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An elderly woman with leg swelling and pain

A 70-YEAR-OLD WOMAN presents to her primary care physician with a 3-day history of painful swelling of her right leg. She has no fever, chills, or chest pain, and has not traveled recently. She has had back pain for the last 10 days, which has made her almost immobile. Her medical history includes hypertension and hyperlipidemia. She has never smoked. She consumes alcohol socially.

She has no family history of thromboembolic disease. Her father has a history of myocardial infarction. She has three children and two sisters. She takes acetaminophen as needed for pain.

Physical examination

The patient is afebrile, with respiratory rate 16, heart rate 86, blood pressure 140/85 mm Hg, and oxygen saturation 94% by pulse oximetry while breathing room air.

Cardiovascular examination is within normal limits. Lungs are clear with good expansion. The right calf is swollen and tender. Pulses in the lower extremities are palpable bilaterally. No lymphadenopathy or organomegaly is noted. Rectal examination and stool guaiac testing are negative.

Laboratory tests

- White blood cell count $11.9 \times 10^9/L$ (normal 4.0–11.0)
- Hemoglobin 13.2 g/dL (normal 12.0–16.0)
- Platelet count $230 \times 10^9/L$ (normal 150–400)
- Prothrombin time (PT) and activated partial thromboplastin time are within normal limits.

Hospital course

The patient is taken to the emergency department. Duplex ultrasonography shows a dilated, noncompressible femoral vein in the mid-thigh and popliteal segment of the right leg. A continuous infusion of unfractionated heparin is started. Elevation of the right leg is initiated. On day 4 the swelling and erythema of the leg significantly improve. However, on day 6 her platelet count is $60 \times 10^9/L$.

DIFFERENTIAL DIAGNOSIS

1 What is the most likely cause of thrombocytopenia in this patient?

- Disseminated intravascular coagulation (DIC)
- Thrombotic thrombocytopenic purpura (TTP)
- Heparin-induced
- Factor V Leiden mutation

Heparin is the most likely cause. Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening adverse reaction to unfractionated or low-molecular-weight heparin exposure (TABLE 1).

In 10% to 20% of patients who receive heparin, mild thrombocytopenia develops within the first 1 to 3 days and spontaneously resolves without stopping heparin. Referred to as type 1 HIT, this condition is thought to be benign; it is not mediated by an antibody, and does not convey a thrombotic risk.¹

Type 2 HIT is more serious and is one of the most common immune-mediated adverse drug reactions, characterized by a significant fall in the platelet count and the presence of antibodies against the heparin-platelet factor

She has no family history of thromboembolic disease

TABLE 1

Characteristics of heparin-induced thrombocytopenia (HIT)

Type 1

Benign form of thrombocytopenia
Early onset
Not immune-mediated
Resolves even with persistent heparin treatment

Type 2

Most severe complication of heparin therapy
Immune-mediated (induced by immunoglobulin G)
Usually has a delayed onset (after 4 to 5 days of heparin treatment)
Persistence or brutal aggravation until cessation of heparin

Type 1 HIT is benign, arises early, and resolves despite continued heparin therapy

IV complex. It typically occurs 4 to 5 days after the start of heparin therapy.² The amount of heparin required to cause HIT can be quite small.

The frequency of type 2 varies considerably and probably is related to differences in heparin preparations. It occurs in 1% to 3% of patients receiving therapeutic doses of unfractionated heparin, but much less often with low-molecular-weight heparin.^{1,3} It can be regarded as a prothrombotic state, based on the greatly elevated levels of thrombin-antithrombin complexes.^{4,5}

Current criteria for type 2 HIT include a platelet count less than $100 \times 10^9/L$; any decrease from the baseline count that occurs no sooner than the 4th or 5th day after first heparin exposure, in the absence of other explanations for a diminished platelet count; or a 30% drop in the platelet count along with an objectively documented thrombotic event.^{6,7}

Disseminated intravascular coagulation

DIC presents primarily with extensive skin and mucous membrane bleeding from surgical incisions or venipuncture or catheter sites. Less often, the patient presents with pregangrenous changes in digits, genitalia, and nose. The laboratory manifestations include:

- Thrombocytopenia and the presence of schistocytes or fragmented red blood cells that arise from cell trapping and damage within fibrin thrombi
- Prolonged PT and thrombin time and a

reduced fibrinogen level from depletion of coagulation proteins

- Elevated fibrin degradation products from intense secondary fibrinolysis.

Usually, patients with DIC are much sicker than the above patient. DIC has been said to be associated with HIT in 15% of cases.

Thrombotic thrombocytopenic purpura

TTP is a fulminant, often lethal disorder that may be initiated by endothelial injury and subsequent release of von Willebrand factor and other procoagulant materials from the endothelial cell.

The classic TTP pentad consists of thrombocytopenia, microangiopathic hemolytic anemia, neurologic symptoms, renal function abnormalities, and fever, although all of these need not be present for the diagnosis. It is not associated with large vein thrombosis.

