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**REVIEW**

# Hematology: A comprehensive approach to study and practice

## Hematología: Un enfoque completo para el estudio y la práctica

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## ABSTRACT

Blood is a very particular tissue, which has numerous properties. Hematologic diseases encompass a wide range of conditions, including anemias, coagulation disorders, leukemias, lymphomas, and myelomas. Hematology is a vital field that not only focuses on diseases, but has a significant impact on the individual's individual health. The continuous evolution of knowledge and techniques in this discipline promises to improve clinical outcomes and patients' quality of life. Provide a comprehensive and up-to-date understanding of the components, functions and disorders of blood, as well as the diagnostic methods and treatments available. Aim. Describe a complete approach to study and practice. The methodology used for this research work is framed within a documentary-type bibliographic review, since we are going to deal with topics raised at a theoretical level such as Pediatric Hematology and the most frequent disorders. The technique for data collection consists of electronic materials, the latter such as Google Scholar, PubMed, Science direct, among others, descriptors in health sciences were used. Based on the bibliography found. The Article offers a comprehensive and updated vision of blood and its diseases. This resource is essential for health professionals and students. Promoting an evidence-based approach.

**Keywords:** Hematology; Disorders; Leukopenia; Anemia; Thrombocytopenia.

## RESUMEN

La sangre es un tejido muy particular, que posee numerosas propiedades. Las enfermedades hematológicas abarcan una amplia gama de condiciones, incluyendo anemias, trastornos de la coagulación, leucemias, linfomas y mielomas. La hematología es un campo vital que no solo se centra en las enfermedades, sino que tiene impacto significativo en la salud individual del individuo. La continua evolución del conocimiento y las técnicas en esta disciplina promete mejorar los resultados clínicos y la calidad de vida de los pacientes. Objetivo general: Proporcionar una comprensión integral y actualizada de los componentes, funciones y trastornos de la sangre, así como de los métodos diagnósticos y tratamientos disponibles. Describir un enfoque completo para el estudio y la práctica, La metodología utilizada para el presente trabajo de investigación, se enmarca dentro de una revisión bibliográfica de tipo documental, ya que nos vamos a ocupar de temas planteados a nivel teórico como es Hematología pediátrica y trastornos más frecuentes. La técnica para la recolección de datos está constituida por materiales electrónicos, estos últimos como Google Académico, PubMed, Science direct, entre otros, se utilizó descriptores en ciencias de la salud. En base a la bibliografía encontrada. El Articulo ofrece una visión integral y actualizada sobre la sangre y sus enfermedades. Este recurso es esencial para profesionales de la salud y estudiantes. Promoviendo un enfoque basado en evidencia.

**Palabras clave:** Hematología; Trastornos; Leucopenia; Anemia; Trombocitopenia.

## INTRODUCTION

Blood is a unique tissue possessing numerous distinct properties. Circulating blood is composed of cellular elements (red blood cells, leukocytes, platelets) suspended in an aqueous solution of salts and proteins (plasma). It is the medium for transporting oxygen and other substances necessary for cell metabolism. Some components offer protection against invasion by foreign organisms. Hematologic diseases encompass a wide range of conditions, including anemias, coagulation disorders, leukemias, lymphomas, and myelomas. Hematology is a vital field that not only focuses on diseases but also has a significant impact on an individual's overall health. The continuous evolution of knowledge and techniques in this field promises to enhance clinical outcomes and improve the quality of life for patients. It provides a comprehensive and up-to-date understanding of the components, functions, and disorders of the blood, as well as the diagnostic methods and treatments available.

### Iron deficiency anemia

Iron deficiency (IDA) and iron deficiency anemia (IDA) according to the World Health Organization (WHO) defines anemia as hemoglobin (Hb) concentration <13 g/dL in men, < 12 g/dL in non-pregnant women > 15 years and children 12-14 years, < 11,5 g/dL in children 6-12 years, and < 11 g/dL in pregnant women and children 6-59 months of age. The earliest phase of iron deficiency (ID) is the depletion of iron stores, which correlates with a decrease in serum ferritin concentration. Ferritin is a hollow iron storage protein: each molecule can take up to 4500 Fe molecules. Its level is not influenced by recent iron intake. It is an acute phase reactant, and its level is elevated in inflammatory processes of any etiology; hepatocellular damage also causes ferritin elevation.[1]

The WHO considers that serum ferritin < 15 µg/L in adults and children older than 5 years and < 12 µg/L in children younger than 5 years, without comorbidities, are diagnoses of DH. In pregnancy, in syndromes associated with inflammation, the diagnosis of DH requires a ferritin < 30 µg/L; in heart failure and chronic renal disease < 100 µg/L. Iron deficiency anemia (IDA) is the most advanced stage of DH. The most commonly used laboratory tests include blood count, reticulocytes, serum iron, transferrin (TIBC) and transferrin saturation (SatT), soluble transferrin receptors (sTfR), sTfR/log ferritin ratio, and Perl staining of bone marrow iron. In the presence of normal folic acid and vitamin B12 levels and normal liver function, FA is typically a microcytic anemia (MCV <80 fl in adults, <71-78 in children). According to age, serum Fe is decreased, as is transferrin saturation (SatT, normal 20-45 %). Note that Fe may be decreased secondary to inflammation/infection or falsely elevated due to recent Fe intake; SatT level decreases with inflammation, advanced age, and malnutrition.[2]

Bone marrow Fe staining detects hemosiderin in erythroblasts and macrophages; like ferritin, it assesses Fe deposits, but it is an invasive and expensive test. The sTfR (soluble transferrin receptor) test is elevated in FA, but its level is not affected by inflammation or chronic disease. It has been proposed for the differential or concurrent diagnosis of FA and inflammatory anemia (IA). Risk factors and causes of iron deficiency anemia include women of reproductive age, infants, preschool children, and adolescents, who are prone to FA due to their high iron requirements. Professional athletes and individuals with obesity are also prone to iron deficiency due to hepcidinemia. Investigating the etiology of FA is essential to inform treatment.[3]

The causes of FA are two: firstly, insufficient Fe intake, which may result from poor nutrition or iron malabsorption, secondary to bariatric surgery, celiac disease, autoimmune or atrophic gastritis due to Helicobacter pylori and other causes; secondly, abnormal blood loss, gastrointestinal, uterine and, rarely, urinary (intravascular hemolysis with chronic hemoglobinuria) are the most common etiology of FA. Additional causes of FA to consider are intestinal parasitosis, especially hookworm duodenal, malaria, and gastrointestinal infections. Prevention of iron deficiency and iron deficiency anemia: In pregnant women, iron supplements 60 mg/day + folic acid 400 µg/day, from the 14th week of gestation until 1 month after delivery; in children, iron supplements (2mg/kg/day) starting at 1 month of age in infants born prematurely and at 4 months of age in those born at term.[3]

The treatment of iron deficiency anemia consists of administering Fe orally early in the morning, when the level of hepcidin is lower, and on an empty stomach because the acid pH of gastric juice favors its reduction to Fe 2+. It is recommended to avoid taking iron with tea, coffee, cereals, and milk, as they can inhibit iron absorption. With oral treatment, the goal is to correct the anemia and restore iron stores. The standard treatment consists of oral (OV.) Fe in the form of sulfate, gluconate, ascorbate, or fumarate salts. Ferrous sulfate (FeSO4) has better absorption, is the most cost-effective, and is widely available. A traditional treatment scheme involves one tablet of SO4Fe 325 mg (65 mg elemental Fe) twice to three times daily for 3-4 months, and in children, 3-6 mg/kg/day of elemental Fe, divided into two to three doses. Several studies have shown a high incidence of secondary unpleasant gastrointestinal (GI) symptoms (epigastric discomfort, metallic taste, nausea, constipation), which can lead to non-adherence to treatment. In cases of GI intolerance, the use of ferrous gluconate, which has lower toxicity, or administering small doses once a day has been proposed.[4]

In elderly and pregnant women, the use of 15 and 50 mg/day showed the same efficacy as the double dosage. Other therapeutic options include the use of oral Fe on alternate days or intravenous Fe. Intravenous (IV) iron therapy is currently considered an adequate therapeutic option in the following clinical situations: gastrointestinal intolerance leading to lack of treatment adherence, and in which alternative doses and OV treatment schedules did not work; AF refractory to treatment, post-bariatric surgery; GI or uterine bleeding exceeding OV Fe intake; chronic kidney disease requiring hemodialysis and erythropoietin. Iron deficiency in these patients is multifactorial, including chronic blood loss, poor absorption due to hepcidinemia, inflammatory bowel disease with persistent anemia despite oral iron supplementation, or during exacerbations of the disease when iron absorption is impaired. In the 2nd and 3rd trimesters of pregnancy, cases of gastrointestinal intolerance, malabsorption, and AF with Hb<10 g/ dL were diagnosed at 34 weeks of gestation. Heart failure (HF) is associated with DH; this contributes to myocardial dysfunction, poor quality of life, and increased mortality. Treatment with intravenous Fe is feasible in hospitals or clinics of medium complexity that have the necessary infrastructure for monitoring cardiorespiratory function and personnel with experience in managing potential adverse reactions.[5]

