Paroxysmal Nocturnal Hemoglobinuria– New Treatment Options and Dealing with Side Effects

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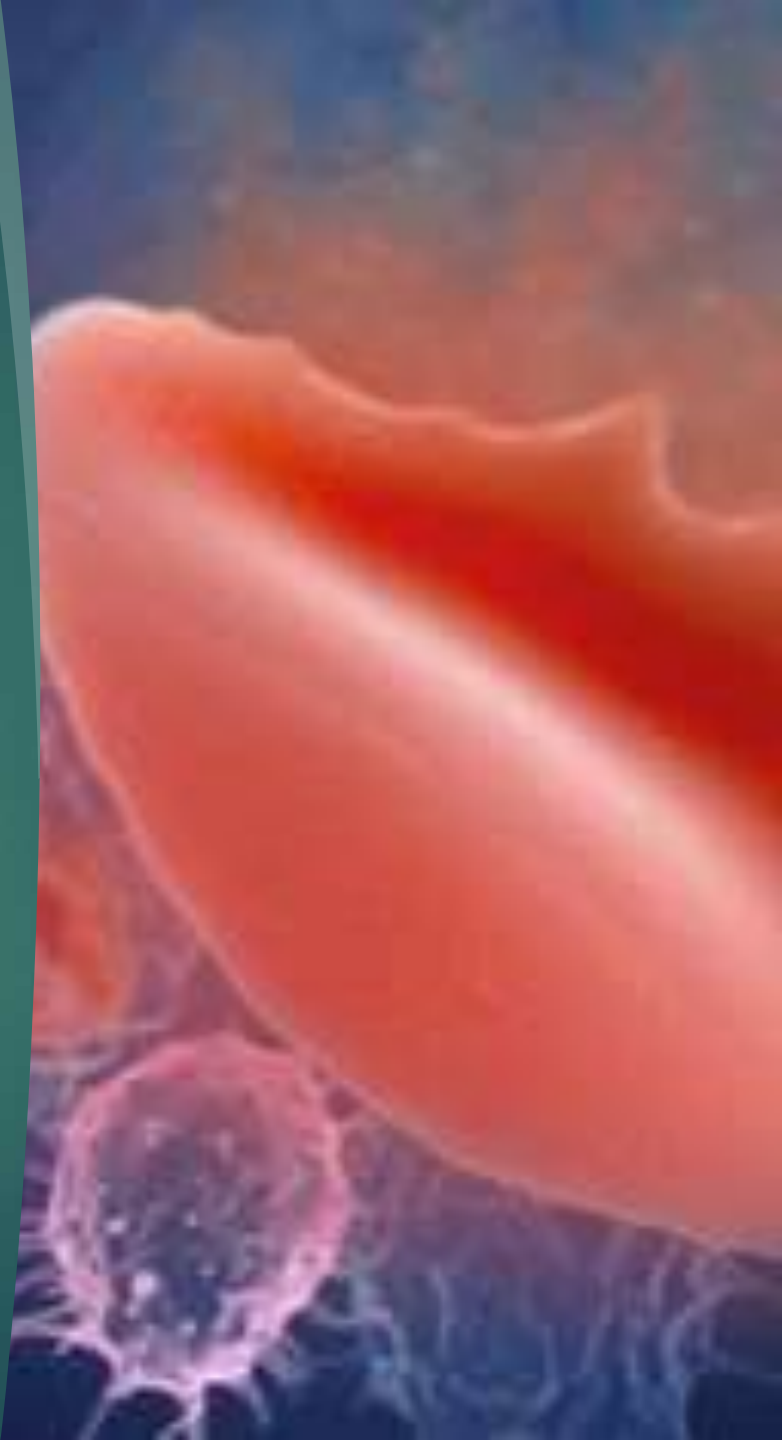
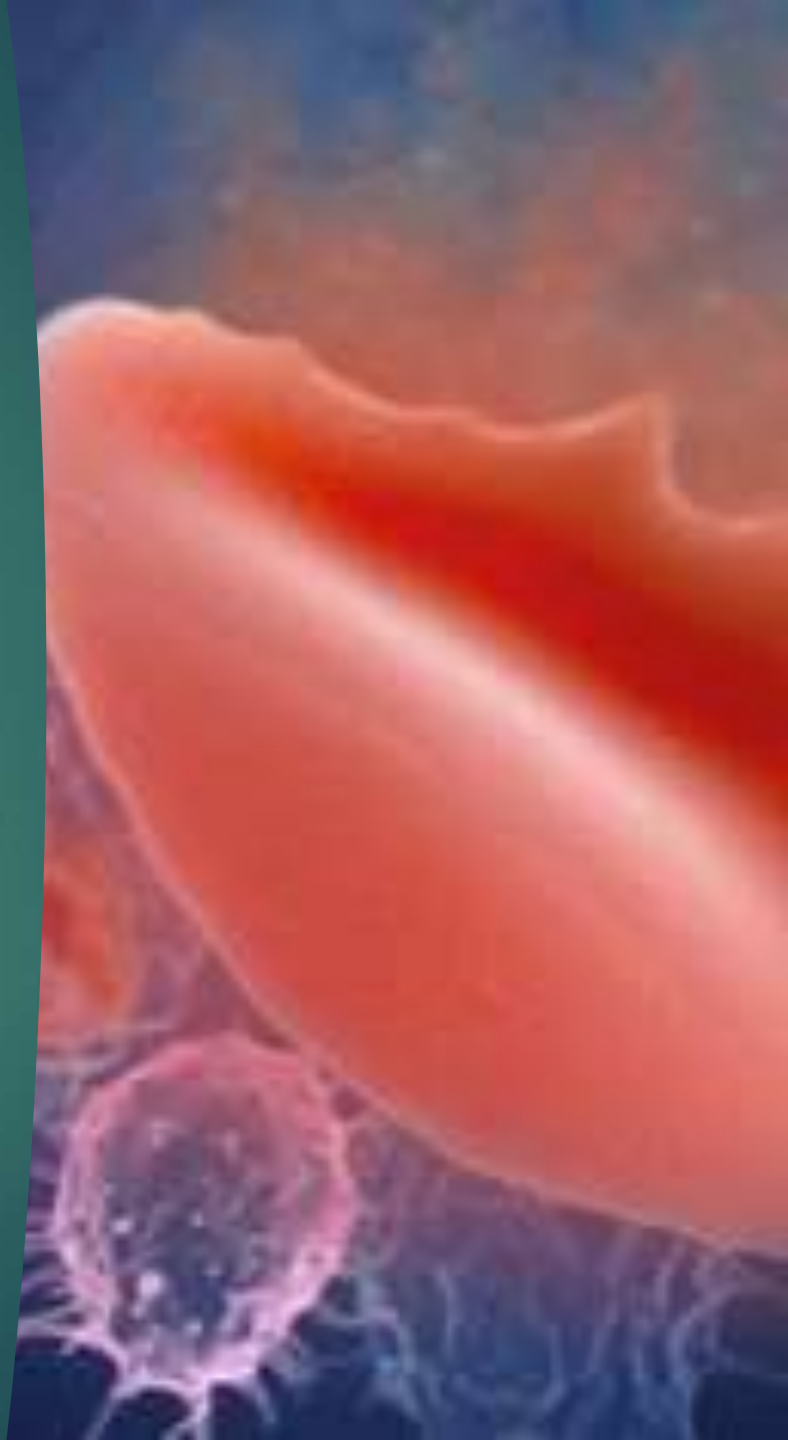
What is PNH

- PNH is a rare acquired disorder, in which red blood cells (erythrocytes) break apart prematurely inside blood vessels
- PNH develops as a result of genetic mutation occurring in bone marrow stem cells (cells that produce all blood cells)
- This mutation makes red blood cells sensitive to destruction (hemolysis) by immune system



