Heparin Induced Thrombocytopenia – Adult – Inpatient– Clinical Practice Guideline

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February 2017

Executive Summary

Guideline Overview

The following guideline is intended to guide the management of heparin induced thrombocytopenia and includes recommendations for diagnosis and treatment agents.

Target Population

Adult patients with suspicion or diagnosis of heparin induced thrombocytopenia

Key Practice Recommendations

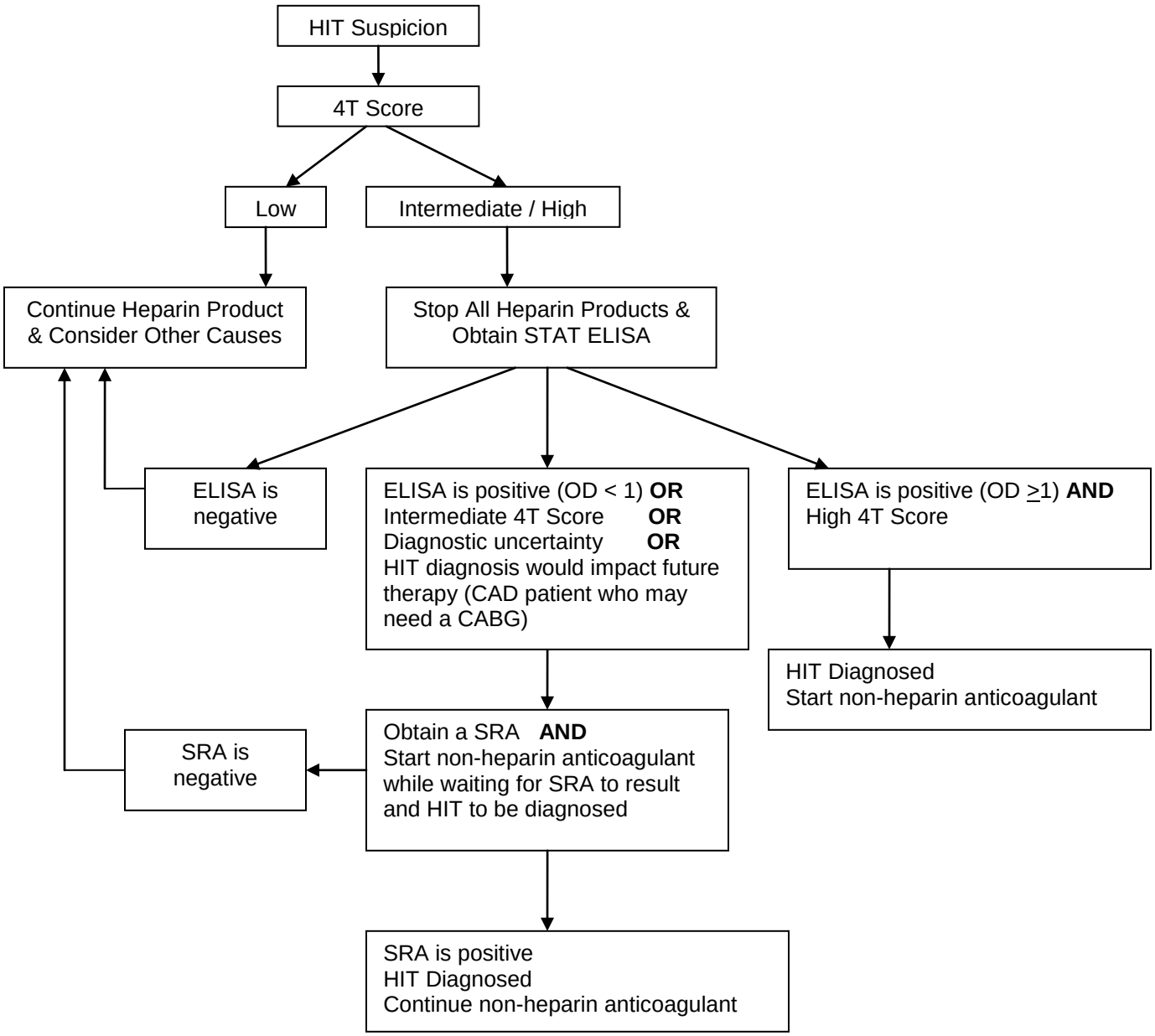
Screening for HIT

1. Clinical assessment can assist in the diagnosis of HIT and clinical prediction tools have been developed to determine the probability of HIT[2-4] ***(Class I, Level C)***
   - 1.1 The most validated has been the 4T score (Table 3)[2,5-7] ***(Class I, Level B)***
   - 1.2 The 4T score has less specificity in critically ill patients. Other causes of thrombocytopenia should be investigated in this patient population ***(Class IIb, Level C)***

