HAEMOLYTIC ANAEMIAS, ACQUIRED DISORDERS.

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- Acquired haemolytic anaemias are predominantly due to extracorpuscular disorders with the exemption of Paroxysmal Nocturnal Haemoglobinuria.
- They are as common if not commoner than inherited haemolytic anaemias.

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CLASSIFICATION OF ACQUIRED HAEMOLYTIC DISORDERS

- ACQUIRED HAEMOLYTIC DISORDERS:
  - -Immune
  - -Non immune

Immune:

- -auto immune
- -allo immune
- -drug induced

Non immune:

- -Red cell fragmentation syndrome
- -March haemoglobinuria
- -Infections
- -Chemical and physical agents.
- -Secondary
- -Paroxysmal nocturnal haemoglobinuria

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IMMUNE HAEMOLYTIC ANAEMIAS

- ANTIBODY MEDIATED
- COMPLEMENT MEDIATED

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IMMUNE HAEMOLYTIC ANAEMIAS

- Antibody-mediated haemolysis is an important cause of acquired haemolytic anaemia.
- Antibodies may be autoantibodies produced by the patient's own immune system and directed against his/her own red cell antigens or they may be alloantibodies.
- Alloantibodies may be produced by the patient and directed against antigens not present on that person's own red cells, but either introduced as foreign red cell antigens or foreign antibodies by blood transfusion.

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- Alloantibodies directed against the patient's red cell antigens might also be introduced from outside the patient, most notably from the mother in haemolytic disease of the newborn.

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- Typically, the immune haemolytic anaemias are distinguished from the non-immune by detecting antibody on the surface of the red cells by the direct antiglobulin test (DAT), also known as the Coombs test.

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AUTO IMMUNE HAEMOLYTIC ANAEMIAS (AIHA)

- Definition: AIHA is an acquired haemolytic disorder in which auto antibody/ies are produced against antigen/s on the surface of red cells.
- The site and severity of red cell destruction depend on structural and functional characteristics of the antibody and efficiency of the mechanism of destruction.

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- The degree of anaemia depends on the rate and acuteness of the destruction and the capacity of the bone marrow to compensate.
- The structural and functional characteristics of the antibodies involved in AIHA are:

-**Immunoglobulin class.**

-Thermal range.

-Complement activation.

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- **Immunoglobulin class:**

Immunoglobulins involved in haemolysis in AIHA are IgG, IgM, IgA while C3c and C3d are the common complement components involved in haemolysis.

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- **Thermal range:**

This is the temperature at which an antibody is most active.

Warm-acting antibodies are most active *in vitro at 37°C.* The antibodies are polyclonal, and IgG antibodies predominate. Where the specificity of the antibody can be determined, it is most commonly in the rhesus blood group complex.

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- Cold-acting antibodies are predominantly IgM and are most actively bound to antigen in the cold (4°C).

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- **Complement activation**

  Autoantibodies against red cell antigens may activate complement on the red cell membrane. Antibody binding to two adjacent sites on the red cell membrane is required to activate the C1 complement component by the classical pathway.

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- IgM molecules are pentameric and a single molecule can bind adjacent sites; IgG molecules will activate complement if they form a ‘doublet’: IgG1, IgG2 and IgG3 can activate complement, whereas IgG4 and IgA do not.

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- In AIHA, complement activation usually stops at the C3 stage, where C3b is bound to the membrane and further proteolysed to form the inactive component C3d, which is detected by the appropriate DAT.
- Complement beyond the C3 stage may lead to the formation of the membrane attack complex and intravascular haemolysis.

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PATHOPHYSIOLOGY OF RED CELL DESTRUCTION

- Red cell destruction could be

-Cell mediated

-Complement mediated.

Cell mediated destruction:

- Human macrophages and monocytes have cell-surface receptors for the Fc portion of IgG and for antigenic determinants present on activated C3. Cellular immune destruction is mediated through these receptors.

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- Spleen and liver have high concentration of these macrophages and monocytes (Kupfer cells in liver). Hence any red cells coated with IgG or complement will be recognized and eventually destroyed in the spleen and liver.

