Contact for Content:
Name: Anne Rose, PharmD - Pharmacy; Anticoagulation Stewardship
Phone Number: (608) 263-9738
Email Address: arose@uwhealth.org

Contact for Changes:
Name: Philip Trapskin, PharmD, BCPS – Drug Policy Program
Phone Number: (608) 263-1328
Email Address: ptrapskin@uwhealth.org

Guideline Author(s):
Anne Rose, PharmD – Pharmacy: Anticoagulation Stewardship

Coordinating Team Members:
John Sheehan, MD – Hematology
Eliot Williams, MD – Hematology

Review Individuals/Bodies:
David Yang, MD – Clinical Lab

Committee Approvals/Dates:
Inpatient Anticoagulation Committee
Pharmacy & Therapeutics Committee (Last Periodic Review: 05/2017)

Release Date: May 2017 | Next Review Date: May 2019
Executive Summary
Guideline Overview
The following guideline is intended to guide the diagnosis and management of heparin induced thrombocytopenia.

Key Practice Recommendations
1. Diagnosis of HIT is based on both clinical (thrombocytopenia or new thrombosis) and laboratory findings. (UW Health moderate quality of evidence, strong recommendation)

2. The heparin induced platelet Ab (ELISA) can be performed in the clinical lab and should be utilized first if laboratory diagnosis is needed. (UW Health low quality of evidence, strong recommendation)
   2.1 A strongly positive ELISA (OD > 1) with a high suspicion for HIT can reliably confirm the diagnosis of HIT (UW Health moderate quality of evidence, strong recommendation)
   2.2 A negative ELISA reliably rules out HIT (UW Health moderate quality of evidence, strong recommendation)

3. A heparin dependant Ab (SRA) may be considered if uncertainty exists in the diagnosis of HIT based on the ELISA results and 4T score. (UW Health moderate quality of evidence, strong recommendation)

4. For all patients with suspected or confirmed HIT: discontinue all heparin (including flushes) and/or low molecular weight heparin orders by any route (UW Health low quality of evidence, strong recommendation)

5. Start a non-heparin anticoagulant immediately upon ELISA confirmation or if awaiting results of the SRA. (UW Health low quality of evidence, strong recommendation)

6. Treatment options
   6.1 Nonsurgical: Fondaparinux or direct oral anticoagulants (DOAC)
   6.2 Surgical: Argatroban
   6.3 Cardiac surgery: Bivalirudin

7. Length of treatment
   7.1 Isolated HIT (HIT without thrombosis): anticoagulation should be continued for 4 weeks
   7.2 HITT: anticoagulation should be continued for at least 3 months and then assess the risk versus benefit of discontinuing therapy.

Companion Documents
1. Appendix B. Decision to treat HIT based on 4T score and lab test interpretation – Heparin Induced Thrombocytopenia – Adult – CPG
2. Appendix C. Selection of non-heparin anticoagulant – Heparin Induced Thrombocytopenia – Adult – CPG
**Scope**

**Disease/Condition(s):** Heparin Induced Thrombocytopenia

**Intended Users:**
- Physicians
- Advanced Practice Providers
- Pharmacists
- Registered Nurses

**Objective(s):** This clinical practice guideline is intended to provide recommendations for the diagnosis and treatment of HIT.

**Target Population:** Adult inpatients with suspicion or diagnosis of HIT

**Interventions and Practices Considered:**
- Assistance with diagnosis of HIT based on clinical presentation and laboratory confirmation
- Assistance with treatment of HIT including parenteral and oral options and patients with a history of HIT requiring cardiac surgery

**Major Outcomes Considered:**
- Frequency of HIT laboratory testing
- Time to platelet count recovery
- Thrombotic event rate
- Drug costs

**Methodology**

**Methods Used to Collect/Select the Evidence:**
Electronic database searches (e.g., PUBMED) were conducted by the guideline author(s) and workgroup members to collect evidence for review. Expert opinion and clinical experience were also considered during discussions of the evidence.

