Immune Thrombocytopenia – Recent Advances

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The disease and its most widely accepted abbreviation, ITP, has variably been defined as , 'idiopathic thrombocytopenic purpura', ' immune thrombocytopenic perpura' and most recently, 'immune thrombocytopenia'. The terminology was agreed and definitions published in 2009 by Rodeghiero *et al*.on behalf of an International Working Group.[1] The abbreviation ITP now stands for immune thrombocytopenia and not immune thrombocytopenic purpura.[1]

ITP is caused by autoantibodies to platelets. The antigenic target in most patients appears to be the platelet GP IIb/IIIa complex. Platelets with antibodies on their surface are trapped in the spleen, where they are efficiently removed by splenic macrophages. [2,3] The mechanism of origin of these antibodies is not known. These antibodies may be directed toward the viral antigens and then cross-react with platelet antigens (Antigenic mimicry). They persist because of the failure of immune surveillance mechanisms to repress these antibodies. These antibodies can also react with the developing megakaryocytes in the bone marrow, leading to decreased production of platelets (ineffective thrombopoiesis).

There is now greater understanding of the mechanisms of thrombocytopenia in ITP, which involve both increased platelet destruction and, in a significant proportion of cases, impaired platelet production. In fact,stimulation of platelet production with thrombopoietin receptor agonists has been a recent successful therapeutic application deriving from this concept.[4]

Diagnosis of ITP:

It is defined as a platelet count of under 100×109/L without any other cause of thrombocytopenia. There is no predictive test for ITP and hence the diagnosis depends on exclusion of other causes of thrombocytopenia. The diagnostic feature is that of isolated bleeding symptoms consistent with thrombocytopenia without any constitutional symptoms; no organomegaly, lymphadenopethy or stigmata of congenital condition on physical examination; CBC showing isolated thrombocytopenia (Platelets less than $100x10^9$ /lit), with normal RBC indices and normal WBCs. Anaemia is present only in presence of significant bleeding . Peripheral smear shows normal RBCs and WBCs and identified platelets are either normal or larger in size.[5]

Bone marrow examination is unnecessary in patients with the typical features of ITP outlined above, irrespective of the age of the patient. The presence of abnormalities in the history, physical examination, or the complete blood count and peripheral blood smear should be further investigated, e.g. with a bone marrow examination or other appropriate investigations, before the diagnosis of ITP is made.[5]

All adult patients with newly diagnosed ITP should undergo testing for HIV and HCV. There is insufficient evidence to support the routine use of anti-platelet, antiphospholipid, and anti-nuclear antibodies, thrombopoietin levels, or platelet parameters obtained on automated analyzers in the evaluation of patients with suspected ITP.[5]

A new staging scheme was also proposed, which defines the following stages of ITP:

Newly diagnosed ITP: months 0–3 after presentation

Persistent ITP: months 4–12

Chronic ITP: greater than 12 months

Refractory ITP: patient has failed splenectomy

Severe ITP: patient has had major clinical bleeding.[1]

ITP occurs in 2 distinct clinical types: (1) an acute self-limiting form observed almost exclusively in children (5 cases per 100,000 persons) and (2) a chronic form, observed mostly in adults (3-5 cases per 100,000 persons) and rarely in children.

Acute ITP

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Acute ITP affects males and females equally and has a peak incidence in children aged 3-5 years. Most patients have a history of an antecedent acute viral syndrome.

The onset is sudden, with symptoms and signs depending on the platelet count. Bleeding is usually mild, unless the platelet count drops below 20,000/μL. With platelet counts from 20,000/μL to 50,000/μL, petechiae and ecchymoses are observed following mild trauma. With platelet counts less than 10,000/μL, generalized petechiae, ecchymoses, and mucosal bleeding occur. With platelet counts below 2000/μL, widespread ecchymoses, hemorrhagic bullae, and retinal hemorrhage occur.

Chronic ITP

This condition is typically observed in adults aged 20-40 years. It has an insidious onset, and a history of an antecedent infection need not be present. Unlike childhood ITP, chronic ITP is more common in females than in males. As in childhood ITP, the bleeding manifestations depend on the platelet count.

Treatment of ITP:

The goal of all treatment strategies for ITP is to achieve a platelet count that is associated with adequate haemostasis, rather than a normal platelet count. The decision to treat should involve a discussion with the patient and consideration of the severity of bleeding, anticipated surgical procedures, medication side effects, and health-related quality of life.

I. Initial Management of ITP

General Considerations for Initial Management:

The majority of patients with no bleeding or mild bleeding(defined here as skin manifestations only, such as petechiae and bruising) can be treated with observation alone regardless of platelet count.

First-line treatment includes

1. Observation,

2. Corticosteroids,

3. IVIg,

]4. Anti-D immunoglobulin (anti-D).

Anti-D should be used with caution given recent FDA warnings of severe hemolysis. It is therefore not advised in patients with bleeding causing a decline in hemoglobin, or those with evidence of autoimmune hemolysis.

Children:

A single dose of IVIg (0.8-1.0 g/kg) or a short course of corticosteroids should be used as first-line treatment.

IVIg should be used instead of corticosteroids if a more rapid increase in platelet count is required.

There is no evidence to support using corticosteroids for longer courses compared to very brief courses.

Anti-D may be considered for first-line therapy in Rh+ non-splenectomized children with recognition of the risks outlined above.

Adults:

Consider treatment for patients with a platelet count < 30 x109/L.

Longer courses of corticosteroids are preferred over shorter courses of corticosteroids or IVIg.

IVIg may be used in conjunction with corticosteroids if a more rapid increase in platelet count is required.

