Heparin-induced thrombocytopenia

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A B S T R A C T

Heparin-induced thrombocytopenia (HIT) is a rare but severe prothrombotic adverse effect of heparin treatment. The underlying cause is formation of highly immunogenic complexes between negatively charged heparin and positively charged platelet factor 4 (PF4). Resulting antibodies against PF4/heparin complexes can activate platelets via the platelet FcγIIa receptor, leading to thrombin generation and thus to the paradox of a prothrombotic state despite thrombocytopenia and application of heparin. Prompt diagnosis of HIT is important in order to change treatment to prevent severe thromboembolic complications. However, this is often difficult, especially in intensive care patients in whom thrombocytopenia is frequent. The commercially available laboratory tests for HIT-antibodies have a high negative predictive value but only a poor positive predictive value. This leads to overdiagnosis and overtreatment of HIT, which also bear the risk for adverse outcomes. Current treatment options are the use of the direct thrombin inhibitors, desirudin, bivalirudin, and argatroban, and the factor Xa-inhibitors, danaparoid and fondaparinux. This review aims at resuming recent data on HIT, thereby providing a framework for diagnosis and treatment of HIT, and some insights into the pathogenesis of this adverse drug reaction.

Introduction

Heparin-induced thrombocytopenia (HIT) is a dangerous complication of heparin treatment and remains the most frequent immune mediated adverse drug reaction involving blood cells.[1] HIT occurs when antibodies against multimolecular complexes formed by negatively charged heparin and the positively charged (platelet protein) platelet factor 4 (PF4)[2] activate platelets via the platelet FcγIIa receptor, leading to platelet microparticle generation and thrombin generation. The most important clinical feature of HIT is a decrease in platelet counts by more than 50% combined with a procoagulatory status that may cause venous and – less frequently – arterial thrombosis.[3] Prompt diagnosis and treatment with an alternative anticoagulant in therapeutic dose are the most important measures to prevent new thromboembolic complications in affected patients. Most physicians find the diagnosis of HIT difficult, particularly when there is evidence of a non-HIT thrombocytopenic disorder. This is especially true in critically ill patients. Laboratory tests for PF4/heparin antibodies are primarily helpful to rule out HIT, as most tests for the detection of HIT-antibodies have high negative but only moderate positive predictive values. A positive test does not confirm HIT, which is especially true for the commercially available antigen tests.

Hence, the problem of not recognizing HIT has turned into a tendency to *over*diagnose HIT with the consequence of unnecessary use of alternative non-heparin anticoagulants. Effective drugs for HIT treatment have been available in North America and Europe for some years,[4,5] but they bear a considerable risk of bleeding.

Pathogenesis of HIT

There are two fundamentally different forms of thrombocytopenia induced by heparin: non-immune-mediated heparin-associated thrombocytopenia (HIT) Type I, which is of minor clinical relevance, and immune-mediated HIT, or HIT Type II.

Non-immune heparin-associated thrombocytopenia (HIT Type I)

Heparin binds to platelets and causes mild platelet activation,[6] which induces a moderate decrease in platelet count, soon after start of heparin in therapeutic doses. These proactivating effects on platelets involve charge related binding of heparin to the glycoprotein (GP) IIb-IIIa complex (integrin αIIbβ3).[7,8] This causes outside-in signaling and thereby activation of phosphatidyl inositol-3 kinase. This potentiates the effects of other platelet agonists.[8] Platelets also bind to immobilized heparin via GPIIb-IIIa. This might be of clinical relevance in intensive care patients, as many intravascular devices and extracorporeal circuits (*e.g.*, in ECMO machines) are coated with heparin.[9] Despite heparin continuation, platelet counts normally recover within 1-2 days. Non-immune HIT does not increase the risk for thrombosis.[3]

Immune heparin-induced thrombocytopenia (HIT)

Platelet-activating antibodies against PF4/heparin complexes cause immune-mediated HIT (or HIT Type II). PF4 is a chemokine stored in platelet α granules and released during platelet activation. Because of its strong positive charge, PF4 binds to negatively charged heparin forming multimolecular complexes, which are highly immunogenic and induce anti-PF4/heparin antibodies. Anti-PF4/heparin IgG antibodies form immune complexes with PF4/heparin complexes, which bind to the platelet FcγIIa receptor resulting in platelet activation and thrombin generation (Figure 1).

In HIT, the platelet count characteristically starts falling 4-10 days after initiation of heparin treatment by more than 50% compared with the highest platelet count value after the start of heparin treatment. In rare cases, the platelet count starts falling after heparin has already been stopped (*delayed-onset HIT*). Such patients typically show strong positive HIT antibody tests caused by high titers of antibodies with autoimmune features, which cause platelet activation in the absence of heparin *in vitro*.[3]

The antibody response in HIT displays an unusual temporal pattern: HIT patients often present with anti-PF4/heparin antibodies of the IgG class, which also occur in heparin-naïve HIT patients as early as 4-5 days after the first heparin application. This is much too early for a primary immune response.

