Heparin-induced thrombocytopenia: a renal perspective

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Abstract | Heparin-induced thrombocytopenia (HIT) is a clinicopathologic syndrome in which one or more clinical events, usually thrombocytopenia or thrombosis, are temporally related to heparin administration and caused by HIT antibodies. Rapid and accurate diagnosis is essential given the high incidence of thrombosis at around the time of initial disease recognition. Discontinuation of heparin and initiation of alternative anticoagulants reduces HIT-associated morbidity and mortality. The clinical consequences of HIT in hemodialysis patients remain unclear, with several studies reporting no clinical sequelae and others describing complications such as thrombocytopenia or clotting of the extracorporeal circuit. Frequent clotting of the extracorporeal circuit has also been reported in HIT-antibody-positive patients on continuous veno-venous hemofiltration. Several recent findings are of particular interest to nephrologists. An acute systemic reaction has been described as a presentation of HIT in hemodialysis patients shortly after administration of an unfractionated heparin bolus. This syndrome is important to recognize as it might mimic a dialyzer reaction. More recently, the presence of a positive HIT-antibody test or increasing titers of HIT antibody were associated with increased mortality in hemodialysis patients, raising the question of whether these antibodies have a role in the increased cardiovascular mortality seen in these patients. HIT-antibody production is often transient and small numbers of hemodialysis patients with undetectable antibody levels have been rechallenged with heparin without adverse clinical consequences.

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Introduction

As a result of its ease of use, short half-life, and low cost, heparin remains the most commonly prescribed anticoagulant in hospitalized patients for both prophylaxis and treatment of thrombotic disorders. One-third of all hospitalized patients in the US, approximately 12 million people, receive heparin annually.[1] For the same reasons, heparin is also the anticoagulant of choice in patients on intermittent and continuous forms of renal replacement therapy.

In 1958, Weismann and Tobin published what was probably the first clinical description of heparin-induced thrombocytopenia (HIT) in their report of 10 patients anticoagulated with heparin who had multiple, recurrent arterial thrombi.[2] In 1973, Rhodes *et al.* demonstrated that sera from patients affected by HIT aggregated normal platelets in the presence of heparin and that this process was mediated by complement-fixing, heparin-dependent antibodies.[3] Subsequently, in 1992, Amiral *et al.* identified the HIT antigen to be a complex of platelet factor 4 (PF4) and heparin.[4]

After briefly reviewing the definition and clinical presentation of HIT, its pathogenesis, diagnosis, epidemiology and risk, we will examine HIT from a nephrological perspective. We will review manifestations of HIT in patients on renal replacement therapy, its recent association with increased mortality in hemodialysis patients, newer aspects of its treatment in the renal patient, and heparin rechallenge in individuals who revert to antibody-negative status.

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Key points

- Heparin-induced thrombocytopenia (HIT) is a clinicopathologic syndrome with one or more clinical events, usually thrombocytopenia or thrombosis, temporally related to heparin administration and caused by HIT antibodies
- The traditional commercial ELISA cutoff value (≥0.4 optical density units) for a positive HIT-antibody test only diagnosed 50% of patients at high to intermediate risk of HIT correctly
- An acute systemic reaction has been described as a presentation of HIT in hemodialysis patients shortly after administration of an unfractionated heparin bolus
- The presence of a positive HIT-antibody test or increasing titers of HIT antibody is associated with increased mortality in hemodialysis patients
- HIT-antibody production is often transient and small numbers of hemodialysis patients with a history of HIT and undetectable antibody levels have been rechallenged with heparin without adverse clinical consequences

Definition and clinical presentation of HIT

HIT is a clinicopathologic syndrome in which one or more clinical events, usually thrombocytopenia and/or thrombosis, are temporally related to heparin administration and caused by HIT antibodies.[5–8] At least five different types of clinical events are associated with HIT: thrombocytopenia; thrombosis; skin necrosis at heparin injection sites; venous limb gangrene; and an acute systemic reaction that occurs 5–30 min after an intravenous bolus of unfractionated heparin (UFH).

HIT typically presents 5–14 days after initiation of heparin therapy. Seroconversion and initial decline in platelet count occurs 5–10 days after initiation of heparin with the nadir between day 7 and day 14.[9] HIT might occur sooner in individuals with previous recent heparin exposure (within the past 100 days), or rarely can occur up to 2 weeks after heparin is discontinued in patients with high titers of platelet-activating IgG antibodies.[10] HIT is associated with a greater than 30–50% decline from baseline in platelet count—often to less than 100×10^9/l.[5] The platelet count nadir in HIT is often less severe (median 60×10^9/l) than in cases where thrombocytopenia is induced by other drugs.[11] A platelet count below 20×10^9/l is seen in less than 10% of HIT cases and the degree of thrombocytopenia correlates with disease severity.[11] Thrombocytopenia usually resolves 1–2 weeks after heparin is discontinued. Failure of thrombocytopenia to resolve during this time frame or while the patient is being treated with an alternative anticoagulant for HIT should prompt a search for a different diagnosis.

Although HIT causes thrombocytopenia, major complications of HIT include thromboembolic phenomena such as pulmonary embolism, deep venous thrombosis, myocardial infarction and limb ischemia. Thrombosis can occur at or shortly after the time of thrombocytopenia, which emphasizes the need for timely diagnosis. A retrospective study of 127 patients with HIT reported that 65 patients had thrombosis at the time of initial diagnosis.[12] Another study reported that 34% of patients already had thrombosis when diagnosed with HIT and an additional 26% developed thrombosis on the day that the platelet count fell to a level that met the criteria for HIT diagnosis.[13] Mortality in individuals with HIT and thrombosis may be as high as 30%.[14] Venous thrombi are four times more common than arterial thrombi in patients with HIT.[7]

In patients with HIT, skin necrosis can appear 5–9 days after heparin exposure and manifests as local erythema and induration that progresses to frank necrosis.[15] Lesions appear at or near injection sites and are initially small, erythematous and painful, but can progress to bullae. Affected areas are often fat-rich regions such as the abdominal wall, but other areas—including distal extremities and the nose—might be involved.

