Diagnosis and management of heparin-induced thrombocytopenia: a consensus statement from the Thrombosis and Haemostasis Society of Australia and New Zealand HIT Writing Group

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Abstract

Introduction: Heparin-induced thrombocytopenia (HIT) is a prothrombotic disorder that occurs following the administration of heparin and is caused by antibodies to platelet factor 4 and heparin. Diagnosis of HIT is essential to guide treatment strategies using non-heparin anticoagulants and to avoid unwanted and potential fatal thromboembolic complications. This consensus statement, formulated by members of the Thrombosis and Haemostasis Society of Australia and New Zealand, provides an update on HIT pathogenesis and guidance on the diagnosis and management of patients with suspected or confirmed HIT.

Main recommendations:

- A 4Ts score is recommended for all patients with suspected HIT prior to laboratory testing.
- Further laboratory testing with a screening immunoassay or confirmatory functional assay is not recommended in individuals with a low 4Ts score. However, if there are missing or unreliable clinical data, then laboratory testing should be performed.
- A positive functional assay result confirms the diagnosis of HIT and should be performed to confirm a positive immunoassay result.
- Heparin exposure must be ceased in patients with suspected or confirmed HIT and initial treatment with a non-heparin alternative instituted.
- Non-heparin anticoagulants (danaparoid, argatroban, fondaparinux and bivalirudin) used to treat HIT should be given in therapeutic rather than prophylactic doses.
- Direct oral anticoagulants may be used in place of warfarin after patients with HIT have responded to alternative parenteral anticoagulants with platelet count recovery.

Changes in management as a result of this statement:

- These are the first Australasian recommendations for diagnosis and management of HIT, with a focus on locally available diagnostic assays and therapeutic options.
- The importance of examining both clinical and laboratory data in considering a diagnosis of HIT cannot be overstated.

Heparin-induced thrombocytopenia (HIT) is a prothrombotic adverse reaction to heparin characterised by platelet-activating antibodies (almost exclusively IgG) that recognise and bind to platelet factor 4 (PF4)–heparin complexes. While antibody formation is common (up to 50% in the setting of cardiac surgery), only a small proportion of patients (0.2–3.0%) develop HIT (ie, thrombocytopenia and/or thrombosis).[1] Thrombosis can be arterial, venous or microvascular. Incidence of HIT varies depending on clinical setting (higher in surgical than medical, rarely in paediatric or obstetric), type of heparin (unfractionated heparin has higher rates than low molecular weight heparin), and dose (therapeutic *v* prophylactic).[2]

PF4 tetramers (cationic) and heparin (anionic) associate by charge and hence certain molar concentrations (1:1 molar ratio) facilitate charge neutralisation, conformational change in PF4-exposing pathogenic epitopes, antibody binding and PF4–heparin–IgG complex formation.[3] PF4 can also bind to other polyanions, including glycosaminoglycans and chondroitin sulfate, and such interactions may play a role in the increasingly reported entity known as spontaneous HIT syndrome; that is, patients with clinical and laboratory features of HIT without exposure to heparin.

Thrombocytopenia and thrombosis in HIT result from the binding of PF4–heparin–IgG complex to FcγRIIa receptors on the platelet surface. Subsequent cross-linking of the receptors leads to intense platelet activation, release of platelet granule content and procoagulant microparticles, thrombin generation, and activation of endothelial cells, neutrophils and monocytes.[4]

HIT is a clinicopathological entity and therefore requires integration of clinical and laboratory results. Accurate diagnosis is important and consultation with an appropriate specialist is recommended as delay in diagnosis and appropriate anticoagulant treatment is associated with an initial 6% daily risk of thromboembolism as well as amputation and death.[5]

Methods

Australian and New Zealand experts in the field of thrombosis and haemostasis who regularly diagnose and treat HIT syndrome were invited to a consensus statement development panel. This group, the Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ) HIT Writing Group, represents THANZ members and received formal endorsement from the THANZ President. A comprehensive literature review, using common online databases, was undertaken for each subsection by at least two authors. Major computerised databases such as Cochrane, MEDLINE and EMBASE were utilised. These searches were further supplemented with review of reference lists and professional society information available from internet sources. A draft for each subsection, collated by its two authors after extensive literature review, was submitted to the lead author (JJ). Following this comprehensive review of the literature, a face-to-face meeting was held over 2 days to discuss specific questions and finalise a draft of the consensus statement. During the meeting, each subsection was presented for further

