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What's new about heparin-induced thrombocytopenia type II

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Introduction

Heparin-induced thrombocytopenia type II (HIT) is an immune-mediated, prothrombotic serious adverse event that can occur due to heparin administration. The platelet-activating immune response is triggered by the interaction of heparin with a specific platelet protein, platelet factor 4 (PF4) [1]. Antithrombosis prophylaxis is a cornerstone in the management of critically ill patients and HIT is, therefore, a major concern in intensive care unit (ICU) patients [1].

Pathophysiology

In this syndrome, PF4/heparin complexes are formed following heparin administration, triggering the release of IgG antibodies, which bind to the PF4/heparin complexes leading to clustering of the platelet Fc receptors (FcγRIIa, FcγRIIIa), platelet activation, and platelet fragmentation into prothrombotic microparticles [2, 3]. CD4 T cells play a critical role in the production of PF4/heparin antibodies [4]. Single nucleotide polymorphisms (SNPs) at the HLA-DRA have been reported to be nominally associated with HIT [5]. HIT antibodies may bind to Fc receptors on monocytes with subsequent production of significant quantities of tissue factor, thereby stimulating thrombosis [3]. Endothelial cell damage may also be implicated in the pathogenesis [6]. The PF4/heparin antibodies can also cross react with PF4 bound to platelets without the need for additional heparin, presumably because of pre-immunization by PF4-coated bacteria [7].

Clinical manifestations

HIT is a clinicopathological syndrome characterized by thrombocytopenia, with or without thrombosis. Thrombocytopenia typically occurs 5–10 days after initiation of heparin therapy [8]. However, rare variants of rapid or delayed onset HIT may occur [1]. Nonetheless, thrombocytopenia has been reported to occur in as many as 40 % of ICU patients as a result of conditions other than HIT, such as sepsis, drug-induced thrombocytopenia, autoimmune diseases, and decompensated cirrhosis [1].

Thrombotic complications occur in 30–70 % of patients with HIT [1]. These include deep vein thrombosis DVT (50 %) and pulmonary embolism (25 %) [1]. Other less common complications include myocardial infarction, cerebrovascular accidents, arterial occlusive lower limb ischemia, sinus vein thrombosis, mesenteric venous or arterial occlusion, repeated occlusion of hemodialysis filters, and skin necrosis [9].

A scoring system, the 4 Ts, has been described to evaluate the pretest probability of the syndrome on the basis of thrombocytopenia, timing of onset, thrombosis, and absence of other causes [10]. The 4 Ts score has a high negative predictive value in the general population and in ICU patients, with low scores (less than 4 points) being suitable for ruling out HIT in most clinical situations [10]. The more recently developed HIT expert probability (HEP) score has been shown to be similar to

Table 1 Available alternative anticoagulants in patients with heparin-induced thrombocytopenia type II (HIT)

Drug	Chemistry/dosage	Mechanism of action	Kinetics	Elimination	Monitoring of therapy	Advantages	Disadvantages
Danaparoid	Heparinoid; mixture of LMW sulfated glycosoaminoglycans	Direct FXa inhibitor Inhibits thromboxane B2 production and blocks antibody-induced platelet activation Little anti-FIIa activity	HL: 24 h after i.v. or s.c. administration	Renal	Anti-FXa levels Target: 0.5–0.8 U/mL (performed with danaparoid standard curve)	Oral administration possible	Long HL in the absence of specific antidote Cross reactivity with HIT antibodies (<10 % of cases) with subsequent thrombosis and persistent thrombocytopenia
Fondaparinux	Synthetic heparin analogue, pentasaccharide anticoagulant	Induces FXa inhibition by binding AT3	HL 18 h	Renal	Anti-FXa activity	Transient therapy in patients under warfarin therapy Prophylaxis and treatment of HIT after orthopedic surgery	Higher risk of bleeding than LMWH Anti-PF4/heparin antibodies are as frequent as with LMWH therapy (clinical HIT is rare probably due to short pentasaccharide chain) Interference with INR (should be considered during therapy with VKA)
Argatroban	Synthetic L-arginine derivative	Direct reversible inhibition of soluble or clot-bound thrombin	HL 50 min after i.v. administration	Hepatobiliary	aPTT 1.5–3 times that of baseline	No cross reactivity with HIT antibodies No antibody formation	HL increases up to 6 h in patients with hepatic dysfunction Possibly increased thrombotic manifestations compared to danaparoid (possibly due to short HL)
Bivalirudin	Synthetic congener of hirudin	Direct thrombin inhibitor	HL 25 min after i.v. administration	20 % urinary 80 % enzymatic proteolysis	aPTT and ACT	Anticoagulation during PCI and cardiac surgery Reduced risk of bleeding in renal/hepatic patients No cross reactivity with HIT antibodies Achieves aPTT targets faster than argatroban	No antidote (consider dialysis, hemofiltration, or plasmapheresis)

HL half-life, *VKA* vitamin K antagonists, *aPTT* activated partial thromboplastin time, *ACT* activated clotting time, *PCI* percutaneous coronary intervention, *s.c.* subcutaneous, *i.v.* intravenous

the 4 Ts in predicting the pretest probability of a diagnosis of HIT [11].

