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The Etiology And Clinical Interpretation of Thrombocytopenia: A Review

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Abstract

Thrombocytopenia can be encountered in a clinical setting with any of a variety of underlying pathological processes. Such pathology may result from decreased platelet production, increased peripheral destruction or abnormal distribution, or excessive consumption; and can be associated with everything from benign temporary conditions to life-threatening diseases. To accurately interpret thrombocytopenia, you need to understand integrated platelet physiology, bone marrow function, immune regulation and hemostasis. Advances in immunohematology and molecular biology in recent decades have shone a searching light on every aspect of thrombocytopenia, from the immune-mediated platelet destruction mechanism to thrombopoietin dysregulation, bone marrow failure and the consumptive coagulopathies. This article reviews what is known to be true about the many factors affecting blood platelet production, and the entire range of causative factors and pathological process entailed in besides deficient thrombopoiesis. Emphasis is placed on those biomarkers related most closely to the clinic and some key diagnostic (differential) points between causes were mentioned. An overall understanding of these levers should facilitate accurate diagnosis of thrombocytopenia along with appropriate risk stratification, and effective patient management.

Keywords: Platelets, Thrombocytopenia, Megakaryocytes, Blood Clotting

Introduction

Thrombocytopenia is the most frequent bleeding disorder encountered by hematologists defined as an abnormally low platelet count with no other explainable cause. Normal value of platelets in adult is defined as < $150*10^9$/L but may be modified based on clinical setting and demographic (Pène et al., 2025). Platelet functions are also critical in primary hemostasis. They preserve the continuity of blood vessels and initiate the blood clotting process when endothelial cells are damaged. If either these cells become too few or poor patients are generally at a greater risk of bleeding-however paradoxically in certain pathophysiologic situations such can occur in the face of thrombotic illness (Yamada & Asakura, 2024; Rasizadeh et al., 2024). Consequently, the clinical evaluation of thrombocytopenia needs an understanding of its varying underlying causes and disease mechanisms, potential prognosis across different clinical conditions, etc. (Provan et al., 2019). Thrombocytopenia is clinically relevant due to its very

wide spectrum of manifestations. These range from totally asymptomatic laboratory findings to life threatening hemorrhage or multisystem organ failure. Levels of thrombocytopenia are often discovered incidentally when undergoing routine blood testing in ambulant settings and may lead to additional clinical testing (Pène et al, 2019). In comparison, thrombocytopenia is common and prognostically relevant in ward patients, particularly critically ill ones. In the context of sepsis, hematological malignancy or traumatic injury, it precedes more morbidity and mortality than would otherwise be predicted. These clinical observations highlight that many low platelet counts are transient or benign but that their diagnosis should be distinguished from the processes leading to adverse pathophysiologic consequences that require treatment intervention (Pène et al., 2025).

Different factors cause thrombocytopenia. This paper describes three main types: because bone marrow does not produce enough blood cells; where blood clots in peripheral vessels so that it cannot be reabsorbed; and abnormal sequestration within the spleen (Jinna and Khandhar, 2023). Infiltration by malignant cells is also responsible as an indicator of decreased production; other cell lineages should show concurrent cytopenias too if there is infiltrative involvement (such as by leukemia). Mechanisms leading to increased destruction may be immunologically or not. Primary immune thrombocytopenia (ITP) tends to a depend upon the immune system (Fattizzo & Barcellini, 2020); both thrombotic microangiopathies (e.g., thrombotic thrombocytopenic purpura) and disseminated intravascular coagulation often develop as complex responses involving various parts of host defenses (Yamada & Asakura, 2024). Therefore, the breakdown of platelets inevitably leads to an increase in blood volume. More often blood passes through the spleen than liver for processing, so as the former organ becomes larger through hypersplenism due to portal hypertension, it carries with it an increased volume of blood which must be sequestered. This framework for classifying is meant to help physicians build up lists of possible diagnoses. But it must be informed by careful history and physical examination together with targeted laboratory examination, so as to avoid wrong diagnosis or unnecessary treatment (Jinna and Khandhar, 2023; Pène et al., 2025).

