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This book discussed on etiology of thrombocytopenia whether it occur due to microbial infections such as Malaria or Kala-azar or due to infection with pathogenic or opportunistic bacteria and also studied others non microbial causes of thrombocytopenia whether its due to congenital defect or associate with pregnancy. In this book we try to give clear picture about thrombocytopenia to enable every medical students to understands this real disaster in order to prevent and treat it accurately.

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# Microbial and non-microbial induced thrombocytopenia

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**Dedication**

*(To my parents*
*& my sons)*

## Acknowledgement

We send many thanks to our colleagues at Khartoum University, faculty of medical laboratory and at Soba university hospital and special thanks to my friend / Ahmed Mustafa Basheir.

**Mosab ,2017**

## Overview

> Platelet is a minute colorless anucleate disklike body of mammalian blood that is derived from fragments of megakaryocyte cytoplasm, that is released from the bone marrow into the blood, and that assists in blood clotting by adhering to other platelets and to damaged epithelium—called also blood platelet, thrombocyte. [(1)]

Platelets are produced during hematopoiesis in a sub-process called thromopoiesis, or production of thrombocytes. Thrombopoiesis occurs from common myeloid progenitor cells in the bone marrow, which differentiate into promegakaryocytes and then into megakaryocytes. Megakaryocytes stay in the bone marrow and are thought to produce protoplatelets within their cytoplasm, which are released in cytoplasmic extensions upon cytokine stimulus. The protoplatelets then break up into hundreds of platelets that circulate throughout the bloodstream, while the remaining nucleus of the ruptured megakaryocyte is consumed by macrophages.

Megakaryocyte and platelet production is regulated by thrombopoietin, a hormone produced by the liver and kidneys. Thrombopoietin stimulates differentiation of myeloid progenitor cells into megakaryocytes and causes the release of platelets. Thrombopoietin is regulated by a negative feedback mechanism based on platelet levels in the body so that high levels of platelets result in lower levels of thrombopoietin, while low levels of platelets result in higher levels of thrombopoietin.

Each megakaryocyte produces between 5,000 and 10,000 platelets before its cellular components are fully depleted. Altogether, around 10^11 platelets are produced each day in a healthy adult. The average lifespan of a platelet is just 5 to 10 days. Old platelets are destroyed by macrophage phagocytosis in the spleen and by Kupffer cells in the liver. Up to 40% of platelets are stored in the spleen as a reserve, released when needed by sympathetically-induced splenic muscle contractions during severe injury. [(2)]

Platelets, or thrombocytes (thromb- + -cyte, "blood clot cell"), are a component of blood whose Function (along with the coagulation factors) is to stop bleeding by clumping and clotting blood vessel injuries. Platelets have no cell nucleus: they are fragments of cytoplasm that are derived from the megakaryocytes of the bone marrow, and then enter the circulation. These unactivated platelets are biconvex discoid (lens-shaped) structures2–3 μm in greatest diameter Platelets are found only in mammals, whereas in other animals (e.g. birds, amphibians) thrombocytes circulate as intact mononuclear cells. [(3)]

Max Schultze published the first accurate and convincing description of platelets as part of a study devoted mainly to the white blood cells in 1865. He recognised them as a normal constituent of the blood and 'enthusiastically recommended' them as an object for further study by 'those concerned with the in-depth study of the blood of humans'. In 1882, Bizzozero demonstrated the value of this recommendation in his much more comprehensive study. He observed them microscopically in the circulating blood of living animals and in the blood removed from the blood vessels. In well-planned experiments, he showed that they were the first component of the blood to adhere to damaged blood vessel walls in vivo and, in vitro, that they were the first components of the blood to adhere to threads that subsequently became covered with fibrin. [4]

Platelets contribute to the hemostatic process in two different ways. First, through their adhesive and cohesive functions that lead to the formation of a hemostatic plug. Second, they can activate Coagulation mechanisms through the exposure of an adequate phospholipidic surface, acting as a catalytic site for the development of coagulation and the consolidation of the hemostatic plug. To promote a correct hemostasis, platelets should ideally retain their adhesive and procoagulant properties.

Platelets possess important secretory functions. During the process of activation, platelets express internal membrane proteins and release adhesive proteins, coagulation and growth factors. Some of the proteins facilitate the cross-talk of platelets with leukocytes and endothelial cells. Thus platelets play and important role in inflammatory and proliferative events and play a critical role for tissue remodeling and wound healing. [5]

# Introduction

**Platelets:**

Platelet is an irregular, disc-shaped element in the blood that assists in blood clotting. During normal blood clotting, the platelets clump together (aggregate). Although platelets are often classed as blood cells, they are actually fragments of large bone marrow cells called megakaryocytes. [6]

**History:**

Platelets were discovered by G. Bizzozero in 1882 and rediscovered in the 1960s after many decades of oblivion. Interestingly enough, their role was initially more clearly associated with thrombosis than with hemostasis. For many years a serious unresolved problem was that the clotting time was normal even in severe thrombocytopenia. The concept of coagulation as an enzymatic cascade had not yet been elaborated. During the 1960s, the interest of many experts moved from the interaction of platelets with the process of blood coagulation to the interaction of these cells with the vascular wall (adhesion) and each other (aggregation). The discovery of the role of ADP as the principle of platelet aggregation stimuli was rapidly followed by other important discoveries such as the aggregating properties of collagen and thrombin, the release reaction, the metabolism of arachidonic acid, and the inhibitory effect of aspirin. The use of aspirin as a potential antithrombotic drug has made the history of clinical trials in the last 30 years. The last two decades have been characterized by an explosion of cell and molecular biology approaches. There are presently people who study platelet signal transduction or platelet-leukocyte interactions but who know almost nothing about hemostasis or thrombosis! This is due not only to the intrinsic limitations of the biological approach but also to the progressive recognition of the role of platelets in other physiopathologic and clinical conditions such as inflammation, cancer growth and dissemination, and organ transplant rejection. Overlooked for more than two centuries after the microscope was made available to hematologists, considered as an artifact or a Cinderella, the platelet has mainly been considered in the past 30 years as a dangerous cell to be inhibited by (ever more expensive) drugs. But the taming of the shrew is far from being achieved. [7]

## Thrombopoiesis

Platelets are one of the many key components of the blood that is required for normal functioning of the body. It is significant to stop bleeding and the loss of blood through platelet plug formation and blood clotting. This is a cellular component of blood and is formed in the bone marrow. Bone marrow is a place where all the cellular components of the blood are formed using stem cells that have the capacity to divide endlessly and get converted into many types of different cellular lines. There are two types of bone marrow; namely, the red and the yellow bone marrow. The red marrow is where the blood cells gets formed. Read Platelets and Blood Clotting.

**Ten steps of platelets formation:**

Megakaryocyte and platelet production is regulated by thrombopoietin**.** This is a hormone produced in the kidneys and liver. The following steps will explain the platelet formation from its birth to disposition:

1. The first cell:

When an embryo is born, it consists a type of cell called totipotent cell. Totipotent cells are capable of dividing into any cell of the body, be it bone or brain, liver or lung, and eye or ear. This cell gives rise to all the cells and has an unmatched capacity to divide. It forms the hematopoietic cells which then give birth to all the cells of the blood. These stem cells keep on dividing to keep the pool of totipotent cells alive.

2. Birth mother of all blood cells:

The first ancestors from blood line of cells in the lineage of platelets are *hematopoietic stem cells*. These stem cells are pleuripotent, which means that they can grow into any form of blood cell lines including red blood cells, white blood cells and the platelets. This is the first cell that gives birth to all other cells in the blood. Hematopietic cells give birth to progenitor cells under the influence of colony stimulating factors which require chemicals to direct a particular type of

cell to divide into another particular type of cell. For example, the GM-CSF or granulocyte monocyte colony stimulating factor gives rise to blood cell lines from hematopietic cells. These cells also keep on dividing to keep the pleuripotent pool alive.

3. The progenitor cells:

Progenitor cells are the committed cell types in this lineage. Once formed, they can only give rise to the next cell line depending on the chemical influence provided. That is to say that the progenitor cells are committed to form the given cell type and will not form any other cell type.

One type of progenitor cell will only ever give rise to a particular cell type.

4. Pooling of the cell lines:

These different types of cell lines are forming together from a common ancestor. The cell lines pool in their respective areas and separate from one another.

5. Megakaryoblasts:

The progenitor cells form the megakaryoblast under the stimulating effect of colony stimulating factors. These factors are the essential requirement for the formation of platelets. These are immature cells and found only in the bone marrow. In certain type of diseases, these cells are released early into the circulation and can be seen on a peripheral blood smear.

6. Megakaryocyte formation:

The megakaryoblasts mature under the effect of the same colony stimulating factors to give rise to megakaryocyte. The role of colony stimulating factors in the formation of platelets is limited to this step. Erythropoietin takes the task of the formation of platelets from here on.

7. Megakaryocyte maturation:

Megakaryocytes mature under the influence of erythropoietin. Erythropoietin is formed by the liver and kidneys and is released into the blood from where it reaches the bones and enters the bone marrow. It then shows its effects on the maturation of megakaryocytes. In diseases involving liver and kidneys where erythropoietin production is compromised, the number of platelets also reduces due to the lack of optimization of this step.

8. Megakaryocyte extrusion from bone:

Megakaryocytes are the precursors of platelets. This is the last step with regards to the involvement of the bone marrow and all the other further steps, takes place outside the bone and in the blood. Megakaryocytes are extruded from the bone through the capillaries and are released into the blood.

