CLINICAL PRACTICE GUIDELINES

August 2006 MOH/P/PAK/115.06 (GU)

MANAGEMENT OF IMMUNE THROMBOCYTOPENIC PURPURA

MINISTRY OF HEALTH MALAYSIA

ACADEMY OF MEDICINE

Statement of Intent

This clinical practice guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily ensure the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

Review of the Guidelines

This guideline was issued in August 2006 and will be reviewed in August 2008 or sooner if new evidence becomes available.

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GUIDELINES DEVELOPMENT AND OBJECTIVES

Guideline Development

The development group for this guideline comprised of paediatricians, physicians, haematologists and an obstetrician from the Ministry of Health Malaysia and Ministry of Education.

The evidence search was carried out using Pubmed, Ovid and general search engines with 'idiopathic thrombocytopenic purpura'; 'immune thrombocytopenic purpura'; 'platelet count'; autoimmune thrombocytopenic purpura'; 'refractory thrombocytopenic purpura'; ITP; thrombocytopenia AND therapy as the key words. For paediatric AND pregnancy articles the previous search terms were combined with 'child' and 'children' and pregnancy respectively. The search excluded secondary causes of ITP e.g. 'drug induced thrombocytopenia'; 'secondary immune thrombocytopenia'. "Related articles were selected and out of these, relevant articles were chosen and graded using the modified version of those used by the Catalonia Agency for Health Technology Assessment (CAHTA) Spain.

This guideline was also adapted from other international guidelines on Management of Idiopathic Thrombocytopenic Purpura which include Guidelines for the Investigation and Management of Idiopathic Thrombocytopenic Purpura in Adults, Children and in Pregnancy by British Society for Haematology and Idiopathic Thrombocytopenic Purpura: A practice guideline by American Society of Haematology. This guideline is also based on the findings of a systematic review of current medical literature, taking into consideration local practices. The draft guideline was posted on both the Ministry of Health Malaysia and Academy of Medicine, Malaysia websites for comment and feedback. This guideline has also been presented to the Technical Advisory Committee for Clinical Practice Guidelines and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

A systematic approach to the treatment modalities was suggested depending on the conditions associated with ITP. This is summarised as an algorithm of management of ITP in adults, children and pregnancy.

Objectives

The main aim of the guideline is to enable practitioners to make informed evidence based decisions on the diagnosis and management of Immune Thrombocytopenic Purpura (primary or idiopathic).

Clinical Questions

The clinical questions of this guideline are:

i) What is the clinical spectrum of Immune Thrombocytopenic Purpura?
ii) How is Immune Thrombocytopenic Purpura diagnosed?
iii) How can patients with Immune Thrombocytopenic Purpura be treated optimally?

Target Population

This guideline is developed for the management of patients with Immune Thrombocytopenic Purpura in children, adults and pregnant mothers.

Target Group

This guideline is applicable to all primary care providers, physicians, paediatricians, obstetricians and others involved in treating patients with Immune Thrombocytopenic Purpura.

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The draft guideline was reviewed by a panel of independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence supporting the recommendations in the guideline.

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TABLE OF CONTENTS

1. INTRODUCTION

Immune thrombocytopenic purpura (ITP) affects both children and adults. It is an autoimmune disorder characterised by persistent thrombocytopenia (peripheral platelet count of less than 150 $x10^9$/L) due to autoantibody binding to platelet antigen(s) causing their premature destruction by the reticulo-endothelial system, in particular the spleen.

In childhood, the peak age is 2-4 years, girls and boys are equally affected, and in most children the disease is self-limiting with spontaneous recovery occurring in several weeks to several months. In adults, ITP is most common among young women and the disease is more insidious in its onset and chronic in its course [1 Level 9]. The true incidence of ITP is still unknown. In children, the overall incidence of ITP is 4 – 5.3 per 100,000 [2 Level 8 ; 3 Level 6]. It has been reported that the incidence of chronic adult ITP is around 5.8-6.6 new cases per 100,000 population per year in the USA [4 Level 9].

2. ITP IN ADULTS

2.1 Clinical Features

In adults, ITP typically has an insidious onset, with no prodromal illness. Symptoms and signs are highly variable, ranging from the common asymptomatic patient with mild bruising or mucosal bleeding to frank haemorrhage from any site, the most serious of which is intracranial.

The most common manifestation in ITP is mucocutaneous bleeding with purpura, epistaxis, gingival bleeding and menorrhagia. Overall, bleeding symptoms are uncommon unless the ITP is severe (platelet count < $30x10^9$/l) [1 Level 9]. The degree of bleeding is largely dependent on the platelet count and patients with platelet counts below $10x10^9$/l (and usually below $5x10^9$/l) are at greatest risk of bleeding, including intracranial haemorrhage.

2.2 Diagnosis

There is no gold standard diagnostic test to confirm ITP. The diagnosis of ITP remains clinical and is based principally on the exclusion of other causes of thrombocytopenia by the history, physical examination, full blood count, peripheral blood film and autoimmune screen.

a. Clinical

ITP can be defined as isolated thrombocytopenia with no clinically apparent associated conditions or other causes of thrombocytopenia (e.g. HIV

infection, systemic lupus erythematosus, lymphoproliferative disorders, myelodysplasia, drug-induced thrombocytopenia, congenital/hereditary non-immune thrombocytopenia, or pregnancy) [5 Level 9].

Patients with isolated abnormalities on serologic tests (e.g. positive tests for antinuclear or antiphospholipid antibodies) but without a clinically evident disorder (e.g. systemic lupus erythematosus) are included within the diagnosis of ITP [6 Level 8 ; 7 Level 8].

Patients with thrombocytopenia and an associated clinically apparent autoimmune disease may have an illness comparable to ITP. Lists of conditions which must be considered and excluded in the diagnostic evaluation of a patient with suspected ITP are as in Table 1.

Table 1: Differential Diagnoses

Falsely low platelet count

In vitro platelet clumping caused by EDTA-dependent or cold-dependent agglutinins.

