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ANEMIA: A COMPREHENSIVE REVIEW OF PATHOPHYSIOLOGY DIAGNOSIS AND MANGEMENT

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ABSTRACT
Anemia is a major global health concern affecting all age groups, especially children, women of reproductive age, and pregnant women. It is characterized by reduced hemoglobin concentration or red blood cell mass, resulting in impaired oxygen delivery. Causes include nutritional deficiencies, chronic diseases, infections, genetic disorders, and socioeconomic factors. This review summarizes the pathophysiology, classification, diagnostic evaluation, and management of anemia. Laboratory tools such as complete blood count, peripheral smear, and reticulocyte count are essential for diagnosis. Early detection and targeted treatment can reduce morbidity and improve quality of life.

KEYWORDS: Anemia, Hemoglobin, Red Blood Cells, Peripheral Blood Smear, Blood Transfusion, Public Health.

INTRODUCTION

Anemia is a global health problem.[1] One of the biggest health burdens in India and many other developed countries of the world is pediatric anemia, which causes a slower rate of growth, impaired development, and delayed wound healing.[2] RBCs oversee delivering oxygen (O_2) to every organ in the body system through a protein called hemoglobin (Hb), and when RBC and Hb levels are low, the body's cells are struggling and do not obtain enough oxygen.[3] Young children and pregnant women bear the brunt of this condition, with an estimated global prevalence of 43% and 5%, respectively. Prevalence is 37.70% in school-age children, 35% in non-pregnant women, and 18% in adult males. The World Health Organization (WHO) defined anemia as having a hemoglobin level of less than 11 g/dL for girls and less than 12 g/dL for boys under the age of 15.[4] Hemoglobin levels between 10 and 12.9 g/dL in men and 10 to 11.9 g/dL in women were considered mild anemia; hemoglobin levels between 7 and 9.9 g/dL were considered moderate anemia; and hemoglobin levels below 7 g/dL were considered severe anemia.

Adolescent iron deficiency impairs growth, increases susceptibility to infections, reduces cognitive performance, and increases the probability of unfavorable pregnancy outcomes.[5] Poor diet contributes to almost 60% of iron-deficient cases. Gender differences are primarily seen after puberty. Menstruation in females causes recurring blood loss, while increasing testosterone in post-pubertal boys increases the synthesis of erythropoietin (EPO).[6] Anemia can be congenital, acquired, acute, or chronic. Anemia can result from decreased RBC production or increased hemolysis. Anemia is defined clinically based on the mean corpuscular volume (MCV) of red blood cells (RBCs): normocytic (MCV within normal range for age). Microcytic or macrocytic. Additional red cell indices, such as the reticulocyte count, can help identify the cause of anemia.[6]

ETIOLOGY

Food insecurity, clean water, and sanitation are examples of distal factors that contribute to the determinants of anemia, according to anemia etiology. And, finally, the most obvious causes of anemia (such as illness, inflammation, nutritional deficits, and hemoglobin abnormalities).

Numerous factors are connected to one another. For instance, poor socioeconomic status is linked to an increased risk of anemia in women and children, and poverty is a major driver of health and nutrition.Similarly, a higher risk of anemia was linked to lower levels of schooling.[7]

Whether anemia is hypo proliferative (corrected reticulocyte count <2%) or hyperproliferative (corrected reticulocyte count >2%) determines its cause.

Microcytic anemia (MCV<80 fl), normocytic anemia (MCV 80-100 fl), and macrocytic anemia (MCV>100 fl) are further classifications of hypo proliferative anemias based on mean corpuscular volume.[8]

Anemia may be caused by several factors: nutrient deficiencies, an inadequate diet (or the inadequate absorption of nutrients), infections, inflammation, chronic diseases, gynecological and obstetric conditions, and inherited red blood cell disorders.

Infections can be another important cause of anemia, depending on the local burden of infectious diseases, such as malaria, tuberculosis, HIV, and parasitic infections. Infections can impair nutrient absorption and metabolism (e.g. malaria, ascariasis) or can cause nutrient loss (e.g. schistosomiasis, hookworm infection). Many different chronic conditions can cause inflammation and lead to anemia of inflammation or anemia of chronic disease.[9]

HIV infection causes anemia through a wide range of mechanisms including ineffective production or excessive destruction of red blood cells, blood loss, and side effects of drug treatment. Consistent heavy menstrual losses, maternal blood volume expansion during pregnancy, and blood loss during and after childbirth, particularly in cases of postpartum hemorrhage, commonly lead to anemia.

Additionally, in some regions, inherited red blood cell disorders are a common cause of anemia. These include conditions such as α- and β-thalassemia due to abnormalities of hemoglobin synthesis, sickle cell disorders due to changes in the hemoglobin structure, other haemoglobinopathies due to hemoglobin gene variants, abnormalities of red cell enzymes, or abnormalities of the red blood cell membrane.[9]

Hereditary spherocytosis (HS) is a diverse collection of illnesses that disrupt the membrane proteins of erythrocytes, causing the erythrocytes to be less deformable and to degrade more quickly in the spleen.[10]

EVALUATION OF ANEMIA

Anemia clinical evaluation is a common issue in healthcare.[11] Over the last ten years, major development have been achieved in the pathophysiology of several different causes of anemia, as well as in technology and the methods used to perform a number of common clinical examinations.[12] In this article we will go through the current laboratory assessment of anemia.

The main objectives of diagnostic tests should be:
(1) Figuring out whether anemia is present.
(2) Figuring out the underlying cause.

