











Figure 2. The 4 T's Score and diagnostic tree.

Source: Up to date, <http://www.utdol.com>

One of the prospective studies showed that the 4Ts score calculation, due to operator inexperience, resulted in misclassification in ~2% of cases [28] Patients with intermediate and high 4T score should have further laboratory test to confirm the diagnosis of HIT [12].

**HIT expert probability score**

It is described by Cuker, uses eight clinical features and an expert opinion for diagnosis of HIT. It demonstrated improved correlation between the serologic HIT testing and inter-observer agreement; it required a prospective validation [29].

**Lillo-Le Louët model score**

This scoring is used only for the post-cardiopulmonary bypass patients, scoring points are based on timing, duration of thrombocytopenia and the duration of cardiopulmonary bypass [30].

**Laboratory tests**

For the diagnosis of HIT it is necessary to have presence of anti-PF4/heparin antibodies in patient's serum, or activation of platelets by either functional or immunoassay.

**Functional or platelet activation assays**

The commonly used are 14C-SRA, platelet aggregation, and recently flow-based platelet activation assays detect antibodies capable of binding and cross-linking platelet. These functional assays are specific but not sensitive. The Specificity is more than 95% with PPVs of 89% to 100%

and a low sensitivity of 56% to 100%. These assays are technically difficult to perform and available only in few medical centers [31].

**Immunoassay**

In contrast the immunoassays measure the presence of anti-PF4/heparin antibodies using enzyme-linked immunosorbent assay, particle gel or immune-turbid metric. The advantages of immunoassays are technically simple and highly sensitive (>99%), but lower specificity of 30 to 70% in the diagnosis of HIT [32].

**DIFFERENTIAL DIAGNOSIS**

HIT should be differentiated from disseminated intravascular coagulation (DIC), heparin toxicity and hyper-responsive thrombocytopenia. It is important to differentiate these clinical entities from HIT as their management is different from that of HIT. DIC is the activation of intravascular coagulation leading to thrombocytopenia, bleeding occurs in diseases ranging from sepsis to trauma and obstetrics. It is differentiated from HIT by prolonged coagulation parameters with elevated fibrinogen degradation products [33].

In acute heparin toxicity there is overdose of heparin, it can be fatal. Commonly manifested as wound bleeding, oozing mucosal membrane and in more severe case intraventricular hemorrhage. It is differentiated from HIT by abnormal activated prothrombin time and thrombocytopenia [34]. In hyper-responsive thrombocytopenia platelets are actively involved and consumed, seen in acute bronchial asthma

patients leading to bronchoconstriction with airway inflammation and thrombocytopenia. It can be differentiated from HIT by the signs and symptoms of primary disease causing hyperactive response [35].

### COMPLICATIONS

The more frequently seen complications in HIT patients are venous/arterial thrombosis, skin lesions and acute platelet activation syndrome.

Venous thromboembolic complications are four times common than arterial thrombosis. The thrombosis mainly occurs in the larger vein, bilateral deep venous thrombosis and pulmonary embolism. Rarely can it cause thrombotic stroke, adrenal hemorrhagic infarction or cerebral venous sinus thrombosis. Arterial thrombosis can cause myocardial or brain infarction [36]. Skin necrosis or/and erythematous plaques occur at the site of heparin injections. Acute platelet activation syndrome in HIT patients will manifest by an acute inflammatory response with fever and chills. In spite of the severe thrombocytopenia the hemorrhagic complications occurs in around 6% HIT patients [37].

### Management

To simplify we will discuss the HIT management in following subheadings:

**Immediate interventions:** These patients need immediate treatment for reduction of the risk of life-threatening thrombosis. The treatment should be started based on a strong clinical suspicion of HIT and on an intermediate or high probability 4 T's score while the laboratory test results are awaited. These initial interventions are discontinuation of all heparin, reversal of warfarin and initiation of a non-heparin anticoagulant. Two major goals of these interventions are to halt platelet activation as early as possible and to provide therapeutic anticoagulation with a non-heparin-anticoagulant to reduce the risk of thrombosis.