Immune thrombocytopenia is one of the most intensively studied clinical conditions producing low platelet counts. Primary ITP is an autoimmune disease in which antibodies destroy platelets and little or no new ones are made (Mititelu et al., 2024). Recent work underscores the many different immune-mediators involved, from autoantibodies to T-cells that are dysregulated and from proinflammatory cytokines which attack both parts of peripheral platelets surviving in circulation as well as those in the marrow where they are born, accounting for variable extent and course. Like in primary ITP there is a parallel problem in patients whose thrombocytopenia results from systemic connective tissue disease or by infection and drugs. This complex pattern of illness requires clinical attention tailored to the specific circumstances of patient care as well as made-to-measure research strategies (Martínez-Carballeira et al., 2024).

Infections are an important cause of of thrombocytopenia, particularly certain geographic regions or times during viral epidemics. For example: HCV, Human Immunodeficiency Virus and dengue fever have long been recognized to make platelets disappear and bone marrow twitch, through complex, pathogen-specific mechanisms which are now a focus object of recent new pathophysiologic research (Rasizadeh et al., 2024). Similarly, sepsis and critical diseases, which are characterized by systemic inflammation and endothelial activation, may lead to thrombocytopenia through consumptive coagulopathy & bone marrow depression. In particular some recent studies have found that this subgroup of patients with high chances for immunodeficiency can display different prognoses even when severity varies widely (Pène et al., 2025).

Improvements in diagnostic algorithms have also helped clinicians discern the underlying cause of thrombocytopenia. In addition to the basic full blood count, specialized tests for platelet function (and immune markers), microscopic examination of the peripheral blood smears to find evidence suggestive of clumping or other morphological abnormalities in platelets and dynamic observation to follow changes in platelet counts are all increasingly recognized as being part of modern etiologic assessment (Jinna and Khandhar, 2023). Furthermore, the concept of relative thrombocytopenia – defined as a significant drop from baseline but without absolute values falling below

established levels of concern – has been found to be of relevance in certain clinical situations. It is particularly relevant for patients in critical condition or with long-term compound disease where changes over time in platelet counts might herald something more dire on the horizon (Pène et al., 2025).

Due to this broadening knowledge of causes, complications and everchanging trends in diagnosing became necessary. This review provides an informative and updated overview of thrombocytopenia taking into account recently published scientific papers this year to elucidate findings of the major causes, including diagnosis, patient prognosis implications on care options and how these implications may differ depending upon context from those normally taken into account; in both general or specialized settings for clinical practice.

Methodology of the Review

For this narrative review, we searched major electronic databases such as PubMed, Google Scholar and some specific medical databases systematically for the literature in its field. The search was directed to peer-reviewed literature on etiology, pathophysiological processes, and clinical application of thrombocytopenia. To capture the most updated clinical perspectives, studies and clinical guidelines were weighted for recency including research in 2024 and 2025. Selection criteria were focussed on articles pertinent to lack of platelet production, increased destruction in the periphery and aberrant sequestration, as well as on new development in immunohematology and molecular biology. By integrating data from a wide range of clinical contexts from ambulatory routine testing to critical care and sepsis, this approach warrants that common as well as devastating causes of thrombocytopenia are covered.

