HITs and misses in 100 years of heparin

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Heparin was discovered 100 years ago, and the heparin-induced thrombocytopenia syndrome was described 40 years ago. That the most powerful anticoagulant of the last century can also produce the most extreme prothrombotic diathesis is but one of the paradoxes that surround heparin-induced thrombocytopenia. Standard treatment is alternative anticoagulation. Advances continue to be made regarding pathophysiology, prevention, and treatment. Currently, an epidemic of overdiagnosis threatens the well-being of patients, so efforts to educate clinicians on when and how to make this diagnosis are pressing.

Learning Objectives

- To review the evolution of knowledge about heparin-induced thrombocytopenia (HIT) in order to better understand current principles of diagnosis and treatment
- To be updated on new findings on pathophysiology, testing, diagnosis, treatment, and prevention of HIT
- To learn when and how to consider HIT (how to interpret clinical parameters and test results) so as not to miss the diagnosis or contribute to harmful overdiagnosis

Introduction

Heparin therapy has saved the lives and limbs of uncountable patients (millions), but a paradoxic reaction to heparin can produce an extreme prothrombotic diathesis that costs thousands their lives or limbs yearly. I am proud that this statement about heparin-induced thrombocytopenia (HIT) has become trite because of my role in making it so.[1] Yet, even as prevailing awareness increases (long predicted to be the solution), HIT and concerns for HIT plague patient outcomes.

Heparin

Heparin is a highly sulfated glycosaminoglycan bearing the highest-density negative charge of any known biologic molecule.[2] Some credit its discovery to medical student Jay McLean in 1916, but others attribute key findings over the next few years to one of his Johns Hopkins professors, William Henry Howell. (Some versions of this story read like a mystery novel.[2]) Clinical application was pioneered by Charles Best and colleagues in Toronto.

Commercial heparins are derived mainly from porcine intestine or bovine lung, with only the former being currently approved in the United States (though new bovine heparins may be on the horizon). From 1 hog (of the 1.2 billion slaughtered yearly), 3 doses of unfractionated heparin (UFH) or 1 dose of low-molecular-weight heparin (LMWH) can be generated. China supplies more than half the world's porcine UFH and close to 90% of the US supply. This was brought into sharp focus 10 years ago by the oversulfated chondroitin sulfate contamination, estimated to have caused 100 patient deaths.[2] LMWHs are extracted from UFH by different techniques. Fondaparinux is synthesized to contain the minimum 5-sugar sequence needed for an anticoagulant effect. Heparins bind to antithrombin, increasing by orders of magnitude its inhibition of serine protease procoagulant proteins IIa (thrombin), IXa, Xa, and XIa. LMWHs inhibit factor Xa to a greater degree than thrombin; fondaparinux purely inhibits factor Xa.

HIT

Early history of HIT

Thrombocytopenia was seen in some heparin-exposed patients after its introduction into the clinic. Surgical case series in 1958 and 1964 documented 21 patients who had repetitive thromboses while on heparin, succumbing to the complications or recovering only after drug cessation.[3,4] These reports do not mention platelet counts (likely not measured). In the mid-1970s, Bell and colleagues[5] found that platelets commonly fall in heparin-treated patients and advanced low-grade disseminated coagulation as the mechanism. Others demonstrated an immunologic mechanism.[6-8] Responding to published queries, Babcock allowed that thrombotic complications had accompanied HIT in his patients. Forty years ago, Donald Silver's surgical group in Missouri put together the clinical features of the HIT syndrome.[9]

Clinical features of HIT

Classically, platelets fall (>50% from baseline in the great majority) beginning 5-12 days after heparin exposure. On presentation with HIT, half of patients display a new thrombosis, either venous or arterial. Venous thromboses have predominated, depending on the underlying disorder; relatively more deep vein thromboses/pulmonary emboli occur after orthopedic surgery, whereas more strokes and other arterial occlusions occur after cardiovascular surgery.[10,11] Thromboses may occur at unusual sites, such as cerebral venous sinuses, splanchnic

