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Peripheral Cytopenia: A Review Of Clinical Spectrum And Management Approaches

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Abstract

This review study thoroughly examined the causes, mechanisms, symptoms, diagnosis, and therapy options for peripheral cytopenia, namely anemia, leukopenia, and thrombocytopenia. The report outlined the several underlying factors that contribute to cytopenia, including dietary deficits, autoimmune illnesses, and bone marrow problems. The paper explored the range of symptoms and the level of severity that may occur based on the exact kind of blood cell lineage impacted and the underlying cause of cytopenia. Diagnostic techniques such as complete blood count and peripheral blood smear examination are emphasized, along with treatment strategies including pharmacotherapy, blood transfusions, and stem cell transplantation. Moreover, the study explored the developing topic of nanomedicine in the treatment of cytopenias, with a specific emphasis on the advancement of iron nanoparticles for anemia, targeted drug delivery systems for neutropenia, and platelet-coated nanoparticles for managing thrombocytopenia. In summary, this review offers a thorough analysis of peripheral cytopenia and highlights the transformative potential of nanomedicine in reshaping its therapy options.

Keywords: Anaemia, Leucocytopenia, Nanomedicines, Peripheral cytopenia, Pharmacotherapy.

1. Overview of peripheral cytopenia

Hematopoiesis, a process in which multipotent hematopoietic stem cells called haemocytoblasts develop to form a communal myeloid progenitor cell that subsequently produces thrombocytes, leucocytes/White blood cell (WBCs), and erythrocytes/Red blood cells (RBCs) is the process that produces blood corpuscles in the bone marrow [1]. The conditions known as pancytopenia or cytopenia are caused by defects in the bone marrow, hemocytoblasts, or the direct degeneration of erythrocyte, leucocyte, and thrombocyte cells [2]. This disorder is often defined as a decrease in peripheral blood lineages, which can be brought on by increased cell sequestration or destruction, aplasia, or bone marrow invasion [3]. Pancytopenia is classified as single-lineage or multi-lineage in general. While the count of cells of more than one kind is reduced in multiple lineage pancytopenia, the count of cells of only one type erythrocytes, thrombocytes, or leukocytes is reduced in single lineage pancytopenia [4]. haemoglobin (Hb) < 11 g/dL, platelet count < 10 g/dL, WBCs < 3500 cells/mm³, and are the cell counts that are reached in pancytopenia. A decrease in the quantity of one or more blood cell types circulating in the peripheral circulation is the hallmark of peripheral cytopenia. A decrease in RBCs, WBCs (leukocytes), or platelets, can be one example of this. Numerous things, such as underlying medical diseases, drugs, infections, or autoimmune illnesses, can contribute to its pathogenesis. Depending on the form of cytopenia and its underlying cause, there are differences in symptoms and therapy strategies [5].

The prevalence of peripheral cytopenia can vary widely depending on the population studied, the specific type of cytopenia, and the underlying causes. For example: Anemia is one of the most common blood disorders worldwide. According to the World Health Organization (WHO), anemia affects about 1.62 billion people globally, which is approximately 24.8% of the population. The prevalence of anemia is higher in developing countries, particularly among children, women of reproductive age, and the elderly [6]. The prevalence of leukopenia also varies depending on the population and the definition used. For example, one study found that the prevalence of mild leukopenia (white blood cell count $< 4.0 \times 10^9$ /L) was 7.7% in the Chinese population [7]. However, the prevalence of leukopenia can be higher in certain conditions, such as autoimmune disorders or after chemotherapy. Thrombocytopenia is less common than anemia or leukopenia. The prevalence of thrombocytopenia also varies depending on the population studied and the definition used. One study found that the prevalence of mild thrombocytopenia (platelet count $< 150 \times 10^9$ /L) was 9.5% in the Japanese population [8].

Anemia can have multiple etiologies, such as genetic, environmental, chronic disease-related, infectious, iatrogenic, and hemorrhaging causes as seen in figure 1. Peripheral cytopenia may have a complex etiology including several underlying diseases and causes. Bone marrow disorders such aplastic anemia, myelodysplastic syndromes, and leukemia may cause cytopenia. Autoimmune hemolytic anemia, immune thrombocytopenia (ITP), and autoimmune neutropenia may also cause blood cell destruction [9]. Lack of iron, vitamin B12, and folate, which are needed to make red blood cells, may cause anemia. HIV, hepatitis, and parvovirus B19 may cause cytopenia in bone marrow. Certain treatments, notably chemotherapy, may impair bone marrow activity, causing cytopenia. Medication reactions, infections, and autoimmune illnesses may cause hemolysis, the excessive destruction of erythrocytes. Splenomegaly-induced hypersplenism traps and eliminates blood cells, causing cytopenia. Toxic compounds like benzene may harm bone marrow and produce cytopenia [9]. Familial Fanconi anemia and congenital neutropenia may produce peripheral

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cytopenia. Chronic illnesses including renal and hepatic disease may also limit blood cell creation or enhance their breakdown, causing cytopenia.

The diagnosis of peripheral cytopenia or pancytopenia entails a comprehensive assessment of the patient's medical history, a thorough physical examination, and the performance of several laboratory tests, such as a complete blood count (CBC) and analysis of a peripheral blood smear. The course of treatment is contingent upon the root cause and may encompass the administration of drugs, blood transfusions, and the control of underlying disorders.

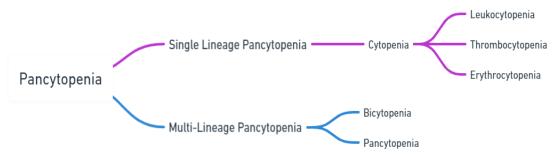


Figure. 1 Factors affecting Cytopenia.

