

Guide to Understanding ITP (Immune thrombocytopenia)



Immune thrombocytopenia (ITP)

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*** *Italicized words are explained in the Glossary of this brochure.*

1 What is ITP?

Immune Thrombocytopenia (ITP) is a bleeding disorder characterized by a low amount of *platelets (thrombocytes)* in the blood; platelet counts are below $100'000 \times 10^6/L$. Other blood components such as red and white blood cells remain normal. ITP is also known as immune thrombocytopenia's former names, idiopathic thrombocytopenic purpura and immune thrombocytopenic purpura.

In ITP, the platelets are attacked and prematurely removed by the body's immune system. Normally, the immune system helps to fight off infections and diseases. If the immune system mistakenly attacks part of a person's own body, this is called an *autoimmune disease*.

In ITP mostly abrupt bleeding occurs and is associated with a platelet count of below $20'000 \times 10^6/L$. The most feared complication is bleeding in the brain, which is very rare but can be life threatening.

In most children with ITP, bleeding signs occur within 1 to 6 weeks after a common infectious disease, such as a cold or the flu. ITP may also occur after rubella, rubeola, chicken pox, hepatitis or after a live virus vaccination.

At the time of diagnosis nobody knows how long ITP will persist. Due to the duration ITP can be either an acute, self-limiting condition or a chronic autoimmune disease (see).

ITP can also be described as

- Autoimmune thrombocytopenic purpura AITP
- Morbus Werlhof
- Purpura hemorrhagica

Thrombocytopenia can also occur

- In association with other disorders such as infection (for example HIV) or autoimmune disorders
- Due to low production of platelets. As thrombocytopenia after cancer drugs, irradiation and/or transplantation.
- After a transfusion (*alloimmune* thrombocytopenia).
- When certain drugs (other than cancer drugs) are taken. This is observed more frequently in adults than in children.

2 Who can get ITP?

- ITP is a rare bleeding disorder that affects 3-4 of 100'000 children. It affects both children and adults, male and female. Slightly more boys are affected at young age, but ITP is more common in female adolescents and adults.
- ITP is more common in white than in black children and its severity and duration may display geographic variations.
- Familial ITP where more than one family member is affected is rare, and the precise nature of inheritance remains unclear.
- ITP is not contagious.

3 What are platelets?

Platelets are small blood cells that are involved in blood clotting and wound repair. They are produced in the bone marrow along with red and white blood cells. The circulating number of platelets in the blood is normally within a range of $150'000$ to $400'000 \times 10^6/L$. Platelets have a life span of 7 to 10 days.

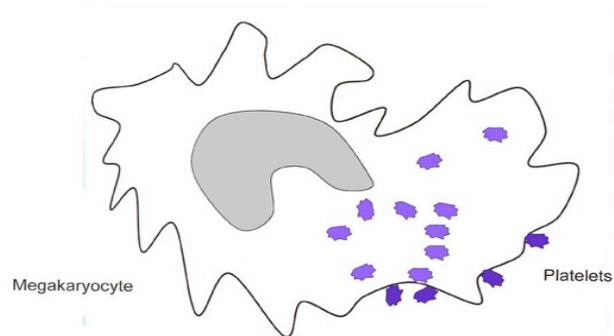


Figure 1: Platelets are produced in *megakaryocytes* in the bone marrow.

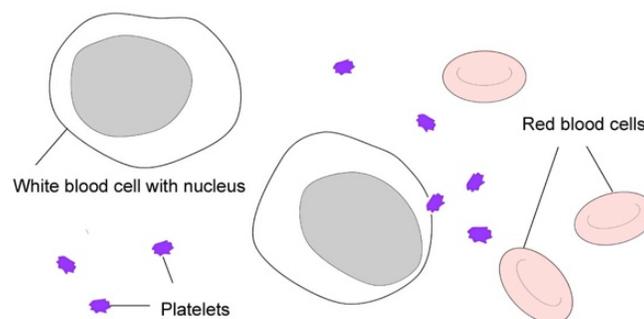


Figure 2: Components of the blood are white blood cells (with nucleus), red blood cells and platelets

	Platelets	Red Cells	White Cells
<i>Size</i>	1-2 micrometer	7	14
<i>Lifetime</i>	7-10 days	120 days	30 days
<i>Function</i>	Blood clotting and wound repair	Deliver oxygen throughout the body	Defense against bacteria and viruses

Table 1: Size and lifetime of platelets, red and white blood cells

Platelet counts of an individual are variable every day as production and turnover of platelets every day is very high, the size is small and the number is high. Platelets function differently individually so one patient with platelet counts below $10'000$ - $20'000 \times 10^6/L$ may have bleeding signs, whereas another patient may have none.

