Initial management of immune thrombocytopaenia in adults based on risk stratification

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ABSTRACT

Patients with immune thrombocytopaenia (ITP) have a 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 evidence supports 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 need 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.

INTRODUCTION

Immune thrombocytopaenia (ITP) is an ancient disease but still poorly understood. Thought to be a disease of platelet production in the past,[1] better understanding of the disease has elaborated the antibody-mediated suppression of normal thrombopoiesis coupled with peripheral platelet destruction.[2] ITP generally has a benign course, but fatal bleeding has been noted. In the systematic review by Neunert *et al*,[3] the incidence of bleeding was 9.6% for severe non-intracranial bleeding and 1.4% for intracranial haemorrhage 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 individualised 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 the heterogeneous nature of the disease, poor correlation with platelet count and variable platelet function at similar counts.[4] 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*[5] reported older age (>60 years), history of bleeding and bleeding symptoms at presentation to correlate with a higher risk of bleeding. Similar correlation with age and bleeding risk was reported by Cohen *et al*,[6] with an estimated risk of bleeding of 0.4% vs 13% for patients aged <40 years and >60 years, respectively. A long-term follow-up study with a median follow-up time of 121 months (range 7–434 months) by Vianelli *et al*,[7] 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*[3] demonstrated a higher risk of bleeding, especially intracranial haemorrhage in adults, with chronic ITP.

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 scores.[8] Additionally, a recent use of any anticoagulant or antiplatelet agent, any underlying coagulopathy, and 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 an individual's risk of bleeding. In 2002, Godeau *et al*[9] developed one of the early bleeding scores to estimate the severity of bleeding. They assigned points for clinical bleeding manifestations (cutaneous purpura, oral and nasal mucosal bleeding, macroscopic haematuria, overt gastrointestinal haemorrhage, 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 patients' age.[8] Page *et al*[10] proposed an ITP-specific bleeding scale comprising 11 site-specific grading of bleeding. Recognising the need for uniform reporting of bleeding, the International Working Group on ITP proposed a consensus-based, ITP-specific bleeding assessment tool to standardise

Table 1 Correlation of clinical and laboratory variables with risk of bleeding in ITP

Clinical/Laboratory findings	Risk of bleeding	Comments
Bleeding symptoms present vs absent at diagnosis[5]	18% vs 0.8% per patient-year	Incidence rates of major bleeding. Retrospective study.
History of haemorrhage vs 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 to 0.28, p<0.05	Moderate inverse correlation with bleeding scores when platelet count <60 000/mm^3. Prospective study.

ITP, immune thrombocytopaenia; r, Spearman's rank correlation coefficient.

description of bleeding manifestations in ITP.[11] 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 *et al*[9] and Page *et al*[10] may be advantageous, and the latter has been validated in subsequent studies.[3] 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 thrombocytopaenia.[12] 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 centres perform 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*[13] investigated 175 patients with platelet counts below 20×10^9/L and reported that the mean platelet volume was significantly lower in patients with versus without bleeding. 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 results.[14] Subsequent larger studies, however, did not confirm a correlation between mean platelet volume and bleeding.[10 12] Leader *et al*[15] 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 cut-off may limit its utility.

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 reproducibility.[16] Prospective studies have shown that absolute immature platelet fraction compared with platelet count correlates better with bleeding, especially in patients with severe thrombocytopaenia.[12 17] This is of significant value since the measurement of immature platelet fraction is readily available in many centres.

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 thrombocytopaenia.[12 17 18] Maximum amplitude has been demonstrated to be an independent predictor of the risk of bleeding.[17] Hence, TEG could be valuable especially when a clinician faces uncertainty about the risk of bleeding. It could also potentially guide decisions regarding hospitalisation 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 x 10^9/L or when bleeding symptoms are present. In these situations, further decisions such as the choice and intensity of treatment may preferably be individualised based on the predicted risk of bleeding.

When to hospitalise?

The indications and benefits of hospitalisation have not been studied in patients with ITP; however, hospitalisation 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 the management of ITP considered hospitalisation appropriate in patients with platelet count less than 20 x 10^9/L and mucosal bleeding. The role of hospitalisation is unclear in patients with severe thrombocytopaenia but with minor purpura or no symptoms.[19 20] In such situations, risk stratification based on the aforementioned clinical and laboratory parameters may allow identification of patients at a higher risk of bleeding and inform decisions regarding hospitalisation 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 have emerged as a better option. Cheng *et al*[24] reported the first prospective study evaluating HD-DXM in first-line management of ITP 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/mm^3 without further treatment during a follow-up of 2–5 years. Subsequently, Wei *et al*[25] performed a randomised trial to compare the outcomes of one or two cycles of HD-DXM with prednisone. HD-DXM resulted in a higher overall initial response (82.1% vs 67.4%, p=0.044) and complete response (50.5% vs 26.8%, p=0.001), a shorter median time to response (3 vs 6 days, p<0.001), a lower risk of bleeding, and similar long-term sustained response. A recent meta-analysis of nine randomised trials[26] (n=1138) confirmed similar findings and demonstrated a lower risk of toxicities with HD-DXM.

