Aplastic anemia and PNH: an overview

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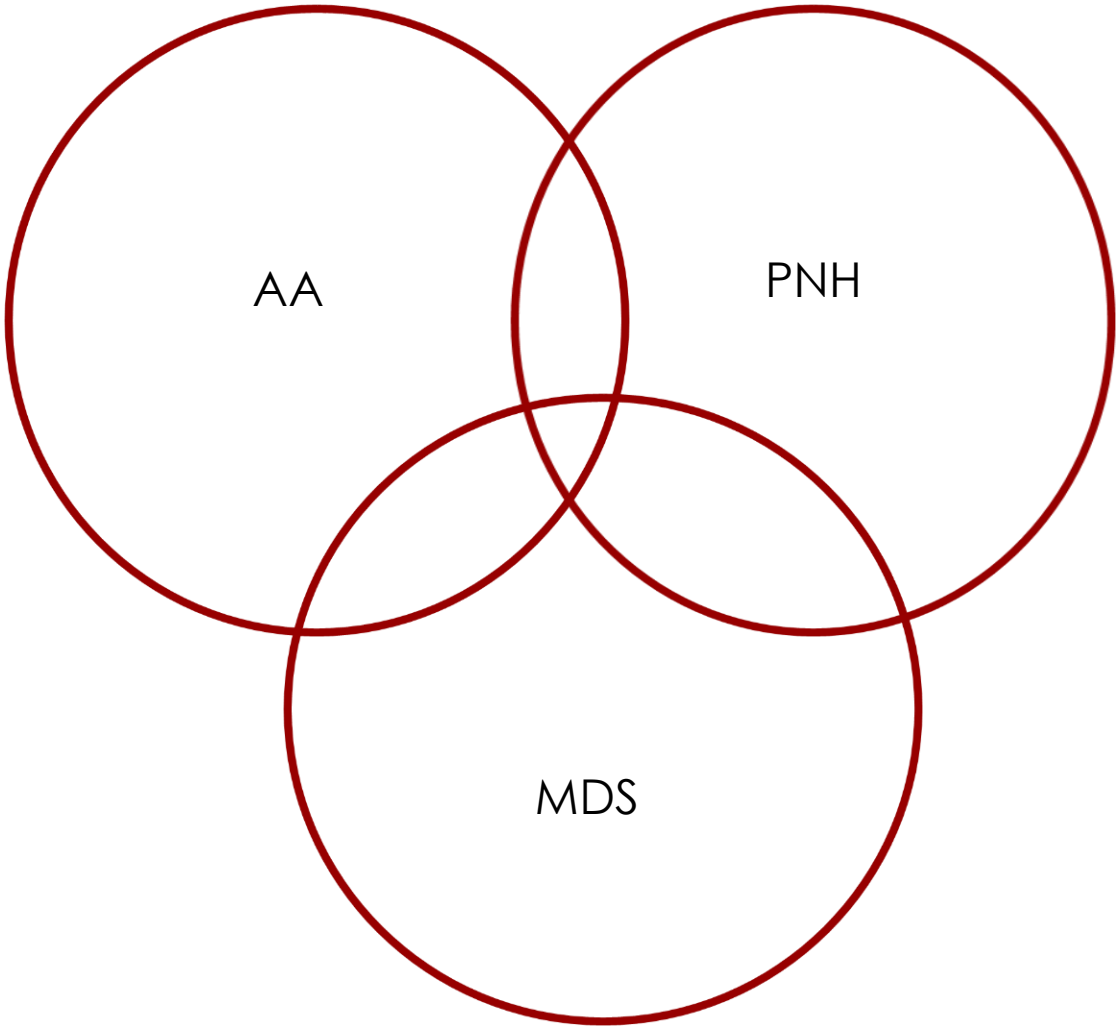
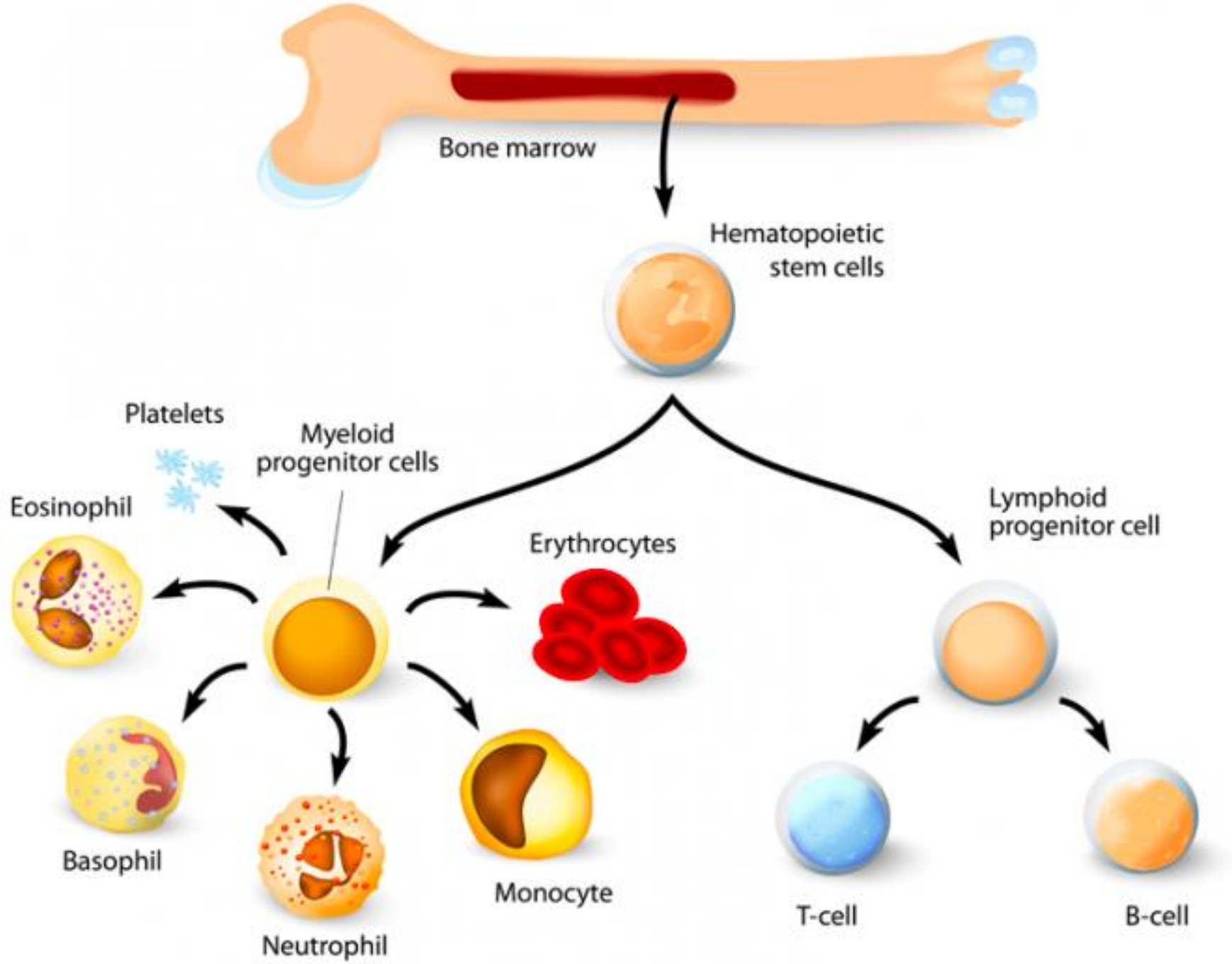
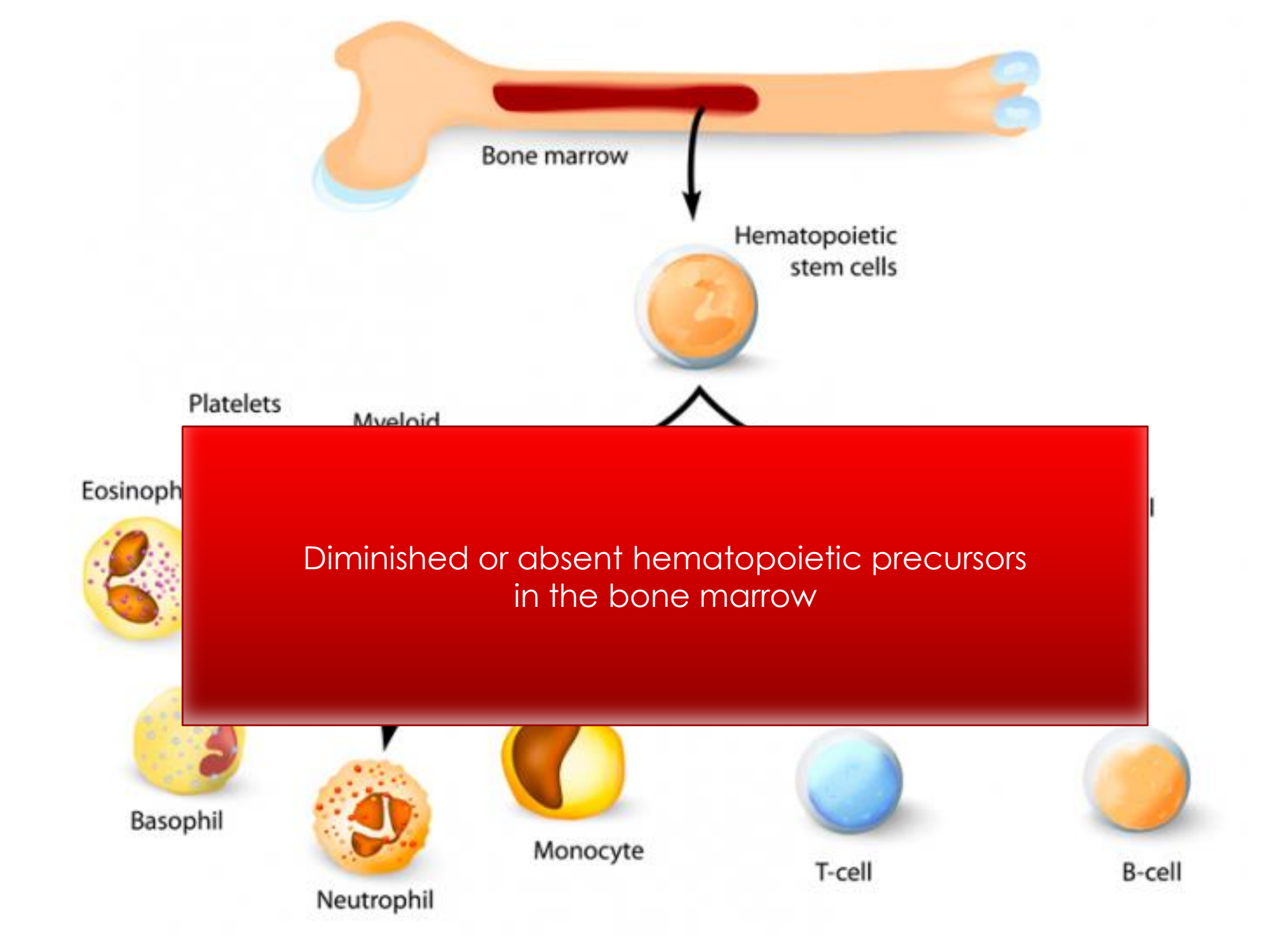
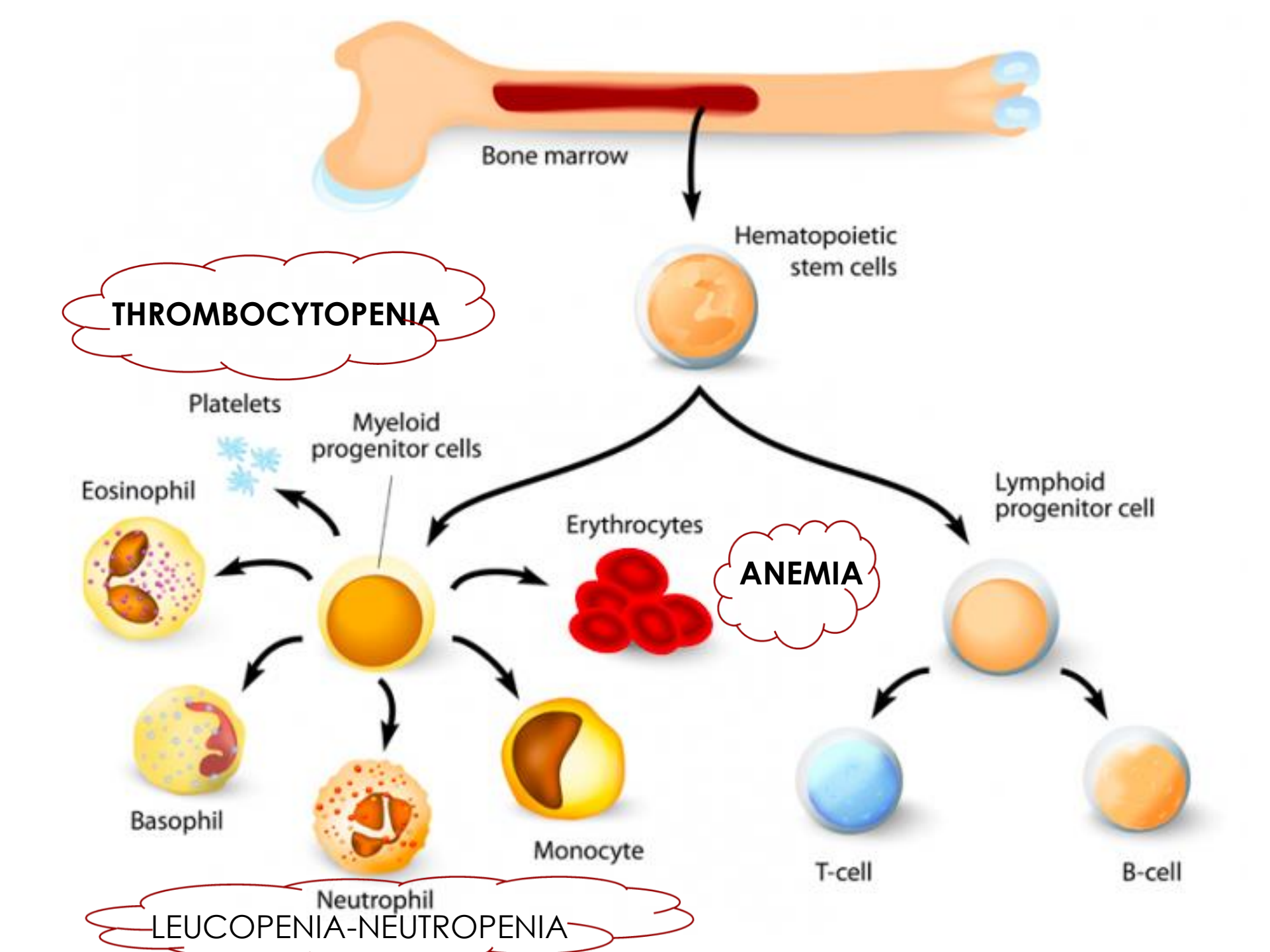