**Methods Used to Formulate the Recommendations:**
The workgroup members agreed to adopt recommendations developed by external organizations and/or arrived at a consensus through discussion of the literature and expert experience. All recommendations endorsed or developed by the guideline workgroup were reviewed and approved by other stakeholders or committees (as appropriate).

**Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:**
Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Figure 1 in Appendix A).

**Rating Scheme for the Strength of the Evidence/Recommendations:**
See Appendix A for the rating scheme(s) used within this document.
**Cost Analysis:**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Price per dose/vial ($)</th>
<th>Price per day ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argatroban 50 mL vial</td>
<td>149.48 per vial</td>
<td>Varies based on bags per day</td>
</tr>
<tr>
<td>Apixaban 5 mg</td>
<td>9.14 per dose</td>
<td>18.28</td>
</tr>
<tr>
<td>Bivalirudin 250 mg/5 mL</td>
<td>380.98 per vial</td>
<td>Varies based on bags per day</td>
</tr>
<tr>
<td>Dabigatran 150 mg</td>
<td>5.23 per dose</td>
<td>10.46</td>
</tr>
<tr>
<td>Fondaparinux (5 mg, 7.5 mg or 10 mg)</td>
<td>33.43 per dose</td>
<td>33.43</td>
</tr>
<tr>
<td>Rivaroxaban 15 mg</td>
<td>8.46 per dose</td>
<td>16.92</td>
</tr>
</tbody>
</table>

**Recognition of Potential Health Care Disparities:** Patients with HIT or HITT requiring at least 30 days of anticoagulant therapy it is important to consider both drug and monitoring costs to the patient. While warfarin is the least expensive medication, the cost for monitoring the INR should be considered. Additionally, the availability of INR monitoring and access, including transportation, to clinic facilities should be considered. Direct oral anticoagulants and fondaparinux may have medication assistance programs for patients who qualify and require minimal monitoring.

**Definitions**

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 occurring in 1 to 3% of patients receiving unfractionated heparin (UFH) and 0.8% of patients receiving low molecular weight heparin (LMWH). See Table 2. 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. An estimated 17-55% of patients with HIT develop venous thrombosis complications. If left untreated the event can be life or limb-threatening.

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

<table>
<thead>
<tr>
<th>Patient Population (after 4 days exposure)</th>
<th>Incidence of HIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical (post-operative)</td>
<td></td>
</tr>
<tr>
<td>Heparin – Prophylactic or Therapeutic</td>
<td>1-5%</td>
</tr>
<tr>
<td>Heparin – Flush</td>
<td>0.1-1%</td>
</tr>
<tr>
<td>LMWH – Prophylactic or Therapeutic</td>
<td>0.1-1%</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>1-3%</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>1-5%</td>
</tr>
<tr>
<td>Medical</td>
<td></td>
</tr>
<tr>
<td>Heparin – Prophylactic or Therapeutic</td>
<td>0.1-1%</td>
</tr>
<tr>
<td>LMWH – Prophylactic or Therapeutic</td>
<td>0.6%</td>
</tr>
<tr>
<td>ICU</td>
<td>0.4%</td>
</tr>
<tr>
<td>Cancer</td>
<td>1%</td>
</tr>
</tbody>
</table>

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 (UW Health moderate quality of evidence, strong recommendation)

1.1 The most validated has been the 4T score (Table 3) (UW Health moderate quality of evidence, strong recommendation)

1.1.2 The 4T score has less specificity in critically ill patients but can still be utilized to assist with diagnosis. Other causes of thrombocytopenia should be investigated in this patient population (UW Health low quality of evidence, weak/conditional recommendation)

1.2 Low 4T scores have a low probability of HIT: 0-3% (UW Health moderate quality of evidence, strong recommendation)

1.2.1 If a low 4T score is calculated then no further diagnostic testing is recommended. Other causes of thrombocytopenia should be investigated. (UW Health moderate quality of evidence, strong recommendation)

1.2.2 Table 4 lists medications that may cause thrombocytopenia

1.3 An intermediate or high 4T score requires laboratory confirmation for diagnosis (UW Health moderate quality of evidence, strong recommendation)
Table 3. 4T Score – Scoring is based on the summation of all categories

