

Association of the blood groups with mostly public Diseases

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Abstract

The ABO blood group system is identified in 1900. Its principle that antigens as sugars physically exposed on the exterior of red blood cells *RBCs* differ between individuals, who have immunological tolerance only toward what occurs in their own bodies. As a result, many humans express isoantibodies-antibodies against isoantigens, natural components present in the bodies of other members of the same species but not themselves. Isoantibodies may be present against the A and/or B antigens in people who do not themselves have the same antigens in their own blood. These antibodies act as haemagglutinins, which cause blood cells to clump and break apart if they carry the foreign antigens, because A and B antigens are chemically modified from a precursor form that is also present in type O individuals, people with type A and B antigens can accept blood from type O individuals; identification of ABO and Rh gene frequencies among human populations has various benefits in transfusion medicine, transplantation and disease risk. The food, bacterial, viral, or plant antigens have epitopes similar enough to A and B glycoprotein antigens lead to create antibodies in the first years of life, Anti-A antibodies are originate from immune response towards influenza virus, Anti-B antibodies are originate from antibodies produced against Gram-negative bacteria.

The ABO antigen is expressed on the von Willebrand factor (vWF) glycoprotein which participates in control of bleeding; individuals with group O predisposes to bleeding as 30% of the total genetic variation due to this group normally have significantly lower plasma levels of vWF (and Factor VIII) than other blood groups. The individuals with A1 AB, and B blood groups have a 14% reduced risk of squamous cell carcinoma; B antigen links with increased risk of ovarian cancer; type O blood is associated with a reduced risk of pancreatic cancer but increased risk of peptic ulcer and infection with cholera while gastric cancer has reported to be more common in blood group A especially in patient with *Helicobacter pylori* infection. The blood types A and AB are associated with an increased risk of nasopharyngeal carcinoma; in 2019, a recently evidence showed a higher risk for renal cell cancer was found in non-O blood group women, but not in men. . Many studies indicate the individuals with group A and B are less likely to have Diabetes Mellitus than group AB.

Introduction

1. ABO system

The ABO blood group system is widely credited to have been discovered by the Austrian scientist Karl Landsteiner, who identified the O, A, and B blood types in

1900 . Landsteiner originally described the O blood type as type "C", and in parts of Europe it is rendered as "0" (zero), signifying the lack of A or B antigen. Landsteiner was awarded the Nobel Prize in Physiology or Medicine in 1930 for his work (1) The central principle of the ABO system is that antigens – in this instance, sugars physically exposed on the exterior of red blood cells – differ between individuals, who have immunological tolerance only toward what occurs in their own bodies. As a result, many humans express isoantibodies – antibodies against isoantigens, natural components present in the bodies of other members of the same species but not themselves. Isoantibodies may be present against the A and/or B antigens in people who do not themselves have the same antigens in their own blood. These antibodies act as haemagglutinins, which cause blood cells to clump and break apart if they carry the foreign antigens, Because A and B antigens are chemically modified from a precursor form that is also present in type O individuals, people with type A and B antigens can accept blood from type O individuals; Anti-A and anti-B antibodies (called *isohaemagglutinins*), which are not present in the newborn, appear in the first years of life. Anti-A and anti-B antibodies are usually IgM type, which are not able to pass through the placenta to the fetal blood circulation. O-type individuals can produce IgG-type ABO antibodies (2). The precursor to the ABO blood group antigens, present in people of all common blood types, is called the H antigen. Individuals with the rare Bombay phenotype (*hh*) do not express antigen H on their red blood cells. As the H antigen serves as a precursor for producing A and B antigens, the absence of the H antigen means that the individuals also lack A or B antigens as well (similar to O blood group), , the H antigen is absent, hence the individuals produce isoantibodies to antigen H as well as to both A and B antigens. If they receive blood from someone with O blood group, the anti-H antibodies will bind to the H antigen on the red blood cells ('RBC') of the donor blood and destroy the RBCs by complement-mediated lysis. Therefore, people with Bombay phenotype can receive blood only from other *hh* donors (although they can donate as though they were type (O). Some individuals with the blood group A1 may also be able to produce anti-H antibodies due to the complete conversion of the entire H antigen to A1 antigen (3).

