A 64-year-old woman who is hospitalized with endocarditis and whose condition is clinically stable while she is receiving intravenous antibiotic agents has had a decrease in platelet count from 161,000 per cubic millimeter on day 7 of hospitalization to 60,000 per cubic millimeter on day 9. She has been receiving low-molecular-weight heparin at a dose of 40 mg per day since admission. How should her case be further evaluated and treated?

The Clinical Problem

In contrast to other conditions caused by enhanced consumption, impaired production, or destruction of platelets, which lead to bleeding complications, immune-mediated heparin-induced thrombocytopenia (HIT) does not induce bleeding but rather results in a paradoxical prothrombotic state. This prothrombotic action makes the early recognition of HIT very important. HIT occurs in approximately 1 in 5000 hospitalized patients, with a large variability among patient populations. Patients who receive unfractionated heparin for 7 to 10 days are at the highest risk; incidence rates of 1 to 3% have been reported after cardiac surgery. Thromboembolic complications develop in approximately 50% of patients with confirmed HIT. Venous thrombosis of the large vessels of the lower limbs and pulmonary embolism are the most frequent complications, followed by peripheral arterial thrombosis and then stroke; myocardial infarction is uncommon. Thrombotic complications may also affect other vessels, including the cerebral sinus or splanchnic veins.

The onset of HIT characteristically occurs between 5 and 10 days after heparin is started, both in patients who receive heparin for the first time and in patients with reexposure. However, there are exceptions. For one, major surgery resets the clock (i.e., the window of 5 to 10 days restarts), even if the patient has recently received heparin (e.g., HIT can develop 5 to 10 days after surgery in patients who have been undergoing hemodialysis for a long time). Second, in persons who have received heparin within the previous 90 days (especially, ≤30 days), there may be persistent circulating anti-platelet factor 4 (PF4)–heparin antibodies, and HIT can start abruptly on reexposure to heparin (rapid-onset HIT); in this case, HIT is sometimes complicated by an anaphylactoid reaction within 30 minutes after a heparin bolus. Otherwise, once the typically transient antibodies have disappeared (median, 50 to 85 days, depending on the assay used), the regeneration of antibodies requires at least 5 days (no earlier anamnestic response). In some patients, HIT develops or worsens after heparin has been discontinued (delayed-onset HIT). These patients can present with thrombosis up to 3 weeks after the...
start of heparin exposure. Note that in some cases, a single heparin bolus is sufficient to induce the syndrome, so the start of heparin is the only fixed time point.

A rare but often catastrophic form of HIT is spontaneous or autoimmune HIT, which develops in the absence of heparin exposure, most often after major surgery (especially knee replacement) or recent infection. In contrast to typical HIT, in which the platelet count increases within 2 to 5 days after the start of an alternative anticoagulant, autoimmune HIT may persist for weeks.

**PATHOGENESIS**

HIT is induced by IgG antibodies recognizing neoepitopes on the positively charged chemokine PF4 within PF4–polyanion complexes (Fig. 1). The resulting immune complexes cross-link Fcγ receptors on platelets (Fcγ RIIa) and monocytes (Fcγ RI), thus activating them. Further enhanced by the alteration of endothelial cells, the activation of platelets and monocytes increases thrombin generation. Increased thrombin, not thrombocytopenia, causes the clinical problems.

In addition to binding heparin, PF4 binds other polyanions, such as nucleic acids and lipopolysaccharides on bacteria. This phenomenon may explain cases of spontaneous HIT after major surgery (causing DNA, RNA, or glycosaminoglycan release) or bacterial infection. An interesting concept is that conformationally changed PF4 in complex with nonheparin polyanions (e.g., on the bacterial surface) induces primary immunization. These PF4–polyanion complexes serve as a danger signal and result in the rapid generation of IgG antibodies, which facilitate opsonization and phagocytosis of PF4-coated bacteria, even against PF4-labeled pathogens that the immune system has not encountered before. This mechanism, however, results in HIT when it is misdirected during heparin treatment as a secondary immune reaction toward platelets coated with PF4–heparin complexes, which results in early production of high-titer IgG antibodies. Anti–PF4–heparin antibodies are produced by B cells (probably marginal-zone B cells), which can mediate a transient antibody response.

