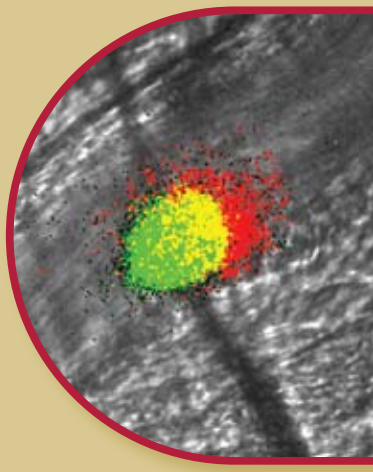
QUICK REFERENCE

2009 Clinical Practice Guideline on the Evaluation and Management of Heparin-Induced Thrombocytopenia (HIT)



Adam Cuker[1] and Mark A. Crowther[2]
[1]University of Pennsylvania, Philadelphia, PA; [2]St. Joseph's Hospital and McMaster University, Hamilton, Ontario, Canada

Presented by the American Society of Hematology, adapted in part from the: American College of Chest Physicians Evidence-Based Clinical Practice Guideline on Antithrombotic and Thrombolytic Therapy (8th Edition).

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 heparin exposure	
Fall in platelet count begins 48 hours after heparin exposure	In patients with previous heparin exposure within last 100 days
Nadir platelet count ≥ 20 x 10^9/L	May be < 20 x 10^9/L in cases associated with thrombosis and 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
Absence of alternative causes of thrombocytopenia	Such as infection, other medications known to cause thrombocytopenia, cardiopulmonary bypass within previous 96 hours, etc.
Absence of petechiae and other significant bleeding	

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.

B. The 4Ts: A clinical probability scoring model

4T's	2 Points	1 Point	0 Points
Thrombocytopenia	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
Timing 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
Thrombosis 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
oTher causes of thrombocytopenia	None apparent	Possible	Definite

High probability: 6-8 points; intermediate probability: 4-5 points; low probability: ≤3 points.

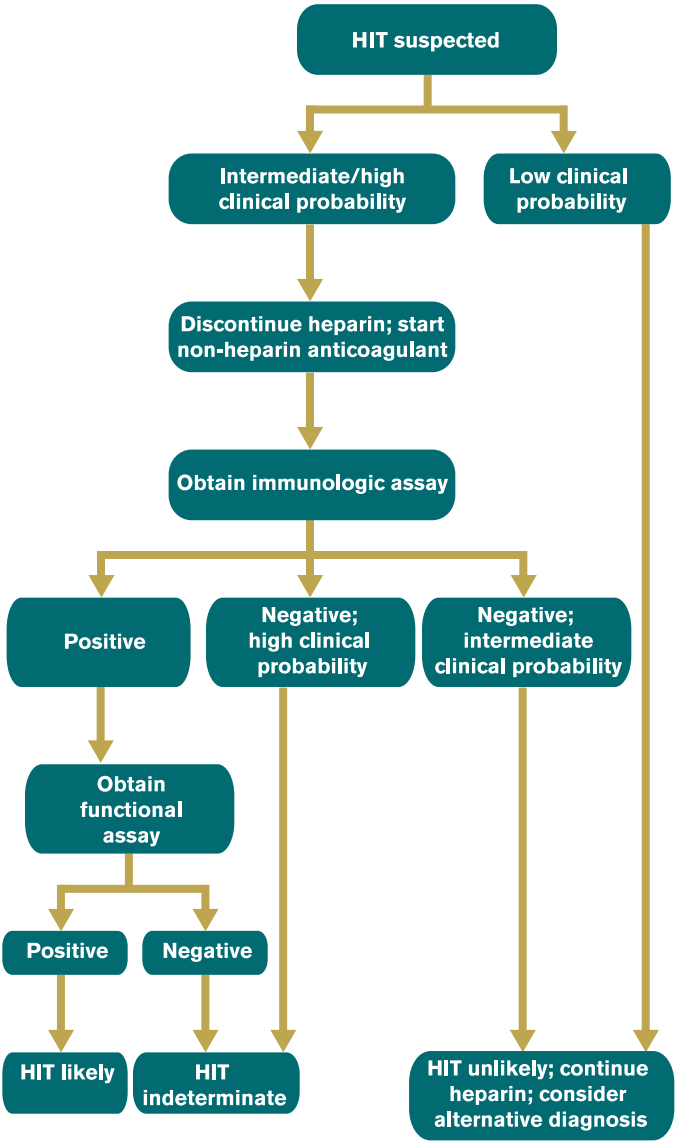
Adapted from Lo GK et al., J Thromb Haemost 2006. The 4Ts model has not been externally validated. It may be used as a guide for clinicians, but should not substitute for clinical judgment. In clinical studies, the 4Ts model has demonstrated excellent sensitivity (low probability score indicates low probability of HIT), but limited specificity (intermediate or high probability score may or may not indicate the presence of HIT).

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 2. IgG-specific ELISA 3. PGIA	>95%	50-89%	OD of ELISA result correlates with clinical probability of HIT
Functional	Detects antibodies that induce heparin-dependent platelet activation	1. SRA 2. HIPA 3. PAT	>90%	>90%	Not available at many centers; may require referral to a reference laboratory

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

III. Diagnostic and Initial Treatment Algorithm



Adapted from Arepally GM and Ortel TL, N Engl J Med 2006.