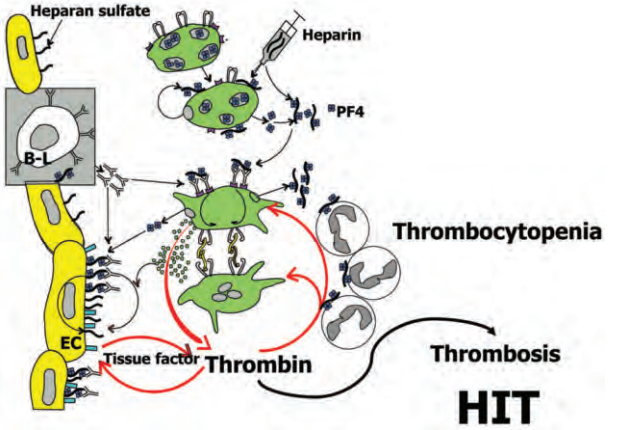

Figure 1. Pathogenesis of heparin-induced thrombocytopenia (HIT) (taken from[4]). Heparin produces mild platelet activation, resulting in the release of platelet factor 4 (PF4) from platelet α-granules and in the formation of immunogenic PF4/heparin complexes. B lymphocytes generate IgG that recognize the PF4/heparin complexes; the Fc *tails* of the IgG bind to platelet FcγII receptors, resulting in Fc receptor clustering and consequent strong platelet activation. Platelet aggregation is mediated by GPIIb-IIIa. Platelet-derived microparticles that accelerate thrombin generation are produced. The HIT antibodies also recognize PF4 bound to endothelial heparan sulfate, leading to tissue factor expression on endothelium. HIT antibodies also can activate monocytes. In all, increased thrombin generation can explain some of the unusual clinical manifestations of HIT (*e.g.*, venous limb gangrene and disseminated intravascular coagulation) and provides a rationale for treatment that reduces thrombin generation (adapted from).[4]
Abbreviations: B-L, B-lymphocyte; EC, endothelial cell.

PF4 also binds to bacteria and forms antigenic complexes on bacterial surfaces. These complexes are recognized by anti-PF4/heparin antibodies from heparin-treated patients.[10] Mice with polymicrobial bacterial sepsis generate anti-PF4/heparin-reactive IgM antibodies[10] and in a cross-sectional population study, a strong association between periodontal disease (which is frequently associated with bacteremia) and anti-PF4/heparin antibodies has been observed.[11] Thus, early production of IgG antibodies in HIT might be due to preimmunization against complexes of PF4 formed on bacterial surfaces,[10] and HIT might be a misdirected bacterial host defense mechanism (Figure 2).

While this concept might explain the presence of anti-PF4/heparin antibodies in healthy humans who very unlikely received heparin[12,13] before, and also the early occurrence of anti-PF4/heparin-IgG in HIT, there are other features of the HIT immune response that are still unclear. HIT antibodies persist on average only for 50-100 days,[14] and memory B-cells are not detectable in HIT-patients.[15] In line with these ex-vivo data is the clinical observation that after approximately 100 days, re-exposure to heparin in HIT patients does usually not cause recurrence of HIT. These features do not fit the concept of HIT as a typical secondary immune response either.

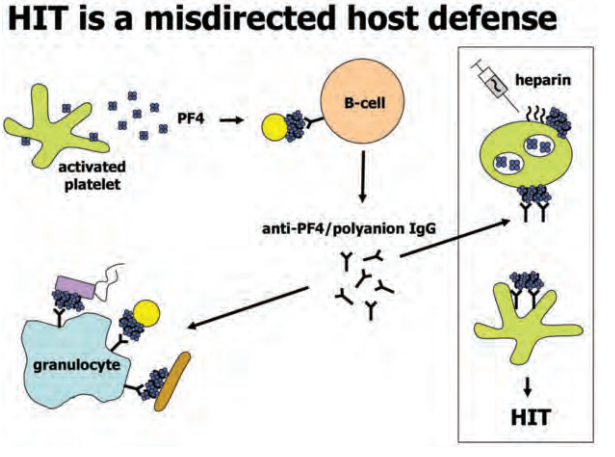

Figure 2. Schematic representation of the mechanism by which PF4 mediates anti-bacterial host defense and concurrently primes for heparin-induced thrombocytopenia (taken from[10]). Bacteria activate platelets, which release positively charged PF4 interacting with polyanions at the bacterial surface. This generates clusters of PF4, which initiate antibody production by B-cells. Once antibodies are induced, they can bind to all bacterial strains, which form PF4 clusters on their surface. Antibody binding to PF4-coated bacteria facilitates binding to granulocytes through Fc-receptors and subsequently phagocytosis. On the other hand, these antibodies can induce a severe adverse drug reaction, heparin-induced thrombocytopenia. During heparin treatment, heparin binds to platelets. This mediates formation of PF4/heparin complexes on the platelet surface. These platelet/PF4/heparin complexes mimic PF4 bound to bacteria and the anti-PF4/polyanion antibodies bind to the platelet surface by their Fab where they activate platelets by cross-linking the platelet Fc-receptors with their Fc. This finally results in massive thrombin generation via a cascade involving activated platelets, platelet microparticles, endothelial cells, and monocytes leading to heparin-induced thrombocytopenia and new thrombosis. Blue symbols indicate PF4. Yellow circles, brown rods, and violet rectangles symbolize different bacterial species.

