

GUIDELINE

HEPARIN-INDUCED THROMBOCYTOPENIA

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Revision Date:

I. **PURPOSE:**

A. Heparin-induced thrombocytopenia (HIT) is a serious and life threatening condition. As such, a high clinical suspicion, accurate assessment/diagnosis, and initiation of prompt and effective treatment are necessary. This institutional guideline incorporates established current clinical practice recommendations and provides evidence-based recommendations for:¹⁻¹⁶

1. Assessment of a clinical suspicion of HIT
 - a. General approach
 - b. Structured pretest clinical probability assessment
 - c. Appropriate use and interpretation of laboratory assays
 - d. Confirming or refuting a diagnosis of HIT
2. Management of patients with suspected and/or confirmed acute HIT.
3. Approach to patients with a history of HIT who re-enter the healthcare system.
4. Appropriate selection and use of non-heparin anticoagulants.

II. **GUIDELINE:**

A. Establishing a diagnosis of Heparin Induced Thrombocytopenia (HIT)

Heparin induced thrombocytopenia is a complex clinical-pathologic syndrome that is difficult to accurately diagnose; available laboratory assays have limitations and cannot be used as a sole means of arriving at a diagnosis. Evaluation requires a high index of clinical suspicion combined with both careful clinical assessment, and appropriate laboratory use and interpretation. Clinical assessment is mandatory. This guideline provides tools for the clinician in the assessment and diagnosis of HIT.

B. Clinical Assessment and Management of Suspected HIT

1. The hallmark of HIT is the development of acute thrombocytopenia in the setting of heparinoid (heparin or low molecular weight heparin) exposure.
2. Importantly, there are many other causes of thrombocytopenia in the hospitalized patient. Many of these are more frequent than HIT. (TABLE 1 and TABLE 2).
3. Approach the diagnosis of HIT using the flow-sheet on PAGE 2 (FIGURE 1).

C. Management of patients with a history of HIT

1. Patients with a HIT diagnosis within past 90 days – use non-heparin anticoagulant as clinical situation dictates.
 - a. Patients with a HIT diagnosis greater than 90 days in past – use a non-heparin anticoagulant as clinical situation dictates, OR order ELISA to see if HIT antibodies are detectable – if negative then short period of exposure to heparin/LMWH acceptable.