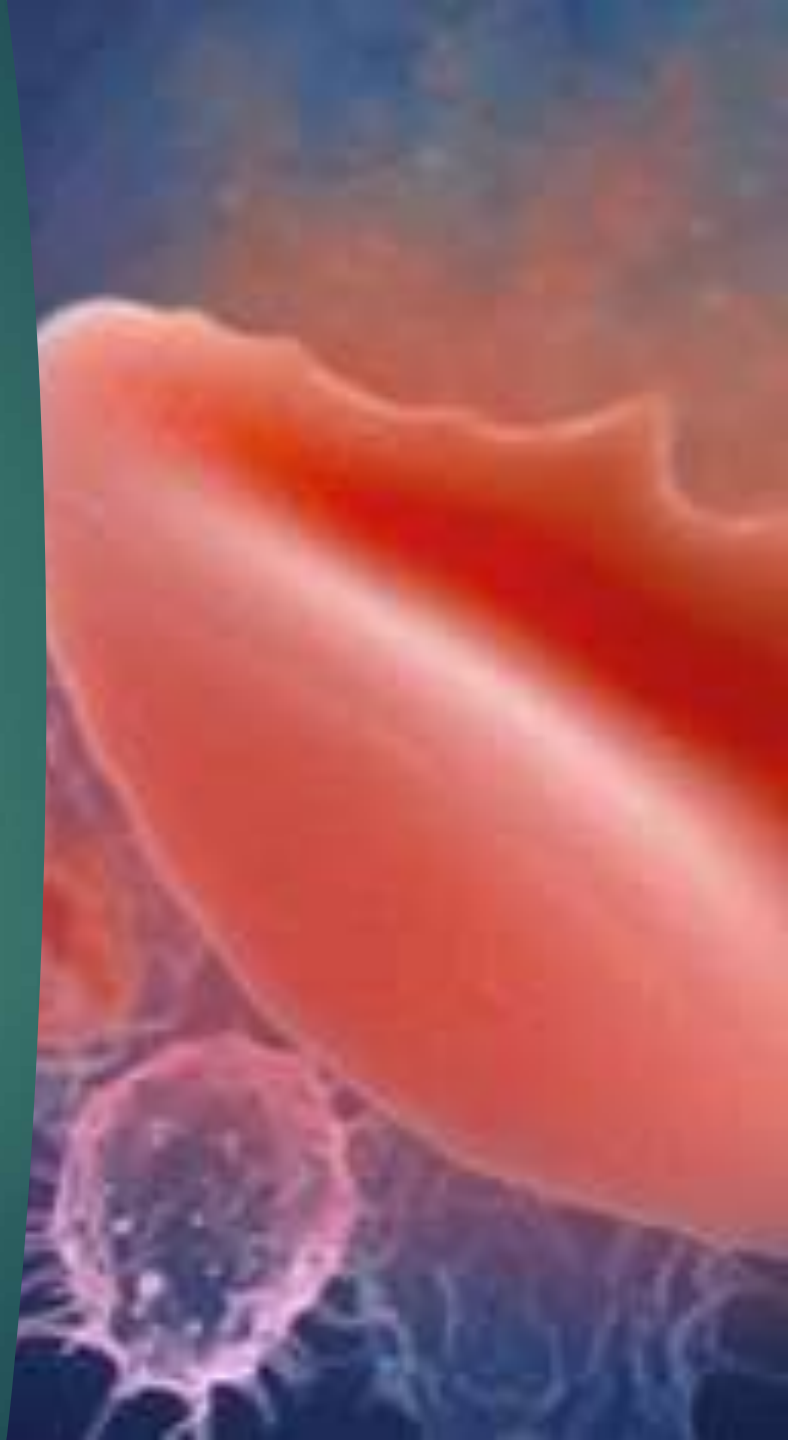
What is PNH

- "Paroxysmal" means "sudden and transient "
- "Nocturnal" refers to belief that cell break happens mostly at night
- "Hemoglobinuria" means that hemoglobin (red blood pigment) can be seen in the urine



PNH is unacurate name

- PNH is not paroxysmal, nor nocturnal and hemoglobinuria is seen in the minority of patients
- Hemolysis happens constantly (it does not occur only at night)
- Urine gets more concentrated overnight which leads to dramatic change in urine color in the morning

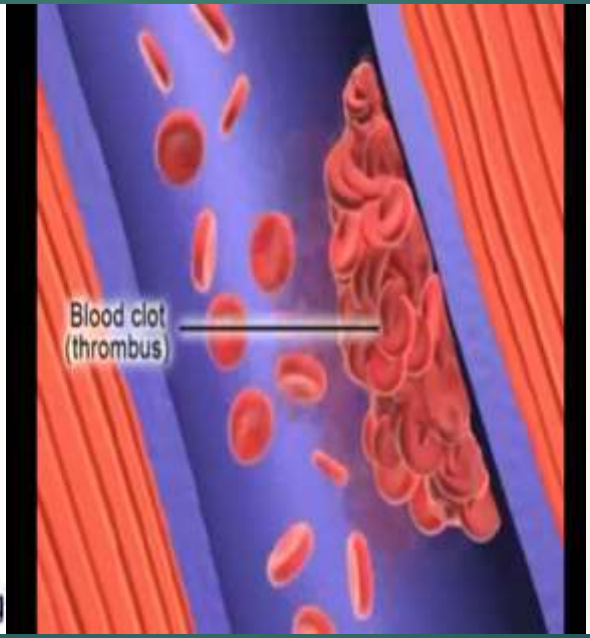


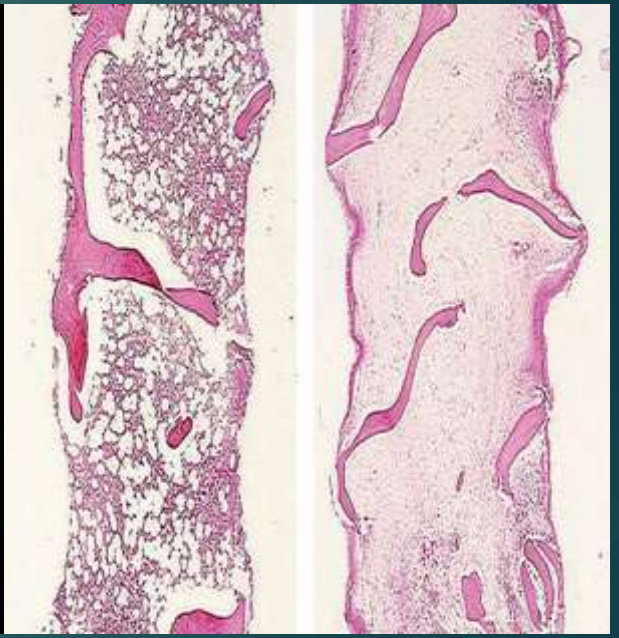
Symptoms of PNH

Haemoglobinuria due to intravascular (occurring inside the vessels) hemolysis

Thrombosis (blood clots and strokes)

Bone marrow failure(low blood counts)





Symptoms of PNH vary greatly from one person to another

Affected individuals usually do not exhibit all of the symptoms associated with the disorder

PNH facts

- PNH is a rare disease, which makes clinical research and drug development difficult
- It is not known how many people are suffering from PNH
- It is estimated that 4,000 – 6,000 people in the U.S are diagnosed with PNH

PNH facts

- Both genders are affected equally
- PNH occurs at any age, but more frequently found among young adults
- Average age at diagnosis is 32-42
- PNH is rare in small children

