Acquired Haemolytic Anaemia

I-Corpuscular causes:

Acquired membrane defect:

PNH.

II- Extra corpuscular causes: (all r aquired)

A- Abnormal plasma constituents:

1- Immune H.A:

i-Auto immune:

warm Ab type

cold Ab type

ii- Allo immune:

Haemolytic transfusion reaction

Haemolytic disease of the newborn (HDN)

Allografts as post marrow transplantation.

iii- Drug immune

2-Drugs & toxins

3-Lipid disorders;

Abetalipoproteinaemia

Liver dis.

Vit E def.

B- Abnormal physical environment:

1- Blood vessel abnormalities:

- Microangiopathic H.A
- e.g: thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome (HUS).
- Marsh haemoglobinuria.
- Red cell fragmentation syndrome: in arterial grafts, cardiac valves.

- Malignant hypertension, pre-eclampsia, DIC.

2- Hypersplenism

3-severe burns

4- Infections:

Malaria, bartonella bacilli

Paroxysmal Nocturnal Haemoglobinuria (PNH)

Def:

- An acquired clonal disease, resulting from somatic mutation affecting haemopoietic stem cells.
- Resulting in defective production of the glycosyl phosphatidyl inositol-anchor (GPI-anchor)
- GPI-anchor proteins are not expressed on surface of haemopoietic cs (RBCs, WBCs & platelets)
- Resulting in ↓ production of WBCs, platelets & production of abnormal RBCs.
- Commonly arises in a damaged marrow e' a previous history of aplastic anaemia.
- It is ch. by pancytopenia e' ↑ retics

Pathogenesis:

RBCs:

PNH is a chronic IVH caused by ↑ sensitivity of RBCs to **complement mediated lysis**, due to acquired membrane abnormality, resulting in loss of certain membrane proteins w' protect against lysis.

DAF: Decay Accelerating Factor (**CD 55)**

MIRL: Membrane Inhibitor of Reactive Lysis **(CD 59)**

Cells are classified acc. to susceptibility to complement mediated lysis into:

Type I PNH : normal susceptibility to complement

„ II „ : intermediate „ „

„ III „ : marked „ „

Platelets:

↓DAF → ↑sensitivity to complement → lysis platelets & abnormal functions → thrombosis or bleeding

Granulocytes:

↓DAF → ↑ sensitivity to complement → ↓ graulocytes &chemotactic function

- PNH red cells are deficient in all GPI anchored protein, but 2 are important in protecting red cells from destruction: **CD55 (DAF)** and **CD59 (MIRL).**
- Without these proteins, red cells don't have their normal protection against the complement system.
- In PNH, you have uncontrolled, complement mediated hemolysis (destruction of red cells). This happens all the time, and is accelerated when you have an event that activates the complement system (infection).

C/P:

Onset: insidious

Course: prolonged

Severity: mild to severe

Age: any age, 6-82 ys

Sex: F > M

No familial tendency

The most common presentation is ch. H.A.

Haemoglobinuria : ¼ pts.

1- Haemoglobinuria:

Mostly it occurs irregularly

It ↑after infections, surgery, stress, exercise, etc…..

Nocturnal Hb-uria in few patients:

urine is dark in colour in the morning & clears during the day.

2- Episodes of haemolysis:

Ppt by : infections, surgery, stress, exercise, etc…..

due to activation of complement .

- Ch. H.A.: pallor, weakness ……

3- Bleeding:

Due to thrombocytopenia

4- Thrombosis:

Due to platelet activation by complement or ADP released from destroyed RBCs

It may be venous or arterial

Hepatic veins: hepatomegaly, pain , ascites.

Cerebral veins: headache

Mesentric, portal & splenic veins:

Pain in the abdomen & lower part of the back.

In pregnancy: abortion

5- Renal symptoms:

Haematuria, proteinuria, renal hypertension or renal failure.

6- Infections:

Due to ↓graulocytes & ↓its function

Lab diagnosis:

1- Evidence: 3

2- CBC:

Pancytopenia , MHA , ↑retics, but out of proportion to degree of anaemia

3- BM:

Normocellular e' erythroid hyperplasia or aplasia

Absent iron stores

4- Iron studies:

↓ serum iron (due to iron loss in urine)

↓ ,, ferritin

↑ TIBC

5- urine:

Hb-uria

Haemosiderinuria

6- Diagnostic tests:

A- Ham's test:

- Acidification of serum to ph 6.5-7 → activates alternative C pathway.
- Patient's RBCs r destroyed (lysed) by **both** acidified serum of donor & patient's himself i.e: defect in patient's RBCs
- **D.D: HEMPAS:** patient's RBCs r lysed by acidified serum of donor only