Frequency

The frequency of HIT differs notably, depending on type of heparin (bovine unfractionated heparin > porcine unfractionated heparin > low molecular weight heparin > fondaparinux), patient group (post-surgery > medical > obstetrical/pediatric),[16-20] extent of trauma (major > minor),[21] gender (female > male),[22] and duration of heparin treatment[3] (5-10 days > 0-4 days). The frequency of HIT ranges between less than 0.1% (*e.g.*, obstetrical patients treated with LMWH) and 5% (thrombosis prophylaxes with UFH after major orthopedic surgery).[20] In critically-ill patients, HIT is an uncommon cause for thrombocytopenia, as only 1% of ICU patients have HIT as the explanation for their thrombocytopenia.[23-25] This low incidence despite frequent bacterial infections might be explained by the immunosuppressed state of critically ill patients.

Diagnosis of HIT (Figure 3)

Anti-PF4/heparin antibodies can be found fairly frequently in heparin-treated patients, but only a minority of patients with these antibodies develops clinical HIT.[26] HIT is a *clinicopathologic syndrome*,[3] which demands both the presence of clinical features (thrombocytopenia, thrombosis) and pathologic anti-PF4/heparin antibodies. Thus, clinical assessment *and* laboratory testing are necessary to confirm the diagnosis of HIT.

There are several scoring systems for HIT.[27-29] Currently the best established pretest model is the 4Ts score,[30] which provides a standardized assessment of the clinical probability of HIT. The "Simple Scoring System"[29] and the HIT Expert Probability Score (HEP) are other proposed scoring systems. The latter is based on eight criteria and in a study by Cuker *et al.*[28] it showed greater inter-observer agreement compared to the 4Ts score. Both scoring systems are not widely validated yet. The criteria used in the 4 Ts score are the main clinical features of HIT (Thrombocytopenia, Timing of platelet count fall, Thrombotic complications), and the likeliness of oTher (=not heparin-associated) causes for thrombocytopenia. The score can indicate a low (0-3 points), intermediate (4-6 points), or high (7-8 points) clinical probability of HIT.

Timing of platelet count fall (Figure 4)

As it takes at least 4 days for B-cells to produce IgG-antibodies in larger quantities, HIT is nearly ruled out if thrombocytopenia occurs before day four of heparin treatment. An exception is rapid onset-HIT, which occurs in patients who developed anti-PF4/heparin antibodies during a previous exposure to heparin, typically within 30 days (rarely up to 100 days), and in whom the antibodies are still present. In these patients, the platelet count often falls within hours after re-exposure to heparin.[14,31] In case of acute systemic reactions upon intravenous UFH bolus (suggesting HIT-mediated platelet activation), a platelet count should be determined immediately, as a low platelet count would strongly implicate HIT in this clinical context.

Thrombocytopenia

The relative decrease in platelet count is more meaningful than the absolute platelet count. In HIT, platelet counts typically decrease by more than 50% of the highest platelet count measured during heparin treatment. Sometimes, the platelet count does not fall below 150 Gpt/L and they rarely fall below 20 Gpt/L. In the case of very low platelet counts, and especially when bleeding symptoms occur, other causes of thrombocytopenia are much more likely than HIT.

In critically ill patients, thrombocytopenia is usually caused by other reasons than HIT (Figure 4). It occurs within the first days of intensive care treatment and is

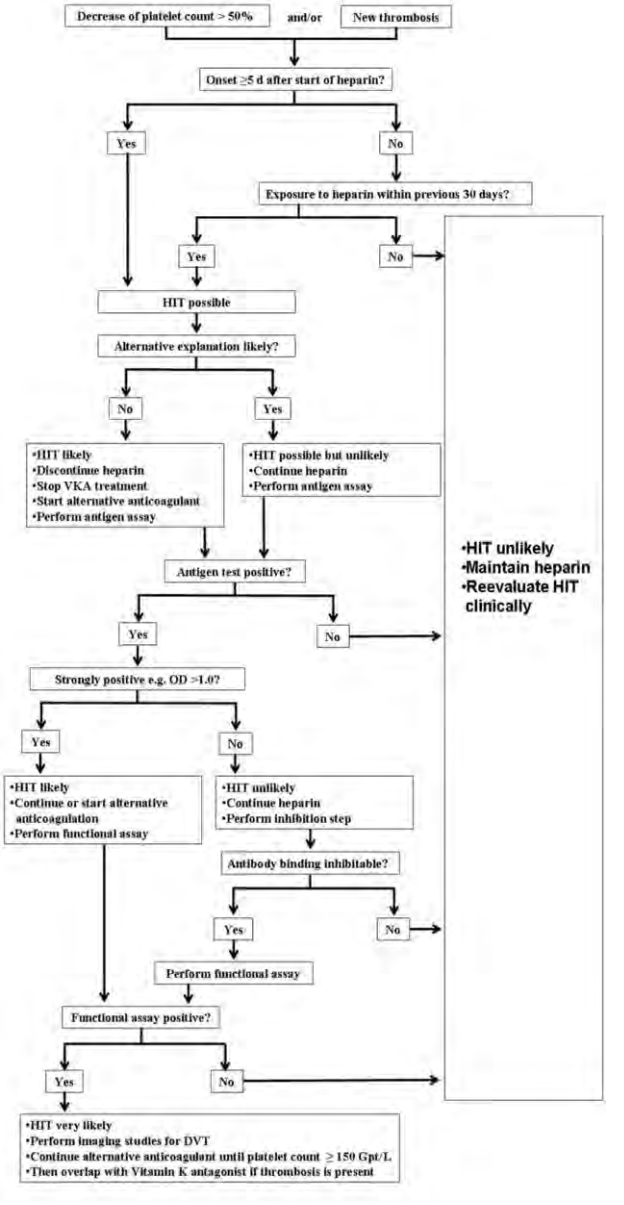

Figure 3. Diagnostic and therapeutic algorithm for HIT adapted from Selleng *et al.*[117]
AA=Alternative nonheparin anticoagulants. VKA=Vitamin K antagonists. DVT=Deep vein thrombosis.

often present at admission. However, a patient who develops a new platelet count fall that begins 5 to 10 days after major surgery must be assumed to have HIT unless proven otherwise because a platelet count fall during this time frame is not expected as it is occurring within the period of expected rising platelet counts following surgery (Figure 4).

