Heparin-Induced Thrombocytopenia[1]

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Abstract
Heparin-induced thrombocytopenia (HIT) is a relatively common immune-mediated disorder with the potential for serious thromboembolic complications. It is associated with the use of unfractionated heparin (UFH) and may be defined as a decrease in platelet count during or shortly after exposure to this anticoagulant. HIT occurs in up to 5% of patients who are exposed to UFH. Characteristic signs of HIT are a drop in platelet count of >50% and/or new thromboembolic complications during heparin therapy. Two types of HIT are recognized. Nonimmune heparin-associated thrombocytopenia is due to a direct interaction between heparin and platelets. The other type of HIT, immune-mediated HIT, is caused by heparin-dependent IgG (HIT-IgG) that recognizes a complex of heparin and platelet factor 4 (PF4), leading to platelet activation via the platelet Fc gammaRIIa receptor. Regular platelet count monitoring is best suited for early diagnosis of HIT, especially if UFH is used. Functional and antigen assays are available to confirm HIT. Heparin withdrawal and treatment with an agent that directly inhibits thrombin or decreases thrombin generation should be initiated prior to laboratory confirmation because of the rapidity with which thrombotic complications occur following platelet decline. The alternative anticoagulants, danaparoid (a heparinoid), argatroban (a synthetic direct thrombin inhibitor), and lepirudin (a recombinant direct thrombin inhibitor), are available for further anticoagulation in patients affected with HIT. At present, the most effective measure to reduce the risk of HIT is to use low-molecular-weight heparin (LMWH) instead of UFH, if possible, since LMWH is less frequently associated with HIT. Any patient who is treated with heparin is at risk for developing HIT, however there is no consensus regarding the necessity to obtain informed consent from patients about this possible risk before heparin treatment.

Key words
Heparin-induced thrombocytopenia (HIT), heparin, danaparoid, lepirudin, argatroban, thrombocytopenia

Definition

Heparin-induced thrombocytopenia (HIT) is a relatively common immune-mediated disorder associated with the use of unfractionated heparin (UFH) and may be defined as a decrease in platelet count during or shortly after exposure to this anticoagulant.

Use of Heparin

Heparin is the most frequently used anticoagulant in patients who are hospitalized. In Germany, about 80 million daily doses of heparin are given each year. Besides bleeding complications, which are usually only clinically relevant if heparin is used in therapeutic dosages, immune-mediated HIT is the most important adverse effect of heparin. Until recently, HIT was a complication almost exclusively observed in patients who were hospitalized. However, due to increasing outpatient treatment with heparin, HIT is now also occurring in this population.

Differential Diagnosis

In presence of unexpected thrombocytopenia, pseudothrombocytopenia should be excluded first (**Table 1**). This is especially important in patients who also receive GPIIb/IIIa inhibitors, which increase the incidence of pseudothrombocytopenia.

Early stages of septicemia are often associated with platelet counts of ~50,000/µL in severely ill patients. In these patients, clinical differentiation from HIT is often very difficult. Frequently, early occlusions of hemofilters used for renal replacement therapy indicate the procoagulatory HIT syndrome in these patients.

In patients with severe pulmonary embolism, massive thrombin generation with a concomitant decrease of platelet counts mimick HIT. Since pulmonary embolism also typically occurs in the same postoperative time frame as HIT, differentiation from HIT without laboratory diagnosis is often impossible.

The clinical presentation is different in acute autoimmune thrombocytopenia (Greinacher *et al*., 2001), other drug-dependent thrombocytopenias (Greinacher *et al*., 2001), GP IIb/IIIa inhibitor-induced thrombocytopenia (Greinacher *et al*., 2001), and posttransfusion purpura (Lubenow *et al*., 2000), all of which are characterized by very low platelet counts associated with hemorrhages.

Other diseases associated with low platelet counts also differ from HIT in regard to the onset of thrombocytopenia. A decrease in platelet counts develops acutely , without a time delay of 5 to 14 days in diabetic ketoacidosis (hyperreactive platelets), during thrombolysis (platelet activation by fibrin-split products and thrombin release), in septic endocarditis (septic emboli), and in paroxysmal nocturnal hemoglobinuria (activation of complement) (Warkentin, 2001).

Table 1: Differential diagnoses of heparin-induced thrombocytopenia

Diagnosis	Differentiating Features
pseudothrombocytopenia	often normal platelet count in citrated blood, platelet aggregates in blood film
nonimmunologic heparin-associated thrombocytopenia	after 1-2 days of therapeutic anticoagulation with UFH. Platelet count rarely <100,000/µL or decreases >30% (diagnosis by exclusion, no diagnostic test)
massive pulmonary embolism	almost clinically indistinguishable from HIT, if occurring 5-14 days following start of heparin
DIC/sepsis	often insidious onset, bleeding complications, consumption of clotting factors
drug-induced thrombocytopenia	usually 7-10 days following introduction of a new drug. Platelets <20,000/µL, bleeding complications
autoimmune thrombocytopenia	not associated with heparin medication
diabetic ketoacidosis	acute thrombocytopenia with onset of illness
GP IIb/IIIa inhibitor-induced thrombocytopenia	begins within 12 h of IIb/IIIa-inhibitor infusion, platelets <20,000/µL, bleeding complications (important differential diagnosis: pseudothrombocytopenia)
post-transfusion purpura (PTP)	7-14 days after transfusion in preimmunized patients (>95% women), platelets <20,000/µL, bleeding complications

