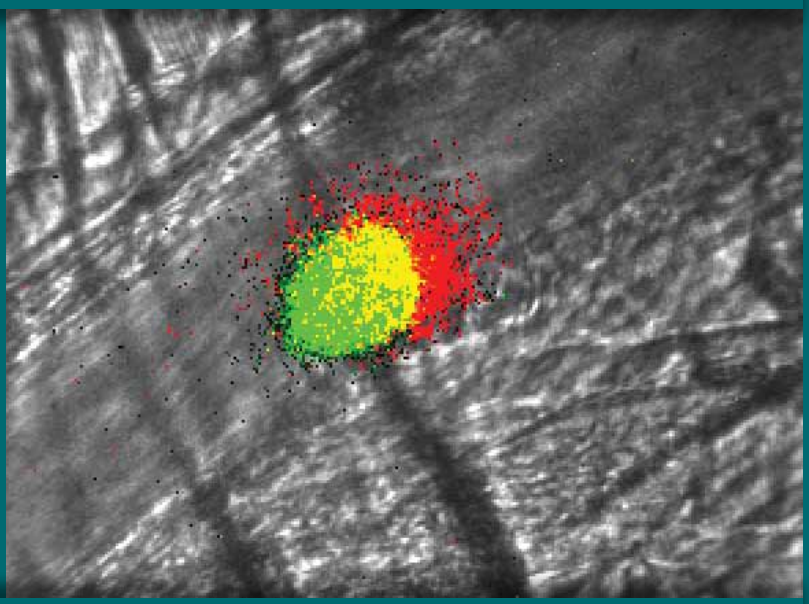
QUICK REFERENCE

# 2013 Clinical Practice Guideline on the Evaluation and Management of Adults with Suspected Heparin-Induced Thrombocytopenia (HIT)



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AMERICAN SOCIETY OF HEMATOLOGY®

# I. History and Physical Examination: Evaluating the Clinical Probability of HIT

## A. Features of the history and physical examination that support a diagnosis of HIT

| Feature | Comments |
|---|---|
| Fall in platelet count ≥ 50% | From highest platelet count after heparin exposure; platelet count fall is 30–50% in 10% of cases |
| Fall in platelet count begins 5–14 days after immunizing heparin exposure | Heparin administered during or soon after surgery is more likely to be immunizing |
| Fall in platelet count begins within 24 hours after heparin exposure | May occur in patients with previous heparin exposure within last 100 days |
| Nadir platelet count ≥ 20 x $10^9$/L | Nadir may exceed lower limit of normal range (i.e. 150 x $10^9$/L ) in patients with high baseline platelet counts. May be < 20 x $10^9$/L in cases associated with DIC |
| Venous or arterial thrombosis | Occurring ≥ 5 days after heparin exposure and up to 30 days after heparin cessation |
| Skin necrosis | At subcutaneous heparin injection sites |
| Anaphylactoid reaction | Within 30 minutes after intravenous heparin bolus or subcutaneous injection |
| Absence of alternative causes of thrombocytopenia | Such as infection, other medications known to cause thrombocytopenia, cardiopulmonary bypass within previous 96 hours, intra-aortic balloon pump, extracorporeal membrane oxygenation, etc. |
| Absence of petechiae and other mucocutaneous bleeding | Adrenal hemorrhage secondary to adrenal vein thrombosis may occur in association with HIT |

## B. The 4Ts: A clinical probability scoring system

| 4Ts | 2 Points | 1 Point | 0 Points |
|---|---|---|---|
| **T**hrombocytopenia | Platelet count fall > 50% and platelet nadir ≥ 20 x $10^9$/L | Platelet count fall 30–50% or platelet nadir 10-19 x $10^9$/L | Platelet count fall < 30% or platelet nadir < 10 x $10^9$/L |
| **T**iming of platelet count fall | Clear onset between days 5–14 or platelet fall ≤ 1 day (prior heparin exposure within 30 days) | Consistent with days 5–14 fall, but not clear (e.g. missing platelet counts) or onset after day 14 or fall ≤ 1 day (prior heparin exposure 30–100 days ago) | Platelet count fall ≤ 4 days without recent exposure |
| **T**hrombosis or other sequelae | New thrombosis (confirmed); skin necrosis at heparin injection sites; anaphylactoid reaction after IV heparin bolus | Progressive or recurrent thrombosis; Non-necrotizing (erythematous) skin lesions; Suspected thrombosis (not confirmed) | None |
| o**T**her causes of thrombocytopenia | None apparent | Possible | Definite |

High probability (6–8 points), intermediate probability (4–5 points), low probability (≤3 points).