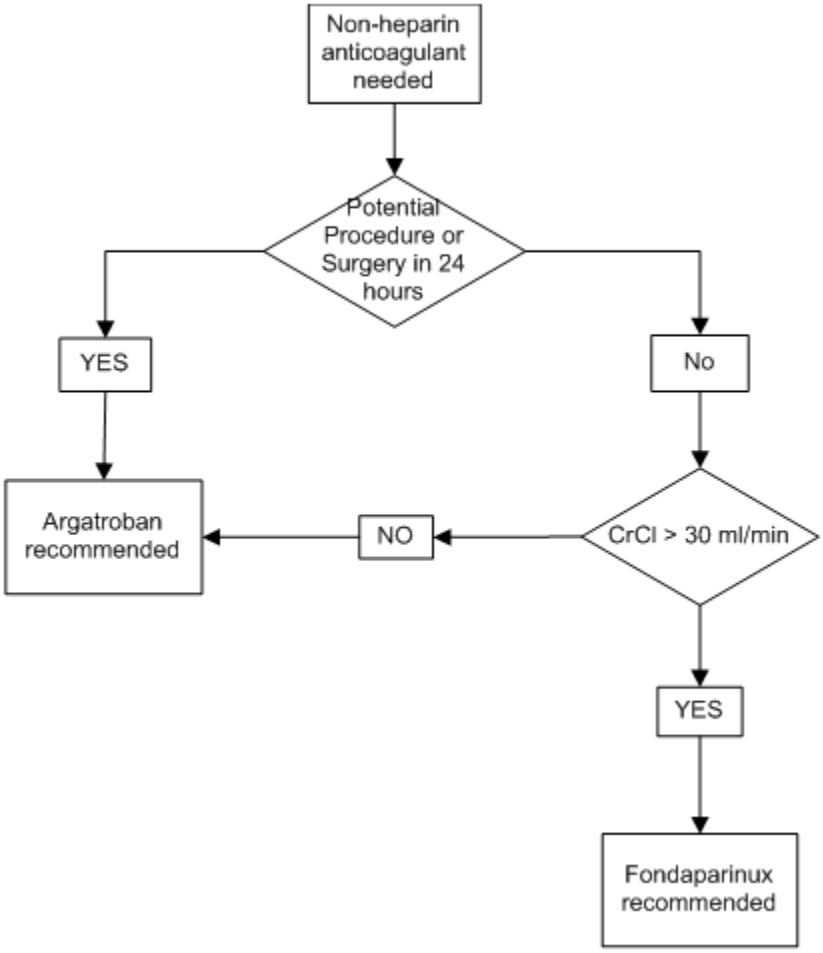
Table 3. 4T Score – Scoring is based on the summation of all categories[2]

4T	2 Points	1 Point	0 Points
Thrombocytopenia	• PLT fall > 50% AND nadir ≥ 20 AND no surgery within previous 3 days	• PLT fall > 50% but surgery within previous 3 days • PLT fall 30-50% or nadir 10-19K	• PLT fall < 30% • Any PLT fall with nadir <10K
Timing of PLT count fall	• Fall 5-10 days after heparin • Fall within 1 day after heparin and exposed to heparin within past 5-30 days	• Fall 5-10 days after heparin but unclear (e.g. missing PLT) • Fall in 1 day after heparin with exposure in past 31-100 days • Fall after 10 days	• Fall ≤ 4 days without recent heparin exposure
Thrombosis or other sequelae	• Confirmed new thrombosis • Skin necrosis at injection site • Anaphylactoid reaction to IV heparin bolus • Adrenal hemorrhage	• Recurrent VTE while on therapeutic anticoagulants • Suspected thrombosis • Erythematous skin lesions at heparin injection sites	• Thrombosis suspected
O**t**her causes of Thrombocytopenia	• No alternative explanation for platelet fall	• Sepsis without proven source • Thrombocytopenia associated with initiation of ventilator • Other	• Within 72 hrs of surgery • Confirmed bacteremia or fungemia • Chemo/radiation within 20 days • DIC due to non-HIT cause • Post-transfusion purpura • Drug induced thrombocytopenia • Other
Clinical Suspicion Scoring: 0-3 = Low, 4-5 = Intermediate, 6-8 = High			

2. Decision to Treat HIT Based on 4T Score and Lab Test Interpretation



3. Decision to Treat HIT With Non-Heparin Anticoagulant



Companion Documents

Appendix B: *Heparin Induced Thrombocytopenia – Adult- CPG*
Decision to Treat HIT Based on 4T Score and Lab Test Interpretation

Appendix C: *Heparin Induced Thrombocytopenia – Adult- CPG*
Decision to Treat HIT With Non-Heparin Anticoagulant

IP – HIT (Heparin Induced Thrombocytopenia) Adult- Supplemental – Order Set 3596

Pertinent UWHC Policies & Procedures

None identified

Patient Resources:

None identified

Scope

Disease/Condition(s):

Heparin induced thrombocytopenia (HIT)

Intended Users:

- Physicians
- Advanced Practice Providers
- Registered Nurses
- Pharmacists

CPG objective(s):

This clinical practice guideline is intended to provide recommendations for the diagnosis and treatment of HIT.

Target Population:

Adult patients with suspicion or diagnosis of HIT

Interventions and Practices Considered:

The guideline contains strategies and recommendations designed to assist clinicians in the diagnosis and treatment of HIT. It focuses on the initial presentation of signs and symptoms of HIT to determine the appropriate diagnostic tests, as well as, provides recommendations for treatment if a patient is diagnosed with HIT. It also provides information for patients with documented heparin allergy due to either recent or previous HIT diagnosis undergoing cardiac procedures.

Major Outcomes Considered:

The major outcome considered in this guideline is for the recovery of platelet levels and the prevention of thrombosis caused by HIT through the selection of an antithrombotic agent best suited for patient specific risk factors and cost considerations.

