INTRODUCTION

ITP or immune thrombocytopenic purpura is an autoimmune disorder characterized by increased platelet destruction & platelet count < 1 lakh. It is seen in both children & adults. In children, it is usually acute and self limited whereas in adults it usually is insidious in onset and chronic. Pathogenesis of the disease is complex.

CLASSIFICATION

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not associated with a secondary cause</td>
<td>Associated with other diseases like infections, autoimmune diseases, malignancies, etc</td>
</tr>
<tr>
<td>Childhood onset</td>
<td>Adult onset</td>
</tr>
<tr>
<td>Sudden onset</td>
<td>Insidious in onset</td>
</tr>
<tr>
<td>Usually acute</td>
<td>chronic</td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>Young adults</td>
</tr>
<tr>
<td>Equal incidence in boys &amp; girls</td>
<td>Female preponderance</td>
</tr>
<tr>
<td>Preceding viral infection</td>
<td>No such history</td>
</tr>
<tr>
<td>Self limited</td>
<td>indolent</td>
</tr>
</tbody>
</table>

The guidelines on ITP are published by the American Society of Hematology (ASH)-2011 & International ITP Working Group (IWG)-2009.
NEW IWG DEFINITIONS

Newly diagnosed- < 3 months
Persistent - > 3 months
Chronic - > 12 months
Severe- Bleeding symptoms at presentation needing remediation OR Occurrence of fresh bleeding symptoms requiring increase in dose or new drug
Refractory- Presence of severe ITP after splenectomy
Response -Platelet count > 1 lakh measured on 2 occasions 7 days apart OR Platelet count >30000 and a greater than twofold increase in platelet count from baseline measured on 2 occasions 7days apart

EPIDEMOLOGY

Multimodal incidence with one peak in childhood and second and third peaks in young adults and the elderly. The incidence of primary ITP in adults is 3.3/100000 adults per year .Prevalence is 9.5 per 100000 adults. There is predilection for female patients in younger adults but equal prevalence among elderly ( > 65 years ) males & females

PATHOGENESIS

1-Pathologic antiplatelet antibodies – Harrington et al in 1951 described a factor in the plasma of ITP patients which when transfused into normal subjects induced thrombocytopenia in them. It was later identified as antiplatelet autoantibody against glycoproteins in the platelet membrane. Dixon and Ross in1975 quantified the platelet associated IgG .These autoantibodies are produced by B cell, driven by CD4+ helper T cells.

2-T-cell–mediated destruction of platelets -In ITP, there is Th1 bias, compared with Th2 characterised by increased expression of genes involved in the Th1 cell response-INF gamma and IL-2 receptor-beta leading to autoimmunity. The direct cytotoxic effect of T cells also leads to increased expression of cytotoxic genes like granzyme a, granzyme b and perforin causing platelet destruction. T cells are also involved in the release of cytokines which also interfere with megakaryocyte maturation and/or platelet release

3-Fc Receptors and Role of Spleen- Platelets coated with IgG autoantibodies undergo an accelerated clearance through FC gamma receptors expressed by tissue macrophages, predominantly in the spleen and liver . The destruction of platelets by the mononuclear phagocyte system (MPS) leads to presentation of additional platelet antigens to the immune system . therefore, autoantibodies have specificity directed to multiple glycoproteins—anti-GP IIb/IIIa ,anti-GPIb/IX and anti-GPla/IIa

3-Impaired megakaryocytopoiesis –There is compensatory increased platelet production in patients with ITP but it is inadequate, indicating that antiplatelet glycoprotein antibodies & T cells have effects not only on platelets but also on megakaryocytes leading to impaired platelet release

Virus-associated ITP

Acute ITP often occurs following a viral illness. Viral infection is cleared normally but initiates ITP. Mechanism is molecular mimicry or B-cell stimulation. Commonly seen with HIV, HCV, EBV

Bacteria-associated ITP: H. pylori

Increased prevalence of H. Pylori is seen in patients with ITP with a response rate of between 38% and 73% in patients in whom H. pylori is eradicated. Patients with newly diagnosed ITP and those with milder thrombocytopenia are more likely to improve in their platelet counts following eradication of H. pylori

Drug-associated ITP

Drug induced development of immune dysregulation & autoimmunity can be seen with
Alemtuzumab & purine analogs

Genetics factors in ITP

ITP has been diagnosed in monozygotic twins and in several families indicating propensity for autoantibody production in family members. However, no consistent association between ITP and specific MHC class I or class II polymorphisms have been identified.