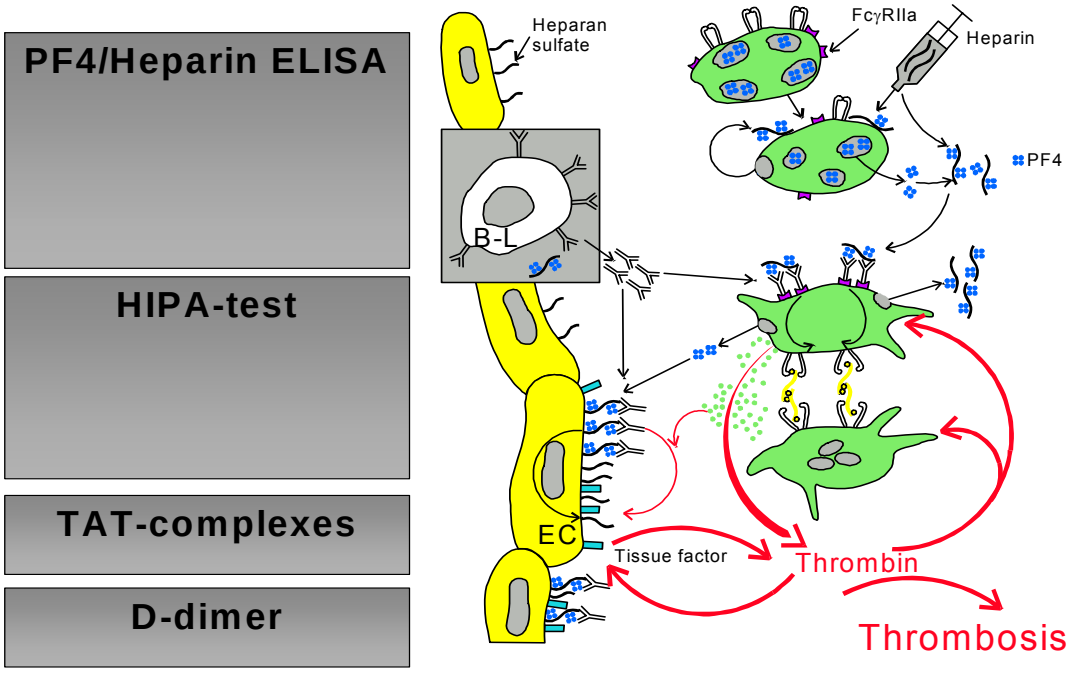
Pathogenesis

HIT is caused by antibodies to platelet factor 4 (PF4) complexed with heparin. Although PF4 is the most important protein involved in the immune response of HIT (Amiral 1992; Greinacher *et al*., 1994), neutrophil-activating peptide 2 (NAP-2) and interleukin 8 (IL8) also play a role (Regnault *et al*., 2003). At least two PF4 neo- or crypto-antigens are exposed (expressed on the surface of PF4) after binding to heparin (Visentin *et al*., 2001; Li ZQ *et al*., 2002). Interaction with PF4 depends on the

molecular weight of heparin. Longer and more highly sulfated heparin chains are more immunogenic than low-molecular weight heparin (LMWH) or even the synthetic pentasaccharide (Greinacher *et al*., 1995). In clinically symptomatic patients, HIT antibodies are mostly of the IgG subclass, (Amiral *et al*., 1996), with or without IgM or IgA HIT antibodies (Suh *et al*., 1997), (Amiral *et al*., 1996). The most important receptor for the IgG immune complexes on the platelet surface is the Fc gammaRIIa (FcγRIIa) receptor. Cross-linking of FcγRIIa results in platelet activation (Denomme, 2001).
Thrombin is the key enzyme in HIT (Warkentin *et al*., 1997; Greinacher *et al*., 2000). Thrombin generation in HIT is enhanced by concomitant activation of platelets (Chong *et al*., 1994) and the clotting cascade, generation of platelet microparticles (Warkentin *et al*., 1994), activation of endothelial cells (Cines *et al*., 1987) and monocytes (Pouplard *et al*., 2001) (**Figure 1**).

HIT can be described by a 3-step model. The first step is the immune reaction, *i.e*., generation of HIT antibodies. The second step consists of platelets activation and increased thrombin generation. This switch from a primary immune reaction to a procoagulatory syndrome occurs only in a subset of patients. No parameter has yet been found to identify these patients. Whether the procoagulatory syndrome manifests as thrombosis in a third step depends on individual patient characteristics. Some patients are able to compensate clotting activation; in others, venous or arterial clots form. The known genetic risk factors for thrombosis, *i.e.* Factor V Leiden, the prothrombin or MTHFR polymorphism, and known platelet-receptor polymorphisms, do not seem to be major risk factors for developing HIT-associated thrombosis (Carlsson *et al*., 2003).