Guideline Metrics:

Treatment therapies will be periodically reviewed to determine guideline compliance and cost considerations.

Methodology

Methods Used to Collect/Select the Evidence:
Completed a comprehensive literature search of electronic databases; conducted an in-depth review of relevant abstracts and articles; conducted a thoughtful discussion and interpretation of findings; ranked strength of evidence underlying the current recommendations that have been provided.

Methods Used to Assess the Quality and Strength of the Evidence:
Comprehensive review of the literature from 2003 to 2014. Search terms that were used in the literature review include: 'heparin induced thrombocytopenia,' 'argatroban,' 'fondaparinux,' 'bivalirudin,' 'HIT and cardiac surgery,' and '4T Score'

Rating Scheme for the Strength of the Evidence:
A modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology have been used to assess the quality and strength of evidence in this clinical practice guideline.[1]

Cost Analysis:
Table 1. Cost Analysis of HIT Treatment Options

Medication	Price per dose/vial ($)
Argatroban 50 mg vial	158.18
Bivalirudin 250 mg vial	910.50
Fondaparinux 7.5 mg dose	102.89

Definitions[2]

1. Heparin induced thrombocytopenia (HIT): immune mediated drug reaction resulting in platelet activation, increased thrombin production and increased risk for venous and arterial thrombosis.
2. Isolated HIT: HIT without thrombosis
3. HITT: HIT with thrombosis
4. Acute HIT: thrombocytopenia with a positive HIT antibody
5. Sub-acute HIT: recovered platelets with a positive HIT antibody

Introduction

HIT is an immune associated thrombocytopenia. HIT occurs in 1 to 3% of patients receiving unfractionated heparin (UFH) and 0.8% of patients receiving low molecular weight heparin (LMWH).[3] Table 2 outlines estimated incidence of HIT in medical and surgical patients. HIT is an immunologic reaction to heparin with a typical onset of five to fourteen days after the initiation of heparin. HIT can also present within minutes to hours in patients who have been previously exposed to heparin within the past 100 days.[2-4] An estimated 17-55% of patients with HIT develop venous thrombosis complications. If left untreated the event can be life or limb-threatening.[2]

Due to HIT being an immune reaction, it can develop from any source of heparin: intravenous, subcutaneous, heparin flushes, or heparin-coated vascular catheters.[2-4] HIT is more common with intravenous administration, larger doses, and longer duration of treatment.[2-4] Risk for developing HIT is influenced by the duration and type of exposure, the dose and specific patient populations.[2]

Table 2: Incidence of HIT

Patient Population (after 4 days exposure)	Incidence of HIT
Post-operative	
Heparin – Prophylactic or Therapeutic	1-5%
Heparin – Flush	0.1-1%
LMWH – Prophylactic or Therapeutic	0.1-1%
Cardiac surgery	1-3%
Orthopedic surgery	1-5%
Medical	
Heparin – Prophylactic or Therapeutic	0.1-1%
LMWH – Prophylactic or Therapeutic	0.6%
ICU	0.4%
Cancer	1%

Recommendations

Screening for HIT

1. Clinical assessment can assist in the diagnosis of HIT and clinical prediction tools have been developed to determine the probability of HIT[2-4] ***(Class I, Level C)***
   1.2 The most validated has been the 4T score (Table 3)[2,5-7] ***(Class I, Level B)***
   1.3 The 4T score has less specificity in critically ill patients. Other causes of thrombocytopenia should be investigated in this patient population ***(Class IIb, Level C)***

Table 3. 4T Score – Scoring is based on the summation of all categories[2]

4T	2 Points	1 Point	0 Points
Thrombocytopenia	• PLT fall > 50% AND nadir ≥ 20 AND no surgery within previous 3 days	• PLT fall > 50% but surgery within previous 3 days • PLT fall 30-50% or nadir 10-19K	• PLT fall < 30% • Any PLT fall with nadir <10K
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Thrombosis or other sequelae	• Confirmed new thrombosis • Skin necrosis at injection site • Anaphylactoid reaction to IV heparin bolus • Adrenal hemorrhage	• Recurrent VTE while on therapeutic anticoagulants • Suspected thrombosis • Erythematous skin lesions at heparin injection sites	• Thrombosis suspected

Other causes of Thrombocytopenia	• No alternative explanation for platelet fall	• Sepsis without proven source • Thrombocytopenia associated with initiation of ventilator • Other	• Within 72 hrs of surgery • Confirmed bacteremia or fungemia • Chemo/radiation within 20 days • DIC due to non-HIT cause • Post-transfusion purpura • Drug induced thrombocytopenia • Other
Clinical Suspicion Scoring: 0-3 = Low, 4-5 = Intermediate, 6-8 = High			

2. Low 4T scores have a low probability of HIT: 0-3%[2] ***(Class IIb, Level C)***
   2.1 Other causes of thrombocytopenia should be investigated. Table 4 lists medications that may cause thrombocytopenia

Table 4. Drugs that can induce thrombocytopenia[2]

Causative Drug	
Relatively common	
Glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban)	
Quinine	Carbamazepine
Quinidine	Vancomycin
Sulfa Antibiotics	
Less Common	
Amitriptyline	Furosemide
Amoxicillin	Metronidazole
Pipercillin	Naproxen
Nafcillin	Phenytoin
Cephalosporins	Propranolol
Celecoxib	Ranitidine
Ciprofloxacin	Rifampin
Fentanyl	