### Heparin alternative

HIT patients stopping heparin alone will not be sufficient as these patients remain at risk for subsequent thrombosis. Anticoagulation is required in HIT patients having essential procedures or emergencies, acute coronary syndrome and thromboembolic phenomenon. Alternative anticoagulant should be free from generating HIT antibodies or cross-react with anti-heparin-platelet factor 4 antibodies. Vital aspects of selection of these alternative anticoagulant agents are familiarity, safety with efficacy, patient's organ functions, clearance of agents, the urgency of anticoagulation, need for reversal and the monitoring techniques [38].

Heparin alternatives available are direct thrombin inhibitors, which directly inhibit thrombin generation (argatroban, bivalirudin), selective factor X inhibitors (danaparoid, Fondaparinux) and the vitamin K antagonist warfarin or

direct oral anticoagulants (DOACs) apixaban, edoxaban, rivaroxaban or dabigatran.

### TREATMENT

In HIT patients the higher risk of thrombosis is from the time of diagnosis of HIT to the starting of alternative anticoagulation agents. Hence the management of HIT patient should be started without delay and waiting for the results of confirmatory laboratory tests [39]. The management of HIT patients is summarized by 6 "A"s [40].

- 1) Avoid and stop all heparin (any form, any route, heparin flush or heparinized catheters).
- 2) Administer direct thrombin inhibitors (alternative anticoagulation).
- 3) Anti-PF4/heparin antibody test for confirmation of diagnosis.
- 4) Avoid platelet transfusion.
- 5) Await platelet recovery.
- 6) Assess lower extremity thrombosis.

LMWHs (Low molecular weight heparin) are contraindicated in patients with HIT due to their cross-reaction with heparin antibodies, and in acute phase of HIT warfarin is contraindicated as it paradoxically worsens the thrombosis due to a drastic decrease in protein C levels [41]. Warfarin can be used only after the alternative anticoagulation and platelet count improves to more than 150,000/uL.

### Choice of anticoagulation

**Urgency of anticoagulation:** In patients with an acute thrombosis, a parenteral agent is required to achieve the therapeutic anticoagulation as early as possible, by argatroban, bivalirudin, danaparoid or a DOAC (direct oral anticoagulant).

**Urgent reversal possibilities:** For patients requiring invasive procedure or those with higher risk for bleeding, we have to use an anticoagulant agent which can be reversed quickly. In these patients either argatroban or bivalirudin are the choice as they have a short half-lives and effects will be vanished within 1 h following discontinuation if they have no organ dysfunction.

**Renal impairment/failure:** In these patients commonly argatroban is used in the therapeutic doses, when platelet counts are stabilized, warfarin can be used, with close monitoring. Rivaroxaban and apixaban can be used in patients with end-stage renal failure and atrial fibrillation.

**Hepatic impairment/failure:** In these patients danaparoid, fondaparinux or bivalirudin in therapeutic doses are the drug of choice. The DOACs can be used in mild hepatic insufficiency and not advisable in moderate to severe liver disease.

**Both renal and hepatic insufficiency:** In this group of patients argatroban or bivalirudin is used at reduced dosages. When patient is stably anticoagulated can be shifted to warfarin. Apixaban is increasingly used in patients with renal impairments.

**Other considerations:** The local availability, institutional or/and clinician familiarity/preference and cost should be considered while selecting the anticoagulation in HIT patients. Patients cannot be on an intravenous agent, fondaparinux or one of the DOACs may be used and patients who cannot take an oral agent, fondaparinux or direct thrombin inhibitors are the anticoagulation of choice. These patients with HIT require therapeutic rather than prophylactic dosing, with the exception of patients with combined renal and hepatic impairment.

**Duration of anticoagulation therapy:** It's based on concurrence of thrombosis. The American and British guidelines recommend therapeutic dose anticoagulation for 4 weeks in patients with isolated HIT and up to 3 months for HIT patients with thrombosis [42,43].

## PHARMACOLOGY OF ALTERNATIVE ANTICOAGULATION

### DTI (Direct Thrombin Inhibitors)

DTI are the medications of choice in patients with HIT. These agents neither interact with heparin-dependent antibodies nor need an anti-thrombin as a cofactor. DTI have a predictable anticoagulant effect. They rapidly stop the thrombin storm and prevent new thrombus formation.

The DTI are argatroban, lepirudin, desirudin, bivalirudin, melagatran, and ximelagatran. Last 2 medications are no more available in the market. As per the structural configuration DTI are divided into 2 groups.

