A Review on Drug Induced Hematological Disorders

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ABSTRACT

- **Objectives**

The hematological disorders that affect white blood cells, red blood cells, platelets and the coagulation system may be sometimes induced by drugs. This paper aims to emphasize the wide variety of drug-induced hematological disorders and to highlight the treatment options of these disorders.

- **Methods**

Based on many case reports and several researches, in this literature drug-induced hematological disorders are reviewed. In this study we focus on individual drugs, their mechanism of action and the process how these drug induced disorders are happen.

- **Results**

There are several drug-induced hematological disorders such as hemolytic anaemias, methemoglobinemia, red cell aplasia, sideroblastic anaemia, megaloblastic anaemia, polycythemia, aplastic anaemia, leukocytosis, neutropenia, eosinophilia, immune thrombocytopenia, microangiopathic syndromes, hypercoagulability, hypoprothrombinemia, circulating anticoagulants, myelodysplasia and acute leukemia. Some of the traditional medicines known to cause hematologic abnormalities have been replaced by newer drugs (developed formulations), including biologics, accompanied by their own syndromes and unintended side effects.

- **Conclusions**

Through a number of varieties of mechanisms, drugs can cause toxicities that affect a wide range of hematological disorders. Physicians should be alert about the possibility of iatrogenic drug-induced hematologic problems.

- **Key Words**

Drug-induced anaemia; aplastic anaemia; agranulocytosis; hemolytic anaemia; megaloblastic anaemia; thrombocytopenia; methemoglobinemia; sideroblastic anaemia; pure red cell aplasia

I. INTRODUCTION

There are several mechanisms and etiologies that lead to hematological disorders. Drug-induced hematological disorders can affect RBC, WBC, platelets and the coagulation system, which encompasses nearly the whole hematological spectrum. Adverse drug reaction can cause harmful effect to the both bone marrow and peripheral blood cells. Every year lots of drug induced hematological instances are reported because the population consumes millions of doses of drugs. Despite the fact that most of the drugs have a relatively low risk, but it can induce more than one adverse event. This is frequently associated with dosage and duration of the drug. This problem can be solved by discontinuing of these offending drugs and by choosing alternate therapy. However, in certain circumstances, the negative effect is permanent, and patient may die. Sometimes, it is difficult to determine the frequency of adverse reaction of a drug. Aplastic anaemia, agranulocytosis, hemolytic anaemia, megaloblastic anaemia and thrombocytopenia are some of the drug-induced hematological disorders. Anti-neoplastic drugs, as well as chloramphenicol and its metabolites, have a direct harmful effect on bone marrow. Immunological mechanisms can induce hemolytic anaemia. The drug may affect the immune system by acting as a hapten, causing the production of autoantibodies or antidrug antibodies. Drugs that act on erythrocytes with enzyme deficiencies (such as glucose-6-phosphate dehydrogenase deficiency) can cause hemolysis [1].

❖ **Aplastic Anaemia**

Aplastic anaemia is a bone marrow failure disease that includes peripheral pancytopenia and bone marrow hypoplasia [2]. It is a dangerous and uncommon condition with unknown etiology. If the pluripotent stem cells are damaged, then it can cause drug-induced aplastic anaemia. In this disease normal amount of erythrocytes, neutrophils and platelets are reduced. The yearly incidence of

aplastic anaemia is around 2 incidences per million people. There are two types of aplastic anaemia: inherited and acquired [3]. Inherited aplastic anaemia is a hereditary condition that causes fatty infiltration, bone marrow suppression and the loss of circulating blood cells. Fanconi's anaemia, Blackfan diamond anaemia and congenital dyskeratosis are among them. Drugs, radiation, viruses, chemical exposures can cause acquired aplastic anaemia.

The following criteria can be used to make a diagnosis -

i. WBC count 3500 cells/mm^3 or less
ii. Platelet count 55000 cells/mm^3 or less
iii. Hb value 10gm/dl or less [3]

- If neutrophils are less than 1500 cells/mm^3, platelets are less than 50,000 cells/mm^3 and Hb is less than 10 gm/dl, then it can be considered that aplastic anaemia is in moderate stage.
- When neutrophils are less than 500 cells/mm^3, platelets are less than 20,000 cells/mm^3, and reticulocytes are less than 1%, then it is considered as severe condition.
- When the neutrophil count is less than 200 cells/mm^3, it is considered as highly serious condition [3-5].

NSAIDs, anticonvulsants, antithyroid drugs, antituberculous drugs, antirheumatic drugs are linked to the development of aplastic anaemia. Some specific drugs mentioned include chloramphenicol, butazone, sulfonamide, gold salts, penicillamine, amidopyrine, trimethoprim/sulfamethoxazole, methimazole, and felbamate [6–9]. Few drugs that are linked to cause aplastic anaemia can also frequently result in mild bone marrow suppression, indicating that little damage may occasionally develop to more serious damage (perhaps due to host metabolism). The treatment for drug induced aplastic anaemia is to stop taking the substance that caused it. Along with antibiotic treatment, blood transfusion is often advised. Even if the neutrophil count continues to drop, granulocyte colony-stimulating factor has been employed. Corticosteroids can be used to treat purpura. Bone marrow transplantation can be used to treat irreversible drug-induced aplastic anemia [10].

