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THROMBOSIS AND HEMOSTASIS

Comment on Marchetti et al, page 1171

Diagnosing HIT: the need for speed

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In this issue of *Blood*, Marchetti et al describe a novel diagnostic algorithm for heparin-induced thrombocytopenia (HIT) based on the 4Ts score and 2 rapid immunoassays (IAs) that correctly classified >95% of patients within a 60-minute analytical window.[1]

HIT is a high-stakes diagnosis that must be made promptly and accurately. Failure to suspend heparin and initiate a nonheparin anticoagulant in patients with HIT is associated with an initial 6.1% daily rate of thrombosis, which may be limb- or life-threatening.[2] On the other hand, unnecessary treatment with a nonheparin anticoagulant in patients without HIT is costly and is associated with an incidence of major bleeding as high as 44%.[3]

The 2018 American Society of Hematology (ASH) HIT guidelines recommend a diagnostic algorithm for HIT based on the 4Ts score and the antiplatelet factor 4/heparin enzyme–linked immunosorbent assay (ELISA). HIT is excluded in patients with a low probability 4Ts score, whereas ELISA testing is advised in patients with an intermediate- or high-probability 4Ts score.[4] An important drawback of this algorithm is the time it takes. Because the ELISA has an analytic turnaround time (TAT) of 3 to 4 hours and is run in batch no more than once per day at most centers, same-day results are often not available. As a result, patients with intermediate- and high-probability 4Ts scores, many of whom do not have HIT, must be treated empirically with a nonheparin anticoagulant while awaiting test results.[5] In recognition of this limitation, the ASH guideline identified "integration of emerging rapid immunoassays into diagnostic algorithms" as a pressing research priority.[4]

Marchetti et al took this imperative to heart. Using Bayesian analysis like other HIT investigators before them,[5-7] they developed a diagnostic algorithm for HIT based on the 4Ts score, a rapid chemiluminescent IA (CLIA), and a rapid particle-gel IA (PaGIA) in 2 derivation cohorts from their center in Lausanne, Switzerland. They subsequently validated the algorithm in a separate, prospective cohort of consecutive patients with suspected HIT at the same institution. They used the heparin-induced platelet aggregation (HIPA) assay as the reference standard for HIT.[1]

The algorithm was highly effective in classifying HIT status. Of the 687 patients in the validation cohort, 655 (95.3%) were classified correctly by the algorithm. Only 12 patients (1.7%) were misclassified. All 12 of these patients tested negative by HIPA, but were classified as having HIT by the algorithm (false-positives). Importantly, there were no false-negatives. The remaining 20 patients (2.9%) were not classifiable by the algorithm and required additional testing to clarify HIT status.[1]

So how does the diagnostic algorithm of Marchetti et al stack up against the algorithm espoused in the ASH guidelines?[4] To address this question, we modeled the diagnostic accuracy of both algorithms in a hypothetical sample of 1000 patients with suspected HIT (see table). We assumed a prevalence of HIT of 7.9%, consistent with the prevalence observed in the validation cohort of Marchetti et al. As shown (see table), the Marchetti algorithm performed at least as well as the ASH algorithm. It correctly classified all 79 patients with HIT and 95.4% of patients without HIT, whereas the ASH algorithm correctly classified only 72 of the patients with HIT (91.1%) and 93.2% of patients without HIT. All told, the Marchetti algorithm misclassified 42 patients (4.2%), whereas the ASH algorithm misclassified 70 patients (7.0%).

Although superior diagnostic accuracy is an important plus of the Marchetti algorithm, it offers another key advantage

Test accuracy per 1000 patients with suspected HIT for 2 diagnostic algorithms

	ASH algorithm	Marchetti algorithm
Tests	4Ts score; IgG-specific ELISA (low threshold)	4Ts score; CLIA; PaGIA
True-positive	72	79
False-negative	7	0
False-positive	63	42
True-negative	858	879

Test accuracy is modeled on 1000 hypothetical patients with suspected HIT. We assumed a disease prevalence of 7.9%, the same prevalence as observed in the validation cohort of Marchetti et al. For the Marchetti algorithm, we assumed that the 2.9% of patients determined to be unclassifiable by the algorithm would be treated empirically for HIT; those patients ultimately found to have HIT by the reference standard were therefore classified as true-positives whereas those ultimately found not to have HIT were classified as false-positives. For the ASH algorithm, we used a sensitivity and specificity of 0.921 and 0.542, respectively, for the 4Ts score and 0.98 and 0.85, respectively, for the immunoglobulin G (IgG)–specific ELISA, the same values that were used in the ASH 2018 guideline on HIT.[4]

compared with the ASH algorithm: timely classification. The Marchetti algorithm relies on 2 rapid IAs, each with an analytical TAT of ~30 minutes. Thus, almost all patients can be classified by the algorithm within a 1-hour analytical window (apart from the 2.9% of patients who could not be classified), sparing the need for unnecessary treatment with a nonheparin anticoagulant in large numbers of HIT-negative patients. In contrast, the ASH algorithm relies on the ELISA and its slower TAT to classify patients with an intermediate- or high-probability 4Ts score. In our model, 422 HIT-negative patients had an intermediate- or high-probability 4Ts score and would have potentially required empiric treatment of HIT for some amount of time under the ASH algorithm while awaiting ELISA testing.

The promising results of Marchetti et al notwithstanding, we believe their algorithm is not ready for broad adoption quite yet. First, all patients were recruited from, and all CLIA and PaGIA testing was performed in, a single center. The authors plan a multicenter trial to determine whether their findings are generalizable to other institutions and other clinical laboratories, a crucial step given challenges in interlaboratory agreement observed with other HIT assays.[8] Second, the HIPA may be an imperfect reference standard. Indeed, a small percentage of patients in the validation cohort had a clinical course and IA profile strongly suggestive of HIT even though they were classified as HIT-negative by HIPA. An ideal reference standard would incorporate clinical adjudication in addition to laboratory assessment.[9] Third, the authors did not apply the HIPA to all subjects, which could introduce verification and misclassification bias. Fourth, the algorithm is very complex and is unlikely to be usable unless it is built into an electronic platform such as smartphones or the electronic health record. Finally, the CLIA and PaGIA are not available in all jurisdictions. For example, the PaGIA is not marketed in the United States.

Identification and management of patients with suspected HIT is a multistep pathway involving clinical recognition, ordering HIT laboratory testing, performing phlebotomy, transporting the sample to the laboratory, running the test(s) (ie, analytical TAT), providing the results to the clinical team, ordering a nonheparin anticoagulant, delivering the medication to the patient's unit, and, finally, administering the medication. There is potential for delay at any of these steps. The Marchetti algorithm holds great promise for reducing analytical TAT. However, in a disease like HIT for which there is a need for speed, we must continue to focus on minimizing delays at all steps along the pathway.

Conflict-of-interest disclosure: A.C. has served as a consultant for Synergy; institutional research support has been received on A.C.'s behalf from Alexion, Bayer, Novo Nordisk, Pfizer, Sanofi, Spark, and Takeda. D.B.C. has received relevant research support from Alexion and Aplagon, and served as a consultant to Rigel, Dova, and CSL Behring. ■

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TRANSPLANTATION

Comment on Ghannam et al, page 1185

The double-edged sword of AlloHCT for SCD

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In this issue of *Blood*, Ghannam and colleagues report on the development of myeloid malignancy in 3 individuals with homozygous sickle cell disease (SCD).[1] This represented a total of 4% (3 of 76) of their cohort transplanted for SCD from 2004 to 2018. Participants with severe SCD had 4 common features: (1) before transplant, clonal hematopoiesis of indeterminate potential (CHIP)-related mutations were detected in the blood of both individuals assessed; (2) all received nonmyeloablative, allogeneic hematopoietic cell transplant (AlloHCT) using total body irradiation (TBI) (300 to 400 cGy) and alemtuzumab-based conditioning; (3) participants received mobilized peripheral blood stem cells; (4) the myeloid malignancy occurred 2 to 5 years after a failed allograft.

In 2 large population studies, SCD patients, independent of AlloHCT, have an increased risk of developing hematology malignancies.[2,3] Others have reported no increased incidence of myeloid malignancies associated with hydroxyurea therapy in SCD. Plausible underlying mechanisms for an increased risk of hematology