Management of the multiple phases of heparin-induced thrombocytopenia

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Introduction

Heparin-induced thrombocytopenia (HIT) is a prothrombotic disorder mediated by IgG antibodies that recognise ultra-large complexes of platelet factor 4 (PF4) and heparin or other endogenous glycosaminoglycans (1). Initial diagnosis is based on an estimation of clinical probability and identification of circulating anti-PF4/heparin antibodies by immunoassay. The diagnosis is confirmed by demonstration of heparin-dependent platelet-activating antibodies in the patient's serum using a washed platelet functional assay. Treatment involves cessation of heparin and initiation of a non-heparin anticoagulant.

The clinical and immunologic response to discontinuation of heparin in a patient with acute HIT follows a predictable pattern. Platelet count recovery occurs within seven days of suspension of heparin in 90% of patients, though it may take weeks in a minority of patients (2, 3). Washed platelet functional assays become negative a median of 50 days after discontinuation of heparin. Circulating anti-PF4/heparin antibodies are no longer detectable by immunoassay at a median of 85 days (3).

This stereotyped sequence of events allows HIT to be conceptually separated into phases (▶ Table 1). In suspected HIT, the patient is thought to have HIT based on clinical grounds, but the results of confirmatory laboratory testing are not yet available. Once laboratory confirmation of the diagnosis is made, the patient is said to have acute HIT. Acute HIT, a period of markedly increased thrombotic risk, persists until platelet count recovery. Subacute HIT A is defined as the interval following platelet count recovery but before the washed platelet functional assay becomes negative. Subacute HIT B is the phase after the washed platelet functional assay becomes negative, but before the immunoassay becomes negative. Finally, once anti-PF4/heparin antibodies are no longer detectable by immunoassay, the patient is said to have remote HIT.

This construct is useful because it reflects the multiple phases in which HIT is encountered and the different management questions with which clinicians are confronted in clinical practice. The objective of this review is to address key management questions that arise during each of the five phases of HIT.

Summary

The clinical course of heparin-induced thrombocytopenia (HIT) may be separated into five sequential phases: 1. suspected HIT, 2. acute HIT, 3. subacute HIT A, 4. subacute HIT B, and 5. remote HIT. Each phase confronts the clinician with a unique set of management questions. In this review, the phases of HIT are defined and key management questions associated with each phase are discussed. Among patients with Suspected HIT, I use the 4Ts score to determine which patients have a sufficiently high probability of HIT to justify discontinuation of heparin and initiation of a non-heparin parenteral anticoagulant. An algorithm for selecting an appropriate non-heparin anticoagulant based on the patient’s clinical stability, renal and hepatic function, drug availability, and physician comfort is provided. In patients with Acute HIT, I generally avoid prophylactic platelet transfusion and inferior vena cava filter insertion because of a potential increased risk of thrombosis. I perform 4-limb screening compression ultrasonography. In patients with symptomatic thromboembolism or asymptomatic proximal deep-vein thrombosis, I treat with anticoagulation for three months. In patients without thrombosis, I discontinue anticoagulation upon platelet count recovery. I do not transition patients to an oral anticoagulant until platelet count recovery (i.e. Subacute HIT A). I increasingly choose direct oral anticoagulants over vitamin K antagonists in this setting because of their greater convenience and safety. In Subacute HIT B and Remote HIT, I use heparin for cardiovascular surgery, whereas I use bivalirudin in patients with Acute HIT and Subacute HIT A in whom surgery cannot be delayed.

Keywords
Heparin-induced thrombocytopenia, management, treatment

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Suspected HIT
Which patients with suspected HIT should receive empiric treatment for HIT?

Owing to the ubiquity of thrombocytopenia and heparin exposure in hospitalised patients and the limited specificity of clinical diagnosis, patients with suspected HIT far outnumber those in whom the diagnosis is confirmed (4). The clinician’s challenge is to distinguish patients with a very low probability of HIT in whom empiric therapy is not warranted and may inflict harm from those with a reasonable probability of HIT in whom prompt suspension of heparin and initiation of a non-heparin anticoagulant could be limb- or life-saving.