More specialized assays will be discussed later in this article. First, standard testing (complete blood count, reticulocyte count, and blood smear) will be reviewed.[13]

HISTORY AND PHYSICAL EXAMINATION

To identify the patient's medical history and physical examination in order to determine whether anemia is present. Family history is most useful for identification of heredity hemolytic disorder, heredity bleeding disorder, congenital vascular abnormalities such as heredity hemorrhagic telangiectasias. Early greying of the hair, burning sensations on the tongue, skin changes, ulcers around the mouth's angles, and discomfort and brittleness of the fingernails are all signs of anemia brought on by a lack of certain nutrients.[14]

Urinary or hematologic diseases may be indicated by abnormal urine color that suggests blood or hemoglobin. Uncomplicated hemolytic anemia lacks bilirubin, although elevated urobilinogen may cause darker urine.[14]

Petechiae, ecchymoses, and bruises may indicate hemostatic problems, platelet or liver involvement, or blood loss. Anemia may be an early indicator of underlying illnesses such as liver disease, renal disease, infections, endocrinopathies, or cancers. Physical examination provides hints: sternal pain may indicate marrow enlargement, while scleral icterus indicates hemolysis or poor erythropoiesis. Infections or cancers can be found by examining the liver, spleen, and lymph nodes.[15]

An evaluation of the volume of blood lost during menstruation is another crucial piece of information for women. Approximately 50 millilitres of blood, or about 25 milligrams of elemental iron, are typically lost during a period. Both the frequency of pregnancies and abortions and the time since the last one are major indicators of iron loss. It is important to record the presence or absence of fever, since it may indicate collagen vascular disease, lymphoma, infection, or other neoplasms. Walking difficulties and paresthesias are indicative of pernicious anaemia.[15]

LABORATORY INVESTIGATION

Laboratory testing should be carried out in in combination with a thorough history and clinical examination, with an understanding of how the results will lead further research and treatment in accordance with local routes within specific healthcare settings as well as national standards for gastrointestinal and gynaecology. A complete blood count (CBC), Peripheral blood smear examination, reticulocyte count, direct antiglobulin test (DAT), and serum bilirubin assessment are a part of the initial basic laboratory evaluation.[16]

Nowadays, almost everyone uses computerised cell counters for comprehensive blood counts. While haematocrit, mean corpuscular haemoglobin (MCH), and

mean corpuscular haemoglobin concentration (MCHC) are computed, these devices directly measure mean corpuscular volume (MCV), haemoglobin concentration, and erythrocyte count.

When erythrocytes are distorted, such as in Sickle Cell Anemia or Iron Deficiency Anaemia, calculated parameters become incorrect. Automated haematocrit is unaffected by plasma trapping, which can inaccurately raise values in cases with rigid or malformed cells, in contrast to spun hematocrit. Without a real change in red cell mass, this could result in significant differences between automated and manual haematocrit tests. Haemoglobin is still the most reliable and consistent parameter for evaluating anaemia since it can be measured directly. The most prevalent cause of anaemia in the world is iron.[12]

According to the World Health Organization (WHO), anaemia is a situation in which the body's physiological requirements are not fulfilled by the amount of red blood cells (and hence, their ability to deliver oxygen). Furthermore, a recognised definition of haemoglobin concentration below age and gender-specific criteria is as follows: <130 g/l for adult men, <120 g/l for adult women who are not pregnant, and paediatric values that rise with age, beginning at <110 g/l for children aged 6 to 59 months.[17] The general anaemia cut-offs have remained unchanged since 1968, with the exception that the initial age group of children 5-14 years of age was separated, and a 5 g/l lower cut-off was given to children 5-11 years of age to mirror observations among non-iron deficient children in the USA.[18] The haemoglobin cutoff of 110 g/l for pregnant women was initially stated in the 1968 report, in addition the results from the article Preventing and controlling anemia through primary health care, Iron deficiency anemia: assessment, prevention and control, a guide for programmed managers.[19]

The concepts of "microcytic," "normocytic," and "macrocytic" anemia were developed as a result of observations that red blood cell size can assist in differentiating the possible aetiology. Another method of classifying anemia focuses on the underlying process, differentiating between a decrease in red blood cell synthesis and an increase in red blood cell loss. Hemolysis and blood loss are the main factors to take into account if the reticulocyte count rises. Low reticulocyte counts may indicate impaired marrow production due to nutritional deficiencies (iron, vitamin B12, folate, copper), marrow failure (aplastic anaemia, pure red cell aplasia, myelodysplasia, leukaemia), lack of growth factors (lack of erythropoietin due to chronic renal disease), or myelopathic processes (cancer, infection). A blood smear might also provide important diagnostic information as to the cause of anaemia.

After anaemia is detected, testing for specific reasons may include a wide range of laboratory tests, depending on the classification. Diagnostic testing can assess renal function, inflammation, nutritional deficits, thalassaemia, sickle cell disease, haemolysis, and myeloma.[20,21,22,23,24]

MICROCYTIC ANEMIA

Microcytic anaemia, defined as a mean corpuscular volume (MCV) of less than 80 fL,is mostcommonlycaused byirondeficiency anaemia and thalassaemia syndromes, but other causes include chronic disease anaemia, lead poisoning, sideroblastic anaemia, and certain haemoglobinopathies. The diagnostic technique begins with confirming microcytosis on a complete blood count, followed by evaluating red cell indices such as haemoglobin level, erythrocyte count, and red cell distribution width (RDW), which aid in distinguishing iron deficiency anaemia from thalassaemia minor.[14]

Iron deficiency anaemia progresses predictably, starting with depleted bone marrow iron stores and low serum ferritin, then decreasing serum iron and increasing total iron-binding capacity (TIBC). As the disorder advances, haemoglobin levels decline and microcytosis occurs, characterised by an increase in RDW and a decrease in erythrocyte count.[11]

Thalassaemia minor, on the other hand, exhibits disproportionately severe microcytosis with a normal or raised erythrocyte count and a normal RDW, indicating homogeneous red cell size; these distinctions serve as the foundation for indices such as the Mentzer.[25]

If thalassaemia is suspected, a haemoglobin test is required to confirm. In β-thalassaemia minor, haemoglobin A_2 levels are elevated (4–6%), and haemoglobin F may also increase, although coexisting iron deficiency can mask these findings. α-thalassaemia is typically diagnosed by exclusion or genetic testing, as iron tests and haemoglobin electrophoresis may be normal. To accurately discriminate between causes, the diagnostic strategy focuses on a step-by-step examination that includes red cell indices, iron studies, and haemoglobin analysis.[25]