B- Sucrose lysis test:

+ ve as sucrose activates classical C pathway

D.D: HEMPAS: - ve

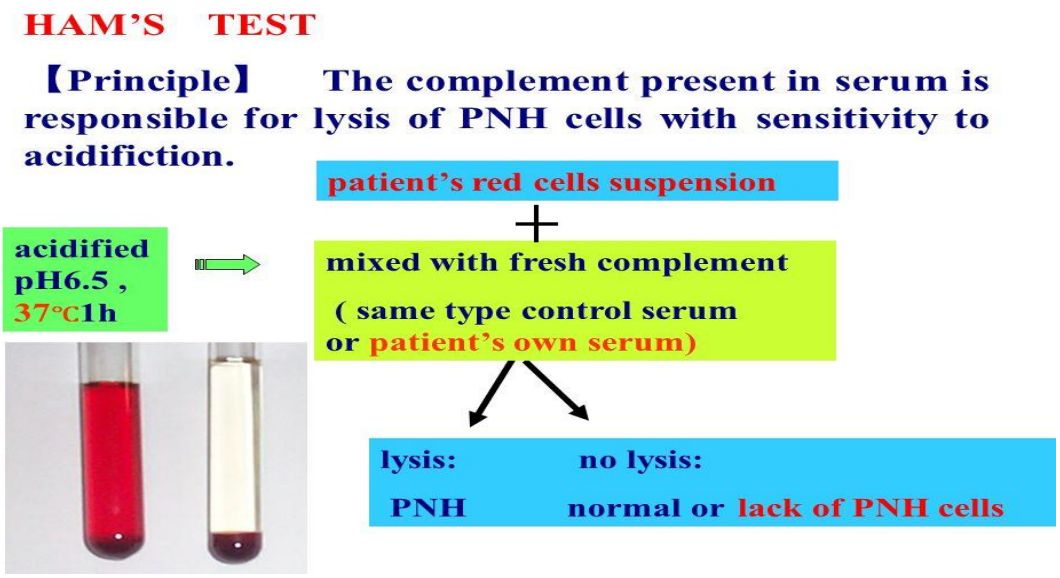
C- Flow cytometry:

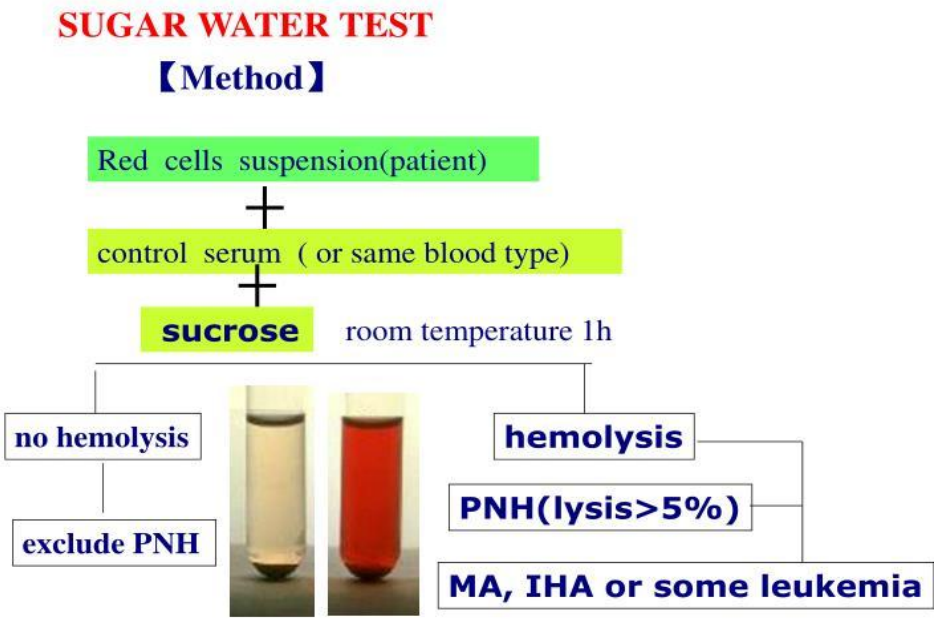
For CD 55 & CD 59 on RBCs

D.D:

HEMPAS (CDA II)

- No leukopenia
- No thrombocytopenia
- Ham's test, sucrose lysis test
- Congenital
- BM findings r characteristic

- 

- 

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IMMUNE HEMOLYTIC ANEMIA

- **Autoimmune Hemolysis**
  - Warm autoimmune hemolysis
  - Cold autoimmune hemolysis
- **Alloimmune Hemolysis**
  - Hemolytic Transfusion Reaction
  - Hemolytic Disease of the Newborn
- **Drug-Related Hemolysis**

Immune H.A

I- Auto immune H.A

- These anaemias r due to Ab production by the body against its own red cells
- They r characterized by shortened red blood cell (RBC) survival and the presence of auto antibodies directed against autologous RBCs.
- They r ch. by a + ve coomb's test
- They r divided into warm & cold types according to whether the Ab react better e' red cells at 37℃ or 4℃

Classification:

AIHA r classified according to:

1- Thermal amplitude of Ab into:

Warm : Ab reacts at 37℃ → 80%

Cold: „ „ 4℃ → less common

2- presence or absence of a cause:

1ry : idiopathic

2ry:

- lymphoproliferative dis.

- Ovarian tumors
- Chronic inflammatory diseases
- SLE
- Infection

AIHA Classification

- **Warm autoimmune hemolytic anemia**
  - Idiopathic,
  - Secondary
    - Lymphoproliferative disorders, autoimmune diseases
- **Cold autoimmune hemolytic anemia**
  - **Cold agglutinin syndrome**
    - Idiopathic,
    - Secondary- mycoplasma, infectious mono, LPD
  - **Paroxysmal cold hemoglobinuria**
    - Idiopathic,
    - Secondary- measles, mumps, syphilis
- **Drug-induced IHA**
  - Autoimmune, Drug adsorption, Neoantigen

Table 5.5 Immune haemolytic anaemias: classification.

Warm type	Cold type
Autoimmune	
Idiopathic	*Idiopathic*
Secondary	*Secondary*
SLE, other 'autoimmune' diseases	Infections—*Mycoplasma* pneumonia; infectious mononucleosis
CLL, lymphomas	Lymphoma
Drugs (e.g. methyldopa)	Paroxysmal cold haemoglobinuria (rare, sometimes associated with infections, e.g. syphilis)
Alloimmune	
Induced by red cell antigens	
Haemolytic transfusion reactions	
Haemolytic disease of the newborn post stem cell grafts	
Drug induced	
Drug–red cell membrane complex	
Immune complex	

1- Warm AIHA:

Characteristics of Ab:

- Ig class : Ig G
- Temp of reactivity: 37 ℃
- Polyclonal
- Incomplete Ab
- Specificity directed against Rh Ag
- Complement plays a minor role in haemolysis
- Direct coomb's test is + ve either

  Type I: Ig G alone on RBCs

  Type II: Ig G + complement on RBCs

  Type III: complement alone on RBCs
- Indirect coomb's test is + ve using O +ve RBCs

Classification:

1ry : idiopathic

2ry:

- CLL & lymphoma
- Ovarian tumors
- Chronic inflammatory diseases
- SLE & other autoimmune dis
- Drugs: methyl dopa
- Viral infection:

Ab formed against virus cross react e' RBCs

Or Ab-virus complex becomes adsorbed on RBCs surface & complement fixation occurs → haemolysis

Pathogenesis:

EVH in spleen

MQ of spleen have receptors for F.C portion of Ig G

RBCs coated by Ig G will be phagocytosed by MQ either:

Partially → spherocytes

Completely→ haemolysis

C/P:

- Anaemia:
- Of varying severity
- Sudden or gradual onset
- Sometimes compensated H.A occurs
- Rare IVH
- Jaundice
- Splenomegaly

Lab findings:

Evidence: 3

CBC:

- NNA
- Spherocytes
- Sometimes platelets ↓ → Evan syndrome

- DAT : + ve
- Indirect : + ve e' O + ve cells

BM:

Erythroid hyperplasia

2 ry causes

1-Post viral AIHA

Mostly in childern

1-2 weeks after viral infection → haemolysis , self limited

Mechanism:

Viral infection → alter RBCs Ag → Auto Abs

Virus + Ab adsorbed on RBCs surface initiating RBCs destruction

Ab against virus cross-react e' RBCs Ag

2-SLE:

Have:

- Ab against RBCs
- ,, ,, platelets
- Anti-DNA Ab
- Ab in case of SLE fix complement → more haemolysis

3- CLL & lymphomas:

Abs against RBCs r mostly due to altered immune mechanism

4-Other immune disorders:

e.g: thymoma

5- Ovarian tumors:

Teratoma, dermoid cyst

ttt:

- Steroids → suppress RES → ↓ Ab synthesis
- Splenectomy
- Immune suppression . High dose Igs

2- Cold AIHA (cryopathic H.A)

Characteristics of Ab:

- Ig class : Ig M or biphasic Ig G
- Temp of reactivity: 4 ℃
- Monoclonal, except if immune response is against infection (polyclonal)
- Complete Ab (Ig M)
- Specificity against I, i or P Ags
- Complement plays a major role in haemolysis
- Direct coomb's +ve : only complement is detected on RBC surface
- Indirect coomb's +ve: e' adult cells containing I Ag,
  or e' foetal cells containing i Ag

Classification:

I- Cold agglutinin syndrome: Ig M Abs

1- Idiopathic:

Monoclonal Ig M , presented at old age

Ig M against I, i Ags

Years later: patient may suffer from B-lympho- proliferative disorders

2- Secondry:

Infections: in adults, presented e'↑ titer of naturally occurring cold agglutinin

Self limited

- **Mycoplasma:** polyclonal Ig M against Ii Ags
- **IMN:** ,, ,, ,, i Ags
- **B-lymphoproliferative disorders:**
  Polyclonal Ig M produced by malignant cells

II- Cold haemolysin syndrome:

1- Idiopathic:

Paroxysmal Cold haemoglobinuria (PCH)

2- Secondry:

Viral infections

Congenital & 3ry syphilis in adults

Biphasic Ig G against P Ags

Pathogenesis:

I- Cold agglutinin syndrome:

On exposure to cold: in extremities

Ig M agglutinate RBCs → ↓blood flow → Acrocyanosis

Ch by gradual onset of dark purplish discoloration of the skin especially peripheral parts of the body, may be painful →

activation of Complement

In core temp. , release of Ig M w' re-circulate & bind to other RBCs

Complement either:

Undergoes complete activation from C1 → C9 → haemolysis

OR:

Undergoes incomplete activation to C3b only & RBCs coated by C3b pass to MQ of liver w' contain receptors for C3b & phagocytosis will occur either completely → haemolysis

Or incompletely → spherocytosis e' C3dg on its surface & these r the cells w' can be detected by Coomb's test

Clinically

-pallor

-Acrocyanosis

-mild splenomegaly

-mild jaundice

D.D:

	Acrocyanosis	**Reynaud's**
Blanching phase	No	Yes
Colour	Dark purplish	Blue
Erythema	Occurs after cyanosis	No

II- Cold haemolysin :

Paroxysmal cold haemoglobinuria (PCH):

Biphasic Ig G **(Donath-Landsteiner Ab. DLA)**

During severe chilling: Ab+ C bind RBCs at 37oC in the central circulation ⟶ activation of C from C1⟶ C9 ⟶ IVH ⟶ haemoglobinaemia, haemoglobinuria, etc….

Clinically:

Bouts of haemoglobinuria on exposure to cold

Diagnosis:

Cold agglutinin syndrome **Ig M**	**Cold haemolysin syndrome** **Biphasic Ig G**
CBC: • Anaemia: mild to moderate • Retics: < of warm AIHA • No spherocytes • Auto agglutination in the film **Serological:** Serum of the patient, agglutinate saline suspended RBCs at lower temp. ⟶ reversed by warming	• Evidence of IVH • Detection of DLA • Patient's fresh serum+ RBCs at 4oC ⟶ warming at 37oC ⟶ intense haemolysis • **Complement assay** ↓C following attack

II- Drug Induced H.A

Mechanisms:

1- Hapten or drug adsorption:

e.g: **Penicillin**

Ab is directed against a drug – red cell membrane complex

Ab (Ig G)≠ Ag (drug + RBCs membrane complex)

Diagnosis:

Clinically:

H.A manifested e' drug intake & gradually disappears when the drug is stopped

Lab:

Direct coomb's: + ve as in WAIHA

Indirect coomb's:

+ ve only in the presence of the drug

II- Auto- Antibody production:

e.g: **α methyl dopa**

- Ab is directed specifically against RBCs Ag (Rh)
- It occurs in 10 % of patient's using α methyl dopa
- Coomb's test: becomes + ve after several months of using the drug & persists for several months after stopping the drug
- Ab is not directed against the drug, but the drug alters Rh Ag making it→ foreign , so induce Immune mechanism

Diagnosis:

- Indirect coomb's : + ve in absence of drug
- Direct coomb's : + ve as in WAIHA

III- Innocent bystander:

e.g: **Quinidine**

- Drug is fixed loosely to RBCs membrane
- Complement is fixed during Ag/Ab reaction → activation of C → haemolysis of RBCs → Hb-uria
- Because the drug is loosely fixed to the membrane, it wash away during preparation of direct coomb's & only C can be detected on RBCs

Diagnosis:

Clinically:

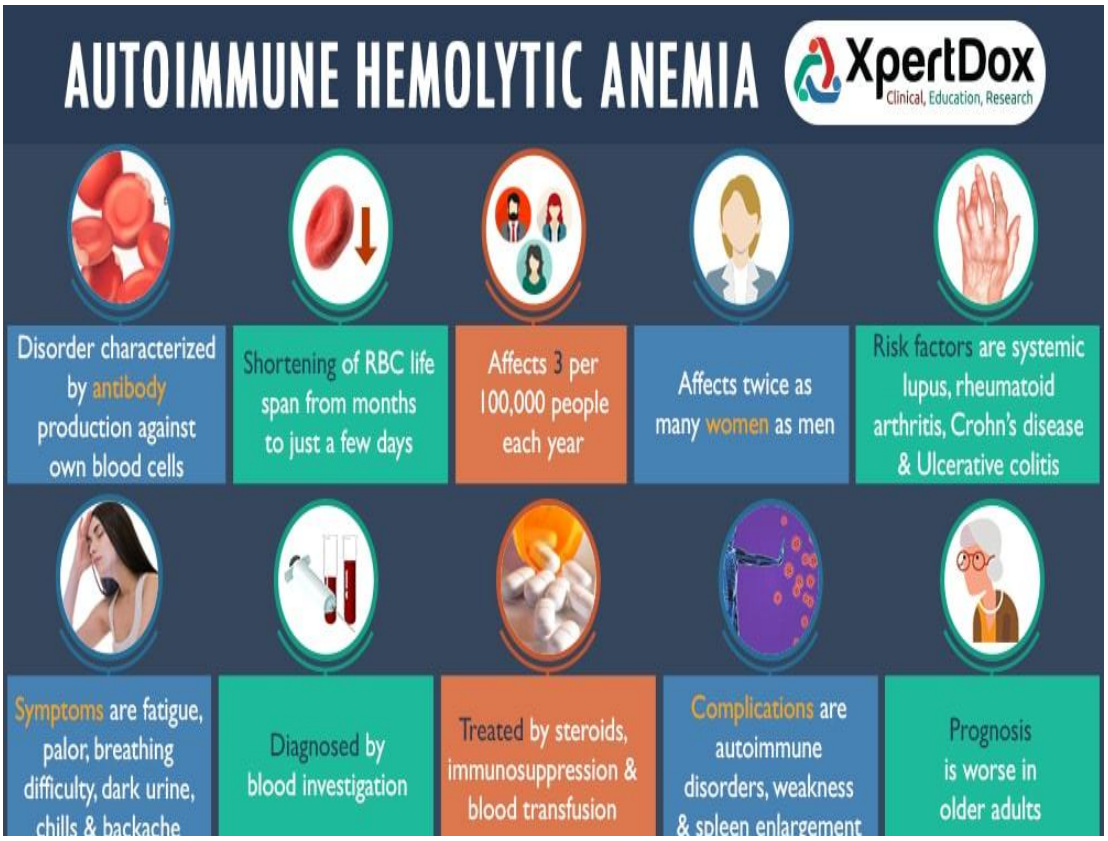
- Moderate to severe anaemia
- Hb-uria
- Disappearance of symptoms on stopping the drug

Lab:

- Direct coomb's:+ve as in CAIHA (by anti C)
- Indirect coomb's: + ve only in the presence of drug

Treatment AIHA

WAIHA	CAD	PCH	Drug-IHA
Folate Corticosteroids 20% complete response	Folate Avoid cold Treat secondary cause	Folate Avoid cold	Treat if hemolysis present
Splenectomy 60-75% response rate	Chlorambucil Cytoxan, α-Interferon	Treat infection	Folate Stop drugs
Cytotoxic drugs	Plasmapheresis	? Plasmapheresis	Corticosteroids-severe cases
Transfuse –least incompatible	Transfuse-I+, blood warmer	Transfuse- P+, blood warmer	Transfuse


AUTOIMMUNE HEMOLYTIC ANEMIA
XpertDox
Clinical, Education, Research
Disorder characterized by antibody production against own blood cells
Shortening of RBC life span from months to just a few days
Affects 3 per 100,000 people each year
Affects twice as many women as men
Risk factors are systemic lupus, rheumatoid arthritis, Crohn's disease & Ulcerative colitis
Symptoms are fatigue, palor, breathing difficulty, dark urine, chills & backache
Diagnosed by blood investigation
Treated by steroids, immunosuppression & blood transfusion
Complications are autoimmune disorders, weakness & spleen enlargement
Prognosis is worse in older adults