Monitoring of platelet counts

About 50% of thromboses in HIT occur very closely to the platelet count decrease. It is therefore unlikely that platelet count monitoring will help to identify many patients before the thrombosis occurs, *i.e.*, platelet count monitoring will not prevent many HIT-related thromboses. The main reason to recommend monitoring of platelet counts is to recognize that the thrombosis might be HIT related. This is especially relevant in patients after major surgery in whom the platelet count increases substantially during the first two weeks after surgery, often to values that are more than double as high as the pre-surgery platelet count value. Without monitoring of platelet count during the post-surgery period, it will not be possible to recognize the platelet count fall, *e.g.*, in a patient with a presurgery platelet count of 200,000/μL, and a platelet count increase after hip replacement to 450,000/μL, until day 9, followed by a decrease to 180,000/μL at day 10 associated with a new thrombosis due to HIT. Monitoring of platelet count from on day 5 of heparin treatment is therefore recommended in patients undergoing major surgery, especially if they receive unfractionated heparin. Medical patients and patients undergoing minor surgery usually do not show a reactive platelet count increase, thus obtaining a platelet count baseline value at the time of start of heparin will be sufficient.[32]

Thrombotic complications

The risk of thromboembolism in HIT is high – ranging from 35 to 70%, depending on the patient group.[20,33] HIT can cause venous, arterial, and microcirculatory thrombosis. The most common thrombotic complication is lower limb deep vein thrombosis (DVT). Thrombotic events mostly occur in patients being at high baseline risk of thrombosis, such as post-orthopedic surgery patients, in vessels with intravenous lines, or as clotting within extracorporeal circuits (*e.g.*, dialysis filters). Arterial thrombosis in HIT usually involves the distal aorta and lower limb arteries causing limb ischemia, less frequent are stroke, myocardial infarction, or occasionally occlusions of brachial, mesenteric, and renal arteries. Sometimes systemic reactions like shivering, fever, tachycardia, hypertension, chest pain, dyspnea, headache, or nausea following intravenous administration of heparin[34] or necrotizing and erythematous skin lesions at the heparin injection sites[35,36] are the first (or only) symptoms of HIT.

Laboratory testing

Two types of serology tests for heparin-dependent antibodies are currently available: functional (platelet activation) tests and (PF4-dependent) immunoassays. Typical HIT patients test positive in both assays (Figure 3).

Antigen assays

Antigen assays are based on detection of the antibodies binding to PF4/polyanion complex. Three types of