4 How is ITP diagnosed?

ITP is diagnosed by a platelet count of below $15'000-20'000 \times 10^6/L$ and by excluding other diseases such as infection, autoimmune or *immunodeficiency disorders* or cancer. A bone marrow examination may be done to rule out diseases such as bone marrow failure, leukemia or metastatic cancer and to verify that there are adequate platelet forming cells.

5 What are the symptoms of ITP?

- In some cases, thrombocytopenia without bleeding symptoms is diagnosed by a routine blood count.
- The bleeding depends on the degree of thrombocytopenia and varies individually.

A person with ITP may have bleeding signs such as bruises and tiny red or purple dots on the skin (*petechiae*). Nosebleeds, bleeding from the mouth, intestines, in muscles and joints may also occur. Women may be affected by heavy menstrual bleeding. Bleeding in the brain is very rare but can be life threatening if it occurs. According to a study in 2001 with 2,031 children, life threatening bleeding occurs in 0.2% within the first 12 months. The risk is greater during initial phase of ITP and if the platelet count is below $10'000 \times 10^6/L$, but can occur at any time in ongoing ITP.

Grading/Severity		Bleeding Manifestation	Management	
1	Minor/mild, normal life style	Few petechiae and small bruises	<ul style="list-style-type: none"> ▪ Occasional nose bleeds, stopped by applied pressure ▪ Blood blisters in the mouth ▪ No other bleeding 	Consent for observation
2	Moderate, troublesome life style	Numerous new petechiae and large bruises (> 5 cm)	<ul style="list-style-type: none"> ▪ Intermittent nose bleeds longer than 15 min. despite applied pressure ▪ Intermittent bleeding from gums, lips, mouth, esophagus, intestines. Blood in urine, hematemesis melena?? 	Punctual intervention to reach stage 1
3	Severe, life threatening	Extensive petechiae and large bruises	<ul style="list-style-type: none"> ▪ Continuous bleeding form gums, lips, mouth, throat ▪ Suspected internal bleeding (brain, lung, muscles, joints, others) 	Intervention

Table 2: Staging of bleeding in ITP, modified from Buchanan, Adix et al and Bolton Maags et al. and recommended management (Imbach)

6 What forms of ITP are there?

Newly Diagnosed ITP – The *acute* form of ITP is temporary and lasts for less than 3 months. It is the most common form of ITP in children. It typically occurs 1-6 weeks following an infection caused by a virus. This ITP is transient, meaning that the disease will go away on its own within weeks and months and will not return. Of children with ITP, 80-90% have acute ITP.

Persistent ITP – The persistent form disappears after within 3 to 12 months.

Chronic – The *chronic* form of ITP is long-lasting (over 12 months of duration or longer) and affects more adults than children. However, teenagers and children can also get this form of ITP. Chronic ITP predominantly affects women. 10 to 20% of children and the majority of adults have chronic ITP.

Recurrent – The *recurrent* form of ITP is defined as episodes of thrombocytopenia at intervals of over 3 months and occurs in 1-4% of children with ITP.

A different classification can be made to bleeding symptoms. Sometimes patients have a very low platelet count, although they have no sign of bleeding. This is usually discovered during a routine check-up and is called **asymptomatic** ITP. The **symptomatic** form of ITP includes minor to severe bleeding (Chapter 5, Table 2).

If there are no other signs of illness in relation to ITP, we speak of **primary** ITP. ITP can be associated with other illnesses such as infection or autoimmune disease, or occur after transfusion or taking certain drugs, for instance cancer drugs. This form is called **secondary** ITP (Chapter 1).

7 What causes ITP?

No one knows for sure what causes ITP, but multiple factors are likely to be involved such as environmental (for instance infections or certain drugs), self marker molecules, and heredity. Decades of studying immune response has provided us with an understanding that the body may overreact after an infection and produce antibodies which attach to platelets and mark them as 'foreign'. These platelets are then rapidly removed.

For information and better understanding of the the immune system, see Box 3 in the appendix.

8 What course will ITP take?

At the time of diagnosis, we do not know how long ITP will persist.