❖ **Agranulocytosis / Neutropenia**
Agranulocytosis is an uncommon disorder in which the quantity of WBC (granulocytes and immature granulocytes) in the circulating blood is severely reduced [10]. The elderly women are more prone to drug-induced agranulocytosis. The incident rate of agranulocytosis in Europe is 1.6 to 9.2 cases per million when compared to the US, where it is slightly higher ranging from 2.4 to 15.4 cases per million population [11]. For the development of this form of agranulocytosis, various mechanisms of action have been proposed. These are listed below –

1) Destruction of neutrophils by drug antibodies,
Example - Chlorpromazine, procainamide, clozapine, dapsone, sulphonamides, carbamazepine, phenytoin, indomethacinetc

2) The development of a lupus-like syndrome,
Example - Penicillin, quinidine, levamisole

3) The toxic depression of bone marrow
Example - Phenothiazine, chlorpromazine, tricyclic antidepressants [11]

Various analgesics, psychotropics, anticonvulsants, antithyroid drugs, antihistaminics, antirheumatics, GI medications, antimicrobials, cardiovascular drugs and chemotherapeutic drugs all can cause drug-induced neutropenia. [12–14]. Some drugs such as penicillins, which function as haptens and trigger the production of antibodies against neutrophils, are linked to immune-mediated processes. Neutrophils' apoptosis is accelerated by clozapine and neutrophils are destroyed by complement mediated action of propylthiouracil. Granulopoiesis is inhibited by medications such as β-lactam antibiotics, carbamazepine and valproate in a dose-dependent manner. A number of drugs, including ticlopidine, bulsufan, methamizole, ethosuximide and chlorpromazine, have direct harmful effects on myeloid precursors.

Primary therapy involves restoring an appropriate neutrophil count (Corticosteroid therapy can help in this condition), withdrawing the offending drugs from patients, antibiotics administration, when necessary giving them recombinant human granulocyte colony-stimulating factor are all methods of treating drug induced neutropenia (rhG-CSF). Sargramostim and filgrastim are the most effective drugs in reducing the duration of neutropenia [10]. Particularly in patients with deep neutropenia, the administration of CSFs can reduce the duration of neutropenia, frequency of infection, and lower death rates [14]. Rituximab, an anti-CD20 antibody used to treat benign autoimmune disorders and B cell lymphoproliferative disorders, can cause neutropenia, usually of delayed onset [15].

❖ Neutrophilia

Neutrophilia is most frequently caused by infection or inflammation, while it might be associated to myeloproliferative disorders. If there are too many neutrophils in the bloodstream, then leukocytosis may develop. Leukocytosis can be drug induced. By stimulating the release of neutrophils from the bone marrow, glucocorticoids can cause neutrophilia [16]. Despite variations, glucocorticoids generally do not cause leukocytosis more than 20000/uL. Such an increase in WBC counts may indicate the presence of an infection [17]. By releasing neutrophils from the marginated pool, adrenaline and epinephrine cause neutrophilia [16]. Prior to the development of CSFs, lithium was utilised to treat neutropenia despite it causes mild neutrophilia [18]. G/GM-CSF, which is widely used to reduce the severity and duration of neutropenia from chemotherapy, usually causes leukocytosis. Drugs including trimethoprim-sulfamethoxazole, various antibiotics, and granulocyte colony stimulating factor can cause Sweet's Syndrome (acute febrile neutrophilic dermatosis), which is characterised by sensitive erythematous skin lesions, fever and neutrophilia [19]. This condition may be paraneoplastic or idiopathic.

❖ Eosinophilia

Eosinophilia can be caused by both intrinsic hematologic disorders as well as secondary to a variety of systemic disorders including allergens and drugs [20]. Drugs most commonly linked with eosinophilia are gold salts, penicillins, sulfas, allopurinol, phenytoin and carbamazepine. 'Drug Rash with Eosinophilia' and 'Systemic Symptoms (DRESS syndrome)' is the term used to describe the concomitant occurrence of eosinophilia, rash, fever and visceral involvement such as pneumonitis, hepatitis, nephritis, adenopathy or carditis [21]. Antibiotics and anticonvulsants are mostly linked with DRESS.

❖ Polycythemia

Smoking, prolonged hypoxia, malignancies, few medications can cause polycythemia, which can either be primary (polycythemia vera) or secondary. With excessive usage of rHuEPO or anabolic steroids, drug-induced polycythemia might be seen. Abusing of such type of drugs by athletes can cause higher risk of thrombosis [22]. The use of diuretics in conjunction with volume contraction can cause pseudopolycythemia, in which hemoconcentration elevates the hematocrit but real red blood cell's mass is not increased.

