Review

Heparin-Induced Thrombocytopenia

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Heparin-induced thrombocytopenia, an adverse drug reaction which appears occasionally and is associated with high morbidity and mortality, is without parallel in clinical medicine. Heparin, a drug with primarily anticoagulant properties, through immunologically mediated reactions occasionally turns procoagulant, thereby paradoxically transforming an antithrombotic intervention into one that promotes thrombosis.

There are two types of heparin-induced thrombocytopenia (HIT).[1] The first, HIT type I, is characterized by a transitory and slight reduction in the platelet count, rarely below $100x10^9$/L, that appears during the first 1-2 days after the onset of therapy. The patients are usually asymptomatic, while thrombocytopenia resolves spontaneously and does not require discontinuation of the drug. The origin of HIT I is not completely known, but is thought to be related to a phenomenon of heparin-induced platelet clamping, as well as to a decrease in the platelet count.[2,3] Thromboembolic complications do not occur in this type of thrombocytopenia.[1]

The second type, HIT type II, is rare but far more serious, usually develops 5 to 15 days after the initiation of heparin therapy (occasionally after months) and is characterized by a significant reduction in platelets (to below $100x10^9$/L or >30% decrease).[1,4] It is immunologically mediated, through the formation of antibodies against heparin/platelet factor 4 (PF4) complex, which is believed to be the principal cause of the prothrombotic complications associated with type II HIT.[5] Several terms have been used to describe HIT and its complications, such as heparin-induced thrombocytopenia and thrombosis (HITT), "white clot syndrome" when arterial thrombosis occurs, subacute HIT, indicating that thrombocytopenia has resolved but HIT antibodies remain detectable.[1,5]

Epidemiology

The true incidence of HIT II is not well defined. Most reported studies are retrospective and differ regarding the factors that determine the incidence of HIT II, such as the characteristics of patients considered, the type of heparin administered, dosage, route of administration, duration of therapy, definition of thrombocytopenia, and laboratory tests employed for diagnostic confirmation (Table 1).

Some of the above factors were studied in a double blind, placebo-controlled study of unfractionated heparin (UFH) or low-molecular-weight-heparin (LMWH) administered following orthopedic surgery.[6] In this study, the frequency of serologically confirmed HIT caused by UFH given to 332 patients was 1% at 7 days and 3% at 14 days, when thrombocytopenia was defined as a platelet count fall to $<150x10^9$/L that began after 5 days of heparin. In contrast, none of the 333

Table 1. Epidemiology of heparin-induced thrombocytopenia.

General:	<5% due to treatment with bovine heparin
	1% due to treatment with porcine heparin
	<1% due to prophylaxis
	20-30% with thrombotic complications
Incidence depends on:	patient characteristics
	type of heparin
	route of administration
	dose
	duration of therapy
	definition of thrombocytopenia
	confirmation by laboratory test

patients who received LMWH (enoxaparin) developed HIT using this definition. However, when thrombocytopenia was defined as a >50% fall in platelet count that began after 5 days of heparin therapy, the frequency of HIT for UFH and LMWH was approximately 5.7% and 1%, respectively.

The relationship between the incidence of HIT II (defined only by clinical criteria), dosage and type of UFH used appeared in the study of Warkentin et al, in which the incidence was about 5% for therapeutic doses of bovine UFH, and 1% for porcine UFH, while it was <1% with prophylactic doses of porcine heparin.[7] In other prospective studies the incidence of HIT II varied from 1-30% in patients treated with high doses of intravenous UFH, while it was <2% in patients administered low doses of subcutaneous heparin.[1,8]

Several studies support the view that the possibility of development of HIT II differs among different study population. Surgical patients appear to be more likely to develop HIT than medical patients.[9] About 15% of orthopedic surgery patients who receive UFH for two weeks develop HIT antibodies, while one third of these patients (5% overall) develop clinical HIT (defined as a 50% or greater drop in platelet count).[10] In contrast, although 50% of cardiac surgery patients form HIT antibodies following heart surgery, only about 5% of these (2-3% overall) develop clinical HIT.[10,11]

In a double-blind, placebo-controlled study, the development of HIT was compared in 3,171 patients with angina at rest or non-Q-wave myocardial infarction, who were randomly assigned to receive either LMWH (enoxaparin) or continuous UFH for 2 to 8 days. No patients in either treatment group developed HIT, possibly due to the brief duration of therapy.[12]

