

**MANAGEMENT OF IDIOPATHIC THROMBOCYTOPENIC
PURPURA IN ADULT- A REVIEW ARTICLE**

Mohammad Ferdous Ur Rahaman¹, Farzana Rahman², Mohammad Salman³, Md.Abdul Kader⁴, Md Abul Kalam Azad⁵

Abstract

Idiopathic thrombocytopenic purpura (ITP), also known as primary immune or autoimmune thrombocytopenic purpura, is a common cause of thrombocytopenia and bleeding complications in children and adults. It may be confused with other causes of thrombocytopenia and is treated with agents that vary in efficacy, toxicity, and cost.

Clinical presentation varies in children and adult. In children, ITP is usually an acute, self-limited disorder that resolves spontaneously; in adults, it is typically a chronic disorder with a more insidious onset. In about one third of adults with ITP, the condition is persistent and relatively resistant to most treatments. Available evidence suggests that only about 5% of adults with chronic ITP have spontaneous remission. The principal therapeutic options for ITP include glucocorticoids, intravenous immunoglobulin and splenectomy. Other treatments have been used for refractory cases; these include intravenous anti-Rh (D), azathioprine, cyclophosphamide, danazol, vinca alkaloids, ascorbic acid, colchicine, interferon-alpha, combination chemotherapy, protein A, immunoadsorption, cyclosporine, epsilon-aminocaproic acid, plasma exchange, and accessory splenectomy.

Key words- Thrombocytopenia, Idiopathic thrombocytopenic purpura, Splenectomy.

Introduction:

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by persistent thrombocytopenia (peripheral blood platelet count < 150 x 10⁹ / l) due to autoantibody binding to platelet antigen(s) causing their premature destruction by the reticuloendothelial system, and in particular the spleen¹.

Primarily a disorder of increased platelet destruction, ITP is caused by the development of autoantibodies to platelet-membrane antigens², Platelets coated with IgG

autoantibodies undergo accelerated clearance through Fc receptors that are expressed by tissue macrophages, predominantly in the spleen and liver.

The level of thrombopoietin is not increased³, reflecting the presence of the normal megakaryocyte mass. A detailed analysis of autoantigen specificity has been published⁴. The first antigen to be identified was recognized on the basis of the failure of immune, thrombocytopenic purpura antibodies to bind to platelets that were genetically deficient in the glycoprotein IIb/IIIa complex. Antibodies that react with glycoproteins Ib/IX, Ia/IIa, IV, and V and diverse other platelet determinants have since been identified^{5,6}, and the presence of antibodies against multiple antigens is typical⁵.

Clinical Features

ITP in adults is quite distinct from the typically acute disorder seen in childhood. In adults, ITP typically has an insidious onset, with no preceding viral or other illness. Symptoms and signs are highly variable and range from the fairly common asymptomatic patient with mild bruising, mucosal bleeding (e.g. oral or gastrointestinal tract) through to frank haemorrhage from any site, the most serious of which is intracranial. Overall, bleeding

1. Dr. Mohammad Ferdous Ur Rahaman
Department of Medicine
Bangabandhu Sheikh Mujib Medical University (BSMMU).

2. Dr. Farzana Rahman
Department of Hematology
Bangabandhu Sheikh Mujib Medical University (BSMMU).

3. Dr. Mohammad Salman
Anwar Khan Modern Medical College. Dhanmondi, Dhaka.

4. Dr. Md.Abdul Kader
Department of Medicine
Bangabandhu Sheikh Mujib Medical University (BSMMU).

5. Dr. Md Abul Kalam Azad
Department of Medicine
Bangabandhu Sheikh Mujib Medical University (BSMMU).

Address of Correspondence:
Dr. Mohammad Ferdous Ur Rahaman
Department of Medicine

Bangabandhu Sheikh Mujib Medical University (BSMMU).
Shahbagh, Dhaka. E-mail: dr.ferdous73@hotmail.com
Mobile: 01711615865

Physical examination

The physical examination is used to:

Assess the type, severity and extent of bleeding and to exclude conditions that might cause non-immune thrombocytopenia

