Heparin-induced thrombocytopenia in solid organ transplant recipients: The current scientific knowledge

Volker Assfalg, Norbert Hüser

Volker Assfalg, Norbert Hüser, Department of Surgery, Klinikum rechts der Isar der Technischen Universität München, D-81675 Munich, Germany

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Correspondence to: Volker Assfalg, MD, Department of Surgery, Klinikum rechts der Isar der Technischen Universität München, Ismaningerstr. 22, D-81675 Munich, Germany. volker.assfalg@tum.de
Telephone: +49-89-41402121
Fax: +49-89-41404870

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Abstract

Exposure to heparin is associated with a high incidence of immunization against platelet factor 4 (PF4)/heparin complexes. A subgroup of immunized patients is at risk of developing heparin-induced thrombocytopenia (HIT), an immune mediated prothrombotic adverse drug effect. Transplant recipients are frequently exposed to heparin either due to the underlying end-stage disease, which leads to listing and transplantation or during the transplant procedure and the perioperative period.

To review the current scientific knowledge on anti-heparin/PF4 antibodies and HIT in transplant recipients a systematic PubMed literature search on articles in English language was performed. The definition of HIT is inconsistent amongst the publications. Overall, six studies and 15 case reports have been published on HIT before or after heart, liver, kidney, and lung transplantation, respectively. The frequency of seroconversion for anti-PF4/heparin antibodies ranged between 1.9% and 57.9%. However, different methods to detect anti-PF4/heparin antibodies were applied. In none of the studies HIT-associated thromboembolic events or fatalities were observed. More importantly, in patients with a history of HIT, reexposure to heparin during transplantation was not associated with thrombotic complications. Taken together, the overall incidence of HIT after solid organ transplantation seems to be very low. However, according to the current knowledge, cardiac transplant recipients may have the highest risk to develop HIT. Different alternative suggestions for heparin-free anticoagulation have been reported for recipients with suspected HIT albeit no official recommendations on management have been published for this special collective so far.

Key words: Heparin-induced thrombocytopenia; Heparin-induced thrombocytopenia; Heparin; Organ; Transplantation

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Core tip: Heparin-induced thrombocytopenia (HIT) II is a life-threatening complication of heparin therapy. Transplant recipients frequently are exposed to high doses of heparin before, during, and after transplantation. This review gives a systematic overview...
on the current scientific knowledge and existing publications on anti-platelet factor 4/heparin antibodies and HIT in transplant candidates and recipients.

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INTRODUCTION

Heparin plays a pivotal role in peri-operative anticoagulation therapy to prevent thrombosis and thrombembolism.

During the course of the underlying disease, nearly all patients who finally undergo solid organ transplantation, are exposed to prophylactic or therapeutic dose heparin (e.g., dialysis due to endstage renal disease; cardiac assist devices because of heart failure). During organ perfusion for procurement and within the transplant procedure heparin is used to prevent formation of blood clots.

Heparin application entails several risks for the transplant recipients who need careful observation to prevent additional morbidity and mortality. Heparin interferes with platelets. It may directly activate platelets, causing a mild, reversible decrease in platelet counts, so-called heparin-induced thrombocytopenia (HIT) type I. In contrast to clinically irrelevant HIT type I, immune mediated HIT type II is of major clinical importance.

If not recognized early during its development this relevant adverse reaction of heparin paradoxically triggers potentially lethal venous and arterial thromboses. Clinical manifestation of HIT type II is very heterogeneous. Therefore, HIT type II should be considered in every patient who develops thrombocytopenia, thrombosis, embolism, vascular obliteration, or skin necroses during heparin therapy.

HIT type II is caused by IgG antibodies binding with complexes of negatively charged heparin molecules and a positively charged, soluble platelet protein platelet factor 4 (PF4). When several of these antibodies bind with PF4/heparin complexes, immune complexes are formed that activate platelets via the platelet Fc-receptor. Activated platelets provide the catalytic surface for enhanced thrombin generation, which is the reason for an increased risk for thrombosis, especially when other risk factors for thrombosis are present.