**Divalent DTI:** lepirudin and desirudin are 65-amino acid, polypeptides; the amino terminal binds to the catalytic site whereas carboxyl terminal irreversibly binds to the exosite of thrombin. Bivalirudin is a 20-amino acid derivative of hirudin, the peptide bond slowly cleaved from the catalytic site on thrombin; hence it is a reversible inhibitor of thrombin with shorter half-life. Lepirudin and desirudin are given by intravenous and subcutaneous routes, and half-life is 60 and 120 min, respectively, both of them are excreted through the renal system, hence requires dose adjustment in renal insufficiency patients. The initial loading dose is 0.4 mg/kg, then 0.15 mg/kg/h. Bivalirudin is given intravenously, largely cleared by peptidase but 20% is excreted through the kidneys, and needs dose adjustment in patients with renal impairment [44]. Patients receiving lepirudin should be monitored 4 h after the initiation of therapy and the target activated partial thromboplastin time (aPTT) should be 1.5-2.5 times, Desirudin does not need monitoring except in patients with renal impairment. Bivalirudin should be monitored by activated clotting time

(ACT) in patients with renal insufficiency or increased risk of bleeding.

**Monovalent DTI:** Argatroban is l-arginine-based molecule, shorter activity and reversibly binds to thrombin. It has a half-life of 50 min and mainly excreted through the liver and requires dose adjustment in patients with hepatic impairment. It is given by intravenous route and monitored with aPTT levels [45]. Ximelagatran is a prodrug, given by the oral route and metabolized in the liver to active form, whereas melagatran has a predictable anticoagulation effect and longer half-life. Its clearance is not affected by liver impairment or moderate renal insufficiency and hence there is no need to monitor the levels unless the renal impairment is severe [46]. The major concern with DTI is the risk of bleeding and it is higher with lepirudin and desirudin when compared with argatroban and no specific antidote is available for DTI. PCC (Prothrombin complex concentrate) is increasingly used in reversing the DTI anticoagulation effect.

**Danaparoid** is a heparinoid derivative, interacts with anti-thrombin III to inhibit factor Xa. It is not available in USA, but used in few other countries. It has cross-reactivity with antibodies in 15% of the patients [47]. It's given subcutaneously or intravenously. Disadvantages are, it needs anti Xa level monitoring, has a long half-life (around 25 h), has renal excretion and absence of a reversal agent.

**Fondaparinux** is a synthetic pentasaccharide, it selectively inhibits factor Xa. The therapeutic dose of fondaparinux ranges from 5 to 10 mg/day, subcutaneously, although the levels can be measured, not required routinely. The disadvantages includes long half-life of around 17 hours, renal elimination and the lack of an antidote [48].

**(DOACs) Direct oral anticoagulants** are the oral anticoagulants that directly act on thrombin that is dabigatran or factor Xa inhibition, these are apixaban, edoxaban, rivaroxaban, they are not stimulating HIT antibodies. There is more experience was with rivaroxaban use in HIT patients. DOAC can be given as initial therapy or can be preceded by a parenteral agent in these patients.

### SPECIAL SCENARIOS WHERE HEPARIN IS NEEDED BUT CANNOT BE USED DUE TO HIT

If patients on hemodialysis, percutaneous coronary Intervention (PCI), cardiopulmonary Bypass (CPB), unstable angina, thromboembolism, indwelling devices, valve replacement or intra-aortic balloon pump, develop HIT, they will require alternative anticoagulation therapy.

### Hemodialysis

HIT antibodies are positive in up to 17% of the patients on hemodialysis with a significantly higher mortality. The manifestation of HIT in these patients varies from acute

systemic reaction to frequent clotting in the extracorporeal circuit or increase in the number of failed arteriovenous fistula. When HIT is suspected in these patients: all forms of heparin should be stopped and start DTI or danaparoid or regional citrate anticoagulation. Argatroban has advantage in these patients as no dose adjustment is required; the recommended dose is an initial bolus of 250 mcg/kg at the start of dialysis then continuous infusion of 2 mcg/kg/min until 1 h before the end of dialysis session. Only bolus dose of lepirudin recommended at the beginning of dialysis session. This DTI has to be monitored with aPTT [49].