<table>
<thead>
<tr>
<th>Category</th>
<th>2 Points</th>
<th>1 Point</th>
<th>0 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>PLT fall &gt; 50% AND nadir &gt; 20 AND no surgery within previous 3 days</td>
<td>PLT fall &gt; 50% but surgery within previous 3 days</td>
<td>PLT fall &lt; 30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PLT fall 30-50% or nadir 10-19K</td>
<td>Any PLT fall with nadir &lt;10K</td>
</tr>
<tr>
<td>Timing of PLT count fall</td>
<td>Fall 5-10 days after heparin</td>
<td>Fall 5-10 days after heparin but unclear (e.g. missing PLT)</td>
<td>Fall ≤ 4 days without recent heparin exposure</td>
</tr>
<tr>
<td></td>
<td>Fall within 1 day after heparin and exposed to heparin within past 5-30 days</td>
<td>Fall in 1 day after heparin with exposure in past 31-100 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fall after 10 days</td>
<td></td>
</tr>
<tr>
<td>Thrombosis or other sequelae</td>
<td>Confirmed new thrombosis</td>
<td>Recurrent VTE while on therapeutic anticoagulants</td>
<td>Thrombosis suspected</td>
</tr>
<tr>
<td></td>
<td>Skin necrosis at injection site</td>
<td>Suspected thrombosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anaphylactoid reaction to IV heparin bolus</td>
<td>Erythematous skin lesions at heparin injection sites</td>
<td></td>
</tr>
<tr>
<td>Other causes of</td>
<td>No alternative explanation for platelet fall</td>
<td>Sepsis without proven source</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>Thrombocytopenia associated with initiation of ventilator</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Within 72 hrs of surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Confirmed bacteremia or fungemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemo/radiation within 20 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DIC due to non-HIT cause</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-transfusion purpura</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug induced thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Suspicion Scoring: 0-3 = Low, 4-5 = Intermediate, 6-8 = High

Table 4. Drugs associated with thrombocytopenia

<table>
<thead>
<tr>
<th>Causative Drug</th>
<th>Relative Commonness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycoprotein IIb/IIIa antagonists</td>
<td>abciximab, eptifibatide, tirofiban</td>
</tr>
<tr>
<td>Quinine</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Sulfa Antibiotics</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td></td>
</tr>
<tr>
<td>Piperacillin</td>
<td></td>
</tr>
<tr>
<td>Nafcillin</td>
<td></td>
</tr>
<tr>
<td>Cephalosporins</td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
</tr>
</tbody>
</table>

Confirming Diagnosis of HIT

2. Diagnosis of HIT is based on both clinical (thrombocytopenia or new thrombosis) and laboratory findings. (UW Health moderate quality of evidence, strong recommendation)

2.1 Routine laboratory screening without signs or symptoms of HIT is not recommended (UW Health moderate quality of evidence, strong recommendation)

2.2 The heparin induced platelet Ab (ELISA) can be performed in the clinical lab and should be utilized first if laboratory diagnosis is needed. (UW Health low quality of evidence, strong recommendation)
2.3 After reviewing clinical and laboratory data if diagnosis remains uncertain consider a hematology or vascular surgery consult (UW Health low quality of evidence, weak/conditional recommendation).

Table 5. Laboratory Tests for Diagnosing HIT\textsuperscript{1,9,10}

<table>
<thead>
<tr>
<th>Test</th>
<th>Lab Test Name</th>
<th>Performed at UW Lab</th>
<th>Turn Around Time</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA Enzyme Linked Immunosorbent Assay</td>
<td>Heparin Induced Platelet Ab</td>
<td>YES</td>
<td>3 hours (STAT) *if after 4pm call lab to arrange for STAT testing</td>
<td>&gt; 95%</td>
<td>50-89%</td>
</tr>
<tr>
<td>SRA Serotonin Release Assay</td>
<td>Heparin Dependant Ab – Serotonin Release Assay</td>
<td>NO</td>
<td>48 hours</td>
<td>&gt; 90%</td>
<td>&gt; 90%</td>
</tr>
</tbody>
</table>

