A Review : Thrombocytopenia

Aishwarya Bhandari[1], Ashwini Andhale[2], Dr.Hemant Kamble[3], Santosh Waghmare[4]
[1, 2, 3] Dept of Pharmacology
[4]Dept of Pharmaceutical Chemistry
[1, 2, 3, 4] Loknete Shri Dadapatil Pharate College of Pharmacy, Tal-Shirur, Dist- Pune

Abstract- *Thrombocytopenia is the result of falling the number of platelet from 150,000/microL. There are three main reasons of thrombocytopenia, a-Decreasing of making platelet b-Increasing of destruction platelet c-Changing of distribution platelet. Pseudothrombocytopenia must be kept in mind too. Both hereditary and acquired reasons help thrombocytopenia have wide spreaded, but acquired causes are more common with increasing age. Thrombocytopenia separates three stages as numerical. Mild: 100,000 - 150,000/microL,Moderate: 50,000 - 100,000/microL. Severe: < 50,000/microL. However, thrombocytopenia is not usually detected clinically until the platelet count has fallen to levels below 100,000/microL. Severe thrombocytopenia, such as intracerebral and intra-abdominal bleeding may be life threatening. So diagnosing the treatment immediately can save the life. Transfusion of platelet may not need in all thrombocytopenias. Treatment of the underlying disease may be sufficient. The reason of thrombocytopenia can be temporary but also can be caused severe diseases. Causes of thrombocytopenia change development levels of countries, according to geographical distribution and application centers .*

Keywords- Thrombocytopenia; Etiology; Platelets, Diagnosis, Pathophysiology, Treatment

I. INTRODUCTION

Primary immune thrombocytopenia (ITP) is a haematological autoimmune disorder characterised by bleeding and a low platelet count of less than 100×10^9/L . There are several factors contributing to the onset of ITP, and the exact mechanisms behind how host immune response turns against own system (autoimmunity) and leads to ITP are still incompletely understood. There is growing evidence suggesting that the main event during ITP is a misbalanced interaction between effectors and regulatory immune cells . This lack of an equitable response leads to a distorted immune tolerance, resulting in increased platelet clearance by immune cells, as well as an impairment in thrombopoiesis. Earlier studies suggested that a low platelet count is largely a consequence of anti-platelet antibodies opsonizing the cells and hence an increased clearance from the circulation . However, lately, it has been demonstrated by many researchers that cytotoxic T cells also play a vital role in ITP pathomechanism by impairing megakaryopoiesis. Thrombocytopenia is a common finding in critically ill veterinary patients, regardless of the diagnosis at admission. There are four primary causes of thrombocytopenia: hypoproliferation (lack of production), sequestration, consumption (utilization), and destruction. Sampling or laboratory artifact may also lead to falsely low platelet counts. The critical care veterinarian's job is to diagnose the cause of the thrombocytopenia, determine whether the platelet count is low enough to intervention, and prescribe appropriate treatment.

Heparin-induced thrombocytopenia (HIT) is a life and limb-threatening complication of heparin exposure. Here, we review the pathogenesis, incidence, diagnosis, and management of HIT. The first step in thwarting devastating complications from this entity is to maintain a high index of clinical suspicionhe spleen harbors 30% of the total platelet mass and splenomegaly can result in thrombocytopenia due to platelet sequestration. Dilutional thrombocytopenia is seen after major surgery or with transfusion of large amounts of non-platelet-containing blood products . Incidental or gestational thrombocytopenia in pregnancy is characterized by mild or moderate thrombocytopenia. Although the cause is unknown, it should be carefully discriminated from other more serious causes of thrombocytopenia .This review article, while not exhaustive, aims to summarize the major and/or life-threatening causes of thrombocytopenia and some molecularly characterized congenital causes of thrombocytopenia.

Several conventional and nonconventional therapies have been link to ITP pathophysiology leading to a better understanding of ITP disease processes. T cells and dendritic cells are the driving cells leading to the initiation and perpetuation of ITP.A better understanding of antiplatelet auto antibodies, particularly anti-GPV, and their relationship to ITP disease classification are now identified.

