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Review Article

Overview on Drugs Causing Anemia

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Abstract

Some drugs can induce anemia by different mechanisms, and some different mechanisms are still a hypothesis needs to be studied. Anti-malaria drugs and some antibiotics can cause hemolysis by different mechanisms. There are several hypotheses for the potential cause of hemolysis following these treatment. Bone marrow suppression and anemia are frequent side effects of Zidovudine, an antiretroviral drug used to treat acquired immunodeficiency syndrome (AIDS). Hepatitis C Virus (HCV) drugs may cause reductions in hemoglobin (Hb) level due to hemolysis and suppression of hematopoiesis, increase rates of Sustained Virological Response (SVR) and severe pancytopenia and aplastic anemia with some regimen of advanced liver disease. Other drugs may also induce anemia like ACE Inhibitors, Phenytoin, and Proton-pump inhibitor. The treatment of drug-induced anemia will depend on the condition of the patient and the responsible drug should be stopped or adjustment of the dose.

Keywords: *Anemia; Anti-HCV; Anti-HIV; Antimalarial Drugs; Antibiotic; Proton Pump Inhibitor*

Introduction

Drug-induced immune hemolytic anemia occurs rarely (1 in 1 million population). This finding shows a sudden reduction of hemoglobin (Hb) after treatment with the supposed drug [1]. Hemolytic anemia induced by the drug (DIHA) is often needed to provide the optimal serological tests to verify the diagnosis. Cefotetan, ceftriaxone, and piperacillin are the most frequently drugs associated with DIIHA. This type of anemia is most commonly assigned to drug-dependent antibodies that can only be found in the presence of drug (e.g. cephalosporin antibodies). DIIHA can also be associated with antibodies which are drug-independent; such antibodies do not need the presence of the drug to obtain reactions *in vitro* (e.g. fludarabine).

Drug induced hemolytic anemia produce RBCs autoantibodies that affect the immune system; these findings clinical and laboratory are similar to autoimmune hemolytic anemia (AIHA), other than the remission associated with stop of the drug.

Some of the DIIHA mechanisms are debatable. The most appropriate mechanism includes the drug, like penicillin, that binds to protein covalently and the RBCs become covered with the drug *in vivo* and the drug IgG antibody adhere to the drug-covered RBCs and consequently removed by macrophages. The immune complex mechanism, suggest that most drugs are able to bind to RBC membrane proteins. The RBCs combined membrane and the drug can be immunogenic; the IgM or IgG antibodies formed can usually activate the complement, resulting in acute intravascular lysis and sometimes renal failure; mortality are more common in such group. The cause why and how some drugs induce RBC autoantibodies, sometimes causing AIHA is still unknown.

Aim of the Study

The aim of this review is to overview some drugs that can cause anemia, their therapeutic uses, their correlation with anemia and lastly how to treat theses anemias.

Drugs Causing Anemia

Anti-Malarial Drugs

Sulfadoxine-Pyrimethamine, Chlorproguanil-dapsone (CD), Mefloquine (MQ)

Therapeutic uses

It's a part of intermittent propable treatment of Malaria in Infants. Preventive intermittent treatment in infants is a complete therapeutic program of antimalarial medicine given to infants through routine immunization, regardless of whether the child is infected with malaria [1].

Correlation with anemia

It has been linked to hemolysis in symptomatic Glucose-6-phosphate dehydrogenase deficient (G6PDd) children. Few studies have explored the effects of G6PD status on hemolysis in children treated with intermittent preventive treatment in infants (IPTi) antimalarial regimens

Artemisinin-Based Combination (ACTs)

Therapeutic uses

Derivatives of Artemisinin are the main antimalarial treatment, both for simple and severe malaria. Artemisinin has rapid onset of action, good tolerability, and safety [2].