In conclusion, the frequency of clinical and laboratory confirmed (antibody formation) HIT II seems to be about 2% when UFH is used, while it is much lower in patients who receive LMWH.[6,9,10]

Pathophysiology

The immunologic basis of HIT II has been fully elucidated. Heparin, a highly sulfated glycosaminoglycan, can form multimolecular complexes with platelet factor 4 (PF4), a protein located within platelet a-granules that exhibits a high affinity for heparin.[13] For unknown reasons, some patients generate antibodies (heparin-induced antibodies, HIA) that recognize PF4 when it is complexed to heparin.[14] These antibodies are usually IgG class, less frequently IgM or IgA. The immune complexes composed of HIA-IgG/PF4/heparin are connected with platelet FcγIIa receptors, resulting in strong platelet activation.[15] This activation causes additional PF4 release, which leads to the formation of new immune complexes, resulting in further activation and thrombocytopenia. Additionally, platelet activation causes platelet membrane changes, including the formation of procoagulant microparticles that lead to thrombin generation.[16] Furthermore, the multimolecular complexes of glycosaminoglycan and PF4 can cause endothelial injury, which in turn expresses tissue factor. As a result, activation of coagulation cascade occurs, leading to thrombin generation. This hypercoagulable state can persist for many days or weeks, which can explain the presence of arterial and venous thrombosis regardless of the cessation of heparin.[1,15,16]

Clinical Picture

The clinical picture of the syndrome is summarized in table 2. Three characteristic features of HIT II can be helpful in distinguishing it from other causes of thrombocytopenia: 1) the timing of the onset of thrombocytopenia, 2) the severity of the thrombocytopenia and 3) the presence of thrombosis or other characteristic sequelae.[4,17] Apart from the above features, this syndrome is also characterized by several clinical and treatment paradoxes (Table 3).[18]

The typical presentation of a HIT II is a platelet count decrease that begins 5 to 10 days after starting heparin therapy.[1,4,17] In some cases, there is a rapid fall in the platelet count (rapid-onset HIT), starting within minutes or hours of heparin administration. Recent heparin use (within the past 3 months) and

Table 2. Heparin-induced thrombocytopenia: clinical picture.

Thrombocytopenia with or without one of the following:
A. Venous thrombosis
Deep venous thrombosis
Coumarin-induced venous limb gangrene
Pulmonary embolism
Cerebral venous thrombosis
Adrenal venous thrombosis
B. Arterial thrombosis
Lower limb artery thrombosis
Cerebrovascular accident
Myocardial infarction
Other
C. Skin lesions (at heparin injection sites)
Erythematous plaques
Skin necrosis
D. Acute systemic (allergic) reactions:
Post-intravenous heparin bolus
E. Disseminated intravascular coagulation with hypofibrinogenemia

circulating HIT antibodies explain this profile. Rarely, thrombocytopenia and thrombosis attributable to HIT II can begin several days after discontinuation of heparin (delayed-onset HIT).[4,13,17]

The severity of thrombocytopenia, which varies between 50 and $70x10^9$/L (seldom $<19x10^9$/L), is often disproportionate to clinical symptoms. Petechiae or hemorrhagic events are not frequent.[13] In contrast, thrombosis, which appears in 30-75% of patients, is the major complication of HIT II. It may appear even in the absence of thrombocytopenia and is associated with a fall in the initial platelet count.[19] Both arterial and venous thrombosis can complicate the course of HIT II. Arterial thrombosis seems to be more frequent in patients with cardiovascular diseases, whereas venous thrombosis is found more often in patients undergoing post-surgical prophylaxis.[20] The most common arterial complications are thromboses of the large vessels, with gangrene and limb amputation, stroke, myocardial infarction, and cardiac thrombosis.[5,13,21,22] Deep venous thrombosis (DVT) and pulmonary embolism are the commonest among venous complications, while hemorrhagic adrenal necrosis, closure of arterial-venous fistula in a dialyzed patient and disseminated intravascular coagulation have been reported.[4,5,8] A severe complication is limb gangrene and DVT that appears during treatment with oral anticoagulants (coumarins). Other complications include allergic reactions within 5-30 minutes after i.v. heparin infusion, and skin necrosis at the site of subcutaneous heparin injection (10-20% of HIT II patients).[17]

