Accepted Manuscript

Heparin induced thrombocytopenia in the critically ill patient

James M. East, M.D., Christine Cserti- Gazdewich, M.D., John T. Granton, MD.

PII: S0012-3692(17)33223-3

DOI: 10.1016/j.chest.2017.11.039

Reference: CHEST 1472

To appear in: *CHEST*

Received Date: 12 April 2017

Revised Date: 22 November 2017

Accepted Date: 29 November 2017

Please cite this article as: East JM, Gazdewich CC-, Granton JT, Heparin induced thrombocytopenia in the critically ill patient, *CHEST* (2018), doi: 10.1016/j.chest.2017.11.039.

Heparin induced thrombocytopenia in the critically ill patient.

James M East M.D.[1], Christine Cserti- Gazdewich M.D.[2], John T Granton MD.[1].

[1] Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario. [2] Division of Hematology, University Health Network, Toronto, Ontario.

Corresponding author
John T Granton
11-124 Munk Building, Toronto General Hospital
585 University Ave
Toronto, Ontario
M5G 2N2

Email: john.granton@uhn.ca

Disclosures
Dr Granton's institution has received funds to support research in pulmonary hypertension from Bayer and Actelion Pharmaceuticals.

Abstract word count 140

Word count of main paper 4622

References 108

Tables 4

Figures 1

Abstract

Heparin induced thrombocytopenia (HIT) is associated with significant morbidity and mortality. Critically ill patients are commonly thrombocytopenic and exposed to heparin. Although HIT should be considered, it is not usually the cause of thrombocytopenia in the medical-surgical ICU population. A systematic approach to the critically ill patient with thrombocytopenia using clinical features, complemented by appropriate laboratory confirmation should lead to a reduction in inappropriate laboratory testing and reduce the use of more expensive and less reliable anticoagulants. If deemed as being intermediate or high risk for HIT or if HIT is confirmed by the serotonin release assay, Heparin should be stopped, Heparin-bonded catheters removed, and a direct antithrombin or fondaparinux should be initiated to reduce the risk of thrombosis. Coumadin is absolutely contraindicated in the acute phase of HIT and if administered its effects must be reversed by vitamin K.

Introduction:

Heparin induced thrombocytopenia (HIT) was first described in 1977,[1,2] twenty years after the first report of heparin-associated thrombosis[3]. Early recognition is important because of the high morbidity and mortality from arterial and venous thrombosis. It is caused by platelet-activating IgG antibodies binding the neoepitopes of PF4/heparin complexes, which were originally elucidated in 1992[4,5]. The diagnosis and treatment is particularly challenging in critically ill patients, owing to a high baseline prevalence of thrombocytopenia, risks for thrombosis from interruption in anticoagulation, or bleeding from the use of alternative anticoagulants in suspected or proven HIT. In this article, we provide an overview of HIT and an approach to diagnosis and treatment in the critically ill patient, and complement earlier reviews on this topic[6-9].

Incidence:

The incidence of HIT varies based on the patient population and type of heparin exposure, and ranges from 1 to 5%[10] (Table 1). Risk factors associated with HIT include surgical patients (OR 3.25)[11], female sex (OR 2.37)[11], exposure to unfractionated heparin (UFH, 0.6-2.6%) vs. low molecular weight heparin (LMWH, 0.2-0.3%)[12,13] (OR 5.29)[11], and an elevated BMI. A BMI of 30-39kg/m^2 having an OR of 2.94 (95% confidence interval [CI] 1.2 – 7.5) and a BMI >40 kg/m^2 having an OR of 6.98 (95% CI 1.6 – 28.2)[14] for the development of HIT. Thrombocytopenia in critically ill patients is common, and often leads clinicians to consider HIT as a cause. However, HIT is not usually the culprit and the incidence has been reported only at 0.02-0.45%[15]. A single center German study of 12,528 patients reported an incidence of HIT of 0.21% in a medical / surgical ICU[15]. One of the largest prospective studies of the incidence of HIT was the Heparin induced thrombocytopenia Evaluation in Critical care study embedded within the PROTECT Trial[16,17] - a prospective evaluation of UFH vs LMWH (dalteparin) in 3764 critically ill patients[11]. Using the serotonin release assay (SRA) to confirm the diagnosis, the overall incidence of HIT was 0.40%, or 0.53% with UFH and 0.26% with dalteparin. Within cardiac ICU's using UFH this rate is substantially higher at 1-3%[18,19].

Pathogenesis:

HIT is a condition that results from the host production of platelet-activating IgG antibodies directed against Heparin - Platelet glycosaminoglycan / Platelet Factor -4 (PF4) complexes that form following the exposure to heparin[4,20]. PF4 is a positively charged chemokine released from the alpha granules of activated platelets[4]. PF4 binds the negatively charged heparin anion in patients receiving either therapeutic or prophylactic doses of heparin[20]. Once ligated, these IgG antibodies cause cross-linkage of the platelet Fc-gamma receptor IIA (FcγRIIa)[21]. This in turn activates platelets,[21] leading to the release of platelet derived microparticles that accelerate thrombin formation and thrombotic complications of HIT[22]. The gene coding for FcγRIIa has two allotypes that differ in their ability to bind IgG immune complexes[23]. The 131R allotype was recently shown to confer a higher risk of thrombosis[24]. The authors of that study implicated the increased thrombotic risk to be related to an increase in cell activation by antibodies to PF4-Heparin and a lower inhibitory effect of endogenous IgG (presumably owing to lower IgG2 binding of the 131R allotype). Typically in a heparin- naive individual, HIT related thrombocytopenia occurs at least 5 days after heparin exposure due to the time required for primary antibody formation[25,26]. The risk for thrombosis may continue after platelet count recovery, and the binding of monocytes to PF4 to form antigenic complexes has also been implicated in thrombotic complications[27,28].

Diagnosis:

There are many clinical mimics of HIT and the development of anti-PF-4 antibodies does not always lead to HIT. Therefore there are two requisites for the clinical diagnosis of HIT. First the patient must exhibit a clinical picture consistent with HIT, and second the patient's heparin-dependent antibodies must be platelet activating.

Clinical Features:

The accurate diagnosis of HIT first requires recognition and understanding of its clinical presentation based on the severity of the thrombocytopenia, the timing of its occurrence, the presence of alternative explanations, and thrombotic complications.

Thrombocytopenia

HIT related thrombocytopenia usually manifests as a > 50% reduction in platelet count (10% will have 30-50% reduction)[29]. The platelet nadir is usually ≥ $20x10^9$/L (~90% of HIT patients)[8]. However, thrombocytopenia alone does not differentiate HIT from other, possibly equally concerning aetiologies of thrombocytopenia in ICU patients. Twenty to 25% of critically ill medical patients and 35-41% of surgical / trauma patients will have thrombocytopenia (platelet counts < 100 $x10^9$/L)[30-32]. In the PROTECT study, the incidence of mild (100 to 149 10^9/L), moderate (50 - 99 10^9 / L), and severe (< 50 10^9 / L) thrombocytopenia was 15.3%, 5.1% and 1.6% respectively[33]. The severity of the thrombocytopenia however may help the clinician differentiate HIT from auto immune, drug-dependent or marrow- suppressive (e.g. sepsis) causes, since these entities often have platelet nadirs <$20x10^9$/L.

Timing

The timing of HIT related thrombocytopenia can vary. The typical course is between 5-10 days post heparin exposure (day 0)[25]. A more rapid onset occurs in patients previously exposed to heparin. In these patients, platelet counts fall on day 1 of exposure[8,25]. HIT antibodies can remain detectable on average 50-85 days after heparin exposure,[25] with the anamnestic (booster or immune re-activation) principle also applying to the faster secondary response in the latter scenario. These two predominant patterns of onset are reflected in the 4 T's score (4Ts)[34] described in more detail below.