Patients with HIT and deep venous thrombosis can develop distal ischemic limb necrosis without arterial occlusion—so-called venous limb gangrene. Warkentin *et al.* found that patients with venous limb gangrene were more likely to have received warfarin than were those with arterial thrombosis.[16] They also noted that peak international normalized ratio (INR) was higher in patients with venous limb gangrene than in those without (5.8 versus 3.1), which indicates that the anticoagulant effect of warfarin was greater in those with venous limb gangrene. A reduction in protein C activity induced by warfarin disturbs the procoagulant–anticoagulant balance and leads to failure of regulation of thrombin generation by the protein C anticoagulant pathway. This creation of a second procoagulant state—in addition to HIT—further predisposes an individual to venous limb ischemia.

An acute systemic reaction that occurs 5–30 min after an intravenous bolus of UFH has been described as a manifestation of HIT.[17] Nephrologists should be aware of such a reaction since it can masquerade as an acute dialyzer reaction. This reaction can manifest in two ways: as an acute inflammatory reaction characterized by fever and chills; or as a cardiorespiratory presentation with signs and symptoms that include hypotension, tachycardia, tachypnea, flushing, headache, dyspnea, chest pain and cardiopulmonary arrest. Dyspnea can be so severe that it mimics a pulmonary embolism ("pseudopulmonary embolism syndrome")[18] and is thought to result from release of interleukin 6 and von Willebrand factor from endothelial injury. This syndrome was also described in a hemodialysis patient with HIT who received only a heparin catheter lock without a bolus of UFH.[19] Vascular collapse ensued and the patient died. Thrombocytopenia in this setting is often transient and platelet count should be checked as soon as possible after symptoms appear to aid in verifying the diagnosis.

Pathogenesis

The pathogenesis of HIT has been well described in several reviews[2,7] and will only be briefly summarized below. Rhodes *et al.* first showed HIT to be an immune-mediated process in 1973.[5] Heparin binds to PF4, causing a conformational change that results in exposure of neoepitopes on PF4 that act as antigens.[6] IgG antibodies are

typically formed, although IgA and IgM antibodies have also been described.[20] The role of non-IgG antibodies in the pathogenesis of HIT is unclear, and the vast majority of pathogenic antibodies in HIT are of the IgG subclass. The heparin–PF4 complex, once formed, binds to the platelet surface and neo-epitopes are recognized by the Fab region of the HIT antibody, resulting in formation of a heparin–PF4–antibody complex on the platelet surface, which leads to platelet activation.[21] Activated platelets then release additional PF4, which also binds to the platelet surface. Platelets undergo aggregation and initiate thrombosis. Thrombotic complications might also be related to other immune-mediated injuries such as direct endothelial damage and activation.[22,23] The risk of thrombosis increases with the degree of thrombocytopenia.[24]

Box 1 | Diagnostic criteria for HIT

- Thrombocytopenia occurring typically 5–10 days after the start of heparin therapy
- Presence of any acute thrombotic event
- Normal platelet count before heparin administration
- Thrombocytopenia (a decrease in platelet count by >30% to below 100×10^9/l or a drop in platelets >50% from baseline)
- No other cause of thrombocytopenia
- Resolution of thrombocytopenia after heparin cessation
- HIT-antibody seroconversion

Abbreviation: HIT, heparin-induced thrombocytopenia.

Diagnosis

HIT should be suspected in any patient who develops thrombocytopenia during or shortly after heparin therapy. Recently hospitalized patients presenting with thromboembolism are at high risk of HIT.

HIT is a clinicopathologic diagnosis: laboratory findings must be interpreted together with clinical information. Diagnostic criteria are shown in Box 1.[1] The British Hemostasis and Thrombosis Task Force recommended use of the "4 T's", as described by Warkentin *et al.*, for estimating pretest HIT probability (Table 1).[25]

Two studies prospectively evaluated use of the 4 T's clinical scoring system for the diagnosis of HIT in consecutive inpatients.[26,27] The renal function of patients was not reported in either study. The first study examined 100 patients in Canada and 236 patients in Germany.[26] In both centers, a low pretest clinical score for HIT was excellent in ruling out a diagnosis of HIT (63/64 patients in Canada and 55/55 patients in Germany). Although patients with intermediate or high scores were more likely to test positive for HIT by enzyme-linked immunosorbent assay (ELISA), a large amount of variability existed between the two institutions (intermediate scores predicted clinically significant HIT antibodies in 28.6% of patients in Canada versus 7.9% in Germany; high scores predicted clinically significant HIT antibodies in 100% of patients in Canada versus 21.4% in Germany). The second study evaluated use of the 4 T's for the diagnosis of HIT in 213 patients in France.[27] In individuals with low pretest 4 T's score the post-test probability of HIT diagnosis was zero, regardless of ELISA result. Patients with an intermediate 4 T's score had a 0.6% post-test probability of HIT if they had a negative ELISA and a 58.2% post-test probability of HIT if they had a positive ELISA. Individuals with high 4 T's scores had a 16% post-test probability of HIT if their ELISA was negative and a 98% post-test probability of HIT if they had a positive ELISA.

