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A Review: Thrombocytopenia

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ABSTRACT

Thrombocytopenia is defined as a platelet count that falls below its normal range. The normal value of platelets for an adult is 150000 to 450000/ microliter. A platelet count of more than 450000/microliter is called thrombocytosis and a platelet count of less than 150000/microliter is called thrombocytopenia. Various types of thrombocytopenia occur based on theircause such as immune thrombocytopenic purpura, heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, immune thrombocytopenia, and drug-induced thrombocytopenia. Various causes of thrombocytopenia are due to some of the drugs, diseases and disorders, chemical exposures, microorganisms, and some rare conditions that cause blood clots. The underlying pathophysiology of thrombocytopenia is decreased platelet production, increased platelet destruction, and platelets redistribution. The effective diagnosis and treatment may help the patient improve in their quality of life and help to achieve an optimal therapeutic outcome. The scope of this review is to describe thrombocytopenia, types, etiology, pathophysiology, diagnosis, pharmacological treatment, non-pharmacological treatment, and its prevention.

KEY WORDS: *Thrombocytopenia, Etiology, Types, Pathophysiology, Sign and Symptoms, Diagnosis, Treatment*

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INTRODUCTION:

Platelets are also called thrombocytes. Platelets are small colorless cell fragments that are present in the blood. In 1841, George Gulliver drew pictures of platelets. He used a twin-lens compound microscope. In 1842, William Addison drew pictures of a platelet fibrin clot. In 1864, Lionel Beale was the first to publish a drawing showing platelets. When a count of platelets falls below its normal range is called thrombocytopenia. The normal value of platelets in adults is 150,000/microliter to 450000/ microliter.[1] In blood vessel injuries, platelets form plugs and stop bleeding by clumping.[2] Platelets helped in clot formation and stopped or prevented bleeding and it helps to maintain the integrity of the blood vessels walls. In the bone marrow, platelets are made. Bone marrow is present inside the bones and it is a sponge-like tissue. Stem cells are present in the bone marrow that develops into red blood cells (RBC), White blood cells (WBC), and platelets. [3,4,5] Thrombopoietin regulates platelet production.[6] In a healthy body, platelets can live about 10 days.[16]When the platelet count reduces below 100,000/microliter, spontaneous bleeding will occur.[1,7]Aplastic anemia and Leukemia are blood diseases that are associated with thrombocytopenia. They contribute to the impaired production of platelets. A complete blood count test shows platelets numbers.[8] The reasons for thrombocytopenia are making decreasing numbers of platelets, destruction of platelets increased, and distribution of platelets changing.[10]Low platelets occur when the damage of bone marrow cannot make enough of its platelets, Severe bleeding causes lost platelets due to surgery and traumatic injury and, many platelets are removed by the spleen because of the filter process.[3]The Reducing the risk of thrombocytopenia is avoiding alcohol consumption because alcohol slows platelet production, avoiding environmental toxins as it can reduce platelet production, avoiding thrombocytopenia caused medications, and receiving medical professionals recommend drugs and vaccinations.[17]Severe thrombocytopenia such as intracerebral and intraabdominal bleeding may be life-threatening and diagnosing the condition immediately can save the life.

Three stages of thrombocytopenia based on their platelet count:

- Mild: 100,000 to 150,000/ microliter.
- Moderate: 50,000 to 100,000/microliter.
- Severe: < 50,000/microliter.[10]

When platelets count exceeds 450000/microliter the condition is termedthrombocytosis. There are two types of thrombocytosis, one of these is primary thrombocytosis and the other is secondary thrombocytosis. Primary thrombocytosis is caused by alterations targeting hematopoietic cells and secondary thrombocytosis is caused by external causes such as chronic inflammation, cancer, and iron deficiencies.[25]

TYPES:

Various types of thrombocytopenia are there based on their cause:

1. Immune thrombocytopenic purpura:

It is an acquired immune-mediated disorder. There are no known conditions or agents known to induce thrombocytopenia. It is also called idiopathic. Secondary immune thrombocytopenic purpura means some other underlying conditions like lympho proliferative disorders, Infections, and autoimmune disorders.

Example: Systemic lupus erythematosus, antiphospholipid syndrome, Grave's disease, and sarcoidosis.

2. Heparin-induced thrombocytopenia:

It occurs when the patient was treated with Heparin. There is no previous exposure but the platelets count starts to decline 5 to 10 days later. Recent Heparin exposure is the reason for platelet count declination. It is a life-threatening disorder. Patients with Heparin-induced thrombocytopenia having a 50% decrease in platelet count from baseline. When compared with surgical patients, medical patients have a lower incidence.