The production of the H antigen, or its deficiency in the Bombay phenotype, is controlled at the H locus on chromosome 19. The H locus is not the same gene as the ABO locus, but it is epistatic to the ABO locus, providing the substrate for the A and B alleles to modify. The H locus contains three exons that span more than 5 kb of genomic DNA, and encodes the fucosyltransferase that produces the H antigen on RBCs. The H antigen is a carbohydrate sequence with carbohydrates linked mainly to protein (with a minor fraction attached to ceramide moiety). It consists of a chain of β -D-galactose, β -D-N-acetylglucosamine, β -D-galactose, and 2-linked, α -L-fucose, the chain being attached to the protein or ceramide. The ABO locus, which is located on chromosome 9, contains seven exons that span more than 18 kb of genomic DNA.

Exon 7 is the largest and contains most of the coding sequence. The ABO locus has three main allelic forms: A, B, and O. The A allele encodes a *glycosyltransferase* that bonds α -N-acetylgalactosamine to the D-galactose end of the H antigen, producing the A antigen. The B allele encodes a *glycosyltransferase* that bonds α -D-galactose to the D-galactose end of the H antigen, creating the B antigen.

In the case of the O allele, when compared to the A allele, exon 6 lacks one nucleotide (guanine), which results in a loss of enzymatic activity. This difference, which occurs at position 261, causes a frameshift those results in the premature termination of the translation and, thus, degradation of the mRNA. This results in the H antigen remaining unchanged in the case of O groups (4).

1.2. Role of ABO antigens in transfusion medicine

The blood donor and recipient to be ABO-compatible for a transfusion, the recipient must not be able to produce Anti-A or Anti-B antibodies that correspond to the A or B antigens on the surface of the donor's red blood cells (since the red blood cells are isolated from whole blood before transfusion, it is unimportant whether the donor blood has antibodies in its plasma).

If the antibodies of the recipient's blood and the antigens on the donor's red blood cells do correspond, the donor blood is rejected. On rejection, the recipient may experience Acute hemolytic transfusion reaction (AHTR). In addition to the ABO system, the Rh blood group system can affect transfusion compatibility. An individual is either positive or negative for the Rh factor; this is denoted by a '+' or '-' after their ABO type. Blood that is Rh-negative can be transfused into a person who is Rh-positive, but an Rh-negative individual can create antibodies for Rh-positive RBCs.

Because of this, the AB+ blood type is referred to as the "universal recipient", as it possesses neither Anti-B nor Anti-A antibodies in its plasma, and can receive both Rh-positive and Rh-negative blood. Similarly, the O- blood type is called the "universal donor"; since its red blood cells have no A or B antigens and are Rh-negative, no other blood type will reject it.

Identification of ABO and Rh gene frequencies among human populations has various benefits in transfusion medicine, transplantation and disease risk (5)

Blood group inheritance by phenotype only

Blood type	O	A	B	AB
O	O	O or A	O or B	A or B
A	O or A	O or A	O, A, B or AB	A, B or AB

B	O or B	O, A, B or AB	O or B	A, B or AB
AB	A or B	A, B or AB	A, B or AB	A, B or AB

1.3. Subgroups

The A blood type contains about twenty subgroups, of which A1 and A2 are the most common (over 99%). A1 makes up about 80% of all A-type blood, with A2 making up almost all of the rest. These two subgroups are interchangeable as far as transfusion is concerned, but complications can sometimes arise in rare cases when typing the blood. With the development of DNA sequencing, it has been possible to identify a much larger number of alleles at the ABO locus, each of which can be categorized as A, B, or O in terms of the reaction to transfusion, but which can be distinguished by variations in the DNA sequence. There are six common alleles in white individuals of the ABO gene that produce one's blood type (6)