9. Megakaryocyte breakage and pro platelet release:

Nuclear death and cellular breakage occurs as soon as the megakaryocytes are released into the blood and even as they are being released into the blood through the capillaries. The megakaryocytes at this stage have pro platelet outgrowths which break off from the main body of the megakaryocytes. These pro platelet extensions carry with them the protein forming machinery of the cells.

10. Platelets:

Platelets are finally formed from the breaking off of pro platelets into further smaller pieces in the blood. These platelets can be counted in the blood though diagnostic procedures like taking a blood sample from the peripheral blood and putting it in a cell counter. This helps in detecting any abnormally high or abnormally low number of platelets. In order to see the platelet morphology, a peripheral blood smear is made and seen under a microscope. A smear is a spread of blood taken from a periphery like a limb and spread on a slide.

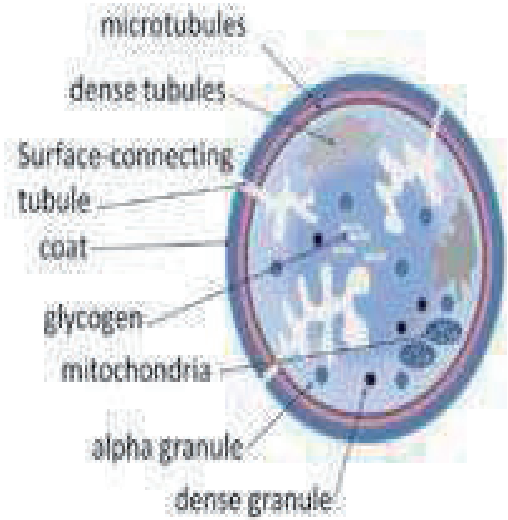
These basic ten steps about platelet formation suggest that a lot can possibly go wrong when it comes to platelet count or morphology. Any defect or drug that interferes with just one of these steps may lead to an abnormal number, growth, or decrease in platelet formation. In order to diagnose a patient who presents with symptoms suggestive of platelet dysfunction such as Bleeding or clotting, a physician has to take into account all these steps and examine each step for factors that may have affected the platelet count, in combination with the assessment of symptoms, diagnostic examinations and results of platelet count and morphology.

Also, it is important to note that all the blood cells originate from a single cell. In fact, all cells originate from a single cell and a defect at an early stage may present later with a disease at much later stage. Therefore, at the time of platelet formation, which continues throughout life, it is important for the bone marrow to be safe. One small change in the environment of platelet

formation or other blood cell production can result in a huge difference in the normal functioning of the body. [8]

## Platelet structure and distribution:

Platelets are irregularly shaped, have no nucleus, and typically measure only 2–3 micrometers in diameter. Platelets are not true cells, but are instead classified as cell fragments produced by megakaryocytes. Because they lack a nucleus, they do not contain nuclear DNA. However, they do contain mitochondria and mitochondrial DNA, as well as endoplasmic reticulum fragments and granules from the megakaryocyte parent cells. Platelets also contain adhesive proteins that allow them to adhere to fibrin mesh and the vascular endothelium, as well as to a microtubule and microfilament skeleton that extends into filaments during platelet activation. Less than 1% of whole blood consists of platelets. They are about $1/10^{th}$ to $1/20^{th}$ as abundant as white blood cells. [9]




**(Figure 1: Platelet structure)**

## Hemostasis

Hemostasis or haemostasis is a process which causes bleeding to stop, meaning to keep blood within a damaged blood vessel (the opposite of hemostasis is hemorrhage). It is the first stage of wound healing. This involves blood changing from a liquid to a gel. Intact blood vessels are central to moderating blood's tendency to clot. The endothelial cells of intact vessels prevent blood clotting with a heparin-like molecule and thrombomodulin and prevent platelet aggregation with nitric oxide and prostacyclin. When endothelial injury occurs, the endothelial cells stop secretion of coagulation and aggregation inhibitors and instead secrete von Willebrand factor which initiate the maintenance of hemostasis after injury.

Hemostasis has three major steps:

1) Vasoconstriction

2) Temporary blockage of a break by a platelet plug

3) Blood coagulation, or formation of a fibrin clot.

**Process:**

Hemostasis occurs when blood is present outside of the body or blood vessels. It is the instinctive response for the body to stop bleeding and loss of blood. During hemostasis three steps occur in a rapid sequence. Vascular spasm is the first response as the blood vessels constrict to allow less blood to be lost. In the second step, platelet plug formation, platelets stick together to form a temporary seal to cover the break in the vessel wall. The third and last step is called coagulation or blood clotting. Coagulation reinforces the platelet plug with fibrin threads that act as a "molecular glue". Platelets are a large factor in the hemostatic process. They allow for the creation of the "platelet plug" that forms almost directly after a blood vessel has been ruptured. Within seconds of a blood vessel's epithelial wall being disrupted platelets begin to adhere to the sub-endothelium surface. It takes approximately sixty seconds until the first fibrin strands begin to intersperse among the wound. After several minutes the platelet plug is completely formed by fibrin. Hemostasis is maintained in the body via three mechanisms:

1. **Vascular spasm**: Damaged blood vessels constrict. Vascular spasm is the blood vessels' first response to injury. The damaged vessels will constrict (vasoconstrict) which reduces the amount of blood flow through the area and limits the amount of blood loss. This response is triggered by factors such as a direct injury to vascular smooth muscle, chemicals released by endothelial cells and platelets, and reflexes initiated by local pain receptors. The spasm response becomes more effective as the amount of damage is increased. Vascular spasm is much more effective in smaller blood vessels.

2. **Platelet plug formation**: Platelets adhere to damaged endothelium to form platelet plug (primary hemostasis) and then degranulate. This process is regulated through thromboregulation. Platelets play one of the biggest factors in the hemostatic process. Being the second step in the sequence they stick together (aggregation) to form a plug that temporarily seals the break in the vessel wall. As platelets adhere to the collagen fibers of a wound they become spiked and much stickier. They then release chemical messengers such as adenosine diphosphate (ADP), serotonin and thromboxane A2. These chemicals are released to cause more platelets to stick to the area and release their contents and enhance vascular spasms. As more chemicals are released more platelets stick and release their chemicals; creating a platelet plug and continuing the process in a positive feedback loop. Platelets alone are responsible for stopping the bleeding of unnoticed wear and tear of our skin on a daily basis.

The second stage of hemostasis involves platelets that move throughout the blood. When the platelets find an exposed area or an injury, they begin to form what is called a platelet plug. The platelet plug formation is activated by a glycoprotein called the Von Willebrand factor (vWF),

which are found in the body's blood plasma. When the platelets in the blood are activated, they then become very sticky so allowing them to stick to other platelets and adhere to the injured area.

There are a dozen proteins that travel along the blood plasma in an inactive state and are known as clotting factors. Once the platelet plug has been formed by the platelets, the clotting factors begin creating the Blood Clot. When this occurs the clotting factors begin to form a collagen fiber called fibrin. Fibrin mesh is then produced all around the platelet plug, which helps hold the fibrin in place. Once this begins, red and white blood cells become caught up in the fibrin mesh which causes the clot to become even stronger.

3. **Blood coagulation** – Clots form upon the conversion of fibrinogen to fibrin, and its addition to the platelet plug (*secondary hemostasis*). Coagulation: The third and final step in this rapid response reinforces the platelet plug. Coagulation or blood clotting uses fibrin threads that act as a glue for the sticky platelets. As the fibrin mesh begins to form the blood is also transformed from a liquid to a gel like substance through involvement of clotting factors and pro-coagulants. The coagulation process is useful in closing up and maintaining the platelet plug on larger wounds. The release of Prothrombin also plays an essential part in the coagulation process because it allows for the formation of a thrombus, or clot, to form. This final step forces blood cells and platelets to stay trapped in the wounded area. Though this is often a good step for wound healing, it has the ability to cause severe health problems if the thrombus becomes detached from the vessel wall and travels through the circulatory system; if it reaches the brain, heart or lungs it could lead to stroke, heart attack, or pulmonary embolism respectively. However, without this process the healing of a wound would not be possible. [10]

## Platelets life span

Platelets are cell fragments which are mainly an essential component when it comes to blood clotting and coagulation. The platelets along with the red blood cells and white blood cells, function together for the regulation and normal functioning of blood in our body. The blood cells have each of their own different life span as well as different functions. Among these three, the platelets are the smallest but one of the most important factors in blood clotting. If the platelets don't get regulated properly, such as when they don't get renewed at normal intervals, then the blood dysfunction or disorder might occur.

The general lifespan of a platelet is about 10 days. The normal platelet count in the human blood ranges from 150,000 to 450,000 per micro liter of blood. The platelet count varies in different

locations and organs. But in cases of medical conditions, the platelets count may either increase or decrease in the blood. One of the most common condition of platelet count changes is the popularly known thrombocytopenia where the levels drop below normal. There are actually several reasons that may have resulted to the drop in platelets. In such condition, there will be a necessity for immediate medical help due to the risk for bleeding. Moreover, thrombocytopenia can also act as a catalyst to trigger other idle diseases in the body. So it is of utmost importance to maintaining and watching proper balanced diet to deal with a low platelet count. On the other hand, an abnormal increase in platelets which is also due to specific causes is referred to as thrombocytosis.