The most extensively studied tool for this purpose, the 4Ts score (5), segregates patients into low, intermediate, or high clinical probability on the basis of four criteria (Thrombocytopenia, Timing of platelet count fall, Thrombosis and other sequelae, and likelihood of other causes of thrombocytopenia). A low probability 4Ts score has a negative predictive value of 99.8% (95% confidence interval [CI] 97.0–100.0) whereas an intermediate and high probability 4Ts score have a positive predictive value of 14% (9–22) and 64% (40–82), respectively (6).

I calculate a 4Ts score in all patients with suspected HIT. Patients with an intermediate or high probability 4Ts score are treated empirically for HIT while awaiting laboratory confirmation. In patients with a low probability 4Ts score, heparin is continued when indicated and other etiologies of thrombocytopenia are sought.

Several cautions regarding the 4Ts score are warranted. First, missing data or incorrect information may lead to a faulty 4Ts score and inappropriate management decisions (7–9). Thus every effort should be made to obtain complete and accurate information. If key data (e.g. platelet counts) are not available, it may be prudent to err on the side of a higher 4Ts score (8). Second, some reports suggest that the 4Ts score does not perform as well in the intensive care and post-cardiac surgery settings (9). Other scoring systems show promise but have not been adequately validated for clinical use (10–12).

How should patients with an intermediate or high probability of HIT be treated?

All heparin including low-molecular-weight heparin, heparin flushes, and heparin-bonded catheters should be discontinued immediately. Suspension of heparin alone is not sufficient to prevent thrombosis (13). Therefore, a non-heparin parenteral anticoagu-
Table 2: Parenteral anticoagulants for the treatment of HIT.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clearance (half-life)</th>
<th>Initial dosing</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argatroban</td>
<td>Hepatobiliary (40–50 min)</td>
<td>Bolus: None Continuous infusion: Normal organ function → 2 µg/kg/min Liver dysfunction (bilirubin &gt; 1.5 mg/dl) → 0.5–1.2 µg/kg/min Heart failure, anasarca, post-cardiac surgery → 0.5–1.2 µg/kg/min</td>
<td>Adjust to APTT 1.5–3.0 times baseline</td>
</tr>
<tr>
<td>Bivalirudin¹</td>
<td>Enzymatic/Renal (25 min)</td>
<td>Bolus: None Continuous infusion: Normal organ function → 0.15 mg/kg/h Renal or liver dysfunction → dose reduction may be appropriate</td>
<td>Adjust to APTT 1.5–2.5 times baseline</td>
</tr>
<tr>
<td>Desirudin³</td>
<td>Renal (2 h)</td>
<td>15 or 30 mg SC every 12 h</td>
<td>None</td>
</tr>
</tbody>
</table>

Indirect factor Xa inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clearance (half-life)</th>
<th>Initial dosing</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danaparoid</td>
<td>Renal (24 h)</td>
<td>&lt;60 kg → 1500 units 60–75 kg → 2250 units 75–90 kg → 3000 units &gt;90 kg → 3750 units Accelerated initial infusion: 400 units/h × 4 h, then 300 units/h × 4 h Maintenance infusion: Normal renal function → 200 units/h Renal dysfunction → 150 units/h</td>
<td>Adjust to danaparoid-specific anti-Xa activity of 0.5–0.8 units/ml³</td>
</tr>
<tr>
<td>Fondaparinux²</td>
<td>Renal (17–24 h)</td>
<td>&lt;50 kg → 5 mg SC daily 50–100 kg → 7.5 mg SC daily &gt;100 kg → 10 mg SC daily CICr 30–50 ml/min → use caution CICr &lt;30 ml/min → avoid use</td>
<td>None³</td>
</tr>
</tbody>
</table>

APTT, activated partial thromboplastin time; CICr, creatinine clearance; h, hour; min, minute; SC, subcutaneous. ¹Not approved for treatment of HIT. ²Some authorities do not routinely monitor danaparoid, particularly in patients with normal renal function. ³Some authorities monitor using fondaparinux-specific anti-Xa activity.