Confirming Diagnosis of HIT

3. Diagnosis of HIT is based on clinical (thrombocytopenia or new thrombosis) and laboratory findings.[2-4] ***(Class I, Level A)***
   3.1 Routine laboratory screening for patients without symptoms of HIT is not recommended ***(Class I, Level C)***

Table 5. Laboratory Tests for Diagnosing HIT[2,8,9]

Test	Performed at UW Lab	Turn Around Time	Sensitivity	Specificity
ELISA Enzyme Linked Immunosorbent Assay	YES	2 hours (STAT) *if after 4pm call lab to arrange for STAT testing	> 95%	50-89%
SRA Serotonin Release Assay	NO	48 hours	> 90%	> 90%

4. If intermediate or high clinical suspicion for HIT (as scored by 4T) then order an ELISA test first[2]
   4.1 The optical density (OD) of the ELISA can identify the probability of HIT[2] ***(Class IIa, Level C)***
      4.1.1 An OD < 1: weak positive; more likely to be HIT negative
      4.1.2 An OD $\geq$ 1: strong positive; more likely to be HIT positive
   4.2 For ELISA with OD < 1 but a high suspicion for HIT, based onhigh 4T score, consider ordering an SRA test to confirm HIT diagnosis ***(Class I, Level C)***
   4.3 If uncertainty exists in the diagnosis of HIT based on ELISA and/or 4T scores, consider ordering a SRA test to confirm HIT diagnosis. ***(Class I, Level C)***
   4.4 A strongly positive ELISA (OD $\geq$1) or a positive SRA in a symptomatic patient 5-14 days after heparin initiation reliably confirms the diagnosis of HIT[2,8,9] ***(Class I, Level C)***
   4.5 For patients undergoing planned cardiac surgery or other procedure where high dose heparin may be used (ECMO) an SRA may be used to reliably rule out HIT (Class IIb, Level C)
   4.6 A negative ELISA or SRA reliably rules out HIT[8,9] ***(Class I, Level C)***
   4.7 Consider a hematology or vascular surgery consult if diagnosis remains uncertain ***(Class IIb, Level C)***

Treatment of HIT

5. Discontinue all heparin (including flushes) and low molecular weight heparin orders by any route ***(Class I, Level A)***

6. If on warfarin less than 7 days when HIT diagnosed:
   6.1 Discontinue warfarin until platelet count has recovered to 100-150x10^9/L ***(Class IIa, Level C)***
   6.2 Administer phytonadione 10 mg orally or intravenous ***(Class IIa, Level C)***

7. Obtain bilateral lower extremity ultrasonography to evaluate for deep vein thrombosis, even if clinical findings are absent ***(Class IIb, Level C)***
   7.1 Consider bilateral upper extremity ultrasonography if central infusion lines are present ***(Class IIb, Level C)***

8. Start a non-heparin anticoagulant immediately upon ELISA confirmation or if awaiting results of the SRA. ***(Class I, Level B)***

Anticoagulant Treatment Options for HIT

9. Fondaparinux
   Fondaparinux is a synthetic pentasaccaride that selectively binds to antithrombin III which results in an indirect inhibition of factor Xa. When given subcutaneously, fondaparinux has a half-life of 17-21 hours. It is eliminated by renal excretion with 80% excreted unchanged[10].
   9.1. Therapeutic dosing should be based on age, renal function and total body weight (TBW) ***(Class IIb, Level C)***

Table 6. Therapeutic Fondaparinux Dosing[10-12]

Age ≤ 75 AND CrCl > 80 mL/min Total Body Weight (kg)	Dose
< 50	5 mg subcutaneous daily
50 - 100	7.5 mg subcutaneous daily
> 100	10 mg subcutaneous daily

9.2 For renal dosing of fondaparinux refer to UW Health Renal Dosing Guidelines

9.3 The safety and efficacy of fondaparinux has not been completely established for HIT ***(Class IIb, Level C)***

9.4 Should not be used in patients with bacterial endocarditis or scheduled neuraxial anesthesia or spinal puncture ***(Class IIb, Level C)***

10. Argatroban

Argatroban directly inhibits thrombin. When given intravenously the half-life is dependent on hepatic function. In patients with normal hepatic function the expected half-life is 40 minutes. In patients with impaired hepatic function the half-life is prolonged to 180 minutes.[13]

10.1 Dosing is based on TBW ***(Class IIa, Level C)***

10.2 No initial bolus is needed. Infusion rates should be initiated and adjusted based on recommendations in table 8 and 9. ***(Class IIa, Level C)***

Table 8. Argatroban Initial Infusion Rate[13,14]

Indication for dose adjustment	Initial Infusion rate
Normal hepatic function	2 mcg/kg/min
Moderate hepatic function	0.5 mcg/kg/min
Heart Failure, Multiple organ system failure, severe anascara, cardiac surgery	0.5-1.2 mcg/kg/min

Table 9. Argatroban Dose Adjustments[13,14]

Hepatic function	PTT	Adjustment
Normal hepatic function	< 1.5 x baseline PTT	Increase by 0.5 mcg/kg/min
	Goal 1.5 - 3.0 x baseline PTT *(*Maximum 100 seconds)*	Continue same rate
	> 3 x baseline PTT	Decrease by 0.5 mcg/kg/min
Moderate hepatic function	< 1.5 x baseline PTT	Increase by 0.25 mcg/kg/min
	Goal 1.5 - 3.0 x baseline PTT *(*Maximum 100 seconds)*	Continue same rate
	> 3 x baseline PTT	Decrease by 0.25 mcg/kg/min

