HEPARIN-INDUCED THROMBOCYTOPAENIA/THROMBOSIS: A CLINICO-PATHOLOGIC REVIEW

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ABSTRACT

Background: Heparin is widely used for the prophylaxis of venous thrombo-embolism and pulmonary embolism. Thrombocytopenia and the sequelae of thrombosis are uncommon adverse effects of therapy which are associated with high morbidity and mortality.

Objective: To review the clinical-pathologic features of heparin induced thrombocytopenia/thrombosis.

Data sources: Reputable haematology journals and the internet in English. Searches included thrombosis, heparin, and heparin induced thrombocytopenia.

Data selection: Only relevant journals and internet sources were selected for this review. In particular leading journals in thrombosis and anticoagulants.

Data extraction: High quality abstracts, papers and internet articles were the main source of information.

Data synthesis: Information from the selected abstracts and papers was used for the paper.

Conclusion: The clinical effects of heparin induced thrombocytopenia/thrombosis (HIT/T) include venous and arterial events the latter of which include limb ischaemia, myocardial infarction and stroke. The pathogenesis of this complication is related to the formation of heparin-platelet factor 4 antibodies which can be demonstrated in the laboratory by functional and immunoassays. Management requires alternative anticoagulation with agents that have no cross reactivity with heparin platelet factor 4 antibodies. These agents include danaparoid, direct thrombin inhibitors and newer agents like fondaparinux and rivaroxaban with anti Xa activity.

INTRODUCTION

Heparin, is a naturally occurring protein with a molecular weight of 6-30 kda. It is a highly sulfated glycosaminoglycan composed of alternating uronic acid and glucosamine residues. Heparin was introduced into clinical practice in the 1960’s and is now firmly established in the the management of venous thromboembolism (1).

Unfractionated heparin, (UFH) is effective in the prevention and treatment of venous thromboembolism (VTE). UFH has also been in use for the early treatment of patients with unstable angina and acute myocardial infarction, for patients who have cardiac surgery under cardiac bypass, in patients who have vascular surgery, during and after coronary angioplasty, in patients with coronary stents and for flushing of intravenous catheters in intensive care unit and renal settings.

Low molecular weight heparin, (LMWH) is presently produced by chemical or enzymatic digestion of UFH and have molecular weights of less than 8.0 kda. In 1986, nandroparin was approved as the first LMWH for peri and post operative VTE prophylaxis. Since then LMWH have been widely used as anticoagulants for venous VTE, pulmonary embolism and for haemodialysis/haemofiltration (2).

Despite the therapeutic benefits as an anticoagulant, there are a number of side effects associated with the use of heparin. These include bleeding, allergic reactions, skin necrosis, osteoporosis and thrombocytopenia.

Thrombocytopenia is a well recognised and serious complication of heparin therapy and occurs regardless of the dose, age, gender or route of administration. This phenomenon associated with heparin therapy is known as the syndrome of heparin induced thrombocytopenia (HIT).
Paradoxically some of the patients with heparin induced thrombocytopenia develop arterial or venous thrombosis. Failure of early recognition of this complication results in variable but relevant rates of morbidity and mortality.

Heparin induced thrombocytopenia with thrombosis, (HIT/T) was described in 1958 by Weismann and Tobin in 10 patients who developed emboli while on treatment with heparin. This complication was described as the white clot syndrome due to the appearance of white platelet thrombi occluding the lumen of blood vessels. Six of the patients died as a result of recurrent multiple arterial emboli (3). In 1964 Roberts et al (4) described an additional 11 patients who manifested arterial thromboemboli following heparin therapy. Rhodes et al (5) observed the relationship between the development of thrombocytopenia and thrombosis in the early 1970s.

The last 40 years has witnessed a considerable interest and awareness of HIT with over 1000 publications on the topic, since the first case described by Weismann and Tobin (3). Today there is better understanding of its clinical presentation, pathophysiology and management options.

**CLINICAL FEATURES OF HIT**

Incidence of heparin induced antibody formation, thrombocytopenia and thrombosis: The overall frequency of HIT is difficult to precisely define because the risk is associated with the type of heparin, the dose of heparin, study design and most importantly the clinical situation (6).