PCI in large clinical trials and is approved in this setting for patients with and without HIT (20). Protocols have also been established for patients undergoing cardiac surgery with or without cardiopulmonary bypass (21, 22). Assessment of bivalirudin in hospitalised patients, including patients with combined hepatic and renal dysfunction, is limited to retrospective studies (23, 24). In the operating room and catheterisation suite, bivalirudin is monitored by activated clotting time. Elsewhere, the APTT is used.

Desirudin is a renally cleared recombinant hirudin. It is licensed in the U.S. for thromboprophylaxis after hip arthroplasty. It is not approved for treatment of HIT. In the PREVENT-HIT trial, patients with HIT were randomised to argatroban or fixed-dose desirudin. The trial closed prematurely after only 16 patients had been enrolled due to poor accrual. In the eight desirudin-treated subjects, there were no new thrombotic or major bleeding events (25).

Danaparoid is an amalgam of glycosaminoglycans with antithrombin-dependent anti-Xa activity. It is approved for the treatment of HIT in multiple jurisdictions, but not in the U.S., where it was withdrawn from the marketplace. In an open-label trial, patients with HIT and thrombosis were randomised to danaparoid or dextran-70. Recovery from thrombosis was greater in the danaparoid arm (56% vs 14%, p=0.02) (26). Danaparoid is given intravenously as a bolus followed by accelerated initial infusion and then maintenance infusion. Prophylactic-dose danaparoid should be avoided in patients with HIT because of a relatively high rate of breakthrough thrombosis (14). 

Fondaparinux, a synthetic pentasaccharide, is an antithrombin-dependent inhibitor of factor Xa. It is approved for the treatment and prevention of venous thromboembolism, but is not approved for treatment of HIT. However, it is widely used in this setting, and appears to have similar efficacy and safety to approved agents (28–30). Although anti-PF4/heparin antibody formation is com-
mon in postoperative patients receiving thromboprophylaxis with fondaparinux, and a small number of cases of HIT possibly caused by fondaparinux in this setting have been reported, the risk of fondaparinux causing further thrombocytopenia when used to treat HIT appears to be negligible (31, 32). Fondaparinux is administered by once-daily subcutaneous injection and does not require routine monitoring.

Which parenteral non-heparin anticoagulant should be selected?

Choice of anticoagulant should be based on the patient's hepatic and renal function, clinical stability, drug availability, and physician comfort. An algorithm for selecting an agent is shown in Figure 1. Several advantages and disadvantages of parenteral non-heparin anticoagulants should be borne in mind when selecting an agent.

Argatroban and danaparoid, the only agents licensed for management of HIT, are associated with important limitations. Both drugs are expensive. Management is complex, involving continuous intravenous infusion, frequent laboratory monitoring, and dose adjustment. The therapeutic indices for these agents are narrow. They carry a ~1% daily risk of major haemorrhage and do not reduce frequency of limb amputation or death (17, 26, 27, 33). The availability of danaparoid has been limited by worldwide shortages. Monitoring of argatroban (and bivalirudin) by APTT may be confounded by HIT-associated consumptive coagulopathy and result in underdosing (34). Argatroban also raises the international normalised ratio (INR), complicating transition to vitamin K antagonists (VKAs) (35). Fondaparinux reduces the complexity of HIT management. It does not require routine monitoring or dose adjustment, is administered subcutaneously, and has a negligible effect on the INR, thereby facilitating transition to outpatient therapy. For these reasons, it is my preferred agent in stable patients with acceptable renal function (► Figure 1).

Are there investigational therapies for the management of acute HIT?

Direct oral inhibitors of thrombin (e.g. dabigatran) and factor Xa (e.g. rivaroxaban, apixaban, edoxaban) do not cross-react with HIT antibodies (36), but published experience with these agents in patients with acute HIT is limited (19), and low trough levels may not provide adequate protection for highly prothrombotic states such as HIT (37). Accordingly, use is not recommended outside of a clinical trial. A single-arm study of rivaroxaban for HIT was closed early due to slow accrual (38).

