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Letters to Blood

TO THE EDITOR:

Managing antithrombotic therapy in immune thrombocytopenia: development of the TH2 risk assessment score

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The management of anticoagulation in patients with immune thrombocytopenia (ITP) is challenging. This difficult clinical scenario is becoming increasingly common as the ITP population ages[1] and indications for anticoagulation broaden.[2] The clinical challenge stems from the fact that a low platelet count increases the risk of bleeding but does not protect against thrombosis. In addition, the risk of thrombosis may be heightened by ITP itself[3-5] or its treatments.[6-9] In this report, we describe how anticoagulation was managed in ITP patients with platelets counts $<50 \times 10^9$/L and whether thrombotic or bleeding events ensued. To help guide treatment decisions regarding anticoagulation, we developed the Thrombosis and Thrombocytopenia (TH2) risk assessment score and applied it to this cohort.

Patients were identified from the McMaster ITP Registry, a prospective, longitudinal observation study of consecutive adults referred for thrombocytopenia.[10] ITP was defined per established guidelines.[11] We identified all ITP patients with platelet counts $<50 \times 10^9$/L who were receiving anticoagulation for any indication. The decision to continue or discontinue anticoagulation was left to the treating hematologist. Bleeding assessments were done prospectively.[12] We defined major bleeding as grade 2 bleeding that did not involve the skin. This study was approved by the Hamilton Integrated Research Ethics Board.

Between 2010 and 2017, 314 patients with ITP were enrolled in the registry, including 13 (29.5%) who were receiving anticoagulation and had a platelet count $<50 \times 10^9$/L. The median age was 74 years, interquartile range, 64-81; and 53.8% were female. Indications for anticoagulation were atrial fibrillation ($n = 6$) or venous thrombosis ($n = 7$). Four patients were also receiving antiplatelet agents. Median follow-up was 9 months (IQR, 4.5-24) during which time there were 41 patient encounters, representing opportunities for clinicians to withhold or continue anticoagulation. Treatment decisions and subsequent clinical outcomes were available for 32 encounters (78.0%).

Anticoagulation was withheld for 10 patients during 22 encounters (median platelet count, 14×10^9/L [range, 1-40]; major bleeding was present at 5/22 encounters; and additional ITP treatments were administered at 17/22 encounters). Among the 10 patients whose anticoagulation was interrupted, 6 (60.0%) developed new thrombotic events, 2 of which were fatal (Table 1). Three patients developed thrombotic events despite subsequently resuming anticoagulation for a median of 7 days (range, 3-35 days). Anticoagulation was continued for 3 patients during 10 patient encounters (median platelet count, 38×10^9/L [range, 7-49 $\times$ 10^9/L], major bleeding was present at 2/10 encounters; and additional ITP treatments were administered at 6/10 encounters). In this group, no subsequent major bleeds occurred, and 1 new thrombotic event occurred in a patient with metastatic squamous cell cancer despite continuation of warfarin. Information on anticoagulation treatment decisions was not recorded for 9 patient encounters (median platelet count, 27×10^9/L; range, 12-49). No subsequent thrombotic or major bleeding events were reported in that group.

We developed the TH2 score based on a literature review and a review of existing thrombosis and bleeding tools (Table 1).[13,14] The TH2 score includes 2 thrombosis items and 2 bleeding items. The thrombosis items are: (1) high thrombotic risk (atrial fibrillation with congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke, vascular disease, age 65 to 74 years, and sex category >5,[13] unprovoked, recurrent, or cancer-associated thrombosis,[15] or antiphospholipid antibody syndrome); and (2) administration of ITP therapies with a known thrombotic risk including intravenous immune globulin[6] or thrombopoietin receptor agonists in the previous 14 days[7,8]; or splenectomy in the previous 30 days.[9] Each thrombosis item is assigned a score of +1. The bleeding items for the TH2 score are: (1) platelet count $<20 \times 10^9$/L and (2) major bleeding at the time of the clinical encounter.[16] Each bleeding item is assigned a score of −1. An overall score that is nil or positive indicates a net increased risk of thrombosis; an overall score that is negative indicates a net increased risk of bleeding. Age was not included in the risk score because it is associated with an increase in both the risk of thrombosis[3,5] and bleeding.[16,17]

We retrospectively applied the TH2 score to the cohort of ITP patients with platelets $<50 \times 10^9$/L while receiving anticoagulation ($n = 13$). The TH2 score was positive or nil at 27/32 encounters (84%). Repeat scores measured once the platelet count increased $>50 \times 10^9$/L after a median 11.5 days (range, 2-129 days) were positive or nil at 32/32 encounters (100%). For all 7 new thrombotic events, the preceding TH2 score was either positive or nil (Table 2).

