

Heparin induced thrombocytopenia in critically ill: Diagnostic dilemmas and management conundrums

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Abstract

Thrombocytopenia is often noted in critically ill patients. While there are many reasons for thrombocytopenia, the use of heparin and its derivatives is increasingly noted to be associated with thrombocytopenia. Heparin induced thrombocytopenia syndrome (HITS) is a distinct entity that is characterised by the occurrence of thrombocytopenia in conjunction with thrombotic manifestations after exposure to unfractionated heparin or low molecular weight heparin. HITS is an immunologic disorder mediated by antibodies to heparin-platelet factor 4 (PF4) complex. HITS is an uncommon cause of thrombocytopenia. Reported incidence of HITS in patients exposed to heparin varies from 0.2% to up to 5%. HITS is rare in ICU populations, with estimates varying from 0.39%-0.48%. It is a complex problem which may cause diagnostic dilemmas and management conundrum. The diagnosis of HITS centers around detection of antibodies against PF4-heparin complexes. Immunoassays performed by most pathology laboratories detect the presence of antibodies, but do not reveal whether the antibodies are pathological. Platelet activation assays demonstrate the presence of clinically relevant antibodies, but only a minority of laboratories conduct them. Several anticoagulants are used in management of HITS. In this review we discuss the incidence, pathogenesis, diagnosis and management of HITS.

Key words: Heparin; Thrombocytopenia; Critically ill; Diagnosis; Management

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Core tip: Thrombocytopenia is common in critically ill patients. While there are several causes of thrombocytopenia, heparin induced thrombocytopenia syndrome (HITS) is an uncommon cause often difficult to diagnose and manage. This article summarises the current diagnostic techniques and management options with a focus on critically ill patients with HITS.

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INTRODUCTION

It has been over 90 years since the discovery of heparin^[1], and by the 1930s heparin was being used clinically as an anticoagulant^[2]. Embolic events during heparin therapy were first described in 1957 and were followed by subsequent reports; however thrombocytopenia as a result of heparin therapy was not described until 1969^[3-6]. The central features of heparin induced thrombocytopenia (HIT) syndrome (HITS) - thrombocytopenia, thrombosis and its immune pathogenesis - weren't recognized until the early 1970s^[7].

Heparin and its derivatives are used frequently in the critically ill, either as thromboprophylaxis or for anticoagulation in patients with thromboembolic diseases. Thrombocytopenia occurs in 15%-58% of ICU patients^[8,9]. Critically ill patients might suffer from a variety of acquired thrombotic risk factors related both to a host of chronic conditions such as obesity, hypertension, and diabetes mellitus, as well as acutely acquired conditions such as the postoperative state, sepsis, trauma, malignancy, other clonal disorders, etc.^[10]. Hence, diagnosis of HIT syndrome is one of exclusion in the critically ill.

As HIT syndrome is a highly prothrombotic state, affected patients require ongoing anticoagulation with alternative anticoagulation such as the use of antithrombin anticoagulants or anti factor Xa agents^[11,12].

As none of these agents have effective antidotes, management of bleeding associated with these agents is fraught with uncertainty.

HITS has been classified into two subtypes: HITS type 1: Benign non-immune condition occurring in 30%-40% patients exposed to heparin. platelets counts rarely fall below 100000/mcl. Heparin can be safely continued in this scenario and this condition is not discussed any further in the review; HITS type 2: Life threatening condition caused by antibodies against complexes of platelet factor 4 (PF4) and heparin, though occasionally other antigens may be implicated. Further discussion will relate to "type 2 HITS" only.

In this review, we focus on diagnostic dilemmas and management challenges associated with this complex problem.