**Factors affecting platelets life span:**

1**-** Genetics:

One of the most important factors that determine a platelet life span is genetics. It has been found out through many researches that the normal platelet count in human blood is deeply associated with the genes. The life span of these platelets are also advanced and rooted in the way how a person lives and carries his lifestyle. Studies have shown that the lifestyle influences heredity or genes. The normal life span as we have read earlier is just about 10 days. But with genetic influence, this can either increase or decrease, accordingly.

2-Age:

Age is one of the prime factors that affects the life span of a person's platelet in the blood. It does not only serve as one of the factors that determine platelet life span, but also affects the count of platelets. With the progressions of age, the capacity of body system and regulation gets reduced affecting the growth and formation of platelets in human blood. As age increases, the body's ability to hold a 10 day platelet life span decreases.

3- Sialic acid:

Sialic acid plays a very crucial role in regulating the life span of platelets in the human blood. Among the rated 7 to 10 days, which is the regular time for platelet cycle, the sialic acid, helps to regular it to a bigger extent. Galatactose, which helps to determine the sialic acid presence, can rapidly change or alter the life spans of platelets. The functionalities of the sialic acid is not fully recognized, but have been found to have a very crucial role in the life span of platelets.

4- Prevalent diseases:

If a human body carries any medical condition that may be affecting platelets, then the life cycle of platelets will certainly get affected. If the platelets are not produced enough to keep a balance with the death of platelets, the body suffer will from thrombocytopenia. In thrombocytopenia, the platelet count becomes visibly low, and the resultant medical disorder can lead to serious medical conditions. Pregnancy is also another common factor that can lead to low platelet count, but normal platelet life span remains intact.

5- Food habits:

A person's food habits and diet regime is also one of the most important factor that determines the platelet count as well as the life span of platelets. There are certain foods that can help increase platelet count as well as alter its life span. Foods such as green leafy vegetables, foods with high zinc and whole grain, keep platelets healthy and increase count.

6- Prolonged Medicine intake:

It is very much known to us that those popularly known pain killers, helps ease our pain for the time being, but in the long run, there are certain factors in our blood that are acutely affected by these medicines. The medicines, can have the capacity to directly create a negative impact on the blood and various other organs, especially if not monitored carefully. The composition of the blood can possibly get to an imbalanced state due to the effects of these medicines. With prolonged intake of pain relievers, it doesn't just affect the platelets but can even lead to organ failure.

7- Bone Marrow:

The platelets are developed or produced inside the bone marrow. So if there comes a disorder associated with the bone marrow, the platelet life spans get affected and probably decreases. In case of acute medical disorders like leukemia or other forms of cancer, the bone marrow is involved and so does the platelet count and life span.

8- Blood Transfusion:

Medical conditions that could have resulted from improper blood transfusion is one of the common factors that can influence the regulation and life span of platelets.

Also, blood transfusion may be given in cases of acute injury or for the purpose of any other blood related disorder in the body, but since it will be an injection of a foreign blood, there may be body reaction resulting to tendencies on platelet life span changes.

9- Congenital thrombocytopenia:

In cases of this platelet related medical disorder of *congenital thrombocytopenia*, the platelet count becomes lower than the normal range. It even drops down to a range of about 100,000 per

micro liters of blood. This make the body fail to maintain a proper life circulation rate of platelet from 7 to 10 days, and instead decreased to 5 days or less.

10- Abnormal accumulation of cells:

If in any part of the body where cells gets accumulated abnormally, the platelet count and its life cycle can potentially be impaired. The accumulation is mostly common in and around the bone marrow which makes the life span of platelet lower and ineffective. [11]

## Platelets count test

A platelet count is used to detect the number of platelets in the blood. The test is included in a complete blood count (CBC), a panel of tests often performed as part of a general health examination.

Platelets are tiny fragments of cells that are essential for normal blood clotting. A platelet count may be used to screen for or diagnose various diseases and conditions that can cause problems with clot formation. It may be used as part of the workup of a bleeding disorder, bone marrow disease, or excessive clotting disorder, to name just a few.

The test may be used as a monitoring tool for people with underlying conditions or undergoing treatment with drugs known to affect platelets. It may also be used to monitor those being treated for a platelet disorder to determine if therapy is effective.

A platelet count may be performed in conjunction with one or more platelet function tests, which assess the function of platelets, and other tests that evaluate coagulation such as PT and PTT. If results are not within the normal interval, a number of other tests may be performed to help give clues as to the cause. Sometimes a blood smear may be done in follow up to examine the platelets under a microscope. This would help to determine, for example, whether platelets might truly be low in number or have clumped together during testing.

**When is it ordered?**

A platelet count is often ordered as a part of a complete blood count (CBC), which may be done at the time of a routine health examination.

It may be ordered when a person has signs and symptoms associated with low platelets or a bleeding disorder, such as:

- Unexplained or easy bruising
- Prolonged bleeding from a small cut or wound
- Numerous nosebleeds
- Gastrointestinal bleeding (which can be detected in stool samples)
- Heavy menstrual bleeding
- Small red spots on the skin called petechiae—may sometimes look like a rash
- Small purplish spots on the skin called purpura, caused by bleeding under the skin

Testing may also be done when it is suspected that an individual has too many platelets. An excess of platelets can cause excessive clotting or sometimes bleeding if the platelets are not functioning properly. However, people with too many platelets often have no signs or symptoms, so the condition may be found only when a platelet count is done as part of a health check or for other reasons.

**What does the test result mean?**

A low platelet count, also called thrombocytopenia, and accompanying signs and symptoms may be caused by a number of conditions and factors. The causes typically fall into one of two general categories:

- Disorders in which the bone marrow cannot produce enough platelets
- Conditions in which platelets are used up (consumed) or destroyed faster than normal

Examples of conditions causing a low platelet count include:

- Idiopathic thrombocytopenia (ITP), also known as immune thrombocytopenic purpura, is the result of antibody production against platelets.
- Viral infections such as mononucleosis, hepatitis, HIV or measles

- Certain drugs, such as aspirin and ibuprofen, some antibiotics (including those containing sulfa), colchicine and indomethacin, H2-blocking agents, hydralazine, isoniazid, quinidine, thiazide diuretics, and tolbutamide, are just a few that have been associated with drug-induced decreased platelet counts.
- Heparin-induced thrombocytopenia (HIT) results in low platelets when a person who is on or received heparin therapy develops an antibody. (For more on this, see the article on HIT Antibody)
- Leukemia, lymphoma, or another cancer that has spread (metastasized) to the bone marrow—people with cancers often experience excessive bleeding due to a significantly decreased number of platelets. As the number of cancer cells increases in the bone marrow, normal bone marrow cells are crowded out, resulting in fewer platelet-producing cells.
- Aplastic anemia—a condition in which the production of all blood cells is significantly reduced
- Long-term bleeding problems (e.g., chronic bleeding from stomach ulcers)
- Sepsis, especially that caused by a serious bacterial infection with Gram-negative bacteria
- Cirrhosis
- Autoimmune disorders, such as lupus, where the body's immune system produces antibodies that attack its own organs or tissues, causing increased destruction of platelets
- Chemotherapy or radiation therapy, which may affect the bone marrow's ability to produce platelets

- Platelet consumption may be observed in various diseases and conditions. For example, disseminated intravascular coagulation (DIC), thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) can result in fewer circulating platelets in the blood.
- Exposure to toxic chemicals, such as pesticides, arsenic, or benzene

If the platelet count falls below 20,000 per microliter, spontaneous bleeding may occur and is considered a life-threatening risk. A person with a very low count may be given platelets through a transfusion. See Blood and Blood Components in the Blood Banking article for more details.

**A high platelet count** may be referred to as thrombocytosis. This is usually the result of an existing condition (also called secondary or reactive thrombocytosis) such as:

- Cancer, most commonly lung, gastrointestinal, ovarian, breast or lymphoma
- Anemia, in particular iron-deficiency anemia and hemolytic anemia
- Inflammatory conditions such as inflammatory bowel disease (IBD) or rheumatoid arthritis
- Infectious diseases such as tuberculosis
- If an individual has had their spleen removed surgically
- Use of birth control pills (oral contraceptives)

Some conditions may cause a temporary (transitory) increased platelet count. These may include:

- Recovery from significant blood loss such as from trauma or major surgery
- After physical activity or exertion
- Recovery from excess alcohol consumption and vitamin B12 and folate deficiency

Rarely, thrombocytosis is caused by a bone marrow disorder. An example is thrombocythemia, also called primary or essential thrombocythemia, a rare myeloproliferative disorder in which the bone marrow produces an extremely high number of platelets. Often there are no signs and symptoms and the condition is discovered when testing is done for a health check or for other reasons.

Individuals who have this condition may be at risk of excessive clotting (thrombosis) due to the excess platelets, but they may have bleeding problems, as the platelets may not function normally. This disorder is often associated with a mutation in the gene called JAK2. A test for this mutation should be performed if a health practitioner suspects that an individual has the disorder. More than half of the people with essential thrombocythemia have the *JAK2* mutation. People with other myeloproliferative or myelodysplastic disorder, such as chronic myeloid leukemia, polycythemia vera or certain subtypes of myelodysplastic syndrome, may also have markedly higher platelet counts.

Some people have platelets that tend to "pool" or collect (sequester) in their spleen, resulting in a low platelet count. However, these individuals typically do not experience any signs or symptoms related to this condition.

Living in high altitudes, strenuous exercise, and having recently delivered a baby (post-partum) may cause increased platelet numbers. Drugs that may cause increased platelet counts include estrogen and birth control pills (oral contraceptives).