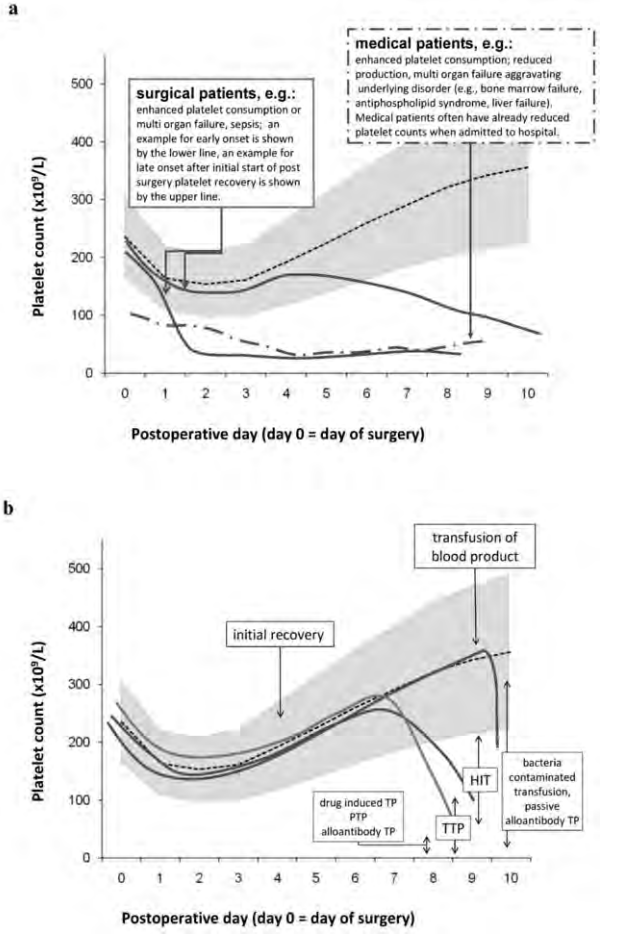

Figure 4. Typical platelet count courses in patients with different causes of thrombocytopenia (taken from[117]). The grey background area shows the platelet count course of 553 patients after cardiopulmonary bypass surgery without thrombocytopenia.
a: Early onset thrombocytopenia in surgical (solid line) and medical patients (dot-dash line) are caused by major platelet consumption, *e.g.*, sepsis, multiorgan failure, or aggravation of the underlying disease. The second solid line indicates a platelet count pattern typical for late onset complications in a surgical ICU patient. The first decrease in platelet counts is caused by major surgery. After initial start of platelet counts recovery, late onset non-immune complications cause a gradual decrease of platelet counts.
b: Late onset rapid decrease of platelet counts are typical for immune-mediated thrombocytopenia, which typically occur in the second week of treatment (after surgical intervention, heparin, other drugs). The arrows indicate the typical range of platelet count nadirs. Transfusion-related passive alloimmune thrombocytopenia can occur any time but is closely related to transfusion of plasma containing blood products.[116]
Abbreviations: HIT, heparin-induced thrombocytopenia; PTP, post-transfusion purpura; TP, thrombocytopenia; TTP, thrombotic thrombocytopenic purpura.

immunoassays have been described: (1) solid-phase enzyme immunoassay (EIA), (2) fluid-phase EIA, and (3) particle gel assay. Antigen assays are widely available and show high sensitivity approaching 100%,[37] which makes them perfect to rule out HIT, but all share the problem of a low specificity for clinically relevant antibodies due to detection of non-platelet-activating anti-PF4/heparin antibodies.[1] Assays detecting only IgG-antibodies show higher specificity[38-40] for HIT because only HIT-antibodies of the IgG class are considered to be able to activate platelets via the FcγRIIa.[41] However, still only half of the PF4/heparin IgG positive sera are also platelet activating.

Results of the enzyme immunoassays (EIAs) are usually reported in optical densities (OD), whereby higher OD values correlate with a higher probability for a positive functional assay, a higher 4T score, and an increased risk for thrombosis.[33,42-44] Specificity of antibody testing can be further increased by the so-called inhibition step: addition of high concentrations of heparin (100 U/mL) disrupts the formation of PF4/heparin complexes and thereby the binding of HIT-antibodies.[45,46] Judging only sera positive, whose reactivity is inhibited by at least 50% by high-dose heparin, notably reduces the rate of false-positive results[47](caused by antibodies binding to PF4 alone). However, binding of high-titer anti-PF4/heparin antibodies may not be inhibited by this step. Combing both approaches, the magnitude of the OD level and the inhibition step,[48] seems to be reasonable to increase further the specificity of immunoassays in HIT-laboratory investigation.

The particle-based immunoassay uses gel centrifugation technology. Its sensitivity and specificity is somewhere between the enzyme immunoassays and the washed platelet activation assays (functional assays). Specificity can be increased by titrating a patient's serum (sera being positive at a 1:8 dilution indicate a high likelihood for HIT) but sensitivity reaches only about 95%, *i.e.*, up to 5% of HIT patients might be missed.[49] Therefore, patients with a high clinical probability and a negative particle based immunoassay should be evaluated in another test system.

Two automated assays, one based on the agglutination of latex particles and the other on chemiluminescence, have recently been introduced. The latex agglutination assay[39] can only be performed with plasma (as its endpoint is based on clotting) and it cannot differentiate between IgG, IgM, or IgA antibodies. The chemiluminescence assay is based on binding of anti-PF4/heparin antibodies. It can be performed with serum or plasma and differentiate between different immunoglobulin classes. It shows a wide range of reactivity and might thus provide additional information compared to the EIAs.[50] These automated assays might allow greater standardization and better comparability of results obtained in different laboratories.

In situations where no functional HIT test is available, a combination of a carefully obtained clinical score, and the magnitude of the reactivity in the antigen assay (usually assessed by OD, or by titration in the particle agglutination test) is a possibility to guide management. In case of an intermediate or high score and a strongly positive antigen test (OD >1.5, or a dilution of 1:32 still reacting positive in the agglutination test), the likelihood for HIT is high, and the patient should be treated accordingly by an alternative anticoagulant. This approach, however, will result in a considerable proportion of patients unnecessarily treated with an alternative anticoagulant.

Functional assays

Functional assays are much more specific for clinically relevant antibodies and essential for confirmation of HIT. Yet, they are technically demanding and not available in all laboratories. As a general rule, it is recommended that functional assays for HIT be performed, unless the EIA is negative (high negative predictive value); or the EIA yields a strong-positive result (>2.0 OD units) and the clinical picture also strongly indicates the diagnosis of HIT– in this situation, the diagnosis of HIT seems assured. However, particularly when a non-HIT diagnosis seems plausible or probable, a weak (0.4 to 1.0) or moderate (1.0 to 2.0) EIA result should prompt further testing by a functional assay.

Washed platelet assays are currently the gold standard. In the serotonin release assay (SRA), platelet activation is measured by the release of radioactive serotonin. The heparin-induced platelet activation assay (HIPA) has comparable specificity and sensitivity but does not require the use of radioactive materials.

Functional assays using platelet-rich plasma[51] and flow cytometry[52] are generally less sensitive than the washed platelet assays. A novel whole blood impendence aggregometry assay might be a future option for many laboratories to run a functional assay without the need of washing platelets. First studies report a reasonable sensitivity for platelet-activating HIT antibodies if a highly sensitive donor is used for whole blood donation.[53,54] However, in our laboratory, this assay was considerably less sensitive than the washed platelet assay (HIPA test; unpublished data).