D. Use of non-heparin anticoagulation options

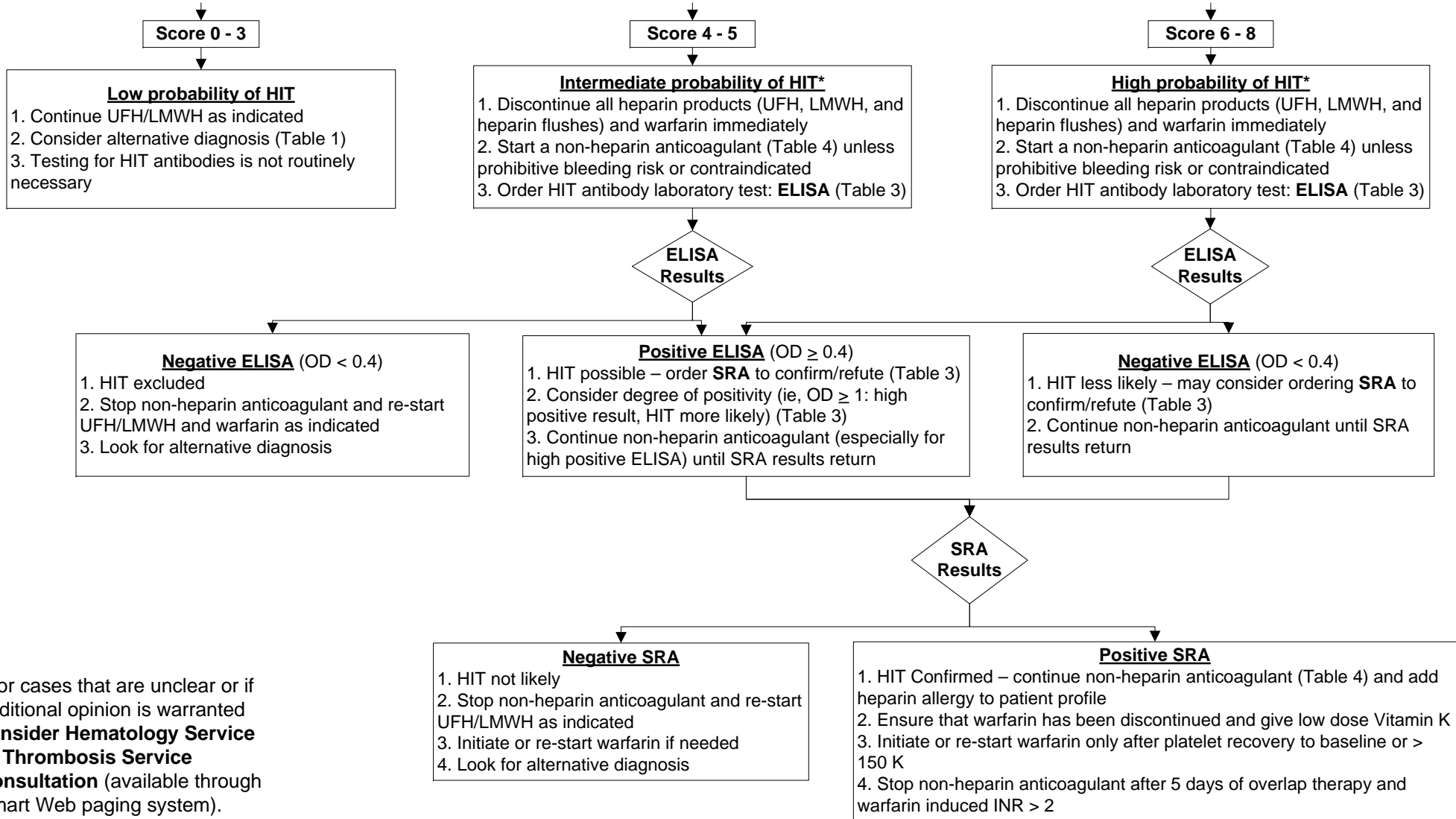
1. Do not administer if patient has a contraindication to selected medication. (See TABLE 4 for a comparison of non-heparin anticoagulants and CPOE links)
2. Consider Hematology or Thrombosis Service consult.

**Figure 1.
HIT Management
Guideline**

Confirm thrombocytopenia is present.
Assess for overtly obvious alternative cause, including other medications that cause thrombocytopenia. See Tables 1 & 2

Assess the pre-test probability of HIT by calculating the **4T's score** – Add up score in each category; Maximum score = 8

4T's Parameter	2 Points each	1 Point each	0 Point each
Thrombocytopenia	Decrease >50% from baseline or nadir >20 K	Decrease 30%-50% from baseline or nadir 10-19 K	Decrease <30% from baseline or nadir <10 K
Timing of platelet count drop with heparin exposure	Onset Days 5-10 or ≤1 day (if heparin exposure in prior 30 days)	Onset Days 5-10 but unclear due to missing data; Onset after Day 10 or ≤ 1day with heparin exposure in the past 31-100 days	Platelet count decrease <4 days without recent exposure
Thrombosis or other complications	New thrombosis, skin necrosis, or acute systemic reaction after heparin bolus	Progressive, recurrent, or suspected thrombosis; erythematous skin lesions while on heparin	None
Other explanations	No other possible causes are evident	Possible	Definite



*For cases that are unclear or if additional opinion is warranted consider Hematology Service or Thrombosis Service Consultation (available through Smart Web paging system).