❖ Myelodysplasia and Acute Leukemia

Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDSs) are clonal hematopoietic disorders linked with cytopenias, impaired bone marrow maturation and eventually uncontrolled blast proliferation. Although the two disorders are different from one another, they share a continuous spectrum and many instances of MDS progress into AML. The vast majority of MDS and AML cases are idiopathic; however radiation and toxin exposure can increase the risk. MDS can be drug induced [23, 24]. MDS most commonly caused by alkylating agents, which include nitrogen mustard, cyclophosphamide, melphalan, busuflan and chlorambucil. Myelodysplasia and leukaemia are also linked with procarbazine and nitrosoureas. Myelodysplastic condition frequently precedes leukaemia caused by these drugs. Prior to the development of t-MDS or AML, there may be a latent phase of 2 to 8 years. The morphological subtypes of these leukemias are generally FAB M1 or M2. Complex chromosomal abnormalities are usual, frequently with deletions of trisomy 8 and chromosomes 5 and 7. Topoisomerase II inhibitors, which include the epipodophyllotoxins (etoposide and teniposide), anthracyclines (daunomycin, epirubicin, and doxorubicin) and mitoxantrone are linked to a specific syndrome of secondary leukaemia. Leukemia caused by these drugs typically manifests without a preceding MDS and has a shorter latency period than leukaemia caused by alkylating agents, frequently less than 2 years. Morphologically, acute myelomonocytic leukemias with a karyotypic anomaly involving 11q23 are frequently found. In patients receiving adjuvant chemotherapy for breast cancer, the risk of acute leukemia increases with age, with the intensity of therapy and with the use of breast radiotherapy [25]. Many of these patients have received in combination of alkylating agents and anthracyclines, both of these are leukemogenic. According to some studies, an increased risk of AML has been seen in breast cancer patients who received G-CSF along with adjuvant chemotherapy. Secondary MDS and leukaemia risk are related to stem cell transplantation, which is used in high risk, relapsed and refractory hematologic malignancies. It is still unclear that either pre transplant treatment or the transplant itself caused the condition. Radioimmunotherapy, developed for non-Hodgkins lymphoma, may be

associated with some risk of leukemogenesis. However, as with transplant patients, some of the risk may be related to stem cell damage from prior therapies or even an increased risk associated with the underlying disease itself. Small numbers of patients treated with radioimmunotherapy alone have demonstrated an apparent low risk for leukemia [26].

❖ **Hemolytic Anaemia**

Hemolytic anaemia is described as the destruction of RBC, including cell membrane lysis and the removal of blood cells by phagocytosis [10]. The severity and morbidity of hemolytic anaemia will be determined by the induction mechanism. The two fundamental mechanisms are -

1) A direct influence on the red blood cell's metabolic process (G_6PD deficiency)
Example - Dapsone, nalidixic acid, vitamin C, aspirin etc
2) An immunological mechanism involving both red blood cells and the drug.
Example - Cimetidine, insulin, penicillin, sulphonamides etc.

Hemolytic anaemia is of two types: immune hemolytic anaemia and nonimmune hemolytic anaemia. According to a study conducted by George Garratty, it is reported that one in every one million of the population have immune hemolytic anaemia and one in every eighty thousands of the population have autoimmune hemolytic anaemia. [11, 27]

• **Immune Hemolytic Anaemia (IHA)**

In immune hemolytic anaemia red blood cells are destroyed by antibodies that acting against antigens on the erythrocyte membrane. IHA may be idiopathic or secondary related to infections, autoimmune diseases, lymphoproliferative disorders or drugs. IHA is mediated by either IgG or IgM antibodies. Patients have increased LDH, anaemia, reticulocytosis, indirect hyperbilirubinemia and positive Coombs test when they first appear. Drug-dependent or drug-independent antibodies may be linked to drug-induced IHA [28]. Few drugs may cause nonimmunologic protein adsorption into drug treated red blood cells. Alpha-methyl DOPA is an example of a drug independent autoantibody that allows IHA to continue for a long time even after the drug is withdrawn. Cephalosporins, nonsteroidal anti-inflammatory drugs (NSAIDS), levaquin, oxaliplatin, teicoplanin have a link to

cause IHA [28, 29]. Intravenous Rh (D) immune globulin, which is used to treat immune thrombocytopenic purpura in non-splenectomized Rh (D) positive patients, intentionally induces a mild hemolysis. However, severe hemolysis with renal failure, disseminated intravascular coagulation and mortality have been reported in rare number of cases [30]. The autoimmune hemolytic anaemia linked with chronic lymphocytic leukaemia has been found to be precipitated or exacerbated by fludarabine, a purine nucleoside chemotherapeutic drug. However, combining fludarabine with rituximab and cyclophosphamide may reduce the risk [31].