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1 Grades and strengths of recommendations and quality of supporting evidence[6,7]

Grade and strength of recommendation*		Quality of supporting evidence	
1	Strong	A	High: further research is very unlikely to change our confidence in the estimate of effect
		B	Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
		C	Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
2	Weak	A	High
		B	Moderate
		C	Low
Good practice point			Supporting evidence insufficient to meet even the lowest grade of evidence; recommendation therefore based on consensus opinion of the writing panel

* Strength of recommendation reflects the extent to which investigators can be confident that desirable effects of an intervention outweigh undesirable effects. ◆

review by all authors. Further revisions were made by consensus in that meeting as well as subsequently by email. Each subsection was individually discussed to provide pertinent recommendations. The GRADE method (Grading of Recommendations Assessment, Development and Evaluation) was used to generate these recommendations (Box 1).[6,7] All members of the panel contributed equally and recommendations represent consensus between members following reviews of the evidence. The consensus statement only applies to adults.

Diagnosis

Clinical scoring and prediction tools

Clinical probability scores aim to determine the pre-test probability that a patient's thrombocytopenia is due to the presence of pathogenic platelet-activating HIT antibodies. Thrombocytopenia and non-pathogenic HIT antibodies are common in hospitalised patients; clinical scores can guide therapy while tests are awaited, and they also assist in decision making once laboratory tests are available. The most widely used HIT clinical probability score is the 4Ts score[8] (Box 2). A low probability score (≤ 3) is associated with a high negative predictive value for HIT (0.998; 95% CI, 0.970–1.000). The positive predictive value of combined high and intermediate probability scores is only 0.22 (0.15–0.31).[9]

Other clinical scoring systems include the HIT expert probability score,[10] and those proposed by Messmore and colleagues[11] and, in the setting of thrombocytopenia following cardiopulmonary bypass surgery, Lillo-Le Louët and colleagues.[12] Although promising, the latter scoring systems require further validation in larger cohorts before recommendations regarding their use can be made.

The accuracy of any clinical scoring system is dependent on the acquisition of correct clinical information and clinical expertise. In some cases, clinical scores are not possible owing to unavailable, missing or incorrect data. In these settings, the clinical score may be unreliable and clinician discretion and an individualised approach are important in determining further investigation and/or a decision to initiate an alternative anticoagulant.[9]

Laboratory testing

There are two broad classes of HIT tests: immunological assays that detect heparin-PF4 antibodies (Box 3), and functional assays that measure heparin-dependent platelet activation and aggregation by these antibodies (Box 4).[13–30] However, all HIT tests suffer several limitations related to sensitivity and specificity, or to complexity and accessibility.[16]

Blood should be collected at least 4 hours after the last administration of heparin for all patients with clinically suspected HIT.[31,32] Serum or double-spun citrate platelet-poor plasma should be prepared within 4 hours of collection, aliquoted and stored appropriately.

Immunoassays detect antibodies against heparin–PF4 complexes — these include both pathogenic and non-pathogenic HIT antibodies.[32,33] However, these assays generally have an excellent negative predictive value (Box 3).[13,16,34] They can be divided into two categories — qualitative and quantitative assays (Box 3) — with the qualitative assays associated with lower specificity than most IgG-specific enzyme-linked immunosorbent assays.

In a clinical setting with a high prevalence of HIT, laboratories should aim to offer a rapid (screening) test to assist clinicians in making or excluding the diagnosis of HIT, ideally within 24 hours.[35,36]

2 Pre-test probability of heparin-induced thrombocytopenia (HIT): 4Ts score*

4Ts category	2 points	1 point	0 points
Thrombocytopenia	Platelet count fall > 50% and platelet nadir ≥ 20×10^9/L	Platelet count fall 30–50% or platelet nadir $10–19 \times 10^9$/L	Platelet count fall < 30% or platelet nadir < 10×10^9/L
Timing of platelet count fall	Clear onset days 5–10 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5–10 fall, but not clear (eg, missing platelet counts); onset after day 10; or fall ≤ 1 day (prior heparin exposure 30–100 days ago)	Platelet count fall ≤ 4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction following intravenous unfractionated heparin bolus	Progressive or recurrent thrombosis; non-necrotising (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

* Low probability for HIT: score, ≤ 3; intermediate probability for HIT: score, 4–5; high probability for HIT: score, 6–8. Adapted with permission from Lo et al.[8] ◆