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abdominal veins, and adrenal veins (bilateral hemorrhagic adrenal necrosis). HIT ranks high among the causes of these unusual clots, so it deserves consideration whenever these are encountered. A point of emphasis is that thromboses are often catastrophic, with amputations and mortality common sequelae, especially if the disease is not recognized and treated promptly and appropriately.[10,12]

Case 1. In 1976, a 58-year-old man had back surgery for traumatic vertebral fractures. Heparin was started a few days later for proximal leg deep vein thrombosis. On day 7 of heparin, he had increased leg swelling, shortness of breath, hemoptysis, and confirmed pulmonary emboli. His platelets had fallen by 75% to 83 $\times$ 10^9/L. Suspected HIT was serologically confirmed by the intense aggregation of normal platelets when heparin was added to the patient's plasma. Heparin was stopped, warfarin (10 mg/d) begun, and an inferior vena cava (IVC) filter placed. On day 4 of warfarin, the patient's prothrombin time was supratherapeutic, and a necrotic lesion appeared on the patient's thigh, leading to death resulting from sepsis and respiratory failure.

Comment. This previously reported case[13] was the first HIT diagnosis made by the author at a time when an association with thrombotic complications was not appreciated. Over the next 10 years, I collected 44 additional cases of HIT with thrombotic complications in Baylor-affiliated hospitals in Houston,[10,14] underscoring that though this problem was once underrecognized, it has always been around. This case underscores that stopping heparin is inadequate without effective alternative anticoagulation and that early, unopposed, and excessively dosed warfarin can worsen thrombotic risks, including skin necrosis and venous limb gangrene.[13,15] IVC filters are highly problematic (see *Vena cava filters* below). Given the limited therapeutic options at the time, what else could have been done?

Epidemiology

Any exposure to heparin (including only catheter flushes) puts a patient at risk for HIT.[10] The risk with UFH is ~10 times higher than with LMWH. Interestingly, the other major risk factor is the clinical context in which heparin is given. The risk is highest after cardiovascular or orthopedic surgery, higher in general surgery than in medical patients, and lowest for obstetric patients. The risk after cardiovascular surgery is 0.5% to 2% and after orthopedic surgery as high as 5%, and it may be increased with inflammatory disorders.[11] Dose and duration may be risk factors. Any increased risks in women or with platelet Fcγ receptor polymorphisms[16] have not informed clinical practice.

Pathophysiology

Platelet factor 4 (PF4) modified by heparin was found by Amiral and colleagues to be the relevant antigen in HIT.[17] When stoichiometry is favorable, PF4–heparin antibody immune complexes coat the platelet surface and activate platelets through their Fc receptors. The thrombotic diathesis results from platelet activation, release of thromboplastic platelet microparticles, endothelial activation and injury resulting from cross-reactivity of the antibodies with endogenous glycosaminoglycans lining the endothelial surface, and monocyte procoagulant expression. Understanding how an immune response so frequently emerges to the autoantigens PF4 and heparin has been advanced by findings that PF4–heparin complexes activate complement and selectively bind to B lymphocytes through complement receptors.[18]

Diagnosis

Clinical diagnosis and 4Ts score

HIT must be considered whenever a patient in the hospital or who has recently been in the hospital has a fall in platelet count or a new blood clot (Table 1). Documented heparin exposure is helpful, but use is ubiquitous, so exposure cannot be dismissed if not charted (eg, heparin flushes during catheter placement). The degree of concern for HIT depends on whether characteristic clinical features are present. The "4Ts" score is a validated clinical decision tool, awarding 0-2 points for each of 4 parameters: (1) a typical fall in platelet count, (2) typical timing after beginning heparin, (3) whether accompanying thromboses are present, and (4) whether other explanations are possible or likely. A score of 0-3 excludes HIT with 99% negative predictive value.[19] Moderate (4-5) or strong (6-8) scores generally mandate eliminating all heparin exposures and initiating alternative anticoagulation. The positive predictive values of moderate and strong clinical scores are only 14% and 64%, respectively, emphasizing the need for serologic confirmation. There can be some subjectivity to awarding points for clinical features, and the 4Ts score is dependent on complete and accurate clinical data. It should be emphasized that, to avoid contributing to harmful overdiagnosis (discussed in *The overdiagnosis epidemic* below), serologic tests should not be ordered when the clinical probability score is low. Examples of situations where serologic testing is not warranted are (1) a dialysis patient (chronically exposed to heparin for months or years) whose platelets fall coincident with a febrile illness or (2) as "screening" before a cardiovascular procedure.