• **Nonimmune Hemolytic Anaemia**

Glucose-6-phosphate dehydrogenase (G_6PD) deficiency is the most common cause of red blood cell enzymopathy, which is linked with nonimmune hemolytic anaemia. Infection, fava beans and drugs all have the potential to cause this hemolysis. Inherited mutation and the associated degree of deficiency are dependent by the sensitivity of various drugs. In generally, drug induced hemolysis is self-limited. Being X-linked, this affects men more frequently and severely. Numerous drugs have been linked to hemolysis including primaquine, phenazopyridine, nitrofurantoin, sulfonamide [32]. Ribavirin has been linked to anaemia when administered in combination with peginterferon to treat hepatitis C. Through oxidative membrane damage, ribavirin accumulates inside red blood cells, depletes ATP and promotes hemolysis. Ribavirin should be stopped or prefer low dose to treat anaemia, but such strategies may compromise the efficacy of the antiviral therapy. According to a study, erythropoietin can help to control anaemia [33].

❖ **Megaloblastic Anaemia**

Megaloblastic anaemia is defined by the presence of a hypercellular bone marrow with large, abnormal hematopoetic progenitor cells (megaloblasts). Megaloblastic anaemia can be congenital or acquired. Thrombocytopenia and leukopenia occur in this anaemia. When DNA synthesis in the bone marrow is inhibited but RNA synthesis continues, then megaloblastic anaemia develops. In this anaemic condition, development of defective macrocytic red blood cells occur [27]. Drugs can cause megaloblastic anaemia in two ways:

i. By preventing the absorption of B_{12} (cobalamin) or folic acid and

ii. By directly reducing DNA synthesis without depleting folate or vitamin B_{12}.

Drugs that interfere with DNA synthesis (such as antimetabolites, alkylating drugs, and few antinucleosides) are used to treat HIV and other viruses [34]. In methotrexate therapy, 3 to 9% of patients develop megaloblastic anaemia, which is caused by the irreversible suppression of the dihydrofolate reductase enzyme [35]. Methotrexate causes megaloblastic anaemia in a dose-dependent manner and when large intravenous dosages are given, calcium leucovorin should be used. If cotrimoxazole is given in low or high dosage, patients with vitamin B_{12} deficiency are more likely to develop megaloblastic anaemia [35, 36]. In cotrimoxazole induced megaloblastic anaemia, a trial dose of folic acid of 5 to 10 mg four times a day is given. Megaloblastic anaemia is also linked with trimethoprim (in high, prolonged dosages) and pyrimethamine, which bind with greater affinity to bacterial than human dihydrofolate reductase. This association mostly seen in individuals who are already at risk for folic acid deficiency. Folate-related alterations that cause megaloblastic anaemia have been associated to antibiotics like sulfasalazine and anticonvulsants like phenytoin, perhaps due to problems with absorption. Decreased cobalamin levels have been reported with long-term usage of histamine 2-receptor antagonists and proton pump inhibitors (such as omeprazole) [37, 38]. These drugs may reduce the absorption of B_{12} that is bound to proteins, but clinically significant B_{12} deficiency seems to be uncommon despite their widespread use. If chemotherapy causes drug-induced megaloblastic anaemia, then it is considered as a side effect. Folate supplements are used to treat megaloblastic anaemia caused by anticonvulsant drugs [10].

❖ **Thrombocytopenia**

Thrombocytopenia is defined as a drop in platelet count below 150 x 10^9/L, although signs and symptoms of hemorrhage (bleeding) are rare, until the count drops below 100 x 10^9/L [39]. Drug-induced thrombocytopenia has an incidence rate of 10-18 occurrences per million [40]. Selective bone marrow suppression and immunological mechanism in which platelet agglutination is caused by antibody formation are associated with drug-induced thrombocytopenia [41, 42]. Thrombocytopenia can be caused by drugs such as thiazide diuretics within 7 to 10 days of using them. Because platelet precursors are more

susceptible to cytotoxic drugs than other stem cells. Immune-mediated thrombocytopenia is characterised by an IgG-mediated response. Several mechanisms for the development of this form of thrombocytopenia have been proposed, some of them are listed below –

i. Hapten induced immune thrombocytopenia
Example - Penicillin, cephalosporin
ii. Drug depended antibody mechanism
Example - Quinine, anticonvulsants, NSAIDs