Other less common presentations of HIT have been more recently described. A more delayed onset of HIT may begin or worsen up to 3 weeks after discontinuation of heparin, owing to higher levels of circulating HIT antibodies at the time, with strong serum-induced platelet activation despite the absence of heparin[35,36]. A spontaneous or naturally-occurring seroconversion to heparin may occur (perhaps by endogenous hepa*ran*-targeting), such that the patient develops the HIT syndrome, albeit without heparin exposure[37]. Finally, protamine/heparin antibodies have been found to produce a similar clinical picture or potentiate the severity of concomitant HIT[38]. This tends to occur earlier than HIT (<5 days) and in post-operative cardiac patients exposed to both heparin and protamine[38].

Thrombosis & systemic events

Thrombotic events can occur in 25-68% of patients with HIT and may occur before the onset of thrombocytopenia[12,39-43]. The frequency of thrombotic events reported may vary because of differences in the patients studied (medical vs surgical vs critically ill) and initial methods of case finding and diagnosis of thrombosis (clinical vs subclinical). In the initial PROTECT study, 17 patients (12 UFH group, 5 Dalteparin) became SRA positive a mean of 8 days (range 1 to 20 days) after study enrollment. Of these patients, there were 2 cases of prevalent VTE and 7 incident cases of VTE [2 PE, 6 DVT (one patient had

both PE and DVT)] and two incident arterial thrombosis (1 also had VTE) during the course of the study. Six of the 17 patients died in the ICU (personal communication, Deborah Cook) [2]. The thromboses in HIT are often extensive with venous thrombosis occurring more frequently than arterial, and lower limb thrombosis occurring more frequently than upper limb[8,44]. Thromboses can occur in atypical locations including adrenal veins[45], central circulation[36] and mesenteric veins[8]. Interestingly in the PROTECT study, patients treated with dalteparin not only had lower rates of seroconversion, but also had less thrombocytopenia and thrombosis[11]. Furthermore, in two patients, the platelet counts recovered despite the ongoing use of dalteparin.

Warfarin use is absolutely contraindicated in HIT as it enhances the prothrombotic state by acutely producing an acquired protein C deficiency, which may not be sufficiently counterbalanced by bridging antithrombotic agents. The acute protein C deficiency may promote macro and micro vascular thrombosis with preserved arterial flow, and cause skin necrosis and venous gangrene[46]. For this reason, vitamin K must be administered immediately in patients with HIT who received warfarin. Finally, acute anaphylactic reactions can occur immediately after heparin administration in patients with circulating HIT antibodies[44].

Does your patient have HIT?

Several scores have been developed to quantitatively assess the likelihood of a patient having HIT and help inform the next course of action (Figure 1). Depending on the pretest probability of HIT, this could involve initiating immediate heparin-free antithrombotic treatment plus serological testing, or serologic testing alone to confirm the diagnosis. These scores include the 4Ts[34], modified 4Ts (m4Ts)[47] and HIT expert probabilities (HEP)[48] scores. All attempt to quantify the pretest probability of having HIT by delineating low, intermediate and high clinical suspicion of HIT and ultimately guide the decision to treat and/or proceed with serological testing. It is important to recognize that none of these HIT risk scores have been extensively validated in critically ill patients. Therefore caution needs to be taken in using them to rule out HIT in this population. Based on the small number of studies evaluating the utility and performance characteristics of the HIT scores in the critically ill, it is our practice to use the 4T score in this population[16,47,49,50]. A 4 T score less than 4 represents a low probability of HIT (Table 2). A 4Ts score ≥ 4 can be sub-divided into intermediate (4-5) and high (6-8) risk for HIT. These correlate with a positive predictive value (PPV) ranging from 0.14-0.21and 0.64-0.78 respectively. The modest PPV of this cut off illustrates the need for confirmatory testing in HIT[49,51].

It is also important to consider the dynamic nature of HIT and the practical limitations of the HIT risk scores. For example, omissions of previous exposures to heparin, occurrences of thrombosis prior to the onset of HIT related thrombocytopenia and imprecise calculation of the timing component of the 4Ts score may yield erroneously low 4Ts scores [2]. Therefore, the 4Ts scores should be re-evaluated in patients with an initial low probability HIT risk score if the diagnosis of HIT remains a concern. Crowther et al in a follow sub-study of the original PROTECT trial, demonstrated that the agreement in the 4-T scores determined by study coordinators and scores determined by adjudication was not ideal with agreement on the 4T category in 71% of the patients (Kappa = 0.23)[2]. One of the main pitfalls they found related to knowledge about prior heparin exposure. This gap affected the ability to accurately time the onset of either thrombocytopenia or thrombosis with first exposure to heparin. This led to the finding of a positive serotonin release assay in 6 patients with an initially low 4T score. Knowledge of heparin exposure prior to the ICU admission would have modified the score to a higher probability value, reducing the number of false negatives[2]. This finding emphasizes the need to carefully evaluate the domains of the 4T score and ensure that research and clinical personnel are well trained in its application. Their results also illustrate

the pitfalls in interrupting heparin or resorting to the use of alternate, more complex agents with a narrower therapeutic window based on a clinical HIT score alone.

Current guidelines recommend investigating for a diagnosis of HIT if a patient is receiving or has received heparin within the last 14 days and the platelet count falls by ≥ 50% and/or a thrombotic event occurs between day 5-14 following the initiation of heparin, even if heparin has been discontinued at the time of thrombosis/thrombocytopenia onset[52,53]. If there is a clinical suspicion of HIT, a confirmatory diagnostic test is required to make the diagnosis. The current recommendations regard a 4Ts score of ≥ 4 (intermediate probability of HIT) as grounds for performing a serological test for the presence of HIT IgG antibodies[49].

A staged laboratory diagnostic approach is recommended. The first stage is an immunologic assay such as the PF4/heparin enzyme-linked immunosorbent assay (ELISA) followed by a second stage washed platelet functional assay such as a SRA or heparin-induced platelet activation (HIPA). Functional assays such as the SRA are considered the gold standard for the diagnosis of HIT. However, SRAs are technically difficult, expensive and only performed at select laboratories. In addition, these samples are usually batched resulting in turnaround times of up to 4 days[54]. As a result, the SRA is typically reserved as a confirmatory test after a positive ELISA in patients with intermediate to high risk 4Ts scores[55].

ELISA testing is commonly used as the initial test for HIT due to low cost and rapid turnaround time[56]. It has a high sensitivity but low specificity for HIT; helping to rule out the condition if negative. The low specificity relates to the frequent development of non-pathologic antibodies to PF4/heparin complexes[56]. Immunologic assays were originally only poly-specific ELISAs. However, they have expanded in recent years to include 5 different classes of assay including ELISA: PaGIA, PIFA, lateral flow immunoassay, CLIA, and latex agglutination assay[57]. The immunologic assay used in any given center is highly variable usually driven by cost and turnaround time (e.g. batched samples vs. real time results).

Most immunologic assays are expressed as both positive/negative and (ideally) quantitatively using optical density. Optical density thresholds for positive results vary by the ELISA manufacturer and by institution. The most common cut off of a positive result is >0.4 OD units (sensitivity 99.99)[58]. However, the higher the OD units used as the threshold, the higher the positive predictive value of the assay[56]. Every increase in OD by 0.5 results in an increase in the likelihood of positive SRA by OR 6.39, and every increase in OD by 1.0 causes an increased likelihood of a positive SRA by OR 40.81[56]. Patients with ELISA OD >2.0 have a 91-100% chance of positive SRA with a 90% chance of thrombosis[55].

