HEPARIN-INDUCED THROMBOCYTOPENIA

SUMMARY

Heparin-induced thrombocytopenia (HIT) is a known complication of heparin exposure. The 4Ts scoring system is a screening tool that accurately rules out HIT. Solid-phase enzyme-immunoassays are an objective tool for ruling out HIT, but a positive test requires platelet activation tests such as the serotonin release assay to confirm the diagnosis of HIT. Once HIT is suspected, all forms of heparin should be discontinued. Patients should be started on a non-heparin anticoagulant as there remains a risk of thrombosis even after heparin is stopped. Patients can be bridged to warfarin after they are stable and their platelets are above 150,000/mm^3 with a goal INR of 2-3. Alternatively, patients may be initiated on a direct oral anticoagulant. Treatment should last for 1-3 months.

RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **Heparin usage should be discontinued immediately in patients suspected of having HIT**
  - **The 4T's scoring system can be used to screen for HIT**
    - **A low probability score can be used to exclude HIT without further testing**
  - **Enzyme-immunoassays have a 99% sensitivity and can be used to rule out HIT**
    - **Positive enzyme-immunoassays require further testing to confirm HIT**
  - **Platelet activation tests, such as the serotonin release assay, are the gold standard for diagnosis of HIT and should be sent if the enzyme-immunoassay is positive**
  - **For patients with confirmed HIT, use of a non-heparin anticoagulant is recommended**
    - **Treatment should last for at least 4 weeks if no thrombotic complications have occurred**
    - **Treatment should last for at least 3 months if thrombotic complications have occurred**
    - **Bridge to warfarin only after the patient is stable and platelets are above 150,000/mm^3 with a goal INR of 2-3**
    - **Argatroban, bivalirudin, and rivaroxaban may be considered for initial treatment of HIT**
- **Level 3**
  - **Fondaparinux, apixaban, dabigatran, and edoxaban may be used as an alternative means of anticoagulation**

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

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INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is an immune IgG mediated condition that occurs secondary to heparin exposure. Negatively charged heparin forms a complex with positively charged platelet factor 4 (PF4) (1). This induces the formation of anti-PF4/heparin IgG antibodies. This complex then binds and activates platelets, which undergo aggregation and removal from the circulation resulting in thrombocytopenia. This usually occurs 5 to 14 days after initial exposure with a ten-fold higher incidence in patients receiving unfractionated heparin (UFH) compared to low-molecular weight heparin (LMWH).The overall incidence of HIT is roughly 0.8-5% with surgical patients having the greatest risk (2). Approximately 25-50% of patients diagnosed with HIT develop thrombotic complications (3).

SCREENING AND DIAGNOSIS

Diagnosing HIT remains difficult. The 4T's scoring system is a pretest-screening tool that was developed to help screen for patients with HIT. It takes into account the magnitude of thrombocytopenia, the timing of heparin exposure, thrombosis or other sequelae of HIT, and other causes of thrombocytopenia. A score of 0-3 denotes a low probability of hit, 4-5 intermediate probability, and 6-8 a high pretest probability of HIT (1) (Table 1).

Table 1: 4T's Score

4Ts Category	2 points	1 point	0 points
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥ 20,000 /mm^3	Platelet count fall 30-50% or platelet nadir 10-19,000 /mm^3	Platelet count fall < 30% or platelet nadir < 10,000 /mm^3
Timing of platelet count fall	Clear onset between days 5-10 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5-10 fall, but not clear (e.g. missing platelet counts); onset after day 10; or fall ≤1 day (prior heparin exposure 30-100 days ago)	Platelet count ≤ 4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction post intravenous unfractionated heparin bolus	Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

Cuker et al. 2011 performed a meta-analysis on the predictive value of the 4Ts. Thirteen studies with 3068 patients collectively were reviewed. They concluded that patients with a low probability 4Ts score had a negative predictive value of 0.998. This held true regardless of the prevalence of HIT, the party responsible for scoring or the composition of the study population. The same could not be said about those with intermediate and high probability score (1).

Berry et al. 2011 found the 4Ts scoring system to not be accurate in critically ill ICU patients. They suggest that the 4Ts, which are usually the initial step in determining the presence of HIT, not be used in critically ill ICU patients. Their data showed that 8.6% of patients who scored a low probability were HIT positive (4).