Alternative temporal scenarios

Clinicians must be cognizant of 2 alternative temporal scenarios. Rapid-onset HIT occurs when patients with prior, relatively recent heparin exposure are reexposed to heparin. Thrombocytopenia can sometimes ensue within minutes as a result of preformed antibody and may precipitate dramatic cardiorespiratory collapse, sometimes mistaken for acute pulmonary embolism.[20] Delayed-onset HIT occurs when a recently exposed patient develops a new blood clot despite receiving no ongoing heparin for a few days to weeks. On representation, platelets may not be low, but they will always fall promptly if heparin is resumed because the nature of the problem is not immediately recognized (see case 5 below). This is most common after heart surgery, accounting for 10% to 15% of patients with HIT who I see. PF4/heparin antibody titers are uniformly very high.[21,22]

Serologic confirmation of HIT

"Functional" platelet aggregation–based assays were developed first but are now rarely used for screening, despite improvements by the use of washed platelets. With identification of PF4/heparin as the relevant antigen, "antigen" enzyme-linked immunosorbent assay (ELISA) or enzyme immunoassay quickly became dominant. When ordered and interpreted properly, these can unquestionably be a boon for clinicians and patients. Advantages of the ELISAs are that they are widely and quickly available, easy to perform, and highly reproducible and are highly sensitive—specificity is the issue. An optical density (OD), a surrogate for antibody titer, of 0.4 was advanced as a cutoff between positive and negative. Warkentin and colleagues[23] found pathogenic platelet-activating antibodies in $<2\%$ with "positive" ELISA results of OD 0.4-1.0, in only 10% with 1.0-1.4, in 50% with 1.4-2.0, and in 90% only when OD was >2.0. ELISA results should not be reported as "positive" or "negative"; rather, the OD value should be interpreted by the ordering physician in the clinical context.[24]

Table 1. Diagnosis of heparin-induced thrombocytopenia

Consider HIT whenever a patient exposed to heparin (or has reasonably supposition of exposure):
Has a significant fall in platelet count and/or
Has new blood clot
Formulate clinical probability estimate (4Ts score awards 0-2 points for each of the following parameters):
Thrombocytopenia, is it typical (at least 30% to 50% fall)
Timing of platelet fall (5-12 d after heparin initiation; consider also alternate temporal scenarios)
Thrombotic complications contemporaneously (consider more strongly if unusual sites)
Other likely explanations for low platelets and/or clots
If moderate or strong suspicion, order serologic test (ELISA):
<0.4, "negative"; 0.4-1.0, <2% to 5% have platelet-activating antibodies
1.0-1.4, 10% to 20% have activating antibodies; 1.4–2.0, 50% have activating antibodies
>2.0, 90% have activating antibodies
If diagnosis is clear on the basis of clinical probability and ELISA (great majority), no need for confirmatory serology.
If clinical probability is low, there is no reason for ordering serologic tests (can lead to harm).

ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia; 4Ts score, thrombocytopenia, timing after beginning heparin, whether accompanying thromboses or other sequelae are present, and whether other explanations are possible or likely.

The serotonin release functional assay emerged in the 1980s as a specific and sensitive "gold standard" and is still widely used for serologic confirmation. Multiple constraints challenge its utility for clinical decision making. It is technically demanding, has limited availability, does not supply results in "real time," is poorly reproducible from one reference laboratory to another, requires "pedigree" platelet donors known to react well in the assay, is subject to important nuances in specimen handling, and so forth.[25] Newer assays are trying to fill the void, but none has been established to meet needs for sensitivity, specificity, and rapid reproducibility. Of note is a PF4-dependent platelet activation assay being developed by the same Milwaukee laboratory that pioneered the most widely used ELISA in the United States.[26] A collaboration between laboratories to establish comparative assay performance should be encouraged. Clinicians should understand that no confirmatory laboratory test is required when a HIT diagnosis has been clearly established or ruled out by clinical scoring and ELISA results.