1.4. The origin theories

It is possible that food and environmental antigens (bacterial, viral, or plant antigens) have epitopes similar enough to A and B glycoprotein antigens. The antibodies created against these environmental antigens in the first years of life can cross-react with ABO-incompatible red blood cells that it comes in contact with during blood transfusion later in life. Anti-A antibodies are hypothesized to originate from immune response towards influenza virus, whose epitopes are similar enough to the α -D-N-galactosamine on the A glycoprotein to be able to elicit a cross-reaction. Anti-B antibodies are hypothesized to originate from antibodies produced against Gram-negative bacteria, such as *E. coli*, cross-reacting with the α -D-galactose on the B glycoprotein (7)

1.5. Bleeding and thrombosis (von Willebrand factor)

The ABO antigen is also expressed on the von Willebrand factor (vWF) glycoprotein which participates in hemostasis (control of bleeding). In fact, having type O blood predisposes to bleeding as 30% of the total genetic variation observed in

plasma vWF is explained by the effect of the ABO blood group, and individuals with group O blood normally have significantly lower plasma levels of vWF (and Factor VIII) than do non-O individuals. In addition, vWF is degraded more rapidly due to the higher prevalence of blood group O with the Cys1584 variant of vWF (an amino acid polymorphism in VWF the gene for ADAMTS13 (vWF-cleaving protease) maps to the ninth chromosome (9q34), the same locus as ABO blood type. Higher levels of vWF are more common amongst people who have had ischaemic stroke (from blood clotting) for the first time. The results of this study found that the occurrence was not affected by ADAMTS13 polymorphism, and the only significant genetic factor was the person's blood group (8)

1.6. Disease risks

Compared to O group individuals, non-O group (A, AB, and B) individuals have a 14% reduced risk of squamous cell carcinoma and 4% reduced risk of basal cell carcinoma. Conversely, type O blood is associated with a reduced risk of pancreatic cancer. The B antigen links with increased risk of ovarian cancer. Gastric cancer has reported to be more common in blood group A and least in group O. Those in the O blood group have an increased risk of infection with cholera, and those O-group individuals who are infected have more severe infections. The mechanisms behind this association with cholera are currently unclear in the literature. ABO blood group incompatibilities between the mother and child does not usually cause hemolytic disease of the newborn (HDN) because antibodies to the ABO blood groups are usually of the IgM type, which do not cross the placenta. However, in an O-type mother, IgG ABO antibodies are produced and the baby can potentially develop ABO hemolytic disease of the newborn (9).

The relationship of blood group with diseases

2.1. Beyond immunohematology

The antigens of the ABO blood group system (A, B and H determinants, respectively) are complex carbohydrate molecules on the extracellular surface of red blood cell membranes. However, along with their expression on red blood cells, ABO antigens are also highly expressed on the surface of a variety of human cells and tissues, including the epithelium, sensory neurons, platelets, and the vascular endothelium. Thus, the clinical significance of the ABO blood group system extends beyond transfusion medicine and several reports have suggested an important involvement in the development of cardiovascular, oncological and other diseases (10). The strongest association found concerned peptic ulcer; statistically significant associations also were found for gastric carcinoma and pernicious anemia. Patients with pernicious anemia were distributed between groups A and O in the ratio 1:0.78, The incidence of gastric carcinoma was also greatest in persons with blood type A; that of peptic ulcer was greatest in persons with blood type O. The data suggested, but

did not suffice to prove, an association of blood group with pulmonary and mammary carcinoma. No evidence was found of association with carcinoma of the colon and rectum, leukemia, ulcerative colitis, or congenital anomalies (11).