- Strategy for Thrombocytopenia
- All patients with enterohemorrhagic diarrhea, especially in endemic or epidemic areas for *E. coli* should be admitted in specialized units.

Epidemiological and familial histories should be taken. Stools should be collected promptly and tested specifically for *E. coli* O157:H7 with culture, Polymerase Chain Reaction (PCR), serology and anti-O157-antibody titer in serum. PCR and testing for anti-LPS antibodies of prevalent serotypes should be conducted.

All patients with relapsing diarrhea associated HUS, with the presence of a family history of the syndrome in their family or with insidious onset should be screened for complement proteins and ADAMTS13 protease. When Pneumococcus infection is suspected, a bacterial culture of sterile body fluids should be conducted.

PATHOPHYSIOLOGY

Decreased platelet production:

- Bone marrow failure presents in aplastic anemia, PNH
- Bone marrow suppression is a feature with exposure to certain drugs, such as valproic acid, daptomycin, certain chemotherapy agents, and irradiation
- Chronic alcohol abuse
- Inherited thrombocytopenia)
- Viral infection
- Systemic conditions like nutrient deficiencies (folate, vitamin B12), sepsis, myelodysplastic syndrome impairs platelet production in the bone marrow - these conditions also associated with decreased production of other cell lines leading to anemia and leukopenia

Increased platelet destruction:

In normal conditions, platelets get removed by monocytes/macrophages of the reticuloendothelial system. The life span of platelets is 8 to 10 days.

In immune-mediated thrombocytopenia, anti-platelet autoantibodies bind to platelets and megakaryocytes, resulting in increased platelet destruction by the reticuloendothelial system and decreased platelet production.

Anti-platelets antibodies are present in primary ITP, drug-induced ITP, lymphoproliferative disorders, autoimmune conditions like SLE and in chronic infections like HEP C, HIV, and Helicobacter pylori.

Non-immune mediated increased platelet destruction occurs in mechanical valve replacement patients, preeclampsia/HELLP syndrome, DIC, and thrombotic microangiopathy. In conditions like DIC and thrombotic microangiopathy, increased platelet consumption within thrombi takes place.

Dilutional thrombocytopenia:

Dilutional thrombocytopenia presents in massive fluid resuscitation and massive blood transfusion.

Redistribution of platelets: In normal individuals, one-third of platelet mass is in the spleen. In conditions that cause splenomegaly and increases spleen congestion (cirrhosis) results in increased platelet mass in spleen and a decrease in circulating platelets.

Thrombocytopenia is caused by several mechanisms. The two most common ones are decreased production in the bone marrow and increased destruction of platelets (immune thrombocytopenia purpura, drug induced, etc) in the peripheral blood. Thrombocytopenia due to dilution can occur in patients receiving multiple transfusions or in pregnant women as a result of increased plasma volume. Platelets are consumed in hypersplenism and disseminated intravascular coagulation. Pseudo or spurious thrombocytopenia is a relatively common cause of thrombocytopenia due to EDTA related platelet clumping . Review of peripheral smear is diagnostic. Total platelet mass in the body is regulated by the balance between production and clearance of platelets. In hypoplastic thrombocytopenias, such as aplastic anemia or chemotherapy-induced thrombocytopenia, platelet counts are decreased due to reduced platelet production. In ITP, platelet mass shrinks as a result of accelerated platelet clearance, which is mainly due to autoantibody-mediated destruction by macrophages in spleen, and moderately impaired platelet production due to antibody- and/or cytotoxic T cell-mediated megakaryocytic damage.

Opsonized platelets by autoantibodies are destroyed by macrophages in spleen and peptide fragments expressed with MHC class II stimulate helper T cells, following activation of autoreactive B cells. Impaired Tregs fail to suppress this vicious cycle. Autoantibodies also suppress megakaryocytopoiesis. Autoreactive cytotoxic T cells may play a role in the destruction of platelets and megakaryocytes. Thrombopoietin receptor (TPO-R) agonists stimulate megakaryocyte proliferation and maturation. Rituximab targets CD20-positive B cells.

TYPES OF THROMBOCYTOPENIA

Idiopathic (or immune) thrombocytopenic purpura (ITP) - Immune thrombocytopenia (ITP) is a disorder that can lead to

easy or excessive bruising and bleeding. The bleeding results from unusually low levels of platelets — the cells that help blood clot.