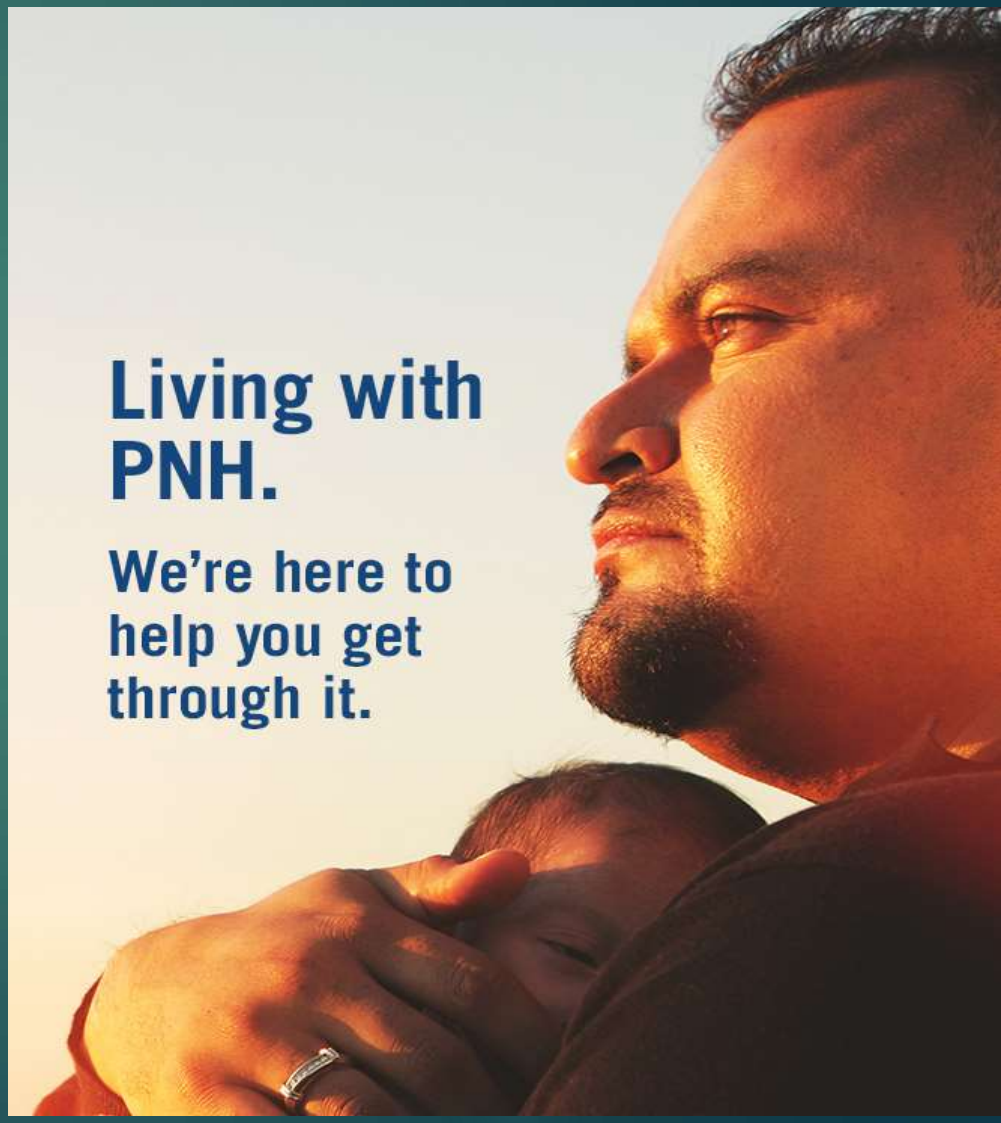
PNH facts

Country	**UK**	**France**	**USA**	**Japan**
Median age at diagnosis	42 yrs	34.2 yrs	30 yrs	45 yrs
Median survival*	10 yrs	22 yrs	23.3 yrs	25 yrs
Thrombosis	39%	30.7% (10yrs after diagnosis)	31.8%	4.3%
Prior aplastic anemia	29%	30%	29%	37.8%
Transformation to leukemia/MDS	0%	7.6% (10yr incidence)	1.7%	2.9%

*Before eculizumab (Soliris®) was introduced main cause of death was venous thrombosis followed by complications of due to bone marrow failure

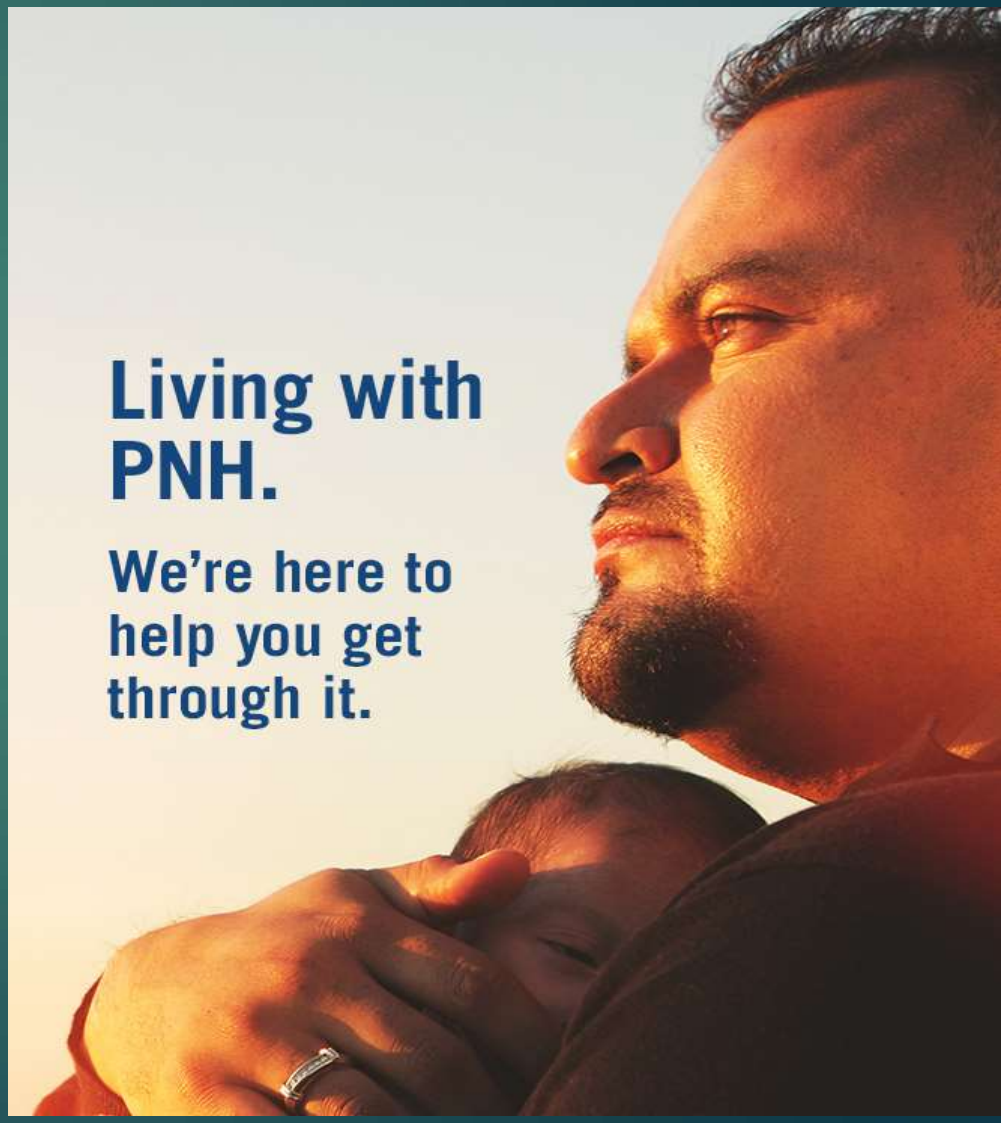
PNH is disabling and life-threatening disease