The diagnosis of HIT requires laboratory confirmation. HIT antibodies can be detected by both functional and immunologic assays. Functional tests measure platelet activation in the presence of patient serum and heparin. These tests—which include the ^{14}C-serotonin release assay and the platelet aggregation assay—rely on the capability of HIT antibody to activate platelets. The ^{14}C-serotonin release assay remains the gold standard among functional tests. It has very high sensitivity (88–94%) and specificity but is performed in only a small number of reference laboratories.[28] The ^{14}C-serotonin release assay can also detect antigens other than PF4 that might, rarely, be involved in the pathogenesis of HIT (for example, interleukin 8 and neutrophil-activating peptide 2). The platelet aggregation assay is less sensitive (35–85%) than the ^{14}C-serotonin release assay.[4]

The solid-phase ELISA immunoassay is very sensitive (90–98%) but has low specificity (50–93%),[29] which results in the frequent detection of HIT antibody in the absence of clinical disease. Commercial ELISA assays identify anti-PF4/heparin IgG, IgA and IgM antibodies. Very few, if any, of the IgA and IgM antibodies are pathogenic. In addition, as not all IgG antibodies are pathogenic, specificity cannot be improved by simply employing an assay that does not detect IgA and IgM antibodies. Advantages and disadvantages of functional and immunologic assays are summarized in Table 2.

The commercial ELISA assay has the potential to substantially overdiagnose HIT. A commercial ELISA assay is reported as positive if the optical density (O.D.) is ≥0.4 O.D. units. To address the problem of overdiagnosis, Lo *et al.* employed a combination of assessment of pretest probability employing the 4 T's scoring system with testing for HIT antibodies using several methods. They found that an intermediate to high pretest probability score combined with a commercial ELISA (EIA-GTI kit, GTI Diagnostics, Waukesha, WI) optical density of ≥1.2 O.D. units was associated with a positive gold standard ^{14}C-serotonin release assay diagnosis of HIT in 16 of 16 patients.[30] An additional 16 patients with an intermediate O.D. ≥0.4 but <1.2 that would be considered a positive test did not have HIT and were felt to have other causes of thrombocytopenia. Therefore, using the traditional commercial ELISA cutoff value (≥0.4 O.D. units) for a positive HIT-antibody test would have correctly diagnosed only 50% of patients with high to intermediate probability. One patient would be potentially

Table 1 | Estimating pretest probability of HIT: the "4 T's"*

Category	2 points	1 point	0 point
Thrombocytopenia	>50% fall in platelet count, or nadir of 20–100 × 10^9/l	30–50% fall in platelet count, or nadir of 10–19 × 10^9/l	30% fall in platelet count or nadir <10 × 10^9/l
Timing of platelet count fall	Day 5–10, or ≤day 1 with recent heparin exposure‡	>Day 10 or unclear timing (but fits with HIT)	≤Day 1 (no recent heparin)
Thrombosis or other sequelae	Proven thrombosis, skin necrosis, or acute systemic reaction after intravenous heparin bolus	Progressive, recurrent, or silent thrombosis; erythematous skin lesions	None
O**T**her cause for thrombocytopenia	None evident	Possible	Definite

*Points assigned in each of four categories are totaled, and pretest probability of HIT by total points is as follows: 6–8 = high; 4–5 = moderate; 0–3 = low. ‡Within past 30 days (2 points); 30–100 days previously (1 point). Abbreviation: HIT, heparin-induced thrombocytopenia.

Table 2 | Advantages and disadvantages of diagnostic tests for HIT

	Functional tests	Immunologic assays
Pros	Highly sensitive and specific Detect pathogenic antibodies Can detect other antigens besides PF4 ^{14}C-serotonin release assay is gold standard test	Highly sensitive Less operator dependent than functional tests Readily available
Cons	^{14}C-serotonin release assay requires radioisotopes Performed in only a few reference laboratories Operator dependent	Low specificity Detect nonpathogenic IgA and IgM antibodies Many IgG antibodies detected are nonpathogenic

Abbreviations: HIT, heparin-induced thrombocytopenia; Ig, immunoglobulin; PF4, platelet factor 4.

misdiagnosed for each one correctly diagnosed, and many patients would be exposed to the risks associated with unnecessary alternative methods of anticoagulation. Individuals with a higher O.D. value (≥1.2 O.D. units) have an excellent correlation with diagnosis by the gold standard ^{14}C-serotonin release assay.

These findings indicate that high-titer IgG antibodies are responsible for HIT and that clinical laboratories should consider reporting the actual O.D. value in addition to whether the test is positive or negative. These important findings await validation in other centers and in individuals with kidney disease.

Epidemiology and risk of HIT

Although all individuals receiving heparin, regardless of type or dose, are at risk of HIT, not all develop the clinical syndrome. The incidence of HIT depends on the patient population, as well as type and source of heparin used. Patients treated with low-molecular-weight heparin (LMWH) have been observed to have a much lower likelihood of developing HIT than those treated with UFH.[31] The risk of HIT in medical patients who have received LMWH might be higher in those with prior heparin exposure.[32] A meta-analysis of five studies showed that unfractionated bovine heparin is more likely to cause HIT than unfractionated porcine heparin.[33]

Manifestations of HIT in hemodialysis patients

The presence of HIT antibody in patients undergoing hemodialysis has been reported in at least 15 studies involving 3,818 patients from 8 countries (Table 3) and ranges from 0% to 17.4%.[34–48] All but one of these studies involved prevalent patients.[34] The type of heparin used was reported in 1,668 patients. HIT antibodies were demonstrated by ELISA in 8.1% of the 1,450 patients exposed to UFH and in 1.8% of 218 patients dialyzed with LMWH. The frequency of a positive ELISA was lower in studies that measured only IgG HIT antibody complexes[36,44] than in those that measured complexes containing IgG, IgA or IgM.[41,46,48] Functional assays were performed in 730 patients exposed to UFH and positive results reported in 3.7%. Functional assays were positive in some patients whose ELISA assay did not detect HIT antibody.