AA
PNH
MDS

Aplastic anemia


Bone marrow
Hematopoietic stem cells
Platelets
Myeloid progenitor cells
Eosinophil
Erythrocytes
Lymphoid progenitor cell
Basophil
Neutrophil
Monocyte
T-cell
B-cell


Bone marrow
Hematopoietic stem cells
Platelets
Eosinoph
Diminished or absent hematopoietic precursors in the bone marrow
Basophil
Neutrophil
Monocyte
T-cell
B-cell


Bone marrow
Hematopoietic stem cells
THROMBOCYTOPENIA
Platelets
Myeloid progenitor cells
Eosinophil
Erythrocytes
ANEMIA
Lymphoid progenitor cell
Basophil
Monocyte
T-cell
B-cell
Neutrophil
LEUCOPENIA-NEUTROPENIA

Aplastic anemia

- Misnomer
  - Affects other cell types
- Rare disease
  - 2-4 patients per million per year
- Can be diagnosed at any age, in any race

Causes of AA

Congenital

- Fanconi anemia
- Dyskeratosis congenita
- Shwachman-Diamond syndrome
- Amegakaryocytic thrombocytopenia
- Reticular dysgenesis

Acquired (80%)

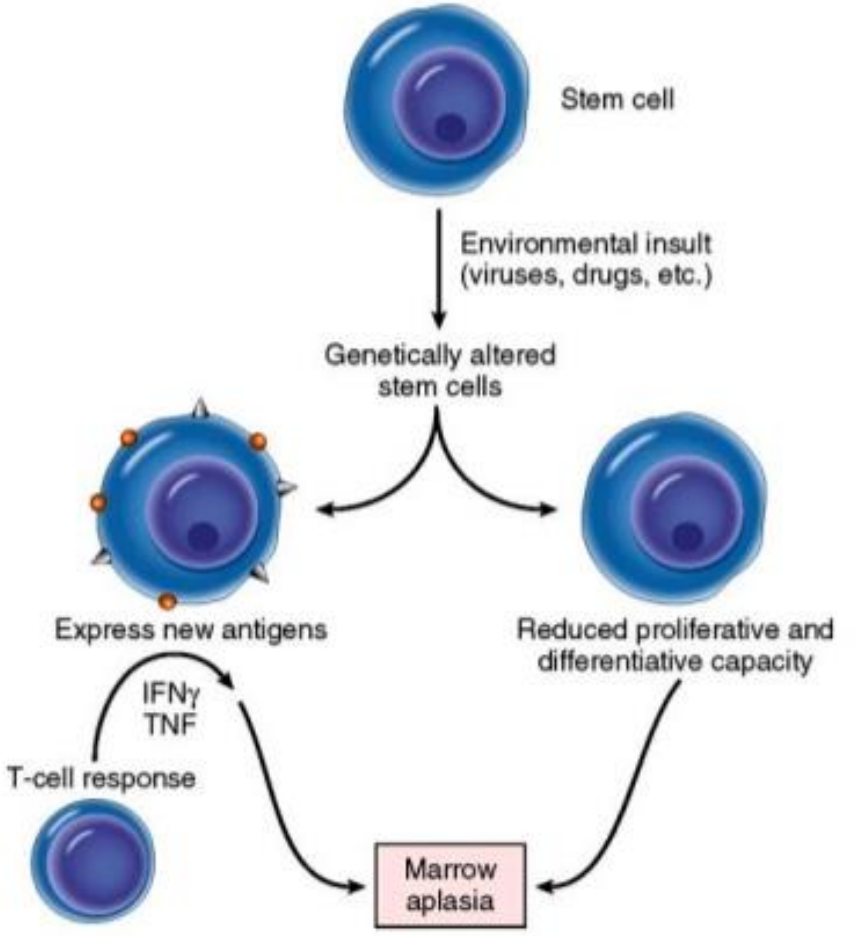
- **Idiopathic (75%)**
- Drugs
  - Gold, NSAID, antiepileptic, antibiotics, anti-thyroid
- Chemical exposition
  - Industrial chemicals, benzene, insecticides
- Radiation exposition
- Viruses
  - Parvovirus B19, HIC, hepatitis viruses
- Immune disorders
- Pregnancy
- PNH
- Anorexia nervosa

Clinical manifestations

- Anemia
  - Fatigue, dyspnea, cardiac problems
- Thrombocytopenia
  - Bleeding
- Leucopenia
  - Infection, fever

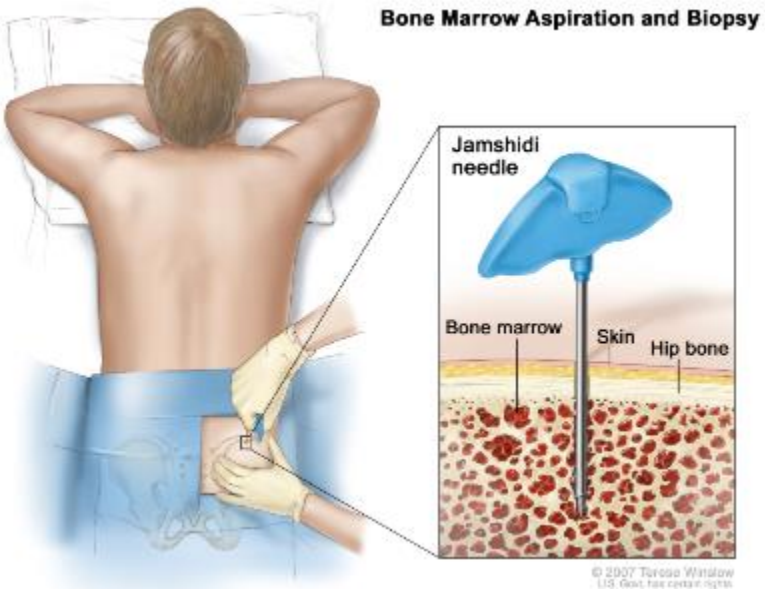
What causes idiopathic AA ?

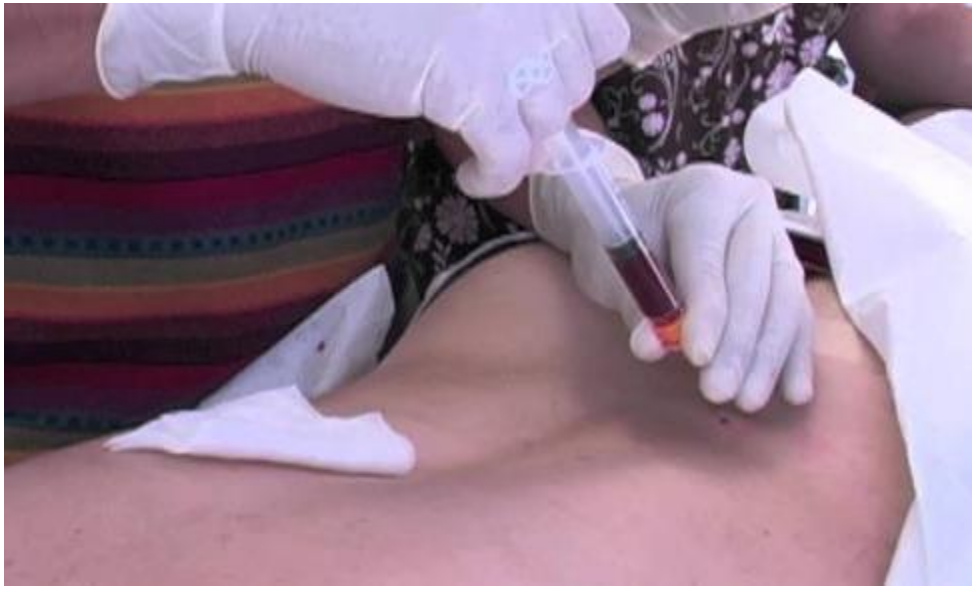
Immune-related bone marrow destruction



Evaluation and diagnostic

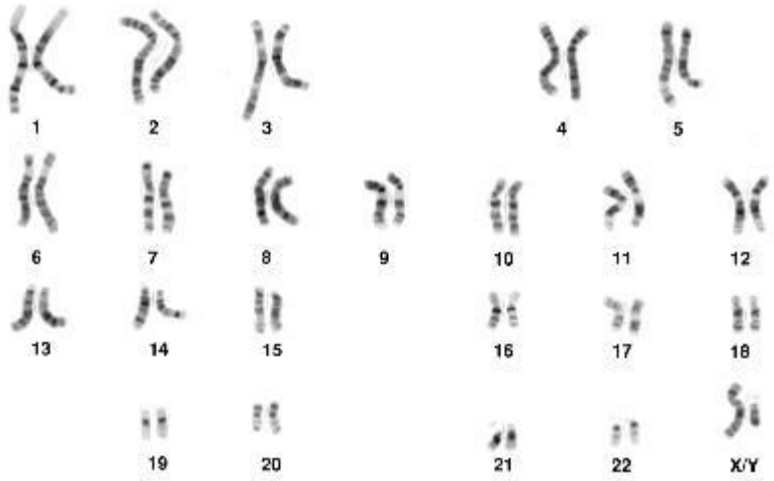
- Complete history
  - Medication review, specific exposure, known diseases
- Bone marrow aspiration and biopsy



