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Initial Management of Immune Thrombocytopenia in Adults Based on Risk Stratification

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Abstract

Patients with immune thrombocytopenia (ITP) have wide spectrum of disease severity, and bleeding risk even at similar platelet counts. Hence, additional clinical and laboratory factors may be considered in the evaluation of bleeding risk in ITP. Risk stratification based on predicted bleeding risk may help to identify high-risk patients and guide the initial management of ITP in adults requiring treatment. Recent evidences support the use of high dose dexamethasone therapy over prednisone in the initial management of ITP because of improved initial response rates, shorter median time to response and better safety profile. A risk-stratified approach to management of ITP is hoped to reduce bleeding complications in high-risk patients, however, the outcomes of such management approach needs to be studied prospectively. Additionally, whether therapy intensification or combination of dual therapy such as intravenous immunoglobulin or rituximab in combination with dexamethasone can reduce bleeding complications in high-risk ITP should be studied in the future.

Keywords

Immune thrombocytopenia; Bleeding risk; Thromboelastography; Steroids; Dexamethasone

Introduction

Immune thrombocytopenia (ITP) is an ancient disease but still poorly understood. Thought to be a disease of platelet production in the historical past¹, better understanding of the disease has elaborated the antibody-mediated suppression of normal thrombopoiesis coupled with peripheral platelet destruction². ITP generally has a benign course but fatal bleeding has been noted. In the systematic review by Neunert et al³, the incidence of bleeding was

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9.6% for severe non-intracranial bleeding and 1.4% for intracranial hemorrhage in adults with ITP. Considering the incidence and prevalence of the disease, the population at risk is not trivial. Although physicians treat most patients with steroids initially in a similar fashion, an individualized risk assessment should preferably guide various aspects of their management. In this review, we discuss the utility of various clinical and laboratory parameters to identify high-risk patients and the optimal initial management aimed to reduce the risk of bleeding.

Estimating the Risk of Bleeding

Estimating bleeding risk in ITP is challenging due to heterogeneous nature of the disease, poor correlation with platelet count and variable platelet function at similar counts⁴. Hence, incorporating various clues presented in the history and physical examination, bleeding risk scores along with laboratory tests beyond platelet count could be helpful (**Table 1**).

Clinical symptoms and signs

Multiple retrospective studies in ITP have assessed the value of several clinical symptoms and signs that could predict an increased risk of bleeding. In 1991, Cortelazzo et al. reported older age (>60 years), prior history of bleeding and bleeding symptoms at presentation to correlate with a higher risk of bleeding⁵. Similar correlation with age and bleeding risk was reported by Cohen et al with an estimated risk of bleeding of 0.4% versus 13% for patients aged <40 years and >60 years, respectively⁶. A long-term follow-up study with median follow-up time of 121 months (range 7–434 months) by Vianelli et al⁷, however, failed to confirm any correlation between older age and increased bleeding risk; the risk of fatal bleeding of <0.3% in their series was lower than the risk of 4–5% historically reported in most of the other studies. Of note, all these studies included mixed populations including a majority of patients with chronic ITP. The chronicity of ITP may also correlate with the risk of bleeding. Neunert et al. demonstrated a higher risk of bleeding, especially intracranial hemorrhage in adults, with chronic ITP³.

Oral mucosal bleeding or ‘wet purpura’ has been conventionally considered an alarm sign by most experts and is given a higher weightage in bleeding risk estimation scores⁸. Additionally, a recent use of any anticoagulant or antiplatelet agent, any underlying coagulopathy, liver or kidney disease may also correlate with an increased risk of bleeding. These clinical data are easy to obtain and may provide useful information.

Integrated bleeding scores

Different groups have formulated bleeding scores in attempts to estimate individual’s risk of bleeding. In 2002, Godeau et al. developed one of the early bleeding scores to estimate the severity of bleeding⁹. They assigned points for clinical bleeding manifestations (cutaneous purpura, oral & nasal mucosal bleeding, macroscopic hematuria, overt gastrointestinal hemorrhage, major menorrhagia and/or metrorrhagia, bleeding on the fundus oculi) and age over 60 years. This scoring system was subsequently modified to capture the risk of major bleeding; one of the modifications included assigning greater weightage for patient’s age⁸. Page et al proposed an ITP-specific bleeding scale comprising of 11 site-specific grading of

bleeding¹⁰. Recognizing the need for uniform reporting of bleeding, International Working Group on ITP proposed a consensus-based ITP specific bleeding assessment tool to standardize description of bleeding manifestations in ITP¹¹. It suggested the concept of 'SMOG' where bleeding manifestations were grouped into three major domains: skin (S), visible mucosae (M), and organs (O), with gradation of severity (G) from 0 to 5. While this system is advantageous in terms of being detailed and extensive, the time and effort it requires along with the descriptive rather than predictive nature may limit its clinical utility. From this perspective, the scoring systems used by Godeau and Page may be advantageous, and the latter has been validated in subsequent studies³. Nevertheless, consistent adoption of any of these scoring systems should give an estimate of the bleeding risk over time, and warn the clinician when the risk increases significantly.