The risk of HIT complications in the hemodialysis population remains unclear. Several studies have reported no clinical sequelae despite positive antibody tests.[35,36,38,39,43] Other studies have reported HIT complications in patients on hemodialysis, primarily thrombocytopenia, frequent clotting of the extracorporeal circuit,[34,40,41] or an increase in the number of failed arteriovenous fistulae.[47] The majority of the studies[34–48] were cross-sectional and two of them had follow-up periods of only 3 months[38] and 6 months.[36] Their cross-sectional nature and the short duration of follow-up might have resulted in failure to detect HIT-related clinical events. Two studies warrant additional discussion.

In the only study that examined incident hemodialysis patients, Yamamoto *et al.* reported that clotting of the extracorporeal circuit was a manifestation of HIT. They examined 154 patients with end-stage renal disease ($n = 104$) or acute kidney injury ($n = 50$) newly treated with hemodialysis between 1993 and 1995.[34] The following criteria were used for clinical suspicion of HIT:

Table 3 | Studies of HIT-antibody positivity in hemodialysis patients

Country[reference]	*n*	Heparin	Follow-up	Patient population	Number of patients with HIT antibodies by ELISA	Number of patients with HIT antibodies by functional tests
Japan[34]	154	Porcine UFH	Incident patients	Incident AKI/ CHD patients	5 by ELISA (3.2%)	4 by HIPA (1 of whom was ELISA negative)
Germany[35]	165	NA	CS study; not stated	CHD	NP	7 by HIPA
Germany[36]	70	UFH	6 months	CHD	2 (2.8%) IgG only	NP
US[37]	45	Porcine UFH	CS study; not stated	CHD	0 (0%) IgG, IgA or IgM	NP
Netherlands[38]	261	128 UFH 133 LMWH	3 months	CHD	3 IgG, 1 IgM (3.1%) in UFH group 1 IgG (0.7%) in LMWH group	NP
USA[39]	81	NA	CS study; not stated	CHD	1 (1.2%)	NP
Japan[40]	305	220 UFH 85 LMWH	2 years	CHD	4 (1.8%) in UFH group 3 (3.5%) in LMWH group	NP
Sweden[41]	100	UFH	6–8 months	CHD	6 (6%)	17 by HIPA
Canada[42]	419	UFH	2.5 years	CHD	54 (12.9%); only 9 IgG	5 by SRA
Italy[43]	50	Porcine UFH	CS study; not stated	CHD	6 (12%): 3 IgG, 3 IgM	NP
US[44]	57	Porcine UFH	2.2 years	CHD	2 (3.5%) IgG only	1 by HIPA (but ELISA was equivocal)
US[45]	1,203	NA	Not clear	CHD	NP	45 by HIPA
Chile[46]	207	UFH	Not clear	CHD	36: 20 IgM; 11 IgG; 5 IgA	Functional studies only performed in subset of patients with positive ELISA
Japan[47]	105	NA	Not clear	CHD	2	NP
US[48]	596	NA	3.6 years	CHD	63 (10.6%) IgG, IgA or IgM	NP
Totals	*3,818*	*1,450 patients exposed to UFH; 218 patients exposed to LMWH*	–	–	*117/1,450 patients (8.1%) exposed to UFH and 4/218 patients (1.8%) exposed to LMWH were positive for HIT antibodies by ELISA*	*27/730 patients (3.7%) exposed to UFH had a positive HIT functional assay*

Abbreviations: AKI, acute kidney injury; CHD, chronic hemodialysis; CS, cross-sectional; ELISA, enzyme-linked immunosorbent assay; HIPA, heparin-induced platelet aggregation; HIT, heparin-induced thrombocytopenia; IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A; LMWH, low-molecular-weight heparin; NA, not applicable; NP, not performed; SRA, ^{14}C-serotonin release assay; UFH, unfractionated heparin.

occlusion of the extracorporeal circuit; increased circuit pressures; formation of clot in drip chambers; clotted dialyzer fibers; and acute thrombocytopenia with more than a 20% decrease in platelet count. Of 154 patients, six were noted to have clot formation in the extracorporeal circuit. Five of the six patients had a positive ELISA for HIT antibody and four of six had positive functional assays (heparin-induced platelet aggregation). All six patients had a decline in platelet count and were diagnosed with HIT. Heparin was stopped in these patients and argatroban was used as an alternative anticoagulant. All patients safely continued on hemodialysis. The authors state that clot formation in the dialyzer or extracorporeal circuit is the first sign of HIT in hemodialysis patients. This study is the only one that has found an association between a positive test for HIT antibody and extracorporeal circuit clotting. Two other studies noted an association between HIT-antibody titer and extracorporeal circuit clotting.[40,41] The number of patients with a positive HIT-antibody test in each of those studies was small (7/135[40] and 2/71[41]) and it remains unclear as to whether clotting of the extracorporeal circuit is a manifestation of HIT.