**KEY CLINICAL POINTS**

**HEPARIN-INDUCED THROMBOCYTOPENIA**

- Heparin-induced thrombocytopenia (HIT) is characterized by a decrease in the platelet count of more than 50% from the highest platelet count value after the start of heparin, an onset 5 to 10 days after the start of heparin, hypercoagulability, and the presence of heparin-dependent, platelet-activating IgG antibodies.
- Use of a scoring system that takes into account the timing and magnitude of the platelet count fall, new thrombosis, and the likelihood of other reasons for thrombocytopenia is helpful in assessing the pretest probability of HIT.
- Delayed-onset HIT develops after the cessation of heparin, and spontaneous or autoimmune HIT develops in the absence of heparin exposure.
- Platelet factor 4–heparin antibody tests should be ordered only if clinical features reasonably suggest HIT. These tests have a high negative predictive value but a low positive predictive value.
- Treatment of acute HIT requires the cessation of heparin and the initiation of therapeutic-dose anticoagulation with an alternative agent (argatroban, danaparoid, fondaparinux, or bivalirudin).
- Warfarin should be avoided in patients with acute HIT.

**STRATEGIES AND EVIDENCE**

**RISK OF HIT**

The risk of HIT depends on the type of heparin and the patient population. The incidence is up to 10 times as high among patients receiving unfractionated heparin as it is among those receiving low-molecular-weight heparin, and HIT occurs more frequently among patients who have had major surgery than among those who have had minor surgery or are receiving medical therapy. HIT is rare in obstetrical patients, although in contexts other than pregnancy, women are at slightly higher risk than men.

**DIAGNOSIS**

The diagnosis of HIT is based on a decrease in the platelet count of more than 50% or throm-
Figure 1. Pathogenesis of Heparin-Induced Thrombocytopenia.

The adverse drug effect known as heparin-induced thrombocytopenia (HIT) shows many similarities to a bacterial host defense mechanism. Platelet factor 4 (PF4) that is released from platelet α-granules binds to polyanions such as heparin or polyanions on the surface of bacteria and undergoes a conformational change. This results in immunogenic PF4–polyanion (heparin) or PF4–polyanion (bacteria) complexes. After activation, B lymphocytes (probably marginal-zone B cells) generate anti–PF4–polyanion IgG. These antibodies can bind to different PF4-coated bacteria and opsonize them. However, these antibodies also bind to PF4–heparin complexes, forming immunocomplexes. The Fc parts of the IgG bind to platelet Fcγ RIIa receptors, resulting in Fcγ-receptor clustering and consequent strong platelet activation and aggregation. This intravascular platelet consumption causes a decrease in the platelet count and the production of platelet-derived microparticles that accelerate thrombin generation. In addition, HIT antibodies activate monocytes (by means of the Fcγ R1) and (directly or indirectly) endothelial cells, inducing additional tissue-factor expression. The resulting increase in thrombin generation leads to an increased risk of thrombosis among patients with HIT, providing a rationale for treatment that reduces thrombin generation.
bosis beginning 5 to 10 days after the start of heparin, in association with the appearance of platelet-activating HIT antibodies, as shown by means of a functional assay or inferred by means of a strong positive immunoassay. The fall in platelet count in HIT occurs rapidly (over a period of 1 to 3 days) and is assessed relative to the highest platelet count after the start of heparin. The typical nadir is 40,000 to 80,000 platelets per cubic millimeter, but the count may remain in the normal range (e.g., a decline from 500,000 to 200,000 per cubic millimeter). In less than 10% of patients, the decrease in platelet count is less pronounced (30 to 50% of the highest preceding value). Rarely, the platelet count may fall below 20,000 per cubic millimeter, especially when HIT is associated with other causes of thrombocytopenia, such as consumptive coagulopathy.