Laboratory assessment

Platelet count does not correlate well with a predictable bleeding risk, especially in patients with severe thrombocytopenia¹². Hence, the results of additional tests could be incorporated to improve the accuracy of estimating the risk of bleeding. Other tests that may help to predict the risk of bleeding include mean platelet volume, immature platelet fraction, and absolute immature platelet fraction; many centers performing some of these tests routinely. Additionally, thromboelastography (TEG) and flow cytometry to assess platelet function may be valuable.

A high mean platelet volume reflects giant, immature platelets in circulation. In 1982, Eldor et al. investigated 175 patients with platelet counts below $20 \times 10^9/L$ and reported that mean platelet volume was significantly lower in patients with versus without bleeding¹³. A mean platelet volume of 6.4 fl or higher was associated with a lower risk of bleeding. A study evaluating gastrointestinal bleeding in Henoch-Schonlein purpura also found similar results¹⁴. Subsequent larger studies, however, did not confirm a correlation between mean platelet volume and bleeding^{10,12}. Leader et al. performed a review of multiple studies and suggested that mean platelet volume may be useful to predict bleeding in the right clinical setting but its variability in measurements and lack of consistent cutoff may limit its utility^{15,15}.

Immature platelets are the platelet analogue of reticulocytes. Newly released immature platelets contain dense RNA, and flow cytometry is able to measure this subset relative to total platelet count, with good reliability and reproducibility¹⁶. Prospective studies have shown that absolute immature platelet fraction compared to platelet count, correlates better with bleeding, especially in patients with severe thrombocytopenia^{12,17}. This is of significant value since the measurement of immature platelet fraction is readily available in many centers.

TEG has been widely used in surgery and trauma to assess bleeding risk in real time. In ITP, clot firmness parameters on TEG such as Maximum Clot Firmness or Maximum Amplitude correlate with bleeding better than platelet count in patients with severe thrombocytopenia^{12,17,18}. Maximum Amplitude has been demonstrated to be an independent predictor of the risk of bleeding¹⁷. Hence, TEG could be valuable especially when a clinician faces uncertainty about the risk of bleeding. It could also potentially guide

decisions regarding hospitalization or intensification of therapy in addition to steroids due to high estimated bleeding risk.

Management

In ITP, treatment is considered in adults when the platelet count is less than 30,000/mm³ or when bleeding symptoms are present. In these situations, further decisions such as the choice and intensity of treatment may preferably be individualized based on the predicted risk of bleeding.

When to hospitalize?

The indications and benefits of hospitalization have not been studied in patients with ITP; however, hospitalization of patients at high risk of bleeding may allow close monitoring and early interventions in case of a bleeding. The 1996 American Society of Hematology guidelines on management of ITP considered hospitalization appropriate in patients with platelet count less than 20,000/mm³ and mucosal bleeding. The role of hospitalization is unclear in patients with severe thrombocytopenia but with minor purpura or no symptoms^{19,20}. In such situations, risk stratification based on the aforementioned clinical and laboratory parameters may allow to identify patients at a higher risk of bleeding and inform decisions regarding hospitalization or close outpatient monitoring.

Choice of initial therapy

Historically, prednisone has been the widely accepted standard of care in a newly diagnosed patient with ITP who does not warrant aggressive rise in platelet counts due to bleeding. Initial responses to prednisone therapy range around 50–60% but long-term remission rates are generally less than 30%^{21–23}. The duration of treatment lasts several weeks to months, thus resulting in a risk of long-term steroid toxicities. In this context, short courses of high dose dexamethasone (HD-DXM) given usually as a pulse dosing of 40 mg daily for 4 days, has emerged as a better option. Cheng et al. reported the first prospective study evaluating HD-DXM in first-line management of ITP²⁴, which resulted in an initial response of 85% after a single course. Approximately half of patients who had an initial response maintained a platelet count of more than 50,000/mm³ without further treatment during a follow-up of 2 to 5 years. Subsequently, Wei et al. performed a randomized trial to compare the outcomes of 1 or 2 cycles of HD-DXM to prednisone²⁵. HD-DXM resulted in a higher overall initial responses (82.1% vs 67.4%, $P = .044$) and complete responses (50.5% vs 26.8%, $P = .001$), a shorter median time to response (3 vs. 6 days, $p < 0.001$), a lower risk of bleeding and similar long-term sustained responses. A recent meta-analysis of nine randomized trials²⁶ ($n=1138$) confirmed similar findings and demonstrated a lower risk of toxicities with HD-DXM.