**Vitamin B12 deficiency anemia**

Vitamin B12 (vitB12), or cyanocobalamin, is an essential nutrient for various metabolic functions and cellular DNA synthesis. Requirements are 2-2,5 µg/day; it is obtained from a diet with foods of animal origin (red meat, poultry, eggs, milk). Tissue stores contain 3-10 mg, so that symptoms of deficiency are not observed until after 3-5 years of establishment.[6]

VitB12 obtained from food is separated from animal proteins by the action of pepsin and gastric hydrochloric acid; it then binds to lipocortin (protein of salivary origin), from which it dissociates in the duodenum by the action of pancreatic proteases, and travels to be absorbed in the distal ileum bound to intrinsic factor (IF) (protein synthesized in the parietal cells of the gastric fundus). The complex formed by vitamin B12 and IF binds to receptors in the ileal cells, is absorbed by endocytosis, and passes into the bloodstream bound to transcobalamin II. It is then transported to the liver and the rest of the body. A minor proportion of 1-2 % is absorbed through passive diffusion.[7]

This is of great physiological interest and, as we shall see, also in terms of treatment, since it is independent of the different pathways and factors required; it does not depend on the IF, the integrity of the distal ileum, the existence of gastric alterations, or selective malabsorption of cobalamin. Among the various causes that can lead to its deficit, the following stand out: Low exogenous intake in the diet, as occurs in strict vegetarians. Effects of poor digestion, such as atrophic gastritis (whether or not due to Helicobacter pylori), achlorhydria, and gastrectomy. Malabsorption, as in pernicious anemia, ileum diseases (Crohn's disease, regional enteritis, celiac disease), or after ileum resection.[7]

The consumption of drugs that interact with its absorption: proton pump inhibitors suppress gastric hydrochloric acid secretion and IF production, which decreases its absorption; on the other hand, metformin interferes with its absorption as a consequence of the reduction of intestinal free calcium, necessary for the uptake of the vitB12-FI complex in the ileum; other drugs with similar effect are anti-H2 drugs, colchicine, aminosalicylates, cholestyramine, neomycin.[7]

It is common to find symptoms secondary to anemia, such as weakness, tachycardia, fatigue, skin pallor, and dizziness; also, digestive disorders, Hunter's atrophic glossitis, and anorexia. Neurological alterations derived from myelin deficiency should also be highlighted, which causes involvement of the lateral and posterior cords of the spinal cord and, consequently, alteration of vibratory and proprioceptive sensitivity. Earlier on, paresthesias, weakness, ataxia, and poor coordination may occur, as well as alteration of the osteotendinous reflexes, signs of pyramidal involvement, irritability, forgetfulness, dementia, and even frank psychosis. The diagnosis is made by requesting serum vitamin B12 and folate levels in cases of Macrocytic anemia or isolated macrocytosis. This assessment helps determine whether iron deficiency or thalassemia coexist, as macrocytosis may be masked. Additionally, pancytopenia, glossitis, or oral ulcers may be present in the population at risk for vitamin deficiency. Request serum vitB12 without including folate in case of the presence of unexplained neurological symptoms, such as paresthesias, numbness, motor coordination deficit, memory or cognitive problems, and personality changes, regardless of the results of the hemogram.[8]

On the other hand, recommendations are provided for determining serum vitamin B12 Levels in asymptomatic patients with normal blood counts. People without risk factors for deficiency. People who are receiving vitamin B12 or folate supplements unless there is a suspicion of treatment abandonment. In general, there are no population screening criteria. Some authors propose analyzing the concentration of vitamin B12 every 5 years in all adult patients up to 50 years of age and annually in those over 65 years of age. Data that usually confirm the suspicion include a blood smear with an increased mean corpuscular volume or hypersegmentation of neutrophils. Low reticulocytes, leukopenia, and thrombopenia. Biochemistry, where we dosed elevated iron, bilirubin, lactate dehydrogenase, and low vitamin B12 (with or without decreased folic acid). Schilling's test, anti-parietal cell, and anti-intrinsic factor antibodies.[9]

Deficiency manifests when vitamin B12 levels are below 300 pg/mL, a condition that may take several years to develop. Reference ranges vary between laboratories; however, in general, levels below 150pmol/Ll (200 pgmLl) are considered compatible with a deficiency, while levels of 151-299pmol/Ll (200-400 pgmLl) are considered borderline values. In this case, deficiency is possible, but additional, more sensitive tests (methylmalonic acid and homocysteine determination: both must be elevated in the case of vitamin B12 deficiency) or empirical treatment with vitamin B12 and assessment of the rise in reticulocyte levels after one week. Levels above 300 pmol/l (400 pg/ml) are considered normal. In certain situations, false positive data are produced, with low levels of vitamin B12, without the patient actually having a deficiency; in others, false negatives, such as those described in the figure 4 Treatment consists of the administration of vitB12 to correct or prevent the deficiency, usually for life. There are different routes of treatment; intramuscular is the most well-known and commonly used. It is administered sequentially, with 1000 µg administered per day. For 1 week, subsequently, 1000 µg per week for 4-8 weeks, then 1000 µg monthly for life.[10]

It is the route of choice in patients with evident and severe neurological impairment secondary to the deficit. It is also helpful in patients who do not respond to oral therapy, have an intolerance to the oral route, experience vomiting or diarrhea, or suffer from cognitive dysfunction or memory loss (not that it is the route of choice, but due to the increased likelihood of therapeutic noncompliance in these cases). The less used and less known oral route. It is based on the possibility of passive intestinal absorption, independent of factors or functional alterations of the digestive system. Oral supplementation at doses of 1000 µg per day can achieve adequate serum levels. Oral replenishment: At least as effective as the intramuscular route, it has a lower incidence of side effects since it avoids the complications inherent to injection and also has fewer relative contraindications (anticoagulation). It generates a lower number of consultations and home care.[10]

**Glucose-6-phosphate dehydrogenase deficiency**

Glucose-6-phosphate dehydrogenase deficiency is the most frequent enzymatic alteration at the erythrocyte level. The characteristic debut is a previously healthy patient in whom certain drugs, infections, or food trigger a hemolytic crisis. In the latter context, the clinical picture secondary to the ingestion of fava beans is known as favism. Glucose-6-phosphate dehydrogenase (G6PDH) is an enzyme present in red blood cells that maintains their homeostasis by protecting them from oxidative stress. Its deficiency is the most frequent enzymatic alteration in erythrocytes. In our environment, in previously healthy patients, it is manifested by episodes of hemolysis triggered by some drugs, infections, or food, which in case of being associated with the intake of fava beans is called favism.[11]

There are different forms with considerable clinical variability. The type I form, which is rare, is characterized by very low enzyme activity and presents with chronic non-spherocytic hemolysis. Favism, or type II, has an enzyme activity of less than 10 % and causes hemolytic crises, as is the clinical case presented, and is the most prevalent form, typical of the Mediterranean and Asia. Type III has activity between 10 % and 60 %, is typical of black American males, and is not uncommon. Types IV and V have even higher enzymatic activity, low clinical expressivity, and very low prevalence, frequent in Africa.[12]

Due to genetic variability, symptomatology can be very variable, from very mild forms, typically in patients from Africa, to severe hemolytic anemias, as in patients from Mediterranean areas, or cases triggered by fava beans (favism).[13] In our environment, in most cases, patients will be asymptomatic throughout their lives, except for the presence of intravascular hemolytic crises that are usually triggered in the presence of certain factors associated with oxidative stress, such as infections, ingestion of fava beans or some drugs and chemicals, especially quinine, acetylsalicylic acid, anti-inflammatory drugs.[14] The treatment of hemolytic crisis with severe anemia is red blood cell transfusion. Except in severe acute episodes and some chronic forms, patients do not require exhaustive medical supervision and can lead an everyday life. However, they should be adequately informed about their disease and the triggers of hemolytic crises. Quality of life and vital prognosis are usually not affected.[15]

**Sickle cell disease**

Sickle cell disease (SCD), also known as sickle cell anemia, is an autosomal recessive disorder that affects millions of people worldwide, making it one of the most common single-gene diseases; it is considered global health problems by international organizations such as the United Nations and the World Health Organization (WHO), where the most affected regions are sub-Saharan Africa and the tropical areas of Asia and America.[16]

It is defined as the most prevalent autosomal recessive structural hemoglobinopathy worldwide. It is caused by a point mutation in the gene encoding the beta globin chain, whose product, known as hemoglobin S (HbS), is less soluble than adult hemoglobin and fetal hemoglobin. The lower solubility of HbS facilitates its polymerization under hypoxic conditions, leading to the formation of sickled red blood cells and resulting in structural and functional changes. In addition, pathological sickle erythrocytes have a greater adherence to the vascular endothelium, which generates aggregation of these in the microvasculature, being that structural

abnormalities and cumulative damage of the cell membrane of these erythrocytes, causing chronic hemolysis which increases the viscosity of the plasma, which contributes to the alteration of blood flow through the capillaries and postcapillary venules of tissues with high oxygen demand, together with the reduction of the deformity of sickle erythrocytes, which can be mechanically sequestered in the microcirculation to promote vas occlusion and multiorgan pathology.[17]