Laboratory investigation:

The finding of thrombocytopenia on a routine blood count may be the first indication of autoimmune thrombocytopenia. Thrombocytopenia should be confirmed by examination of the blood film to exclude pseudo-thrombocytopenia due to EDTA-dependent platelet agglutination. The blood film should also be examined to exclude acute or chronic leukaemia, myelodysplasia, megaloblastic anaemia, microangiopathic anaemia, inherited thrombocytopenias and pseud thrombocytopenia. An autoimmune profile / screen should be carried out to exclude other underlying autoimmune diseases. If the history, physical examination, blood count and blood film examination are consistent with the diagnosis of ITP, with no atypical findings, it can be argued that additional investigations such as bone marrow examination and assays for platelet antibodies are unnecessary. If atypical findings are present particularly those suggesting alternative haematological diagnoses, additional investigations including bone marrow examination should be carried out.

Bone marrow sampling should be reserved for patients who are older than 60 years, or have atypical features, or have a poor response to first line (e.g. prednisolone) treatment or in whom splenectomy is being considered⁸

Assays for antibodies to specific platelet membrane glycoproteins (GP) I_b / II_a and I_b / IX are less sensitive (50-65%) but more specific (90%) in ITP^{9,10}.

Management:

The requirement for treatment varies from patient to patient, and is dictated by factors such as clinical status (asymptomatic, bruising, bleeding or planned intervention likely to induce bleeding in a patient with ITP who is thrombocytopenic).

Observation (No Specific Initial Treatment):

In general, patients with platelet counts exceeding $30 \times 10^9 / l$, require no treatment unless they are undergoing any procedure likely to induce blood loss including surgery, dental extraction or delivery¹¹. Clinically important bleeding with trauma rarely occurs at platelet counts $> 50 \times 10^9 / l$.

Recommendation for "safe" platelet counts in

adults"

- Dentistry $> 10 \times 10^9 / L$
- Extractions $> 30 \times 10^9 / L$
- Regional dental block $> 30 \times 10^9 / l$
- Minor surgery $> 50 \times 10^9 / l$ » Major surgery $> 80 \times 10^9 / l$
- Platelet counts $> 50 \times 10^9 / l$ are safe for normal vaginal

delivery in patients with otherwise normal coagulation. Platelet counts $> 80 \times 10^9 / l$ are safe for caesarean section, spinal or epidural anaesthesia in patients with otherwise normal coagulation. First line therapy

First line therapy comprises oral corticosteroids and intravenous immunoglobulin (IVIg). Splenectomy is often cited as first line therapy but this mode of treatment is seldom used.

Prednisolone: Prednisolone is the initial therapy for most patients with ITP who require treatment. Some two-thirds of patients will respond to prednisolone at 1 mg/kg body weight per day for 2-4 weeks, tapering off over several weeks¹². Reported response rates vary widely (from 3% to 50%)¹³. Patients who fail to respond to treatment with corticosteroids or require unacceptably high doses of corticosteroid in order to maintain a safe platelet count should be considered for splenectomy¹².

Intravenous immunoglobulin (IVIg): Pooled normal human immunoglobulin is effective in elevating the platelet count in 75% of patients, of which 50% will achieve normal platelet counts. However, responses are transient and 3-4 weeks following IVIg treatment, platelet counts drift back to pre-treatment levels¹³, and there is little evidence of a lasting effect. Another single randomized study showed no difference in efficacy between the two dosing schedules 0.4 g/kg/d for 5 days and 1 g/kg/day as a single infusion¹⁴.

Splenectomy: Splenectomy has been used for many years, before steroid therapy was introduced in 1950¹³, as a means of prolonging the survival of antibody-coated platelets. The procedure is not strictly 'curative' since opsonization still takes place but the effector of platelet destruction is removed. Two-thirds of patients with ITP who undergo splenectomy will achieve a normal platelet count, which is often sustained with no additional therapy.

Predicting response to splenectomy. Various indicators of the likely response to splenectomy have been reviewed including response to oral steroids, which has a low predictive value, response to high dose IVIg which, in two small series, correlated well with response to splenectomy¹⁵, and indium-labelled autologous platelet scanning which appears to be the most sensitive predictor of response to splenectomy, to date¹⁶.