PATHOGENESIS

Heparin mediated thrombocytopenia is an immunologic disorder mediated by antibodies to heparin-PF4 complex^[13-16]. The Fab fragments from the IgG subclass of antibodies to PF4 bind platelet associated PF4. The Fc fragments of these antibodies bind to FcγIIa receptors on the same or adjacent platelets, resulting in cross linking causing platelet activation. This results in generation of platelet microparticles that have procoagulant activity. This prothrombotic phenomenon is the principal difference between thrombocytopenia induced by heparin and other drugs such as quinine^[17]. This marked release of the platelet microparticles is associated with massive thrombin generation, which explains the increased risk of thrombosis associated with HITS^[18]. Significantly fewer platelet microparticles are generated in the presence of very high amounts of Heparin or in its absence, suggesting a stoichiometric relationship between HIT-IgG antibodies and heparin^[17]. In addition to the increased thrombin generation in HITS, HITS antibodies also bind to endothelium-bound heparin resulting in release of tissue factor (TF) contributing to the overall prothrombotic state^[19]. Recently, Monocytes have been found to bind hPF4 onto their surface and form antigenic complexes leading to monocyte activation and ultimately culminating in expression of TF. Both monocyte and endothelial activation may explain recurrence of thrombosis in many patients treated with direct thrombin inhibitors as none of them target these cells^[20]. This may also explain the fact that HITS predisposes to both arterial and venous thrombosis even though it is primarily a platelet activation disorder. HIT-IgG antibodies also inhibit the generation of activated protein C by thrombin/thrombomodulin in the presence of PF4, augmenting the thrombotic state^[21].

It seems that there might be a crucial period of exposure to heparin in patients who develop HITS. Patients, who suffer from conditions associated with high amounts of PF4 release prior to exposure to heparin, tend to be at a higher risk of developing HITS. For example, amongst elective hip replacement patients who receive preoperative low-molecular weight heparin (LMWH) are at a lower risk of HITS as compared to patients who receive post-operative thromboprophylaxis. This phenomenon of "point immunization" is probably explained by the fact that stoichiometrically optimal concentrations of heparin-PF4 are most likely to occur when PF4 is released prior to exposure to heparin^[22]. Free nucleic acids in plasma can induce similar conformational changes in PF-4 as are induced by heparin, mainly because of the highly anionic Phosphate entities on the nucleic acid molecules. This finding may further explain the propensity for certain subgroups of patients (such as those with major

tissue damage) to develop pathological antibodies to heparin-PF4 complexes^[23].

Two key determinants of antigenicity of a heparin preparation are chain length (approximately 1000 Da) and minimal amount of sulfation per saccharide unit. This explains lower risk of HITS with LMWH preparations as compared to unfractionated heparin (UFH)^[24].

Occasionally, HITS can be caused by antibodies to other antigens such as neutrophil activating peptide-2 or interleukin 8.

EPIDEMIOLOGY

Reported incidence of HITS in patients exposed to heparin varies from 0.2% to up to 5%^[25]. HITS is rare in ICU populations, with estimates varying from 0.39%-0.48%^[26]. The incidence of HITS varies widely depending on the preparation of heparin, sex of the patients, and clinical population. The risk of HITS is higher amongst women [Odds ratio (OR) = 2.37]; among surgical patients as compared with medical patients (OR = 3.25); and patients on UFH vs patients receiving LMWH (OR = 5.29)^[27]. Amongst surgical patients, although post-cardiac surgery patients tend to have a higher risk of developing HIT-IgG than post-orthopaedic surgical group (20% vs 3.2%), patients are much more likely to develop HITS after Orthopaedic surgery (OR = 21.1)^[28]. Patients with major trauma are more likely to be Heparin-PF4 antibody positive and develop HITS as compared to patients with minor trauma^[29]. HITS is very rare in obstetric or pediatric patients.

CLINICAL FEATURES

Heparin induced thrombocytopenia is characterized by thrombocytopenia and thrombotic manifestations after exposure to unfractionated heparin or low molecular weight heparin.

Thrombocytopenia

Onset of thrombocytopenia is usually between 5-10 d after the exposure, but it is faster (within a few hours to a day) if the patient has been exposed to heparin within 100 d of current exposure^[30].

Platelet count usually drops to 50% or less of the baseline platelet count. Drop in platelet counts 30%-50% of baseline occurs in 10% of the cases^[25].

Platelet counts usually do not fall below 20000/mcl. Lower platelet counts may be observed if HITS causes disseminated intravascular coagulation (DIC).

Bleeding is very rare as a complication of thrombocytopenia.

Recovery typically takes 4-14 d after cessation of heparin.

Pattern of thrombocytopenia occurring after the inciting event (such as cardiothoracic surgery) is important as well. A continuous decline after cardiopulmonary bypass is less likely to be due to HITS. A fall

in platelet count of at least 40% between 5-10 d post cardiopulmonary bypass is likely to be due to HITS^[31].

Thrombotic manifestations

Thrombotic manifestations develop in 20%-50% of the patients. HITS that is not associated with thrombotic phenomena is known as "isolated HITS".