Formerly known as idiopathic thrombocytopenic purpura, ITP can cause purple bruises, as well as tiny reddish-purple dots that look like a rash.

Children may develop ITP after a viral infection and usually recover fully without treatment. In adults, the disorder is often long term.

If you don't have signs of bleeding and your platelet count isn't too low, you may not need any treatment. If your symptoms are more severe, treatment may include medications to boost your platelet count or surgery to remove your spleen.

Thrombotic thrombocytopenic purpura (TTP) -

Thrombotic thrombocytopenic purpura (TTP) is a rare blood disorder. In TTP, blood clots form in small blood vessels throughout the body.

The clots can limit or block the flow of oxygen-rich blood to the body's organs, such as the brain, kidneys, and heart. As a result, serious health problems can develop.

The increased clotting that occurs in TTP also uses up platelets (PLATE-lets) in the blood. Platelets are blood cell fragments that help form blood clots. These cell fragments stick together to seal small cuts and breaks on blood vessel walls and stop bleeding.

With fewer platelets available in the blood, bleeding problems can occur. People who have TTP may bleed inside their bodies, underneath the skin, or from the surface of the skin. When cut or injured, they also may bleed longer than normal.

"Thrombotic" (throm-BOT-ik) refers to the blood clots that form. "Thrombocytopenic" (throm-bo-cy-toe-PEE-nick) means the blood has a lower than normal number of platelets. "Purpura" (PURR-purr-ah) refers to purple bruises caused by bleeding under the skin.

Bleeding under the skin also can cause tiny red or purple dots on the skin. These pinpoint-sized dots are called petechiae (peh-TEE-kee-ay). Petechiae may look like a rash.

Haemolytic Uraemic Syndrome (HUS) -Atypical hemolytic-uremic syndrome is a disease that primarily affects kidney function. This condition, which can occur at any age, causes abnormal blood clots (thrombi) to form in small blood vessels in the kidneys. These clots can cause serious medical problems if they restrict or block blood flow. Atypical hemolytic-uremic syndrome iAtypical hemolytic-uremic syndrome is a disease that primarily affects kidney function. This condition, which can occur at any age, causes abnormal blood clots (thrombi) to form in small blood vessels in the kidneys. These clots can cause serious medical problems if they restrict or block blood flow. Atypical hemolytic-uremic syndrome is characterized by three major features related to abnormal clotting: hemolytic anemia, thrombocytopenia, and kidney failure.

Hemolytic anemia occurs when red blood cells break down (undergo hemolysis) prematurely. In atypical hemolytic-uremic syndrome, red blood cells can break apart as they squeeze past clots within small blood vessels. Anemia results if these cells are destroyed faster than the body can replace them. can lead to unusually pale skin (pallor), yellowing of the eyes and skin (jaundice), fatigue, shortness of breath, and a rapid heart rate.

Thrombocytopenia is a reduced level of circulating platelets, which are cells that normally assist with blood clotting. In people with atypical hemolytic-uremic syndrome, fewer platelets are available in the bloodstream because a large number of platelets are used to make abnormal clots. Thrombocytopenia can cause easy bruising and abnormal bleeding.

Thrombocytopenia is a reduced level of circulating platelets, which are cells that normally assist with blood clotting. In people with atypical hemolytic-uremic syndrome, fewer platelets are available in the bloodstream because a large number of platelets are used to make abnormal clots. Thrombocytopenia can cause easy bruising and abnormal bleeding.

As a result of clot formation in small blood vessels, people with atypical hemolytic-uremic syndrome experience kidney damage and acute kidney failure that lead to end-stage renal disease (ESRD) in about half of all cases.

Dignostic Testing-

Although there is no test capable of reliably diagnosing ITP, a laboratory evaluation is recommended at diagnosis to screen for potential causes of secondary ITP, uncover infections resulting in thrombocytopenia that may resolve with proper treatment, and rule out other causes of thrombocytopenia.[4] [5] Alternative causes of

thrombocytopenia, and the recommended assessments to rule out these disorders.