3 Characteristics of heparin-induced thrombocytopenia immunological assays available in Australia

Assay	Result	Principle	Advantages	Disadvantages
Particle gel immunoassay	Qualitative	Agglutination test using coloured polystyrene particles coated with heparin–PF4	Rapid turnaround time	Requires specific manufacturer centrifuge Result assessed by visual inspection Not IgG-specific Occasional false negatives[14,15] Low positive predictive value (< 50%)
Lateral flow assay	Qualitative	IgG-specific lateral flow qualitative immunochromatography	Rapid turnaround time (fastest of all heparin-induced thrombocytopenia assays) Highly sensitive[16–18]	Result assessed by visual inspection Poor inter-observer reproducibility for weak antibodies Occasional false negatives[18] Low positive predictive value (< 50%)[18–21]
Automated latex-based assay	Quantitative	Latex agglutination assay	Rapid turnaround time	Requires instrumentation Not IgG-specific[22] Expensive
Automated chemiluminescence-based assay	Quantitative	Chemiluminescence assay	Rapid turnaround time Very high negative predictive value[18,19,23]	Requires specific manufacturer instrument Expensive Occasional false negatives[18]
ELISA				
Lifecodes PF4 IgG (Immucor GTI Diagnostics)	Quantitative	ELISA, polyvinylsulfate–PF4 surface bound	Reporting of optical density and cut-off[18,24–27] High negative predictive value Possible confirmatory step with high heparin[14,24–27]	Longer turnaround time due to batch testing Usually not available for single patient on-demand testing
Zymutest HIA IgG (Aniara)	Quantitative	ELISA, heparin bound and suspension platelet PF4	Reporting of optical density and cut-off[18,24–27] High negative predictive value Possible confirmatory step with high heparin concentration[14,24–28]	Longer turnaround time due to batch testing Usually not available for single patient on-demand testing
Asserachrom HPIA – IgG (Stago)	Quantitative	ELISA, PF4–heparin surface bound	Reporting of optical density and cut-off[18,24–27] High negative predictive value Possible confirmatory step with high heparin concentration[14,24–28]	Longer turnaround time due to batch testing Usually not available for single patient on-demand testing

ELISA = enzyme-linked immunosorbent assay; PF4 = platelet factor 4. ◆

We recommend that laboratories utilise immunological assays which selectively detect the IgG isotype to improve specificity[14,37] and report where available the actual optical density or strength of reaction,[27] inhibition by supra-therapeutic heparin[23–25] and the cut-off point for a positive test, rather than simply reporting the test result as positive or negative. The sensitivities, specificities and likelihood ratios for quantitative tests depend on the cut-off points chosen.[38]

Depending on the local needs, volume of tests and resources, particle gel immunoassay, lateral flow assay, automated chemiluminescence and enzyme-linked immunosorbent assay are acceptable options for screening. Turnaround times vary depending on the test used.

Functional HIT assays are designed to detect pathogenic anti-PF4–heparin antibodies that can activate platelets in the presence of heparin, confirming a clinical diagnosis of HIT. These include serotonin release assay, heparin-induced platelet activation assay and heparin-induced multiple electrode aggregometry. These assays rely on the activation of normal (responsive) donor platelets in the presence of patient serum (typically heat inactivated) or plasma, using both low dose (0.1–1.0 IU/mL) and high dose (50–200 IU/mL) heparin as a confirmatory step (Box 4). Laboratories performing functional assays must have a strategy to identify responsive donors.[29] Functional assays used by laboratories should be validated against the gold standard: serotonin release assay.

Diagnostic algorithm

HIT is a clinicopathological diagnosis, requiring the integration of both the clinical picture and laboratory results for accurate diagnosis and management. The diagnosis of HIT (or its exclusion) ideally requires a sequential combinatorial approach (Box 5). Every effort should be made to obtain an accurate 4Ts score.[8,9]

In relation to the diagnostic algorithm, it is important to note the following caveats:

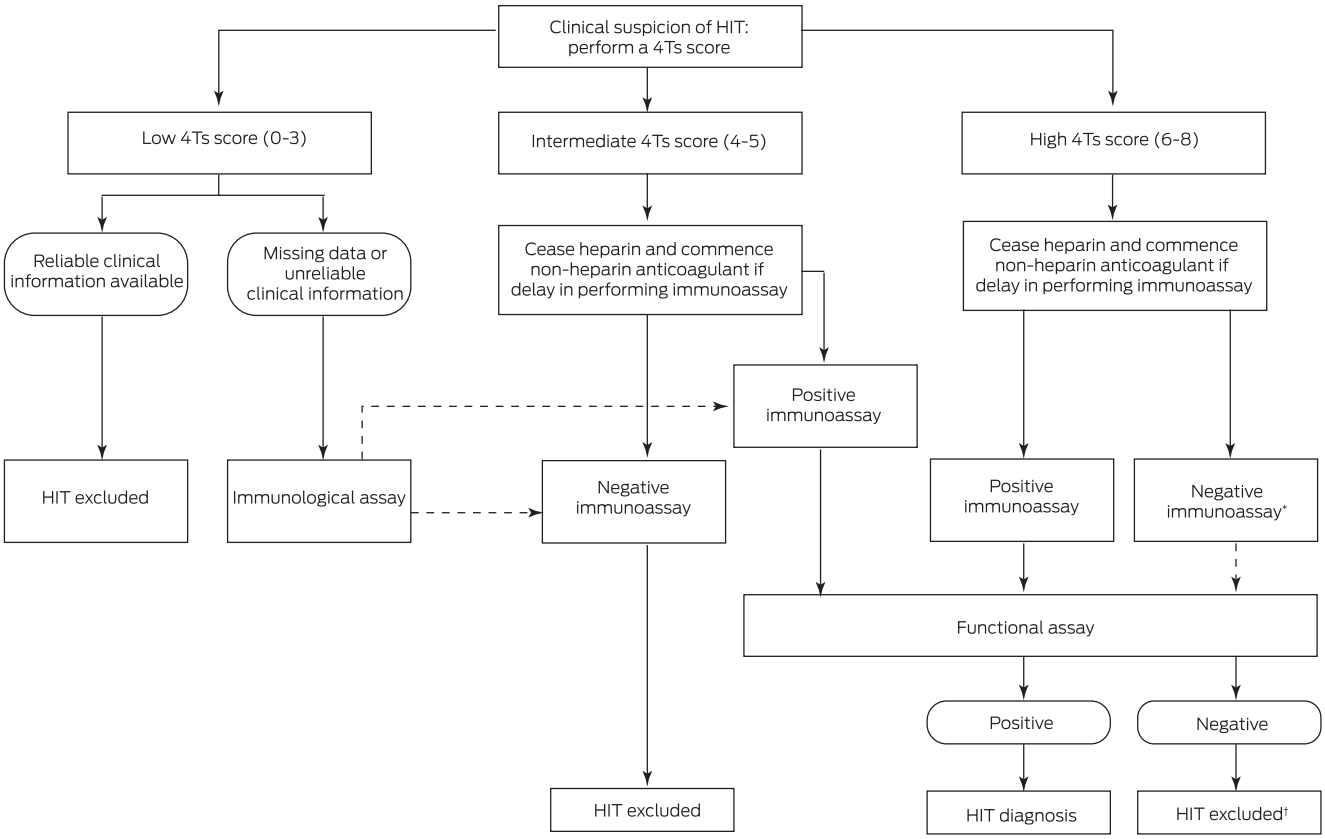
- Low 4Ts score: if reliable clinical information is available, there is no need to perform testing and HIT is excluded.[9] However, if there are missing data or unreliable information, then an immunological assay should be performed.
- High 4Ts score: if the immunoassay result is negative, it is recommended to treat the patient as not having HIT (ie, continue with heparin) until further clarification is attained, which can occur with clinical reassessment and/or functional assay, or if a functional assay is not available, by repeating the immunoassay or performing an alternative high sensitivity immunoassay.

4 Characteristics of functional heparin-induced thrombocytopenia (HIT) assays available in Australia*

Assay	Donor platelets	Availability	Requirements	Interpretation of positive result	Advantages	Disadvantages
Serotonin release assay	Washed platelets	Offered once or twice a month in a single laboratory	Platelets from a high responder donor[29] Laboratory expertise Radioactivity beta counter	Serotonin release > 20% with low dose heparin and < 20% with high dose heparin or < 50% of release with low dose[30]	Considered the gold standard	Long turnaround time due to batch testing Use of radioactive material Complex Requires fresh responsive platelets
Heparin-induced multiple electrode aggregometry	Whole blood	Performed on demand if suitable high responder donor available	Platelets from a high responder donor[29] Whole blood impedance aggregometer	Typical sigmoid curve Aggregation with low dose heparin ≥ 30 U and with high dose heparin AUC < 50% of the AUC for low dose heparin[29]	Quick turnaround time (20 minutes) Simple assay, easy to perform Sensitivity and specificity close to serotonin release assay[29]	Requires fresh responsive platelets