LABORATORY TESTS

Laboratory tests can help confirm clinical suspicions of HIT, but should not delay treatment. There are two categories of tests for HIT: immunoassays and platelet activation tests. Immunoassay tests detect HIT antibodies by measuring binding activity to a reference PF4 complex. If the antibodies are present, they will bind to these complexes. The results are reported as optical density values (OD). OD values of <0.4 are considered a negative test (5).

Warkentin et al. 2011 reported an almost 99% sensitivity of the solid-phase enzyme-immunoassays (EIAs) for anit-PF4/heparin antibodies. Therefore, a negative test can rule out HIT. Unfortunately, EIAs do not have a high specificity as they also detect clinically insignificant anti-PF4/heparin antibodies caused by non-HIT factors. This could potentially lead to over diagnosis of HIT (6). Berry et al. 2011 reported that in surgical ICU patients a PF4 range of 0.4 to 2.0 OD carries a true positive value of 8% while a PF4 > 2.0 OD increased the true positive rate to 65% (4). This suggests that higher OD values should be considered more predictive of HIT.

Platelet activation tests detect the degree of platelet activation by anti-PF4/heparin antibodies in the patient's serum. Multiple platelet activation test exist, but vary in their functionality. Standard light transmission platelet aggregometry detects aggregation of normal platelets when placed in the presence of plasma from a patient suspected of having HIT. HIT antibodies produce activation of platelets at 0.1-0.5 iu/ml of heparin that is not present at 100 iu/ml of heparin. This method has a sensitivity of 85% and donor platelet selection is important as one in seven donors may be responsive (7).

To increase the sensitivity of platelet activation tests, washed platelet assays are used. One such test is the serotonin release assay (SRA), which carries a sensitivity and specificity >95%. For this reason, the SRA remains the gold standard for the diagnosis of HIT. Unfortunately, this test carries a high cost and slow turnaround time as only a few centers perform the test due to the use of radiation and technical demands of conducting the test (8).

TREATMENT

Once an intermediate or high risk of HIT is suspected, all exposure to heparin should be stopped including low molecular weight heparin as this may cross-react with the heparin induced antibodies. Simply stopping heparin exposure is not enough, as up to 50% of patients will have a thrombotic event within a month of stopping heparin if they are not placed on alternative anticoagulation (9). Direct thrombin inhibitors (DTI) are the most widely studied and utilized initial anticoagulants in patients with HIT. Table 2 shows the most commonly used anticoagulants, dosing, and other considerations.

<u>Parenteral Anticoagulants</u>

Argatroban is an intravenous DTI and is recommended for patients with acute HIT based on two non-randomized studies that compared it with historical controls in patients with acute HIT. Outcomes evaluated included a composite of all-cause mortality, all-cause amputation, or new thrombosis, as well as the incidence of bleeding events. The incidence of all-cause mortality, all-cause amputation, and new thrombosis were significantly reduced in the argatroban arms compared to historical controls, with similar incidence of bleeding events between the groups (10,11). Of note, patients with hepatic impairment (Child-Pugh B), it is recommended to reduce the initial dose due to prolonged clearance. It is not recommended to use argatroban in patients with a Child-Pugh score >10. Argatroban also predictably affects INR and a higher therapeutic range is needed while transitioning to warfarin.

Bivalirudin is a DTI that does not have FDA approval for the management of acute HIT, however it is recommended as an option for the management of HIT by the American Society of Hematology (12). This recommendation stems from a retrospective review of 461 patients treated for HIT (13). The rates of new thrombosis and bleeding events were similar to those found in studies evaluating argatroban, and there were no cases of patients requiring amputation. Additionally, Vo and colleagues compared treatment with bivalirudin to argatroban in 68 patients (argatroban = 48, bivalirudin = 20) with suspected HIT. At 30 days, they found that the rate of thromboembolic events, bleeding, and mortality were similar between both groups. They also found that the time to therapeutic targets were faster in the bivalirudin patients, and concluded that bivalirudin is a safe and effective alternative to argatroban for the treatment of HIT (14). Bivalirudin unpredictably affects INR, and it is not recommended to transition to warfarin from bivalirudin.

