B. Transitioning to warfarin

- HIT patients are at risk of venous limb gangrene during initiation of warfarin.
- Warfarin should not be initiated until platelet count is ≥ 150 x 10^9/L (Grade 1B).
- Initial warfarin dose should be ≤ 5 mg/day. Larger loading doses should be avoided (Grade 1B).
- A parenteral non-heparin anticoagulant should be overlapped with warfarin for ≥ 5 days and until INR has reached intended target (Grade 1B).
- Because argatroban raises the INR, the following steps should be taken when transitioning a patient from argatroban to warfarin:
  1. Stop argatroban when INR on combined argatroban and warfarin is ≥ 4.
  2. Repeat INR in 4-6 hours.
  3. If INR is ≤ 2, restart argatroban.
  4. Repeat procedure daily until INR ≥ 2 is achieved.

If argatroban dose is >2 mcg/kg/min

- If argatroban dose is ≤ 2 mcg/kg/min
  - Warfarin should be taken when transitioning a patient from argatroban to warfarin.

Because argatroban raises the INR, the following steps should be taken (Grade 1B):

- Parenteral non-heparin anticoagulant should be overlapped with warfarin for ≥ 5 days and until INR has reached intended target (Grade 1B).
- For all patients, anticoagulation management should be based on an individualized risk/benefit assessment.

C. Duration of anticoagulation

- Bilateral lower extremity compression ultrasonography should be performed in all patients with HIT, whether or not there is clinical evidence of lower-limb DVT (Grade 1C), because the finding of DVT may influence the recommended duration of anticoagulation.
- For patients with HIT-associated thrombosis (i.e., HITT), anticoagulate for a defined course (typically 3-6 months) as with other provoked thrombosis.
- For patients with HIT without thrombosis (i.e. isolated HIT), anticoagulation should be considered for at least 30 days after the diagnosis of HIT, anticoagulation for at least one month should be considered.
- For all patients, anticoagulation management should be based on an individualized risk/benefit assessment.

D. Platelet transfusion

- Due to theoretical risk that platelet transfusion may precipitate thrombosis in HIT, prophylactic platelet transfusions should not be given to patients with confirmed or strongly suspected HIT (Grade 2C).
- Platelet transfusion may be appropriate in situations of diagnostic uncertainty, high bleeding risk, or clinically significant bleeding.

V. Heparin Re-Exposure in Patients with a History of HIT

A. Cardiac and vascular surgery

- HIT laboratory testing should be used to determine the safety of exposing a patient with a history of HIT to intravenous heparin.
- Warfarin should not be initiated until platelet count is ≥ 100 x 10^9/L (Grade 1B).
- Platelet transfusion may be appropriate in situations of diagnostic uncertainty, high bleeding risk, or clinically significant bleeding.

B. Cardiac catheterization/percutaneous coronary intervention

- American College of Chest Physicians Evidence-Based Clinical Practice Guideline on Antithrombotic and Thrombolytic Therapy (8th Edition).

Guidelines provide the practitioner with clear principles and strategies for quality patient care and do not establish a fixed set of rules that preempt physician judgment.

For further information, please see the complete guidelines on the Chest Web site at www.chestjournal.org/content/133/6_suppl/340S.long or refer to the Practice Guidelines section of the ASH Web site at www.hematology.org/copd/resources/guidelines. You may also contact the ASH Policy & Practice Department at 202-776-0544.