Enzyme linked immunosorbent assay (EIA) can detect the anti-PF4/heparin antibodies underlying HIT. However, in the context of HIT, only anti-PF4/heparin IgG antibodies are relevant, as IgM and IgA antibodies cannot bind to the platelet Fc receptor and can therefore not induce platelet activation with subsequent thrombin generation. Platelet activating antibodies can be identified by functional assays such as serotonin release assay (SRA) and heparin induced platelet activation assay (HIPA). This stepwise emergence of seroconversion (EIA), activating antibodies (SRA/HIPA), thrombocytopenia, and HIT II associated thrombosis (HIT thrombotic syndrome: HITT S) has previously been illustrated as an “iceberg model of HIT” (Figure 1). As only a minority of anti-PF4/heparin antibodies induces HIT, the diagnosis of HIT requires both, clinical and serological findings.

Unfortunately, a major criterion of HIT, a platelet count decrease by more than 50%, is not very specific after major surgery due to a frequent post-operative decrease in platelet counts for surgery-related reasons. However, HIT occurs typically between day 5 and 14 after starting heparin treatment and is often associated with new thrombosis. Taking these criteria together, the diagnosis of HIT becomes likely if the platelet count decreases by > 50% between days 5 and 14 after starting heparin treatment, especially if accompanied by new thrombotic complications. Basically, patients receiving heparin need routine laboratory controls of platelet counts to detect an emerging thrombocytopenia and HIT II. To this day, no screening procedure exists to detect patients at risk of HIT II. In case of suspected HIT II it is important to stop heparin application immediately, initiate laboratory investigations, and switch to a heparin-free anticoagulation regimen such as danaparoid, lepirudin, argatroban, or fondaparinux.

In daily clinical practice the 4Ts score (Table 1) has been repeatedly shown to serve as a reliable tool to assess the individual probability of HIT II. A high 4T score together with a positive functional assay are regarded as being confirmatory for HIT. A negative PF4/heparin EIA rules out HIT with very high likelihood. However, a positive PF4/heparin EIA on its own is not very informative. Therefore, according to the “classic” definition of HIT an intermediate to high pretest probability and detection of platelet activating antibodies (SRA/HIPA) are required for a reliable diagnosis of HIT. Less stringent criteria often lead to an inappropriate change to alternative, heparin-free anticoagulation, which causes both an increased risk of bleeding and increased treatment costs. Most importantly, this overdiagnosis may lead to patients being delisted from the transplant list.

In regard to disease specific impacts on HIT, comprehensive and reliable data mainly exist based on patient series from cardiac surgery, orthopedic surgery, and vascular surgery. However, reports and systematic studies on HIT in solid organ transplant recipients are rare and inconclusive.

In this review we give a systematic overview of the current scientific knowledge about anti-PF4/heparin antibodies and HIT in patients undergoing organ transplantation.
transplantation and discuss appropriate diagnostic and therapeutic strategies for transplant physicians.

RESEARCH STRATEGY

The authors independently performed a systematic PubMed literature search on articles published in English. The following keywords were used: Transplantation AND heparin-induced thrombocytopenia OR HIT antibodies OR HIT disease OR HIT II OR anti-PF4/heparin. The search was performed on May 31st, 2015. In addition, the authors’ libraries and the Internet were searched. The following medical subject headings were used: Heparin-induced thrombocytopenia after heart OR lung OR liver OR pancreas OR kidney OR organ transplantation; risk factors in transplantation; and HIT development. Papers deemed relevant by the authors were retrieved.

RESULTS

Transplant recipients frequently are multimorbid patients with major diseases of the cardiovascular, hematologic, the coagulation, and the endocrinologic systems, which each can trigger thrombocytopenia. This is why relevant side-effects of drugs, thrombocytopenia associated to the underlying disease, sepsis, disseminated intravascular coagulation, and post transfusion purpura always have to be considered in every individual case of thrombocytopenia in ICU patients[21]. However, a platelet count drop is also well known to occur after major surgery and extracorporeal circuitry such as heart-lung machine or cell saver® autotransfusion[22]. Drug-induced immune thrombocytopenia has been reported for calcineurin inhibitors[23], mycofenolate, and anti-thymocyte globulin (ATG)[24,25]. Therefore, other syndromes and diseases have to be taken into consideration within the postoperative setting after solid organ transplantation to carefully distinguish between physiologically and pathologic thrombocytopenia such as HIT II.

