Normocytic Hemolytic Anemia Causes

Normocytic hemolytic anemia refers to an anemic state in which the average RBC volume is maintained with an MCV between 80-100 fL and hemolysis of red blood cells occurs intravascularly (occurring within blood vessels) or extravascularly (occurring in the liver or spleen, where macrophages consume abnormal RBCs or those tagged by antibodies). There are numerous causes of hemolytic anemia. These can be divided into either intrinsic (etiology related to the components of the RBC itself) or extrinsic (etiology related to pathology outside of the RBC) categories. Note that two separate categorization systems are used simultaneously: intravascular vs. extravascular; and intrinsic vs. extrinsic.



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Intrinsic Hemolytic

Hereditary Spherocytosis
Hair-Red-Kid with Sphere-cell
Patients with hereditary spherocytosis have spherical RBCs, which are due to mutations in structural membrane proteins that maintain RBC shape, such as ankyrin and spectrin. These defective RBCs are destroyed extravascularly by the spleen. Spherocytes can be visualized on blood smear. A related disorder with similar pathology is hereditary elliptocytosis.

RBC Enzyme Deficiency
Red Blood Cell Enzyme Broken
In certain RBC enzyme deficiencies, RBCs are unable to maintain proper metabolism for cell maintenance and repair. Cells are subject to many environmental stressors throughout their lifespan, and depend on enzymes to prevent them from enduring oxidative damage and membrane damage. Without these enzymes, cells are less robust, have shorter half-life, and are subject to hemolysis.

Hemoglobin C Defect
He-man-globe (C) Cat
Hemoglobin C defect is due to an autosomal recessive inherited mutation in the beta-globin chain, in which glutamic acid is substituted with lysine. Hemoglobin C crystals can be visualized on blood smear. Due to these defective RBCs, hemolysis may occur, leading to anemia. These patients tend to have less severe symptoms and fewer hospitalizations than those with sickle cell anemia.

Paroxysmal Nocturnal Hemoglobinuria (PNH)
Pirate of the Night He-man-globe-urinates
PNH is due to the absence of glycosylphosphatidylinositol (GPI), a protein that serves as a cell membrane anchor for other protective proteins to attach and prevent the complement-mediated destruction of RBCs, neutrophils, and platelets. Intravascular hemolysis often occurs at night in these patients, as the complement cascade is activated by sleep-induced respiratory acidosis. They often have hemoglobinuria when they wake up due to the hemolysis. Patients with PNH are at higher risk for thrombosis, as the products of rapid cell turnover may pathologically activate the coagulation cascade.

Sickle Cell Anemia
Sickle Anemone
Sickle cell anemia is a common autosomal recessive genetic disease, due to the substitution of glutamic acid for valine on the beta-globin chain. These structural mutations cause RBCs to form into the sickle-shaped blood vessels and occlude blood vessels, leading to organ damage and severe pain crises. These defective RBCs are destroyed via hemolysis, both intravascularly and extravascularly via the reticuloendothelial system. Nuclear remnants known as Howell-Jolly bodies may be visualized on blood smear.

Extrinsic Hemolytic

Autoimmune
Auto-in-moon
The immune system can cause a hemolytic anemia. IgG antibodies that bind RBCs when body temperature is at or above 37° Celsius and can cause hemolytic anemia are known as warm agglutinins. IgM antibodies that bind RBCs at temperatures below 37° Celsius and induce hemolytic anemia are

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known as cold agglutinins; this phenomenon occurs in Mycoplasma pneumoniae and EBV infections. In drug-induced hemolytic anemia, RBC destruction occurs when antibodies are created in response to that drug or when pre-existing antibodies attach to the drug-RBC complex. Drugs usually cause a warm-type hemolytic anemia, and examples include levofloxacin, quinidine, alpha-methyldopa, and NSAIDs.

Microangiopathic

Microscope-angel

Several pathophysiologic conditions cause microangiopathic hemolytic anemias, such as disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), and hemolytic uremic syndrome (HUS). In these disease states, microthrombi made from coagulation cascade factors (DIC) or platelets (TTP/HUS) form within the vessels, leading to blood vessel occlusion and ischemia. As RBCs travel through the narrowed lumen, they are sheared and hemolyzed intravascularly. Sheared RBCs are known as schistocytes or helmet cells.

Mechanical Destruction

Machine Destructing

RBCs can also be mechanically sheared as they pass through stenotic or prosthetic heart valves, producing schistocytes. These deformed RBCs are hemolyzed, potentially leading to anemia.

Prosthetic Cardiac Valves

Prosthetic Heart Valves

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Infection

Infectious-bacteria

In infections such as malaria, Plasmodium parasites reproduce within the RBCs. When reproduction is complete, the Plasmodium protozoa lyse the cell to release progeny in the blood, causing hemolysis. This cycle of reproduction, cell lysis, and distribution of progeny in the blood is the basis behind the cyclical fevers of malaria.

Snake Venom

Snake

Snake venom contains phospholipase A2, which cleaves the RBC membrane, leading to hemolysis.

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