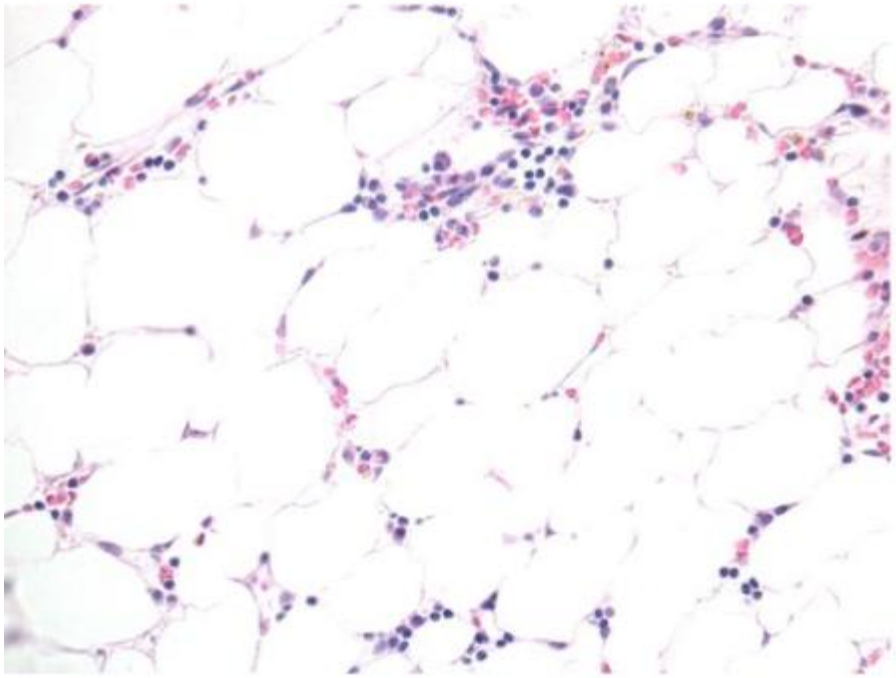


Tests on the marrow

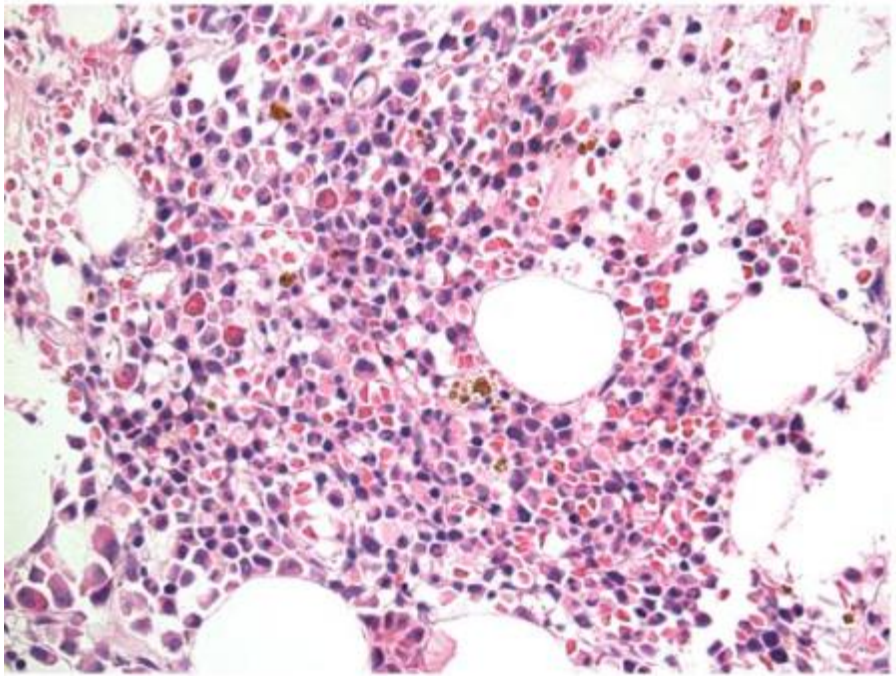
- Flow cytometry for PNH
- Cytogenetic analysis



Normal Karyotype



Bone marrow biopsy in AA



Normal bone marrow biopsy

Aplastic anemia severity

- Severity of cytopenias can be variable
  - Moderate
  - Severe
  - Very severe

- When is it severe or very severe
  - High risk of complications if no treatment given
  - High rate of mortality at 1 year if not treated (70%)

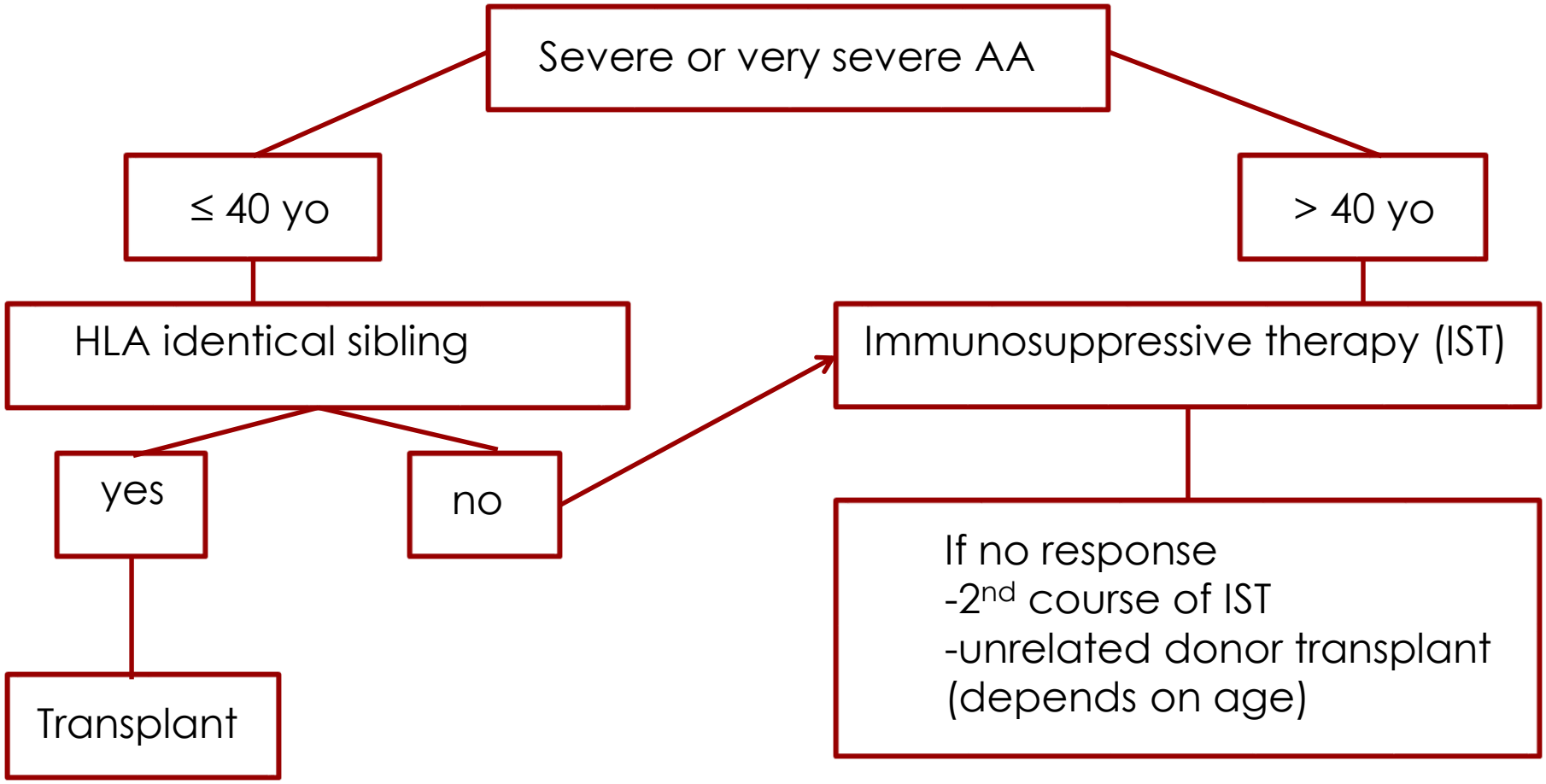
Indications for treatment

- Patients with severe and very severe AA require treatments
- Patients with non-severe AA will be followed and treated at progression
- Because of the prognosis if left untreated, treatment goal is to improve the long-term control of the disease

Treatment overview

- Remove the offending agent if needed
- Supportive treatment
  - Antibiotics for infection
  - Transfusions
- Definitive treatment
  - Immunosuppressive therapy
  - Allogeneic stem cell transplant

Treatment schema



Immunosupressive therapy

- Modulates the body's immune system
- Prevents the immune system from attacking the bone marrow stem cells
  - Cells can grow and blood counts improve

Immunosupressive therapy

- Combination of
  - 1) Antithymoglobulins (iv x 5 days)
    - ATG produced by immunizing animals against human lymphoid tissue

  - 2) Cyclosporine (oral)

Immunosupressive therapy complications

- Infusion reactions to the ATG
- Serum sickness
  - Rash, joint pain, fever, itchiness
- High blood pressure
- Kidney failure
- Gums swelling
- Unwanted hair

Immunosupressive therapy

- Chances of response after 1st treatment (horse ATG)
  - Approximately 60- 70% at 3-6 months
- Relapse in 30-40% of patients
- Chances of response after 2nd treatment (rabbit ATG)
  - 30% (range from 20-60% in different trials)

Blood 2006;108(8):2509

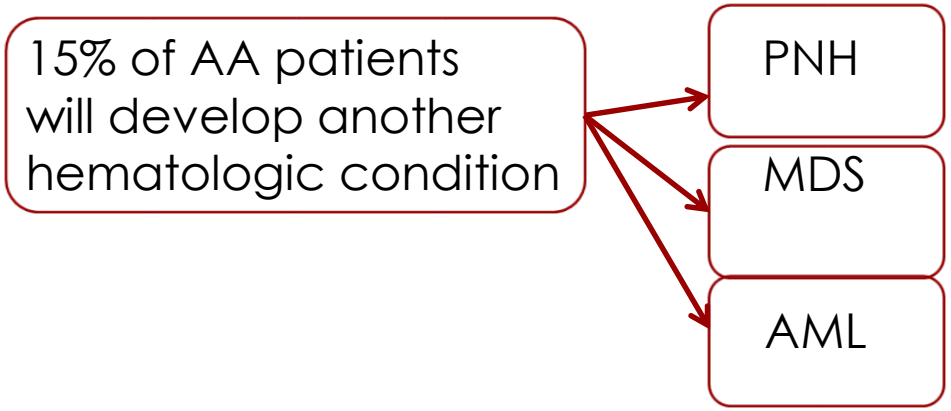
Elthrombopag (REVOLADE®)