Thrombocytopenia is a common problem in cardiovascular patients, but the etiology and management of this condition may be different than those in other populations. Around the time that percutaneous coronary interventions are performed, the drugs most commonly associated with thrombocytopenia are the glycoprotein (GP) IIb/IIIa receptor inhibitors and heparin. Thienopyridines only rarely cause thrombocytopenia. Patients with non-ST-elevation acute coronary syndromes may be exposed to prolonged heparin infusions, GPIIb/IIIa inhibitors, and thienopyridines. After open-heart surgery, as opposed to other surgical procedures, the platelet count falls, primarily due to platelet damage and destruction in the bypass circuit and hemodilution.

Immune thrombocytopenia

1. Assess pretest probability for HIT (e.g., using the 4Ts). Patients with a low pretest probability (score ≤3) need no further testing and heparin can be maintained.
2. If the EIA is negative, HIT is very unlikely and heparin can be maintained. A positive result in a screening EIA indicates the presence of anti-PF4/heparin antibodies. If an IgG EIA is weakly positive (OD<1.0), the antibodies are most likely non-platelet-activating. A confirmatory step using high heparin should be performed; if reactivity is not inhibited, HIT is very unlikely and heparin can be maintained.
3. An IgG EIA (OD>1.0) indicates an increased risk for platelet-activating antibodies. These sera should ideally be assessed by a washed platelet activation assay. Demonstration of platelet-activating antibodies makes HIT very likely. A negative functional assay makes HIT unlikely and heparin can be maintained/restarted.
4. Clinical reassessment should support a final confirmation or exclusion of the diagnosis. However, it is a misconception to automatically retest patients whose EIA is negative (as the EIA is positive even during the earliest phase of HIT)

Table 1
Alternative etiologies of isolated thrombocytopenia to consider in the diagnosis of immune thrombocytopenia

Alternative diagnosis	Recommended evaluation	Additional testing to consider
Chronic infections • HIV • HCV • *Helicobacter pylori*	Serologic evaluation for HIV, HCV, and *H. pylori*	More sensitive *H. pylori* testing (e.g., urea breath test, stool antigen) may be considered in patients from high-prevalence locations
Systemic autoimmunity (especially systemic lupus erythematosus and antiphospholipid antibody syndrome)	History and physical examination	Targeted serologic testing (e.g., antinuclear antibody, anti–double-strand DNA antibody, antiphospholipid antibodies) in patients with concerning findings on history and physical
Chronic liver disease	History and physical examination Liver panel (transaminases, bilirubin, alkaline phosphatase)	Liver imaging (e.g., ultrasound) in cases suspicious for occult liver disease
Splenomegaly	History and physical examination	Abdominal ultrasound to assess spleen size
Malignancy	History and physical examination Age-appropriate cancer screening	Targeted evaluation as indicated based on history and physical examination
Primary bone marrow disorders (e.g., myelodysplastic syndrome, aplastic anemia, leukemia, Gaucher's disease)	Complete blood count Peripheral blood film	Bone marrow evaluation can be considered in patients with unexplained concomitant anemia, leukopenia, or leukocytosis or steroid- and IVIG-nonresponsive patients
Substances and drugs • Prescription medications (e.g., valproic acid) • Heparin agents (precipitation of heparin-induced thrombocytopenia) • Over-the-counter medications/supplements • Alcohol abuse • Tonic water (containing quinine) • Environmental toxin exposure	History	Targeted laboratory evaluation as indicated based on history

Heamolytic uremic Syndrom - All patients with enterohemorrhagic diarrhea, especially in endemic or epidemic areas for *E. coli* should be admitted in specialized units.

Epidemiological and familial histories should be taken. Stools should be collected promptly and tested specifically for *E. coli* O157:H7 with culture, Polymerase Chain Reaction (PCR), serology and anti-O157-antibody titer in serum. PCR and testing for anti-LPS antibodies of prevalent serotypes should be conducted.

All patients with relapsing diarrhea associated HUS, with the presence of a family history of the syndrome in their family or with insidious onset should be screened for complement proteins and ADAMTS13 protease. When Pneumococcus infection is suspected, a bacterial culture of sterile body fluids should be conducted.