Figure 1: Pathogenesis of HIT



HIT-IgG antibodies bind to epitopes on the antigen complex, thus forming immune complexes that become localized to the platelet surface. The IgG immune complexes can cross-link the platelet FcgRIIa receptors, resulting in FcgRIIa-dependent platelet activation. The activated platelets trigger a cascade of events, leading ultimately to activation of the coagulation pathways. This results in thrombin generation.
Activated platelets release their granule proteins including PF4, which leads to formation of more multimolecular PF4/heparin complexes, thereby setting up a vicious cycle of platelet activation.
The activated platelets bind fibrinogen, recruit other platelets, and start to form a primary clot.
Procoagulant, platelet-derived microparticles are released, providing a phospholipid surface for amplifying thrombin generation. Tissue factor expression on activated endothelial cells and monocytes further enhances thrombin generation.
The left part of the figure shows which pathophysiological steps are detected by the assays currently available. PF4/heparin-ELISAs detect the presence of HIT antibodies only; functional tests, for example the HIPA assay, show whether these antibodies are able to activate platelets. None of the available so-called HIT tests can predict the risk of a patient developing a thrombosis. Increased thrombin formation can be demonstrated by prothrombin fragments F1+2 or thrombin antithrombin (TAT) complexes. D-dimers indicate if a patient has already developed a thromboembolic complication

Clinical Presentation

Two types of HIT are recognized: nonimmune heparin-associated thrombocytopenia and immune-mediated heparin-induced thrombocytopenia (HIT).

Nonimmune heparin-associated thrombocytopenia

Heparin is a strongly negatively charged polysaccharide. It binds to positively charged proteins and cell surfaces (Greinacher *et al*., 1993; Horne, 2001). Thus, heparin can directly bind to platelets, which results in a moderate decrease of platelet counts in about 25% of patients in the first days of therapeutic heparin treatment. Platelet counts rarely decrease by more than 30% (Burgess *et al*., 1997). In patients with peripheral arterial disease, severe burns, or anorexia nervosa, the platelet count decrease may be more severe (Reininger *et al*., 1996). There is no specific diagnostic tool to identify these patients; the diagnosis is, rather, one of exclusion of other causes. In the literature, nonimmune heparin-associated thrombocytopenia is often called HIT type I. A change of treatment is usually unnecessary in nonimmune HIT since platelet counts normalize spontaneously, despite maintenance of heparin.

Immune-mediated heparin-induced thrombocytopenia (HIT)

HIT is a clinico-pathological syndrome characterized by clinical symptoms (primarily, decreased platelet counts and new thromboembolic complications) and specific antibodies.

HIT typically manifests between day 5 and day 14 after the start of heparin therapy, but may occur earlier if the patient received heparin within the last 3 months (Lubenow *et al*., 2002; Warkentin *et al*., 2001). This delayed onset is caused by the biology of B-cells, which require at least 5 days for sufficient antibody production. Subsequently, platelet counts decrease rapidly by more than 50% within another 1 to 2 days (Warkentin, 2001). To calculate the relative decrease of platelet counts, it is important to use the highest platelet count value after start of heparin therapy, as a reactive thrombocytosis is known to occur in many patients after major surgery. Therefore, a rapid fall in platelet count from 500,000/µL to 200,000/µL is a very strong indicator of HIT, even though these platelet counts are still within the normal range. In ~10% of patients, platelet counts never decrease below 150,000/µL. Usually platelet counts are between 30,000 and 80,000/µL and decrease to values below 20,000/µL in fewer than 10% of patients. These patients often suffer from secondary disseminated intravascular coagulopathy (DIC) (Warkentin, 2001).

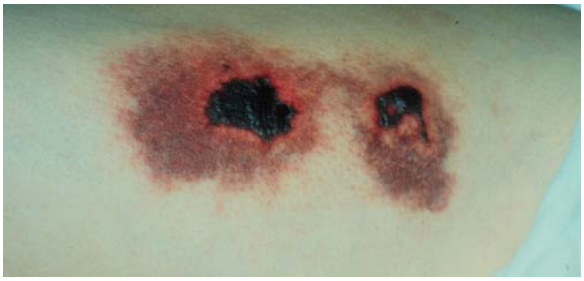
Paradoxically, bleeding complications are rare in HIT, but they should be expected in patients with platelet function defects (*e.g.*, caused by uremia in endstage renal insufficiency or in clotting disorders such as DIC. Patients tend to develop new thrombotic complications, which worsen dramatically if treated by an increase in heparin dose.The risk of developing HIT-associated thrombo-embolic complications (TECs) ranges between 50% and 75%, depending on the patient group and the antibody titer. In clinical studies addressing the risk of HIT-induced thrombosis, the odds ratio (OR) for deep vein thrombosis (DVT) ranges between 20% and 40% for orthopedic surgery and medical patients (Warkentin *et al*., 1995; Girolami *et al*., 2003). The OR for pulmonary embolism in orthopedic surgery patients was found to be as high as 93.4 in one prospective trial (Warkentin *et al*., 1995).

Early reports on HIT stressed its association with arterial thrombosis. Newer data indicate that about 65% of all thromboses in HIT are venous. In a retrospective analysis of more than 400 patients with HIT, we found that nearly 50% of patients with thrombosis also developed pulmonary embolism. Other thromboses often affect the lower limb veins -less frequently limb arterial embolism, myocardial infarction, stroke, sinus-vein thrombosis (Pohl *et al*., 1999), mesenteric veins- arteries, and induce skin lesions, which manifest as inflammation and necrosis at the heparin injection site (**Figure 2**). Acute neurological deficits, such as retro- and anterograde amnesia or systemic reactions with hypotension, following a heparin bolus are also seen, but less frequently.

In some patients, thromboses manifest without a decrease in platelet counts. Typically, these patients do not show postoperative reactive thrombocytosis but maintain a stable platelet count. When heparin is stopped, platelet counts usually increase rapidly to much higher levels. Therefore, in all patients who present with a new thrombosis within 2 weeks after heparin was given, platelet counts must be checked before the start of heparin therapy to rule out delayed onset HIT.