Thrombosis can affect both arterial and venous beds. However, Venous thromboembolic complications are twice as likely as compared to arterial thrombotic phenomena. About 10%-20% patients suffer DIC.

Risk of thrombosis is higher for days to weeks after heparin is discontinued, even after normalization of the platelet counts^[11].

Risk of thrombosis is higher in patients with higher level of antibodies to PF4-heparin complexes^[32].

Other clinical manifestations that should raise the suspicion of HITS in appropriate clinical scenario: (1) acute anaphylactoid/anaphylactic reactions after heparin administration: Heparin induced anaphylactoid and anaphylactic reactions are two distinct pathophysiological entities. Heparin induced anaphylactoid reactions are due to activation of platelets and leukocytes in patients harbouring anti heparin-PF4 antibodies, typically administered a heparin bolus after prior exposure to heparin. Heparin induced anaphylactic reaction is due to a contaminant (oversulphated chondroitin sulphate or OSCS) activating the contact system resulting in the clinical manifestations. However, patients exposed to OSCS contaminated heparin are more likely to develop pathological HITS antibodies^[33]; (2) heparin induced skin lesions: These painful or pruritic necrotic lesions develop at the site of injection, beginning on day 5 or later after exposure to heparin or LMWH. Non-necrotic lesions at the injection sites are almost always due to delayed hypersensitivity to heparin rather than a manifestation of HITS, especially after exposure to LMWH rather than Unfractionated heparin^[34]; (3) heparin induced skin necrosis and venous gangrene: especially in the presence of coumarin, attributed to both macro and micro vascular thrombosis with preserved arterial flow. Inhibition of activated protein C by heparin PF4 antibodies could be a strong contributory factor^[21]; and (4) transient global amnesia^[35].

These manifestations curiously, tend to occur in the absence of thrombocytopenia^[25].

DIAGNOSIS

The diagnosis of HITS centers around detection of antibodies against PF4-Heparin complexes. Immunoassays performed by most pathology laboratories detect the presence of antibodies, but do not reveal whether the antibodies are pathological. Platelet activation assays demonstrate the presence of clinically relevant antibodies, but only a minority of laboratories conduct them. Before elaborating further on the diagnostic assays, it is vital to consider the following

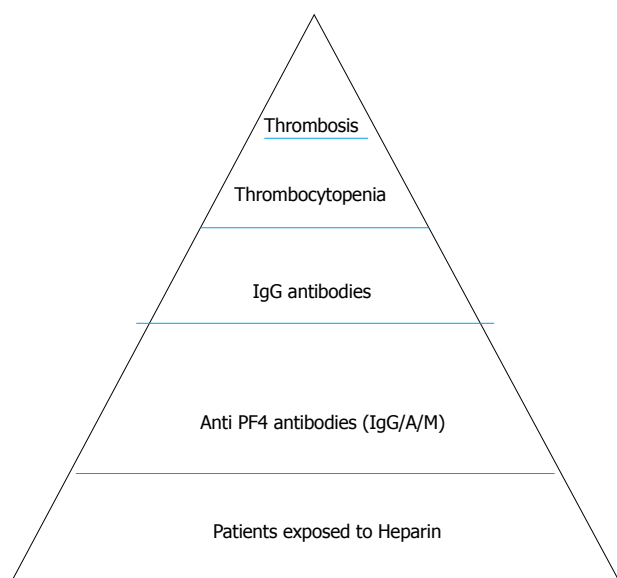


Figure 1 Iceberg model for heparin induced thrombocytopenia syndrome as proposed by Warkentin *et al.*^[37]. The size of various iceberg sections and the portion seen, can vary in proportion to the other sections depending on the population of patients, preparation of heparin used, *etc.*

facts: (1) heparin-PF4 antibodies can exist naturally in people unexposed to heparin in the past^[36]; (2) only IgG subclass of antibodies are pathological. Hence assays which are not IgG specific are likely to yield a higher false positive result; (3) out of the patients who are anti heparin/PF4IgG positive, only a minority will be positive by the "Gold Standard" platelet activation assays; (4) not all patients with platelet activating antibodies develop the clinical syndrome of HITS; and (5) fraction of the patients with heparin/PF4 antibody depends on the patient population and the type of heparin preparation used.

The above phenomena observed have been conceptualized as an "iceberg model" by Warkentin *et al.*^[37], and highlight the fact that HITS is a clinicopathological syndrome rather than just a laboratory diagnosis (Figure 1).