DISCUSSION

As noted in the introduction, the combined clinical and laboratory proof of HIT II has to be performed
according to the “classic definition of HIT”\(^{[4,15,16]}\) to avoid overdiagnosis. Unfortunately, the diagnosis of HIT is difficult in critically ill patients as both leading symptoms of HIT (thrombocytopenia and thrombosis) are not specific\(^{[21]}\). Although the absence of anti-heparin/PF4 antibodies has a high negative predictive value to exclude HIT, it is not sufficient to detect these antibodies without further satisfying the stepwise criteria (Figure 1) including the 4Ts pretest clinical score\(^{[13,14]}\) for the diagnosis of HIT\(^{[7,9-11,15]}\).

Our literature research revealed six studies, nine case reports, and six series on anti-PF4/heparin antibodies or HIT in solid organ transplant candidates and recipients. Detailed data on different organ transplants, type of study, number of patients investigated, performed laboratory diagnostics, time of HIT investigation, and the clinical course and outcome of the recipients are provided in supplementary Table 1.

**THORACIC ORGANS**

*Heart transplantation*

The treatment of seriously ill cardiac patients is a demanding challenge for the interdisciplinary team of physicians. The risk for HIT is proposed to be high due to high doses of heparin used in cardiac surgery and a vast release of PF4 from platelets because of the platelets’ contact to cardiopulmonary bypassing\(^{[20]}\).

Patients with a history of HIT who need extracorporeal circulation within a surgical procedure require careful planning of anticoagulation therapy. Respective considerations on HIT prevention have been published in several case reports\(^{[27-35]}\) and are explicitly discussed in the guidelines published by both the American College of Physicians (ACCP)\(^{[12]}\) and the British Society of Hematology\(^{[30]}\).

In prospective studies a relevant discrepancy was observed between detection of anti-PF4/heparin antibodies (EIA positive: 27%-50% of the patients) and the capability of these antibodies to activate platelets (SRA or HIPA positive: 7%-40% within the EIA positive patients)\(^{[26,37,38]}\). The development of clinically relevant HITTS was reported to range between 1% and 3%\(^{[39]}\) and is therefore considerably smaller in regards to the high rate of seroconversion. An investigation on HIT in pediatric patients revealed a comparable frequency of 1%-2%\(^{[17,40]}\).

According to the ACCP guidelines heparin is recommended for anticoagulation during cardiopulmonary bypass in patients with a history of HIT provided that anti-heparin/PF4 antibody testing is negative at the time of surgery\(^{[42]}\). This advice is based on the fact that an anamnestic response and antibody production cannot emerge that fast to develop fulminant HITTS\(^{[41,42]}\).

Nevertheless, for all cases of proven HIT (defined as positive antibody detection plus thrombocytopenia) several alternative regimens have been published\(^{[43]}\) starting with strategies to adjourn surgery through to complex heparin-free combination therapies.

However, cardiac transplant surgeons have to draw on the latter regimens because heart transplantation cannot be deferred. Selleng et al.\(^{[44]}\) addressed this complex situation in candidates awaiting heart transplantation and defined the state of regenerating platelet counts but still detectable anti-PF4/heparin IgG antibodies in EIA as “subacute HIT”. When platelet-activating antibodies were not detectable by the functional assay HIPA, the authors demonstrated that heart transplantation can be performed despite using heparin for anticoagulation without serious complications. Furthermore, the article provides useful recommendations and structured strategies for choosing perioperative anticoagulation in recipients with a positive history of HIT\(^{[45]}\).

However, these patients already are under critical surveillance of transplant physicians and hematologists and receive an adapted anticoagulation therapy because of known anti-heparin/PF4 antibody seroconversion before transplant. The true challenge for transplant physicians is rather the sufficiently early recognition of a de-novo HIT development or postoperative reactivation within the complex clinical setting of a just transplanted recipient. This differentiation is rather difficult because on the one hand many cardiac patients have long-term heparin therapy (LMWH) and on the other hand postoperative thrombocytopenia can usually be ascribed to reasons other than HIT\(^{[46]}\). This is why a scoring system comparable to the 4Ts system was developed to assess the HIT probability after cardiopulmonary bypass surgery\(^{[46]}\). Heart transplant recipients should be monitored with the same due skill, care and diligence as other cardiac surgery patients. For these patients routine screening is not recommended\(^{[7,12,47]}\). However, HIT laboratory diagnostic should be started immediately in every case of intermediate or high risk in the 4Ts system\(^{[12,17]}\).