- It is progressive disease
- Symptoms and disease progression vary greatly from one person to another
- Some individuals may have mild symptoms that remain stable for many years
- Others may have serious symptoms that can progress to cause life-threatening complications



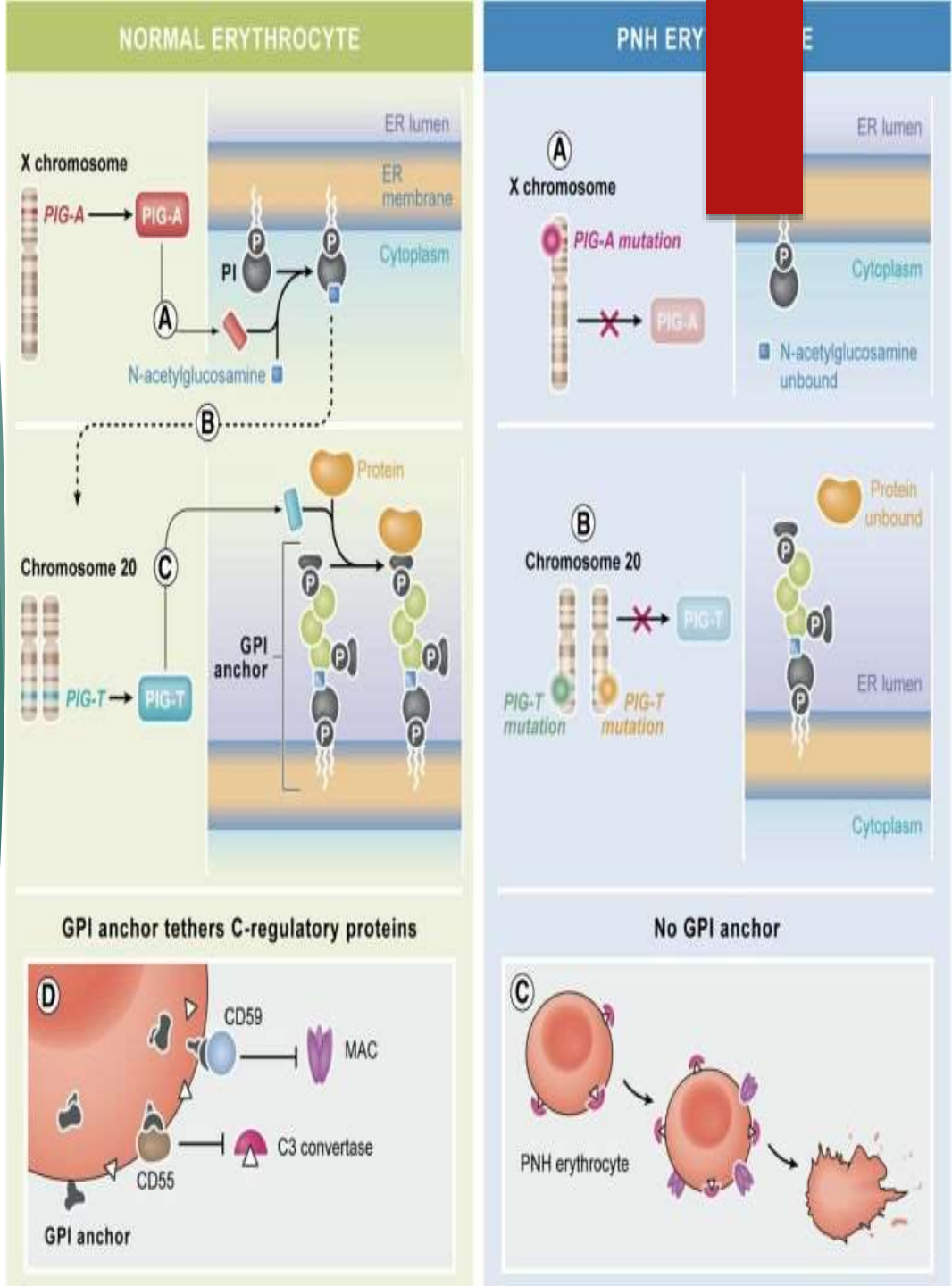
PNH is disabling and life-threatening disease

- Quality of life is diminished in PNH patients
- Early intervention is critical
- Reported symptoms may vary between visits and patients
- It is important to discuss symptoms in detail at each visit to the doctor



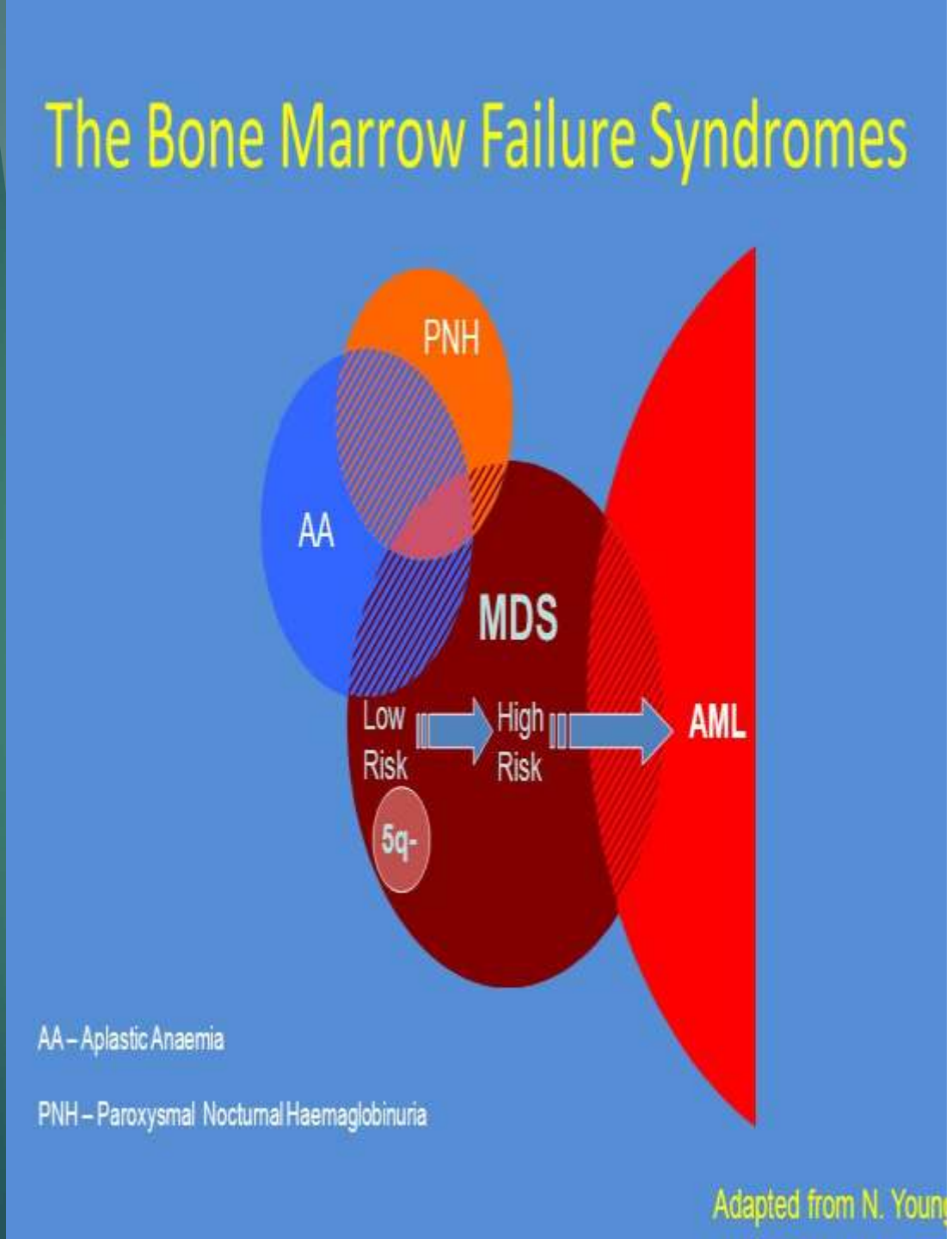
Why PNH develops

- ▶PNH happens because of mutation of the PIGA gene which leads to development of cells deficient for protein called GPI anchor
- ▶This mutation is a somatic mutation, which means that it develops after conception; it is not inherited and is not passed on to children.
- ▶This mutation occurs randomly, for no apparent reason
- ▶"PNH" blood cells are extremely susceptible to destruction by a part of the immune system known as the complement system