One series from Japan suggested a possible relationship between dialysis vintage and HIT-antibody positivity. The authors examined 305 prevalent hemodialysis patients for HIT-antibody presence by ELISA.[40] Of seven patients who tested positive for HIT antibody, three had been on hemodialysis for less than 1 year; none of 62 patients on hemodialysis for more than 10 years was HIT-antibody positive.

Unexpected filter clotting during continuous venovenous hemofiltration (CVVH) has been described as a complication of HIT.[49] Unexpected clotting was defined as repeated clotting (≥2 episodes) within a 24–48 h period with no obvious cause. During a 2-year period, 87 patients were examined and 28 of these patients met criteria for frequent clotting. Eight patients tested positive for HIT antibodies and 21 patients showed negative test results. No differences in platelet counts were found between groups. CVVH duration was significantly shorter (5 versus 12 h) and urea reduction ratio significantly lower (17% versus 44%) in antibody-positive patients compared with antibody-negative patients.

In summary, whether extracorporeal circuit clotting is a manifestation of HIT remains unclear. It is likely that

many patients diagnosed with HIT by nonspecific assays such as ELISA did not have true HIT, which confounds interpretation of the majority of the studies. Future studies will hopefully help resolve this issue with more accurate diagnosis.

Mortality

Four studies have examined the association between mortality and HIT-antibody test results in hemodialysis patients.[42,44,45,48] de la Vega *et al.*[44] showed a relationship between mortality and high HIT-antibody titer and two other studies reported increased mortality associated with a positive HIT-antibody test.[42,45] By contrast, a study of a large cohort of 596 hemodialysis patients found no association between HIT-antibody-positive status and mortality.[48] An examination of these studies in more detail suggests a possible explanation for this discrepancy.

de la Vega *et al.* reported that the all-cause mortality rate was significantly higher among patients in the highest tertile of PF4-heparin antibody levels than in those in the two lower tertiles after adjusting for Framingham risk score (hazard ratio 2.47; 95% CI 1.07–5.72).[44] Of 54 patients on chronic hemodialysis who received porcine heparin and were analyzed for HIT antibody, only three had positive laboratory tests by ELISA or heparin-induced platelet aggregation. Mean follow-up was 1.7 years. Eight of 13 cardiovascular deaths were in the highest tertile (hazard ratio versus lower tertiles 4.14; 95% CI 1.32–13). Surprisingly, patients in the highest tertile for PF4-antibody titer had a lower rate of vascular access thrombosis than those in the two lower tertiles (hazard ratio 0.13; 95% CI 0.02–0.95).

Carrier *et al.*[42] and Mureebe *et al.*[45] reported that a positive HIT-antibody test in hemodialysis patients was associated with increased mortality. Carrier *et al.* studied the association between PF4–heparin antibodies and mortality among 419 patients on chronic hemodialysis followed for a median of 2.5 years.[42] IgG-specific PF4 antibodies were found to be an independent predictor of mortality (adjusted hazard ratio 2.68; 95% CI 1.08–6.63). ELISA-positive patients with an indeterminant serotonin release assay had an even higher unadjusted hazard ratio for death (3.61; 95% CI 1.14–11.43). However, the numbers of patients in these groups were small—9 and 4, respectively. Mureebe *et al.* followed 1,203 chronic hemodialysis patients over a 5-year period.[45] Overall, 45 patients tested positive for HIT antibodies by heparin-induced platelet aggregation (3.7%), 35 of whom were compared with 23 control subjects. Thrombotic and hemorrhagic complications were significantly more common in the HIT-antibody-positive group than in controls (60% versus 8.7%, respectively). In addition, mortality rate was significantly higher in HIT-antibody-positive patients than in controls (28.6% versus 4.35%, respectively). It should be noted that both of these studies employed functional assays to detect HIT antibodies.

By contrast, Asmis *et al.*[48] reported that HIT-antibody positivity did not predict development of any of the four clinical outcomes examined (arterial cardiovascular events, venous thromboembolism, vascular access occlusion or death), nor did it predict thrombocytopenia. These researchers collected sera from 596 chronic hemodialysis patients 6 months after enrollment in the CHOICE (Choices for Healthy Outcomes In Caring for End-stage renal disease) study.[48] Patients were followed for a mean of 3.6 years. Six months after enrollment in CHOICE, 63 of 596 (10.3%) chronic hemodialysis patients tested positive for an IgG, IgA, or IgM HIT antibody. HIT-antibody positivity did not predict the development of any of the four clinical outcomes examined.

Interestingly, the two studies that showed an association with mortality employed functional assays to detect HIT antibodies, whereas the study that did not detect an association employed a less-specific immunologic assay. It is likely that several patients in the study reported by Asmis *et al.* with a positive ELISA did not have true HIT. Whether HIT-antibody levels below the threshold for ELISA positivity (<0.4 O.D. units) have a role in the pathogenesis of the increased cardiovascular morbidity and mortality of hemodialysis patients is an intriguing hypothesis that warrants further investigation.

Treatment options

Results of HIT-antibody testing might not be immediately available and treatment should not be delayed pending laboratory confirmation in patients judged to be at high risk of HIT on the basis of clinical findings. Early treatment is critical as thrombus formation occurs at a very high rate in the first few days after onset of thrombocytopenia.[6,50] In patients at high risk of HIT, all heparin therapy, including that used to flush or lock catheters, should be discontinued and alternative non-heparin anticoagulants should be started. Heparin-coated catheters or devices should also be avoided as they have been reported to initiate HIT.[51] Clinical judgment must be used in patients at moderate risk of HIT, while in low-risk patients LMWH can be continued until laboratory confirmation is obtained.[25] In patients with HIT, warfarin should not be initiated until the patient's platelet count normalizes, and prophylactic platelet transfusions should be avoided. Although heparin is not thought to be absorbed across the peritoneal membrane to any notable degree, Kaplan *et al.* reported a patient who developed HIT as a result of UFH exposure during an episode of peritonitis.[52] HIT was confirmed serologically using a functional assay (the ^{14}C-serotonin release assay). In addition, a recent study of peritoneal dialysis patients found that the incidence of HIT-antibody positivity was similar in peritoneal (9.3%) and hemodialysis patients (10.6%).[48] Therefore, changing from hemodialysis to peritoneal dialysis in a patient with HIT seems unlikely to be beneficial.