10.3 The maximum infusion rate is 10 mcg/kg/min ***(Class IIa, Level C)***

10.4 PTT should be measured every 2 hours after initiation or rate adjustment
10.5 Once 2 consecutive PTT are in target range then PTT may be checked daily

11. Laboratory Monitoring[13] ***(Class IIb, Level C)***
    11.1 Platelets should be monitored daily for recovery. Once they have normalized (100-150 x 10^9/L) they may be monitored less often.
    11.2 CBC should be monitored every 48 hours while hospitalized and on an anticoagulant.
    11.3 Creatinine should be monitored as clinically indicated.

12. Transitioning

    Transition from parenteral anticoagulant to oral anticoagulant should occur only in a stable patient and after platelet recovery to at least 150 K/uL. ***(Class I, Level C)***[2]
    12.1 Fondaparinux to warfarin[2]
        12.1.1 Once platelet count normalizes start warfarin 5 mg daily ***(Class I, Level C)***
        12.1.2 When INR is therapeutic after a minimum of 5 days on dual anticoagulation, fondaparinux may be discontinued ***(Class I, Level C)***
    12.2 Argatroban to warfarin[2,15 13]
        12.2.1 Reduce infusion rate to achieve a PTT level just above 1.5 x normal before initiating warfarin at 5 mg daily. **(Class I, Level C)**
        12.2.2 The combination of argatroban and warfarin creates a laboratory discrepancy which reports falsely elevated INR values
        12.2.3 If the INR is > 4 and after a minimum of 5 days on dual anticoagulant therapy, argatroban can be discontinued and the INR repeated in 4-6 hours. ***(Class I, Level C)***
        12.2.4 If the repeat INR off of argatroban is sub-therapeutic the infusion should be resumed at the previous rate and the procedure repeated daily until the INR on warfarin alone is therapeutic. ***(Class I, Level C)***
    12.3 Target-specific oral anticoagulant (TSOAC)[16-19]
        12.3.1 Stop fondaparinux and start TSOAC at the time of next scheduled fondaparinux dose ***(Class IIb, Level C)***
        12.3.2 Start TSOACs (apixaban, dabigatran, or rivaroxaban) within 2 hours of stopping the argatroban infusion ***(Class IIb, Level C)***

13. Special Populations
    13.1 Urgent cardiac surgery with acute or sub-acute HIT or cardiac catheterization or percutaneous coronary intervention[2]
        13.1.1 Recommend bivalirudin (***Class IIb, Level C)***
        13.1.2 Dosing is based on TBW to a max of 150 kg
        13.1.3 No initial bolus needed. Infusion rates should be initiated and adjusted based on recommendations in tables 10 and 11.

Table 10. Initial Bivalirudin Infusion Rate[20-24]

Estimated Creatinine Clearance (mL/min)	Initial Bivalirudin Infusion Rate (mg/kg/hr)
> 60	0.15
30 – 60	0.08
< 30 / Renal Replacement Therapy	0.05

Table 11. Bivalirudin Dose Adjustments[15,25-28]

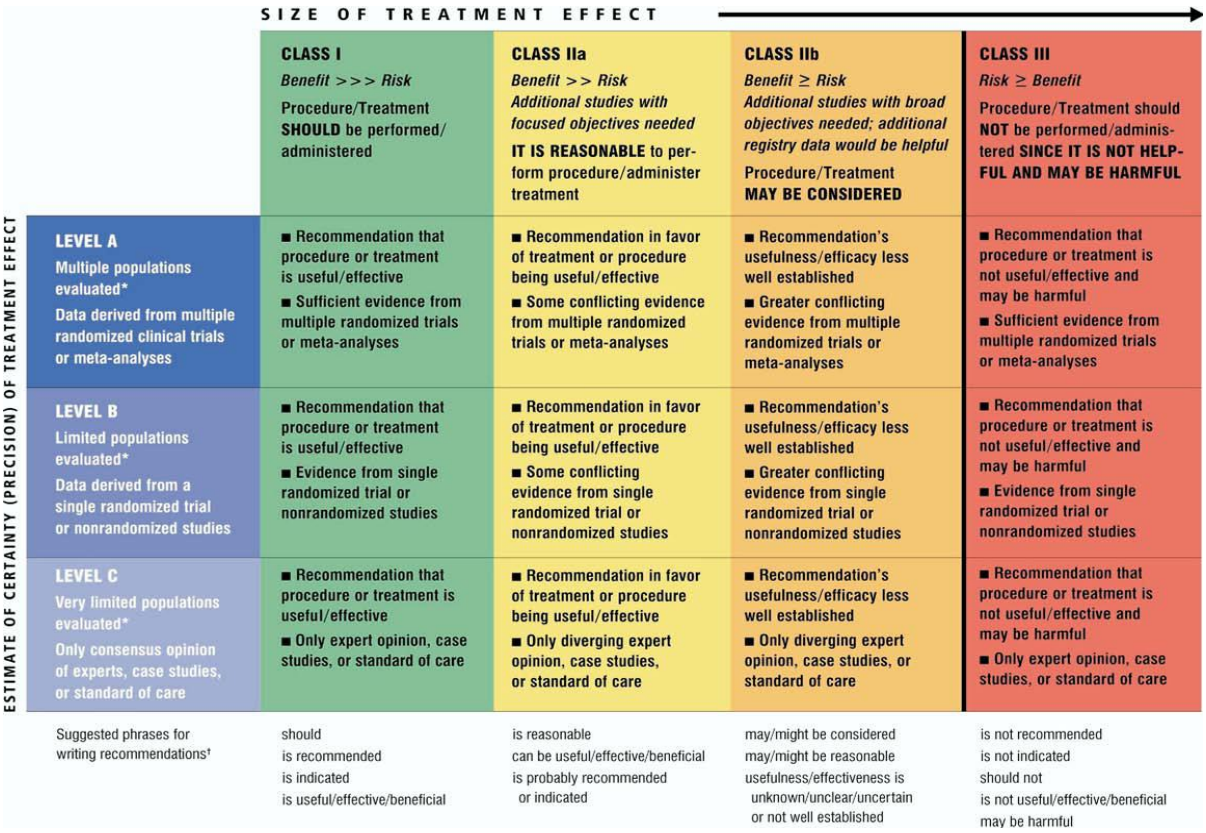
PTT (seconds)	Dose Adjustment	Monitoring Recommendation
< 1.5 x baseline	Increase infusion by 20%	Recheck PTT 2 hrs after rate change
1.5 to 2.5 x baseline	Continue current rate	Recheck PTT in 2 hrs; if within therapeutic range 2 consecutive times, check PTT every 12 hours.
>2.5 - 3 x baseline	Decrease infusion by 20%	Recheck PTT 2 hrs after rate change
>3 x baseline	Hold for 1 hour, then restart at 50% lower rate	Recheck PTT 2 hrs after rate change