3. Thrombotic thrombocytopenic purpura:

One of the rare disease conditions is Thrombotic thrombocytopenic purpura (TTP). In small blood vessels, it forms blood clots. Some of the blood vessels are present in the brain, kidneys, and heart. Neurological changes, renal manifestation, and fever present. Without treatment it is fatal. Primarily, it occurs in adults. In children with acute renal failure, bloody diarrhea, and abdominal pain, the hemolytic uremic syndrome is said to be Thrombotic thrombocytopenic purpura. The most common causative organism in hemolytic uremic syndrome is Shiga toxin which is produced by Escherichia coli.

4. Immune thrombocytopenia:

Abnormal immune reaction. It destroys their platelets. The immune system recognizes platelets as foreign substances.

5. Drug-induced thrombocytopenia:

Quinine is one of the most common causes of drug-induced thrombocytopenia. It occurs within 5 to 7 days of exposure to drugs. Usually resolves 7 to 14 days after discontinuation.[3,10]

ETIOLOGY:

1. Drugs:

- Antiplatelet agents: Abciximab, Eptifibatide, Tirofiban.
- Anticoagulants: Heparin; Heparin-induced thrombocytopenia.
- Analgesics: Acetaminophen
- NSAIDs: Ibuprofen, Naproxen, Amiodarone
- Antibiotics: Cimetidine, Piperacillin, Vancomycin
- Anti-seizure medications: Carbamazepine
- Sulfonamides: Trimethoprim-sulfamethoxazole.
- Histamine 2 blocker: Cimetidine
- Vaccines: Measles, Mumps, and rubella vaccine.

2. Diseases and disorders:

- Alcoholism and Alcohol use disorder
- Autoimmune disease: Systemic lupus erythematosus, Rheumatoid arthritis, Henoch-schonlein purpura (small blood vessels).
- Splenomegaly.
- Bone marrow diseases: Myelodysplastic syndromes and certain lymphomas. Leukemia and Aplastic anemia.

3. Treatments:

- Chemotherapy
- Radiotherapy

4. Chemical exposures:

- Arsenic
- Benzene and
- Pesticides.

5. Microorganisms:

- Chickenpox virus.
- Hepatitis C.
- Cytomegalovirus.
- Epstein-Barr virus
- Human immunodeficiency virus
- Parvovirus
- Severe bacterial infection in blood i.e., Sepsis
- Helicobacter pylori.

6. Some rare conditions that cause blood clots:

- Thrombotic thrombocytopenic purpura (TTP)
- Disseminated Intravascular coagulation (DIC).[4,11-15]

SYMPTOMS:

- Bleeding gums
- Blood in the stool(black), urine (haematuria), or vomit
- Red or pink urine
- Heavy menstrual periods
- Rectal bleeding
- Purpura or easy bruising
- Rash: Tiny red-purple or dots on lower legs.
- Superficial bleeding into the skin: pinpoint-sized reddish-purple.
- Prolonged bleeding from cuts
- Bleeding gums or nose
- Fatigue
- Splenomegaly
- Severe headache
- Muscle pain
- Joint pain
- Dizziness
- Feeling weak[2,7,12,16]

PATHOPHYSIOLOGY:

1. Decreased platelet production:

In aplastic anemia, there is the presence of bone marrow failure. Exposure to certain drugs (valproic acid, daptomycin, certain chemotherapeutic agents, and irradiation) bone marrow suppression may occur. Vitamin B12 deficiencies and folate deficiencies, myelodysplastic syndrome, Sepsis impairs platelet production in the bone marrow. The above-mentioned conditions associated with decreased production of other cell lines cause leukemia and Aplastic anemia.

2. Increased platelet destruction:

In a healthy human, platelets get removed by monocytes or macrophages of the reticuloendothelial system. Anti-platelets autoantibodies bind to platelets and megakaryocytes and cause increased destruction of platelets in immune-mediated thrombocytopenia.

Antiplatelet antibodies are present in:

A. Primary Idiopathic Thrombocytopenic purpura (ITP)
B. Drug-induced Idiopathic Thrombocytopenic purpura (ITP)
C. Lymphoproliferative disorders
D. Autoimmune conditions like Systemic lupus erythematosus.
E. Chronic infections like HIV and Helicobacter pylori.