The process of vascular occlusion is now considered a form of reperfusion injury in which oxidative stress and inflammation lead to chronic organ damage. The organs in which the risk is most significant are those with venous sinuses, where blood flow is slower, and oxygen tension and pH are lower, such as the spleen and bone marrow. Additionally, organs with terminal blood circulation, including the eyes and the head of the femur or humerus, are also at risk. In the lung, there is a high risk of vascular occlusion and infarction, but no organ or tissue is protected against these injuries. The symptoms produced by vascular occlusion with consequent hypoxia can be acute, such as episodes of pain associated with painful vasoocclusive crises (CVOD), osteomyocclusive osteomyofibular pain, or acute chest syndrome (ACS), or of insidious onset, including retinopathy and aseptic necrosis of the femoral or humeral head. As the patient ages, acute and chronic tissue damage can produce irreversible changes in organs such as the central nervous system, lungs, kidneys, and liver. In recent years, it has been proposed that there are two subphenotypes in AD, characterized by distinct clinical, hematological, and biochemical features: the hyperhemolytic subphenotype and the vascular occlusive subphenotype.[17]

The first is characterized by exaggerated hemolysis, with a predominance of anemia, as evidenced by lower hemoglobin levels and higher values of reticulocytes, lactate dehydrogenase, indirect bilirubin, and plasma hemoglobin. The second is characterized by a predominance of vascular occlusion, accompanied by higher hemoglobin levels. Reticulocytosis, indirect bilirubin, lactate dehydrogenase, and plasma hemoglobin have less elevated values. In the hyperhemolytic subphenotype, malleolar ulcer, priapism, and pulmonary hypertension are frequent, and in the vascular occlusive subphenotype, acute chest syndrome and painful crises are more common. The existence of these two subphenotypes is not yet fully established, especially in children; however, it is common for patients to exhibit a clinical picture characterized by the recurrence of some manifestations and the absence of others. It is also necessary to know that sickle cell disease patients live under constant psychosocial stress, not only because they suffer from an incurable chronic disease but also because of its unpredictable clinical features. Recurrent CVOD makes it difficult for them to attend school or work regularly and lowers their self-esteem.[18]

At the moment, there is no cure for sickle cell disease except bone marrow transplantation. This will be available only to a limited number of people after the criteria for transplantation have been established and agreed upon. The lack of drugs or treatments that cure the disease is mainly due to the absence of good animal models for experimentation. Recent advances in DNA technology have enabled the introduction of intact human genes into the germ line of mice, thereby generating transgenic animals. Transgenic mouse models for sickle cell disease provide the opportunity to experiment with new treatments, drugs, and antisickling agents to treat these diseases. It also allows the study of the initiation of vaso-occlusive crises and their pathophysiological consequences in sickle cell disease.[18]

Unfortunately, except for BMT, there is no other curative treatment for sickle cell disease associated with these diseases. The clinical pharmacotherapy of complications has managed to increase the life expectancy and quality of life of these patients, which previously averaged 15 years and is now 45 years. Comprehensive management of these patients begins by providing appropriate genetic counseling to populations at risk, and it is also essential to achieve diagnosis as early as possible. Currently, in the United States, 48 of the 50 states have screening programs for hemoglobinopathies and other genetic diseases in all newborns (newborn screening). Statistics indicate that when only at-risk populations (African American, Hispanic, Mediterranean, etc.) are screened, 20 % of infants with severe hemoglobinopathies are missed.[19]

Once the diagnosis has been established, the core of effective disease management is prophylaxis and treatment of the characteristic symptoms. Attempts to modify or inhibit the sickling process have employed various therapeutic approaches; however, none have been demonstrated to be sufficiently safe or to yield positive results in adequate clinical trials for these patients. Recent therapeutic approaches to managing sickle cell disease are described in this publication.[19]

In sickle cell disease (SCD), the rate of infection is extremely high during the first three years of life and remains consistently higher than the rate in the normal population. Individuals with SCD should receive the following vaccines: polio (OPV), Diphtheria-Pertussis-Tetanus (DPT), hepatitis B, Haemophilus influenzae type B, and measles-rubella (MMR). The pneumococcal vaccine should be administered at 12 months and 24 months of age and then repeated every 5 years for life. Influenza vaccine should be given at 12 months of age and repeated annually with the strains available for each year. In sickle cell disease, infections are the leading cause of mortality. Susceptibility is increased, especially to encapsulated organisms, due to the compromise of splenic function.[20]

All infants with sickle cell disease, HbSS, sickle cell disease with Hb C (Hb SC disease), and Hb-S Beta

thalassemia disease should begin penicillin therapy as early as possible before the age of one month. Children should receive 125 mg of penicillin V potassium orally, twice daily, until they are 3 years of age. Then, the dose should be increased to 250 mg orally, twice daily, until at least 5 years of age. Different classes of antibiotics, which are appropriate and effective for treatment in normal individuals, can be used for the same indications in SCD patients. However, caution should be exercised with trimethoprim-sulfamethoxazole because of its side effects in patients who may have Glucose-6-Phosphate-Dehydrogenase (G6PD) deficiency because of the potential for causing a hyperhemolytic crisis.[20]

Chelation therapy with deferoxamine mesylate (Desferal Mesylate) is usually necessary for many polytransfused individuals with SCD. When serum ferritin levels exceed 1500 ng/mL, this therapy should be considered. If deferral is used, annual hearing and ophthalmologic evaluations are necessary. The use of iron for sickle cell disease is not indicated unless iron deficiency is proven.[20]

Several agents are under investigation and are in various stages of evaluation for long-term use as a treatment for SCD. Hydroxyurea and butyrate compounds increase the production of gamma (γ) chains, which, when combined with alpha (α) chains, form fetal hemoglobin (Hb F). Hemoglobin F inhibits the polymerization of deoxyhemoglobin S, thereby benefiting the patient. Recombinant erythropoietin in combination with these drugs has the potential to elevate clinical levels of Hb F.[20]

**Autoimmune hemolytic anemias**

Autoimmune hemolytic anemia (AIHA) results from the destruction of red blood cells in patients whose bodies have formed antibodies that are specific to antigens on their red blood cells. This type of anemia accounts for 5 % of all anemias, with an incidence ranging from 0,4 to 2,0 per 100 000 inhabitants, and is more frequent in female patients. It can occur at any age; however, it has been observed that two-thirds of patients presenting the pathology are older than 50 years. The causes of this type of anemia are diverse and range from physiological states such as pregnancy (incidence 1/ 50 000) to the use of a drug; however, the vast majority of cases are secondary to some pathology.[21]

Symptomatology in the vast majority of patients is masked by the underlying condition, making its clinical manifestations nonspecific. These can range from the absence of symptoms if the destruction of red blood cells is mild and develops gradually to presenting symptoms similar to those of any anemia if the hemolysis is severe or rapid. Alternatively, cases may occur in which hemolysis persists for several months, manifesting as jaundice and an increase in the size of the spleen. The pathophysiologic mechanisms of RBC destruction vary and depend on the antibody or immunoglobulin involved, which may be of the IgG or IgM isotype, causing extravascular or intravascular hemolysis, respectively.[22]

Recognition of the most common forms of AHAI was achieved through the development of the direct and indirect Coombs' tests in 1945, which are now referred to as the direct antiglobulin test (DAP) and indirect antiglobulin test (IAT). Fundamentally, the DAP is used to determine whether red blood cells have surface-bound immunoglobulin G (IgG) and/or complement by first using polyspecific antiglobulin serum containing anti-IgG and anti-complement antibodies. If the reaction is positive, the red cells are then challenged with monospecific antiglobulin serum to detect individual IgG and complement, containing anti-IgG and anti-complement antibodies. For the performance of this test, various techniques have been described, including liquid phase hemagglutination (tube), column agglutination (gel test), flow cytometry, and molecular techniques such as immunoblotting.[23]

In AHAI, the antibodies produced are generally directed against erythrocyte antigen systems and react at different temperatures, allowing them to be classified according to the isotype of the autoantibody formed in hemolytic anemia by hot antibodies when it is an immunoglobulin G (IgG), by cold antibodies, if the immunoglobulin is M (IgM), anemias by biphasic antibodies, capable of binding to the erythrocyte at low temperatures (4°C) and causing lysis of the hematocyte when the blood returns from the capillary circulation to the venous circulation (37°C), mixed type, where both hot and cold antibodies can be present as responsible for the hemolytic picture and the group of AHAI caused by the use of some drugs. AHAI produced by warm antibodies corresponds to 80 % of AHAI.[23]

Warm antibodies produce AHAI. It is more frequent in women between the third and fourth decades of life. It can be idiopathic in 50 % of cases or secondary to diseases such as lymphoproliferative syndromes, systemic lupus erythematosus, and chronic lymphocytic leukemia, among others. The course can be either acute or chronic, with periods of remission and exacerbation. The predominant subclass of IgG formed is IgG1 and, in smaller proportion, IgG3, being the two subclasses of immunoglobulin G, the ones that fix complement with greater avidity; IgG3 turns out to be more efficient since it requires some hundreds of molecules, concerning IgG1 that requires 10 000 molecules to produce the same effect. Erythrocyte sensitization occurs at 37°C and may cause extravascular hemolysis by phagocytosis in reticuloendothelial cells in spleen sinusoids when the amount of IgG bound to the erythrocyte is low or phagocytosis by macrophages at the liver level if the amount of IgG coating the erythrocytes is high. There has been complement activation up to C3b, which contributes

to opsonization. It has also been described that erythrocytes opsonized with IgG can bind to the Fc receptor of macrophages, causing damage to the cell membrane and giving rise to microspherocytes, which will also be removed in the spleen sinuses. When AHAI develops with idiopathic thrombocytopenic purpura (ITP), it is known as Evans syndrome.[24]

AHAI produced by cold antibodies, Known as cold agglutinin syndrome, is a rare condition. The immunoglobulin isotype formed is IgM, accounting for 10-20 % of AHAI. Its incidence is higher in older people. The hemolysis produced by these antibodies is most efficient between 0 °C and 20°C. They differ from the irregular natural cold antibodies because, in this pathology, the antibody exhibits a greater thermal range and high titers. It can occur idiopathically but is usually associated with infections, particularly Mycoplasma pneumonia infection, and the presence of antigen I antibodies. Cases have also been described in infectious mononucleosis, HIV, hepatitis C, influenza, cytomegalovirus, rubella, chickenpox, measles, syphilis, malaria, and bacterial endocarditis, among others. The hemolysis that occurs in these cases is intravascular, as IgM is efficient in activating complement, ultimately leading to the formation of the membrane attack complex (C9), and the endothelial reticulum system is also involved. The IgM antibody binds to red blood cells at temperatures below 37ºC. As the red cells return to body temperature, IgM dissociates, leaving only C3b bound to the erythrocyte surface. The released IgM can then bind to other cells at low temperatures.[21] While the C3b-coated red cell is detected by specific receptors on macrophages of the endothelial reticulum system (particularly the liver), it undergoes phagocytosis.[25] This process is usually self-limiting.