Having cognizance of a general HIT incidence of 1% to 3%, Hourigan et al.\(^{[48]}\) performed a retrospective analysis on cardiac transplant recipients. Overall, thrombocytopenia was found in 26 of 46 patients. Thrombocytopenia was the decisive factor to initiate anti-PF4/heparin antibody testing using EIA. Antibodies were detected in 11 recipients, but in 10 cases seroconversion had already occured before transplantation. Therefore, these patients also have to be assigned to the above-mentioned population with HIT development due to heparin application during the pre-transplant period. Only one patient who suffered from CMV pneumonitis was suspected for HIT 10 mo after transplant. However, the limitation of Hourigan et al.\(^{[48]}\) study is that no functional assay on platelet activating antibodies was performed to meet the “classic” definition of HIT development. This liberal definition of HIT, which is only based on thrombocytopenia and a positive result in EIA, might explain the high frequency of HIT as reported in their retrospective study. Nevertheless, Hourigan et al.\(^{[48]}\) recognized thromboembolic events in 5 EIA-positive
patients (45% of the EIA-positive and 11% of all investigated patients) but unfortunately they failed to promptly perform a functional test to confirm the true evidence of HIT. Furthermore, thromboses occurred exclusively before heart transplantation and therefore were non-transplant related anyway. Interestingly, the authors reported on no significant difference in mortality between EIA-positive and EIA-negative patients on the one hand and EIA-positive patients and those patients with thromboses on the other hand, respectively.

Hassan et al[49] performed the most comprehensive study on HIT in transplant recipients and they consider the mentioned potential of overdiagnosis[15,16]. The authors therefore consistently distinguished between “HIT antibody positivity” (4Ts score > 3 points and EIA positive) and “HIT” (plus positive SRA). A total number of 2587 transplant patients (thoracic and abdominal organs) from one center were retrospectively evaluated. Due to unexpected thrombocytopenia HIT was initially assumed in approximately 10% of the patients. Therefore, the 4Ts scoring system pretest probability was calculated and anti-heparin/PF4 EIA was subsequently performed. Seroconversion was observed in 1.9% of all investigated patients. Compared to the investigation of Hourigan et al[48], this study mainly reports on antibody detection after transplantation. SRA verification was performed in 29% (14/48) of the seroconverted patients and revealed positive results in 11 of 14 cases (78%). Assuming that 78% of all antibody positive patients were SRA positive, the frequency of HIT (susicious 4Ts test and both EIA and SRA positive) would be 1.5% in the whole investigated population. The study actually revealed “HIT” according to the authors’ definition in 3.6% of the heart recipients and 0.9% of the lung recipients. Interestingly, thromboembolic events were found in 23% of all the anti-heparin/PF4 antibody positive patients and in 2.4% of the cardiac graft recipients, respectively. However, no thrombotic event was observed in recipients with low 4Ts scores and no single case of HIT-associated death was revealed in this comprehensive analysis[49].

Both analyses are limited due to their retrospective single center design and the difficulties to generalize these results to the heterogeneous transplant population[48,49].

Lung transplantation
No data are available besides the results by Hassan et al[49] (see heart transplantation).

ABDOMINAL ORGANS
Kidney transplantation
Kidney transplant recipients have a high frequency of pretransplant heparin exposure due to dialysis. Therefore, an increased risk of HIT-associated syndromes and complications could be assumed in this collective. Strict heparin exposure can only be avoided in those candidates who are either planned for preemptive transplantation or who perform CAPD.