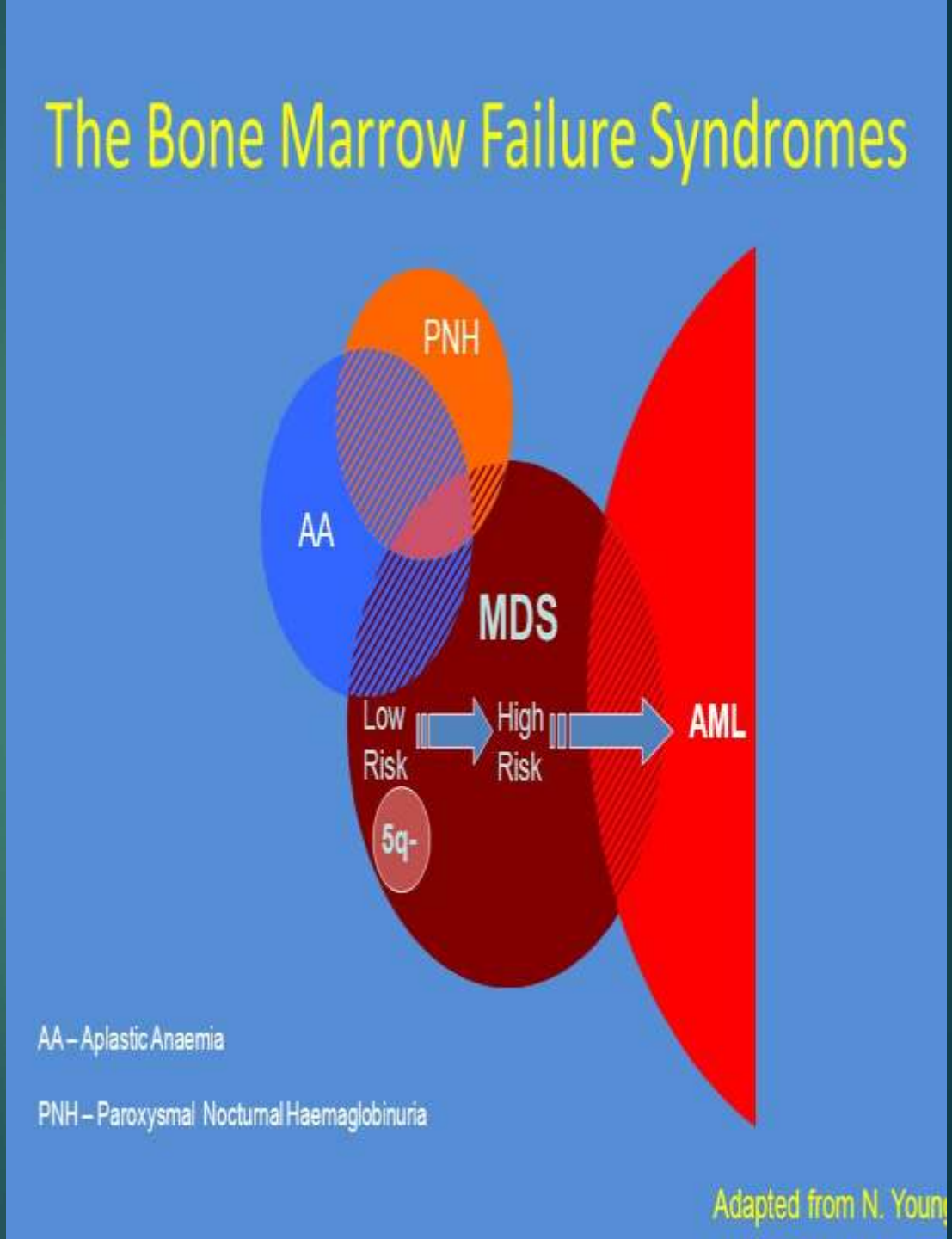
PNH related diseases

- PNH cells are not cancerous but rarely, individuals with PNH may develop leukemia
- PNH is closely related to aplastic anemia
- Aplastic anemia is anemia is a rare disorder caused by profound, almost complete bone marrow failure



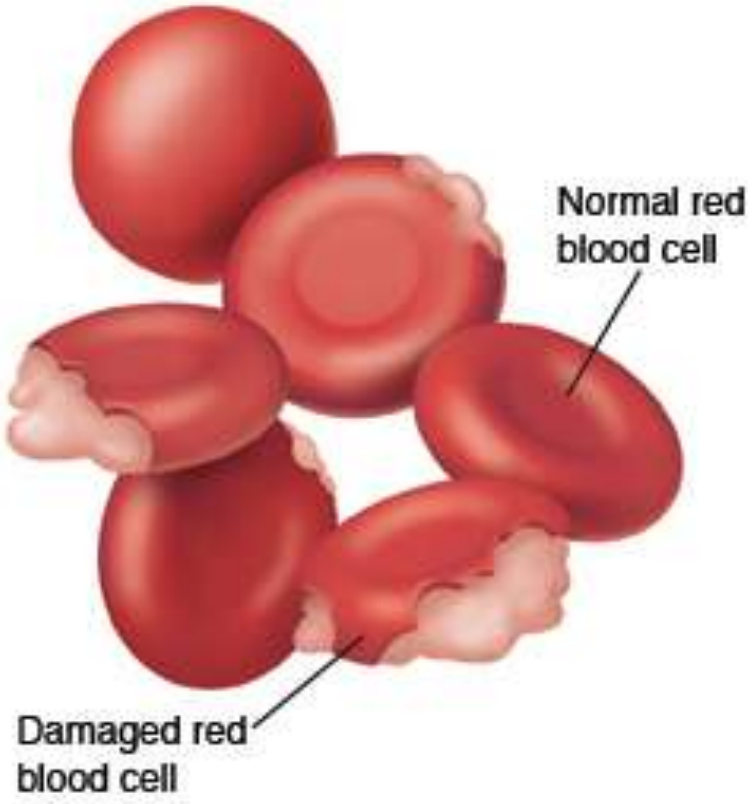
PNH related diseases

- PNH cells can also be detected in patients with myelodysplastic syndrome
- Myelodysplastic syndrome (myelodysplasia) is a rare group of blood disorders that occur as a result of improper development of blood cells within the bone marrow
- Usually percentage of PNH cell is low (typically <10-15%)