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I. History and Physical Examination: Evaluating the Clinical Probability of HIT

A. Features of the history and physical examination that support a diagnosis of HIT

- **Features**
  - Significant bleeding
  - Absence of petechiae and other thrombocytopenia
  - Skin necrosis at subcutaneous heparin injection sites

**II. Laboratory Diagnosis**

**II. Laboratory Diagnosis**

<table>
<thead>
<tr>
<th>Category</th>
<th>Assay</th>
<th>Example</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunologic</td>
<td>Detects antibodies against PF4- (\text{PF4}^-) or HSPGs, regardless of their capacity to activate platelets</td>
<td>ELISA</td>
<td>&gt;95%</td>
<td>50-90%</td>
</tr>
<tr>
<td>Functional</td>
<td>Detects antibodies that induce heparin-dependent platelet activation</td>
<td>SRA, HIPA, PAI</td>
<td>&gt;90%</td>
<td>90-100%</td>
</tr>
</tbody>
</table>

B. The 4Ts: A clinical probability scoring model

**4Ts Table**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Points</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall in platelet count (&gt;50)%</td>
<td>2</td>
<td>Clear onset within 5-14 days (prior to heparin exposure)</td>
</tr>
<tr>
<td>Fall in platelet count (\leq 10)%</td>
<td>1</td>
<td>Clear onset within 1 day (prior to heparin exposure)</td>
</tr>
<tr>
<td>Thrombosis or Other sequelae</td>
<td>2</td>
<td>New thrombosis (confirmed)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>Progressive thrombocytopenia</td>
</tr>
<tr>
<td>No other causes of thrombocytopenia</td>
<td>0</td>
<td>None apparent</td>
</tr>
</tbody>
</table>

High probability: 6-8 points; intermediate probability: 4-5 points; low probability: ≤3 points.

Adapted from Lo GK et al., J Thromb Haemost 2006. The 4Ts model has demonstrated excellent sensitivity (low probability score indicates low probability of HIT), but limited specificity (intermediate or high probability score may or may not indicate the presence of HIT).

C. The 4Ts: A clinical probability scoring model

<table>
<thead>
<tr>
<th>4Ts</th>
<th>2 Points</th>
<th>1 Point</th>
<th>0 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall in platelet count (&gt;50)%</td>
<td>Clear onset within 5-14 days (prior to heparin exposure)</td>
<td>Clear onset within 1 day (prior to heparin exposure)</td>
<td>None apparent</td>
</tr>
<tr>
<td>Fall in platelet count (\leq 10)%</td>
<td>Clear onset within 1 day (prior to heparin exposure)</td>
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<tr>
<td>Thrombosis or Other sequelae</td>
<td>New thrombosis (confirmed)</td>
<td>Progressive thrombocytopenia</td>
<td>None apparent</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Progressive thrombocytopenia</td>
<td>None apparent</td>
<td>None apparent</td>
</tr>
</tbody>
</table>

D. The 4Ts: A clinical probability scoring model

<table>
<thead>
<tr>
<th>4Ts</th>
<th>2 Points</th>
<th>1 Point</th>
<th>0 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall in platelet count (&gt;50)%</td>
<td>Clear onset within 5-14 days (prior to heparin exposure)</td>
<td>Clear onset within 1 day (prior to heparin exposure)</td>
<td>None apparent</td>
</tr>
<tr>
<td>Fall in platelet count (\leq 10)%</td>
<td>Clear onset within 1 day (prior to heparin exposure)</td>
<td>None apparent</td>
<td>None apparent</td>
</tr>
<tr>
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<tr>
<td>Thrombocytopenia</td>
<td>Progressive thrombocytopenia</td>
<td>None apparent</td>
<td>None apparent</td>
</tr>
</tbody>
</table>

II. Laboratory Diagnosis

**Assay**

**Method**

**Example**

**Sensitivity**

**Specificity**

**Comments**

**III. Diagnostic and Initial Treatment Algorithm**

**Intermediate/high clinical probability**

**Low clinical probability**

**IV. Treatment**

**A. Non-heparin anticoagulants: selection, dosing, and monitoring**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Direct recommendation</th>
<th>Initial dosing</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argatroban</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argatroban</td>
<td>Continuous infusion:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
I. History and Physical Examination: Evaluating the Clinical Probability of HIT

A. Features of the history and physical examination that support a diagnosis of HIT

1. History and Physical Examination:

- A. Features of the history and physical examination that support a diagnosis of HIT
- B. The 4Ts: A clinical probability scoring model
- III. Diagnostic and Initial Treatment Algorithm
- IV. Treatment

Cover Image: In skin microscopy showing monocyeles (in red), platelets (in green), and areas of overlap (in yellow) being incorporated into a growing thrombus in a mouse model of HIT. Courtesy of L. Rauova and M. Poncz, Children's Hospital of Philadelphia.

