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 stopped. Patients should be started on an alternative form of anticoagulation 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. Treatment should last for 1-3 months.

RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **Heparin usage should be stopped 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 are the gold standard for diagnosis of HIT and should be sent if the enzyme-immunoassay is positive**
  - **For patients with confirmed HIT, alternative means of anticoagulation are needed**
    - **Treatment should last for 4 weeks if no thrombotic complications have occurred**
    - **Treatment should last for 3 months if thrombotic complications have occurred**
    - **Bridge to warfarin after the patient is stable and platelets are above 150,000/mm^3 with a goal INR of 2-3**
- **Level 3**
  - **Argatroban should be used for an alternative means of anticoagulation**

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 10 days after exposure and has an incidence of roughly 3% with 1% of patient demonstrating thrombosis (2-4).

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.

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 (5) (Table 1).

Table 1

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 (5). 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.

Berry et al. 2011 found the 4Ts scoring system to not be accurate in critically ill ICU patients (6). 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.

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 (7). The results are reported as optical density values (OD). OD values of <0.4 are considered a negative test (6,7).

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 (8). 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% (6). 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 0.1-0.5iu/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 (9).

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 turn around time as only a few centers perform the test due to the use of radiation and technical demands of conducting the test (10).

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 (2,11). Direct thrombin inhibitors (DTI) are the most widely used initial anticoagulants in patients with HIT. Table 2 shows the most commonly used anticoagulants, dosing, and other considerations. Once the patient is stable and their platelet count is greater then 150,000/mm^3, they can be transitioned to warfarin with a five-day overlap (2). Treatment is recommended for 2-6 months with an INR range between 2-3 (12).

Table 2

Anticoagulant	Dosing (13)	Half life / Elimination	Considerations
Argatroban (DTI)	2 mcg/kg/min 0.5 mcg/kg/min (in critically ill)	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 • 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 minor adjustment for patients with renal dysfunction • 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 • Bleeding complication occur in 8.1% of patients
Fondaparinux (Xa inhibitor)	Not established for HIT	17-20 hours Renal	• No studies at present to confirm efficacy in HIT but due to theoretical lack of cross reactivity with HIT antibodies suggests usefulness in treating HIT • Irreversible

Some new anticoagulants have recently been released and even though they have not been studied specifically for HIT, in vitro studies have shown some promise. Dabigatran is a reversible DTI and rivaroxaban is reversible factor Xa inhibitor. 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 (1). 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. 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 80 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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