Facts:

- 80% of children no longer have ITP 6 months after they are diagnosed, independent of treatment. The younger the child, the less risk of developing chronic ITP.
- Complete *remission* is gained in 90% of children with ITP within 3-7 years.
- It seems that the severity of bleeding decreases with time. (A reduction of the severity of disease in children with ongoing ITP over time was documented in a study of children with ITP at 6 months and at 12 months after diagnosis.)
- Infants with ITP have a significantly favourable outcome in comparison with children aged 1-18 years.
- Increased risk for chronic ITP includes a history of bleedings for more than 4 weeks before diagnosis, female gender, age over 10 years and higher than $20'000 \times 10^6/L$ at diagnosis.

9 How will ITP change my life style?

Depending on the severity of ITP, certain precautions are recommended. Parents and the child/adolescent with ITP are generally worried about bleeding signs. They are concerned about the low platelet counts and perturbed by life style restrictions. Nobody can foresee if rare, severe bleeding will or will not occur in the individual child.

It is important for parents and patients to be informed about the mostly benign character of ITP and the low risk of long-term or secondary ITP. With this in mind, parents support the child with the hope to belong to the major group of good outcomers. Positive thinking and behaving until the next medical visit will help your child who is an 'existentialist'. This means a child will feel comfortable when parents are happy with her/him, when she/he has fun in daily life, can compete with school comrades, enjoy the next special event (birthday, vacation, annual holidays, visit of a performance etc.). For activity restrictions due to bleedings the child and parents need to find compensation with alternatives and avoid spoiling and pampering which produce fear!

10 How should ITP patients be managed?

Despite a low platelet count, treatment may not be necessary. For instance when there are no or mild bleeding signs and the platelet count is above $10'000-20'000 \times 10^6/L$. Nonetheless, the patient should be carefully monitored; this is also called 'observation' or 'watchful waiting'.

Observation and/or treatment is recommended according to a Staging System (Table 2). Treatment is necessary when troublesome bleeding (stage 2) or severe/emergency bleeding (stage 3) occurs. The goal is to reach stage 1. Therapeutic measures in acute ITP should be maintained until bleeding has ceased and the platelet count has reached levels above $10'000-20'000 \times 10^6/L$ platelets (stage 2, Table 2).

Treat the bleeding, not the platelet count! Instead of solely treating a low platelet count, treatment should be given for bleeding.

11 What types of treatment are there?

Recent insight into what might cause ITP has formed the base for a more biologic therapeutic treatment approach. Instead of suppressing the immune system, this therapy focuses on 'fine tuning' to help coordinate immune responses.

Some *immunomodulating* medications are antibody concentrates from healthy blood donors (IVIg, Anti D) or monoclonal antibodies (for instance Anti-CD20). They compete with the autoantibodies related to ITP and cause an alteration in the immune response. The exact mechanisms of action are not yet fully understood.

A new treatment form is stimulation of platelet production by megakaryocytes in the bone marrow. Two new thrombopoietin receptor agonists are available: Romiplostim/N-plateR for weekly subcutaneous administration and Eltrombopag/PromactaR or RevoladeR in tablet form for daily oral

use. Both have less side effects than the other medications, but long-term adverse effects have to be studied.

Many other treatments are associated with side effects (Table 3), some of which (for instance high dose corticosteroids) may be worse than the disease itself. While treatment can effectively raise the platelet count, most medications suppress the disturbed immune response of ITP, but do not treat the underlying (mostly unknown) cause of low platelet count, which may fall again when therapy is stopped.

Splenectomy as a therapeutic intervention is restricted to cases with uncontrollable bleeding in children.

Standard Treatment	Type of Medication	Rate of Response	Main Adverse Effects
IVIg	Immunoglobulins	> 95%	Headache, nausea, fever. Rarely aseptic transient meningitis
Anti-(Rh)D	Immunoglobulins	> 80%	Breakdown of red blood cells, hemolysis
Corticosteroids	Immunosuppressive drug	75-79%	Weight gain, hyperglycemia, facial swelling, hypertension, behavioral abnormalities. Long-term treatment: growth retardation, cataract
Treatment - Refractory ITP			
Anti CD20 (Rituximab)	Monoclonal Antibody	70%	Fever, headache, dizziness, nausea, vomiting, low blood pressure
Thrombopoietin Receptor Agonist (TRA)	Platelet production stimulator	80%	Headache, nausea, vomiting or diarrhea in about 2%,
Splenectomy	Surgical removal of the spleen	70%-80%	Risk of fatal bacterial infections, dysfunction of kidneys, abnormally low number of white blood cells
Vinca alkaloids (Vincristine, Vinblastine)	Cytostatic drug	63-68%	Transient neuropathy, constipation, lymphopenia
Azathioprine	Cytostatic drug	50-70%	Abnormally low number of white blood cells, hair loss
Cyclophosphamide	Cytostatic drug	60-80%	Abnormally low number of white blood cells, hair loss, infertility
Cyclic high dose steroids	Immunosuppressive drug	see above ???	see above ???
Denazol	Immunosuppressive drug	10-80%	Weight gain, headache, hair loss, liver dysfunction, muscle pains, virilization, disturbances of menstrual bleeding
Vitamin C		15%	
Cyclosporin	Immunosuppressive drug	50-60%	Kidney dysfunction, abnormally low number of white blood cells, abnormal hair growth
Interferon alpha	Cytokine	25%	Fever, headache, dizziness, nausea