Case 2. A 74-year-old man underwent coronary artery bypass surgery. His intensive care unit (ICU) stay was prolonged by postoperative transient atrial fibrillation and volume overload. Preoperative platelets of 200×10^9/L recovered postoperatively to 182×10^9/L, then fell on the sixth postoperative day to 70×10^9/L. He had no signs of thrombosis (negative venous and arterial ultrasounds). Serologic tests were strongly positive for HIT, and heparin was stopped. Four days later, the patient's platelets had recovered to 132×10^9/L, and this clinically improved patient was awaiting transfer out of the ICU when he had a lethal ventricular arrhythmia.

Comment. The treating physicians of this previously reported case[27] have no doubt in blaming this death on thrombosis of the coronary bypass grafts, a complication seen in other cases of HIT. The case emphasizes the point below that all cases of HIT, even "isolated" cases (no thrombosis), require effective alternative anticoagulation.

Treatment

The most logical solution for the half of HIT patients who do not already have a thrombotic complication (or a mechanical heart valve or other pressing demand for anticoagulation) would seem to be to just stop the heparin. Such cases without thrombosis have been labeled *HIT* (vs *HITT* [heparin-induced thrombocytopenia with thrombosis]) and are now commonly called *isolated HIT*. Warkentin and colleagues[28] found that half of patients with isolated HIT had new thrombotic events within 1 month if not afforded effective alternative anticoagulation; 5% died (see cases 1 and 2 above). I have argued that the terms *HIT* and *HITT*, as well as *type 1* and *type 2 HIT*, should long ago have been abandoned because they confuse clinicians into believing that some cases of true HIT are benign and do not warrant anticoagulation. If one desires abbreviations, I have recommended that isolated HIT be designated *HITTY* (*HIT without thrombosis yet*).[10] On moderate suspicion for HIT, standard care for all cases is alternative anticoagulation (except for the direst bleeding contraindications).

Steroids were not efficacious in early reports, and antiplatelet agents proved inadequate. The defibrinating agent ancrod was used until more effective agents became available. On the basis of European trials, lepirudin was the first drug approved for HIT by the US Food and Drug Administration (FDA). A direct thrombin inhibitor (DTI), it is a recombinant form of the leech salivary protein hirudin. Because of increased risks for bleeding and for antibody formation that could prolong anticoagulant effects or produce anaphylaxis on reexposure, the drug is no longer manufactured. Another hirudin, desirudin, has not gained wide use.

Warfarin

Initiating early warfarin once seemed a reasonable strategy, and most so treated have had the good fortune to recover. Nevertheless, warfarin can precipitate disastrous outcomes, such as venous limb gangrene, central skin necrosis, or worsening of preexisting thrombosis. Warfarin is prothrombotic in the first days of use because of effects on the short-lived vitamin K–dependent natural anticoagulant protein C, particularly problematic in the extreme hypercoagulable milieu of HIT. Warfarin should not be started early (before platelet recovery), unopposed (adequate anticoagulation must be established with an appropriate agent), or in an excessive dose (thrombotic complications are highest with supratherapeutic international normalized ratio, which early reflects factor VII activity and correlates with protein C).[13,15] These caveats on warfarin initiation apply to any active thrombotic diathesis, not just HIT. A tragic mistake can be inadequate overlap of warfarin with an effective anticoagulant.

Case 3. A middle-aged woman underwent mastectomy for breast cancer with postoperative heparin prophylaxis. Readmitted with an acute abdomen on postoperative day 11, she underwent resection of ischemic/necrotic bowel. Postoperatively, she required pressors and had a tender quiet abdomen and a cold pulseless leg. Her platelet count was 30×10^9/L, and the result of a platelet aggregation assay for HIT was strongly positive. With her husband's consent, argatroban was initiated as part of a multicenter clinical trial. Her platelet count rose quickly as her leg became warm and viable. Months later in the clinic, the patient was well (her colostomy having been taken down).