The artemisinin class of antimalarials following the spread of drug resistance in Plasmodium Falciparum isolates to previously used first-line drugs. Artemisinin were demonstrated to show unparalleled rapid parasite clearance, excellent tolerability, and were assumed to be exceptionally safe in the treatment of malaria [2]. Due to a high rate of recrudescence when used as monotherapy, the use of artemisinin has been recommended in combination with partner drugs for the treatment of uncomplicated malaria, in the form of Artemisinin combination therapies (ACT). Artesunate, artemether, and dihydroartemisinin became the most widely employed oral artemisinin derivatives used in ACT.

The intravenous administration of artesunate - a water-soluble artemisinin derivative readily hydrolyzed to the active metabolite dihydroartemisinin - was demonstrated to lead to improved survival rates compared to standard quinine therapy for severe P. Falciparum malaria.

Correlation with anemia

Hemolysis associated with the use of Artemisinin derivatives was therefore defined as the onset of hemolysis evidenced by a decrease in hemoglobin and an increase in lactate dehydrogenase (LDH) after the complete clearance of asexual parasitemia from peripheral blood [3]. The onset and duration of hemolysis after the administration of Artemisinin derivatives was categorized into the two main patterns of 'delayed' and 'persistent' hemolysis, two distinct patterns of hemolysis after the use of Artemisinin therapy have been described and classified. These encompass a delayed onset and a persistent pattern of hemolysis ('Delayed hemolysis' was defined as the occurrence of a decrease in haemoglobin associated with low haptoglobin or increased LDH at > 7 days following the initiation of Artemisinin treatment 'Persistent hemolysis' was defined as continuing hemolysis starting from or around day 7 of Artemisinin treatment and persisting beyond day 9% of the total patient population suffering from severe malaria and treated with Artemisinin derivatives required blood transfusions late hemolysis. late onset hemolysis has predominantly been described after the use of intravenous Artesunate. Increased reticulocyte counts during hemolysis contradict the hypothesis of direct bone marrow suppression by artemisinin drug [4].

Intravenous Artesunate

Therapeutic uses

The treatment of uncomplicated Plasmodium Falciparum malaria [5].

Correlation with anemia

It kills young circulating ring stage parasites before they sequester in the microcirculation, could explain the delayed hemolysis. This mechanism explains the rapid action of Artesunate [6]. Most of the killed ring stage parasites are cleared rapidly by the spleen by 'pitting' of erythrocytes whereby the dead parasite is removed from within the erythrocyte. These 'once infected' erythrocytes are returned to the circulation but they have a reduced lifespan of about 7 - 15 days. The delayed destruction of 'once infected' erythrocytes correspond with the time course of post-treatment delayed anemia seen clinically.

Oral Artemether and Lumefantrine

Therapeutic uses

The combination of Artemether and Lumefantrine is used to treat certain kinds of malaria. Artemether and Lumefantrine are not used for malaria prevention. It works by killing the organisms that cause malaria [7].

Correlation with anemia

They kill all erythrocytic stages of malaria parasites, including the ring stages and early schizonts which causing hemolytic anemia [8].

How to treat the anemia

Hemolytic anemia treatments include blood transfusion, medications, plasmapheresis, surgery, blood and marrow stem cell transplantation, and change the lifestyle. Patients with mild hemolytic anemia no treatment is needed, as long as the condition doesn't worsen. Severe hemolytic anemia can be fatal if it's not treated properly.

Hepatitis C Virus (HCV) drugs

Ribavirin (RBV)

Therapeutic uses

Ribavirin (RBV) is an antiviral nucleoside analog commonly used in combination with interferon for the treatment of chronic hepatitis C [9].

Correlation with anemia

Anemia is likely related to extensive RBV accumulation in erythrocytes subsequent to active unidirectional transmembrane transport. Toxicity of RBV is through the inhibition of intracellular energy metabolism and oxidative membrane damage, leading to an enhanced extravascular hemolysis by the reticuloendothelial system [10]. On the other hand, pronounced variability in the correlation between RBV concentration and Hb reduction limits the prediction of anemia based on plasma or erythrocyte concentrations in individual patients and points towards additional factors determining individual susceptibility to RBV-induced anemia. Recent studies suggest that erythrocyte oxidative defense mechanisms may play an important role in RBV-induced anemia.