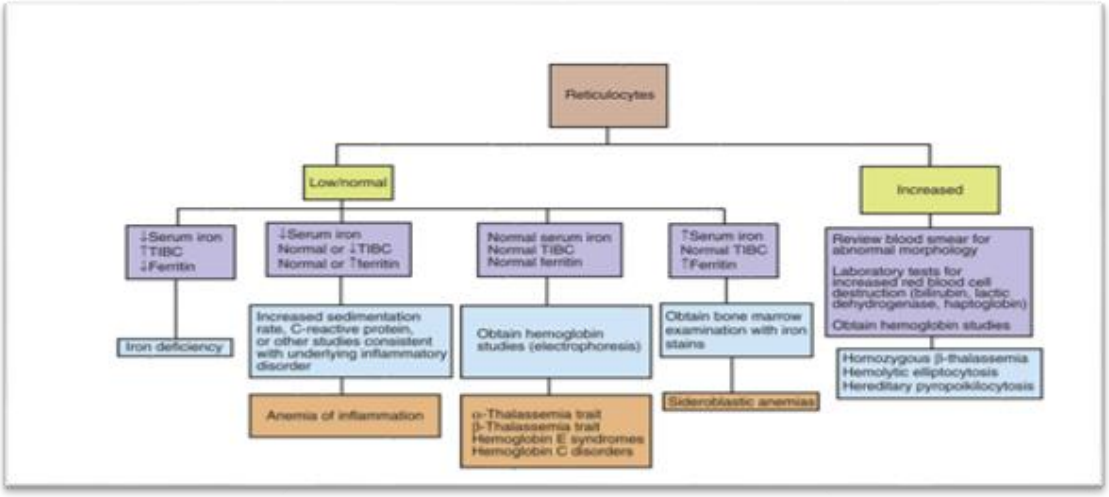

Fig. No 1: Diagnostic approch to a patient with microcytic anemia. Increases, decreases, TIBC, total iron-binding capacity.[14]

NORMOCYTIC ANEMIA

Normocytic anaemia (MCV 80-100 fL) is a diverse set of illnesses that necessitates a comprehensive diagnostic strategy focused on measuring bone marrow response. After verifying anaemia with a normal MCV, the most crucial step is to assess the reticulocyte count, which measures erythropoietic activity.[26] An increased reticulocyte count indicates an appropriate marrow response and suggests that the anemia is due to hemolysis or acute blood loss.

Further evaluation includes a clinical history, haemolysis markers such as increased bilirubin and lactate dehydrogenase with low haptoglobin, and peripheral smear abnormalities such as schistocytes and polychromasia, which can distinguish haemolysis from haemorrhage.[14]

In contrast, a low or abnormally normal reticulocyte count implies a decline in red cell synthesis. The next step is to do suitable laboratory tests to rule out secondary reasons such as chronic renal disease (owing to low erythropoietin levels), anaemia from chronic inflammation, and endocrine or liver diseases.[26]

If these are ruled out or if additional cytopenias are present, intrinsic bone marrow disorders such as aplastic anaemia, leukaemia, myelofibrosis, or marrow infiltration should be considered; peripheral smear abnormalities such as nucleated red cells or teardrop cells may provide clues, but bone marrow examination is required for confirmation. A subset of patients with severe reticulocytopenia and isolated anaemia appear to have selective erythroid suppression, as shown in pure red cell aplasia, transitory erythroblastopenia of childhood, or aplastic crises.[14]

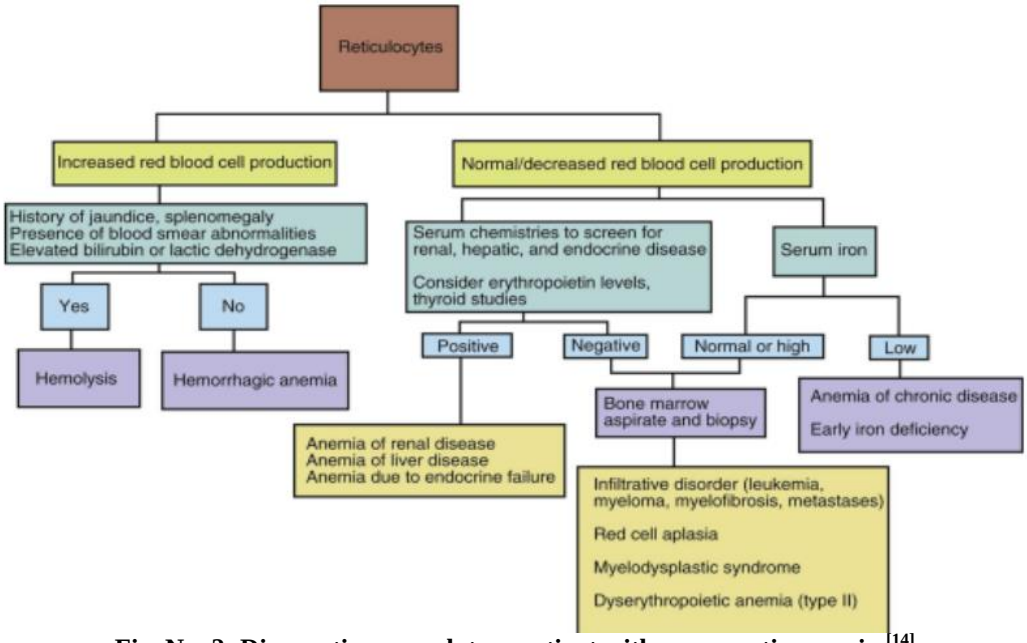

Fig. No. 2: Diagnostic approch to a patient with normocytic anemia.[14]

MACROCYTIC ANEMIA

Macrocytic anaemia with a normal or low reticulocyte count usually indicates **reduced erythrocyte production**, which is an uncommon cause of anaemia in children. Causes include nutritional deficiencies, genetic disorders, congenital dyserythropoietic anaemias, bone marrow replacement disorders, drug-induced suppression, viral infections, and other rare conditions.[26] Depending on the stage and underlying disease, anaemia may also appear normocytic or microcytic, especially in nutritional and infectious causes. Mild macrocytosis (MCV 100–110 fL) is relatively common and may occur even without anaemia, but it should not be ignored as it can be an early sign of reversible conditions such as pernicious anaemia, where neurological or psychiatric features may precede haematological changes.[14]

The diagnostic approach begins by classifying macrocytic anaemia into **megaloblastic and non-megaloblastic types** based on morphological and biochemical features, which is the key initial step. Macrocytic anaemia is defined by low haemoglobin (<12 g/dL in females and <13 g/dL in males) with MCV ≥100 fL. Evaluation starts with the **reticulocyte count**: if elevated, it suggests increased red cell turnover and prompts assessment of haptoglobin, where low levels indicate haemolysis and normal/high levels suggest acute blood loss. If the reticulocyte count is normal or low, it indicates decreased production, and further tests such as vitamin B12, folate, TSH, and liver function tests (PT, AST, ALT, GGT) are performed. Abnormal results suggest deficiencies or systemic disease, while normal findings warrant bone marrow examination to assess for dysmyelopoiesis, completing a structured diagnostic flow.[27]

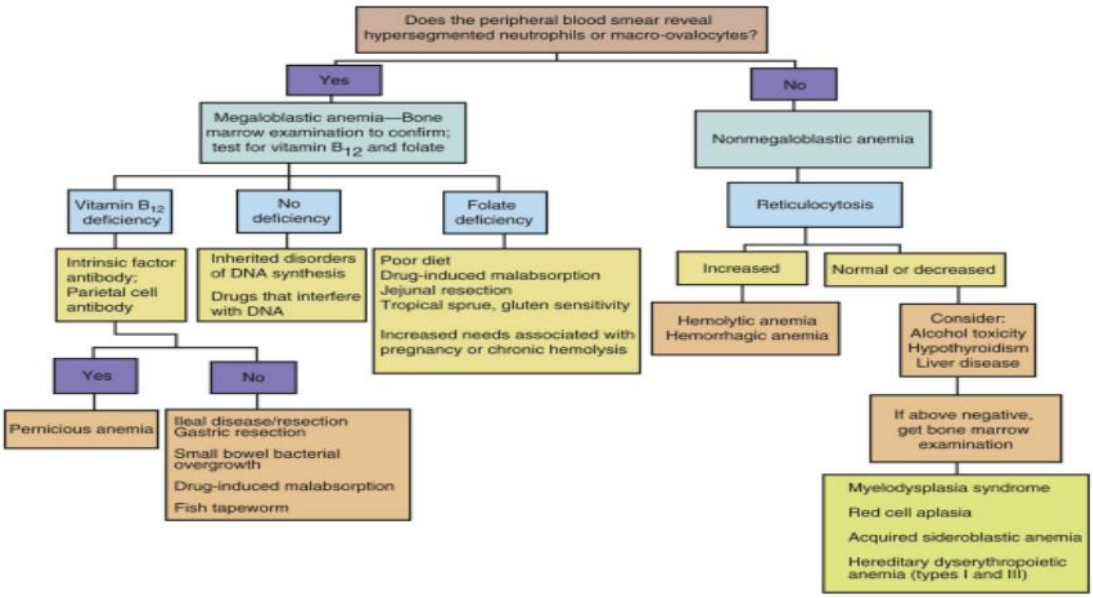

Fig. No. 3: Diagnostic approch to a patient with macrocytic anemia.[14]

COMPLETE BLOOD COUNT

The complete blood count (CBC) is a straightforward, inexpensive, and commonly available laboratory test that reveals important information about red blood cells, white blood cells, and platelets. Despite its widespread use, it is frequently misinterpreted, despite the fact that careful examination can reveal crucial diagnostic signals in illnesses such as anaemia, infection, inflammation, and haematologic disorders.[28] The CBC includes important parameters such as haemoglobin concentration, haematocrit, RBC count, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), leukocyte count with differential, and platelet count, which can be measured directly or calculated from other values.[26] Modern automated analysers count and size cells using electrical impedance and light scatter techniques. RBCs travelling through an electric field emit pulses proportional to cell volume, which can be used to calculate RBC count and MCV, while haemoglobin is quantified using spectrophotometry after cell lysis. Derived indices such as MCH, MCHC, and haematocrit are derived using primary values. The RBC size distribution is represented as a histogram, from which red cell distribution width (RDW) is calculated, representing variation in cell size and aiding in the detection of aberrant red cell populations even when the peripheral smear appears normal. Automated analysers also produce flags and histograms that may suggest aberrant populations such as blasts, platelet clumping, or RBC agglutination, necessitating additional human smear analysis.[29]

One significant restriction is that haematocrit is computed rather than physically measured, therefore it may differ from spun haematocrit due to plasma entrapment during centrifugation; this variance increases in aberrant RBC forms such as spherocytes or sickle cells. In most circumstances, haemoglobin is a more reliable measure of oxygen transport.[30] "rule of 3s," in

which haemoglobin is approximately three times the RBC count and haematocrit is approximately three times the haemoglobin, is a valuable clinical screening tool; large divergence indicates analytical or biological artefacts such as cold agglutination or severe leukocytosis. Overall, the CBC should be understood as a pattern-based diagnostic tool that relies on the combination of indices, histograms, and clinical correlation to ensure appropriate diagnosis.[31]

PERIPHERAL BLOOD SMEAR

The initial step in a peripheral blood smear examination should be to examine the smear quality. Poor preparation can result in misleading artifacts, therefore the smear must have a good feathered edge with evenly distributed, non-overlapping red cells. Areas of stacking, excessive overlap, or stain precipitation should be avoided for interpretation.[28]

At low power, the overall staining, cell dispersion, and distribution of cells are evaluated. This helps in identifying rouleaux formation, which indicates increased plasma proteins, and autoagglutination, which suggests immune-mediated red cell clumping. It also provides a quick overview of anemia pattern, helping to broadly classify it as microcytic, normocytic, or macrocytic.[28]

Anaemia is then classified based on red blood cell size and central pallor. Microcytic hypochromic cells suggest iron deficiency, thalassaemia, chronic disease, or sideroblastic anaemia, whereas macrocytic cells suggest vitamin B12/folate deficiency, liver disease, alcoholism, or bone marrow stress. Assessment of central pallor also helps in judging the severity of hypochromia.Red cell shape abnormalities and inclusions provide strong diagnostic clues. Howell-Jolly bodies indicate hyposplenism; basophilic stippling is seen in lead poisoning, thalassaemia, and increased red cell turnover; and bite cells suggest oxidative injury, commonly seen in G6PD deficiency. Additional shapes such as schistocytes suggest microangiopathic hemolysis, while teardrop cells indicate marrow infiltration or fibrosis.[32]

White blood cell morphology further supports diagnosis. Hypersegmented neutrophils are characteristic of vitamin B12 or folate deficiency, toxic granulation and Döhle bodies suggest bacterial infection or inflammation, and blast cells indicate acute leukaemia. Rare findings like abnormal granules may suggest specific syndromes such as Chédiak–Higashi syndrome.Platelets should be evaluated for number, size, and clumping. Clumping may cause pseudothrombocytopenia due to EDTA effect, while large or giant platelets suggest increased turnover or bone marrow disorders. Platelet morphology also helps assess bleeding or marrow response in hematological disease.[28]

The blood smear contains three types of cells: red blood cells (RBCs), white blood cells (WBCs), and platelets, with RBCs being the majority. Pathologists examine peripheral blood smears (PBS) to determine RBC and WBC size, shape, and colour, as well as platelet count. Any variation in RBC form, volume, or haemoglobin content indicates aberrant cells, which are reflected in red cell indices.[33]

Anaemia is largely characterised according to RBC morphology: microcytic hypochromic, normocytic normochromic, and macrocytic forms. It can also be associated with iron deficiency anaemia, sickle cell anaemia, thalassaemia, hereditary spherocytosis, haemolytic anaemia, and aplastic anaemia based on distinctive RBC alterations. In addition to morphology, anaemia is characterised using clinical characteristics such as RBC count, MCV, MCH, MCHC, haematocrit (PCV), and RDW, all of which are required for correct diagnosis. When these parameters are aberrant, haematologists frequently use PBS evaluation, and morphological and clinical data work together to promote effective anaemia classification.[33]

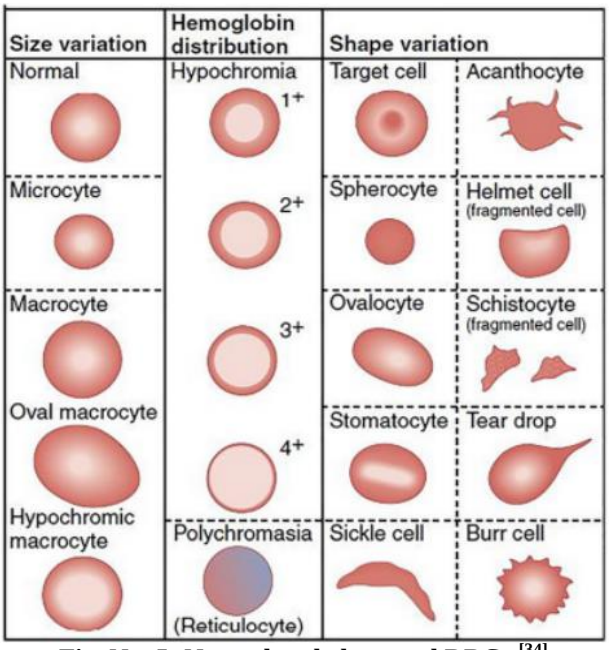

Fig. No. 5: Normal and abnormal RBCs.[34]

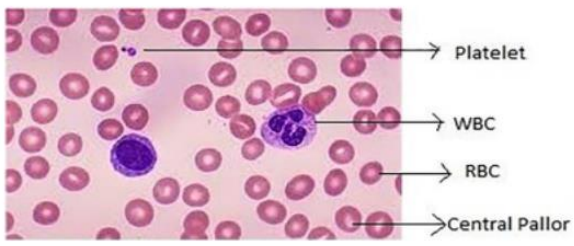

Fig. No 4: Microscopic view of blood smear image.[34]

CLASSIFICATION OF ANEAMIA

NUTRITIONAL DEFICIENCIES

When concentrations of hematological nutrients—those involved in RBC generation or maintenance—are insufficient to satisfy those demands, nutritional anemias

occur.[35] Inadequate nutritional intake, increased nutrient losses (such as blood loss from parasites, childbirth-related hemorrhage, or significant monthly losses), altered nutritional metabolism (e.g., VA or riboflavin deficiency impacting mobilization of iron reserves) or decreased absorption (e.g., lack of intrinsic factor to aid vitamin B12 absorption, excessive phytate diet, or Helicobacter pylori infection that impairs iron absorption). Although nutrient supplementation is a popular preventive and therapeutic approach for nutritional anemias, such as iron supplementation for the prevention of IDA, the bioavailability and, consequently, absorption from various nutrient supplement preparations can differ, potentially limiting their impact.[36]

A number of these elements, including riboflavin, folic acid, and vitamins A, B6, and B12, are necessary for the regular synthesis of red blood cells (RBCs); other nutrients, such vitamins C and E, may protect RBCs by acting as antioxidants.[37]

IRON DEFICIENCY ANEMIA

Iron deficiency is the most common nutritional deficiency among children in developing nations, but it is still a common cause of anemia in children and adolescents in industrialized nations, even though the incidence is declining due in part to iron fortification of infant formulas and cereals. Even in the absence of anemia, the connection between iron shortage and cognitive impairments—some of which may be reversible—is more significant than anemia.[38]

ID arises when dietary iron intake is insufficient over time to meet iron requirements, particularly during times of life when iron requirements are very high (e.g., during periods of rapid growth and development, such as infancy and pregnancy) or when iron losses outweigh iron intake. Storage iron depletion, iron deficient erythropoiesis, and IDA (defined as concurrent ID plus anemia) are the three stages that ID usually progresses through.[39] WHO advises utilizing soluble transferrin receptor (sTfR) or serum ferritin to determine iron status.[40],[41]

VITAMIN B12 DEFICIENCY

Reduced intake, decreased absorption, or genetic deficiencies of vitamin B12 absorption, transport, or metabolism are indicators of vitamin B12 deficiency in pediatric patients.Poor growth, developmental delay, and neurologic abnormalities including weakness or irritability are common symptoms of vitamin B12 insufficiency.[42] Megaloblastoid macrocytic anemia caused Vitamin B12 deficiency manifest as hypersegmented neutrophils in peripheral blood and megaloblastoid maturation of granuloctics and erythroid lineages in the bone marrow.The challenges of using serum Vitamin B12 levels to identify tissue inadequacy is becoming more wide acknowledged.[43]

FOLATE DEFICIENCY

Folate deficiency is more prevalent in people that eat little in the way of legumes and green leafy vegetables and rely on either wheat or rice as a staple food.[44] Similar to vitamin B12 deficiency, folate deficiency manifests as a megaloblastoid macrocytic anemia and shows identical morphologic features. Both serum and red cell folate concentration lack diagnostic specificity and, like vitamin B12 deficiency, the use of metabolite assays are more accurate.[43] Folate deficeincy is particularly dangerous for pregnant women, premature babies and those who live in areas where malaria is endemic since folate is necassary for the formation of malarial parasites.[37][45]