Common causes of thrombocytopenia

Pregnancy (gestational thrombocytopenia, preeclampsia)
Drug-induced thrombocytopenia (common drugs include heparin, quinidine, quinine, and sulfonamides)
Viral infections, e.g. HIV, infectious mononucleosis, hepatitis
Hypersplenism due to liver disease

Other causes of thrombocytopenia that mimic ITP

Myelodysplasia
Congenital thrombocytopenia eg. Wiskott-Aldrich syndrome, von Willebrand disease type 2B
Thrombotic thrombocytopenic purpura-Haemolytic uremic syndrome
Chronic disseminated intravascular coagulation

Thrombocytopenia associated with other disorders

Autoimmune diseases eg. systemic lupus erythematosus
Lymphoproliferative disorders eg. chronic lymphocytic leukaemia, non-Hodgkin's lymphoma

Adopted with permission from George et al 1998.

b. Laboratory

The finding of thrombocytopenia on a routine blood count may be the first indication of immune thrombocytopenia.

Thrombocytopenia needs to be confirmed on peripheral blood film examination to exclude pseudo-thrombocytopenia. Pseudo-thrombocytopenia due to EDTA-dependent platelet agglutination is a cause of spuriously low platelet count. This condition occurs in about 0.1% of adults, and is easily confirmed by the finding of a normal platelet count using a sample taken in citrate or heparin rather than EDTA anticoagulant [8 Level 9].

An autoimmune screen should be carried out to exclude other autoimmune diseases which may be associated with thrombocytopenia, e.g. systemic lupus erythematosus or antiphospholipid syndrome. HIV antibody testing should also be done in patients with risk factors for HIV infection [5 Level 9].

If the history, physical examination, blood count and peripheral blood film examination are compatible with a diagnosis of ITP and do not include atypical findings, additional investigations such as bone marrow examination and assays for platelet antibodies are not indicated [5 Level 9].

Recommendations: Indications for Bone Marrow Examination

- over 60 years of age
- prior to splenectomy
- presence of atypical features
- poor response to first line treatment (eg. prednisolone) [5 Level 9] (Grade C)
- relapsed ITP following complete remission [9 Level 8] (Grade C)

Assays for anti-platelet antibodies such as direct platelet immunofluorescence test (PIFT) and assays for antibodies to specific platelet membrane glycoproteins (GP) IIb/IIIa and Ib/IX are not sensitive or specific enough to be recommended as routine tests in the diagnosis of ITP [10 Level 8 ; 11 Level 8].

However, these tests may be useful in distinguishing between immune and non-immune thrombocytopenia in complex cases such as combination of bone marrow failure associated with immune-mediated thrombocytopenia,

ITP patients refractory to first and second line treatment, drug-dependent immune thrombocytopenia, miscellaneous disorders (rare) e.g. monoclonal gammopathies and acquired auto-antibody mediated thrombasthenia [5 Level 9].

2.3 Management of Chronic ITP

Most adults with ITP have a good outcome except for a small subset that has severe symptomatic ITP. Eighty-five percent of patients who had platelet >30x 10^9/L had long term mortality risk equal to the general population even without treatment. Patients who suffered major bleeding during their follow up had median platelet counts of 10x 10^9/L [12, Level 6].

These findings favour treating patients with platelet count <30x 10^9/L and/or symptomatic ITP. This will reduce the risks of infection through immunosuppression [12 level 6; 13 , Level 6 ; 14 , Level 8].

Recommendations : When to Treat

Patients with platelet counts exceeding 30 x 10^9/L require no treatment. Treat when symptomatic or when platelet count < 30x10^9/L unless they are undergoing surgical procedures (Grade C)

'Safe' Platelet Thresholds for Procedures

Platelet counts considered "safe" in adults undergoing procedures :
Dentistry > 10 x 10^9/L
Extractions > 30 x 10^9/L
Regional dental block > 30 x 10^9/L
Minor surgery > 50 x 10^9/L
Major surgery > 80 x 10^9/L (Grade C)

a. First Line Treatment

i. Corticosteroid

Two thirds of patients will respond to prednisolone at 1mg/kg body weight/day for 2-4 weeks [15 Level 9; 16 Level 8]. However long term remission is seen only in 10-20% of patients [16 Level 6; 17 Level 8].

The response to oral steroids is slower compared to intravenous methylprednisolone [18 Level 3].

ii. Intravenous Immunoglobulin (IVIG)

IVIG is effective in elevating the platelet count in 75% of patients, of whom 50% will achieve normal platelet counts. However the responses are transient lasting between 3 to 4 weeks [19, Level 9]. Combination of IVIG/ oral prednisolone seemed to be more effective than IV methylprednisolone/ oral prednisolone in adults with severe ITP [20, Level 2]. There is no difference between the two dosing of IVIG 0.4g /kg/day for 5 days and 1 g/kg/day for two days [21, Level 2].

Adverse effects with intravenous immunoglobulin are common but generally mild including fever, chills, rigors, headache and backache [20, Level 2].

Recommendations : First Line Therapy in Adults

Oral corticosteroids are used as first line therapy at 1 mg/kg body weight /day (max 60 mg) for 2-4 weeks tapering off over several weeks (Grade B).

Intravenous methylprednisolone (30 mg/kg body weight/day with total maximum daily dose of 1 gram for 3 days) is an alternative to oral prednisolone where more rapid response is required (Grade B).

Intravenous immunoglobulin (1g/ kg body weight /day for 2 days or 0.4 g/kg/day for 5 days) is useful in severe ITP who require rapid rise of platelet count. (Grade A)

b. Second Line Treatment

i. Splenectomy

Splenectomy is considered as second line therapy with two thirds of patients achieving a complete remission [22 Level 8; 16 Level 8; 23 Level 8; 24 Level 8; 25 Level 8; 5 Level 9; 26 Level 9]. The rest will experience a lesser increase or only transient normalization of platelet counts. Most relapses occur within the first 6 months after splenectomy, however, a small percentage of patients continue to relapse thereafter [16 Level 8; 27 Level 8].

Predicting response to splenectomy

There are conflicting data on the predictive value of the response to steroids [28 Level 8; 29 Level 8; 30 Level 8; 31 Level 8; 32 Level 8; 23 Level 8] and IVIG [33 Level 8; 34 Level 8; 30 Level 8; 29 Level 8; 35 Level 8; 23 Level 8; 32 Level 8] on splenectomy but in general they do not have a high predictive value.

The most sensitive indicator of response to splenectomy is the indium-labelled autologous platelet scanning with more than 90% response if platelet destruction is primarily in the spleen [36 Level 8]. However, platelet sequestration studies are difficult to perform and currently not available in Malaysia.

The timing of splenectomy does not appear to affect the response rate [22 Level 8; 36 Level 8; 30 Level 8; 31 Level 8; 23 Level 8; 32 Level 8].