Table 3: Treatment options for ITP patients, response rate and main adverse effects

Treatment mode	Response within 3 days
No treatment (observation)	9 of 16 patients = 56%
IVIg (0.8g/kg bodyweight)	34 of 35 patients = 97%
Intravenous Anti(Rh)D immunoglobulin (25 µg/kg bodyweight, 2x per day)	31 of 38 patients = 82%
Corticosteroids (4 µg/kg bodyweight, daily)	45 of 57 patients = 79%

Table 4: Rate of recovery after Standard Treatment

12 What research is being done?

3-4 of 100,000 children are affected by ITP per year, which amounts to over 200,000 cases worldwide per year.

Decisions on how to manage patients with ITP have for many years been based on opinions of experts in this field. For the past decade, efforts have been made to gain more knowledge about this heterogeneous disease by promoting more evidence-based research. This means that definitions, classifications, the description of the natural history of ITP, treatment guidelines etc. must be based on solid scientific research.

Basic aims of **clinical research** are to answer questions such as

- What is the natural history of ITP, especially chronic ITP, and the outcome of the disease?
- When should ITP be treated with medication?
- Which medication is best suited for which patient? (Treatment optimization studies)
- Which ITP patients will develop chronic ITP?
- How can risk groups concerning the severity of disease be determined?
- What kind of management may be most suitable and most effective for which patient?
- How can the quality of life of patients with ITP be best enhanced?

Because ITP is a rare disorder, information on patients with ITP is being collected in registries with the help of many medical centers. These registries will help answer the above questions or give useful hints as how future studies should be designed.

While some defects of the immune system have been described, the cause for loss of self tolerance is still unknown. Recent development in **Genetics** and **Genomics** provide tools for investigating possible predisposing factors to ITP such as the likelihood of losing self tolerance or developing autoantibodies.

Studying the **Pathogenesis** of the disease includes having a closer look at the cells of the immune system, how immune responses are triggered and regulated. This research also enables the development of refined laboratory tests for diagnostics.

A networking community of researchers from different fields has been established to achieve a better understanding of this heterogeneous disease (see www.itpbasel.ch). Research of ITP as a disease model may be valuable to other autoimmune disorders as well.

13 Where can I find more information on ITP?

www.itpfoundation.org The ITP Foundation is a non-profit organization focusing on ITP in children and youth. They seek to raise awareness of ITP among the general public, medical and health care professionals, and elected officials. In addition, they work to fund vital medical research into various aspects of ITP, including its cause, treatment and cure, and, to provide financial assistance to the families of children with ITP.

Dr. Paul Imbach is a resident Medical Advisory Board of Directors for the ITP Foundation.

www.itpbasel.ch The Intercontinental Childhood ITP Study Group (ICIS) was founded in 1997 by physicians in the field of hematology to analyze the multiple diagnostic and therapeutic aspects of acute and chronic childhood Idiopathic Thrombocytopenic Purpura (ITP). There are many questions, such as the natural history of childhood ITP, which need to be clarified as well as questions concerning diagnosis and therapy of ITP, such as the identification of early predictors of chronic ITP.

The Intercontinental Childhood ITP Study Group (ICIS) was founded in 1997 by physicians in the field of hematology to analyze the multiple diagnostic and therapeutic aspects of acute and chronic childhood Idiopathic Thrombocytopenic Purpura (ITP).

ICIS provides a long-term concept for prospective studies and new, evidence-based definitions of ITP by worldwide cooperation of physicians. Within 9 years, over 500 physicians from over 60 countries have participated or are participating in ICIS projects, and over 4'300 patients have been registered anonymously.

Dr. Paul Imbach is ICIS Chairperson of the Hematology/Oncology Unit of University Children's Hospital in Basel, Switzerland.