TTP has been associated with the use of mitomycin C, tamoxifen, bleomycin, cytosine arabinoside, and daunomycin. Noncancer chemotherapeutic and other drugs suspected of causing TTP include immunosuppressive agents (eg, cyclosporine A), crack cocaine, ticlopidine, clopidogrel, oral contraceptives, penicillin, and rifampin.

Factor V Leiden mutation

Factor V Leiden mutation is the most common cause of hereditary thrombophilia. The major clinical manifestation is deep vein thrombosis with or without pulmonary embolism. It is usually not accompanied by thrombocytopenia.

CHOOSING A LABORATORY TEST

2 Which test is most helpful at this point to diagnose HIT?

- Antiphospholipid antibody assay
- Antinuclear antibody assay
- Mixing study
- Antiplatelet factor IV antibody assay

In patients who have never received heparin, giving heparin or low-molecular-weight heparin for 4 or more days can trigger an antibody response to the complex of heparin and platelet factor IV. Immunoglobulin G (IgG) and IgM antibodies are provoked by the com-



plex of heparin and platelet factor IV on the platelet surface.⁸

Laboratory assays for antiplatelet factor IV help confirm the diagnosis of HIT. The heparin-induced platelet aggregation test or the serotonin release assay, with or without an additional antigen assay such as the enzyme-linked immunosorbent assay (ELISA), detects antibodies to the heparin-platelet factor IV complex. For the detection of HIT, the serotonin release assay has a sensitivity of 88%, a specificity of about 100%, a positive predictive value of about 100%, and a negative predictive value of about 81%.^{9,10} The ELISA has a sensitivity of 97%, a specificity of 86%, a positive predictive value of 93%, and a negative predictive value of 95%.

Antiphospholipid antibodies belong to the family of antibodies that react with negatively charged phospholipids. The antiphospholipid antibody syndrome includes arterial or venous thrombosis in the presence of antiphospholipid antibodies or a lupus anticoagulant. This predominantly affects women of reproductive age (ie, 15 to 55 years).

Antinuclear antibodies are, by definition, present in some systemic autoimmune disorders. The mixing study is indicated when the partial thromboplastin time is prolonged in the absence of heparin therapy. But neither antinuclear antibody testing nor a mixing study is helpful in a patient with the above history of acute thrombocytopenia after starting heparin.

■ COMPLICATIONS OF TYPE 2 HIT

3 Which of the following is the most common complication of immune-mediated heparin-induced thrombocytopenia (type 2 HIT)?

- Bleeding
- Thrombosis
- Hypotension
- Fever

Thrombosis is the most common and can produce devastating complications, including necrosis of the extremities, stroke, myocardial infarction, and pulmonary embolism (TABLE 2). Indeed, pulmonary embolism occurs more often than all arterial thrombotic events com-

TABLE 2

Criteria for identifying heparin-induced thrombocytopenia with thrombosis

- Heparin exposure > 4 days (in patients without prior heparin exposure)
- Decrease in platelet count by 50% from baseline OR decrease in platelet count to less than $100 \times 10^9/L$
- Absence of other causes of thrombocytopenia
- Development of new or extension of existing thrombosis while receiving heparin therapy
- Confirmation by laboratory testing
- Return to normal platelet count when heparin is discontinued

bined.¹¹ Lower-extremity deep vein thrombosis is the most frequent thrombotic manifestation of type 2 HIT.

Some studies suggest that the heparin-platelet factor IV antibody complex may also promote thrombosis by inducing the production of tissue factor by monocytes.¹² HIT is associated with platelet activation. This may explain why HIT is uniquely associated with thrombosis rather than bleeding. Thrombocytopenia due to immune-mediated HIT is rarely severe, with platelet counts typically above $20 \times 10^9/L$, so spontaneous bleeding is unusual.

Antibodies are generally not detectable 50 to 85 days after heparin is stopped. Recent studies indicate that HIT antibody formation does not recur more quickly or more often in patients with previous HIT, and there is no anamnestic response against HIT antigens.¹³ Under special circumstances, a patient with a remote history of type 2 HIT may be safely re-exposed to heparin for short periods if no antibodies are detectable. This should be done under direct supervision of a physician familiar with the disease.³

4 Which one of the following is the next best step?

- Discontinue heparin and start a direct thrombin inhibitor
- Discontinue heparin and start warfarin
- Discontinue heparin and give protamine
- Do not discontinue heparin because the thrombocytopenia is self-limited