3. Platelet's redistribution:

In a healthy adult, one-third of the platelet mass is in the spleen. In thrombocytopenia, Splenomegaly and increased spleen congestion occur. This results in increased mass in the spleen and decreased platelet production in blood circulation.[15]

DIAGNOSIS:

- Physical examination
- Medical history: General eating habits, alcohol consumption, OTC medications and herbal remedies, quinine-containing beverages. (Often in tonic water and nutritional health products, quinine is present as a substance). Signs of bleeding under the skin (bruises or spots on the skin), Enlargement of the spleen (platelets trapping).
- Complete blood count: It helps to measure the number of red blood cells (RBCs), White blood cells (WBCs), and platelets in the blood. Thrombocytopenia results show low platelet levels
- Prothrombin time (PT) and partial thromboplastin time (PTT) tests: This helps to measure the time taken for blood clotting.
- Automated counter: To determine the severity of thrombocytopenia. It is examined with the help of a microscope.
- Bone marrow biopsy: Sample observed under a microscope.
- Blood smear: It helps to check the appearance of platelets with the help of a microscope.[2,4,17-19]

TREATMENT:

- **PHARMACOLOGICAL MANAGEMENT:**

1. Corticosteroids: The first choice of drug is Corticosteroid. These are also called steroids. It helps to slow down the destruction of platelets by decreasing the production of antibodies against platelets. The example of corticosteroids is Prednisone, Dexamethasone, Methylprednisolone.

Dose: Prednisone; For adults: 1-2 mg/kg/day with taper Dexamethasone 40 mg/day x 4 days for 1-3 cycles orally or intravenously. For children: 2-4 mg/kg orally divided 2 times a day for 5-7 days.[20]

ADR: Irritability, stomach irritation, weight gain, difficulty sleeping, mood changes, and acne.[21,22]

2. Immune globulin: Immune globulin injection. It is used for critical bleeding. The example for Immune globulin is IV gamma globulin and anti-D Immune globulin. IV gamma globulin temporarily slows the rate of platelet destruction.

Dose: 0.8 – 1 gram/kg for 1 dose.[20]

ADR: Headache, fatigue, nausea, chills.

3. Thrombopoietin mimetics: These are the drugs that boost platelets production. It helps our bone marrow produce more platelets. Recently FDA approved drugs for patients who do not respond to

steroids. It may also increase the risk of blood clots. The examples of Thrombopoietin mimetics are Romiplostim and Eltrombopag.

Dose: Romiplostim: 1 mcg/kg subcutaneous q Week Eltrombopag: 50 mg oral qDay.[24]

ADR: upper respiratory tract infection, nasopharyngitis, anemia, pyrexia.

4. Rituximab: It helps to increase platelet counts by reducing immune system response. The results can be seen after 4 to 6 hours. The risk of Rituximab may damage platelets and reduce the effectiveness of vaccinations.[25]

5. Platelets or blood transfusion: Receiving healthy blood or platelets. Replacement of lost blood with transfusion of packed red blood cells or platelets.[2]

- **NON - PHARMACOLOGICALMANAGEMENT:**

1. Surgery: Splenectomy is the removal of the spleen. This removes the main source of platelets destruction. This procedure is done in adults who have immune thrombocytopenia (ITP). It is a permanent solution and effective treatment.[21,22]

2. Vitamin B12: It helps to keep our blood cells healthy. For example, beef liver and eggsare rich in vitamin B12.[23]

3. Vitamin B (Folate): It helps blood cells. Example: peanut, black-eyed peas, kidney beans, orange, orange juices.

4. Iron: It is essential to produce healthy blood cells. Example: Mussels, pumpkin seeds, lentils, beef.

5. Vitamin C: It helps our platelets group together and functions efficiently. It also helps to increase platelets by increasing iron absorption. Example: Mangoes, pineapple, broccoli, tomatoes, cauliflower.[22]

6. Plasma exchange.[2,21]

7. Lifestyle modification:

- Avoid injuries-causing activities such as sports (boxing, martial arts, and football)
- Moderate intake of alcohol if at all.
- Caution for over-the-counter medications. Example: Aspirin, Ibuprofen can prevent platelets from working properly[24]

PREVENTION:

Usually, thrombocytopenia cannot be prevented. Some of the steps which help to prevent health problems associated with thrombocytopenia:

- Avoid contact with toxic chemicals
- Be aware of medications that cause thrombocytopenia.
- Avoid injuries or trauma.
- Avoid drinking alcohol.[14]

CONCLUSION:

Thrombocytopenia is defined as a platelet count that falls below its normal range. The normal value of platelets in adults is 150,000/microliter. This review focuses on thrombocytopenia, types, etiology, pathophysiology, diagnosis, pharmacological treatment, non-pharmacological treatment, and prevention. Successful treatment of thrombocytopenia is the understanding of the underlying pathophysiological process in the disease development. Patients who have thrombocytopenia should take preventive measures and due to the complexity of this condition management of thrombocytopenic conditions requires an inter professional team of health care professionals to achieve an optimal patient outcome.

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