Mildly decreased platelet counts may be seen in women before menstruation. Up to 5% of pregnant women may have a lower platelet count at term.

Inherited disorders caused by genetic defects in platelets include Glanzmann's Thrombasthenia, Bernard-Soulier disease, Chediak-Higashi syndrome, Wiskott-Aldrich syndrome, May-Hegglin

syndrome, and Down syndrome. The occurrence of these genetic abnormalities, however, is relatively rare.

Bruising for no apparent reason, bleeding from the nose, mouth, or rectum without obvious injury, excessive or prolonged menstrual periods, or the inability to stop a small wound from bleeding within a reasonable period of time may indicate a platelet deficiency.

Generally, there are no lifestyle changes that you can make that would increase your platelet count. Treatment for a low platelet count usually involves addressing the underlying condition that is causing it. If your condition is mild and your platelet count is only slightly low, you may not require any treatment. If it is caused by a drug, your healthcare provider may switch you to a different one. If it is due to an autoimmune disorder, your practitioner may prescribe a drug that helps to suppress the immune system. People with serious conditions and/or platelet counts that are significantly decreased may be at risk of excessive bleeding, so they may be transfused with platelets.

Mean platelet volume (MPV) and platelet distribution width (PDW) are calculations performed by automated blood analyzers. MPV reflects the average size of platelets present in a person's sample of blood while PDW reflects how uniform the platelets are in size. These calculations can give the doctor additional information about platelets and/or about the cause of a high or low platelet count. Larger platelets are usually relatively young and more recently released from the bone marrow, while smaller platelets may be older and have been in circulation for a few days.

A high number of large platelets (high MPV) in a person with a low platelet count suggests the bone marrow is producing platelets and releasing them into circulation rapidly. Conversely, the MPV may be low in people with low platelet counts due to a disorder affecting production by the bone marrow. A normal PDW indicates platelets that are mostly the same size, while a high PDW means that platelet size varies greatly, a clue that there may be a disorder affecting platelets.

Often, abnormal results will prompt additional testing. Under certain conditions, platelets may clump together and falsely appear to be low in number and/or large in size so a blood smear may be performed to examine platelets directly using a microscope.

Giant platelet" is a term used to describe platelets that are abnormally large, i.e., as large as a normal red blood cell. These may be seen in certain disorders such as immune thrombocytopenic purpura (ITP) or in rare inherited disorders such as Bernard-Soulier disease. However, as mentioned in the previous question, a direct examination with a blood smear may be necessary to determine whether the platelets are truly giant or platelets have clumped together during testing. If platelets are clumping, repeat testing may be performed using a different collection tube containing a different anticoagulant that prevents or minimizes platelet clumping.

Immature platelet fraction (IPF) is the relative number of immature platelets (also called reticulated platelets) in the blood. Platelets are produced in the bone marrow and are normally not released into the bloodstream until they have matured. When platelet numbers in the blood are low (thrombocytopenia), it stimulates the bone marrow to produce platelets faster. When the need is great and when production cannot keep up with "demand," then an increased number of immature platelets will be released into the bloodstream.

This IPF test result would be one of the values reported when blood is evaluated using an automated hematology analyzer. The IPF may be used to help a healthcare provider determine the likely cause of a person's thrombocytopenia, that is, decrease in production by the marrow (IPF is low) versus increased loss of platelets in the blood (IPF is higher). Lab test results including platelet count and IPF can also help determine if a person needs a platelet transfusion and help monitor bone marrow recovery, such as after a bone marrow transplant. Other uses are being studied and the test's ultimate clinical utility has not yet been well determined.

If the cause of the abnormal result is not apparent and cannot be determined from your medical history and physical examination, your healthcare provider may choose to order additional tests. Depending on the suspected cause and results from a CBC and blood smear, various follow-up tests may be performed. A few examples include:

• Tests for inflammatory conditions such as CRP, ESR or tests for autoantibodies that target platelets

• Tests for infectious diseases including bacteria and viruses

• Tests for bleeding disorders such as PT, PTT, fibrinogen

• Tests for kidney failure

• Iron studies or vitamin B12 and folate levels

• Tests for liver disease

• In unexplained, serious cases, a bone marrow biopsy. [12]

The reference range of platelets is 150-450 billion/L of blood. [13]

## Thrombocytopenia

Thrombocytopenia means you don't have enough platelets, cells in your blood that stick together to help it clot. It might not cause you any health problems at all. But if you do have symptoms like bleeding too much, treatments can help.

**Causes**

Platelets are made in your bone marrow, the spongy tissue inside your bones. You can get thrombocytopenia if your body doesn't make enough of them, or if they're destroyed faster than they can be made.

Your body might not make enough platelets if you have a:

- Blood disorder that affects bone marrow, called aplastic anemia
- Cancer such as leukemia or lymphoma, which damages your bone marrow
- Platelet-lowering disease that runs in your family, like Wiskott-Aldrich or May-Hegglin syndrome
- Virus such as chickenpox, mumps, rubella, HIV, or Epstein-Barr

Chemotherapy or radiation treatment for cancer destroys stem cells that form platelets. If you've been in contact with chemicals like pesticides and arsenic, your body might slow down the process of making platelets.

Your platelets can be damaged by:

- Autoimmune diseases such as lupus or idiopathic thrombocytopenic purpura (ITP), where your own body attacks healthy cells
- Medicines, such as antibiotics that contain sulfa, heparin used to prevent blood clots, and antiseizure drugs such as phenytoin (Dilantin) and vancomycin.
- Rare diseases that make blood clots form in the body, such as thrombotic thrombocytopenic purpura (TTP) and disseminated intravascular coagulation (DIC)
- Viruses like mononucleosis or cytomegalovirus

Sometimes, you don't have enough platelets because they get trapped in your spleen, an organ that fights infection. And women may get thrombocytopenia during pregnancy, because their bodies get rid of platelets more quickly than usual.

**Symptoms**

Sometimes you don't have any symptoms from thrombocytopenia. When you do, the main one is bleeding.

You can bleed outside or inside your body. Sometimes it can be heavy or hard to stop. Some people get nosebleeds or bleeding gums.

You might also have:

- Blood in your urine or bowel movement
- Headaches
- Heavy menstrual periods
- Purple or red bruises, called purpura
- Tiny red or purple spots on your skin, called petechiae. [14]

## Congenital thrombocytopenia:

Congenital thrombocytopenias represent a very small percentage of the thrombocytopenias that are seen by hematologists and oncologists. Even when chemotherapy-induced thrombocytopenia and overt infections are excluded and only isolated thrombocytopenia is considered, at least 95% of these cases in both children and adults will be primarily autoimmune thrombocytopenia (ITP) or drug-induced thrombocytopenia. However, more and more routine platelet counts are obtained allowing the identification of asymptomatic or mildly symptomatic children and adults,

which increases the number of isolated thrombocytopenias referred to specialists. Even in adults, a small percentage of cases represent a type of congenital thrombocytopenia (CTP), and a number of cases of CTP have been misdiagnosed as ITP and the patients subjected to splenectomy and/or cyclophosphamide, among other inappropriate therapies. Recent developments, especially in identification of molecular defects, have highlighted the manifestations of the congenital cases of nonimmune thrombocytopenia and improved the ability to identify and distinguish among them.

## Family History

The most obvious feature suggesting CTP, while nonspecific, is the presence of a family history of thrombocytopenia. This should immediately raise suspicion of CTP, rather than ITP, especially if more than two family members are involved and/or the family members are closely related, especially parent and child or maternal uncle and nephew. Many types of CTP have an autosomal dominant inheritance, but several are X-linked or autosomal recessive, which means that the affected child or adult may be the propositus/index case. A family history of "ITP" has been reported, for example, in familial autoimmune disease in which the family history may be more consistent with systemic lupus (SLE). Based on anecdotal experience, the infrequent cases of familial ITP often appear coincidental, e.g., two cousins. In the past, cases of familial CTP have been considered (and reported) to be ITP because of the presence of platelet-associated antibodies using tests now known to have low specificity. While current testing that is antigen-specific (involves a specific platelet glycoprotein such as GPIIb/IIIa) has greater predictive value than tests in which the whole platelet is the target, it remains to be demonstrated that this testing will distinguish ITP from CTP, especially in those subsets in which there may be an autoimmune component.

## Nonresponse to ITP Treatment:

In cases where it is necessary to distinguish CTP from ITP, the most definitive finding available by history or clinically, prior to specific laboratory investigation for CTP including review of the smear where diagnostic, is the "failure" to respond to ITP-specific therapy. This includes not only IVIG and IV anti-D, but also splenectomy and steroids. It also potentially includes other immune-modulating therapies such as azathioprine, cyclophosphamide, and anti-CD20. While the lack of response in patients with CTP to these treatments is a universally accepted criterion based on anecdotal experience, an exact definition of lack of response has not been established or verified. For example, there are no well-defined response thresholds, i.e., how high does the platelet count have to go after treatment with IVIG to diagnose ITP and exclude CTP? Arbitrarily, a peak platelet response to treatment > 30,000/μl increase from baseline would suggest that the case in question is not CTP. Conversely, a < 10,000/μl peak increase is compatible with CTP, although it just as compatible with a diagnosis of "refractory" ITP. Numbers in between might favor ITP but are even more ambiguous. A confusing feature is that some children with Wiskott-Aldrich syndrome and velocardiofacial syndrome (also known as

DiGeorge syndrome) respond to corticosteroids, IVIG, and/or splenectomy either because there is an immunological component to the thrombocytopenia or because impeding the clearance mechanism for aberrant platelets helps to offset impaired platelet production. Since "spontaneous" fluctuation in the platelet count may occur (for example as a result of a viral infection), the assessment of two treatment responses is probably more helpful as a diagnostic criterion.