Fondaparinux is an intravenous factor Xa inhibitor that carries a low risk of cross reactivity with heparin antibodies, suggesting a potential role in the management of HIT. The 2018 ASH guidelines for the management of HIT suggest fondaparinux as a non-heparin anticoagulant that can be considered for use (12). Lobo and colleagues prospectively evaluated the use of fondaparinux in 7 patients with acute HIT

and compared them to 10 historical controls treated with either lepirudin or argatroban. They found similar rates of recurrent VTE and bleeding and suggested that it was safe for use in these patients (15). Grouzi and colleagues completed a single center retrospective analysis of 24 patients treated with fondaparinux and compared to 20 patients treated with lepirudin. All treated patients in both groups experienced platelet recovery, and none experienced recurrent VTE or major bleeding (16). Lastly, Kang and colleagues retrospectively evaluated 239 patients who received a non-heparin anticoagulant (fondaparinux = 133, danaparoid = 59, argatroban = 47) for suspected or confirmed HIT. A propensity score based on age, gender, creatinine, 4T scores, and comorbidity index was used to match the fondaparinux to control patients receiving either danaparoid or argatroban. The rates of new thrombosis and bleeding were similar in both groups (17).

Danaparoid is an IV factor Xa inhibitor that is not currently available in the United States. It is recommended as an option for the management of HIT by the ASH guidelines, as well. Chong and colleagues compared the effects of danaparoid versus dextran 70 in a prospective randomized controlled trial. The study enrolled 42 patients (danaparoid=25, dextran 70=17) with recent thrombosis and a probable clinical diagnosis of HIT. All patients received concurrent treatment with warfarin starting on day one. The primary endpoint was proportion of thromboembolic events with complete clinical resolution by the time of discharge from the hospital. Danaparoid patients had significantly higher rates of clinical resolution compared with the dextran group (56% vs 14%; p=0.02), and there was no major bleeding observed in either group (18). Magnani and colleagues conducted an analysis of 1478 case reports of danaparoid use for treatment of HIT. They found a composite outcome incidence of all-cause mortality, new/extended thromboembolism, or amputation of 23%, and a major bleeding rate of 8.1%. These rates compared favorably to lepirudin (=1465) and argatroban (n=722) as the composite outcome incidence was 20.6% and 34.9%, respectively. The authors also found a platelet cross-reactivity rate of 3.2%, and therefore recommended that danaparoid cross-reactivity is conducted when considering danaparoid for use (19).

Oral Anticoagulants

Once the patient is stable and their platelet count is greater than 150,000/mm^3, they can be transitioned to warfarin (12). Parenteral anticoagulation should overlap with warfarin for at least 5 days and until the INR is 2.0-3.0 for at least 24 hours (20). When monitoring overlap therapy with parenteral direct thrombin inhibitors, the manufacturer's guidelines for INR monitoring should be followed, if available, as the INR and bleeding risk are altered with co-administration.

Direct oral anticoagulants (DOACs) including rivaroxaban, apixaban, dabigatran, or edoxaban may be utilized as an alternative to warfarin for primary and secondary treatment of HIT, however, data supporting the use of these agents in HIT is limited. A prospective study conducted by Warkentin et al. evaluated the use of rivaroxaban as initial treatment and as secondary treatment after initial non-DOAC treatment prior to and after platelet recovery. Additionally, they conducted a literature review on the use of rivaroxaban, apixaban, edoxaban, and dabigatran. Overall, they found 0% incidence of new objectively confirmed thrombosis at 30 days and no major hemorrhage. They concluded that DOACs may be safe and effective for both primary and secondary treatment of HIT. However, the most experience with DOACs is reported with rivaroxaban (21).

Treatment for HIT is recommended for 1 month (without thrombotic complications) to3 months (with thrombotic complications) or until platelet recovery, whichever is longer (12).

