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*Editorial Comment*

# Heparin-induced thrombocytopaenia (HIT)—an overview: what does the nephrologist need to know and do?

Tina Dutt[1] and Michael Schulz[2]

[1]Department of Haematology, Royal Liverpool University Hospital, Liverpool, UK and [2]Department of Nephrology, Royal Liverpool University Hospital, Liverpool, UK

*Correspondence and offprint requests to:* Tina Dutt; E-mail: tina.dutt@rlbuht.nhs.uk

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## Introduction

In an era where medical and critical care patients are more commonly subject to thromboprophylaxis, prompt recognition and appropriate treatment of Heparin-induced thrombocytopaenia (HIT) is required to reduce the risk of serious thrombotic events. In this issue of the Clinical Kidney Journal, Thong *et al.* present two cases of HIT after initiation of dialysis therapy with heparin as anticoagulant (see 'Management of heparin-induced thrombocytopaenia (HIT) in patients with systemic vasculitis and pulmonary haemorrhage' in this issue). This prompts us to present the following overview on diagnosis and management of patients with HIT requiring regular dialysis therapy.

## Pathophysiology

Heparin-induced thrombocytopaenia is defined as a decrease in platelet count during or shortly following exposure to heparin [1]. Although it is almost a century since the discovery of heparin, the defining features of HIT were first described in the early 1970s [2] followed by increasing reports of a condition suspected to have an underlying immunological basis. We now know that HIT is a potentially devastating immune-mediated reaction caused by the development of IgG antibodies against the complex of heparin and platelet factor 4 [3]. IgG/PF4/heparin complexes bind and activate circulating platelets through their Fc receptors promoting thrombin generation and platelet aggregation. Paradoxically, this is clinically manifested by an increased propensity for arterial/venous thrombosis despite a falling platelet count. The condition often will affect patient groups who are already at an increased thrombotic risk due to their clinical predicament such as those with renal failure or requiring renal replacement therapy. Such patients will often have coexistent causes for thrombocytopaenia other than HIT.

## Incidence

A critical assessment of immune-mediated HIT suggests a frequency of 0.2–5.0% in patients exposed to heparin for more than 4 days with an overall incidence of 2.6% noted in a meta-analysis [4]. Most patients have undergone a proximate immunizing exposure to unfractionated or less commonly low-molecular-weight heparin (LMWH). The risk of developing HIT appears to be up to 30 times lower with LMWH than with the administration of unfractionated heparin (UFH), although it remains controversial whether the reduced risk is also true for the long-term use of LMWH [5–8]. LMWHs with their reduced polysaccharide chain length have superior pharmacokinetic properties compared with UFH in patients with normal renal function. One could debate however whether these potential advantages apply for patients with renal failure. The principle limitation is that LMWHs are predominately cleared by the renal route and therefore their biological half-life is significantly prolonged in renal failure. However, currently there is a trend for many dialysis units in the UK for reasons of convenience (one off bolus dose) and efficacy to use LMWHs instead UFH.

Currently, unfractionated or LMWHs are used in the majority of renal units to prevent clotting in the extracorporeal circuit. In addition, heparin is also used as line-lock solution in some patients with catheter-only dialysis access. Therefore, the vast majority of patients on standard maintenance haemodialysis therapy have either heparin injected three times per week or some might arguably even be exposed to it permanently. This potentially presents a significant problem in patients who need heparin for regular haemodialysis therapy, although the incidence rate for this population is currently not well researched. Certain patient groups, including post-cardiac surgery and female gender, may increase the risk of developing HIT.

It is likely that HIT was previously a condition overlooked or underdiagnosed, which may have led to a lower presumed incidence.

## Presentation

HIT can manifest clinically in a number of ways: thrombocytopaenia, thrombosis, skin necrosis at heparin injection sites, venous limb gangrene and the more recently

described acute systemic reaction 5–30 min following IV UFH bolus [9]. The condition can be classified as HIT 1 or HIT 2. Type 1 HIT occurs as a direct result of heparin on platelet activation and resolution of thrombocytopaenia occurs spontaneously. HIT 2 represents an immune disorder as described below.