The diagnosis of HITS centers around the pretest probability of HITS being the cause of the drop in platelet count and/or the thrombotic phenomenon observed. In light of this the "4-T's" scoring system was introduced (Table 1)^[38]. Low pretest probability score ruled out HITS in all but one of the 119 patients studied.

Patients with intermediate or high pre-test probability of HITS should be investigated further with enzyme linked immunosorbent assay (ELISA) based methods^[12].

These assays use heparin-PF4 or polyvinyl sulfate-PF4 immobilised onto microtiter plates as antigens. Antibodies in the patient's plasma bind to these antigens and is detected using goat anti human IgG/A/M bound to alkaline phosphatase. Substrate, subsequently added, changes colour in presence of the enzyme. The intensity of the colour change is measured as optical density (OD)

and is directly proportional to the concentration of the antibodies^[39]. Even though these tests are very sensitive (negative predictive values of close to 100%), they tend to yield a high number of false positive results for HITS, depending on the manufacturer of the assay kit and the clinical population. Higher rates of false positive ELISAs are noted in patients post cardiac surgery and those with antiphospholipid antibody (APLA) syndrome. Anti PF4 antibodies rather than anti PF4/heparin antibodies are responsible for false positive ELISA in sera with APLA syndrome^[40].

Following measures may be taken to increase the specificity of ELISA based assays (Table 2): (1) using IgG specific assays: As IgG antibodies are pathogenic, using specific assays targeting IgG antibodies rather than non-specific assays improves the specificity of the test without sacrificing the sensitivity of the assay; (2) using higher OD cut offs: As higher titers of antibodies are associated with a greater probability of HITS, using higher cutoff values (for example 1.0 instead of 0.4) might increase the specificity of the assay. However, this comes at cost of sacrificing sensitivity of the assay; and (3) confirmatory step using high concentration of heparin: As heparin and anti heparin-PF4 antibodies have a stoichiometric relationship, re-performing the ELISA test with higher concentrations of heparin may confirm the presence of anti heparin-PF4 antibodies. However, this approach requires the test to be performed twice, increasing the cost and the turn around time. It can also be falsely negative if the titre of the antibodies is very high.

Diagnosis of HITS should be confirmed with functional platelet assays in patients with intermediate pretest probability and positive ELISA or in patients with high pretest probability with negative ELISA (Figure 2).

Selection of platelet donors can be potentially critical for these assays as certain polymorphisms on the Fc γ RIIa receptors affects the response of platelets to the activating monoclonal antibodies^[41].

Serotonin release assay (SRA) is the gold standard test for diagnosis of HITS. It utilizes washed donor platelets incubated with ¹⁴C-labelled serotonin. It is considered positive when more than 20% serotonin is released at therapeutic heparin concentrations (0.1-0.3 IU/mL), but not at supra-therapeutic heparin levels (10-100 IU/mL)^[42]. In Australia, out of 675 SRAs requested to the only centre performing this assay between 2010-2012, around 19% were positive for HITS. Interestingly, amongst cases in which 4T score was available, almost 96% had intermediate or high probability 4T score^[43].

Whole blood impedance aggregometry (WBIA) is emerging as a useful alternative to SRA with faster turnaround time (around 15 min), does not use washed platelets and no radioactive waste products. The laboratories running this assay still need access to high reactive platelet donors as using less responsive platelet donors might result in false negative WBIA. The agreement of WBIA with SRA improves if a higher cut

Table 1 4T score as studied by Lo *et al*^[38]

Points (0, 1, or 2 for each of 4 categories: maximum possible score = 8)			
	2	1	0
Thrombocytopenia	> 50% fall or platelet nadir $\geq 20 \times 10^9/L$	30%-50% fall or platelet count $10-19 \times 10^9/L$	Fall < 30% or platelet nadir $< 10 \times 10^9/L$
Timing of fall in platelet count	Clear onset between day 5-10 ¹ ; or less than 1 d (if history of heparin exposure within 30 d)	Consistent with d 5-10 fall, but not clear (<i>e.g.</i> , missing platelet counts) or onset of thrombocytopenia after d10 or fall ≤ 1 d (prior heparin exposure 30-100 d ago)	Platelet count fall < 4 d without recent heparin exposure
Thrombosis or other sequelae (<i>e.g.</i> , Skin lesions)	New thrombosis; skin necrosis; acute systemic reaction post unfractionated heparin bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
Other cause of thrombocytopenia	None apparent	Possible other cause is evident	Definite

4T score: 6-8 = High; 4-5 = Intermediate; 0-3 = Low

¹5-10 d after exposure to heparin or low molecular weight heparin.