3. A heparin induced platelet Ab (ELISA) should be ordered for intermediate or high suspicion of HIT (as scored by 4T)\textsuperscript{1}. (UW Health low quality of evidence, strong recommendation)

3.1 The optical density (OD) of the ELISA can identify the probability of HIT\textsuperscript{1} (UW Health low quality of evidence, strong recommendation)

3.1.1 An OD < 1: weak positive; more likely to be HIT negative

3.1.2 An OD ≥ 1: strong positive; more likely to be HIT positive

3.2 A strongly positive ELISA (OD ≥ 1) with a high suspicion for HIT can reliably confirm the diagnosis of HIT\textsuperscript{1,9,10} (UW Health moderate quality of evidence, strong recommendation)

3.3 The ELISA method can be associated with false positive results.\textsuperscript{1} An SRA may be needed to confirm diagnosis – see Section 4.

3.4 A negative ELISA reliably rules out HIT\textsuperscript{9,10} (UW Health moderate quality of evidence, strong recommendation)

4. A heparin dependant Ab (SRA) may be considered if uncertainty exists in the diagnosis of HIT based on the ELISA results and 4T score\textsuperscript{1,9,10} (UW Health moderate quality of evidence, strong recommendation)

4.1 In a weakly positive ELISA with an intermediate/high suspicion for HIT (based on 4T score) consider sending a SRA for confirmation. (UW Health low quality of evidence, strong recommendation)

4.2 A positive SRA reliably confirms the diagnosis of HIT\textsuperscript{1,9,10} (UW Health moderate quality of evidence, strong recommendation)

4.3 A negative SRA reliably rules out HIT\textsuperscript{9,10} (UW Health moderate quality of evidence, strong recommendation)

5. The following steps should be done for all patients with suspected or confirmed HIT

5.1 Discontinue all heparin (including flushes) and/or low molecular weight heparin orders by any route (UW Health low quality of evidence, strong recommendation)

5.2 Discontinue and reverse warfarin with phytonadione\textsuperscript{1} (UW Health low quality of evidence, strong recommendation)

5.2.1 If started less than 7 days when HIT diagnosed

5.2.2 Resume warfarin when platelet count has recovered to 100-150 \times 10^{9}/L

5.3 Obtain bilateral lower extremity ultrasonography to evaluate for deep vein thrombosis, even if clinical findings are absent (UW Health low quality of evidence, weak/conditional recommendation)
5.3.1 Consider bilateral upper extremity ultrasonography if central infusion lines are present (UW Health low quality of evidence, weak/conditional recommendation)

5.4 Start a non-heparin anticoagulant immediately upon ELISA confirmation or if awaiting results of the SRA.¹ (UW Health low quality of evidence, strong recommendation)

Anticoagulant Treatment Options for HIT

6. 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 unchanged¹¹. While fondaparinux has demonstrated similar efficacy and safety outcomes compared to traditional treatment in small studies and case reports, its use has not been completely established for treatment of HIT.¹¹-¹⁴

6.1 Therapeutic dosing should be based on renal function and total body weight (TBW)¹¹– In patients with CrCl > 80 mL/min see Table 6 (UW Health low quality of evidence, weak/conditional recommendation)

6.1.1 For CrCl < 80 mL/min refer to UW Health Renal Dosing Guidelines

Table 6. Therapeutic Fondaparinux Dosing¹¹-¹⁴

<table>
<thead>
<tr>
<th>CrCl &gt; 80 mL/min</th>
<th>Total Body Weight (kg)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 50</td>
<td>5 mg subcutaneous daily</td>
</tr>
<tr>
<td></td>
<td>50 - 100</td>
<td>7.5 mg subcutaneous daily</td>
</tr>
<tr>
<td></td>
<td>&gt; 100</td>
<td>10 mg subcutaneous daily</td>
</tr>
</tbody>
</table>

6.2 Prophylactic dosing of fondaparinux for suspected or confirmed HIT may also be considered at a dose of 2.5 mg daily if there is not an indication for therapeutic anticoagulation¹⁸ (UW Health low quality of evidence, weak/conditional recommendation)