Diagnosis

HIT II is a clinicopathologic syndrome that is often under-diagnosed.[22] A high index of suspicion, association of symptomatology with heparin therapy and serological confirmation are required for the diagnosis. The clinical diagnosis of HIT II is based on the following criteria: 1) the occurrence of thrombocytopenia during heparin therapy, 2) resolution of thrombocytopenia after cessation of heparin, and 3) exclusion of other causes.[1,23] The clinical diagnosis should be confirmed by a laboratory test for HIT antibodies. For that purpose two types of laboratory tests are available: the immunoassays and the functional assays. The first, ELISA assays, have a sensitivity of approximately 80% to 90% and can detect antibodies against heparin/PF4 complexes. The functional assays include various methods of platelet aggregation tests, the C-serotonin-release assay and flow cytometric platelet activation assay.[14,20,21] The

Table 3. Heparin-induced thrombocytopenia: medical paradoxes.

Paradox	Comment
Coumarins increase risk of microvascular thrombosis in acute HIT (venous limb gangrene, skin necrosis)	Coumarins are contraindicated in acute HIT. Treatment should be initiated after restoration of platelet count to near normal or at least $100x10^9$/L
LMWH is contraindicated for treatment of acute HIT, despite its lower frequency of causing HIT	In vivo crossreactivity (of 50%) when used to treat UFH-induced HIT
Platelet transfusions are contraindicated in acute HIT	Spontaneous bleeding is uncommon despite thrombocytopenia Platelet transfusion may contribute to thrombotic risk
High risk of thrombosis persists even after heparin is stopped	Treatment with alternative anticoagulation is recommended

Table 4. Clinical Scoring System.

Clinical features	Score
Decrease in platelet count <50% and >30%	+1
Decrease in platelet count >50%	+2
Timing of thrombocytopenia after heparin exposure:	
>5 days for patient's exposure for first time	+2
<5 days for patient re-exposure	+2
Thrombotic complications during heparin treatment	+2
Skin necrosis at heparin injection sites	+1
Improvement in platelet count after heparin withdrawal	+2
Infectious causes of thrombocytopenia-sepsis	-1
Recent chemotherapy	-1
Thrombotic complication before the onset of heparin treatment	-1
HIT II unlikely/low probability	<1
HIT II intermediate probability	1-3
HIT II high probability	>3

role of the above tests is to detect antibodies that activate the platelets. Immunoassays can detect IgG, IgA, or IgM, even in low titers that have no clinical importance. In contrast, functional tests are capable of detecting the same antibodies but in higher titers.[1,15,16] At this time, both methods complement one another and neither is 100% sensitive.[15]

Due to the difficulties reported in interpreting the above serologic methods, various score systems have been proposed for the estimation of the clinical probability of HIT II (including clinical symptoms and laboratory values). These systems are based on the severity of thrombocytopenia, the recovery following drug withdrawal, onset of thrombotic complications, and the exclusion of other causes of thrombocytopenia. A diagnosis of HIT II is highly probable when the score is >3, intermediate from 1-3 and low when the score is < 1 (Table 4).[16]

As mentioned above, the diagnosis of HIT II is primarily clinical and is confirmed by laboratory results. In cases of thrombocytopenia or thrombosis associated with heparin administration a positive test, immunoassay or functional, is sufficient to confirm the diagnosis of HIT II. If the test chosen initially is negative and the clinical likelihood of the syndrome is high, an alternative assay is tested. If the second assay is positive the diagnosis is confirmed. In the case that the second assay is also negative, the diagnosis is questionable even if the clinical picture is suggestive of HIT type II.[16,17] There are disorders that strongly mimic HIT ("pseudo-HIT"), such as thrombocytopenia associated with pulmonary embolism and disseminated intravascular coagulation (DIC), cancer-associated DIC and thrombosis, purpura fulminans with DIC, in which serologic tests are negative. In contrast, acute dyspnea that mimics pulmonary embolism ("pseudo-pulmonary embolism") or adult respiratory distress syndrome (ARDS) may be the presenting manifestation of HIT type II syndrome.[24-26]

Treatment

Despite the variety of treatment options for HIT type II, the best therapeutic strategy has not yet been clearly established. The treatment paradoxes in the acute phase of HIT type II are depicted in table 3.[18] The clinical significance of the above is to know what to avoid in the acute phase of the syndrome: 1) anticoagulant therapy (warfarin) with vitamin K antagonists is contraindicated due to the risk of venous-limb gangrene and skin reactions; 2) LMWH is contraindicated as an alternative to UFH (high risk of in-vivo cross reactivity) despite its lower frequency of causing the syndrome; 3) platelet transfusion is relatively contraindicated due to increased risk of new thrombotic complications; 4) discontinuation of heparin alone does not protect against thrombosis. It is estimated that 40-50% of cases of HIT type II show thrombotic complications despite cessation of heparin.[27]