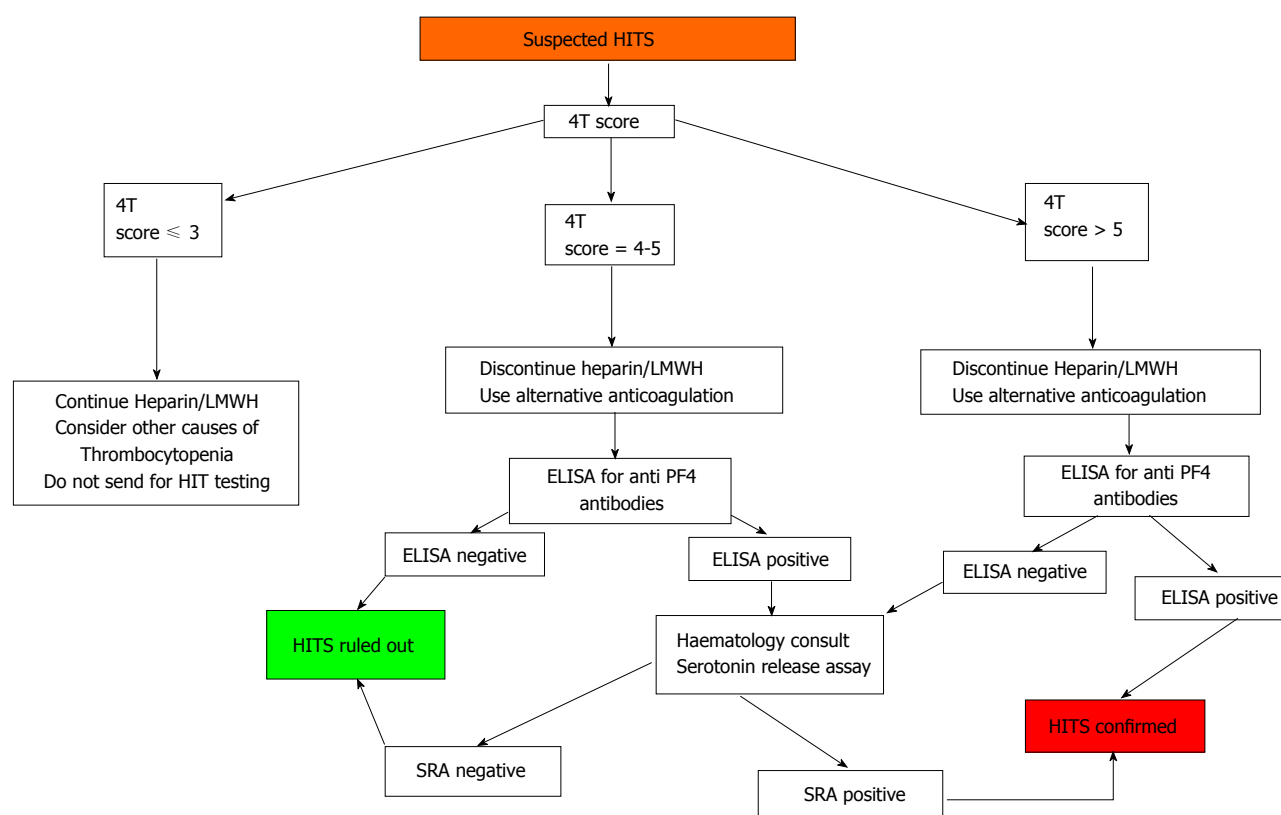


Figure 2 Diagnostic algorithm for Heparin induced thrombocytopenia syndrome. Note that Confirmatory assays for HITS should be considered on the basis of pre test probability rather than ELISA alone. HITS: Heparin induced thrombocytopenia syndrome; SRA : Serotonin release assay. ELISA : Enzyme linked immunosorbent assay.

off of 50% instead of 20%, and if a high dose heparin confirmatory step is used^[44].

TREATMENT

Once a presumptive diagnosis of HITS is made on the basis of pretest probability and anti PF4 antibody assays, therapeutic dosing of alternative anticoagulant is needed along with cessation of the offending agent. Patients are hypercoagulable for days to even weeks despite normalization of platelet counts^[11]. Hence, patients may need to be transitioned to oral anticoagulants once

platelet counts have normalized.