Other novel therapies that target steps in the pathogenesis of HIT proximal to activation of coagulation are in preclinical development and may provide effective therapy without the bleeding risk associated with anticoagulants. Examples include PF4 antagonists and non-pathogenic anti-PF4/heparin monoclonal antibodies which interfere with formation of PF4/heparin complexes, FcγRIIA blockers which prevent binding of HIT immune complexes to activating receptors on platelets, and inhibitors of splenic tyrosine kinase and Ca^{2+}-diacylglycerol regulated guanine nucleotide exchange factor I which disrupt intracellular pathways triggered by immune complex binding (39–42).

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### Figure 1: An algorithm for selecting a parenteral non-heparin anticoagulant for management of acute HIT.

- **Is the patient stable?**
  - Yes
  - No

- **Is there renal dysfunction (Clcr < 30 mL/min)?**
  - Yes
  - No

- **Is there hepatic dysfunction (Bilirubin > 1.5 mg/dL)?**
  - Yes
  - No

- **Fondaparinux**
  - Bivalirudin
  - Danaparoid

- **Argatroban**
  - Bivalirudin
  - Danaparoid

- **Bivalirudin**
  - Danaparoid

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What is the appropriate duration of anticoagulation?

As with other thromboembolic events secondary to a transient provoking factor, three months of anticoagulation is generally sufficient for patients with HIT complicated by thrombosis. For patients with isolated HIT, the optimal duration of anticoagulation is controversial. In a historical series of 62 untreated patients with isolated HIT, the cumulative incidence of thromboembolism at 30 days was 53%. The majority of events occurred within 10 days of heparin cessation, a period corresponding to platelet recovery (13). At a minimum, anticoagulation should therefore be continued in patients with isolated HIT until platelet recovery. Some experts recommend a longer course of treatment (e.g. 4–6 weeks) (19).

Should asymptomatic patients undergo screening compression ultrasonography of the limbs?

Silent deep-vein thrombosis (DVT) is common in patients with HIT (43), but it is unknown whether identification of silent DVT should influence the duration of anticoagulation. I perform four-limb ultrasound in all patients with isolated HIT and continue anticoagulation for three months in those with proximal DVT.

Is platelet transfusion safe in patients with acute HIT?

There is a theoretical concern that platelet transfusion may precipitate thrombosis in patients with HIT, though published evidence is conflicting and has important limitations (44–46). In a retrospective cohort study, there were no thrombotic complications after platelet transfusion in 37 patients with a positive anti-PF4/heparin enzyme immunoassay. In view of the limited specificity of this assay (47) and lack of confirmation with a washed platelet functional assay, it is likely that many of the patients in the study did not have HIT (45). Conversely, analysis of a large inpatient administrative dataset demonstrated an increased risk of arterial thrombosis in patients with HIT who received platelet transfusion during their hospital admission. In this study, a diagnosis of HIT was based solely on diagnostic codes and could not be verified, a temporal relationship between platelet transfusion and thrombosis could not be assessed, and the analysis was not adjusted for severity of thrombocytopenia (46). This last limitation is of particular relevance because lower platelet count nadirs are not only more likely to prompt platelet transfusion, but are also associated with increased thrombotic risk in patients with HIT (48).

Because HIT generally manifests as a prothrombotic rather than a haemorrhagic diathesis, prophylactic platelet transfusion is rarely indicated. Transfusion may be appropriate in the setting of serious bleeding or prior to a procedure with high bleeding risk (e.g. spinal or intracranial procedures). It may also be considered in patients with severe thrombocytopenia (< 20 x 10^9/l) or concomitant coagulopathy who are receiving treatment with a therapeutic intensity alternative anticoagulant.

Should inferior vena cava filters be inserted in patients with acute HIT?