Morbidity of suspected diagnosis

Given the high false positive rate of screening tests (e.g. ELISA), a significant proportion of patients with 4Ts ≥4 will receive non-heparin anticoagulation until confirmatory testing excludes or establishes the diagnosis HIT. This period of diagnostic uncertainty exposes patients to a series of potential harms at an additional cost to the health care system. Costs include ordering of additional testing and the antithrombotic agents. Risks include those relating to the misdiagnosis of the thrombocytopenia itself (which may indeed be pro-hemorrhagic rather than pro-thrombotic) and the risks associated with use of non-reversible antithrombotic agents. Some studies report major bleeding rates of 6-30%, illustrating the perils associated with the over-diagnosis of HIT[43,59]. This is not to dissuade from both the consideration and empiric treatment of HIT, but it is important to consider the increased morbidity and mortality of patients that have 4Ts ≥4[59,60].

Pitfalls:

In ICU populations, up to 41.3% of patients develop thrombocytopenia from any cause[61]. This potential source of confusion is compounded by the fact that HIT assay positive patients tend to have other more common causes of thrombocytopenia than patients who are HIT assay negative[47]. With an OD threshold of >0.4 up to 60% of patients will test positive for PF4/heparin antibodies with no clinical signs of HIT and no increased rate of death or thromboembolism[62]. Thus, without a clinical context suggestive of HIT (4Ts ≥4) the routine screening for HIT antibodies is not recommended. The other causes of thrombocytopenia form an important component of the 4Ts score and should be considered. (Table 3).

One particularly difficult overlap is disseminated intravascular coagulation (DIC). DIC and HIT are not different by median platelet counts, PT, aPTT, fibrinogen, DIC score or overt DIC[63]. Mixed evidence exists for the ability of quantitative D-dimers to separate the two entities[63,64]. One study demonstrated that among limited-availability tests such as thrombin/antithrombin complex (TAT) and plasmin/alpha 2-plasmin inhibitor complex (PIC), levels were higher in DIC compared to HIT, although further evaluation is required before incorporation into clinical decision making[64]. Fibrinogen levels were only decreased in 5.4% of DIC patients, illustrating its weakness as a screening test for DIC[65]. Two scores have been developed for the diagnosis of DIC; the Japanese Ministry of Health and Welfare score (JMHW) and the International Society on Thrombosis and Haemostasis (ISTH) score. The ISTH score has a sensitivity of 91% and a specificity of 97%[65]. In addition, with the exception of the setting of DIC during hematologic malignancy, the scores show concordance of 93%[66]. Finally, the concurrent presentation of HIT with DIC is also well described, further complicating the ability to diagnose these conditions in a critically ill patient[64]. If suspecting either HIT or DIC, clinicians should take steps to ensure they have the correct diagnosis so as to treat appropriately for both conditions until one or both are appropriately ruled out, so as to avoid the morbidity and mortality associated with missing either.

Drug induced thrombocytopenia is common and can be confused with HIT. In general, the platelets fall 7-20 days after commencing the offending agent. The challenge in critically ill patients is finding the culprit agent as many medications can cause thrombocytopenia and are often administered concurrently. Drug induced thrombocytopenia tends to lead to extremely low platelets counts ($<20x10^9$/L) and by extension more bleeding complications as opposed to thrombosis[15].

Intravascular devices may cause platelet destruction and produce thrombocytopenia that is temporally related to either the initiation or senescence of a device (e.g. Extra-corporeal membrane oxygen [ECMO], CVVHD, IABP, etc.)[15]. The caveat is that repeat filter/device clotting should equally raise concerns for HIT associated thrombosis since most devices depend for their patency on the use of UFH as the first-line anticoagulant, and/or have heparin impregnated in the circuit materials themselves (http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm135347.htm). ECMO patients are screened far more frequently than most other ICU patients despite extremely low incidence of confirmed HIT[60].

The onset of immune thrombocytopenia (ITP) or anti-phospholipid antibody syndrome (APLA) would not be temporally linked to heparin dosing, while the immunopathogenesis of either is also distinct. However, there is no accepted antibody test for ITP, and 20-25% of ITP is not even B-cell (antibody) mediated, (e.g. there is a T-cell mediated immunopathology). On the other hand, there are many direct-immune-detection tests (eg. Anticardiolipin antibodies, ELISA) and functional assays (eg. Lupus Anticoagulant titres, Hexagonal Phase Phospholipid confirmation, or platelet neutralization procedure) for APLA.

Acute liver failure causes both thrombocytopenia and "rebalanced hemostasis" despite an increase in INR[67]. Rather than being prone to bleeding, a mismatched decrease in the production of various

coagulant and anticoagulant factors may associate instead with a hypercoagulable state in some patients. As a result, as with the above examples, patients with Budd-Chiari syndrome should cue clinicians to suspect the possibility of HIT and thus should also have 4Ts calculated to assess the appropriateness for further screening if at high risk for HIT.

Treatment:

Given the high mortality and morbidity associated with ongoing heparin use in HIT patients, immediate management changes must occur in suspected or confirmed HIT.

If a patient has confirmed HIT or moderate-high clinical suspicion of HIT (4Ts $\geq$ 4), then all heparin products should be discontinued, and all heparin-containing devices removed (e.g. heparin-bonded central venous catheters).

In addition to stopping heparin, a non-heparin, non-vitamin K antagonist anticoagulant should be started immediately[52,53]. Currently, the only guideline-supported alternatives include intravenous direct thrombin inhibitors (lepirudin, argatroban and bivalirudin) or indirect factor Xa inhibitors (danaparoid and fondaparinux)[52,53]. Although there is emerging evidence that novel/direct oral anti-coagulants (rivaroxaban, dabigatran and apixaban) may be a safe alternative to treat HIT[68-71], they are not incorporated into current HIT guidelines[52] and do not yet have regulatory approval for this indication[52,53].

Transfusion thresholds for states of "thrombotic thrombocytopenia" are not established, and studies in some conditions (such as thrombotic thrombocytopenic purpura or antiphospholipid antibody syndrome) may not be generalizable to HIT[72,73]. Platelet needs or hazards in the patient with suspected HIT may not be different from those with other forms of platelet insufficiency. Given the high bleeding risk of ICU patients, and peri-operative patients in particular, the bleeding risk (by deferring platelet transfusion) may outweigh that of theoretical thrombosis (with platelet transfusion). If HIT is confirmed, then consultation from hematology or thrombosis services should help guide platelet thresholds in a HIT confirmed patient on an individualized basis.

Argatroban:

Argatroban is a direct thrombin inhibitor and is currently the only FDA approved treatment of HIT. It is recommended first-line in patients with renal insufficiency. Given the high prevalence of acute kidney injury and/or chronic renal failure in ICU populations, argatroban has been the mainstay of treatment for the treatment of HIT. Its half-life is 40-50min. In patients who have heart failure, liver failure or severe anasarca, or who are post cardiac surgery, reduced initial infusions are recommended, with subsequent q2-4h adjustments using the aPTT (target aPTT 1.5-3 times patient baseline)[52,53]. Careful monitoring is required as comorbidities may affect the aPTT and necessitate infusion rate modifications to remain within the therapeutic window. Furthermore, patients requiring EMCO may require modified dosing. A 9-patient cohort found that the 2 mcg/kg/min dose resulted in significant bleeding and that a lower 0.2 mcg/kg/min resulted in clinically significant anticoagulation without additional bleeding[74]. Although the average maintenance dose required was 0.15mcg/kg/min, it should be noted that HIT positive patients with active clot formation may require up-titrated doses to achieve clinical anticoagulation beyond these levels[75].