Current knowledge on the association between the ABO blood group system and various human diseases are summarised in this narrative review

2.2. ABO blood group and cardiovascular disorders

The ABO blood group is determined by the presence of A and B antigens on the surface of the red blood cells (RBCs). In addition to RBCs, these antigens are widely expressed on the membranes of a wide variety of cells, including platelets, vascular endothelium and epithelium, as well as in saliva and body fluids, the ABO blood group antigens consist of terminal carbohydrate molecules which are synthesized by the sequential action of the ABO glycosyltransferases. The ABO glycotransferase (transferase A, alpha 1,3-N-acetylgalactosaminyltransferase; transferase B, alpha 1,3-galactosyltransferase) gene encodes proteins related to the ABO blood group system. The active ABO glycotransferases catalyze the addition of specific monosaccharides to a common core precursor antigen (H) to form distinct A and B antigens (11a)

It has long been known that the ABO blood type has a profound influence on haemostasis, being a major determinant of the von Willebrand factor (VWF), VWF levels are approximately 25% higher in individuals who have a blood group other than O; The active ABO A and B glycosyltransferase enzymes, found in the Golgi system of endothelial cells, generate terminal carbohydrate modifications, i.e. A and B antigens, on the existing VWF "H" oligosaccharides, whereas the enzymatically inactive ABO O group protein cannot modify these VWF H antigens (12). The addition of A or B terminal carbohydrate antigens to VWF in endothelial cells might influence circulating VWF levels and function through several mechanisms, including the alteration of the rate of VWF synthesis and/or secretion, the regulation of VWF proteolysis by ADAMTS13, the modulation of VWF clearance, the modification of VWF biological activity or perhaps a combination of these events. A number of clinical and experimental studies have assessed whether the ABO blood group could influence the traditional risk factors for arterial or venous thrombotic events. Advances in our understanding of the physiologic importance of various endothelial and platelet-derived circulating glycoproteins are elucidating the mechanisms through which the ABO blood group may determine overall cardiovascular disease risk (13). VWF binds and transports FVIII, the correlation between the ABO gene and FVIII is most likely mediated via VWF, As increased plasma levels of VWF and Factor VIII are associated with greater risk of thrombosis In a (Genom Wide Associated Studies) published in 2009, SNPs rs8176750, rs8176746 and rs8176719, which tag the A2, B, and O ABO blood groups, respectively, showed that genetically inferred blood type O had 67% lower risk of VTE than non-O blood groups. Additionally, the A2 blood group had 47% lower risk of VTE when compared to the other non-O blood groups (13a)

As regards coronary heart disease (CHD), its association with the ABO blood group is supported by evidence indicating that elevated VWF-FVIII levels are a risk factor for CHD and by genome-wide association studies (GWAS) documenting that variants at ABO loci are associated with increased levels of plasma lipid and inflammatory markers (i.e., soluble intercellular adhesion molecule 1, E-selectin, P-selectin and tumor necrosis factor- α), which are well known risk factors for CHD; the association of non-O blood groups with a variety of vascular disorders. The authors observed a consistent relation between non-O blood group and an increased CHD risk [odds *ratio*] (OR): 1.25; 95% confidence interval (CI): 1.14–1.36] (14)

Meta-analysis of data from the Health Professionals Follow-up Study, Nurses' Health Study and five other prospective cohort studies in which several thousands of participants were enrolled and they concluded that individuals with non-O blood group had an 11% [relative risk (RR): 1.11; 95% CI: 1.05–1.18; $p=0.001$] increased risk of developing CHD compared to that in O blood group individuals (15). These results were replicated by another recent study conducted retrospectively by our group in which we observed a statistically significant difference of prevalence of O blood group in CHD patients *vs* healthy controls (40.9% *vs* 44.5%; $p=0.01$) (16). The contrasting results of the study conducted by Jukic and colleagues, who performed ABO genotyping in patients with acute myocardial infarction and controls and did not find a statistically significant difference in the OO/non-OO genotype distribution (OR: 1.41; 95% CI: 0.94–2.11), show that the issue of the association between ABO blood group and CHD is still unclear and deserves further investigations (17). Soluble levels of multiple adhesion molecules, mostly derived from endothelial cells and platelets, have been associated with coronary heart disease, Blood group ABO antigens are known to be carried by several platelet GPs, for example, GPIb, GPIIb, GPIIIa, and platelet endothelial cell adhesion molecule (PECAM); that play important roles in platelet function, so GPIIb is an integral component of the GPIIb-GPIIIa fibrinogen receptor complex, which represents the critical final common pathway for platelet-driven thrombosis in hemostasis and pathologic arterial thrombosis including acute MI (17a)