Laboratory diagnosis

Two types of assay are available to test for the presence of HIT antibodies: antigen and functional assays. Enzyme immunoassays (EIAs) are the tests most commonly used to detect HIT antibodies. EIAs are highly sensitive and can detect a broad range of PF4/heparin antibodies, including IgG, IgA, and IgM antibodies [1]. The optical densities (OD) of these assays correlate with the clinical manifestations and severity of complications of HIT [1] and an OD greater than 1 has been recently shown to increase their positive predictive value [12]. The use of IgG-specific EIAs and the application of a high-dose heparin confirmatory step may increase the specificity of these tests [13].

The particle gel immunoassay (PaGIA) is another antigen assay with intermediate sensitivity and specificity [14]. The PaGIA may be used as a rapid screening test pending the results of ELISA and functional assays [14]. The particle immunofiltration test (PIFA) is another screening test but has poor performance in terms of specificity and sensitivity [15]. A rapid lateral flow immunoassay (LFIA) has recently been reported to be highly sensitive in ruling out a diagnosis of HIT, with a positive predictive value similar to that of ELISA [16].

Functional assays, such as heparin-induced platelet activation (HIPA) and serotonin release assays (SRA), are based on in vitro activation of platelets as evidence of the presence of relevant IgG-HIT antibodies [17]. These assays have high specificity but are technically demanding, have a high turnaround time, and can be performed only by experienced laboratories [1]. The specificity of functional assays is increased by adding heparin in excess to inhibit platelet activation, and by showing Fcγ receptor IIA-dependent activation using a blocking monoclonal antibody (clone IV.3) [7].

Other evolving functional tests that may be useful in the diagnosis of HIT include whole blood impedance aggregometry (WBIA), flow cytometry, and the thrombin generation assay using a calibrated automated thrombogram (CAT) [13].

The diagnosis of HIT should be established taking into consideration clinical manifestations and laboratory evidence [1]. Only a subset of patients with positive antigen assays have platelet-activating antibodies, of which only a few patients develop thrombocytopenia and subsequent thrombosis [1]. Functional and antigen assays may be used in combination to achieve the highest performance in terms of specificity and sensitivity [18].

Management of patients with HIT

In patients with suspected (high pretest probability) or confirmed HIT, heparin administration, whether unfractionated or low molecular weight, should be discontinued and prophylactic platelet transfusions should be discouraged [19]. Alternative therapeutic anticoagulation should be initiated without delay, while awaiting confirmatory laboratory testing [19]. The choice of alternative anticoagulant should be based upon availability, associated patient comorbidities, and the expertise of the medical staff. Candidates include direct thrombin inhibitors (DTIs) and factor Xa (FXa) inhibitors (Table 1). In the presence of thrombocytopenia, vitamin K antagonist (VKA) therapy should be postponed until the platelet count has recovered, otherwise it may increase the risk of thrombosis [19].

Synthetic oligosaccharides, such as non-PF4-binding agents that are structurally modified from the fondaparinux base, are in development [20]. DTIs and FXa inhibitors may have limited efficacy because they only target inhibition of one coagulation factor [20]. Using these drugs in combination has been suggested but data are lacking on the efficacy and safety of this approach [20]. Therapeutic agents that prevent the formation of PF4/heparin complexes or promote their breakdown or that prevent platelet activation by HIT immune complexes could represent a new approach [21].

Oral thrombin and FXa inhibitors, such as dabigatran, rivaroxaban, and apixaban, are not yet approved in patients with HIT but may be effective in this context [22]. The pharmacodynamics of these agents would be of major concern in critically ill patients because of the predominance of factors that limit the bioavailability of oral medications in these patients.

Therapeutic plasma exchange can rapidly remove HIT IgG antibodies and allow administration of heparin in certain situations, such as urgent cardiac surgery [23].

Conflicts of interest The author declare that he does not have any conflict of interest in relation to the current manuscript.

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