Under the guidance of

Howard A. Liebman, MD
Director, Fellowship Program in Hematology
Medical Director, Special Hemostasis Laboratory, Norris Cancer Hospital
Director, University of Southern California, Gaucher Center
University of Southern California

Diane J. Nugent, MD
Medical Director of CHOC Hematology and Blood & Donor Services
Chief of the PSF Division of Hematology
Children’s Hospital of Orange County, California

ITP Primer
An educational brochure provided by Cangene bioPharma
DEFINITIONS

ITP can be separated into 2 forms: primary (idiopathic) and secondary ITP.1

**Primary ITP** is an autoimmune disorder characterized by thrombocytopenia (peripheral blood platelet count <100,000/µL) in the absence of other causes or disorders that may be associated with thrombocytopenia.2

**Secondary ITP** is a thrombocytopenia associated with chronic infections (HIV, HCV, H. pylori); Autoimmune disease (SLE, immune thyroid disease, etc.); Immune deficiency disorders (CVID, ALPS); Lymphoproliferative disorders (CLL, lymphoma, Hodgkin’s disease); and drug-induced thrombocytopenia (quinine).

PHASES OF ITP

**Newly diagnosed:** historically referred to as acute ITP, this refers to a patient diagnosed within the past 3 months

**Persistent:** this is a newly created category that indicates a patient diagnosed within the past 3 to 12 months—includes patients not reaching spontaneous remission or not maintaining complete response off therapy

**Chronic:** lasting for more than 12 months; historically, chronic referred to >6 months duration

**Severe:** presence of bleeding symptoms requiring treatment at presentation, or new bleeding requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose

**Refractory:** primary ITP with the following characteristics:

- Failure to achieve a response or loss of response following splenectomy
- Requires treatment to minimize the risk of clinically significant bleeding

PATHOPHYSIOLOGY OF ITP

In ITP, platelet destruction is mediated by antibodies against platelet glycoproteins.5 It is now known that decreased platelet counts are a result of both platelet destruction and in some patients decreased platelet production.5 Antibodies directed against platelet glycoproteins have also been shown to inhibit megakaryocyte maturation and therefore platelet production.

Recent evidence has also shown that the thymic (T cell) lymphocyte plays an important role in this disorder. Cytotoxic T lymphocytes may also destroy platelets and damage megakaryocytes. Defective T lymphocyte regulatory cells may contribute to the persistent nature of adult ITP.

Abbreviations used in this brochure

- **ALPS**  Autoimmune Lymphoproliferative Syndrome
- **CLL**  Chronic Lymphocytic Leukemia
- **CMV**  Cytomegalovirus
- **CVID**  Common Variable Immune Deficiency
- **EBV**  Epstein Barr Virus
- **HCV**  Hepatitis C Virus
- **HIV**  Human Immunodeficiency Virus
- **SLE**  Systemic Lupus Erythematosus
## Childhood versus Adult ITP

### Epidemiology

<table>
<thead>
<tr>
<th>Topic</th>
<th>Children</th>
<th>Adults</th>
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</table>
| **INCIDENCE and PREVALENCE** | Between 4.0 and 5.3 per 100,000 per year  
Incidence of acute: between 1.9 and 6.4 per 10^5 children/year.  
Incidence of chronic: approximately 0.46 per 100,000 children per year and prevalence of 4.6 per 100,000 children. | Incidence estimates of chronic ITP vary significantly ranging from 1.6 to 3.9 per 10^5 adults/year.  
Overall female : male prevalence rate ratio ranges from 1.2 to 1.9 |
| **AGE** | Most common age of occurrence: 2-years, followed by adolescence.  
Children 8-14 more likely to acquire chronic than 7 years or younger. | Suggestion of higher prevalence in males over age 75 and less than 18 years |
| **PREDOMINANCE** | Slight male predominance  
Male to female ratio 1.2 | Slight female predominance in adult chronic ITP |

### Pathophysiology and Characteristics

<table>
<thead>
<tr>
<th>Topic</th>
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</tr>
</thead>
</table>
| **TRIGGERS** | Infections and vaccination, especially the MMR vaccine.  
Suggestion that ITP may have seasonal variation has not been confirmed. | Patients with autoimmune disorders and women in pregnancy have historically recorded an overall higher incidence of ITP; however, no statistical findings are consistently reproducible in well-powered studies. |
| **PATHOPHYSIOLOGY** | B-cell mediated  
Primarily peripheral destruction of platelets | Primarily B-cell mediated, some suggestion of T-cell involvement  
Peripheral destruction of platelets, can involve megakaryocytes  
Decreased platelet production may also be a factor |
| **PRESENTATION ONSET PLATELET COUNT** | **ACUTE**  
Most with symptoms < 1 week often after viral infection  
Most < 20,000/µL | **INSIDIOUS**  
Most symptoms > 2 months  
Most < 20,000/µL |
| **COURSE** | Overall: 85% acute, 15% chronic  
Young children: more likely to be acute  
Adolescents: More likely to be chronic | More likely to be chronic. |
| **CHRONIC DISEASE** | Atypical | Typical |
| **CEREBRAL HEMORRHAGE** | <1% | 3%; increases with age > 60 years |
| **MORTALITY OF CHRONIC, REFRACTORY DISEASE** | 2% | 5%; increases with age > 60 years |
CLINICAL FEATURES OF ITP

Signs and symptoms vary widely – many patients have no symptoms or minimal bruising.