The first prospective study investigating the incidence of thrombocytopenia during heparin therapy was reported by Bell et al in 1976. The incidence of thrombocytopenia (platelet count of < 100 x 10^9/l) was found to be 30.7%. Subsequent studies found that the incidence of heparin induced thrombocytopenia was lower than this initial report particularly with the recognition of the immune mechanisms of thrombocytopenia.

In a review of 14 prospective clinical studies reported between 1980 and 1989 and involving a total of 1,336 patients the frequency of the risk of HIT was approximately 3.4%. Remarkably HIT associated thrombosis was found only in 1% of patients. In most of the studies cited in that review a confirmatory test for the diagnosis of HIT was not performed (7).

Schmitt and Adelman (8) reviewed 23 randomised or cohort prospective studies of 2160 patients. Utilising reproducible thrombocytopenia (platelet count less than 100 x 10^9/l) as criteria in the absence of laboratory confirmation, the incidence of HIT was found to be 1.1% with intravenous porcine heparin and 2.9% with bovine heparin. No thrombocytopenia was observed with subcutaneous administration of heparin. This difference however was not statistically significant.

Two well designed randomised studies have been described in literature. The first is a study by Warkentin et al (9) involving 665 orthopaedic patients and comparing the incidence of HIT with standard UFH and LMWH. Using a threshold platelet count of 150 x10^9/l, HIT developed in 2.7% of patients with standard UFH. None of the patients on LMWH developed HIT. The frequency of heparin induced antibodies was 7.8% with UFH and 2.2% with LMWH.

The other study was the multicenter trial by Lindhoff et al (10) involving 1137 patients randomly assigned to therapy with standard UFH or LMWH for the treatment of DVT. This study found a significantly higher incidence of heparin induced antibody formation in the UFH group than in the LMWH heparin group (20.7% vs 7.5% p<0.001). The patients on short term (5-7 days) treatment with LMWH did not develop heparin induced antibodies or HIT. Although the frequency of HIT was similar for both UFH and long term treatment LMWH groups (0.53%) the incidence of thrombosis events was higher in the former (50% vs 0%). An important observation in this study was the increase in the titre of heparin induced antibodies 14 days after stopping heparin treatment.

Analysis of the studies published between 1996 and 2005 indicate a high incidence of antibody formation in patients undergoing cardiac surgery (range 25-64%) (11,12). Despite this high frequency the incidence of thrombocytopenia and thrombosis are much lower than in patients receiving prophylactic heparin therapy for orthopaedic surgery in which the frequency of antibody formation is much lower (7.8-14.1%) (13).

Neurological patients receiving UFH also demonstrated a high incidence of antibody formation (20.5%) and thrombocytopenia (2.5%) with 80% of HIT patients developing thrombosis (14). However similar patients treated with with LMWH demonstrated a much lower incidence of antibody formation (1.8%) with no sequelae of thrombocytopenia and thrombosis (15).

The incidence of antibody formation in medical patients in one large study was found to be 1% with an even lower frequency of thrombocytopenia (0.5%). This low incidence of HIT was also seen in other studies involving medical in patients but the proportion of patients with HIT developing thrombosis was high (50-67%) (16-18). Analysis of renal patients on haemodialysis also indicate a low incidence of antibody formation (combined incidence 2.6%) with very few patients noted to be thrombocytopenic and none with thrombotic complications (19-23).
Preliminary results from the CATCH registry (Complications After Thrombocytoopaenia Caused by Heparin) indicate an incidence of HIT in 0.2% of patients who have received heparin for more than 96 hours (n=1020) and 2.1% for patients receiving heparin in coronary care units (n=164). Final results from this study which aims to clarify the incidence evaluation and outcome of HIT in over 7000 patients, are keenly awaited (24).

Clinical manifestation of HIT: The predominant clinical features of HIT are thrombocytoopaenia and the sequelae of thrombosis. Despite the thrombocytoipaenia, which can be severe, bleeding is not a feature of this syndrome. Thrombosis though not very common, can be extensive resulting in increased morbidity and mortality (25).

Thrombocytoopaenia occurs in 90% of patients with immune HIT. Typically the thrombocytoopaenia is of moderate severity with median platelet count of approximately 50-70 x 10^9/l and very few patients have platelet counts of less than 15x10^9/l. Ironically these patients are at an even greater risk of thrombosis compared to patients with less severe thrombocytoapaenia (7).