Case 4. A 30-year-old woman with diabetes insipidus as well as gingival and skin lesions was diagnosed with Langerhans cell histiocytosis. On an outpatient basis, 2-chlorodeoxyadenosine was infused over 7 days, and the patient's central catheter was flushed daily with heparin. On day 9 of therapy, she was admitted with shortness of breath, severe pleuritic pain, and a platelet count of 55×10^9/L. With initiation of therapeutic LMWH, her platelet count fell within hours to 19×10^9/L; her oxygenation deteriorated; and there emerged new headache, facial edema, and severe bilateral arm pain and swelling. Imaging showed bilateral subclavian vein thromboses; superior caval thrombosis; and bilateral pulmonary emboli, including a right main pulmonary artery clot. She was transferred with an IV heparin drip; argatroban was substituted immediately. The patient's PF4/heparin antibodies came back in high titer. All her signs and symptoms resolved over 8 days, and she remains well years later.

Comment. Cases 3 and 4 illustrate key clinical features of HIT, including the catastrophic potential, worsening by delayed recognition, and the sometimes dramatic efficacy of DTI therapy. Case 3 was the first patient we treated with argatroban as part of the ARG-911 trial, an historically controlled prospective study of suspected cases of HIT.[29] Case 4 has been reported previously.[27] Neither patient would likely have survived without effective alternative anticoagulation. The only heparin exposure in case 4 was catheter flushes, proven unnecessary in most situations, clearly so here with continuous medication infusion. I have long stressed this as a cause or propagating factor for HIT.[10]

Danaparoid

Danaparoid is a heparinoid molecule with a long half-life (24 hours), renal clearance, and cross-reactivity with PF4/heparin antibodies that is rarely clinically relevant. An array of subcutaneous or IV dosing strategies have been proposed for different scenarios. HIT efficacy was demonstrated by a registry and an attempted randomized trial against dextran (which suffered low accrual). This drug has been unavailable in the United States for 15 years but remains favored by some international experts. An in vitro study showed that danaparoid was able to disrupt PF4–heparin antibody immune complexes, thus possibly mediating benefits beyond anticoagulation.[30]

Argatroban

Argatroban is an arginine-derived DTI developed in Japan. The FDA approved its use for HIT on the basis of historically controlled clinical trials in the mid- to late 1990s. It is given by IV infusion, monitored by partial thromboplastin time, hepatically cleared, and thus contraindicated with significant liver disease. Some nuances are that its approved starting dose is too high for most patients; its significant and variable effects on prothrombin time international normalized ratio can be challenging during warfarin transition; and, like other agents monitored by partial thromboplastin time, it is subject to confounding by coexistent coagulopathies.[29,31,32]

Bivalirudin

Bivalirudin is a synthetic modified hirudin. It is FDA approved for angioplasty, including in those "with HIT or at risk for HIT." It has been used successfully for HIT, including in those with multiorgan failure, where argatroban or lepirudin would be problematic.[33] It has favorable pharmacokinetics, is cleared mainly by serum proteases and only 20% renal, and is familiar to cardiologists (by virtue of its use with angioplasty).

Fondaparinux

Fondaparinux is a subcutaneous product with a long half-life (24 hours) and renal clearance. It is very rare for this drug to cross-react with PF4/heparin antibodies. This has become favored in "less-sick" patients with HIT or as a second-line therapy after ICU patients have been stabilized. It allows once-daily subcutaneous dosing without monitoring and no interference with warfarin transition, although renal clearance can be problematic.[34]

New oral anticoagulants

Increasing use of new direct oral anticoagulants (eg, as post-orthopedic prophylaxis or for atrial fibrillation) should result in a lowered incidence of HIT, a realistic hope. These drugs (eg, rivaroxaban, apixaban) should also be valuable for treatment, especially for milder cases or for those past the acute stage. Indeed, preliminary experience is favorable.[35,36]