Post-operative complications

Splenectomized patients have a small risk for overwhelming sepsis with an estimated mortality rate of 1.2% [37 Level 1].

Operative mortality rates are < 2 % in most series [38 Level 8; 12 Level 8; 24 Level 8].

Recommendations : Prevention of Post Splenectomy Sepsis
At least 2 weeks before surgery, the patient should be immunized with a polyvalent pneumococcal vaccine, Hemophilus influenzae b (Hib) conjugate vaccine and meningococcal polysaccharide vaccine. (Grade B)
A booster dose of pneumococcal vaccine should be given every 5 years. (Grade B)
Prophylactic antibiotics with oral penicillin 250 mg bd or erythromycin 500 mg bd should be given. (Grade C)
The optimal duration of antibiotic prophylaxis is still uncertain (Grade C) but is recommended lifelong in the UK guidelines. (Grade C)

Accessory spleen

The presence of an accessory spleen should be considered in patients who fail to respond to splenectomy or relapse following an initial response.

ii. Danazol

Response can be as high as 60% especially in older females and those who have undergone splenectomy [39 Level 5]. It is used as a steroid-sparing agent in steroid responsive patients who require longer term high dose steroids or in patients who are refractory to steroids. The usual dose is 200 mg 2-4 times daily [39 Level 5] and a trial of at least 6 months should be allowed.

iii. Azathioprine

Approximately 20% of patients may achieve a sustained complete response with this agent while 30 to 40% may have a partial response [40 Level 9]. The recommended dose for ITP is 2 mg/kg/day usually up to a maximum of 150mg/day [26 Level 9]. The treatment should be continued for up to 4 to 6 months before a patient is considered non-responsive [41 Level 8; 42 Level 8].

Azathioprine is associated with few side effects, even with prolonged use [43 Level 9; 41 Level 8]. The potential side effects include a reversible leucopenia and elevated transaminases. Secondary malignancies and myelodysplastic syndrome have been reported [**44 Level 9**].

iv. Dapsone

Responses are seen in 50% of patient with platelet counts < 50 $x10^9$/L with sustained responses in 25% of patients. Half of all patients with chronic ITP treated with dapsone will show some response within 3 weeks [45 Level 3]. It is less effective in severe cases especially those who have undergone splenectomy [46 Level 4]. The usual dose is 75-100 mg orally [45 Level 3].

v. Anti-D

This is effective only in Rh(D) positive non-splenectomized patients with response rate of up to 75 to 90% of adults with ITP. The effect last for more than 3 weeks in 50% of responders [47 Level 8]. The usual dose is 50-75mcg/kg [48 Level 8; 47 Level 8; 49 Level 8]. However this drug is not readily available in Malaysia.

Recommendations : Second Line Therapy in Adults

Patients not responding to steroids or requiring persistently high doses require second line therapy. The choice of therapy must be individualized. The treatment options are:

- Splenectomy.
- Danazol
- Azathioprine
- Dapsone
- Anti-D

Grade C

c. Refractory ITP

Refractory ITP is defined as failure to respond to first or second line treatment. This group accounts for 5.6% of all patients with ITP and are expected to have the worst outcome with a 4.2 fold increased mortality risk [12 Level 6].

The cornerstone of management is to raise the platelet counts to a safe level of more than 30 X 10^9/L taking into account coexisting risk factors for bleeding, patient's level of acceptance of modifications in lifestyle, tolerance or lack of tolerance to treatment, and the potential toxic effects of each intervention [12 Level 6]. Elderly patients are both more likely to have severe bleeding and to suffer debilitating side effects from treatment [50 Level 3].

Treatment Options

i. Eradication of Helicobacter Pylori

The regression of ITP has been reported after eradication of *Helicobacter pylori* [51 Level 5].

ii. Intravenous Immunoglobulin (IVIG)

Repeated infusions of IVIG are reserved for intervention during serious bleeding and to raise platelet count before surgical procedure. It is often lifesaving, but refractoriness can develop [12 Level 6].

iii. Vinca Alkaloids

The overall response is 50% in splenectomized patients, but is usually not sustained [52 Level 8]. It may cause a transient increase in the platelet count lasting between 1 and 3 weeks in two-thirds of patients treated. The dose for vincristine is 1 mg (occasionally 2 mg) or vinblastine 5-10 mg weekly for 4-6 weeks.

iv. High Dose Methylprednisolone

Two studies have shown that high dose methylprednisolone is effective in the treatment of patients with refractory ITP [53 Level 9; 18 Level 3].

v. Cyclosporin A

Cyclosporin A can be used as monotherapy or in combination with steroids. Two small case series reported responses between 50-80% [54 level 8; 55 Level 8]. The cyclosporin dose is between 2.5 to 5 mg/kg/day in divided doses. The patient should be treated for at least 4 weeks before a response can be observed. The side effects may limit widespread practical use.

vi. Mycophenolate Mofetil

Mycophenolate mofetil had been shown to be of value in some patients with autoimmune cytopenias including refractory ITP [56 Level 8; 57 Level 5] with overall response of 62%. The dose is 1.5 to 2.0 g/day. Side effects are quite tolerable with slight nausea and diarrhoea.

vii. Anti-CD20 Antibody (Rituximab)

The overall response rate is reported between 40 to 50%. Younger patient have a better response [58 Level 8]. Twenty eight percent of patients will have sustained response more than 6 months. The recommended dose is 375 mg/m^2 rituximab weekly for 4 weeks [58 Level 8; 59 Level 8].

viii. Combination chemotherapy

Combination chemotherapy including cyclophosphamide, vincristine with prednisone has been reported to give a response of 80% with prolonged sustained effect [60 level 5]. The side effects include myelosuppression and risk of secondary malignancies, and hence should be used with caution.

ix. Others

Other modalities for treatment include liposomal doxorubicin [61 Level 8] anti CD52 (Campath-1H) [62 Level 5] and protein A immunoadsorption [63 Level 5]. Bone marrow transplant should only be considered in the experimental context until there is a bigger clinical trial to prove its efficacy [64 Level 9; 65 Level 9].

Recommendations : Management of Refractory ITP in Adults

For patients who have platelet counts between 10 to 30 X 10^9/L (Grade B) without other risk factors for bleeding, treatment is not indicated unless surgery is planned. (Grade C)

Modalities of treatment include eradication of Helicobacter Pylori, Intravenous Immunoglobulin (IVIG), high dose methylprednisolone, cyclosporin A, mycophenolate mofetil, rituximab, and combination chemotherapy. (Grade C)

d. Emergency Treatment

There is no published data on the efficacy of different treatments for the management of urgent, life-threatening bleeding. The serious consequences of severe, life-threatening bleeding justify the use of several regimens.