High titer HIT antibodies, which recognize an epitope on PF4 even in the absence of heparin, are usually detectable in these patients (Warkentin *et al*., 2001). Presumably these patients develop an autoimmune phenomenon, which, in some aspects, mimicks posttransfusion purpura (Lubenow *et al*., 2000).

Figure 2: Typical appearance of a heparin-induced skin necrosis: erythematous edge with clearly visible irregularly demarcated central necrosis.



Prognosis

Until recently, mortality in HIT was as high as 20%, with a similar percentage of patients surviving with major complications (*e.g.*, limb loss, stroke). Improvements in early diagnosis of HIT and new treatment options have resulted in a much better prognosis for patients with HIT in recent years. However, mortality remains as high as 6% to 10%, and the risk for limb loss is similar.

Laboratory Diagnosis

As screening patients for HIT antibodies has not yet been proven beneficial, it is currently not recommended for any patient population. Laboratory testing for HIT antibodies is only relevant to confirm or to rule out clinical diagnosis of HIT (Warkentin *et al*., 2001).

All functional assays are independent of the antigen towards which HIT antibodies are directed in an individual patient, but they primarily identify HIT antibodies of the IgG-class. The serotonin-release assay (SRA) remains the gold standard of HIT-antibody tests. However, it is technically demanding, time consuming and uses radioactivity. Therefore, the heparin-induced platelet activation test (HIPA), although still technically demanding (*e.g.*, performing platelet rich plasma or washing of platelets), is the most widely used washed-platelet functional assay in Europe. Other functional assays for diagnosis of HIT have been described. The results do not differ substantially from each other, as long as washed platelets are used.

Antigen assays (*e.g.*, enzyme-linked immunosorbent assays [ELISAs]) are now commercially available (Amiral 1992; Visentin 2001). All these assays detect antibodies that bind to PF4/heparin or PF4/polyvinylsulfate complexes bound to a solid phase. PF4/heparin complexes are either bound to a microtiter plate or to microbeads (microcolumn assay) (Alberio *et al*., 2003; Eichler *et al*., 2002). These assays detect HIT antibodies of the IgG, IgM, and IgA classes. However, they cannot detect HIT antibodies directed to proteins other than PF4 (*e.g.*, NAP-2 or IL-8).

Although antigen assays and functional HIT assays have similar sensitivities in patients with clinical manifestations of HIT, they do not detect the same patient groups. About 5% of patients with clinically symptomatic HIT will be positive in only one assay. Thus, for high sensitivity, a combination of both assays is required (Greinacher *et al*., 1994).

Antigen assays have a higher sensitivity than functional assays in patients who are clinically asymptomatic. Therefore, functional assays seem better than antigen assays to predict clinically manifest HIT (Warkentin *et al*., 2000).

This also suggests that clinical probability of HIT must be taken into account when results of HIT assays are interpreted. If a patient presents with the typical decrease of platelet counts 5 to 10 days after the start of heparin therapy, and one of the assays (functional or antigen assay) is positive, HIT is very likely (Warkentin *et al*.,2003). Conversely, if a post-cardiac-surgery patient develops severe complications but not the typical platelet count decrease, and a positive PF4-heparin antigen assay does not necessarily indicate HIT. More likely this is a simple coincidence because the chance of developing HIT antibodies that are detectable by an antigen assay in a post-cardiac surgery patient is about 50%. However, if both functional and antigen assays are negative in a patient with clinically suspected HIT, then HIT is very unlikely (Warkentin *et al*., 2001).

The 3-stage model of the pathogenesis of HIT, described above, is also relevant for interpretation of HIT assay results. Antigen assays can only detect the first step of the cascade, the immune response (**Figure 1**). Functional assays also involve the second step, *i.e.* whether the antibodies in a specific patient are able to activate platelets. The most important final step of the cascade, *i.e*. thrombosis manifestation, cannot be tested with any of the so-called HIT assays. In our experience, the stronger the antibodies are, either showing a high optical density in the ELISA, a high serotonin release in the SRA, or a short lag time in the HIPA test, the higher is the likelihood for thrombotic complications. However, it is unknown whether this applies to all patients.

The easiest method to identify HIT early is to determine platelet counts. However, optimal frequency of platelet-count monitoring is debated. **Table 2** provides suggestions by several experts in the field (Greinacher *et al*., 2003; Warkentin, 2002).

Table 2: **Optimal frequency of platelet-count monitoring in different HIT patient populations**

1. Patients at highest risk for HIT (1%-5%) Postoperative patients, who are treated with unfractionated heparin (UFH) for thrombosis prophylaxis after major surgical/orthopedic procedures: platelet counts during heparin medication at least every other day from day 4 to 14[1] (or until end of heparin medication). All patients receiving UFH in therapeutic doses: daily platelet counts[2] from days 4 to 14[1] (or until end of heparin medication). Patients at medium risk for HIT (0.1%-1.0%) Medical/gynecologic patients, receiving UFH for prophylaxis; thrombosis prophylaxis with low-molecular-weight-heparin (LMWH) after major surgical/orthopedic procedures; postoperative patients, in whom UFH is used for catheter flushes: platelet counts during heparin medication every 2 to 3 days from days 4 to 14[1] (or until end of heparin medication, if feasible).[3] Patients at low risk for HIT (<0.1%) Medical/gynecologic patients, receiving LMWH for prophylaxis or therapy; medical patients in whom UFH is used for catheter flushes; patients receiving LMWH for prophylaxis after minor surgery: platelet count monitoring not necessary.[4,5]
2. The most important period to diagnose HIT with typical onset is between days 4 to 14[1] after start of heparin, the highest platelet count from day 4 (inclusive) being the baseline value.
3. In patients reexposed to heparin within 100 days, a platelet count 24 h after reexposure will detect those with rapid-onset HIT due to circulating HIT antibodies.
4. In patients who develop a thrombosis during or soon after heparin medication, or in whom an unusual clinical event occurs in conjunction with heparin (*e.g.*, heparin-induced skin lesions or acute systemic reaction after heparin bolus), a platelet count should be performed immediately and should be compared with previous values.
5. Even a platelet count nadir above $150x10^9$/L can be a decrease of >50% from baseline, thus indicating HIT; less pronounced drops in platelet numbers in HIT can be associated with thrombotic events as well.