Thrombocytoapaenia by standard definition is based on a fall in platelet count below 150x10^9/l but this definition has been found to be inappropriate for HIT because of the existence of clinical situations where the platelet count may not fall below the lower limit of the reference (26). In about 10% of patients with HIT the platelet nadir count never falls to less than 150x10^9/l. This may be because HIT complicates a postoperative course that is characterised by thrombocytosis and occasionally because of chronic thrombocytosis.

Following a secondary analysis of a clinical trial Warkentin et al (27) proposed an improved definition for thrombocytoapaenia; a fall in platelet count of 50% or greater from the postoperative peak. This improved definition had superior operating characteristics and identified many more patients with HIT while retaining the same high specificity as observed with the standard definition.

Thrombosis is the most important complication of HIT. Indeed some cases of HIT are only identified after development of a new thrombotic event. Both arterial and venous thrombo-embolic complications are seen in HIT patients (25).

The thrombosis described in the early studies of Weisman et al (3) as well as by Roberts et al (4) were mainly arterial in site. These thrombi appeared pale or pearly white in colour and when examined microscopically showed platelet rich contents. As a result of these observations the term “white clot” syndrome was designated for this condition (3). More recent studies have demonstrated a higher incidence of venous thrombosis occurring as part of the spectrum of the thrombo-embolic complication in HIT patients (26).

Thrombosis is strongly associated with HIT. In a randomised double blind clinical trial involving 665 patients, eight out of nine patients with HIT developed thrombosis compared with 117 of 656 patients without HIT (88.9% vs 17.8% odds ratio 36.9% p< 0.001). In this study venous thrombosis predominated with seven patients developing DVT and pulmonary embolism, while one patient developed mesenteric artery thrombosis (13).

In a 14 year retrospective study carried out by Warkentin and Kelton (26) on 127 patients with HIT, 61% of patients had venous thrombotic events while arterial events occurred in 14% patients giving a ratio of 4:1. The venous thrombotic events included DVT and PE. Limb ischaemia, myocardial infarction and thrombotic stroke formed the spectrum of arterial events. Two cases of adrenal haemorrhage and one case of sudden death were also reported in this study (26).

Nand et al (28) found an overall incidence of 29% for thromboembolic complication in their study of 108 consecutive patients with HIT. Venous thrombosis was more frequent than arterial thrombosis (62% vs 25%; ratio V/A 2.5:1). Pulmonary embolism was seen in two patients and 14 patients had DVT. The arterial events seen in this study included limb ischaemia, cerebrovascular accidents and myocardial infarction secondary to by pass graft occlusion. A mortality rate of 15.6% was found in this study.

Skin manifestations of HIT have been reported in literature. Warkentin (29) reported six patients with skin lesions and serological evidence of HIT. Four patients developed painful erythematous plaques while the other two manifested overt skin necrosis. Two of the patients developed thrombocytoapaenia and both had severe venous and arterial thrombosis.

All six patients had received UFH for postoperative prophylaxis with skin manifestations localised to the injection site. Tietge et al (30) presented a case report of a 76 year old male with skin necrosis induced by subcutaneous injection of LMWH. This adverse event occurred at a distant position from heparin injection sites with thrombocytoapaenia being notably absent.

CLINICAL DIAGNOSIS OF HIT

Thrombocytoapaenia in hospitalised patients can result from numerous causes. These include bone marrow failure, haemodilution, bacteraemia, disseminated vascular coagulation and non heparin medication. Although HIT may not be the most common cause of acute thrombocytoapaenia, failure to recognise it may cause significant morbidity and mortality.

Once thrombocytoapaenia is confirmed, the diagnosis of HIT should be formulated on the basis of clinical criteria and the in vitro demonstration of heparin dependant antibodies (31).
To evaluate the clinical probability of HIT various scoring systems have been proposed. A clinical scoring system, the four T’s based upon the assessment of Thrombocytopenia, Timing, Thrombosis and absence of other causes for thrombocytopenia have been proposed by Warkentin (32). Preliminary evaluation suggests that HIT is unlikely when a low score (<3) is obtained and very likely with a high score (≥6). An intermediate score (4-5) indicates a clinical profile compatible with HIT but other causes such as sepsis may be present. Laboratory testing for HIT antibodies is especially valuable in these patients (32).