**Platelet counts**
- <100,000/µL with no evidence of an underlying reason for thrombocytopenia

**Minor bleeding**
- Petechiae – small, purplish, hemorrhagic spots on the skin
- Ecchymoses – superficial bleeding under the skin or a mucous membrane (bruising)
- Purpura – any rash in which blood cells leak into the skin or mucous membranes, usually at multiple sites

**Major bleeding**
- Gastrointestinal and genitourinary bleeding
- Intracranial hemorrhage
  - 0.1-0.5% incidence in children with ITP
  - Risk factors: head trauma, concomitant meds that affect platelet function
  - 25% mortality / 25% neurologic sequelae
- Skin or mucosal hemorrhage
- Epistaxis - hemorrhage from the nose (nosebleed)
- 3% of children have clinically significant bleeding
- Severe bleeding more likely in children with PLT < 10,000/mm³

Large ecchymotic area over the thigh following minor trauma. The platelet count at the time was 7000/µL.

Petechiae were originally described as “flea bites.”

DIAGNOSIS OF ITP

**ADULTS**

ITP is largely diagnosed by excluding other etiologies of thrombocytopenia. The following should be used to make an accurate diagnosis and to inform future treatment decisions:

Suggested diagnostics include:
- Patient and family history
- Physical exam
- Complete blood count, reticulocyte count, and peripheral blood smear
- Direct antiglobulin (Coombs) test or DAT
- Blood group Rh(D) typing
- Bone marrow examinations in patients older than 60 years of age, in patients with systemic symptoms or abnormal signs, or in some patients in which splenectomy is being considered.
- HIV/HCV/H. pylori testing

Other tests may provide additional information including tests for:
- Platelet-specific antibody
- Antiphospholipid antibodies (eg, cardiolipin, lupus anticoagulant)
- Antithyroid antibodies and thyroid function
- Pregnancy test
- Antinuclear antibodies
- Viral PCR for parvovirus and cytomegalovirus

**CHILDREN**

ITP in children is usually acute and can resolve spontaneously. It can develop following an acute viral infection. Diagnosis of ITP in children, like adults, is by exclusion of other etiologies and may include congenital disorders of thrombocytopenia and immune dysfunction such as Wiskott Aldrich, or giant platelet syndromes. Along with recommendations listed above for adults, suggested diagnostics include:

- Direct review of the smear to evaluate platelet size
- Bone marrow evaluation (recommended if ITP persists)
- Infectious etiology (HIV/EBV/CMV/H. pylori)
  - Antinuclear antibodies
  - Antiphospholipid antibodies
  - Autoimmune disease (ANA, anti-DNA or lupus panel)
  - Antiphospholipid panel
- Measurement of serum immunoglobulins (IgG, IgA, IgM)
- History including review of medication usage

**Predictors of Chronic ITP in Children**

Compared to acute ITP, the major predictors of chronic ITP are:
- Age >10 years
- Gradual onset of symptoms
- Initial platelet count >20,000/µL
ADULT ITP TREATMENT STRATEGIES
(see Table)
The goal of treatment is to achieve a safe platelet count to decrease bleeding risk. Patients with platelet counts <30,000/µL should be treated for ITP. Patients with higher platelet counts (≥50,000/µL) should also be treated if they have any of the following characteristics:9

• Bleeding due to platelet dysfunction or another hemostatic defect, trauma, surgery
• Clearly identified comorbidities for bleeding
• Are receiving anticoagulation therapy
• A profession or lifestyle that predisposes them to trauma

Emergency Management of Patients with ITP
Some patients with ITP may need their platelet counts raised quickly to undergo surgical procedures, or because they have active CNS, GI, or GU bleeding, or are at high risk of bleeding. Two treatments are recommended for patients with uncontrolled bleeding:

• Combination of prednisone and IVIg
• High-dose methylprednisolone

Other therapies that can quickly raise platelet counts include:

• Platelet transfusions alone or in combination with IVIg
• Emergency splenectomy
• vinca alkaloids

CHILDHOOD ITP TREATMENT STRATEGIES
Watch and wait is appropriate for many children with no or only minor bleeding symptoms. Multiple factors when deciding to treat/not to treat include:9

• Bleeding symptoms
• Platelet count
• Parental perspective

First Line Treatments include:

• IV anti-D
• IVIg single dose

Immunosuppressive therapy is more commonly used before cytotoxic medications, i.e following BM aspirate, consider prednisone in refractory acute. Other options include rituximab and dexamethasone pulse dosing.