This process is usually self-limiting, as over time, the C3b components are hydrolyzed to their inactive form (C3d) by the C3 inactivator, preventing them from being recognized by macrophages. Although the syndrome generally has a mild course, in some cases, it can be life-threatening. The characteristic clinical manifestation of this syndrome is acrocyanosis.[24]

AHAI is produced by biphasic antibodies, also known as paroxysmal hemoglobinuria, a condition associated with fever. In this type, the autoantibodies produced are of the IgG type, with specificity towards the P antigen. It is rare (2 %) and usually occurs in children, secondary to infections. Its clinical course is chronic and presents with hemoglobinuria after exposure to cold, chills, vomiting, fever, and renal, abdominal, and lower limb pain. The antibody binds to the erythrocyte at cold temperatures, and then the antigen-antibody complex separates. Therefore, phagocytosis does not occur, and hemolysis occurs at 37°C, resulting in acute destruction at the intravascular level due to complement activation. This characteristic (essential to be demonstrated in the laboratory) is called Donath-Landsteiner antibodies.[25]

Drug-induced AHAI Several drugs have been identified that can cause AHAI and positive PAD by different mechanisms and can be classified according to the mechanism of action of the drug. They account for 16-18 % of autoimmune hemolytic anemias.[25]

**Polycythemia vera**

Polycythemia vera (PV) is one of several forms of "myeloproliferative neoplasms" (MPN), a term used to group several types of blood cancers that share several standard features, in particular, the "clonal" production of one or more blood cell lines. All clonal diseases (types of cancer) begin with one or more changes in the DNA of a single cell: the cells found in the marrow or blood are descended from that single mutant cell. PV is the result of uncontrolled production of blood cells, especially red blood cells, as a result of mutations acquired in the early stages of a blood-producing cell. Because this early-stage cell can form not only red blood cells but also white blood cells and platelets, any combination of these cell lines can be affected.[26]

The cause of PV is not fully understood. Almost all patients with PV have a mutation of the JAK2 (Janus kinase 2) gene. This mutated gene probably plays a role in the onset of PV. However, its precise role in causing the disease remains to be studied. Most patients with PV have no family history of the disease. However, occasionally, there is more than one family member with the disease. PV is more common among Jews of Eastern European descent than among other Europeans or Asians. The incidence of PV is approximately 2,8 per 100 000 males and 1,3 per 100 000 females across all races and ethnic backgrounds. The prevalence (estimated number of persons alive with a diagnosis of the disease in a population on a specific date) is approximately 22 cases per 100 000 persons. This prevalence has been demonstrated in several small studies. The average age at which PV is diagnosed is between 60 and 65 years of age. It is rare in people younger than 30 years of age.[27]

Diagnostic criteria for PV: More specific symptoms: history of thrombotic events at any level, pruritus (almost always related to hot baths, erythromelalgia (pain and burning in hands and feet associated with erythema and cyanosis), splenomegaly (70 %). Absence of secondary causes. Nonspecific symptoms: headaches, fatigue, flushing, numbness of the extremities. Laboratory studies include peripheral blood, characterized by panmyelosis (erythrocytosis, leukocytosis, and thrombocytosis), mild reticulocytosis, and regular blood cell morphology. Microcytosis and hypochromia may be observed. Bone marrow: Hypercellular for age, with the presence of panmyelosis (trilinear proliferation), predominantly erythroid, megakaryocytic (small megakaryocytes, polylobulated and tending to cluster), and granulocytic. There is usually an absence of iron, and different degrees of fibrosis may be found.[27]

Signs, symptoms, and complications of PV occur as a consequence of too many red blood cells and often too many platelets in the blood. The increased number of white blood cells does not predispose the patient to an increased risk of infection or cause any other significant effects. The presence of too many red blood cells can make the patient's blood more viscous so that it does not flow efficiently. High platelet counts may contribute to the formation of thrombi. Underlying vascular disease, which is common in older people with PV, can increase the risk of clotting complications. Clots can cause problems such as stroke, heart attack, deep vein thrombosis, or pulmonary embolism. Blood clots occur in approximately 30 percent of patients before a diagnosis of PV is made. During the first 10 years after diagnosis, 40 to 60 percent of untreated patients with PV may develop blood clots.[26]

A diagnosis of PV is considered a diagnosis if the patient's red blood cell counts are elevated. Three measurements of the concentration of red blood cells in the blood can be used to diagnose PV: hematocrit, hemoglobin concentration, and red blood cell count. These measurements are included in a standard blood test called a complete blood count (CBC). In a patient with PV, if the normal hematocrit of 45 percent increases by one-third to a value of 60 percent, the corresponding normal hemoglobin concentration of 150 grams per liter (g/L) of blood would also increase by one-third to 200 g/L of blood. The corresponding amount of red blood cells would also increase by one-third. Therefore, for diagnostic purposes, any of these three measurements can be used.[27]

PV is not curable, but it can usually be managed effectively for very long periods. Careful medical observation and therapy are crucial to maintaining hematocrit concentration at near-normal near-normal levels. The goals of treatment for this disease are to control symptoms and decrease the risk of complications. Therapies aim to lower the hematocrit concentration to normal or near-normal values and reduce the platelet count if the numbers are high or rise over time. A presenting symptom in many patients with PV is aquagenic pruritus. Aspirin and antihistamines may be beneficial for patients. Other treatment options include phototherapy and ultraviolet light. Interferon alpha or pegylated interferon has been effective in treatment over the years.[28]

Patients with low-risk PV are usually given a phlebotomy and low-dose aspirin. High-risk patients require medical treatment to permanently reduce their hematocrit concentration, eliminate the need for phlebotomy, and reduce the risk of clot formation. All patients receive low-dose aspirin, provided they have a platelet count of less than or equal to one million per $mm^3$. Phlebotomy is typically the initial step in treatment for most patients. A volume of blood is drawn at regular intervals to lower the hematocrit concentration to a normal level within weeks or months. The procedure is identical to that used to donate blood at a blood bank. The immediate effect of phlebotomy is to lower the hematocrit concentration, which usually results in an improvement of specific symptoms, such as headaches, ringing in the ears, and dizziness.[28] Over time, phlebotomy can reduce the hematocrit level to a normal level.

Over time, phlebotomy can lead to iron deficiency. In many cases, it may be the only form of treatment required for patients. Acceptable disease control may be achieved by drawing a blood sample every three months. After phlebotomy, patients may feel tired and need a short rest.[29]

Regarding medication. Patients taking anagrelide may experience side effects, including fluid retention, heart and blood pressure problems, headaches, dizziness, nausea, and diarrhea. Patients who have extremely high platelet counts, bleeding complications, blood clots, or severe systemic symptoms that do not respond to low-dose aspirin or phlebotomy may also be treated with myelosuppressive drugs. Drug therapy to suppress the marrow production of red blood cells and platelets can be used as an alternative to phlebotomy, such as hydroxyurea, which is the most commonly used myelosuppressive chemotherapy drug for PV and is administered orally. It helps to reduce both hematocrit concentration and platelet count.[30]

**Primary immune thrombocytopenia**

Primary immune thrombocytopenia (ITP) is an acquired autoimmune disease with no identifiable cause. The pathogenesis of this condition is complex, with humoral and cellular dysregulation leading to progressive thrombocytopenia as a consequence of production defects and increased platelet destruction. Especially adults may present a hemorrhagic risk that requires medical intervention, and, in addition, the quality of life of the patients is impaired. The fact that the presentation, characteristics, and clinical course are highly variable and heterogeneous makes decision-making regarding diagnosis, treatment, and follow-up of patients particularly difficult. In 2020, the latest recommendations for the management of patients with ITP were published and were a milestone for bringing together all the evidence produced in the last 10 years, which witnessed significant changes in the management of these patients.[31]

The terminology adopted in this document is consistent with the consensus statement of the ITP International Working Group (ITP IWG), published in 2009. ITP is defined as a platelet count < 100× 109/L in the absence of other causes that may be associated with thrombocytopenia. When thrombocytopenia occurs as a consequence of other conditions involving immune-related destruction of these cells, such as the presence of human immunodeficiency virus (HIV) or hepatitis C virus (HCV), systemic lupus erythematosus (SLE), chronic lymphocytic

leukemia (CLL) or the use of certain drugs, it is referred to as secondary immune thrombocytopenia. In terms of stages, the time elapsed since diagnosis determines whether ITP is termed as newly diagnosed, up to 3 months from diagnosis, persistent, 3 to 12 months from diagnosis, chronic, or more than 12 months after diagnosis.[31]

**Classification**

- Newly diagnosed or newly diagnosed ITP: those cases within the first 3 months of disease progression.
- Persistent ITP: those cases with evolution between 3-12 months since diagnosis. It includes patients who do not achieve spontaneous remission or do not maintain a complete response after discontinuation of the proposed therapy.
- Chronic ITP: those cases with evolution longer than 12 months.
- Severe ITP: those cases that debut with severe hemorrhagic manifestations and require the use of intensive treatment schemes constantly.