RIBOFLAVIN DEFICIENT

In both high-income and low-income countries, riboflavin deficiency has been reported in pregnant and lactating women, infants, school-age children, adolescent girls, and the elderly. This is particularly true in areas with low consumption of meat and milk/dairy products, which are the main sources of riboflavin.[46] An essential component of iron metabolism is riboflavin's function as a cofactor in redox processes. In animals, riboflavin shortage can reduce iron mobilization from storage, decrease iron absorption, increase iron losses, and affect globin formation.It is believed that many populations suffer from riboflavin insufficiency.[37][46] Some studies, but not all of them, have demonstrated that giving children and pregnant women riboflavin supplements in addition to iron supplements had a stronger impact on hemoglobin concentration than iron supplements alone.[47]

VITAMIN A DEFICIENCY

VAD is common in various LMICs, especially among WRA, PSC, and pregnant women. Based on serum retinol concentrations, the WHO projected that 190 million PSC and 9.1 million pregnant women from regions at risk of VAD were VA deficient in 2005. This amounts to a third of PSC and 15% of pregnant women from these countries.[48] Even when given without iron supplements, VA supplementation has been demonstrated to raise Hb concentrations, hematocrit, and several iron status indices. Retinoids' role in erythropoiesis, VA's significance for immunological function, and VA's well-established role in iron metabolism are some of the ways that VAD is hypothesized to induce anemia.[49]

NORMOCYTIC ANEMIA

Normocytic anemia with elevated reticulocyte count

This broad category of pediatric anemias includes acquired conditions like immune hemolysis and microangiopathic conditions like hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and disseminated intravascular coagulation, as well as inherited disorders of the erythrocyte membrane, cellular metabolism, and unstable hemoglobin.

Hemolysis, or the early destruction of erythrocytes, is a characteristic of several of these illnesses. Poor erythrocyte deformability that results in splenic trapping and subsequent phagocytosis, antibody-mediated destruction via phagocytosis or direct complement activation, fragmentation brought on by microthrombi or direct mechanical trauma, oxidation, or direct cellular destruction are some of the mechanisms of hemolysis.[50]

[Erythrocyte membrane disorders]
Erythrocyte membrane disorders can occur at any age, during pregnancy, the neonatal stage, childhood, and some are undetectable until later in life.

1. Herediatry Spherocytosis
The main erythrocyte membrane proteins, such as ankyrin-1, b-spectrin, band3, a-spectrin, and protein4.1R, are linked to qualitative or quantitative changes in the hereditary spherocytosis (HS) syndromes.[51]

2. Herediatry Elliptocytosis
The hereditary elliptocytosis (HE) syndromes are found during unrelated laboratory testing, are usually asymptomatic, and mostly affect people of African heritage. Hemolytic HE and the associated disorder hereditary pyropoikilocytosis (HPP), in which hemolysis, anemia, and jaundice may be severe, are the exceptions.A variation of HE is called HPP. The MCV is low (50–65 fl), hemolysis is severe, and the blood smear shows erythrocyte morphology similar to thermal burns, including elliptocytes, poikilocytes, pyknocytes, fragmented cells, and microspherocytes.[16]

3. Herediatry Stomatocytosis
A diverse range of conditions known as the hereditary stomatocytosis (HSt) syndromes12 are typified by aberrant erythrocyte permeability to potassium and sodium, changing the water content.Hemolytic anemia, hyperbilirubinemia, and hydrops fetalis have all been reported in perinatal HSt subtypes; nonimmune hydrops fetalis unrelated to the severity of fetal anemia has been reported in additional subtypes.[52]

Defects of erythrocyte metabolism
Erythrocyte metabolism disorders are a small but significant category of hereditary illnesses. Often referred to as congenital nonspherocytic hemolytic anemia (CNSHA), this category include erythrocyte membrane problems, thalassemia or sickle cell disease (SCD), and disorders not caused by immune-mediated disruptions. These include anomalies in the metabolism of glucose, nucleotides, or glutathione.These conditions exhibit considerable clinical, laboratory, and genetic heterogeneity, much like the HS syndromes. Hemolysis is caused by an enzyme or antioxidant deficit or poor function.[16]

Glucose-6-phosphate dehydrogenase (G6PD) deficiency G6PD insufficiency is the most prevalent erythrocyte metabolic disorder, affecting 400 million people globally.[26] Reduced glutathione (GSH) detoxifies intracellular oxidants in healthy erythrocytes. The incapacity to produce NADPH in G6PD deficiency results in low levels of GSH, which leaves oxidants free to harm vital erythrocyte proteins. Methemoglobin and intracellular Hb precipitates called Heinz bodies are produced when Hb sulfhydryl groups are oxidized. Because their primary source of NADPH is the hexose monophosphate shunt, erythrocytes are especially vulnerable to oxidative stress.[16]

Neonatal jaundice (NNJ), CNSHA, and acute hemolysis following exposure to an oxidative stressor are the three clinical syndromes that G6PD deficiency is commonly divided into. On the second or third day of life, NNJ usually manifests. Severe cases that result in kernicterus or even death have been reported, albeit the severity varies.[16]

Unstable Hbs One underappreciated and underdiagnosed etiology of dominantly inherited CNSHA is unstable hemoglobinopathies, which are caused by structural anomalies of the a-orb-globin chain.[53] Early in infancy, two unstable Hbs exhibit hemolytic anemia. When combined with g-globin, the mutant a-globin known as Hb Hasharon results in an unstable Hb. The 10-fold greater affinity between a and b chains than between a and g chains is the reason why mutant Hb Hasharon chains are no longer unstable when linked with b-globin. A mutation in the g-globin chain causes Hb F Poole to be unstable. Hemolytic anemia in early infancy is caused by Hb Hasharon, Hb F Poole, and other unstable Hb variations that affect fetal Hb structure and function. This condition goes away once the fetal-to-adult Hb changeover takes place.[16]

Microangiopathic hemolysis: Microangiopathic hemolytic anemia and thrombocytopenia can result from thrombotic microangiopathy, which is the production of clots in tiny blood arteries throughout the body. The most frequent causes of microangiopathic hemolysis in children include TTP, hemolytic uremic syndrome (HUS), and disseminated intravascular coagulation.[16]

