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Practice Guideline: Disease Management

Evidence-Based Recommendations for the Management of Immune Thrombocytopenia (ITP)

Effective Date: March 2013

CancerCare Manitoba Guideline

Disease Management – Immune Thrombocytopenia

Developed by: Hematology Disease Site Group

ACKNOWLEDGEMENT AND SPONSORSHIP DISCLAIMERS

There are no relevant conflicts of interest to disclose.

Preface

At CancerCare Manitoba (CCMB) the Clinical Practice Guidelines Initiative (CPGI) seeks to improve patient outcomes in terms of survival and quality of life through the development, dissemination, implementation and evaluation of guidelines for the management of common clinical scenarios encountered by cancer patients throughout the province.

This practice guideline was created through the efforts of a large interdisciplinary group from CCMB in collaboration with community partners. Members of the CCMB Hematology Disease Site Group have participated in its development.

The Hematology DSG will review and update this document every two years, unless emerging evidence from scientific research, or practice issues requiring urgent resolution dictate a need for more immediate change in content.

Purpose

This document is intended as a guide to facilitate an evidence-based, shared approach to the clinical management of immune thrombocytopenia (ITP).

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology/hematology patients, which may include (but is not limited to): physicians, surgeons, nurses, radiation therapists, pharmacists, psychosocial oncology caregivers and dieticians at CCMB, Community Cancer Program Network (CCPN) sites, Uniting Primary Care in Oncology Network (UPCON) clinics and WRHA Community Oncology Program sites.

Disclaimer

This guideline document should be viewed as an evidence-based practice tool, and as such, it does not represent an exhaustive text on the subject of ITP. Clinicians are advised to use it in their practice concomitantly with information from other evidence-based sources.

Use of this guideline in the clinical setting should not preclude use of the practitioner's independent clinical judgment, nor should it replace consultation with the hematologist when indicated.

It is the responsibility of the practitioner to develop an individualized disease or symptom management plan for each patient under his/her care, and ideally this should take place within the context of a multidisciplinary team. The needs and preferences of the patient and the family should always be reflected in the plan of care.

Contents

Summary of Recommendations

The recommendations in this document are meant to apply to patients 18 years of age or older with primary immune thrombocytopenia (ITP).

1. All patients with suspected ITP require a complete history and physical examination. Investigations should include CBC, peripheral blood smear, reticulocyte count, pregnancy test (in women of childbearing age), direct antiglobulin test, Rh determination and serology for HIV, Hepatitis B and C. ANA, antiphospholipid antibody testing, and quantitative immunoglobulins should be performed if clinically indicated.
   Level of Evidence IV

2. A bone marrow aspirate and biopsy is suggested in patients over 60 years old, patients with poor response to immune suppression, findings on history and physical suggestive of malignancy, blood count abnormalities aside from thrombocytopenia, and prior to splenectomy. *Level of Evidence IV*

3. Due to the higher risk of bleeding we recommend a platelet count treatment threshold of 30 x 10^9/L be adhered to in patients over 60 years old. For patients younger than 60, a threshold of 20-30 x 10^9/L with consideration of other risk factors for bleeding and platelet count trend should be used.
   Level of Evidence IIb-III

4. Patients needing emergency therapy (life threatening bleeding, need for urgent procedure) should be treated with dexamethasone 40 mg orally daily for 4 days AND IVIG 1g/kg. *Level of Evidence IIa*
   As an adjunct, anti- D immune globulin and platelet transfusion can be administered.
   Level of Evidence Ib, Level IV respectively

5. In patients requiring non-emergency initial treatment (platelet count < 20-30 x 10^9/L) dexamethasone 40 mg orally for four days is recommended. *Level of Evidence IIa*

   - Prednisone (1 mg/kg daily) can be used in patients not expected to tolerate high dose dexamethasone. *Level of Evidence IIb*

   - While IVIG 1g/kg, and IV anti-D immune globulin (Ig) 50-75 ug/kg are also effective for most patients, they are much more costly and provide only transient responses. In patients needing a transient boost in platelet count (e.g. for a procedure) or unable to tolerate steroids, both are reasonable options*. IVIG *Level of Evidence IIa;* IV anti-D *Level of Evidence Ib.*
     *Note: For reasons of cost and convenience of administration, anti-D Ig is preferred to IVIG for Rh-positive patients.

6. Initial therapy should be monitored with twice weekly CBC until platelet count response, with subsequent CBC weekly for one month. *Level of Evidence IV*

7. Most patients do not require hospital admission. However, short hospital admission, until cessation of bleeding and demonstrated improvement in platelet count, is recommended at presentation for patients

requiring emergency treatment (major bleeding) or those at high risk of bleeding (See Section VII). *Level of Evidence IV*

8. Patients eligible for second line (and subsequent) treatment are those with: a) persist ITP with platelet counts < 20 - 30 x 10^9/L; b) inability to maintain platelet count with corticosteroids; or c) need for relief from corticosteroid side effects. *Level of Evidence IV*

9. We recommend consideration of laparoscopic splenectomy for second line treatment. *Level of Evidence IIb*

10. Patients should be counseled regarding the benefits and risks of splenectomy including lifelong risk of serious bacterial infection and should be provided with instructions regarding febrile illness. Pre-splenectomy vaccination, in accordance with current Canadian Immunization Guidelines, should be completed at least two weeks prior to splenectomy. *Level of Evidence IIb*

11. Rituximab 375 mg/m^2 IV weekly for four doses should be administered to patients with refractory ITP who have failed splenectomy or who are not candidates for splenectomy. *Level of Evidence IIa*

12. There are multiple treatment options to be considered after splenectomy and rituximab in patients with persistent or chronic ITP; these recommendations can be found in Table 3 (*Section IX*).

