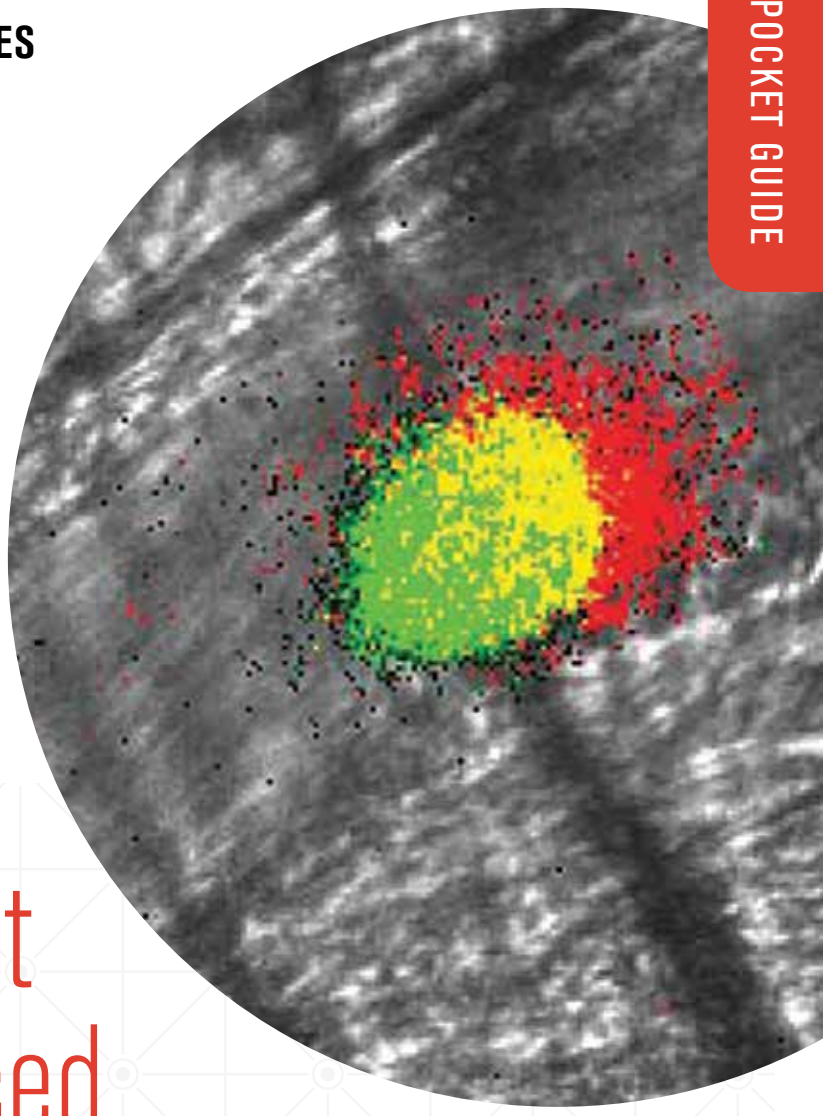
ASH CLINICAL PRACTICE GUIDELINES
VENOUS THROMBOEMBOLISM (VTE)

POCKET GUIDE



Diagnosis and Management of Heparin-Induced Thrombocytopenia (HIT)

A POCKET GUIDE FOR THE CLINICIAN

DECEMBER 2018

Allyson M. Pishko, MD, *University of Pennsylvania*
Lori-Ann Linkins, MD, MSc, *McMaster University*
Theodore E. Warkentin, MD, *McMaster University*
Adam Cuker, MD, MS, *University of Pennsylvania*

The recommendations in this guide are based on the 2018 American Society of Hematology (ASH) Clinical Practice Guidelines for Management of VTE: HIT

Evaluating the Clinical Probability of HIT

In patients with suspected HIT, the ASH guideline panel **recommends** using the 4Ts score to estimate the probability of HIT rather than a gestalt approach ✓.

THE 4Ts: A CLINICAL PROBABILITY SCORING SYSTEM[1,2]

4Ts	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; adrenal hemorrhage	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)

Missing or inaccurate information may lead to a faulty 4Ts score and inappropriate management decisions. Every effort should be made to obtain accurate and complete information necessary to calculate the 4Ts score. If key information is missing, it may be prudent to err on the side of a higher 4Ts score. Patients should be reassessed frequently. If there is a change in the clinical picture, the 4Ts score should be recalculated.