Although monitoring of platelet counts facilitates the recognition of HIT, it is difficult to justify in many patients, especially outpatients. Monitoring should be considered when the risk of HIT is relatively high (>1%), such as among patients who have undergone cardiac surgery and those receiving unfractionated heparin after major surgery (other than heparin received for intraoperative flushes or catheter-related flushes). After major surgery, patients typically have a reactive platelet count increase that exceeds the baseline value (i.e., the value before the receipt of heparin) after the first postoperative week. Given the typical time window of HIT, platelet count monitoring on days 5, 7, and 9 allows for the early recognition of HIT in the majority of patients. Even if HIT manifests thereafter, the platelet count on day 9 is close to the peak post-surgery platelet count. Monitoring platelet counts on these days facilitates later recognition of a fall in the platelet count of more than 50%, which can be missed when only the lower presurgery baseline value is considered. Even with platelet count monitoring, however, the first thrombotic complication may not be preventable, because in approximately 20% of patients it occurs shortly before, or concomitant with, the platelet count decrease (Fig. 2).

Scoring systems can be helpful in estimating the probability of HIT. A widely used scoring system is the 4T score, which evaluates four indicators: the relative platelet count fall, the timing of the onset of the platelet count fall, the presence or absence of thrombosis, and the likelihood of another cause, with scores on the individual components ranging from 0 to 2 and higher scores indicating a higher likelihood of HIT. A total score of less than 4 points has a very high negative predictive value (97 to 99%) (Table 1), whereas the positive predictive value is low (10 to 20% for an intermediate score [4 or 5 points] and 40 to 80% for a high score [6
to 8 points)).\textsuperscript{32} A falsely low score may result from missing platelet count values or coexisting conditions that may also underlie thrombocytopenia. For patients with missing values or coexisting conditions and for those whose score is intermediate or high, laboratory tests are needed to rule out HIT.

### Additional Laboratory Testing

Anti–PF4–heparin enzyme immunoassays have an excellent negative predictive value (98 to 99%)\textsuperscript{34} but a low positive predictive value, owing to the detection of clinically insignificant anti–PF4–heparin antibodies. In systematic serosurveillance studies, clinically evident HIT developed in only a minority (2 to 15%) of heparin-treated patients who had anti–PF4–heparin antibodies detected by means of enzyme immunoassay.\textsuperscript{35,36} In patients with thrombocytopenia who have a negative test, repeat testing is generally not indicated in the absence of a new decrease in the platelet count or a thrombotic event. Anti–PF4–heparin antibodies are always present before the platelet count begins to decline,\textsuperscript{37} and seroconversion after an initially negative test for anti–PF4–heparin antibodies nearly always detects coincidental, clinically irrelevant antibodies. Overdiagnosis and associated overtreatment of HIT are probably more common than underrecognition, given the high frequency of thrombocytopenia among early postoperative and critically ill patients and the low specificity of the assays.

Several strategies can be used to increase the specificity of PF4–heparin enzyme immunoassays. One strategy is the restriction of the assay to IgG antibodies, because only IgG activates platelets and monocytes by means of Fcγ receptors, yet some commercial assays detect combined IgG, IgA, and IgM. Also, the magnitude of anti–PF4–heparin reactivity on enzyme immunoassay should be considered, because greater reactivity correlates with a greater likelihood of HIT; an optical density of less than 1.0 on enzyme immunoassay is rarely associated with clinically relevant anti–PF4–heparin antibodies.\textsuperscript{38} However, optical-density values are arbitrary units and may vary among laboratories.\textsuperscript{39} Inhibition of the enzyme immunoassay by high concentrations of heparin also increases specificity, but the most relevant, very strongly reacting antibodies may not be inhibited.\textsuperscript{34}

Diagnostic accuracy for HIT is improved with the use of both an anti–PF4–heparin enzyme immunoassay and a functional test (e.g., a platelet-activation assay). In particular, platelet-

