

ASH CLINICAL PRACTICE GUIDELINES VENOUS THROMBOEMBOLISM (VTE)



Diagnosis & Management of Heparin-Induced Thrombocytopenia

An Educational Slide Set

American Society of Hematology 2018 Guidelines for Management of Venous Thromboembolism

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Clinical Guidelines

American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparininduced thrombocytopenia

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ASH Clinical Practice Guidelines on VTE

- 1. Prevention of VTE in Surgical Hospitalized Patients
- 2. Prevention of VTE in Medical Hospitalized Patients
- 3. Treatment of Acute VTE (DVT and PE)
- 4. Optimal Management of Anticoagulation Therapy
- 5. Prevention and Treatment of VTE in Patients with Cancer

6. Heparin-Induced Thrombocytopenia (HIT)

- 7. Thrombophilia
- 8. Pediatric VTE
- 9. VTE in the Context of Pregnancy
- 10. Diagnosis of VTE



How were these ASH guidelines developed?

PANEL FORMATION

Each **guideline panel** was formed following these key criteria:

- Balance of expertise (including disciplines beyond hematology, and patients)
- Close attention to minimization and management of conflicts of interest

CLINICAL QUESTIONS

10 to 20 clinicallyrelevant questions generated in PICO format (population, intervention, comparison, outcome)

Example: PICO question

"In patients with suspected HIT and an intermediate probability 4Ts score, should non-heparin anticoagulants be provided at therapeutic or prophylactic intensity?"

EVIDENCE SYNTHESIS

Evidence summary generated for each PICO question via systematic review of health effects plus:

- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

MAKING RECOMMENDATIONS

Recommendations made by guideline panel members based on evidence for all factors.



How patients and clinicians should use these recommendations

	STRONG Recommendation ("The panel recommends")	CONDITIONAL Recommendation ("The panel suggests")
For patients	Most individuals would want the intervention.	A majority would want the intervention, but many would not.
For clinicians	Most individuals should receive the intervention.	Different choices will be appropriate for different patients, depending on their values and preferences. Use shared decision making .



Objectives

By the end of this module, you should be able to

- 1. Describe a <u>diagnostic algorithm</u> for patients with suspected heparin-induced thrombocytopenia (HIT)
- 2. Compare <u>non-heparin anticoagulants</u> for the treatment of acute HIT
- 3. Describe recommendations for managing anticoagulation for <u>cardiac surgery</u> in patients with a previous history of HIT





HIT is an iatrogenic disorder usually mediated by IgG antibodies that bind **PF4-heparin** complexes These antibodies cause a hypercoagulable state by activating platelets and procoagulant microparticles

One-third to one-half of patients with HIT develop venous, arterial, or microvascular thrombosis Unfractionated heparin (UFH) associated with 10-fold increase in risk of HIT compared with LMWH





82 year old male

Past Medical History: Diabetes, hypertension, congestive heart failure

Medications: Metformin, ramipril, aspirin, furosemide

Admitted to: Internal Medicine ward with exacerbation of congestive heart failure, secondary to poor compliance with diet and diuretics

Treated with:

- Intravenous furosemide, nitroglycerin patch
- *Subcutaneous unfractionated heparin (UFH)* 5,000 IU Q12H started on admission date for DVT prophylaxis





- Bloodwork: Day 0 is admission date
- No fever, no other new medications. Normal blood pressure and heart rate. No signs or symptoms of venous thromboembolism.
- No bleeding or bruising
- No exposure to heparin in the 3 months prior to this admission

Date	Day 0	+1	+2	+3	+4	+5	+6	+7
Platelets (x 10 ⁹)	200	220	206	210	220	230	150	67



Considering your patient's progressive thrombocytopenia and heparin exposure, you are concerned about the possibility of HIT.

Which of the following most accurately describes his clinical probability of HIT?

- A. Probably low probability, given overall clinical context
- B. Probably high probability, given overall clinical context
- C. Low probability, based on 4Ts score
- D. Intermediate probability, based on 4Ts score
- E. High probability, based on 4Ts score



Recommendation

In patients with **suspected HIT**, the panel recommends using the <u>**4Ts score**</u> to estimate the probability of HIT <u>**rather than a gestalt approach**</u> (strong recommendation, moderate certainty)

Remarks:

- Missing or inaccurate information may lead to a faulty 4Ts score and inappropriate management
- 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.
- Reassess frequently. If there is a change in clinical picture, the 4Ts score should be recalculated.