Vancomycin is also associated with thrombocytopenia and exhibit drug-dependent antibodies in the serum [43]. Patients with renal insufficiency may experience prolonged thrombocytopenia, which is most likely due to delay in drug clearance. Antimicrobials (sulfanomides, rifampin, linezolid), anti-inflammatory drugs, antineoplastics, antidepressants, benzodiazepines, anticonvulsants (carbamazepine, phenytoin, valproic acid), as well as cardio vascular and antihypertensive drugs are linked to immune thrombocytopenia [44, 45]. Heparin is well known to be associated with thrombocytopenia, sometimes with arterial or venous thrombosis, which, in most cases, poses a greater threat than the risk of bleeding [46, 47]. Antibodies against the complex of heparin and platelet factor 4 (PF4), can lead to activation of platelets and initiate thromboses are the cause of heparin-induced immune thrombocytopenia. Low molecular weight heparins are less frequently associated with heparin-induced thrombocytopenia than unfractionated heparins. For patients who have recently been exposed to heparin and still have PF4 antibodies, there is often a delay of 5 to 10 days. However, in patients who have previously been exposed to heparin and have developed an anamnestic response, thrombocytopenia can happen within hours or within a few days. Sometimes heparin-induced acute allergic responses, skin necrosis, and venous gangrene can happen. In the appropriate clinical setting, the diagnosis is supported by evidence of antiheparin antibodies, which can be detected by a number of assays. These include the more accurate functional tests (such as detecting C-14 serotonin platelet release in the presence of heparin and serum) and the more sensitive serologic assays (such as ELISA). In addition to discontinuing the use of heparin, treatment includes anticoagulation to lower the risk of thrombosis, usually start with argatroban, bivalrudin, or lepirudin initially, with transition to warfarin. Anticoagulation should be

continued for several weeks even after the platelet count returns to normal due to the high risk of thrombosis at that time. Abciximab (a chimeric Fab fragment), eptifibatide, and tirofiban (ligand mimetic inhibitors) are widely used in coronary angioplasty to reduce thrombosis by impairing platelet function through inhibiting the interaction between GP IIb/IIIa and fibrinogen. However, they can also cause severe thrombocytopenia in a small number of patients in addition to the intended platelet dysfunction, most likely via a drug-dependent antibody-mediated mechanism [48]. This can start at any time, within hours to days, and usually resolves spontaneously in 2–5 days. It could happen during the initial or subsequent infusions. Most of the patients recover without complications though sometimes severe bleeding may occur. If there is considerable bleeding, platelet transfusions may be given. Drugs which are associated to cause thrombocytopenia should be stopped and adequate platelet levels should be restored. Quick recovery can occur by the rapid elimination of these drugs from body. When the platelet count is dangerously low, platelet transfusion should be performed. If drug allergy is found, corticosteroids can be used. Aspirin and NSAIDs reduce platelet counts, thus these should be avoided. Quinine and heparin are two drugs worth highlighting. Quinine can be found in over-the-counter (OTC) drugs, tonic water, and soft drinks. When anticoagulants are required, an alternative to heparin, such as snake venom or prostacyclin, should be used.

❖ **Methemoglobinemia**

Methemoglobinemia is a hematological disorder, which is characterised by abnormal formation of methemoglobin (MetHb), which causes impairment in the transport of oxygen and prevents the release of oxygen effectively to body tissues. MetHb is formed when hemoglobin or reactive oxygen species are deoxygenated (ROS). The superoxide or peroxides change the state of iron in the heme group from ferrous (Fe_2+) to ferric (Fe_3+) through oxidization. The normal levels of MetHb values in adults should be in between < 0.14 - 0.175 gm/dl and 0.12 - 0.153 gm/dl [36, 39]. MetHb levels in methemoglobinemia are greater than 1% of Hb levels in the blood [34-38]. Methemoglobinemia is a rare inherited gene mutation that can be induced by specific foods or drugs. Methemoglobinemia can be acquired or congenital (caused by defects in the enzymatic degradation of haemoglobin). Anoxia, cyanosis,

low oxygen saturation and chocolate-brown color arterial blood are the initial symptoms seen in most of the patients. Oxidizing drugs or metabolically activated oxidizing agents (such as nitroglycerin, dapsone, sulphonamides, primacine, phenytoin, phenacetin, and prilocaine) cause acquired methemoglobinemia. Oxidative hemolysis can be induced by phenazopyridine, a drug used to treat cystitis [49]. Dapsone is used to treat leprosy, dermatitis herpetiformis and as a prophylacxis of pneumocystis carinii, is converted to a hydroxylamine derivative [50]. According to a recent study, this is the most frequent reason for methemoglobinemia [51]. Methemoglobinemia can be induced by primaquine and local anaesthetics such as topical or spray benzocaine (used prior to upper endoscopic procedures) and prilocaine [52, 53]. Amyl nitrite and isobutyl nitrite have been implicated also [54]. It is most common in those who drink untreated water with high levels of nitrate and nitrite [55, 56]. Acquired methemoglobinemia is a serious condition that can develop to severe consequences such as hemolytic anaemia, which can be fatal. Methylene blue solution and supplementary oxygen are routinely used to treat methemoglobinemia because of its rapid action. Methylene blue is not recommended as a treatment option for G_6PD deficiency patients, as it causes methemoglobinemia and increases hemolysis [57]. The offending drugs, inducing substances or causative agents of methemoglobinemia must be stopped and replaced with 1 to 2 mg/kg of 1% methylene blue solution given intravenously for at least 20 minutes. Supplemental oxygen is very much effective for asymptomatic patients [58]. Confirmational diagnosis is done by the measurement of methemoglobin on arterial blood gas sampling.