Ideal anticoagulant for treatment of HITS should have following characteristics: (1) should have no risk of generating HITS antibodies; (2) should have robust evidence supporting its use in HITS; (3) should be able to provide predictable anticoagulation and be able to be monitored by an widely available assay; (4) should have short half life; (5) should be easily reversible by an antidote which is readily available; (6) should have a low risk of bleeding and other adverse effects; (7) metabolism and elimination should be reliable and independent of renal or hepatic dysfunction; (8)

Table 2 Characteristics of various assays for heparin induced thrombocytopenia syndrome

	4T score ≤ 3 ^[73-76]	ELISA ^[77]	IgG specific ELISA ^[77]	OD cut off ≥ 1.0 ^[78]	Heparin confirmation step for IgG specific ELISA ^[79]	Serotonin release assay ^[80]	Whole blood impedance Aggregometry ^[44]
Sensitivity	-	100%	100%	80%	94%	100%	90.3%-93.6%
Specificity	-	81%	89%	85%	90%-93%	95%-97%	89%-96%
PPV	-	28%	40%	42%	45%	NA	84.4%-94.8%
NPV	100%	100%	100%	84%	99.50%	NA	-

PPV: Positive predictive value; NPV: Negative predictive value; NA: Not applicable as serotonin release assay is the gold standard assay for diagnosis of heparin induced thrombocytopenia syndrome.

Table 3 Characteristics of alternative anticoagulants

Drug	Route of elimination	Plasma half life	Monitoring	Interaction of antibodies with HITS antibodies	Antidote
Lepirudin	Renal	60 min, up to 200 h in anuric patients ^[81,82]	aPTT (1.5-2 times baseline) ACT on CPB ECT (Not affected by presence of VKAs or UFH)	None	None ?Haemofiltration ^[47]
Desirudin	Renal	2-3 h	None	None	None
Danaparoid	Renal	24 h	Anti-Xa activity (0.5-0.8 U/mL)	Possible, but very rare	None
Argatroban	Hepatic	40-50 min	aPTT (1.5-3 times baseline) ACT on CPB	None	None
Bivalirudin	Enzymatic 80% (Thrombin), renal 20%	25 min	aPTT (1.5-2.5 times baseline) ACT on CPB	None	None ?Haemofiltration ^[52]
Fondaparinux	Renal	17-20 h	None, Anti Xa levels with renal impairment	Case reports only ^[45,61,62]	None

aPTT: Activated partial thromboplastin time; ACT: Activated clotting time; ECT: Ecarin clotting time; CPB: Cardiopulmonary bypass; HITS: Heparin induced thrombocytopenia syndrome; UFH: Unfractionated heparin.

should be safe to use in special subgroup of patients such as those who are pregnant or need to go on to cardiopulmonary bypass; and (9) should be easily available in both oral and intravenous preparations for easy transition between short and longer term anticoagulation.

Unfortunately, such an anticoagulant doesn't exist. Most of the problems from anticoagulation in HITS arise because of the lack of familiarity with non-heparin anticoagulants.

Following are the different categories of anticoagulants which can be used for HITS, based on the clinical scenario (Tables 3 and 4): (1) direct thrombin Inhibitors: Univalent direct thrombin inhibitors (argatroban; dabigatran), bivalent direct thrombin inhibitors [recombinant hirudins (lepirudin, desirudin); synthetic hirudin (bivalirudin)]; and (2) factor Xa antagonists: danaparoid, fondaparinux, rivaroxaban, apixaban.

DIRECT THROMBIN INHIBITORS

Lepirudin

A recombinant hirudin derived from yeast cells, Lepirudin was the first drug approved by United States Food and Drug Administration, for the treatment of HITS in 1998. Even though it reduced new thromboembolic manifestations, it increased the risk of major bleeding

in a combined analysis of 3 prospective trials with historical controls^[45].

Retreatment with lepirudin can increase the risk of anaphylaxis almost half the patients will develop antibodies to lepirudin on initial use. The risk of antibody formation can be reduced by avoiding the bolus and reducing the duration of infusion as much as possible^[46].

Although no antidote is available, use of activated Factor VII to control bleeding and haemofiltration has been described^[47,48].

Argatroban

Argatroban is a synthetic L-arginine derivative, which is tolerated well by patients with moderate renal dysfunction^[49].