AUC = area under the curve. *Where functional HIT testing is not available, local testing protocols may wish to investigate whether serial dilution of plasma increases specificity of particle gel immunoassay, and/or high level positivity better associates with pathogenic HIT; however, this is not the recommended approach and ideally a functional assay should be performed. ◆

5 Heparin-induced thrombocytopenia: diagnostic algorithm



* If the immunoassay is negative, it is recommended to treat the patient as not having HIT until further clarification is attained, which can occur with clinical reassessment and/or a functional assay, or if a functional assay is not available, repeating the immunoassay or performing an alternative high sensitivity immunoassay. † If the immunoassay is positive and the functional assay is negative, we recommend examining the optical density of the immunoassay result and the sensitivity of the functional assay to guide patient management. Retesting can also be considered.[27] If the clinical suspicion of HIT remains high despite negative testing and/or the patient's clinical condition changes, there is a need to reassess the possibility of HIT and retesting should be considered.[39] ◆

- Intermediate and high 4Ts score: if the immunoassay result is positive, it is recommended to treat the patient as having HIT until results of a functional assay are available.
- High 4Ts score: if the immunoassay result is positive and the functional assay result is negative, we recommend examining the optical density of the immunoassay result and the

6 Anticoagulants used for the treatment of heparin-induced thrombocytopenia (HIT)*

	Argatroban	Bivalirudin	Danaparoid	Fondaparinux
Mechanism of action	Direct thrombin inhibitor	Direct thrombin inhibitor	Mostly anti-Xa	Anti-Xa
Half-life (normal renal function)	39–51 minutes	25 minutes	Anti-Xa 25 hours	17–20 hours
Dosing in HIT*	Continuous IV infusion, no bolus Starting infusion: • critically unwell patients: life-threatening TE, 2.0 µg/kg/min; non-life threatening TE,1.0 µg/kg/min; no thrombosis, 0.5 µg/kg/min • non-critically unwell patients: normal hepatic function, 2.0 µg/kg/min; hepatic impairment, 0.50 µg/kg/min Target APTT, 1.5–3.0 × patient baseline APTT Measure APTT 2-hourly until two consecutive results in target range and then a minimum of daily Do not exceed APTT of 100 s	Continuous IV infusion, no bolus Starting infusion: CrCl > 60 mL/min, 0.15 mg/kg/h; CrCl 30–60mL/min, 0.08 mg/kg/h; CrCl < 30 mL/min avoid use Target APTT, 1.5–2.5 × patient baseline APTT Measure APTT 4-hourly until two consecutive results in target range; consider initial 2-hourly monitoring in patients at high risk of bleeding	IV bolus plus monitored infusion Bolus: weight < 60 kg, 1500 U; 60–75 kg, 2250 U; 75-90 kg, 3000 U; > 90 kg, 3750 U Accelerated initial infusion: 400 U/h × 4 h;then 300 U/h × 4 h Maintenance infusion: normal renal function, 200 U/h; renal dysfunction, 150 U/h	Weight-based daily dosing Weight < 50 kg, 5 mg SC daily; 50-100 kg, 7.5 mg SC daily; > 100 kg, 10 mg SC daily CrCl: 30–50 mL/min use caution; < 30 mL/min avoid use
Monitoring	APTT	APTT	Anti-Xa	Anti-Xa
Renal impairment	No dosage adjustment necessary in renal dysfunction	Avoid when CrCl < 30 mL/min	Avoid when CrCl < 30 mL/min	Contraindicated when CrCl < 30 mL/min (however, can be given with appropriate monitoring in haemodialysis patients (Box 7)
Hepatic impairment	Reduce dose in moderate to severe hepatic impairment (Child–Pugh class B and C)	No dose adjustment	Contraindicated in severe hepatic insufficiency	No dose adjustment
Clearance	Mainly hepatic metabolism	Combination of renal mechanisms and proteolytic cleavage	Renal	Renal
Effect on PT/INR during transition to warfarin	Yes	Yes	Minimal	Not affected

