One HIT Wonder!

Jeffrey Bien, MD; Luai Al Rabadi, MD;
Tom G DeLoughery, MD; Michael Heinrich, MD
Oregon Health & Sciences University

U.S. Department of Veterans Affairs
Veterans Health Administration
VA Portland Health Care System

Introduction

A patient with high pre-test probability for Heparin-Induced-Thrombocytopenia (HIT) is treated empirically for the condition despite a negative PF4 assay, later found to be a false negative.

Background

A 75 year-old woman with a history of:

- atrial fibrillation on chronic anticoagulation
- remote past deep vein thrombosis
- mitral regurgitation
- chronic heart failure
- coronary artery disease

was admitted with acute decompensation of heart failure and recurrent rapid ventricular response.
Cardiac evaluation revealed an atrial thrombus for which she was started on a continuous heparin infusion.
Unfortunately, she required urgent and complex cardiac surgery, specifically:

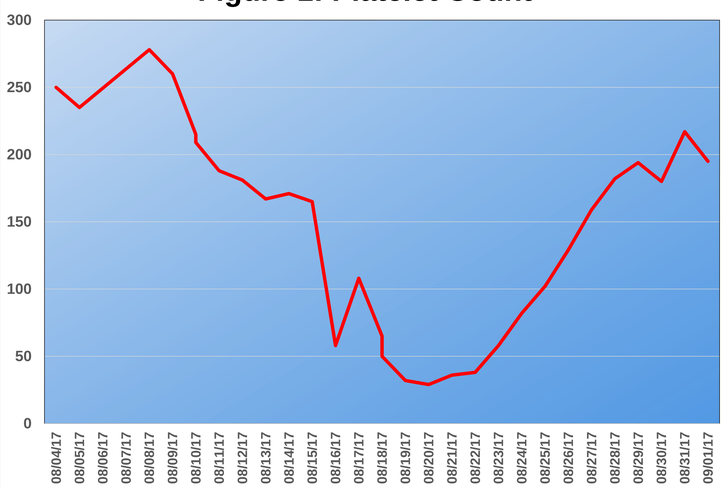
- coronary artery bypass graft
- both mitral and tricuspid valve repair
- a MAZE procedure
- left atrial appendage ligation

necessitating an intra-aortic balloon pump in place for several days.

Clinical History

The patient remained on a continuous heparin infusion for 9 days, through her cardiac surgery. Whereas platelets upon presentation were 250K/cu mm, they began to drop on day 6 of heparin infusion; reaching an eventual nadir of 29K/cu mm by day 14 of heparin exposure **(Figure 1).**

Figure 1: Platelet Count



All heparin products were stopped by day 14 of admission, at this point the patient is presumptively treated with argatroban. The platelet counts subsequently recovered.

An anti-PF4 ELISA assay curiously returned negative.

Concomitant Thromboses

Along with thrombocytopenia, the patient, was also found to have multiple thromboses **(figure 2)**:

- DVT in the internal jugular vein
- DVT in the subclavian & axillary veins
- PICC line clot
- 2x arterial line clot
- DVT of left common & deep femoral vein
- Multiple superficial venous thrombi

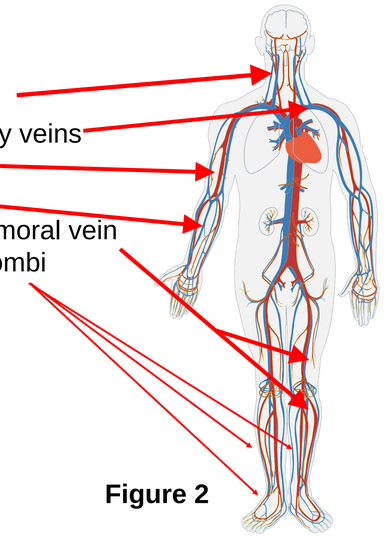


Figure 2

Characteristics of HIT

Heparin Induced Thrombocytopenia (HIT) is one of the most thrombogenic processes known.

The process results from an autoantibody complexing with the neoantigen formed by endogenous platelet factor 4 (PF4) and heparin. With the formation of the antibody-antigen complex, platelet activation, release, and aggregation occurs, causing widespread thrombosis and subsequent thrombocytopenia. Venous thromboses are common; arterial thrombi less so. Other sequelae include skin necrosis, limb/organ ischemia and death.

Evaluation is performed via a combination of a clinical score ("4T" - **Table 1** below) in conjunction with with reflex to a functional assay.

ThType equation here.e 4 T's

"T" of Interest	Finding	Patient's Score
Thrombocytopenia	Platelet count fall >50% & Platelet nadir ≥ 20	+2
Timing of Fall	Clear onset between days 5-10	+2
Thrombosis	New thromboses	+2
O**T**her Causes	No apparent other causes	+2
Total		**=8! (maximum score)**

Table 1

The performance characteristics of the 4T Score are that of high negative predictive value (99.8% [97-100]) with a "low probability" score, but poor positive predictive value (14% "intermediate" and 64% "high probability" scores).

Our patient has achieved the maximum possible score using this tool, suggestive of a high pre-test probability of HIT, though not on its own diagnostic.

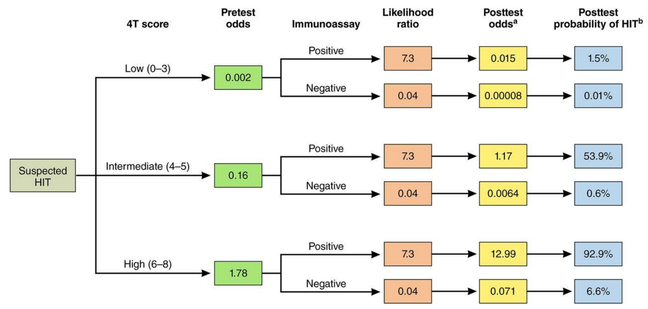
Discussion

In most clinical practice, a negative HIT ELISA (anti-PF4 testing) is sufficient to rule out HIT, due to the highly sensitive nature of the immunoassay. One such study comparing ELISA results with optical density <1.00 to serotonin release assays (SRA) ("gold standard" functional assay) found 95-99% sensitivity; this was corroborated on multiple follow up tests.

Nevertheless, given our extremely high clinical suspicion based on the 4Ts testing and other risk factors, our patient was treated presumptively for HIT before the SRA result returned. This functional assay testing in our patient confirmed a falsely negative ELISA result.

A Bayesian Approach

Based on the work of Nagler et al., hematologist Adam Cuker has proposed a Bayseian approach to diagnosing HIT based on both the 4T score and an upfront immunoassay **(Figure 3).**



Adam Cuker Blood 2016;127:522-524

Figure 3

The posttest probability of HIT in our clinical scenario is calculated to be 6.6%.

Teaching Points

- When clinical suspicion is at odds with a diagnostic test result, err on the side of caution
- There is utility in a Bayesian approach when evaluating diagnostic assay characteristics

References

- Cuker, A. (2016). Does my patient have HIT? There should be an app for that. *Blood*, *127*(5), 522–524. https://doi.org/10.1182/blood-2015-11-679811
- Cuker, A., Gimotty, P. A., Crowther, M. A., & Warkentin, T. E. (2012). Predictive value of the 4Ts scoring system for heparin-induced thrombocytopenia: a systematic review and meta-analysis. *Blood*, *120*(20), 4160–4167. https://doi.org/10.1182/blood-2012-07-443051
- Husseinzadeh, H. D., Gimotty, P. A., Pishko, A. M., Buckley, M., Warkentin, T. E., & Cuker, A. (2017). Diagnostic accuracy of IgG-specific versus polyspecific enzyme-linked immunoassays in heparin-induced thrombocytopenia: a systematic review and meta-analysis. *Journal of Thrombosis and Haemostasis: JTH*, *15*(6), 1203–1212. https://doi.org/10.1111/jth.13692
- Nagler, M., Bachmann, L. M., Cate, H. ten, & Cate-Hoek, A. ten. (2016). Diagnostic value of immunoassays for heparin-induced thrombocytopenia: a systematic review and meta-analysis. *Blood*, *127*(5), 546–557. https://doi.org/10.1182/blood-2015-07-661215
- Smythe, M. A., Koerber, J. M., & Mattson, J. C. (2007). The incidence of recognized heparin-induced thrombocytopenia in a large, tertiary care teaching hospital. *Chest*, *131*(6), 1644–1649. https://doi.org/10.1378/chest.06-2109
- Warkentin, T. E., Sheppard, J. I., Moore, J. C., Sigouin, C. S., & Kelton, J. G. (2008). Quantitative interpretation of optical density measurements using PF4-dependent enzyme-immunoassays. *Journal of Thrombosis and Haemostasis: JTH*, *6*(8), 1304–1312. https://doi.org/10.1111/j.1538-7836.2008.03025.x