B. The 4Ts: A clinical probability scoring model

<table>
<thead>
<tr>
<th>Feature</th>
<th>1 Points</th>
<th>2 Points</th>
<th>3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Platelet count &lt; 50% and nadir count &lt; 20 x 10⁹/L</td>
<td>Platelet count &lt; 30% of nadir platelet count</td>
<td>Platelet count &lt; 10 x 10⁹/L</td>
</tr>
<tr>
<td>Thrombus or Other sequelae</td>
<td>New thrombus (confirmed)</td>
<td>Progressive or recurrent thrombosis</td>
<td>Non-necrotizing skin lesions; Suspected skin ischemia (not confirmed)</td>
</tr>
<tr>
<td>Absence of alternative causes of thrombocytopenia</td>
<td>None</td>
<td>Possible</td>
<td>Definite</td>
</tr>
</tbody>
</table>

High probability: 6-8 points; intermediate probability: 4-5 points; low probability: ≤3 points.

Adapted from Lo GK et al., J Thromb Haemost 2006. The 4Ts model has not been externally validated. It may be used as a guide for clinicians, but should not substitute for clinical judgment. In clinical studies, the 4Ts model has demonstrated acceptable accuracy (low probability score indicates low probability of HIT), but limited specificity (intermediate or high probability scores may or may not indicate the presence of HIT).

II. Laboratory Diagnosis

<table>
<thead>
<tr>
<th>Assaying Category</th>
<th>Mechanism</th>
<th>Examples</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunologic</td>
<td>Detects antibodies against PF4/heparin complexes</td>
<td>ELISA for anti-β2GPI, ELISA for anti-β2GPI/heparin complexes</td>
<td>≥95%</td>
<td>50-80%</td>
<td>OQ of result correlates with clinical probability of HIT</td>
</tr>
<tr>
<td>Functional</td>
<td>Detects antibodies that induce thrombin-dependent platelet activation</td>
<td>SRA, HIPA, PAT</td>
<td>≥90%</td>
<td>90%</td>
<td>Not available at many centers; may require referral to a reference laboratory</td>
</tr>
</tbody>
</table>

Bolus: Weight 200-500 kg: ≤500 U/hr; ≤60-75 kg: ≤2500 U/hr; ≤75 300 kg: ≤3000 U/hr; ≤500 kg: ≤3500 U/hr

I. History and Physical Examination: Evaluating the Clinical Probability of HIT

A. Features of the history and physical examination that support a diagnosis of HIT

I. History and Physical Examination:

- Nadir platelet count ≥ 20 x 10^9/L May be < 20 x 10^9/L in cases associated with previous heparin exposure within last 100 days
- Fall in platelet count begins 5-14 or platelet counts) or ≤ 10 x 10^9/L
- Platelet count fall ≥ 50% from highest platelet count after heparin exposure; platelet count fall 50-99% or platelet nadir < 20 x 10^9/L

II. Laboratory Investigation

- Skin necrosis At subcutaneous heparin injection sites
- Non-necrotizing thrombosis; Suspected lesions; Suspected thrombosis (not confirmed)
- Clear onset after day 14 or fall ≤ 50% from highest platelet count after heparin exposure within last 30 days

III. Diagnostic and Initial Treatment Algorithm

A. Non-heparin anticoagulants: selection, dosing, and monitoring

Adapted from Warkentin TE et al., Chest 2008.