- TPO agonist studied in patients with aplastic anemia refractory to IST
- 43 patients
  - 40% with improvement in their counts at 3-4-months
- REVOLADE® is indicated for the treatment of adult patients with severe aplastic anemia (SAA) who have had an insufficient response to immunosuppressive therapy (product monograph)

BLOOD 2014;123(12)

Survival determinants

- Age at diagnostic
- Severity of the disease
- Response to treatment
- Evolution of the disease



Survival

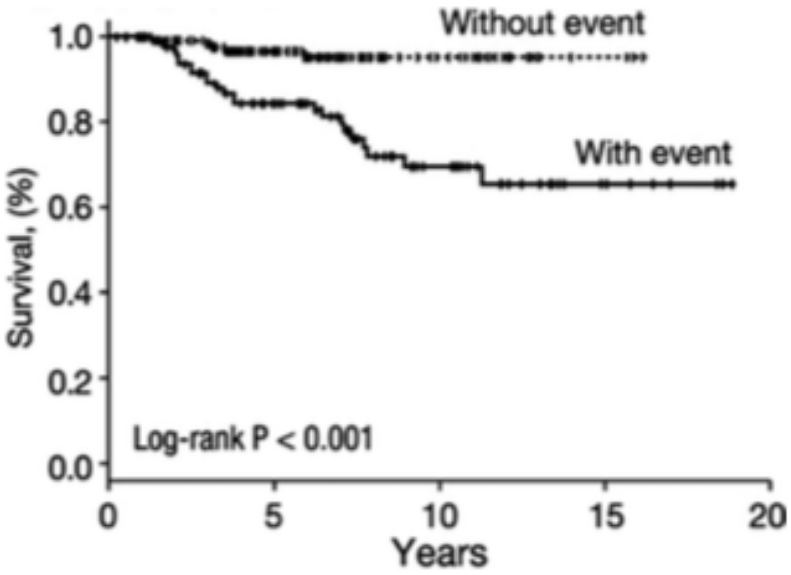


Figure 2. Survival after response to immunosuppression in severe aplastic anemia. A large cohort (N = 243) of NIH patients who responded to treatment with the standard regimen of horse ATG plus cyclosporine was analyzed. Shown are long-term outcomes including the negative impact of a complicating event. Events were defined as relapse (need for further immunosuppression after protocol treatment) and clonal evolution (myelodysplasia/acute myeloid leukemia; almost always accompanied by a new cytogenetic abnormality in the BM). Approximately half of the patients did not experience a clonal event and poor survival was largely a consequence of disease progression. Data were censored for transplantation.[1]

ASH education book 2013

Conclusion

- Idiopathic aplastic anemia is a failure of bone marrow stem cells caused by an immune attack
  - Many other causes
- It can affect all blood cells
- Can be severe and needs treatment
- Effective treatments are available

PNH

What is PNH ?

- Rare disease
  - 1-5 people affected per million population [1]
- Main problem is red cells destruction in the circulation (hemolysis)
  - Gives rise to many problems…

PNH RBC Lysis (hemolysis)
PNH RBCs are lysed, and contents are released into the surrounding plasma.

Source: soliris.net

1:Rosse WF. Epidemiology of PNH. Lancet. 1996;348:573–7.

What is PNH ?

- Chronic and severe disease
  - Life long disease
  - Many organs can be affected
- Life threatening

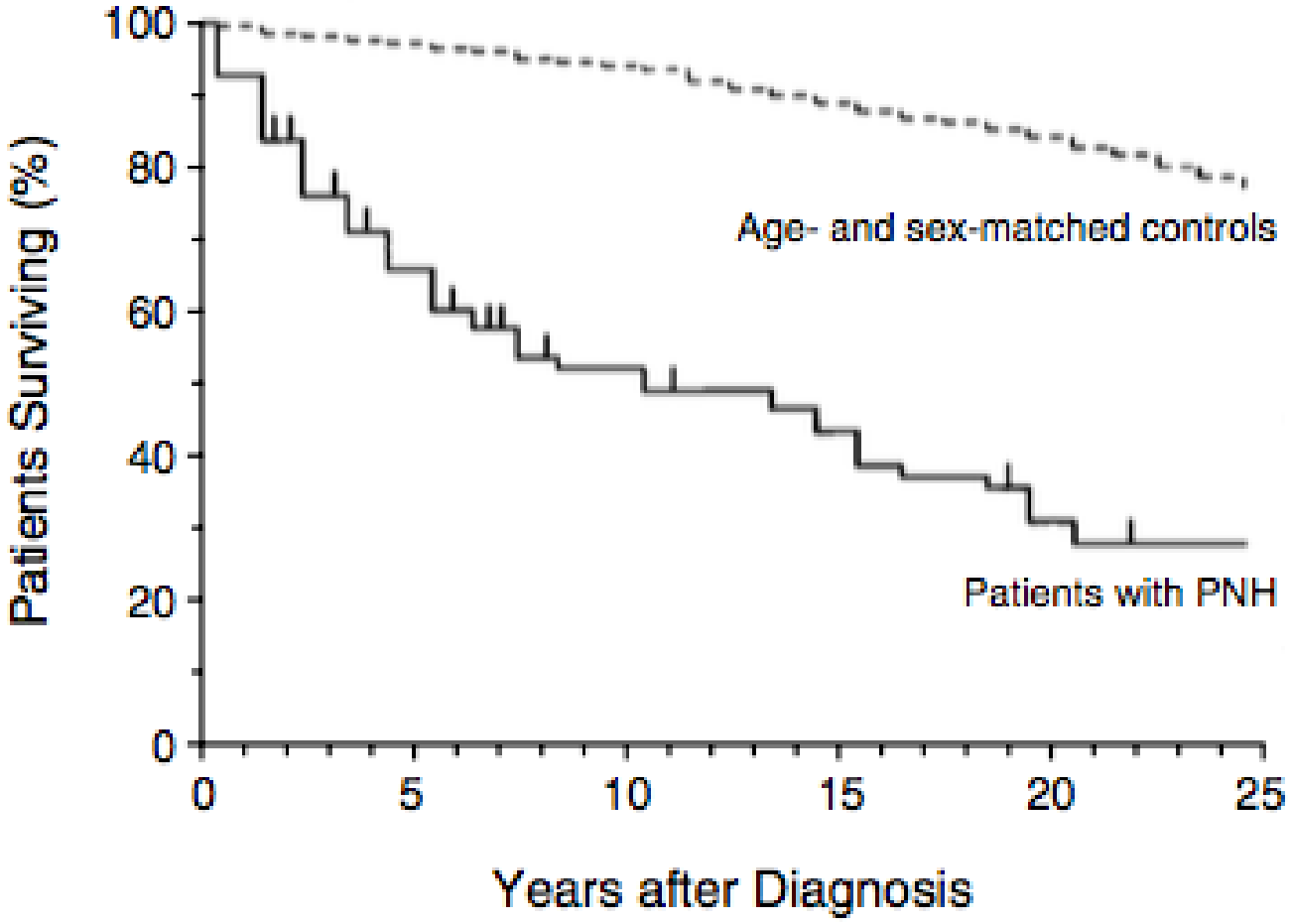


Figure 2. Actuarial Survival from the Time of Diagnosis in 80 Patients with PNH.

The median survival was 10 years. The expected survival of an age- and sex-matched control group is shown for comparison.

NEJM 1995;333(19):1255

What does PNH mean ?

- Paroxysmal = sudden recurrence
- Nocturnal = at night
- Hemoglobinuria= presence of free hemoglobin in the urine
  - Resulting from destruction of red cells (hemolysis)

Clinical manifestations

- Anemia (hemolysis)
  - Fatigue, shortness of breath
- Thrombosis (venous or arterial)
- Others
  - Fatigue
  - Abdominal pain, oesophageal spasm
  - Chronic kidney disease
  - Pulmonary hypertension
  - Erectile dysfunction
- Bleeding, infection
  - In case of associated marrow failure

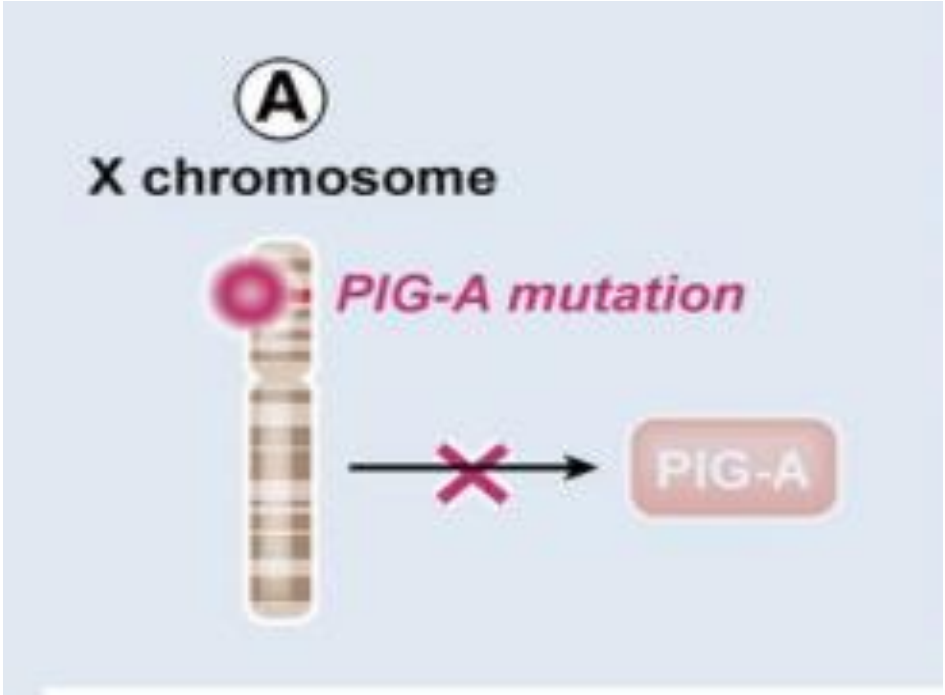
Clinical manifestations

- Anemia
  - Fatigu
- Thromb
- Others
  - Fatigu
  - Abdo
  - Chron
  - Pulmo
  - Erectile dysfunction
- Bleeding, infection
  - In case of associated marrow failure

Impact on quality of life

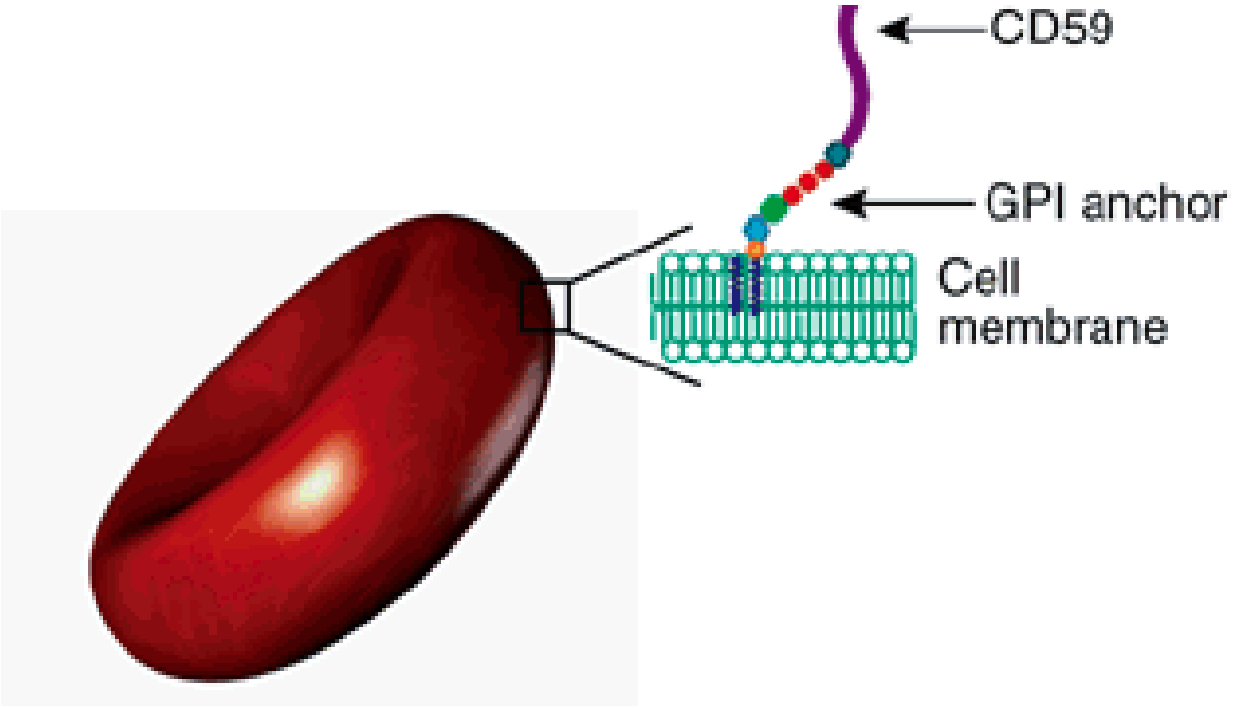
What causes PNH ?