2. Classification of cytopenia based on the affected blood cell lineages (Anaemia, leukopenia, thrombocytopenia)

The categorization of cytopenia according to the specific blood cell lineages that are impaired is beneficial for comprehending the root reasons and directing the approach to treatment. The treatment of cytopenia typically involves targeting the root cause, such as administering iron supplements for iron deficiency anemia or using drugs to increase the WBCs or platelets production. Cytopenia can be categorized into three primary classifications based on the specific blood cell lineages that are affected: Anemia, leukopenia, and thrombocytopenia are medical conditions characterized by a decrease in red blood cells, white blood cells, and platelets, respectively [10].

- Anemia (Erythrocytopenia): Anemia is defined as a reduction in the quantity of RBCs or a reduction in the concentration of hemoglobin in the bloodstream. As a result, the blood's capacity to transport oxygen to tissues and organs is diminished. WHO has established the reference range for hemoglobin concentration at 13.0 g/dL for males and 12.0 g/dL for women. However, these normal levels may need to be adjusted based on specific factors and circumstances such as pregnancy, ethnicity, age, and the laboratory methods used [11]. Anemia can be categorized according to the dimensions and hue of red blood cells, which aids in identifying the root cause. Prevalent forms of anemia encompass:
- ➤ **Hemolytic anemia:** Resulting from the untimely breakdown of erythrocytes, this syndrome might arise from autoimmune disorders, infections, or hereditary factors [12].
- > Aplastic anemia: Resulting from bone marrow injury, which hinders the generation of red blood cells [13].
- ➤ Leukopenia (Leukocytopenia): Leukopenia is characterized by a reduction in the quantity of white blood cells (leukocytes) present in the bloodstream. White blood cells play a crucial role in the body's immune system, and a reduction in their quantity might elevate the susceptibility to infections [14]. Leukopenia can be categorized according to the specific subtype of white blood cells that are impacted, such as:
- > **Neutropenia:** A reduction in the quantity of neutrophils, which play a crucial role in combating bacterial infections [15].
- **Lymphopenia:** A reduction in the quantity of lymphocytes, which play a crucial role in the body's immunological system [16].
- **Eosinopenia:** A reduction in the quantity of eosinophils, which play a role in allergic reactions and combatting parasitic illnesses [17].
- Thrombocytopenia: Thrombocytopenia is defined as a reduction in the quantity of platelets (thrombocytes) present in the bloodstream. Platelets play a crucial role in the process of blood clotting, and having a low platelet count might elevate the likelihood of experiencing bleeding and bruises [18].

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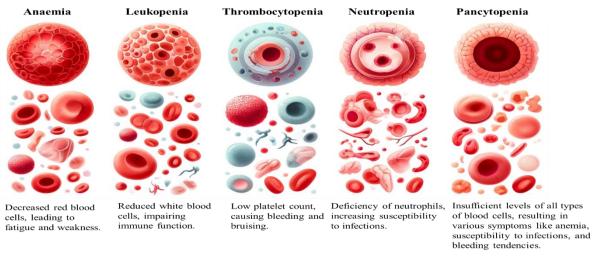


Figure 2. Types of cytopenia

3. Explaining the pathophysiological processes of each cytopenia

Cytopenias are medical diseases marked by a decrease in the quantity of blood cells, which includes red blood cells (anemia), white blood cells (leukopenia), and platelets (thrombocytopenia) [19]. Each form of cytopenia is characterized by unique underlying pathophysiological mechanisms:

> Anemia:

- **Decreased Production:** Anemia can occur when the bone marrow's ability to produce RBCs is hindered owing to nutrient deficiencies (like iron, vitamin B12, or folate), bone marrow disorders (such aplastic anemia or myelodysplastic syndromes), or chronic diseases (such as chronic renal disease or chronic inflammation) [19].
- **Increased Destruction:** Hemolytic anemias occur when red blood cells are prematurely destroyed, either because of inherent causes such as genetic illnesses like sickle cell anemia and thalassemia, or external ones such autoimmune reactions, infections, and toxins [20].
- **Blood Loss:** Anemia can also occur because of sudden or long-term loss of blood, for example, due to bleeding in the gastrointestinal tract, menstruation, or injury [20].

Leukopenia:

- **Decreased Production:** Leukopenia, also known as low white blood cell count, can be caused by bone marrow abnormalities such as aplastic anemia and myelodysplastic syndromes, infections like HIV and viral hepatitis, nutritional deficiencies in vitamin B12 and folate, or certain drugs such as chemotherapy and immunosuppressants [21].
- Increased Destruction or Sequestration: Leukopenia can occur because of conditions such as autoimmune illnesses, hypersplenism (enlarged spleen trapping white blood cells), or some infections, which cause an increase in the destruction or sequestration of white blood cells [22].

> Thrombocytopenia:

- **Decreased Production:** Thrombocytopenia may occur due to bone marrow illnesses such as aplastic anemia, leukemia, or myelodysplastic syndromes, as well as infections like HIV or hepatitis C, or because of drugs that restrict platelet formation [23].
- **Increased Destruction or Sequestration:** Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by the specific targeting and destruction of platelets by antibodies. Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS) are medical conditions defined by the activation and depletion of platelets, resulting in low platelet count [24].