More consistent data are available in the literature regarding the ABO blood group-related risk of venous thromboembolism (VTE), group O subjects had lower concentrations of both FVIII and VWF as compared to those of non-O individuals; After adjustment for FVIII and VWF levels, the risk of VTE among non-O blood group subjects remained significantly higher than that among individuals with O blood group (18)

Similar results were observed in a retrospective case-control study of a large number of Italian patients with deep vein thrombosis and controls (712 cases and 712 controls), in which it was found that having a non- O blood group increased the risk of deep vein thrombosis by 2.2 times over that of individuals with group O, this due to and the rate of VWF proteolysis by ADAMTS13, being higher in blood group O as

compared to non-O individuals. Thus, the absence of VWF terminal carbohydrate modifications in individuals with ABO blood group O increases the susceptibility to and rate of proteolysis by ADAMTS13 (19)

2.3 ABO group with cancer

A- Gastric cancer

More recently, in 2019, a large prospective population-based study carried out within a well-defined cohort of Swedish and Danish blood donors included in the Scandinavian Donations and Transfusions database (known as the “SCANDAT” database) involved more than one million donors who were followed for up to 35 years. This study confirmed that blood group A is indeed associated with a higher risk of gastric cancer compared to blood group O; the extent of the association was similar to those previously reported as Poisson regression analyses showed an adjusted incidence rate *ratio* of 1.20 (95% CI: 1.02–1.42), (20)

In 2012, Wang and co-workers published a case-control study, which showed that the risk of gastric cancer in individuals with blood group A was significantly higher than that in subjects with non-A groups (A, B, and AB) (OR: 1.34; 95% CI: 1.25–1.44). On the other hand, subjects with blood group O had a reduced risk of gastric cancer (OR: 0.80; 95% CI: 0.72–0.88). In addition, the authors combined their data with those from the PubMed database from 1953 to the end of 2010 and carried out a meta-analysis (15,843 gastric cancer cases and 1,421,740 controls) that resulted in similar findings: (i) the odds *ratio* of gastric cancer in group A individuals was 1.11 (95% CI: 1.07–1.15); and (ii) the odds *ratio* of group O individuals was 0.91 (95% CI: 0.89–0.94), the authors also found that the *ratio* of *Helicobacter pylori* infection in blood group A patients was significantly higher than in non-A blood group subjects; The results of this study suggest that ABO blood group can be considered a risk factor for progression towards gastric cancer in patients with *H. pylori* infection but the association is highly dependent on *H. pylori* cytotoxin-associated gene A (*CagA*) status, which is responsible for the secretion of the CagA virulence protein that is injected in the cytosol of host cells and can play a relevant role in the development of precancerous lesions (21)

H. pylori is now known as a causative agent leading to peptic ulceration and gastric cancer. In addition, non-secretion of blood group antigens is a significant risk factor for gastro-duodenal disease; The blood group antigen-binding adhesin (BabA) mediates the adherence of *H. pylori* to ABO/Lewis b (Le^b) blood group antigens in the gastric pit region of the human stomach mucosa, This interaction is important not only for the adhesion of *H. pylori* to the stomach surface but also to anchor the bacterial secretion system to the host cell surface (21a).