The 4Ts Score: Clinical Probability Model

Our patient:

Platelets 67, > 50% drop.Onset of drop on day +6.No thrombosis.No other cause for thrombocytopenia.

HIGH probability: 6-8 points

INTERMEDIATE probability: 4-5 points

LOW probability: ≤ 3 points

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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 (con- firmed); skin necrosis at heparin injection sites; anaphylactoid reaction after IV heparin bolus; adrenal hemorrhage	Progressive or recurrent thrombosis; Non-nec- rotizing (erythematous) skin lesions; Suspected thrombosis (not con- firmed)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite



Your patient's 4Ts score indicates a high clinical probability for HIT.

What diagnostic tests would you recommend at this point to confirm or exclude a diagnosis of HIT?

- A. None; patient is high probability and diagnosis is confirmed
- B. Immunoassay only (ex. HIT PF4/heparin ELISA)
- C. Functional test only (ex. serotonin release assay)
- D. Immunoassay, and if positive then perform functional test





HIT Immunoassay Tests Detect the presence of anti-PF4/heparin antibodies		Functional HIT Assays Assays that detect antibodies capable of binding and activating platelets		
•	ELISA (detect IgG) ELISA (detect polyspecific antibodies)	•	Serotonin release assay (SRA) Heparin-induced platelet activation test	
•	IgG-specific chemiluminescent assay Particle gel immunoassay (PaGIA)	•	(HIPA) Platelet aggregation test (PAT) Elow cytometry-based assays	





Recommendation

- If there is an **intermediate- or high-probability 4Ts score**, the panel **recommends an immunoassay** (strong recommendation, moderate certainty)
- If the **immunoassay is positive** and a functional assay is available (locally or as a send-out test to a reference laboratory), the panel suggests a **functional assay** (conditional recommendation, moderate certainty)

Remark:

• Likelihood of HIT increases with a higher 4Ts score and a higher ELISA OD (Optical Density)



A *diagnostic algorithm* of intermediate/high 4Ts score, followed by immunoassay, followed by functional testing results in:

- Few false negatives (missed HIT diagnoses), and
- Few or no false positives (incorrect diagnoses of HIT)







What management strategy would you recommend while awaiting the HIT ELISA test results?

- A. Continue heparin as the diagnosis of HIT is not confirmed
- B. Stop heparin, wait for ELISA result
- C. Stop heparin, start non-heparin anticoagulant at prophylactic intensity
- D. Stop heparin, start non-heparin anticoagulant at therapeutic intensity
- E. Stop heparin, transfuse platelets





In patients with suspected HIT and <u>HIGH PROBABILITY</u> 4Ts score:

• The panel recommends discontinuation of heparin and initiation of a non-heparin anticoagulant at **therapeutic intensity** (strong recommendation, moderate certainty)

In patients with suspected HIT and <u>INTERMEDIATE PROBABILITY</u> 4Ts score:

- The panel recommends **discontinuation of heparin** (strong recommendation, moderate certainty)
- The panel suggests initiation of non-heparin anticoagulant at <u>prophylactic intensity</u> if patient is at high bleeding risk, <u>therapeutic intensity</u> if patient not at high bleeding risk

In patients with INTERMEDIATE-risk 4Ts score who have high bleeding risk, there could be greater harm with therapeutic-intensity treatment (bleeding) with less potential benefit, because fewer such patients will have HIT



Therapeutic versus Prophylactic Intensity

- Non-heparin anticoagulant at therapeutic intensity is recommended over prophylactic intensity based on *very low certainty of evidence*
 - 3 small studies comparing therapeutic versus prophylactic anticoagulation with Danaparoid, Lepirudin, or Fondaparinux
 - Danaparoid showed 50% reduction in thrombosis with therapeutic dosing
 - No difference in outcomes with Lepirudin and Fondaprainux
- However, strong recommendation based on likely large magnitude of benefit (prevention of thrombosis)

Schindewolf *Thromb Res* 2012 Greinacher A *Circulation* 1999 Farner *Thromb Haemost* 2001