Physiology and production of platelets

Platelets (or thrombocytes) are small, anucleate cellular cytoplasmic fragments essential in the maintenance of hemostasis and vascular integrity and play important roles in inflammatory and immune responses. Despite their main function is to clog up leaks in blood vessels, the blot and stop bleeding immediately after injury from external forces, new evidence has now confirmed that platelets are complicated cells which communicate with the innate immune system, angiogenesis, and cell-to-cell messaging (Machlus & Italiano, 2013). As such, a deep comprehension of the physiology and production of platelets is essential for correctly diagnosing thrombocytopenia as well as distinguishing among its different etiologies in the clinical setting (Sun et al., 2021). Megakaryocytes are the precursor cells of platelets, which are specialized cells in the hematopoietic system located predominantly in bone marrow. Thrombopoiesis – the full term for platelet production – is tightly regulated by thrombopoietin (TPO), a glycoprotein hormone that's secreted predominately in liver and to a lesser extent, kidneys and stroma cells. When TPO attaches to c-MPL, its receptor on megakaryocyte precursors, cell proliferation, polyploidization and cytoplasmic maturation can be stimulated allowing mature megakaryocytes to emerge capable of producing thousands of platelets each (Kaushansky; 2024). When platelet mass in blood is reduced this also leads to an increase of its circulating mass concentration of TPO through a negative feedback loop mechanism which accelerates production and therefore the equilibrium (Vainchenker et al., 2013).

Recent studies have broadened our understanding of how megakaryocytes develop, showing that thrombopoiesis isn't confined to the bone marrow alone. The lungs also serve as an active site of platelet production, and it contributes significantly to overall platelet output. This is especially true under conditions of pressure on the system as seen in inflammatory states or bone injury. It is therefore apparent from this finding that platelet production is in a continual and active state, rearranging itself throughout the body as the overall physiologic needs dictate (Lefrançais et al., 2017).

When thrombopoiesis occurs, maturing megakaryocytes stretch out long cytoplasmic arms into the lumen of bone marrow sinusoids. Blood flow-induced shear stress then breaks off these tubular projections as platelets. Microtubules, actin filaments, and motor proteins like dynein and kinesin all play a role in the structural remodeling needed to release platelets (Machlus & Italiano, 2013). Once they have entered general circulation, platelets have a life expectancy of 7-10 days before being primarily removed from the bloodstream via the macrophages in spleen and liver. The bodies of old platelets in circulation are stripped of their sialic acid sugars and identified by the Ashwell-Morell receptor, which also stimulates hepatic TPO production; this

serves to further tighten regulation over platelet homeostasis (Semple & Freedman, 2010).

Functionally, inactive platelets stay around in the form of a thick circumferential coil of microtubules and a layer of cortical actin. But when a blood vessel is damaged--collagen or von Willebrand factor (vWF) are exposed on the subendothelial level --glycoprotein receptor mediated adhesion occurs for platelets, including GPIb-V-IX and GPVI. This leads to activation, with cytoplasmic calcium release, rearrangement of the cytoskeleton and granules. Platelet granules contain different bioactive substances including ADP, serotonin and thromboplastin in addition to coagulation factors; these help to amplify adhesion and increase the size of clots. Activated platelets change their shape, they grow pseudopods and develop an irregular form for aggregation. Then integrin αIIbβ3 binds to fibrinogen bridges between the cells to complete this process (Sun et al., 2021).

Furthermore, platelets are not only involved in hemostasis, but also participate on the immune and inflammation processes. They cooperate with leukocytes, which release antimicrobial peptides and bridge the endothelial with cytokines or chemokines. This versatility is exemplified by platelet-anaesthetic aggregates for instance which are critically useful in the body's defense against pathogens but also contributes to those circumstances when overstimulation becomes harmful as seen in sepsis, or any of a variety of viral infections provoking microvessel damage. This complexity of what might be considered to be a relatively simple cell highlights how platelet activities may account for difference between similar disease ranging from syndromes sans across clinical challenge (Semple & Freedman, 2010).

Etiology of thrombocytopenia

Thrombocytopenia is defined as a rapid decline in the number of platelets within the blood, characterized typically by a count below 150×10^9/L Thrombocytopenia has diverse pathological mechanisms, and it exists in many different clinical situations. Understanding why it appears is crucial for better diagnosis, risk assessment and treatment decisions. Disease processes can result in thrombocytopenia: diminished platelet production, increased platelet destruction, or abnormal platelet storage, distribution or availability. For each of these there are a variety of different ailments with different prognoses (Provan et al., 2019).