B. The 4Ts: A clinical probability scoring model

- High probability: 6-8 points; intermediate probability: 4-5 points; low probability: <3 points

- Adapted from Lo GK et al., J Thromb Haemost 2006. The 4Ts model has not been externally validated. It may be used as a guide for clinicians, but should not substitute for clinical judgment. In clinical studies, the 4Ts model has demonstrated excellent sensitivity (low probability score indicates low probability of HIT), but limited specificity (intermediate or high probability score may or may not indicate the presence of HIT).

IV. Treatment

- Adjust dose to anti-factor Xa level of 0.5-0.8 U/ml (if assay is available).
- Monitor APTT every 4 hours during dose titration.
- Adjust dose to APTT of 1.5-2.0 times patient baseline.
- Monitor APTT every 4 hours during dose titration.
- No specific recommendations given minimal data supporting efficacy and appropriate dosing in HIT.
I. History and Physical Examination: Evaluating the Clinical Probability of HIT

A. Features of the history and physical examination that support a diagnosis of HIT

B. The 4Ts: A clinical probability scoring model

III. Diagnostic and Initial Treatment Algorithm

IV. Treatment

Covers Image: (in skin microscopy showing monocytes in red), platelets (in green), and areas of overlap (in yellow) being incorporated into a growing thrombus in a mouse model of HIT. Courtesy of L. Rauova and M. Poncz, Children’s Hospital of Philadelphia.

D. Platelet transfusion

- Due to theoretical risk that platelet transfusion may precipitate thrombosis in HIT, prophylactic platelet transfusions should not be given to patients with confirmed or strongly suspected HIT (grade 1C).
- Platelet transfusion may be appropriate in situations of diagnostic uncertainty, high bleeding risk, or clinically significant bleeding.

V. Heparin Re-Exposure in Patients with a History of HIT

A. Cardiac and vascular surgery

- HIT laboratory testing should be used to determine the safety of exposing a patient with a history of HIT to intravenous heparin.
- For all patients, anticoagulation management should be based on an individualized risk/benefit assessment.
- Anticoagulation for at least one month should be considered.
- For all patients, anticoagulation management should be based on individualized risk/benefit assessment.
- For patients with HIT without thrombosis (i.e. isolated HIT), anticoagulate for a defined course (typically 3-6 months) as appropriate for other provoked thromboses.
- For patients with HIT-associated thrombosis (i.e. HITT), anticoagulation should be considered.
- For patients with HIT without thrombosis (i.e. isolated HIT), anticoagulation for at least one month should be considered.
- For all patients, anticoagulation management should be based on an individualized risk/benefit assessment.

B. Transitioning to warfarin

- HIT patients are at risk of venous limb gangrene during initiation of warfarin.
- Warfarin should not be initiated until platelet count is ≥150 x 10^9/L (Grade 1B).
- Initial warfarin dose should be ≤5 mg/day. Larger loading doses should be avoided (Grade 1B).
- A parenteral non-heparin anticoagulant should be overlapped with warfarin for ≤5 days and until INR has reached intended target (Grade 1B).
- Because argatroban raises the INR, the following steps should be taken when transitioning a patient from argatroban to warfarin:
  1. If argatroban dose is <2 mcg/kg/min
     1. Stop argatroban when INR on combined argatroban and warfarin is ≥2
     2. Repeat INR in 4-6 hours
     3. If INR is ≥2, restart argatroban
     4. Repeat procedure daily until INR ≥2 is achieved
  2. If argatroban dose is ≥2 mcg/kg/min
     1. Reduce argatroban dose to 2 mcg/kg/min
     2. Repeat INR in 4-6 hours
     3. Stop argatroban when INR on combined argatroban and warfarin is ≥4
     4. Repeat INR in 4-6 hours
     5. If INR is ≥2, restart argatroban
     6. Repeat procedure daily until INR ≥2 is achieved