Treatment of HIT

Treatment principles of HIT include:[55] discontinuation of heparin; initiation of an alternative non-heparin anticoagulant; performing imaging studies for lower-limb deep-vein thrombosis; postponing/avoiding vitamin K antagonists; minimizing platelet transfusions; and avoiding inferior vena cava filters.

As laboratory confirmation of HIT may take up to several days and non-heparin anticoagulants[56-58] entail a notable bleeding risk, the clinician often faces the challenge to weight the risk of HIT-induced thrombotic complications against the risk of major bleeding complications caused by an alternative anticoagulant. An antidote does not exist for any of the alternative anticoagulants. To decide whether to continue or to withdraw heparin, the use of a systematic scoring system (see above) can be helpful. In a two-center study,[30] less than 2% (2/119) of patients who were classified as having a low (0-3) 4T score showed pathogenic, platelet activating antibodies. Thus, in patients with a low 4T score it is reasonable to maintain heparin until laboratory test results are available (Figure 3).

In patients with an intermediate (4-5) or high (6-9) 4T score, however, HIT is more likely and decision making

depends on the interpretation of both, laboratory test results, and clinical presentation.

Two different approaches to alternative anticoagulation are available: indirect antithrombin (AT)-dependent inhibitors of factor Xa (danaparoid, fondaparinux); and direct thrombin inhibitors (r-hirudin, argatroban, bivalirudin).

Direct thrombin inhibitors

All direct thrombin inhibitors (DTIs) inhibit the activity of both free and clot-bound thrombin, while the indirect inhibitors inhibit only free thrombin. DTIs are usually monitored by the activated partial thromboplastin time (APTT, target range: 1.5-3-fold prolongation), which is strongly dependent on the prothrombin concentration in the patient blood.[59] This can cause false high APTT levels in patients with low levels of prothrombin (*e.g.*, caused by liver impairment, recent treatment with vitamin K antagonists, DIC). These patients are often at the highest risk for new thrombosis, as low prothrombin is a surrogate marker for consumption of clotting factors or deficiency in Protein C. When the false prolonged APTT prompts inappropriate dose reduction of the DTI, this can result in new thrombosis, especially microvascular occlusions and limb loss.[1,60] In general, interpretation of all clotting parameters is difficult in patients treated with DTIs, which interact with all functional clotting assays. Argatroban has the strongest effect on functional clotting parameters,[61] followed by bivalirudin, lepirudin, and desirudin. Implementation of nomograms for dosing and monitoring of direct thrombin inhibitors likely improves safety of treatment.[62]

Lepirudin (Refludan®; Celgene Pharmion Ltd)

The recombinant hirudin/lepirudin has been formally studied in HIT. The other hirudins have very similar characteristics, which likely allow transfer of some of the experiences made with lepirudin. Desirudin (Revasc; Canyon Pharmaceutics), another recombinant hirudin, is available in Europe and the United States, and in several developing countries as rhirudin rb variant (*Thrombexx*, Rhein-Minapharm, Egypt).

Lepirudin yielded a significantly better overall-outcome in patients with acute HIT[58,63,64] (combined endpoint: new thromboembolic complications, limb amputations, death and major bleeding) compared with a historical control group in three studies.[56] Major bleeding events were substantially more frequent and strongly associated with creatinine levels.

The pharmacokinetic of all hirudins strongly depends on renal function as the kidneys clear more than 98% of the drug. In view of high bleeding rates observed under the dosage regimen provided by the manufacturer,[56,57,65] the bolus should be omitted unless there is limb- or life-threatening thrombosis, and dosages for the continuous infusion should be largely reduced depending on renal function.

Thirty to seventy percent of patients developed antibodies to lepirudin.[56] In most patients, these antibodies have minor clinical relevance. Their most frequent effect is prolongation of the half-life, as the complexes of hirudin-anti-hirudin-antibodies can no longer be filtrated by the kidneys. Rarely the antibodies inhibit the function of hirudin. Both antibody effects can be easily compensated by a dose decrease or increase, respectively. A rare but potentially life threatening complication of anti-hirudin antibodies is anaphylaxis, which is IgG not IgE mediated. Circulating anti-hirudin-IgG antibodies form immune complexes with hirudin, causing activation of macrophages. Anaphylactic reactions have only been observed in preimmunized patients after i.v. bolus applications.[66,67] Therefore, re-exposure with hirudin is more likely to be associated with anaphylactic reactions compared with first time treatment. Avoidance of bolus application strongly reduces the risk for anaphylaxis.

Desirudin (Revasc®/Iprivask®; Canyon Pharmaceuticals)

Is also a recombinant hirudin with similar characteristics to lepirudin, including dependency of pharmacokinetics from renal function and immunogenicity. Antibodies induced by lepirudin show 100% crossreactivity to desirudin and vice versa.[68]

Desirudin was the first direct-thrombin inhibitor approved in the United States by the Food and Drug Administration for the prevention of DVT after major orthopedic surgery in 2004.[69] It has been assessed in a small number of patients with clinical suspicion of HIT with fixed-dose, subcutaneous administration (15 mg s.c. every 12 hours) in comparison with APTT adjusted intravenous argatroban.[70] None of the eight patients treated with desirudin developed major bleeding or new thrombosis. Clinical studies enrolling more patients are warranted for further evaluation.