### Table 1. 4T Scoring System for Evaluating the Pretest Probability of Heparin-Induced Thrombocytopenia.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute thrombocytopenia</td>
<td></td>
<td>Platelet count decrease of &gt;50% and nadir ≥20,000/mm³</td>
<td>Platelet count decrease of 30–50% or nadir 10,000–19,000/mm³</td>
<td>Platelet count decrease of &lt;30% or nadir ≤10,000/mm³</td>
</tr>
<tr>
<td>Timing of onset</td>
<td></td>
<td>Day 5–10, or day 1 if recent heparin exposure</td>
<td>&gt;Day 10 or unclear exposure</td>
<td>≤Day 4 with no recent heparin exposure</td>
</tr>
<tr>
<td>Thrombosis</td>
<td></td>
<td>New thrombosis or anaphylactoid reaction after heparin bolus</td>
<td>Progressive or recurrent thrombosis</td>
<td>None</td>
</tr>
<tr>
<td>Other cause of thrombocytopenia</td>
<td></td>
<td>None</td>
<td>Possible</td>
<td>Definite</td>
</tr>
<tr>
<td>Total score</td>
<td></td>
<td>6–8, indicating high score</td>
<td>4 or 5, indicating intermediate score</td>
<td>0–3, indicating low score</td>
</tr>
</tbody>
</table>

* Adapted from Lo et al.\textsuperscript{31} A low 4T score (0 to 3 points) has a high negative predictive value. The day that heparin was started is considered as day 0. The onset of heparin-induced thrombocytopenia (HIT) is defined as the day that the platelet count begins to decrease. Patients in whom the score is difficult to apply, owing to missing platelet count values or coexisting conditions causing thrombocytopenia, and those with an intermediate or high score require further evaluation. This score can be included on ordering forms for HIT laboratory testing (e.g., www2.medizin.uni-greifswald.de/transfus/ fileadmin/user_upload/doku_thrombo_gerinnung/platelet_lab_request_form.pdf).
activation assays with the use of washed platelets (e.g., serotonin-release assay and heparin-induced platelet-activation test, both with the use of high heparin inhibition) are much more specific than enzyme immunoassays for clinically relevant antibodies and also detect the rare antibodies with other specificities. A negative functional assay essentially rules out HIT. These assays are restricted to specialized laboratories and are usually applied as second-line tests in the diagnostic workup of HIT.

HIT assays should not be used to screen asymptomatic patients and should be interpreted only in the context of the pretest probability of HIT.33,34 A low or intermediate 4T score together with a negative antigen test rules out HIT, whereas an intermediate or high score together with a positive functional assay makes HIT very likely (Fig. 3).

In a subgroup of patients, anti–PF4–heparin antibodies show very high optical densities (>2.0) and strongly activate platelets even in the absence of heparin. First recognized in delayed-onset HIT,9 these autoreactive antibodies mediate spontaneous HIT. They may also be transiently present during the first 5 to 7 days in typical HIT, without affecting treatment.40,41 In patients with strongly suspected or confirmed HIT, duplex ultrasonography can rule out subclinical deep-vein thrombosis, which may affect the duration of treatment.1 In patients with HIT who have abdominal pain or hypotension, bilateral adrenal hemorrhage associated with adrenal-vein thrombosis should be considered; severe headache should prompt the consideration of cavernous sinus thrombosis.

TREATMENT

Key interventions in patients with highly suspected or confirmed acute HIT are the prompt cessation of heparin (if still being administered) and the initiation of an alternative anticoagulant at a therapeutic dose. Prophylactic-dose anticoagulation is insufficient28 to compensate for massive thrombin generation, even if the patient has no apparent thrombosis. Vitamin K antagonists (e.g., warfarin and phenprocoumon) should not be given until HIT has abated (e.g., the platelet count has increased to >150,000 per cubic millimeter at a stable plateau for 2 consecutive days), because they increase the risk of venous limb gangrene and limb loss by decreasing the level of protein C. When vitamin K antagonists are initiated, overlap with an alternative anticoagulant is needed.29