13. In pregnant patients found to have thrombocytopenia, etiologies unique to pregnancy (HELLP) or more common in pregnancy (TTP) must be considered prior to diagnosis with ITP. In addition to standard recommended investigations for ITP bilirubin, liver enzymes, LDH, INR, and fibrinogen should be assessed. *Level of Evidence IV*

14. In pregnant patients with ITP indications for initiating treatment during the first two trimesters are the same as the non-pregnant patient (*Level of Evidence IV*). Platelet count should be monitored every two weeks in the third trimester with treatment to maintain platelet count above 50 x 10^9/L. *Level of Evidence IV*

    - First line treatment options are corticosteroids or IVIG with limited evidence for use of other treatments. Given lack of safety data, rituximab and other steroid sparing agents should be avoided in pregnancy. *Level of Evidence IV*

15. For pregnant patients with ITP the mode of delivery should be determined based on obstetrical indications. *Level of Evidence III*

    - Procedures associated with hemorrhagic risk to the fetus should be avoided (scalp electrodes, forceps, vacuum assist, etc). *Level of Evidence IV*

    - At delivery the platelet count should be measured from umbilical cord blood, and if depressed follow up is recommended. *Level of Evidence III*

16. Treatment for HIV-associated thrombocytopenia is similar to treatment of the patient without HIV, with the caveat that treatment must also be directed at the underlying HIV infection with anti-retrovirals (*Level of Evidence IIa*). It is recommended that corticosteroids be used sparingly in this patient population and avoided

altogether with confirmed or suspected tuberculosis, CMV or HCV co-infection (*Level of Evidence IIa).*

17. Treatment of HCV-associated ITP should include IVIG, IV anti-D immune globulin and splenectomy. Corticosteroids have lower response rates, are associated with increased viral load with potential hepatic compromise, and therefore should be avoided. Many patients with thrombocytopenia will respond to treatment directed at HCV with interferon/ribavirin. Referral to Hepatology to initiate this treatment is recommended. *Level of Evidence IIa*

18. Helicobacter pylori eradication can result in platelet count improvement. Given the relative ease of testing and treating for this infection we recommend doing so in all patients with persistent ITP. *Level of Evidence IIa*

19. For procedures or operations recommended platelet targets can be found in Section XIII. If patients are not at target, suggested treatments are corticosteroids, IVIG, or IV anti-D depending on urgency for procedure (the latter two have quicker response). Consider addition of an antifibrinolytic agent especially for dental procedures (tranexamic acid 10 mg/kg/dose 3-4 times/day; typical dose 1,000 mg po TID).
Level of Evidence IV

CancerCare Manitoba

Practice Guideline: Disease Management

Evidence-Based Recommendations for the Management of Immune Thrombocytopenia (ITP)

I. Introduction and Scope of Guideline

This document is an evidence-based consensus of the CancerCare Manitoba Hematology Disease Site Group (HDSG) for the diagnosis and management of adults with Immune Thrombocytopenia (ITP).

ITP is an acquired immune mediated disorder with isolated thrombocytopenia. Mechanisms of disease include platelet destruction via auto-antibodies and impaired platelet production. The severity of disease is variable ranging from fatal hemorrhage to asymptomatic thrombocytopenia. Physicians' choice of medical management of indication for starting treatment can be quite variable.

This guideline is developed as an adaptation of recently published, *"International consensus report on the investigation and management of primary ITP"* with review of additional relevant evidence and consideration of available resources in Manitoba.[1] The goal is to provide recommendations for initiation of treatment and sequence of pharmacologic/non-pharmacologic treatment for adults with primary ITP. Special patient populations such as the pregnant patient with ITP and those with HIV or Hepatitis C virus/secondary ITP are considered in sections X and XI.

Recommendations are intended for use in ambulatory and inpatient settings, each recommendation is given appropriate evidence level (*see Appendix 1*)

References

1. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-86.

II. Method for Guideline Adaptation

Organizing Committee

- General Hematology Disease Site Group (HDSG), CancerCare Manitoba
- Author: Dr. Pam Skrabek wrote this guideline as a required administrative project during her Hematology residency program.
- Supervisors – Dr. David Szwajcer and Dr. Donald Houston
- Reviewers: HDSG members and Chair (Dr. Donald Houston)
- Conflicts of interest: None relevant to disclose

Health Topic

Guideline for the management of patients with primary ITP

Population: adults diagnosed with primary ITP

- Exclusions: secondary immune thrombocytopenia (i.e. Chronic Lymphocytic Leukemia), children (<18 years old)

Intervention: therapeutic management

- Indications for initiation of treatment
- Pharmacologic treatment options
    - Recommended sequence of initiation
- Indications for and timing of splenectomy

Target audience:

- General Hematologist
- Other subspecialists (General Internal Medicine, Emergency Room Physicians)
- General Practitioners

Outcomes:

- Response assessment
- Expected time to response
- Duration of response
- Criteria for changing management plan

Context for Guideline:

- In ITP there is heterogeneity amongst physicians with respect to when to initiate treatment and how to

treat. This guideline is meant to be a summary of diagnosis and treatment of acute and chronic ITP.