6.3 Should not be used in patients with bacterial endocarditis or scheduled neuraxial anesthesia or spinal puncture¹¹ (UW Health low quality of evidence, strong recommendation)

7. 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.¹⁶

7.1 Dosing is based on TBW¹⁶ (UW Health low quality of evidence, strong recommendation)

7.2 No initial bolus is needed. Infusion rates should be initiated and adjusted based on recommendations in table 8 and 9. (UW Health low quality of evidence, strong recommendation)

7.3 The maximum infusion rate is 10 mcg/kg/min (UW Health low quality of evidence, strong recommendation)
Table 8. Argatroban Initial Infusion Rate\textsuperscript{16,17}

<table>
<thead>
<tr>
<th>Indication for dose adjustment</th>
<th>Initial Infusion rate Based on total body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal hepatic function</td>
<td>2 mcg/kg/min</td>
</tr>
<tr>
<td>Moderate hepatic function</td>
<td>0.5 mcg/kg/min</td>
</tr>
<tr>
<td>Heart Failure, Multiple organ system failure, severe anascara, cardiac surgery</td>
<td>0.5-1.2 mcg/kg/min</td>
</tr>
</tbody>
</table>

Table 9. Argatroban Dose Adjustments\textsuperscript{16,17}

<table>
<thead>
<tr>
<th>Hepatic function</th>
<th>PTT</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal hepatic function</td>
<td>&lt; 1.5 x baseline PTT</td>
<td>Increase by 0.5 mcg/kg/min</td>
</tr>
<tr>
<td></td>
<td>Goal 1.5 - 3.0 x baseline PTT (*Maximum 100 seconds)</td>
<td>Continue same rate</td>
</tr>
<tr>
<td></td>
<td>&gt; 3 x baseline PTT</td>
<td>Decrease by 0.5 mcg/kg/min</td>
</tr>
<tr>
<td>Moderate hepatic function</td>
<td>&lt; 1.5 x baseline PTT</td>
<td>Increase by 0.25 mcg/kg/min</td>
</tr>
<tr>
<td></td>
<td>Goal 1.5 - 3.0 x baseline PTT (*Maximum 100 seconds)</td>
<td>Continue same rate</td>
</tr>
<tr>
<td></td>
<td>&gt; 3 x baseline PTT</td>
<td>Decrease by 0.25 mcg/kg/min</td>
</tr>
</tbody>
</table>

7.4 PTT should be measured every 2 hours after initiation or any rate adjustment (\emph{UW Health low quality of evidence, strong recommendation})

7.5 Once 2 consecutive PTTs are in target range then PTT may be checked daily (\emph{UW Health low quality of evidence, strong recommendation})

8. Direct Oral Anticoagulants (DOACs)

The use of DOACs (i.e. dabigatran, rivaroxaban, apixaban) has recently been reported as possible alternative treatment options for HIT. Case reports and small case series are the only data currently available as large randomized, controlled trials are unlikely to occur due to the low prevalence of HIT. To date each of these agents have shown promising outcomes regarding platelet recovery and preventing thrombotic events with no major bleeding events.\textsuperscript{18-25} They offer an easier alternative for treatment as they have standardized dosing, minimal monitoring and oral administration.\textsuperscript{18} Between the 3 DOAC options rivaroxaban has the most case reports and case series data.\textsuperscript{21-25}

8.1 When selecting a DOAC for treatment of HIT it is important to consider patient risk factors. DOAC should be avoided in patients with: (\emph{UW Health low quality of evidence, weak/conditional recommendation})

8.1.1 Creatinine clearance < 30 mL/min or hemodialysis\textsuperscript{26,27}
8.1.2 Weight: < 50 kg, > 120 kg or BMI > 35 kg/m\textsuperscript{2}\textsuperscript{26,29}
8.1.3 The potential for procedure or surgery in 24 hours\textsuperscript{26,27}
8.1.4 Critical illness

8.2 Rivaroxaban 15 mg by mouth twice daily until platelet count recovers then decrease dose to 20 mg daily\textsuperscript{21-25} (\emph{UW Health low quality of evidence, weak/conditional recommendation})