Two drugs are approved for the treatment of HIT — the direct thrombin inhibitor argatroban (in the United States, Canada, the European Union, and Australia) and the antithrombin-dependent factor Xa inhibitor danaparoid (in Canada, the European Union, and Australia).29 An analysis of prospective cohorts showed a reduced risk of the composite outcome of new thrombosis, death due to thrombosis, or amputation related to thrombosis in patients treated with argatroban, as compared with historical controls (hazard ratio for the composite outcome among patients with HIT without thrombosis, 0.33; 95% confidence interval [CI], 0.20 to 0.54; hazard ratio for the composite outcome among patients with HIT with thrombosis, 0.30; 95% CI, 0.25 to 0.62).41 An analysis of outcomes with danaparoid29 that was provided on a compassionate-use basis showed a rate of treatment success (platelet count recovery without new thrombosis and absence of major adverse events requiring drug cessation) that was higher than 90%.46 In a small, open-label, randomized trial comparing danaparoid with dextran 70 for the treatment of HIT with thrombosis, the rates of recovery from thromboembolism were significantly higher with danaparoid.45 Fondaparinux and bivalirudin are also used in this context, although they have not been approved by the Food and Drug Administration for this indication. Case series have shown good outcomes in patients with HIT treated with fondaparinux29,46 or bivalirudin.28,47

Argatroban is frequently used in critically ill patients. It has a relatively short half-life, which is independent of renal function, but it requires intravenous administration. Because argatroban affects the international normalized ratio, the transition to warfarin has to follow a special protocol.28 An underrecognized issue is that the activated partial-thromboplastin time may be falsely high when argatroban is given to patients who have additional coagulopathies (e.g., consumptive coagulopathy or impaired liver function) or to patients who have received pretreatment with warfarin. This situation may lead to underdosing of argatroban, with the risk of progressive microvascular thrombosis and ischemic limb loss. This limitation may be overcome
Figure 3. Diagnosis of HIT.

The flowchart provides a guide to decision making regarding a patient who is suspected to have HIT. Antigen assays for PF4–heparin antibodies are widely available, whereas functional assays with the use of washed platelets, such as the serotonin-release assay (SRA) or the heparin-induced platelet-activation (HIPA) test, are restricted to specialized laboratories. In centers where a functional assay is unavailable or cannot be obtained promptly, other options include the use of high reactivity of the antigen test (e.g., optical density [OD], >1.0) as a surrogate marker for clinically relevant antibodies or incorporating the 4T score in interpretation (dashed lines), although the overdiagnosis of HIT remains possible. The 4T scoring system evaluates four indicators (the relative platelet count fall, the timing of the onset of the platelet count fall, the presence or absence of thrombosis, and the likelihood of another cause), with scores on the individual components ranging from 0 to 2 and higher scores indicating a greater likelihood of HIT. In the case of a high 4T score and a negative result on the PF4–heparin IgG antibody immunoassay, consider that laboratory error may be a cause of a false negative result. Even if short-term treatment decisions are made without confirmation of the presence of platelet-activating, heparin-dependent antibodies, efforts should be made to rule out or confirm the presence of these antibodies to guide the future treatment of the patient.
by the use of an ecarin-based clotting assay (which has limited availability) or the plasma-
diluted thrombin time assay (for which an in-
house standard for argatroban is required).

Danaparoid can be administered intravenous-
ly or subcutaneously, whereas fondaparinux is
given only subcutaneously. These two drugs can
be reliably monitored by anti–factor Xa assays,
but they have long half-lives and in patients with
renal insufficiency, a dose adjustment will be
necessary. Subcutaneous injection makes these
drugs easier than argatroban to use outside the
intensive care unit. In addition, danaparoid in-
terferes with the immune mechanism of HIT by
disrupting PF4–heparin complexes.48 Exacerba-
tions of HIT have been reported infrequently
with the use of either danaparoid or fondaparinux.
Although most cases of exacerbations are attrib-
utable to autoimmune HIT antibodies and are
independent of these drugs, a small percentage
of patients have true in vivo and in vitro cross-
reactivity. If manifestations of HIT worsen de-
spite sufficient levels of anti–factor Xa activity in
patients taking danaparoid or fondaparinux, treat-
ment should be switched (e.g., to argatroban).

Prophylactic platelet transfusions should be
avoided in patients with HIT. The risk of bleed-
ing is very low, and such transfusions can in-
crease the risk of thrombosis.49

AREAS OF UNCERTAINTY

Whereas in vitro data suggest that dabigatran,
rivaroxaban, and apixaban might also be used to
treat patients with HIT,50 more data are needed
before these drugs can be recommended in the
context of acute HIT. A concern is whether
trough levels are sufficient to prevent thrombin
generation by strongly reactive anti–PF4–heparin
antibodies.