In the case of high clinical suspicion of HIT type II (with or without thrombosis) all heparin treatment should be discontinued immediately without waiting for HIT antibody test results. Several cases of thromboembolic complications associated with heparin "flushes" (for maintaining the patency of central venous or peripheral arterial catheters) and the use of heparin-coated pulmonary arterial catheters have been reported.[28] Since HIT II patients are at high risk of thrombotic complications even after discontinuation of heparin, treatment with a rapidly acting alternative anticoagulant to heparin is mandatory.

Alternatives to heparin anticoagulants

The alternative anticoagulant drugs to heparin include the direct thrombin inhibitors lepirudin (Refludan®) and argatroban (Novastan®), as well as the low-molecular-weight heparinoid danaparoid sodium (Orgaran®) (Table 5).

Lepirudin

Lepirudin (recombinant hirudin, r-hirudin, Refludan®) is a recombinant direct thrombin inhibitor that binds

Table 5. Heparin-induced thrombocytopenia: alternative anticoagulant.

Anticoagulant	Dosing	Pharmacokinetics	Comments
Agents approved for HIT type II			
Danaparoid sodium (Orgaran)	Bolus:2250U Infusion: 400U/hx4h 300U/hx4h 200U/h with monitoring by antifactor Xa (0.5-0.8U/ml)	Renal metabolism Dose reduction in RF	Approved for treatment and prevention of HIT thrombosis (Europe, Canada, Australia). Rarely in vivo crossreactivity with heparin/PF4 complex
Lepirudin (Refludan)	Bolus: 0.4 mg/kg	Renal metabolism Dose reduction in RF	Approved for HIT-associated Thrombosis (Europe, USA) Allergic reactions, antibodies
Argatroban (Novastan)	2 μg/kg/min without initial bolus, target aPTT range 1.5-2.5 x baseline	Hepato-biliary excretion	Approved for prevention and treatment of HIT-associated thrombosis (USA, Canada)
Agents under investigation for HIT II			
Bivalirudin (Angiomax)	0.15-0.20 mg/kg/h without bolus aPTT 1.5-2.5 x baseline	Enzymic excretion	Approved in USA for percutaneous coronary intervention (non-HIT) limited experience
Fondaparinux (Arixtra)	Uncertain	Renal excretion	Approved for DVT prophylaxis in orthopedic surgery, lack of in-vivo cross-reactivity with heparin/PF4 complex

RF: Renal failure

thrombin, forming an irreversible 1:1 complex. Hirudin's half-life is approximately 80 min, but is increased dramatically in renal insufficiency. The anticoagulant activity of the drug is monitored by measuring the activated partial thromboplastin time (aPTT). The usual dose is 0.4 mg/kg bolus followed by 0.15 mg/kg/h by continuous infusion, adjusted for a target aPTT (prolongation of aPTT 1.5-2.5 to the control). For prophylactic use it may be preferable to omit the initial bolus and to use a lower target aPTT range (1.5-2.0). The drug has been approved for prophylactic and treatment use in HIT II patients (Table 5). As a foreign protein for the body, the drug can cause the development of anti-hirudin antibodies when administered for >8 days in about 50-80% of cases. The formation of these antibodies prolongs the aPTT but does not increase the hemorrhagic complications. Thus, daily monitoring of aPTT should be performed throughout the course of lepirudin treatment.[30,31]

Argatroban

Argatroban is a synthetic drug derived from L-arginine. It is a small molecule that acts as a reversible, direct and selective thrombin inhibitor. Argatroban has similar in vitro potency for inhibiting both fibrin clot-bound and soluble thrombin. The half-life is 40-50 min. Argatroban is cleared by the liver, and when administered in patients with liver disease, the elimination half-life is doubled (in such patients the initial dose of the drug should be decreased to 25%). Argatroban is not excreted renally, therefore a dose reduction is not required in cases of renal failure. The pharmacologic properties of the drug give it a potential safety advantage over lepirudin. The anticoagulant activity of the drug is monitored by the aPTT with target therapeutic range 1.5-3 times baseline.[1,16]