Adapted from Lo et al., *J Thromb Haemost* 2006;4:759. The 4Ts has not been compared with intuition-based diagnosis. It may be used as a guide for clinicians but should not substitute for clinical judgment. In a meta-analysis, the negative predictive value of a low probability 4T score was 99.8% (i.e. a low probability score reliably excludes HIT). The positive predictive values of intermediate and high probability scores were 14% and 64%, respectively (Cuker et al., *Blood* 2012;120:4160).

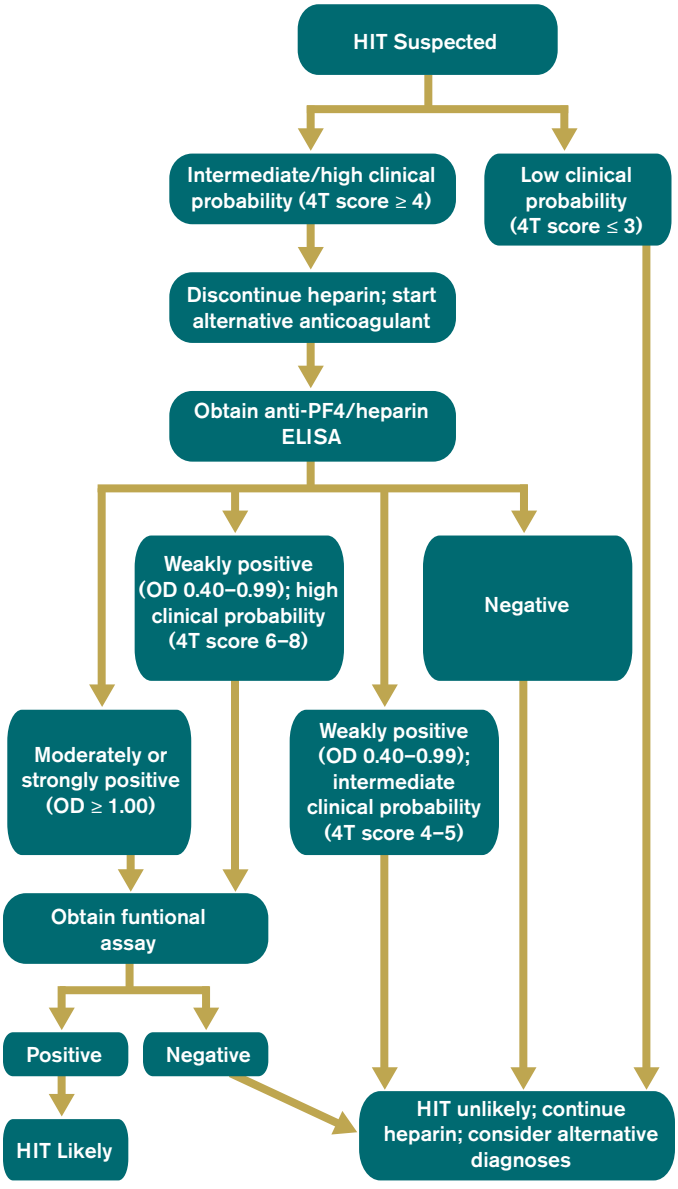
# II. Laboratory Diagnosis

| Assay category | Mechanism | Examples | Sensitivity | Specificity | Comments |
|---|---|---|---|---|---|
| Immunologic | Detects antibodies against PF4/heparin, regardless of their capacity to activate platelets | 1. Polyspecific ELISA<br>2. IgG-specific ELISA<br>3. PaGIA | >95% | 50–89% | OD of ELISA result correlates with clinical probability of HIT and odds of a positive functional assay |
| Functional | Detects antibodies that induce heparin-dependent platelet activation | 1. SRA<br>2. HIPA | 90–98% | 90–95% | Not widely available; requires referral to a reference laboratory |

PF4, platelet factor 4; PaGIA, particle gel immunoassay; OD, optical density; SRA, serotonin release assay; HIPA, heparin-induced platelet activation assay.

# III. Diagnostic and Initial Treatment Algorithm

Adapted from Cuker et al., *Blood* 2012;119:2209. OD, optical density.