Patients who have HIT with thrombosis re-
quire therapeutic-dose anticoagulation for at least
3 months. However, in patients who have HIT
without thrombosis, the duration of therapeutic-
dose anticoagulation after the platelet count has
reached a stable plateau (ideally >150,000 per
cubic millimeter)28 is unresolved.

High-dose intravenous immune globulin G
(e.g., at a dose of 2 g per kilogram of body
weight over a 2-day period) interferes with HIT
by blocking platelet Fcγ receptors. Limited data
suggest that this drug may be an option (along
with anticoagulation) in patients at high risk for
thrombosis and bleeding (e.g., those who are preg-
nant or have sinus-vein thrombosis complicating
HIT) or in patients who have autoimmune HIT.31

PF4 forms complexes with negatively charged
nucleic acids and aptamers,20 which cross-react
with anti–PF4–heparin antibodies. Aptamers and
other nucleic acid–based drugs are entering
clinical application, and it is unclear whether
they can induce HIT.

In patients with a history of HIT who require
cardiac surgery, postponing surgery until plate-
let-activating anti–PF4–heparin antibodies dis-
appear and then using heparin intraoperatively
is a safe approach.6,28,52 Another option in urgent
situations is the removal of platelet-activating
anti–PF4–heparin antibodies by plasmapheresis,
as described in anecdotal reports.53 Otherwise,
bivalirudin is a compatible anticoagulant for
cardiac surgery if platelet-activating anti–PF4–
heparin antibodies are present. However, its use
requires special approaches to avoiding stagna-
tion of blood (which results in degradation of
bivalirudin).28

GUIDELINES

The guidelines of the American College of Chest
Physicians (ACCP)28 and national European guide-
lines54-56 address HIT. In the absence of data
from randomized trials, most recommendations
are supported by low-grade evidence. All these
guidelines recommend the use of a scoring sys-
tem to determine the probability of HIT before
testing is performed and note the need for
therapeutic-dose anticoagulation in cases of acute
HIT. Guidelines differ with each other regarding
specific recommendations about which patients
should undergo routine platelet count monitor-
ing and the frequency of monitoring. The ACCP
guidelines recommend assessing patients at high
risk (>1%) for HIT every 2 to 3 days between day
4 and day 14.28

CONCLUSIONS AND
RECOMMENDATIONS

The patient described in the vignette had a
marked decrease in the platelet count after several
days of therapy with low-molecular-weight hepa-
рин, which raises concern about HIT. Calculation
of the 4T score is recommended to determine
her risk of HIT. Her score of 5 points (decrease in platelet count, 2; timing, 2; thrombosis, 0; and likelihood of other reasons, 1, since her endocarditis is stable and the platelet count is too high for antibiotic-induced immune thrombocytopenia) places her at intermediate risk. Although routine screening for PF4–heparin antibodies is strongly discouraged, patients at intermediate or high risk should undergo this testing. A positive anti–PF4–heparin IgG enzyme immunoassay is necessary for the diagnosis of HIT but is nonspecific. A strongly positive test (optical density, >1.5) or positive platelet-activation assay would strongly support the diagnosis of HIT. Treatment involves the prompt cessation of heparin and the initiation of an alternative anticoagulant (argatroban or danaparoid, both of which are approved for this indication, or fondaparinux or bivalirudin, with use of these agents supported by case series).

Dr. Greinacher reports receiving fees for serving on an advisory board from Instrumentation Laboratory; consulting fees from Bayer HealthCare, Macopharma, Merck Sharp & Dohme, and W.L. Gore and Associates; travel support from Boehringer Ingelheim; fees for the planning and participation in a Continuing Medical Education program from Bristol-Myers Squibb; grant support from Macopharma; and institutional fees to his university from Boehringer Ingelheim. He also reports an agreement in development with BioMarin Nederland and Nanjing King-phenibiochemical Pharmaceutical, which will provide institutional but no personal fees. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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