Accessory splenic tissue. The presence of an accessory spleen (or spleens) should be considered in patients who fail to respond to splenectomy or relapse following an

initial response. Imaging techniques have shown the presence of accessory splenic tissue in up to 12% of such patients¹⁷.

Second line therapy Second line therapy is used for patient who failed to first line therapy or who have a chronic refractory ITP (This defines patients who fail to respond to first line treatment or require unacceptably high doses of corticosteroids to maintain a safe platelet count.) The actual percentage of patients defined as having refractory ITP varies from 11% to 35%¹². When considering second line therapy, the original first line therapies (corticosteroids, IVIg or splenectomy) should be reconsidered, and implemented if possible¹³, although the doses may have to be altered compared with those used in first line therapy. Conventional second-line treatment approaches are as follows -

High dose corticosteroids: As an alternative to prednisolone, study reported favourable responses in refractory patients using an oral high dose dexamethasone regimen, comprising 40 mg of dexamethasone daily for 4 days, repeated every 28 day for six cycles. Ten patients were treated in this small study with favorable responses in all patients which sustained for at least 6 months¹⁸.

Methylprednisolone: Parenteral steroids such as methylprednisolone have been used as second and third line treatments for patients with refractory ITP. One study reported the results of nine adult patients with platelets $<50 \times 10^9/l$, all of whom were treated initially with oral corticosteroids (prednisolone at 1 mg/kg/d). Methylprednisolone was given at 30 mg/kg/day for 3 days, 20 mg/kg/day for 4 days then 5, 2 and 1 mg/kg/day each for 1 week. The platelet count became normal within 3-5 days in all patients, although in seven of nine the response lasted only a few weeks before dropping to pre-treatment levels¹⁹. The effect of methylprednisolone was compared with IVIg in 22 adult patients with a control series (17 patients treated with standard oral corticosteroids)²⁰.

High dose IVIg: High dose intravenous immunoglobulin at a dose of 1 g/kg per day for two consecutive days, often in combination with corticosteroids, will raise the platelet count rapidly in a proportion of patients²¹. Side effects, particularly headaches, may occur, but if successful can be given on an intermittent basis or substituted with intravenous Anti-D²².

Intravenous anti-D: Intravenous anti-D has been shown to elevate the platelet count in 79-90% of adults²². Anti-D treatment is suitable for Rh(D) positive patients who are not splenectomized.

Vinca alkaloids: This group of drugs may cause a transient increase in the platelet count lasting between 1 and 3 weeks in two-thirds of patients treated. Around 50% of splenectomized patients will respond, but sustained responses are observed in less than 10% of patients^{13,23}. Danazol: Danazol, an attenuated androgen, appears to be especially effective in patients with overlap syndromes between ITP and lupus and can often be used as a corticosteroid-sparing agent in responsive patients who require longer term unacceptably high doses. The outcome of 22 patients, of which 15 had undergone splenectomy, treated with danazol at a dose of 200 mg 2-4 times daily for more than 2 months. Around 60% showed elevation of the platelet count above $50 \times 10^9/l$ that was sustained for more than 2 months²⁴.

Azathioprine: case series^{25,26} suggest that about 20% of patients may achieve a normal platelet count, sustained for several months to years without treatment. Another review²⁷ of the use of azathioprine 150 mg per day for a median of 18 months shows Platelet responses in 64% of patients and were complete in 45% of these.

Cyclosporin A: In a recent study²⁸, 20 patients with ITP all of whom were refractory to corticosteroids and half of whom had undergone splenectomy, were treated with cyclosporin A for at least 4 weeks. The dose was reduced by 50 mg/day every 2 weeks in those showing responses.

Dapsone: In a series of 66 adults with chronic ITP and platelet counts $< 50 \times 10^9/l$, treated with dapsone at 75-100 mg orally, responses were observed in 33 of 66 patients (50%), with a median duration of treatment required to achieve a response of 21 days. Sustained responses were observed in 19 patients²⁹.