[1] Adapted from Lo et al., J Thromb Haemost 2006;4:759 and Warkentin et al., J Thromb Haemost 2010;8:1483.

[2] The 4Ts score may be used as a guide for clinicians but should not substitute for clinical judgment.

Laboratory Diagnosis

In patients with a low-probability 4Ts score, the ASH guideline panel **recommends against** HIT laboratory testing ✓. HIT laboratory testing may be appropriate for patients with a low-probability 4Ts score if there is uncertainty about the 4Ts score (for example, due to missing data).

If there is an intermediate- or high-probability 4Ts score, the ASH guideline panel **recommends** using an immunoassay ✓. If the immunoassay is positive and a functional assay is available, the ASH guideline panel **suggests** a functional assay C.

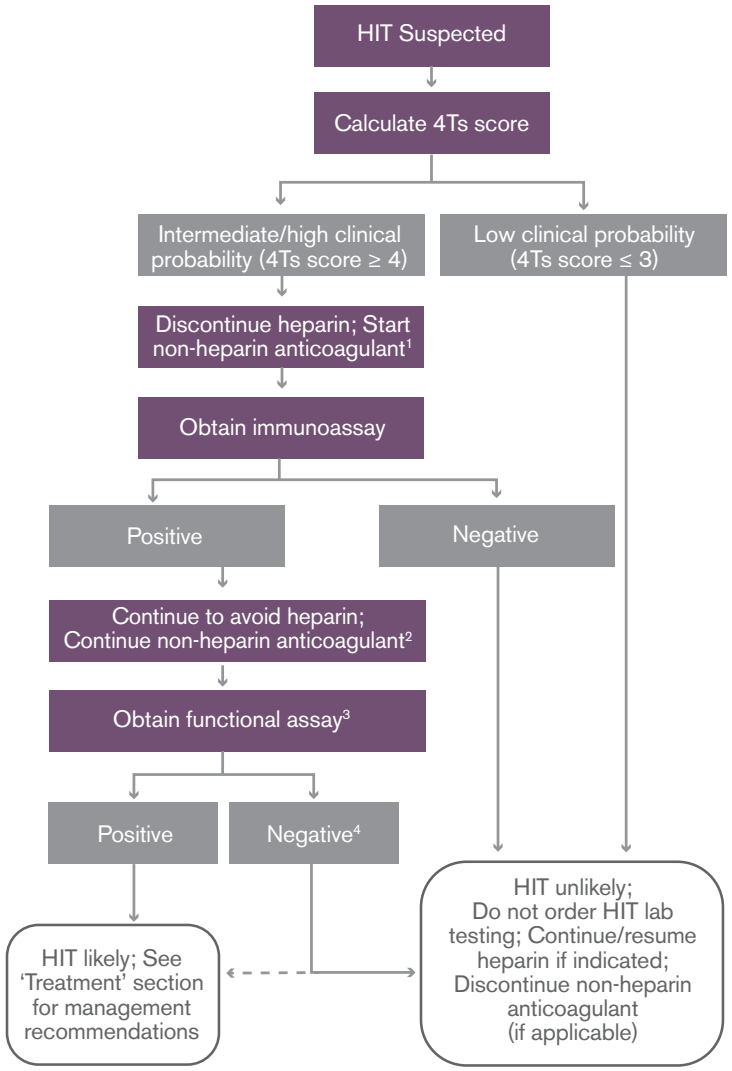
Assay Category	Mechanism	Examples			Comments
Immunoassay	Detects antibodies against PF4/heparin, regardless of their capacity to activate platelets	Polyspecific ELISA IgG-specific ELISA Rapid immunoassays[1]	>95%	80-90%	The likelihood of HIT increases with a higher 4Ts score and a higher ELISA optical density.
Functional platelet activation assay	Detects antibodies that induce heparin-dependent platelet activation	SRA HIPA	90-98%	90-95%	Not widely available; requires referral to a reference laboratory

ELISA, enzyme-linked immunoassay; HIPA, heparin-induced platelet activation assay; PF4, platelet factor 4; SRA, serotonin release assay

[1] Includes chemiluminescence assay, lateral flow immunoassay, latex agglutination assay, particle gel immunoassay

Different immunoassays and functional assays are available. The choice of assay may be influenced by diagnostic accuracy, availability, cost, feasibility, and turnaround time. If an ELISA is used, a low threshold is preferred over a high threshold.