C. Duration of anticoagulation

- Bilateral lower extremity compression ultrasonography should be performed in all patients with HIT, whether or not there is clinical evidence of lower-limb DVT (Grade 1B), because the finding of DVT may influence the recommended duration of anticoagulation.
- For patients with HIT-associated thrombosis (i.e. HITT), anticoagulate for a defined course (typically 3-6 months) as appropriate for other provoked thromboses.
- For patients with HIT without thrombosis (i.e. isolated HIT), the optimal duration of anticoagulation is unknown. Because there is an elevated risk of thrombosis extending at least 30 days after the diagnosis of HIT, anticoagulation for at least one month should be considered.
- For all patients, anticoagulation management should be based on an individualized risk/benefit assessment.
B. Transitioning to warfarin
- HIT patients are at risk of venous limb gangrene during initiation of warfarin.
- Warfarin should not be initiated until platelet count is ≥ 150 x 10^9/L (Grade 1B).
- Initial warfarin dose should be ≤ 5 mg/day. Larger loading doses should be avoided (Grade 1B).
- A parenteral non-heparin anticoagulant should be overlapped with warfarin for ≤ 5 days and until INR has reached intended target (Grade 1B).
- Because argatroban raises the INR, the following steps should be taken when transitioning a patient from argatroban to warfarin:
  - If argatroban dose is >2 mcg/kg/min
  1. Stop argatroban when INR on combined argatroban and warfarin is ≥4
  2. Repeat INR in 4-6 hours
  3. If INR is ≥4, restart argatroban
  4. Repeat procedure daily until INR ≥4 is achieved
  5. Reduce argatroban dose to ≤2 mcg/kg/min
  6. Repeat INR in 4-6 hours
  7. Stop argatroban when INR on combined argatroban and warfarin is ≥4
  8. Repeat INR in 4-6 hours
  9. If INR is ≥4, restart argatroban
  10. Repeat procedure daily until INR ≥4 is achieved
- Bleeding risk should be considered.
- Platelet transfusion should be given to patients with confirmed or strongly suspected HIT to prevent further thrombosis.
- Due to the thrombotic risk that platelet transfusion may precipitate thrombosis in HIT, prophylactic platelet transfusions should not be given to patients with confirmed or strongly suspected HIT (Grade 2C).
- Platelet transfusion may be appropriate in situations of diagnostic uncertainty, high bleeding risk, or clinically significant bleeding.

C. Duration of anticoagulation
- For all patients, anticoagulation management should be based on clinical evidence of lower-limb DVT (Grade 1C), bilateral lower extremity compression ultrasonography should be performed in all patients with HIT, whether or not there is clinical evidence of lower-limb DVT (Grade 1C), because the finding of DVT may influence the recommended duration of anticoagulation.
- For patients with HIT-associated thrombosis (i.e., HIT-T), anticoagulate for a defined course (typically 3-6 months) as a non-heparin anticoagulant should be used. 2American College of Chest Physicians Grading System: 1=strong recommendation; 2=weak recommendation; 3=weak recommendation; 4=based on high quality evidence; 5=based on moderate quality evidence; C=based on low quality evidence.
- Platelet transfusion should be given to patients with confirmed or strongly suspected HIT to prevent further thrombosis.
- Due to the thrombotic risk that platelet transfusion may precipitate thrombosis in HIT, prophylactic platelet transfusions should not be given to patients with confirmed or strongly suspected HIT (Grade 2C).
- Platelet transfusion may be appropriate in situations of diagnostic uncertainty, high bleeding risk, or clinically significant bleeding.