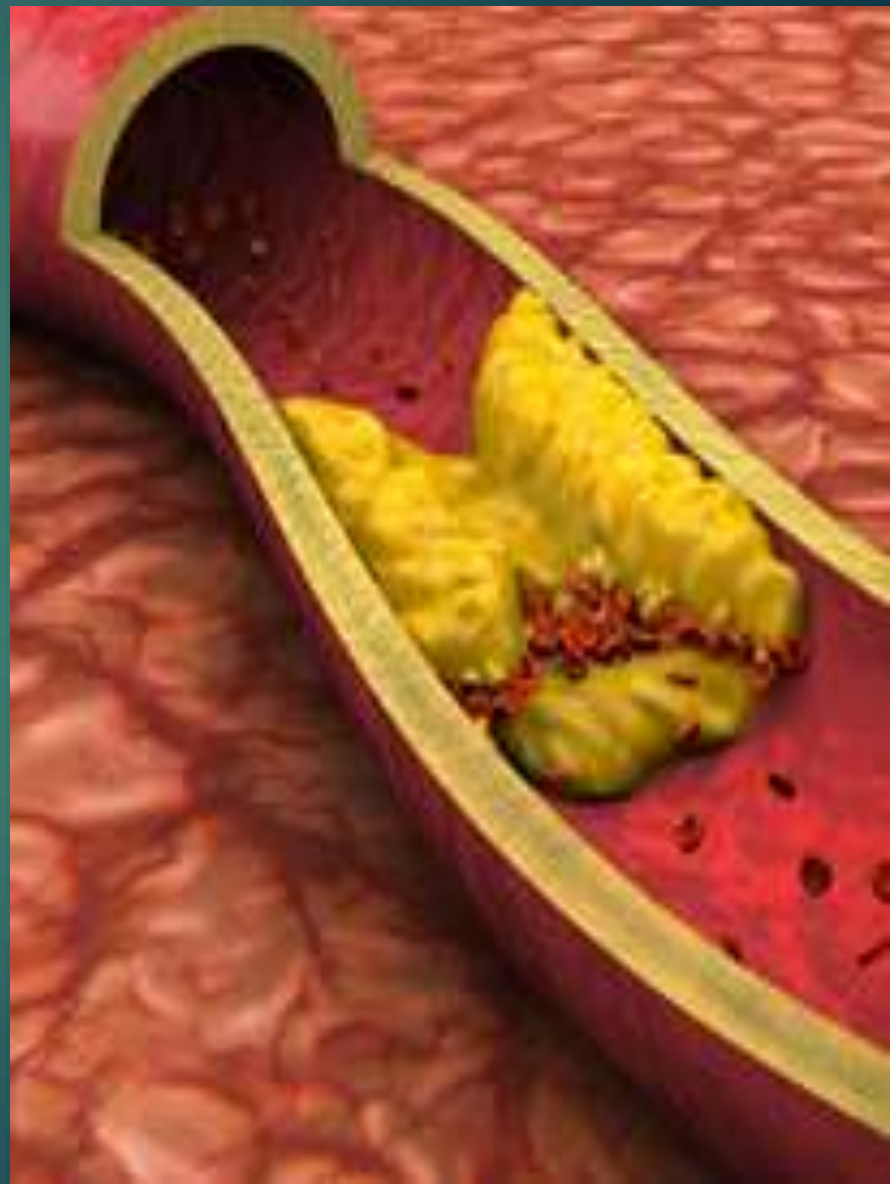
Blood cell destruction (hemolysis) is a hallmark of PHN

- Hemolysis leads to
1. Anemia
2. Dark urine
3. PNH symptoms
4. Blood clots



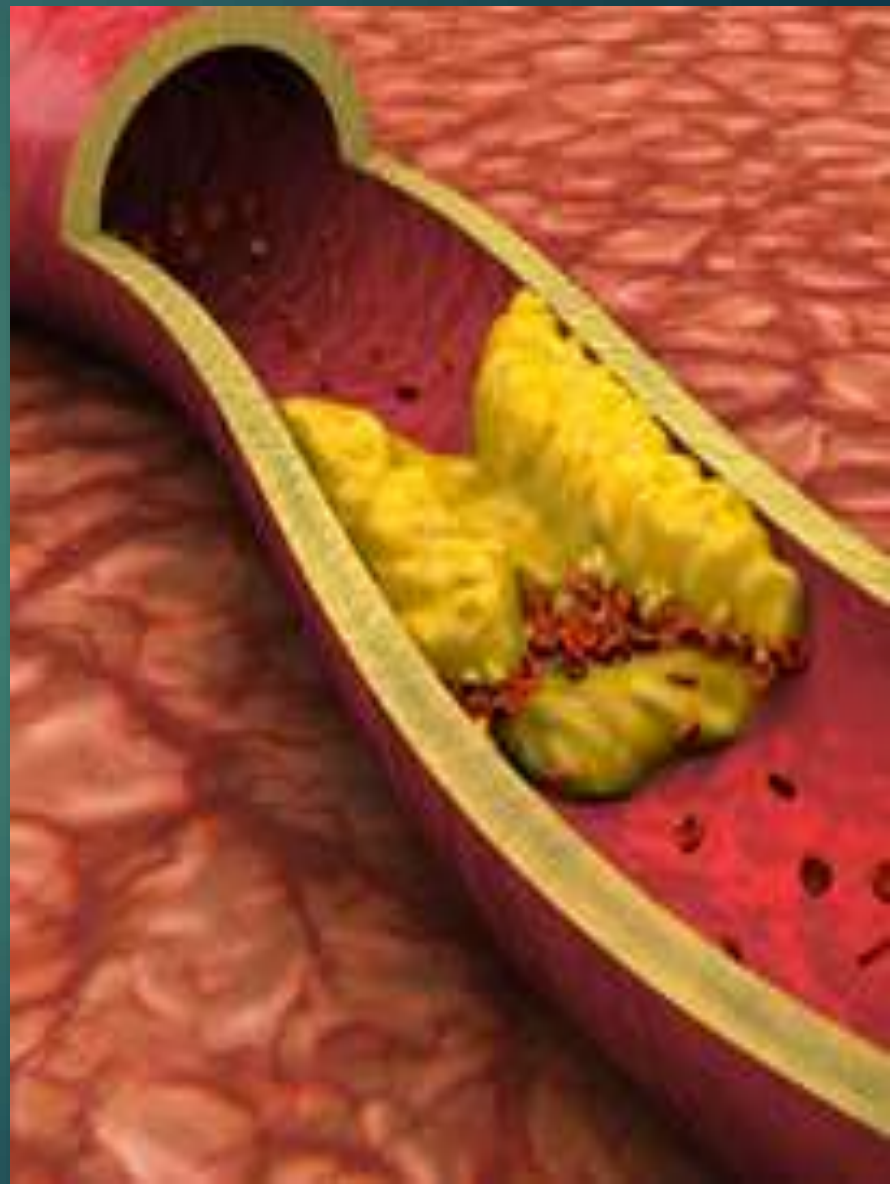
Blood clots (thrombosis)

- Thrombosis usually happens when there is a high number of PNH cells (>50%)
- Before the introduction of Soliris blood clots happened in 30% to 44% of all PNH patients
- Blood clots often happen in unusual places
- Liver (hepatic) vein thrombosis is called Budd-Chiari syndrome which can lead to jaundice, abdominal pain, enlarged liver and fluid accumulation in the abdomen



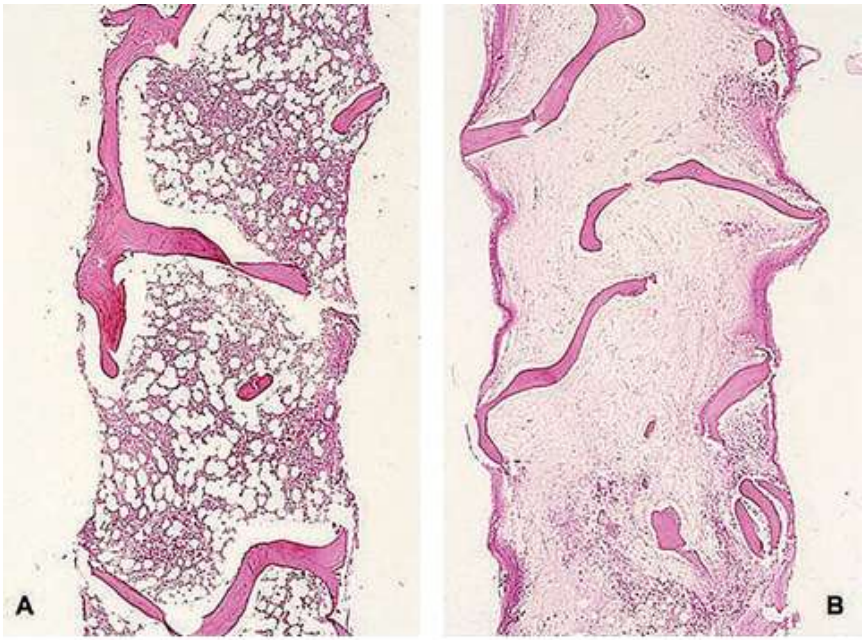
Blood clots (thrombosis)