Literature Search

1. Initial search January 2010
2. Search engines/databases
    - Pubmed
    - EMBASE
    - www.guidelines.gov
    - www.g-i-n.net
3. Search terms
    - Pubmed
        - "purpura, thrombocytopenic, idiopathic" (MESH) *and* (guideline *or* management guideline ***or*** practice guideline)
        - "purpura, thrombocytopenic, idiopathic" (MESH) *and* (practice guidelines as topic" (MESH) *or* "evidence-based practice" (MESH) *or* "practice guideline" (publication type)
    - EMBASE
        - exp practice guideline *and* (exp idiopathic thrombocytopenic purpura *or* exp immune thrombocytopenia)
4. Exclusion Criteria
    - Published prior to the year 2003
    - Guidelines focusing on population outside of that defined above (i.e. > 18 years old, secondary ITP)
    - Opinion based reviews
    - All documents that are not clinical practice guidelines
    - Documents published only in languages other than English
5. Retrieved Guidelines
    - British Committee for Standards in Haematology General Haematology Task Force. *Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy.* Br J Haematol 2003;120:574-96.
    - Stevens W, Koene H, Zwaginga JJ, et al. *Chronic idiopathic thrombocytopenic purpura: present strategy, guidelines and new insights.* Neth J Med 2006;64:356-63.
    - Rodeghiero F, Stasi R. Gernsheimer T, et al. *Standardization of terminology, definitions and*

outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113:2386-93.

- Provan D, Stasi R, Newland AC, et al. *International consensus report on the investigation and management of primary immune thrombocytopenia.* Blood 2010;115:168-86.

6. Assessment of Guidelines
7. Selection: Due to a systematic and comprehensive search strategy and the current nature of this guideline with involvement of international committee members the *"International consensus report on the investigation and management of primary immune thrombocytopenia"* was selected as the primary document to be adapted. Original references sourced within the document were reviewed as cited when appropriate. The Blood publication was utilized for definitions of terms.
8. Draft Guideline

Review and Finalization Process

Review

1. Project supervisors
   - Dr. David Szwajcer and Dr. Donald Houston reviewed the draft, and made recommendations in August 2010
   - Revisions were made and the document was circulated to HDSG members in September 2010
2. Hematology Disease Site Group Committee
   - Document was reviewed in detail at the HDSG meetings on 22 September and 24 November 2010
   - After considering treatment efficacy, toxicities in the local context a consensus document was completed

Update December 2010/January 2012

Limited literature search for trials, and original research studies published in time since adapted guideline was published.

- Pubmed
  - search term ITP (MESH major topic); "limits" – clinical trials, meta-analysis, practice guidelines, randomized control trials, English, adult, published in the last two years
- Results = 21
- Revisions made to a number of sections.

Next Review and Revision

Due January 2014

Implementation

- Recommendations were tailored to a local context as described above. This document will be disseminated to HDSG members, put on a local shared drive and further distribution through existing CCMB channels.

III. ITP Definitions

In addition to small or poor quality trials interpretation of evidence is hampered by heterogeneity in terminology used in trials. In an effort to standardize terminology an international working group met in 2007 and set standard definitions.[1] Historically the ITP stood for "idiopathic thrombocytopenic purpura", a major recommendation was to replace the term "idiopathic" with "immune" to reflect disease pathogenesis. Also, it was decided that "purpura" was inappropriate because patients do not necessarily have this manifestation.[1] The recommended term therefore is, intuitively Immune Thrombocytopenia (ITP**)**. This document will utilize the definitions as proposed by this working group.

Table 1. ITP Definitions[1]

Primary ITP	• Isolated thrombocytopenia plt < 100 x 10^9/L in the absence of other disorders associated with thrombocytopenia • Diagnosis of exclusion without a specific diagnostic test or clinical criteria	
Secondary ITP	All forms of immune-mediated thrombocytopenia other than primary ITP	
Phases of the disease	Newly diagnosed ITP	Within 3 months of diagnosis
	Persistent ITP	3 – 12 months from diagnosis
	Chronic ITP	> 12 months
	Severe ITP	Bleeding significant* enough to require treatment at presentation of thereafter; bleeding despite intervention or requiring additional treatment

* Note: A definition of significant bleeding was not provided by the International Working Group, thus this is a decision left up to the treating physician.

Table 2. Definitions of Therapeutic Response[1]

Quality of Response	
Complete Response (CR)	plt $\geq$ 100 x 10^9/L* and absence of bleeding
Response (R)	plt $\geq$ 30 x 10^9/L*, 2 fold increase from baseline and absence of bleeding
No Response (NR)	Fails to fulfill above criteria
* Platelet counts confirmed on two separate occasions at least 7 days apart	

References

1. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113:2386-93.

IV. Diagnosis of ITP

There is no specific test to rule in or rule out ITP. A diagnosis is made when history, physical examination, complete blood count and peripheral blood smear do not suggest an alternative etiology for thrombocytopenia.

All patients evaluated for thrombocytopenia require a complete history and physical examination. Important historical features include demographics; prior medical history (include screening for predisposing condition i.e. SLE); medications including non-prescription drugs and alcohol/illicit drug use; comprehensive bleeding history and family history. Physical examination should concentrate on search for bleeding manifestations as well as potential underlying causes of thrombocytopenia (e.g. evidence of splenomegaly).