Treatment of the anemia

Determination of RBV concentrations has little value in the management of anemia. The only proven effective prevention of RBV-induced anemia is the concomitant administration of erythropoietin. Future research on RBV pharmacokinetics as well as erythrocyte antioxidant defense mechanisms, may improve safety and efficacy of RBV therapy and guide the development of new treatments for RBV-induced anemia and alternative antiviral agents [11].

Telaprevir

Therapeutic uses

Telaprevir is the first direct-acting antivirals approved for chronic hepatitis C in combination with peg-interferon alfa and Ribavirin. Pancytopenia due to myelotoxicity caused by these drugs may occur.

Correlation with anemia

Severe pancytopenia and especially aplastic anemia, are not rare during triple therapy with Telaprevir in patients with the advanced liver disease. Close monitoring is imperative in this setting to promptly detect serious hematological disorders and to prevent further complications [12]. Addition of the new directly acting antivirals (DAAs), Telaprevir clearly improved sustained virological response

(SVR) rates in patients with chronic hepatitis C. However, also increased the risk of serious adverse events (SAEs). One of the most common adverse events associated with triple therapy compared to standard peg-interferon and Ribavirin (PR) regimens is anemia. Interferon-related bone marrow suppression and Ribavirin related hemolytic anemia are common and may lead to dose-reduction, especially in patients with baseline cytopenia. Interferon results in bone marrow suppression and Ribavirin lead to hemolysis, while PIs may cause direct bone marrow toxicity (as suggested in a few reports in the setting of HIV infection in patients with portal hypertension or advanced cirrhosis. Finally, the risk of hematological abnormalities could also be influenced by genetic factors.

Overall incidence of severe aplastic anemia is low, as it is estimated to occur in only 2 - 4 million people per year. Antibiotics, anti-inflammatory drugs, and anticonvulsants are among the currently licensed drugs which have been associated with aplastic anemia [13].

Treatment of the anemia

Early discontinuation of antiviral therapy after AA diagnosis. Supportive care with Granulocyte-colony stimulating factor (G-CSF) and blood and platelet transfusions was administered. One patient received cyclosporine [14].

Human immunodeficiency virus (HIV) antiretroviral drugs

Zidovudine

Therapeutic uses

Zidovudine is a reverse transcriptase inhibitor antiretroviral drug used to treat Human Immunodeficiency Virus (HIV). The combination with other Antiretroviral drugs has greater effect in decreasing HIV replication and elevating CD4 cells count [15].

Correlation with anemia

All types of blood cells are produced in the bone marrow; a drug that damages the bone marrow can cause shortages in all of these cells. Bone marrow suppression and anemia are frequent side effects of Zidovudine, an antiretroviral drug used to treat acquired immunodeficiency syndrome (AIDS) [19].

Treatment of the anemia

Conservative management of hematologic toxicity includes dosage reduction or cessation of therapy, diagnosis and treatment of chronic debilitating diseases, and supportive care, such as blood transfusions [16]. New investigational agents, including hematopoietic growth factors, are being studied to combat the toxicities associated with Zidovudine. The efficacy of these agents has yet to be established. Recent advances in drug efficacy at reduced dosage and in combination therapy promise to permit the use of Zidovudine with markedly reduced toxicity [17].

Antibiotics causing anemia

Penicillin

Therapeutic uses

It is an antibiotic that kills susceptible bacteria by specifically inhibiting the trans-peptidase that catalyze the final step in cell wall biosynthesis, the cross-linking of peptidoglycan [18].

Penicillin G is also used as a prophylaxis of recurrent rheumatic fever [19].