There are four case reports on anti-PF4/heparin antibodies and HIT in renal transplantation up to the present day. However, according to the recommended criteria for manifest HIT disease (HITTTS) no report fulfills the “classic” criteria as the 4Ts pretest score was not performed[50-53] no functional test on the activating potential of the EIA-positive anti-PF4/heparin antibodies was further analyzed in either SRA or HIPA[51,52], or was even SRA-negative[50]. In two cases the renal graft was lost due to proven thrombosis[50,51] but the association with HIT cannot be determined because of the inadequate diagnostic approach. One case report[53] addresses an adolescent patient with end-stage renal disease who performed thrombocytopenia after eight months of repeated heparin exposure during dialysis, which is untypical for HIT. Even though both anti-PF4/heparin EIA and SRA were positive, the patient did not have a manifest thromboembolic event, had not been transplanted at that time, but showed additional major procoagulatory disorders potentially accountable for thrombocytopenia and thrombosis. The authors reported on a heparin-free hirudin-based perioperative anticoagulatory regimen and successful kidney transplantation, which could serve as recommendation in cases of (suspected) HIT.

Liver transplantation
Chronic end-stage liver disease is frequently associated with coagulation disorders and secondary thrombocytopenia due to portal hypertension and hypersplenism[54]. These preexisting disorders in liver transplant candidates make clinical recognition of HIT difficult because a significant drop in the platelet count according to the 4Ts system’s definition tends to be rather small when the baseline value is already reduced below the normal range. This is why a reactive thrombocytopenia in the postoperative course of a liver transplant recipient may easily mislead the accountable physicians to assume HIT, prompt HIT testing, and impetuously change anticoagulation to a heparin-free protocol with all its risks and side-effects. Therefore, the assessment of the clinicopathological syndrome of HIT is especially demanding in liver transplantation. Both clinical findings in recipients and published data have to be questioned carefully with regards to the correct adherence to the “classic” definition of HIT to avoid overdiagnosis.

In literature, three case reports and four studies have been published within this field so far. Unfortunately and as criticized before, the inadequately implemented stepwise diagnostics and evidence of “classic” HIT[15,16] displays a substantial problem in interpretation of the results from these data. All three
case reports concern liver transplant recipients with a history of anti-PF4/heparin antibody seroconversion or proven HIT before transplantation. In these reports no data are available regarding HIT-antibodies after transplant.

Amongst the comprehensive studies on postoperative HIT-antibodies after liver transplant a retrospective study on 205 recipients revealed only 1.95% anti-PF4/heparin antibody positive (EIA) patients but information on the number of patients tested through EIA is missing. No single case of HIT-associated thrombosis or thromboembolism was found after liver transplantation in this study though the definition of HIT rather meets a "liberal" definition of HIT compared to the suggested "classical" iceberg model.

In a prospective series of 52 living donor liver transplant recipients, Kaneko et al. investigated anti-PF4/heparin antibody seroconversion starting before surgery until three weeks after transplant. This study revealed a low incidence of antibodies (5.6%), no detection of antibodies in two patients with postoperative thrombosis, and no proof of HIPA-positive antibodies in two patients with suspicious postoperative platelet courses. However, recipients with anti-PF4/heparin antibodies in EIA did not develop thrombosis despite continuation of heparin therapy. These findings could mostly be confirmed by the results of the two studies we performed on anti-PF4/heparin antibodies after liver transplantation.

In a first retrospective analysis the authors evaluated the incidence of anti-PF4/heparin antibodies in patients undergoing liver transplantation. The analysis revealed a remarkably high frequency of anti-PF4/heparin antibody seroconversion in 30.4% of the recipients. However, none of them developed HIT-associated thromboembolic complications within the characteristic period between day 5 and 14 after the beginning of heparin therapy. In a univariate and multivariate analysis of potentially causative factors for antibody production the authors ruled out suspected impact from cell saver® autotransfusion, transfusion, and postoperative dialysis. The only trigger that could be identified in multivariate analysis and binary logistic regression was patient’s age with a cutoff at 59 years in chi-square testing and an increased risk for patients of 59 years and older. Unfortunately, due to the retrospective character of the analysis the authors could not further distinguish between antibody subclasses (IgG, IgA, and IgM) and their activating features in SRA or HIPA.

Therefore, Bakchou et al. initiated a prospective cohort analysis on 38 consecutive deceased donor whole organ liver transplant recipients. In their study, patient sera were investigated for the different anti-PF4/heparin antibody subclasses, their activating power in HIPA, thrombocytopenia, and HIT-associated thromboembolic events according to the “classic” definition of HIT until post-operative day 21.