8.2.1 Platelet count recovery defined as \( \geq 150 \times 10^9/L \) or to previous baseline
8.2.2 If thrombosis confirmed continue 15 mg twice daily for 21 days then decrease to 20 mg daily\textsuperscript{27}
8.3 Dabigatran 150 mg by mouth twice daily\textsuperscript{19,20} (UW Health low quality of evidence, weak/conditional recommendation)

8.4 Apixaban 5 mg by mouth twice daily\textsuperscript{30} (UW Health low quality of evidence, weak/conditional recommendation)

8.5 For duration of therapy see Section 10.

9. Special Populations

9.1 Urgent cardiac surgery with acute or sub-acute HIT or cardiac catheterization or percutaneous coronary intervention\textsuperscript{1}

9.1.1 Bivalirudin is recommended (UW Health low quality of evidence, weak/conditional recommendation)

9.1.2 Dosing is based on TBW to a max of 150 kg (UW Health low quality of evidence, strong recommendation)

9.1.3 No initial bolus is needed. Infusion rates should be initiated and adjusted based on recommendations in tables 10 and 11. (UW Health low quality of evidence, strong recommendation)

Table 10. Initial Bivalirudin Infusion Rate\textsuperscript{31-35}

<table>
<thead>
<tr>
<th>Estimated Creatinine Clearance (mL/min)</th>
<th>Initial Bivalirudin Infusion Rate (mg/kg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>0.15</td>
</tr>
<tr>
<td>30 – 60</td>
<td>0.08</td>
</tr>
<tr>
<td>&lt; 30 / Renal Replacement Therapy</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Table 11. Bivalirudin Dose Adjustments\textsuperscript{36-40}

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

9.2 Urgent cardiac surgery with a history of HIT and a negative HIT antibody\textsuperscript{1}

9.2.1 Recommend unfractionated heparin during the procedure (UW Health low quality of evidence, weak/conditional recommendation)

9.2.2 Recommend a non-heparin anticoagulant post operatively (UW Health low quality of evidence, weak/conditional recommendation)
10. Transitioning Therapies

Transitioning from a parenteral anticoagulant to oral anticoagulant should occur only in a stable patient and after platelet recovery to at least 150 K/uL or upon return to usual baseline. *(UW Health low quality of evidence, strong recommendation)*

10.1 Fondaparinux to warfarin\(^1,11\)
   10.1.1 Once platelet count normalizes start warfarin 5 mg daily *(UW Health low quality of evidence, strong recommendation)*
   10.1.2 Dose adjust warfarin until the INR is > 2. When INR is within a therapeutic range for two consecutive results and after a minimum of 5 days, discontinue fondaparinux. *(UW Health low quality of evidence, strong recommendation)*

10.2 Argatroban to warfarin\(^1,16,36\)
   10.2.1 Adjust infusion rate to achieve a PTT level just above 1.5x normal before starting warfarin at 5 mg daily. *(UW Health low quality of evidence, strong recommendation)*
   10.2.2 The combination of argatroban and warfarin creates a laboratory discrepancy which falsely elevates INR values. During the combination target an INR of ≥ 4.
   10.2.3 Once the INR is > 4 and after a minimum of 5 days on dual anticoagulant therapy, argatroban can be held and the INR repeated in 4-6 hours. *(UW Health low quality of evidence, strong recommendation)*
   10.2.4 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. When this occurs argatroban can be discontinued. *(UW Health low quality of evidence, strong recommendation)*

10.3 Parenteral to DOAC\(^11,16,20,26,27,41\)
   10.3.1 Stop fondaparinux and start DOAC at the time of next scheduled fondaparinux dose. *(UW Health low quality of evidence, strong recommendation)*
   10.3.2 Stop argatroban infusion and start DOAC at the same time. *(UW Health low quality of evidence, strong recommendation)*

11. Duration of Anticoagulation
   11.1 Isolated HIT (HIT without thrombosis): anticoagulation should be continued for 4 weeks\(^1\)
   11.2 HITT: anticoagulation should be continued for at least 3 months and then assess the risk versus benefit of discontinuing therapy.\(^2\)