Diagnostic and Initial Treatment Algorithm



[1] If the patient has an intermediate-probability 4Ts score, has no other indication for therapeutic-intensity anticoagulation, and is judged to be at high risk for bleeding, the panel suggests treatment with a non-heparin anticoagulant at prophylactic intensity rather than therapeutic intensity. If the patient has an intermediate-probability 4Ts score and is not judged to be at high risk for bleeding or has another indication for therapeutic-intensity anticoagulation, the panel suggests treatment with a non-heparin anticoagulant at therapeutic intensity rather than prophylactic intensity. In a patient with a high-probability 4Ts score, the panel recommends treatment with a non-heparin anticoagulant at therapeutic intensity.

[2] For all intermediate/high-probability patients with a positive immunoassay, including those who were receiving prophylactic-intensity treatment with a non-heparin anticoagulant prior to the availability of the immunoassay result, the panel recommends treatment with a non-heparin anticoagulant at therapeutic intensity.

[3] In some settings, a functional assay may not be available and decisions may need to be made based on the results of the 4Ts and immunoassay. A functional assay may not be necessary in patients with a high 4Ts score and a strongly positive immunoassay (e.g., an ELISA > 2.0 optical density units).

[4] Most patients with a negative functional assay do not have HIT and may be managed accordingly. However, depending on the type of functional assay and the technical expertise of the laboratory, false-negative results are possible. Therefore, a presumptive diagnosis of HIT may be considered for some patients with a negative functional assay, especially if there is a high-probability 4Ts score and a strongly positive immunoassay. This is represented in the figure by a dashed line.

Treatment

In patients with acute HIT complicated by thrombosis (HITT) or acute HIT without thrombosis (isolated HIT), the ASH guideline panel **recommends** discontinuation of heparin and initiation of a non-heparin anticoagulant ✓. When a non-heparin anticoagulant is being selected, the ASH guideline panel **suggests** argatroban, bivalirudin, danaparoid, fondaparinux, or a direct oral anticoagulant (DOAC) C.

NON-HEPARIN ANTICOAGULANTS FOR TREATMENT OF ACUTE HIT

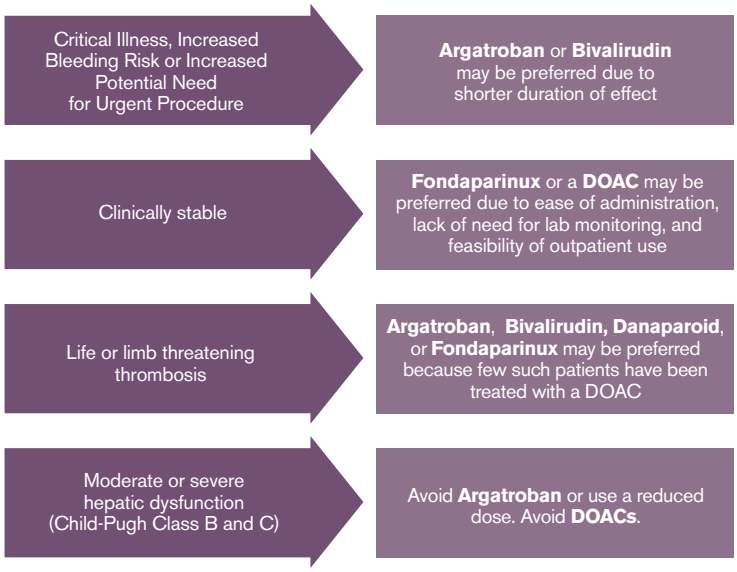
Drug	Dosing	Laboratory Monitoring
Argatroban	Bolus: None Continuous infusion: Normal organ function → 2 µm/kg/min Liver dysfunction (bilirubin > 1.5 mg/dl) → 0.5–1.2 µm/kg/min Heart failure, anasarca, post-cardiac surgery → 0.5–1.2 µm/kg/min	Adjust to APTT 1.5–3.0 times baseline
Bivalirudin	Bolus: None Continuous infusion: Normal organ function → 0.15 mg/kg/h Renal or liver dysfunction → dose reduction may be appropriate	Adjust to APTT 1.5–2.5 times baseline
Danaparoid	Bolus: <60 kg, 1,500 units 60–75 kg, 2,250 units 75–90 kg, 3,000 units >90 kg, 3,750 units Accelerated initial infusion: 400 units/h × 4 h, then 300 units/h × 4 h Maintenance infusion: Normal renal function → 200 units/h Renal dysfunction → 150 units/h	Adjust to danaparoid-specific anti-Xa activity of 0.5–0.8 units/mL
Fondaparinux1	<50 kg → 5 mg daily 50–100 kg → 7.5 mg daily >100 kg → 10 mg daily	None
Apixaban1,2	HITT: 10 mg twice daily × 1 week, then 5 mg twice daily Isolated HIT: 5 mg twice daily until platelet count recovery	None
Dabigatran1,2	HITT: 150 mg twice daily after ≥5 days of treatment with a parenteral non-heparin anticoagulant Isolated HIT: 150 mg twice daily until platelet count recovery	None
Rivaroxaban1,2	HITT: 15 mg twice daily × 3 weeks, then 20 mg daily Isolated HIT: 15 mg twice daily until platelet count recovery	None

