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GUIDELINE

BSH GUIDELINES

Diagnosis and management of heparin-induced thrombocytopenia: Third edition

Deepa J. Arachchillage[1,2] | **Jecko Thachil**[3] | **Julia A. M. Anderson**[4] | **Peter Baker**[5] | **Anthony Poles**[6] | **Steve Kitchen**[7] | **Mike Laffan**[1,2] | **on behalf of the BSH Committee**

[1]Centre for Haematology, Department of Immunology and Inflammation, Imperial College London, London, UK

[2]Department of Haematology, Imperial College Healthcare NHS Trust, London, UK

[3]Department of Haematology, Manchester Royal Infirmary, Manchester, UK

[4]Department of Haematology, Edinburgh Royal Infirmary, Edinburgh, Scotland

[5]Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals NHS Trust, Oxford, UK

[6]Bristol NHS Blood and Transplant Centre, Bristol, UK

[7]Department of Haematology, Royal Hallamshire Hospital, Sheffield, UK

Correspondence
BSH Guidelines Administrator, British Society for Haematology, 100 White Lion Street, London, N1 9PF, UK.
Email: bshguidelines@b-s-h.org.uk

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METHODOLOGY

This guideline was compiled according to the BSH process at (https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org. A literature search was carried out using the terms given in Appendix until August 2022.

REVIEW OF THE GUIDELINE

The review of the guideline followed the standard BSH guidelines procedure. Following review of the draft guideline by the BSH Haemostasis and Thrombosis Task Force and the BSH Guidelines Committee, it was placed on the members section of the BSH website for comment (sounding board).

INTRODUCTION

This guideline updates and widens the scope of the previous British Society for Haematology (BSH) Clinical guidelines for Diagnosis and Management of Heparin-Induced Thrombocytopenia: Second Edition[1] to include functional assays in the diagnosis of heparin-induced thrombocytopenia (HIT), when to use direct-acting oral anti-coagulants, and the role of intravenous (IV) immunoglobulins and plasma exchange in the management of HIT and spontaneous HIT.

HIT is an immune-mediated, highly pro-thrombotic disorder of platelet activation caused by pathogenic antibodies against a platelet factor 4 (PF4)–heparin complex. It is the most frequent drug-induced immune thrombocytopenia and may lead to life-threatening thrombosis. There are two distinct forms of HIT: type I, also known as heparin-associated thrombocytopenia, which is a non-immunological response to heparin treatment, mediated by a direct interaction between heparin and circulating platelets causing platelet clumping or sequestration, and type II, which is immune mediated.

Type I HIT is more frequent than type II, affects around 10%–30% of patients and occurs early, within the first 48–72 h following heparin exposure.[2] It generally causes transient, mild thrombocytopenia, and the platelet count returns to normal within 4 days of heparin discontinuation. Type I HIT is benign and is not associated with thrombosis. In contrast, type II HIT is much less frequent, and its incidence ranges from 0.1% to 7% depending on the type of heparin, duration of heparin exposure and patient population. Unfractionated heparin (UFH) is associated with ~10-fold greater risk of HIT than low molecular weight heparin (LMWH).[3,4] HIT typically occurs within 5–14 days of first exposure to heparin and is associated with a significantly increased risk of thrombosis.[5] Unlike type I HIT, thrombosis is more frequent in type II HIT and occurs in around 25%–50% of patients.[6,7] When used hereafter in this guideline, 'HIT' refers to type II HIT.

The complex formed by the binding of heparin to PF4 acts as an immunogen, leading to immunoglobulin (Ig)G antibody production by B cells. Although IgG is the main driver in the pathogenesis of HIT, there is some evidence to suggest IgM and IgA may also have a pathogenic role.[8,9] The antibodies form a heparin–PF4-IgG molecular complex that binds to platelets via platelet FcγRIIa causing platelet activation and aggregation with the release of more PF4 and microparticles, leading to complement and coagulation activation. Furthermore, activation of monocytes through FcγRIIa leads to the expression of tissue factor and binding of HIT antibodies to PF4/glycosaminoglycan complexes on the surface endothelial cells (ECs) causing their activation, creating a pro-coagulant state.[10]

Platelet activation, aggregation and the activation of complement, monocytes and ECs all lead to thrombosis with thrombocytopenia. Removal of immune complex-coated platelets by the reticuloendothelial system contributes further to thrombocytopenia.[11] Anti-PF4–heparin immune complexes are able to induce NETosis via interaction with FcγRIIa on neutrophils and through neutrophil–platelet interactions. In a microfluidic system and mouse model, it has been shown that HIT immune complexes are able to induce thrombi containing neutrophils, extra-cellular DNA, citrullinated histone H3 and platelets, whereas depletion of neutrophils abolished thrombus formation.[12] Thrombosis in HIT may be venous, arterial, microvascular or a combination and can affect virtually any tissue or organ.[10,13,14] The immunogenicity of PF4–heparin complexes is affected by heparin chain length and the level of sulphation.[15] This may explain the higher incidence of HIT following exposure to UFH compared to LMWH and the near absence of risk with fondaparinux.[16,17] The diagnosis of HIT is based on the key aspects of the clinical history combined with confirmation of PF4-heparin antibodies presence by laboratory tests. Final confirmation can come from a demonstration that the antibodies can mediate platelet activation.

In addition to classical HIT triggered by heparin and featuring predominantly heparin-dependent antibodies, disorders that are caused by anti-PF4 antibodies are broadly categorised as follows[18]:

1. Autoimmune HIT (aHIT); a severe subtype of HIT that features both heparin-dependent and heparin-independent platelet-activating antibodies.[19] aHIT disorders include 'delayed-onset HIT' (thrombocytopenia that begins or worsens despite heparin cessation), 'persistent HIT' (HIT that persists beyond a week after stopping heparin), heparin 'flush' HIT and most cases of fondaparinux-associated HIT.[19] aHIT is caused by similar IgG antibodies that are reactive against PF4–heparin complexes but which activate platelets even in the absence of pharmacological heparin.[20]
2. Spontaneous HIT (non-heparin triggers such as knee replacement surgery and infection); predominantly heparin-independent platelet-activating antibodies.[21]
3. Thrombocytopenia and thrombosis with highly pathogenic anti-PF4 antibodies with heparin-independent platelet-activating properties following the adenovirus-based COVID-19 vaccine (vaccine-induced thrombosis and thrombocytopenia: VITT), which is discussed in the Guidance produced from the Expert Haematology Panel (EHP)[22] and adenovirus-associated VITT-like disorder that occurs following recent adenovirus infection.[23]

In these disorders, the antigen site(s) on PF4 that support anti-PF4 antibodies with heparin-independent reactivity are distinct from those with heparin-dependent reactivity seen in classical HIT.