14 About the Author – Dr. Paul Imbach

Paul Imbach is a Consultant to the University Children's Hospitals in Basel and Aarau, Switzerland. He is emerited Professor in Pediatrics, Dean of Education and Extraordinarius of the Pediatric Oncology/Hematology Medical Faculty, University of Basel. Professor Imbach obtained his medical degree at the Universities of Basel and Zurich in 1971, prior to receiving his paediatric board certificate in 1977. His discovery of the immunomodulatory effects of human immunoglobulin G concentrate IVIg in ITP was published in 1981. Professor Imbach is Chairman of the Intercontinental Cooperative ITP Study Group, with over 70 participating hospitals and clinics worldwide, and a board member of the ITP Foundation in the USA. He is President of the cord blood stem cell project Stiftung, and past President of both the Swiss 'Make a Wish' Foundation and European Society for Paediatric Haematology and Immunology. Professor Imbach is the author or co-author of numerous articles published in international peer-reviewed journals such as The Lancet and Blood.

– Biography provided by the European Hematology Association

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Intercontinental Cooperative ITP Study Group
[http://www.itpbasel.ch/](http://www.itpbasel.ch)

APPENDIX

Box 1: Patient – Ken

As a healthy four year old boy, Ken, had an infection of the upper respiratory tract two weeks ago. Now his parents observed multiple red dots (petechiae) and large bruises on his chest and his legs. A nose bleed (epistaxis) which could only be stopped by pressure after 15 minutes led to a consultation with the family physician who examined no other signs with exception of the bleedings and the blood analysis showed isolated thrombocytopenia of $12'000 \times 10^6/L$ (normal range is $150'000-400'000 \times 10^6/L$), and sent the boy to the pediatric hematologist who confirmed the diagnosis of post-infectious idiopathic thrombocytopenic purpura (ITP).

The physician and parents agreed on observation and regular platelet counting. The next day bleeding in the mouth occurred and the platelet count was $7'000 \times 10^6/L$. A single intravenous treatment with 0.8 g per kg bodyweight of human immunoglobulin concentrate was given. One day later Ken's platelet count was $18'000 \times 10^6/L$, the next day $34'000 \times 10^6/L$ and no new bleeding signs were observed.

Later on, some petechiae and bruises could be recognized and the platelet counts fluctuated between $15'000$ and $90'000 \times 10^6/L$, thereafter, in the course of 4 months his platelet counts had reached normal values and Ken was again a healthy boy.

Comments

Transient ITP in children occurs mostly during or after an infection in an otherwise healthy child. Behind the thrombocytopenic bleeding seems to be a prolonged disturbed recovery of the child's immune system. Severe, spontaneous bleeding is rare and occurs with platelet counts below $10'000 \times 10^6/L$. Care and management of ITP is through observation or standard treatment (Chapter 11, Table 3).

Difficulty

Bleeding is fearful for the parents and the child. The physician cannot predict, which child is at risk for severe bleeding (at diagnosis the rate is 3 of 100 children) and the duration of ITP. Seldom does a child with ITP have second episode or a relapsing-remitting form of ITP. The duration of ITP varies individually between weeks and up to 12 months. Ongoing chronic and secondary ITP are seen in less than 10-20 percent of children.

Box 2: Patient - Katja

Katja was 11 years old when she observed bruises and petechiae on her skin, especially after sport activities. Blood analysis showed a platelet count of $8'000 \times 10^6/L$ and she received 0.8g/body weight of intravenous immunoglobulin (IVIG). Platelets increased to $24'000 \times 10^6/L$ within 3 days, but she relapsed three weeks later with $4'000 \times 10^6/L$ platelets and repetitive bleeding signs as in stage 2. Corticosteroids during 14 days showed an increase of platelets to $35'000 \times 10^6/L$. Katja experienced imperative appetite, weight gain and sleeping problems as side effects to the steroids. During the 18 months she had repetitive skin and nose bleeding, especially during sport activities, despite biweekly alternative application of IVIG and Anti-D immunoglobulins, respectively. After an accidental trauma with head injury she developed headache and unconsciousness and epilepsy. After the emergency transportation to the hospital intracranial bleeding (bleeding in the head) was diagnosed. Emergency treatment was given and neurosurgery had to be performed. She recovered and afterwards she had splenectomy (removal of the spleen) which resolved her stage 3 mild to severe ITP, with platelet counts of $30'000-70'000 \times 10^6/L$ (stage 1) in subsequent years.