Decreased Platelet Production

The primary causes of thrombocytopenia due to impaired platelet production are bone marrow disease. Hematopoietic stem cells or megakaryocyte maturation disorders for example aplastic anemia, myelodysplastic syndromes (MDS), leukemia and marrow infiltration by solid tumors can sharply reduce the platelet output (Moore & Krishnan, 2023). Viral infections, including hepatitis C, HIV, Epstein–Barr virus and more recently SARS-CoV-2, directly suppress megakaryopoiesis through stem cell injury or inflammatory cytokine-mediated marrow suppression (Banerjee et al, 2020).

Nutritional deficits are also significant contributors. Deficiency of vitamin B12 and folate produce DNA synthesis disorders which cause megaloblastic changes in hematopoietic precursors, and during its formation reduce platelets. Copper deficiency, though rarer, has also been blamed for reversible pancytopenia (Vască et al., 2022). Chemotherapeutic agents and radiotherapy are the main iatrogenic causes—they act on rapidly dividing cells and so house megakaryocyte maturation but do not affect the surrounding tissue very much. Many drugs, including linezolid, valproate, heparin and alcohol, are also able to directly cause bone marrow toxicity in a dose-dependent fashion with thrombocytopenia resulting (Provan et al., 2019). Deficiency of thrombopoietin is another common reason for reduced platelet production. In advanced liver disease, decreased hepatic synthesis of TPO results in chronic thrombocytopenia which is often complicated by portal hypertension and hypersplenism. Similarly, rare congenital disorders such as congenital amegakaryocytic thrombocytopenia and thrombocytopenia with absent radius (TAR) syndrome may be a result of defective TPO signalling or megakaryocyte differentiation (Tripodi & Mannucci, 2011).

Increased Platelet Production

Accelerated platelet destruction is one of the most commonly recognized causes of thrombocytopenia. Immune-mediated thrombocytopenia is caused by autoantibodies to platelet surface glycoproteins (most

commonly GPIIb/IIIa or GPIb/IX) that lead to increased clearance by splenic macrophages. The most widely practiced example is primary immune thrombocytopenia (ITP), which is defined by isolated thrombocytopenia with a careful exclusion of secondary causes. Recent studies from since the year 2015 have pointed out different mechanisms including dysfunctional regulatory T-cell function, skewed B-cell responses, platelet apoptosis contributing to the pathophysiology of ITP (Pietras et al.., 2024). Evidence: Secondary immune thrombocytopenia develops in conjunction with autoimmune diseases like systemic lupus erythematosus, lymphoproliferative disorders, and chronic infections such as HIV or HCV. Drug-induced immune thrombocytopenia (DITP) is caused by the development of antibodies recognizing platelets in a drug-dependent manner; common drugs include quinine, sulfamethoxazole, vancomycin, and some anticonvulsants (Aster & Bougie, 2007). HIT is a unique immune-mediated syndrome with antibodies to platelet factor 4 (PF4)–heparin complexes. HIT is shafted because it is a condition that results thrombosis rather than bleeding pathophysiologically indicating that the inter-dependent processes of platelet activation (i.e., thrombosis) and immune-mediated destruction are actually quite complex (Greinacher, 2015). Meanwhile, non-immune mechanisms of platelet destruction also contribute. DIC, sepsis-induced coagulopathy, and thrombotic microangiopathies (TMA) including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) lead to massively increased consumption of platelets in microthrombi. TTP is associated with a severe deficiency of ADAMTS13, which in turn causes accumulation of large circulating vWF multimers that contribute to platelet adhesion in the microcirculation and result in marked thrombocytopenia. In patients with prosthetic heart valves or devices that involve extracorporeal circulation there is also mechanical destruction (Joly et al., 2017).

Anomalous Distribution and Sequestration

The spleen commonly stores one-third of the human body's platelets, so splenomegaly from portal hypertension, infiltrative diseases, cancer of hematopoietic lineage, or a congestive spleen increases sequestration and diminishes the circulating platelet pool (Tripodi & Mannucci, 2011). Out of immune, marrow produce source, the splenic pool thrombocytopenia is generally mild and with rare uncontrolled bleeding, though when combined on top of liver disorder or coagulation function failure it can be severe indeed.

In massive transfusion, a marked decline in platelets may also occur because the blood replaces or greatly dilutes itself with crystalloid and red cells that have already been packed for later use. Similarly, so is pregnancy-induced thrombocytopenia — comprising gestational thrombocytopenia and pre-eclampsia-related decreases which reflect haemodilution, increased platelet activation and consumption mechanisms (Mangla & Hamad, 2022).

Pathophysiology of thrombocytopenia

When either production, life span or distribution of the platelets is altered by pathological processes in someone 's bone marrow, peripheral blood or immune system, the result is thrombocytopenia. The specific mechanisms involved in these diseases can vary, but most thrombocytopenias share at least one cause if not all three of these - megakaryocytopoiesis impairment induced by MDS or other diseases; immune-mediated platelet destruction; a state which makes it difficult for nothing from the coagulation cascade to form; and congestion somewhere unexpected. Advances in haemotology have made sense of much of the etiology linking many different diseases to low thrombocyte counts over the past ten years (Provan et al., 2019).

Megakaryocytopoiesis Terribly impaired

In order for platelet production to go on, healthy haematopoietic stem cells are needed, together with probably intact megakaryocyte maturation and their own stimulant, thrombopoietin (TPO). Disease at any one of these points results in thrombocytopenia. In escape scenarios such as aplastic anemia or myelodysplastic syndrome (MDS) where marrow progenitors are singled out by clonal mutations, less but not more megakaryocytes are developed and they are immature (Moore & Krishnan, 2023). Somatic mutations in genes like TET2, ASXL1, and RUNX1—frequently present in MDS—interfere with megakaryocyte differentiation and chromosomal remodeling. These produce ineffective thrombopoiesis in a variety of cells

with abnormal shapes and decreased numbers of platelets made (Crisan, 2000).

Many infectious viruses, including HIV, hepatitis C virus, cytomegalovirus and SARS-CoV-2, can inhibit megakaryopoiesis either by directly infecting the marrow or through a variety of cytokines that they release upon contact with tissue. High levels of interferon-γ, tumor necrosis factor-α and interleukin-6, amongst others all act to injure megakaryocytic progenitors and alter the responsiveness of thrombopoietin. Another well-recognized mechanism is that of chemotherapy-induced thrombocytopenia, in which cytotoxic agents block DNA synthesis and therefore mitosis in megakaryocytic precursor cells, thus reducing both the total number and potential output of their progeny platelets (Banerjee et al, 2020).

Blood cells finally express the chemokine receptor macrophage-stimulating 1 (MST1), according to a recent study. MST1-deficient mice demonstrate higher levels of B cells in their spleens and blood than normal mice, as well as more extensive proliferation and migration of these cells. However, when the researchers examined result bore out over long periods, they found MST1's effect tends to diminish with age. The same observation could be made for statistical differences between young and old individuals in terms of life span (Zhu et al., 2022).

Platelet production may be seriously affected by insufficient TPO levels. Since the liver is the main site of TPO synthesis in human beings, persistent liver disease has led to where there is no more TPO to produce proteins for each time a plate is released and causing chronic severe forms of thrombocytopenia. If the TPO receptor (MPL) or transcription factors in megakaryocyte development are defective from an earlier stage, such patients will suffer severe early-onset thrombocytopenia compounded by impaired signal transduction and reduction of proplate cycles (Tripodi & Mannucci, 2011).