A 50% fall in the platelet count due to HIT typically occurs 5–10 days after commencing heparin, however, if patients have been exposed to heparin in the preceding 3 months there can be a more rapid fall due to pre-existing antibodies. It is worthy to note that a 50% fall in the platelet count does not automatically render the platelet count abnormally low; therefore, a drop from 400 to $200 \times 10^9$/l could still have implication. Severe thrombocytopaenia ($<15 \times 10^9$/l) is unusual, with a median nadir reported around $55 \times 10^9$/l [10]. Despite thrombocytopaenia, bleeding is rare [11]. Mortality in patients with HIT and thrombosis can be up to 30% [12] and patients with central venous catheters and HIT develop upper limb venous thrombosis more frequently than those without HIT [13].

For the dialysis population, it is important to recognize that HIT seems to occur at any stage of heparin therapy but seems to be more likely in the first 5–10 days of heparin. Delayed-onset HIT is also described [14]. It is arguably under-recognized in dialysis patients who have many coexisting conditions to account for mild-to-moderate thrombocytopaenia (increased platelet consumption, immunosuppression, drugs and uraemia). When blood passes through the extracorporeal circuit in haemodialysis an activation of platelets can be observed. Usually at the beginning of dialysis the platelet count decreases marginally, although in most cases by the end of the dialysis session the original readings return [15]. However, there have been cases of haemodialysis patient reports in which significant decreases in the platelet count (50% or more) during dialysis was observed, resulting in mild degrees of pre-dialysis thrombocytopaenia [15]. Hence, the challenges for the nephrologists considering HIT can be multiple.

The clinical features can be non-specific and vary between an asymptomatic drop in the platelet count with increased clotting in extracorporeal dialysis circuit 'despite sufficient anticoagulation' to failing venous access, which is difficult to diagnose as clotting in the dialysis circuit and chronic access dysfunction are common dialysis-related problems. Acute local injection site reactions are described in 10–20% of patients with HIT [16]. Severe HIT-associated systemic (anaphylactoid) reactions or sudden cardiovascular events or acute thromboembolic events (so-called white clot syndrome with predominately arterial platelet rich thrombosis) can easily be mistaken for a dialysis-related symptom because infections with septicaemia or cardiovascular events in a vasculopathic dialysis population are expected complications. Clotting of the dialysis circuit as per Cases 1 and 2 in the accompanying article is not an uncommon presentation. The initial presumption of 'insufficient anticoagulation' may have devastating consequences as the reflex response would be to increase the heparin dose.

In most countries it seems to be common practice to monitor blood results in patients in a chronic haemodialysis programme on a monthly basis; however, there may arguably be a case to monitor the full blood count in the first weeks of starting dialysis much more frequently. The BCSH guidelines for HIT suggest that all patients receiving any type of heparin should have a baseline platelet count. Further, higher risk patients such as cardiopulmonary bypass grafting and obstetric cases should have routine platelet count monitoring testing from Days 4 to 14 or until heparin is stopped. The same could be extrapolated to patients with renal failure; however, a formal guideline for detection and management of HIT in renal patients would be of value.

Given the multitude of reasons for a drop in platelet count or clotting complications in haemodialysis patients, constant vigilance and awareness of the potential mode of presentation of HIT is absolutely crucial for all haemodialysis staff, bearing in mind that in many countries the provision of haemodialysis and monitoring of its day-to-day complications lays predominantly in the hands of nurses.

## Diagnosis

HIT is a clinical–pathological syndrome where an observed fall in the platelet count should prompt the clinician to first weigh the likelihood of a diagnosis of HIT on clinical grounds.

The 4T scoring system is most widely known and is used to assess how compatible the clinical picture is with a diagnosis of HIT (see Table 1). Interestingly, scoring systems used to assess the clinical pre-test probability of HIT [17] may underscore patients who have a similar likelihood for both HIT and other causes for thrombocytopaenia such as patients with renal failure.

Because of the challenges of clinical diagnosis, physicians rely heavily on laboratory testing; however, it is important to recognize that HIT antibody formation may occur without consequential thrombocytopenia and the full clinical HIT picture.

Laboratory testing to detect antibody formation in HIT can be broadly classified into platelet activation assays or immunological assays targeted towards PF4 or heparin. Functional tests, which measure platelet activity in the presence of the patient's serum and heparin, e.g. heparin-induced platelet aggregation and the serotonin release assay offer greater specificity; however, these tests are complex and technically demanding. Consequently, most centres tend to perform the ELISA with the limitation that low titre antibodies of no clinical significance may be detected. As it is only IgG antibodies that activate platelets, IgG-specific immunological assays are now commercially available [18, 19]. A further consideration in interpreting the test results relates to the absolute optical density (OD) values, a marker of antibody levels where increased levels correspond to a greater risk of HIT [20]. The 2012 BCSH Guidelines suggest that a cut-off point for a positive test should be used when using an immunological ELISA to look for HIT antibodies, rather than simply reporting a positive or negative [21]. A retrospective study of the trend of sequential quantitative results obtained using an ELISA immunoassay showed that initial high negative OD values (0.7–1.0) have a significant chance of becoming clearly positive (>1.0) with repeat testing suggesting sequential testing in such cases [22].