IV. Treatment

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

Agent	Graded recommendation[1]	Initial dosing	Monitoring
Danaparoid[2]	1B	**Bolus:** Weight <60 kg ▸ 1500 U Weight 60-75 kg ▸ 2250 U Weight 75-90 kg ▸ 3000 U Weight >90 kg ▸ 3750 U **Accelerated initial infusion:** 400 U/hr x 4 hrs, then 300 U/hr x 4 hrs **Maintenance infusion:** Normal renal function ▸ 200 U/hr Renal insufficiency ▸ 150 U/hr	Adjust dose to anti-Xa level of 0.5-0.8 U/ml (if assay is available).
Lepirudin	1C	**Bolus:**[3] 0.2 mg/kg (only if life- or limb-threatening thrombosis is present) **Continuous infusion:**[3] Cr <1.0 mg/dl ▸ 0.10 mg/kg/hr Cr 1.0-1.6 mg/dl ▸ 0.05 mg/kg/hr Cr 1.6-4.5 mg/dl ▸ 0.01 mg/kg/hr Cr >4.5 mg/dl ▸ 0.005 mg/kg/hr	Adjust dose to APTT of 1.5-2.0 times patient baseline. Monitor APTT every 4 hours during dose titration.
Argatroban	1C	**Bolus:** None **Continuous infusion:** Normal organ function ▸ 2 mcg/kg/min Liver dysfunction (total serum bilirubin >1.5 mg/dl), heart failure, post-cardiac surgery, anasarca ▸ 0.5-1.2 mcg/kg/min	Adjust dose to APTT of 1.5-3.0 times patient baseline. Monitor APTT every 4 hours during dose titration.
Bivalirudin[4]	2C	**Bolus:** None **Continuous infusion:** Normal organ function ▸ 0.15 mg/kg/hr Renal or hepatic insufficiency ▸ dose reduction may be necessary	Adjust dose to APTT of 1.5-2.5 times patient baseline.
Fondaparinux[5]	2C	No specific recommendations given minimal data supporting efficacy and appropriate dosing in HIT	

Adapted from Warkentin TE et al., Chest 2008.

[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

[2]Not available in U.S.

[3]Lower than FDA-approved dosing.

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

[5]Not approved for treatment of HIT.

B. Transitioning to warfarin

- HIT patients are at risk of venous limb gangrene during initiation of warfarin.
- Warfarin should not be initiated until platelet count is ≥ 150 x 10^9/L (Grade 1B).
- Initial warfarin dose should be ≤ 5 mg/day. Larger loading doses should be avoided (Grade 1B).
- A parenteral non-heparin anticoagulant should be overlapped with warfarin for ≥ 5 days and until INR has reached intended target (Grade 1B).
- 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

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

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

C. Duration of anticoagulation

- Bilateral lower extremity compression ultrasonography should be performed in all patients with HIT, whether or not there is clinical evidence of lower-limb DVT (Grade 1C), because the finding of DVT may influence the recommended duration of anticoagulation.
- For patients with HIT-associated thrombosis (i.e. HITT), anticoagulate for a defined course (typically 3-6 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 at least 30 days after the diagnosis of HIT, anticoagulation for at least one month 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, prophylactic platelet transfusions should not be given to patients with confirmed or strongly suspected HIT (Grade 2C).
- Platelet transfusion may be appropriate in situations of diagnostic uncertainty, high bleeding risk, or clinically significant bleeding.

V. Heparin Re-Exposure in Patients with a History of HIT

A. Cardiac and vascular surgery

- HIT laboratory testing should be used to determine the safety of exposing a patient with a history of HIT to intraoperative heparin:

Clinical picture	Laboratory profile		Recommended intraoperative anticoagulation[1, 2]
	Immunologic assay	Functional assay	
Remote HIT	Negative	Negative	1. Use UFH (Grade 1B)
Subacute HIT	Positive	Negative	1. Delay surgery, if possible, until immunologic assay becomes negative (Grade 1B) 2. If surgery cannot be delayed, use UFH (Grade 2C)
Acute HIT	Positive	Positive	1. Delay surgery, if possible, until functional and immunologic assays become negative (Grade 1B) 2. If surgery cannot be delayed, use bivalirudin (Grade 1B)

[1]If pre- or post-operative anticoagulation is indicated, a non-heparin anticoagulant should be used. [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 UFH, unfractionated heparin.

B. Cardiac catheterization/percutaneous coronary intervention

Clinical picture	Laboratory profile		Recommended intraprocedural anticoagulation[1]
	Immunologic assay	Functional assay	
Remote HIT	Negative	Negative	1. Use a non-heparin anticoagulant [bivalirudin (Grade 1B), argatroban (Grade 1C), lepirudin (Grade 1C), or danaparoid (Grade 1C)] 2. If a non-heparin anticoagulant is not available, use UFH
Subacute HIT	Positive	Negative	1. Use a non-heparin anticoagulant [bivalirudin (Grade 1B), argatroban (Grade 1C), lepirudin (Grade 1C), or danaparoid (Grade 1C)]
Acute HIT	Positive	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.

This document summarizes selected recommendations from the: American College of Chest Physicians Evidence-Based Clinical Practice Guideline on Antithrombotic and Thrombolytic Therapy (8th Edition).

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.

For further information, please see the complete guidelines on the Chest Web site at *www.chestjournal.org/content/133/6_suppl/340S.long* or refer to the Practice Guidelines section of the ASH Web site at *www.hematology.org/policy/resources/guidelines*. You may also contact the ASH Policy & Practice Department at 202-776-0544.

American Society of Hematology
1900 M Street NW, Suite 200
Washington, DC 20036

www.hematology.org