- Mutation in the PIG-A gene, located on the X chromosome
  - Has to be there to produce a normal protein
  - Protein is implicated in the formation of a molecule (GPI-anchor)
- Acquired mutation
  - Not hereditary



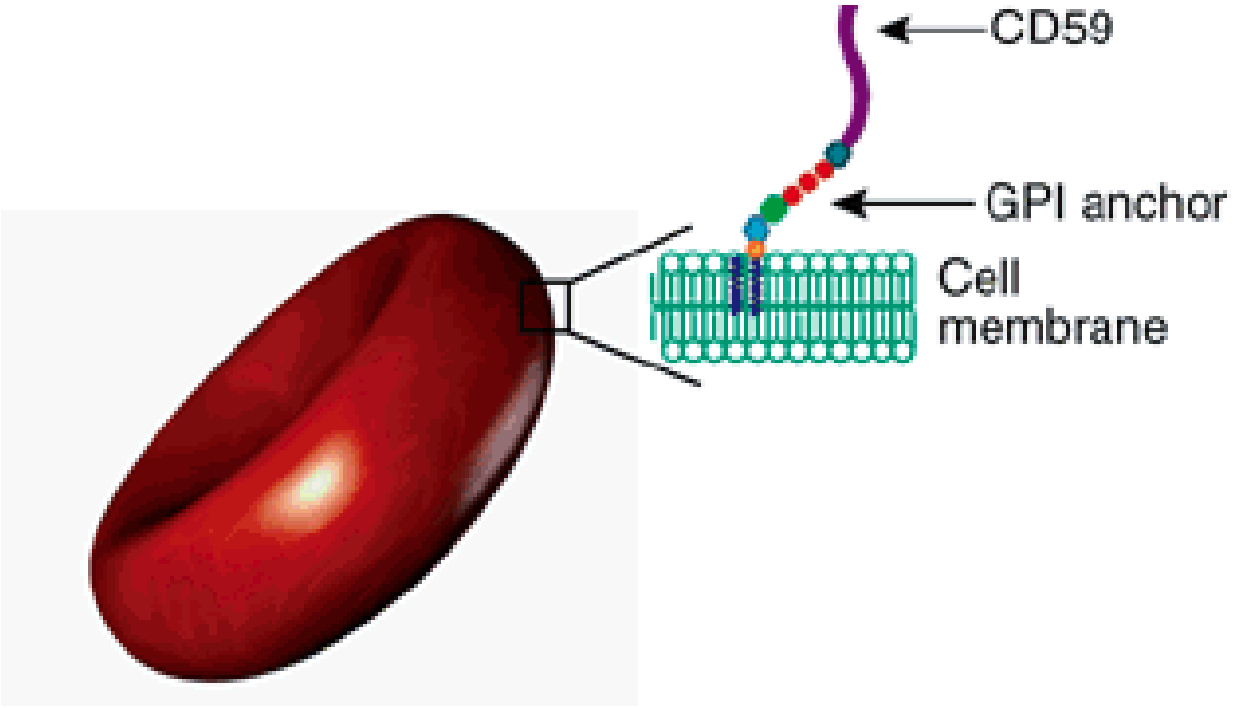
Source: Blood Journal and nature.com

What causes PNH ?



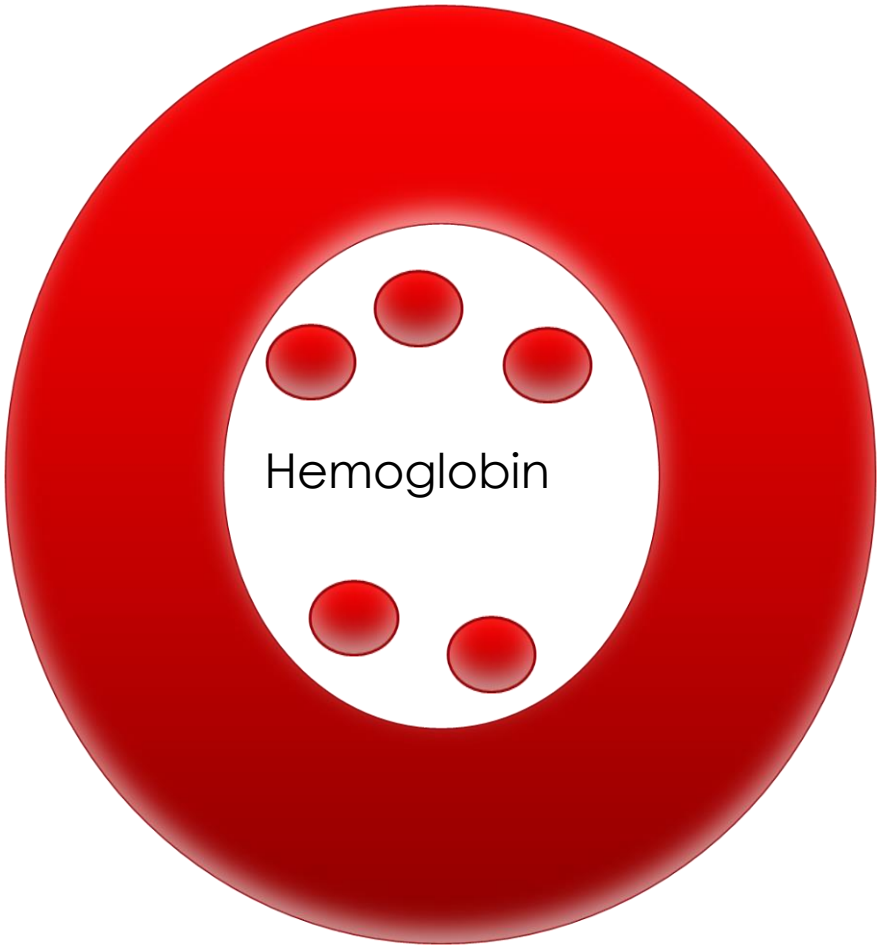
Source: nature.com

What causes PNH ?

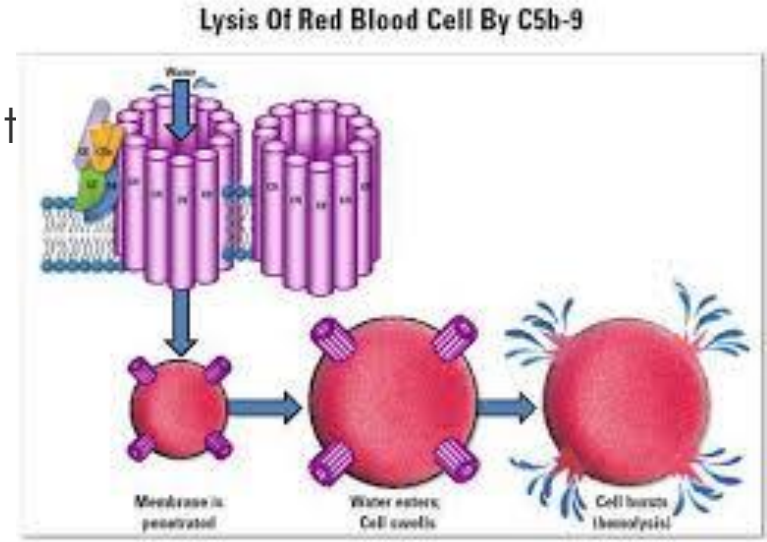


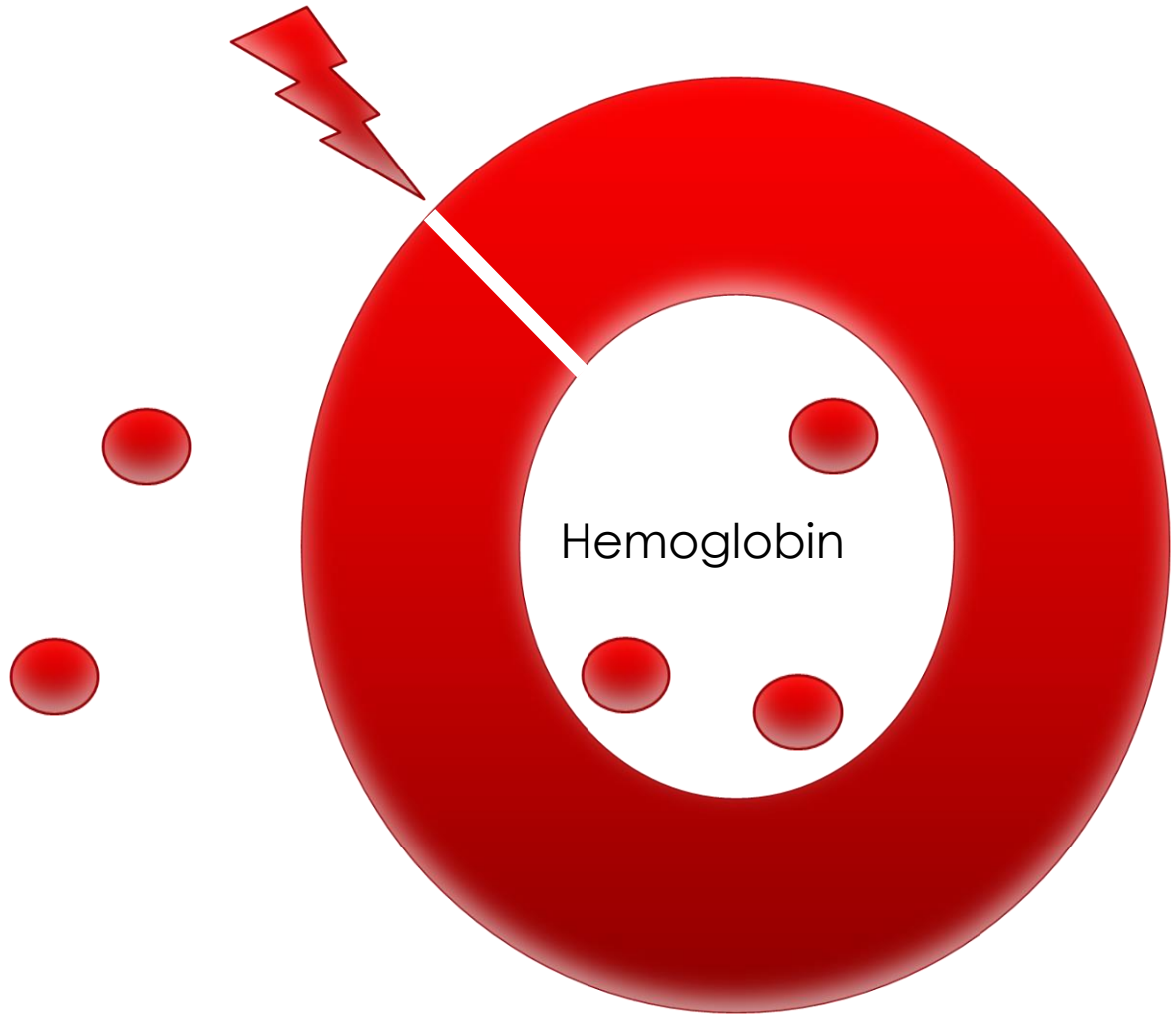
Relationship with red cells destruction (hemolysis)??

