Heparin Induced Thrombocytopenia; a diagnostic challenge

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For the diagnosis of heparin induced thrombocytopenia (HIT), a structured diagnostic work-up helps to reduce the risk of false positive results. If relying completely on laboratory results or completely on clinical features, HIT will often be wrongly assigned as being the underlying mechanism for the thrombocytopenia and possible thrombo-embolic events.[1] Clinical features and laboratory results complement each other in the diagnosis of HIT.

The important first step is a clinical probability score, by using the 4T clinical HIT probability scoring list, e.g. as published by Lo et al.[2,3] For this score, it is necessary to analyze some relevant clinical features, including: the fall in platelet counts and the chronological relationship with heparin administration, the occurrence of thrombo-embolic events and the presence of possible other causes for thrombocytopenia. HIT can be excluded for patients with a low clinical HIT probability score, and laboratory investigations should be avoided. On the other hand, laboratory investigations are necessary for patients with intermediate or high clinical HIT scores.

Laboratory HIT tests, either investigate the presence of antibodies of the IgG class against the complex platelet factor (PF)4-heparin[4,5], or the activation, via Fc-gamma-receptor IIa (FcγRIIa), of washed platelets incubated with the patients serum in the presence of heparin.[6,7] Several PF4-heparin antibody immunoglobuline G (IgG) enzyme-immunoassays (EIA) are available of which we use a PF4-heparin EIA method. Although, these EIA are commercially available, inter-laboratory variation in OD reactivity of these assays are known to occur and validation of the method before routine use is recommended.[8]

The negative predictive value of the EIA is very high (>95%) and a negative EIA result, excluding the presence of PF4-heparin specific IgG antibodies, rules out HIT. For weak positive EIA results, one can use high heparin concentrations to see if the positive reactions disappear. If not, it is less likely that the weak positive reaction is caused by PF4-heparin specific antibodies. Take care, due to variation in reactions the 'high heparin concentration' results can be difficult to interpret.[4,5,8,9]

Unfortunately, the positive predictive value of the EIA is low, ranging from ± 10% to ± 90% depending on the OD values.[4,5,8] Therefore, a positive EIA result needs confirmation in a washed platelet activation (functional) assay.[6,7] Several functional assays, e.g. the serotonin release assay (SRA)[6] and the heparin induced platelet activation assay (HIPAA)[7], can be used. In our laboratory, the HIPAA according to Greinacher et al.[7] is used. The HIPAA is positive if within several minutes aggregation of donor platelets, exposed to the optimal concentration of heparin and PF4-heparin specific antibodies of the IgG class in the patient's serum, occurs. As controls, the aggregation should not occur in the presence of high concentration of heparin, causing destruction of the PF4-heparin complexes and after blocking the binding of PF4-heparin antibodies to FcγRIIa on platelets with FcγRIIa specific monoclonal antibodies. Platelet suspensions of at least four donors should be tested in functional assays for inter-donor variability in platelet reactivity. The accuracy of the SRA and the HIPAA are comparable, with approximately 94% sensitivity and 99% specificity.[6-8,10]

If the clinical HIT probability score is high, heparin should be discontinued (take care; alternative anticoagulation is necessary) until laboratory test results are available. For an intermediate clinical score, heparin can be continued until the EIA result is available. If the EIA result is positive, heparin should be replaced until the HIPAA result is available.

You will probably notice that this EIA, HIPAA order is not optimal, but it is determined by the practicality of these tests. The different HIT diagnostic steps are shown in Table 1 and Figure 1 (see next page).

References

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Table 1: HIT diagnostic possibilities and consequences for heparin treatment.

clinical probability score	**EIA**	**HIPAA**	**Heparin treatment**	**conclusion**
low				no HIT
intermediate	negative		continue	no HIT
intermediate	positive, OD>1.5	negative	replace after EIA result, consider to restart after re-evaluation*	needs re-evaluation
intermediate	positive, OD<1.5	negative	replace after EIA result, restart after HIPAA result	no HIT
intermediate	positive	positive	replace after EIA result	HIT
high	negative		replace after clinical score, restart after EIA result	no HIT
high	positive, OD>1.5	negative	replace after clinical score, consider to restart after re-evaluation	needs re-evaluation
high	positive, OD<1.5	negative	replace after clinical score, restart after HIPAA result	no HIT
high	positive	positive	replace after clinical score	HIT

EIA: enzyme immunoassay HIPAA: Heparin induced platelet activation assay

* For re-evaluation, platelet counts after replacement of heparin can be included. If still in doubt, consider re-testing.

Figure 1: HIT laboratory cascade