Frequent platelet count monitoring beginning on day 5 of heparin use is important for the early diagnosis of HIT and should be performed in high risk patients especially cardiac and orthopaedic surgery patients using UFH. Patients receiving therapeutic doses of UFH should have their platelet count monitored on alternate days until day 14 or until UFH is stopped whichever occurs first. For patients who have received heparin in the past 100 days prior to re-exposure, a baseline platelet count should be obtained before commencing heparin and a repeat within 24 hours followed by alternate day monitoring (33).

Pathogenesis of HIT: The major determinant in the pathogenesis of immune HIT is the formation of heparin/platelet factor complexes and the development of antibodies directed against these complexes (34).

The binding of heparin induces a conformational change exposing several antigenic epitopes of the PF4 molecule between the 3rd and 4th cysteine residues (35). This region appears to be the major antigenic site with a second site (site 2) identified at proline 34 which is the amino acid preceding the third cysteine moiety.

The heparin-platelet factor 4 complexes with the exposed antigenic sites are recognised by antigen presenting cells and subsequently these complexes are presented to helper T cells resulting in the production of antibodies. A number of studies have confirmed the highly immunogenic nature of HPF4 complexes and the role of T cells in anti HPF4 antibody formation (36, 37).

The complexes of heparin PF4 form on the surface of activated platelets where they are subsequently recognised by HIT antibodies. HIT antibodies bind to HPF4 complexes on platelets through their Fab portion. The HPF4 antibody also binds to Fc receptors on platelets thereby inducing further platelet activation and enhancing more expression of PF4 moieties on the platelet surface (38, 39).

HIT is also associated with direct endothelial damage. Heparan sulphate is a glycosaminoglycan found on endothelial cells and is less sulphated than heparin. Excess platelet factor 4 secondary to platelet activation can bind to heparin and these heparin-PF4 complexes are recognised by HIT antibodies resulting in immune mediated vascular injury with endothelial activation (40).

| Points (0,1 or 2 for each of four categories: maximum possible score = 8) |
|---------------------------------|-----------------|-----------------|-----------------|
| Thrombocytopenia                | >50% platelet fall to |
|                                 | Nadir > 20×10^9/1 |
| Timing of onset of platelet fall (or other sequelae of HIT) | day 5-10, or |
|                                 | < day 1 with recent |
|                                 | heparin (past 30 days) |
| Thrombosis or other sequelae    | Proven new thrombosis: |
|                                 | skin necrosis or acute |
|                                 | systemic reaction after |
|                                 | 1v heparin bolus |
| •Ther cause(s) of platelet fall | None evident |
|                                 | Possible |
|                                 | Definite |

Pretest probability score: 6-8 high 4-5 intermediate 0-3 low

Table 1

*Testimating pretest probability of HIT: the “four T’s”*
Laboratory testing for HIT

Laboratory testing for the diagnosis of HIT have evolved following better understanding of its immuno pathological mechanisms. Two types of laboratory tests are available for establishing a diagnosis of HIT functional assays and immunoassays.

Functional assays are tests that are based on platelet aggregation or activation. Frantantoni et al in 1975 (41) described the first platelet aggregation test following the observation that heparin added to platelet rich plasma of HIT patients caused aggregation. Further the serum from HIT patients also effected the release of 3H – serotonin from normal platelets.

In 1986 Sheridan et al (42) developed a more sensitive and specific assay that measured platelet release instead of aggregation. The principle of this test is based on the release of C-serotonin by washed platelets at therapeutic concentrations and inhibition with very high concentrations of heparin. This test is regarded as the “gold standard” for laboratory diagnosis.

The heparin induced platelet activation assay (HIPA), developed by Greinacher and colleagues in 1991 is a platelet aggregation assay performed in microtitre wells using washed platelets. In this test visual detection is employed for determination of platelet aggregation (43).

Following molecular characterisation and antigenicity of the heparin/PF4 complexes, immunoassays have been developed for the detection of heparin induced antibodies. The first enzyme linked immunoabsorbent assay (ELISA) was developed in 1995 by Amiral et al (44) using macromolecular complexes of HPF4 as the target antigen immobilised to a solid phase. Commercial assays using PF4/polyvinyl sulphonate as target antigens have been subsequently developed.