Secondary ITP

Seen with Antiphospholipid syndrome, Systemic lupus erythematosus, Evans syndrome, Post-hematopoietic cell transplantation ITP, Sarcoidosis, Chronic lymphocytic leukemia, Autoimmune lymphoproliferative syndrome, etc...

CLINICAL FEATURES

Childhood ITP-Typically develops in a healthy child with a preceding history of viral infection presenting with petechiae or mucosal bleeding. It is a self-limited with spontaneous recovery in the majority.

Adult ITP-Insidious in onset with no preceding viral or other illness. Sometimes it may be incidentally detected in an asymptomatic patient.

Petechiae, purpura, and easy bruising are the most common manifestations. Epistaxis, gingival bleeding, and menorrhagia are common. Overt gastrointestinal bleeding and gross hematuria are rare. Intracranial hemorrhage is very uncommon. Wet purpura & retinal haemorrhages herald life threatening bleeds. Younger patients tolerate low platelet levels better than the elderly. Bleeding can be aggravated by antiplatelet drugs like aspirin, viral infections or trauma.

Anemia in ITP

ITP per se, does not cause anemia. Chronic blood loss can lead to iron deficiency anemia contributed by nutritional anemia. Evan’s syndrome can cause ITP with associated autoimmune hemolytic anemia.

Correlation between bleeding and the platelet count

Bleeding in ITP is less severe at equivalent platelet counts than in thrombocytopenia due to marrow aplasia or chemotherapy-induced marrow suppression. Bleeding tendency generally occurs with platelet counts < 30,000/cu mm. Major severe bleeding occurs with platelet counts < 20,000/cu mm, usually < 10,000/cu mm.
APPROACH

- History: Drugs, herbal medication, systemic diseases
- Physical examination: normal except bleeding manifestation and anemia, No splenomegaly
- Determine the type of bleeding and distinguish ‘platelet-type’ from ‘coagulation-type’
- Assess the severity, extent and duration of bleeding
- Determine the presence of medical conditions, which may be associated with autoimmune thrombocytopenia
- Identify conditions, which may aggravate risk of bleeding: peptic ulcer, renal stones, and severe hypertension

ITP is a diagnosis of exclusion. Only two criteria need to be satisfied
1. Isolated thrombocytopenia is present (except for other coincidental abnormalities such as iron deficiency)
2. Clinically apparent associated conditions (eg, systemic lupus erythematosus, antiphospholipid syndrome, chronic lymphocytic leukemia) are not present

INVESTIGATIONS

1. **Peripheral Smear**: For evidence for other causes of thrombocytopenia & to exclude “pseudothrombocytopenia”- due to EDTA dependent platelet agglutinins

   Artifacts affecting platelet counting
   - Cold-dependent platelet agglutinins and autoantibodies causing “rosetting” of platelets around neutrophils or monocytes
   - Giant platelets
   - Cryoglobulin particles may be counted as platelets

<table>
<thead>
<tr>
<th>Features consistent with diagnosis of ITP</th>
<th>Features not consistent with diagnosis of ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia: Platelet size normal or larger. Predominant giant platelets (approaching the size of erythrocytes) should be absent</td>
<td>Predominant giant platelets</td>
</tr>
<tr>
<td>Normal red cell morphology</td>
<td>Red blood cell poikilocytosis, schistocytosis, macrocytes, nucleated red cells, polychromatophilia (unless as a response to bleeding)</td>
</tr>
<tr>
<td>Normal white blood cell morphology</td>
<td>Leukocytosis or leukopenia, morphology immature or abnormal leucocytes (in childhood ITP atypical lymphocytes oreosinophilia may be seen)</td>
</tr>
</tbody>
</table>

2. Autoimmune screening
3. LFT, USG abdomen to exclude CLD
4. HIV, HCV
5. Coomb’s test
6. Antiplatelet Antibodies— neither sensitive nor specific for ITP & not recommended in the diagnostic work-up
7. Helicobacter pylori—IWG recommends H pylori stool antigen testing in all patients with ITP
8. Bone Marrow Examination

   IWG guidelines suggest to do bone marrow examinations in patients 60 years old or more with newly diagnosed ITP. However, ASH guidelines 2011
do not suggest bone marrow examination in any patient population if diagnosis of ITP is sure.

But, a marrow examination is mandatory in patients with lassitude, protracted fever, bone or joint pain & unexplained macrocytosis or neutropenia.