Bivalirudin (Angiox®; The Medicines)

Is a synthetic peptide derived from hirudin. Its activity is reversible as it is cleaved by thrombin itself.[71] It has a short half-life (20 minutes), which is increased in patients with renal impairment but much less than in the case of hirudins. If it is used for extracorporeal circulation, *e.g.*, for cardiac surgery or extracorporeal lung assist, it is important to avoid any stasis of blood in the extracorporeal circuit, as in non-flowing blood, thrombin rapidly cleaves bivalirudin, resulting in clotting.[72]

Argatroban (Novastan®, Argatra®; Mitsubishi Pharma)

Is a small molecule, reversible, direct thrombin inhibitor.[73,74] Argatroban is metabolized in the liver.[75] It has a short plasma half-life of 39-51 minutes.[76] Altogether 754 patients in the three studies received argatroban for treatment of HIT and HIT-associated thrombosis syndrome (HITTS).[77] Argatroban reduced new thrombosis but did not decrease all-cause mortality or limb amputation. However, bleeding events were similar between the argatroban-treated patients and historical controls.

Over recent years, dosing schedules for argatroban have been changed, particularly for ICU patients,[78] who require significantly lower argatroban doses than previously recommended.[79] A recent consensus publication summarizes current recommendations for dose adjustments of argatroban in critically ill patients.[80] In patients with no symptoms for impaired liver function/perfusion, a starting dose of 1.0 μg/kg/min argatroban is recommended. In critically ill patients, a starting dose of 0.5 μg/kg/min should be used and titrated upwards until the target APTT range is reached, meanwhile the APTT

should be monitored every 2 hours. Then monitoring every 8-12 hours is sufficient. If for interventional procedures or any other reason the administration of argatroban is interrupted, most of its efficacy will be lost after 2-4 hours in a patient with normal metabolism.

Argatroban is usually monitored by APTT. Because commercially available APTT kits exhibit different sensitivities to argatroban, laboratories should generate their own dose response calibration curve. As argatroban prolongs the INR, during argatroban/warfarin overlapping therapy, the INR reflects the combined effects of both drugs. Serious thrombotic events had been observed in patients with HIT when argatroban was prematurely discontinued when the INR was 2-3 during overlapping therapy. After stopping argatroban, the INR became subtherapeutic (<2). It may be more appropriate to stop argatroban when the INR is 4 and to repeat the INR a few hours later to ensure that the INR remains in the therapeutic range of 2-3.[77]

Dabigatran-etixilate (Pradaxa®; Boehringer Ingelheim)

Is a reversible, direct thrombin inhibitor, which is orally administered. It is an attractive alternative anticoagulant in patients with a history of HIT. No information on the use of dabigatran in acute HIT is available. Dabigatran does not interact with PF4 or platelet activation by PF4/heparin antibodies.[81]

Factor Xa inhibitors

The indirect FXa inhibitors, danaparoid and fondaparinux, catalyze inhibition of FXa by antithrombin (AT). They do not significantly prolong the APTT or the INR,82 which facilitates overlapping VKA treatment. With rivaroxaban and apixaban, the first direct FXa inhibitors are now available.

Danaparoid is the only FXa inhibitor approved for HIT treatment, but otherwise data on its efficacy are limited, while for the other drugs, much more data exist in non-HIT prothrombotic disorders. Even more important, the other drugs are much more frequently used in daily clinical practice, which may reduce potential errors in monitoring and dosing when used in the infrequent HIT patient.

Danaparoid (Orgaran®; MSD)

Is the most established anticoagulant for HIT treatment outside the United States. It has been tested in a small, randomized controlled trial,[83] against dextran-70. A further non-randomized study using contemporaneous controls showed similar efficacy as lepirudin in treatment of HIT-associated thrombosis at comparable bleeding rates, but a slightly weaker efficacy when administered in prophylactic dose (yet at a much lower bleeding risk of 0% *vs.* 17.2% with lepirudin).[84]

Danaparoid is a mixture of heparan sulfate, dermatan sulfate, and chrondroitin sulfate and isolated from porcine intestinal mucosa. Despite its heparin-like structure, anti-PF4/heparin antibodies do not show clinically relevant cross-reactivity with danaparoid.[85] It shows a unique feature by disrupting preformed PF4/heparin complexes,[86] which might contribute to its therapeutic efficacy.

Danaparoid shows a predictable dose-response with less need for monitoring. It has a long half-life (mean 25 hours after s.c. administration) and its pharmacokinetic depends to 30% on renal function. Dosage should be reduced accordingly in patients with severe renal impairment. Danaparoid does not alter the INR. Overlapping treatment with VKA does not differ from the protocol used for LMWH.

During the last years, the manufacturer had substantial difficulties to maintain supply, which resulted in recurrent shortages of the drug. As a result, many hospitals have already replaced danaparoid by other alternative anticoagulants (most often argatroban and fondaparinux).