[1]First day of heparin treatment=day 0.
[2]Daily platelet counts are feasible, since blood has to be taken for aPTT monitoring of heparin therapy.
[3]Platelet-count monitoring can be difficult to perform in outpatients.
[4]Platelet-count monitoring according to the section "Patients at medium risk of HIT" should be performed in patients who received one or more doses of UFH before changing to LMWH.
[5]In these patients, a preheparin baseline platelet count should be obtained.

Incidence

HIT occurs in up to 5% of patients who are exposed to unfractionated heparin (UFH)

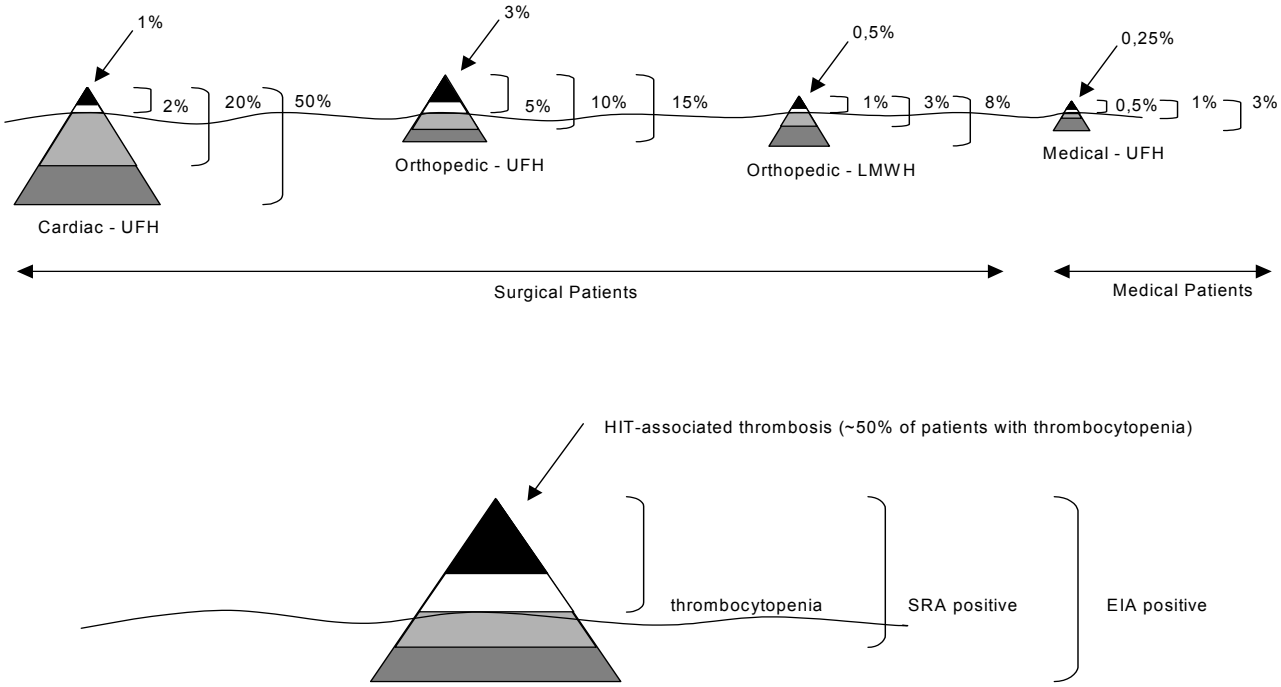
As shown in several prospective trials, only a minority of patients developing HIT antibodies will also develop clinical symptoms of HIT. This pattern is very well described by the "iceberg model" of HIT (Lee and Warkentin, 2001) (**Figure 3**). Additionally, the incidence of HIT strongly depends on the type of heparin used. UFH causes HIT ~10 times more frequently than LMWH (Warkentin *et al*., 1995; Ganzer *et al*., 1999). The widespread use of LMWH has resulted in a substantial decrease in the incidence of HIT. HIT incidence depends also on the patient population: patients receiving heparin following major surgery are at a higher risk of developing HIT than medical patients. In surgical patients, prospective trials showed that HIT incidence ranges from 2.3% to 3% following hip replacement surgery (Warkentin *et al*., 1995) and from 2% to 2.5% following cardiac surgery (Pouplard *et al*., 1999; Warkentin, and Greinacher, 2003).

In medical patients, HIT should be primarily expected in cardiac patients and in patients receiving UFH in intensive care units. Patients with acute stroke who receive UFH seem also to be at risk for HIT (Harbrecht *et al*., 2002). HIT is rare during hemodialysis, and when it occurs, it is usually during the second or third week following start of chronic dialysis. Also, dialysis patients who undergo a surgical procedure seem to be at increased risk for developing HIT within 2 weeks following surgery (Tholl *et al*., 1997).

