A comparison of danaparoid and lepirudin in heparin-induced thrombocytopenia. *Thromb Haemost* 2001;85:950-7.
46. Warkentin TE, Kelton JG. Delayed-onset heparin-induced thrombocytopenia and thrombosis. *Ann Intern Med* 2001; 135:502-6.
47. Rice LMD, Attisha WKMD, Drexler AMSRN, Francis JLP. Delayed-onset heparin-induced thrombocytopenia. *Ann Intern Med* 2002;136:210-5.
48. Warkentin TE, Greinacher A, Craven S, Dewar L, Sheppard JA, Ofosu FA. Differences in the clinically effective molar concentrations of four direct thrombin inhibitors explain their variable prothrombin time prolongation. *Thromb Haemost* 2005;94:958-64.
49. Potzsch B, Klovekorn WP, Madlener K. Use of heparin during cardiopulmonary bypass in patients with a history of heparin-induced thrombocytopenia. *N Engl J Med* 2000;343:515.

Copyright © 2006 Massachusetts Medical Society.