Ideal number of cycles of High Dose Dexamethasone

Various prospective studies have used 1–6 cycles of High dose Dexamethasone as initial therapy of ITP. Cycles have been repeated as early as after 10–14 days or repeated after 28 days of the prior cycle. Mazuconi et al determined a higher response rate with 3 cycles of HD-DXM, compared to 2 cycles²⁷. However, the response rates reported in the randomized

trial with 1–2 cycles of HD-DXM²⁴ was similar to those reported by Mazuconi et al^{26,27}. Hence, an additional cycle of HD-DXM repeated at 10 days may be a reasonable first-line strategy based on presently available evidence.

Predicting the risk of steroid failure

Though the initial response rates are better with high dose dexamethasone therapy, a significant proportion of patients may relapse and become steroid refractory²⁷. Earlier identification of patients who are unlikely to benefit from repeated courses of HD-DXM might allow use of more effective therapy and avoidance of toxicities from further doses of steroids. In the trial by Wei et al.²⁵, patients who did not respond to the first cycle of HD-DXM by 10 days received an additional cycle at day 10. Persistent non-responders exited the study to receive other therapies. Cheng et al also demonstrated that a low platelet count at day 10 was associated with a lack of response to further therapy with steroid and a higher risk of relapse within 2 months²⁴. These factors might be worth considering while making the decision to move to second line therapy such as rituximab, avoiding further steroid exposure without significant benefit.

Conclusion

In an era of personalized medicine, ITP is no exception particularly given its varied spectrum of disease severity, bleeding risk and response to therapy²⁸. Various factors discussed previously can help to risk stratify and guide the initial management of ITP in adults requiring treatment. A risk-stratified approach to management of ITP is hoped to reduce complications in high-risk patients, while saving costs and hospitalization in low-risk patients, however, prospective clinical trials are warranted to study the outcomes of such risk stratified management approaches.

We have proposed an algorithm describing a tailored approach for ITP management in Figure 1. Bleeding risk can be used to determine if patients can be managed as an outpatient or an inpatient. Patients with high bleeding risk may be hospitalized and managed with HD-DXM and additional medications including considerations for intravenous globulin and/or anti-D, while those with low risk can be managed in outpatient setting with HD DXM. TEG may be used to direct therapy for intermediate risk group. Additional therapies including rituximab, transfusion support, thrombopoietin-mimetics, and splenectomy may be needed in cases not responding to HD-DXM. While the algorithm is based on established risk factors for bleeding in ITP, the benefit of algorithm in reducing the risk of bleeding is unclear and needs prospective confirmation.

In future, a prospective observational study can be designed to examine different clinical predictors of bleeding in all patients with ITP. Variables significantly associated with bleeding risk, based on multivariate analysis, can be incorporated in a predictive model. Each predictor may be graded to calculate a score and stratify the risk of bleeding. Multinational multi-institutional collaboration will be needed for a large study size. Additionally, future clinical trials should address whether therapy intensification or combination of dual therapy such as intravenous globulin or rituximab in combination with dexamethasone can reduce bleeding complications in high-risk ITP.

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Multiple choice questions

Question: Platelets counts correlate well with the risk of bleeding in ITP. True or False?

Answer: False

Question: Different scoring system may be used to estimate the risk and severity of bleeding in ITP. True or False?

Answer: True

Q. In ITP, treatment is considered in adults when the platelet count is less than 30,000/mm³ or when bleeding symptoms are present. True or False?

A. True

Q. High dose dexamethasone is the preferred initial choice of therapy for ITP in most patients. True or False?

A. True

Q. Long duration of treatment with prednisone is better than pulse dosing of high dose dexamethasone for 4 days. True or False?

A. False

Main messages

- Clinical and laboratory findings along with bleeding scoring systems are helpful in estimating the bleeding risk in patients with ITP.
- Treatment of ITP should be initiated when the platelet count is less than 30,000/mm³ or when bleeding symptoms are present.
- High dose dexamethasone is the initial choice of treatment for ITP.

Current research questions

- How do you risk-stratify patients to guide initial management of ITP?
- When do you start treatment for ITP?
- What are the initial treatment options for ITP?

Figure 1.
Proposed algorithm for initial management of ITP in adults based on risk stratification

Table 1:

Correlation of Clinical & Laboratory Variables with Risk of Bleeding in ITP

Clinical/Laboratory Findings	Risk of Bleeding	Comments
Bleeding symptoms present versus absent at diagnosis ⁵	18% vs. 0.8% per patient-year	Incidence rates of major bleeding Retrospective study
History of previous hemorrhage versus none ⁵	OR 27.5, p<0.005	Retrospective study
Age in years: ⁵ 40–60 vs. <40 > 60 vs. <40	OR 2.8, p = Not significant OR 28.9, p<0.01	Retrospective study
Absolute immature platelet fraction ¹²	r = – 0.34 to 0.60, p<0.005	Moderate to strong inverse correlation with bleeding scores Prospective study
Maximum amplitude/maximum clot firmness on thromboelastography ¹²	r = – 0.26–0.28, p<0.05	Moderate inverse correlation with bleeding scores when platelet count <60,000/mm ³ Prospective study

OR – Odds Ratio; r - Spearman's rank correlation coefficient