### **Percutaneous coronary interventions and cardiopulmonary bypass**

Hypercoagulability in HIT patients in combination with endovascular disruptions in PCI and CPB increases the risk of thrombosis. Argatroban, bivalirudin and danaparoid are the frequently used in PCI. If it is possible CPB surgeries should be postponed till PF4-heparin antibodies are negative, if cannot be delayed the bivalirudin, lepirudin, argatroban or danaparoid can be used.

### **Unstable coronary syndrome**

These patients may need full anticoagulation for longer period, initially the intravenous argatroban is used successfully in HIT patients with unstable coronary syndrome and later on they can be managed with DOACs [50].

### **Multiple organ failure and HIT**

Critically ill HIT patients with multiple organ dysfunction/failure and may have hepatic/renal impairment or failures, the dose of DTI must be adjusted with monitoring of the coagulation parameters and organ functions. The lack of antidote will put critical patients at the risk of potential risk of bleeding. Bivalirudin demonstrated better safety as it is cleared predominantly by the enzymatic cleavage.

### **Pregnancy and HIT**

Fortunately HIT is rare in pregnancy. When a HIT patient becomes pregnant may require thromboprophylaxis and/or treatment for thrombosis. It is of extreme important to use an anticoagulant that causes the minimal risk to the developing fetus. Danaparoid, subcutaneous lepirudin and Fondaparinux are commonly used; there is limited literature available about their effects on fetus and newborn [51].

### **MORBIDITY AND MORTALITY**

Early diagnosis and earlier management of HIT can reduce the morbidity and mortality, 20% of HIT patients with thrombosis need amputation [52]. In HIT patients treated with DTI, mortality decreases to 16% and the incidence of new thrombus decreases to 5.8% [53]. Small doses of thrombolytic agents were used locally in HIT patients with good results in massive pulmonary embolism or arterial

thrombosis [54]. Ralph-Edward successfully managed a case of massive pulmonary embolism in a patient with HIT by embolectomy [55]. The immune memory in Hit patients lasts for 90 days in around 35% of patients. Immunoassay is positive up to 1 year [56]. Platelets come to the normal range in a week of discontinuation in approximately 65% of patients [57]. After the platelet count recovery, patients will be at risk for thrombosis for 4 to 6 weeks because of circulating anti-PF4/heparin antibodies. Patients who are re-exposed to the heparin months to years after antibody disappearance do not manifest anamnestic responses. In a small study of 17 patients with HIT who are re-exposed to heparin for cardiac surgery, a higher proportion of patients developed anti-PF4/heparin antibodies (65%) relative to the incidence described in the literature (~27% to 51%) [58].

### **PREVENTION**

By following measures below will decrease the HIT occurrence (a) Keeping heparin therapy for shorter duration and starting warfarin early if expecting prolonged anticoagulation. (b) Avoiding bovine and fractional heparin and using LMWH. (3) Stopping the use of heparin flush for central and arterial catheters. (d) Heparin-free dialysis and not using heparin lock [59]. Sunnybrook Health Sciences Center, Toronto/Canada, implemented the "Avoid Heparin" campaign: in this campaign they replaced the use of UFH with LMWH for thromboprophylaxis and/or treatment, removed UFH from catheter flushes and nursing units. By this campaign the investigators found a significant reduction in percentage of occurrence of HIT [60,61].

### **CONCLUSION**

For more than 100 years from the time of discovery, heparin remained most frequently used anticoagulant in the clinical practice. Its use is increasing as the patient population is getting older and number of vascular surgeries is increasing day by day. Heparin has advantages of rapid, shorter duration of Action and easy reversibility. The heparin induced thrombocytopenia (HIT) is a known but potentially life threatening complication of heparin use, it's more frequent in females, young and surgical patients. HIT is diagnosed by 4T's score in combination with laboratory test. The functional laboratory test (platelets aggregation test) is more specific but less sensitive and not routinely done. Immunoassay is commonly done laboratory test, it is sensitive but not specific. Optical density will increase the specificity of Immunoassays. Thrombocytopenia and thrombosis are common complications but the hemorrhage is rare in HIT patients. The management of HIT is summarized by 6 "A" Avoid heparin, alternative anticoagulation, anti PF4 antibodies detection, avoid platelet transfusions, await platelet recovery and asses for thrombosis. HIT can be prevented by use of porcine heparin, low molecular weight heparin, shorter duration of intravenous therapeutic heparin, avoiding heparin flush for central venous and arterial catheters and heparin lock.



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