In summary, the diagnosis of HIT should only be entertained if the clinical picture fits. A pre-test probability of at least 4 using the 4T Scoring System should be taken together with the type of assay used and the quantitative result to determine a post-test probability. In routine clinical practice, as many clinicians do not have direct access to the complete portfolio of laboratory assays, it would be

**Table 1.** Estimating the pre-test probability of HIT; the 4Ts score [17]

| 4Ts | 2 points | 1 point | 0 point |
|---|---|---|---|
| **T**hrombocytopenia | >50% platelet count fall to nadir ≥20 | 30–50% platelet count fall or nadir 10–19 | <30% platelet count fall or platelet nadir <10 |
| **T**iming[a] of onset of platelet count fall or other sequelae of HIT | Days 5–10 or ≤Day 1 with heparin exposure (within 30 days) | >Day 10 or timing unclear; or <Day 1 with recent heparin exposure (past 31–100 days) | <Day 4 (no recent heparin exposure) |
| **T**hrombosis or other sequelae | New thrombosis (proven); skin necrosis; or acute systemic reaction post-intravenous unfractionated heparin bolus | Progressive or recurrent thrombosis; erythematous skin lesions, suspected thrombosis (not proven) | None |
| O**t**her causes for thrombocytopaenia | None evident | Possible | Definite |

Maximum possible score 8, pretest probability score 6–8 indicates high, 4–5 intermediate and 0–3 low. Adapted from Warkentin TE, HIT Diagnosis and Management, Circulation, 2004 [17].
[a]First day of immunizing heparin exposure considered Day 0.

reasonable to discuss suspected cases and investigation with the haematology team and laboratory.

## Treatment

Once clinically suspected, the principles of treatment involve cessation of all heparin formulations and initiation of an appropriate alternative anticoagulant. Discontinuation of the trigger alone is not sufficient as there needs to be targeted treatment against the thrombin storm as well as protection against subsequent thrombotic events, which occur in as many as 40–50% of the patients over the next several days or weeks [23]. Reflex platelet transfusion directed towards a thrombocytopaenia or minor bleeding is also contraindicated and should only be reserved for life-threatening haemorrhage to avoid potential exacerbation of thrombotic risk [24].

If HIT is suspected in a dialysis patient, dialysis needs to be performed heparin free. There are a number of options ranging from dialysis with either continuous pre-dilution with saline or regular bolus injection of saline to short, daily dialysis. However, saline infusions are labour intensive and seem to have a high treatment failure rate and daily dialysis is not always feasible. Using one of the available alternative anticoagulants might be a more long-term option. Currently, three non-heparin anticoagulants that do not cross-react with HIT antibodies, danaparoid, lepirudin and argatroban are available for anticoagulation in HIT.

Where HIT occurs with unfractionated heparin, LMWH should not be used as an alternative due to up to 50% cross-reactivity. Although the HIT syndrome in itself is rarely associated with bleeding, the alternative anticoagulant treatment options carry a bleeding risk and therefore should be carefully chosen.

The ideal alternative for patients on haemodialysis might be argatroban, a synthetic thrombin inhibitor, as it is not excreted by the kidneys and does not require a renal dose adjustment [23]. Monitoring is recommended using the activated partial thromboplastin time (APTT) aiming for a target range of 1.5–3.0. Standard initial dosing is 2 ug/kg/min as a continuous infusion except for critical care patients where the SmPC suggests 0.5 ug/kg/min. Standard initial dosing is recommended as a continuous infusion except for critical care patients where the SmPC provides a reduced dosing regimen. When transferring patients on to oral anticoagulation with warfarin, argatroban-induced prolongation of the prothrombin time needs to be taken into account. The two drugs should be overlapped for at least 5 days and an INR of 4–5 achieved for 2 consecutive days before discontinuing the argatroban. It remains unclear if argatroban is dialysable. Whilst one author demonstrated that there was only an insignificant amount of argatroban removed through dialysis compared with endogenous clearance, the product labelling suggests that ∼20% of the drug can be cleared through haemodialysis [25].