Either IVIg (1g/kg for one dose, repeated as necessary) or anti-D (in appropriate patients) may be used as a first-linetreatment if corticosteroids are contraindicated.

2. General Considerations for Subsequent Management:

If previous treatment with corticosteroids, IVIg, or anti-D has been successful, these options may be used as needed to prevent bleeding.

If previous treatment with corticosteroids, IVIg, or anti-D has been unsuccessful, subsequent treatment may include splenectomy, rituximab, thrombopoietin receptor agonists,or more potent immunosuppression.

Adults who have a platelet count > 30 x 109/L and are asymptomatic following splenectomy do not require further therapy.

In children, splenectomy or other interventions with potentially serious complications should be delayed for at least 12 months, unless warranted by severe disease unresponsive to other measures or due to quality of life considerations.

Special consideration in ITP :

Secondary ITP - HIV- associated:

Treatment of the underlying HIV infection with antiviral therapy should be considered prior to other treatment options unless the patient has clinically significant bleeding.

IVIg, corticosteroids, or anti-D may be used initially for patients requiring further therapy.

Splenectomy is considered preferable to other agents in symptomatic patients who have failed initial drug therapy.

Secondary ITP - H. pylori- associated:

Routine testing for *H.pylori* is not recommended in asymptomatic children with unresolved ITP.

Screening for *H.pylori* should be considered in adults for whom eradication therapy would be undertaken if testing were positive.

Eradication therapy for *H.pylori* should be administered to patients who are found to have infection.

MMR-related ITP:

Children with a history of ITP who are not immunized should receive their scheduled first MMR vaccine.

In children with either non-vaccine or vaccine-related ITP who have already received their first dose of MMR vaccine, vaccine titers can be checked. If the child displays full immunity, no further MMR vaccine should be given. If the child does not have adequate immunity, then the child should be re-immunized at the recommended age.

ITP in Pregnancy:

Pregnant patients requiring treatment should receive either corticosteroids or IVIg.

For pregnant women with ITP, the mode of delivery should be based on obstetric indications.

Table 1 . Causes of **Secondary ITP**

A. **Autoimmune Diseases :** Systemic lupus erythomatosus, Antiphospholipid syndrome, Autoimmune hepatitis, Autoimmunr thyroiditis

B. **Lymphoproliferative disorders :** Chronic lymphatic leukaemia, Hodgkin's lymphoma, Large granular lymphocytic leukaemia

C. **Infections :** HIV, Hepatitis C, HelicobacterPylori

D. **Myelodysplasia**

E. Gammaglobulinemia, hypogammaglobulinemia, immunoglobulin A deficiency

F. **Drugs:** quinidine, gold, heparin, penicillin, procainamide, α -methyldopa, sulfamethoxazole

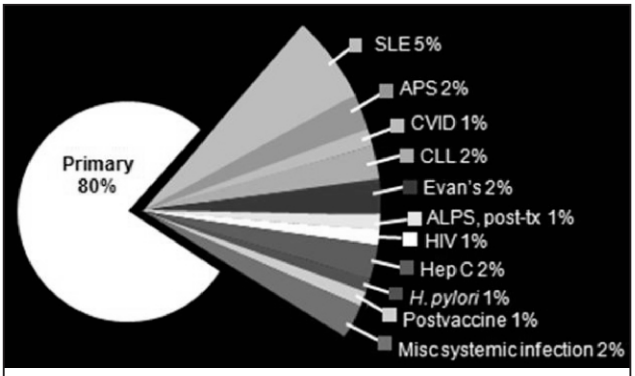

Fig 1 : Secondary ITP.8

Table 2 : Drugs useful in ITP[7]

Clinical Situation	Therapy Option
1st line Initial treatment of newly diagnosed ITP	IV IG Steroids :Dexamtehasone, Methyl Prednisolone, Prednisolone Anti D
2nd Line	– Azathioprine – Cyclosporin A – Cyclophosphamide – Danazol – Dapsone – Mycophenolate mofetil – Rituximab – Splenectomy – TPO-receptor agonists – Vinca alkaloids
Treatment for refractory ITP patients (patients failing first and second-line therapies)	Category A:Treatment options with sufficient data – TPO-receptor agonists Category B:Treatment options with minimal data and considered to have potential for considerable toxicity – Campath-1H – Combination of first- and second-line therapies – Combination chemotherapy – Haemopoietic stem cell transplantation (HSCT)

	Children	Adult
Splenectomy	- Children with persistant bleeding after primary treatment like steroids, Iv Ig, or Anti D - Children who have need for improved quality of life	- Adults who have failed corticosteroid therapy, with similar efficacy with open or laparoscopic procedures.
Rituximab	- Children with significant bleeding after primary treatment - Need for improved quality of life - Alternative to splenectomy. - Failure after splenectomy6	- For adults at risk of bleeding who have failed one line of therapy such as corticosteroids, IVIg, or splenectomy.6
Thrombopoietin Receptor Agonists	Studies are ongoing, but there are no published data to guide the use of these agents in children.	-Relapse or persistant disease after splenectomy - Relapse or persistant disease after primary treatment - For patients who want to avoid spelectomy or have contraindication for splenectomy
High dose Dexamethasone	- May be considered for children or adolescents with ITP who have significant ongoing bleeding and/or have a need for improved quality of life despite conventional treatment. - Also may be considered as an alternative to splenectomy in children with chronic ITP or in those who have failed splenectomy.	No comment in current guidelines.
Immunosupression	Multiple agents have been reported; however data for any one specific agent remain insufficient for specific	Multiple agents have been reported; however data for any one specific agent remain insufficient for specific
	recommendations.	recommendations.

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