Sufficient evidence exists to support the use of three non-heparin based agents in patients with HIT: the direct thrombin inhibitors, lepirudin and argatroban, and the factor Xa inhibitor, danaparoid. At this time, sufficient data do not exist to justify use of dermatan sulfate,

nafamostat mesilate, prostacyclin or fondaparinux.[53] Regional citrate anticoagulation can be employed in individuals with a history of HIT. An excellent summary of therapeutic options for the hemodialysis patient with HIT is provided by Fischer.[53]

Lepirudin

Lepirudin was the first direct thrombin inhibitor in clinical use. It is irreversible and binds to both free and clot-bound thrombin. Originally produced from the salivary glands of the medicinal leech *Hirudo medicinalis*, lepirudin is now available in recombinant form. In individuals with normal renal function, lepirudin has a half-life of 1 h when administered intravenously and 2 h when administered via the subcutaneous route. Lepirudin is cleared primarily by the kidney and its half-life can be as long as 316 h in patients on hemodialysis.[54]

In 2006, the British Task Force on Thrombosis and Hemostasis concluded that lepirudin at doses adjusted to achieve an activated partial thromboplastin time (aPTT) 1.5–2.5 times the baseline value reduces the risk of death, new thrombosis or limb amputation in patients who have HIT, with or without thrombosis.[55] More recently, it was recommended that to reduce bleeding risk in individuals without a severe thrombotic disorder, the loading dose be omitted and the aPTT target range be reduced to 1.5–2.0 times the baseline value.[56] Studies of lepirudin in patients with and without renal impairment have been reviewed extensively elsewhere.[57,58] Lepirudin dose must be reduced markedly in patients with renal disease and recommended doses in all patient groups have continued to decline over the past few years. A correlation between residual renal clearance and lepirudin clearance has been reported.[54,59] This finding might be particularly relevant in patients with acute kidney injury, in whom glomerular filtration rate might be changing on a daily basis, making use of this agent particularly problematic.

The most recent guidelines from the American College of Chest Physicians for the treatment and prevention of HIT suggest avoiding an initial bolus dose of lepirudin in all patients and starting with an infusion rate adjusted for renal function as follows: 0.10 mg/kg per hour for those with serum creatinine levels <90 μmol/l, 0.05 mg/kg per hour for those with serum creatinine levels within the range 90–140 μmol/l; 0.01 mg/kg per hour for those with serum creatinine levels within the range 140–400 μmol/l and 0.005 mg/kg per hour for those with serum creatinine levels >400 μmol/l.[58] The British Task Force also stated that the risk of serious bleeding complications with lepirudin is related to the degree of elevation of the aPTT ratio, lepirudin levels and elevation of serum creatinine level.[55]

In their meta-analysis, Greinacher *et al.* found that lepirudin-treated patients had a lower incidence of death, thromboembolic complications, and limb amputations than historical controls.[60] However, the cumulative incidence of bleeding was higher in patients treated with lepirudin than in historical controls (42% versus 23.6% at 40 days). In addition, bleeding requiring transfusion was more common in lepirudin-treated patients (18.8% versus 7.1% at 35 days). No intracranial bleeds or fatal bleeding episodes occurred in lepirudin-treated patients.

Lepirudin is very immunogenic; up to 40% of patients develop antihirudin antibodies after 5–10 days of treatment.[61] These antibodies can result in reduced drug clearance and increased bleeding risk. Fatal anaphylactic reactions can occur with initial and repeat exposure to lepirudin (frequencies 0.015% and 0.16%, respectively).

Lepirudin is easily dialyzed as it is not protein bound, has a molecular weight of only 6.98 kDa and a low volume of distribution (0.20–0.25 l/kg). Hemodialysis has been used successfully to remove lepirudin that was given as an iatrogenic overdose.[62] In general, high-flux polysulfone dialyzers have the highest sieving coefficients while low-flux dialyzers show no notable lepirudin removal.[63,64] Exceptions to this rule exist, however, and knowledge of an individual dialyzer's sieving coefficients and clearance for recombinant hirudin (lepirudin) is important.

Recommended doses of lepirudin for patients with chronic kidney disease on hemodialysis or CVVH are shown in Table 4. Lepirudin treatment is generally monitored using the aPTT method. It should be noted, however, that significant assay variability exists between different aPTT reagents[53] and that a linear correlation is found only with lepirudin concentrations up to 0.5 μg/ml, a level that is often exceeded in patients on hemodialysis.[65,66] An aPTT ratio of 1.5–2.5 times baseline corresponds to a lepirudin concentration of 0.6–1.4 μg/ml. Therefore, aPTT will underestimate the action of lepirudin at higher lepirudin concentrations in patients on hemodialysis. The ecarin clotting time or ecarin chromogenic assay, which are more linear at higher lepirudin concentrations, are preferred over the aPTT for monitoring lepirudin blood levels if available.[67] They should be used to monitor rare patients who have both a prolonged aPTT from the lupus anticoagulant and HIT.[68] These methods are not, however, widely available.