Postulated mechanism for heparin-induced thrombocytopenia and thrombosis. Heparin binds to platelet factor 4, which induces an IgG antibody (1). Formation of PF4-heparin-IgG immune complexes occurs (2), which triggers platelet activation via binding to Fc receptors (3). Platelet activation results in further elaboration of PF4 (4a), as well as prothrombotic microparticle release (4b). PF4 binds to endothelial bound heparin-like molecules and promotes immune-mediated endothelial damage (5), which further raises the risk for thrombosis.
Heparin induced thrombocytopaenia poses a serious challenge for patients who require anticoagulation. Available evidence indicates that the risk for thrombosis in the days to weeks after stopping heparin therapy is at least 20% and possibly as high as 50% in HIT patients presenting with isolated thrombocytopaenia. This evidence supports the view that alternate therapy with a rapidly acting anticoagulant should be initiated when heparin therapy is discontinued (45).

The optimal anticoagulant therapy for HIT remains uncertain. Oral anticoagulants such as warfarin are ineffective and potentially deleterious during the first several days of use in patients with acute HIT. A syndrome of venous limb gangrene has been linked with procoagulant/anticoagulant balance during the use of warfarin to treat HIT (47).

The use of alternative anticoagulants is advocated for the treatment of patients with HIT based on the understanding that these agents do not cross react with anti HPF4 antibodies and are effective and safe for the prophylaxis or treatment of thrombosis (46).

LMWH appear to be attractive for the treatment of HIT/T patients in view of their reduced immunogenic potential as compared to UFH. However LMWH have a high in vitro cross reactivity rate with heparin dependant antibodies reaching almost 100% in some very sensitive assays. LMWH less likely, but can also cause HIT, and when used in its treatment there is a significant risk of recurrent or progressive thrombocytopaenia with or without thrombosis. As a result of these drawbacks and with the availability of other anticoagulants options LMWH are not recommended for the management of patients with HIT (48).

Newer anticoagulants which have been used with varying degrees of success for the management of HIT/T include danaparoid sodium (Orgaran), lepirudin (Refudan TM) and argatroban. Danaparoid is a mixture of low molecular weight anticoagulant glycosaminoglycans. In contrast to LMWH it contains no heparin fragments and has a different glycosaminoglycans back bone structure.

Earlier studies with danaparoid carried out by Chong et al (49) demonstrated an in vitro cross reactivity rate with HIT antibodies of 18%. Other reports indicate in vitro cross reactivity rates of 10-50% depending on the sensitivity of the method used but in vivo cross reactivity has not been commonly observed (50). Danaparoid treatment without prior in vitro cross reactivity is therefore assumed to be a reasonable therapeutic option (51).

Magnani (52) presented an overview of 230 patients treated with orgaran on a “compassionate” basis. 92.8% of patients responded adequately to treatment as gauged by recovery or stabilisation of platelet counts and control of thrombotic events. A total of 59 deaths were reported of which seven (30%) were attributed to orgaran use. The remaining 52 deaths were due to severity of the preexisting disorders (52).

Treatment failures with Danaparoid have been reported. In the overview by Magnani (51), there were 15 treatment failures in patients receiving danaparoid and also within 48 hours of stopping orgaran therapy. Treatment failure manifested as bleeding (two patients), persistence of thrombocytopaenia (five patients), appearance of thrombocytopaenia (four patients) and thromboembolic events (four patients) (52).

Danaparoid is a useful and safe alternative to other anticoagulants in HIT patients and can be used in a variety of clinical settings with success and may be considered as first choice alternative parental anticoagulant in patients due to its relative low cost and ease of use.

Hirudins are a group of highly homologous polypeptides extracted from the salivary glands of the medicinal leech Hirudo medicinalis. They have an extremely high and specific binding for thrombin and are consequently potent anticoagulants. Hirudins have the property of inhibiting platelet activation induced by thrombin and efficiently inhibit fibrin bound thrombin. Recombinant hirudins have now been produced and

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### MANAGEMENT OF HIT AND HIT/T

Heparin induced thrombocytopaenia poses a serious challenge for patients who require anticoagulation. Available evidence indicates that the risk for thrombosis in the days to weeks after stopping heparin therapy is at least 20% and possibly as high as 50% in HIT patients presenting with isolated thrombocytopaenia. This evidence supports the view that alternate therapy with a rapidly acting anticoagulant should be initiated when heparin therapy is discontinued (45).