Comments

Chronic ITP occurs at a rate of 10-20% of children. Most of the time, the severity of bleeding diminishes with duration of chronic ITP. One of four children/adolescents (25% or less than 4% of all children with ITP) have long-term severe ITP of stage 3 (Chapter 5, Table 2). Rarely are such children or adolescents diagnosed with

secondary ITP, meaning that their ITP is associated with another autoimmune disorder, a chronic viral disease or other disorders. The hematologist will exclude secondary ITP by clinical examinations and lab tests. Katja continues to have mild chronic ITP. Since her spleen was removed, she takes penicillin daily as a risk prophylaxis against life threatening infection. Her quality of life is comparable to that of her colleagues. After splenectomy, however, some patients can relapse to severe ITP (stage 2 or 1) within several years.

Box 3: Immune System

7.1 How does the immune system work?

The key to a healthy immune system is its remarkable ability to distinguish the body's own cells and foreign cells. The body's immune defenses normally coexist peacefully with cells that carry distinctive 'self' marker molecules. But when cells or organisms carrying markers designated as 'foreign' are encountered, they quickly launch an attack. Anything that triggers this *immune response* is called an *antigen*. In abnormal situations, the immune system can mistake self for a nonself and launch an attack against the body's own cells or tissues. The result is called an autoimmune disease.

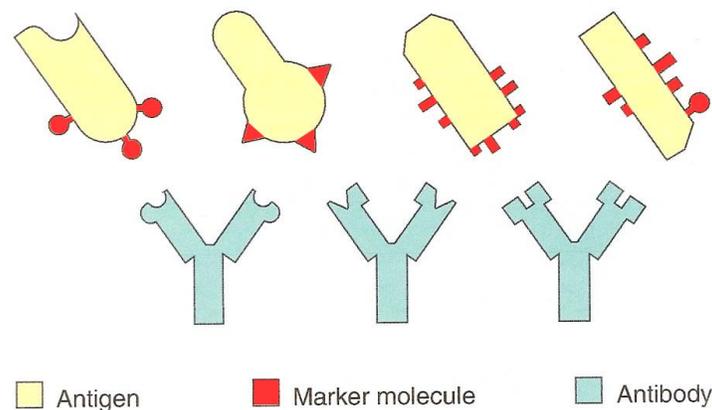


Figure 3: Antigens carry marker molecules that identify them as foreign

7.2 Immune cells

Key players of the immune system are white blood cells called *lymphocytes* and *granulocytes*. They travel throughout the body using blood vessels and lymphatic vessels. To work effectively, most immune cells need the cooperation of other white blood cells. They produce and respond to different *cytokines* and other signals to grow into specific immune cell types. Among the many types of white blood cells are:

- Antigenpresenting cells and T cells. These cells are able to direct and regulate immune responses and communicate by release of chemical messengers called cytokines.
- B cells mainly work by secreting antibodies into the body's fluids and tissues. The antibody matches an antigen much as a key matches a lock. Whenever antigen and antibody interlock (Figure 3), they form an *immune complex*.
- *Phagocytes* are large white blood cells that can ingest foreign particles, cells or microbes by engulfing them.

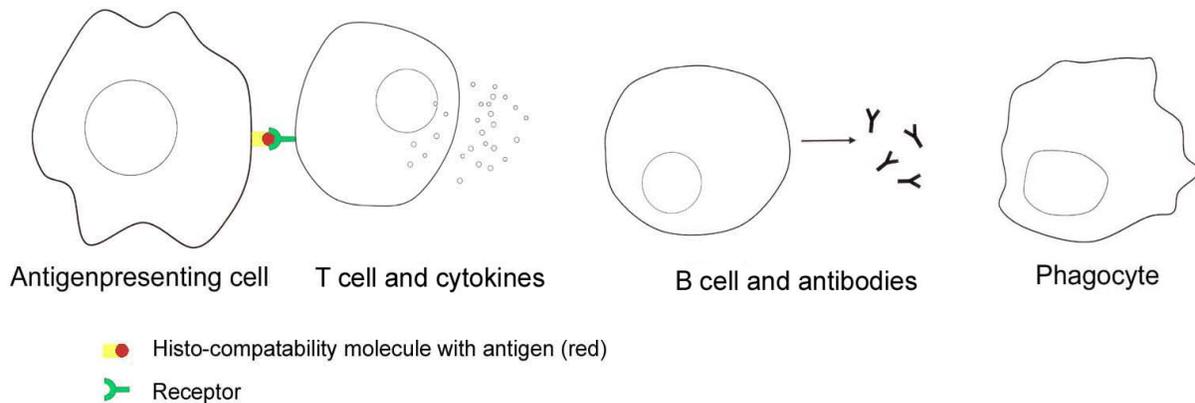


Figure 4: Key players of the immune system

7.3 Different mechanisms seem to lead to the different forms of ITP

- Acute ITP may be due to a crossreactive immune response directed against an infectious antigens. Immune complexes, originated in relation to infection or another underlying disease, may bind to the platelet, or circulating antigens or antibodies may alter the platelet membrane, so that the platelets are *sensitized*, marking them as foreign. Sensitized platelets are cleared by the immune system, mainly in the *spleen*, liver and bone marrow.
- Chronic ITP may be perpetuated by a immune response that is constantly stimulated by self molecules and cytokine production, increased activation of T-cells and increased production of specific antibodies.