Even though the half life is short and use in mild to moderate renal dysfunction is safe, rebound hypercoagulability after cessation of infusion, and spurious prolongation of Prothrombin time when given with warfarin are significant issues, especially when transitioning to longer term oral anticoagulation.

A severity of illness based dosing regime for continuous renal replacement therapy in critically ill is available but not validated^[50].

Bivalirudin

Bivalirudin is a hirudin based synthetic direct thrombin

Table 4 Dosage and availability of anticoagulation agents for heparin induced thrombocytopenia syndrome

Drug	Bolus	Dosage	Dosage in renal impairment	Dosage in hepatic impairment	Availability in Australia
Lepirudin	Only if life or limb threatening thrombosis. 0.4 mg/kg <i>iv</i>	0.1-0.15 mg/kg per hour	Cr. Cl. 45-60: 50% of original infusion rate. Cr. Cl. 30-44: 30% of original infusion rate. Cr. Cl. 15-29: 15% of original infusion rate according to body weight. Avoid if Cr. Cl. Lower or use 0.005 mg/kg per hour if on haemofiltration	No change	Discontinued
Desirudin	None	15-30 mg <i>sc bd</i> . Limited data	Not recommended given paucity of data	No change	Not available
Danaparoid	IV according to body weight. < 60 kg: 1500 U; 60-75 kg: 2250 U; 75-90 kg: 3000 U; > 90 kg: 3750 U	400 U/h IV × 4 h followed by 300 U/h IV × 4 h followed by 200 U/h <i>iv</i>	Reduce dose by 30% and monitor antiXa activity	No change	Available
Bivalirudin	None	0.15-0.2 mg/kg per minute	Cr. Cl 10-29: 0.06 mg/kg per minute; Cr. Cl < 10: 0.015 mg/kg per minute <i>iv</i>	No change	Available
Fondaparinux	None	< 50 kg: 5 mg <i>sc</i> ; 50-100 kg: 7.5 mg <i>sc</i> ; > 100 kg: 10 mg <i>sc</i>	Cr. Cl 30-50: monitor closely. Cr. Cl < 30: Contraindicated	No change	Available
Argatroban	None	2 mcg/kg per minute <i>iv</i>	No change	0.5 mcg/kg per minute	Not available

Cr. Cl.: Creatinine clearance in mL/min; *sc*: Subcutaneous; *iv*: Intravenous.

inhibitor, which binds to free as well as bound thrombin reversibly. It has the shortest half-life amongst the direct thrombin inhibitors and has higher reversibility as up to 80% is eliminated by enzymatic proteolysis^[51]. Due to better pharmacokinetic profile, this is the agent used most widely in patients needing cardiopulmonary bypass. hemodialysis, haemofiltration or plasmapheresis may be used to reverse its effect, even though the data available for efficacy of these therapies is limited^[52].

Desirudin

Desirudin is a recombinant hirudin and is a bivalent, irreversible direct thrombin inhibitor. There is very limited data about use of Desirudin for HITS. An open label randomized pilot trial comparing Desirudin with Argatroban for HITS (PREVENT-HIT) was closed because of poor accrual^[53,54].

FACTOR XA INHIBITORS

Fondaparinux

Fondaparinux is a sulfated pentasaccharide derivative of heparin which binds to antithrombin, inhibiting factor X^[55]. Even though the frequency of heparin - PF4 antibody is similar to Low molecular weight heparins, Fondaparinux induced antibodies are seldom pathogenic^[56,57].

The risk of bleeding while treating HITS is around 5%. Even though some cases of HITS caused by Fondaparinux have been described in literature, benefits such as ease of administration, predictable pharmacokinetics in patients with normal renal function and lack of effect on aPTT makes it an attractive option in patients in whom benefits outweigh low risk of exacerbation of HITS^[45,58-62].

Danaparoid

Danaparoid, a mixture of low molecular sulphated glycosaminoglycans, Heparan, dermatan and chondroitin sulphate is a factor Xa inhibitor. The requirement for monitoring anti Xa levels in most of the critically ill patients developing HITS and risk of cross reaction with heparin-PF4 antibody (< 10% patients) are the factors which need to be considered before using Danaparoid for HITS^[63].

TRANSITION TO ORAL VITAMIN K ANTAGONISTS

For isolated HITS, alternative anticoagulation with or without transition to oral vitamin K antagonists is recommended for up to 4-6 wk. For HITS associated with thrombosis, switching to warfarin followed by continuation of warfarin therapy for 3 mo is recommended.