Correlation with anemia

The development of immune hemolytic anemia in patients receiving parenteral penicillin depends on Two factors: first, the coating of the patient's red cells with penicillin and second, the ability of the patient to synthesize large amounts of IgG penicillin antibody. The former will occur in most patients receiving 15 mega units a day or more [22].

Immune reaction: The antigen is a hapten-protein complex formed by penicillin combined covalently with proteins both on the red cell membrane and in the serum. The penicillin can react with red cell protein direct, possibly through the B-lactam ring. Penicillin-induced hemolytic anemia does not seem to occur in patients receiving low doses of penicillin [22].

Treatment of this anemia

The hemolysis will be ceased on stopping the drug, severe hemolysis requires blood transfusion. There is no reported beneficial effect from the corticosteroid [20].

Cephalosporin

Therapeutic uses

Cephalosporins have an important role in the treatment of infectious diseases. The third-generation cephalosporins have enhanced activity against gram-negative bacilli, as well as most other enteric organisms plus Serratia Marcescens [21]. Ceftriaxone is sometimes given before surgery to prevent infections that may develop after the operation [21].

Correlation with anemia

Cephalosporins are known to interact with the RBC membrane without causing hemolysis by modifying it and causing non-immunologic protein adsorption [22]. First generation Cephalosporins are thought to cause hemolysis by IgG adsorbing to the RBC membrane and activating complements which leads to hemolysis. Ceftriaxone appears to have a slightly different mechanism through an immune-complex reaction in which IgM antibodies are directed against Ceftriaxone and cause erythrocyte destruction through complement activation [22,23].

Treatment of this anemia

Stop the drug, and if the hemolysis is severe, immediate transfusion of RBCs is indicated. Corticosteroids can also be used to induce remission of antibody production, but this therapy has limited effect. Treatment with corticosteroids for severe warm-reactive autoimmune-hemolytic anemia include intravenous Methylprednisolone [23]. Plasmapheresis and intravenous immunoglobulin dosed at 1 gram per kilogram were also used successfully in one case. Intravenous immunoglobulin is a potent inhibitor of the reticuloendothelial system and therefore is thought to rid the body of the Ceftriaxone induced antibodies on RBCs.

Ethambutol

Therapeutic uses

Ethambutol is an antimycobacterial agent that is most commonly used in combination with other drugs in the treatment of tuberculosis. It is also used as part of a combination regimen in the therapy of Mycobacterium Avium complex (MAC) infections in patients with or without concomitant infection with human immunodeficiency virus (HIV) [24].

Correlation with anemia

Immunohaematological analysis confirmed diagnosis of drug-induced autoimmune hemolytic anemia (AIHA) induced by the presence of immunoglobulin G (G1) þ complement. At least four mechanisms may individually or collectively cause drug-induced immune-hemolytic anemia: self-absorption, modification of the membrane, immune complex, and immune system changes. It is thought that this immune complex (drug-antibody þ drug) may bind to red cells or activate complements that bind to red cells. For this reason, the RBCs will be 'innocent spectators' [25].

Treatment of this anemia

Stopping the drug that is causing the problem may relieve or control the symptoms. It may need to take prednisone to suppress the immune response against the red blood cells. Special blood transfusions may be needed to treat severe symptoms [23].

Other drugs

ACE Inhibitors

Therapeutic uses

The antihypertensive drugs Angiotensin-Converting Enzyme inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) are in wide use for treatment of hypertension [25]. This is due to their renoprotective and cardioprotective effects in patients with compelling diseases like diabetes mellitus (DM) and congestive heart failure (CHF) [26].

In clinical practice, ACEI/ARB drugs are used for many purposes, from prevention of proteinuria and progression to renal failure in diabetic patients, and as first-line treatment of hypertensive patients with concurrent CHF and DM, to decrease the progression of heart failure and enhance survival in CHF patients [26]. It was found that the use of ACEIs was associated with a decrease in Hgb levels, while the use of ARBs was not [27].