Management of Persistent and Chronic ITP in Children
Treatment options in children with persistent or chronic ITP are similar to options for adults, except that cytotoxic therapies should only be used with extreme caution.

• Splenectomy for ITP is less common in the pediatric population.
• Limited clinical data on the use of TPO-R agonists in children.

Refractory ITP
Rodeghiero, et al convened to define standard terminology and definitions for primary ITP. Based upon their recommendations, “Response” (R) is defined as any platelet count between 30 and 100 x 10⁹/L and at least doubling of the baseline count. “No response” (NR) is defined as any platelet count lower than 30 x 10⁹/L or less than doubling of the baseline count.

DEFINITION (all should be met)

• Failure to achieve at least R or loss of R after splenectomy
• Need of treatment(s) (including, but not limited to, low dose of corticosteroids) to minimize the risk of clinically significant bleeding.
• Primary ITP confirmed by excluding other supervened causes of thrombocytopenia

DEFINITION OF ON-DEMAND THERAPY

• Any therapy used to temporarily increase the platelet count sufficiently to safely perform invasive procedures or in case of major bleeding or trauma

DEFINITION OF ADJUNCTIVE THERAPY

• Any non-ITP specific therapy that may decrease bleeding (eg, antifibrinolytic agents, hormonal agents, DDAVP, recombinant factor VIIa, fibrin sealants). Platelet transfusion is also included.

DEFINITION OF RESPONSE TO THERAPY IN REFRACTORY ITP

• Ability to maintain a platelet count sufficient to prevent clinically significant bleeding
• Ability to decrease toxic therapy (eg, corticosteroids) does not qualify for response but should be reported

DEFINITION OF RESPONSE TO ON-DEMAND THERAPY

• Control of bleeding in the specific situation
• Achievement of a platelet count sufficient to perform procedure or minimize bleeding from trauma

DDAVP indicates deamino arginine vasopressin.
* May not be applicable in children or in patients with accessory spleen.
† Bleeding symptoms measured by a validated scale whenever possible (requires further studies).
‡ Specific platelet thresholds cannot be provided, but in most instances, a platelet count of 50-70 x 10⁹/L would fulfill this criterion.
§ A strict definition of response in terms of predefined platelet count cannot be given and may not be appropriate when considering the risk/benefit ratio in refractory ITP, because the trade off between efficacy of a specific treatment and its short and long-term toxicity varies among patients.
**ADULT AND CHILDHOOD TREATMENT STRATEGIES**

**First Line** 5, 9

**Corticosteroids**
(eg, prednis(ol)one, dexamethasone, methylprednisolone)
Corticosteroids interfere with the clearance of antibody-coated platelets and induce nonspecific T-cell immunosuppression. They reduce bleeding by increasing platelet counts and by direct effects on blood vessels.

Unlike oral daily dosing of prednis(ol)one, dexamethasone is frequently administered as pulse dosing; eg, high daily dose for 4 days, given every 14 days for 4 cycles.

- Side effects include: mood swings, weight gain, anger, anxiety, insomnia, Cushingoid faces, dorsal fat, diabetes, fluid retention, osteoporosis, skin changes including thinning, alopecia, hypertension, GI distress and ulcers, avascular necrosis, immunosuppression, psychosis, cataracts, opportunistic infections, adrenal insufficiency, hypertension, and anxiety. Side effects tend to increase with repeated administration.
- Because of side effects, especially osteoporosis and aseptic necrosis of the hip, long-term use of corticosteroids is not recommended.

**Intravenous anti-D (anti-D)** 1, 5, 9, 12, 13

Intravenous anti-D is appropriate for use in Rh(D)-positive patients with intact spleens, including:

- Children with acute or chronic ITP
- Adults with chronic ITP
- Children and adults with ITP secondary to HIV infection

Anti-D can be administered in 3 to 5 minutes, however, the use of anti-D is not indicated for non-ITP causes of thrombocytopenia. It interferes with the clearance of antibody-coated platelets, and rapidly raises platelet count in 1-3 days. 1

- Common side effects include: hemolytic anemia (dose-limiting toxicity), headache, fever/chills.
- Additional rare, but serious side effects may include: intravascular hemolysis (IVH) and very rarely disseminated intravascular coagulation (DIC).

**Intravenous immunoglobulin (IVIg)** 1, 5, 9, 14

IVIg may be administered over several hours for up to 3 days. IVIg interferes with the clearance of antibody-coated platelets and interferes with B-cell participation in antibody synthesis. It also rapidly raises platelet counts within days.