B- Other types of cancer

A case-control study was conducted with 1,538 patients affected by nasopharyngeal carcinoma and 1,260 controls. A relatively higher risk was observed among cases with blood types A or AB, with odds ratios of 1.287 (95% CI 1.072–1.545; $p=0.007$) and 1.390 (95% CI: 1.007–1.919; $p=0.045$), respectively, after adjusting for gender, age, smoking status, and family history of cancer. These results suggest that blood types A and AB are associated with an increased risk of nasopharyngeal carcinoma as compared with blood type O. Obviously, further studies are needed to confirm this association and to explore the mechanisms involved (22). Data from large prospective cohort studies indicate that the ABO blood group is associated with the risk of developing skin, ovarian and lung cancers, while no association was found with colorectum and breast cancers (23).

In addition, very recently a higher risk for renal cell cancer was found in non-O blood group women, but not in men. However, also for this type of cancer, additional studies are needed to confirm the association detected (24)

2.4 ABO system with infectious disease

The concept of evolutionary selection based on pathogen-driven blood group changes is currently supported by studies on the genetic characterization of the ABO blood group in many countries. These studies suggest a potential selective advantage of the O allele influencing the susceptibility to several different pathogens responsible for diseases such as severe malaria, *H. pylori* infections and severe forms of cholera. The positive selective pressure could have been caused by the absence of the A and B antigens (that can be used as receptors by infectious agents) and by the presence of anti-A and anti-B antibodies (25).

The ABO system is important because the original allele, encoding glycosylation with the A sugar, acts as an adhesion ligand with infected red blood cells thus promoting rosette formation with uninfected red blood cells and adhesion to vascular endothelium, which cause vaso-occlusion and severe disease. The least rosette formation is observed in individual with blood group O (26). By GWAS, the association between ABO polymorphism and the incidence of severe malaria. They identified two previously unknown loci associated with severe falciparum malaria in patients and controls from Ghana, West Africa. One of the loci was identified on chromosome 1q32 within the *ATP2B4* gene, which encodes the main calcium pump of red blood cells. The second was indicated by an intragenic single nucleotide polymorphism on chromosome 16q22.2, possibly linked to a neighboring gene encoding the tight-junction protein MARVELD3, which is expressed on endothelial cells and might, therefore, have a role in micro vascular damage caused by endothelial adherence of parasitized erythrocytes (27).

2.4.1. ABO Hemolytic disease of the newborn

Anti-A and anti-B antibodies are usually IgM and do not pass through the placenta, but some mothers "naturally" have IgG anti-A or IgG anti-B antibodies, which can

pass through the placenta. Exposure to A-antigens and B-antigens, which are both widespread in nature, usually leads to the production of IgM anti-A and IgM anti-B antibodies but occasionally IgG antibodies are produced. Some mothers may be sensitized by fetal-maternal transfusion of ABO incompatible red blood and produce immune IgG antibodies against the antigen they do not have and this is called (environmental factor) (28)

third of all ABO incompatible pregnancies maternal IgG anti-A or IgG anti-B antibodies pass through the placenta to the fetal circulation leading to a weakly positive direct Coombs test for the neonate's blood. However, ABO HDN is generally mild and short-lived and only occasionally severe due to IgG - antibodies that enter the fetal circulation from the mother find A (or B) antigens on many different fetal cell types, leaving fewer antibodies available for binding onto fetal red blood cells, as soon as Fetal RBC surface A and B antigens are not fully developed during gestation and so there are a smaller number of antigenic sites on fetal RBCs (29)

The antibodies in ABO HDN cause anemia due to destruction of fetal red blood cells and jaundice due to the rise in blood levels of bilirubin a by-product of haemoglobin break down. If the anemia is severe, it can be treated with a blood transfusion, however this is rarely needed. On the other hand, neonates have underdeveloped livers that are unable to process large amounts of bilirubin and a poorly developed blood-brain barrier that is unable to block bilirubin from entering the brain. This can result in kernicterus if left unchecked. If the bilirubin level is sufficiently high as to cause worry, it can be lowered via phototherapy in the first instance or an exchange transfusion if severely elevated (30)