The risk/benefit profile for anti-coagulation should be personalized when selecting the starting dose, followed by close adjustments based on the clinical response. The bleeding rates in critically ill range from 7.4 to 21.9%, with the only predictive risk factor being major surgery prior to commencing treatment[43,59,76]. Argatroban has been used for perioperative anticoagulation for ventricular assist devices.

However, because limited case studies have shown high breakthrough rates of intraventricular thrombus (14.2%), risk of bleeding (57.1%) and mortality (57.1%), it is not routinely used in this setting[77].

Bivalirudin

A direct thrombin inhibitor, bivalirudin is recommended as first line for patients requiring emergent cardiopulmonary bypass for cardiac surgery. It is also recommended as one of the first line agents for percutaneous coronary interventions. The initial dose is 0.15mg/kg/h and is adjusted to achieve aPTT at 1.5-2.5 times baseline[78]. Dose adjustments for hepatic dysfunction (0.14mg/kg/h), renal/hepatic dysfunction (0.03-0.05mg/kg/h) and continuous renal replacement therapy (0.03-0.04mg/kg/h) are required[78]. Bivalirudin has been used in ventricular assist devices but with mixed results and its use in these patients requires some caution[79,80].

Indirect factor Xa inhibitors

Danaparoid and fondaparinux are highly effective in the management of HIT but are of limited clinical usefulness in ICU populations due to their long half-lives and renal clearance.

Fondaparinux, a FXa-binding heparin-subunit pentasaccharide which does not bind to PF4, is an ideal therapy for HIT patients with creatinine clearance >30mL/min. It is given subcutaneously and does not routinely require monitoring[81]. However, the guidelines only recommend fondaparinux for HIT in pregnant patients where danaparoid is unavailable or in patients with a history of HIT with a new (unrelated) thrombosis until transitioned to warfarin[52]. There have been case reports of HIT complicating fondaparinux use[82]. Despite this, up to 50% of HIT was treated with fondaparinux in a multi-center German registry[83]. Retrospective analysis of patients with HIT treated with fondaparinux has found similar thrombosis, bleeding and mortality rates to those treated with danaparoid and argatroban[84] . It has also been found to be more cost effective versus other recommended agents[85]. However, no prospective evidence is currently available to recommend its routine use for treatment of HIT[52].

Immunotherapies

There are limited reports on the use of plasmapharesis to treat refractory or severe HIT[86,87]. Plasmapheresis has also been advocated to reduce the risk of thrombosis in patients undergoing cardiac surgery who a preoperative history of HIT and a current positive anti-heparin/platelet factor 4 (anti-HPF4) antibody titer[88]. Despite these reports there is limited clinical data to support plasmapheresis as routine practice. Exogenous immunoglobulin administration (ivIg) has been the subject of several case reports to treat HIT[89-91]. Padmanabhan et al reported 3 patients with refractory HIT and venous / arterial thrombosis[90]. All three were reported to respond to ivIg administration (two patients had 1 gram/kg administered on 2 consecutive days while the other had the same dose two days apart). In vitro data from the patient's sera suggested that immunoglobulin was effective at inhibiting the activation of platelets pretreated with low levels of PF4 in the serum of patients with severe documented HIT (using a PF4-dependent P-selectin expression assay). Interestingly 2 of the patients had the FcγRIIa RR131 allotype and seemed to respond to treatment. It is important to emphasize that ivIg has been associated with thrombosis. In addition, a consensus statement on the clinical use of ivIg advised against its use to treat HIT[92]. Therefore, the use of ivIg to treat HIT must be considered on a case by case basis and ideally properly evaluated in the context of a clinical trial.

Outcomes of HIT

Outcomes vary considerably based on the severity of HIT and clinical condition of the patient. Overall, thrombotic events occur in 20-68% of patients with HIT[42-44,78,93]. Mortality rates even with treatment vary from 14.5-25%[42,43,94], despite HIT associated thrombosis only directly causing death in 0-1.7% of cases[42,43]. Table 4 shows several study outcomes from HIT patients treated with bivalirudin and argatroban.

Future Directions of Management:

More research validating the utility and performance of the HIT risk scores is needed to help guide clinical decision making. Based on our interpretation of the literature we have provided a rather conservative approach to the diagnosis of HIT in the critically ill population (Figure 1). We recognize the inherent limitations as it relates to the use of the 4T score and emphasize the dynamic nature of HIT. Therefore patients with ongoing clinical suspicion of HIT who have an initial low risk 4T score should be re-evaluated for changes in their risk score. In addition, we suggest that in the patient with intermediate risk of HIT consultation with a hematologist is appropriate to avoid the inherent complications of interrupting Heparin administration with more toxic and less reliable anticoagulants.

With the recent development of reversal agents for Xa inhibitors[95], the utility of danaparoid and factor X-specific direct oral anticoagulants (DOACs) may emerge in ICU populations as useful agents for the management of HIT. Given that these drugs do not interact with PF4, they are theoretically invisible as targets of antibody-mediated HIT[96]. Small case studies have already demonstrated the effectiveness of DOACs in non-ICU populations[68,71,97]. However, the current dearth of precision-monitoring options for DOACs in challenging titration situations remains a concern for ICU patients[98]. Prospective trials are necessary to demonstrate DOAC effectiveness and safety in ICU populations, particularly in a fixed-dosing context with assay limitations, prior to their use in HIT.

Furthermore, prospective trials are needed to examine the effectiveness and safety of fondaparinux in preserved renal function patients. Fondaparinux may be a cost effective and safer management strategy, and experience in its use is described by several specialist centers throughout the world. Likewise, larger studies are required for ECMO patients with HIT both for the validation of the 4Ts score and the best treatment in this unique population.

The results of the PROTECT study support the use of a LMWH prophylaxis instead of UFH to decrease the incidence and morbidity of suspected and confirmed HIT[16,99]. Therefore we advocate for the adoption of LMWH thromboprophylaxis in ICU patients.

Conclusion

HIT is a complex clinical pathological condition that threatens both surgical and medical critical care patients with unchecked morbidity and mortality if not quickly diagnosed and treated. However in the critically ill population HIT is likely over diagnosed. Over diagnosis can lead to adverse consequences such as interruption in therapeutic heparin – resulting in unintended thrombosis as well as use of expensive and inappropriate diagnostic testing. The empiric use of direct thrombin inhibitors or indirect factor Xa inhibitors may be associated with increased costs and morbidity relating to bleeding or thrombosis if sub therapeutic doses are used. Monitoring of these agents in the context of renal or hepatic dysfunction is also problematic. To avoid these pitfalls, HIT should only be considered in the context of a high clinical probability quantified by using available prediction scores. Although these scores have not been fully evaluated in the ICU population; used in the proper clinical context they should help inform the decision to proceed with serological confirmatory testing.

Legend Figure 1

Algorithm for the Diagnosis and treatment of Heparin induced thrombocytopenia (HIT).