Recommended Diagnostic Tests for All Patients with Suspect ITP[1]

- CBC and reticulocyte count
- Peripheral blood smear review
- Direct antiglobulin test
- Blood group and Rh determination
- HIV, hepatitis serology
- H. pylori (suggested test is Urea Breath Test)*
- Pregnancy test in women of childbearing potential

* For patients with chronic ITP see Section XI.

Tests to Consider in Select Patient Populations[1]

- Bone marrow examination – consider in pts > 60, signs or symptoms of systemic disease, CBC abnormalities aside from thrombocytopenia, poor response to standard therapy, pre-splenectomy
- ANA*
- Antiphospholipid antibodies**
- Baseline immunoglobulin levels

* If signs or symptoms of SLE

** If suspected Antiphospholipid Antibody Syndrome

References

1. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-86.

V. Initial Management of ITP

Background

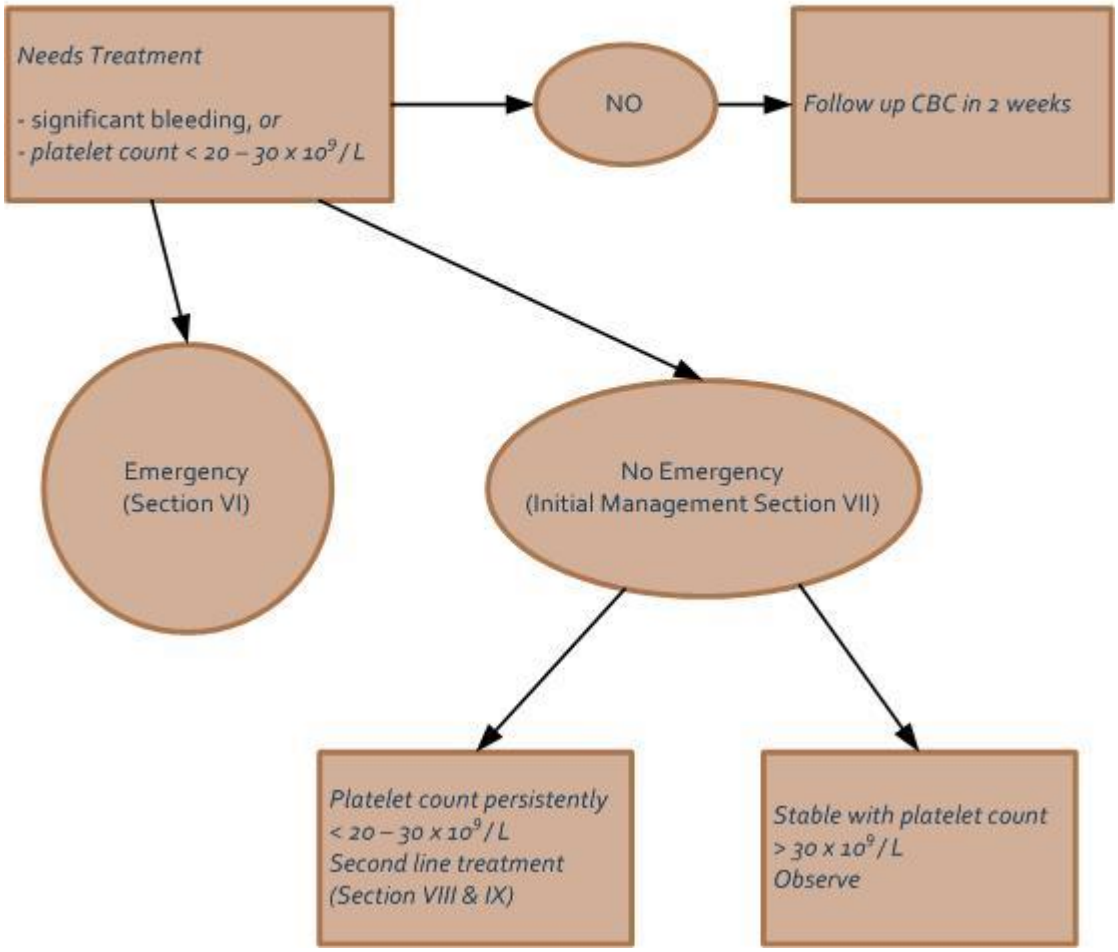
Indications for intervention rather than a "watch and wait" strategy are somewhat subjective as the goal of treatment is to prevent major bleeding rather than correct the platelet count. Most authors recommend treatment threshold for adults of less than 30 x 10^9/L due to very low incidence of major bleeding above this level.

Patient's risk of bleeding is dependent on many factors such as concurrent illness, trauma, anti-platelet or anticoagulant medication. Previous history of major hemorrhage should be regarded as a major risk factor for recurrent event (RR 27.5).[1] There is an increased incidence of bleeding for a given level of thrombocytopenia with increasing age.[1] In a compilation of 17 case series (n=1817) of patients with ITP and platelet count less than 30 x 10^9/L the risk of fatal hemorrhage was 0.4%, 1.2% and 13% per year for ages < 40, 40–60, and > 60 respectively.[2] Over a two year course 76% of patients over 60 with ITP and platelet count < 30 x 10^9/L will have a major bleeding event.[2]

Recommendations

Due to the higher risk of bleeding we recommend that a treatment threshold of 30 x 10^9/L be adhered to in patients over 60 years old. For patients less than 60 years, a platelet threshold of 20-30 x 10^9/L with consideration of other risk factors for bleeding should be used. *Level of Evidence IIb-III*.