INCIDENCE OF HIT

Several reviews have addressed the incidence of HIT in different circumstances.[24] The incidence of PF4–heparin antibodies is much higher than the HIT syndrome itself.[25]

Several factors have been reported to affect the incidence of HIT, but these are not consistent between studies, and most of the studies include only a small number of patients. In general, it appears that lower frequencies are seen with LMWH versus UFH, prophylactic versus therapeutic doses, medical versus surgical patients and minor versus major trauma.[4,26] However, to determine which patients merit monitoring, the absolute risk should be considered. In the meta-analysis by Martel, which contained predominantly orthopaedic patients, the incidences were 0.2% with LMWH and 2.6% with UFH.[4] The reported incidence of HIT following cardiac surgery was 1.1%, and in patients supported with extracorporeal membrane oxygenation (ECMO), it was 6.6%.[27,28] Although PF4–heparin antibodies developed after cardiac surgery within 30 days in 50% of around 950 cases (as measured in a polyspecific enzyme-linked immunosorbent assay [ELISA][29] using a cut-off optical density [OD] of 0.4 with >50% inhibition by excess heparin), this was not associated with any increase in death or thromboembolism. Therefore, HIT testing should be confined to cases with sufficiently high clinical suspicion that HIT may be present. Audits have confirmed that using lower-specificity assays alone can lead to substantial overdiagnosis of HIT.[30]

A retrospective analysis of 25 653 medical inpatients found rates of HIT of ≤0.2% in patients on prophylactic LMWH, treatment dose LMWH and prophylactic UFH, but 0.7% on treatment dose UFH.[31] In another study of medical inpatients, the incidence of HIT with subcutaneous UFH was 0.8% (CI 0.1–1.6) and 1.3% for those on prophylaxis.[32] A study of neurology patients showed similar results.[33] A prospective study of medical patients given LMWH for prophylaxis or treatment reported an incidence of 0.8%, but this figure may be an overestimate.[34,35] A Cochrane review concluded the risk of UFH following surgery was 2.2%, compared to 0.5% in patients receiving LMWH.[36]

The risk of HIT is very low in obstetric patients given LMWH. A systematic review identified 2777 pregnancies in which LMWH was given.[37] In the 2603 pregnancies given LMWH as prophylaxis, there were two cases of thrombocytopenia not thought to be related to heparin, and in the 174 given LMWH as treatment, there was one case of thrombocytopenia also not thought to be related to heparin treatment. In a large administrative database including 66 468 antepartum hospitalisations, 66 741 delivery hospitalisations and 16 325 postpartum readmissions where women received pharmacological prophylaxis, 10 women during antepartum, one during delivery and 14 during postpartum had readmissions involving HIT.[38] Of these women, none had arterial thrombosis, limb amputation, heart failure or death related to HIT.[38]

PRESENTATION AND ASSESSMENT

If HIT is suspected in a patient receiving heparin on the basis of a fall in the platelet count, the probability of HIT should initially be judged on clinical grounds. Four features are particularly helpful in estimating the likelihood of HIT[39]:

1. *Timing*. If HIT develops, the platelet count typically begins to fall 5–10 days after starting heparin and is rare after 15 days but may occur in less than 24 h in patients who have received heparin in the previous 3 months. In patients undergoing cardiopulmonary bypass, a significant fall in the platelet count is very common in the first 72 h (h) postsurgery.[40] In these patients, platelet recovery followed by a secondary fall in counts between postoperative days 5–14 is much more suspicious of HIT than a low count that persists beyond Day 4.[41]
2. *Degree of thrombocytopenia*. In HIT, the platelet count usually falls by at least 30%–50% from baseline; the median nadir is 55×10^9/L. The 'baseline' should be taken as the highest platelet count immediately preceding the putative HIT-related fall.[39] Severe thrombocytopenia (platelet count $<15 \times 10^9$/L) is unusual but is associated with higher thrombotic risk.[42]
3. *Thrombosis*. Up to half of the patients who develop HIT will have associated thrombosis. This is most commonly venous but may be arterial or atypical, such as adrenal haemorrhage, necrosis at injection sites and gangrene.
4. *Presence of an alternative explanation*. In ill patients, this may include drugs, liver failure, sepsis and non-HIT disseminated intravascular coagulation (DIC) (as severe HIT, especially aHIT, may present as overt DIC).

These factors form the basis of the '4Ts' scoring system (Table 1) to assess the pretest probability of HIT.[43] A low 4Ts score (≤3) carries a high negative predictive value (0.998; 95% confidence interval, 0.970–1.000) and so heparin use (platelet count permitting) can continue without further testing. An alternative, more detailed HIT Expert Probability (HEP) score was developed and performed better than the 4Ts score in a retrospective study,[44] but in a subsequent prospective study, its sensitivity and specificity were similar to the 4Ts score. However, it performed better than the 4Ts score for trainees and in ICU patients, where assessment is complicated by multiple alternative aetiologies.[45,46] Either system is therefore acceptable, but in both cases, the positive predictive value is poor, and a positive score (≥4) should be followed by laboratory testing. The positive predictive value of the 4Ts score in identifying HIT in patients post cardiopulmonary bypass and ECMO was only 0.562 (18/32) and 0.25 (15/60), respectively,[27] suggesting that in these patient populations, a low 4Ts score may not be sufficient to exclude HIT.[27] A large variability in calculating the 4Ts score by clinicians was noted, and the experience of attending physicians in calculating the score was crucial. The value of the 4Ts score in the diagnosis or exclusion of HIT can be markedly improved by its calculation jointly by the treating physician and an on-call haematologist with experience in the diagnosis and management of HIT.[27,47]

Monitoring of platelet count

There is a good case for platelet monitoring in patients who have a significant risk of developing HIT. The risk/benefit has not been calculated formally, but consensus exists that an incidence <0.1% in a particular patient group does not require monitoring but >1% does. As detailed above, many groups appear to fall between these limits, and recommendations are therefore somewhat subjective.

The value of detecting HIT is high. Even if heparin is discontinued, the risk of developing thrombosis within 30 days is 50%.[48] In the Nationwide Inpatient Sample (NIS) study of 97 508 discharges coded for HIT, the in-hospital mortality was 10·1% (SE 0.2) compared to 2.1% (0.01) of 149 811 891 discharges for non-HIT (adjusted OR 4.075 [95% CI 3.846–4.317]; $p < 0.0001$).[49]

The harm from monitoring arises largely from the false positive rate, making the correct application of the 4Ts score and laboratory testing of paramount importance. False positives will result in an increase in major haemorrhage due to inappropriate therapeutic anti-coagulation in thrombocytopenic patients, sometimes with non-heparin anti-coagulants with a higher bleeding risk.