In patients with HIT who are at average bleeding risk, the panel suggests <u>against</u> <u>routine platelet transfusion</u> (conditional recommendation, low certainty)

Remark:

• Platelet transfusion may be an option for patients with active bleeding or at high bleeding risk

Low certainty for beneficial or adverse effects of platelet transfusions in HIT Mixed results from observational studies

→ One large database study (n = 6,332) suggested increase in arterial thrombotic events (adjusted odds ratio 3.4, 95% CI 1.2 to 9.5); other small cohort studies suggest no difference

Goel *Blood* 2015 Refaai *J Thromb Haemost* 2010





Case 1: HIT Laboratory Test Results

- Your HIT immunoassay (ELISA) results are reported back that afternoon as optical density (OD) = 1.8 (NORMAL OD is < 0.4 at your lab).
- You ask your lab to send a sample to your local reference lab for a confirmatory functional assay (serotonin release assay).
- Your patient continues to be clinically stable with no symptoms or signs of pulmonary embolism, deep vein thrombosis, or arterial thrombosis.





Your patient has acute isolated HIT (without thrombosis), and platelet count is currently 67.

Which of the following non-heparin anticoagulants would NOT be appropriate at this point?

- A. Argatroban
- B. Warfarin (vitamin K antagonist)
- C. Rivaroxaban
- D. Fondaparinux
- E. Danaparoid



Recommendation

In patients with acute HITT or acute isolated HIT, the panel recommends <u>against</u> initiation of a VKA prior to platelet count recovery (platelets $\geq 150 \times 10^9$ /L) (strong recommendation, moderate certainty)

Remarks:

- Also applies to those taking VKA at onset of acute HITT or acute isolated HIT
- In these patients, VKA would be discontinued and intravenous Vitamin K administered concomitant with initiation of a non-heparin anticoagulant

In case series, early initiation	Warfarin-induced	Venous limb	Recurrent	Limb amputation
of VKA associated:	skin necrosis	gangrene	thrombosis	



Recommendation

- In patients with acute HIT complicated by thrombosis (HITT) or acute HIT without thrombosis (isolated HIT), the panel *recommends* **discontinuation of heparin** and initiation of a **non-heparin anticoagulant** (*strong recommendation, moderate certainty*)
- The panel suggests argatroban, bivalirudin, danaparoid, fondaparinux or a direct oral anticoagulant (DOAC)



Rationale for Anticoagulant Selection

- Using a non-heparin anticoagulant (compared with stopping heparin +/- starting VKA) associated with:
 - Fewer thrombotic events
 - BUT probably increase in risk of major bleeding
- No direct comparisons of DOACs vs. parenteral anticoagulants in HIT
- Small numbers of patients treated with DOACs in case series
 - Few thrombotic events (*rivaroxaban 1/46, apixaban 0/12, dabigatran 1/11*)
 - Benefits and harms of DOACs compare favorably to parenteral agents





Rationale for Anticoagulant Selection

Clinical Context	Implications for Anticoagulant Selection
Critical illness Increased bleeding risk Possible urgent procedures	 Argatroban or Bivalirudin (shorter duration of effect) If <i>moderate or severe hepatic dysfunction</i> (Childs-Pugh B or C), may be advisable to avoid argatroban or use a reduced dose
Life- or limb-threatening VTE (massive PE or venous limb gangrene)	 Parenteral non-heparin anticoagulant preferred (Argatroban, Bivalirudin, Danaparoid, Fondaparinux) Few such patients treated with DOACs
Clinically stable patients at average bleeding risk	 Fondaparinux or DOACs reasonable Most published DOAC experience with Rivaroxaban