TREATMENT – Initial thrombopoietic cytokines Interleukin-1 (IL-1), IL-3, and IL-6 are pleiotropic cytokines that act early in the phases of megakaryocytopoiesis, and they all have *in vitro* thrombopoietic activity. However, clinical application of these cytokines for the treatment of thrombocytopenia was hampered by side-effects and/or

marginal efficacy, and therefore these agents did not undergo any further clinical development.

The treatment for thrombocytopenia can vary depending on how low a person's platelet count becomes. If the platelet count falls within 100,000–150,000 per microliter (µl)Trusted Source of blood, the blood can still clot, meaning that the increase in the risk of bleeding is not significant.

In these cases, a doctor may suggest monitoring the condition rather than treating it. A person may need regular blood tests to monitor the platelet count over time.

When the platelet count falls below 100,000 per µl, a person may develop spontaneous bleeds. This form of thrombocytopenia usually requires immediate treatment that focuses on managing the cause of thrombocytopenia. The treatment may involve:

- addressing underlying conditions, such as infections or nutritional deficiencies
- stopping any drugs that could be reducing the platelet count
- starting medications that stimulate platelet production
- undergoing blood or platelet transfusions
- undergoing plasma exchange therapy removing the spleen

If someone develops moderate or severe thrombocytopenia while pregnant, a doctor may admit them to the hospital for monitoring. In some cases, they may recommend early delivery.

Treatment is guided by the severity and specific cause of the disease. Treatment focuses on eliminating the underlying problem, whether that means discontinuing drugs suspected to cause it or treating underlying sepsis. Diagnosis and treatment of serious thrombocytopenia is usually directed by a hematologist. Corticosteroids may be used to increase platelet production. Lithium carbonate or folate may also be used to stimulate platelet production in the bone marrow.[26]

II. CONCLUSION

Management of severe thrombocytopenia remains a significant challenge to practicing hematologists and oncologists. Although platelet transfusions remain the standard of care for acute management of this disorder, administration of platelets is associated with a number of problems including availability, cost, immunogenicity, and transmission of infection. Additionally, there is good reason to suspect that prevention will be a preferable option to therapy, much as is true in many other areas of medical practice. Therefore, since currently available means for treating chemotherapy-induced thrombocytopenia are inadequate, investigators are actively developing rationally targeted pharmacologic interventions for this problem. Despite the somewhat naïve hopes that primitive-acting cytokines might be effective therapy for this disorder, several candidate molecules in this regard have failed to fulfill this promise. rHuIL-11 is the only therapeutic agent currently approved for this problem. However, treatment with rHuIL-11 is associated with significant risk of side effects and only modest efficacy.

REFERENCES

[1] Estcourt, Lise J; Malouf, Reem; Hopewell, Sally; Doree, Carolyn; Van Veen, Joost (2018-04-30). Cochrane Haematological Malignancies Group (ed.). "Use of platelet transfusions prior to lumbar punctures or epidural anaesthesia for the prevention of complications in people with thrombocytopenia". Cochrane Database of Systematic Reviews. **4**: CD011980. doi:10.1002/14651858.CD011980.pub3. PM C 5957267. PMID 29709077.

[2] Chapman, Kent; Seldon, Michael; Richards, Ross (2012). "Thrombotic microangiopathies, thrombotic thrombocytopenic purpura, and ADAMTS-13". Seminars in Thrombosis and Hemostasis. **38** (1): 47–54. doi:10.1055/s-0031-1300951. PMID 22314603.

[3] Gresele, Paolo; Fuster, Valentin; Lopez, Jose A.; Page, Clive P.; Vermylen, Jos (2007). Platelets in Hematologic and Cardiovascular Disorders: A Clinical Handbook. Cambridge University Press. ISBN 9781139468763. Retrieved 2015-04-30.