Antibody testing in subclass-specific EIA directly before surgery revealed pre-existing seroconversion of 13.2% (IgG), 7.9% (IgA), and 57.9% (IgM), respectively. Interestingly, 80% of the recipients with pre-operative anti-PF4/heparin antibodies presented decreasing titers after transplantation and none of them developed HIT. These data confirm previous recommendations that liver transplant candidates with a history of positive HIT-testing but without activating features should not be excluded from the waitinglist.

After surgery 15.2% of the recipients developed de novo IgG antibodies and two of the recipients (6.1%) showed activating IgG-antibodies in HIPA. Overall, none of the liver transplant recipients developed HITTS in their systematic study. Furthermore, recipients who were clinically suspected to suffer from HIT according to 4Ts pretest clinical scoring system did not develop platelet activating antibodies in HIPA. Therefore, HIT can be assumed to be very unlikely in these recipients. This observation raises the question whether the 4Ts system is suitable to estimate the probability of HIT without restrictions in transplant recipients. The 4Ts scoring system has not been investigated in this special subgroup of patients so far.

Heparin-free anticoagulation is difficult to monitor in critically ill patients and entails a relevant risk of bleeding complications. According to the reported findings, changing anticoagulation to a heparin-free regimen should be reconsidered in liver transplant recipients with non-activating anti-PF4/heparin antibodies.

Pancreas transplantation
No data are available.

CONCLUSION
Due to repeated and usually high-dose heparin application before and after transplant surgery, HIT could be expected to occur frequently in organ recipients. Furthermore, standardized organ procurement procedures use heparin for donor anticoagulation, which causes an inevitable exposure of the recipient to heparin. This review questions the assumption of a relevant role of HIT in these patients according to present investigations.

First, the “classic” definition of HIT needs to be established as a common basis to allow for convincing and comparable results of research. Second, clinicians need to distinguish carefully between data on HIT before and after transplantation.

Several publications reported on uneventful cases of heparin re-exposure of transplant patients with a positive history of HIT, when anti-heparin/PF4 antibodies were not detectable in EIA anymore. Different heparin-free anticoagulation regimens were given (hirudin, bivalirudin, lipirudin) but
the recipients had one inevitably heparin exposure during surgery due to the usage of UFH during organ procurement. These reports consistently confirm the hypothesis that the risk of early-onset HIT after heparin re-exposure is small after cessation of heparin more than 100 d prior to surgery \[^{32,56,57}\]. According to the current knowledge as depicted in this review we suggest that: A patient with a history of HIT more than 100 d ago and negative anti-PF4/PF4 EIA and SRA/HIPA can be re-exposed to heparin during surgery for organ transplantation; organs from donors treated with heparin can be transplanted to these patients; organs rinsed with heparin can be transplanted to these patients; and patients with a history of HIT need not be delisted from the waiting-list.

To this day, only few systematic investigations on HIT in solid organ transplant recipients (after transplantation) have been published. Thereof, most data exist on anti-PF4/heparin antibody seroconversion after liver transplantation. The most conclusive studies consistently report on no HIT-associated thromboembolic events despite anti-PF4/heparin antibodies in EIA between 1.9% to 57.9% and continuation of heparin therapy \[^{49,59-61}\].

Available research shows that on the one hand immunosuppressed solid organ transplant recipients are capable to develop anti-PF4/heparin antibodies, and on the other hand apparently do not suffer from HIT according to the “classic” definition and as displayed in the iceberg model \[^{0-11}\]. These findings could potentially be displayed carefully in an adjusted iceberg model with a broad basis below the waterline but apparently only little mass and no summit above (Figure 2). Until now research has not provided any reliable information on clinically apparent HIT in this special cohort, which is displayed by the question mark in the depiction. Nevertheless, we point out that this illustration has to be handled with care as strong evidence from comprehensive prospective trials is missing.

Routine screening for anti-PF4/heparin antibody seroconversion is not recommended to avoid an increase in false-positive results with unnecessary change of anticoagulation \[^{7,12,47,49}\]. The true incidence of HIT after solid organ transplantation and its morbidity and mortality appears to be rather low \[^{49,59-61}\]. Nonetheless, cardiac transplant recipients possibly have the highest risk of developing HIT among transplanted patients in general \[^{49}\].

In the absence of large prospective studies, no conclusive recommendations on the acute therapeutic management of HIT-suspected recipients can be provided besides switching to heparin-free anticoagulation.

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