# IV. Treatment

## A. Non-heparin anticoagulants: selection, dosing, and monitoring

| Agent | Initial dosing | Monitoring |
|---|---|---|
| Argatroban | **Bolus:** None<br>**Continuous infusion:**<br>Normal organ function→2 mcg/kg/min[1]<br>Liver dysfunction (total serum bilirubin >1.5 mg/dL), heart failure, post-cardiac surgery, anasarca→0.5–1.2 mcg/kg/min[2] | Adjust dose to APTT of 1.5–3.0 times patient baseline. Monitor APTT every 4 hours during dose titration. |
| Danaparoid[3] | **Bolus:**<br>Weight <60 kg→1500 U<br>Weight 60–75 kg→2250 U<br>Weight 75-90 kg→3000 U<br>Weight >90 kg→3750 U<br>**Accelerated initial infusion:**<br>400 U/hr x 4 hrs, then 300 U/hr x 4 hrs<br>**Maintenance infusion:**<br>Cr < 2.5 mg/dL→200 U/hr<br>Cr ≥ 2.5 mg/dL→150 U/hr | Adjust dose to danaparoid-specific anti-Xa level of 0.5–0.8 U/ml (if assay is available). |
| Bivalirudin[4] | **Bolus:** None<br>**Continuous infusion:**<br>Normal organ function→0.15 mg/kg/hr<br>Renal or hepatic insufficiency→dose reduction may be necessary | Adjust dose to APTT of 1.5–2.5 times patient baseline. |
| Fondaparinux[5] | <50 kg→5 mg SC daily<br>50-100 kg→7.5 mg SC daily<br>>100 kg→10 mg SC daily<br>$Cl_{Cr}$ 30–50 ml/min→use caution<br>$Cl_{Cr}$ <30 ml/min→contraindicated | Some experts recommend adjusting dose to a peak anti-Xa activity of 1.5 fondaparinux-specific U/ml. Others do not recommend routine monitoring. |
| NOACs[6] | At the time of writing, none of the NOACs (e.g. rivaroxaban, dabigatran, apixaban) had been assessed for treatment of patients with suspected or proven HIT and none had FDA approval for this indication. Until supporting data are available, their use cannot be endorsed. | |

The American College of Chest Physicians suggests argatroban or danaparoid over other non-heparin anticoagulants (Grade 2C). Argatroban is preferred in patients with renal insufficiency (Grade 2C) (Linkins et al., *Chest* 2012;141:e495S).

However, other experts believe that fondaparinux is an important treatment option, especially in stable, non-critically ill patients (Cuker et al., *Blood* 2012;119:2209; Warkentin, *Hematology* (Am Soc Hematol Educ Program) 2011;143).

[1]Some experts recommend a starting dose of 1 mcg/kg/min in patients with normal organ function.

[2]Lower than FDA-approved dosing.

[3]Not available in U.S.

[4]FDA-approved for patients with HIT only during percutaneous coronary intervention.

[5]Not FDA-approved for treatment of HIT; use is based largely on case series and anecdotal experience.

[6]NOACs, novel oral anticoagulants.

## B. Transitioning to warfarin

- HIT patients are at risk of venous limb gangrene and skin necrosis during initiation of warfarin.
- Warfarin should not be initiated until platelet count is ≥ 150 x $10^9$/L (Grade 1C).
- Initial warfarin dose should be ≤ 5 mg/day. Larger loading doses should be avoided (Grade 1C).
- A parenteral non-heparin anticoagulant should be overlapped with warfarin for ≥ 5 days and until INR has reached intended target (Grade 1C).
- Because argatroban raises the INR, the following steps should be taken when transitioning a patient from argatroban to warfarin:
  - If argatroban dose is ≤ 2 mcg/kg/min and patient has normal hepatic function
    1. Stop argatroban when INR on combined argatroban and warfarin is >4
    2. Repeat INR in 4–6 hours
    3. If INR is <2, restart argatroban
    4. Repeat procedure daily until INR ≥ 2 is achieved
  - If argatroban dose is >2 mcg/kg/min and patient has normal hepatic function
    1. Reduce argatroban dose to 2 mcg/kg/min
    2. Repeat INR in 4–6 hours
    3. Stop argatroban when INR on combined argatroban and warfarin is >4
    4. Repeat INR in 4–6 hours
    5. If INR is <2, restart argatroban
    6. Repeat procedure daily until INR ≥ 2 is achieved
- An alternative option is to convert from argatroban to fondaparinux, which has minimal effect on the INR, before transitioning to warfarin.