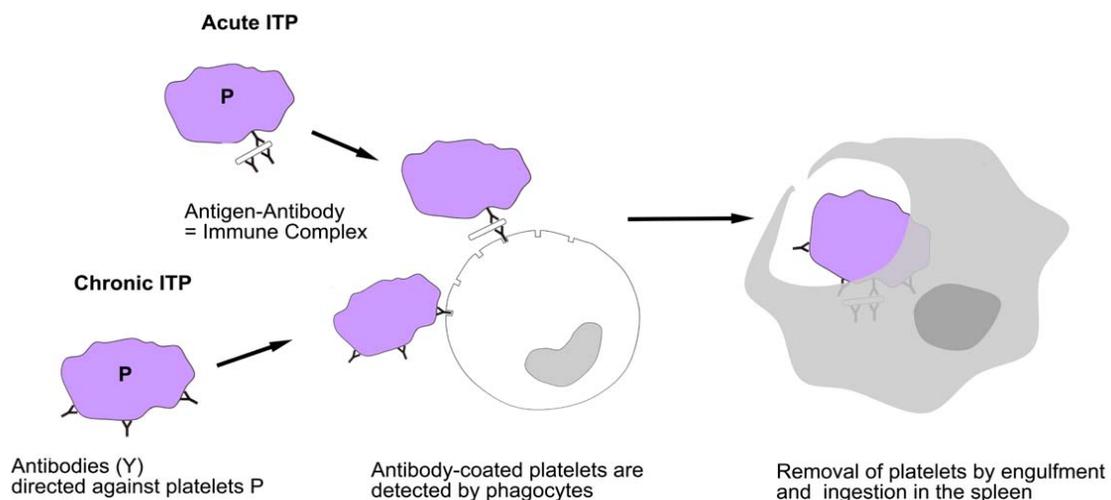


Figure 5: Sensitized platelets are detected by phagocytes, engulfed and digested.

However, both forms of ITP appear to result from an altered feedback mechanism critical for the termination of the immune response. The severity of thrombocytopenia reflects the balance between platelet production and the accelerated clearance of sensitized platelets.

7.4 Multiple defects to the immune system have been described in patients with ITP

- A T cell can only recognize an antigen if it is presented along with molecules that are marked as self (molecules of the genetic histocompatibility system). It has been observed that serum level of histocompatibility molecules are enhanced in ITP.
- Increased levels of chemical messengers such as cytokines have been detected in ITP as well as in other autoimmune disorders.
- After the immune cells have done their job, they are usually disintegrated through a process called programmed cell death (apoptosis). This process might be impaired, leaving immune cells in circulation that should have been cleared in the immune system.

Box 4 – ITP Timeline

Discovery of ITP

1735	The bleeding disorder Morbus maculosus hemorrhagicus was first described by Werlhof.
1842	Platelets were identified under the microscope for the first time.
1916	The first splenectomy was performed in Prague. After that, splenectomy became the main treatment for chronic ITP even though the role of the spleen in the disease was not clear.
1950	ITP has something to do with a disturbed immune response. Harrington et al. observed that newborns of mothers with chronic ITP often had a transient decrease in their platelet counts, suggesting there was something in the <i>blood plasma</i> that had been transferred through the placenta from the mother to her baby. He then injected <i>plasma</i> from a patient with ITP to himself and other volunteers and promptly developed classical transient ITP, proving that some factor in the blood plasma leads to thrombocytopenia.
since 1950	Since 1950 corticosteroids – a human (stress) hormone and other immunosuppressants (see treatment of refractory ITP) have been used to increase the platelet count, however, with frequent side effects. Thus, the question to treat or not to treat ITP in patients without severe bleeding continues to be discussed by doctors and patients.
1965	Shulman showed that a certain type of antibody in the ITP plasma is involved and, importantly, that it binds to self as well as nonself platelets. Since 1975, laboratory techniques have demonstrated that high levels of these antibodies can be found in the majority of patients with thrombocytopenia.
1981	Imbach observed that the certain fractions of antibodies from healthy blood donors (intravenous immunoglobulins) can be used therapeutically and raises the platelet counts in patients with acute and chronic ITP. Two years later Salama described the use of Anti-D-immunoglobulin in ITP. ITP becomes a model for immunomodulatory treatment of many diseases with autoimmune traits.
1982	Van Leeuwen provided the first evidence for autoantibodies in chronic ITP and found out that the antibodies bind to a protein called glycoproteins (Gp) IIb and IIIa on the platelet. In 1987, 2 methods were developed which can detect both platelet-associated and free plasmic autoantibodies.
1991	Semple documented that chronic ITP was associated with a T-helper cell defect in which T cells secrete a chemical messenger called interleukin-2 upon stimulation with self platelets.
2000	The role of phagocytosis and the crucial receptor on the phagocyte in ITP was shown by Ravetch.
2010	Thrombopoietin Receptor Agonists as new platelet stimulating treatment form registered