Reexposure to heparin

Patients with a remote history of HIT have a risk for redevelopment of PF4/heparin antibodies on reexposure. Although the incidence of full-blown recurrent HIT may be low with proper precautions, a few fatal and near-fatal recurrences have been seen.[37,38] Given that there are highly effective alternative anticoagulants for most situations where heparin is used (eg, fondaparinux, bivalirudin, new oral anticoagulants [NOACs]), reexposure to heparin can rarely be justified. An exception is on-pump cardiovascular surgery, where UFH is preferred for its unique properties, such as having well-established dosing protocols, established bedside monitoring, and complete reversibility with protamine. Guidelines allow reexposure to heparin on pump in those with past HIT, but postoperative alternative anticoagulation and close monitoring are required.[33,39] If cardiovascular surgery cannot be postponed with acute HIT, guidelines and published experience suggest bivalirudin as a relatively safe alternative agent, but unfavorable anecdotal experiences suggest this may be an area with unmet needs.

Non-anticoagulant therapies

Vena cava filters. Almost from the beginning of the recognition of HIT, expert opinion has cautioned against the use of vena cava filters. Indeed, there has been recent general pushback on overuse of these devices, with the best established use being for deep vein thrombosis with a contraindication to anticoagulation, and perhaps for failure of adequate anticoagulant therapy.[40,41] HIT actually is a situation where anticoagulation is strongly mandated and effective. My group presented evidence of the markedly increased risk for thromboses in patients with HIT in whom IVC filters have been placed[42]; we are now updating our retrospective data showing a thrombosis risk of ~70% when a filter has been inserted vs 15% in those without (J. Pacheco, L. Rice, unpublished data, September 2017). Caval thrombosis and venous limb gangrene leading to amputation are among the complications seen when thrombogenic foreign material is inserted during this extreme hypercoagulable maelstrom.

Thrombolytic therapy. Few reports and my own experience have found benefit in some patients, but deaths due to intracranial hemorrhage have also been seen. Thrombolytic therapy can be considered in desperate circumstances.

Plasma exchange. Although generally disappointing for immunoglobulin G–mediated autoimmune disorders, there have been anecdotal reports of success with this intervention for HIT. Plasma exchange can be reasonably considered in relatively desperate clinical situations, such as before urgent cardiovascular surgery.[43]

Intravenous immunoglobulin. A few anecdotes and a small in vitro study have reported the efficacy of intravenous immunoglobulin in HIT, although many of the cases had poorly documented disease. Recently, a few dramatic responses have been reported along with supporting evidence from the Milwaukee laboratory that high-dose immunoglobulin can block platelet activation by PF4–heparin immune complexes through Fc receptor blockade.[43,44]

Prevention

HIT can be prevented by avoiding heparin exposure. LMWH can and should replace UFH for most heparin indications. Increasing use of NOACs for thromboprophylaxis and for primary treatment of thrombosis would clearly reduce the incidence of HIT. Monitoring platelet counts in high-risk patients has also been advocated to allow early intervention and reduce complications, but that strategy is limited because no situations engender a risk >2% to 5%, and serious complications can occur despite monitoring. There is no role for monitoring antibody tests in patients exposed to heparins, and attempts to do this contribute to overdiagnosis and harm.

The "Avoid-Heparin Initiative" was instituted in 2006 at a tertiary care hospital in Toronto, replacing UFH with LMWH for all prophylactic and therapeutic indications except for heart surgery and dialysis. Cases of adjudicated HIT fell from 10.7 to 2.2 per 10 000 admissions, accompanied by substantial decreases in suspected HIT, in serologic tests ordered, and in hospital costs.[45]

The overdiagnosis epidemic

An epidemic of HIT overdiagnosis has arisen such that, when I have been called for HIT in recent years, I have found that only 1 in 3 has it, an experience shared by other consultative hematologists. Consider 2 representative cases this month. A 50-year-old man was transferred from another state for possible heart transplant, with argatroban being infused. Transplant consideration was put on hold while a strategy was pondered for his HIT. Contact with the referring hospitalist revealed that his platelets had fallen in concert with intra-aortic balloon pump placement and not temporally related to heparin, that his ELISA OD had been 0.5, and that his serotonin release functional assay results (not followed prior to the call) were negative. Another patient had urgent percutaneous coronary intervention postponed when she reported "heparin antibodies" (as she had been instructed) during admission 12 years ago. Retrieved records revealed that she had never seen a hematologist and that her ELISA OD had been 0.06.