The most essential element in the treatment of HIT and HIT/T remains discontinuation of all heparin including heparin line flushes, subcutaneous heparin and heparin coated indwelling catheters. The persistent prothrombotic tendency associated with HIT, the presence of thrombus in HIT/T and the patients original indication for heparin therapy all warrant the use of an alternative anticoagulant agent after heparin cessation (46).

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have been shown to be effective against venous thrombi and platelet rich thrombi in arteries.

Lepirudin is a recombinant form of hirudin derived from yeast cells and is a highly specific direct and irreversible inhibitor of thrombin binding to it with a ratio of 1:1. It differs structurally from heparin thus eliminating cross-reactivity and can be monitored using the ubiquitous activated partial thromboplastin time assay (aPTT) (50).

A meta-analysis of two prospective studies in patients with HIT and TEC showed a reduction in the combined endpoint of death, limb amputation and new TECs in lepirudin treated patients compared with a historical control population (a placebo control trial was considered unethical given the natural history of HIT/T). These better outcomes resulted primarily from a statistically significant reduction of new TECs (10.1% vs 27.2%) at day 35 (53).

Agatroban is a direct competitive inhibitor of thrombin derived from L-arginine. It binds reversibly to the thrombin catalytic site and inhibits the reactions that are induced by soluble and clot bound thrombin. In addition agatroban inhibits activation of factors V, VIII XIII and protein. Agatroban is monitored by the aPTT aiming for a target of 1.5-3 times the control value (53). Antibody formation has not been reported with agatroban (54).

Two large multicentre prospective studies with historical controls evaluating the efficacy and safety of agatroban in HIT and HIT/T have been reported. In the first study (ARG 911) the composite end point incidence (death, amputation or new thrombosis) was significantly reduced in the agatroban HIT treated patients versus control. For the HIT/T patients the time to event analysis clearly favored the agatroban treated arm with significant reduction in new thrombotic events and death due to thrombosis. An interesting observation was the more rapid rise in platelet count in agatroban treated patients. Major bleeding rates were not different between the agatroban treated patients and control subjects in either study arms (55).

The second multicentre non randomized prospective study showed similar results regarding time to event analysis of composite endpoint with a significant reduction in the incidence of death due to thrombosis in patients with HIT/T (55).

Fondaparinux is a new synthetic selective inhibitor of activated coagulation factor X and has been shown to be an effective and safe antithrombotic agent in a number of thrombotic disorders. Fondaparinux does not bind to PF4 and has negligible cross-reactivity with HIT antibodies. Savi et al (56) performed a serologic study to determine cross-reactivity of HIT sera with fondaparinux in a prospective blinded study. This study showed that fondaparinux was significantly less reactive than UFH in the evaluable assays. The results of this study favor the possibility of fondaparinux as a therapeutic option for prophylaxis and treatment of thrombosis in HIT patients (56).

Additional treatments in HIT have not been assessed systematically. They may be considered as additional treatment options in individual patients and include antiplatelet agents such as aspirin, iloprost and platelet glycoprotein 11b/111a inhibitors (57). Intravenous immunoglobulins, (IVg), have been shown to block activation of platelets by HIT antibodies and there have been case reports of increased platelet counts after administration of IVlg (58). Plasmapheresis as a therapeutic adjuvant has been cited in a number of case studies where a dramatic improvement in the plate count and marked reduction of thrombosis have been reported (59-61).

HIT is now a well recognized adverse effect of heparin therapy. Though uncommon, recognition of HIT is important because of the potential to develop serious complications of thrombosis. The formation of heparin-platelet factor 4 complexes and the subsequent but variable evolution of the humoral response are central to the pathogenesis, clinical manifestation, laboratory diagnosis and treatment of HIT.

The frequency of heparin induced antibody formation, thrombocytopenia and thrombotic complications vary in different populations, with orthopaedic and medical in-patients demonstrating a higher incidence of thrombo-embolic complications following HIT. The diagnosis of HIT requires awareness and a high index of suspicion coupled with the results of highly sensitive and specific laboratory tests. Treatment consists of immediate cessation of heparin therapy and institution of anticoagulants that do not exhibit cross-reactivity to HIT antibodies. Despite the increased awareness there is a significant degree of morbidity and mortality which can be prevented by early recognition and platelet count monitoring.

REFERENCES