**Diagnosis**

1. Isolated thrombocytopenia, platelet counts less than 100 x $10^9$/L.
2. Intact or hyperplastic megakaryopoietic system.
3. Erythropoietic and granulopoietic system intact.
4. Exclusion of other causes of thrombocytopenia.

Responses to therapy can be defined as follows: a response occurs when a platelet count of greater than 30 × 10^9/L has been reached, which is at least twice the baseline count. Complete response if values > 100× 109/L are reached and non-response, with counts < 30× 109/L or less than a doubling of the baseline figure. In addition, severe ITP is considered to be a pathology that presents with hemorrhagic symptoms sufficient to indicate treatment, which typically occurs with platelet counts < 20× 109/L. The term refractory ITP refers to the primary lack of response (or relapse) to splenectomy and is additionally severe if it is associated with bleeding or the risk of bleeding requiring therapy.[32]

Although the adoption of this terminology has allowed the establishment of a standardized framework in which to interpret the data from the different studies, there are several limitations, which are currently being addressed in future consensus documents:[33,34] Taking into account that, at present, different therapeutic lines are used in second and subsequent lines that do not necessarily include splenectomy, the designation of refractory ITP should be reviewed. The differentiation between ITP stages is artificial and does not accurately reflect established differences in diverse pathophysiological behaviors. Over the last decade, the emergence of new medical therapies has revealed the possibility of sustained responses following medication withdrawal, known as treatment-free responses. However, the definition of this concept has not yet been agreed upon, and data are needed to support its validity. In this way, the inclusion of a new therapeutic target in trials and even in clinical practice could be a goal to aspire to.[35]

**Hodgkin's lymphoma**

Hodgkin's lymphoma (HL) is a primary malignant disease of lymphoid tissue characterized by the presence of a small number of tumor cells, usually less than 1 %, named Reed-Sternberg cells (RSC) and lymphocytic-histiocytic cells (L&H), accompanied by a significant polymorphous inflammatory cellular infiltrate composed of lymphocytes, plasma cells, histiocytes and eosinophils.H), which are accompanied by a significant polymorphous inflammatory cellular infiltrate composed of lymphocytes, plasma cells, histiocytes and eosinophils; a variable degree of fibrosis and effacement of the standard lymph node architecture.[36] The diagnosis of HL is histopathologic, by excisional biopsy of a lymph node or extranodal tissue. However, in the latter case, it is advisable to biopsy a lymph node as well, except when there is no doubt.[36]

The 2008 WHO classification and the new one of 2016 retain the two types proposed in 1997: nodular lymphocyte-predominant Hodgkin's lymphoma and classical Hodgkin's lymphoma, which in turn are divided into nodular sclerosis, mixed cellularity, lymphocytic depletion, and lymphocyte-rich. The four subtypes of classical HL difier in their clinical features: growth pattern, fibrosis, composition of the cellular milieu, number and degree of Reed-Sternberg cell atypia, and frequency of Epstein-Barr virus infection. However, the immunophenotype of the tumor cells is the same in all four variants; however, this is not the case for the nodular lymphocytic subtype. Classic HL accounts for approximately 95 % of all HL cases, and most cases exhibit expression of CD30 and CD15 but not CD45. HL has evolved from a fatal disease to one of the most curable neoplasms. More than 75 % of all newly diagnosed adult patients can be cured with combination chemotherapy or radiation therapy (RT). Mortality from the disease has declined much faster than any other cancer over the past five decades. Currently, the relative survival rate at one year is approximately 92 %; at 5 years and 10 years, it is 86 % and 80 %, respectively. This is due to advances in staging methods and the recognition of prognostic factors, the use of more effective drugs, more accurate and refined RT fields, more rational combinations of the various

therapeutic modalities, and more possibilities to treat complications observed during or after treatment, as well as the development of cooperative clinical trials. In the last 30 years, advances in the treatment of HL have achieved cure in about 75-80 % of patients, with standard chemotherapy or with the combination of this and RT. Still, significant problems are caused by the toxicity of the treatments. Therefore, the main objective of current treatment protocols is to achieve a cure for patients with fewer side effects.[37]

Although globally, the results of the treatment are positive, there are about 15 % of cases with advanced stages relapse, and only 50 % of them achieve a second remission. In patients over 60 years of age, treatment outcomes tend to be less favorable. The characterization of patients with HL is vital for determining the appearance of complications, sequelae, and their direct relationship with the treatments used, as well as the risk factors for their development. This enables the development of strategies that contribute to improving patient survival.[37]

75 % of all newly diagnosed patients with adult Hodgkin's lymphoma can be cured with a combination of chemotherapy and radiotherapy. Careful staging and treatment determination by a multidisciplinary team of cancer specialists are needed to determine the optimal treatment for this type of patient. The mortality rate of adult Hodgkin's lymphoma has declined much more rapidly than any other cancer due to the excellent results achieved by radiotherapy, modern immunotherapy, and effective combination chemotherapy.[37]

The ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) polychemotherapy scheme remains the gold standard in almost all HL situations. Wide-field radiotherapy is used less and less. The affected-field RT technique is generally recommended, with doses not exceeding 36 Gy in most cases.[38]

**Pillars of treatment**

- Greater use of prognostic factors for therapeutic decisions.
- Less use of laparotomy and lymphography in staging, greater confidence in imaging techniques.
- Greater use of chemotherapy in localized stages.
- Reduction of treatment toxicity: fewer cycles of polychemotherapy, combinations of drugs with lower toxicity, reduction of fields and irradiation dose.
- Use of intensive and high-dose chemo-radiotherapy schemes with hematopoietic progenitor cell transplantation.[39,40]

**Non-Hodgkin's lymphoma**

Non-Hodgkin lymphomas (NHL) constitute a heterogeneous group of lymphoproliferative cancers that exhibit distinct patterns of behavior and varied responses to treatment. Like Hodgkin's lymphoma, non-Hodgkin's lymphoma usually originates in lymphoid tissues and can spread to other organs. However, NHL is much less predictable than Hodgkin's lymphoma and has a greater predilection to spread to extranodal sites. The prognosis depends on the histologic type, stage, and type of treatment.[41]

NHL can be divided into three groups according to their prognoses: indolent, aggressive, and very aggressive lymphomas. The fast-growing types of NHL have a shorter natural history, but a significant number of these patients can be cured with intensive combination chemotherapy regimens. In general, with modern treatments for patients with NHL, the overall five-year survival is approximately 50 % to 60 %. Between 30 % and 60 % of patients with aggressive or very aggressive NHL can be cured.[41]

The diagnosis of non-Hodgkin's lymphoma is typically made histopathologically through hematoxylin-eosin staining. It must be performed by surgical biopsy of the lymph node or an extranodal suspicious site to evaluate the nodal architecture and cell type. This histological diagnosis is complemented by immunohistochemistry to determine the origin of the tumor. FNA (fine-needle aspiration biopsy) is inconclusive.[41]

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The anamnesis is aimed at looking for B symptoms and predisposing factors. A careful physical examination should be performed, with attention to all peripheral lymph node chains, the spleen, liver, and Waldeyer's ring, as well as an assessment of performance status. The classification of non-Hodgkin's lymphoma can be very confusing (even to physicians) because there are so many types, and several different systems have been used. The most recent classification system is that of the World Health Organization (WHO). The WHO system categorizes lymphomas based on their microscopic appearance, the chromosomal characteristics of the lymphoma cells, and the presence of specific proteins on the cell surface. The most common types of lymphomas are presented below, categorized by whether they are B-cell or T-cell lymphomas. Some rare forms of non-Hodgkin's lymphoma are not discussed in this document.[40]

Non-Hodgkin's lymphoma (NHL) is one of the most common cancers, accounting for about 4 % of all cancers.