HIT-associated thrombosis demonstrates a propensity to occur at sites of vessel injury (49, 50). Inferior vena cava filters may have serious consequences including caval thrombosis, progression of DVT, and ischaemic limb necrosis (51). They do not protect against arterial thrombembolism or obviate the need for anticoagulation and their use in HIT should generally be avoided.

Subacute HIT A

When and how should patients be transitioned to oral anticoagulation?

Patients with HIT who are taking a VKA are at risk for venous limb gangrene, a potentially catastrophic thrombotic complication of the microvasculature secondary to depletion of protein C (52, 53). To prevent this complication, VKAs should be avoided in patients with HIT until platelet count recovery. There is no universally accepted definition of platelet recovery. Some clinicians define recovery as a platelet count ≥ 150 x 10^9/l. I define recovery as a rise in platelet count to a stable plateau (a platelet count ≥ 150 x 10^9/l that increases by 10% or less over 3 consecutive days), recognising that not all patients with HIT have a platelet count nadir below 150 x 10^9/l (54). When a VKA is initiated, large loading doses (e.g. warfarin > 5 mg/day) should be avoided and the VKA should be overlapped with a parenteral anticoagulant for at least five days and until the INR has reached the intended target. If a patient is on a VKA at the time HIT is diagnosed, it should be discontinued immediately and reversed with vitamin K (19).

Transitioning from argatroban to a VKA presents a unique challenge because of the effect of argatroban on the INR. Algorithms have been developed to guide this transition and avoid under-anticoagulation (55). The INR should be measured daily while co-administering these agents. After an overlap of at least five days, argatroban may be discontinued when the INR is > 4. The INR should be measured again 4–6 hours after argatroban has been discontinued. Aragatroban should be resumed if the repeat INR is below the target range. This procedure should be repeated daily until the desired INR is achieved on VKA alone.

Although the direct oral anticoagulants (DOACs) are not recommended for initial treatment of HIT, they represent a suitable alternative to VKAs after platelet count recovery and do not require overlap with parenteral anticoagulation or routine laboratory monitoring. I increasingly prefer DOACs to VKAs in this setting because of their greater convenience and lower bleeding risk (56).

Can patients with subacute HIT A be re-exposed to heparin?

As with acute HIT, heparin should be scrupulously avoided in patients with subacute HIT A due to the risk of disease exacerbation and thrombosis. If a patient requires cardiovascular surgery, the
procedure should be delayed at least until the functional assay becomes negative (i.e. subacute HIT B) and ideally until anti-PF4/heparin antibodies are no longer present (i.e. remote HIT). If surgery cannot be delayed, a non-heparin anticoagulant such as bivalirudin (21, 22) should be used (Table 3). An alternative approach involves preoperative plasma exchange to remove platelet-activating antibodies and enable intraoperative heparin. This approach appears to be safe, but has not been extensively studied (57, 58).

Subacute HIT B and remote HIT
In patients with subacute HIT B or remote HIT who require cardiovascular surgery, what should be used for intraoperative anticoagulation?

The safety of intraoperative heparin in remote HIT was first established in a series of 10 patients undergoing cardiac surgery. None developed recurrent HIT or recrudescence of HIT antibodies (59). There is growing evidence that use of intraoperative heparin is also safe in patients with subacute HIT B. In three patients with subacute HIT B who required urgent heart transplantation, exposure to intraoperative heparin did not result in clinical recurrence (60). Similar findings were observed in a recently published series of 10 patients (61).

In patients with subacute HIT B, surgery should ideally be postponed until the anti-PF4/heparin immunoassay has become negative. In patients with subacute HIT B in whom surgery cannot be delayed and in patients with remote HIT, I prefer intraoperative heparin over a non-heparin anticoagulant (Table 3). Whenever a patient with a history of HIT is re-exposed to heparin, exposure should be strictly limited to the intraoperative setting. If pre- or post-operative anticoagulation is indicated, a non-heparin anticoagulant should be prescribed.

In patients with subacute HIT B or remote HIT who require coronary angiography, what should be used for intraprocedural anticoagulation?