Table 1. Alternative Causes of Acute Thrombocytopenia⁴

Disease States	Drugs	Other
<ul style="list-style-type: none"> • Sepsis • Disseminated intravascular coagulation • Thrombotic thrombocytopenic purpura • Hemolytic uremic syndrome • Hypersplenism 	<ul style="list-style-type: none"> • Heparin • Chemotherapy • Alcohol • Other Medications – See TABLE 2 below 	<ul style="list-style-type: none"> • Laboratory error (eg, platelet clumping) • Dilutional – large volume transfusion or crystalloid infusion • Peripheral destruction (eg, ventricular–assist device, post-cardiac surgery)

Table 2. Drug-induced Causes of Thrombocytopenia¹⁶

Medications strongly associated with drug-induced thrombocytopenia ^{a, b, c}	
Abciximab Efalizumab Heparin Tirofiban Vancomycin	
Medications potentially associated with drug-induced thrombocytopenia ^{a, b, d}	
Analgesics	Antitubercular agents
Acetaminophen Diclofenac Ibuprofen Naproxen Sulindac Tolmentin	Ethambutol Isoniazid
	Cardiovascular agents
	Amiodarone Captopril Chlorothiazide Digoxin Eptifibatide Hydrochlorothiazide Methyldopa Minoxidil Nitroglycerin Procainamide Quinidine Tirofiban
Antibiotics	
Ampicillin Linezolid Piperacillin Rifampin Sulfisoxazole Trimethoprim/Sulfamethoxazole Vancomycin	
Anticonvulsants	Gastrointestinal agents
Carbamazepine Phenytoin Valproate	Cimetidine Famotidine Ranitidine Sulfasalazine
Antidiabetic agents	
Chlorpropamide Glyburide	Miscellaneous agents
Antifungals	Aminosalicic acid Chlordiazepoxide-clidinium bromide Danazol Diazepam Diazoxide Deferoxamine Etretinate Gold salts Interferon alpha Octreotide Quinine Simvastatin
Amphotericin B Fluconazole Terbinafine	
Antipsychotics	
Chlorpromazine Haloperidol Thiothixene	
Antiretrovirals	
Adefovir dipivoxil Lopinavir/ritonavir	

a. Not an all-inclusive list. Contact the Drug Information Service (801-581- 2073) for more information.

b. Chemotherapy-induced thrombocytopenia is not included.

c. Data from at least one randomized controlled clinical trial.

d. Data from at least one published case-report or case-series.

Table 3. Laboratory Testing for HIT Antibodies^{4,5}

HIT Antibody Test	Description
Enzyme-linked immunosorbent assay (ELISA) <ul style="list-style-type: none"> ELISA only (ARUP#0051052) <u>OR</u> ELISA with Reflex to SRA (ARUP#0051249) – automatic SRA ordered with positive ELISA 	a. High sensitivity for detection of heparin antibodies but poor specificity for pathogenic antibodies. b. Test turnaround 1-2 days; may be ordered as STAT test. c. Consider degree of positivity based upon result reported as optical density (OD) units 1. OD \geq 1.0: HIT likely 2. OD 0.4 – 1.0: HIT less likely – weak positive result 3. OD <0.4: HIT highly unlikely
Serotonin release assay (SRA) <ul style="list-style-type: none"> SRA Heparin Dependent Platelet Antibody (ARUP#0093196) 	a. Gold standard for diagnosis of HIT - higher diagnostic specificity than immunoassay. b. Test turn-around time 3-7 days c. Negative result challenges the diagnosis of HIT d. Positive result is consistent with HIT diagnosis