The most recent estimates from the American Cancer Society regarding non-Hodgkin's lymphoma indicate that by 2026, Approximately 69 740 people will be diagnosed with non-Hodgkin's lymphoma. This includes both adults and children. Approximately 19 020 people will die from this cancer. The average U.S. lifetime risk of non-Hodgkin lymphoma is about 1 in 50. Each person's risk may be affected by certain risk factors listed in the next section.[42,43]

Mortality rates for non-Hodgkin's lymphoma have been declining since the late 1990s. Although some types of NHL are among the most frequent childhood cancers, more than 95 % of cases occur in adults. The kinds of NHL seen in children are often very different from those seen in adults. For more information, see our paper on Non-Hodgkin's Lymphoma in Children.[44] Although NHL can occur at any age, approximately half of patients are older than 65 years. The risk of non-Hodgkin's lymphoma increases over the life course. The aging population of people living in the United States is likely to contribute to an increase in cases of non-Hodgkin's lymphoma over the next several years.[45]

**Acute Myeloid Leukemia**

Acute myeloid leukemia is a neoplastic involvement of hematopoietic stem cells in which there is a clonal overproduction of hematopoietic stem cells. It is considered a heterogeneous group of diseases.[46]

Previous chemotherapies, chemical exposure to some substance, or idiopathic genetic mutations have been proposed as triggering factors of the disease. The clinical manifestations of the disease are mainly centered on hematopoietic germline involvement. However, cases have been documented where extramedullary clinical features such as myeloid sarcomas and cutaneous leukemia are present.[46]

The diagnosis of this entity is based on an essential pillar for medical action. This pillar is applicable in any pathological situation. The study of bone marrow samples constitutes a vital element. It involves the quantification of the cells as well as the analysis of their structural components. The study of the genome, especially its modifications, is a key aspect of the field.[47]

Only a count of more than 20 % belonging to the ballasts or genetic alterations is sufficient to diagnose the disease. The World Health Organization, in its guidelines, recognizes six types of acute myeloid leukemia: acute myeloid leukemia with recurrent genetic abnormalities, acute myeloid leukemia with changes related to myelodysplasia, treatment-related myeloid neoplasms without further specification, myeloid sarcoma, and myeloid proliferations associated with Down syndrome.[47]

Worldwide, 80 % of cases of acute myeloid leukemia occur in adults. However, in infants, it represents 33 % of neoplasms. Treatment includes two types of therapies: initial induction therapy and post-remission therapy. The objective of the former is to achieve complete remission—however, the second attempts to halt the progression of a pathological relapse. The patient's functional status is a key element to be considered when initiating treatment protocols.

On the other hand, the biological state of the disease and the patient's objectives are key factors to be considered. However, approximately 1/3 of treated patients need new interventions due to relapses. Significant progress in research and knowledge about the human genome has enabled the subclassification of Acute Myeloid Leukemia into distinct groups. Each group has specific characteristics based on immunophenotype. It has ensured better clinicopathology, as well as the search for accurate treatments, which are defined in the various National Protocols.[47]

The use of monoclonal antibodies is becoming increasingly critical. Blinatumomab is a drug for the previous preparation of the patient candidate for transplantation. Its mechanism involves stimulating T lymphocyte cells to focus their action on B lymphocytes. Chemotherapy is the most widely used therapeutic means in any neoplastic process. Specifically, in Acute Myeloid Leukemia, it is only applied to patients who clinically present with characteristics that allow them to survive the treatment. It is known as 7+3 therapy. Cytarabine is infused for 7 days, but a 3-day cycle of daunorubicin (an anthracycline) is previously performed. The results have shown a considerable improvement in 80 % of patients with favorable prognosis and 60 % for intermediate patients. This therapy has been improved with the introduction of new drugs, such as Gemtuzumab oligomycin, which has decreased the risk of relapse.[48]

In reviews, the benefits of two new drugs, which are being combined with classic chemotherapy, have been presented (7+3). Vosaroxin is considered a superior effector to traditional anthracyclines (daunorubicin). Volasertib, on the other hand, induces the accelerated maturation and subsequent death of cancerous myeloblastic cells.[46]

A study on the use of anthracyclines was conducted at the Institute of Hematology and Immunology in our country. It showed a higher probability of survival in the 50-59 age group, at 80 %, compared to younger people. However, the outstanding group showed a relapse at 27 months after treatment. The authors consider that, although age is an essential factor to be taken into account in many pathological entities, it may not be a strong determinant in acute myeloid leukemia.[46]

Cytotoxic chemotherapies are used in patients with the possibility of relapse. However, morbidity is high

when attempting to eliminate the relapse rate. The FLT3 complex is a potent inducer of cell maturation in the bone marrow. In pathological conditions, it is a double-edged sword if its genetic sequence is altered, as in 30 % of cases of acute myeloid leukemia. From this follows the action of the FLT3 inhibitor, which, although still in the clinical trial phase, shows encouraging results.[47,48]

Our economy exhibits remarkable regulatory mechanisms for internal control. It highlights cellular developmental checkpoints through which cancerous myeloblastic cells evade Immune System regulators. On this basis, potent inhibitors have been developed that induce brief but effective immune responses. Like the previous one, they are in clinical trials. Alemtuzumab is considered a synthetic antibody for treatment. It focuses its action on the induction of cell death through the involvement of antibodies and the complement system. In other words, it is based on the elimination of cancer cells in the periphery. These clinical trial phase studies indicate that efforts to improve treatment protocols are ongoing. However, these projects are primarily focused on adults.[49]

**Multiple Myeloma**

Multiple myeloma (MM) is characterized by the neoplastic proliferation of a clone of plasma cells that, in most cases, produces a monoclonal protein. This proliferation in the bone marrow frequently invades adjacent bone, causing destruction of the skeleton and leading to bone pain and fractures. In addition, other essential features include anemia, hypercalcemia, and renal failure.[50]

The incidence is approximately 4 to 5 times 100 000, with higher incidence in the black population, and the average age at diagnosis is 65 years (only 3 % of cases are younger than 40). In recent years, there has been an increase in the number of cases, which is related to earlier diagnoses. More than 70 % of the cases are normocytic normochromic anemia. Ninety-eight percent of cases have a serum or urinary paraprotein at the time of diagnosis. Protein electrophoresis reveals a monoclonal peak in approximately 80 % of patients, hypogammaglobulinemia in around 10 %, and a regular appearance in the remainder. Immunoelectrophoresis in serum shows an IgG paraprotein in 53 %, IgA in 20 %, light chains only in 17 %, IgD in 2 %, and an abiclonal gammopathy in 1 %. Additionally, 7 % have no serum paraprotein.[51]

Urine studies show paraprotein in 75 % of patients. The light chain study shows a kappa/lambda ratio of 2:1. In the myelogram and bone marrow biopsy, plasma cells may represent from 10 % to 100 % of the nucleated cells. Radiological studies of the skeleton reveal lesions in more than 80 % of cases, which may be characteristic osteolytic lesions associated with sacabocados, osteoporosis, and fractures. The most affected bones are the vertebrae, the skull, the thoracic cage, the pelvis, and the proximal regions of the femur and humerus.[52]

Hypercalcemia and increased creatinine can be detected in 20 % of cases at diagnosis.

*Diagnostic criteria*

The minimal criteria for the diagnosis of MM are More than 10 % plasma cells in the bone marrow. Presence of a paraprotein in the serum (usually greater than 3 g/dL). Presence of a urinary paraprotein ¾ Osteolytic lesions Criterion 1 and at least one of the other three are required. These data should not be related to metastatic carcinoma, connective tissue disease, lymphomas, or chronic infection. The differential diagnosis should be made with monoclonal gammopathy of unknown cause and with latent myeloma.[52]

At present, therapeutic options for patients with symptomatic MM range from dexamethasone pulses to with or without thalidomide, conventional chemotherapy, and high-dose chemotherapy with hematopoietic cell transplantation (HCT). The treatment decision depends on the patient's age, overall health, and personal preferences. The five current strategies in MM therapeutics are as follows:

- High-dose corticosteroids (dexamethasone or methylprednisolone).
- Thalidomide (alone or in combination with high doses of dexamethasone)
- Conventional chemotherapy: VAD, melphalan/prednisone, cyclophosphamidaprednisone, VMCP, MOAP,
- HCT, autologous or allogeneic, peripheral blood progenitor cells
- Proteosome inhibitors (bortezomid) Recommendations
- If the patient is under 60 years of age and there is a possibility of autologous peripheral blood hematopoietic progenitor cell transplantation, induction treatments that do not contain alkylating agents such as the VAD scheme are recommended.
- If the patient is under 50 years of age, the possibility of allogeneic transplantation should be evaluated and an HLA study should be performed.
- In patients older than 60 years and patients who do not have criteria for autologous HCT, the recommended regimen is melphalanprednisone. This is not strict and depends on the patient's condition.
- Patients with renal damage should be treated with VAD, high doses of dexamethasone or dexamethasone-thalidomide. Induction treatment will be maintained for at least 6 months, until a favorable therapeutic response is obtained.

During induction treatment, protein electrophoresis and blood chemistry studies will be performed every two months. High doses of corticosteroids, dexamethasone at a dose of 40 mg/day per v/o, x 4 consecutive days, in a scheme similar to VAD. A 60-70 % response rate is reported. Among the advantages reported are easy administration, the absence of hematologic toxicity, suitability for elderly patients or those with poor general health, and the elimination of alkylating agents. It is recommended in patients who are contraindicated for cytotoxic chemotherapy, have severe pancytopenia, or require extensive radiotherapy. It is helpful as initial therapy in patients presenting with renal impairment.[52] Methylprednisolone pulses: 2 g 3 times/week for at least four weeks. Less toxicity reported than dexamethasone.