Patients failing first and second line therapies

Fortunately, most adult patients with chronic refractory ITP are able to tolerate marked thrombocytopenia relatively well²³, and are able to have a normal or near normal quality of life. For those who fail to respond to standard first and second line therapy and who require treatment, the options are limited and include: (i) interferon- α (IFN- α), (ii) anti-CD20, (iii) Campath 1H, (iv) mycophenolate mofetil, (v) protein A columns, and (vi) other treatments.

IFN- α : There are several case series that report on the use of IFN- α in refractory ITP, and have shown that 25% of patients can achieve a platelet count of over $100 \times 10^9/l$ for between 1 week and 7 months after the IFN- α treatment".

Anti-CD20 antibody (Rituximab): (chimaeric anti-CD20 monoclonal antibody) has been evaluated in a single study³⁰ in which 25 patients with ITP resistant to 2-5 therapeutic options were treated with 375 mg/m²

rituximab weekly for 4 weeks. Five patients showed a complete response and a partial response was seen in a further five. In seven patients the responses were sustained for over 6 months.

Protein A immunoadsorption column: One case series³¹ reported that 18 of 72 patients achieved a platelet count $>100 \times 10^9/l$, which was sustained in 16 patients. **Plasmapheresis:** There are several reports, the largest of which documented the treatment of 14 patients, some of whom had acute ITP. Five of nine with acute ITP responded to Plasmapheresis. Another study³² has reported success using a combination of Plasmapheresis and IVIg for patients with chronic refractory ITP.

Campath-1H: A more recent study of the use of Campath-1H in patients with a variety of cytopenias has shown that it was well tolerated with encouraging responses³³.

Mycophenolate mofetil: This antiproliferative immunosuppressant has been shown to be of value in some patients with autoimmune cytopenias including refractory ITP. However, the numbers of patients treated to date are small and larger studies are required³⁴.

Combination chemotherapy: This mode of therapy may be useful for patients who have failed other therapies but in whom the need to elevate the platelet count is less urgent, e.g. patients who are not actively bleeding. One case series³⁵ reported their results in 10 patients with refractory ITP. A complete response was seen in six patients, a partial response was observed in two and two died of intracerebral haemorrhage.

Ascorbic acid (vitamin C): Case series³⁶ reported that 15% of patients had increased platelet counts, but other medications were being taken concurrently.

Colchicine: One case series³⁷ report conflicting data regarding the effectiveness of colchicine. The principal adverse effect of colchicine is dose-dependent diarrhea.

Aminocaproic acid: In contrast to other modalities discussed in this section, aminocaproic acid has not been used to increase the platelet count but rather to diminish bleeding symptoms. One case series³⁸ of seven patients suggested that it helped control bleeding.

Emergency Treatment in Adult Patients

Hospitalization

There have been no studies to evaluate the effectiveness of hospitalizing adults with ITP.

Hospitalization is appropriate for patients with severe, life-threatening bleeding, regardless of the platelet count, as well as for patients with platelet counts $<30 \times 10^9/l$, who have significant mucous membrane bleeding or who are inaccessible or noncompliant.

Treatment

Urgent treatment is required for adults with severe thrombocytopenia (e.g. platelets $<30 \times 10^9/l$) and who have active bleeding from the gastrointestinal or genitourinary tracts, into the central nervous system or other sites. In this situation, treatment is aimed at elevating the platelet count to a "safe" level quickly (i.e. in less than 24h). Clearly,

many of the treatments discussed earlier take much longer to achieve this effect, and therapies that work almost immediately include platelet transfusion, intravenous methylprednisolone and IVIg. Platelet transfusion is indicated for controlling severe hemorrhage.

Conclusion

Currently several treatment options are available, each of which has been shown to be effective to some extent. Controversy exists regarding the optimal dose and duration of corticosteroid and also the route of administration of corticosteroid. Treatment options differ in chronic or refractory ITP.