Appropriate interventions include platelet transfusions, high-dose parenteral glucocorticoid (e.g. methylprednisolone 30 mg/kg daily for 3 days), and IVIG, either alone or in combination with corticosteroids [26 Level 9].

Conditions requiring urgent treatment in adults with ITP are:

1. active bleeding from the gastrointestinal or genitourinary tracts
2. intracranial bleed
3. bleeding into important structures e.g. upper airway

The aims of treatment are to elevate platelet count quickly (within 24 hours) and to arrest bleeding.

Recommendations : Emergency treatment

1. i.v. methylprednisolone 500mg to 1g/day for 3 days
2. IVIG 1g/kg/day for 2 consecutive days
3. Platelet transfusion

Emergency splenectomy is considered if above measures fail to increase platelet count to safe level i.e. above $50x10^9$/L. (Grade C)

Indications for platelet transfusion in ITP

Platelet transfusion in ITP is only given in the following situations:

1. life-threatening haemorrhage e.g. intracerebral haemorrhage (ICH)
2. severe thrombocytopenia < 10×10^9/L and patient has to undergo an emergency surgery

High dose i.v. steroids and IVIG must also be given together to raise the platelet counts and to stop the haemorrhage. Platelet survival is increased if the platelets are transfused immediately after IVIG infusion [66 Level 9].

Recommendations : Platelet Transfusion Dosage

- 6-8 U of platelet concentrate, or 1 U/10 kg body weight. (Grade C)

  1 U of platelets to increase count of a 70-kg adult by 5-10 x 10^9/L and an 18-kg child by 20 x 10^9/L (Grade C)

3. ITP IN CHILDREN

In children, ITP is usually an acute, self-limiting disorder that resolves spontaneously. The clinical onset is usually acute, with a spectrum of bleeding severity ranging from superficial (petechiae, purpura) to life-threatening. Hepatosplenomegaly or lymphadenopathy is absent. The majority will give a history of a viral infection in the preceding 2-4 weeks. 75% of patients remit spontaneously with 70% achieving platelet count of more than 50 $x10^9$/L by the fourth week of illness [67 Level 9].

The diagnosis can be made clinically based principally on the history, physical examination (no stigmata of malignant disease or congenital thrombocytopenia), full blood count (isolated thrombocytopenia), and examination of the peripheral blood smear (exclude abnormal cells).

Bone marrow examination is seldom required. Less than 4% of 127 children had a different diagnosis from ITP following bone marrow examination [68 Level 8]. It is only indicated if the patient is not responding to therapy or before starting steroids (to avoid partially treating an undiagnosed acute leukaemia) [26 Level 9].

The need for other investigations depends on clinical indications : ANF and DNA antibodies in those progressing into chronic ITP, CMV serology in those under 1 year of age, immunoglobulin levels in those with recurrent infections and HIV screening for those at risk e.g. parents with HIV infection, intravenous drug users. Coagulation profile is needed for those with suspected non-accidental injury, inherited bleeding disorders or meningococcal infection.

Recommendations : Diagnosis of ITP in Children

Full blood count with differential and a peripheral blood film examination are the only two recommended laboratory investigations in a child with typical clinical features of ITP (Grade C)

Bone marrow examination is only indicated in patients not responding to therapy or before starting steroids. Additional investigations are done as clinically indicated (Grade C)

3.1 Management of Acute ITP

Outpatient observation and monitoring will suffice for those with platelet count > 20 $x10^9$/L without bleeding tendencies. Precaution with physical activities, avoidance of contact sports and seeking immediate medical attention if bleeding occurs should be advised [69 Level 9]. A repeat platelet count should be performed within the first 7-10 days to ensure there is no evidence of a serious evolving marrow condition. Otherwise, the count can be repeated only when clinically indicated [69 Level 9].

Hospitalisation is required in acute severe life-threatening or mucosal bleeds regardless of platelet count or if platelet count is < 20 $x10^9$/L without bleeding but with poor access to health care. Hospital admission also depends on parents' request and on their confidence in homecare [70 Level 9].

Treatment is indicated if there is a life threatening bleeding episode (e.g. ICH) regardless of platelet count or if the platelet count is < 20 $x10^9$/L with mucosal bleeding [5 Level 1].

There is insufficient evidence to guide treatment in those with platelet count of <10 $x10^9$/L without bleeding manifestations. Treatment should be individualized.

The choice of treatment is : IVIG 0.8 g/kg as a single dose [71 Level 1] or oral steroids (oral prednisolone 2 mg/kg/day for not more than 14 days or oral prednisolone 4 mg/kg/day for 4 days) [72 Level 6].

Both steroids and IVIG may shorten the thrombocytopenic phase in responsive cases but do not influence outcome of disease. They are both effective in raising platelet count more rapidly compared to no treatment [73 Level 1]. However, there is no direct evidence indicating either treatment is superior to the other, reduces bleeding complications or mortality from ITP or influences progression to chronic ITP [74 Level 9; 26 Level 9; 2 Level 8].

Recommendations : Management of Acute ITP in Children

Hospitalisation is required in acute severe life-threatening or mucosal bleeds regardless of platelet count or if platelet count is < 20 $x10^9$/L without bleeding but with poor access to health care. (Grade C)

Management of ITP should not depend only on platelet numbers but also on clinical severity. IVIG and oral steroids are the recommended choices of treatment but they do not influence the final outcome of the disease. (Grade A)

Treatment options include :
- IVIG 0.8 g/kg as a single dose, or
- oral prednisolone 2 mg/kg/day for not more than 14 days, or
- oral prednisolone 4 mg/kg/day for 4 days

3.2 Management of Chronic ITP

Chronic ITP in children is defined as persistent thrombocytopenia after 6 months of onset, is strikingly different from that in adults with complete, spontaneous remission seen in the majority [75 Level 6; 76 Level 6]. There is a wide spectrum of manifestations. However, there is insufficient evidence in the literature to determine the best management for these patients [77 Level 9].

As far as possible, allow the disease to remit spontaneously. However, other causes of thrombocytopenia e.g. SLE should be considered. Asymptomatic patients can be left without therapy with advice regarding precautions during physical activities, contact sports, dental/surgical procedures and menses.