Ideal number of cycles of HD-DXM

Various prospective studies have used one to six cycles of HD-DXM as initial therapy for ITP. Cycles have been repeated as early as after

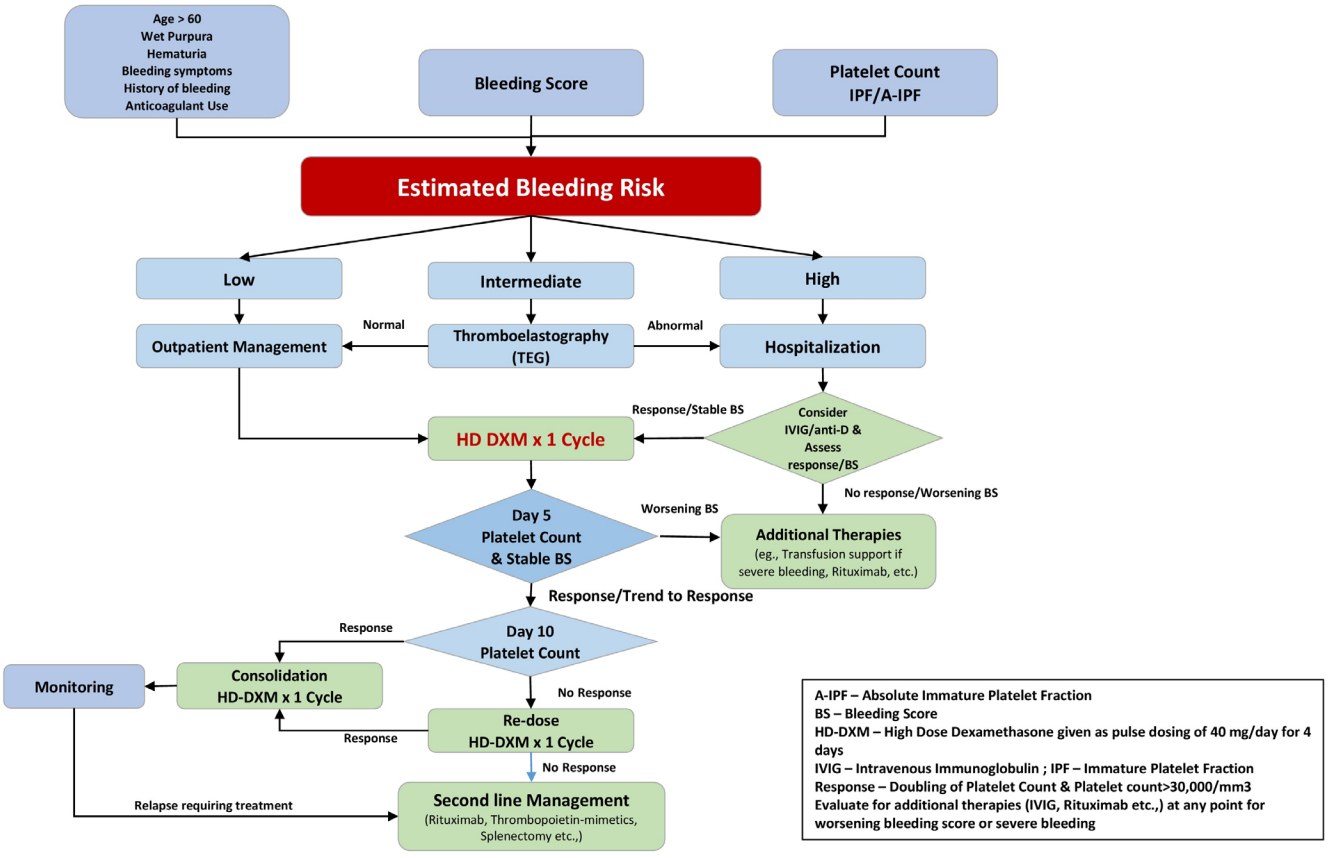

Figure 1 Proposed algorithm for initial management of immune thrombocytopaenia in adults based on risk stratification.

10–14 days or repeated after 28 days of the prior cycle. Mazzucconi *et al*[27] determined a higher response rate with three cycles of HD-DXM, compared with two cycles. However, the response rates reported in the randomised trial with one to two cycles of HD-DXM[24] were similar to those reported by Mazzucconi *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

Although the initial response rates are better with HD-DXM therapy, a significant proportion of patients may relapse and become steroid-refractory.[27] 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 months.[24] 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 personalised medicine, ITP is no exception particularly given its varied spectrum of disease severity, bleeding risk and response to therapy.[28] 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 hospitalisation 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 hospitalised 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 an 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

Self assessment questions

1. Platelets counts correlate well with the risk of bleeding in immune thrombocytopaenia (ITP). True or False?
2. Different scoring system may be used to estimate the risk and severity of bleeding in ITP. True or False?
3. In ITP, treatment is considered in adults when the platelet count is less than 30x 10^9/L or when bleeding symptoms are present. True or False?
4. High-dose dexamethasone is the preferred initial choice of therapy for ITP in most patients. True or False?
5. Long duration of treatment with prednisone is better than pulse dosing of high-dose dexamethasone for 4 days. True or False?

Main messages

- Clinical and laboratory findings along with bleeding scoring systems are helpful in estimating the bleeding risk in patients with immune thrombocytopaenia (ITP).
- Treatment of ITP should be initiated when the platelet count is less than 30 x 10^9/L 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 immune thrombocytopaenia (ITP)?
- When do you start treatment for ITP?
- What are the initial treatment options for ITP?

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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Answers

1. False.
2. True.
3. True.
4. True.
5. False.

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