❖ **Sideroblastic Anaemia**

Sideroblastic anaemia is a group of disorders characterized by the presence of ringed sideroblast (erythroblasts contain iron-positive granules surrounding the nucleus) in the bone marrow, exhibit impaired heme biosynthesis in erythroid progenitors. Sideroblastic anaemia is a kind of anaemia that can be inherited or acquired. The inherited mechanisms of transmission include X linked, autosomal dominant or autosomal recessive. When compared to inherited types, acquired sideroblastic anaemia is more prevalent. Some persons can develop sideroblastic anaemia as a result of alcohol addiction [58]. Chemotherapy-induced myelodysplasias and secondary acute

leukemias can cause sideroblastic anaemia [59]. Linezolid, a drug used to treat respiratory problems and skin infections, has been linked to mitochondrial toxicity. When it suppresses the synthesis of mitochondrial proteins, it binds to mitochondrial ribosomes [60]. Isoniazid, chloramphenicol, penicillamine, busulfan, triethylenetetramine dihydrochloride (a chelating agent used to treat Wilson's disease) and few drugs cause reversible sideroblastic anaemia [61, 62]. Pyridoxine can be used to treat reversible drug-induced sideroblastic anaemia caused by isoniazid and penicillamine [63]. Discontinuation of these offending drugs is the primary treatment option for this anaemia [64].

❖ **Pure Red Cell Aplasia (PRCA)**
Pure red cell aplasia is defined as normocytic anaemia, reticulocytopenia (abnormal decrease of reticulocytes) and erythroblastopenia (bone marrow fails to make red blood cells) in the bone marrow [65]. It can be inherited or acquired. The drug's mechanism may involve one or more of the following: -
i.   Drug's interference with nucleated red cell metabolism ,
iii.   Immune-mediated responses, including antibody production against red cell precursors ,
iv.   DNA synthesis inhibition [66].

When compared to aplastic anaemia, pure red cell aplasia has comparatively normal leukocyte and platelet counts. Pure red cell aplasia may develop together with a thymoma, lymphoid malignancy, parvovirus, rheumatoid arthritis, pregnancy. Malnutrition, autoimmune diseases, drugs including immunosuppressants (azathioprine, FK506, antithymocyte globulin), antibacterials (linezolide, isoniazid, rifampin, chloramphenicol), antivirals (interferon-alpha, lamivudine, zidovudine), fludarabine, anticonvulsants (diphenyldrantoin, carbamazepine, valporic acid), as well as chloroquine, allopurinol, ribavirin, gold salts and infections like mononucleosis, viral hepatitis, parvovirus B_{19} and tuberculosis are the most common causes of acquired pure red cell aplasia [67,68,69]. Pure red cell aplasia is an acute self-limiting and can be idiopathic or secondary condition. Pure red cell aplasia and cholestatic liver damage are both life-threatening side effects linked with dapsone therapy. Pure red cell aplasia has been reported to develop after prolonged exposure to recombinant human erythropoietin (rHuEPO), particularly the brand Eprex, which is mostly used in Europe [70–73]. Patients became anti-EPO

antibody negative and transfusion independent after rHuEPO withdrawal and several months of immunosuppressive therapy (cyclosporine A). Subcutaneous injection can cause pure red cell aplasia in renal failing patients. Corticosteroid in the form of oral prednisone is used as a treatment option for pure red cell aplasia. Corticosteroid helps the bone marrow make more red blood cells. If corticosteroid will be successful in treating the disease, it will be apparent during the first 2 -4 weeks of treatment (the number of red blood cells will increase over this time).

❖ **Thrombotic Microangiopathies**
Microangiopathic hemolytic anaemia, thrombocytopenia and signs of microvascular occlusion are the symptoms of thrombotic microangiopathies. It is caused by excess platelet aggregation. Low levels of the metalloprotease ADAMTS13, which causes the cleavage of von Willebrand factor (vWF), have been often linked with thrombotic microangiopathies. Two main thrombotic microangiopathies are hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). Thrombotic microangiopathies can be developed as a result of toxins, pregnancy, infections (including HIV, Shigella and E. coli), drugs or idiopathic causes. Drug-induced thrombotic microangiopathies have a long history, although its mechanism is not fully understandable [74–77]. Immune-mediated or direct toxicity causing factors are mostly proposed. Autoantibodies to the ADAMTS13 protease are found in some individuals with drug-induced thrombotic microangiopathies. Thrombotic microangiopathies incidence appears to be dose-dependent in few patients, and in many cases, there are no "hints" of a mechanism at all. A drug named immunosuppressant cyclosporine A (CyA) is frequently blamed for causing thrombotic microangiopathies. Patients receiving treatment for rheumatoid arthritis and uveitis are also frequently found with CyA-induced thrombotic microangiopathies. This condition is associated with the mechanism of Dose-related toxicity. Once CyA treatment is reduced or discontinued, thrombotic microangiopathy often goes away. The chemotherapy treatments mitomycin-C, gemcitabine, and cisplatin as well as α-interferon and tacrolimus are associated with thrombotic microangiopathies [74–76]. It could be challenging to distinguish between drug-induced thrombotic microangiopathies from anaemia, thrombocytopenia and microangiopathy associated