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Complement mediated destruction

- Intravascular complement-mediated haemolysis is a minor mechanism for red cell destruction in most patients with AIHA.
- In a small proportion of patients, such a mechanism may predominate and produce severe intravascular haemolysis.
- Complement-induced intravascular haemolysis in warm AIHA is most likely to occur when more than one class or subclass of Ig is present on the red cell surface.

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- In cold AIHA syndromes, intravascular haemolysis may be precipitated by exposure to cold. In such cases, lytic as well as agglutinating antibodies with a high thermal range may be present.

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- From these, AIHA can be classified into

-WARM AIHA.

-COLD AIHA.

According to the thermal range of the antibody with red cells (37^0c or 4^0c).

WARM AIHA could be:

1. Idiopathic
2. Secondary to

   -other auto immune disorders e.g SLE, RA.

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-Chronic lymphocytic leukaemia

-Lymphomas.

-Drugs.

3. If associated with immune thrombocytopenic purpura, it is called Evan's syndrome.

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- In warm AIHA, red cells are coated with immunoglobulin, usually IgG alone or with complement.
- These IgG/complement coated red cells are taken up by macrophages of reticuloendothelial system (RES) because they have receptors for the Ig Fc fragment.
- Part of the coated membrane is lost so the cells become progressively more spherical to maintain its volume (microspherocyte).

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- The cells will be eventually prematurely destroyed especially in the spleen.
- CLINICAL FEATURES:

  -Occurs at any age

  -both sexes are equally affected.

  -Presesnts as haemolytic anaemia of varying severity

  -Splenomegally is common.

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-The disease remits and relapses.

LABORATORY FEATURES:

-Haematological and biochemical findings of extravascular haemolysis.

-Spherocytosis is prominent on blood film.

-Coomb's test is positive.

-The antibodies (on the red cell surface and in the serum) are best detected at 37^0c

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TREATMENT:

1. Remove underlying cause/s.
2. Give steroids. Prednisolone is the usual first line drug. Starting dose of 60mg/day in adults and later tapered down.
3. Splenectomy in those who fail to respond to steroids.
4. Immunosuppresion with azathioprine, cyclophosphomide, chlorambucil etc may be tried.

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5. Monoclonal antibodies e.g CD20 (rituximab) for those associated with lymphomas.
6. Folic acid supplement
7. Red cells transfusion.
8. High dose immunoglobulin. These immunoglobulins compete with the auto antibodies in binding to red cell, hence reducing haemolysis.

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COLD AIHA

- Cold AIHA could be:

  1.Idiopathic

  2. Secondary to:

  -lymphoproliferative diseases

  -Infections.

In cold AIHA, auto antibodies attach to red cells mainly in the peripheral circulation where blood is cooled e.g tip of toes or fingers.

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- The antibodies are usually IgM and they bind to red cells maximally at 4^0c.
- IgM fixes complements well, hence haemolysis is predominantly intravascular.
- The IgM could be monoclonal as in idiopathic cold haemaglutitnin syndrome or polyclonal as in those due to infections.

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- CLINICAL FEATURES:

-Chronic haemolytic anaemia aggravated by cold.

-Features of intra vascular haemolysis.

-mild jaundice.

-splenomegally

-acrocyanosis (purplish skin discolouration) at the tip of fingers and toes due to agglutination of red cells in small vessels.

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- LABORATORY FEATURES:

  is similar to that of warm AIHA but spherocytosis is less prominent.

TREATMENT:

1. Keep patient warm.
2. Treat underlying causes.
3. Alkylating agents e.g chlorambucil may be useful.

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PAROXYMAL COLD HAEMOGLOBINURIA

- Form of cold AIHA.
- A rare syndrome.
- Caused by Donath-Landsteiner antibody, an IgG antibody against P blood group antigens. The antibody binds to P antigen in the cold but causes lysis with complement in warm condition.
- Presents with acute intravascular haemolysis after exposure to cold.