Symptomatic children may need short courses of treatment (as for acute ITP) during periods of "relapse" or for surgical procedures. Prolonged steroid therapy or regular infusions of IVIG are not justified [75 Level 6].

For those with persistent bleeding problems, second-line therapies include steroids e.g. dexamethasone (oral 1mg/kg) given on 4 consecutive days every 4 weeks for 4 months [78 Level 8] or oral methylprednisolone for 7 days (30 mg/kg for 3 days followed by 20 mg/kg for 4 days) every 4 weeks for maximum of 6 courses [79 Level 8] and anti-D immunoglobulin 45-50 ug/kg immunoglobulin in Rh positive patients [80 Level 6]. Second-line therapy should only be started following consultation with a paediatric haematologist.

Recommendations : Management of Chronic ITP in Children

Allow chronic ITP children to remit spontaneously as far as possible (Grade B)

Use of steroids or IVIG should be for acute bleeding manifestations only (Grade B)A paediatric haematologist should be consulted if second-line therapy is required (Grade C)

3.3 Refractory ITP

Splenectomy is rarely indicated in children with ITP as spontaneous remissions continue to occur up to 15 years from diagnosis [75 Level 6]. It is important to note that the risk of dying from childhood ITP is very low (0.002%) whilst the mortality associated with post-splenectomy sepsis is 1.4 – 2.7% [36 Level 8; 81 Level 8].

However, splenectomy is justified when there is a life threatening bleeding event or severe lifestyle restrictions and where there has been no or only transient success with intermittent IVIG, pulsed steroids or anti-D [82 Level 9].

Up to 70% of children achieve complete remission post-splenectomy [83 Level 6]. It is important to ensure pre-splenectomy immunization against pneumococcus, haemophilus and meningococcus . Post-splenectomy patients require life-long penicillin prophylaxis and 5-yearly pneumococcal booster (CDC 1993).

Agents that have been used when first and second-line therapies fail include Rituximab [84 Level 8] and cyclosporin [54 Level 8]. Children who reach this stage should be managed by a paediatric haematologist.

Recommendation : Management of Refractory ITP in Children
In children with symptomatic refractory ITP, splenectomy is an option. There is insufficient evidence to recommend third-line immunomodulating agents (Grade C)

3.4 Emergency Treatment

Serious bleeding e.g. severe epistaxis, GIT bleeding or bleeding causing a drop in haemoglobin concentration was seen in 17% of 332 pts over 10 years [85 Level 9]. However, the most serious form of bleeding i.e. intracranial bleeding has a very low incidence of 0.1 to 0.5 % [86 Level 8 ; 87 Level 8 ; 88 Level 8].

The following methods have been employed in cases of serious bleeding / intracranial haemorrhage :

Platelet transfusion
A rapid increase in the platelet count is necessary in life-threatening haemorrhage. The immediate administration of a larger than usual (8-12

units per sq meter) transfusion of donor platelets plus i.v. methylprednisolone 30 mg/kg (maximum 1 gm) over 20 to 30 minutes have been advocated [89 Level 6; 4 Level 6].

Intravenous methylprednisolone

The usual dose used is 30 mg/kg/day for three days. Seventy percent of children have been reported to show an unsustained rise in platelet counts [90 Level 8; 91 Level 8; 92 Level 8].

Intravenous immunoglobulins (IVIG)

Infusion of IVIG has been reported to cause a rapid rise in platelet count to at least above 30 $x10^9$/L in 80% of children. A single dose of 0.8 g/kg or 1 g/kg [71 Level 8] has been shown to be as effective as doses of 0.25 – 0.5 g/kg/day for two days in a randomized multicentre study [93 Level 5].

Combination IVIG and methylprednisolone

Several authors have combined IVIG with methylprednisolone to increase the platelet count rapidly in life-threatening bleeds [94 Level 8] reported 11of 11 patients had increased platelet count above 40 $x10^9$/L following infusion of IVIG plus methyl-prednisolone and this was sustained for at least 24 hours (Level 8). In a consensus statement, [5 Level 9] also reported on the efficacy of this combination.

Emergency splenectomy

This measure will lead to a rapid increase in platelet count; at least 75% of patients will respond [95 Level 9 ; 96Level 8]. If this procedure is to be performed, the laparoscopic method is preferred. Laparoscopic splenectomy has been associated with a shorter hospital stay, diminished blood loss and lower cost compared to an open procedure [97 Level 9 ; 98 Level 9].

Recommendations : Emergency Treatment

In the event of life-threatening haemorrhage, a two-to-three fold transfusion of donor platelets is required. (Grade C)

Concomitant use of IVIG alone (0.8 g/kg stat) or in combination with methylprednisolone (30mg/kg/day; max 1 gm for three days) is recommended. Emergency splenectomy (preferably laparoscopic) may be justified. (Grade C)

4. ITP IN PREGNANCY

Thrombocytopenia in pregnancy is relatively common, occurring in 7 to 10% of unselected pregnancies. However, ITP only accounts for approximately 3% of these cases [99 Level 9] as compared to gestational or incidental thrombocytopaenia of pregnancy (74%) and hypertensive disorders of pregnancy (21%) [100 level 6].

ITP in pregnancy must be differentiated from other causes of thrombocytopenia.

Table 2 Differential Diagnoses

1. Gestational or incidental thrombocytopaenia of pregnancy (mild thrombocytopaenia >70 x 10^9/L occurring in late gestation)
2. Pre-eclampsia
3. HELLP syndrome
4. Thrombotic thrombocytopenic purpura (TTP)
5. Disseminated intravascular coagulation (DIC)
6. Antiphospholipid syndrome
7. Folate deficiency
8. Viral: Dengue, HIV, HCV
9. Drug-related
10. Spurious due to platelet clumping or macrothrombocytes

Modified from British Committee for Standards in Haematology General Haematology Task Force (2003)

4.1 Diagnosis

a. Clinical

The diagnosis of ITP in pregnancy remains one of exclusion as there is no confirmatory laboratory test [101 Level 9]. Therefore it is important to obtain a detailed history and physical examination to exclude other secondary causes and to assess the clinical severity of haemostatic defects [102 Level 9].

b. Laboratory

The aim of investigation is to confirm thrombocytopenia and to exclude secondary causes. If gestational thrombocytopenia is suspected, only regular monitoring of platelet counts is required without further investigations [103 Level 9; 100 level 6].