Box 5 - Glossary

Terms	Definitions
Acute ITP	Short-term ITP with bleeding signs. This form of ITP that goes away and does not occur again.
Adverse effect	Harmful side effects
Antibody, autoantibodies	Molecules (also called immunoglobulins) produced by a B cell in response to an antigen. When an antibody attaches to an antigen, it helps the body destroy or inactivate the antigen. Autoantibodies react against the body's own tissues.
Antigen	A substance or molecule that is recognized by the immune system. The molecule can be from foreign material such as bacteria or viruses. In ITP, platelets are mistakenly recognized as foreign.
Autoimmune disease	A disease that results when the immune system mistakenly attacks the body's own tissues. Examples include Type I Diabetes, Rheumatoid arthritis, and Systemic Lupus Erythematosus, Multiple sclerosis, ITP.
Blood plasma	The liquid component of blood.
Chronic ITP	Persisting or lasting ITP.
Cytokine	A natural protein that works as a chemical messenger to direct and regulate the immune system.
Cytostatic drug	An agent the suppresses cell growth and multiplication. Mainly used against cancer cells.
Genetics, Genomics	While genetics is the study of genes, genomics includes comparing the whole set of genetic makeup. This has been made possible by the Human Genome Projekt.
Idiopathic	'Of unknown cause'
Immune complex	Clusters of interlocking antigens and antibodies. If not removed, they can cause damage.
Immunodeficiency	A state in which the immune system's ability to fight infectious disease is compromised or entirely absent
Immunoglobulins	A family of large protein molecules, also known as antibodies, produced by B cells.
Immunomodulating drugs	Drug that influence the regulation of the immune response.
Immune response	Reaction of the immune system to foreign substances
Immunosuppressant drugs	Drugs that prevent inflammation and immune response. Prevent the production of antibodies against platelets in ITP
ITP	Idiopathic Thrombocytopenic Purpura (id-ee-o-PATH-ick thromb-bo-cy-toe-PEE-nick PURR-purr-ah)
Lymphocytes	White blood cells that circulate throughout the lymphatic system
Megakaryocytes	'Mother' cell in the bone marrow that produces thrombocytes
Pathogenesis	Cause of the disease.
Petechiae	(Peh-TEE-kee-ay) small reds dot that appear on the skin and mucosa and may look like a rash.
Persistent ITP	ITP lasting 3 to 12 months
Platelet (thrombocytes)	A cellular of blood. Other components are white and red blood cells.
Platelet count	Determines how many platelets are in the blood. A blood sample is needed.
Recurrent ITP	Episodes of ITP that occur again in time.
Refractory ITP	ITP that is persistant.
Relapse	Occurs when a patient again shows symptoms of ITP after an episode without ITP.
Remission	Is the state of absence of disease in patients with a chronic illness.
Sensitized platelets	Antibody-coated platelets are sensitized, meaning that the immune system turns against them and initiates their removal.
Splenectomy	Removal of the spleen by surgery, also performed by laparoscopic surgery

Spleen	(minimal invasive surgery). An organ on the left of the abdomen, behind the stomach and close to the diaphragm. The spleen is an important center for immune system activities, for antibody production as well as cell removal (platelets, red cells etc.).
Thrombocytes	(THROM-bo-sites) platelets
Thrombocytopenia	Thrombo-site-oh-PEE-nee-ah. A lower than normal amount of platelets in the blood (below $150'000 \times 10^6/L$).
Transient, newly diagnosed ITP	Short-term ITP with bleeding signs. This form of ITP that goes away within weeks and does not occur again.