Approach to hemolysis

GNT Block

COLOR INDEX:

- Main text
- Dr. Notes
- Male's text
- Femal's text
- Important
- Extra

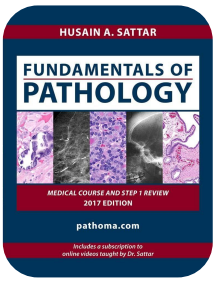
Editing file:

Objectives

- To be able to define haemolysis and hemolytic anemia.
- To be able to classify hemolytic anemias into congenital and acquired types, and to know the etiological factors in each division.
- To understand the difference between intravascular and extravascular haemolysis, and to recognize the laboratory features of each.
- To appreciate some major examples of congenital disorders resulting in hemolysis like HS and G6PD deficiency.
- To understand the role of autoantibodies in the production of hemolytic anemias and to know the types of disease with which they are associated
- To understand some causes of non-immune acquired hemolytic anemias.

Click HERE for summarised Podcast & written TEXT! ZERO TO FINALS

Click on PATHOMA for a revision and more info!



Our YouTube's playlist for this lecture!

This lecture was given by: Dr. Osamah T.Khajoh and Prof. Fatma Al Qahtani

*No objectives was found in new male slides

Introduction to Hemolysis

Hemolysis

Hemolysis is a state with a **short lifespan** of a mature red blood cell

Not marked (mild)
Can be compensated

- Increased red cell output from the marrow.
- Stimulated by erythropoietin
- Will be sufficient.

Marked
Can **NOT** be compensated

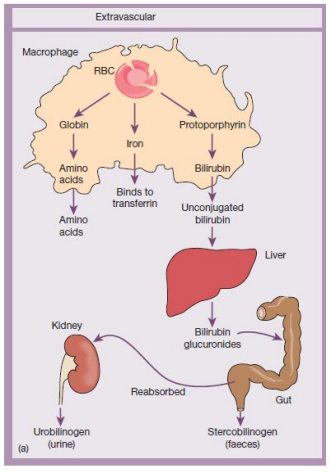
- More marked reductions in red cell lifespan.
- 5-10 days from usual 120 days

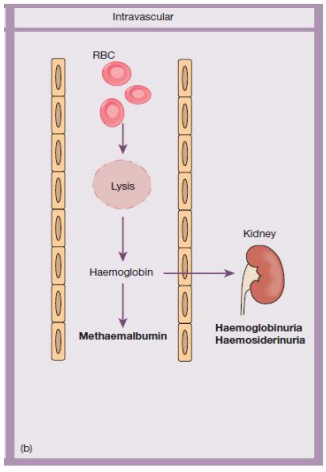
Will result in hemolytic anemia.

Extravascular hemolysis	Intravascular hemolysis
Excessive removal of RBCs by **macrophages** of the (liver, spleen and bone marrow)[1] from the circulation by phagocytosis macrophages of the Reticuloendothelial system (Organs) **Majority of hemolytic anemia**	Red blood cells are caused to rupture and release their hemoglobin (Hb) **directly into circulation.**

The extra/intravascular site of red cell destruction may give clues to the underlying etiology of the hemolysis.

Extra Row	
hemolysis occurs in the reticuloendothelial system, which occurs in **normal and pathological** hemolysis.	hemolysis is taking place within vessels. Never in normal physiology, **always pathological.**





Hemolysis

Male Slides

Laboratory investigation

A) Features of increased red cell breakdown:

serum bilirubin raised, unconjugated and bound to albumin; urine urinobilinogen increased; **serum haptoglobins absent** because the haptoglobins become saturated with hemoglobin and the complex is removed by RE cells.

B) Features of increased red cell production:

Reticulocytosis; bone marrow erythroid hyperplasia; **the normal marrow myeloid : erythroid ratio of 2 : 1 to 12 : 1 is reduced to 1 : 1 or reversed.**meaning there is a pressure on bone marrow to produce more RBC`s

C) Damaged red cells:

morphology (e.g. microspherocytes, elliptocytes, fragments); osmotic fragility; specific enzyme, protein or DNA tests.

General Management

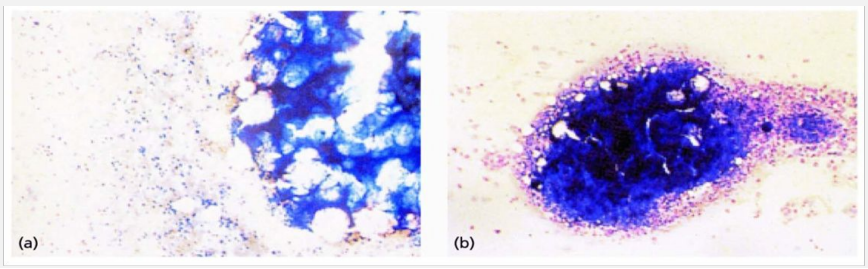
- Remove the underlying cause (e.g.methyldopa).
- Corticosteroids.
- Monoclonal antibody. Anti-CD20 (rituximab)(used with the acquired immune haemolytic anemia).
- Splenectomy may be of value in those who fail to respond well.
- Immunosuppression: Anti-CD52 (Alemtuzumab), azathioprine, cyclophosphamide,chlorambucil, ciclosporin and mycophenolate.
- It may be necessary to treat the underlying disease, e.g. chronic lymphocytic leukemia or lymphoma
- Folic acid.
- Blood transfusion.
- High-dose immunoglobulin.
- Bone marrow Transplant.
- Gene therapy.

Hemolysis

Laboratory evidence of hemolysis

Type of hemolysis	Intravascular hemolysis	Extravascular hemolysis
Hyperbilirubinemia	A rise in unconjugated **bilirubin** concentration in the plasma.	
Serum lactate dehydrogenase (LDH) an enzyme present in red cells	↑ ↑	↑
Macrocytosis (high MCV)	may also develop secondary to folate deficiency. How? hemolysis will increase the bone marrow demand for folic acid leading to deficiency.	
↑ reticulocyte count	An **increase** in the absolute reticulocyte count is an indication of increased erythropoietic activity. The number of reticulocytes in the blood is expressed either as: 1. percentage of the total number of red cells 2. absolute number per liter of blood in normal adults, the percentage is in the range of 0.5–3% and the absolute count is (20 - 100 X 10^9/L)	
Polychromasia	a bluish discoloration of RcBC due to **reticulocytosis**	
examination of the bone marrow	if examination of the bone marrow is undertaken, there will be evidence of **increased erythropoiesis.** Marrow shows erythroid hyperplasia are also hypercellular, due to the replacement of fat cells by erythroid precursors.	
haptoglobin (molecule binds to free Hb)	↓ or absent	↓ mild
Methaemalbuminaemia*	✓ when Free Hb can bind to albumin to form methemalbumin.	-
Hemoglobinuria	✓ Free Hb in the urine (note the difference from **hematuria**, which describes the presence of intact red cells in the urine).	-
Hemosiderinuria	✓	-
Hemoglobinemia	✓	-
On peripheral blood film	**Schistocytes:** Red cell fragmentation	**Spherocytosis** (spherocyte)

Note: *Now rarely used in investigating a patient



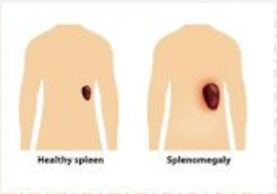
(A) A normocellular marrow fragment: about half its volume consists of hematopoietic cells (staining blue) and the remainder of unstained rounded fat cells.
(B) A markedly hypercellular marrow fragment, as might be seen in the response to haemolysis: virtually all the fat cells are replaced by hematopoietic cells.

Hemolysis

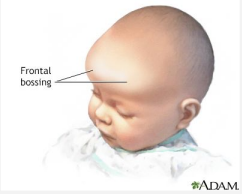
Clinical features of hemolysis :

1. **Pallor** and jaundice secondary to the elevated bilirubin levels
   Pallor is a sign of anemia and jaundice is a sign of hemolysis

2. Splenomegaly might be seen.

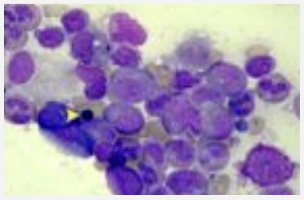


3. Long term complications of chronic hemolysis;
   Expansion of erythropoiesis in the marrow cavities, thinning of cortical bone, bone deformities (e.g. frontal and parietal bossing) and very occasionally pathological fractures Signs of increased hematopoiesis



4. Pigment gallstones are seen commonly Signs of increased hematopoiesis

5. Risk of episodes of **pure red cell aplasia (PRCA)** especially with **parvovirus B19.** (Very common in haemolytic anemia)



Hemolytic Anemia

EXTRA

Hemolytic anemias are defined as anemias characterized by an excessive breakdown of red blood cells (RBCs).
They can be classified according to the **cause of hemolysis** (intrinsic or extrinsic) and by the **location of hemolysis** (intravascular or extravascular).

By RBC Pathology	
Type	**Definition**
Intrinsic hemolytic anemia	Increased destruction of RBCs due to a defect within the RBC
Extrinsic hemolytic anemia	Abnormal breakdown of normal RBCs

By location of RBC Breakdown	
Type	**Definition**
Intravascular hemolytic anemia	Increased destruction of RBCs within the blood vessels
Extravascular hemolytic anemia	Increased destruction of RBCs by the reticuloendothelial system (primarily the spleen)

Based on presence at birth	
Type	**Definition**
Congenital hemolytic anemia	Hereditary conditions including defects of erythrocyte membrane proteins, red cell enzymes and globin chains
Acquired hemolytic anemia	Normal RBC's. However, some other disease or factor causes the body to destroy red blood cells and remove them from the bloodstream.

Hemolytic Anemia

Hemolytic anemia

It is a **shorten in the lifespan** of an RBC that **cannot** be overcome by ability of bone marrow production.(Can not be compensated)

Classification

congenital

The underlying defect is typically **intrinsic** to the red cell itself, affecting the red cell's membrane, its enzymes, or its hemoglobin.

acquired

The underlying defect are due to defects **extrinsic** or outside the RBCs (except PNH= Paroxysmal nocturnal hemoglobinuria)and can be divided into those with an immune basis and those without.

مهم جدا لو حفظنا الجدول هذا ممتاز :Dr.F

Congenital Hemolytic Anemia **

Etiology	Conditions
Membrane defects (Membraneopathy)	1. Hereditary **spherocytosis(HS)** 2. Hereditary **Elliptocytosis (HE)** 3. Hereditary **Pyropoikilocytosis (HPP)**
Enzyme defects (Enzyomopathy)	1. **G6PD** def. 2. **Pyruvate kinase** def.
Globin defects(another lecture)	Sickle cell anemia

Acquired Hemolytic Anemia **

Etiology		Conditions
Immune	**Autoimmune**	1. Warm autoimmune hemolytic anemia (**WAHA**) 2. Cold Hemagglutinin disease (**CHAD**)
	Alloimmune	1. hemolytic transfusion reactions 2. hemolytic disease of the newborn
Non-immune		1. Mechanical 2. Microangiopathic haemolytic anemia (**MAHA**) 3. Infection

Congenital Hemolytic Anemias

Overview of Membranopathies

- The red cells undergo significant deformations while traversing the circulation. Thus, flexible red cell cytoskeleton is essential.
- Key components of The RBCs cytoskeleton is formed by **structural proteins** that include:
  1. α Specretin. **2.** Protein 4.1. **3.** β Spectrin. **4.** Actin. **5.**Ankyrin
- While connections linking the **cytoskeleton** to the overlying red cell **phospholipid** bilayer include:
  1. Band 3. **2.** Glycophorin C. **3.** Rh-associated glycoprotein
- Defects in any of these proteins can jeopardize the integrity of the red cells and shorten its lifespan

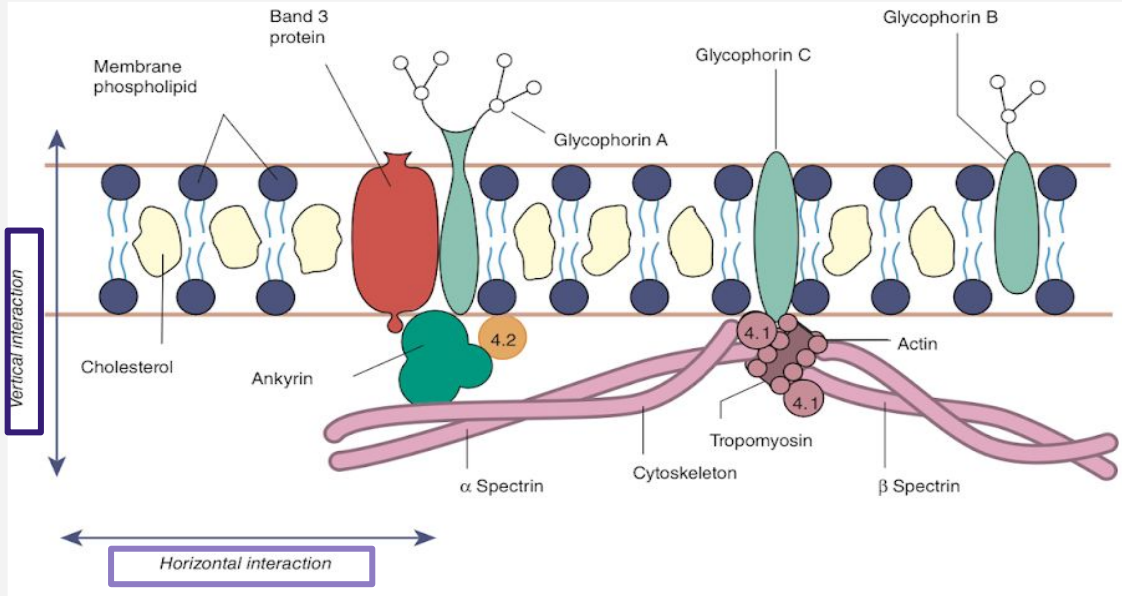


Figure 2.12 The structure of the red cell membrane. Some of the penetrating and integral proteins carry carbohydrate antigens; other antigens are attached directly to the lipid layer.

- RBCs membranes are made of Cytoskeleton attached to Bilayer phospholipid.
- The cytoskeleton proteins form (horizontal connections) on the internal side of the red cell membrane and are important in maintaining the biconcave shape.
- At the head end, of the cytoskeleton, the β spectrin chains attach to ankyrin which connects to band 3, the transmembrane protein that acts as an anion channel forming (vertical connections).
- Defects in proteins of the horizontal interactions→ Hereditary Pyropoikilocytosis (HPP)
- Defects in proteins of the vertical interactions→ Hereditary spherocytosis (HS)

Congenital Hemolytic Anemias

Hereditary Spherocytosis (HS) It is an autosomal dominant disease caused by mutations of proteins that attach RBC cytoskeleton to RBC membrane leading to loss of the membrane, RBC becomes more spherical(spherocyte)

1.Membranopathy: A. Hereditary Spherocytosis (HS)

Overview

- HS is the most common membranopathy **with 60%** related to **Ankyrin protein gene**. Loss of Ankyrin gene leads to secondary reductions in spectrin and protein 4.1 leading to a **spheroid shape**, distribution in vertical connection
- RBCs are destroyed by **splenic** macrophages **(extravascular hemolysis)**

Presentation

- 20% of all HS patients have **mild disease**
- The majority of patients have **moderate disease** characterized by a Hb concentration of 8-11 g/dl
- A small percentage have **severe disease** requiring intermittent or even regular transfusion

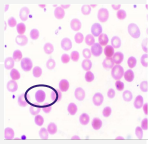
Complication

Pigment gallstones. Increased hemolysis of red blood cells leads to increased bilirubin levels, which may cause the formation of a pigmented

- Megaloblastic anemia occasionally found. Folate and vitamin B12 deficiency may develop due to chronic hemolysis leading to megaloblastic anemia
- Aplastic crisis may occur **secondary to parvovirus** B19. .How? The main target cells of parvovirus B19 are erythroid precursor cells in bone marrow leading to further destruction of RBCs and Aplastic crisis which is when the body fails to produce blood cells in sufficient numbers

Diagnosis

Family History, Mild jaundice, pallor and **splenomegaly**



peripheral blood film	**Presence of Spherocytes** In HS there will be ↑MCHC so the RBC will look more dense without central pallor
Laboratory findings	anemia, reticulocytosis and ↑ plasma bilirubin
Special tests	• The eosin-5-maleamide **(EMA)** binding test (**definitive evidence**) by **flow cytometry**. • The red cell membrane proteins genes, by **molecular testing**. • **Protein electrophoresis** on a denaturing polyacrylamide gel.

Treatment

1. **Folic acid** supplementation.
2. **Splenectomy**.
   - For children with severe disease
   - **Splenectomy** ↑ the risk of significant **infection**, encapsulated organisms. This risk is especially marked in children under the age of 5.
   - **Preoperative preparation**: Administration of pneumococcal and meningococcal vaccine and *Haemophilus influenzae* type b vaccine.(as prophylactic)
   - **Post splenectomy:** Prophylactic penicillin V is advised lifelong

Congenital Hemolytic Anemias

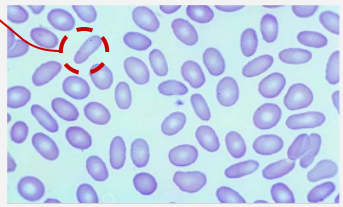
Q. How **Hereditary Spherocytosis (HS)** can lead to **splenomegaly**?
A. The spleen is a filtering organ in the body and the main site of destruction for the abnormal red cells in HS, spherocytes have a hard time passing through due to their irregular shape causing back up in the spleen and eventually splenomegaly

Q. What is The eosin-5-maleamide (**EMA**) binding test?
A. It's the test of choice in HS, and it will show decreased binding between dye (eosin-5-maleimide) and RBC membrane proteins, which shows ↓ RBCs fluorescence. Binding is quantified

Q. Why do we perform **splenectomy** in HS?
A. Having spherocytes isn't the problem, spleen eating them is, so a Splenectomy removes the primary "graveyard" for spherocytes eliminating anemia and hyperbilirubinemia and lowers the high reticulocyte number to nearly normal levels.

1.Membranopathy: B. Hereditary Elliptocytosis (HE)

- Relatively common condition, with many cases showing defects in α spectrin protein, **(horizontal interaction)**
- Most patients are clinically asymptomatic, some will have a chronic symptomatic hemolytic anemia.
- showing very characteristic elongated **(elliptical) red cell shape** on peripheral blood film



1.Membranopathy: C. Hereditary Pyropoikilocytosis (HPP)

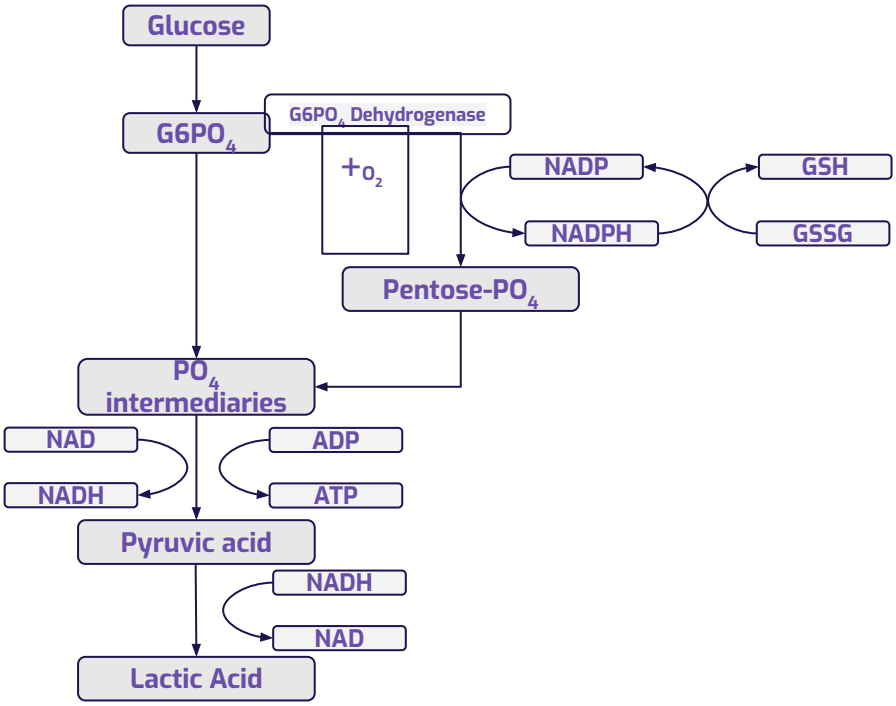
- Described as **Severe** disturbance of multimerization of spectrin with severe hemolytic anemia from infancy and a **bizarre peripheral blood morphology**, including microspherocytes and poikilocytes

Congenital Hemolytic Anemias

Overview of Enzymopathies

- Hemolytic anemias may also result from congenital abnormalities of the **enzymes required for energy transfer** in glucose **metabolism (example: G6PD)**
- The red cell needs a continuous supply of energy for
- It need supply because it becomes fragile / can't handle stress or pressure)
  - Maintenance of membrane flexibility and cell shape
  - Regulation of sodium and potassium pumps
  - Maintenance of Hb in the reduced ferrous form which protects from an **oxidative stress**

G6PD Enzyme



A schematic diagram of the pathway of **glucose metabolism in the red cell**, to show the important role of **G6PD**. A **decreased** activity of the enzyme leads to a **deficiency** of the reducing compounds **NADPH** and **GSH.**

This deficiency makes RBCs more susceptible to oxidative stress and can result in episodic hemolytic anemia

بكل اختصار حنا نحتاج G6DP عشان نطلع NADPH
والي يستخدم للتخلص من ال Oxidative stress

2.Enzymopathies: A. G6PD deficiency

Definition: Various mutations in the G6PD gene on the **X chromosome** results in this disorders with a **male predominance.**

G6PD deficiency often protects against malaria

It's X chromosome (**recessive**) with a male predominance. G6PD deficiency **protects** against **malaria,** an infection **by plasmodium falciparum.**

Congenital Hemolytic Anemias

2.Enzymopathies: A. G6PD deficiency

Deficiency of glucose-6-phosphate dehydrogenase G6PD, the first enzyme of the hexose monophosphate/pentose-phosphate shunt

↓

Will prevent the normal generation of NADPH, with subsequent erythrocyte sensitivity to oxidative stress.

The RBC is exposed to oxidants
(e.g. some medications)

↓

Hb is converted to methemoglobin and denatured.

Denatured Hb then **precipitates**

↓

forming inclusions in the red cell called **Heinz bodies**(Remainings of haemoglobin)
(detected by supravital staining)

Splenic macrophages (extravascular) **remove Heinz bodies**
(this is not hemolysis!)

↓

forming inclusion-free cells called **Bite cells** (خلايا مقضومة)
the resulting inclusion-free cells display unstained areas at their periphery (Bite cells, caused by removal of Heinz bodies from RBC)

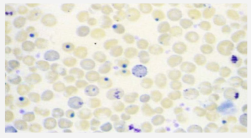
Bite cells will lead to **hemolysis**

↓

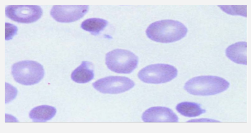
Bite cells lead to predominantly **intravascular hemolysis** (during acute insult) which begins 1-3 days post exposure to the oxidative stressor, with anemia being maximal about 7-10 days after exposure

↓

Patient may report dark reddish urine due to hemoglobinuria.
Screening test and assays for detecting G6DP deficiency are available



Membrane-bound **Heinz bodies** consisting of denatured hemoglobin (supravital staining with methyl violet)



Patient with G6PD deficiency who had received primaquine.
These red cells are irregular in shape, are abnormally dense and show a poorly staining area just beneath part of the cell membrane (MGG stain)

Treatment of G6PD deficiency

1. In most cases it is self-limiting
2. Avoidance of oxidative precipitants to hemolysis.
3. Packed red cell transfusion may be required in cases of severe hemolysis
4. In children, rehydration is needed to avoid acute kidney injury.

Congenital Hemolytic Anemias

Favism/أنيميا الفول

- **Syndrome** in which an **acute hemolytic anemia** occurs after the ingestion of the **broad bean** (Vicia fava) in individuals with a **deficiency of G6PD** (commonly of the Mediterranean type)

- Usually affects **children**:
  1. **Severe anemia** develops rapidly
  2. Often accompanied by **hemoglobinuria**.

2.Enzymopathies: B. Pyruvate Kinase Deficiency

- Pyruvate kinase deficiency is another relatively common example of enzymopathies
- There is usually a **chronic hemolytic anemia** and some patients may benefit from **splenectomy**.

3.Hemoglobinopathies

- Defects in the structure of Hb.
- Structural variants of the globin chains may affect the lifespan of the red cell, **with sickle cell anemia being the best-described example.**
- A tendency of the HbS variant to **polymerize** under conditions of low oxygen tension leads to distortion of the erythrocyte in the well-recognized sickle shape.

Evaluation of Hb electrophoresis

Male Slides

Dr: All of this in OSPE, so i will not ask u about it here

Golden Rules to Evaluate Hemoglobin Electrophoresis

- You must know the CBC results (RBC count, Hb, MCV, MCH, RDW & Plt).
- Peripheral blood film might be useful (target, sickle, pencil, rhomboidal, golf).
- Different methods have their own issues (gel: alkaline or acid, HPLC & capillary electrophoresis)
- Family history and molecular tests are critical in difficult cases and to confirm the diagnosis.
- As a physician, do not under estimate the medical history and clinical examination.
- Are all normal hemoglobin variants present? And if present, are they in normal amount?
- Beta thalassemia trait has a higher Hb A2 (>3.6) & beta thalassemia major has a very high Hb F (>80%).
- Is there any abnormal Hb? What is the percentage?
- Sickle cell trait has 35% - 45% Hb S. If it is >45%, it is a sickle cell disease (when high Hb A2 then likely S/beta thal). • 10) Alpha thalassemia reduced other abnormal Hb level, in trait state.

Acquired Hemolytic anemia

Acquired Hemolytic anemia

In Acquired hemolytic anemias, red cells may be destroyed either by **immunological** or by **non-immunological** mechanisms.

Immunological causes

Antigens on the surface of red cells react with **antibodies** and might cause complement activation.

Pathogenesis

Extravascular hemolysis

IgG-coated red cells interact with the Fc receptors on macrophages in the spleen, and are then either completely or partially phagocytosed. When the phagocytosis is partial, the damaged cell will return to the circulation as a spherocyte.

Intravascular hemolysis

Sometimes, membrane attack complex (C5-C9),complement, leads to it.

Subtypes of Immunological Acquired Hemolytic anemia

Autoantibodies Autoimmune	Alloimmune
• Antibodies formed by the body against one or more **antigenic** constituents of the individual's own tissues. • These include: **autoimmune hemolytic anemia (AIHA)** and some **drug-related** hemolytic anemias. • Auto means the human's body itself synthesis the Ab	• Antibodies produced by one individual reacts against **red cells** of another, as in hemolytic **transfusion** reactions and **hemolytic disease of the newborn** • Allo means the human gain Ab from other factors, for example: blood / organ transplantation

Autoimmune hemolytic anemias are a collection of disorders characterized by the destruction of red blood cells via antibody-mediated hemolysis.
They are classified as **type II (cytotoxic) hypersensitivity reactions.**

Acquired Hemolytic anemia

autoimmune hemolytic anemia (AIHA)

Classification of AIHAs Male dr: not important		
Causes	**Etiology**	
Warm-reactive antibodies "IgG Subtype"	**Idiopathic**	• Chronic lymphocytic leukemia (CLL) • Lymphoma • **Systemic lupus erythematosus (SLE)** • Some drugs
Cold-reactive antibodies (Cold haemagglutinin disease CHAD) "IgM Subtype"		• Infections: **Mycoplasma pneumoniae** and Infectious mononucleosis • Lymphomas
Paroxysmal cold haemoglobinuria		• Some viral infections • Congenital & tertiary syphilis
Paroxysmal nocturnal hemoglobinuria (PNH)		
Drug-related hemolytic anemias.		

1.AIHA: A.Warm AIHA

Warm Agglutinin Disease is characterized by heat sensitive (warm) antibodies binding to RBCs, which triggers inappropriate phagocytosis of these RBCs

Overview

- '**Warm**' autoantibodies react best with the red cell antigen at 37°C and are usually of **IgG** subtype.
- Antibody-coated red cells undergo partial or complete phagocytosis in the **spleen** and by the Kupffer cells of the **liver.** kupffer cells are macrophages of the liver
- There may be partial activation of the complement cascade.

Etiology

- **Idiopathic**
  - Hemolysis dominates the clinical picture and no evidence can be found of any other disease.
- Secondary to a primary disease like:
  - Chronic lymphocytic leukemia (CLL)
  - Systemic lupus erythematosus (SLE).

mnemonic:
- The **M**ilkshake is **cold**
- **G**loves keep me **warm**

Acquired Hemolytic anemia

1.AIHA: A.Warm AIHA

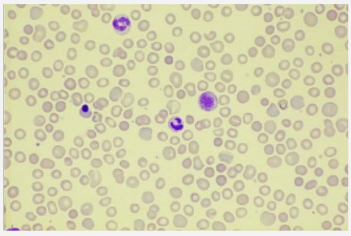
Critical diagnostic investigation:

Direct antiglobulin test (DAT)

Direct antiglobulin test (DAT) also known as **Coomb's test,** helps to distinguish between autoimmune (positive Coombs test) and non-autoimmune anemias (negative Coombs test).

Findings in the peripheral blood.

1. Anemia
2. Reticulocytosis
3. Spherocytosis Extravascular
4. Rare nucleated red cells



Blood film from a patient with idiopathic AlHA (warm-reactive antibody) showing prominent **spherocytosis** and polychromasia.

Treatment

1. **Prednisolone** — can limit hemolysis.
2. **Splenectomy** — should be considered if reduction in hemolysis is not maintained when the dose of steroids is lowered
3. **Immunosuppressive therapy** — An alternative option, the anti-CD20 monoclonal antibody rituximab, as well as immunosuppressants such as azathioprine or cyclophosphamide.

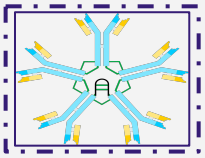
Acquired Hemolytic anemia

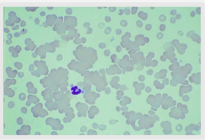
Cold Hemagglutinin Disease (CHAD) is characterized by heat sensitive (cold) antibodies binding to RBCs, which causes agglutination and lysis of these RBCs

1.AIHA: B.Cold AIHA

Overview

- 'Cold' antibodies react best at temperatures below 32°C (usually below 15°C) and, since they are usually of **IgM** subtype, are capable of agglutinating red cells.
- Cold antibodies bind to the red cell surface in the cooler superficial blood vessels of the peripheries. IgM subtype, **pentameric** structure **(check pic),** permits direct agglutination of red cells coated with antibody; they are therefore sometimes termed cold agglutinins.





Numerous red cells agglutinated from a patient with idiopathic CHAD
Clumped RBCs

Symptoms

Symptoms of CHAD are worse during cold weather

- **Acrocyanosis** [1] provoked by exposure to cold painful cyanosis of the extremities
- The direct activation of the complement system leads to red cells lysis and, consequently, to hemoglobinemia and hemoglobinuria (intravascular hemolysis).

Treatment

- Rituximab may be effective , Steroids or Splenectomy is prohibited.
- Chronic idiopathic CHAD is managed initially simply by keeping the patient warm

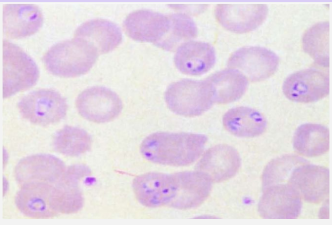
Acquired Hemolytic anemia

Acquired Non-immune Hemolytic Anemias

- Several of the mechanical causes of acquired non-immune hemolytic anemia are **summarized in table. Note that some drugs cause hemolysis by immune mechanisms.**

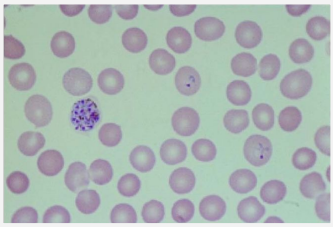
Causes of Acquired Non-immune Hemolytic Anemias	
Mechanical trauma to RBC	• Abnormalities in the heart & large blood vessels • Aortic valve prosthesis, severe aortic valve disease • Microangiopathic haemolytic anaemia • Haemolytic uremic syndrome (HUS) • Thrombotic thrombocytopenic purpura (TTP) • **Disseminated intravascular coagulation (DIC)** • Metastatic malignancy, Malignant hypertension • March haemoglobinuria
Infections Most common cause **	• Clostridium perfringens (welchii) • **Malaria** • bartonellosis
Drugs, *chemicals & venoms	• Oxidant drugs and chemicals, arsine • Acute lead poisoning, copper toxicity • Venoms of certain spiders and snakes
Burns	
Hypersplenism	

A. Plasmodium Falciparum Malaria



Blood film from a patient with **plasmodium falciparum malaria** showing several parasitized red cells, Red cells heavily parasitized with malaria may be subject to intravascular lysis.

B. Plasmodium Vivax Malaria



Blood film from a patient with **plasmodium vivax malaria** showing two parasitized red cells, each containing a single parasite (ring form or early trophozoite and an ameboid late trophozoite). Another red cells contains a schizont. Some of the parasitized cells are slightly enlarged

Acquired Hemolytic anemia

Acquired Non-immune Hemolytic Anemias

Mechanical Damage to Red cells

Red cells are mechanically damaged when they impact upon abnormal surfaces.

Disseminated Intravascular Coagulation (DIC)

- Inappropriate activation of the coagulation cascade produces fibrin strands which are thought to cause mechanical destruction of red cells.
- Such damage usually results in the presence of red cell fragments (**schistocytes**) Triangular in shape, in the blood film. sign of intravascular hemolysis

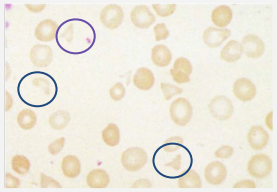


Figure: Fragmented red cells (schistocytes) in the blood film of a patient with a malfunctioning aortic valve prosthesis
Dr.F: Someone presented with malfunctioning aortic valve and has haemolytic anemia = Blood fragmentation = schistocytes

Drugs

- While immune mechanisms of drug-induced haemolysis are well described, there are also non-immune mechanisms by which the red cell lifespan may be shortened.
- Chemicals, such as benzene, toluene (methylbenzene) and saponin, which are **fat solvents**, act on the red cell membrane directly and disrupt its lipid components, inducing hemolysis.

Hypersplenism

- Overactive spleen results in the reduction in the lifespan of red cells, granulocytes and platelets that may be found in patients with splenomegaly due to any cause.
- The cytopenias found in these patients are also partly caused by **increased pooling** of blood cells within the spleen and might be treated with a **splenectomy**. (Splenectomy is to prevent pooling)

Summary

Thanks to team 439

Laboratory Findings of Hemolysis	
Extravascular Haemolysis involves RBC destruction by reticuloendothelial system (The majority of hemolytic anemia)	**Intravascular Haemolysis** involves destruction of RBCs within vessels
Hyperbilirubinemia (unconjugated)	
Increase Serum Lactate dehydrogenase (**LDH**, marked in intra)	
Reticulocytosis: Increased **reticulocyte count**. Which indicates increased **erythropoietic activity.**	
examination of the bone marrow shows: 1-increased Erythropoiesis 2-Erythroid hyperplasia.	
Spherocytosis on the peripheral blood film. (Spherocyte)	**Reduction** of serum **Haptoglobin**
	Hemoglobinuria, Haemoglobinaemia and **Hemosiderinuria** .
	Schistocytes: red cell fragmentation

Hemolytic Anemia: is a shorten in lifespan of RBC that can't be compensated by bone marrow. Hemolytic anemias can be classified into:

A) Congenital Hemolytic Anemia: The defect is **intrinsic** to RBC itself, affecting Red cell:

Membrane	**Hereditary spherocytosis (HS)** Most common	**Causes:** loss of **Ankyrin** then leads to secondary reductions in **spectrin**, and **protein 4.1** leading to a spheroid shape, vertical interaction. Destroyed by splenic macrophages, **extravascular hemolysis.** Peripheral smear shows **spherocytosis**.
	Hereditary Elliptocytosis (HE)	**Causes:** defects in **α spectrin,** horizontal interaction**.** Peripheral smear shows **elliptical/elongated RBC's.**
	Hereditary Pyropoikilocytosis (HPP) sever form from HE (homozygous mutation)	
Its Enzymes	**1- G6PD Deficiency** (G6PD gene mutation on **X** chromosome) predominantly intravascular, could be extravascular	**Blood film shows: 1-Heinz bodies 2- Bite cells** (in a patient exposed to **Oxidants**). **Favism:** causes an **acute hemolytic anemia** after the ingestion of the broad bean in G6PD deficiency patients. Affects **children**. **Severe anemia** develops & accompanied by **hemoglobinuria**.
	2 - Pyruvate kinase deficiency Extravascular	
Its hemoglobin	Sickle cell anemia	

B) Acquired Hemolytic Anemia: The cause is typically due to **extrinsic** defects, outside the red cell (**except *PNH**)

Immune	**Autoimmune**	**Warm Autoimmune Hemolytic Anemia** Extravascular	Autoantibodies react best with the red cell antigen at 37°C and are usually of **IgG**. Secondary to: SLE and CLL. **Peripheral smear shows spherocytosis. Critical diagnostic investigation:** Direct antiglobulin test (DAT), known as Coomb's test
		Cold Hemagglutinin Disease (CHAD) Intravascular	Antibodies react best below 32°C, they are usually of **IgM**.
	Alloimmune		
Non-immune	**Most commonly due to infection of: Malaria,** Clostridium perfringen, and bartonellosis. **Some drugs**		

Members board

Team Leaders:

Aleen AlKulyah **Remaz Almahmoud** **Sultan albaqami**

Team Members:

- **Milaf alotaibi**
- **Reuf Alahmari**
- **Deema almadi**
- **huda bin jadaan**
- **Elaf moatabi**
- **Aseel Alsaif**
- **Razan alsoteehi**
- **Maryam Alghannam**
- **Raghad Alqhatani**
- **Lama Alotaibi**
- **AlJoharah Alwohaibi**
- **Aroub Almahmoud**
- **Dana Almuhaisen**
- **Ryan alghizzi**
- **Feras Mazen**
- **Mishal Aldakhail**
- **Abdullah Alzamil**
- **Khalid Alanezi**
- **Mohammed Manee**
- **Ziad Alhabardi**
- **Zeyad Alotaibi**
- **Omar Alamri**
- **Moath Alhudaif**
- **Faris Alzahrani**
- **Abdullah Alkodari**

Special thanks to 442 team

HEMATO.TEAM43@GMAIL.COM

haematology Team