Recommendations : Investigations for Thrombocytopenia in Pregnancy

The important investigations include :

1) Full blood count
2) Peripheral blood film: to exclude platelet clumping and red cell fragmentation (in TTP, pre-eclampsia, HELLP or DIC)
3) Coagulation screen (PT, APTT, fibrinogen, D-dimer)
4) Liver function tests
5) HIV screening
6) ANA
7) Lupus anticoagulant/ anticardiolipin antibody
   - for patients with past history of unexplained pregnancy losses/ thrombosis [102] level 9 (Grade C)

Bone marrow examination is unnecessary unless there is suspicion of myelodysplastic syndrome, leukaemia or lymphoma [104] Level 9 (Grade C)

4.2 Management

Although pregnancy is not discouraged in woman with preexisting ITP, maternal and foetal complications can occur. Close collaboration between haematologist, obstetrician, neonatologist and anaesthetist is needed to ensure a good pregnancy outcome [26] Level 9.

Platelet counts in women with ITP may decrease as pregnancy progresses and need to be monitored closely as follows:

1st to 2nd trimester	:	monthly
3rd trimester	:	2 weekly
at term	:	weekly

The principal of management in ITP during pregnancy is to do least harm to both the mother and the foetus. The decision to treat is based on assessment of the risk of significant haemorrhage.

Corticosteroids are considered safe with regards to potential teratogenecity and foetal toxicity as 90% of the administered dose is metabolized in the placenta [105] Level 6.

Intravenous immunoglobulin is effective and safe for use in pregnancy. It's effect is transient and last for about a month [104 Level 9].

Splenectomy should be avoided if possible or should be deferred to the second trimester to prevent miscarriage [26 Level 9].

Anti-D Immuneglobulin among Rh positive non-splenectomized women can be considered as second line therapy [106 Level 9].

Androgen analogues such as danazol and all the other potential teratogenic agents like cyclophosphamide or vinca alkaloids are strictly prohibited in pregnant women.

Recommendations : Modalities of Treatment for ITP in Pregnancy
Corticosteroids and IVIG are effective and safe in pregnancy and are used as first line therapy. (Grade B)
Androgen analogs such as danazol and cytotoxic agents are contraindicated in the treatment of ITP in pregnancy due to its teratogenecity. (Grade C)
Splenectomy is considered only if above measures fail to elevate the platelet counts and patient has serious bleeding. This is best deferred until the second trimester to prevent miscarriage. (Grade C)

a. Management before 36 weeks

Management can be divided into 3 groups based on clinical presentation and platelet count.

1) Asymptomatic patients with mild to moderate thrombocytopenia (platelet count >20 x 10^9/L)
   a. No treatment is required
   b. To expect further drop of platelet during 3rd trimester

2) Symptomatic patients or those with moderate to severe thrombocytopenia (platelet count <20 x 10^9/L)

a. Corticosteroid prednisolone 1mg/kg/day with rapid taper to keep <30mg/day (safe from adverse foetal effects)

AND/ OR

b. IVIG 1g/kg (according to pre-pregnant weight) every month

3) Severe thrombocytopaenia (platelet count <10 x 10^9/L)

The approach in managing these groups of patients is to deliver the minimum amount of therapy necessary.

a. high dose corticosteroid (methylprednisolone/dexamethasone)

AND

b. periodic high dose IVIG 1g/kg x 2 days

Splenectomy during 2nd trimester is considered if above measures fail to elevate the platelet count.

Recommendations : When to treat?

- Platelet count < 20 x 10^9/L before 36 weeks
- Symptomatic bleeding at any trimester
- Platelet count < 30 x 10^9/L after 36 weeks (Grade C)

b. Management after 36 weeks

The mother should be assessed at 36 weeks by both the haematologist and the obstetrician.

- platelet count >30 x 10^9/L
  - safe for normal vaginal delivery in patients with otherwise normal coagulation [108] Level 9
- platelet count <30 x 10^9/L
  - admit for pulsed IVIG and close monitoring

The mode of delivery in a mother with ITP is based on obstetric indications [109] Level 9.

Caesarian section is only for obstetric indications and the patient will require:

i. iv corticosteroids if platelet count between 30-50 x 10^9/L
ii. IVIG and iv corticosteroids if platelet count <30 x 10^9/L
iii. IVIG and iv corticosteroids plus platelet transfusion if platelet count <10 x 10^9/L

Recommendations : Mode of delivery

The mode of delivery in mothers with ITP is decided primarily by obstetrical indications (Grade C)

The use of vacuum extraction and complicated instrumental delivery should be avoided if possible (Grade C)

c. Management in labour

Platelet count above 50 x 10^9/L is safe for caesarian section under general anaesthesia but not epidural anaesthesia. Epidural anaesthesia is best avoided because of the risk of epidural haematoma and cord compression. However, patients who prefer epidural analgesia need to be admitted earlier for IVIG infusion in order to raise the platelet counts to a safe level >80 x 10^9/L [104 Level 9].

If platelet counts are less than 50 x 10^9/L and patient requires immediate caesarian delivery, administer IVIG and methylprednisolone. Give platelet transfusion just prior to surgery.

'Safe' Platelet Thresholds for delivery

- vaginal delivery: > 30 x 10^9/L
- caesarean section: > 50 x 10^9/L
- epidural anaesthesia: > 80 x 10^9/L

(Grade C)

5. NEONATAL CARE

The overall incidence of thrombocytopenia in newborns born to mothers with ITP is reported to vary from 14.3 to 37.5% [110 Level 8; 111 Level 8]. Severe thrombocytopenia (<50 X 10^9/l) occurs in 8.9 to 14.7% [48 Level 8; 112 Level 8]. Bleeding is fortunately a rare event [113 level 8] with overall incidence of intracranial haemorrhage about 0 to 1.5% [48 Level 8].

Prediction of neonatal thrombocytopenia is difficult, and there is no relationship with maternal platelet counts. Infants from splenectomized mothers were more likely to have thrombocytopenia [110 Level 8; 113 Level 8] as were mothers who had presence of circulating antiplatelet antibody [110 Level 8]. Thrombocytopenia is more likely if there is a previous sibling with thrombocytopenia [115 Level 8].

Cordocentesis and foetal scalp sampling to measure foetal platelet counts carry more risks than potential benefits and are not recommended [26 Level 9]. The application of scalp electrodes for monitoring in labour should be avoided [26 Level 9].