Fondaparinux (Arixtra®; GSK)

Is a promising drug for future treatment of HIT (Arixtra®; GSK), a synthetic pentasaccharide that has exclusive antithrombin-dependent anti-FXa activity.[87] Fondaparinux has a long half-life of 17-21 hours in patients with normal renal function and it strongly accumulates in patients with renal impairment. It shows weak binding to PF4 *in vitro* and forms a small amount of multimolecular complexes with PF4,[88] which are sufficient to induce an immune response as frequent as the LMWH enoxaparin.[89,90] However, the number of complexes is too small to cause major platelet activation after antibody binding. The reported cases of fondaparinux-induced HIT are likely due to the same mechanisms that are thought to underlie *delayed-onset HIT*:[91] After preimmunization with PF4/heparin or PF4/fondaparinux complexes respectively, some HIT patients develop autoantibodies against PF4 that show strong platelet-activating potency even in the absence of heparin or fondaparinux. This phenomenon is thought to be extremely rare, and the risk of causing HIT-like complications is considered to be negligible and routine platelet count monitoring is not recommended.[55]

Fondaparinux has not been systematically studied in HIT patients but the pooled data of several observational studies and case reports[92-97] suggest efficient prevention of new thrombosis in HIT patients (none of 71 patients with suspected HIT who were treated with fondaparinux, of whom 25 had a positive result in the functional assay, developed new thrombosis).[91] Bridging therapy with low-dose fondaparinux until HIT test results arrive might be reasonable in patients with low clinical suspicion of HIT. Considering the extensive experience using fondaparinux for prophylaxis and treatment of thrombosis in non-HIT patients, fondaparinux appears to be an appropriate drug for treatment of HIT.

Rivaroxaban (Xarelto®; Bayer)

Is an oral, direct FXa inhibitor, which does not interact with PF4 or PF4/heparin antibodies.[81] It is an attractive alternative anticoagulant in patients with a history of HIT. No information on the use of rivaroxaban in acute HIT is available.

Vitamin K antagonists (VKA)

Are dangerous in acute HIT as they cause a decrease in Protein C. This facilitates induction of microcirculatory thrombosis resulting in venous limb gangrene.[98,99] Vitamin K antagonists should not be initiated before platelet count has recovered (to at least 150 Gpt/L), or better to a stable plateau at two consecutive days, and always with an overlap with an alternative anticoagulant for at least five days and then until INR has reached the therapeutic levels.[55]

Patients receiving VKA at the time of HIT diagnosis should be given vitamin K (10 mg p.o./ 5-10 mg *i.v.*) to reverse vitamin K depletion.[55]

As the risk for thrombotic events remains high in HIT for 2-4 weeks[100] after initiation of alternative anticoagulation, until the antibody titer decrease, VKA anticoagulation can be considered for up to 4 weeks in patients with isolated thrombocytopenia.[101]

Recurrence of HIT

Several case series indicate that patients with a history of HIT are not at an increased risk for recurrence of HIT when they are reexposed to heparin.[14,102-107] This is compatible with laboratory studies, which failed to demonstrate memory B-cells in patients with PF4/heparin antibodies.[15] However, as the patient may develop HIT twice by chance, it is recommended to restrict the use of heparin in patients with a history of HIT to indications for which no established treatment schedule with an alternative anticoagulant is available, or to situations in which UFH has major advantages. One exception of this recommendation might become hemodialysis.

Hemodialysis

Most cases of HIT in patients on renal replacement therapy occur within the first two weeks after start of chronic dialysis, and patients should be monitored for a platelet count decrease during this period. Thereafter, the PF4/heparin antibodies are usually without clinical relevance. According to cross sectional studies, approximately 10% of hemodialysis patients have developed PF4/heparin antibodies six months after initiation of hemodialysis.[108] However, acute inflammatory events, especially surgery, can trigger HIT[109] even in patients who have received heparin during dialysis for years, and patients should be monitored for changes in the platelet count for the first two weeks after surgical interventions.

In dialysis patients with a history of HIT (>100 days), re-exposure to heparin only rarely induces recurrence of HIT when antibody tests are negative before re-exposure. Several reports suggest that re-exposure to heparin is feasible in these patients.[103,104]

Systematic data about alternative anticoagulants in hemodialysis patients with HIT are sparse.[110,111]

Cardiovascular surgery

Up to 70% of patients who underwent cardiovascular surgery develop anti-PF4/heparin antibodies. About 50% of these are IgG antibodies but only about 20% also activate platelets.[112-114] Despite this high prevalence of anti-PF4/heparin antibodies, only 1-2% of post-cardiac surgery patients develop clinical HIT. This raises the risk of overdiagnosing HIT in this patient group especially if only antigen assays are used to confirm the diagnosis. This problem is further aggravated by the high prevalence of a fall in platelet counts after cardiac surgery. In most patients, thrombocytopenia after cardiac surgery is caused by platelet consumption and typically occurs within the first 4 days. But in patients with low platelet counts persisting after day four after surgery, the misdiagnosis of HIT is frequent when these patients then develop (clinically irrelevant) PF4/heparin antibodies and test positive in a PF4/heparin antigen test. Therefore, it is highly recommended to test post-cardiac surgery patients also in a functional assay to avoid overdiagnosis.

The most appropriate anticoagulatory management in patients with a history of HIT during cardio-pulmonary bypass surgery is to use UFH, if the patient tests negative for PF4/heparin antibodies, but pre and postoperative anticoagulation should be performed with non-heparin anticoagulants. Until the antibodies are boosted (if at all), heparin is no longer in the circulation, and the antibodies cannot bind. In case of urgent surgery, intraoperative administration with UFH is also feasible in patients with a negative functional assay[115] (even when the immunoassay is still positive). If the functional assay is still positive, it is recommended to use an alternative anticoagulant for intraoperative anticoagulation.[55]

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