Figure 1
Initial Management Algorithm for ITP



General measures to reduce bleeding should be considered for all patients (*Level of Evidence IV*):

- Avoidance of activities at high risk for injury (i.e. boxing, high impact sports) with use of protective equipment (helmets) for activities such as biking, skateboarding, and riding motorcycles.
- Discontinue anti-platelets, anticoagulation and non selective – NSAIDs (note Celecoxib does not have significant anti-platelet effect) in patients with bleeding (if this is not possible in non bleeding patients the treatment threshold should be increased to 50 x 10^9/L).[3]
- Patients should be educated about local measures to achieve hemostasis (RICE – rest, ice, compression, elevation).

- Tranexamic acid 1000 mg TID should be prescribed for patients with mucosal bleeding.

  NOTE: contraindicated in patients with upper urinary tract bleeding.

- When menorrhagia is a symptom of ITP, oral contraceptives or progesterone-eluting IUD are recommended and referral to Gynecology should be made to facilitate this.

References

1. Cortelazzo S, Finazzi G, Buelli M, Molteni A, Viero P, Barbui T. High risk of severe bleeding in aged patients with chronic idiopathic thrombocytopenic purpura. Blood 1991;77:31-3.
2. Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. Arch Intern Med 2000;160:1630-8.
3. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-86.

VI. Emergency Management of ITP

Background

This section applies to scenarios where there is life threatening or severe bleeding, or a need to increase platelet count within 24 hours or less. **All patients requiring emergency treatment should be hospitalized.**

Emergency Treatment - ITP
Dexamethasone 40 mg po daily x 4 days * *Level of Evidence IIa* ***and*** IVIG 1 g/kg IV x 1 day ** *Level of Evidence IIa* + / - 1 adult dose platelets (must be in combination with above) *Level of Evidence III-* + / - IV anti-D 50-75 microgram/kg *** *Level of Evidence Ib-IIa*

*Alternative: Prednisone 1 mg/kg daily (see discussion Section VIII). IV methylprednisolone has been reported to be effective in patients not responding to initial treatment.[1] There is no need for routine use upfront as a combination of IVIG and prednisone or dexamethasone has a rapid response in the majority of patients.[2]

** Most patients will respond to one dose of IVIG. If there is no response repeat IVIG on Day 3.

*** Must be Rh +, non-splenectomized patient without suspicion of concurrent autoimmune hemolytic anemia (anemia, reticulocytosis, increased indirect bilirubin/LDH)

References

1. Alpdogan O, Budak-Alpdogan T, Ratip S, et al. Efficacy of high-dose methylprednisolone as a first-line therapy in adult patients with idiopathic thrombocytopenic purpura. Br J Haematol 1998;103:1061-3.

2. Godeau B, Chevret S, Varet B, et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. Lancet 2002;359:23-9.

VII. Non-Emergent First Line Management of ITP

Recommendations

Corticosteroids

Given efficacy and low cost, corticosteroids are recommended as first line treatment in non-emergency scenarios with dexamethasone 40 mg po for four days as recommended regimen. *Level of Evidence IIa*

An acceptable alternative is prednisone 0.5-2 mg/kg/day until platelet count >30-50 x 10^9/L with subsequent tapering dose. *Level of Evidence IIb*

Using prednisone, 70-80% of patients will respond in days to weeks however with discontinuation of prednisone few have sustained response.[1] Administration of a single cycle of dexamethasone 40 mg/day resulted a platelet response (increase by at least 20 by Day 3 and platelets >100 by Day 7) in 85% of patients.[2,3] Among the responders, 50% had maintenance of platelet count over 50 with no further treatment required during the follow up period of 30.5 months.[2] Two further studies by the GINEMA group looked at high dose dexamethasone (40 mg/day) with a total of 6 cycles (Q28 days) or 4 cycles (Q14 days). Response rates were similar to the initial study; however higher rates of long term response were seen.[3] The optimal number of cycles is not known, although there was no significant difference in long term response between 3 and 4 cycles.[3] In both of these studies, despite the high doses of corticosteroids, low rates of adverse events were seen.[2,3] There have been no published studies randomizing patients to high dose dexamethasone compared to standard dose prednisone. The available evidence suggests that a shorter course of more potent steroids may minimize risks of corticosteroids with better chance of long term response.

For this reason we suggest dexamethasone 40 mg po daily for 1-3 cycles (given Q14-28 days) first line however standard dose prednisone is an acceptable alternative.

IVIG and IV anti-D

While IVIG and IV anti-D are also effective for most patients, they are much more costly and provide only transient responses. In patients needing a transient boost in platelet count (e.g. for a procedure), or who are unable to tolerate steroids, both are reasonable options.