13.2 Urgent cardiac surgery with a history of HIT and a negative HIT antibody[2]
- 13.2.1 Recommend unfractionated heparin during the procedure (***Class IIb, level C)***
- 13.2.2 Recommend a non-heparin anticoagulant post operatively (***Class IIb, level C)***

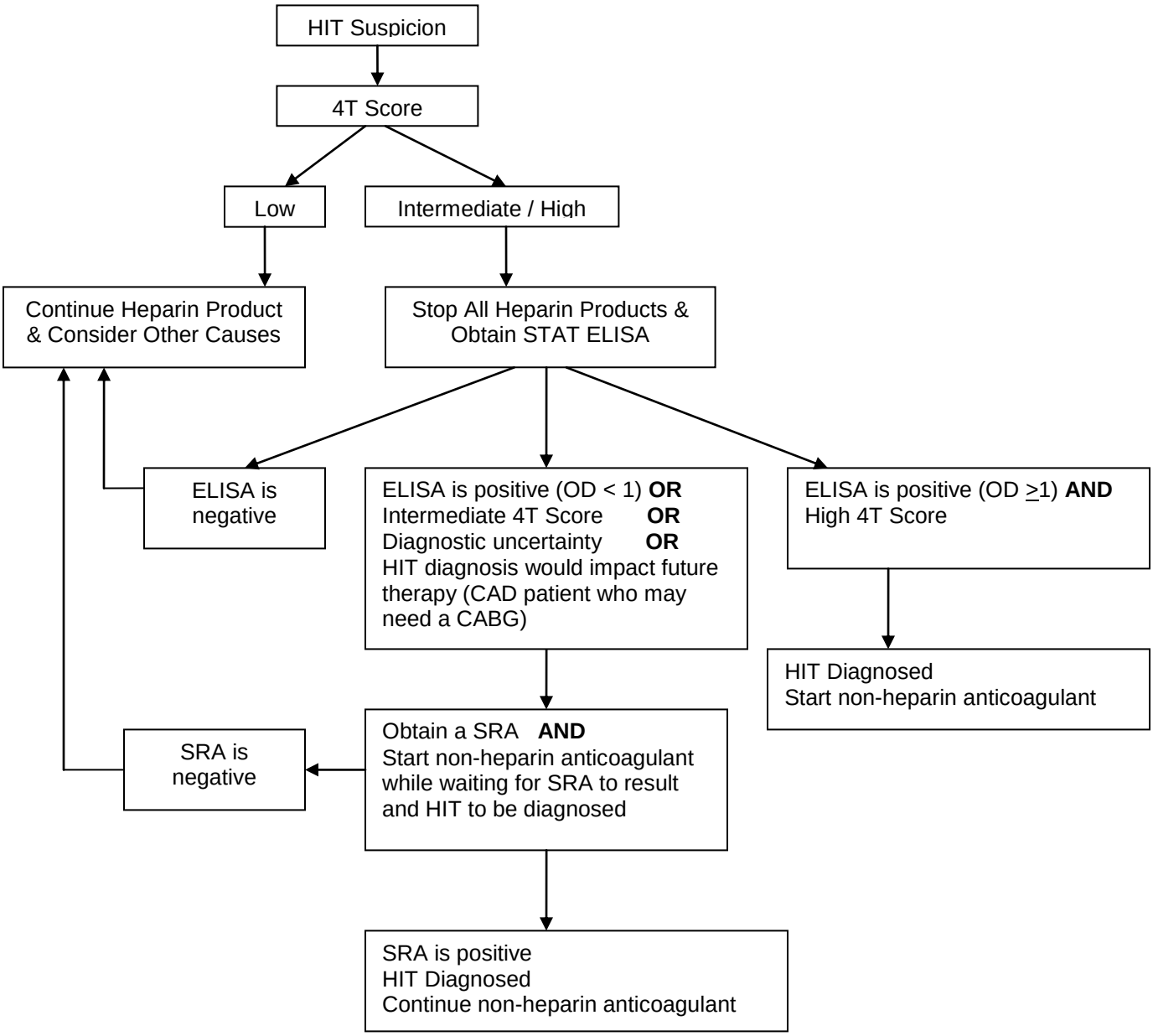
14. Duration of Anticoagulation
- 14.1 Isolated HIT (HIT without thrombosis): anticoagulation should be continued for 4 weeks after diagnosis of HIT[2]
- 14.2 HITT: anticoagulation should be continued for at least 3 months and then assess the risk versus benefit of discontinuing therapy.[2]