Correlation with anemia

ACEIs and ARBs mechanism of action and their effects on hemoglobin level is not well understood. ACEIs may interfere with the production of erythropoietin (EPO) [27]. ACEI related decrease in hemoglobin may affect the modulation of multiple factors interacting with erythroid marrow progenitors [26]. There is an association documented between ACEI treatments, decrease in Hgb and suppression of EPO production.

Angiotensin II increases proliferation of early erythroid progenitors but no effect on the progenitors of other cell lines and ARB completely abolishes this effect. These observations focus on a possible inhibitory effect of these drugs on bone marrow.

Phenytoin

Therapeutic uses

It reduces seizures by blocking voltage-gated channels (Na^+ or Ca^{2+}), interfering with excitatory glutamate transmission and enhancing inhibitory γ-aminobutyric acid (GABA)-ergic impulses. Some antiepilepsy drugs have multiple effects within the CNS, whereas the mechanism of action for some agents is poorly defined. Anti-epilepsy drugs suppress seizures but do not "cure" or "prevent" epilepsy [28].

Correlation with anemia

One of the hypotheses suggested that phenytoin elevates the pH of the small intestine and inhibits the intestinal conjugate activity impairing the intestinal absorption of floats. Other hypotheses involves direct competition between folate and phenytoin for uptake sites, inhibition of folate inter-converting enzymes, increased catabolism of floats and induction of folate catabolic enzymes and inhibition of central appetite centers by phenytoin thereby leading to decreased tissue folate concentrations [29].

Treatment of the anemia

The teratogenic effects of anticonvulsant drugs are explained by the decreased blood folate levels and have been to be prevented with folic acid supplementation during the peri-conceptional period. However, folate supplementation in phenytoin-treated patients, as in phenytoin-treated pregnant epileptic patients to prevent the risk of neural tube defects and other common teratogenic effects of anticonvulsant drugs, is also not considered to be safe because of the risk of precipitation of seizures in an otherwise stabilized epileptic patients [33]. There is also accumulating evidence that folic acid supplementation in peri-conceptional period might prevent other major birth defects including congenital heart disease, oro-facial clefts, and anomalies of the urinary tract. However, this is still controversial since there are also studies that do not show any correlation between folate fortification and the incidence of these birth defects [30].

Proton-pump inhibitor

Therapeutic uses

1. Gastroesophageal reflux disease.
2. Peptic ulcer disease.
3. Non-ulcer dyspepsia.
4. Prevention of stress-related mucosal bleeding.
5. Gastrinoma and other hypersecretory conditions [31].

Correlation with anemia

Acid suppression is of interest as a potential primary risk factor for iron deficiency, as a contributing risk factor and as an impediment to iron-replacement therapy [31].

Metabolism of iron *in vivo* is controlled by the hepcidinferroportin axis [32]. Iron absorption decreases when Hepcidin production is enhanced [32]. On the contrary, when Hepcidin production is decreased, such as patients with liver damage, the iron absorption rate rises inappropriately. Hence, even when iron absorption is inhibited by PPIs, the Hepcidin-Ferroportin system provides negative feedback, thereby enhancing iron absorption. Therefore, patients with iron-deficiency anemia caused by PPI use may have a problem somewhere in the Hepcidin-Ferroportin system.

Treatment of the anemia

In anemias caused by malabsorption, intravenous iron administration is recommended. Follow up of treated patients should be done regularly to evaluate the therapeutic response. Blood samples should be taken on a regular basis to check CBC, reticulocyte count as well as liver function test, serum iron, ferritin and transferrin saturation. Therapy should be stopped if any abnormality is seen in any of these parameters [33].

Conclusion

Drug-induced immune hemolytic anemia (DIIHA) is a rare condition that occurs primarily as a result of drug-induced antibodies and the diagnosis of DIIHA is often difficult because of the similarities with autoimmune hemolytic anemia and the inconstant sensitivity of immunologic tests that sometimes required repetitive assessment. A possible signal was detected for peginterferon alfa-2a, ribavirin and flu vaccine in the occurrence of autoimmune hemolytic anemia.

