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: heparin-induced thrombocytopenia

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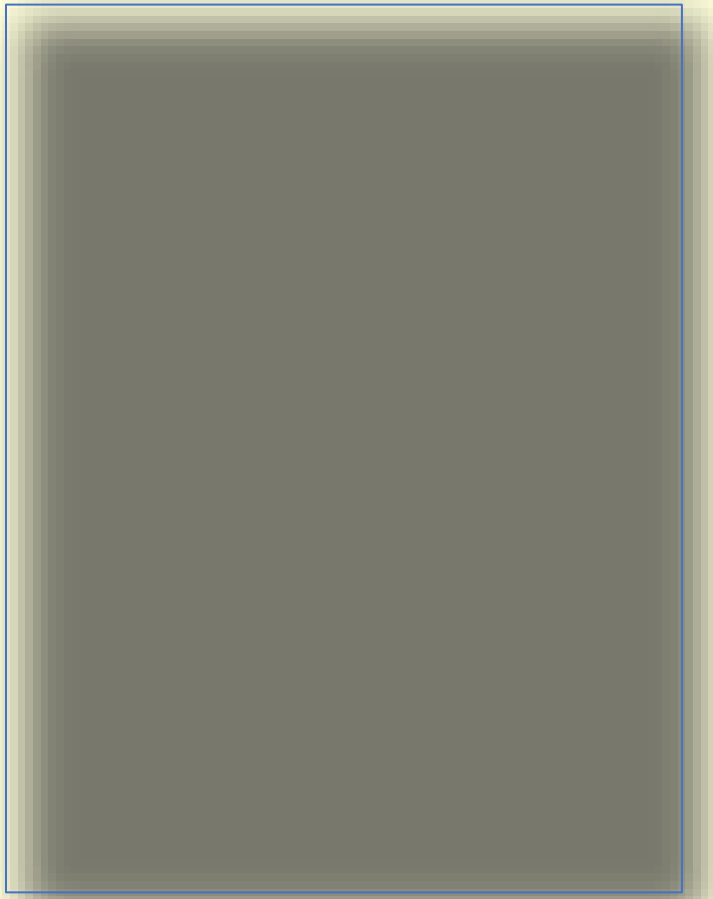

ASH Clinical Practice Guidelines on VTE

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.

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

HIT is a profoundly hypercoagulable state

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

Case 1: Medical Inpatient Admission

82 year old male

Past Medical History: Diabetes, hypertension, congestive heart failure

Medications:

Case 1: 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 bleeding or bruising

No exposure to heparin in the 3 months prior to this admission

Date	
Platelets (x 10^9)	

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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 4Ts score to estimate the probability of HIT rather than a gestalt approach

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.

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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.