- Common side effects include: headache, fever, chills, and fatigue.
- Additional rare, but serious side effects may include: renal toxicity, aseptic meningitis, and thrombotic reactions

**Second Line** 5, 15, 16, 17, 18, 19

Other than the thrombopoietin receptor agonists (TPOs), medications indicated for other conditions, such as chemotherapeutic agents, are often clinically used and reported in the medical literature to be useful for refractory/second line ITP treatment. However, these medications are not approved by the FDA for the treatment of ITP. (Medications are listed alphabetically. Safety information is available from their manufacturers or in their prescribing information.)

**Immunosuppressive and cytotoxic**

Therapies such as vincristine interfere with the clearance of antibody-coated platelets. Therapies that induce non-specific T-cell immunosuppression include: azathioprine, cyclophosphamide, cyclosporin A, and vincristine. Mycophenolate mofetil interferes with B-cell participation in antibody synthesis.

**Danazol**

An attenuated androgen administered p.o. that interferes with the clearance of antibody-coated platelets and includes nonspecific T-cell immunosuppression.

**Dapsone**

An oral sulfone and moderate corticosteroid sparing agent. Necessitates frequent blood work as hemolysis, leukopenia and methemoglobinemia can occur.

**Rituximab**

Rituximab interferes with B-cell participation in antibody synthesis. Side effects may include infusional reactions, rare reports of progressive multifocal leukoencephalopathy (PML).

**Splenectomy**

Complete response is seen in approximately two thirds of patients. Surgical complications from splenectomy include bleeding, infection, and thromboembolism. Long-term risks include sepsis and thrombotic disorders.

**Thrombopoietin (TPO) receptor agonists**

Eltrombopag and romiplostim are indicated for the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. They increase platelet counts by binding to TPO-R and stimulating platelet production. Responses are achieved in approximately 85% of treated patients, however, chronic treatment is required to maintain platelet counts. Potential side effects of these treatments include: thrombotic events, reticulin deposition in the bone marrow, hepatotoxicity (eltrombopag).
## Treatment Options for Adult ITP Patients

### FIRST-LINE TREATMENTS: FDA APPROVED FOR ITP TREATMENT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Approximate Response Rate*</th>
<th>Approximate Time to Response*</th>
<th>Sustained Response After Treatment Discontinuation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CORTICOSTEROIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Up to 90% initially respond</td>
<td>Several days to several weeks</td>
<td>Depending on cycles may be as high as 50%-80%</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Can go to 95%</td>
<td>High-dose methylprednisolone (HDMP) vs prednisone 4.7 days vs 8.4 days</td>
<td>23% patients (&gt;50 x 10^9/L at 39 mos)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>70%-80%</td>
<td>Several days to several weeks</td>
<td>Uncertain</td>
</tr>
<tr>
<td>IV Anti-D</td>
<td>Up to 80%</td>
<td>1-3 days</td>
<td>In some patients</td>
</tr>
<tr>
<td>IVIG</td>
<td>Up to 80%</td>
<td>1-3 days</td>
<td>In a few patients</td>
</tr>
</tbody>
</table>

### SECOND LINE TREATMENTS: SURGICAL & FDA APPROVED

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Approximate Response Rate*</th>
<th>Approximate Time to Response*</th>
<th>Sustained Response After Treatment Discontinuation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenectomy</td>
<td>80%</td>
<td>1–24 days</td>
<td>Up to 66% of patients</td>
</tr>
<tr>
<td>TPO: Eltrombopag</td>
<td>Up to 80%</td>
<td>15 days</td>
<td>No</td>
</tr>
<tr>
<td>TPO: Romiplostim</td>
<td>Up to 89%</td>
<td>1–4 weeks</td>
<td>No</td>
</tr>
</tbody>
</table>

### SECOND LINE TREATMENTS: PRODUCTS NOT FDA APPROVED FOR ITP TREATMENT**

- Azathioprine
- Cyclosporine
- Cyclophosphamide
- Danazol
- Dapsone
- Mycophenolate Mofetil (MMF)
- Rituximab
- Vinblastine

*Approximate response rate, time to response and response after treatment are provided based upon Provan et al and are not meant to assess comparative effectiveness between different product classes.

**Information contained in Provan et al, and is not intended to support the use of these agents in the treatment of ITP patients. The safety and effectiveness of these products in ITP treatment have not been established with the FDA.

### RESPONSE TO TREATMENT:

- **Response:** ≥30,000/µL and at least 2x baseline platelet counts without bleeding
- **No response:** platelet count <30,000/µL or less than 2-fold increase of baseline platelet count or bleeding
- **Loss of response:** below 30,000/µL or less than 2-fold increase of baseline platelet count or bleeding
References


13. WinRh o SDF® prescribing information, March 2010.


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