Patients with HIV are at risk of both primary and secondary hematological disorders. Many cases were reported of patients with HIV and cryptococcal meningitis who developed severe hemolytic anemia, thrombocytopenia, renal failure and lactic acidosis while on treatment with amphotericin B and co-trimoxazole.

Levels of Hb are reduced during the first year of use of ACEIs and to a lesser extent with use of ARBs. This association is dose dependent and is not explained by patient adherence.

High proportion of cardiovascular, particularly surgical patients with ischemic and valvular heart disease utilized proton pump inhibitor in prolonged courses. Prolonged courses of PPIs were connected with existence and worsening of red blood count indexes, older age, and lesser weight of patients and underutilization of cardioprotective drugs.

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Bibliography

1. Poirot E., *et al*. "Risks of Hemolysis in Glucose-6-Phosphate Dehydrogenase Deficient Infants Exposed to Chlorproguanil-Dapsone, Mefloquine and Sulfadoxine-Pyrimethamine as Part of Intermittent Presumptive Treatment of Malaria in Infants". *PLoS ONE* 10.11 (2015): e0142414.

2. Sinclair D., *et al*. "Artemisinin-based combination therapy for treating uncomplicated malaria". *Cochrane Database of Systematic Reviews* 3 (2009): CD007483.

3. Rolling T., *et al*. "Post-treatment haemolysis in severe imported malaria after intravenous artesunate: case report of three patients with hyperparasitaemia". *Malaria Journal* 11 (2012): 169.

4. Rehman K., *et al*. "Haemolysis associated with the treatment of malaria with artemisinin derivatives: a systematic review of current evidence". *International Journal of Infectious Diseases* 29 (2014): 268-273.

5. Sowunmi A., *et al*. "Anaemia following Artemisinin-Based Combination Treatments of Uncomplicated Plasmodium falciparum Malaria in Children: Temporal Patterns of Haematocrit and the Use of Uncomplicated Hyperparasitaemia as a Model for Evaluating Late-Appearing Anaemia". *Chemotherapy* 62.4 (2017): 231-238.

6. Ndour PA., *et al*. "Measuring the Plasmodium falciparum HRP2 protein in blood from artesunate-treated malaria patients predicts post-artesunate delayed hemolysis". *Science Translational Medicine* 9.397 (2017): eaaf9377.

7. White NJ., *et al*. "Clinical Pharmacokinetics and Pharmacodynamics of Artemether-Lumefantrine". *Clinical Pharmacokinetics* 37.2 (1999): 105-125.

8. Wernsdorfer WH. "Coartemether (artemether and lumefantrine): an oral antimalarial drug". *Expert Review of Anti-infective Therapy* 2.2 (2004): 181-196.

9. Stefan R., *et al*. "Ribavirin-Induced Anemia: Mechanisms, Risk Factors and Related Targets for Future Research". *Current Medicinal Chemistry* 13.27 (2006): 3351-3357.

10. Soota K and Maliakkal B. "Ribavirin induced hemolysis: A novel mechanism of action against chronic hepatitis C virus infection". *World Journal of Gastroenterology: WJG* 20.43 (2014): 16184-16190.

11. Poordad F., *et al*. "Effects of Ribavirin Dose Reduction vs Erythropoietin for Boceprevir-Related Anemia in Patients With Chronic Hepatitis C Virus Genotype 1 Infection Randomized Trial". *Gastroenterology* 145.5 (2014): 1035-1044.e5.

12. Lens S., *et al*. "Aplastic anemia and severe pancytopenia during treatment with peg-interferon, ribavirin and telaprevir for chronic hepatitis C". *World Journal of Gastroenterology: WJG* 21.17 (2015): 5421-5426.

13. Marsh JCW., *et al*. "Guidelines for the diagnosis and management of aplastic anaemia". *British Journal of Haematology* 147.1 (2009): 43-70.