[4] Arnold DM, Nazi I, Warkentin TE, Smith JW, Toltl LJ, George JN, Kelton JG. Approach to the diagnosis and management of drug-induced immune thrombocytopenia. Transfus Med Rev. 2013;27:137–45. doi: 10.1016/j.tmrv.2013.05.005. [PMC free article] [PubMed]

[5] 9. Huxtable LM, Tafreshi MJ, Rakkar ANS. Frequency and management of thrombocytopenia with the glycoprotein IIb/IIIa receptor antagonists. Am J Cardiol. 2006;97:426–9. doi: 10.1016/j.amjcard.2005.08.066. [PubMed]

[6] Cines DB, Bussel JB, Liebman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. Bloo Chakravarty EF, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. Blood. 2011;117:1499–506. doi: 10.1182/blood-2010-07-295444. d. 2009;113:6511–21. doi: 10.1182/blood-2009-01-129155. [PMC free article] [PubMed]

[7] McCrae KR. Thrombocytopenia in pregnancy. Hematology Am Soc Hematol Educ Program. 2010;2010:397–402. [PubMed] [Google Scholar]

[8] 36. Gernsheimer T, James AH, Stasi R. How I treat thrombocytopenia in pregnancy. Blood. 2013;121:38–47. doi: 10.1182/blood-2012-08-448944. [PubMed] [CrossRef] [Google Scholar]

[9] 37. Eser B, Guven M, Unal A, Coskun R, Altuntas F, Sungur M, Serin IS, Sari I, Cetin M. The role of plasma exchange in HELLP syndrome. Clin Appl Thromb Hemost. 2005;11:211–7. doi: 10.1177/107602960501100211

[10] Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of "hypersplenic" thrombocytopenia. J Clin Invest. 1966;45:645–57. doi: 10.1172/JCI105380

[11] Patel PD, Samanich JM, Mitchell WB, Manwani D. A unique presentation of Wiskott-Aldrich syndrome in relation to platelet size. Pediatr Blood Cancer. 2011;56:1127–9. doi: 10.1002/pbc.22920. [PubMed] [CrossRef] [Google Scholar] http://f1000.com/prime/718390785

[12] ussel JB, Kaufmann CP, Ware RE, Woloski BM. Do the acute platelet responses of patients with immune thrombocytopenic purpura (ITP) to IV anti-D and to IV gammaglobulin predict response to subsequent splenectomy? Am J Hematol. 2001;67:27–33. doi: 10.1002/ajh.1072

[13] Wood JH, Partrick DA, Hays T, Ziegler MM. Predicting response to splenectomy in children with immune thrombocytopenic purpura. J Pediatr Surg. 2010;45:140–4. doi: 10.1016/j.jpedsurg.2009.10.026. discussion 144.

[14] McCrae KR. Thrombocytopenia in pregnancy. Hematology Am Soc Hematol Educ Program. 2010;2010:397–402.

[15] Chakravarty EF, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. Blood. 2011;117:1499–506. doi: 10.1182/blood-2010-07-295444.

[16] Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117:4190–207. doi: 10.1182/blood-2010-08-302984.

[17] Swisher KK, Terrell DR, Vesely SK, Kremer Hovinga JA, Lämmle B, George JN. Clinical outcomes after platelet transfusions in patients with thrombotic thrombocytopenic purpura. Transfusion. 2009;49:873–87. doi: 10.1111/j.1537-2995.2008.02082

[18] Ozkan MC, Sahin F, Saydam G. Immune thrombocytopenic purpura: new biological therapy of an old disease. Curr Med Chem. 2015;22(16):1956-62. Review. Citation on PubMed

[19] Provan D, Newland AC. Current Management of Primary Immune Thrombocytopenia. Adv Ther. 2015 Oct;32(10):875-87. doi: 10.1007/s12325-015-0251-z. Epub 2015 Oct 26. Review. Citation on PubMed or Free article on PubMed Central

[20] Smalisz-Skrzypczyk K, Romiszewski M, Matysiak M, Demkow U, Pawelec K. The Influence of Primary Cytomegalovirus or Epstein-Barr Virus Infection on the Course of Idiopathic Thrombocytopenic Purpura. Adv Exp Med Biol. 2016;878:83-8.

[21] Neunert C, Noroozi N, Norman G, Buchanan GR, Goy J, Nazi I, Kelton JG, Arnold DM. Severe bleeding events in adults and children with primary immune thrombocytopenia: a systematic review. J Thromb Haemost. 2015 Mar;13(3):457-64. doi: 10.1111/jth.12813. Epub 2015 Jan 14. Review.