LMWH – low molecular weight heparin, PF4 – platelet factor 4, ELISA - enzyme-linked immunosorbent assay, SRA – serotonin release assay

References

1. Rhodes GR, Dixon RH, Silver D. Heparin induced thrombocytopenia: eight cases with thrombotic-hemorrhagic complications. *Annals of surgery.* 1977;186(6):752-758.
2. Crowther M, Cook D, Guyatt G, et al. Heparin-induced thrombocytopenia in the critically ill: interpreting the 4Ts test in a randomized trial. *J Crit Care.* 2014;29(3):470 e477-415.
3. Weismann RE, Tobin RW. Arterial embolism occurring during systemic heparin therapy. *AMA archives of surgery.* 1958;76(2):219-227.
4. Amiral J, Bridey F, Dreyfus M, et al. Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. *Thromb Haemost.* 1992;68(1):95-96.
5. Crafoord C. Preliminary Report on post operative treatment with heparin as a preventative of thrombosis. *Acta Chirurgica Scand.* 1936;79:407-426.
6. Warkentin TE, Anderson JA. How I treat patients with a history of HIT. *Blood.* 2016.
7. Bakchoul T. An update on heparin-induced thrombocytopenia: diagnosis and management. *Expert Opin Drug Saf.* 2016:1-11.
8. Warkentin TE. Heparin-induced thrombocytopenia in critically ill patients. *Semin Thromb Hemost.* 2015;41(1):49-60.
9. Greinacher A. CLINICAL PRACTICE. Heparin-Induced Thrombocytopenia. *N Engl J Med.* 2015;373(3):252-261.
10. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126(3 Suppl):311S-337S.
11. Warkentin TE, Sheppard JA, Sigouin CS, Kohlmann T, Eichler P, Greinacher A. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. *Blood.* 2006;108(9):2937-2941.
12. Cook D, Meade M, Guyatt G, et al. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med.* 2011;364(14):1305-1314.
13. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood.* 2005;106(8):2710-2715.
14. Bloom MB, Zaw AA, Hoang DM, et al. Body mass index strongly impacts the diagnosis and incidence of heparin-induced thrombocytopenia in the surgical intensive care unit. *J Trauma Acute Care Surg.* 2016;80(3):398-404.
15. Selleng K, Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia in intensive care patients. *Crit Care Med.* 2007;35(4):1165-1176.
16. Crowther M, Cook D, Guyatt G, et al. Heparin-induced thrombocytopenia in the critically ill: interpreting the 4Ts test in a randomized trial. *J Crit Care.* 2014;29(3):470.e477-415.
17. Warkentin TE, Sheppard JA, Heels-Ansdell D, et al. Heparin-induced thrombocytopenia in medical surgical critical illness. *Chest.* 2013;144(3):848-858.
18. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia and cardiac surgery. *The Annals of Thoracic Surgery.* 2003;76(6):2121-2131.
19. Selleng S, Selleng K, Wollert HG, et al. Heparin-induced thrombocytopenia in patients requiring prolonged intensive care unit treatment after cardiopulmonary bypass. *J Thromb Haemost.* 2008;6(3):428-435.
20. Greinacher A, Potzsch B, Amiral J, Dummel V, Eichner A, Mueller-Eckhardt C. Heparin-associated thrombocytopenia: isolation of the antibody and characterization of a multimolecular PF4-heparin complex as the major antigen. *Thromb Haemost.* 1994;71(2):247-251.
21. Kelton JG, Sheridan D, Santos A, et al. Heparin-induced thrombocytopenia: laboratory studies. *Blood.* 1988;72(3):925-930.

22. Warkentin TE, Hayward CP, Boshkov LK, et al. Sera from patients with heparin-induced thrombocytopenia generate platelet-derived microparticles with procoagulant activity: an explanation for the thrombotic complications of heparin-induced thrombocytopenia. *Blood.* 1994;84(11):3691-3699.
23. Bruhns P, Iannascoli B, England P, et al. Specificity and affinity of human Fcgamma receptors and their polymorphic variants for human IgG subclasses. *Blood.* 2009;113(16):3716-3725.
24. Rollin J, Pouplard C, Sung HC, et al. Increased risk of thrombosis in FcγRIIA 131RR patients with HIT due to defective control of platelet activation by plasma IgG2. *Blood.* 2015;125(15):2397-2404.
25. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med.* 2001;344(17):1286-1292.
26. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. *Am J Med.* 1996;101(5):502-507.
27. Kasthuri RS, Glover SL, Jonas W, et al. PF4/heparin-antibody complex induces monocyte tissue factor expression and release of tissue factor positive microparticles by activation of FcgammaRI. *Blood.* 2012;119(22):5285-5293.
28. Rauova L, Hirsch JD, Greene TK, et al. Monocyte-bound PF4 in the pathogenesis of heparin-induced thrombocytopenia. *Blood.* 2010;116(23):5021-5031.
29. Cuker A. Recent advances in heparin-induced thrombocytopenia. *Curr Opin Hematol.* 2011;18(5):315-322.
30. Stephan F, Hollande J Fau - Richard O, Richard O Fau - Cheffi A, Cheffi A Fau - Maier-Redelsperger M, Maier-Redelsperger M Fau - Flahault A, Flahault A. Thrombocytopenia in a surgical ICU. 1999(0012-3692 (Print)).
31. Hanes SD, Quarles DA, Boucher BA. Incidence and risk factors of thrombocytopenia in critically ill trauma patients. *Ann Pharmacother.* 1997;31(3):285-289.
32. Thiele T, Selleng K, Selleng S, Greinacher A, Bakchoul T. Thrombocytopenia in the intensive care unit-diagnostic approach and management. *Semin Hematol.* 2013;50(3):239-250.
33. Williamson DR, Albert M, Heels-Ansdell D, et al. Thrombocytopenia in critically ill patients receiving thromboprophylaxis: frequency, risk factors, and outcomes. *Chest.* 2013;144(4):1207-1215.
34. Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost.* 2006;4(4):759-765.
35. Warkentin TE, Kelton JG. Delayed-onset heparin-induced thrombocytopenia and thrombosis. *Annals of internal medicine.* 2001;135(7):502-506.
36. Warkentin TE, Bernstein RA. Delayed-onset heparin-induced thrombocytopenia and cerebral thrombosis after a single administration of unfractionated heparin. *N Engl J Med.* 2003;348(11):1067-1069.
37. Warkentin TE, Makris M, Jay RM, Kelton JG. A spontaneous prothrombotic disorder resembling heparin-induced thrombocytopenia. *Am J Med.* 2008;121(7):632-636.
38. Bakchoul T, Jouni R, Warkentin TE. Protamine (heparin)-induced thrombocytopenia: a review of the serological and clinical features associated with anti-protamine/heparin antibodies. *J Thromb Haemost.* 2016;14(9):1685-1695.
39. Girolami B, Prandoni P, Stefani PM, et al. The incidence of heparin-induced thrombocytopenia in hospitalized medical patients treated with subcutaneous unfractionated heparin: a prospective cohort study. *Blood.* 2003;101(8):2955-2959.
40. Prandoni P, Siragusa S, Girolami B, Fabris F. The incidence of heparin-induced thrombocytopenia in medical patients treated with low-molecular-weight heparin: a prospective cohort study. *Blood.* 2005;106(9):3049-3054.
41. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. *The American journal of medicine.* 1996;101(5):502-507.