References:

1. Woods VL, Oh EH, Mason D, & McMillan R. Autoantibodies against the platelet glycoprotein IIb/IIIa complex in patients with chronic ITP. *Blood* 1984b; 63: 368-75.
2. George JN, El-Harake MA, Ruskob GE. Chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 1995; 331:1207-11.
3. Emmons RVB, Reid DM, Cohen RE. Human thrombopoietin levels are high when thrombocytopenia is due to megakaryocyte deficiency and low when due to increased platelet destruction. *Blood* 1996; 87:4068-71.
4. McMillan R. Autoantibodies and autoantigens in chronic immune thrombocytopenic purpura. *Semin Hematol* 2000; 37:239-48.
5. He R, Reid DM, Jones CE, Shulman NR. Spectrum of IgG classes, specificities, and titers of serum antiglycoproteins in chronic idiopathic thrombocytopenic purpura. *Blood* 1994; 83:1024-32.
6. Escher R, Muller D, Vogel M, Miescher S, Stadler BM, Berchtold P. Recombinant human natural autoantibodies against GPIIb/IIIa inhibit binding of autoantibodies from patients with AITP. *Br J Haematol* 1998; 102:820-8.
7. George JN, Woolf SH, & Raskob GE. Idiopathic thrombocytopenic purpura: a guideline for diagnosis and management of children and adults. *American Society of Hematology. Ann Int Med* 1998; 30: 38-44. S.Mak YK, Yu PH, Chan CH, Chu YC. The management of isolated thrombocytopenia in Chinese adults: does bone marrow examination have a role at presentation? *J Clin Lab Haematol* 2000; 22: 355-58.