12. Laboratory Monitoring\(^1,11,16,26,27\) *(UW Health low quality of evidence, strong recommendation)*
   12.1 Platelets should be monitored daily for recovery. Once they have normalized (100-150 x 10^9/L) they may be monitored less often.
   12.2 CBC should be monitored every 48 hours while hospitalized and on an anticoagulant.
   12.3 Creatinine should be monitored as clinically indicated.
UW Health Implementation

Potential Benefits:
- Standardized approach to diagnosis of HIT
- Selection of optimal treatment based on patient specific factors

Potential Harms:
- Hemorrhagic complications
- Thrombotic complications

Qualifying Statements:
Neither fondaparinux nor the DOACs are FDA approved for the treatment of HIT. Current existing data is from case reports and/or case series. There are no randomized, controlled trials using these medications for the treatment of HIT. The workgroup agreed that case reports and case series will likely be the only available data as HIT is a rare occurrence which makes large randomized trials a challenge for this disease state. The workgroup reviewed the available data and felt the benefit to using these agents (as described in the guideline) outweighed the lack of strong clinical data. Recommendations were graded to reflect the lack of controlled clinical data.

Pertinent UW Health Policies & Procedures
1. None identified

Guideline Metrics
1. VTE Performance Measure – VTE 4 – UFH with dosage and platelet monitored by protocol
2. Frequency for HIT laboratory testing and false positive ELISA HIT results
3. Time to platelet count recovery
4. Thrombotic event rate

Implementation Plan/Clinical Tools
1. Guideline will be posted on uConnect in a dedicated location for Clinical Practice Guidelines.
2. Guideline will be posted on the uwhealth.org/anticoagulation webpage.
3. Release of the guideline will be advertised in the Physician/APP Briefing newsletter.
4. Content and hyperlinks within clinical tools, documents, or Health Link related to the guideline recommendations (such as the following) will be reviewed for consistency and modified as appropriate.

Order Sets & Smart Sets
IP – HIT (Heparin Induced Thrombocytopenia) Adult – Supplemental – Order Set [3596]

Disclaimer
Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This 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.

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Contact: CCKM@uwhealth.org
Last Revised: 05/2017
Appendix A. Evidence Grading Scheme(s)

Figure 1. GRADE Methodology adapted by UW Health

GRADE Ranking of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are confident that the effect in the study reflects the actual effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>The true effect may differ significantly from the estimate.</td>
</tr>
<tr>
<td>Very Low</td>
<td>The true effect is likely to be substantially different from the estimated effect.</td>
</tr>
</tbody>
</table>

GRADE Ratings for Recommendations For or Against Practice

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.</td>
</tr>
<tr>
<td>Weak/conditional</td>
<td>Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.</td>
</tr>
</tbody>
</table>
Appendix B. Decision to treat HIT based on 4T score and lab test interpretation – Heparin Induced Thrombocytopenia – Adult – CPG

HIT Suspicion

4T Score

Low

Intermediate / High

Continue Heparin Product & Consider Other Causes

Stop All Heparin Products & Obtain STAT ELISA

Negative ELISA

Negative SRA

Positive ELISA (OD < 1) AND Intermediate 4T Score OR Diagnostic uncertainty OR HIT diagnosis would impact future therapy (CAD patient who may need a CABG)

Obtain a SRA AND Start non-heparin anticoagulant while waiting for SRA to result and HIT to be diagnosed

Positive SRA

HIT Diagnosed

Continue non-heparin anticoagulant

Positive ELISA (OD ≥1) AND High 4T Score

HIT Diagnosed

Start non-heparin anticoagulant

CPG Contact for Changes:
Name: Philip J Trapskin, PharmD, BCPS
Phone Number: 263-1328
Email Address: ptrapskin@uwhealth.org
Revised: 2/2017

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Contact: CCKM@uwhealth.org
Last Revised: 05/2017
Appendix C. Selection of non-heparin anticoagulant – Heparin Induced Thrombocytopenia – Adult – CPG

Non-heparin anticoagulant needed

Procedure/surgery in 24 hrs

Recommend Argatroban

CrCl > 50 mL/min

YES

Recommend Fondaparinux or DOAC

NO

NO
References