Newer automatic blood cell analyzers are superior to the previous generation in their recognition of platelets, especially large platelets, so that size measurements appear to be more reliable than they had been in the past. However, particularly for very small or very large platelets, and for very low platelet counts, the accuracy of the MPV obtained in standard laboratories remains to be determined and may vary from case to case, so that visual inspection of the smear remains the "gold standard" for platelet size in clinical practice. If platelets appear very large (the size of red cells or even larger), this would be compatible with Bernard-Soulier syndrome or the MYH9 defects, e.g., May-Hegglin syndrome. Döhle-like bodies in neutrophils also suggest May-Hegglin syndrome. The presence of very small platelets is most consistent with Wiskott-Aldrich, whether the complete syndrome or the XLT form. Platelet clumping may suggest von Willebrand type IIb, although pseudothrombocytopenia would need to be excluded either by using citrate as the anticoagulant or by making smears directly from a drop of blood. Microcytosis suggests the XLT-T form involving a mutation in the DNA face of GATA-1.

Specific Inherited Thrombocytopenias:

Amegakaryocytic thrombocytopenias

Congenital amegakaryocytic thrombocytopenia (CAMT) typically presents as severe thrombocytopenia that is often recognized on day 1 of life or at least within the first month. CAMT is often initially confused with fetal and neonatal alloimmune thrombocytopenia, but the neonate fails to improve and responds only to platelet transfusion. Eventually a "diagnostic" bone marrow is performed; a marrow biopsy may be required which can be technically difficult in a neonate. Ten percent to 30% of cases have orthopedic or neurologic abnormalities. Intracranial hemorrhage is not rare (5 of 24 cases in one survey [PR Merola et al, manuscript in preparation]), and treatment other than platelet transfusions is largely ineffective.

Fifty percent of the 24 cases in the same survey progressed to aplastic pancytopenia within the first 5 years of life; 1 case of leukemia was also seen (PR Merola et al, manuscript in preparation). The underlying defect in the majority of cases is a mutation in the TPO-receptor, c-mpl (PR Merolta et al, manuscript in preparation). In the absence of a signal from thrombopoietin (TPO), megakaryocytes do not proliferate. The prevailing hypothesis to explain the development of aplastic pancytopenia is that c-mpl is also required for stem cell maturation. Therefore, in the absence of its anti-apoptotic effects of TPO, stem cell depletion may lead to aplasia.

While certain cytokines (interleukin [IL]-3, granulocyte-macrophage colony-stimulating factor [GM-CSF], IL-11) may have limited efficacy in individual patients, none are consistently effective and their use may result in substantial toxicity. TPO, or a thrombopoietic agent, seems

unlikely to be of use because the underlying defect is a mutation in c-mpl. Platelet transfusions are administered for very low counts and as prophylaxis in patients who have had major bleeds. Matching strategies are generally pursued only in the context of developing refractoriness to leukocyte -reduced random donor units. The only effective treatment thus far has been allogeneic stem cell transplant (HSCT). An approach to gene therapy is being pursued in which insertion of a dimerized artificial TPO receptor is intended to convey a growth advantage to stem cells that take up and express the vector, allowing them to eventually replace the marrow. [15]

## Drug induced thrombocytopenia

Although drugs are a common cause of acute immune-mediated thrombocytopenia in adults, the drug etiology is often initially unrecognized. Most cases of drug-induced thrombocytopenia (DITP) are caused by drug-dependent antibodies that are specific for the drug structure and bind tightly to platelets by their Fab regions but only in the presence of the drug.

Typically, DITP occurs 1 to 2 weeks after beginning a new drug or suddenly after a single dose when a drug has previously been taken intermittently. However, severe thrombocytopenia can

occur immediately after the first administration of antithrombotic agents that block fibrinogen binding to platelet GP IIb-IIIa, such as abciximab, tirofiban, and eptifibatide. Recovery from DITP usually begins within 1 to 2 days of stopping the drug and is typically complete within a week. Drug-dependent antibodies can persist for many years; therefore, it is important that the drug etiology be confirmed and the drug be avoided thereafter.

Drug-induced thrombocytopenia (DITP), which also includes thrombocytopenia induced by beverages, foods, and herbal remedies, is an important clinical problem for hematologists. DITP typically appears suddenly, is often severe, and can cause major bleeding and death.

In many patients, the drug etiology is not initially recognized. In hospitalized patients, unexpected thrombocytopenia may be attributed to complications such as sepsis. In previously asymptomatic patients, DITP is often misdiagnosed as immune thrombocytopenic purpura (ITP) with resulting inappropriate treatment. Even when the diagnosis of DITP is considered, a drug etiology may not be apparent because patients may not think that self-regulated medications, beverages, foods, or herbal remedies are relevant to their bleeding symptoms and therefore they may not report them to their physician. [16]

Thrombocytopenia is any disorder in which there are not enough platelets. Platelets are cells in the blood that help the blood clot. A low platelet count makes bleeding more likely.

When medicines or drugs are the causes of a low platelet count, it is called drug-induced thrombocytopenia.

Drug-induced thrombocytopenia occurs when certain medicines destroy platelets or interfere with the body's ability to make enough of them.

There are two types of drug-induced thrombocytopenia: immune and nonimmune.

If a medicine causes your body to produce antibodies, which seek and destroy your platelets, the condition is called drug-induced immune thrombocytopenia. Heparin, a blood thinner, is the most common cause of drug-induced immune thrombocytopenia.

If a medicine prevents your bone marrow from making enough platelets, the condition is called drug-induced nonimmune thrombocytopenia. Chemotherapy drugs and a seizure medicine called valproic acid may lead to this problem.

- Furosemide
- Gold, used to treat arthritis
- Nonsteroidal anti-inflammatory drugs (NSAIDs)

- Penicillin
- Quinidine
- Quinine
- Ranitidine
- Sulfonamides
- Linezolid and other antibiotics

Decreased platelets may cause:

- Abnormal bleeding
- Bleeding when you brush your teeth
- Easy bruising
- Pinpoint red spots on the skin

Treatment
The first step is to stop using the medicine that is causing the problem.

For people who have life-threatening bleeding, treatments may include:

- Immunoglobulin therapy (IVIG) given through a vein
- Plasma exchange (plasmapheresis)
- Platelet transfusions
- Corticosteroid medicine. [17]

**Heparin-Induced Thrombocytopenia:**

Heparin-induced thrombocytopenia (HIT) is a complication of heparin therapy. There are two types of HIT. Type 1 HIT presents within the first 2 days after exposure to heparin, and the platelet count normalizes with continued heparin therapy. Type 1 HIT is a nonimmune disorder that results from the direct effect of heparin on platelet activation.

Type 2 HIT is an immune-mediated disorder that typically occurs 4-10 days after exposure to heparin and has life- and limb-threatening thrombotic complications. In general medical practice, the term HIT refers to type 2 HIT.

HIT must be suspected when a patient who is receiving heparin has a decrease in the platelet count, particularly if the fall is over 50% of the baseline count, even if the platelet count nadir remains above 150 x $10^9$/L. Clinically, HIT may manifest as skin lesions at heparin injection sites or by acute systemic reactions (e.g., chills, fever, dyspnea, chest pain) after administration of an intravenous bolus of heparin.

Unlike other forms of thrombocytopenia, HIT is generally not marked by bleeding; instead, venous thromboembolism (e.g., deep venous thrombosis, pulmonary embolism) is the most common complication. Less often, arterial thrombosis (e.g., myocardial infarction) may occur. For that reason, the disorder is sometimes termed heparin-induced thrombocytopenia and thrombosis (HITT).

Heparin-induced thrombocytopenia (HIT) is caused by antibodies that bind to complexes of heparin and platelet factor 4 (PF4), activating the platelets and promoting a prothrombotic state. HIT is more frequently encountered with unfractionated heparin (UFH) than with low molecular weight heparin (LMWH).

The risk of HIT is highest with prolonged use of heparin for postoperative thrombophylaxis. However, case studies have also demonstrated the possibility of developing HIT with minimal heparin exposure via intravascular flushes to maintain the patency of indwelling arterial or venous catheters.

Fondaparinux is a synthetic pentasaccharide that catalyzes the inhibition of factor Xa (but not thrombin) by antithrombin, and thus inhibits thrombin generation. A study suggested that fondaparinux may be associated with formation of anti–PF4/heparin antibodies but, in contrast to LMWH, is unlikely to cause HIT because of the poor reactivity of antibodies against PF4/fondaparinux.

Men have significantly less risk than women for thrombotic manifestations in HIT. Women diagnosed with HIT and thrombosis are 1.7 times more likely than men to have a new HIT-associated thrombotic event.

The higher frequency of HIT in females was found most strikingly in patients treated with UHF. There was no relationship between sex and the risk for HIT in patients treated with low molecular weight heparin (LMWH). LMWH in prevention of HIT may have the greatest absolute benefit in females undergoing surgical thromboprophylaxis. [18]

**Rifampicin-induced thrombocytopenia:**

In the treatment of tuberculosis there are special therapeutic problems related to adverse effects of drugs, compliance to treatment, and microbial resistance. Thrombocytopenia is an uncommon but potentially fatal adverse effect of certain anti-tubercular drugs when the incriminating drug is taken by a susceptible individual. We report a case of rifampicin-induced thrombocytopenia, which although rare, needs attention.