There are two risk groups for HIT in children: one group consists of newborns and toddlers with complex cardiac malformations requiring cardiac surgery; the other group consists of adolescents who receive UFH after developing a thrombosis. To date, all HIT cases reported in children were induced by UFH (Klenner *et al*., 2003).

Also, characteristics of HIT patients have changed. Until recently, the majority of patients who developed HIT were those who had had major orthopedic surgery, whereas in 2003, most are intensive care patients or post-cardiac-surgery patients. In general, this shift in patient populations has been towards UFH-treated group rather than LMWH-treated group.

Figure 3: Variable frequency of HIT antibody formation and clinical HIT among different patient populations treated with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH).



A schematic "iceberg," shown below, illustrates the relationship between HIT-associated thrombosis, thrombocytopenia, HIT antibodies detected by serotonin release assay (SRA), and HIT antibodies detected by enzyme-immunoassay (EIA). The size of the iceberg reflects the relative frequency of HIT antibody formation by EIA, *i.e.*, the cardiac-surgery-UFH iceberg is about six times larger than the orthopedic-LMWH iceberg (50% vs 8% frequency of HIT antibody formation). Noteworthy aspects include the observation that HIT-associated thrombosis is most common in orthopedic-UFH patients, even though HIT antibody formation is most common in cardiac-UFH patients, as well as the observation that orthopedic-LMWH has a higher frequency of thrombosis than does medical-UFH.

Treatment

Patients groups

Treatment strategies in HIT depend on the clinical status of the patient:

Patients with isolated seroconversion

The detection of HIT antibodies without other symptoms, such as an otherwise unexplained decrease in platelet counts, a new thrombotic complication, or skin reactions at the heparin injection site, does not require a change in heparin treatment.

Patients with HIT but no thrombosis

About 50% of patients in whom HIT is diagnosed do not have a known thrombotic complication. HIT is usually suspected when there is an otherwise unexplained decrease in platelet counts. In a retrospective analysis of 62 patients with isolated HIT, 52.8% developed a new thrombosis in the 30 days following discontinuation of heparin (Warkentin, 1996). As a result, these patients should be anticoagulated with an alternative anticoagulant. The high rate of clinically manifest thromboses might also be caused by clinically asymptomatic thromboses at the time of acute HIT, which, over the following weeks, trigger a clinically symptomatic thrombosis. Therefore, in these patients deep venous thrombosis (DVT) should be excluded for example by duplex sonography (Wallis *et al*., 1999). Anticoagulation should at least be maintained until platelet numbers have normalized, *i.e*. reaching a stable, nonrising count on 2 consecutive days (Greinacher *et al*., 2001). In a retrospective analysis, we recently provided evidence that HIT patients with isolated thrombocytopenia benefit from therapeutic-dose anticoagulation (Farner *et al*., 2001). Danaparoid in low dose (750 U tid), currently the only treatment approved in Europe for these patients, is most likely insufficient to control thrombin generation.

Platelet transfusions are relatively contraindicated in patients with acute HIT.

Patients with HIT and thrombosis

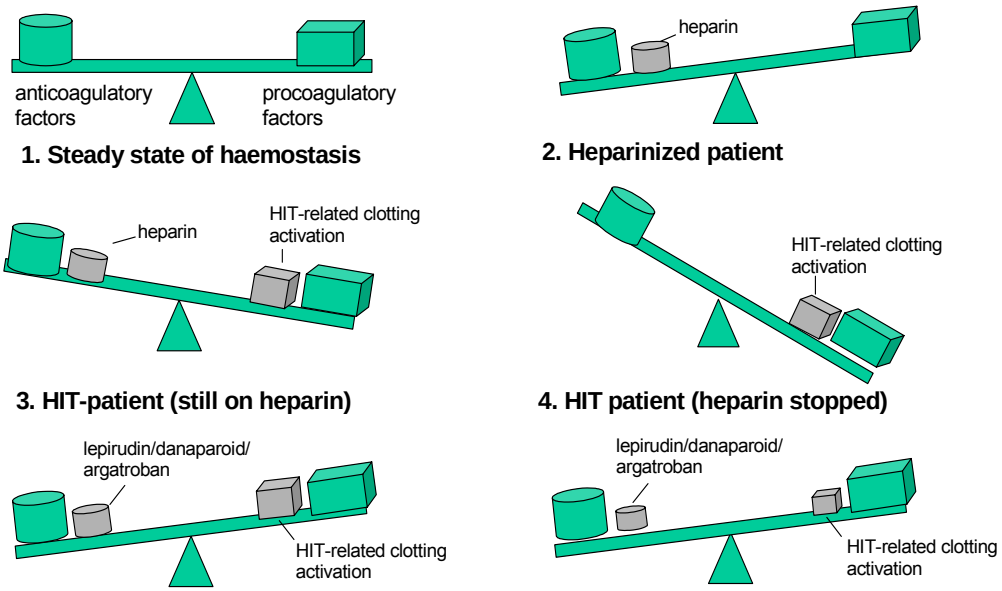
It is generally accepted that patients with acute thrombosis require therapeutic-dose anticoagulation. This is especially important during the first days of HIT, due to the massive generation of thrombin in patients with HIT (Greinacher *et al*., 2000).