2.5. Association of Diabetes Mellitus with ABO Blood Group

Diabetes mellitus is a common medical problem having significant morbidity and predisposition, although environmental factors do play mortality. It has a genetic inherited traits, blood groups their role in its genetic expression. Like many other are also genetically predetermined and therefore may have an association with diabetes mellitus. Identification of a positive association with blood groups might reflect increased susceptibility to and a negative association protection against diabetes mellitus, DM is generally divided as insulin-dependent Diabetes Mellitus (IDDM or type I), characterized by the body's failure to produce insulin and requires the person to inject insulin and non -insulin-dependent diabetes mellitus (NIDDM or type 2), characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency (30a). Many studies indicate the individuals with group A and B are less likely blood while those with blood group AB are more likely to have Diabetes Mellitus whereas blood group O has no difference Blood group positive is less frequent in diabetics when compared to healthy controls whereas blood group Rh negative is more frequent in diabetics. This higher frequency reflects a positive association of Rh negative blood group with diabetes (31). The

possible explanation of these conflicting findings is that probably racial and geographical factors have a role in genetic expression of disease (32)

2.6. Anemia and blood transfusion

Anemia goes undetected in many people, and symptoms can be minor or vague. The signs and symptoms can be related to the underlying cause or the anemia itself. Most commonly, people with anemia report feelings of weakness, or fatigue, general malaise, and sometimes poor concentration. They may also report dyspnea (shortness of breath) on exertion. In very severe anemia, the body may compensate for the lack of oxygen-carrying capability of the blood by increasing cardiac output. The patient may have symptoms related to this, such as palpitations, angina (if pre-existing heart disease is present), intermittent claudication of the legs, and symptoms of heart failure. On examination, the signs exhibited may include pallor (pale skin, lining mucosa, conjunctiva and nail beds), but this is not a reliable sign. There may be signs of specific causes of anemia, e.g., koilonychia (in iron deficiency), jaundice (when anemia results from abnormal break down of red blood cells — in hemolytic anemia), bone deformities (found in thalassemia major) or leg ulcers (seen in sickle-cell disease). In severe anemia, there may be signs of a hyperdynamic circulation: tachycardia (a fast heart rate), bounding pulse, flow murmurs, and cardiac ventricular hypertrophy (enlargement). There may be signs of heart failure. Pica, the consumption of non-food items such as ice, but also paper, wax, or grass, and even hair or dirt, may be a symptom of iron deficiency, although it occurs often in those who have normal levels of hemoglobin. Chronic anemia may result in behavioral disturbances in children as a direct result of impaired neurological development in infants, and reduced scholastic performance in children of school age. Restless legs syndrome is more common in those with iron-deficiency anemia (33)

Causes

A- Impaired production

- **Disturbance of proliferation and differentiation of stem cells**
 - Pure red cell aplasia
 - Aplastic anemia affects all kinds of blood cells. Fanconi anemia is a hereditary disorder or defect featuring aplastic anemia and various other abnormalities.
 - Anemia of renal failure by insufficient erythropoietin production
 - Anemia of endocrine disorders
- **Disturbance of proliferation and maturation of erythroblasts**

- Pernicious anemia is a form of megaloblastic anemia due to vitamin B₁₂ deficiency dependent on impaired absorption of vitamin B₁₂. Lack of dietary B₁₂ causes non-pernicious megaloblastic anemia
- Anemia of folic acid deficiency, as with vitamin B₁₂, causes megaloblastic anemia
- Anemia of prematurity, by diminished erythropoietin response to declining hematocrit levels, combined with blood loss from laboratory testing, generally occurs in premature infants at two to six weeks of age.
- Iron deficiency anemia, resulting in deficient heme synthesis
- Thalassemias, causing deficient globin synthesis
- Congenital dyserythropoietic anemias, causing ineffective erythropoiesis
- Anemia of renal failure (also causing stem cell dysfunction)
- **Other mechanisms of impaired RBC production**
 - Myelophthistic anemia or myelophthisis is a severe type of anemia resulting from the replacement of bone marrow by other materials, such as malignant tumors or granulomas.
 - Myelodysplastic syndrome
 - anemia of chronic inflammation (34)