Treatment of tuberculosis has been a therapeutic challenge since long. Most anti-tubercular drugs are relatively safe but serious reactions are not uncommon. Adverse reactions due to rifampicin are either dose related or allergic. Thrombocytopenia is an uncommon but potentially fatal

adverse effect seen with certain anti-tubercular drugs, including rifampicin. To identify the offending agent in a patient taking several medications, it poses a challenging clinical problem.

Confirmation of drug-induced thrombocytopenia at the time of initial presentation is not often possible as tests for drug-dependent anti-platelet antibodies are not available in most laboratories. Discontinuation of suspected drug leading to resolution of thrombocytopenia provides a strong evidence of drug-induced thrombocytopenia. Rifampicin-induced thrombocytopenia was first reported in 1970. It is usually reversible if detected early and treated appropriately. Other drugs known to cause thrombocytopenia are quinine, quinidine, chloroquine, sulfonamides, tolbutamide, chlorothiazide, digoxin, penicillamine, amphotericin B, sedatives, anticonvulsants, methyldopa, and aspirin. [19]

**Vancomycin induced thrombocytopenia:**

Vancomycin-induced thrombocytopenia is a rare adverse reaction that may be overlooked because no specific diagnostic test is currently available. We herein report a patient with vancomycin-induced immune thrombocytopenia who was diagnosed by the detection of vancomycin-dependent anti-platelet antibody with flow cytometry. An IgG antibody in the patient's serum reacted with platelets only in the presence of vancomycin. Severe thrombocytopenia gave rise to life-threatening gastrointestinal bleeding, which was quickly resolved after effective platelet transfusion following the cessation of vancomycin administration.

The flow cytometric test is useful for the differential diagnosis of thrombocytopenia and platelet transfusion should be performed after the cessation of vancomycin administration. Platelet transfusion in patients with vancomycin-induced thrombocytopenia is likely to be ineffective because of immune destruction of platelets. The failure of platelet transfusion during vancomycin administration has been reported.

A recent study reported that platelet transfusion failed to elevate the platelet counts in 11 of 14 patients However, platelet transfusion was effective in our case. This may be explained by the biological feature of the anti-platelet antibody to react with platelets only in the presence of vancomycin. In our case, platelet transfusion was performed after discontinuation of vancomycin. Similar to our case, successful platelet transfusion was reported in a patient after discontinuation of vancomycin .It should be noted that platelet transfusion must be performed after discontinuation of vancomycin.

Vancomycin is a mainstay in the treatment of MRSA infection in hospitalized patients. Such patients may have many comorbidities and take many drugs, which precipitate thrombocytopenia. The flow cytometric test for vancomycin-dependent antibody may be useful in the differential diagnosis of thrombocytopenia in these patients and lead to successful treatment of patients with potentially life-threatening bleeding. [20]

## Interaction of Platelets with Bacterial Pathogens

Bacteria enter the bloodstream in response to infectious insults, via surgical procedures or indwelling catheters, and sepsis occurs in up to 6–30% of all intensive care unit patients.

The balance of pro- and anti-inflammatory reactions critically determines the severity and lethality of sepsis, a fact that turns the spotlight onto understanding the immune reaction in order to develop appropriate therapies.

Bacterial contact with the platelets is a key event for the pathogenesis of sepsis, as deduced from the correlation between sepsis outcome and decreased platelet numbers: the more profound the thrombocytopenia the more severe the sepsis and the greater the mortality of affected patients.

There are two main causes for the bacteria-induced thrombocytopenia:

- Bacteria induce platelet activation. Activated platelets show shortened survival and are targets of phagocytic clearance.
- Bacterial compounds induce apoptosis and cytotoxic effects in platelets.

The mechanisms that finally lead to the loss of platelets and their attributed immune functions can decisively compromise the antibacterial immune defense. The subsequent thrombocytopenia might be regarded as a normal consequence of immune exhaustion. However, it might also be regarded as targeted bacterial evasion strategies to eliminate a central innate immune cell from circulation with a kinetic that exceeds *de novo* generation in the bone marrow ; thus, thrombocytopenia represents a status that helps the bacteria to survive in the bloodstream. There is yet a third aspect: those mechanisms of platelet activation or apoptosis that finally result in thrombocytopenia can also lead to thrombosis, thus contributing to tissue damage in the pathogenesis of bacterial infections.

Mechanisms for pathogen-induced thrombocytopenia.
Pathogens can interfere with platelet production in the bone marrow by either infecting the precursor megakaryocytes, by induction of autoimmune antibodies that trigger elimination of the megakaryocytes or by disturbance of thromopoiesis via dysregulated cytokines or thrombopoietin. Pathogens can also target circulating platelets and induce apoptosis or cell lysis. In addition, platelet activation after contact with the microorganisms shortens their lifespan. Furthermore, pathogens can induce removal of platelets from the circulation by stimulating their sequestration in organs or by triggering their clearance by phagocytes.

**Platelet Activation as a Putative Reason for Thrombocytopenia:**

Platelets have a broad spectrum of tools to sense the presence of bacteria and/or their secreted products and react on these signals with a multistep activation process. Consequences of this platelet activation might be their deposition in microvascular thrombi or their clearance from the circulation by phagocytes. Both processes give rise to reduced platelet numbers in the circulation and can explain sepsis-induced thrombocytopenia.

Bacteria-induced platelet activation can be triggered by several mechanisms. One possibility is the adhesion of bacteria to platelet membrane receptors as described above, such as GPIIb-IIIa, GPIb, complement receptors, FcÛRIIa or TLRs .This adhesion can include a direct interaction between the bacterial surface structures and a platelet receptor, but also an indirect mechanism when bacteria are covered by plasma proteins (fibrinogen, fibronectin, vWF, complement factors

and IgG) and attach to platelets via the corresponding receptors. A bacterial species can also use both pathways to get in contact with the platelets, demonstrated, for example, by S. aureus and Streptococcus sanguinis.

The platelet TLR4 is one important pattern recognition receptor and binds to lipopolysaccharides from Gram-negative bacteria. Studies using an animal model for bacterial sepsis revealed that TLR4 is particularly relevant for bacteria-induced platelet activation with subsequent thrombocytopenia.

Bacteria can stimulate platelets not only as a consequence of adhesion, but also via secretion of soluble compounds that bind to platelet surface structures and trigger activation. This mechanism is described for S. aureus, Streptococcus pneumoniae, Streptococcus pyogenes and Porphyromonas gingivalis. The latter, a Gram-negative oral pathogen that is involved in the pathogenesis of periodontitis, secretes a family of cysteine proteases that stimulate the protease-activated receptors 1 and 4 on the platelet surface with subsequent increase in intracellular calcium and platelet aggregation.

Another example is Shiga toxin-producing *Escherichia coli*. Infection by this pathogen is associated with hemolytic uremic syndrome and a key feature of this disease is thrombocytopenia. Culture filtrates of Shiga toxin-producing *E. coli* that contained all released bacterial compounds specifically induced downregulation of CD47, the receptor for thrombospondin-1, and reduced surface CD47 correlated with platelet activation and phagocytosis by macrophages.

Activated platelets, as they occur in bacterial infection and infection-induced inflammation, represent a threat to homeostasis, since exposition of phosphatidylserine and release of granule contents might exaggeratedly trigger the coagulation. Therefore neutrophils attach to activated platelets by several surface receptors and clear them from circulation. The initial binding event involves P-selectin exposed on stimulated platelets and the corresponding counter-receptor PSGL-1 on resting neutrophils. Subsequently, neutrophils upregulate the active form of $\alpha_M$ù$_2$, which binds to fibrinogen on the surface of activated platelets. The final engulfment of the platelets by neutrophils is dependent on the recognition of platelet phosphatidylserine.

**Bacteria-induced Apoptosis & Disintegration of Platelets as a Putative Reason for Thrombocytopenia:**

The second putative reason for thrombocytopenia in sepsis is the damage of platelets, when bacteria either initiate the apoptotic program in platelets or disturb platelet integrity.

The common sepsis inducers *E. coli* and *S. aureus* as well as their secretion products α-toxin and α-hemolysin, respectively, are capable of inducing apoptosis in platelets. Both bacteria and their secreted toxins can trigger the calpain-mediated degradation of the platelet protein Bcl-$x_L$.

Since Bcl-$x_L$ represents a crucial factor for platelet survival, its proteolytic elimination is a key step for initiating the apoptotic program. Furthermore, the bacterial cell wall component

peptidoglycan, purified from *S.* aureus, is also able to trigger apoptotic processes like mitochondrial depolarization, caspase-3 activation and membrane scrambling.