## C. Duration of anticoagulation

- Bilateral lower extremity compression ultrasonography may be considered in patients with HIT, whether or not there is clinical evidence of lower-limb DVT, because silent DVT is common and its presence may influence the recommended duration of anticoagulation.
- For patients with HIT-associated thrombosis (i.e. HITT), anticoagulate for a defined course (typically 3 months) as with other provoked thromboses.
- For patients with HIT without thrombosis (i.e. isolated HIT), the optimal duration of anticoagulation is unknown. Because there is an elevated risk of thrombosis extending 2 to 4 weeks after heparin is stopped, anticoagulation for up to 4 weeks should be considered.
- For all patients, anticoagulation management should be based on an individualized risk/benefit assessment.

## D. Platelet transfusion

- Due to theoretical risk that platelet transfusion may precipitate thrombosis in HIT, and because patients with HIT do not have a hemorrhagic diathesis, platelet transfusions should not be given to patients with confirmed or strongly suspected HIT except for bleeding or an invasive procedure with a high risk of bleeding (Grade 2C).
- Platelet transfusion may be appropriate in situations of diagnostic uncertainty.

## V. Heparin Reexposure in Patients with a History of HIT

### A. Cardiac and vascular surgery

- In patients with a history of HIT, laboratory testing may be used to determine whether HIT is acute, subacute, or remote and the safety of using intraoperative heparin.

| Clinical picture | Laboratory profile | | Recommended *intraoperative* anticoagulation[1, 2] |
|---|---|---|---|
| | Platelet count | Immunologic assay | |
| Remote HIT | Recovered | Negative | 1. Use UFH (Grade 2C) |
| Subacute HIT | Recovered | Positive | 1. Delay surgery, if possible, until immunologic assay becomes negative (Grade 2C)<br>2. If surgery cannot be delayed, use bivalirudin (Grade 2C)[3] |
| Acute HIT | Thrombocytopenic | Positive | 1. Delay surgery, if possible, until functional and immunologic assays become negative (Grade 2C)<br>2. If surgery cannot be delayed, use bivalirudin (Grade 2C)<br>3. Case reports suggest that repeated plasmapheresis may transiently reduce HIT antibody levels, allowing brief heparin re-exposure during surgery[4] |

[1]If heparin is given, it should be limited to the intraoperative setting. If pre- or postoperative anticoagulation is indicated, a non-heparin anticoagulant should be used and heparin exposure scrupulously avoided.
[2]American College of Chest Physicians Grading System: 1, strong recommendation; 2, weak recommendation; A, based on high quality evidence; B, based on moderate quality evidence; C, based on low quality evidence.
[3]Small studies suggest UFH may be used for intraoperative anticoagulation in patients with subacute HIT provided that the functional assay has become negative.
[4]Grade 2C per the American Society of Apheresis (Schwartz et al., *J Clin Apheresis* 2013;28:145).
UFH, unfractionated heparin, is an important option in centers where experience with intraoperative bivalirudin is limited.

### B. Cardiac catheterization/percutaneous coronary intervention

| Clinical picture | Laboratory profile | | Recommended intraprocedural anticoagulation[1] |
|---|---|---|---|
| | Platelet count | Immunologic assay | |
| Remote HIT | Recovered | Negative | 1. Use bivalirudin (Grade 2B) or argatroban (Grade 2C)<br>2. If a non-heparin anticoagulant is not available, use UFH |
| Subacute HIT | Recovered | Positive | 1. Use bivalirudin (Grade 2B) or argatroban (Grade 2C) |
| Acute HIT | Thrombocytopenic | Positive | |

[1]American College of Chest Physicians Grading System: 1, strong recommendation; 2, weak recommendation; A, based on high quality evidence; B, based on moderate quality evidence; C, based on low quality evidence.

Cover Image: *In vivo* microscopy showing monocytes (in red), platelets (in green), and areas of overlap (in yellow) being incorporated into a growing thrombus in a mouse model of HIT. Courtesy of L. Rauova and M. Poncz, Children's Hospital of Philadelphia.

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This document summarizes selected recommendations from: Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition).

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Guidelines provide the practitioner with clear principles and strategies for quality patient care and do not establish a fixed set of rules that preempt physician judgment.

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For further information, please see the complete guidelines on the Chest website at *www.chestjournal.org/content/133/6_suppl/340S.long* or refer to the Practice Guidelines section of the ASH website at *www.hematology.org/practiceguidelines*. You may also contact the ASH Government Affairs, Practice, and Scientific Affairs Department at 202-776-0544.

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