4. Clinical Presentation (Symptoms of Anaemia, leukopenia, thrombocytopenia)

- ➤ Anemia: Individuals suffering from anemia may exhibit symptoms such as exhaustion, debility, pallor (a lack of color in the skin), difficulty breathing, light-headedness, and migraines. Severe instances can result in angina, irregular heartbeats, and dizziness [25].
- ➤ Leukopenia: Leukopenia can present as heightened vulnerability to infections, frequent episodes of fever, and longer durations of sickness. Additionally, patients may encounter oral ulcers, inflamed throat, and dermal infections [25].
- > Thrombocytopenia: Thrombocytopenia may result in the occurrence of effortless or profuse bruising, persistent bleeding from minor lacerations, nosebleeds, and bleeding gums. In more extreme instances, it can lead to the development of petechiae, which are little red spots on the skin, or larger bruises. Healthcare personnel must be able to identify and diagnose cytopenias by recognizing and understanding the important clinical signs and symptoms [26].

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5. Symptoms and severity of cytopenia vary based on the underlying cause and severity.

The manifestations of cytopenia can exhibit significant variation based on the specific blood cell type impacted (RBCs, WBCs, or platelets), the root cause, and the degree of severity. The degree of cytopenia can also differ depending on the root reason and the individual's general well-being. Variables such as age, coexisting medical conditions, and immune system function might impact the intensity of symptoms and the effectiveness of treatment [27].

> Anemia

The symptoms can vary from mild fatigue to severe weakness, accompanied by shortness of breath and chest pain. The severity of these symptoms depends on the extent of red blood cell insufficiency and the speed at which it occurs. Chronic disorders such as iron deficiency anemia can result in the slow onset of less severe symptoms, while acute blood loss anemia can cause quick and severe symptoms that require immediate action [28].

Leukopenia

Minor instances of leukopenia may not result in observable symptoms, but severe leukopenia might give rise to recurrent infections, protracted illnesses, and possibly perilous sequelae. others with weakened immune systems, such as those receiving chemotherapy, may encounter more severe and frequent infections in comparison to others with less severe cases of leukopenia [29].

> Thrombocytopenia

Minor instances may solely cause effortless bruising or nosebleeds, whereas severe thrombocytopenia might result in significant bleeding episodes or hemorrhage. Individuals with mild thrombocytopenia may be asymptomatic, however those with severe thrombocytopenia may face life-threatening bleeding issues [30].

6. Diagnosis of various cytopenias

Various diagnostic techniques are available for identifying anemia, which vary based on the probable etiology and the clinical circumstances. Below are few frequently used techniques:

- ➤ Complete Blood Count (CBC): Hematocrit determination is typically the initial diagnostic test for anemia. This test quantifies the quantity of RBCs, WBCs, and platelets in the bloodstream, together with the levels of hemoglobin (Hb) and hematocrit (Hct). Anemia is commonly characterized as a reduction in the level of hemoglobin (Hb) below the reference range, as observed in the study conducted by Ana Kriselda et al., 2023 [31]. The study involved analyzing venous blood samples from 170 Filipino women aged 18-44 years, using serum ferritin and complete blood count (CBC) tests. Analyzed were the investigative capabilities of the CBC parameters in detecting iron deficiency and anemia, utilizing receiver operating characteristic (ROC) curves. 'Iron deficiency' was characterized by a low ferritin level [31].
- ➤ Peripheral Blood Smear: The study of the Peripheral Blood Smear (PBS) is crucial for assessing hematological diseases. Anemia, leukocytopenia, and thrombocytopenia are identified by peripheral blood smear (PBS). Despite its drawbacks, the manual analysis approach remains in use due to its status as the most potent analytical instrument, albeit it is laborious, error-prone, time-consuming, and necessitates skilled laboratorians. There is a clear requirement for a cost-effective, automated, and reliable method to identify RBCs abnormalities from peripheral blood smears. The automation of PBS analysis is a highly active field of research that has encouraged numerous research groups to create approaches utilizing image processing [32].
- ➤ Platelet Function Tests: These tests assess the platelets' level of functionality. An example of a frequently used test is the bleeding time test, which assesses the duration it takes for bleeding to cease following a minor incision [33].

7. Treatment of pancytopenia or cytopenia

Recombinant proteins such as epoetin alfa (Epogen, Procrit), Filgrastim (Neupogen), Sargramostim (Leukine), and Pegfilgrastim (Neulasta) are bone marrow stimulant medications that are suggested for the management and treatment of cytopenia. Additional therapeutic modalities for pancytopenia include stem cell therapy, bone marrow transplantation, and blood transfusion. Colony stimulating factors (CFUs) are the primary and main treatment for pancytopenia, which is a condition characterized by low levels of all three blood cell types. These CFUs are bone marrow stimulants that help to increase the production of blood cells. Colony-stimulating factors (CSFs) like sargramostim enhance the production of hematopoietic progenitor cells and promote their differentiation into monocytes and neutrophils, hence reducing the risk of neutropenia. An adverse reaction commonly observed with long-term use of sargramostim treatment is hypersensitivity, which is caused by the presence of yeast in the medication. Filgrastim is a recombinant DNA technology product that is utilized to promote the proliferation and differentiation of granulocytes [34].

The negative effects associated with this medication include bone and joint discomfort, ruptured spleen, hypersensitivity reactions, hemoptysis, and alveolar hemorrhage [35]. Epoetin alfa is a man-made version of human erythropoietin, which promotes the formation of red blood cells by stimulating erythropoiesis. The side effects include joint discomfort, allergic reactions, pulmonary embolism, and dyspnea. With continued use, the negative impact becomes increasingly prevalent and lethal. Transfusion of blood is utilized to treat disorders such as thalassemia, a genetic abnormality in hemoglobin that impairs the production of normal red blood cells. In this case, blood transfusion is performed once every 21 days [36]. Pancytopenic disorders are commonly detected in later stages of blood

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transfusion, and thalassemia is often linked to viral infections such as hepatitis C. This process is both unpleasant and laborious, and it also carries the risk of opportunistic diseases such as hepatitis C. Transplantation of bone marrow involves the replacement of damaged and defective bone marrow with healthy bone marrow. The treatment is costly and requires both allogenic and autologous stem cell transplantation. Nevertheless, certain patients experience graft against host illness, which leads to reactions of hypersensitivity. Stem cell treatment employs induced pluripotent stem cells to regenerate human organs [37].