- Abdominal vein thrombosis is associated with bowel infarction and necrosis, which may require surgery
- Thrombosis of veins around the brain can lead to headaches and brain swelling
- Thrombosis of veins in skin leads to painful rash



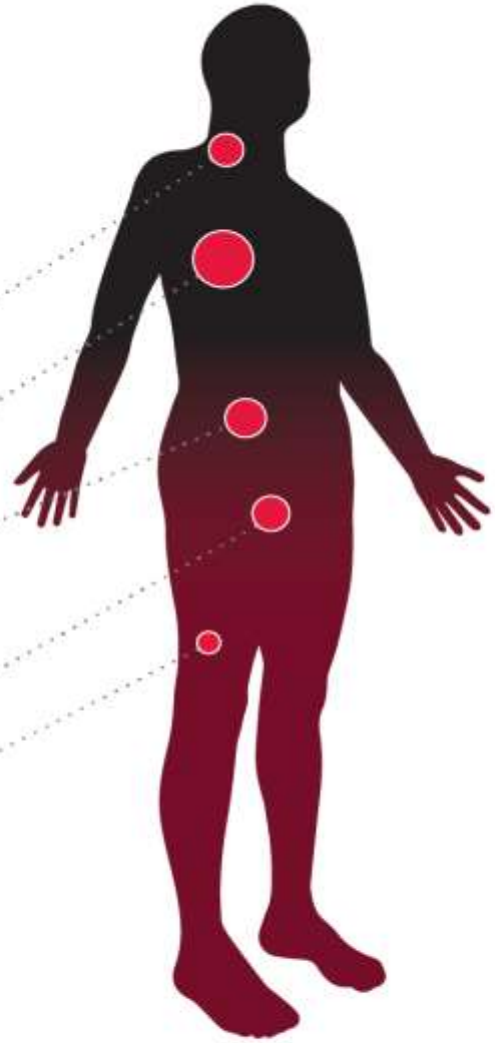
PNH is often associated with bone marrow failure

- Usually presents with anemia
- It can also be associated with low white blood cells, which can lead to increased infections
- It can also be associated with low platelets, which can lead to increased risk of bleeding



Signs and symptoms of PNH may include:

- Extreme tiredness[8]
- Low healthy red blood cell count[9]
- Difficulty swallowing[10]
- Shortness of breath[8]
- Abdominal pain[8]
- Erectile dysfunction*[,8]
- Hemoglobinuria[8]



PNH deaths can be caused by blood clots in the veins and arteries[6,7]

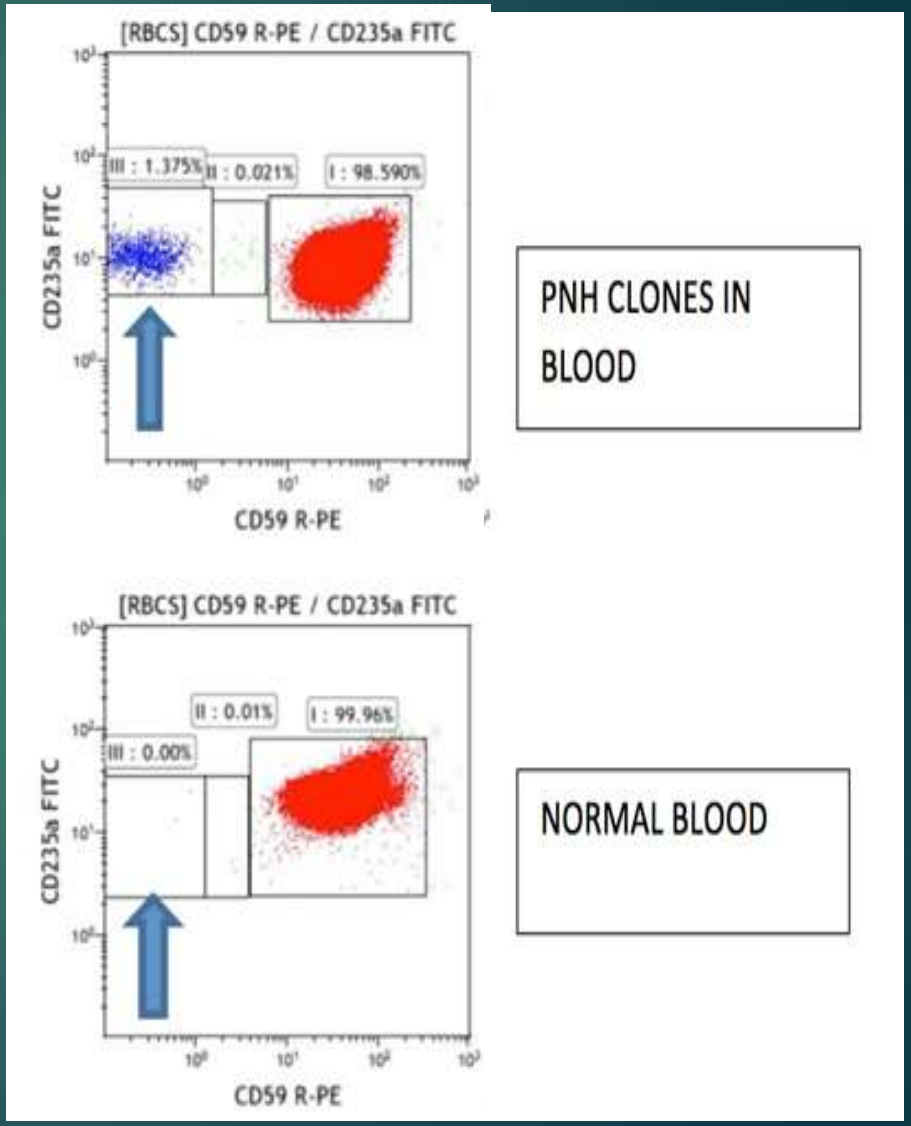
PNH deaths can be caused by kidney failure[6]

Patients with PNH may suffer from pulmonary hypertension, a type of high blood pressure that can affect the arteries of the lung[11]

Adapted from:
Schrezenmeier H, et al. 2014. An analysis of baseline characteristics and disease burden in 856 patients enrolled in the International PNH Registry, as of June 30, 2012, and completed baseline patients' questionnaires relating to symptoms of PNH, QoL, and work.
Nishimura J, et al. 2004. An epidemiologic analysis on 385 patients with PNH from the US and Japan.
Weitz I, et al. 2013. A cross-sectional validation study of self-reported outcomes in 29 patients with PNH.