Companion/Collateral documents

Appendix A: Modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE)



Appendix B: *Heparin Induced Thrombocytopenia – Adult- CPG*
Decision to Treat HIT Based on 4T Score and Lab Test Interpretation



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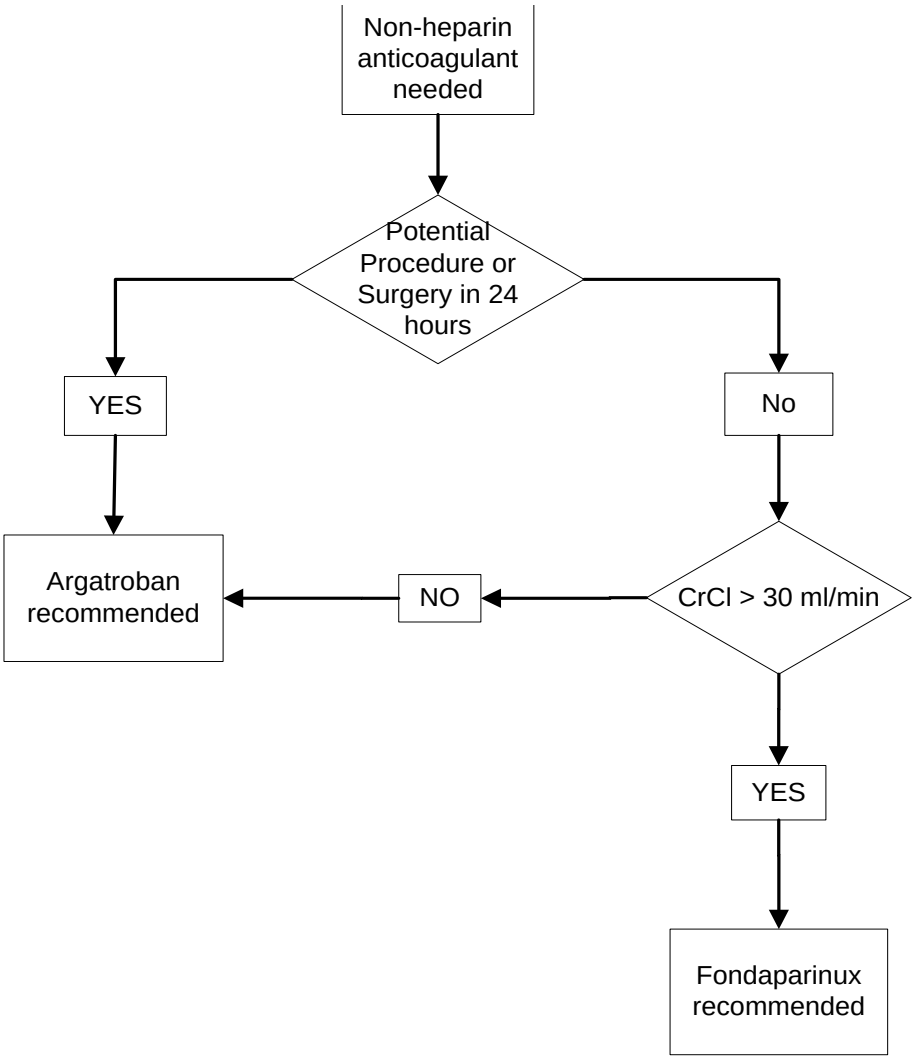
Revised: 12/2014

Appendix C: *Heparin Induced Thrombocytopenia – Adult- CPG*
Decision to Treat HIT With Non-Heparin Anticoagulant



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Revised: 12/2014

UW Health Implementation

Potential Benefits:

The benefits of this guideline include providing recommendations for the diagnosis of HIT through both symptom and lab test interpretation and for selecting the most appropriate treatment option for HIT-based on patient factors and cost analysis.

Potential Harms:

While it is anticipated that the overall safety and quality of HIT management will be improved with this guideline there is a risk for hemorrhagic complications when antithrombotics are used for treatment of HIT.

Implementation Plan/Tools:

Recommendations from this guideline will be incorporated into the Heparin Induced Thrombocytopenia Order Set.