[1] *Not approved for treatment of acute HIT*

[2] *Dosing for treatment of acute HIT is not well-established. Suggested dosing is extrapolated from venous thromboembolism and based on limited published evidence*

Selecting a Non-Heparin Anticoagulant

Choice of agent may be influenced by drug factors (availability, cost, ability to monitor the anticoagulant effect, route of administration, half-life), patient factors (kidney function, liver function, bleeding risk, clinical stability), and experience of the clinician.



TRANSITIONING TO AN ORAL AGENT

In patients with HIT initially treated with a parenteral agent, the ASH guideline panel **suggests** transitioning to a DOAC rather than warfarin C. The ASH guideline panel **recommends against** initiation of warfarin prior to platelet count recovery ✓. Specific guidance on transitioning from a parenteral agent to an oral agent is detailed in the table:

Transition	Timing of Initiation of Oral Agent	Overlap[1]	Additional Comments[1]
Parenteral agent → warfarin	Initiate warfarin once the platelet count has recovered (usually to ≥150 x 109/L).	Overlap parenteral agent with warfarin for ≥ 5 days and until INR has reached the intended target	Argatroban raises the INR. When transitioning from argatroban to warfarin the following steps should be taken: 1.Stop argatroban when INR on combined argatroban and warfarin is > 4. 2. Repeat INR in 4-6 hours. 3. If INR <2, restart argatroban. 4. Repeat procedure daily until INR ≥ 2 is achieved.
Parenteral agent → DOAC	Initiation of DOAC does not require platelet recovery. Transition when patient is clinically stable.	No overlap. Start DOAC within 2 hours of stopping argatroban or bivalirudin infusion, within 8-12 hours after stopping danaparoid infusion, and 24 hours after last dose of fondaparinux.	

[1] *Table provides general guidance on transitioning between agents and is not derived from the 2018 ASH Clinical Practice Guidelines for Management of VTE: HIT.*

SCREENING FOR ASYMPTOMATIC DVT AND DURATION OF ANTICOAGULATION

In patients with acute HIT without clinically apparent thrombosis, the ASH guideline panel **suggests** bilateral lower extremity compression ultrasonography to screen for asymptomatic proximal DVT C.

If an upper extremity central venous catheter is present, the ASH guideline panel **suggests** ultrasonography of the limb with the catheter to screen for asymptomatic DVT C.

In patients with acute HIT without clinically apparent thrombosis and no asymptomatic DVT identified by screening ultrasonography, the ASH guideline panel **suggests** that anticoagulation be continued, at a minimum, until platelet count recovery (usually a platelet count of ≥150 × 10^9/L). The ASH guideline panel **suggests against** continuing treatment for more than three months unless the patient has persisting HIT without platelet count recovery C. In patients with HIT complicated by thrombosis and no other indication for anticoagulation, anticoagulation is typically given for 3-6 months.

PLATELET TRANSFUSION

In patients with acute HITT or acute isolated HIT who are at average bleeding risk, the ASH guideline panel **suggests against** routine platelet transfusion C. Platelet transfusion may be an option for patients with active bleeding or at high bleeding risk.