8. Nanomedicine treatment for anaemia

During this investigation, researchers discovered that there are multiple iron nanocarriers that have been authorized for the anemia treatment on the market. Furthermore, current study has shown a growing focus on using these nanocarriers for the neutropenia treatment. Nanomedicines Research for neutropenia is prioritized over thrombocytopenia and anemia due to its direct association with the management of chemotherapeutics. Administering G-CSF (Growth-colony stimulating factors) is a recommended treatment for neutropenia; nevertheless, it is accompanied by many side effects, such as bone pain caused by the drug's deposition in the peripheral areas. Nanomedicine research in the neutropenia treatment has provided a means to reduce side effects utilizing targeted medication delivery nanocarriers as seen in table

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Table.1 FDA-approved iron oxide nanoparticles for treatment of iron deficiency anemia									
S. No	Product Name	Type	Indication	References					
1	Ferroportin	nanoparticulate Fe3+polyoxohydroxide	Iron deficiency anemia	[38]					
2	Nanotherm	Amino-silane coated superparamagnetic iron oxide nanoparticles	Glioblastoma	[38]					
3	Ferrlecit (Sanofi)	Iron gluconate colloid	Anemia in patients with chronic kidney disease	[38]					
4	CosmoFer/INFeD/ Ferrisat (Pharmacosmos)	Iron dextran colloid	Iron deficient anemia	[38]					
5	DexFerrum/DexIron (American Regent)	Iron dextran colloid	Iron deficient anemia	[39]					
6	Venofer (American Regent)	Iron sucrose colloid	Anemia in patients with chronic kidney disease	[40,41]					

> Pancytopenia targeting by Nano-platforms

Nanoparticles are produced through the synthesis of different materials, such as viruses (viral nanoparticles), polymers (dendrimers, vesicles, nanoparticles, polymeric, micelles), lipids (liposomes), and even inorganic substances. Mediated delivery systems encompass a range of methods, including the use of cells such as monocytes, erythrocytes, macrophages, platelets, natural killer cells, B cells, T cells, and dendritic cells to deliver nanoparticles. A mediated or targeted drug delivery system enhances the effectiveness of medications by delivering them directly to certain tissues, thereby controlling the ratio of drug distribution between target and non-target tissues. This approach reduces the required drug dosage and minimizes the potential toxicity associated with higher doses [42]. Hence, targeted drug administration is an appealing strategy for medications with a restricted therapeutic range and/or those that are effective at extremely low concentrations. The main methods for achieving targeted medicine delivery consist of passive and active affecting methodologies. Passive aim to occurs in the presence of leaky microvasculature, leading to the nanocarriers extravasation at the site of illness. An instance where there is a presence of leaky blood vessels is observed in cases of tumors and inflammatory tissue. Localized diseases such as cancer and inflammatory disorders exhibit permeable blood vessels and include specific receptors that can be targeted for therapeutic purposes. Active targeting involves the use of ligands that specifically bind to receptors that are overexpressed at the desired regions. The ligands have been attached to the circulating nanocarriers surface. This method is beneficial for medications or bioactive substances that are not readily absorbed by cells and need assistance from processes such as endocytosis or fusion to reach the active areas within the cells [42].

> Nanomedicines for anaemia

The development of nanomedicines for the treatment of anemia is an emerging field that is attracting the attention of scientists and engineers worldwide. A variety of nanostructured-based delivery systems for iron are currently being researched. The use of nanostructure enables the safe delivery of iron without causing harm to the gastrointestinal tract. Furthermore, the nanocarriers enhance iron absorption by 1.35 times compared to ferrous sulphate, the conventional medication [43]. The research report indicated that Fe3O4 astragalus polysaccharide core shell nanoparticles

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(Fe3O4@APSNPs) have the potential to be used in the iron-deficient anemia treatment. This suggests the possibility of creating nanocomposites from pure natural ingredients [44]. Various techniques for producing iron nanoparticles have been employed, with one recently discovered method being the one-pot reduction process carried out under the BSA (bovine serum albumin) protection for the purpose of anemia therapy. In a separate study conducted by Garces et al. [45], anemia was successfully treated by administering iron oxide nanoparticles carried by bacteria. The study found that the bacteria were able to enter the enterocytes and attach to the gut wall, demonstrating their probiotic capabilities

Several conventional approaches, such as iron supplementation and iron fortification in food crops, are used to address iron deficiency. Iron biofortified crops are the most effective means of addressing iron deficiency [46]. However, if those who do not have nutrient deficiencies ingest these products, it can pose a substantial danger of developing heart illnesses, kidney ailments, and diabetes. Iron supplements, such as ferrous sulphate and ferrous citrate, are the preferred medications for treating' iron deficiency anemia. However, these treatment methods are linked to numerous gastrointestinal adverse effects and impact the natural microbiota of the digestive system. Furthermore, the uptake of iron is inadequate and extended use of synthetic supplements results in the buildup of iron in cells, leading to cancer, oxidative stress, and lipid peroxidation [47]. Therefore, there is a need for new options that can enhance the absorption of iron, and to achieve this, scientists have concentrated on utilizing nanotechnology for the treatment and control of anemia [47].