TABLE 1 Pretest probability scoring for heparin-induced thrombocytopenia.

	Points (0, 1 or 2 for each of four categories: Maximum possible score = 8)		
	2	**1**	**0**
Thrombocytopenia	>50% fall and platelet nadir $\geq 20 \times 10^9$/L	30%–50% fall or platelet nadir $10–19 \times 10^9$/L	Fall <30% or platelet nadir $<10 \times 10^9$/L
Timing[a] of platelet count fall or other sequelae	Clear onset between days 5 and 10; or ≤1 day (if heparin exposure within past 30 days)	Consistent with immunisation but not clear (e.g., missing platelet counts) or onset. of thrombocytopenia after Day 10; or fall ≤1 day (if heparin exposure 30–100 days ago)	Platelet count fall ≤4 days (without recent heparin exposure)
Thrombosis or other sequelae (e.g., skin lesions)	New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspected. thrombosis not yet proven	None
Other cause for thrombocytopenia not evident	No other cause for platelet count fall is evident	Possible other cause is evident	Definite other cause is present

Note: Pretest probability score: 6–8 = High; 4–5 = Intermediate; 0–3 = Low. d = days. Reproduced from: Lo et al. (2006). With permission from Blackwell Publishing Inc.

[a]First day of immunising heparin exposure considered Day 0; the day the platelet count begins to fall is considered the day of onset of thrombocytopenia. (It generally takes 1–3 days more until an arbitrary threshold that defines thrombocytopenia is passed.)

The cost of monitoring is low; initially a full blood count (FBC), which is frequently indicated for clinical care already should be performed. The burden may be high for patients not in hospitals, but this is likely to be unusual. False positives may also increase costs when monitoring of non-heparin anti-coagulants is required.

A baseline platelet count should be obtained before heparin initiation. The vast majority of cases occur 4–14 days after starting heparin; therefore, platelet monitoring can be restricted to this time period. When there has been exposure to heparin in the preceding 100 days then monitoring should begin immediately. Given the seriousness of the condition, the rapidity of complications and the availability of a simple test, it seems valuable to monitor on at least alternate days.

RECOMMENDATIONS

- **Patients who are to receive any heparin should have a baseline platelet count (1A).**
- **We suggest platelet count monitoring be performed at least every other day from Days 4 to 14 or until heparin is stopped, whichever is longer, in patients on UFH infusion (2C).**
- **We suggest platelet count monitoring be performed at least every other day from Days 4 to 14 or until heparin is stopped in post cardiopulmonary bypass patients receiving LMWH (2C).**
- **We suggest platelet count monitoring be performed at least every other day from Days 4 to 14 or until heparin is stopped for medical or surgical patients receiving UFH by subcutaneous injection at therapeutic or prophylactic doses (2C).**
- **We suggest that routine monitoring of platelet counts in postoperative patients (other than cardiopulmonary bypass patients) receiving LMWH is not required (2C).**
- **We suggest checking a platelet count 24 h after starting heparin in postoperative patients and cardiopulmonary bypass patients who have been exposed to heparin in the previous 100 days and are receiving any type of heparin (2C).**
- **We suggest not routinely monitoring the platelet count in medical patients and obstetric patients receiving LMWH (2C).**
- **HIT should be suspected if the platelet count falls by 30% or more and/or the patient develops new thrombosis, skin allergy or any of the other rarer manifestations of HIT are noted (see Table 1) between Days 4 and 14 of heparin administration, and a clinical assessment should be made (1A).**
- **We suggest calculating the pretest probability score (PTPS) in a patient with suspected HIT (2C).**
- **If the pretest probability score is ≤3, no further laboratory investigation is recommended for the majority of patients, except rarely for patients treated in the intensive care unit (2B).**
- **Laboratory testing to exclude HIT despite a low pretest probability score is suggested in a selected small number of patients treated in intensive care units, especially those supported with extracorporeal membrane oxygenation (ECMO) (2C).**
- **If the pretest probability of HIT is ≥4, heparin should be stopped, and an alternative anti-coagulant started at therapeutic intensity while laboratory tests are performed (1C).**

LABORATORY DIAGNOSIS OF HIT

Historically, functional platelet aggregation (heparin-induced platelet activation [HIPA]) or specific granule content release assays (serotonin-release assay [SRA]) in the presence of heparin, were the only methods available for the demonstration

of anti-PF4/heparin complex antibodies. Although these remain the gold standard for clinically relevant antibodies, the methods are complex and limited to specialist centres. More recently, antigen-based assays have become available on automated platforms and stand-alone devices, shortening the processing time to under 1 h. In some cases, there has been a trade-off in sensitivity and specificity for quicker result generation. The use of more than one immunoassay has been reported to increase the sensitivity and specificity of testing where functional assays are not available.[50]

RAPID SCREENING

Qualitative

Rapid screening tests based on qualitative demonstration of anti-PF4–heparin complex antibodies are available on a range of equipment/devices usually within 1 h. They are widely available in routine diagnostic laboratories with a high degree of sensitivity; however, the trade-off is a lack of specificity for those antibodies that cause platelet activation and/or the detection of non-PF4-heparin antibodies.[51,52] Furthermore, there is no quantification of the antibody concentration present, stratification of which has been used in the assessment of the chances of developing clinical HIT.[53]

Lateral flow immunoassay (LFIA)

Lateral flow-based assays detect antibodies to PF4–heparin complexes that are bound to gold nanoparticles as they move laterally (fluid phase) along a membrane.[54] IgG complexes are immobilised onto the membrane to generate a unique visible line. The assay claims a sensitivity of 100% with reduced false positives compared to other techniques. Reports have shown that fresh samples must be used, with technical issues occurring from frozen or lyophilised material.[55]

Particle gel immuno and immunofiltration assays (PaGIA/PIFA)

The PaGIA uses centrifuge column technology to capture IgG/A/M antibodies for PF4–heparin complexes (bound to red polystyrene beads) as they are spun through a Sephacryl® column. The PIFA relies on the vertical flow of fresh samples in the presence of PF4-coated microspheres through a membrane filter. Low sensitivity and/or specificity have been reported for both assays and, at the time of writing, have been discontinued.[56,57]

Quantitative

Latex immunoassay (LIA IgGAM)

A latex immunoassay is available on the ACL TOP analyzer platform (Werfen, Warrington, UK), in which the patient's potential PF4-heparin antibodies compete with latex beads coated with HIT-like antibodies for PF4/polyvinyl sulfonate (PVS) complexes. This makes the presence of patient antibodies to PF4-heparin inhibit the 'normal' agglutination expected in an inversely proportional manner. The benefit of this assay is that it is performed on a widely available analyser with sensitivity and specificity superior to manual rapid assays. Reports using stratification of values into weak, moderate and strong positivity in conjunction with chemiluminescent-based assays achieved 98% comparability with the gold standard SRA.[50,58]