In children, bone marrow examination is not necessary if management involves observation or intravenous immune globulin. Aspiration should be performed before starting corticosteroids to rule out acute leukemia. The British guidelines for ITP in children recommend bone marrow to be examined before steroid therapy is given.

9. Immunoglobulin levels-IgA deficiency

TREATMENT

Treatment needs an individualised approach. It is to treat the patient & not the platelet count & to provide a safe platelet count to prevent major bleeding, rather than returning the platelet count to normal. Platelet < 30,000 needs treatment whether symptomatic or not whereas asymptomatic & platelet > 30,000 needs no treatment & only observation.

First line drugs

1. Glucocorticoids
   a. Prednisone
      Oral prednisone, 1 mg/kg as a single daily dose for 2-4 weeks. Most adults respond within two weeks. Duration of initial prednisone treatment is determined by the platelet count response. If the platelet count recovers promptly to normal, the prednisone dose is tapered and discontinued. There is no standard regimen for tapering the prednisone dose. It is ideal to taper and discontinue prednisone over four to six weeks after achieving a normal platelet count. Persistent symptomatic and severe thrombocytopenia (platelet count < 10,000/microL) after two weeks of prednisolone needs additional treatment. Similarly, severe bleeding also require additional treatment immediately. If thrombocytopenia recurs after stopping prednisone, it is temporarily resumed until a decision for more definitive treatment is made. Long-term glucocorticoid treatment is not appropriate in view of its side effects.

b. High dose dexamethasone

   40 mg per day (either orally or intravenously) for four consecutive days can produce an early response compared to prednisone.

c. High dose methylprednisolone

   30 mg/kg intravenously over the course of one hour for 1-3 days.

2. Intravenous immunoglobulin and anti-D

   Increase the platelet count in most patients with ITP, including patients who have not responded to corticosteroids.

   Dose—IVIg — 1 g/kg per day, given for one to two days; Anti-D — 50 to 75 mcg/kg per day, given once.

   Anti-D is effective only in Rh-positive patients & in patients who have not had splenectomy. Anti-D causes immune-mediated clearance of the sensitized erythrocytes which occupy the Fc gamma receptors in splenic macrophages, minimizing removal of antibody-coated platelets. Hence, a modest amount of hemolysis is expected.

   No long-term remission is seen with both. They are valuable in a patient with life-threatening bleeding, or in preparing for splenectomy or other surgical procedures. Either IVIg or anti-D may be used as a first-line treatment if corticosteroids are contraindicated.

   Second-line management after failure of initial therapy

1. Splenectomy

   Splenectomy removes the major site where antibody-coated platelets are trapped and destroyed by the reticuloendothelial system & also leads to decrease...
in the B-lymphocytes responsible for anti-platelet antibody production. It is the most effective treatment for ITP with the highest rate of complete and durable remissions, i.e., 60-70%. Complications include risks of surgical procedure, increased susceptibility to serious infection, thrombosis risk, and pulmonary hypertension. Immunization at least two weeks prior to splenectomy for Streptococcus pneumoniae, Haemophilus influenzae B, and Neisseria meningitidis & penicillin prophylaxis daily for at least 1 year after splenectomy are recommended.

2. Rituximab
Rituximab, the anti CD 20 monoclonal antibody is used when glucocorticoids have been ineffective and who are not candidates for splenectomy or who have failed to achieve a response to splenectomy. It is typically administered as a single agent at a dose of 375 mg/m²/week for four weeks. Rituximab after splenectomy is effective in both adults and children with refractory ITP (i.e., ITP for which splenectomy was ineffective). Complications include infusion reactions, prolonged immunosuppression, reactivation of hepatitis B, and very rarely progressive multifocal leukoencephalopathy. Initial response rates are 40% to 60% & long-term response rate is 20% at 5 years post initial rituximab treatment.

CHRONIC REFRACTORY ITP
Defined as ITP with plt < 50000 lasting > 3 months & failed response to splenectomy & rituximab

Management of refractory ITP
- No bleeding & plt > 30000 - observation
- Persistent symptomatic thrombocytopenia between 20000-30000 - thrombopoiesis stimulating agents
  - Lack of response with thrombopoiesis stimulators - observation with supportive care with IVIg or steroid pulse at time of major bleeding
  - Persistent symptomatic thrombocytopenia < 20000 - immunosuppressive agents

Thrombopoiesis-stimulating agents
Are used in ITP in adults with insufficient response to corticosteroids, immunoglobulins, or splenectomy; who have a contraindication to splenectomy and who have failed at least one other therapy; who have failed one line of therapy such as corticosteroids or IVIg and who are not willing for splenectomy. TPO-RA (romiplostim and eltrombopag) are US FDA approved for adults with chronic ITP. Eltrombopag is approved for use in children as well. Side effects include headache, nasopharyngitis, upper respiratory infection, fatigue, transaminitis, thromboembolism, reticulin deposition in bone marrow & rebound thrombocytopenia after discontinuation.