Interestingly, E. coli and S. aureus can affect platelet integrity by another mechanism and thus enhance the level of thrombocytopenia. Their bacterial toxins α-toxin and α-hemolysin stimulate disturbances in the platelet membrane and thus act directly in a cytotoxic manner. α-toxin firmly binds to target membranes and forms ring-structured toxin oligomers, thus causing membrane damage and calcium influx and mimicking the effect of an ionophore. Platelets might be lysed directly, or may be affected by calcium-driven stimulation with subsequent clearance by neutrophils. A similar pore-forming mechanism was detected for the bacterial toxins streptolysin O from *S.* pyogenes*,* where resulting complexes between platelets and neutrophils impeded blood flow and lead to ischemia and tissue necrosis, and for pneumolysin from *S.* pneumonia. [21]

**Brucellosis-induced immune thrombocytopenia mimicking ITP:**

Brucellosis continues to be an important cause of fever in underdeveloped countries and in rural areas of developed world. It is a multisystemic disease, associated with wide variety of symptoms. A wide variety of symptoms, including haematological abnormalities, such as anemia, thrombocytopenia, pancytopenia, disseminate intravascular coagulation and leucopoenia could be seen, all of which are more common than usually thought. In this short study, we present a relatively uncommon haematological manifestation that of isolated thrombocytopenia mimicking idiopathic thrombocytopenic purpura, which we observed in seven of 114 patients who were diagnosed with brucellosis in our hospital over a 2-year period. Having given brucellosis treatment with rifampicin and doxycycline, complete remission was achieved and thrombocyte count returned to normal in all cases. [22]

**Helicobacter pylori-associated immune thrombocytopenia:**

Idiopathic thrombocytopenic purpura (ITP), a disorder characterized by autoantibody-mediated platelet destruction, may be primary or secondary to various illnesses including lymphoproliferative, autoimmune, or infectious diseases. There are increasing data on the association between Helicobacter pylori infection and idiopathic thrombocytopenic purpura and the significant increase in platelet count after bacterial eradication. The aim of this review is to consider the studies so far published on Helicobacter pylori infection and idiopathic thrombocytopenic purpura in order to evaluate a possible pathogenic correlation between these two conditions. A review of the literature data show that Helicobacter pylori eradication in patients with idiopathic thrombocytopenic purpura is effective in increasing platelet count in approximately half of the cases. However, since the studies so far published are few, sometimes controversial and involve small series of patients, further controlled studies on larger numbers of patients with longer follow-up are needed to confirm these preliminary findings. [23]

Improvement of thrombocytopenia after treatment for *Helicobacter pylori* in a patient with immunologic thrombocytopenic purpura:

Immune thrombocytopenic purpura is the most common autoimmune hematologic disease, affecting individuals of different ages. Recently, the bacterium *Helicobacter pylori* entered the

list of causes of immune thrombocytopenic purpura. Here we present the case of a 55-year-old female patient with low platelet counts initially attributed to chronic vaginal bleeding. As corticosteroid therapy was ineffective she was treated for *H. pylori* infection. Within four weeks the patient had a platelet count of $87.17 \times 10^9$/L accompanied by clinical improvement of the symptoms. [24]

**Viral-associated immune thrombocytopenic purpura:**

Chronic immune thrombocytopenic purpura (CITP) is a diagnosis of exclusion that occurs either de novo or secondary to other underlying disorders. Chronic infection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are now well-characterized causes of CITP. Between 6% and 15% of patients infected with HIV may develop thrombocytopenia. Patients with CITP with risk factors for HIV infection should be screened for the virus. Treatment of HIV-related CITP should be directed toward antiviral therapy with highly active antiretroviral therapy (HAART) regimens. Hepatitis C viral infection can also be associated with chronic thrombocytopenia, even in the absence of overt liver disease. While HCV-related

thrombocytopenia is typically less severe than primary CITP, affected patients are at greater risk of major bleeding. Sustained suppression of HCV virus with interferon-ribavirin therapy can improve platelet counts. Screening for HCV infection should be considered in patients with ITP with risk factors for infection, from regions with high rates of infection or in patients with unexplained mild elevations of liver enzymes. [25]

**Thrombocytopenia in chronic hepatitis C:**

Thrombocytopenia in patients with chronic hepatitis C may be the result of several factors: bone marrow inhibition, the decrease of liver thrombopoietin production and an autoimmune mechanism. Clinical variables such as age, gender, severity of liver disease and degree of viremia could influence the severity of platelet reduction. The goal of this study is to determine the prevalent mechanism of thrombocytopenia in patients with chronic hepatitis C and the clinical predictors of its severity. [26]

In patients with untreated hepatitis C, both prevalence and severity of thrombocytopenia increase in parallel with the extent of disease, usually becoming clinically relevant when patients develop extensive fibrosis and/or cirrhosis. Pathogenetic mechanisms include hypersptenism secondary to portal hypertension, bone marrow suppression resulting from either HCV itself or interferon treatment, aberrations of the immune system resulting in the formation of anti-platelet antibodies and/or immune-complexes that bind to platelets and facilitate their premature clearance, development of immunologically-mediated extrahepatic manifestations including mixed cryoglobulinemia with or without associated joint, renal, or cutaneous involvement, and thrombopoietin (TPO) deficiency secondary to liver dysfunction. In chronic liver disease, the natural inverse relationship between TPO and platelet levels is not maintained; therefore, blood TPO levels fail to have clinical relevance or predictive value in assessing the thrombocytopenic status of a given patient. [27]

**Thrombocytopenia in plasmodium falciparum malaria:**

Malaria is usually associated with reduced blood cell counts & mild to moderate thrombocytopenia is a common association of malaria. The cause of thrombocytopenia is poorly understood, but the immune-mediated lysis, sequestration in the spleen and dyspoietic processes in the marrow with diminished platelet production have all been postulated. This study was conducted to evaluate thrombocytopenia in the patients suffering from acute Plasmodium falciparum malaria.

Descriptive case series study was conducted at a tertiary care hospital, Liaquat University of Medical & Health Sciences Jamshoro, over a one-year period. A total of 370 Plasmodium falciparum positive on peripheral blood film were studied. Full blood counts were determined by

using automated Coulter analyzer. Thick & thin smears were stained with Giemsa stains and studied by haematologist. Data was analyzed using the SPSS version 10.0.

Out of 370 patients, 260 were male & 110 were female, with M:F ratio of 2.36:1. Mean age was 34 +/- 1.7 years (range 16-53 years). Hemoglobin values were 12.7 +/- 1.4g% and white blood cells counts were found 12600 +/- 450/microL. Out of 370, 114 (30.81%) had normal platelet counts, and 256 (69.18%) had thrombocytopenia ($p < 0.05$). The mild, moderate and severe thrombocytopenia were found in 39 (10.5%), 180 (48.6%) and 37 (10%) respectively ($p < 0.05$).

We found high frequency of mild to moderate thrombocytopenia in the Plasmodium falciparum malaria. Finding of thrombocytopenia is of diagnostic help as it raises the suspicion of malaria. [28]

**Thrombocytopenia and *Plasmodium falciparum* malaria in children with different exposures:**

Study of thrombocytopenia during acute Plasmodium falciparum malaria in 64 traveller children from Paris (France), 85 children from Dakar (Senegal) with an intermittent exposure (69 with severe attack or cerebral malaria), and 81 children from Libreville (Gabon) with a perennial exposure (43 with severe attack or cerebral malaria). Initial thrombocytopenia was present in 43–58% of children with P falciparum malaria but was not more frequent in severe outcome or cerebral malaria. Low parasitaemia may lead to the misdiagnosis of malaria and delayed treatment when there is associated thrombocytopenia. [29]

**Occurrence of Thrombocytopenia in *Plasmodium vivax* Malaria:**

*Plasmodium vivax* malaria is endemic the state of Sucre in northeastern Venezuela and is commonly associated with mild hematological abnormalities. Although severe thrombocytopenia is commonly reported to be associated with *Plasmodium falciparum* infection and has been reported to occur in patients coinfected with both *P. falciparum* and *P. vivax*, its occurrence has been rarely reported in cases of *P. vivax* malaria. Herein, we describe a series of patients with *P. vivax* malaria who developed thrombocytopenia. Furthermore, many of these cases were associated with severe thrombocytopenia that required platelet transfusion. [30]

Thrombocytopenia is frequently observed in vivax malaria but the exact mechanism has not been elucidated. We studied 27 cases of acute vivax malaria out of which 24 cases had thrombocytopenia. This was the most common hematological finding. None had bleeding from any site. Anemia and splenomegaly were not present in any of the cases. Platelet counts reverted to normal on treatment. Other causes of thrombocytopenia were ruled out by complete history and physical examination, dengue serology and blood culture. DIC was ruled out by peripheral smear examination and measurement of FDP levels. Our study stresses the importance of thrombocytopenia as an early indicator for acute malaria; a finding that is frequent and present even before anemia and splenomegaly set in. The possible mechanisms leading to thrombocytopenia in malaria have been discussed which include immune mechanisms, oxidative

stress, alterations in splenic functions and a direct interaction between plasmodium and platelets. (31)

**Visceral Leishmaniasis and thrombocytopenia:**

Visceral leishmaniasis, also known as kala-azar, is characterized by irregular bouts of fever, substantial weight loss, swelling of the spleen and liver, and anaemia (which may be serious).