RECOMMENDATIONS

- **Lateral flow assays should be performed only on fresh samples to avoid technical problems (1B)**
- **PIFAs should not be used in isolation for first-line HIT screening (1B)**

ENZYME-LINKED IMMUNOSORBENT ASSAYS AND CHEMILUMINESCENCE IMMUNOASSAY (CLIA)

Enzyme-linked immunosorbent assays

ELISA methods for the detection of anti-PF4 antibodies vary in the class of immunoglobulin that is detected and in the way that PF4 is presented for antibody binding. Some include a high-dose heparin confirmation step. In general, they have excellent sensitivity, with 0.97 (CI 0.95–0.99) reported in one meta-analysis using the manufacturer's optical density (OD) cut-offs between 0.3 and 0.5[59] and essentially ruling out HIT.

Heparin-exposed patients often make PF4-heparin antibodies of IgG, IgA and IgM class,[53] but IgG antibodies are thought to have the predominant capacity for triggering platelet activation.[53] The detection of non-pathogenic IgA and IgM classes contributes to the lower specificity of polyspecific methods that detect all three Ig classes described in meta-analyses.[53,59] The specificity of IgG-specific methods was superior to polyspecific ELISAs, with values of 0.87 (CI 0.85–0.88) for IgG specific and 0.82 (CI 0.80–0.84) for polyspecific assays, respectively, in one meta-analysis,[59] with similar results described in another meta-analysis.[60]

Negative predictive values of IgG-specific and polyspecific ELISAs were both 0.99 (CI 0.99–1.00) in a meta-analysis.[59] It is preferable to use IgG-specific assays since they offer superior positive predictive value at 0.56 (CI 0.52–0.61) compared to polyspecific methods at 0.32 (CI 0.28–0.35), although they fall well short of those achieved by functional assays. Positive IgG-specific ELISA alone does not confirm the presence of HIT.

There is variability between the results obtained by different ELISA kits,[59,61] but in general, the stronger the OD signal in an ELISA, the more likely it is that a functional assay will

be positive and therefore that a diagnosis of HIT can be confirmed.[53] The probability of strongly positive SRA HIT antibodies being present reached 50% or more when the OD was 1.4 or higher in an IgG-specific ELISA.[51] A weak positive OD in the range 0.4–1.0 with either of the two methods indicated a low probability of HIT, as defined by a strongly positive SRA.[51] In another study, patients with an OD >1.0 using a commercial kit demonstrated a nearly sixfold increased risk of thrombosis compared to cases with an OD of 0.4–0.99.[62] Use of a higher OD threshold improves the specificity of IgG-specific assays to >90%.[60]

Non-heparin-dependent anti-PF4 antibodies, which can cause VITT and adenovirus-associated VITT-like disorder,[23] can be associated with elevated ODs of more than 1.0 in IgG, and polyspecific ELISA methods are being used for HIT diagnosis, with variability between results obtained with different kits.[63,64]

RECOMMENDATIONS

- **ELISAs used for the initial investigation of possible HIT should have high sensitivity (>95%) and detect only IgG antibodies (1B).**
- **A positive result in an ELISA for anti-PF4 antibodies should be interpreted in conjunction with a clinical estimate of pretest probability to make the diagnosis of HIT (1A).**
- **HIT can be excluded by a negative high-sensitivity ELISA antigen assay (1B).**
- **Reporting the results of an ELISA for anti-PF4 antibodies should include the cut-off for a positive test and the optical density obtained on the test sample (1C).**

Chemiluminescence immunoassay

Currently used commercial CLIA HIT assays have an analysis time of approximately 35 min (i.e. much shorter than current ELISA methods, which take 2–4 h). This facilitates a rapid turnaround time and the ability to offer 24-h test availability. The sensitivity of the IgG-specific CLIA method is >95%.[60,65] The specificity of IgG-specific CLIA was consistently superior to IgG-specific ELISAs in multiple studies and meta-analyses[52,60,65,66] when using the manufacturer's cut-off of 1.0 arbitrary units/mL as a threshold for positivity. A specificity of >94% was reported in most studies.[52,60,65,66] Currently, CLIA provides the best combination of sensitivity/specificity and accessibility for HIT diagnosis in the absence of a functional assay.[67]

Functional platelet activation assays

Platelet activation assays can be subdivided into assays that measure either platelet aggregation or a specific marker indicative of platelet activation. All these assays require a source of donor platelets that have been proven to be responsive to the presence of patient serum containing anti-PF4 antibodies in addition to heparin.

All assays are dependent on the detection of platelet activation in the presence of material from HIT patients and an appropriate concentration of heparin. Confirmation of HIT is supported by inhibition of activation in the presence of an excess heparin concentration.

Sources of donor platelets may be whole blood (WB), washed platelets (WPs) or platelet-rich plasma (PRP). Their complexity means they should only be performed in experienced centres.

Heparin-induced platelet activation assay

The HIPA relies on the visual inspection of platelet aggregation (over regular intervals up to 45 min) in the presence of high and low doses of heparin in a U-bottomed microtitre plate well while being stirred with a steel ball.[68] The assay depends on careful screening/selection of known 'reactive' donors prior to testing. Enhanced sensitivity has been reported by using WP instead of PRP in the assay, considered by some a 'gold standard' reference method.[69,70] HIPA and SRA have a good correlation for positive HIT cases, reaching 84% concordance in a recent retrospective analysis.[71]

Light transmission aggregometry (LTA)

Standard LTA relies on detecting increased light transmission that correlates with the formation of platelet aggregates in the presence of both patient plasma and heparin (0.1–0.5 IU/mL) and which is inhibited by an increased concentration of heparin (100 IU/mL) in the test system.

LTA with WP has been reported to be more sensitive than using PRP.[72] Overall sensitivity has been reported to be between 85%[73] and 69%.[74]

LTA can also be performed using adenosine triphosphate (ATP) release as a measure of platelet activation. LTA-positive results are defined as >20% aggregation in light transmission or detection of ATP production. HIT antibody detection is confirmed by inhibition of aggregation or ATP release by more than 50% in the presence of 100 IU/mL heparin.