Laboratory Diagnostic Testing for HIT

HIT Immunoassay Tests	

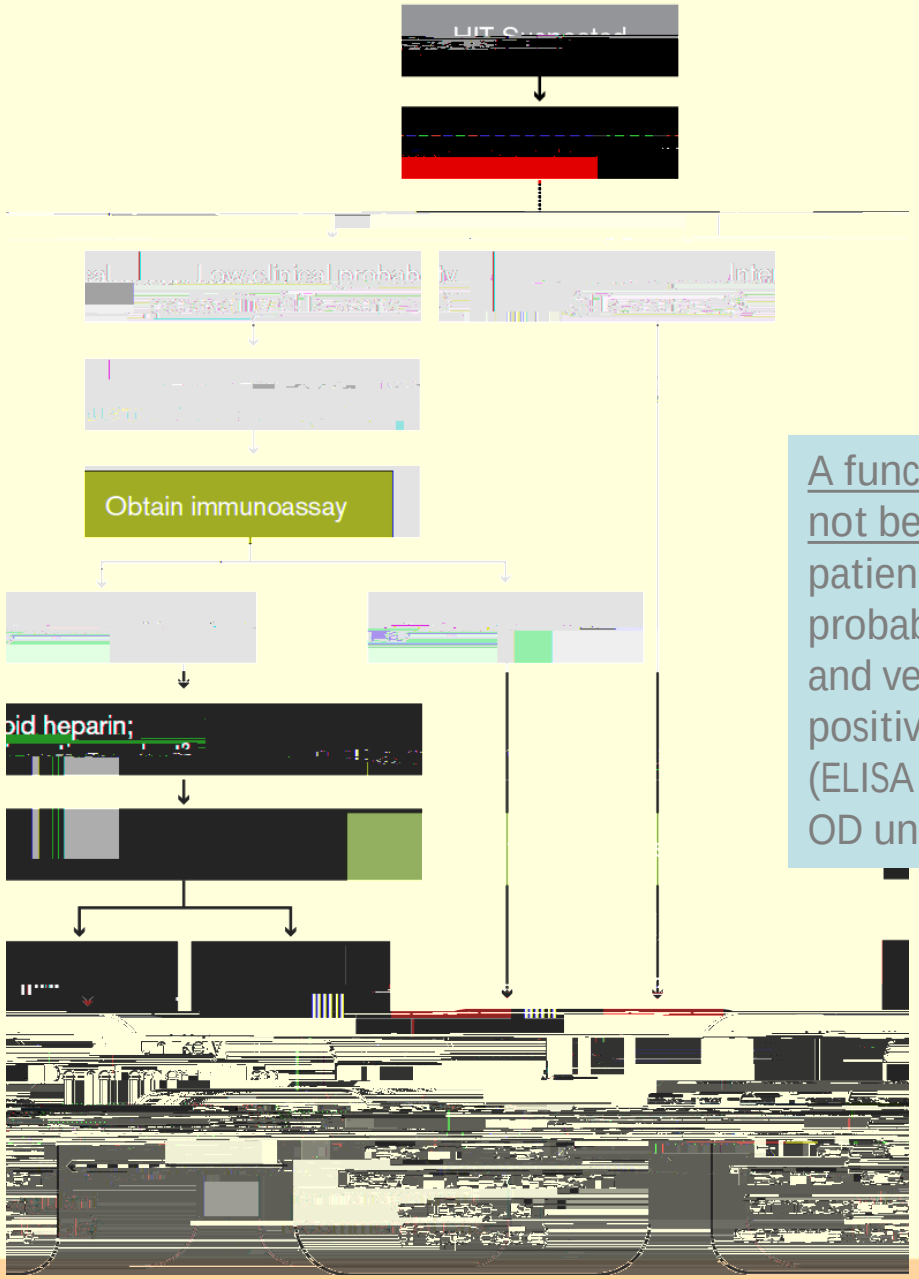
Recommendation

If there is an intermediate- or high-probability 4Ts score, the panel recommends an immunoassay

If the immunoassay is positive and a functional assay is available (locally or as a send-out test to a

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)



A functional assay may not be necessary for patients with high probability 4Ts score and very strongly positive immunoassay (ELISA value of > 2.0 OD units)

¸2dzN LJI·ŭλŜyűΩă ⊓¢ă ăÖ2NŜ λyŘλÖI·ŭŜă high probability for HIT, and you have sent off the HIT ELISA (result is pending). Currently, your patient is receiving subcutaneous UFH 5,000 units twice daily.

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

Recommendation

In patients with suspected HIT and HIGH PROBABILITY 4Ts score:

The panel recommends discontinuation of heparin and initiation of a non-heparin anticoagulant at therapeutic intensity

In patients with suspected HIT and INTERMEDIATE PROBABILITY 4Ts score:

The panel recommends discontinuation of heparin

The panel suggests initiation of non-heparin anticoagulant at prophylactic intensity if patient is at high bleeding risk, therapeutic intensity 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

- 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 2012
Greinacher A 1999
Farner 2001

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 2015

Refaai 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 against initiation of a VKA prior to platelet count recovery (platelets ≥ 150 x 10^9/L) (

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 of VKA associated:	Warfarin-induced skin necrosis	Venous limb gangrene	Recurrent thrombosis	Limb amputation

Rationale for Anticoagulant Selection

Using a non-heparin anticoagulant associated with:

- Fewer thrombotic events
- BUT probably increase in risk of major bleeding

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

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.