Table 4. Comparison of Available Non-heparin Anticoagulants

Property	Argatroban	Desirudin	Fondaparinux	Lepirudin	Bivalirudin
Brand Name	Argatroban	Iprivask	Arixtra	Refludan	Angiomax
Class	Univalent DTI	Bivalent DTI	Factor Xa Inhibitor	Bivalent DTI	Bivalent DTI
Description	Synthetic direct thrombin inhibitor	Recombinant hirudin analog	Synthetic pentasaccharide	Recombinant hirudin analog	Synthetic hirudin analog
Route	Intravenous	Subcutaneous	Subcutaneous	Intravenous	Intravenous
Labeled indication	Thrombosis prophylaxis and treatment in patients with HIT or patients undergoing PCI at risk for HIT	VTE prophylaxis following elective hip replacement surgery	VTE prophylaxis in patients undergoing hip or knee replacement surgery, or abdominal surgery; Treatment of VTE in conjunction with warfarin	Anticoagulation in patients with HIT and thromboembolic disease	Anticoagulation in patients with unstable angina undergoing PTCA or PCI or patients undergoing PCI at risk for HIT
Prophylactic dosing for HIT patients	<ul style="list-style-type: none"> Argatroban Standard Dosing for HIT Argatroban Dosing in Hepatic Dysfunction or Critical Illness 	Prophylaxis only: <ul style="list-style-type: none"> 15 mg subcutaneous every 12 hours Approved by P&T for clinically suspected HIT	Prophylaxis only: <ul style="list-style-type: none"> 2.5 mg subcutaneous every 24 hours 	<ul style="list-style-type: none"> 0.2 - 0.4 mg/kg IV bolus (max 44 mg) 0.15 mg/kg/hr (max 16.5 mg/hour) 	Restricted for use in cardiac cath lab or patients with heparin antibodies undergoing CPB
Treatment dosing for HIT patients	<ul style="list-style-type: none"> Argatroban Standard Dosing for HIT Argatroban Dosing in Hepatic Dysfunction or Critical Illness First line for confirmed acute HIT or HITTS	Not applicable	VTE treatment: <ul style="list-style-type: none"> < 50 kg: 5 mg subcutaneous every 24 hours 50-100 kg: 7.5 mg subcutaneous every 24 hours >100 kg: 10 mg subcutaneous every 24 hours 	<ul style="list-style-type: none"> 0.2 - 0.4 mg/kg IV bolus (max 44 mg) 0.15 mg/kg/hr (max 16.5 mg/hour) 	Restricted for use in cardiac cath lab or patients with heparin antibodies undergoing CPB
Time to Peak	1– 3 hours	1– 3 hours	2 – 3 hours	5– 18 minutes	15–19 minutes
Metabolism and Clearance	Primarily hepatic	Renal	Renal	Renal	Primarily proteolytic cleavage; some renal
Half-life (normal renal function)	39-51 minutes	2-3 hours	17 – 21 hours	1.3 hours	30 minutes
Contraindications and Warnings	<ul style="list-style-type: none"> Hypersensitivity to argatroban Major active bleeding 	<ul style="list-style-type: none"> Hypersensitivity to hirudins Active bleeding Coagulation disorder Avoid in patients with previous desirudin or lepirudin use due to risk of anaphylaxis from antihirudin antibodies 	<ul style="list-style-type: none"> Hypersensitivity to fondaparinux Active major bleeding CrCl <30 mL/minute Body weight < 50 kg (prophylaxis dose only) Bacterial endocarditis 	<ul style="list-style-type: none"> Hypersensitivity to hirudins Active bleeding Coagulation disorder Avoid in patients with previous lepirudin or desirudin use due to risk of anaphylaxis from antihirudin antibodies 	<ul style="list-style-type: none"> Hypersensitivity to bivalirudin Major active bleeding
Monitoring	aPTT; Directly affects INR but adjust dosing per aPTT, not INR increases	No routine monitoring; aPTT with renal impairment or bleeding risk	Platelet count; serum creatinine; stool occult blood tests	aPTT	aPTT, ACT
Dose adjustment	Hepatic impairment	CrCl < 60 mL/minute	CrCl < 50 mL/minute	CrCl < 60 mL/minute	CrCl < 30 mL/minute

Abbreviations: ACT = activated clotting time; aPTT = activated partial thromboplastin time; CPB = cardiopulmonary bypass; CrCl = creatinine clearance; DTI = direct thrombin inhibitor; HIT = heparin-induced thrombocytopenia; HITTS = heparin-induced thrombocytopenia and thrombosis syndrome; INR = international normalized ratio; IV = intravenous; PCI = percutaneous coronary intervention; PT = prothrombin time; PTCA = percutaneous transluminal coronary angioplasty; TT = thrombin time; VTE = venous thromboembolism.

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(More historical information can be obtained from the P&T Minutes)