Argatroban

Argatroban, another direct thrombin inhibitor, is an arginine derivative that reversibly binds thrombin. Argatroban is nonimmunogenic and no reports of anaphylactic reactions associated with this agent exist.[69] Argatroban is approved to treat HIT with and without thrombosis in the US, Canada, and several European countries and has been shown to reduce the risk of thrombotic events (versus the risk in historical controls).[70] In general, no dose adjustment of argatroban is required in renal disease as the drug is primarily hepatically metabolized with a half-life of 39–51 min, and there is minimal renal clearance (16–23%).[71] Systemic argatroban clearance increases about 20% during hemodialysis.[72] When argatroban is used for the prevention of extracorporeal circuit clotting during hemodialysis, the recommended initial dose is a bolus of 250 μg/kg at the start of hemodialysis, followed by a continuous infusion of 2 μg/kg/min until 1 h before the end of the session.[73]

Table 4 | Doses of alternative anticoagulants in patients on dialysis

Drug	Intermittent hemodialysis (3 times weekly)		Continuous dialysis	
	Dose	Monitoring	Dose	Monitoring
Lepirudin	0.02–0.15 mg/kg bolus at start of dialysis	Monitor to maintain 2–3× baseline aPTT; can also monitor with ECT	Initial bolus 0.01 mg/kg; subsequent boluses 0.005–0.01 mg/kg	Monitor to maintain 1.5–2× baseline aPTT; can also monitor with ECT
Argatroban	250 μg/kg bolus; 2 μg/kg/min infusion until 1 h before end of dialysis	Monitor to maintain 1.5–3× baseline aPTT; can also monitor with ECT	0.5–2.0 μg/kg/min	Monitor to maintain 1.5–3× baseline aPTT; can also monitor with ECT
Danaparoid	Before first 2 hemodialysis sessions: 3,750 U (2,500 U*). For subsequent sessions: 3,000 U (2,000 U*) if predialysis anti-Xa is <0.3 U/ml; 2,500 U (1,500 U*) if predialysis anti-Xa is 0.3–0.35 U/ml; 2,000 U (1,500 U*) if predialysis anti-Xa is 0.35–0.4 U/ml; 0 if predialysis anti-Xa is >0.4 U/ml	Monitor anti-Xa levels to maintain within the range 0.5–0.8 U/ml	Initial bolus 2,500 U (2,000 U*); 600 U (600 U*) for first 4 h; 400 U (400 U*) for next 4 h; subsequently, 200–600 U (150–400 U*)	Monitor anti-Xa levels to maintain within the range 0.5–0.8 U/ml

*Doses in parentheses for danaparoid use are for patients weighing <55 kg. Abbreviations: aPTT, activated partial thromboplastin time; ECT; ecarin clotting time.

A literature search by Hursting and Murray in 2008 identified publications describing 644 patients with renal dysfunction who had been treated with argatroban, 446 of whom had HIT.[74] The argatroban package insert recommends a starting dose of 2 μg/kg/min monitored with aPTT to maintain an aPTT value 1.5–3.0 times that at baseline. The dose should be reduced to 0.5 μg/kg/min if hepatic dysfunction is present. The American College of Chest Physicians recommends reducing the initial infusion rate of argatroban to 0.5–1.2 μg/kg/min in patients who have undergone cardiac surgery, have severe anasarca, congestive heart failure or multiorgan failure.[58] Link and colleagues correlated argatroban dose in critically ill patients with HIT on continuous renal replacement therapy with Acute Physiology and Chronic Health Evaluation (APACHE)-II score.[72] The authors developed a regression equation to predict the required argatroban infusion dose for anticoagulation: dose (μg/kg/min) = 2.15–0.06*APACHE-II score.

The literature review by Hursting and Murray found that in eight prospective studies, renal replacement therapy was carried out without hemorrhagic complication in 109 patients treated with argatroban.[74] In two retrospective studies involving 47 patients with HIT treated with argatroban during renal replacement therapy, nonfatal bleeding occurred in 6%.[74]

Once argatroban is discontinued, coagulation parameters return to baseline within 2–4 h. All direct thrombin inhibitors have the problem that no specific reversal agent is available. Argatroban prolongs INR to a greater extent than lepirudin, which complicates therapy during the transition from argatroban to warfarin, as will be discussed.[56]

Danaparoid

Danaparoid is a low-molecular-weight heparinoid. It contains a mixture of heparan sulfate, chondroitin sulfate and dermatan sulfate. Danaparoid binds antithrombin and as a result inactivates factor Xa. Danaparoid therapy is monitored using the anti-factor Xa assay and not by the aPTT method. Measurement of anti-factor Xa levels should be based on a danaparoid calibration curve which is often not done routinely in most laboratories. The advantages of danaparoid include the following: dual inhibition of factor Xa and thrombin; lack of INR prolongation; therapy can be monitored by specific anti-factor Xa levels; and long half-life of danaparoid (25 h). Taken together, these factors result in a decreased risk of warfarin-induced venous limb gangrene that can complicate overlapping therapy with a direct thrombin inhibitor and warfarin.[56] A potential problem with danaparoid is the possibility of crossreactivity with heparin. In addition, renal clearance of danaparoid makes up 40–50% of total plasma clearance and the half-life of this drug can be as long as 4 days in patients with end-stage renal disease.[53] Dialysis patients treated with a bolus of danaparoid might remain anticoagulated in the interdialytic interval, which can be problematic in individuals who no longer have active disease. The manufacturer's recommended doses of danaparoid for intermittent and continuous dialysis are listed in Table 4. Danaparoid is not removed by high-flux dialysis, but it can be removed by plasmapheresis; this method might be the only way to remove the drug in cases of accidental overdose or severe bleeding.[75] Danaparoid was withdrawn from the US market in April of 2002 but is still available for use in Europe and Asia.