Cord blood platelet count should be done and the neonate with thrombocytopenia should be monitored daily. The platelet counts reach a nadir on days 2 to 5 [116 Level 8].

Severe thrombocytopenia (<20 X 10^9/L) or clinical haemorrhage can be treated with IVIG with good response in 75% of patients [117 Level 8]. Life threatening complications should be treated with immediate platelet transfusions and IVIG [26 Level 9].

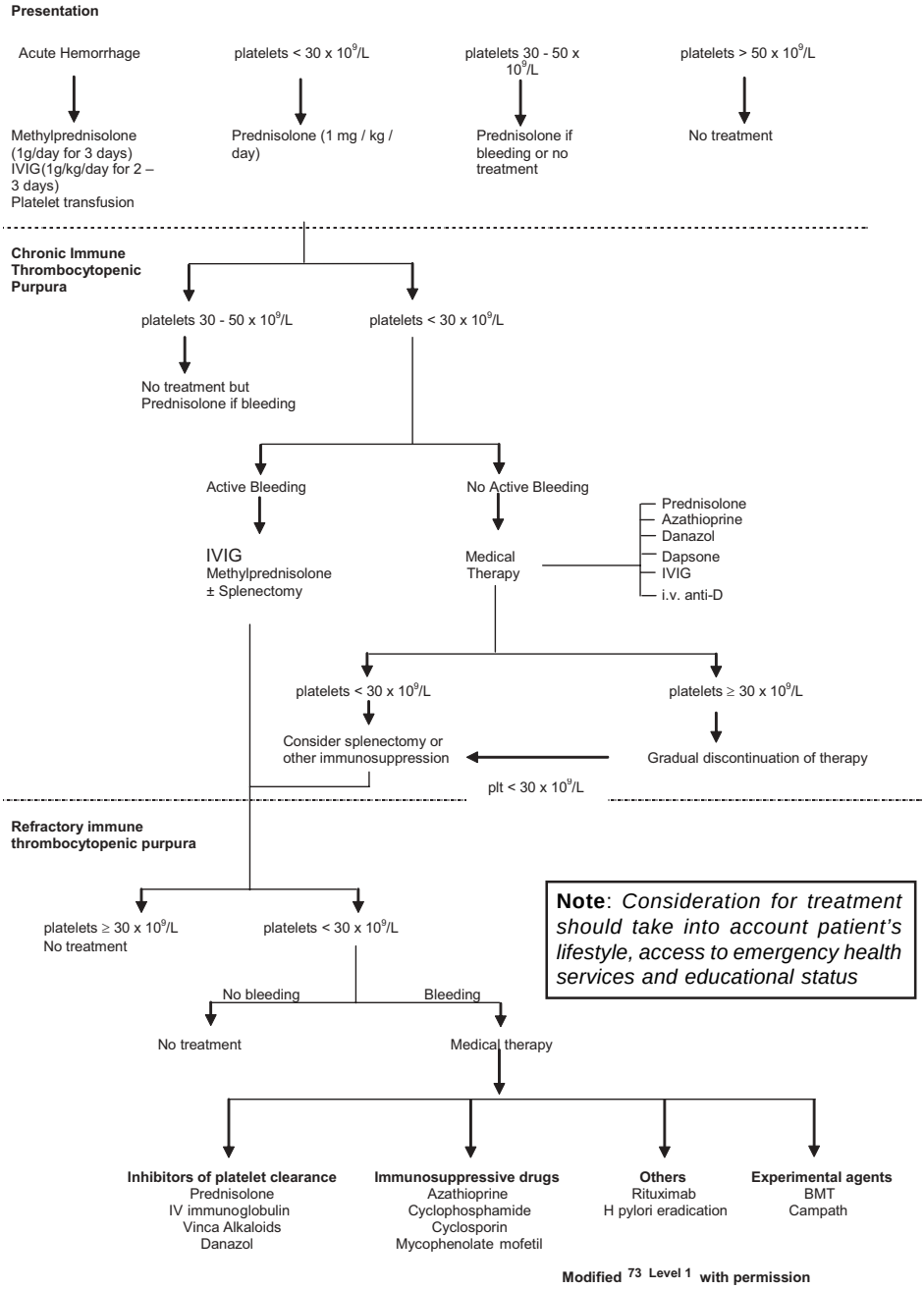
Recommendations : Management of Neonates Born to Mothers with ITP

The neonatology team should be alerted prior to delivery.
(Grade C).

The cord blood platelet count should be done for newborns of mothers with ITP. In those with low platelet counts, the count should be monitored till after the nadir, which is usually from Day 2 to Day 5.
(Grade C)

Treatment is only required when there is clinical bleeding or when the platelet count is < 20 x 10^9/L. The first line therapy is with IVIG (1 g/kg). Newborns with life-threatening haemorrhage should receive concurrent platelet transfusion. (Grade C)

TREATMENT ALGORITHM : ITP IN ADULTS

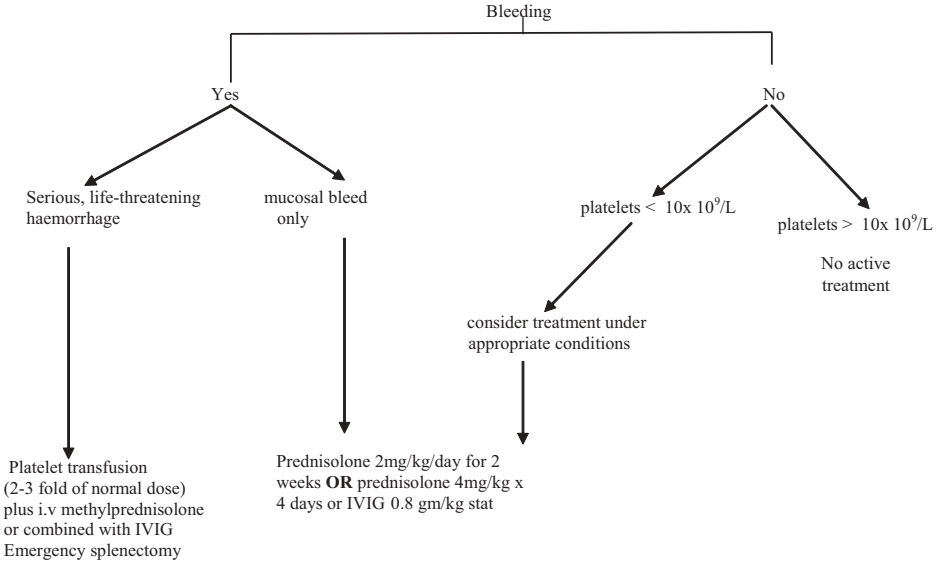


Note: *Consideration for treatment should take into account patient's lifestyle, access to emergency health services and educational status*