> Nanomedicines for neutropenia

The treatment is determined based on the cause, the severity of the problem, and the underlying disease that is causing neutropenia. Nanomedicine enhances the effectiveness, distribution throughout the body, safety, and ability to target specific areas of therapeutic formulations. Neupogen (Filgrastim) received approval from the US-FDA in 1991 for the treatment of neutropenia caused by chemotherapy. This medication is licensed for patients with non-myeloid cancer who are receiving chemotherapy to reduce the occurrence of neutropenia. While the regular administration of filgrastim through injections is linked to pain, especially joint pain, which causes discomfort for patients and may result in noncompliance, leading to missed doses or reduced effectiveness. As a result, alternative methods were employed to administer filgrastim to ameliorate neutropenic symptoms. A recent study was undertaken to treat neutropenia, a condition caused by chemotherapy, in an experimental rat model. The study utilized G-CSF nanoparticles administered in several daily dosages [48]. A nanoparticle system consisting of chitosan with diethylene triaminepentaacetic acid (γPGA-DTPA), and poly (γ-glutamic acid) was developed for the oral delivery of G-CSF medication to treat neutropenia associated with chemotherapy. Several chemotherapeutic drugs, including doxetaxel [49], rapamycin [50], camptothecin [51], cabazitaxel [52], vincristine [53], doxorubicin [54], cisplatin [55], irinotecan [56], and paclitaxel [57], have the potential to cause neutropenia as a side effect. To address this, these drugs are formulated in the form of nanoparticles to counteract the neutropenic condition. Paclitaxel, a chemotherapy medication, has been widely researched and found to cause neutropenia as a side effect. To address this issue, several nanoparticles have been created and examined in different stages of clinical trial [58].

> Nanomedicines for thrombocytopenia

The nanomedicines that target hematological abnormalities are described and organized in Table 2. The diagnosis of heparin-induced thrombocytopenia is performed using a nanoparticle-based lateral flow immunoassay called STicExpert HIT [59]. The management of thrombocytopenia involves the use of nanoparticles that are coated onto platelets. A recent study has discovered a new approach for treating immunological thrombocytopenia, which involves using nanoparticles that mimic antibodies and are disguised within the coating of platelets [60]. Cell membrane-coated nanoparticles are a significant nanoplatform used for various purposes such as immunization, medication delivery, and detoxification. An important component is the capacity of various types of cells to reproduce the surface characteristics and engage with the surface of nanoparticles. many types of cells, like cytotoxic T cells, neutrophils, leukocytes, NKC, erythrocytes, macrophages, platelets are utilized to disguise NPs for the treatment of many illnesses, including thrombocytopenia as seen in table 2 [61]. Table 4 categorized and tabulates key nanomedicines that target hematological abnormalities [62].

Table. 2 Nanoparticles for chemotherapeutic drugs to treat hematological disturbances								
S. NO	Product	Company	Nanoplatform	Drug	Indication			
1	Mepact	Takeda	Liposome	Mifamurtide MTP-PE	Osteosarcoma			
2	Marqibo	Talon	Liposome	Vincristine	Acute lymphoid leukemia			
3	Doxil	Alza	Liposome	Doxorubicin	Multiple myeloma			
4	Oncaspar	Enzon-Sigma-tau	Polymer protein conjugate	L-asparaginase	Leukemia			
5	CPX-351	Celator Pharmaceuticals	Liposome	Cytarabine and daunorubicin	Acute myeloid leukemia			
6	Rexin-G	Epeius Biotechnologies	Targeted protein tagged	Phospholipid/micro- RNA-122	Sarcoma, Osteosarcoma			

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9. Discussion

The discussion section of this review paper examines the mechanisms, prevalence, causes, classification by blood cell lineage (anemia, leukopenia, thrombocytopenia), and clinical manifestations of cytopenia. Pancytopenia can occur when there is a malfunction or destruction of the bone marrow, hematopoietic stem cells, or blood cells. Anemia is a common blood disorder that occurs worldwide, however the frequency of cytopenia varies. Cytopenia can arise from various factors, including bone marrow disorders, autoimmune conditions, nutritional deficiencies, infections, pharmaceutical effects, and inherited abnormalities. A comprehensive medical history, thorough physical examination, and extensive laboratory tests are required to make a diagnosis. Treatment options, such as bone marrow stimulants, blood transfusions, and stem cell treatments, are determined based on the underlying cause. The paragraph emphasized the efficacy of nanomedicine in addressing cytopenia and the utilization of nanostructured iron delivery techniques for anemia treatment. The article examined the use of iron nanocapsules for the secure transportation and assimilation of substances. Chemotherapy-induced neutropenia was treated with filgrastim nanoparticles. The paper also discusses the utilization of nanoparticles in lateral flow immunoassays for diagnosing heparin-induced thrombocytopenia and the use of cell membrane-coated nanoparticles for treating immunological thrombocytopenia. The paragraph discussed cytopenia, including its diagnosis, treatment, and the role of nanomedicine.

10. Conclusion

To summarize, this study emphasizes that cytopenias, such as anemia, leukopenia, and thrombocytopenia, occur due to disturbances in the generation or functioning of blood cells. The process of diagnosis entails gathering the medical history of patient, doing a physical examination, and performing laboratory tests such as a complete blood count (CBC). The treatment options for this condition are diverse and depend on the underlying cause. They may involve the administration of medications, blood transfusions, and the management of any associated underlying conditions. Nanomedicine provides precise drug delivery, minimizing adverse consequences. Iron oxide nanoparticles are used to treat iron deficient anemia, while growth factor nanoparticles are used to accelerate the formation of WBCs or platelets. Gaining a comprehensive understanding of the mechanisms underlying cytopenia is essential for accurate diagnosis and effective treatment. Nanomedicine holds great potential in enhancing the management of this condition.

References

- 1. A.S. Gupta, Bio-inspired nanomedicine strategies for artificial blood components, Wiley Interdiscipl. Rev. Nanomed. Nanobiotechnol. 9 (2017), https://doi.org/10.1002/wnan.1464.
- 2. X. Na, H. Shanfeng, Z. Yang, S. Zonghong, Roles of immune responses in the pathogenesis of immuno related pancytopenia, Scand. J. Immunol. 92 (2020) 12911, https://doi.org/10.1111/sji.12911.
- 3. Shukla, N. Dasgupta, S. Ranjan, S. Singh, R. Chdambaram, Nanotechnology towards prevention of anaemia and osteoporosis: from concept to market, Biotechnol. Biotechnol. Equip. 31 (2020) 863–879, https://doi.org/10.1080/13102818.2017.1335615.
- 4. S.M. Bagwe, P.P. Kale, L.K. Bhatt, K.S. Prabhavalkar, Herbal approach in the treatment of pancytopenia, J. Compl. Integr. Med. 14 (2017), https://doi.org/10.1515/jcim-2016-0053.
- 5. Hepburn AL, Narat S, Mason JC. The management of peripheral blood cytopenias in systemic lupus erythematosus. Rheumatology. 2010 Dec 1;49(12):2243-54.
- 6. Niroula K. PREVALENCE OF ANEMIA AND ASSOCIATED FACTORS AMONG NON-PREGNANT WOMEN OF REPRODUCTIVE AGE (15-49 YEARS) IN DHIMAL COMMUNITY OF DAMAK MUNICIPALITY (Doctoral dissertation).
- 7. Sing CW, Tang CT, Chui CS, Fan M, Lai FT, Li X, Wan EY, Wong CK, Chan EW, Hung IF, Leung AY. COVID-19 vaccines and risks of hematological abnormalities: nested case–control and self-controlled case series study. American Journal of Hematology. 2022 Apr;97(4):470-80.
- 8. Keerthy Aberna A. Role of Platelet Indices in Differentiating the Causes of Thrombocytopenia in a Tertiary Care Hospital (Doctoral dissertation, Madras Medical College, Chennai).
- 9. Kovalyova O, Pasiieshvili L, Frolova T, Andrusha A, Shapkin V, Ivanchenko S. Syndromes and diseases of the blood system: textbook.
- 10. Gangat N, Wolanskyj AP. Anemia of chronic disease. Semin Hematol (2013) 50:232–8. doi: 10.1053/j.seminhematol.2013.06.006
- 11. M.D. Cappellini, I. Motta, Anemia in clinical practice-definition and classification: does hemoglobin change with aging? Semin. Hematol. 52 (4) (2015) 261–269.
- 12. Fattizzo B, Barcellini W. Autoimmune hemolytic anemia: causes and consequences. Expert Review of Clinical Immunology. 2022 Jul 3;18(7):731-45.
- 13. Biswajit H, Pratim PP, Kumar ST, Shilpi S, Krishna GB, Aditi A. Aplastic anemia: a common hematological abnormality among peripheral pancytopenia. North American journal of medical sciences. 2012 Sep;4(9):384.
- 14. Riley LK, Rupert J. Evaluation of patients with leukocytosis. American family physician. 2015 Dec 1;92(11):1004-11.

http://www.veterinaria.org

Article Received:01/03/2024 Revised:31/03/2024 Accepted:16/04/2024



- 15. Newburger PE, Dale DC. Evaluation and management of patients with isolated neutropenia. InSeminars in hematology 2013 Jul 1 (Vol. 50, No. 3, pp. 198-206). WB Saunders.
- 16. Lv Y. Causes of peripheral blood cytopenias in patients with liver cirrhosis portal hypertension and clinical significances. Open Journal of Endocrine and Metabolic Diseases. 2014 Apr 15;2014.
- 17. Gleich GJ, Klion AD, Lee JJ, Weller P. The consequences of not having eosinophils. Allergy. 2013 Jul;68(7):829-35.
- 18. Smock KJ, Perkins SL. Thrombocytopenia: an update. International journal of laboratory hematology. 2014 Jun;36(3):269-78.
- 19. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood. 2004 Oct 15;104(8):2263-8.
- 20. Naik RP, Smith-Whitley K, Hassell KL, Umeh NI, De Montalembert M, Sahota P, Haywood Jr C, Jenkins J, Lloyd-Puryear MA, Joiner CH, Bonham VL. Clinical outcomes associated with sickle cell trait: a systematic review. Annals of Internal Medicine. 2018 Nov 6;169(9):619-27.
- 21. Young NS. Current concepts in the pathophysiology and treatment of aplastic anemia. Hematology 2013, the American Society of Hematology Education Program Book. 2013 Dec 6;2013(1):76-81.
- 22. Olcay L, Yetgin S, Aoshima H. Disorders mimicking myelodysplastic syndrome and difficulties in its diagnosis. London, UK:: IntechOpen; 2016 Sep 7.
- 23. Bento L, Canaro M, Bastida JM, Sampol A. Thrombocytopenia and therapeutic strategies after allogeneic hematopoietic stem cell transplantation. Journal of Clinical Medicine. 2022 Mar 2;11(5):1364.
- 24. Balduini CL, Pecci A, Noris P. Diagnosis and management of inherited thrombocytopenias. InSeminars in thrombosis and hemostasis 2013 Mar (Vol. 39, No. 02, pp. 161-171). Thieme Medical Publishers.
- 25. Massaro F, Andreozzi F, Vandevoorde C, Bron D. Supportive Care in Older Lymphoma Patients to Reduce Toxicity and Preserve Quality of Life. Cancers. 2023 Nov 13;15(22):5381.
- 26. Gharwan H, Groninger H. Kinase inhibitors and monoclonal antibodies in oncology: clinical implications. Nature reviews Clinical oncology. 2016 Apr;13(4):209-27.
- 27. Izak M, Bussel JB. Management of thrombocytopenia. F1000prime reports. 2014;6.
- 28. Stevens GA, Paciorek CJ, Flores-Urrutia MC, Borghi E, Namaste S, Wirth JP, Suchdev PS, Ezzati M, Rohner F, Flaxman SR, Rogers LM. National, regional, and global estimates of anaemia by severity in women and children for 2000–19: a pooled analysis of population-representative data. Lancet Global Health. 2022 May 1;10(5):e627-39
- 29. Parasher A, Saini V, Saini A, Barik RR, Aggarwal A, Khan J. A study of the association of leukopenia with disease severity and mortality in patients diagnosed with COVID-19. International Journal of Advances in Medicine. 2020 Nov;7(11):1721.
- 30. Schlappi C, Kulkarni V, Palabindela P, Bemrich-Stolz C, Howard T, Hilliard L, Lebensburger J. Outcomes in mild to moderate isolated thrombocytopenia. Pediatrics. 2018 Jul 1;142(1).
- 31. Rivera AK, Latorre AA, Nakamura K, Seino K. Using complete blood count parameters in the diagnosis of iron deficiency and iron deficiency anemia in Filipino women. Journal of Rural Medicine. 2023;18(2):79-86.
- 32. KT N, Prasad K, Singh BM. Analysis of red blood cells from peripheral blood smear images for anemia detection: a methodological review. Medical & biological engineering & computing. 2022 Sep;60(9):2445-62.
- 33. Frelinger III AL, Grace RF, Gerrits AJ, Berny-Lang MA, Brown T, Carmichael SL, Neufeld EJ, Michelson AD. Platelet function tests, independent of platelet count, are associated with bleeding severity in ITP. Blood, The Journal of the American Society of Hematology. 2015 Aug 13;126(7):873-9.
- 34. R. Karwasra, S. Faithi, K. Raza, S. Singh, K. Khanna, S. Sharma, N. Sharma, S. Varma, Filgrastim loading in PLGA and SLN nanoparticulate system: a bioinformatics approach, Drug Dev. Ind. Pharm. 46 (2020) 1354–1361, https://doi.org/10.1080/03639045.2020.1788071.
- 35. J. Hoggatt, T.A. Tate, L.M. Pelus, Role of lipegfilgrastim in the management of chemotherapy-induced neutropenia, Int. J. Nanomed. 10 (2015) 2647–2652, https://doi.org/10.2147/IJN.S55796.
- 36. Matzdorff, O. Meyer, H. Ostermann, V. Kiefel, W. Eberl, T. kuhne, I. Pabinger, M. Rummel, Immune thrombocytopenia current diagnostics and therapy: recommendations of a joint working group of DGHO, OGHO, SGH, GPOH, and DGTI, Onclol. Ress. Treat. 41 (2018) 1–30, https://doi.org/10.1159/000492187.
- 37. K.J. Smock, S.L. Perkins, Thrombocytopenia: an update, Int. J. Lab Hematol. 36 (2014) 269–278, https://doi.org/10.1111/ijlh.12214.
- 38. M.F. Aslam, D.M. Frazer, N. Faria N, S.F. Bruggraber, S.J. Wilkins, C. Mirciov, J. J. Powell, G.J. Anderson, D.A. Pereira, Ferroportin mediates the intestinal absorption of iron from a nanoparticulate ferritin core mimetic in mice, Faseb. J. 28 (2014) 3671–3678, https://doi.org/10.1096/fj.14-251520.
- 39. C.L. Ventola, Progress in nanomedicine: approved and investigational nanodrugs, P T 42 (2017) 742–755. https://pubmed.ncbi.nlm.nih.gov/29234213/.
- 40. B.S. Barot, P.B. Parejiya, D.M. Mehta, P.K. Shelat, G.B. Shah, Physicochemical and structural characterization of iron–sucrose formulations: a comparative study, Pharmaceut. Dev. Technol. 19 (2014) 513–520, https://doi.org/10.3109/10837450.2013.795171.

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- 41. T. Di Francesco, G. Borchard, A robust and easily reproducible protocol for the determination of size and size distribution of iron sucrose using dynamic light scattering, J. Pharmaceut. Biomed. Anal. 152 (2018) 89–93, https://doi.org/10.1016/j.jpba.2018.01.029.
- 42. A.C. Anselmo, S. Mitragotri, Nanoparticles in the clinic, Bioeng Transl. Med. 1 (2016) 10–29, https://doi.org/10.1002/btm2.10003.
- 43. E.H. Shafie, S.A. Keshavarz, M.E. Kefayati, F. Taheri, P. Sarbakhsh, M. Reza Vafa, The effects of nanoparticles containing iron on blood and inflammatory markers in comparison to ferrous sulfate in anemic rats, Int. J. Prev. Med. 7 (2016) 117, https://doi.org/10.4103/2008-7802.193092.
- 44. K. Wang, L. Li, X. Xu, L. Lu, J. Wang, S. Wang, Y. Wang, Z. Zin, Y. Ziang, Fe3O4@ Astragalus plysaccharide core-shell nanoparticles for iron deficiency anemia therapy and magnetic resonance imaging in vivo, ACS Appl. Mater. Interfaces 11 (2019) 10452–10461, https://doi.org/10.1021/acsami.8b18648.
- 45. V. Garc´es, A. Rodríguez-Nogales, A. Gonz´ alez A, et al., Bacteria-carried iron oxide nanoparticles for treatment of anemia, Bioconjugate Chem. 29 (2018) 1785–1791, https://doi.org/10.1021/acs.bioconjchem.8b00245.
- 46. T.A. Salaheldin, In-vivo nutritional and toxicological evaluation of nano iron fortified biscuits as food supplement for iron deficient anemia, J. Nano Res. 3 (2016), 00049, https://doi.org/10.15406/jnmr.2016.03.00049.
- 47. M.B.M. Mohamed, S.H.A. Helmy, WO2014135170- Novel Formula of Iron Based Nanocomposite for Rapid and Efficient Treatment of Iron Deficiency Anemia, European patent, 2013. EP2964205A1.
- 48. F.-Y. Su, E.-Y. Chuang, P.-Y. Lin, et al., Treatment of chemotherapy-induced neutropenia in a rat model by using multiple daily doses of oral administration of G-CSF-containing nanoparticles, Biomaterials 35 (2014) 3641–3649, https://doi. org/10.1016/j.biomaterials.2014.01.020.
- 49. D.D. Von Hoff, M.M. Mita, R.K. Ramanathan, et al., Phase I Study of PSMAtargeted docetaxel containing nanoparticle BIND-014 in patients with advanced solid tumors, Clin. Canc. Res. 22 (2016) 3157–3163, https://doi.org/10.1158/1078-0432.CCR-15-2548.
- 50. A.M. Gonzalez-Angulo, F. Meric-Bernstam, S. Chawla, et al., Weekly nabRapamycin in patients with advanced nonhematologic malignancies: results of a phase I trial, Clin. Canc. Res. 19 (2013) 5474–5484, https://doi.org/10.1158/1078-0432.CCR-12-3110.
- 51. G.J. Weiss, J. Chao, J.D. Neidhart, et al., First-in-human phase 1/2a trial of CRLX101, a cyclodextrin-containing polymer-camptothecin nanopharmaceutical in patients with advanced solid tumor malignancies, Invest. N. Drugs 31 (2013) 986–1000, https://doi.org/10.1007/s10637-012-9921-8.
- 52. N. Kommineni, S. Mahira, A.J. Domb, W. Khan, Cabazitaxel loaded nanocarriers for cancer therapy with reduced side effects, Pharmaceutics 11 (2019) 141, https://doi.org/10.3390/pharmaceutics11030141.
- 53. S. O'Brien, G. Schiller, J. Lister, et al., High-dose vincristine sulfate liposome injection for advanced, relapsed, and refractory adult philadelphia chromosomenegative acute lymphoblastic leukemia, J. Clin. Oncol. 31 (2013) 676–683, https://doi.org/10.1200/JCO.2012.46.2309
- 54. C. Mamot, R. Ritschard, A. Wicki, et al., Tolerability, safety, pharmacokinetics, and efficacy of doxorubicin-loaded anti-EGFR immunoliposomes in advanced solid tumours: a phase 1 dose-escalation study, Lancet Oncol. 13 (2012) 1234–1241, https://doi.org/10.1016/S1470-2045(12)70476-X.
- 55. V. Subbiah, J.E. Grilley-Olson, A.J. Combest, et al., Phase Ib/II trial of NC-6004 (Nanoparticle Cisplatin) plus gemcitabine in patients with advanced solid tumors, Clin. Canc. Res. 24 (2018) 43–51, https://doi.org/10.1158/1078-0432.CCR-17-1114.
- 56. R.D.N. Arifa, T.P. Paula, M.F.M. Madeira, et al., The reduction of oxidative stress by nanocomposite Fullerol decreases mucositis severity and reverts leukopenia induced by Irinotecan, Pharmacol. Res. 107 (2016) 102–110, https://doi.org/10.1016/j.phrs.2016.03.004.
- 57. S.K. Williamson, G.A. Johnson, H.A. Maulhardt, et al., A phase I study of intraperitoneal nanoparticulate paclitaxel (Nanotax®) in patients with peritoneal malignancies, Canc. Chemother. Pharmacol. 75 (2015) 1075–1087, https://doi. org/10.1007/s00280-015-2737-4.
- 58. R.K. Singh, S. Pankaj, S. Kumar, V. Rajkota, A retrospective study of efficacy and safety of albumin bound paclitaxel in metastatic breast cancer, World J. Oncol. 5 (2014) 204–209, https://doi.org/10.14740/wjon865w.
- 59. D. Leroux, N. Hezard, A. Lebreton, et al., Prospective evaluation of a rapid nanoparticle-based lateral flow immunoassay (STic Expert® HIT) for the diagnosis of heparin-induced thrombocytopenia, Br. J. Haematol. 166 (2014) 774–782, https://doi.org/10.1111/bjh.12939.
- 60. X. Wei, J. Gao, R.H. Fang, B.T. Luk, A.V. Kroll, D. Dehaini, J. Zhou, H.W. Kim, W. Gao, W. Lu, L. Zhang, Nanoparticles camouflaged in platelet membrane coating as an antibody decoy for the treatment of immune thrombocytopenia, Biomaterials 111 (2016) 116–123, https://doi.org/10.1016/j. biomaterials.2016.10.003.
- 61. V. Vijayan, S. Uthaman, I.K. Park, Cell membrane camouflaged nanoparticles: a promising biomimetic strategy for cancer theragnostics, Polymers 10 (2018) 983, https://doi.org/10.3390/polym10090983.
- 62. T. Tagami, T. Ozeki, Recent trends in clinical trials related to carrier-based drugs, J. Pharmacol. Sci. 106 (2017) 2219–2226, https://doi.org/10.1016/j. xphs.2017.02.026.