Immune thrombocytopenia (ITP) occurs when autoantibodies–primarily discontinuation IgG –click on the platelet membrane glycoproteins GPIIb/IIIa or GPIb/IX (the receptors and ligand, respectively). These opsonized platelets are removed by liver and spleen macrophages then internalized into lysosomes via Fcγ receptor-mediated phagocytosis. Autoantibodies attacking megakaryocytes with proplatelet-bound ITP gradually lead to decreased production of platelet numbers in adults and therefore have this combined peripheral and marrow thrombocytopenia (Pietras et al.., 2024). When immune regulation is out of control. Suppressed regulatory T-cell activities make destructive restoration by cytotoxic T-cells more severe for both platelets and megakaryocytes. There also seems to be increased platelet apoptosis in ITP, accompanied with caspase signaling pathways that are upregulated for a setting in which platelets last shorter than they should. Heparin-Induced Thrombocytopenia (HIT) is an antibody-mediated disease separate from ITP. PF4–heparin complexes trigger a procoagulant state characterized by extensive platelet consumption within intravascular thrombi instead of their destruction. Consequently, thrombocytopenia in HIT reflects a paradoxical combination of immune activation and consumptive loss (Audia et al., 2017).

Consumptive and Mechanical Destruction

Consumptive thrombocytopenia happens when platelets are constantly active and taken up into fibrin-rich thrombus. Disseminated intravascular coagulation (DIC), sepsis, and severe trauma all activate the coagulation system, leading to generalized microvascular thrombosis with massive platelet use-up. High levels of tissue factor present in the circulation, plus other factors such as inflammatory cytokines and damage to endothelial surfaces, cause coagulation activation and depletion of circulating platelets to be sustained (Gando et al., 2016).

TMAs such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are related forms of thrombocytopenia in some patients, severe hypoproproteinemia is the critical factor that tip's balance towards the latter syndrome. Deeply deficient in ADAMTS13, the process of ultra-large von Willebrand factor multimer secretion and binding was observed in the guinea pig model. Platelets that were thus bound together translated into a great drop in platelet count. Prosthetic heart valves, extracorporeal membrane oxygenation (ECMO), and left ventricular assist devices also bring about notable mechanical destruction of platelets in whom high shear stress quickly breaks these cells to pieces with resultant briefst circulatory life (Arias et al., 2022).

Redistribution and Sequestration

Normally, 25–35% of platelets are sequestered by the spleen. However, in such conditions as portal hypertension or certain neuropsychiatric diseases that lead to reflex splenic enlargement, up to 80–90% of platelets may be trapped. Thus results a moderate fall in platelet count (Peck-Radosavljevic, 2017). Note that the production of platelets by bone marrow is clinically unchanged while the effective circulating platelet mass drops considerably. This mechanism is responsible for much of the clinical findings seen in chronic liver disease, hematologic malignancy and storage disease, such as mucopolysaccharidosis type 1-H (Takamatsu et al., 2007).

Conclusion

The pathophysiology of thrombocytopenia is complex and depends on the interaction of immune response, coagulation, bone marrow signaling and vascular characteristics. A knowledge of these processes is essential not only for discrimination between lack of production, peripheral destruction, consumption and sequestration, but also to help navigate in a practical way implications for diagnostic and treatment strategies. The etiology of thrombocytopenia is wide ranging and can be categorized via marrow failure disorders, immune mediated destruction, consumption, or sequestration. It is important to recognize the pathogenesis for diagnosis and treatment. Platelet transfusion remains important, even as our hematologic practice overall has become lymphocyte-hypocentric (with an ill-defined target of depletion of viruses and/or malignant cells in the current arbitrary goals), these continue to be met with armamentaria of new insights into how thrombocytopenia is produced by emergent immunologic and molecular pathways.

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