Multiple electrode aggregometry (MEA)

Multiple electrode aggregometry, also referred to as heparin-induced multielectrode aggregometry (HIMEA), utilises WB as a source of platelets and has been reported to provide results with a sensitivity ranging from 90%[75] to 81%.[76] Specificity has been reported to be 95%, which compares well to results obtained using SRA.[66,67]

Serotonin-release assay

The SRA has been referred to as a 'gold standard' functional assay, mainly due to its high level of specificity and sensitivity.[77–79] However, at present, SRA is not available in the United Kingdom. Several alternative methods have been developed to avoid the use of radioisotopes and to detect serotonin release, namely, high-performance liquid chromatography,[80] ELISA[81] and flow cytometry.[82]

Detection of platelet activation using flow cytometry

Platelet activation can induce extra-cellular expression of specific antigens such as Annexin V and P-selectin (CD62P). Fluorescent-labelled antibodies can be used to detect these using flow cytometry (FC). Applications of FC to detect HIT antibodies include commercial assays such as the Emotest HIT confirm assay (Quadratech, Surrey, UK) and the HIT Alert assay (IQ Products, Groningen, Netherlands). Detection of P-selection expression using FC in one study suggested earlier detection of HIT antibodies, prior to detection by SRA.[83] In comparison to SRA, one study reported a specificity of 100% and sensitivity of 80% using the HIT Alert assay.[84]

- **When confirmation of HIT is required, activation assays should be used to demonstrate inhibition of platelet activation with excess heparin (1A).**
- **It is recommended that donor platelets be confirmed to be sensitive to HIT-positive material prior to use (1B).**

SELECTION OF LABORATORY ASSAYS FOR DIAGNOSTIC ALGORITHM

Key determinants for the choice of assays include time, cost and expertise available to the clinician/service trading off against sensitivity and specificity. A summary of various laboratory assays for the diagnosis of HIT is presented in Table 2. In conjunction with pretest probability scoring, single-assay rapid screening techniques can exclude a number of cases with reasonable certainty with limited time, cost and expertise, making them suitable for peripheral centres. This drops off rapidly if scoring or circumstances are more complex or limited. In this scenario, automated latex-based immune and chemiluminescent assays are preferred and can provide <1 h results 24/7 in a wide range of routine testing environments.[61,66] Combination of these assays with either rapid screening or ELISA-based techniques have been reported to reach near equivalence to the gold standard functional-based assays, although time and cost constraints must be balanced.[85] Functional-based assays are currently mostly reserved for expert centres as a follow-up/second-line consideration, often in conjunction with automated assays.

RECOMMENDATIONS

- **All HIT testing should be performed in conjunction with pretest probability scoring (2A).**
- **HIT reporting should include assay-specific thresholds (1B).**
- **The stratification of numerical assay results should be used to increase sensitivity, specificity and negative predictive value (1B).**
- **Functional assays performed by expert centres should be considered for confirmation of HIT where possible (1A).**

SPONTANEOUS HIT

'Spontaneous HIT' is a rare form of aHIT that occurs without any preceding exposure to heparin[86,87] Spontaneous HIT is associated with unexplained thrombocytopenia and/or thrombosis, with associated laboratory evidence of a high level of PF4-dependent antibodies.[18] Although these patients have no exposure to heparin, they generally have infection or inflammation following surgical interventions.[11] It is possible that chemicals such as glycosaminoglycans released during orthopaedic surgeries or bacterial antigens in the case of infections may trigger the formation of PF4-heparin antibodies. There is evidence to suggest that bacterial cell walls and RNA/DNA nucleotides bind to PF4, resembling HIT antigens and bacterial infections can trigger anti-PF4/heparin antibody formation in mice and humans.[86] Warkentin and colleagues proposed the following criteria for making the diagnosis of spontaneous HIT[86]:

1. thrombocytopenia (with no alternative explanation);
2. thrombosis;
3. no recent heparin exposure;
4. presence of strongly positive PF4-heparin antibodies detected in ELISA (with ≥2 different assays), a strong positive platelet activation assay (>80% peak serotonin release) featuring strong heparin-independent platelet activation (>50% serotonin release at 0 IU/mL heparin), as well as additional heparin-dependent platelet activation seen when using diluted patient serum;
5. presence of other characteristic features of HIT sera (inhibition at 100 IU/mL heparin and with Fc receptor-blocking monoclonal antibody).

These diagnostic criteria mean samples from suspected patients with spontaneous HIT must be sent to specialised laboratories for SRA or another functional assay such as the heparin-induced platelet activation test. This should not delay the initial treatment for these patients. However, strict diagnostic criteria as suggested above will avoid

TABLE 2 Summary of the laboratory assays used to diagnose platelet factor 4 disorders.

Test category	Assay type	Time to complete	Sensitivity	Specificity	Comments	Reference
Semi-quantitative—Immunoassay	IgG lateral flow immunoassay (LFIA)	<1 h	0.95	0.83	Fresh samples are preferred.	Sachs et al.[54]
	IgGAM particle immunofiltration (PIFA)	<1 h	0.27	0.72	High false positive rate has been reported.	Compton et al.[56]
	IgGAM particle gel immunoassay (PaGIA)	<1 h	1.00	0.90	Limited availability in the UK.	Schneiter et al.[57]
Quantitative—Immunoassay (automated)	IgG latex immunoassay (LIA)	<1 h	0.95	0.95	Widely available.	Warkentin et al.[50]
	IgG chemiluminescent immunoassay (CLIA)	<1 h	0.98	0.98	Approaching SRA level in diagnosis HIT and preferred method in the absence of functional assay.	Nagler et al.[61]
Quantitative immunoassay (ELISA)	IgG ELISA	3–4 h	0.98	>0.90	ELISA based. Benefits from high dose heparin step.	Nagler et al.[61]
	IgGAM ELISA	3–4 h	0.97	0.87	Range of characteristics depending on isotypes and thresholds.	Nagler et al.[61]
Functional	Heparin-induced platelet activation (HIPA)	2–3 h	>0.95	>0.95	Microtiter plate-based assay requires source of prescreened PF4-reactive washed donor platelets. Seen as gold standard by some.	Greinacher et al.[68] Eichler et al.[69]
	Light transmission aggregometry (LTA)	2–3 h	0.69–0.85	1.00	Aggregometer-based assay requires source of prescreened PF4-reactive donor platelets.	Brodard et al.[74]
	Multiple electrode aggregometry (MEA)	2–3 h	0.81–0.90	~0.95	Whole blood aggregometry assay.	Morel-Kopp et al.[75] Pishko et al.[142]
	Serotonin-release assay (SRA)	4 h	1.00	>0.95	Original gold standard but not available in the UK due to requirement for radioactive isotopes. Non-isotopic end-point detection can replace the need for ^{14}C including flow cytometry, HPLC and ELISA. Reported risk of false positives.	Tardy et al.[77] Warkentin et al.[79] Fouassier et al.[81]
	Flow cytometry	2–3 h	1.00	0.80	Good sensitivity and specificity but limited availability of equipment and requires pretested donor platelets.	Gobbi et al.[82]