with carcinomatosis in patients with metastatic adenocarcinoma. There is evidence that mitomycin-C; a well-recognized nephrotoxin, causes thrombotic microangiopathies by a dose-dependent direct toxic action on endothelium. Thrombotic microangiopathies have also been linked to the thienopyridines, ticlopidine (an antiaggregating agent) and less commonly clopidogrel [77]. Ticlopidine-related TPA is more likely to develop after 2 two weeks of therapy, to be linked with low ADAMTS13 levels with demonstrable auto-antibodies and to benefit from plasma exchange therapy. Clopidogrel-induced thrombotic microangiopathy tends to occur within the first two weeks of therapy, is less frequently accompanied by low ADAMTS13 levels and auto-antibodies, and is less likely to benefit from plasma exchange. Quinine can also cause thrombotic microangiopathy through immune-mediated mechanism. Antibodies against lymphocytes, granulocytes, endothelial cells and quinine-dependent antibodies such as IgG or IgM reactive with platelet glycoprotein Ib/IX or IIb/IIIa have been discovered in patients with quinine induced thrombotic microangiopathy. Plasma exchange and quinine withdrawal are often effective treatments for thrombotic microangiopathy [78].

❖ **Platelet Dysfunction**
Patients with prolonged bleeding times but having normal platelet counts may have the disorders of platelet function. While it is frequently the intended outcome of some drugs (such as aspirin, clopidogrel, and anti-GP IIb/IIIa inhibitors), causing platelet dysfunction to decrease the risk of thrombosis may also be an undesired side effect [79]. When cyclooxygenase-1 (COX-1) is acetylated, this cause impaired biosynthesis of thromboxane A2 (an essential platelet agonist). Aspirin irreversibly acetylates COX-1, causing its effect persists even when the drug is no longer in circulation. In contrast, nonselective nonsteroidal anti-inflammatory drugs reversibly acetylate COX-1 in order to reduce inflammation. There is some evidence that aspirin affects platelet aggregation in a dose-dependent manner [80]. By inhibiting serotonin uptake, fluoxetine and several tricyclic antidepressants cause malfunction. High dosage pencillins and other β-lactam antibiotics, chemotherapeutic agents (like mithramycin and daunorubicin), immunosuppressants and phenothiazines are some of drugs that can prevent platelet adhesion or aggregation [79].

❖ **Hypercoagulability**
Hypercoagulability can exist, with a tendency for both arterial and venous thrombosis. It can be acquired or inherited. Factor V Leiden, prothrombin G20210A mutation and deficits in the proteins C, S or antithrombin III are few examples of hereditary thrombophilic disorders. Acquired hypercoagulable states can be caused by surgery, trauma, pregnancy, antiphospholipid syndrome, cancer, and drugs. In addition to being widely used as analgesics and anti-inflammatory medications, selective COX-2 inhibitors were also being studied for their potential ability to lower the risk of polyps and colorectal cancer. Selective COX-2 inhibitors have less potential for bleeding and gastrointestinal toxicity than traditional COX inhibitors. However, multiple investigations revealed that celecoxib, rofecoxib, and valdecoxib are linked to an increase in thrombotic cardiovascular events. [81–83] These findings prompted the voluntary removal of rofecoxib from the global market and focused intense scrutiny on pharmaceutical and FDA regulations. Erythropoietin has been linked to an increased risk of thrombosis. While erythropoietin targets hemoglobin levels and significantly improves anaemia caused by renal failure, then it can increase cardiovascular morbidity and mortality [84]. Questions have also been raised about the safety and efficacy of erythropoietin in cancer patients, because some studies indicating an increased risk of mortality and thrombotic risk in erythropoietin treated patients [85]. Guidelines for the safer and more constrained use of these agents in cancer patients are being updated. Hormone replacement therapies including oral contraceptives, tamoxifen (a selective estrogen receptor modulator with some agonist activity) are linked to an increased risk of thrombosis. Use of oral contraceptives (mainly some types of associated progestin), risk of arterial and venous thrombosis may increase with age, inherited thrombophilias and smoking [86]. According to the Women's Health Initiative study, using estrogen and progestin together can cause more than double the risk of venous thrombosis as compared to placebo control [87]. Raloxifene was discovered to have a lower risk of thrombosis and uterine cancer than tamoxifen for the chemoprevention of breast cancer, suggesting that it may be a safer medication in this situation [88]. Similar to tamoxifen, aromatase inhibitors such asanastrazole, letrozole, or exemestane show a reduced risk of thrombosis than tamoxifen when used to treat early or advanced breast cancer [89]. Adjuvant