1. Disseminated intravascular coagulation (DIC) Anemia in critically ill infants and children is frequently caused by DIC. Sepsis, meningitis, necrotizing enterocolitis, respiratory failure, pancreatitis, severe liver failure, certain cancers, and vascular abnormalities are frequently linked to it.[16]
2. HUS Thrombotic microangiopathy with hemolytic anemia, thrombocytopenia, and renal involvement make up the triad of HUS.[54] Acute renal impairment in children, particularly those under five, is frequently caused by HUS.[55]
3. TTP Thrombocytopenia, microangiopathic hemolytic anemia, fever, mucosal and cutaneous bleeding, and ischemia alterations in numerous organs, including the brain, kidney, and heart, are the hallmarks of thrombotic microangiopathy (TTP), which is also indicated by a significant lack of functioning ADAMTS13.[56]

Normocytic anemia with normal or decreased reticulocyte count

Acute Hemorrhage Three of the most frequent causes of trauma in pediatric patients with severe bleeding include assaults, falls, and motor vehicle accidents.When blood loss may be occult (such as from a burst spleen or lacerated liver) as a result of an incident that was not initially reported, like a sports accident or a bicycle fall, a high index of suspicion may be required.[57]

Acute Hemolysis Before a reticulocyte response occurs, patients with acute onset hemolysis may exhibit noticeable normocytic anemia. This could be the manifestation of AIHA following a Mycoplasma or viral infection. Patients with G6PD deficiency, unstable hemoglobin, or metabolic abnormalities may experience severe hemolysis following an acute oxidant exposure. Acute splenic sequestration in SCD and other conditions may cause it. The Thomsen-Friedenreich cryptoantigen, also known as the T antigen, which is present on erythrocytes, platelets, and glomeruli, may be exposed by an enzyme produced by S. pneumoniae infection. The exposed T antigen is bound by antibodies to the T antigen, which are typically present in human serum. This antigen-antibody response causes hemolytic anemia and atypical HUS.[16]

Chronic Disease/Inflammation Acute infection, or anemia of chronic illness, is often mild-to-moderate (Hb values 8–10 g/L) and normocytic with a low reticulocyte count.84. Proinflammatory cytokines (IL-6 in particular, but other cytokines are also involved) released in the host defense response to infection in AI change iron metabolism, causing iron to be sequestered within intestinal enterocytes and cells of the reticuloendothelial system (liver and spleen), reducing RBC production and life span.[58][59][60]

Patients with a wide range of illnesses, infections, cancers, renal disease, rheumatologic disorders, heart failure, chronic lung disease, and GI conditions like ulcerative colitis, Crohn's disease, and celiac disease are found to have anemia of chronic disease/inflammation. Anemia is caused by a number of reasons. These include mild hemolysis, decreased erythroid precursor sensitivity to erythropoietin as a result of cytokines produced by inflammatory cells, and increased hepcidin synthesis caused by inflammation, which binds ferroporatin, prevents iron export from the liver and GI tract, and lowers the amount of iron available to developing erythroid cells.[61]

Transient erythroblastopenia of childhood (TEC) TEC is an uncommon red cell aplasia that typically follows a viral infection in young children or babies.[62]

MICROCYTIC ANEMIA

Microcytic anemia with normal or decreased reticulocyte count

Iron deficiency anemia Worldwide, iron deficiency and iron deficiency anemia are prevalent.[63] Around the age of one year, the American Academy of Pediatrics advises screening all children for anemia. This screening should include evaluating risk factors such as low birth weight, lead exposure, history of prematurity, exclusive breastfeeding without iron supplementation beyond four months, feeding issues, poor growth, low socioeconomic status, Mexican American heritage, and special medical needs.[64]

Iron deficiency is the most prevalent nutritional deficiency among children in developing nations, but it is still a common cause of anemia in children and adolescents in industrialized nations, even though the incidence is declining due in part to iron fortification of infant formulas and cereals. Even in the absence of anemia, the connection between iron shortage and cognitive impairments—some of which may be reversible—is more significant than anemia.[65]

Sideroblastic anemia Congenital sideroblastic anemias (CSAs) are uncommon disorders of mitochondrial dysfunction caused by abnormalities in specific mitochondrial respiratory chain proteins involved in oxidative phosphorylation, heme biosynthesis, iron-sulfur cluster biogenesis, or generalized mitochondrial protein synthesis.[66]

Microcytic anemia with increased reticulocyte count

Disorders of Hb Thalassemia syndromes and sickle cell disease (SCD) are two of the most prevalent monogenic illnesses in the world.[67]

1. Thalessemia A class of hereditary disorders known as thalassemias is characterized by defects in the synthesis of one or more of the globin chains that make up hemoglobin; α-thalassemia is caused by reduced or absent synthesis of the α-globin chain, while β-thalassemia is caused by reduced or absent synthesis of the β-globin chain.[50]
2. Sickle cell disorder It is characterized by sickle-shaped red blood cells (RBCs) that are caused by a faulty β-globin chain. These RBCs cause significant pain and lasting organ damage, clog small blood arteries, damage big blood vessels, and have a considerably shorter life span, which results in chronic hemolytic anemia.[68][69]

MACROCYTIC ANEMIA

Macrocytic anemia with normal or decreased reticulocyte count

Nutritonal deficiencies

Maintaining normal rates of erythropoiesis requires an adequate intake of both folate and vitamin B12. As a result, deficits in both folate and vitamin B12 are major contributors to nutritional anemia, which is brought on by a breakdown in DNA synthesis (megaloblastic anemia).[70]

Anemia and infection

In children in endemic areas, anemia and the diseases that cause it are also leading causes of hospitalization and mortality.[71] Anemia that is more severe may occur as a result of infections. A study conducted on hospitalized children in Malawi revealed a high correlation between severe anemia (Hb concentration < 5g/dL) and both malaria and bacterial infection, but not ID.[72]

1. **Malaria:** One of the main causes of anemia worldwide and a major contributor to severe anemia is malaria. In sub-Saharan Africa, especially in West sub-Saharan Africa, malaria is an even more frequent cause of anemia, accounting for 25% of cases.[73] Increased intravascular and extravascular hemolysis of infected and uninfected red blood cells, bone marrow dyserythropoiesis, and changes in iron mobilization and use are the ways that malaria causes anemia.[74]
2. **Tuberculosis:** The main cause of TB-associated anemia is chronic inflammation, which is indicated by elevated C-reactive protein and proinflammatory cytokine levels.[75] Anemia among pulmonary TB patients is thought to result from AI, as well as increased blood loss from hemoptysis (blood in sputum), decreased RBC production, and poor appetite and food intake, leading to poor nutrient status.[76]