It is easy to understand why physicians might overreact to the possibility of HIT. Catastrophic outcomes have been exacerbated by lack of awareness and late diagnosis, so educational efforts have stressed the need for vigilance. This was reinforced by a burgeoning literature, by personal experiences of physicians and their colleagues, and even by lawsuits (this is a highly litigious area). The lack of specificity of clinical diagnosis contributes to overdiagnosis, as does the use of overly sensitive ELISAs. These tests are being ordered "willy-nilly" on the basis of the misconception that they can provide a simple answer instead of the physician's having to learn about the disease, when and when not to order a test, and how to interpret results. A study of PF4/heparin ELISAs ordered in the ICUs of my institution revealed that 85% of patients had a low 4Ts score and 27% had never been exposed to heparin.[46] My informal survey of several reference laboratories revealed that only ~10% of ordered PF4/ELISAs are "positive" even at a 0.4-OD cutoff and that <5% have an OD >1.0. The problem of inappropriate test ordering is multiplied when the physician cannot interpret results in the context of his patient or when the laboratory reports only a "positive" or "negative" result.

Table 2. Harms of overdiagnosis

Expenses (eg, prolonged hospitalization, alternative anticoagulants)
Alternative anticoagulant bleeding risks
True diagnosis missed or delayed
Procedures, transfers delayed or cancelled
"Branding": diagnosis carried forward on record and affects future care

Another major reason for the overdiagnosis epidemic is a lack of appreciation of the harm that ensues from misdiagnosis (Table 2). As with the cases above, urgent treatments are delayed, transplant lists culled, transfer to outpatient dialysis facilities blocked, and expensive alternative anticoagulants administered by those not familiar with them. Anticoagulants in general have the narrowest therapeutic index, with bleeding risks on the order of 20% in studies of alternative anticoagulants, higher in HIT-misdiagnosed patients.[47] The financial expenses that accompany even a consideration of HIT have been documented. Patients become "branded," affecting their future medical care. I and others have found that when one reviews charts coded with a diagnosis of HIT, one-half clearly do not have it (negative ELISA and/or a hematology note specifically stating there is no HIT).[42]

The future

Reduced numbers of true HIT cases continue to be anticipated on the basis of hoped-for substitutions of LMWH for UFH, replacement of heparins by NOACs in prophylaxis and treatment, emergence of more anticoagulant options, and adoption of other "avoid-heparin policies" such as the one demonstrated to be beneficial in Toronto. Available treatment agents can be highly effective when used properly. Newer approaches in preclinical testing include non-anticoagulant glycosaminoglycans, which can disrupt PF4/heparin complexes and should interrupt the prothrombotic cascade.[48] Emerging diagnostic assays offer hope for improved sensitivity, specificity, simplicity, and availability. Educational efforts remain crucial, but better diagnostic assays may ultimately have more impact on the overdiagnosis epidemic.

Case 5. An 80-year-old woman underwent coronary artery bypass grafting and bioprosthetic aortic valve insertion. She was discharged 8 days later with a platelet count of 186×10^9/L, only to present to an outside hospital on postoperative day 13 with dysarthria, hemiparesis, and an ischemic cortical infarct seen on a computed tomographic scan. Following heparin administration, her platelet count fell to 19×10^9/L. The patient was transferred back to my hospital, where a neurology stroke consultant ordered, "Begin heparin protocol." This was countermanded by the admitting cardiovascular surgeon, who wrote, "Give no heparin until approved by Hematology." Lepirudin was started. PF4/heparin antibodies were detected in high titer the next day. Remarkably, all the patient's neurologic symptoms rapidly cleared as her platelets rose quickly and warfarin transition was accomplished.

Comment. In this delayed-onset case,[27] the possibility of HIT was immediately considered by the cardiovascular surgeon because of thrombocytopenia and thrombosis in a recently exposed patient. There is hope!

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