chemotherapy for breast cancer with CMF (cyclophosphamide, methotrexate, and fluorouracil) is also related to hypercoagulability [90-92]. Protein levels inhibitors C and S may be lower in patients receiving CMF [90]. This decreased production of antithrombin III, protein C and S increases the risk of thrombosis. When used with glucocorticoids, the multiple myeloma medications (thalidomide and lenalidomide) have been linked to an increased risk of thrombosis [96]. Asparaginase, a medication used to treat acute lymphoblastic leukaemia, has been linked to thrombotic problems [93-95]. It is possible to develop arterial and venous thromboses, including cerebral venous sinuses. By hydrolyzing the necessary amino acid asparagine, L-asparaginase prevents protein synthesis. It is recommended to use aspirin, warfarin and heparin as preventative measures. The use of a less intensive once-weekly dexamethasone schedule decreases the thrombotic risk in comparison with the standard 4-day high dose plan in combination with lenalidomide [96]. Skin necrosis may be a side effect of drugs like warfarin or heparin that cause thrombosis. Pre-existing thrombophilic disorders including protein C, S, or antithrombin III deficiency are frequently linked to warfarin-induced skin necrosis [97]. Therapy includes warfarin withdrawal, vitamin K administration and anticoagulation with heparin. However, heparin can also cause skin necrosis, which may be a symptom of the condition of heparin-induced thrombocytopenia [98]. A monoclonal antibody against vascular endothelial growth factor called bevacizumab, which is used to treat metastatic breast, lung, and colon cancers, has been linked to an increased risk of arterial thrombosis, especially in elderly people who are already predisposed to cardiovascular problems [99].

❖ Circulating Anticoagulants
Circulating anticoagulants causes excessive bleeding and inhibit clotting factors from their normal working. Acquired inhibitors of factor VIII are an example of an autoantibody that can be idiopathic or secondary to genetic hemophilia, the postpartum condition, other autoimmune illnesses, cancer, or drugs. Patients with an acquired haemophilia syndrome appear with bleeding who have low F VIII: c levels and demonstrable F VIII inhibitors. Involved drugs include fludarabine, interferon, psychotropics and antibiotics [100]. Antibody activity resolves with cessation of the drug or with the use of immunosuppressive drugs.

Isoniazid has been linked to an acquired inhibitor of factor XIII, which crosslinks and stabilises fibrin [101]. Drugs like chlorpromazine, hydralazine, phenytoin, quinine, and procainamide may cause lupus anticoagulants and antiphospholipid antibodies [102, 103]. In these cases, hypercoagulability is associated rather than hemorrhage.

❖ Hypoprothrombinemia
The most frequent causes of hypoprothrombinemia with prolonged PT/INR are liver illness or vitamin K insufficiency. Broad spectrum antibiotics are associated with hypoprothrombinemia, mainly in individuals who are also malnourished. Sulfonamides, ampicillin, chloramphenicol, tetracyclines, and cefoxitin all are related to the lack of vitamin K-dependent clotting factors [104]. Even though these are no longer widely used, cephalosporins, particularly which contains the N-methyl-thiotetrazole (NMTT) side chain (such as moxalactam and cefoperazone), may be linked to hypoprothrombinemia [105]. However, it is evident that several drugs including antibiotics (notably quinolones, macrolides, and azoles) modify the pharmacokinetics or dynamics of Coumadin (warfarin) while others increase bleeding risk through their own processes (e.g., aspirin, heparin, ticlopidine, and NSAIDs). Before giving such drugs to patients on warfarin, careful monitoring and dosage modifications are required.

II. CONCLUSION
The broad ranges of drug-induced hematological disorders are mediated by a number of mechanisms including immunological effects, interactions with enzyme pathways and direct suppression of hematopoiesis. Aplastic anaemia, megaloblastic anaemia, and haemolytic anaemia are the most frequent drug-induced anemias. Drug-induced anaemia can be caused by either direct immunological response, or drug toxicity. The elimination or withdrawal of the causative drugs is the primary therapy of drug-induced anaemia. As medicines develops, older drugs are no longer used and replaced by the newer formulation of drugs such as penicillin, quinidine, gold and chloramphenicol are becoming absolute. On the other hand, clopidogrel, linezolid, ribavirin and GPIIP/IIIa inhibitors are few newer drugs that have been linked to hematological side effects. Drug induced hematological disorders must be understood by medical professionals for the

occurrence and treatment of these events to the patients.

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