Alternative anticoagulants in HIT

In case of high clinical suspicion of HIT, alternative anticoagulation should be started as soon as possible. A delay in initiating treatment, such as waiting for laboratory results of HIT antibody tests, is associated with high risk of further thrombosis (Greinacher *et al*., 2000).

Similarly, cessation of heparin is not sufficient treatment to avoid new thrombosis (**Figure 4**) (Greinacher *et al*., 2002). In a retrospective analysis (Wallis et al., 1999) compared 113 patients in whom heparin was stopped immediately after clinical suspicion of HIT (0.7 +/- 0.6 days; n=40) with patients in whom heparin was continued (5 +/- 3 days; n=73). Paradoxically, the rate of mortality and thrombotic complications in patients with early cessation of heparin (and no other anticoagulatory treatment) is higher than in patients with ongoing heparin treatment. Most likely, the continuing anticoagulatory effect of heparin partly compensated for the HIT-induced thrombin generation. Due to the central role of thrombin in HIT, agents that decrease the generation of thrombin or directly inhibit thrombin activity (direct thrombin inhibitors) are a logical choice for prevention or treatment of HIT.

Figure 4: Scale model of hemostatic balance



The steady state of the healthy individual (#1) is tipped towards anticoagulation in the patient receiving heparin (#2). HIT-related clotting activation increases the risk of thrombosis (#3), especially if heparin is stopped (#4) without switching to an alternative anticoagulant (#5). Importantly, as HIT-related clotting activation decreases, anticoagulation has to be adjusted accordingly (#6).

Danaparoid

The heparinoid, danaparoid (Orgaran) (Chong *et al*., 2001), approved for prophylaxis and treatment of thrombosis in patients with HIT in the European Union [EU]), inhibits thrombin generation primarily by anti-FXa activity with a half-life of ~24 hours.

Danaparoid, compared to dextran, has been assessed in patients with HIT in a small, randomized trial, and in a large compassionate-use program (Chong *et al*., 2001) with more than 660 patients. In the compassionate-use program, the treating physicians judged treatment to be successful in 93% of cases. New thrombosis was documented in 1.7% of cases. Of the 114 deaths, 14 (17.1%) were associated with danaparoid therapy.

HIT antibodies may cross-react with danaparoid. The *in vitro* cross-reactivity rate, ranging between 7% and 50%, however, depends on the sensitivity of the assay used. A retrospective cohort study did not reveal a difference in outcomes in those patients who showed *in vitro* cross-reactivity and those who did not (Warkentin, 1996). Therefore, treatment can be started without cross-reactivity testing. Clinical signs of cross-reactivity, (*i.e.*, new thrombosis, persistent thrombocytopenia) should prompt a switch to another anticoagulant, such as lepirudin, and confirmatory cross-reactivity testing.

Direct thrombin inhibitors

Lepirudin and argatroban are two direct thrombin inhibitors (DTIs) currently used for

anticoagulation in patients with HIT. Lepirudin is approved in the EU, while both lepirudin and argatroban are approved in the United States (Lewis *et al*., 2001; Greinacher *et al*., 1999).

Lepirudin

Lepirudin, a bivalent inhibitor, binds irreversibly to the catalytic site and the fibrinogen binding site of thrombin (Greinacher *et al*., 2001). Clinical trials demonstrated that lepirudin is effective in patients with HIT, with or without baseline thrombosis (Greinacher *et al*., 1999; Greinacher *et al*., 2000; Eichler *et al*., 2002; Lubenow *et al*., 2002) (**Figures 5a and 5**b). However, bleeding complications were more frequent in patients treated with lepirudin than in historical controls or patients on other treatments (Greinache ret al, 2000; Lubenow et al, 2002), presumably due to a longer treatment period and the often underestimated effect of venal impairment on pharmacokinetics lepirudin. The half-life of lepirudin is strongly dependent on renal function and, in rare cases, it can induce anaphylactic reactions (Greinacher et al, 2003). The risk of bleeding during treatment with lepirudin as well as the risk of severe anaphylaxis, should be reduced by avoiding the bolus and starting the intravenous infusion at a reduced rate of 0.1 mg/kg/hr adjusted to (Partial Thromboplastin Time) aPTT after 4 hours.

Argatroban

Argatroban is a synthetic thrombin inhibitor that binds reversibly to the catalytic site of thrombin. A careful review of the published clinical trials demonstrated that the efficacy data for argatroban are favorable for patients with HIT and isolated thrombocytopenia, but inconclusive for patients with HIT and baseline thrombosis (Lewis *et al*., 2001, Lewis *et al*., 2003) (**Figures 5a and 5b**). As argatroban itself causes an increase in International Normalized Ratio (INR), transition to oral anticoagulants is problematic.

Figure 5a: Comparison of efficacy and safety outcomes in studies evaluating direct thrombin inhibitors in heparin-induced thrombocytopenia with isolated thrombocytopenia.