Abbreviations: ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia; HPLC, high-performance liquid chromatography; PF, platelet factor; SRA, serotonin-release assay.

overdiagnosis in patients with unexplained thrombocytopenia and positive PF4-heparin antibodies by ELISA. The pattern of results in laboratory tests for HIT has been summarised in a number of cases of spontaneous HIT.[19] More recently, there are several case reports of individuals with monoclonal gammopathy of clinical significance (MGCS)[88,89] and, following a recent adenovirus infection, developing anti-PF4 platelet-activating VITT-like antibodies, causing clinical VITT-like syndrome.[23] It is important to have high clinical suspicion and test for the anti-PF4 platelet-activating antibodies using ELISA but not by LIA or CLIA, as the latter two assays typically provide negative results for VITT-like antibodies. At present, there is insufficient evidence to indicate the duration of treatment with a non-heparin anti-coagulant in patients who develop spontaneous HIT.

RECOMMENDATIONS

- **Spontaneous HIT should be suspected in a patient with thrombosis and unexplained thrombocytopenia but no history of exposure to heparin, especially following surgery or infection (2C).**
- **Patients with suspected spontaneous HIT should be investigated with a platelet activation assay and demonstration of inhibition at 100 IU/mL heparin and with Fc receptor-blocking monoclonal antibody (1C).**
- **Patients with a VITT-like syndrome (e.g. patients with MGCS or following recent adenovirus infection developing thrombocytopenia and thrombosis) should be tested for anti-PF4 platelet-activating antibodies using ELISA (2C)**
- **In patients with suspected spontaneous HIT, treatment should not be delayed until all investigations are completed (1C).**

Management of HIT including spontaneous HIT

HIT is a pro-thrombotic disorder. Therapeutic anti-coagulation with an alternative non-heparin anti-coagulant is required in a person with HIT when the PTPS is high or the diagnosis is confirmed.[1] The choice of future thromboprophylaxis is dependent on the previous history of HIT. Patients with confirmed HIT should be given a diagnosis/alert card at discharge from the hospital (the suggested format of a HIT alert card is provided in Figure S1).

In all cases of suspected or proven HIT, any form of heparin should be avoided, including heparin flushes.[1,6,24] In addition, to curtail the pro-thrombotic effect of PF4/heparin complexes in patients with proven HIT, anti-coagulation with an alternate drug to heparin is necessary.[1,6,24] The currently available options include both parenteral and oral formulations. The recommended duration of treatment in a patient with confirmed HIT, in the absence of thrombosis, is an alternative anti-coagulant for at least 4 weeks or until the platelet count is greater than 150×10^9/L, whichever is later.[1] If HIT is associated with a thrombotic complication, 3 months of therapeutic anti-coagulation is warranted.[1]

RECOMMENDATIONS

- **Patients should be therapeutically anti-coagulated for 3 months after classical HIT with a thrombotic complication (1A).**
- **Patients should be therapeutically anti-coagulated for 4 weeks following HIT without a thrombotic complication (1B).**
- **We suggest recording the diagnosis clearly in the patient's medical record and proving the HIT alert card to the patient (2C).**
- **We suggest evaluating and making an individualised plan for the duration of anti-coagulation in patients with spontaneous HIT, as there is insufficient evidence to make a recommendation at present (2C).**

Alternative anti-coagulant (parenteral options)

The two direct thrombin inhibitors that can be used in this setting are argatroban and bivalirudin, and both require continuous intravenous infusion.[90–92] The initial dose of argatroban may require reduction in critically ill patients with liver dysfunction (drug elimination by hepatobiliary clearance), while dose reduction is required in moderate to severe renal dysfunction for bivalirudin.[6,93,94]

It has been recommended that argatroban monitoring be performed using an activated partial thromboplastin time (APTT) with a therapeutic range of 1.5–3.0 times the patients baseline APTT.[95] A number of studies have demonstrated major limitations of APTT for monitoring argatroban[90,96,97] including the variation of APTT based on the method[98] and reagents[96] used for assessment of APTT as well as influence by coagulopathies, lupus anti-coagulant and raised factor VIII levels. Measurement of argatroban concentration is the preferred method of monitoring, with a target of 0.4–1.5 μg/mL suggested by a Swiss guideline.[99] A French guideline recommends a target of 0.25–1.5 μg/mL, especially in patients with a prolonged baseline APTT prior to commencing argatroban, as it is not safe to use APTT to monitor argatroban in such situations.[100] A single-centre retrospective study of 133 patients treated with argatroban compared chromogenic assay (75 patients, target range 0.4–1.2 μg/mL) with monitoring by APTT (68 patients, target range by APTT 50–80 s). The study showed a reduction in argatroban dosing requirements by approximately 67% without an increase in thrombosis. There was no difference in the incidence of bleeding between the two groups.[101] There was no difference in the incidence of bleeding between

the two groups.[101] However, assays to quantify argatroban levels are not readily available in many laboratories in the UK at present.

Two other parenteral indirect anti-coagulants can be used in HIT patients. Danaparoid sodium is administered either by intravenous infusion or subcutaneously, while fondaparinux is given subcutaneously.[102–105] Both of these drugs are cleared through the kidneys and can be measured if required using calibrated anti-Xa assays.

RECOMMENDATIONS

- **Alternative parenteral anti-coagulants to heparin, such as argatroban, bivalirudin, danaparoid and fondaparinux, should be used in the acute management of patients with HIT (1B).**
- **Argatroban, danaparoid and fondaparinux are suggested alternatives to treat spontaneous HIT (2C).**

Alternative anti-coagulant (oral options)

Since HIT is a pro-thrombotic state and vitamin K antagonists (VKAs) can deplete endogenous anti-coagulants, VKAs should be started only after the platelet count has normalised in confirmed HIT.[106] At least 5 days of concomitant parenteral therapy are needed during the transition.[1] Care should be taken when converting direct thrombin inhibitors (argatroban and bivalirudin) to the VKA because the international normalised ratio (INR) may be affected by the thrombin inhibition. In the case of argatroban, during the transition, the target INR should be set at 4; argatroban is stopped once two INR values are in the desired therapeutic range; and subsequently, a repeat INR should be performed 4–6 h later to obtain an accurate INR.