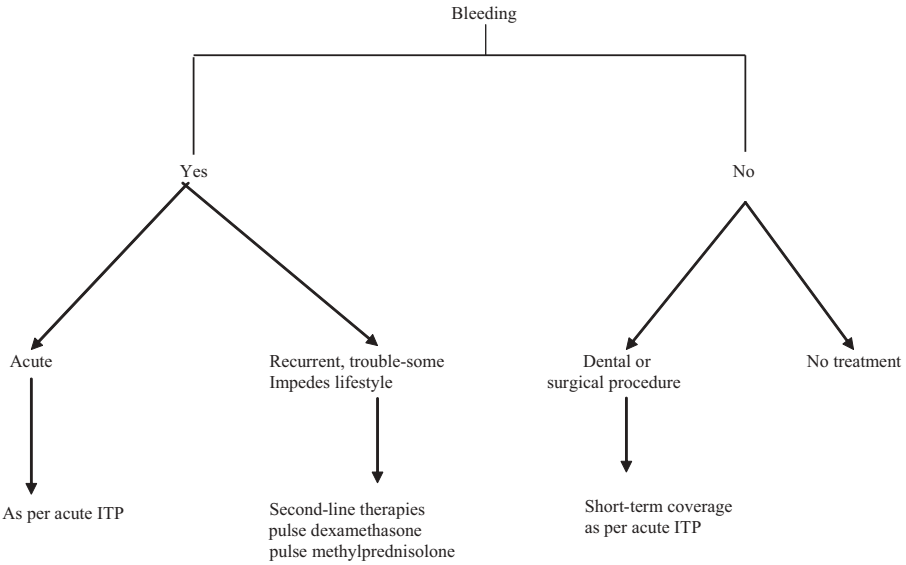
Modified [73] Level 1 with permission

TREATMENT ALGORITHM : ITP IN CHILDREN

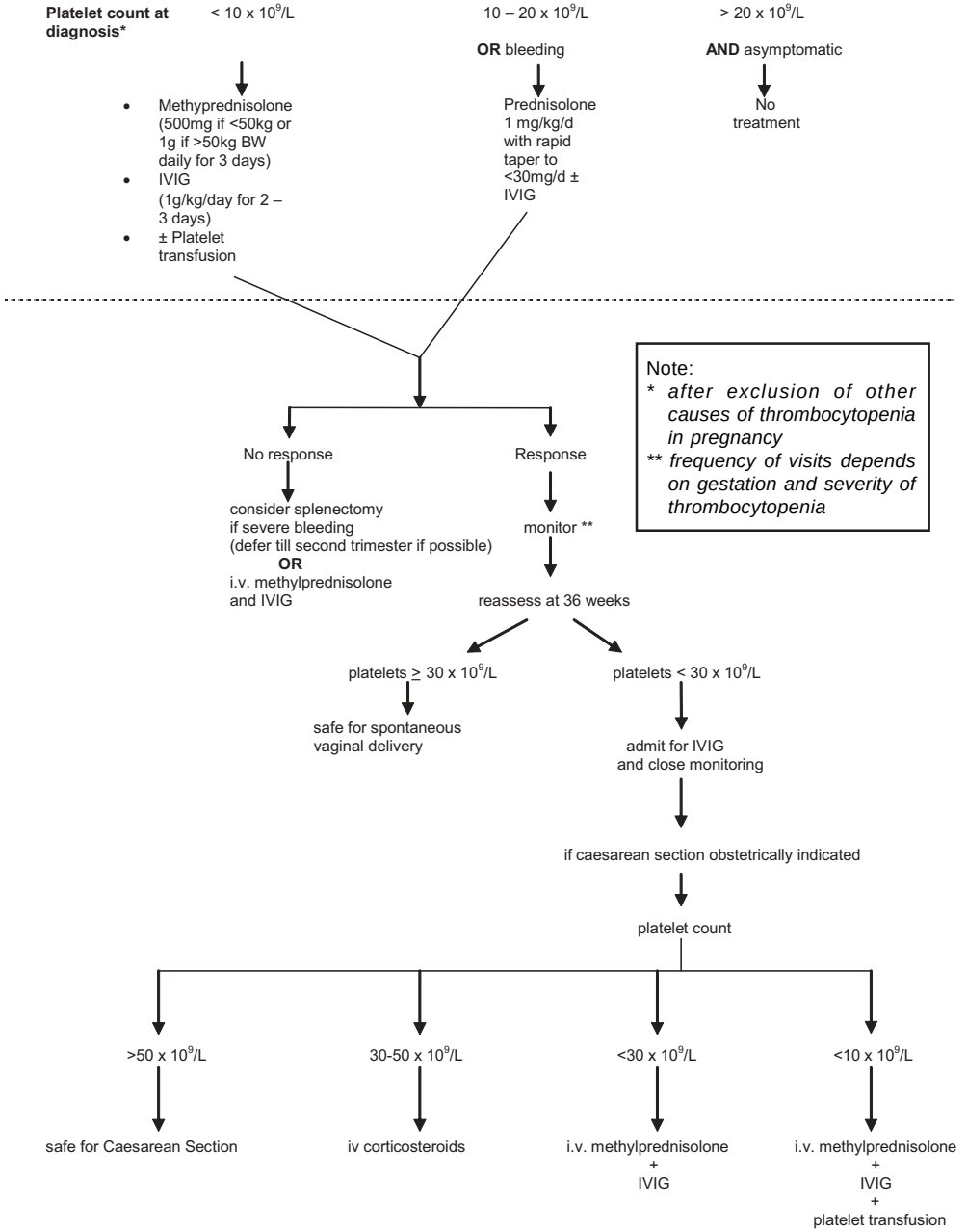
ACUTE PRESENTATION



CHRONIC ITP



TREATMENT ALGORITHM : ITP IN PREGNANCY



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LEVELS OF EVIDENCE SCALE

Level	Strength of Evidence	Study Design
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4	Good to Fair	Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports anecdotes

Adapted from Catalonian Agency for Health Technology Assessment & Research, (CAHTAR) Spain

GRADES OF RECOMMENDATIONS

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality