The Importance of Platelet Counts in Dengue Infection: 35 Cases and Literature Review

Abstract

Dengue infection is a major vector-borne disease. The classical form of this infection has an incubation period of 5 to 8 days followed by fever, violent headache, and chills, with rash developing after 3 to 4 days. A summative report on the platelet count and its clinical correlation to duration of fever in 35 Thai children is presented. Most of the subjects visited to the physician with a complaint for fever. Most patients went to see the physician between the 3rd and the 5th day from the onset of fever. There is no significant correlation between platelet count and duration of fever (ANOVA test, p = 0.28). However, there is a trend of increase platelet count in the later days. In addition, an overview on the previous literatures on platelet count and dengue infection is presented.

Thrombocytopenia
(Low Platelet Count)

Take the Blood Disorders Quiz

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- What is thrombocytopenia?
- What causes thrombocytopenia?
- What are the symptoms of thrombocytopenia?
- When should I seek medical care for thrombocytopenia?
- How is thrombocytopenia diagnosed?
- How is thrombocytopenia treated?
- What are the complications of thrombocytopenia?
What is thrombocytopenia?

Thrombocytopenia is a lower than normal number of platelets in the blood.

Platelets are one of the components of the blood along with white and red blood cells. They play a role in clotting and bleeding. Platelets are made in the bone marrow similar to other blood cells and red blood cells. Platelets originate from megakaryocytes which are large cells found in the bone marrow. The fragments of these megakaryocytes are platelets that are released into the blood stream. The circulating platelets make up about two third of the platelets that are released from the bone marrow, and the other third is typically stored (sequestered) in the spleen.

Platelets, in general, have a brief 7 to 10 days life in the blood, after which they are removed from the circulation. The number of platelets in the blood is referred to as the platelet count and is normally between 150,000 to 450,000 per micro liter (one millionth of a liter) of blood. Platelet counts less than 150,000 are termed thrombocytopenia. Platelet counts greater that 450,000 are called thrombocytosis.

The function of platelets is very important in the clotting system. Platelets are a part of a complicated pathway. They circulate in the blood vessels and become activated if there is any bleeding. Certain chemicals are released from the injured blood vessels or other structures that signal and join the other components of the system to stop the bleeding. When activated, the platelets adhere to one another and to the blood vessel wall at the site of the injury to slow down and stop the bleeding by plugging up the damaged blood vessel or tissue (hemostasis).

It is important to note that, even though, the platelet numbers are decreased in thrombocytopenia, their function usually remains completely intact. Other disorders exist that can cause impaired platelet function despite normal platelet count.

Low platelet count in severe cases may result in spontaneous bleeding or may cause problems with clotting. In mild thrombocytopenia, there may be no adverse effects in the clotting or bleeding system.
Thrombocytopenia (Low Platelet Count) (cont.)

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Low platelet counts, thrombocytopenia, can be caused by a variety of reasons. In general, they can be divided into:

1. decreased platelet production,
2. increased platelet destruction or consumption, or
3. increased splenic sequestration (capturing of circulating platelets in the spleen).

Some of the most common and important causes or thrombocytopenia are outlined below.

**Decreased platelet production**

Decreased platelet production is usually related to a bone marrow problem (agranulocytosis). In most of these conditions, red blood cell and white blood cell productions may also be affected.

- Viral infections affecting the marrow for example:
- parovirus,
- rubella,
- mumps,
- varicella (chickenpox),
- hepatitis C,
- Epstein-Barr virus, and
- HIV.

- Aplastic anemia is a general term used when the bone marrow fails to produce any blood cells (red cells, white cells, and platelets), also called pancytopenia. This can be caused by some viral infections (parovirus or HIV), medications (gold, chloramphenicol, Dilantin, valproate (Depacon), or radiation, or rarely, it can be congenital (Fanconi's anemia).

- Chemotherapy drugs frequently cause bone marrow suppression resulting in thrombocytopenia.

- Some drugs other than chemotherapy can suppress platelet production, such as thiazide diuretics.

- Cancers of the bone marrow and blood (leukemia) or cancers of the lymph nodes (lymphoma) can cause various degrees of thrombocytopenia.

- Cancers from other organs can sometimes infiltrate (invade) the bone marrow and result in impaired production of platelets.

- Long term alcohol can cause direct toxicity of the bone marrow.

- Deficiency of vitamin B12 and folic acid can result in low platelet production by the bone marrow.

Increased platelet destruction or consumption
Increased platelet destruction or consumption can be seen a number of medical conditions. They can be divided into immune related and non-immune related causes.

Many medications can cause low platelet count by causing immunologic reaction against platelets, called drug-induced thrombocytopenia. Some examples may include:

- sulfonamide antibiotics,
  - carbamazepine [(Tegretol, Tegretol XR, Equetro, Carbatrol) anti-seizure drug],
  - digoxin (Lanoxin),
  - quinine (Quinerva, Quinite, QM-260),
  - quinidine (Quinaglute, Quinidex),
  - acetaminophen (Tylenol and others), and
  - rifampin.

- Heparin, a commonly used blood thinner, and similar medications [low molecular weight heparin or enoxaparin (Lovenox)] can occasionally induce an immune response against platelets resulting in rapid destruction of platelets. This condition is termed heparin-induced thrombocytopenia or HIT.

- Idiopathic thrombocytopenic purpura (ITP) is a condition where the immune system attacks platelets. In severe conditions, ITP can result in very low platelet counts. In adults, this is usually a chronic (long standing) condition, whereas, in children, it can be caused acutely after a viral infection. This is usually a diagnosis of exclusion, meaning other more common causes need to be ruled out.
Some rheumatologic condition, such as **systemic lupus erythematosus** (SLE) or other autoimmune conditions (connective tissue diseases), can cause platelet destruction.

**Transfusion of blood products** and organ transplantation can sometimes cause immunologic disturbances resulting in thrombocytopenia.

**Thrombotic thrombocytopenic purpura** (TTP) and **hemolytic uremic syndrome** (HUS) are similar conditions that can cause non-immune related consumptive thrombocytopenia resulting from some viral illnesses, pregnancy, some metastatic cancers, or chemotherapy. Other manifestations of these conditions include kidney insufficiency, **confusion**, **anemia** (hemolytic), and **fever**. HUS is largely seen in children and is generally thought of as an aftermath of an infection with a certain strain of *Escherichia coli* bacteria (E. coli O157:H7) which causes infectious **diarrhea**.

**HELLP syndrome** (hemolysis, **elevated liver tests**, low platelets) is another non-immune thrombocytopenia that may occur during pregnancy and can include elevation of liver enzyme and anemia (specifically, **hemolytic anemia** or rupturing of red blood cells).

Disseminated intravascular coagulopathy (DIC) is a rare but severe condition that may be a **complication** of overwhelming infections, traumas, **burns**, or pregnancy.

Injury to or **inflammation** of blood vessels (vasculitis) and, sometimes, **artificial heart valves** can cause increased destruction of platelets as they pass by.

Severe infections (**sepsis**) or trauma can sometimes cause consumptive thrombocytopenia (without DIC).

**Splenic sequestration**
Splenic sequestration can also lead to low platelet counts as a result of **enlargement of the spleen** for a variety of reasons. When the spleen enlarges, it can retain (**sequester**) more than the usual amount of platelets. Common causes of thrombocytopenia due to splenic enlargement may include advanced **liver disease** (cirrhosis, for example, from chronic **hepatitis B** or **C**) and blood cancers (leukemias or lymphomas).

- Dilutional thrombocytopenia can result from severe bleeding and transfusion of several units transfused red blood cells in a short time.

- Pseudothrombocytopenia (false thrombocytopenia) is also one of a commonly encountered condition where the number of platelets seen on a **complete blood count** analysis (CBC) may falsely appear low because of the clumping of platelets together. This can lead to a smaller number of platelets seen throughout the slide reviewed by the technician. If this is suspected, the blood can be redrawn in a tube with a material that prevents clumping of platelets for repeat analysis.

- Thrombocytopenia can also be present at birth, called neonatal thrombocytopenia. Most of these cases can be caused by processes similar to above, although, they are occasionally related to rare genetic conditions.

**What are the symptoms of thrombocytopenia?**

In many instances, thrombocytopenia may have no symptoms, especially if mild, and it can be detected only incidentally on routine blood work done for other reasons.

If thrombocytopenia is severe, for example less than 20 per micro liter, it can potentially manifest as increase bleeding when a person is cut or injured or increased bleeding during **menstrual period**.
Spontaneous bleeding can also happen with severe thrombocytopenia (less than 10,000 to 20,000 platelets). This type of bleeding usually occurs under the skin or the mucus membrane (the inner lining of the oral cavity, gastrointestinal tract, or the nasal cavity).

**Petechiae** may be seen in patients with very low platelet counts. Petechiae are small (pin head size) red, flat spots seen under the skin on the dependent parts of the body because of increased pressure due to gravity, for example, on the lower legs. These happen because of bleeding out of the tiny blood vessels under the skin or the mucus membrane. Petechiae are generally not palpable or painful.

Other rashes or bruises seen in thrombocytopenia are called **purpura**, which are small, purple spots under the skin as a result of **hemorrhage**. These are typically greater than 3 millimeters in diameter and may represent a confluence of petechiae.

**When should I seek medical care for thrombocytopenia?**

If thrombocytopenia is detected on a routine blood work, it is generally addressed and investigated by the physician who orders the **blood draw**. In people with known thrombocytopenia, follow-up care is decided based on the diagnosis and the severity.

People with thrombocytopenia are, in general, initially cared for by an **internist** or a **family practice** physician. Sometimes, consultation with a doctor who specializes in blood disorders (**hematologist**) is helpful for more thorough investigation or treatment.

**How is thrombocytopenia diagnosed?**

As mentioned earlier, thrombocytopenia is usually detected incidentally from routine blood work done for other reasons. Platelets are a component of the complete blood count (CBC)
which also contains information on red blood cells and white blood cells.

If thrombocytopenia is seen for the first time, it is prudent to repeat the complete blood count in order to rule out pseudothrombocytopenia (see above). If the repeat CBC confirms low platelet counts, then further evaluation can begin.

Once detected, the cause of thrombocytopenia may be investigated by the doctor. The most essential part of this evaluation includes a thorough physical examination and medical history of the patient. In the medical history, the complete list of all medications is routinely reviewed. Some of the other important components of the history include reviewing previous known history of low platelet count, family history of thrombocytopenia, recent infections, any previous cancers, other autoimmune disorders, or liver disease.

A review of the symptoms related to excessive bleeding or bruising can also provide additional information. As a part of a thorough physical examination, special attention may be given to the skin and mucus membrane in the oral cavity for petechiae or purpura or other signs of bleeding. On the abdominal examination, an enlarged spleen (splenomegaly) can provide important diagnostic clues.

The urgency to perform additional testing and evaluation is largely dependent on how low the platelet count is on the blood count, and what the clinical situation may be. For instance, in a person who needs a surgery and has a platelet count of less than 50 the investigation will take precedence over one whose thrombocytopenia was detected on a yearly blood work with a platelet of 100.

A comprehensive review of the other components of the CBC is one of the most important steps in the evaluation of low platelet count. The CBC can tell us whether other blood disorders may be present, such as, anemia (low red cell count or hemoglobin),
erythrocytosis (high red blood cell count or hemoglobin), leukopenia (low white cells count), or leukocytosis (elevated white blood cell count). These abnormalities may suggest bone marrow problems as the potential cause of thrombocytopenia. Abnormally shaped or ruptured red cells (schistocytes) seen on the blood smear may suggest evidence of HELLP, TTP, or HUS (see above).

Another clue in the CBC is the mean platelet volume or MPV, which is an estimate of the average size of platelets in the blood. A low MPV number may suggest platelet production problem, whereas, a high number may indicate increased destruction.

It is important to also review other blood work including the complete metabolic panel, coagulation panel, and urinalysis. Certain abnormalities in these tests can suggest advanced liver disease (cirrhosis), kidney problems (renal failure), or other pertinent underlying medical conditions.

In some causes of thrombocytopenia, such as HIT or ITP, additional testing with antibodies or assays may be done. Bone marrow biopsy can sometimes be performed if a bone marrow problem is suspected.

**How is thrombocytopenia treated?**

The treatment of thrombocytopenia is largely dependent upon the cause and the severity of the condition.

Some situations may require specific or emergent treatments, whereas, others can only be managed by occasional blood draws and monitoring of the platelet levels.

In auto-immune thrombocytopenia or ITP, steroids can be used to weaken the immune system in order to impair the attack on platelets. In more severe cases, intravenous immunoglobulins (IVIG) or antibodies may also be given to slow down the immune process. In refractory cases, splenectomy (removal of the spleen) may be necessary.
If a drug is thought to be the cause of low platelet count, then it may be discontinued by the supervising physician. In patients with HIT, it is very important to remove and avoid the future use of any heparin products, including low molecular weight heparin (Lovenox), immediately to prevent further immune response against the platelets.

If TTP or HUS is diagnosed, the treatment may include plasma exchange or plasmapheresis. In cases with severe kidney failure, dialysis may be necessary.

In general, platelet transfusion is not necessary, unless an individual with low platelets (less than 50,000) has an active bleeding or hemorrhage, or needs a surgery or other invasive procedures. Sometimes, transfusion may be recommended without any bleeding if the platelet count is less than 10,000.

In suspected cases of HIT or TTP, transfusion of platelets is generally not recommended because the new platelets can potentially make the condition worse and more prolonged.

**What are the complications of thrombocytopenia?**

The complications of thrombocytopenia may be excessive bleeding after a cut or an injury resulting in hemorrhage and major blood loss. However, spontaneous bleeding (without any injury or cut) due to thrombocytopenia is uncommon, unless the platelet count is less than 20,000.

Other complications may be related to any other underlying factors or conditions. For example, autoimmune thrombocytopenia related to lupus may be associated with other complications of lupus. TTP or HUS can have many complications including severe anemia, confusion or other neurologic changes, or kidney failure. HIT or heparin induced thrombocytopenia can have devastating complications related to blood clot formation (thrombosis).
Can thrombocytopenia be prevented?

In general, thrombocytopenia can be prevented if the cause is known and it is preventable. If a certain medication is found to induce low platelet count in an individual, then its future use needs to be avoided. Alcohol avoidance should be encouraged in people with known alcohol-induced thrombocytopenia. Current and future use of all heparin products must be avoided in people diagnosed with heparin-induced thrombocytopenia.

Thrombocytopenia At A Glance

- Thrombocytopenia refers to platelet counts lower than the normal range of 150,000 to 450,000.
- Causes of thrombocytopenia can be classified in 3 groups; diminished production, increased destruction, and splenic sequestration.
- Treatment of thrombocytopenia may vary depending on the cause and the severity.