MANAGEMENT OF ANEMIA

The aetiology, laboratory test results, and clinical symptoms determine the initial course of treatment.[77] Whenever possible, the first step in treating anaemia is to address any underlying causes.[78] Individuals who have an underlying illness that results in anaemia should receive treatment or be referred to a subspecialist (such as a gastroenterologist or gynaecologist) for definite treatment.[79]

ORAL IRON THERAPY

Oral iron supplementation is advised as first-line treatment by the American Gastroenterological Association.[80] Adults with iron deficient anaemia must take 120 mg of elemental iron daily for three months; youngsters should take up to 60 mg daily at a dose of 3 mg per kg. After a month of treatment, an increase in haemoglobin of 1 g per dL indicates a sufficient response to therapy.[73] Anaemia is typically treated using a range of easily accessible, safe, and reasonably priced oral ferrous (sulphate, fumarate, gluconate, glycine-sulfate) or ferric (protein-succinylate, mannitol-ovoalbumin, polymaltose complex) iron supplements.A novel paradigm for treating oral ID has recently emerged: low dose (40–60 mg) and/or alternate day (80–100 mg) oral iron supplementation, which has been demonstrated to minimise adverse effects and maximise fractional absorption. When oral iron cannot be taken or is unsuccessful in treating ID, such as when there is inflammation, a requirement for quick iron replenishment, or persistent blood loss, patients should be transferred to IVI.[81]

PARENTERAL IRON THERAPY

The Ganzoni formula (total iron dose = [actual body weight × (15-actual Hb)] × 2.4 + iron storage) can be used to determine a patient's total body iron shortfall. Although using the Ganzoni formula is the optimal method for choosing a dose, it is not practical, in part because product labels specify a certain dosage schedule.[82] Iron dextran may be administered intravenously byinfusion. The infusion rate shouldn't be more than 50 mg/min. The only parenteral iron substance that can be given intramuscularly is iron dextran.

Sodium ferric gluconate is administered as IV infusion of 125 mg may be given over ten minutes.Iron sucrose is given by infusion or intravenous injection. It is advised to provide 100 mg intravenously over a period of five minutes, one to three times each week, until 1,000 mg is administered. No more than 20 mg should be administered each minute.[83]

DIET AND LIFE STYLE MODIFICATION

The National Institutes of Health states that while nuts, beans, vegetables, and fortified grain products supply non-heme iron, lean meat and seafood are the diet's highest sources of heme iron. Essential nutrients from a well-balanced diet aid in the body's production of red blood cells. Particularly crucial for preserving appropriate oxygen levels are iron, vitamin B12, and folate. Haemoglobin, the protein that enables red blood cells to transport oxygen throughout the body, is made using iron.[84] Dietary iron occurs in two forms: heme iron, which is derived from haemoglobin and myoglobin in meals derived from animals, and nonheme iron, which is found in both plant foods and animal tissues. In populations that consume meat, heme iron is thought to contribute 10–15% of total iron intake; yet, due to its higher and more consistent absorption (estimated at 15–35%), it may contribute up to 40% of total absorbed iron.[80,81] Compared to heme iron, nonheme iron is often far less readily absorbed. Every nonheme dietary iron that enters the digestive tract's common iron pool is equally absorbed.[85] Dietary recommendations to lower iron absorption inhibitors (such as tannins and phytates) and boost iron, vitamin B12, and folate-rich food consumption may prevent recurrence and improve therapy efficacy. Both patient education and regular monitoring are necessary for long-term treatment.[86] While day sleepers change their peaks to about 7 hours and switch which analyte reaches its peak first, iron at 19.7 hours and transferrin saturation at 19.3 hours, night sleepers reach their peak iron and transferrin saturation values at 12.6 and 12.8 hours, respectively. Try to obtain iron from diet, but if anaemia persists, take supplements until the body can return to normal. Supplementation should only be used as a last resort after all other lifestyle options have been exhausted.[87]

BLOOD TRANSFUSION

A key component of the therapy of anaemic patients is red blood cell transfusions. There are hazards associated

with these blood transfusions. Red cell transfusions to treat anaemia have an unclear risk-benefit profile, however they may help unfavourable patient outcomes in some circumstances.[88] The spread of infectious infections, immunological suppression, acute respiratory distress syndrome, circulatory overload, and administration errors are among the dangers and problems associated with RBCT.[89] A 2017 study published in the journal Blood TransfusionTrusted Source suggests a more customised evaluation of an individual with anaemia, taking into account haemoglobin levels, other health indicators, and the individual's capacity to receive repeated blood transfusions.[90]

RECENT ADVANCEMENT

Developments in biotechnology, molecular genetics, and health informatics are driving new trends in anaemia research and development.Individualised therapy, in which the course of treatment is modified based on the patient's genetic composition, clinical characteristics, and disease aetiology, is also receiving a lot of attention. Ferumoxytol for the US market and ferric carboxymaltose for the European market are two recently created intravenous iron preparations that show how the pharmaceutical business is coming up with new ideas to get around the drawbacks of conventional iron supplements.[91]

CONCLUSION

Anemia is not merely a laboratory abnormality but a clinical condition that reflects diverse underlying pathological processes requiring thorough evaluation and management. Its multifactorial etiology, including nutritional deficiencies, chronic diseases, infections, and hereditary disorders, necessitates a structured and systematic diagnostic approach. Fundamental tools such as complete blood count, red cell indices, reticulocyte count, and peripheral blood smear remain indispensable for identifying the type and cause of anemia and guiding appropriate treatment strategies.

Early diagnosis and timely intervention are crucial in preventing complications such as impaired growth, decreased cognitive performance, reduced physical capacity, and adverse maternal and fetal outcomes. Importantly, many forms of anemia are preventable and treatable, particularly those related to nutritional deficiencies and other modifiable risk factors.

Therefore, beyond individual patient care, addressing anemia requires a broader public health perspective that includes improving nutritional status, enhancing awareness, strengthening healthcare access, and reducing socioeconomic disparities. A coordinated effort among clinicians, public health systems, and communities is essential to effectively reduce the global burden of anemia and improve overall quality of life.

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