42. Joseph L, Casanegra AI, Dhariwal M, et al. Bivalirudin for the treatment of patients with confirmed or suspected heparin-induced thrombocytopenia. *J Thromb Haemost.* 2014;12(7):1044-1053.
43. Tardy-Poncet B, Nguyen P, Thiranos JC, et al. Argatroban in the management of heparin-induced thrombocytopenia: a multicenter clinical trial. *Crit Care.* 2015;19:396.
44. Gupta S, Tiruvoipati R, Green C, Botha J, Tran H. Heparin induced thrombocytopenia in critically ill: Diagnostic dilemmas and management conundrums. *World J Crit Care Med.* 2015;4(3):202-212.
45. Ketha S, Smithedajkul P, Vella A, Pruthi R, Wysokinski W, McBane R. Adrenal haemorrhage due to heparin-induced thrombocytopenia. *Thromb Haemost.* 2013;109(4):669-675.
46. Kowalska MA, Krishnaswamy S, Rauova L, et al. Antibodies associated with heparin-induced thrombocytopenia (HIT) inhibit activated protein C generation: new insights into the prothrombotic nature of HIT. *Blood.* 2011;118(10):2882-2888.
47. Fiorenza MA, Frazee EN, Personett HA, Dierkhising RA, Schramm GE. Assessment of a modified 4T scoring system for heparin-induced thrombocytopenia in critically ill patients. *J Crit Care.* 2014;29(3):426-431.
48. Cuker A, Arepally G, Crowther MA, et al. The HIT Expert Probability (HEP) Score: a novel pre-test probability model for heparin-induced thrombocytopenia based on broad expert opinion. *J Thromb Haemost.* 2010;8(12):2642-2650.
49. Cuker A, Gimotty PA, Crowther MA, Warkentin TE. Predictive value of the 4Ts scoring system for heparin-induced thrombocytopenia: a systematic review and meta-analysis. *Blood.* 2012;120(20):4160-4167.
50. Uaprasert N, Chanswangphuwana C, Akkawat B, Rojnuckarin P. Comparison of diagnostic performance of the heparin-induced thrombocytopenia expert probability and the 4Ts score in screening for heparin-induced thrombocytopenia. *Blood Coagul Fibrinolysis.* 2013;24(3):261-268.
51. Bayat M, Macedo FY, Ansari AS, Bracey AW, Akinyele S, Salazar M. Evaluation of clinical and laboratory data for early diagnosis of heparin-induced thrombocytopenia. *Am J Health Syst Pharm.* 2015;72(19):1649-1655.
52. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e495S-530S.
53. Cuker A, Crowther M. Clinical Practice Guideline on the Evaluation and Management of Adults with Suspected Heparin-Induced Thrombocytopenia (HIT). *American Society of Hematology.* 2013.
54. Warkentin TE. Demand on-demand testing for the diagnosis of heparin-induced thrombocytopenia. *Thromb Res.* 2016;140:163-164.
55. Warkentin TE, Arnold DM, Nazi I, Kelton JG. The platelet serotonin-release assay. *Am J Hematol.* 2015;90(6):564-572.
56. Warkentin TE, Sheppard JI, Moore JC, Sigouin CS, Kelton JG. Quantitative interpretation of optical density measurements using PF4-dependent enzyme-immunoassays. *J Thromb Haemost.* 2008;6(8):1304-1312.
57. Nagler M, Bachmann LM, Ten Cate H, Ten Cate-Hoek A. Diagnostic value of immunoassays for heparin-induced thrombocytopenia: a systematic review and meta-analysis. *Blood.* 2016;127(5):546-557.
58. Altuntas F, Matevosyan K, Burner J, Shen YM, Sarode R. Higher optical density of an antigen assay predicts thrombosis in patients with heparin-induced thrombocytopenia. *Eur J Haematol.* 2008;80(5):429-435.

59. Doepker B, Mount KL, Ryder LJ, Gerlach AT, Murphy CV, Philips GS. Bleeding risk factors associated with argatroban therapy in the critically ill. *J Thromb Thrombolysis.* 2012;34(4):491-498.
60. Glick D, Dzierba AL, Abrams D, et al. Clinically suspected heparin-induced thrombocytopenia during extracorporeal membrane oxygenation. *J Crit Care.* 2015;30(6):1190-1194.
61. Vanderschueren S, De Weerdt A, Malbrain M, et al. Thrombocytopenia and prognosis in intensive care. *Crit Care Med.* 2000;28(6):1871-1876.
62. Welsby IJ, Krakow EF, Heit JA, et al. The association of anti-platelet factor 4/heparin antibodies with early and delayed thromboembolism after cardiac surgery. *J Thromb Haemost.* 2017;15(1):57-65.
63. Park SH, Jang S, Shim H, et al. Usefulness of anti-PF4/heparin antibody test for intensive care unit patients with thrombocytopenia. *The Korean journal of hematology.* 2012;47(1):39-43.
64. Matsuo T, Matsuo M, Sugimoto T, Wanaka K. Anti-heparin/PF4 complexes by ELISA in patients with disseminated intravascular coagulation. *Pathophysiol Haemost Thromb.* 2007;36(6):305-310.
65. Bakhtiari K, Meijers JC, de Jonge E, Levi M. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. *Crit Care Med.* 2004;32(12):2416-2421.
66. Matsumoto T, Wada H, Nishioka Y, et al. Frequency of abnormal biphasic aPTT clot waveforms in patients with underlying disorders associated with disseminated intravascular coagulation. *Clin Appl Thromb Hemost.* 2006;12(2):185-192.
67. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med.* 2011;365(2):147-156.
68. Linkins LA, Warkentin TE, Pai M, et al. Rivaroxaban for Treatment of Suspected or Confirmed Heparin-Induced Thrombocytopenia Study. *J Thromb Haemost.* 2016.
69. Sharifi M, Bay C, Vajo Z, Freeman W, Sharifi M, Schwartz F. New oral anticoagulants in the treatment of heparin-induced thrombocytopenia. *Thromb Res.* 2015;135(4):607-609.
70. Skelley JW, Kyle JA, Roberts RA. Novel oral anticoagulants for heparin-induced thrombocytopenia. *J Thromb Thrombolysis.* 2016.
71. Walenga JM, Prechel M, Jeske WP, et al. Rivaroxaban--an oral, direct Factor Xa inhibitor--has potential for the management of patients with heparin-induced thrombocytopenia. *Br J Haematol.* 2008;143(1):92-99.
72. Otrock ZK, Liu C, Grossman BJ. Platelet transfusion in thrombotic thrombocytopenic purpura. *Vox sanguinis.* 2015;109(2):168-172.
73. Riviere E, Saint-Leger M, James C, et al. Platelet transfusion and catheter insertion for plasma exchange in patients with thrombotic thrombocytopenic purpura and a low platelet count. *Transfusion.* 2015;55(7):1798-1802.
74. Beiderlinden M, Treschan T, Gorlinger K, Peters J. Argatroban in extracorporeal membrane oxygenation. *Artif Organs.* 2007;31(6):461-465.
75. Phillips MR, Khoury AI, Ashton RF, Cairns BA, Charles AG. The dosing and monitoring of argatroban for heparin-induced thrombocytopenia during extracorporeal membrane oxygenation: a word of caution. *Anaesth Intensive Care.* 2014;42(1):97-98.
76. Hursting MJ, Verme-Gibboney CN. Risk factors for major bleeding in patients with heparin-induced thrombocytopenia treated with argatroban: a retrospective study. *J Cardiovasc Pharmacol.* 2008;52(6):561-566.
77. Hillebrand J, Sindermann J, Schmidt C, Mesters R, Martens S, Scherer M. Implantation of left ventricular assist devices under extracorporeal life support in patients with heparin-induced thrombocytopenia. *Journal of artificial organs : the official journal of the Japanese Society for Artificial Organs.* 2015;18(4):291-299.