9. Brighton TA, Evans S, Castaldi PA, Chesterman CM, Chong BH. Prospective evaluation of the clinical usefulness of an antigen-specific assay (MA1PA) in idiopathic thrombocytopenic purpura and other immune thrombocytopenias. *Blood* 1996; 88: 194-201.
10. Warner MN, Moore JC, Warkentin TE, Santos AV, Kelton JG. A prospective study of protein-specific assays used to investigate idiopathic thrombocytopenic purpura. *Br J Haematol* 1999; 104: 442-47.
11. Yang R, Zhong CH. Pathogenesis and management of chronic idiopathic thrombocytopenic purpura: an update. *Int J Hematol* 2000; 71: 18-24.
12. George JN, el-Harake MA, Raskob GE. Chronic idiopathic thrombocytopenic purpura. *N Eng J Med* 1994; 331: 1207-11.
13. George JN, Woolf SH, Raskob GE, Wasser JS, Aledort EM, Ballem P.I. et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood* 1996; 88: 3-40.
- H. Godeau B, Lesage S, Divin M, Wirquin V, Parcel JP, Bierling P. Treatment of adult chronic autoimmune thrombocytopenic purpura with repeated high-dose intravenous immunoglobulin. *Blood* 1993; 82: 1415-21.
15. Law C, Marcaccio M, Tarn P, Heddle N, Kelton JG. High-dose intravenous immune globulin and the response to splenectomy in patients with idiopathic thrombocytopenic purpura. *N Eng J Med* 1997; 336: 1494-98.
16. Najean Y, Rain JD, Billotey C. The site of destruction of autologous 111 In-labelled platelets and the efficiency of splenectomy in children and adults with idiopathic thrombocytopenic purpura: a study¹ of 578 patients with 268 splenectomies. *Br J Haematol* 1997; 97: 547-50.
17. Facon T, Caulier MT, Fenaux P, Plantier I, Marchandise X, Ribet M, et al. Accessory spleen in recurrent chronic immune thrombocytopenic purpura. *Am J Hematol* 1992; 41: 184-89.
18. Caulier MT, Rose C, Roussel MT, Huart C, Bauters F, Fenaux P. Pulsed high-dose dexamethasone in refractory chronic idiopathic thrombocytopenic purpura: a report on 10 cases. *Br J Haematol* 1995; 91: 477-479.
19. Akoglu T, Paydas S, Bayik M, Lawrence R, Firatli T. Megadose methylprednisolone pulse therapy in adult idiopathic thrombocytopenic purpura. *Lancet* 1991; 337: 56.
20. Von dem Borne AH, Vos JJ, Pegels JG, Thomas LL & van der L. High dose intravenous methylprednisolone or high dose intravenous gammaglobulin for autoimmune thrombocytopenia. *BMJ* 1988; 296: 249-250.
21. Imbach P, Wagner HP, Berchtold W, Gaedicke G, Hirt A, Joller P. et al. Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. *Lancet* 1985; 2: 464-68.
22. Scaradavou A, Woo B, Woloski BM, Cunningham-Rundles S, Ettinger LJ, Aledort LM, et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: experience in 272 patients. *Blood* 1997; 89: 2689-2700.
23. Blanchette V, Freedman J, Garvey B. Management of chronic immune thrombocytopenic purpura in children and adults. *Semin Hematol* 1998; 35: 36-51.
24. Ann YS, Rocha R, Mylvaganam R, Garcia R, Duncan R, Harrington WJ. Long-term danazol therapy in autoimmune thrombocytopenia: unmaintained remission and age-dependent response in women. *Ann Int Med* 1989; 111: 723-29.
25. Bouroncle BA, Doan CA. Refractory idiopathic thrombocytopenic purpura treated with azathioprine. *N Eng J Med* 1996; 275: 630.
26. Bouroncle BA, Doan CA. Treatment of refractory idiopathic thrombocytopenic purpura. *JAMA* 1996; 276: 2049.
27. Quiquandon I, Fenaux P, Caulier MT, Pagniez D, Huart JJ, Bauters F. Re-evaluation of the role of azathioprine in the treatment of adult chronic idiopathic thrombocytopenic purpura. A report on 53 cases. *Br J Haematol* 1990; 74: 223-28.
28. Kappers-Klunne MC, van't Veer MB. Cyclosporin A for the treatment of patients with chronic idiopathic thrombocytopenic purpura refractory to corticosteroids or splenectomy. *Br J Haematol* 2001; 114: 121-25.
29. Godeau B, Durand JM, Roudot-Thoraval F, Tenneze A, Oksenhendler E, Kaplanski G. et al. Dapsone for chronic autoimmune thrombocytopenic purpura: a report of 66 cases. *Br J Haematol* 1997; 97: 336-39.
30. Stasi R, Pagano A, Stipa E & Amadori S. Rituximab chimaeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. *Blood* 2001; 98: 952-57.
31. Ballem PJ, Buskard N, Wittman BK, Wilson RD, Effer S, Farquharson D. ITP in pregnancy: Use of the bleeding time as an indicator for treatment. *Blut* 1989; 59: 132.
32. Bussel JB, Saal S, Gordon B. Combined plasma exchange and intravenous gammaglobulin in the treatment of patients with refractory immune thrombocytopenic purpura. *Transfusion* 1988; 28: 38-41.
33. Willis F, Marsh JC, Bevan DH, Killick SB, Lucas G, Griffiths R. et al. The effect of treatment with Campath-1H in patients with autoimmune cytopaenias. *Br J Haematol* 2001; 114: 891-98.
34. Howard J, Hoffbrand AV, Prentice HG, Mchta A. Mycophenolate mofetil for the treatment of refractory autoimmune haemolytic anaemia and auto-immune thrombocytopenia purpura. *Br J Haematol* 2002; 117: 712-15.
35. Figueroa M, Gehlsen J, Hammond D, Ondreyco S, Piro L, Pomcroy T. et al. Combination chemotherapy in refractory immune thrombocytopenic purpura. *N Engl J Med* 1993; 328: 1226-29.
36. Brox AG, Howson-Jan K, Fauser AA. Treatment of idiopathic thrombocytopenic purpura with ascorbate. *Br J Haematol* 1988; 70: 341.
37. Strother SV, Zuckerman KS, LoBuglio AF. Colchicine therapy for refractory idiopathic thrombocytopenic purpura. *Arch Intern Med* 1984; 144: 2198.
38. Bartholomew JR, Salgia R, Bell WR. Control of bleeding in patient with immune and nonimmune thrombocytopenia with aminocaproic acid. *Arch Intern Med* 1989; 149: 1959.