Table 1. TH2 score with 2 thrombotic risk factors and 2 bleeding risk factors for patients with thrombocytopenia and an indication for antithrombotic therapy

Risk assessment	Score
Thrombotic risk factors	
High thrombotic risk*	+1
Recent ITP treatment†	+1
Bleeding risk factors	
Platelets $<20 \times 10^9$/L	−1
Major bleed (excluding skin) at presentation‡	−1
Overall score	Nil or positive (excess thrombotic risk); negative (excess bleeding risk)

*Atrial fibrillation congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke, vascular disease, age 65 to 74 years, and sex category >5; unprovoked, recurrent, or cancer-associated thrombosis; antiphospholipid antibody syndrome.

†Intravenous immune globulin within 2 weeks or thrombopoietin receptor agonist or splenectomy within 4 weeks.

‡Grade 2 by the ITP Bleeding Score.[12]

The TH2 score was designed to summarize the net risk of thrombosis or bleeding in patients with thrombocytopenia who had a separate indication for anticoagulation, and to help clinicians make an informed decision regarding the use of anticoagulation. Acknowledging the lack of precision, the TH2 score provides an overall direction of risk (positive/nil, indicating a net increased risk of thrombosis; negative, indicating a net increased risk of bleeding) rather than a quantitative risk estimate. When we applied the score retrospectively to a group of patients with ITP, we found that the TH2 score was useful in identifying patients who subsequently developed thrombosis. We also found that the TH2 scores changed quickly over time (days). Our data suggest that many patients had an increased thrombotic risk and that risk assessments should be reevaluated frequently as ITP treatments are administered and the platelet count increases. Overall, for patients with ITP, early resumption of anticoagulation should be considered to mitigate subsequent thrombotic risk.

This study emphasizes the challenge that physicians face when managing ITP patients who require anticoagulation. Little evidence is available to support the decision to withhold or to continue anticoagulation in this population. The TH2 score is a helpful tool to evaluate patients with uncertain bleeding or thrombotic risk. A common example is patients with chronic ITP and a separate indication for anticoagulation who have stable platelet count levels $<50 \times 10^9$/L while receiving a thrombopoietin receptor agonist medication. According to the TH2 score, most of these patients would be well-served to remain on anticoagulation.

Strengths of this study were the use of data from a prospective registry in which all patients were managed by 2 experienced hematologists and bleeding was measured prospectively using a validated ITP bleeding score.[12] Limitations were the retrospective single-center design and the small number patients. Our study did not evaluate other potential biomarkers that could influence the bleeding risk (eg, platelet function tests, immature platelet fraction, platelet autoantibodies[18,19]). Validation of the TH2 score is required in other populations of thrombocytopenic patients, including patients with chemotherapy-induced thrombocytopenia, because there may be differences in platelet reactivity. In addition to withholding or continuing anticoagulation, future studies should consider dose reductions similar to what has been proposed for patients with cancer.[20] The small sample size precluded the use of goodness-of-it models to correlate the risk score with clinical outcomes as has been done with large data sets in atrial fibrillation.[13] Additional validation studies of the TH2 score will require a larger sample to apply established methodology for risk prediction models.[21,22]

Table 2. New thromboembolic events (n = 7) in patients with ITP who developed a platelet count $<50 \times 10^9$/L while receiving AC and their TH2 scores

Patient	Initial TH2 score	AC decision after initial encounter	Repeat TH2 score*	AC decision after repeat encounter	Thrombotic event
1	Negative	Withheld	Positive	Withheld	Fatal ischemic stroke
2	0	Withheld	Positive	Withheld	Fatal PE
3	0	Withheld	Positive	Resumed	Ischemic stroke†
4	Negative	Withheld	Positive	Withheld	Iliac artery thrombus
5	Negative	Continued	0	NA	Arterial and venous limb thrombus‡
6	Negative	Withheld	Positive	Resumed	Arterial limb thrombus
7	0	Withheld	Positive	Resumed	Ischemic stroke†

PE, pulmonary embolism.

*Repeat TH2 score once platelet count improved $>50 \times 10^9$/L.

†Subtherapeutic international normalized ratio after resumption of warfarin.

‡Cancer-associated thrombosis on warfarin (metastatic squamous cell cancer).

The results of our study suggest that the risk of thrombosis is high in patients with ITP who have a separate indication for anticoagulation, especially after ITP therapies are administered and the severe thrombocytopenia improves. Early resumption of anticoagulation should be considered in this population. Future multicenter studies are needed to validate the TH2 risk score and to establish its clinical utility in practice.

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Authorship

Contribution: A.K.B. designed and established the study, collected and analyzed data, and wrote the manuscript; D.M.A. designed and established the study, supervised the research, and edited the manuscript; J.G.K. helped conceive the study and edited the manuscript; and all authors reviewed and approved the final version of the manuscript.

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