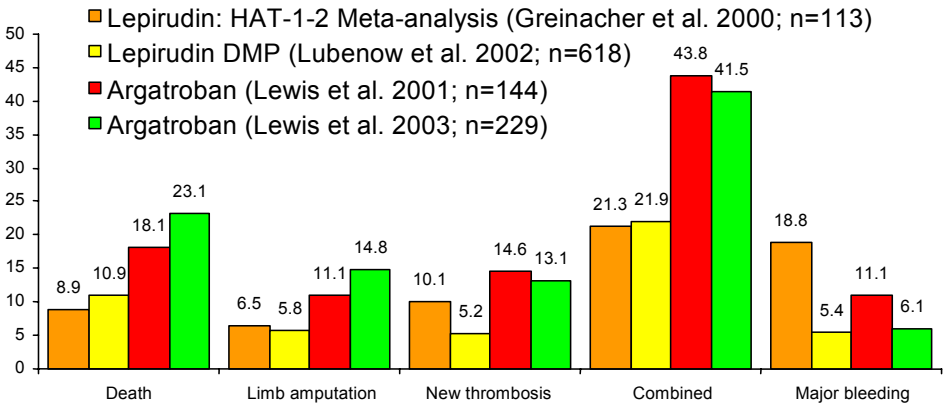
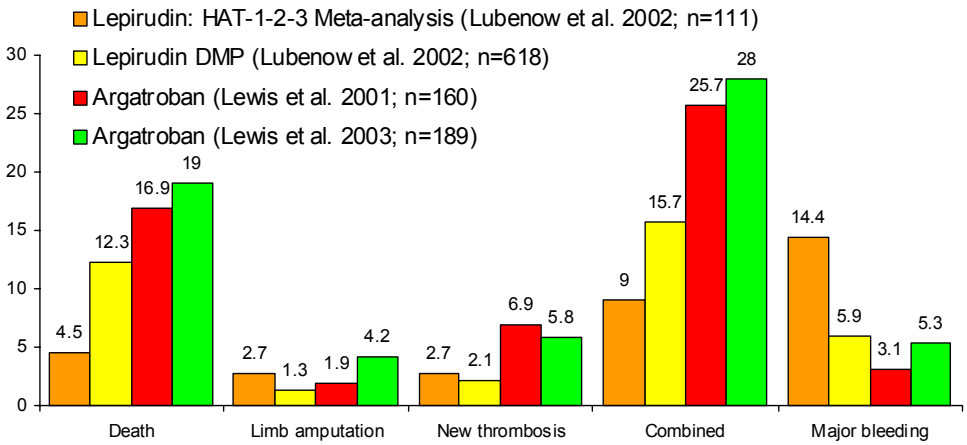


Figure 5b: Comparison of efficacy and safety outcomes in studies evaluating direct thrombin inhibitors in heparin-induced thrombocytopenia with thrombosis.



Oral Anticoagulation

Due to the short half-life of Protein C, there is a procoagulatory imbalance in the clotting system with low Protein C levels at the start of oral anticoagulants (OA), while the procoagulatory clotting factors are still present in high concentrations. In combination with HIT antibodies, this temporary procoagulatory imbalance can trigger microvascular clots with the risk of venous limb gangrene. Therefore, it is of major importance to start OAs in HIT at a low dose and only under therapeutic anticoagulation with a compatible anticoagulant. To avoid the syndrome of venous limb gangrene, OAs should only be started when platelet counts have normalized. Parenteral anticoagulation should only be stopped after therapeutic INR is reached (Warkentin *et al*., 1997; Greinacher *et al*., 2001).
In some patients the INR increases rapidly to therapeutic levels before day 5 of OA treatment. This is usually caused by low FVII levels. If parenteral anticoagulation is stopped in these patients, the risk of new thrombosis is very high.

Other Drugs

LMWHs induce HIT much less frequently than UFH. However, in immunized patients, they can cause serious complications and are contraindicated in acute HIT. The recently approved synthetic pentasaccharide, fondaparinux (Arixtra®), might be suitable for alternative anticoagulation in HIT patients, but this has not been investigated systematically.

Reexposure of Patients With HIT to Heparin

As only patients who received heparin within the last 100 days are at risk of developing early onset of HIT (<5 days), patients with a history of HIT can be reexposed to heparin (Warkentin *et al*., 200; Lubenow *et al*., 2002) briefly. Heparin has been used successfully in cardiopulmonary bypass surgery in patients with a history of HIT, thereby avoiding the use of high-dose alternative anticoagulants for which no antidote is available (Pötzsch *et al*., 2001; Pötzsch *et al*., 2000; Selleng *et al*., 2000).

Legal Aspects of HIT

As HIT is a iatrogenic complication, the medico-legal aspects are of increasing interest. The legal implications of HIT have been discussed from the European and the North American perspective by legal experts (Ulsenheimer, 2001; McIntyre *et al*., 2001). However, the question of informing the patient about the potential complications of HIT before giving heparin has not been addressed up to now. Informed consent is required for most treatments, including information about unwanted effects of treatment, but HIT is hardly mentioned to any patient even though it can occur in up to 5% of certain patient populations. We recently examined whether obtaining informed consent in patients at risk for HIT might result in patient rejection of prophylaxis for thrombosis. This is an important issue, as it would put the patient at high risk for developing a thrombosis due to lack of anticoagulation. In a prospective study, we informed 460 consecutive patients in trauma surgery about the risk of HIT, before starting thrombosis prophylaxis. None of the patients refused thrombosis prophylaxis, and the vast majority (>98%) rated being informed about this potential adverse effect as very positive (Hinz *et al*., 2003).
The incidence of HIT is decreasing due to the more frequent use of LMWHs and other nonheparin anticoagulants. Therefore, informed consent mentioning HIT will also help increase recognition of this condition by the treating physician and the patient as a cause for new thrombosis, thereby avoiding mistreatment with therapeutic doses of heparin.
Whether patients should also be informed about the varying likelihood for HIT, when UFH, LMWHs or other anticoagulants approved for thrombosis prophylaxis are used, is currently unresolved.

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