Confirm HIT with serologic testing

Management of heparin-induced thrombocytopenia

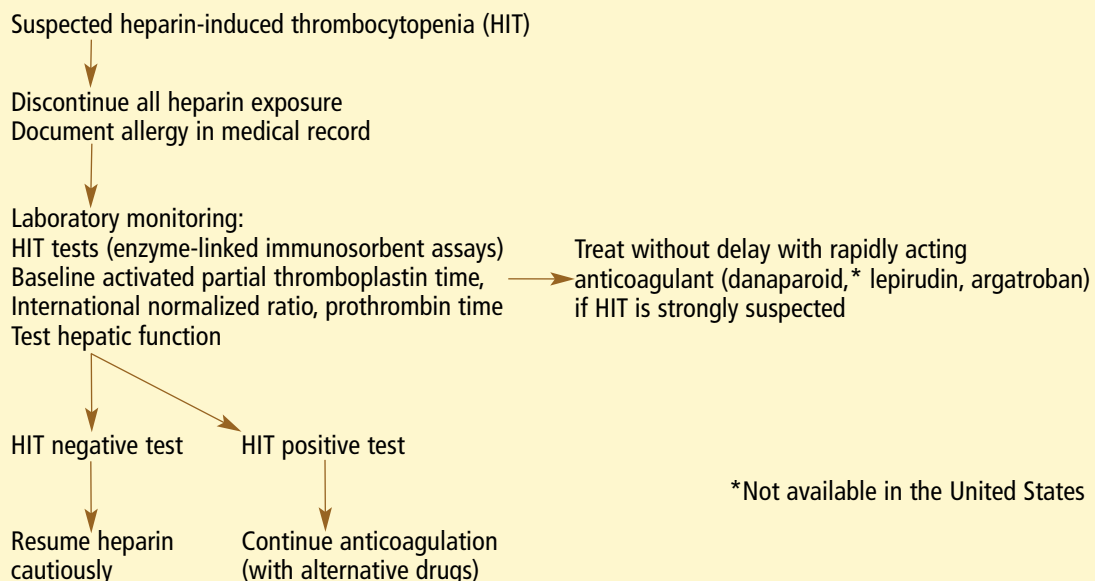


FIGURE 1

The first intervention should be to immediately stop all exposure to heparin, including heparin flushes, and then to start thrombin inhibitor therapy (FIGURE 1).

Warfarin should not be given to patients who already have HIT until the thrombocytopenia resolves. Warfarin in the absence of other anticoagulants should be avoided in patients with HIT until the platelet count rises above $100 \times 10^9/L$.¹⁴ Because of its early effects on protein C, warfarin can precipitate venous limb gangrene and limb loss in the extreme prothrombotic milieu of type 2 HIT.

Protamine has no use in the management of type 2 HIT. Usually the thrombocytopenia in type 1 HIT is self-limiting. Any form of heparin must be discontinued immediately in any patient suspected of having type 2 HIT.

5 All the following can be used after stopping heparin in this patient, except which one?

- Lepirudin
- Danaparoid
- Low-molecular-weight heparin
- Argatroban

Low-molecular-weight heparin should be avoided, since there is a high incidence of cross-reactivity between low-molecular-weight heparin and unfractionated heparin antibodies.

Alternatives to heparin are listed in TABLE 3. Unless it is contraindicated, all patients with recently diagnosed HIT require treatment with a direct thrombin inhibitor, eg, recombinant hirudin, bivalirudin, or argatroban. These agents should also be considered for prophylactic therapy in patients with HIT without thrombosis until the platelet count has recovered.

Danaparoid is an anticoagulant that was withdrawn from the US market in April 2002.

6 Which one of the following statements is false?

- In patients with a history of HIT who require cardiopulmonary bypass, anticoagulation with unfractionated heparin is effective and free of complications
- Recombinant hirudin has been used in different studies as a possible alternative to heparin in cardiopulmonary bypass patients with HIT
- Disadvantages of danaparoid include

Treat with a direct thrombin inhibitor without delay if HIT is strongly suspected

**TABLE 3****Alternatives to heparin**

	ARGATROBAN	DANAPAROID*	LEPIRUDIN	BIVALIRUDIN
Mechanism of action	Synthetic direct thrombin inhibitor (reversible)	Heparinoid with anti-factor Xa activity (irreversible)	Direct thrombin inhibitor (irreversible)	Direct thrombin inhibitor (reversible)
Route of administration	Intravenous	Intravenous	Intravenous	Intravenous
Elimination half-life	40–50 minutes	25 hours	1.3 hours	Approximately 25 minutes
Elimination	Hepatic	Mainly renal	Renal (stop treatment if creatinine clearance is < 15 mL/min)	Renal
US Food and Drug Administration indications	Prevention or treatment of thrombosis in heparin-induced thrombocytopenia (HIT) type	Prevention of postoperative deep vein thrombosis after elective hip surgery, although approved in some countries for treatment of type 2 HIT	Treatment of HIT and HIT with thrombosis	For patients undergoing coronary angioplasty with unstable angina and concomitant aspirin therapy
Anticoagulant monitoring	Activated partial thromboplastin time	Anti-factor Xa levels	Activated partial thromboplastin time	Activated partial thromboplastin time or ecarin clotting time

*No longer available in the United States

its long-lasting anticoagulant activity that cannot be neutralized and significant difficulty in monitoring the anticoagulant effect during the surgery

- Detection of platelet factor IV antibodies is not a contraindication for reexposure to heparin

When one is considering reexposure to unfractionated heparin, platelet factor IV

antibodies should not be detectable. Patients with a history of HIT have successfully undergone anticoagulation with unfractionated heparin.¹⁵ A short exposure to heparin during surgery should not immediately cause HIT antibodies. The disadvantages of using danaparoid are the need to measure levels of anti-factor Xa to monitor its anticoagulant effect, its long half-life (25 ± 100 hours), and the absence of a reversing agent.¹⁶

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