Table 2: Anticoagulants for the Management of HIT

Anticoagulant	Dosing (12,20)	Half-life / Elimination	Considerations
Argatroban (DTI)	2 mcg/kg/min Dose reduction: 0.5 – 1.2 mcg/kg/min	40-50 mins Hepatobiliary	• Increases INR so a higher therapeutic range may be required during the warfarin overlap • Dose reduction is needed in patients with hepatic dysfunction, critical illness, post-cardiac surgery • Reversibly binds to both free and clot bound thrombin
Lepirudin (DTI)	Bolus 0.2-0.4mg/kg max infusion 0.1mg/kg/h (aPTT 1.5-2.5 x baseline)	80 mins Renal	• No longer available in US, Canada, and EU • Half-life is increased in patients with renal dysfunction. • Contraindicated in patients with acute renal failure or on hemodialysis • Irreversibly binds to free and sub-endothelium bond thrombin
Bivalirudin* (DTI)	0.15-0.2 mg/kg/h (aPTT 1.5-2.5 x baseline)	25 mins Both enzymatic and renal	• Only approved for patients with HIT undergoing PCI • Requires dose adjustment for patients with renal dysfunction or on hemodialysis or CRRT • Reversibly binds to active site of thrombin
Danaparoid (Xa inhibitor)	Initial bolus 2250 U,400 U/h x4h, 300 U/h x4h, 200 U/h	24 hours Renal	• No longer available in the US
Fondaparinux* (Xa inhibitor)	<50 kg: 5 mg once daily 50 to 100 kg: 7.5 mg once daily >100 kg: 10 mg once daily	17-24 hours Renal	• Irreversible • 50% dose reduction for CrCl <50 mL/minute • Avoid use in patients on dialysis or with CrCl <30 mL/minute
Warfarin* (Vitamin K antagonist)	Initiate at 2.5 to 5 mg and adjust dose accordingly until INR 2-3	~40 hours Hepatic	• Requires overlap and bridging until INR 2-3 • Full therapeutic effect usually seen within 5 to 7 days • Dosing varies widely and adjustments should be made cautiously
Rivaroxaban*^ (Xa Inhibitor)	15 mg PO BID x 21 days or until platelet recovery, then 20 mg PO daily	5-9 hours Renal	• Should be given with meals • Avoid use in patients on dialysis or with CrCl <30 mL/minute • If isolated HIT without thrombosis, may treat with 15 mg PO BID until platelet recovery
Apixaban*^ (Xa Inhibitor)	10 mg PO BID x7 days or until platelet recovery, then 5 mg PO BID	~8-15 hours Hepatic	• If initially treated with parenteral anticoagulant, can transition to 5 mg twice daily after platelet recovery • Avoid use in patients on dialysis or with CrCl <25 mL/minute • If isolated HIT without thrombosis, initiate at 5 mg PO BID and treat until platelet recovery
Dabigatran*^ (Thrombin inhibitor)	150 mg PO BID after ≥5 days of parenteral therapy	12-17 hours Renal	• May be used as secondary treatment after at least 5 days with parenteral anticoagulant • Avoid use in patients on dialysis or with CrCl • If isolated HIT without thrombosis, may initiate 150 mg PO BID on day 1 and treat until platelet recovery
Edoxaban*^ (Xa Inhibitor)	Not established for HIT	10-14 hours PGP substrate	• May be used as secondary treatment after at least 5 days with parenteral anticoagulant • Avoid use in patients on dialysis or with CrCl <15 or >95 mL/min

*Not approved for treatment of acute HIT
^Dosing for treatment of acute HIT not well established. Suggested dosing is extrapolated from venous thromboembolism and based on limited published experience in HIT.

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Although not commercial available, 2-0, 3-0 desulfated heparin (ODSH) was developed to separate the anticoagulant effects of heparin from the anti-inflammatory effects. Krauel et al. 2011 looked at how dabigatran, rivaroxaban, and 2-0, 3-0 desulfated heparin interacted with PF4/heparin complexes and the interaction of anti-PF4/heparin antibodies with platelets. They found that dabigatran and rivaroxaban did not interact with PF4. ODSH was actually found to prevent PF4/heparin complexes from binding to platelets and reduced the anti-PF4/heparin antibodies binding to PF4/heparin complexes. This suggests that ODSH may help prevent HIT in patients who require heparin (22). Further studies need to be conducted.

There has not been a large prospective study on the deliberate re-exposure to heparin, but in smaller studies re-exposure to heparin after HIT had not been shown to cause rapid-onset of HIT or rapid regeneration of antibodies. HIT antibodies are transient and usually disappear in 50 to 85 days. Once cleared, it is likely that the use of unfractionated heparin is safe in the setting of cardiac and vascular surgery (13).

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