Overlap of direct thrombin inhibitors and warfarin

Patients with documented HIT often require long-term anticoagulation. As a result, they often need to be transitioned from a direct thrombin inhibitor to warfarin. Venous limb gangrene can occur when warfarin is started in the setting of acute HIT. The risk of this complication can be minimized by starting warfarin at relatively low doses and delaying therapy until the platelet count normalizes. Warfarin and the direct thrombin inhibitor should overlap for at least 5 days after the INR is therapeutic.[76] In patients requiring a longer term, non-heparin-based anticoagulant for hemodialysis

once HIT has resolved, regional citrate anticoagulation is an option.[77,78]

Heparin rechallenge

Given the high cost of alternative anticoagulants for hemodialysis and the problems with reversal of direct thrombin inhibitors during cardiac surgery, rechallenge with heparin has been carried out in these clinical settings in a small number of patients.

In patients on hemodialysis

Although anticoagulants other than heparin can be used to maintain extracorporeal circuit patency in patients on hemodialysis, their use is limited by factors such as high cost and the risk of anaphylactic reactions associated with current agents. Hartman *et al.* reported heparin rechallenge in three hemodialysis patients who initially developed HIT following treatment with LMWH.[79] These patients developed 'pseudo-pulmonary embolus' syndrome during dialysis as a manifestation of HIT. The patients were switched to lepirudin and thrombocytopenia resolved within 12 days after the switch. After 53 days, 82 days and 193 days, HIT antibodies were no longer detected by either ELISA or functional assays. These patients were rechallenged with LMWH after HIT antibodies had disappeared from their serum and did well with follow-up periods of 1 month, 7 months and 12 months. In an accompanying editorial, Davenport cautioned that further studies are needed to determine whether rechallenge with heparin is safe in patients who have a positive ELISA but a negative functional assay and whether ELISA assays alone can predict cases in which rechallenge can be safely carried out.[80] Matsuo *et al.* successfully rechallenged a hemodialysis patient who developed HIT with UFH.[81] The patient was switched to argatroban and became seronegative around 40 days after the cessation of heparin treatment and was successfully rechallenged with UFH, without recurrence of HIT, on day 210.[81]

In patients requiring cardiac surgery

Several options can be considered in patients with a previous history of HIT who require cardiac surgery. If possible, the procedure should be delayed until HIT antibodies are no longer detectable. In a study of 10 patients who had previously tested positive for HIT antibodies and were undergoing cardiopulmonary bypass, heparin use was confined to the operative period.[82] Heparin was avoided both before and after the operation. Surgery was carried out safely and all patients made a good recovery. Although alternative agents to heparin can be used during the cardiac surgical procedure itself, such agents are not readily reversible and experience of their use in this setting is limited. Use of heparin rechallenge is based on the principle that it takes a minimum of 5 days for B lymphocytes to produce clinically significant HIT-antibody titers. There does not seem to be immune memory for HIT-associated antigens in patients with previous episodes of HIT who become negative for HIT antibodies.[83]

At least two case reports of patients with renal disease and a previous history of HIT who have undergone cardiac surgery have been published. The first patient had end-stage renal disease on hemodialysis and received lepirudin preoperatively and heparin intraoperatively. Surgery was complicated by massive bleeding requiring transfusion of 18 units of packed red blood cells and the patient subsequently recovered.[84] In the second case, a 44-year-old woman with chronic kidney disease, a serum creatinine concentration of 189 μmol/l and a history of HIT underwent aortic valve replacement. Heparin was used intraoperatively and argatroban postoperatively, without complications.[85]

The situation is much more complicated in individuals who require cardiac surgery and still have detectable HIT antibodies. As clinical HIT can reoccur rapidly with re-exposure to heparin in such patients, heparin is best avoided and alternative agents should be used. The selection of an alternative anticoagulant in this particular circumstance is more completely covered in an excellent review by Greinacher.[83]

Conclusions

The recent literature has reported several key findings with regard to HIT and the hemodialysis patient, but several questions remain. An acute systemic reaction occurring 5–30 min after an intravenous bolus of UFH has been described in dialysis patients and might be confused with a dialyzer reaction. The risk of HIT-associated complications in hemodialysis patients is still not well defined, with several studies reporting no clinical sequelae while others describe thrombocytopenia or extracorporeal circuit clotting. Extracorporeal circuit clotting, however, is a common problem in the dialysis patient and whether it is truly a presentation of HIT awaits confirmatory studies, especially in incident patients. Three of four studies that examined HIT-antibody titers in hemodialysis patients showed a relationship between mortality and either the level of HIT-antibody titer or the presence of a positive antibody titer. Whether levels of HIT antibody that are below the threshold for a positive test have a role in the pathogenesis of the cardiovascular disease that is so prevalent in hemodialysis patients requires further study. HIT-antibody production can be transient and small numbers of hemodialysis patients have been rechallenged without adverse consequences after HIT antibodies were no longer detectable by immunologic and functional assays.

Review criteria

Material for this Review was obtained by searching the PubMed database using the search terms "heparin", "heparin-induced thrombocytopenia", "pseudo-pulmonary embolism syndrome", "hemodialysis", "peritoneal dialysis", "CVVH", "CVVHD", "lepirudin", and "argatroban" for papers published in English. No date restriction was placed on the search.

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