In the last decade, there have been several observational studies, cohort analyses, and case reports of the use of DOACs (oral Xa inhibitors [rivaroxaban, apixaban and edoxaban] and an oral thrombin inhibitor [dabigatran]) for patients with HIT with and without thrombosis.[107,108] An important consideration in many of these cases is that a parenteral anti-coagulant was used first before transition to the DOAC. In a systematic review that included 54 patients with HIT (48% with thrombosis at HIT diagnosis), only one patient had thrombus progression, while three had clinically relevant major bleeding but no HIT-related mortality.[109] It is useful to remember that DOACs should not be used when an arterial thrombotic event occurs during HIT.[6] The choice of anti-coagulant in patients with HIT, depending on the clinical situation, is summarised in Table 3.

RECOMMENDATIONS

- **A vitamin K antagonist with appropriate bridging with a parenteral non-heparin anti-coagulant is recommended as an oral anti-coagulant in HIT once the platelet count has normalised or returned to baseline (1A).**
- **Direct-acting oral anti-coagulants are suggested for use as oral anti-coagulants in patients with clinically stable HIT (2C).**

Role of intravenous immunoglobulin (IVIG) and plasma exchange (PEx) in heparin-induced thrombocytopenia

The optimal application of these therapies is unclear. IVIG may act by competitively blocking FcγRIIa-receptor-mediated heparin-independent platelet activation.[110] PEx likely removes antibodies against PF4/heparin high molecular weight complexes.[111]

Onuoha et al.[112] reported the use of PEx, IVIG and a combination of PEx/IVIG in 113 HIT cases: 26/113 cases used PEx alone and 4/113 cases used IVIG and PEx. A post-treatment platelet count $\geq 150 \times 10^9$/L was achieved in 48% of cases within an average of 6 days. The data suggest 1–2 PEx procedures may be effective in reducing or eliminating PF4–heparin antibodies/immune complexes, with the average volume exchanged being 1.3 (range 1.0–2.0).

Another review collated 36 cases of acute HIT treated with IVIG, alongside alternative anti-coagulation[110] reported between 2014 and 2019: 21/36 were cases of aHIT, with severe thrombocytopenia (platelet nadir 15) and a high frequency of thrombosis, of which 11/21 were rated as having an 'excellent response' and 6 had a 'good response' to a first course of IVIG, with no thrombotic sequelae. To achieve the best response, it is recommended to use the total dose of 2 g/kg over 48 h based on actual body weight, as the treatment failures

TABLE 3 Choice of anti-coagulant in patients with HIT depending on clinical situation.

Clinical scenario	Alternative anti-coagulant to heparin
Patient requiring invasive procedures or with risk of bleeding in the immediate future and patients with very high risk of bleeding	Consider drugs with shorter half-lives for example: argatroban or bivalirudin
Inpatient with renal impairment (creatinine clearance <30 mL/min)	Argatroban
Inpatient with hepatic impairment	Bivalirudin, danaparoid or fondaparinux
Stable patients with no organ impairment	Fondaparinux subcutaneously once daily or oral anti-coagulants once platelet count to normalised or returned to baseline

are usually seen when patients receive doses lower than the recommended total dose of 2 g/kg.

Treatment with IVIG and/or PEx could be considered in patients who have severe HIT syndrome, present with a clear case of aHIT, when there is a lack of access to a non-heparin anti-coagulant or in cases where clinically significant bleeding prevents the use of therapeutic anti-coagulation.

RECOMMENDATION

- **IVIG 1 g/kg for 2 days is suggested for patients with heparin-independent platelet-activating antibodies such as autoimmune HIT, spontaneous HIT and VITT-like disorders or severe HIT, and if a patient has a contra-indication to the use of a non-heparin anti-coagulant (2C).**
- **Treatment with IVIG and/or PEx is suggested in patients who have severe HIT syndrome or are presenting with a clear case of aHIT, when there is a lack of access to a non-heparin anti-coagulant, or in cases where clinically significant bleeding prevents the use of therapeutic anti-coagulation (2C).**

Re-exposure to heparin following the history of HIT, including management of patients with HIT undergoing cardiac surgery, percutaneous coronary intervention and haemofiltration.

Patients who developed HIT should ideally avoid rechallenge with heparin, especially now that several effective alternative anti-coagulants are available. For this purpose, they should be given an alert card and informed that they should not receive heparins in the future unless advised by a specialist. If such individuals require thromboprophylaxis, fondaparinux or a DOAC may be considered to prevent the resurgence of the HIT antibodies.

However, UFH is the preferred anti-coagulant for patients undergoing cardiac surgery and haemofiltration. In clinical practice, there are data to support the safe use of UFH in patients with previous HIT >3 months earlier. The basis for this is that (1) there is no relationship between the day of onset and previous heparin exposure; (2) in patients who develop rapid-onset HIT, the previous exposure to heparin is more recent; generally, in the last 100 days; and (3) HIT antibodies are transient and generally disappear with a median of 50–85 days, depending on the assay.[113] Warkentin et al. assessed the time taken to become negative for heparin-dependent antibodies in 144 patients who initially had positive tests. The median time to a negative test according to the Kaplan–Meier analysis was 50 days (95% CI, 32–64) according to SRA and 85 days (95% CI, 64–124) in the case of the antigen assay.[113]

When it was essential, re-exposure to heparin during cardiac surgery and vascular surgery in patients with previous HIT has been reported several times.[113–115] A systematic review that included 136 patients with a history of HIT had 141 instances of heparin re-exposure.[116] Of these 141 patients, the majority (66%) had re-exposure after 3 months following the diagnosis of HIT, while 11%, 8% and 15% had re-exposure within 1 week, between 1 week and 1 month and 1 month and 3 months following the diagnosis of HIT respectively. Cardiac surgery (76%) was the most common indication for re-exposure to heparin, and vascular surgery was the indication for 11% of the patients. Some patients (11%, 16/141) had plasmapheresis to reduce the PF4-heparin antibodies prior to re-exposure to heparin, while non-heparin anti-coagulants were used as single or combination anti-coagulant treatment following the re-exposure in 63% of patients. Following the re-exposure to heparin, a recurrence of HIT occurred in 2.1% of the patients.[116]

If an individual with a previous diagnosis of HIT requires an intervention where heparin is the most appropriate anti-coagulant, we recommend first to determine whether the antibodies are still present.[87,117] If the antibodies have cleared, rechallenge with heparin in the perioperative setting has been tried successfully by some experts.[24,118] In such patients, preoperative and postoperative use of UFH or LMWH should be avoided, and immediately following the completion of the procedure, an alternative non-heparin-based anti-coagulant such as argatroban, danaparoid sodium or fondaparinux should be started if the patient requires ongoing anti-coagulation or prophylaxis. This takes advantage of the fact that a minimum of 4 days is required to regenerate the HIT antibodies.[119]