Thalidomide has shown effect in patients at debut and relapse. Its mechanism of action is not well known, but it is considered to involve anti-angiogenic activity, interference with adhesion molecules, and cytokine release. It is administered orally daily (usual dose: 50-200 mg/day). It has been combined with high doses of dexamethasone, and 70-80 % of responses have been reported. Dose: thalidomide 50-200 mg / day, dexamethasone 40 mg/day/ppr v/o, days 1-4 (or 1-4, 9 - 12, 17-20) every 28 days. Its combination with conventional chemotherapy is evaluated. Some studies employ an MPT scheme (melphalan 4 mg/m$^2$ per v/o, x 7 days per month; prednisone 40 mg/m$^2$ per v/o, x 7 days per month; thalidomide 100 mg/day, per v/o) and report similar results to those of autologous HCT.[53]

The main toxic effects are sedation, constipation, peripheral neuropathy, and deep vein thrombosis. There is no or minimal hematologic toxicity. Conventional chemotherapy of MM using alkylating agents prolongs survival between 26 and 46 months, with a response being observed in 60 % of cases, the response varying according to the stage. However, at present, many patients start with non-alkylating schemes to eliminate the initial exposure to these drugs before HCT, in which high doses of these drugs will be used. The VAD regimen is effective in 60-80 % of cases and is the non-alkylating regimen of choice for patients who are candidates for HCT, those with renal damage, and those in whom a rapid response is required.[54,55]

**Medullary Aplasia**

Medullary aplasia (MA) or aplastic anemia is a clinical syndrome characterized by pancytopenia and bone marrow with markedly reduced cellularity without evidence of tumor infiltration, myelodysplastic syndrome (MDS), or increased reticulin. Aplastic anemia is a distinct entity characterized by a primary deficiency of hematopoietic progenitor cells (stem cells), leading to bone marrow aplasia or hypoplasia and resulting in pancytopenia. The term "bone marrow failure or marrow failure" is a more encompassing term that describes pancytopenia caused by a variety of mechanisms, such as replacement of marrow tissue by tumor infiltration or fibrosis, and MDS in which hematopoietic progenitor cells are malignant and are present or increased in number but do not mature.[56]

The term "aplastic anemia" has been in use for more than 90 years and is considered by many to be inappropriate, as the condition is defined by pancytopenia, not anemia alone. Furthermore, anemia has less impact on morbidity/mortality than neutropenia or thrombopenia, which are also present. A possible underlying cause should be sought at the time of diagnosis of MA, as well as evidence of an accompanying paroxysmal nocturnal hemoglobinuria (PNH) clone or an abnormal cytogenetic clone.[57]

The annual incidence of AM varies in different geographic regions. In the USA and Europe, it is approximately 2-3 cases per million population, but it is more frequent in Asian countries. In Thailand, it is reported to be 4/million inhabitants in the capital city and 6/million in rural areas; in Japan, the incidence (based on retrospective studies) is reported to be 14/million inhabitants. It is considered that this increased incidence in Asian countries is related to environmental factors, such as increased exposure to toxic chemicals, rather than to genetic factors because this incidence is not observed among Asian populations living in the United States. The exact annual incidence data for South America and Africa are not known but are considered to be similar to those of Asian countries.[57]

AM is a disease of young adulthood but has been reported in all ages and is considered to be a disease of triphasic incidence. There is a small peak in childhood (between 2 and 5 years), which may be related to the presence of hereditary causes. A high incidence is observed in individuals aged 20-25 years, with another peak incidence in people older than 55-60 years. Some point out that the latter is probably related to the inclusion of MDS cases diagnosed as AM.[58]

AM can be congenital or, much more frequently, acquired. The primary primary etiology of acquired AM is exposure to a wide range of drugs, chemicals, ionizing radiation, and certain viruses. Some specific circumstances have been strongly associated with the onset of AM, and perhaps the most impressive picture is the development of aplastic anemia in patients undergoing orthotopic liver transplantation. AM can also occur in patients with various immune disorders and pregnancy. In the latter situation, it is usually self-limited. It resolves with delivery, and it is not precisely known whether the association is coincidental or whether pregnancy plays a role in the development of AM. A large body of clinical and laboratory data now supports the hypothesis that most patients with acquired AM have an immunologic component responsible for the destruction of hematopoietic progenitor cells.[59]

The various studies that should be performed on a patient with SMA are aimed at confirming the diagnosis, excluding other possible causes of pancytopenia with hypocellular marrow, excluding hereditary causes of SMA, screening for an underlying cause of acquired SMA, confirming or excluding a cytogenetic clone or a clone of HPN.[59]

*Diagnostic criteria for MA*

Clinical: manifestations of bone marrow failure. Absence of history or family history. Absence of hepatic/splenomegaly and adenopathy.

Peripheral blood: pancytopenia, absolute reticulocytopenia, morphologically normal blood cells, and slight macrocytosis may be observed in erythrocytes. Bone marrow is profoundly hypocellular, with a decrease in all hematopoietic cellular elements, with medullary spaces composed mainly of fat and stromal elements.[57]

The residual hematopoietic cells are morphologically normal; however, some dysplastic signs may be present in the red blood cell series.There is an absence of malignant infiltration or fibrosis, with normal cytogenetic and HPN studies. The clinical course and prognosis of MA are dependent on disease severity and age. The estimation of seriousness is also crucial in treatment decisions, and the degree of severity is based on the hemogram and bone marrow data.[58]

Seventy percent of patients with AMs or AMms who do not receive successful treatment die within the first year. Patients with AMms have a high mortality and a higher risk of fatal infectious complications. Prognosis is also influenced by age, and in any degree of severity of AM, therapeutic outcomes and outcomes are much worse in older patients. It has been reported that the 5-year overall survival rate of patients with AMms, treated with immunosuppression, is 49 % in patients < 49 years, 40 % in patients between 50 and 60 years, and 21 % in patients > 60 years. Among cases of moderate AM, the overall survival rate at 5 years is 86 %, 72 %, and 54 % in the above age groups.[59]

Treatment of acquired AM should be aimed at three objectives: Elimination or immediate suspension of the probable causative factor or agent if known or suspected. Insistence should be placed on eliminating exposure to environmental toxicants (such as solvents and pesticides) and medications. If, at the time of debut, the patient was taking several drugs that may have been implicated in the development of MA (even if only based on a single case report), all of these medications should be discontinued, and the patient should no longer take them, even if they recover from MA. The standard treatment for a patient diagnosed with MA is allogeneic HCT or immunosuppressive therapy (ITT). Allogeneic HCT from an HLA-identical sibling donor is indicated as first-line treatment in patients with severe spinal cord aplasia (SMAs) or very severe spinal cord aplasia (mSAs). With an HLA-identical sibling donor, age < 40 years (there is controversy with the upper age limit for HCT).[60]

SCT with a combination of anti-thymocyte globulin (ATG) or antilymphocyte globulin (ALG) and cyclosporin-A (CsA) is indicated in patients who are transfusion-dependent and who do not have a sibling donor for HCT. HCT with an unrelated donor can be considered a therapeutic measure in young patients without a matched sibling and who do not respond to immunosuppression. Children with non-severe MA, with an HLA-identical sibling donor, and who are transfusion-dependent may be considered for HCT in cases of non-response to ISCT.[60]

It is essential that before starting specific treatment (HCT or SCT), the patient is clinically stable in terms of bleeding control and treatment of infections. Administering immunosuppressive therapy in the presence of disease or uncontrolled bleeding is dangerous. Some authors recommend that, in certain situations, it may be necessary to proceed with HCT even in the presence of active infections, especially fungal infections, because it is the fastest way to achieve neutrophil recovery and the only way to prevent disease progression. Spontaneous remission in AM is very infrequent, and from a practical point of view, the time to initiate specific treatment should be the time necessary to confirm the diagnosis, stabilize the disease, determine the severity, perform the family HLA study, and decide on the therapeutic strategy. The use of steroids as specific therapy is not recommended due to their ineffectiveness, their action favoring bacterial and fungal colonization, and the risk of gastrointestinal bleeding in a patient with severe thrombocytopenia. Likewise, growth factors (G-CSF, rPET) should not be used in recently diagnosed patients under the erroneous belief that they can stimulate the marrow and achieve healing. Patients with AM should be followed throughout life to monitor for possible relapse or the development of a clonal disorder.[59]

**Transfusion medicine**

Blood transfusion is a simple form of organ transplantation. Blood (the fluid) is transferred from a donor to a patient to correct a deficiency or impairment of function temporarily.[60]

Both the organ and the patient must undergo rigorous screening to ensure compatibility. Transplantation is only indicated when there are specific abnormalities, and the recipient patient is expected to benefit from the procedure. Transfusion can transmit infectious diseases and can result in rejection with serious complications for the recipient.[60] Transfusion is a component of transfusion medicine.