Immunosuppressives
1. 6-mercaptopurine 50-75 mg/m² orally once per day; side effects - Hepatotoxicity, neutropenia, infection, pancreatitis
2. Azathioprine 1-2 mg/kg orally once per day (maximum 150 mg/d); side effects - Hepatotoxicity, neutropenia, infection, pancreatitis
3. Cyclosporin A 5-6 mg/kg/d orally divided into 2 doses per day (titrate to blood levels of 100-200 ng/mL); side effects - Nephrotoxicity, hypertension, tremor, parathesias, gingival hyperplasia
4. Cyclophosphamide 0.3-1.0 g/m² IV repeated once every 2 to 4 weeks 1 to 3 doses; 50-200 mg orally once per day; after response has been achieved, dose can be tapered to 50 mg; side effects - Neutropenia, nausea/vomiting, infertility, secondary malignancy
5. Danazol 50-800 mg/d orally divided into 2 to 4 doses per day; side effects - Hemolytic anemia, viral infection, amenorrhea
6. Dapsone 75-100 mg orally once per day; side effects - Hemolytic anemia (in patients with G6PD deficiency), rash, nausea, methemoglobinemia
7. Mycophenolate mofetil 250-1000 mg orally twice per day; side effects - Headache, diarrhea,
nausea, anorexia, infection

8. Vinca alkaloids - Vincristine: 1 to 2 mg IV once per week for 3 weeks; Vinblastine: 10 mg IV once per week for 3 weeks; side effects - peripheral neuropathy, constipation

Role of platelet transfusion - Provide critical temporary hemostatic support

ITP IN SLE

Is due to immunologic platelet injury & similar to ITP. 5-15% of ITP patients satisfy diagnostic criteria for SLE at presentation. Others may have positive ANA at presentation; A few progress to SLE in several years. High ANA titre & speckled pattern have a high risk of progression to SLE. Thrombocytopenia correlates with SLE disease activity. ITP in SLE to be treated on same grounds as ITP, but role of splenectomy controversial

ITP IN PREGNANCY

ITP is the most common cause of thrombocytopenia in the first trimester. There are no fertility issues for ITP patients. But pregnancy is contraindicated for patients on immunosuppressives except azathioprine. Therapy however does not appear to affect the neonatal risk of thrombocytopenia. Treatment is directed towards maintaining a safe platelet count in the mother, generally considered 30,000 throughout pregnancy & 50,000 towards delivery. Pregnancy needs to be managed like a normal pregnancy. Caesarean is done only for obstetric indications. Epidural anaesthesia requires a platelet count 75000-80000.

First-line therapy include intravenous immunoglobulin (IVlg) or corticosteroids. Prednisolone is the preferred steroid. Both are similarly efficacious in increasing platelet counts. Patients refractory to first-line treatment can be treated with combination of IVlg and corticosteroids. Options for second-line therapy are limited by fetal risk. Azathioprine may be used as a steroid sparing agent as the fetus lacks enzyme for converting azathioprine to its active form. Use of anti-RhD immune globulin, cyclosporine, and rituximab are reported with good outcomes but cannot be routinely recommended. There are a few reports of successful romiplostim therapy & recombinant human thrombopoietin in severe refractory thrombocytopenia in pregnancy

REFERENCES

HARRISON’S PRINCIPLES OF INTERNAL MEDICINE - 19th edition
UPTODATE MEDICINE 2013
API TEXT BOOK OF MEDICINE-10th edition
ASH ITP pocket guide-2011
REVIV ARTICLE – ITP-NEJM MEDICAL PROGRESS 2002
How I treat refractory immune thrombocytopenia; Adam Cuker -Department of Medicine and Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; and Cindy E. Neunert-Department of Pediatrics, Columbia University, New York, NY
Clinical updates in adult immune thrombocytopenia; Michele P. Lambert-Gernsheimer Division of Hematology, The Children’s Hospital of Philadelphia, Philadelphia, PA; and Terry B- Division of Hematology, University of Washington School of Medicine, Seattle, WA
High-dose dexamethasone vs prednisone for treatment of adult immune thrombocytopenia: a prospective multicenter randomized trial-BLOOD article