IVIG 1 g/kg for 1 day *Level of Evidence IIa*

- Initial response in 80%
- Often rapid (within 24 hours) lasts 2-4 weeks
- Can be repeated on Day 3 if inadequate response
- Toxicities
    - common: headache, myalgias
    - less common: renal insufficiency, aseptic meningitis, thrombosis[1,4]

IV anti-D immune globulin 50 ug/kg *Level of Evidence Ib*

- Patients must be Rh+ without splenectomy and have baseline hemoglobin > 100 g/L
- Majority of patients will respond to IV anti-D immune globulin within 4-5 days
- Duration of response is 3 weeks or longer (can be given q4wks)
- Use of higher dose (75 microgram/kg) is associated with improved platelet response and longer duration without increase in adverse events[4]
- Toxicities
    - common: hemolytic anemia, fevers/chills
    - less common: severe hemolysis, DIC

Monitoring

Initial therapies recommended above (corticosteroids, IVIG, IV anti-D) should be monitored with twice weekly CBC until platelet count response, with subsequent CBC weekly for one month. *Level of Evidence IV*

High Risk Patients

It is recommended that short hospital admission, until demonstrated improvement platelet count, be considered at initial presentation for patients at high risk of bleeding. *Level of Evidence IV*

This can include, but is not limited to:

- Age > 60 especially with platelet count < 10 x 10^9/L
- Patient with multiple bleeding risk factors (i.e. anti-platelet agent or renal failure along with severe thrombocytopenia)
- Poorly compliant patient
- Patients from outside of Winnipeg with platelet count < 10 x 10^9/L

References

1. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-86.

2. Cheng Y, Wong RS, Soo YO, et al. Initial treatment of immune thrombocytopenic purpura with high-dose dexamethasone. N Engl J Med 2003;349:831-6.

3. Mazzucconi MG, Fazi P, Bernasconi S, et al. Therapy with high-dose dexamethasone (HD-DXM) in previously untreated patients affected by idiopathic thrombocytopenic purpura: a GIMEMA experience. Blood 2007;109:1401-7.

4. Cooper N. Intravenous immunoglobulin and anti-RhD therapy in the management of immune thrombocytopenia. Hematol Oncol Clin North Am 2009;23:1317-27.

VIII. Splenectomy as Second Line Management of ITP

Recommendations

Considerations for Splenectomy

Patients requiring second line treatment are those with persistent ITP with platelet counts < 20 – 30 x 10^9/L. Second line (and subsequent) treatment is to be considered when unable to maintain platelet count > 20 – 30 x 10^9/L with corticosteroids, or as steroid sparing treatment. We recommend consideration of splenectomy for second line treatment. *Level of Evidence IIb*

Splenectomy should be reserved until at least six months post diagnosis to allow for possible spontaneous resolution of ITP (rare in adults).[1]

Laparoscopic splenectomy is the preferred surgical method due to fewer days in hospital, lower complication rate, and less post-operative pain.[2] There is no difference in relapse rate between open and laparoscopic splenectomy.[2]

Informing the Patient

The following should be discussed with the patient when considering splenectomy for ITP:

Benefits

- Splenectomy has the most evidence to date for potential "cure" of ITP. The complete response (CR) rate is 66% with another 22% achieving partial response.[3] Only 15% of patients that initially respond later relapse in long term follow up studies.[3]

Risks

- Operative mortality with laparascopic splenectomy is 0.2% [3]
- 30 day complication rate is 9.6% [3]
- Long term infectious risk due to increase susceptibility to encapsulated bacteria (Streptococcus pneumoniae, Hemophilus influenza, etc). This risk is presumed to be decreased but not prevented with vaccination (see c. below for recommendations).

Relapse

- In those that relapse, this most often occurs in the first 2 years post splenectomy[4]
- Factors predictive of long-term response have been inconsistent.
    - Age has been found to be predictive of response with younger patients having higher likelihood of success. However, there is no absolute age that can be determined from the evidence to assist the clinician in recommendation for or against splenectomy. Additionally, there are nearly as many studies

that did not find age to be an important determinant as ones that did.[3]

- Postoperative platelet count is associated with risk of relapse in several studies.[4,5,6]
- Post operative platelet count at Day 7 (455 in non-relapsed vs. 277 pts with relapse, P=<0.001).[4]

Pre-Splenectomy Vaccination

Vaccinations to be completed at least 2 weeks pre splenectomy[7] *Level of Evidence IIb**

Hemophilus influenza type B (Act-Hib 0.5 mL IM)

Pneumococcus (Pneumovax 23 0.5 mL IM)

Meningococcus
(1st given Menjugate 0.5 mL IM, then 2 weeks later give Menomune 0.5 mL subcut**)

Asplenia Alert card should be filled out and given to all patients.

Medic-alert bracelets are also recommended.

* Although often logistically difficult, vaccination should be administered when the patient is on little or no immune suppressing medications.

** Both Menjugate (covers Meningococcus C) and Menomune (covers Meningococcus A,C,Y, W-135) are recommended since 2007.[7]

Note: Splenectomy and ITP are associated with thromboembolism, as such thromboprophylaxis should be administered post operatively.[1]

References

1. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-86.

2. Cordera F, Long KH, Nagorney DM, et al. Open versus laparoscopic splenectomy for idiopathic thrombocytopenic purpura: clinical and economic analysis. Surgery 2003;134:45-52.

3. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. Blood 2004;104:2623-34.

4. Vianelli N, Galli M, de Vivo A, et al. Efficacy and safety of splenectomy in immune thrombocytopenic purpura: long-term results of 402 cases. Haematologica 2005;90:72-7.

5. Kang CM, Lee JG, Kim KS, et al. Long-term follow-up of laparoscopic splenectomy in patients with immune thrombocytopenic purpura. J Korean Med Sci 2007;22:420-4.

6. Julia A, Araguas C, Rossello J, et al. Lack of useful clinical predictors of response to splenectomy in patients with chronic idiopathic thrombocytopenic purpura. Br J Haematol 1990;76:250-5.