Danaparoid can also be used however; patients with significant renal disease should receive reduced dosing regimens. Danaparoid is a conjugate of heparin sulphate, dermatan sulphate and chondroitin sulphate and was originally FDA approved for VTE prophylaxis in surgical patients post-op. Relative to heparin, danaparoid has an increased antifactor Xa: anti-factor IIa activity of around 28:1 versus 1:1. The drug has a predictable dose response and therefore monitoring is usually only required in certain patient populations, in particular those with severe renal disease and body weight less than or greater than 55 or 90 kg, respectively [24]. Prophylactic and therapeutic dosing regimens are available; however, studies suggest that low-dose regimes may be associated with a higher rate of new thrombotic events. Monitoring is performed using the anti-Xa assay using danaparoid sodium as the standard. The use of danaparoid has been studied in critically ill patients and those undergoing haemofiltration/haemodialysis. Example regimes for haemofiltration include 100–400 U/h iv to achieve anti-Xa levels of 0.5–1 U/mL and 40 U/kg iv for haemodialysis [25]. Example regimes for haemofiltration and haemodialysis have been reported [26]. It is not known if danaparoid is dialysable.

Lepirudin, a recombinant hirudin, is a natural thrombin inhibitor and has been shown to reduce the risk of death, new thromboembolic complications and limb amputation during treatment [27]. Standard dosing consists of 0.4 mg/kg bolus followed by 0.15 mg/kg/hr and standard dosing consists of a bolus followed by an infusion and monitoring employs the APTT aiming for a range of 1.5–2.5. Lepirudin should not be given if the APTT is >2.5 times the normal. The $t_{1/2}$ of lepirudin is significantly prolonged with reduced renal function and therefore 50% reduced dosing for bolus and infusion is advised where creatinine levels are 1.5–2.0 mg/dL and further caution with greater renal impairment [28]. For dialysis patients, where the $t_{1/2}$ is around 50 h, altered doses have been advised pre-dialysis to successfully maintain anticoagulation through

dialysis [29]. Lepirudin is dialysable if used with high-flux polysulfone dialysers [30].

Although unlicensed in HIT, fondaparinux, a synthetic polysaccharide, has been used favourably in patients with HIT. It lacks the sugar domain necessary to complex with PF4, making the likelihood of inducing HIT extremely low. A number of reports exist detailing its favourable use in HIT, in patients with renal failure [31] and on haemodialysis [32]. The initial daily dose is as per usual (7.5 mg/d for a patient weighing between 50 and 100 kg), but anti-Xa levels are used to judge subsequent doses. Maintenance doses may only require 2.5 or 5 mg daily.

Practice around the duration of treatment for patients with HIT is variable. Prospective studies suggest that the risk for thrombosis can persist for up to 6 weeks; therefore, a minimum of 2 months has been advised. Warfarin initiation can be considered once the platelet count has returned to baseline using a regime overlapping with the specific alternative anticoagulant that the patient has been receiving. Discontinuation of heparin and initiation of warfarin alone is not recommended because of reports of venous limb gangrene most likely secondary to warfarin induce protein C depletion combined with the ongoing thrombotic process [23].

Finally, it is worthwhile to provide affected patients with information about their condition and advice not only about the risk of thrombosis in the acute setting but also to highlight that should they require heparin in the next 120 days, antibody testing may be required as well as the use of alternative anticoagulation. As with other drug-induced adverse events, the patient's case notes should be marked to advise clinicians of future risk.

Accurate recognition, evaluation and appropriate treatment of HIT in renal patients remain a considerable challenge and an optimal management regime is not yet backed by sufficient clinical evidence. Due to the low diagnostic specificity of the widely applied PF4-dependent immunoassays to look for HIT antibodies, ironically there has been a recent epidemic in over-diagnosing HIT. Testing only for IgG class antibodies where the more specific functional assays are not available should improve this. Taking into consideration patient and diagnostic variability, it would seem prudent to discuss management cross-speciality in particular dosing regimens for drugs not typically used outside of the HIT arena. For the future it remains to be seen if the current trend to the increasing use of LMWHs for dialysis will translate into a reduced incidence of HIT in chronic haemodialysis patients. It is yet to be seen what therapeutic role the new oral anticoagulants may play in this niche area.

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