CrCl = creatinine clearance; SC = subcutaneous; TE = thromboembolism; APTT = activated partial thromboplastin time; PT = prothrombin time; INR = international normalised ratio; IV = intravenous. * All dosing recommendations are taken from the Australian product information sheets and/or the comprehensive reviews by Linkins et al[40] and Cuker.[41] These doses apply to adults only. ◆

sensitivity of the functional assay to guide patient management. Retesting can also be considered.[27]

- If the clinical suspicion of HIT remains high despite negative testing and/or the patient's clinical condition changes, there is a need to reassess the possibility of HIT and retesting should be considered. Seroconversion may take up to 4–6 days to develop so it may be necessary to consider retesting at a later time point.[39]
- The importance of a 4Ts score is highlighted by the fact that a low 4Ts score obviates the need for further laboratory testing, and a high 4Ts score would result in a switch from heparin to a non-heparin anticoagulant without an immunoassay result. However, in the acute medical setting, accurate information can be difficult to obtain (ie, timing of heparin commencement, platelet counts, etc) and there may be individual variability in calculating the 4Ts score. In these situations, the result of the screening immunoassay is relied upon to guide further management.

Treatment

In a patient with suspected or proven HIT, continued exposure to heparin (unfractionated or low molecular weight) must be avoided and alternative anticoagulants should be considered. Alternative anticoagulants include anti-factor Xa inhibitors and direct thrombin inhibitors (Box 6 and Box 7) (note that there are no registered anticoagulants approved for HIT in Australia). There are very limited comparative data to guide choice of alternative anticoagulant,[40,48–50] so local experience and access are important factors. In general terms, clinically unstable HIT patients with acute thrombosis (eg, those with critical illness or increased potential need for an urgent procedure) should be managed with monitored infusions (danaparoid, argatroban or bivalirudin). Argatroban is only available in Australia under the Therapeutics Goods Administration Special Access Scheme. Anti-Xa inhibitors (danaparoid and fondaparinux) are more commonly used than direct thrombin inhibitors (argatroban and bivalirudin), as the latter are associated with high rates of bleeding and interfere with coagulation assays when transitioning to warfarin.[41] Fixed dose anticoagulants (fondaparinux) are simpler options for stable patients, including those without thrombosis (isolated HIT).[51,52] Caution is needed when transitioning to warfarin from a direct thrombin inhibitor, as activated partial thromboplastin time and prothrombin time can be affected by both agents. Warfarin should not be introduced until platelet levels are > 150 × 10^9/L

7 Treatment of heparin-induced thrombocytopenia in special patient populations

Patient population	Drug	Dosing protocol*
Percutaneous coronary intervention	Bivalirudin[42]	0.75 mg/kg bolus, followed by 1.75 mg/kg/h for 4 h Check ACT 5 min after bolus; further bolus 0.3 mg/kg if needed
	Argatroban[43]	350 µg/kg bolus For target ACT 300–450 s, initial dosage 25 µg/kg/min Check ACT 5–10 min after initial bolus: if ACT < 300 s, adjust dosage to 40 µg/kg/min; if ACT > 450 s, adjust dosage to 15 µg/kg/min
Cardiopulmonary bypass, on pump	Bivalirudin[44]	Before: 1.0 mg/kg bolus, commence infusion at 2.5 mg/kg/h — target ACT 2.5 × baseline; add 50 mg to pump circuit — avoid stasis in CPB circuit During: continue infusion at 2.5 mg/kg/h; monitor ACT every 30 min — target ACT 2.5 × baseline; increase infusion rate only if ACT levels decrease below target or give repeated fractionated boluses of 0.25 mg/kg
Renal replacement therapy		
Continuous	Argatroban[45]	100 µg/kg bolus: initial infusion 0.5 µg/kg/min — target APTT 1.5–3.0 × baseline
Intermittent haemodialysis	Danaparoid[46]	3750 U bolus before (1250 U if < 55 kg; 5000 U if > 90 kg)
	Fondaparinux[47]	Limited data: 2.5 mg SC or 0.03–0.05 mg/kg IV before; monitor for drug accumulation
	Argatroban[45]	250 µg/kg bolus: initial infusion 2.0 µg/kg/min — target APTT 1.5–3.0 × baseline or ACT 170–230 s