Recommendation

In patients with acute isolated HIT, the panel suggests:

Bilateral lower extremity compression US to screen for asymptomatic proximal DVT

Upper-extremity US in patients with an upper extremity central venous catheter, in the limb with the catheter, to screen for asymptomatic DVT

Case 1: HITT

He is found to have an occlusive left popliteal vein DVT. He continues rivaroxaban 15

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

Remarks:

- Treatment with heparin would be limited to the intraoperative settin

Case 2: Medical Inpatient Admission

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

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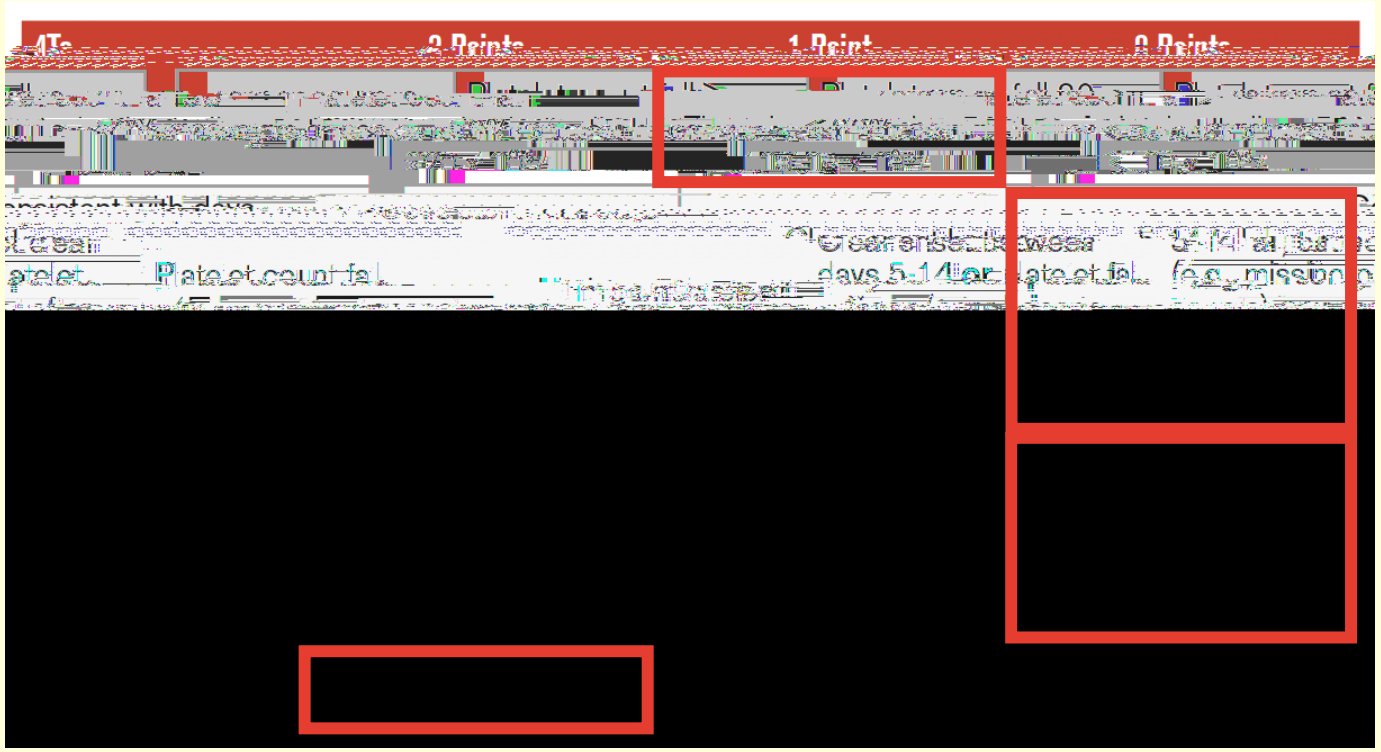
The 4Ts Score: Clinical Probability Model

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



Lo 2006
ASH 2009 Clinical Guide

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

Recommendation

In patients with suspected HIT and low probability 4Ts score, the panel recommends against HIT laboratory testing


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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

Date	Day 0	+1	+2	+3	
Platelets (x 10^9)	200	220	206	145	

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

Acknowledgements