Source: nature.com

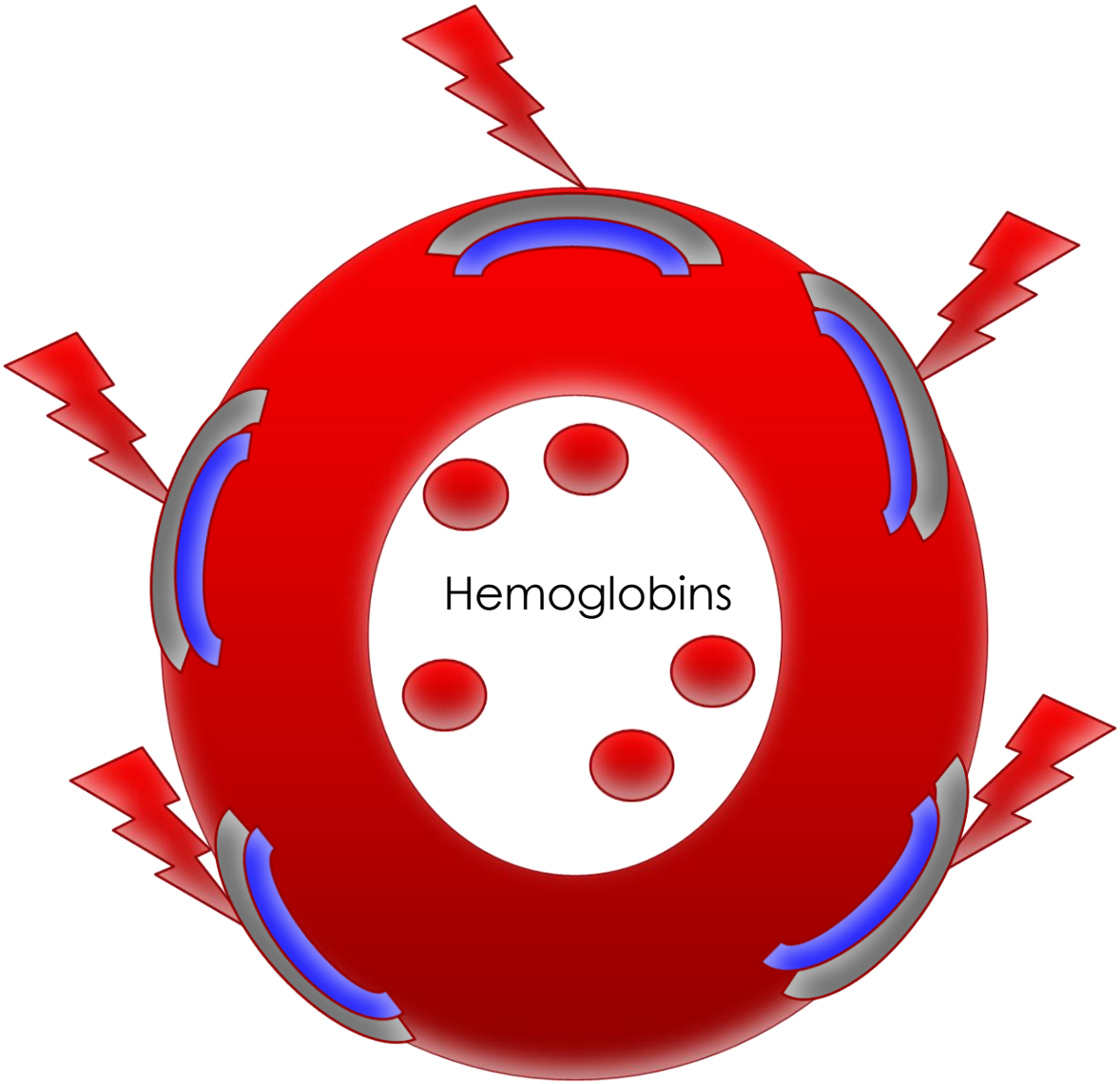

Hemoglobin

- Membrane attack complex (MAC)
  - Part of the complement system, an important component of our immune system
  - Create holes in the cells membrane
  - Role is to destroy dead cells, foreign body
  - Can also destroy good cells




Hemoglobin

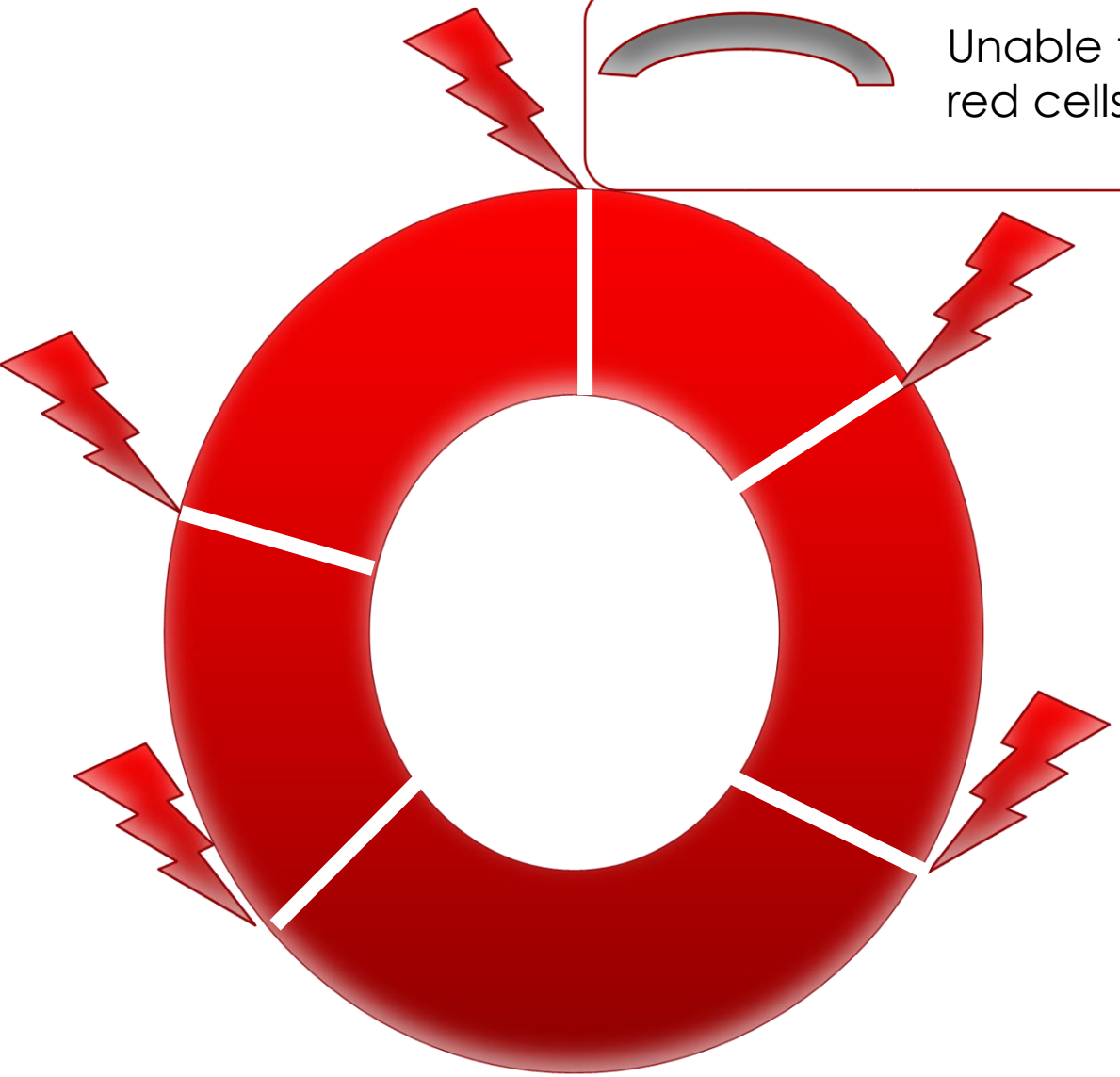
NORMAL INDIVIDUAL



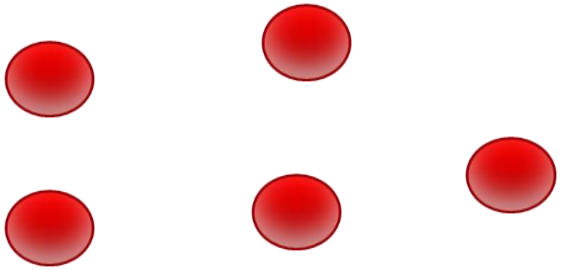
MAC Protectors (proteins)

GPI anchor

PNH PATIENTS



Unable to protect
red cells againt MAC

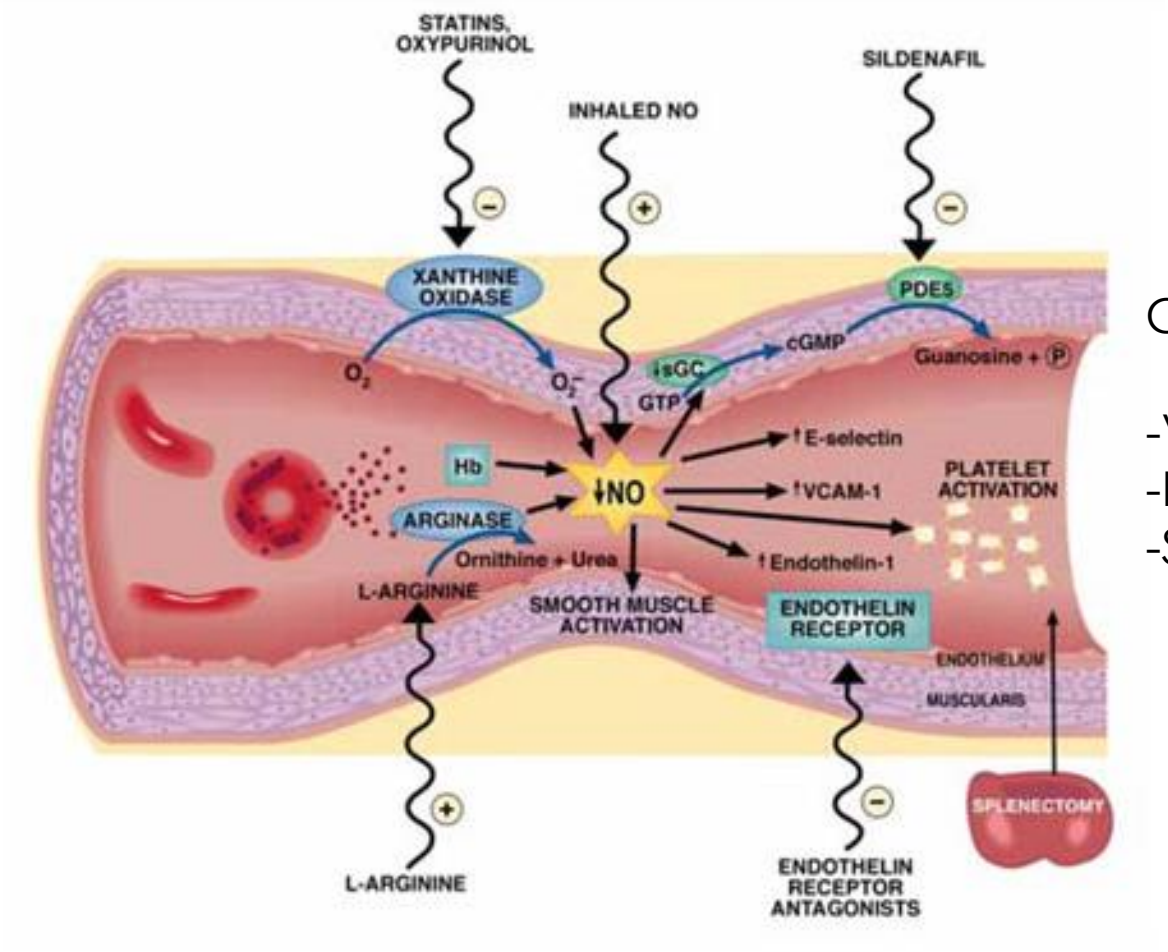


Free Hemoglobin

Consequences of hemolysis

- Anemia
  - Fatigue
  - Dyspnea
- Jaundice
- Dark urine coloration
- Iron and folic acid deficiency
- High LDH levels