In a recent study, patients with HIT Type II (with or without thrombosis) who received 2 μg/kg/min argatroban, had a significant reduction of new thrombosis and limb amputations with a decline of the subsequent mortality rates when compared to controls. Additionally, although bleeding events were similar in both study groups, the argatroban treated patients had a much more rapid increase in the platelet count.[32] Argatroban is approved in the USA for treatment of percutaneous coronary intervention in patients with a history of acute HIT type II.[33]

Danaparoid

The heparinoid danaparoid sodium (Orgaran), derived from porcine intestinal mucosa, consists of heparin sulfate, dermatan sulfate and chondroitin sulfate. In contrast to LMWH, it contains no heparin fragments. It has antifactor Xa activity. A dose regimen for treatment of thromboembolism should be adequate to maintain antifactor Xa activity at 0.5-0.8 U/ml. The elimination half life of the antifactor Xa activity is 24 hours. This prolonged half-life, although advantageous for HIT type II patients with deep venous thrombosis or pulmonary embolism where gradual transition to oral anticoagulants is required, is a disadvantage in cases of acute bleeding, operations or other invasive procedures due to the deficiency of an antidote (cannot be neutralized by protamine sulfate). It has renal clearance and requires dose reduction in renal insufficiency. Rarely, the drug exhibits cross-reactivity with the heparin/PF4 complex. Because of the prolonged elimination half-life, bleeding complications, lack of antidote for anticoagulant effects and routine monitoring test, the drug has limited use. Recently, the drug has been disapproved for prophylaxis and treatment of HIT type II patients in the USA.[16,34,35]

Other anticoagulants

The hirudin analogue bivalirudin (Angiomax®) is approved for percutaneous coronary angioplasty, as an alternative to heparin, while its use in HIT II patients is limited.[36] The pentasaccharide Fondaparinux (Arixtra®) is approved for antithrombotic prophylaxis after orthopedic surgery.[37] This agent does not cross react with antibodies against heparin/PF4 complex, and theoretically should be effective for HIT given that it has potent antithrombotic activity (inhibits antiXa on clot external).

Adjunctive therapy

Antiplatelet agents, aspirin and dipyridamole, which have been used for many years in HIT patients in order to inhibit platelet activation, are ineffective, since aspirin has low antiplatelet activity. For this reason, aspirin is not considered as a principal agent for therapy of HIT type II patients but can be added to therapeutic anticoagulation in patients as an adjunct in HIT patients with arterial thrombosis.

Iloprost, a prostacyclin analog with potent antiplatelet activity, has been successfully used in cardiac surgery in HIT II patients. The drug reversibly inhibits platelet aggregation and has an elimination half-life of 15-30 min. Due to increased risk of hypotensive episodes its use is limited.[38]

Antagonists of platelet glycoprotein IIb/IIIa receptors (GPIIb/IIIa) have been used in combination with direct thrombin inhibitors in HIT II patients during percutaneous coronary angioplasty or coronary by-pass surgery.[39] A study using this regimen showed that platelet activation from heparin/PF4 complex is inhibited when an antagonist of GPIIb/ IIIa is added to the direct thrombin inhibitors. Although the number of series is limited, the clinical use of this combined treatment has shown beneficial results.[13,39]

Immunoglobulin at 1g/kg for two consecutive days has been used as adjunctive therapy for the treatment of HIT II, inhibiting HIT antibody-induced platelet activation via blocking platelet Fc receptors. Intravenous IgG may be used as adjunctive treatment for patients in whom rapid blockade of the Fc receptor is required (HIT in pregnancy, DIC, limb gangrene).[1,16] Thrombolysis with streptokinase, urokinase or rTPA, plasmapheresis and surgical thromboembolectomy have all been used as an adjunctive treatment in HIT type II patients.[4,16]

An approach to HIT in various clinical settings

HIT in coronary artery bypass surgery

For patients who require coronary artery bypass surgery and have either an active or a remote history of HIT, the physician should first decide if heparin or an alternative anticoagulant drug could be used. In cases with a history of HIT but no detectable antibodies heparin can be used at a regular dose during surgery, followed by an alternative anticoagulant beginning in the postoperative period. In those with detectable antibodies or those with low platelet count, where immediate operation is not required, bypass can be delayed for 3-4 weeks and if the platelet count has returned to normal, then heparin is used as in the first case. In a patient who has either acute HIT or who has had HIT within the past 4 weeks and the bypass procedure is essential, two treatment approaches have been described.[40]