Anticoagulant (mechanism, route)	Dosing	Clearance & Monitoring
Argatroban (direct thrombin inhibitor) IV	Bolus: None Infusion: STANDARD (2 mcg/kg/min), REDUCED DOSE for liver dysfunction, CHF, post-cardiac surgery (0.5-1.2 mcg/kg/min)	 Hepatobiliary clearance Adjusted to aPTT 1.5-3.0 times baseline
Bivalirudin (direct thrombin inhibitor) IV	Bolus: None Infusion: STANDARD (0.15 mg/kg/hr); consider REDUCED DOSE for renal or liver dysfunction	 Enzymatic clearance Adjusted to aPTT 1.5-2.5 times baseline
Danaparoid (indirect Xa inhibitor) IV	Bolus: Weight-based (1500-3750 units) Infusion: INITIAL ACCELERATED (400 units/hr x 4 hr, then 300 units/hr x 4 hr), then MAINTENANCE (150-200 units/hr)	 Renal clearance Adjusted to anti-Xa activity 0.5-0.8 units/mL
Fondaparinux (indirect Xa inhibitor) SC	< 50 kg \rightarrow 5 kg daily 50-100 kg \rightarrow 7.5 mg daily > 100 kg \rightarrow 10 mg daily	Renal clearanceNo monitoring
Rivaroxaban (direct Xa inhibitor) PO	<i>HITT:</i> 15 mg twice daily x 3 weeks, then 20 mg daily <i>Isolated HIT:</i> 15 mg twice daily until platelet count recovery (≥ 150)	Renal clearanceNo monitoring



Case 1: Treatment

- You decide to start your patient on rivaroxaban 15 mg PO BID and discontinue subcutaneous UFH.
- Over the next 8 days, your patient's platelet count gradually rises from 67 to 165, and there is no evidence of bleeding.



Your patient has no symptoms of deep vein thrombosis or pulmonary embolism.

Which of the following tests would you suggest to screen for asymptomatic VTE?

- A. There are no symptoms, so imaging is not indicated
- B. Bilateral upper extremity compression ultrasound (US)
- C. Bilateral lower extremity compression ultrasound (US)
- D. CT pulmonary angiogram
- E. Choices C & D



Recommendation

In patients with **acute isolated HIT**, the panel suggests:

- **<u>Bilateral lower extremity compression US</u>** to screen for asymptomatic proximal DVT (conditional recommendation, very low certainty)
- <u>Upper-extremity US</u> in patients with an upper extremity central venous catheter, in the limb with the catheter, to screen for asymptomatic DVT (conditional recommendation, very low certainty)

Ultrasound studies have identified silent lower extremity DVT in 12-44% of asymptomatic patients with HIT





Case 1: HITT

- He is found to have an **occlusive left popliteal vein DVT**. He continues rivaroxaban 15 mg BID for 3 weeks, then takes rivaroxaban 20 mg daily for a total of 3 months.
- At 3 months, his platelet count is normal (205 x 10⁹/L) and he is at his baseline health status. You ask him to stop rivaroxaban.
- 15 months later, he returns to hospital with CHF again and is found to have severe aortic stenosis, with an aortic valve area of 0.6 cm². He requires a valve replacement.





Your patient with a history of HITT requires open heart surgery, with intraoperative anticoagulation while on pump. His platelet count is normal. You repeat his HIT ELISA and OD is 0.2 (NORMAL < 0.4).

What would you suggest that your patient receive for intraoperative anticoagulation?

- A. Preoperative plasma exchange and intraoperative heparin
- B. Intraoperative heparin only
- C. Intraoperative heparin with an antiplatelet agent
- D. Intraoperative bivalirudin only
- E. Intraoperative bivalirudin with an antiplatelet agent





Five Phases of HIT

Phase	Platelet count	Immunoassay	Functional assay	
Suspected HIT	Decreased	?	?	
Acute HIT	Decreased	+	+	
Subacute HIT A	Normal	+	+	
Subacute HIT B	Normal	+	_	
Remote HIT	Normal	_	_	





Recommendation

In patients with **subacute HIT B or remote HIT who require cardiovascular surgery**, the panel suggests **intraoperative anticoagulation with heparin** rather than treatment with a non-heparin anticoagulant, plasma exchange and heparin, or heparin combined with antiplatelet agent (conditional recommendation, very low certainty)

Remarks:

- Treatment with heparin would be *limited to the intraoperative setting*, and avoided before and after surgery
- **Postoperative platelet count monitoring** for HIT may be necessary, even when postoperative heparin is not given, because "delayed-onset (autoimmune) HIT" beginning 5 to 10 days after intraoperative heparin exposure has been reported