78. Kiser TH, Fish DN. Evaluation of bivalirudin treatment for heparin-induced thrombocytopenia in critically ill patients with hepatic and/or renal dysfunction. *Pharmacotherapy.* 2006;26(4):452-460.
79. Garland C, Somogyi D. Successful Implantation of a Left Ventricular Assist Device in a Patient with Heparin-Induced Thrombocytopenia and Thrombosis. *The Journal of Extra-corporeal Technology.* 2014;46(2):162-165.
80. Awad H, Bryant R, Malik O, Dimitrova G, Sai-Sudhakar CB. Thrombosis during off pump LVAD placement in a patient with heparin induced thrombocytopenia using bivalirudin. *Journal of Cardiothoracic Surgery.* 2013;8(1):115.
81. Scully M, Gates C, Neave L. How we manage patients with heparin induced thrombocytopenia. *Br J Haematol.* 2016.
82. Warkentin TE, Chakraborty AK, Sheppard JA, Griffin DK. The serological profile of fondaparinux-associated heparin-induced thrombocytopenia syndrome. *Thromb Haemost.* 2012;108(2):394-396.
83. Schindewolf M, Steindl J, Beyer-Westendorf J, et al. Frequent off-label use of fondaparinux in patients with suspected acute heparin-induced thrombocytopenia (HIT)--findings from the GerHIT multi-centre registry study. *Thromb Res.* 2014;134(1):29-35.
84. Kang M, Alahmadi M, Sawh S, Kovacs MJ, Lazo-Langner A. Fondaparinux for the treatment of suspected heparin-induced thrombocytopenia: a propensity score-matched study. *Blood.* 2015;125(6):924-929.
85. Aljabri A, Huckleberry Y, Karnes JH, et al. Cost-effectiveness of anticoagulants for suspected heparin-induced thrombocytopenia in the United States. *Blood.* 2016;128(26):3043-3051.
86. Chan KM, Cheung CY, Chau KF. Heparin-induced thrombocytopenia due to heparin lock in a hemodialysis patient: a case report. *Hemodialysis international. International Symposium on Home Hemodialysis.* 2014;18(2):555-558.
87. Horlait G, Minet V, Mullier F, Michaux I. Persistent heparin-induced thrombocytopenia: danaparoid cross-reactivity or delayed-onset heparin-induced thrombocytopenia? A case report. *Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis.* 2017;28(2):193-197.
88. Welsby IJ, Um J, Milano CA, Ortel TL, Arepally G. Plasmapheresis and heparin reexposure as a management strategy for cardiac surgical patients with heparin-induced thrombocytopenia. *Anesthesia & Analgesia.* 2010;110(1):30-35.
89. Lei BZ, Shatzel JJ, Sendowski M. Rapid and durable response to intravenous immunoglobulin in delayed heparin-induced thrombocytopenia: a case report. *Transfusion.* 2017;57(4):919-923.
90. Padmanabhan A, Jones CG, Pechauer SM, et al. Intravenous immunoglobulin for treatment of severe refractory heparin-induced thrombocytopenia. *Chest.* 2017.
91. Winder A, Shoenfeld Y, Hochman R, Keren G, Levy Y, Eldor A. High-dose intravenous gamma-globulins for heparin-induced thrombocytopenia: a prompt response. *Journal of clinical immunology.* 1998;18(5):330-334.
92. Anderson D, Ali K, Blanchette V, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. Vol 212007:S9-56.
93. Warkentin TE. HITlights: a career perspective on heparin-induced thrombocytopenia. 2012(1096-8652 (Electronic)).
94. Vo QA, Lin JK, Tong LM. Efficacy and safety of argatroban and bivalirudine in patients with suspected heparin-induced thrombocytopenia. *Ann Pharmacother.* 2015;49(2):178-184.
95. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *N Engl J Med.* 2015;373(25):2413-2424.
96. Krauel K, Hackbarth C, Fürll B, Greinacher A. Heparin-induced thrombocytopenia: in vitro studies on the interaction of dabigatran, rivaroxaban, and low-sulfated heparin, with platelet factor 4 and anti-PF4/heparin antibodies. *Blood.* 2012;119(5):1248.

97. Hantson P, Lambert C, Hermans C. Rivaroxaban for arterial thrombosis related to heparin-induced thrombocytopenia. *Blood Coagul Fibrinolysis.* 2015;26(2):205-206.
98. Dale BJ, Chan NC, Eikelboom JW. Laboratory measurement of the direct oral anticoagulants. *Br J Haematol.* 2016;172(3):315-336.
99. McGowan KE, Makari J, Diamantouros A, et al. Reducing the hospital burden of heparin-induced thrombocytopenia: impact of an avoid-heparin program. *Blood.* 2016;127(16):1954-1959.
100. Warkentin TE, Sheppard JA, Horsewood P, Simpson PJ, Moore JC, Kelton JG. Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood.* 2000;96(5):1703-1708.
101. Pouplard C, May MA, Iochmann S, et al. Antibodies to platelet factor 4-heparin after cardiopulmonary bypass in patients anticoagulated with unfractionated heparin or a low-molecular-weight heparin : clinical implications for heparin-induced thrombocytopenia. *Circulation.* 1999;99(19):2530-2536.
102. Walls JT, Curtis JJ, Silver D, Boley TM, Schmaltz RA, Nawarawong W. Heparin-induced thrombocytopenia in open heart surgical patients: sequelae of late recognition. *The Annals of thoracic surgery.* 1992;53(5):787-791.
103. Walls JT, Boley TM, Curtis JJ, Silver D. Heparin induced thrombocytopenia in patients undergoing intra-aortic balloon pumping after open heart surgery. *ASAIO journal.* 1992;38(3):M574-M576.
104. Singer RL, Mannion JD, Bauer TL, Armenti FR, Edie RN. Complications from heparin-induced thrombocytopenia in patients undergoing cardiopulmonary bypass. *CHEST Journal.* 1993;104(5):1436-1440.
105. Ganzer D, Gutezeit A, Mayer G, Greinacher A, Eichler P. Thromboembolieprophylaxe als Auslöser thrombembolischer Komplikationen. *Zeitschrift für Orthopädie und ihre Grenzgebiete.* 1997;135(06):543-549.
106. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-Induced Thrombocytopenia in Patients Treated with Low-Molecular-Weight Heparin or Unfractionated Heparin. *New England Journal of Medicine.* 1995;332(20):1330-1336.
107. Leyvraz P, Bachmann F, Hoek J, et al. Prevention of deep vein thrombosis after hip replacement: randomised comparison between unfractionated heparin and low molecular weight heparin. *Bmj.* 1991;303(6802):543-548.
108. Louridas G. Heparin-induced thrombocytopenia. *South African journal of surgery. Suid-Afrikaanse tydskrif vir chirurgie.* 1991;29(2):50-52.

Table 1: Incidence of HIT as reported in registries, clinical trials and cohort studies.

Author	Year	Patients	Incidence (%)	Population at risk
Warkentin[100]	2000	100	1.00%	Cardiac
Cook[12]	2011	3746	0.45%	Medical /surgical ICU
Selleng[15]	2007	12528	0.02%	Medical / Surgical ICU
Pouplard[101]	1999	263	3.42%	Cardiac surgery on bypass
Walls[102]	1992	4261	1.92%	Cardiac surgery
Walls[103]	1992	764	4.58%	IABP
Singer[104]	1993	1500	0.75%	CABG, Valve and combined
Ganzer[105]	1997	307	4.89%	Orthopaedic
Warkentin[106]	1995	332	2.41%	Orthopaedic elective hip
Leyvraz[107]	1991	204 205	2% with UFH 0 with LMWH	Orthopaedic elective hip
Louridas[108]	1991	114	4.39%	Vascular Surgery

IABP – intra-aortic balloon pump, CABG – coronary artery bypass graft, ICU – intensive care unit

UFH – Unfractionated heparin, LMWH – Low molecular weight heparin.