If a HIT diagnosis has been made in the previous 100 days, surgery should be delayed, if it is safe to do so, until the disappearance of the antibodies.[6,24] Intraoperative anti-coagulation with a non-heparin anti-coagulant, for example bivalirudin,[120] is used if the surgery cannot be delayed or the antibodies are persistent. Intraoperative anti-coagulation with UFH combined with a platelet inhibitor, for example iloprost, has been used in patients with negative PF4-heparin antibodies.[121]

Bivalirudin has been widely used for patients with a history of HIT requiring percutaneous coronary intervention (PCI). Bivalirudin is licensed for use in patients undergoing PCI without HIT,[122] and therefore, it is reasonable to use it for patients with a relevant history for this indication. If bivalirudin is not available, then therapeutic PEx to remove HIT antibodies can be attempted with the use of UFH if seronegative.[123] In patients rechallenged with heparin, strict platelet count monitoring is required in the following 2 weeks given the risk of recurrent HIT, even when postoperative heparin is not administered.[87]

Patients on haemodialysis need more than a single heparin rechallenge, and hence anti-coagulation with a non-heparin anti-coagulant such as argatroban or danaparoid or the use of citrate will need to be considered because repeated exposure to heparin increases the risk of recurrent HIT.[87,116,124] If the patient has active HIT, they require

ongoing anti-coagulation, and we therefore recommend against the use of citrate.

RECOMMENDATIONS

- **In patients with a history of HIT, re-exposure to heparin should be avoided unless it is essential (1A).**
- **Screening for platelet-activating PF4–heparin antibodies is recommended if rechallenge with heparin is essential in patients with a history of HIT (1A).**
- **If the platelet-activating PF4–heparin antibodies are positive and surgery cannot be delayed, heparin should be avoided, and an alternative anti-coagulant should be used (2B).**
- **A functional assay for PF4-heparin antibodies prior to cardiac surgery is suggested for patients with a history of HIT (2C).**
- **Patients with a history of HIT who are antibody negative (usually after >100 days) requiring cardiac surgery, coronary intervention, including angiography and percutaneous coronary intervention should receive intraoperative UFH in preference to other anti-coagulants, which are less validated for this purpose. Preoperative and postoperative anti-coagulation should be with an anti-coagulant other than UFH or LMWH (1B).**
- **Patients with active or recent HIT (<100 days) requiring surgery should be reviewed to assess whether surgery can be postponed until the patient is antibody negative, after which surgery can proceed as above (1B).**
- **Use of bivalirudin is recommended in patients with active or recent HIT with positive PF4-heparin antibodies requiring cardiac surgery, coronary intervention, including angiography and percutaneous coronary intervention if the procedure cannot be delayed (2B).**
- **Use of PEx +/− IVIG is suggested for patients with HIT needing heparin re-exposure prior to CPB or vascular surgery if bivalirudin is not available and heparin use is essential during the surgery, with a change to a non-heparin anti-coagulant following the surgery (2C).**
- **In patients with a history of HIT requiring hemofiltration, a non-heparin anti-coagulant such as argatroban, danaparoid or citrate is suggested, as repeated exposure to heparin increases the risk of recurrent HIT (1C).**
- **Patients with active HIT requiring haemofiltration should receive a non-heparin anti-coagulant such as argatroban or danaparoid rather than citrate anti-coagulation (2B).**

Heparin-induced thrombocytopenia in pregnancy

HIT is rare in pregnancy[37,125] with most cases occurring following exposure to UFH,[126] and only a few reported after LMWH.[84,126,127] Due to the low incidence, routine monitoring of the platelet count is not deemed necessary if treated exclusively with LMWH.[37] This is supported by a study of 31 pregnant women who received thromboprophylaxis with dalteparin for a median of 33 weeks (6–45 weeks) of whom none developed PF4-heparin antibodies.[128]

The diagnosis of HIT in pregnant women is the same as in non-pregnant women, although care must be taken when using scoring systems to acknowledge the wide differential diagnosis of thrombocytopenia in the different trimesters of pregnancy. A study of 120 pregnant women demonstrated that HIT occurred after a median of 27.5 days of treatment.[125]

Currently available alternative anti-thrombotic drugs that may be used in pregnancy include danaparoid, argatroban and fondaparinux.[129,130]

Individualised written management plans are recommended for intrapartum and postpartum care as these drugs have variable half-lives, may be unfamiliar to the wider team, and confer a risk of intrapartum and postpartum haemorrhage.[126,130]

A small number of case reports describe the successful use of argatroban,[131–133] although it needs to be administered intravenously and bridged to an alternative anti-thrombotic drug prior to discharge.

In a review of 91 pregnancies treated with danaparoid, its use in pregnancy appears safe; it does not cross the placental barrier ($n = 6$) and is not found in breast milk ($n = 5$).[134]

Fondaparinux is well tolerated in pregnancy,[125,135–138] with over 68 reported cases and cohort studies. A retrospective study of 120 women who received fondaparinux in pregnancy (FondaPPP)[125] confirmed a rate of obstetric complications similar to that in the general obstetric population.

Fondaparinux passes the placental barrier to a small extent in vivo,[139] but this is unlikely to be of clinical significance.[129] It is important to recognise the different pharmacokinetic properties of fondaparinux compared to LMWH, with a 24–42-h rule for prophylactic doses and 48 h in women receiving treatment doses of fondaparinux.[125] The recommendation is to avoid neuraxial blockade in patients receiving therapeutic doses.[140] Use in breastfeeding is felt appropriate.[141]

RECOMMENDATIONS

- **Argatroban, danaparoid and fondaparinux are suggested alternatives to treat HIT in pregnancy (2C).**
- **A written management plan for intrapartum and immediate postpartum care is suggested, taking the pharmacokinetic properties of danaparoid, fondaparinux or argatroban into account (2C).**

AUTHOR CONTRIBUTIONS

Deepa J. Arachchillage chaired the writing group. All authors contributed to writing, editing and reviewing the manuscript, including the final submission.

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Correction made on 10 January 2024, after first online publication: The previous reference 99 was deleted, a new reference 101 was added, and the second last paragraph under 'Alternative anti-coagulant (parenteral options)' section was improved for clarity in this version.

CONFLICT OF INTEREST STATEMENT

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a full declaration of interests to the BSH and Task Force Chairs, which may be viewed on request. None of the authors have any relevant conflicts of interest to declare.

REVIEW PROCESS

Members of the writing group will inform the writing group chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force, and the literature search will be re-run every 3 years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made, an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk/guidelines).

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AUDIT TOOL

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ORCID

Deepa J. Arachchillage https://orcid.org/0000-0001-5993-4850
Peter Baker https://orcid.org/0000-0002-6233-5389
Mike Laffan https://orcid.org/0000-0002-8268-3268

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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