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ALLO IMMUNE HAEMOLYTIC ANAEMIA

- Allo antibodies are antibodies produced by an individual and react with red cells of another or antibodies produced by the body against another antigen but also reacts with red cells antigens.
- Allo immune haemolytic anaemia is seen in

1. ABO incompatible blood transfusion
2. Haemolytic Disease of Newborn.

Haemolysis could be intra or extra vascular depending on the type and the nature of the antibodies involved.

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DRUG INDUCED HAEMOLYTIC ANAEMIA

- Drugs cause immune haemolytic anaemia through 3 main mechanisms:

1. Antibody directed against drug/red cell membrane complex, e.g penicillin, ampicillin.
2. Activation of complement via drug/protein (antigen)-antibody complex on red cell membrane, e.g quinidine, Rifampicin.
3. A true AIHA in which the role of the drug is not clear, methyl DOPA.

TREATMENT:

-Removal of the drug from circulation.

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RED CELL FRAGMENTATION SYNDROME

- This syndrome is due to physical damage to red cells in circulation. The syndrome could be divided into two:
- 1. MACRO ANGIOPATHIC HAEMOLYTIC ANAEMIAS.
- 2. MICRO ANGIOPATHIC HAEMOLYTIC ANAEMIAS.

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MACRO ANGIOPATHIC HAEMOLYTIC ANAEMIAS.

Damage to red cells could be from:

1. Abnormal surfaces, e.g artificial heart valves, arterial grafts.
2. Arterovenous malformations.

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MICRO ANGIOPATHIC HAEMOLYTIC ANAEMIAS.

In microangiopathic haemolytic anaemias, red cells pass through,

-fibrin strands as in DIC.

-roughened endothelial surfaces as in vasculitis , e.g poly arteritis nodosa.

-platelets adhered to small, vessels as in thrombotic thrombocytopenic purpura (TTP).

CLICAL FEATURES:

-Lots of red cell fragments on peripheral blood.

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MARCH HAEMOGLOBINURIA

- Caused by damage to red cells between small bones of feet, usually during prolonged marching or running.
- No red cell fragments on blood film.

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INFECTIONS

- Cause haemolytic anaemia in so many ways

1. Acute haemolytic anaemia of G6PD deficiency.
2. Micro angiopathic haemolytic anaemia, e.g pneumococcal and meningococcal septicaemia.
3. Malaria causes haemolysis by extra vascular destruction of parasitised red cells or direct intravascular destruction of red cells loaded with malaria parasites.
4. Black water fever is an acute intravascular haemolysis associated with acute renal failure in Falciparum malariae infestation.

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CHEMICAL AND PHYSICAL AGENTS

- DAPSONE AND SALAZOPYRIN cause oxidative damage and intravascualar haemolysis.
- High levels of cupper in the blood can cause intravascular haemolysis as in Wilson's disease.
- Chemical poisoning, e.g lead, chlorate, arsine cause severe haemolysis.

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PAROXYSMAL NOCTURNAL HAEMOGLOBINURAI

- Is a rare, acquired, clonal intracorpuscular disorder of bone marrow stem cells.
- There is deficient synthesis of glycosylphosphatidylinositol (GPI) anchor.
- GPI attaches several surface proteins to red cell membrane.
- Results from mutation in the X chromosome gene that code for phosphatidylinositol glycan protein A (PIG-A).

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- With absence of GPI anchor, there is no GPI linked proteins, e.g CD55, CD59.
- CD55 and CD59 are Decay Accelerating Factors (DAF) and Membrane inhibitor of reactive lysis (MIRL).
- Absence of DAF and MIRL renders red cells sensitive to lysis by complement resulting into intravascular haemolysis.

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CLINICAL FEATURES

- Males and females equally affected.
- Haemoglobinuria noticed in the first urine after sleep and clears during the day.
- Abdominal pain, often severe, intermitenet and unrelated to meals.
- Thrombotic complications especially of large veins are common

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- Haemosiderinuria are constant features
- Iron deficiency may develop.
- Splenomegally in some patients.

- DIAGNOSIS is made by flow cytometry.

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TREATMENT:

-Iron therapy.

-Anti couagulants with warfarin.

-Immunosuppression.

-Bone marrow transplantation.

- PNH usually remits with median survival of 10 years.

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