Nitric oxide (NO) depletion



Consequences of NO ↓

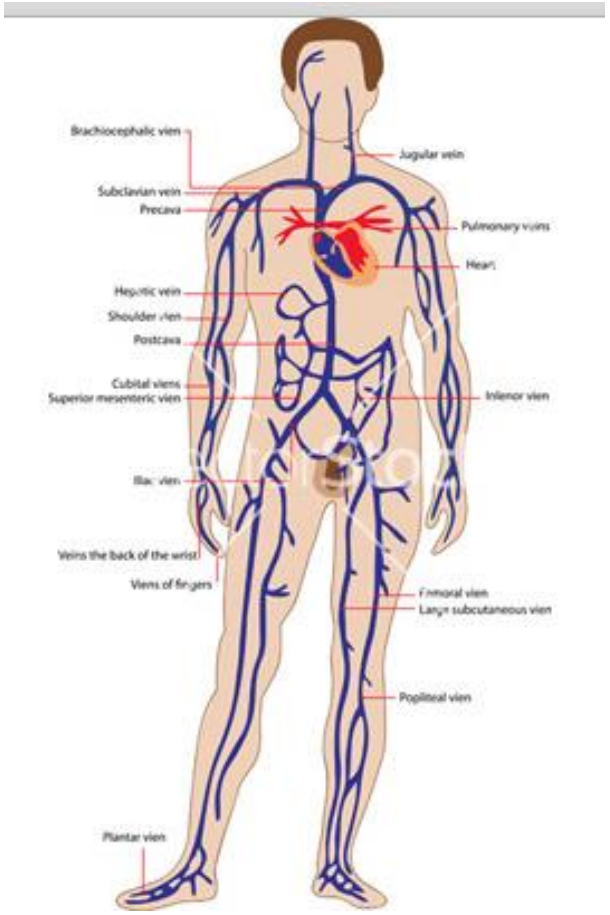
-Vasoconstriction
-Platelet activation
-Smooth muscle contraction

Clinical manifestations of NO depletion

- Fatigue
- Abdominal pain, esophageal spasm
- Chronic kidney disease
- Pulmonary hypertension
- Erectile dysfunction

Thrombosis

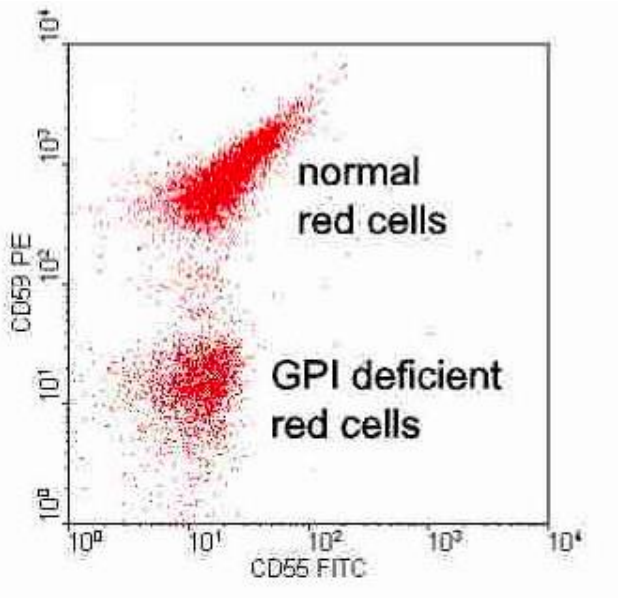
- Leading cause of death
  - Presenting symptom in 5%
  - Occurs in up to 40% during disease evolution
- Can affect both venous and arterial system
- Atypical locations
  - Hepatic, portal, mesenteric, cerebral, dermal
    - Abdominal pain
    - Cirrhosis
- Treated with anticoagulant



How is PNH diagnosed ?

Flow cytometry

- The most important test for diagnostic
- Done on a peripheral blood specimen
- Identifies ≥2 cell lineages with absent or decreased GPI-AP
- Helps to predict severity of disease



What are treatment options?

Treatment options

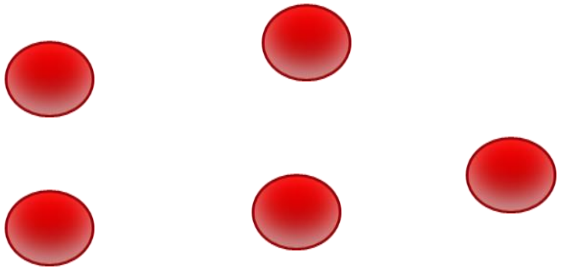
- Supportive treatments
  - Iron supplements
  - Folic acid supplements
  - Transfusions
  - Anticoagulation if thrombosis
- Disease modifying treatments
  - Anti-complement therapy (Eculizumab)
  - Allogeneic transplant

Indications for anti-complement therapy

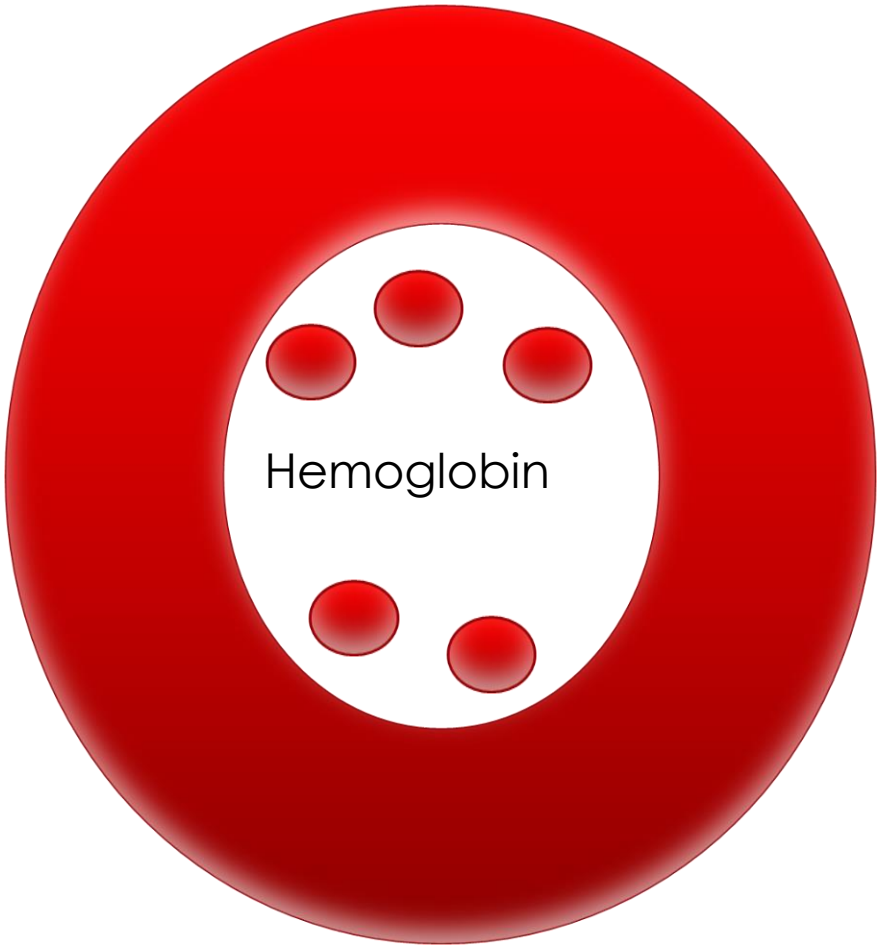
- Severe fatigue
- Thrombosis
- Transfusion dependency
- Symptoms of muscle dystonia (pain)
- Other organ damage

Eculizumab inhibits C5 in the complement system and prevents the formation of the MAC