Transition to warfarin should only be made once platelet count is > 150000/mcl. Warfarin needs to be overlapped with alternative anticoagulation for at least 5 d and until the INR is in the therapeutic range.

Fondaparinux or Danaparoid may be required for transition of Argatroban to oral vitamin K antagonists due to effect of Argatroban on INR.

SPECIAL PATIENT POPULATIONS

Pregnancy

HITS is extremely rare during pregnancy and all the data regarding diagnosis and management is anecdotal. Thrombocytopenia occurs in 7%-8% pregnancies. Most common reason for thrombocytopenia is gestational (haemodilution, increased platelet aggregation due to

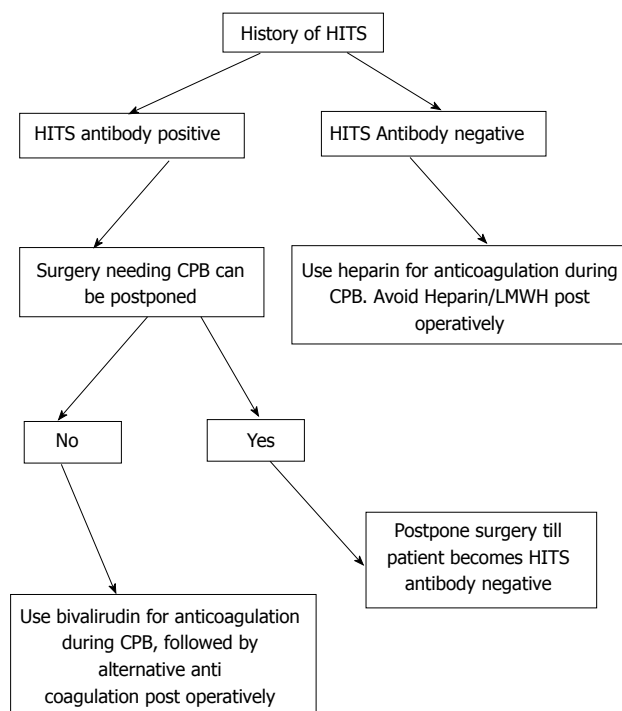


Figure 3 Suggested approach for patients with heparin induced thrombocytopenia syndrome needing cardiopulmonary bypass. HITS: Heparin induced thrombocytopenia syndrome; CPB: Cardiopulmonary bypass.

raised thromboxane A_2 , increased platelet consumption) followed by other causes such as HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, Preeclampsia/eclampsia, acute fatty liver disease of pregnancy, Idiopathic thrombocytopenic purpura, etc.^[64].

In a review of 2777 pregnancies involving exposure to LMWH, none of the patients developed thrombocytopenia attributable to HITS^[65].

Ease of administration, safety in longer term use, and transplacental transfer are special considerations in this group of patients. Despite case reports of the use of argatroban, fondaparinux and danaparoid are preferred because of their subcutaneous administration and availability of large data on longer term use during pregnancy^[66-68].

Cardiopulmonary bypass

Patients with history of HITS that require cardiopulmonary bypass can be managed based on their HITS antibody status (Figure 3).

Bivalirudin is the alternative anticoagulant most well described in literature, however lepirudin and argatroban have also been described^[69-72].

We recommend Bivalirudin for anticoagulation while on cardiopulmonary bypass, as it has been compared directly with heparin in an open label randomized control trial with heparin and protamine reversal. As Bivalirudin is metabolized by thrombin in the blood, care must be taken to avoid any stasis in the venous circuit, surgical field, and the vein grafts. Citrate phosphate

dextrose acetate is used for anticoagulation in the cell saver.

CONCLUSION

The diagnosis of HITS in critically ill patients requires early recognition for successful management. Exclusion of other causes for thrombocytopenia and or thrombosis with special consideration to the temporal relationship of onset of thrombocytopenia with exposure to UFH/LMWH is vital. Use of clinical pretest probability scores such as 4T score in conjunction with more specific assays such as anti-IgG heparin PF4 antibody may reduce over-diagnosis of the disease. Confirmatory tests such as the SRA should be considered for equivocal cases; new tests such as WBIA based assay show promise. Attention to risk of bleeding with invasive interventions, presence and degree of renal/hepatic dysfunction, and availability and cost of alternative anticoagulation agents is important. Finally, patients requiring cardiopulmonary bypass and pregnant patients present rare and challenging scenarios.

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