V. Heparin Re-Exposure in Patients with a History of HIT
A. Cardiac and vascular surgery
- HIT laboratory testing should be used to determine the safety of exposing a patient with a history of HIT to intravenous heparin.
- For patients with HIT without thrombosis (i.e. isolated HIT), anticoagulate for a defined course (typically 3-6 months) as a non-heparin anticoagulant should be used. 2American College of Chest Physicians Grading System: 1=strong recommendation; 2=weak recommendation; 3=weak recommendation; 4=based on high quality evidence; 5=based on moderate quality evidence; C=based on low quality evidence.
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B. Cardiac catheterization/percutaneous coronary intervention
- For patients with HIT without thrombosis (i.e. isolated HIT), the optimal duration of anticoagulation is unknown. Because there is an elevated risk of thrombosis extending at least 30 days after the diagnosis of HIT, anticoagulation for at least one month should be considered.
- For all patients, anticoagulation management should be based on an individualized risk/benefit assessment.
B. Transitioning to warfarin

- HIT patients are at risk of venous limb gangrene during initiation of warfarin.
- Warfarin should not be initiated until platelet count is ≥ 150 x 10^9/L (Grade 1B).
- Initial warfarin dose should be ≤ 5 mg/day. Larger loading doses should be avoided (Grade 1B).
- A parenteral non-heparin anticoagulant should be overlapped with warfarin for ≥ 5 days and until INR has reached intended target (1.5-2.5) (Grade 1B).
- Because argatroban raises the INR, the following steps should be taken when transitioning a patient from argatroban to warfarin:
  1. If argatroban dose is ≤ 1 mcg/kg/min, transition to warfarin:
     - Warfarin should not be initiated until platelet count is ≥ 100 x 10^9/L. (Grade 1B)
     - Repeat procedure daily until INR > 2 is achieved
     - If argatroban dose is ≤ 2 mcg/kg/min:
       1. Reduce argatroban dose to 1 mcg/kg/min
       2. Repeat procedure daily until INR > 2 is achieved

- If argatroban dose is > 2 mcg/kg/min:
  1. Stop argatroban when INR on combined argatroban and warfarin is ≥ 4
  2. Repeat INR in 4-6 hours
  3. If INR is ≤ 3, restart argatroban
  4. Repeat procedure daily until INR ≥ 3 is achieved

C. Duration of anticoagulation

- Bilateral lower extremity compression ultrasonography should be performed in all patients with HIT, whether or not there is clinical evidence of lower-limb DVT (Grade 1C), because the finding of DVT may influence the recommended duration of anticoagulation.
- For patients with HIT-associated thrombosis (i.e., HITT), anticoagulate for a defined course (typically 3-6 months) as per physician judgment.

D. Platelet transfusion

- Due to theoretical risk that platelet transfusion may precipitate thrombosis in HIT, prophylactic platelet transfusions should not be given to patients with confirmed or strongly suspected HIT (Grade 2C).
- Platelet transfusion may be appropriate in situations of diagnostic uncertainty, high bleeding risk, or clinically significant bleeding.

V. Heparin Re-Exposure in Patients with a History of HIT

A. Cardiac and vascular surgery

- HIT laboratory testing should be used to determine the safety of exposing a patient with a history of HIT to intraparacardiac heparin:
  1. Use a non-heparin anticoagulant if a patient has a history of HIT treated with heparin:
     - Delay surgery, if possible, until immunologic assay becomes negative (Grade 1B)
     - If surgery cannot be delayed, use UFH (Grade 2C)

- If a non-heparin anticoagulant is used, a non-heparin anticoagulant should be used:
  1. American College of Chest Physicians Grading System: 1=strong recommendation; 2=weak recommendation; A=based on high quality evidence; B=based on moderate quality evidence; C=based on low quality evidence; UFH, unfractionated heparin.

B. Cardiac catheterization/percutaneous coronary intervention

- If per- or post-operative anticoagulation is initiated, a non-heparin anticoagulant should be used:
  1. Use a non-heparin anticoagulant if a patient has a history of HIT treated with heparin:
     - Delay surgery, if possible, until immunologic assay becomes negative (Grade 1B)
     - If surgery cannot be delayed, use UFH (Grade 2C)

- If a non-heparin anticoagulant is used, a non-heparin anticoagulant should be used:
  1. American College of Chest Physicians Grading System: 1=strong recommendation; 2=weak recommendation; A=based on high quality evidence; B=based on moderate quality evidence; C=based on low quality evidence.

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