14. De Zern AE and Brodsky RA. "Clinical management of aplastic anemia". *Expert Review of Hematology* 4.2 (2011): 221-230.

15. Staszewski S., *et al*. "Efavirenz plus Zidovudine and Lamivudine, Efavirenz plus Indinavir, and Indinavir plus Zidovudine and Lamivudine in the Treatment of HIV-1 Infection in Adults". *New England Journal of Medicine* 341.25 (1999): 1865-1873.

16. Fischl M., *et al*. "Recombinant Human Erythropoietin for Patients with AIDS Treated with Zidovudine". *New England Journal of Medicine* 322.21 (1990): 1488-1493.

17. Brogan KL and Zell SC. "Hematologic toxicity of zidovudine in HIV-infected patients". *American Family Physician* 41.5 (1990): 1521-1528.

18. Yocum RR., *et al*. "The mechanism of action of penicillin. Penicillin acylates the active site of Bacillus stearothermophilus D-alanine carboxypeptidase". *Journal of Biological Chemistry* 255.9 (1980): 3977-3986.

19. Diehl AM., *et al*. "Long-acting repository penicillin in prophylaxis of recurrent rheumatic fever". *Journal of the American Medical Association* 155.17 (1954): 1466-1470.

20. White JM., *et al*. "Penicillin induced Haemolytic Anaemia". *British Medical Journal* 3.5609 (1968): 26-29.

21. Paterson DL and Bonomo RA. "Extended-spectrum β-lactamases: a clinical update". *Clinical Microbiology Reviews* 18.4 (2005): 657-686.

22. Arndt P., *et al*. "Serology of antibodies to second-and third-generation cephalosporins associated with immune hemolytic anemia and/or positive direct antiglobulin tests". *Transfusion* 39.11-12 (1999): 1239-1246.

23. Garratty G. "Drug-induced immune hemolytic anemia". *Hematology. American Society of Hematology. Education Program* 1 (2009): 73-79.

24. Mikusova K., *et al*. "Biogenesis of the mycobacterial cell wall and the site of action of ethambutol". *Antimicrobial Agents and Chemotherapy* 39.11 (1995): 2484-2489.

25. Nicolini A., *et al*. "A rare adverse reaction to ethambutol: drug-induced haemolytic anaemia". *The International Journal of Tuberculosis and Lung Disease* 20.5 (2016): 704-705.

26. Ishani A., *et al*. "Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction". *Journal of the American College of Cardiology* 45.3 (2005): 391-399.

27. Ajmal A., *et al*. "Effect of angiotensin converting enzyme inhibitors and angiotensin receptor blockers on hemoglobin levels". *BMC Research Notes* 6 (2013): 443.

28. Boylan LS., *et al*. "Psychiatric uses of antiepileptic treatments". *Epilepsy and Behavior* 3.5 (2002): 54-59.

29. Blain H., *et al*. "Aplastic anemia induced by phenytoin: a geriatric case with severe folic acid deficiency". *Journal of the American Geriatrics Society* 50.2 (2002): 396-397.

30. Nayyar AS., *et al*. "Phenytoin-Folate Interactions: How Far is Safe Folate Supplementation in Phenytoin Treated Epileptic Patients". Journal of Applied Pharmaceutical Science 2.6 (2012): 230-235.

31. Dado DN., *et al*. "A Case of Severe Iron Deficiency Anemia Associated with Long-Term Proton Pump Inhibitor Use". *Current Therapeutic Research, Clinical and Experimental* 84 (2017): 1-3.

32. Ganz T and Nemeth E. "Hepcidin and Disorders of Iron Metabolism". *Annual Review of Medicine* 62.1 (2011): 347-60.

33. Qamar K., *et al*. "Malabsorption of iron as a cause of iron deficiency anemia in postmenopausal women". *Pakistan Journal of Medical Sciences* 31.2 (2015): 304-308.

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