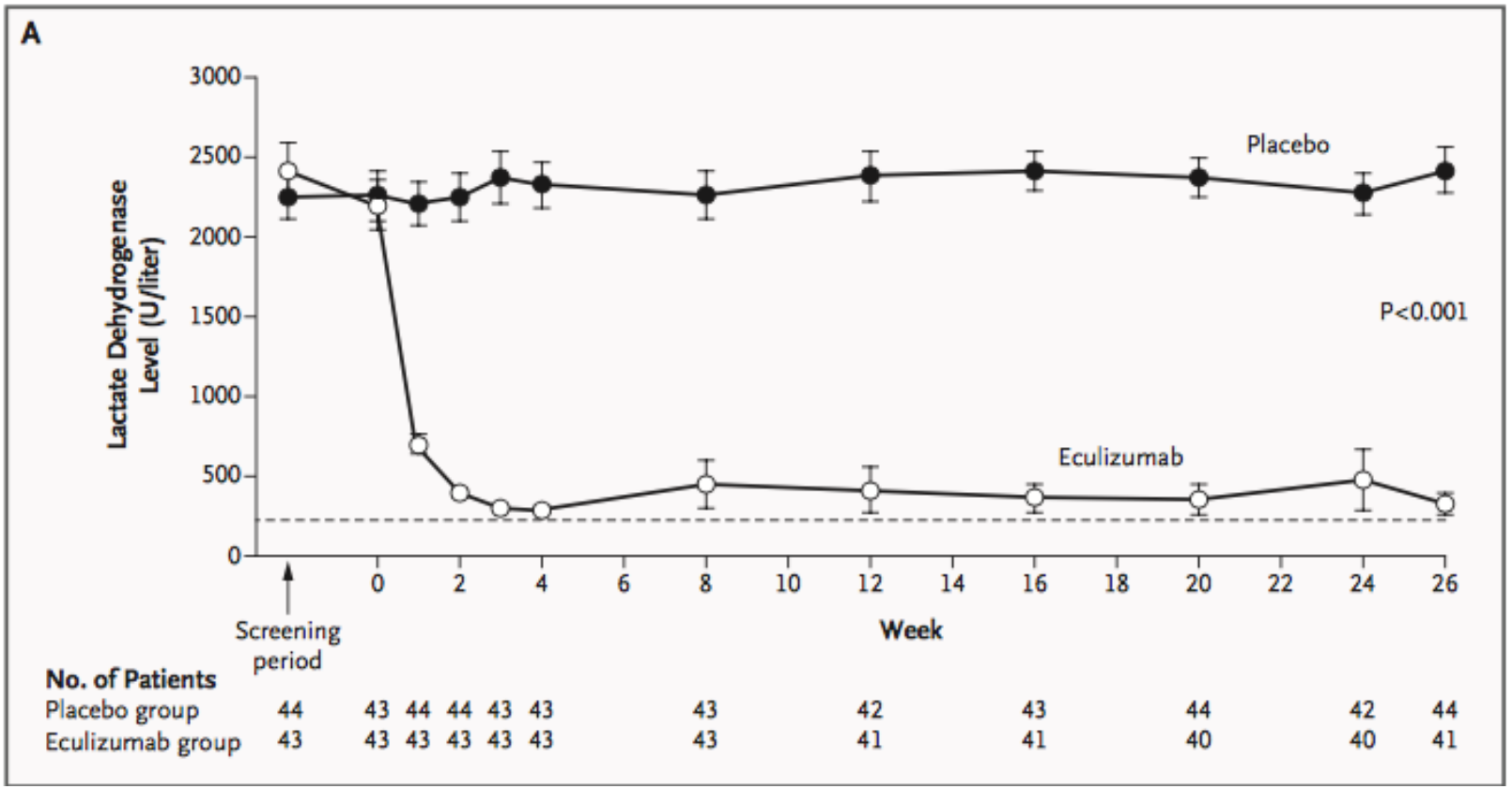
PNH PATIENTS



Free Hemoglobin

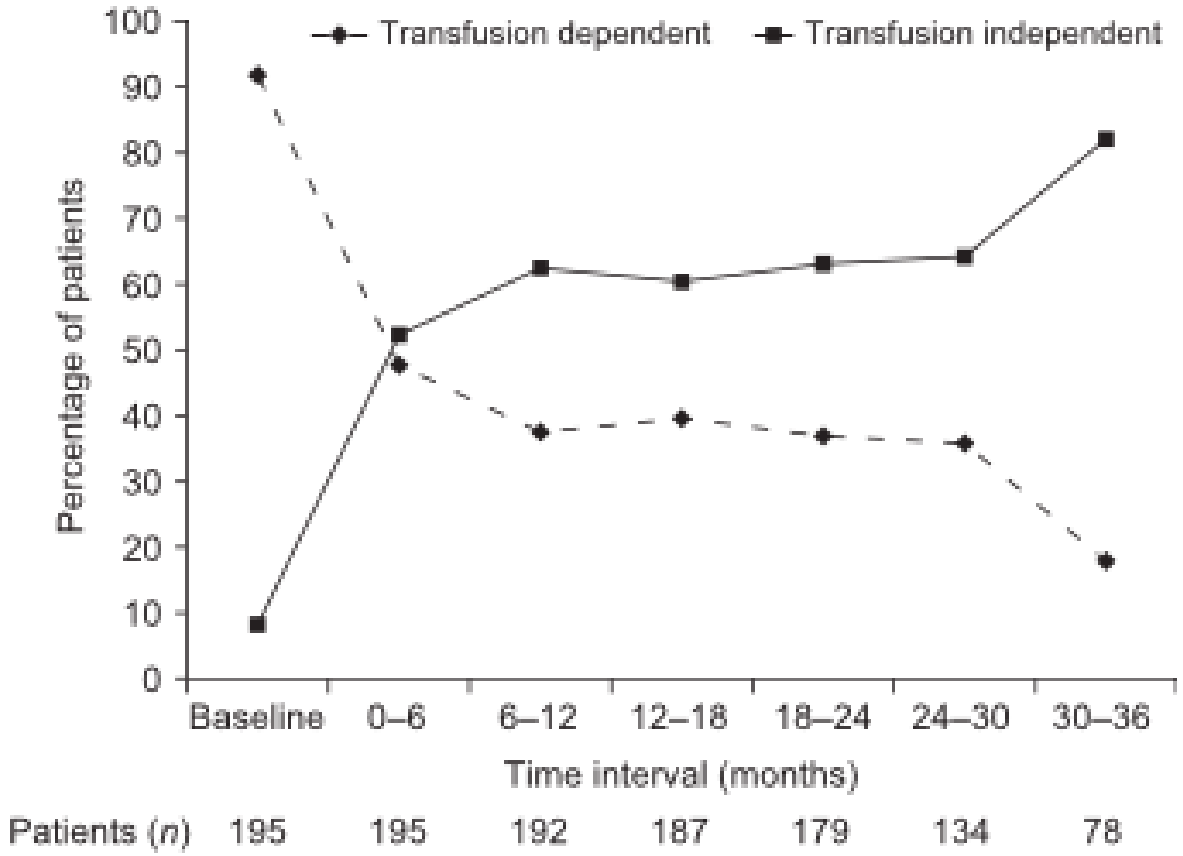

Hemoglobin

Eculizumab efficacy : LDH levels



NEJM 2006;355:1233

Eculizumab efficacy: Transfusion needs



Open-label extension study

British Journal of Haematology, 2013, 162, 62–73

Eculizumab efficacy

- Reduces
  - Hypercoagulability (thrombosis)
  - Smooth muscle dystonia
  - Stabilize or improve kidney function
  - Improve quality of life (fatigue)

- Long term treatment (needs to be given regularly to be effective)

Effect on survival

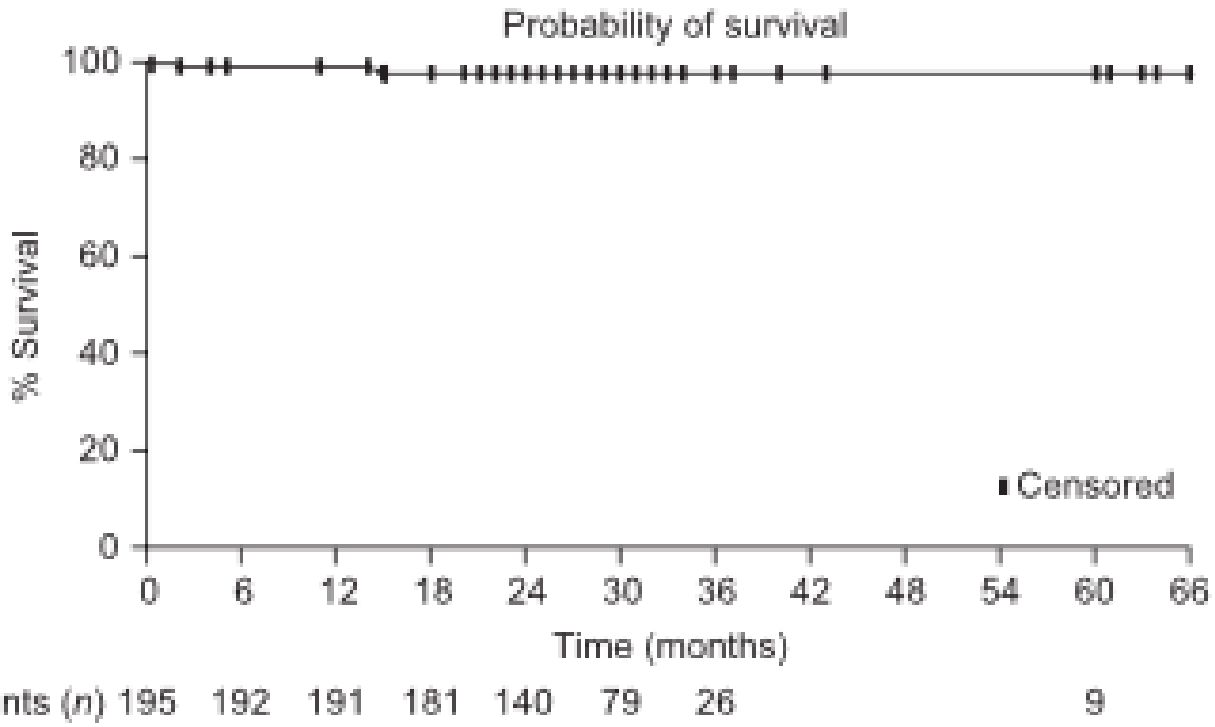


Fig 4. Long-term survival with eculizumab therapy.

British Journal of Haematology, 2013, 162, 62–73

Effect on survival

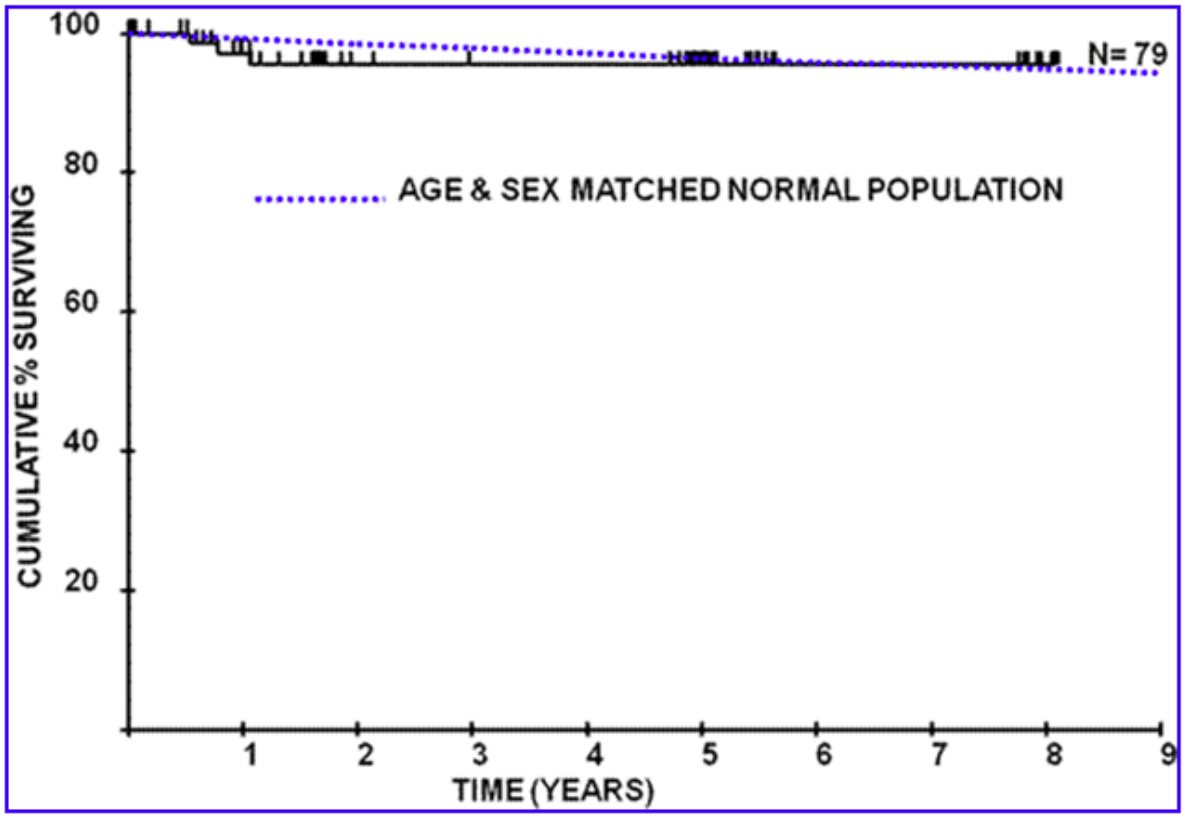


Figure 1 Kaplan-Meier survival plots depicting PNH patients on eculizumab compared to age and sex matched controls

Eculizumab administration

- 600 mg iv once per week x 4
- 900 mg iv one week later
- 900 mg iv every 2 weeks
- Indefinitely

- Monitoring
  - CBC, LDH, reticulocytes
  - Will help to adjust dose and interval between treatments
- Patients needs vaccination against *Neisseria meningitidis*

Allogeneic stem cell transplant

- Is the only curative therapy
- Higher potential for toxicities (short and long term)
- Indications
  - PNH unresponsive to eculizumab
  - Severe aplastic anemia
  - High-risk myelodysplastic syndrome

Conclusion

- PNH is a rare and severe acquired disease affecting many organs
- Decreases life expectance and affects quality of life
- Exist treatments to overcome symptoms and improve survival