Table 2: 4Ts and Modified 4Ts Score

Points	**2**	**1**	**0**
Thrombocytopenia	>50% platelet fall to nadir ≥20	30-50% platelet count fall; or nadir 10-19	<30% platelet fall; or nadir <10
Timing of platelet fall	Days 5-10 or ≤1 day (with heparin exposure in past 30 days)	Consistent with days 5-10 fall but not clear; ≤1 day; (heparin exposure within past 31-100 days); ≥ days	≤4 days (with no picture of rapid onset HIT)
Thrombosis or other sequelae	Proven new thrombosis/skin necrosis or post heparin bolus anaphylactoid reaction	Progressive or recurrent thrombosis, erythematous skin lesions, suspected thrombosis or hemofilter thrombosis	None
Other causes of thrombocytopenia*	No explanation for platelet count fall	Possible other cause is evident	Definite other cause is present

* - Excluded from the modified 4Ts score
HIT – Heparin induced thrombocytopenia
Score originally published Lo et al (2006)[34]

Table 3: Differential diagnosis of HIT and their potential distinguishing clinical features

Condition	**Diagnostic Clues**
Sepsis	SIRS criteria, positive blood cultures
DIC	Increased both PT/APTT, decreased fibrinogen
Massive blood loss	Source of bleeding, large volume transfusions, increased PT/APTT, hypocalcaemia, hypothermia
Thrombotic microangiopathy	Schistocytes on blood film, acute kidney injury, stroke/neurological deficits, hemolysis
Immune thrombocytopenia	Diagnosis of exclusion, no universally accepted antibody test
Drug induced thrombocytopenia	Decreased megakaryocytes on bone marrow, rebound of platelets after discontinuation of drug
Cardiopulmonary bypass / extracorporeal membrane oxygenation	
Intra-aortic balloon pump	

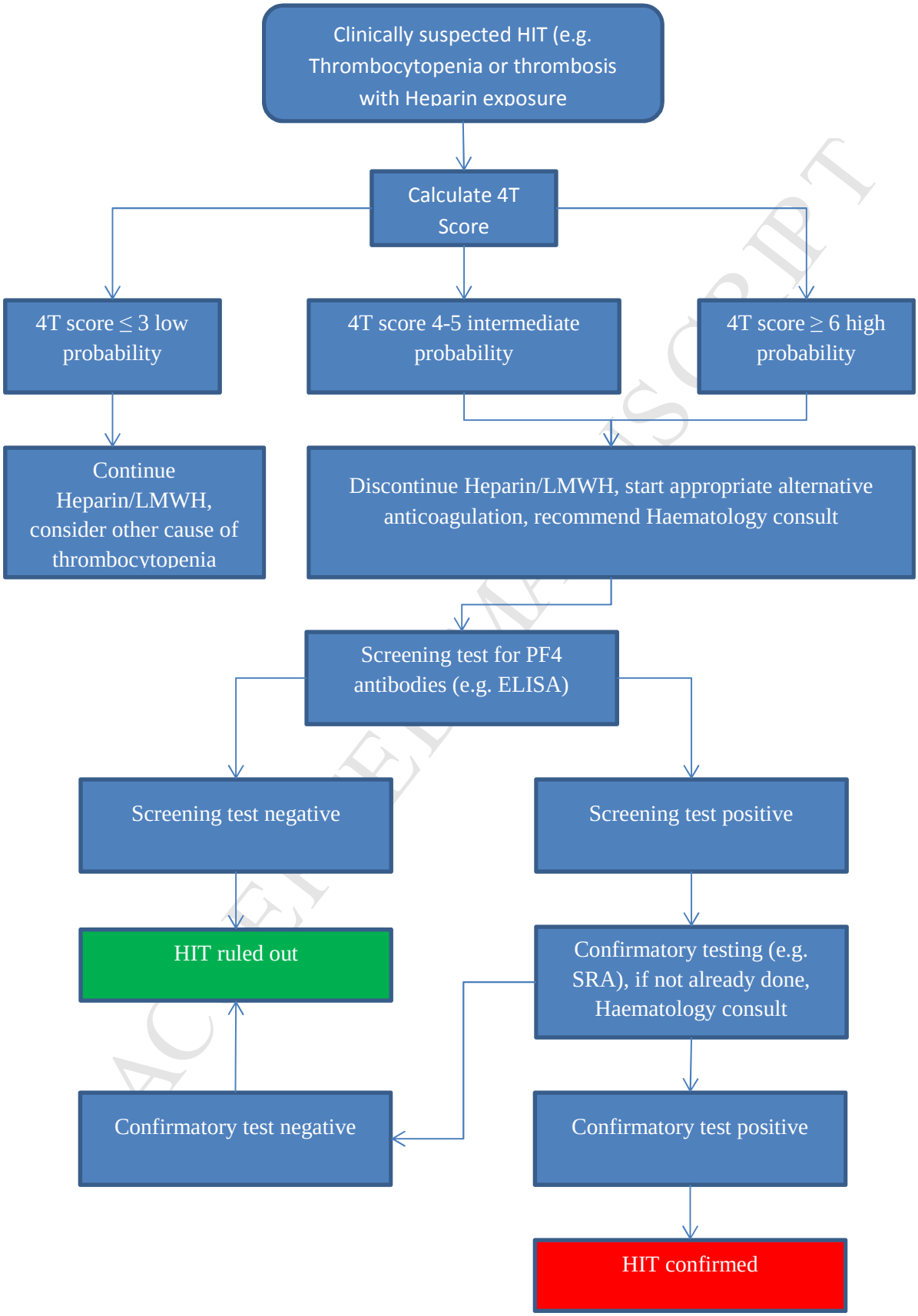
PT – Prothrombin time, APTT – activated partial thromboplastin time

Table 4: Complications of HIT (HIT and HIT treatment related mortality, thrombosis and bleeding

Author	Year	Drug	Patients	Mortality	HIT related mortality	Thrombosis	Amputation	Any Bleed	Major Bleed	Minor Bleed
Joseph[42]	2014	Bivalirudin	124* 262**	9.7% 17.2%	0.8%	70% 52%	0 0	5.6% 11%	4.8% 8.4%	-
Tardy-Poncet[43]	2015	Argatroban	20	25%	0	68.8%	-	-	18.8%	-
Vo[94]	2015	Argatroban Bivalirudin	48 20	19% 25%	- -	8% 15%	0 0	31% 30%	15% 25%	19.00% 5.00%
Kiser[78]	2006	Bivalirudin	18	22%	-	22%	-	-0	-	-

- * Confirmed HIT = presence of a positive immunogenic assay and a patient with suspect HIT.
- ** Suspected HIT= required only a clinical suspicion in the absence of confirmatory testing.
- Major bleeding in studies was defined variably and usually represented a reduction in hemoglobin requiring transfusion or bleeding into a critical site or death.

Figure 1


Clinically suspected HIT (e.g. Thrombocytopenia or thrombosis with Heparin exposure
Calculate 4T Score
4T score ≤ 3 low probability
4T score 4-5 intermediate probability
4T score ≥ 6 high probability
Continue Heparin/LMWH, consider other cause of thrombocytopenia
Discontinue Heparin/LMWH, start appropriate alternative anticoagulation, recommend Haematology consult
Screening test for PF4 antibodies (e.g. ELISA)
Screening test negative
Screening test positive
HIT ruled out
Confirmatory testing (e.g. SRA), if not already done, Haematology consult
Confirmatory test negative
Confirmatory test positive
HIT confirmed