Renal Replacement in Patients with a History of HIT

Phase of HIT	Platelet Count	Immunologic Assay	Functional Assay	Recommended Anticoagulation to Prevent Thrombosis of Dialysis Circuitry
Acute	Low	Positive	Positive	The ASH guideline panel **suggests** argatroban, danaparoid, or bivalirudin rather than other non-heparin anticoagulants C.
Subacute HIT A	Recovered	Positive	Positive	In patients who do not otherwise require therapeutic anticoagulation, the ASH guideline panel **suggests** regional citrate rather than heparin or other non-heparin anticoagulants to prevent thrombosis of the dialysis circuit C.[1]
Subacute HIT B	Recovered	Positive	Negative	
Remote	Recovered	Negative	Negative	

[1] *Citrate is not appropriate for patients with acute HIT, who require systemic rather than regional anticoagulation C.*

Heparin Re-Exposure in Patients with a History of HIT

CARDIAC AND VASCULAR SURGERY

In patients with a history of HIT, HIT laboratory testing may be used to define the phase of HIT and an appropriate strategy for intraoperative anticoagulation.

Phase of HIT	Platelet Count	Immunologic Assay	Functional Assay	Recommended intraoperative anticoagulation[1]
Acute HIT	Low	Positive	Positive	Delay surgery, if possible, until patient has subacute HIT B or remote HIT. If surgery cannot be delayed, the ASH guideline panel **suggests** bivalirudin; heparin with preoperative and/or intraoperative plasma exchange; or heparin with a potent antiplatelet agent (e.g., prostacyclin analogue or tirofiban) C.
Subacute HIT A	Recovered	Positive	Positive	
Subacute HIT B	Recovered	Positive	Negative	The ASH guideline panel **suggests** heparin rather than a non-heparin anticoagulant; heparin following plasma exchange; or heparin with an antiplatelet agent C.
Remote HIT	Recovered	Negative	Negative	

[1] *If heparin is used, exposure should be limited to the intraoperative setting and avoided before and after surgery*

CARDIAC CATHETERIZATION/PERCUTANEOUS CORONARY INTERVENTION

Phase of HIT	Platelet Count	Immunologic Assay	Functional assay	Recommended intraprocedural anticoagulation[1]
Acute	Low	Positive	Positive	The ASH guideline panel **suggests** bivalirudin C. Argatroban may be a suitable substitute if bivalirudin is not available.
Subacute HIT A	Recovered	Positive	Positive	
Subacute HIT B	Recovered	Positive	Negative	The ASH guideline panel **suggests** bivalirudin rather than heparin C. Argatroban may be a suitable substitute if bivalirudin is not available. Heparin is an acceptable alternative if a suitable non-heparin anticoagulant is not available.
Remote HIT	Recovered	Negative	Negative	

[1] *If heparin is used, exposure should be limited to the intraprocedural setting and avoided before and after the procedure*

Strength of Recommendations and Quality of Evidence

The methodology for determining the strength of each recommendation and the quality of the evidence supporting the recommendations was adapted from GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Guyatt GH, et al; GRADE Working Group. 2008;336(7650):924–926. More details on this specific adaptation of the GRADE process can be found in the 2018 ASH Clinical Practice Guidelines for Management of VTE: HIT.[1]

Strength of Recommendation	
✓	**Strong recommendations -** Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
C	**Conditional recommendations -** Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values and preferences.

How to Use This Pocket Guide

ASH pocket guides are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. The information included in this guide is not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the unique clinical presentation of an individual patient, ideally through a shared process that considers the patient's values and preferences with respect to all options and their possible outcomes. Decisions may be constrained by realities of a specific clinical setting, including but not limited to institutional policies, time limitations, or unavailability of treatments. ASH pocket guides may not include all appropriate methods of care for the clinical scenarios described. As new evidence becomes available, these pocket guides may become obsolete. Following the guidance in these pocket guides cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these pocket guides.

The complete 2018 ASH Clinical Practice Guidelines for Management of VTE: HIT[1] include additional remarks and contextual information that may affect clinical decisionmaking. To learn more about these guidelines, visit ***hematology.org/vte***.

Drs. Pishko, Linkins, Warkentin, and Cuker declare no competing financial interests.

[1] *Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia.* Blood Adv. *2018;2(22). In press.*

This and other ASH pocket guides are also available in the ASH Pocket Guides App, available for Android and iOS devices. More information about this and other ASH pocket guides may be found at ***hematology.org/pocketguides***.

American Society of Hematology
2021 L Street NW, Suite 900
Washington, DC 20036
www.hematology.org

For expert consultation on HIT and other hematologic diseases, submit a request to the ASH Consult a Colleague program at ***www.hematology.org/consult*** (ASH members only).