7. Canadian Immunization Guide - 7th Edition 2006. Part 3 Immunization of Immune Compromised Persons. 2010.

IX. Management of Refractory ITP

Refractory ITP is defined as ITP requiring treatment to minimize risk of bleeding (generally platelet count < 30 x 10^9/L) in patients who have either no response to splenectomy, or relapse post splenectomy.[1] Published guidelines suggest more than ten pharmacologic treatment options with no particular order of preference.[2]

Recommendations

Given response rate and potential for long-term duration of response, rituximab 375 mg/m^2 IV weekly for four doses is recommended as treatment in patients not eligible for splenectomy or with relapse post splenectomy. *Level of Evidence IIa*

In ITP rituximab has been shown to result in response (platelet count > 50 x 10^9/L) in 62.5% of patients despite many of them having refractory ITP.[3] Several reports have documented sustained response (up to 56 months) as a result of rituximab.[4,5] The most common side effects are infusion reactions with a small increased risk of infection. Please see the P&T submission document "Rituximab for ITP" submitted to the WRHA/CCMB Oncology Pharmacotherapeutic Subcommittee for further details.

If there is no response to rituximab (wait 12 weeks after last dose given to evaluate response) the following are treatment options:

- If the patient has not yet had a splenectomy this should be again considered.
- There are multiple other medications with efficacy in ITP (see Table 3). All have limited supporting evidence as experience has been published in small, uncontrolled trials and case series. Choice should be made between options below based on patient comorbidities, side effect profile and physician experience. At least a three-month trial is warranted prior to determining lack of response and moving on to the next option.

Table 3. Fourth Line Treatment Options in Patients with Persistent or Chronic ITP in Suggested Order of Use *Level of Evidence IIb-III unless otherwise stated*

Treatment	Dose	Response Rate	Time to Respond	Toxicities/Comments
Azathioprine	1-2 mg/day (start 50 mg max 150 mg)	45-60%	3-6 mths	Fatigue, transaminitis, cytopenias, secondary malignancy Check thiopurine methyltransferase level prior to initiation
Danazol	200 mg BID	67% plt count >50	3-6 mths	Weight gain, hirsuitism, liver dysfunction

Rombiplastin* (Evidence level Ib)	1-10 ug/kg subcut weekly	79-88%	1-4 wks	Requires continual administration Side effects: headache, fatigue, myelofibrosis
Eltrombopag* (Evidence level Ib)	25-75 mg po daily	70-80%	2 wks	Requires continual administration Side effects: headache, myelofibrosis, elevated liver enzymes
Cyclosporin	5 mg/kg/day titrate to levels 100-200 mg/mL	Dose dependent	3-4 wks	HTN, renal impairment, fatigue, tremor
Mycophenylate Mofetil	250 titrated to 1000 mg BID	Up to 70% pts (small series)	4-6 wks	Headache, backache, GI upset
Cyclophosphamide	1-2 mg/kg/day po	39%	1-16 wks	Myelosupression, infection, secondary malignancy
Dapsone	200 mg po BID	Up to 50% (pre-splenenctomy)	3 wks	Must rule out G6PD Skin rash, GI side effects
Vincristine	2 mg weekly IV	Highly variable	5-7 days	Neuropathy (especially with cumulative dose)

* Thrombopoeitin- receptor agonists are not on the provincial formulary. Both romiplostim (weekly subcutaneous injection) and eltrombopag (daily oral medication) result in a good rate of platelet response in patients with refractory ITP.[2] Limitations are lack of sustained response, findings of increased bone marrow reticulin, and cost. In patients who have failed splenectomy and rituximab, and at least one other option listed in Table 3, these new medications should be considered.

References

1. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113:2386-93.

2. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-86.

3. Arnold DM, Dentali F, Crowther MA, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura (Structured abstract). Ann Intern Med 2007;146:25-33.

4. Medeot M, Zaja F, Vianelli N, et al. Rituximab therapy in adult patients with relapsed or refractory immune

thrombocytopenic purpura: long-term follow-up results. Eur J Haematol 2008;81:165-9.

5. Garcia-Chavez J, Majluf-Cruz A, Montiel-Cervantes L, Esparza MG, Vela-Ojeda J, Mexican Hematology Study Group. Rituximab therapy for chronic and refractory immune thrombocytopenic purpura: a long-term follow-up analysis. Ann Hematol 2007;86:871-7.

X. ITP in Pregnancy

This section applies to patients diagnosed with ITP preceding a pregnancy, as well as patients newly diagnosed with ITP during pregnancy. In the latter, it is important to consider that thrombocytopenia in pregnancy can occur for a variety of reasons including etiologies unique to pregnancy (HELLP) or more common in pregnancy (TTP).[1]

Table 4. Considerations in the Differential Diagnosis of Thrombocytopenia in Pregnancy

Diagnosis	Clues*
ITP	Onset any point in pregnancy Prior history thrombocytopenia or autoimmune disease, platelet count < 50 [2]
Gestational thrombocytopenia	Mild thrombocytopenia in 3rd trimester
Pre-eclampsia	Onset 3rd trimester, associated HTN & proteinuria
HELLP syndrome	Microangiopathic hemolytic anemia, elevated AST/ALT
TTP/HUS	Microantiopathic hemolytic anemia, increased LDH
* Additional tests to be done in pregnant women with suspected ITP: INR, PTT, fibrinogen, AST, ALT, bilirubin, LDH [1]	

Recommendations: Treatment of ITP in Pregnancy

During the first two trimesters indications for initiating treatment are no different from the non-pregnant patient. *Level of Evidence IV*

Platelet counts should be monitored every two weeks in third trimester. Consensus is that treatment to increase platelet count above 50 x 10^9/L is warranted in the third trimester *(Level of Evidence IV)*.[1] Neuraxial anesthesia may be declined to women with platelet counts less than 80 x $10^{9/L}$ depending on individual anesthetists' practices.