B- Increased destruction

- Intrinsic (intracorpuseular) abnormalities cause premature destruction. All of these, except paroxysmal nocturnal hemoglobinuria, are hereditary genetic disorders.
 - Hereditary spherocytosis is a hereditary defect that results in defects in the RBC cell membrane, causing the erythrocytes to be sequestered and destroyed by the spleen.
 - Hereditary elliptocytosis is another defect in membrane skeleton proteins.
 - Abetalipoproteinemia, causing defects in membrane lipids
 - Enzyme deficiencies
 - Pyruvate kinase and hexokinase deficiencies, causing defect glycolysis
 - Glucose-6-phosphate dehydrogenase deficiency and glutathione synthetase deficiency, causing increased oxidative stress
 - Hemoglobinopathies
 - Sickle cell anemia
 - Hemoglobinopathies causing unstable hemoglobins
 - Paroxysmal nocturnal hemoglobinuria
- **Extrinsic (extracorpuseular) abnormalities**
 - **Antibody-mediated**

- Warm autoimmune hemolytic anemia is caused by autoimmune attack against red blood cells, primarily by IgG. It is the most common of the autoimmune hemolytic diseases. It can be idiopathic, that is, without any known cause, drug-associated or secondary to another disease such as systemic lupus erythematosus, or a malignancy, such as chronic lymphocytic leukemia.
- Cold agglutinin hemolytic anemia is primarily mediated by IgM. It can be idiopathic or result from an underlying condition.
- Rh disease, one of the causes of hemolytic disease of the newborn
- Transfusion reaction to blood transfusions
- **Mechanical trauma to red cells**
 - Microangiopathic hemolytic anemias, including thrombotic thrombocytopenic purpura and disseminated intravascular coagulation
 - Infections, including malaria
 - Heart surgery
 - Haemodialysis (35)

C- Blood loss

- Anemia of prematurity from frequent blood sampling for laboratory testing, combined with insufficient RBC production
- Trauma or surgery, causing acute blood loss
- Gastrointestinal tract lesions causing either acute bleeds (e.g. variceal lesions, peptic ulcers or chronic blood loss (e.g. angiodysplasia)
- Gynecologic disturbances, also generally causing chronic blood loss
- From menstruation, mostly among young women or older women who have fibroids
- Infection by intestinal nematodes feeding on blood, such as hookworms and the whipworm *Trichuris trichiura*. (36)

D- Fluid overload

Fluid overload (hypervolemia) causes decreased hemoglobin concentration and apparent anemia:

- General causes of hypervolemia include excessive sodium or fluid intake, sodium or water retention and fluid shift into the intravascular space.
- Anemia of pregnancy is induced by blood volume expansion experienced in pregnancy. (37) Anemia is a common problem in critically ill patients admitted to intensive care units (ICUs). Deleterious effects of anemia include increased risk of cardiac-related morbidity and mortality as well as a generalized decrease

in oxygen-carrying capacity. Consequences of anemia may be compounded in this population since critical illness often increases metabolic demands, among the many causes of anemia in the critically ill, some of the most important are sepsis, decreased production of endogenous erythropoietin, and immune-associated functional iron deficiency (38)

Groeger et al found that 16% of patients in medical ICUs and 27% of those in surgical ICUs are transfused on any given day, 85% of patients with an ICU length of stay greater than 1 week received at least 1 blood transfusion, and the mean number of units of blood transfused per patient was 9.5 More than two thirds of ICU transfusions were not associated with acute blood losses ;the transfusion strategies in ICU patients indicated that the liberal use of transfusions may have resulted in higher hospital mortality rates (39)

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