First, alternative anticoagulation with danaparoid sodium or lepirudin or bivalirudin can be provided. Disadvantages of the first drug include a long half-life, the lack of an antidote, the need for antifactor Xa monitoring and in some cases severe

bleeding complications. Drawbacks of lepirudin include the lack of an antidote, the risk for drug accumulation during renal failure and the need to monitor using ecarin clotting time (ECT).[30,40] Bivalirudin has a theoretical advantage over lepirudin due to its shorter half-life and enzymic rather than renal clearance.[36]

A second approach is to administer heparin together with antiplatelet agents such as iloprost, epoprostenol or GPIIa/IIIb antagonist (tirofiban). Both approaches have been used successfully, but experience is limited.[38,40]

HIT in cardiology

In patients who have acute cardiac episodes or require cardiologic interventions (percutaneous angioplasty, percutaneous valve repair) heparin is commonly used to avoid thrombotic complications. Patients with HIT type II who require coronary intervention have increased thrombosis risk, since besides the hypercoagulant feature of the syndrome they have increased risk of thrombus breakdown during the procedure. In such cases, anticoagulation with an alternative drug to heparin is required, though LMWH and danaparoid sodium are contraindicated due to the potential of cross-reactivity with antibodies against heparin/PF4 complex.[6,11,14,40]

Lepirudin, bivalirudin and argatroban have been approved by the FDA for use in patients with active HIT or a history of HIT who are undergoing percutaneous coronary intervention, while several studies concerning the combination of these drugs with inhibitors of GPIIb/IIIa platelet receptors are in progress.[33,41,42] Lepirudin, either alone or in combination with the above inhibitors has been used successfully in these patients in doses sufficient to maintain the aPTT between 200 to 400 seconds.

HIT type II patients re-exposed to heparin

Patients with HIT type II with detectable antibodies should not receive heparin under any circumstances. Recent studies showed that the titers of antibodies against heparin/PF4 complex fell to undetectable levels at a median of 50 to 85 days after heparin withdrawal.[43] Accordingly, heparin should not be given to patients with HIT type II within the previous 120 days, without previous estimation of these titers.[43] In those patients who have had HIT type II and have no detectable antibodies, heparin can be provided during cardiac or other surgery, although alternative anticoagulation is required perioperatively.[40]

Long term treatment of HIT type II

The duration of treatment for patients with HIT II is not well defined. Prospective studies suggest that the risk of thrombotic complications can persist for up to at least 6 weeks. Therefore, anticoagulation is recommended for at least 2 to 3 months. The anticoagulant of choice is the vitamin K antagonist coumarin.[16,40,43] Treatment should be initiated while the patient is under adequate alternative anticoagulant treatment (direct thrombin inhibitors or danaparoid sodium), even if thrombosis is not apparent, because subclinical thrombosis can be present. For that reason, HIT II patients should undergo duplex ultrasonography for deep venous thrombosis.[44] The proper time for coumarin initiation is individualized, but is probably best started when the platelet count is near the normal range.[16,40,45] When coumarin treatment is provided immediately after heparin cessation without normalization of the platelet count, the risk of limb necrosis (gangrene) from deep venous thrombosis is increased.[16,18,46] Affected patients have a typical clinical profile. First, progression to necrosis occurs in a limb with active deep venous thrombosis; second, gangrene occurs only after HIT has been diagnosed, heparin discontinued, and coumarin commenced; and third, patients usually have an INR above therapeutic range. The pathogenesis of this phenomenon is obscure. The paradoxically ongoing thrombin generation, despite coumarin treatment and increased INR, as well as the severe depletion in protein C levels, which is a natural thrombin inhibitor, have all been implicated for venous limb gangrene.[18,46] Recently, a similar complication has been described in two patients with HIT type II and deep venous thrombosis during coumarin transition from direct thrombin inhibitors (lepirudin, argatroban), due to persistent thrombocytopenia.[47]

Unanswered questions

Despite progress towards a better understanding of the pathophysiology and the innovative treatment options, several questions regarding diagnosis and treatment remain unanswered. For example, are all patients who receive heparin equally at risk for developing HIT? Some studies have suggested that poly-

morphism for the FCγRII receptor alters the susceptibility to thrombocytopenia. What is the best policy for those who receive heparin during a coronary artery bypass procedure or other surgery and then develop thrombosis in the postoperative period? Several studies are under way and are expected to help in resolving the unanswered questions in HIT type II syndrome.

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