Mode of delivery should be determined based on obstetrical indications; ITP is not an indication in isolation for cesarean section.[1] *Level of Evidence III*

- Procedures associated with hemorrhagic risk of fetus should be avoided (scalp electrodes, forceps of vacuum assist, etc). *Level of Evidence IV*
- At delivery the platelet count should be measured in neonatal cord blood, and if depressed follow up is recommended. Maternal anti-platelet IgG can cross the placenta, however the incidence of severe

neonatal thrombocytopenia as a result of maternal ITP is low.[2] *Level of Evidence III*

First line treatment options are corticosteroids* or IVIG with limited evidence for other treatments. Given lack of safety data rituximab and other steroid sparing agents should be avoided in pregnancy.[1] *Level of Evidence IV*

- IVIG should be used if rapid platelet response is required (unexpected pre-term delivery or bleeding) or to avoid side effects of corticosteroids.
- Prednisone dose should be minimized to lowest dose necessary (start with 20 mg/day). Do not taper rapidly close to delivery.

*NOTE: Adverse effects of corticosteroids are amplified in pregnancy. Common maternal side effects are development or exacerbation of hypertension, gestational hyperglycemia, excess weight gain, and accelerated bone loss.[2]

References

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2. Stavrou E, McCrae KR. Immune thrombocytopenia in pregnancy. Hematol Oncol Clin North Am 2009;23:1299-316.

IX. Other Special Patient Populations

Recommendation

HIV-associated ITP

Thrombocytopenia is common in patients with HIV infection. This is especially prominent in patients with AIDS and intravenous drug users (possibly as a result of HCV co-infection). In HIV, thrombocytopenia can be attributed to peripheral destruction and impaired platelet production.

- HIV-associated ITP is generally responsive to the same treatments as the non-HIV positive ITP patient.[1] However, in patients with HIV, treatment must also be directed at the underlying cause with anti-retrovirals. *Level of Evidence IIa*
- It is recommended that corticosteroids be used sparingly in this patient population and avoided altogether with confirmed or suspected tuberculosis, CMV, or HCV co-infection.[1] *Level of Evidence IIa*

Hepatitis C Virus-associated ITP

Prevalence of Hepatitis C (HCV) is 2.2% worldwide. Furthermore, in studies of patients with chronic ITP, HCV infection can be found in 20% of patients.[1] Testing all patients regardless of perceived risk is imperative.

Patients with HCV may also have chronic liver disease and associated hypersplenism contributing to thrombocytopenia.

- Treatment of HCV-associated ITP should include IVIG, IV anti-D and splenectomy. Many patients will respond to therapy with interferon/ribavirin, and referral to Hepatology for this is recommended. Corticosteroids have lower response rates and are associated with increased viral load with potential hepatic compromise.[1] *Level of Evidence IIa*

Helicobacter pylori (H.pylori) infection and ITP

H.pylori infection has not been found to be more prevalent in patients with ITP.[2] However, eradication has been associated with a platelet response in approximately 50% of H.pylori positive patients with ITP.[3,4] Studies have largely been done in Japan and it is uncertain how applicable this is to a Canadian population where prevalence and molecular characteristics of the micro-organism differ.

- Given the relative ease of testing for and treating H.pylori, we recommend doing so in all patients with persistent ITP. *Level of Evidence IIa*

References

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4. Arnold DM, Stasi R. Does Helicobacter pylori eradication therapy result in a platelet count improvement in adults with immune thrombocytopenic purpura regardless of H pylori infection? ASH evidence-based review 2008. Hematology Am Soc Hematol Educ Program 2008:31-2.

XII. Preoperative Recommendations

Recommendations

If patients are not at target platelet count suggested treatments are corticosteroids, IVIG, or IV anti-D depending on urgency for procedure (the latter two have quicker response). Consider addition of an antifibrinolytic agent especially for dental procedures (tranexamic acid 10 mg/kg/dose 3-4 times/day, typical dose **1,000** mg po TID).

Platelet Targets[1] *Level of Evidence IV*

- Dental prophylaxis (descaling, deep cleaning) ≥ 20–30 × 10^9/L
- Simple extractions ≥ 30 × 10^9/L
- Complex extractions ≥ 50 × 10^9/L
- Regional dental block ≥ 30 x 10^9/L
- Minor surgery ≥ 50 × 10^9/L
- Major surgery ≥ 80 × 10^9/L
- Major neurosurgery ≥ 100 × 10^9/L
- Obstetrics see Section XI

References

1. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-86.

XIII. Contact Physicians and Contributors

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XIV. Appendices

Appendix 1

Evidence Grading[1]

Evidence Level	Definition
Ia	Evidence obtained form meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained form at least one well-designed controlled study wihtou randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study*
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlated studies and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

* Refers to a situation in which implementation of an intervention is without the control of the investigators, but an opportunity exists to evaluate its effect

Grade of Recommendation	Definition	Level of Evidence
A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation	Ia, Ib
B	Requires the availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation	IIa, IIb, III

C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality	IV

References

1. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-86.

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