If the disease is not treated, the fatality rate in developing countries can be as high as 100% within 2 years. (32)

Visceral leishmaniasis is characterized by diversity and complexity of clinical manifestations ranging from asymptomatic infection to life threatening illness. Experimental evidence and clinical studies indicate multifaceted role of various factors leading to parasite survival and multiplication. In early stage of infection, generation of reactive oxygen and nitrogen intermediates play significant role in curtailing the parasite multiplication while in later phase on

one hand, hepatic resistance is expressed by the dominant role played by nitric oxide synthase (NOS)-2 gene regulation and on the other hand, production of inhibitors of NOS-2 gene expression, interleukin 10 (IL-10) and transforming growth factor beta (TGFbeta) correlate well with reduced parasite killing. The hepatic infection is usually self-limiting due to production of multiple cytokine responses including moderate level of tumour necrosis factor (TNF) while in spleen excess TNF mediates destructive pathology. CD8+ T cells appear to play multiple roles comprising both cytotoxic activity and secretion of cytokines and chemokines. Capacity to produce ThI cytokines is associated with asymptomatic or subclinical self-healing infection. However, in symptomatic patients, Th I cytokine production is not depressed but there appears to be unresponsiveness to the stimuli of these cytokines. Experimental evidences indicate genetic basis for such a phenomenon. [33]

Visceral Leishmaniasis (VL) or Kala Azar is a chronic infectious disease caused by parasites of the Leishmania donovani complex that can cause various hematologic manifestations. It is characterized by fever, enlargement of liver and spleen, weight loss, pancytopenia and hypergammaglobinemia. It is endemic in the Indian subcontinent, mainly seen in the states of Bihar and West Bengal. Patients with VL can present to the haematologist for various haematological problems prior to receiving the diagnosis of VL. Anaemia is the most common haematological manifestation of VL. VL may also be associated with leucopenia, thrombocytopenia, pancytopenia, and hemophagocytosis and disseminated intravascular coagulation. Hematological improvement is noted within a week and complete hematological response occurs in 4-6 weeks of treatment. Relapses are rare and increased risk of being diagnosed with hematolymphoid malignancies on long term follow up is not noted. [34]

**Idiopathic Thrombocytopenic Purpura**

Idiopathic thrombocytopenic purpura (ITP), also known as primary immune thrombocytopenic purpura and autoimmune thrombocytopenic purpura, is defined as isolated thrombocytopenia with normal bone marrow and in the absence of other causes of thrombocytopenia. ITP has two distinct clinical syndromes, manifesting as an acute condition in children and a chronic condition in adults.

ITP is primarily a disease of increased peripheral platelet destruction, with most patients having antibodies to specific platelet membrane glycoproteins. Relative marrow failure may contribute

to this condition, since studies show that most patients have either normal or diminished platelet production.

Acute ITP often follows an acute infection and has a spontaneous resolution within 2 months. Chronic ITP persists longer than 6 months without a specific cause.

Hemorrhage represents the most serious complication; intracranial hemorrhage is the most significant. The mortality rate from hemorrhage is approximately 1% in children and 5% in adults. In patients with severe thrombocytopenia, predicted 5-year mortality rates from bleeding are significantly raised in patients older than 60 years versus patients younger than 40 years, 47.8% versus 2.2%, respectively. Older age and previous history of hemorrhage increase the risk of severe bleeding in adult ITP.

Spontaneous remission occurs in more than 80% of cases in children. However, it is uncommon in adults. [35]

**Pregnancy induced thrombocytopenia**

Gestational thrombocytopenia, also known as incidental thrombocytopenia of pregnancy, is the commonest cause of thrombocytopenia in pregnancy occurring in approximately 75% of cases. It is a diagnosis of exclusion, no confirmatory tests are available. It generally causes mild thrombocytopenia with the majority of cases having platelet counts of 130 to 150 x $10^9$/L. Most experts consider this diagnosis unlikely if the platelet count falls below 70 x $10^9$/L.

It occurs in the middle of the second trimester and the third trimester and is not associated with maternal bleeding. During pregnancy, it is not possible to differentiate between the more severe form of gestational thrombocytopenia and primary immune thrombocytopenia (ITP) as both are diagnoses of exclusion. For the thrombocytopenia to be consistent with gestational thrombocytopenia, women should have no history of thrombocytopenia (except during a previous pregnancy), the thrombocytopenia should resolve spontaneously (usually shortly after delivery) within 1 to 2 months in all cases and the fetus/neonate should not be affected by thrombocytopenia.

Preeclampsia is the second most frequent cause of thrombocytopenia developing in the late second and third trimester and accounts for 21% of the cases of thrombocytopenia at delivery. Thrombocytopenia may be the only initial manifestation of preeclampsia. Platelet counts of in less than 50 x $10^{9/}$L are rare in preeclampsia, occurring in less than 5% of cases. Intravascular hemolysis and elevated LDH and transaminases are less severe than seen in HELLP syndrome.

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening condition characterized by microangiopathic hemolytic anemia, thrombocytopenia, fever, neurologic abnormalities, and renal dysfunction. It occurs due to a deficiency of VWF cleaving protein ADAMTS13. TTP is more common in women (3:2) and occurs in 1 in 25,000 pregnancies. It is not specific to pregnancy but is found with increased frequency in association with pregnancy in 5% to 25% of cases. Laboratory findings reveal microangiopathic hemolytic anemia, negative direct antiglobulin test, and normal coagulation tests (prothrombin time, activated partial thromboplastin time (APTT), fibrinogen, and D-dimers). Renal impairment is usually mild.

Hemolytic uremic syndrome (HUS) is a microangiopathy similar to TTP but with predominantly renal involvement. A useful clinical feature in distinguishing atypical HUS from TTP is the timing of onset; most cases of HUS occur a number of weeks postpartum. Complement abnormalities are present in 90% of cases with pregnancy-related disease.

A pregnant woman with a new presentation of thrombocytopenia should have a full diagnostic assessment including history, physical examination, and laboratory testing. The key initial laboratory assessment at all gestational ages is a peripheral blood smear to confirm that low platelet count is genuine and to rule out microangiopathy. Following this, the level of thrombocytopenia at which to perform additional tests is a matter of debate, with many using a level of less than 100 x $10^9$/L as a cut-off point below which further investigations should be carried out.

Screening for coagulation abnormalities (prothrombin time, antithrombin, fibrinogen, APTT, D-dimers) should be performed, being aware that APTT shortens during pregnancy. Liver function test abnormalities (bilirubin, albumin, total protein, transferases, and alkaline phosphatase) and screening for infectious causes are recommended and antiphospholipid antibodies, lupus anticoagulant, and serology for SLE are also recommended. Thyroid dysfunction is commonly seen in association with pregnancy and with ITP and should be done routinely. A direct antiglobulin test is required to rule out autoimmune hemolysis.

If there is a family history of bleeding or of thrombocytopenia, laboratory investigation for type 2B VWD should be carried out and included in VWF activity, ristocetin-induced platelet aggregation, and multimeric analysis of VWF.

Bone marrow examination is rarely indicated in pregnancy and suspicion of malignancy is one of its few indications. It is not required for the diagnosis of ITP. As in the nonpregnant patient, antiplatelet antibodies are of no value in the diagnosis of ITP in pregnancy. [36]

**Splenectomy as treatment of thrombocytopenia**

A splenectomy is the surgical removal of the spleen, a small, hand-sized organ located in front of the left kidney and behind the stomach. The spleen acts like a large lymph node, helping to maintain a healthy immune system and cleaning the blood of foreign matter.

In ITP, the antibody-coated platelets are often removed from circulation by the spleen. Theoretically, if the spleen is removed, the platelets will remain in the blood stream. The spleen can also be the site of antibody production. Therefore removing the spleen may reduce the amount of anti-platelet antibodies in addition to removing the antibody-coated platelets.

Although the spleen is often the major site of antibody-coated platelet destruction, platelets may also be removed from circulation by the liver, by a combination of the spleen and liver, or within the blood stream. Therefore, splenectomies are not always successful in raising the platelet count and may fail over time, prompting a return of low platelets.

Splenectomies have been used to treat ITP since 1913. About 10% to 15% of people have no meaningful response to the operation. For those who do respond from 30% to 35% relapse over time.[16] The published success rates are about 66%, although the measurement criteria for success and the duration of follow-up are not standardized in the studies.[1] Splenectomies are more successful and last longer in younger people (under 40 years of age).

There are two types of splenectomies: laparoscopic where the spleen is removed through a few small holes in the abdomen and open, requiring a large incision. The laparoscopic splenectomy is preferred, when possible, since the healing time is reduced. It has the same rate of success as an open splenectomy and there are fewer complications.

While a splenectomy may raise the platelet count, it does not eliminate ITP since the antibody-coated platelets remain in circulation. In pregnancy, these antibody-coated platelets may cross the placenta and have the potential for reducing the platelet count of the newborn.

Doctors vaccinate those about to have a splenectomy with polyvalent pneumococcal, meningococcal C conjugate, and H influenzae b (Hib) vaccines. Timeframes may be different for those on other immune suppressing therapies.

A small percent of the splenectomised ITP population develops an accessory (extra) spleen. Occasionally, a second surgery is suggested to remove the accessory spleen if the patient has relapsed following a successful first surgery.

The immediate complication rate from surgery is about 10%, although estimates vary. The fatality rate from the surgery is about one percent for an open splenectomy and much less than that for a laparoscopic procedure. Patients over 65 have a higher complication and fatality rate.

Since the spleen is responsible for making antibodies, filtering the blood, and removing bacteria, those without a spleen have an impaired immune system. Because of this, splenectomised patients have a more difficult time recovering from pneumonia, meningitis, Hib flu, sepsis, hospital-based infections, malaria and other parasitic diseases, babesiosis (a tick-borne disease) and gram-negative bacterial diseases from animal bites.

People who have had a splenectomy have more microparticles in their blood, giving them an increased risk of dementia[4] and heart attacks[6] from blood clots. They are also more prone to blood vessel complications. [37]

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