Disclaimer

CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

References

1. Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA.* 2009;301(8):831-841.
2. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e495S-530S.
3. Shantsila E, Lip GY, Chong BH. Heparin-induced thrombocytopenia. A contemporary clinical approach to diagnosis and management. *Chest.* 2009;135(6):1651-1664.
4. Hassell K. Heparin-induced thrombocytopenia: diagnosis and management. *Thromb Res.* 2008;123 Suppl 1:S16-21.
5. Bryant A, Low J, Austin S, Joseph JE. Timely diagnosis and management of heparin-induced thrombocytopenia in a frequent request, low incidence single centre using clinical 4T's score and particle gel immunoassay. *Br J Haematol.* 2008;143(5):721-726.
6. Denys B, Stove V, Philippé J, Devreese K. A clinical-laboratory approach contributing to a rapid and reliable diagnosis of heparin-induced thrombocytopenia. *Thromb Res.* 2008;123(1):137-145.

7. Warkentin TE, Linkins LA. Non-necrotizing heparin-induced skin lesions and the 4T's score. *J Thromb Haemost.* 2010;8(7):1483-1485.
8. Bakchoul T, Giptner A, Najaoui A, Bein G, Santoso S, Sachs UJ. Prospective evaluation of PF4/heparin immunoassays for the diagnosis of heparin-induced thrombocytopenia. *J Thromb Haemost.* 2009;7(8):1260-1265.
9. Harenberg J, Huhle G, Giese C, et al. Determination of serotonin release from platelets by enzyme immunoassay in the diagnosis of heparin-induced thrombocytopenia. *Br J Haematol.* 2000;109(1):182-186.
10. database] MHSi. *Thomson Healthcare*. Greenwood Village, CO.
11. Grouzi E, Kyriakou E, Panagou I, Spiliotopoulou I. Fondaparinux for the treatment of acute heparin-induced thrombocytopenia: a single-center experience. *Clin Appl Thromb Hemost.* 2010;16(6):663-667.
12. Lobo B, Finch C, Howard A, Minhas S. Fondaparinux for the treatment of patients with acute heparin-induced thrombocytopenia. *Thromb Haemost.* 2008;99(1):208-214.
13. insert] Ap. *GlaxoSmithKline*. Research Triangle Park, NC2009.
14. Verme-Gibboney CN, Hursting MJ. Argatroban dosing in patients with heparin-induced thrombocytopenia. *Ann Pharmacother.* 2003;37(7-8):970-975.
15. Gosselin RC, Dager WE, King JH, et al. Effect of direct thrombin inhibitors, bivalirudin, lepirudin, and argatroban, on prothrombin time and INR values. *Am J Clin Pathol.* 2004;121(4):593-599.
16. Hellerslia V, Mehta P. Transition of Anticoagulants 2014. *Hospital Pharmacy*2014.
17. Mirdamadi A. Dabigatran, a direct thrombin inhibitor, can be a life-saving treatment in heparin-induced thrombocytopenia. *ARYA Atheroscler.* 2013;9(1):112-114.
18. Linkins LA, Warkentin TE. Rivaroxaban for treatment of HIT: a riveting first experience. *Thromb Res.* 2015;135(1):1-2.
19. Walenga JM, Prechel M, Hoppensteadt D, et al. Apixaban as an alternate oral anticoagulant for the management of patients with heparin-induced thrombocytopenia. *Clin Appl Thromb Hemost.* 2013;19(5):482-487.
20. Kiser TH, Fish DN. Evaluation of bivalirudin treatment for heparin-induced thrombocytopenia in critically ill patients with hepatic and/or renal dysfunction. *Pharmacotherapy.* 2006;26(4):452-460.
21. Kiser TH, Burch JC, Klem PM, Hassell KL. Safety, efficacy, and dosing requirements of bivalirudin in patients with heparin-induced thrombocytopenia. *Pharmacotherapy.* 2008;28(9):1115-1124.
22. Runyan CL, Cabral KP, Riker RR, et al. Correlation of bivalirudin dose with creatinine clearance during treatment of heparin-induced thrombocytopenia. *Pharmacotherapy.* 2011;31(9):850-856.
23. Tsu LV, Dager WE. Bivalirudin dosing adjustments for reduced renal function with or without hemodialysis in the management of heparin-induced thrombocytopenia. *Ann Pharmacother.* 2011;45(10):1185-1192.
24. Wisler JW, Washam JB, Becker RC. Evaluation of dose requirements for prolonged bivalirudin administration in patients with renal insufficiency and suspected heparin-induced thrombocytopenia. *J Thromb Thrombolysis.* 2012;33(3):287-295.

25. Dager WE, Dougherty JA, Nguyen PH, Militello MA, Smythe MA. Heparin-induced thrombocytopenia: treatment options and special considerations. *Pharmacotherapy.* 2007;27(4):564-587.
26. Dang CH, Durkalski VL, Nappi JM. Evaluation of treatment with direct thrombin inhibitors in patients with heparin-induced thrombocytopenia. *Pharmacotherapy.* 2006;26(4):461-468.
27. Kiser TH, Mann AM, Trujillo TC, Hassell KL. Evaluation of empiric versus nomogram-based direct thrombin inhibitor management in patients with suspected heparin-induced thrombocytopenia. *Am J Hematol.* 2011;86(3):267-272.
28. Skrupky LP, Smith JR, Deal EN, et al. Comparison of bivalirudin and argatroban for the management of heparin-induced thrombocytopenia. *Pharmacotherapy.* 2010;30(12):1229-1238.