ACT = activated clotting time; APTT = activated partial thromboplastin time; CrCl = creatinine clearance; IV = intravenous; SC = subcutaneous. *These doses are applicable to adults only. ◆

8 Summary of recommendations

- A 4Ts score is recommended for all patients with suspected heparin-induced thrombocytopenia (HIT) prior to laboratory testing (Grade 1B).[8,9]
- Low probability of HIT on 4Ts score: further testing with an immunoassay or functional assay is not recommended (Grade 2C). However, if there are missing or unreliable clinical data, laboratory testing is recommended.[9]
- Intermediate or high probability of HIT on 4Ts score and a positive immunoassay result: initial treatment should include discontinuing heparin and considering a non-heparin alternative (Grade 1C).[40,41]
- Laboratories should provide a rapid, on demand, high sensitivity, IgG selective immunological assay (Grade 1C).[35,36]
- Positive immunoassay results should be confirmed with functional testing, regardless of 4Ts score (good practice point).
- Heparin exposure must be ceased in patients with suspected or confirmed HIT. Continued use of heparin, even in low concentrations, has been associated with adverse outcomes in HIT patients (Grade 1B).[40,41]
- A non-heparin anticoagulant (danaparoid, argatroban, fondaparinux and bivalirudin) should be used to treat HIT (Grade 1B/C).[40,41]
- A non-heparin anticoagulant should be given in therapeutic rather than prophylactic doses (Grade 1C).[40,41]
- Argatroban is the preferred anticoagulant in the presence of severe renal impairment (creatinine clearance < 30 mL/min) (Grade 2C).[40,41]
- Direct oral anticoagulants can be used in place of warfarin after patients with HIT have responded to alternative parenteral anticoagulants (Grade 2C).[53]

and, for patients on warfarin at diagnosis, warfarin should be reversed with vitamin K.[40] Although clinical experience is limited,[41] transition from parenteral anticoagulants to direct oral anticoagulants will avoid interference with laboratory assays and would be expected to provide similar efficacy to warfarin.[53] Patients with isolated HIT should receive therapeutic anticoagulation until platelet levels are > 150 × 10^9/L.[41] Patients with HIT and thrombosis should receive therapeutic anticoagulation for a minimum of 3 months.[41] Platelet transfusions are not recommended to treat thrombocytopenia due to HIT in the absence of clinical bleeding.[41]

Patients with a proven history of HIT should avoid the use of heparin for future procedures.[41] However, there are situations in which heparin use can be considered, such as during cardiopulmonary bypass and percutaneous coronary intervention.[54] In these settings, referral to a haematologist is recommended. In an emergency setting where there is no time for repeat serological testing, if the episode of HIT occurred > 3 months ago, the likelihood of a positive functional assay result is < 5% because of the transient nature of pathogenic platelet-activating HIT antibodies, which have a median time to disappearance of 50–80 days.[55] In this scenario re-exposure to heparin is possible without the results of serological tests. In all other cases, repeat immunological assays and, if positive, functional assays should be performed and the results used to guide treatment decisions. Here, intra-operative re-exposure to heparin may be considered if functional assay results are negative; however, non-heparin anticoagulants should be given for further post-operative anticoagulation.[56] Surgery should be delayed if possible if functional HIT testing results are positive. Bivalirudin and therapeutic plasma exchange are treatment options in this setting if surgery cannot be delayed (Box 6).[56,57] If required, non-heparin anticoagulants should be used in the pre- and post-operative periods.

Similarly, in the context of haemodialysis, heparin use should be avoided. Options include use of regional citrate, saline flushes and use of non-heparin anticoagulants, depending on local expertise and experience[40] (Box 7).

Non-heparin anticoagulants are recommended for patients with a remote history of HIT and who require anticoagulation for prophylaxis or treatment of venous thromboembolism.[40]

Specialist referral is recommended in cases of acute HIT refractory to treatment. Switching to another non-heparin anticoagulant is reasonable if therapeutic levels of current anticoagulants have been achieved. There are increasing reports in the literature of efficacy of intravenous IgG in this setting.[58]

Summary

The diagnosis and management of HIT is an evolving field in medicine, particularly with the recent introduction of newer assays and the availability of direct oral anticoagulants. It is difficult to perform randomised clinical trials involving large numbers of participants; local expertise in caring for patients with HIT is therefore paramount as the level of evidence to guide management is often suboptimal. This consensus statement provides recommendations (Box 8) to be read and referred to with this in mind.

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