Transfusion medicine is a vital component of orthopedic surgery practice. Although transfusion medicine

covers all aspects of blood and blood component administration, its most important feature for the practicing orthopedic surgeon is hemoglobin (Hb) control. Adequate Hb control requires that the surgeon be knowledgeable about transfusion practices, the advantages and disadvantages of different possibilities for Hb control, and strategies to avoid the need for blood administration.[60]

Several hundred antigenic systems have been identified in red cells, but only a few of them (less than 12) are responsible for the majority of alloimmune transfusion reactions. Although the clinical significance of the different erythrocyte antigenic systems has been known for over 100 years, knowledge of the functional significance of many of these systems is relatively recent. For example, blood group antigenic proteins are responsible for the structural integrity of the red cell membrane and also for the transport of substances across the membrane, act as receptors for various complement components, exhibit adhesion properties, and show enzymatic activity. Pretransfusion tests now routinely determine the presence or absence of the major blood group antigens and their antibodies.[60] Blood group antigens are the most common blood group antigens.[61]

Blood group A and B antigens are expressed from birth. The blood group O phenotype is due to the absence of transferase activity, which adds an immunodominant acetylgalactosamine or galactose molecule to the A and B erythrocyte antigens, respectively, which are expressed in large amounts. After the first years of life, healthy individuals develop circulating isoagglutinins against the A or B antigens they lack. The expression of A and B antigens is the primary factor determining red blood cell transfusion practices. Studies are underway to evaluate the use of enzyme activity to convert individuals with group B and A blood to the more common group O phenotype.[62]

Rh is the most complex and immunogenic antigenic system of all blood group-related antigenic systems. It consists of almost 50 antigens, including the major antigens D, C, c, E, and e. Antisera to the D antigen results in agglutination of 85 % of human erythrocytes. In the absence of immunization through transfusion or pregnancy, the presence of antibodies to the Rh system is not routinely detected. However, routine screening of blood samples is necessary to rule out the presence of the D antigen due to its immunogenicity and association with Rh hemolytic disease of the newborn. Although erythrocytes lacking Rh antigens (Rhnull phenotype) are stomatocytes, and Rhnull disease is associated with hemolytic anemia, the role of the Rh antigens has not yet been precisely determined.[62]

In addition to the ABO and Rh systems, the most crucial erythrocyte antigenic systems are the Kell, Duffy, Kidd, and MNS systems. Generally, antibodies to these antigens appear after transfusion treatment or after feto-maternal hemorrhage during pregnancy. Anti-Kell antibodies are relatively frequent and may accelerate the elimination of transfused red blood cells. Negativity for Duffy antigens [Fy(a-b-)] is frequent in blacks. Patients with this phenotype may have alloantibodies that cause delayed hemolytic transfusion reactions. Antibodies to the Kidd antigens (anti-Jka and anti-Jkb) may be difficult to detect during pretransfusion testing and may result in a delayed hemolytic transfusion reaction. Antibodies to the MNS antigens can cause clinically significant hemolysis.[63]

Until the 1980s, blood transfusion was regarded as a relatively risk-free practice. Consequently, transfusions were routinely administered before surgery to patients whose Hb levels were < 10 g/dL. Following the emergence of human immunodeficiency virus (HIV) infection and considering the morbidity and mortality associated with other transfusion-related infections such as hepatitis C virus (HCV), the appropriateness of routine transfusion based on Hb values has been questioned. In the management of surgical patients with anemia, the primary consideration should be the potential immunomodulatory effects rather than the risks of transfusion-related viral infections. Additionally, the oxygen supply capacity of transfused red cells is not optimal, particularly when transfusion is performed with relatively old red cell units. Therefore, transfusion therapy should be practiced according to the following guidelines: patients should only receive the components necessary to correct a specific deficiency, and treatment should aim to restore functional levels of the deficient element rather than normalize analytical values. Red cells are transfused to improve the oxygen-carrying capacity of the blood rather than to correct hypovolemia. Several studies have shown that patients with chronic anemia can perform very well with Hb levels in the range of 7 to 8 g/dL, as they exhibit several compensatory mechanisms that maintain tissue oxygenation in situations of chronic anemia. These mechanisms are modifications in tissue oxygen extraction and utilization, as well as modifications in the oxygen dissociation curve secondary to changes in the erythrocyte level of 2,3-bisphosphoglycerate, pulmonary ventilation/perfusion, and cardiac output. This Hb level is well tolerated in patients who are chronically anemic and otherwise healthy; however, Hb monitoring is often necessary in patients with acute anemia, cardiopulmonary disease, or other concurrent illnesses. A variety of red blood products are available in hospital blood banks, although most of them do not store whole blood.[62]

Red blood cells are the component of choice for treating acute anemia. A unit of packed red cells consists of erythrocytes in a unit of whole blood, excluding most of the plasma. The leukocytes present in a unit of blood may be responsible for various adverse effects such as HLA alloimmunization, transmission of cell-mediated immunity-related viruses, graft-versus-host disease, and immunomodulation. Red cells washed with multiple

steps in saline can be transfused to patients with a history of allergic reactions to plasma proteins. Finally, frozen red cells can be deglycerolized and thus represent a source of rare blood types indicated in patients for whom there are no compatible units.[63]

Attempts to develop red blood cell substitutes have been ongoing for hundreds of years, although they have not yet been commercially available outside of clinical trials. Until the HIV epidemic, the large availability of donated blood and the existence of hospital transfusion services made the procurement of artificial substitutes a low priority. The development of blood substitutes has given rise to several problems that limit their usefulness. For example, they exhibit a short intravascular half-life (≤ 2 days) compared with the 120-day duration of circulating red blood cells. In addition, the absence of the erythrocyte membrane allows for the rapid diffusion of oxygen from the transport molecule to adjacent tissues, resulting in a disruption of the autoregulatory mechanism of the microvasculature. Consequently, as second and third-order third-order arterioles become constricted to modulate excessive tissue oxygen levels, ischemia may occur. Hb molecules then readily trap nitric oxide. When this natural vasodilator is taken up by the large circulating amounts of free Hb, vasoconstriction occurs, and blood pressure may increase.[61]

A variety of infectious agents have been identified in human blood. Although the risk of transfusion-associated disease caused by these agents is currently unknown, the possibility of infection does exist. However, at the dawn of the 21st century, blood used in the United States is safer than it has ever been—thanks to genomic Screening Tests for Transfusion-Related Pathogens. Several factors have contributed to the increased safety of transfused blood, including detailed interviews to exclude high-risk donors, implementation of measures for inactivating lipid-coated viruses, monitoring of infectious disease trends, and the introduction of tests for specific infectious agents. Currently, screening tests for hepatitis B virus (HBV), HCV, HTLV-1 and -2, as well as HIV-1 and -2, are performed.[62]

Screening tests have significantly decreased, but not eliminated, the risk of viral infection due to transfusion. There is a window period during which viremia may occur without antibodies or with such low concentrations of antibodies that they are undetectable; during these periods, circulating levels of antigen may also be too low to be detected by conventional techniques. Therefore, various methods—such as polymerase chain reaction (PCR), reverse transcriptase PCR, ligase chain reaction, nucleic acid sequence amplification, and transcription amplification—have been used to detect silent infections in patients.[62]

Newly discovered transmissible pathogens can also be detected using nucleic acid amplification technology (NAT), which can differentiate between antibody-positive patients (e.g., in neonatal HIV) and actively infected patients, as well as distinguish between strains and detect asymptomatic infections. False-negative results can occur when viral clearance is complete, subthreshold viremia is present, PCR primers are obtained from the least conserved regions of the virus, or when blood has been stored under conditions that favor degradation of the genomic material of the agent in question. The sensitivity of TAN testing is at the level of 10218 g nucleic acids. TAN is currently being used in both the United States and continental Europe for the detection of infectious agents in large quantities of plasma. The application of these tests to individual donations is theoretically attractive but economically very expensive.[64]

The incidence of hemolytic transfusion reactions is approximately 1 in 250 000 to 1 in 1 million. Approximately half of the deaths are attributed to ABO incompatibility due to administrative errors. This eventuality is more frequent in cases treated outside the laboratory and is due to a lack of knowledge of the patient's blood group. Delayed hemolytic transfusion reactions, which occur in approximately 1 out of every 1000 units, are associated with decreased red cell survival and may appear masked as hemolytic anemia of immune origin.[64] The incidence is higher in patients who are treated for hemolytic anemia.

The incidence is higher in patients who receive frequent transfusions. Febrile transfusion reactions are the most frequent adverse effect associated with blood administration. These reactions may be due to a reaction between the recipient's HLA antibodies and the donor's leukocytes, or they may be the consequence of elevated cytokine levels in the transfused unit. Patients with a history of febrile reactions should receive units of blood in which leukocytes have been removed before storage. Transfusional anaphylactic reactions are most often the result of transfusion of anti-IgA IgE antibodies to IgA-deficient recipients. IgA deficiency is relatively standard. Intense washing of cellular blood products is necessary to avoid these reactions. Transfusion-related lung injury may be due to the presence of HLA or antineutrophil antibodies in the donor plasma. The severity of the reaction appears to be related to the patient's overall cardiopulmonary status.[65]

Preoperative autologous donation (PAD) offers several advantages, including the absence of infectious complications and immunomodulation, although the procedure is not entirely without risk. Syncopal or ischemic episodes may accompany the donation process. In addition, reinfusion of autologous units can also lead to the occurrence of adverse effects, sepsis, volumetric overload, and hemolytic transfusion reactions caused by the same type of administrative error that complicates allogeneic transfusions. Because patients in good health may require weeks for regeneration of blood lost during DAP, these patients often have lower Hb levels before surgery than before DAP. The primary issue with this procedure is that many of the donated units are never

utilized. Nearly half of the autologous units donated in the context of total arthroplasty are not transfused. The complex nature of the DAP procedure may render it non-cost-effective.[65]

## CONCLUSIONS

The article provides a comprehensive and up-to-date overview of blood and its diseases. This resource is essential for healthcare professionals and students. It promotes an evidence-based approach.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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