In light of its documented efficacy and safety in large coronary angiography trials (20), I recommend bivalirudin for percutaneous vascular procedures in all patients with a history of HIT. If bivalirudin is not available, heparin is an acceptable alternative in patients with subacute HIT B and remote HIT provided that its use is limited to the procedure, itself.

In patients with subacute HIT B or remote HIT who require hemodialysis, what strategy should be used to prevent thrombosis of the dialysis circuit?

Although anti-PF4/heparin antibodies are present in ~10% of patients on chronic haemodialysis (62, 63), HIT is uncommon (<1%) in this population (64). In patients with a history of HIT, treatment with heparin during haemodialysis is contraindicated. Alternative strategies for prevention of dialysis circuit thrombosis including saline flushing, regional citrate, danaparoid, argatroban, and VKA have been reported but not compared or systematically investigated.

Conclusions

HIT may be conceptualised as occurring in five sequential phases: suspected HIT, acute HIT, subacute HIT A, subacute HIT B, and remote HIT (Table 1). Each phase is associated with a unique set of clinical challenges and questions.

In patients with suspected HIT, I use the 4Ts score to determine which patients warrant empiric treatment for HIT with discontinuation of heparin and initiation of a parenteral non-heparin anticoagulant (Table 2). The choice of parenteral non-heparin anticoagulant is based on a patient’s clinical stability, hepatic and renal function, drug availability, and physician comfort (Figure 1). I prefer fondaparinux in stable patients with acceptable renal function because it is given as a once daily subcutaneous injection, does not require routine monitoring, and has a negligible effect on the INR, thus easing the transition to outpatient therapy. In patients with acute HIT, I generally avoid prophylactic platelet transfusion and inferior vena cava filter insertion because of a potential increased risk of thrombosis. I perform four-limb screening compression ultrasonography. In patients with symptomatic thromboembolism or asymptomatic proximal DVT, I treat with anticoagulation for three months. In patients without thrombosis, I discontinue anticoagulation upon platelet count recovery, though some experts recommend a longer course of treatment. I do not

<table>
<thead>
<tr>
<th>Phase</th>
<th>Functional assay</th>
<th>Immuno-assay</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>Acute/</td>
<td>+</td>
<td>+</td>
<td>1. Delay surgery 2. If surgery cannot be delayed, use an alternative anti-</td>
</tr>
<tr>
<td>Subacute A</td>
<td></td>
<td></td>
<td>coagulant (e.g. bivalirudin) or treat with preoperative plasma exchange</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>until functional assay becomes negative</td>
</tr>
<tr>
<td>Subacute B</td>
<td>-</td>
<td>+</td>
<td>1. Delay surgery 2. If surgery cannot be delayed, use heparin</td>
</tr>
<tr>
<td>Remote</td>
<td>-</td>
<td>-</td>
<td>1. Heparin</td>
</tr>
</tbody>
</table>

Table 3: Recommendations for intraoperative anticoagulation in patients with a history of HIT.
transition patients to an oral anticoagulant until platelet count recovery (i.e. the subacute A phase). I increasingly choose direct oral anticoagulants over VKAs in this setting because of their greater convenience and superior safety profile. If a VKA is selected, it should be overlapped with a non-heparin parenteral anticoagulant for at least five days to avoid venous limb gangrene. In patients with subacute HIT B and remote HIT, I use heparin for cardiovascular surgery, whereas I use bivalirudin in patients with acute HIT and subacute HIT A whose surgery cannot be delayed (Table 3).

Novel treatment strategies that disrupt HIT immune complex formation, abrogate immune complex-mediated platelet activation, and interfere with downstream signaling within activated platelets are under investigation. Additional therapeutic targets are likely to be identified as the pathophysiology of HIT continues to be elucidated. These discoveries may one day alter the paradigm of HIT management as we know it.

Conflicts of interest
AC has served as a consultant for Amgen, Bayer, Bracco, and Genzyme; has received research support from Spark Therapeutics and T2 Biosystems; and has provided expert witness testimony related to heparin-induced thrombocytopenia.

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