82 year old male

Past Medical History: Diabetes, hypertension, congestive heart failure

Medications: Metformin, ramipril, aspirin, furosemide

Admitted to: Internal Medicine ward with exacerbation of congestive heart failure, secondary to poor compliance with diet and diuretics

Treated with:

- Intravenous furosemide, nitroglycerin patch
- *Subcutaneous unfractionated heparin (UFH)* 5,000 IU Q12H started on admission date for DVT prophylaxis



Case 2: Medical Inpatient Admission

- Bloodwork: Day 0 is admission date
- No fever, no other new medications. Normal blood pressure and heart rate. No signs or symptoms of venous thromboembolism
- No bruising or bleeding
- No exposures to heparin in the 3 months prior to this admission

Date	Day 0	+1	+2	+3	+4	+5	+6	+7
Platelets (x 10 ⁹)	200	220	206	145	140	145	130	125



Considering your patient's progressive thrombocytopenia and heparin exposure, you are concerned about the possibility of HIT.

Which of the following most accurately describes his clinical probability of HIT?

- A. Probably low probability, given overall clinical context
- B. Probably high probability, given overall clinical context
- C. Low probability, based on 4Ts score
- D. Intermediate probability, based on 4Ts score
- E. High probability, based on 4Ts score





Our patient:

Platelets 125, 30-50% drop Drop at Day +2 No thrombosis No other cause for thrombocytopenia

HIGH probability: 6-8 points

INTERMEDIATE probability: 4-5 points

LOW probability: ≤ 3 points

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 (con- firmed); skin necrosis at heparin injection sites; anaphylactoid reaction after IV heparin bolus; adrenal hemorrhage	Progressive or recurrent thrombosis; Non-nec- rotizing (erythematous) skin lesions; Suspected thrombosis (not con- firmed)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite



Your patient's 4Ts score (3) indicates a low clinical probability for HIT.

What diagnostic tests would you recommend at this point to confirm or exclude a diagnosis of HIT?

- A. None; patient is low probability and HIT is highly unlikely
- B. Immunoassay only (ex. HIT PF4/heparin ELISA)
- C. Functional test only (ex. serotonin release assay)
- D. Immunoassay, and if positive then perform functional test



Recommendation

In patients with suspected HIT and **low probability 4Ts score**, the panel recommends **against HIT laboratory testing** (strong recommendation, moderate certainty)

Remark:

• 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)







Case 2: Resolution

- Given his low clinical probability, you elect not to send his HIT ELISA assay or functional assay. He continues to receive SC heparin.
- With treatment for CHF, his thrombocytopenia improves. He is discharged with a follow-up outpatient CBC to ensure resolution of thrombocytopenia





Additional Topics in these Guidelines

- Platelet count monitoring in patients receiving heparin
- Prophylactic IVC filter insertion in the setting of acute HIT
- Duration of non-heparin anticoagulant therapy in acute isolated HIT
- Anticoagulant management for percutaneous coronary intervention in patients with acute HIT or previous history of HIT
- Anticoagulant therapy for HIT in renal replacement therapy



Areas of Future Investigation

- Development of novel HIT immunoassays and functional assays
- Outcomes from treatment of acute HIT with DOACs
- Comparisons of DOACs and parenteral non-heparin anticoagulants
- Role of concomitant antiplatelet and anticoagulant therapy in HIT
- Impact of screening for asymptomatic DVT in acute isolated HIT
- Optimal duration of anticoagulation in acute isolated HIT
- Intraoperative anticoagulant management for cardiovascular surgery



In Summary: Back to our Objectives

- 1. Describe a <u>diagnostic algorithm</u> for patients with suspected heparin-induced thrombocytopenia (HIT)
 - 4Ts score, immunoassay, functional assay
- 2. Compare <u>non-heparin anticoagulants</u> for treatment of acute HIT
 - DOACs or parenteral options (Argatroban, Fondaparinux, Danaparoid, Bivalirudin)
- 3. Describe recommendations for managing anticoagulation for <u>cardiac surgery</u> in patients with a previous history of HIT
 - Determination of HIT clinical status with ELISA and/or functional assay helps to determine intraoperative anticoagulation plan



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See more about the **ASH VTE guidelines** at <u>http://www.hematology.org/VTEguidelines</u> Don't miss our updated **HIT Pocket Guide**!