Diagnosis of PNH

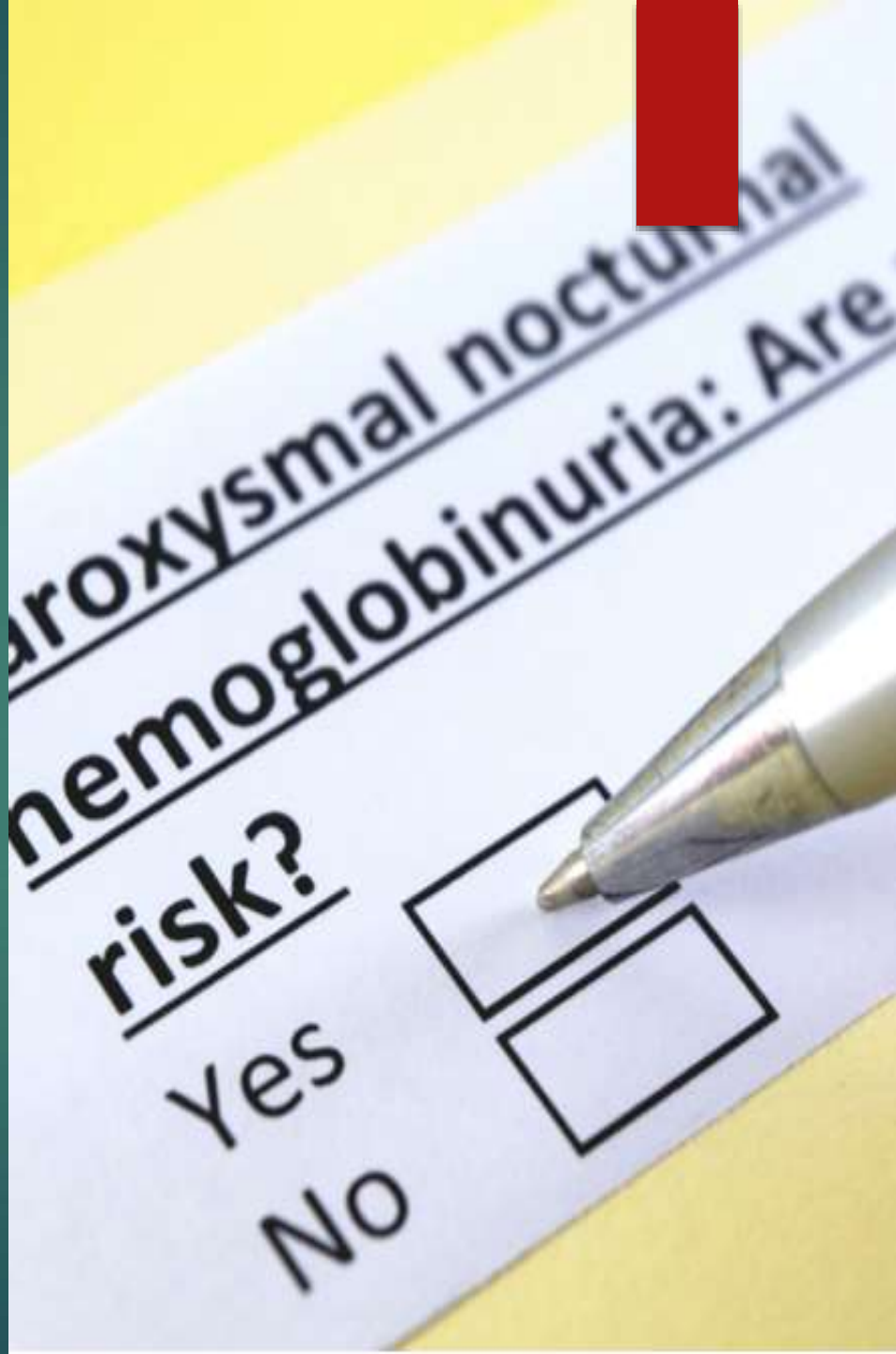
- When PNH is suspected peripheral blood is sent for flow cytometry testing
- Flow cytometry is a computer-based method do discover PNH cells
- This is a very accurate, sensitive and precise test



Poor prognosis of PNH

- If thrombosis develops
- If blood white blood cell or platelet count is low
- Age >55

Treatment



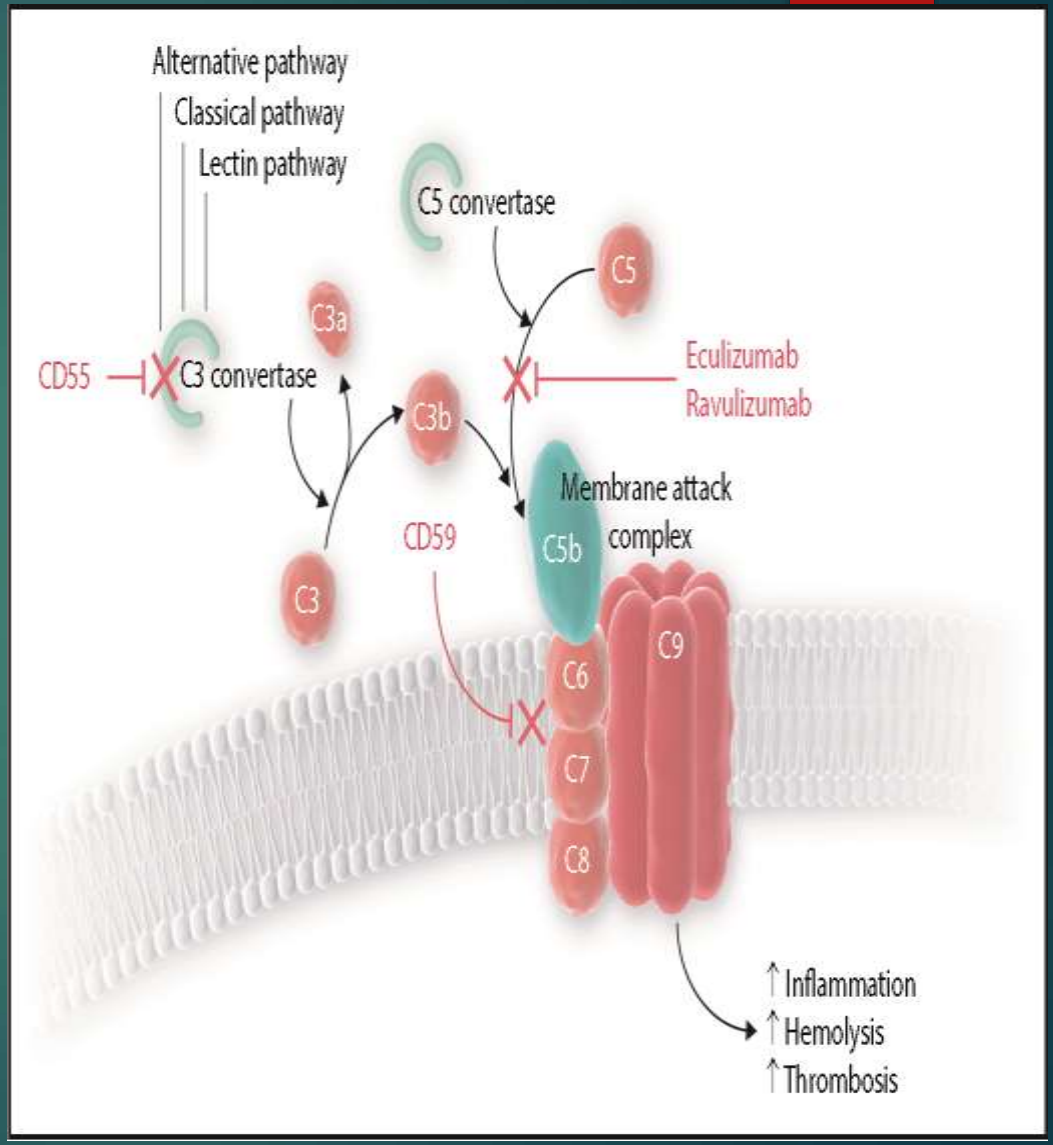
Treatment goals for PNH

- #1 Goal is to decrease hemolysis and therefore:

1. Reduce risk of blood clots
2. Reduce number of transfusions
3. Improve symptoms and quality of life
4. Prevent damage of kidneys, lungs, brain, liver, and gastrointestinal tract

Complement inhibitors

Recently introduced complement inhibitors revolutionized therapy of PNH
In 2007 FDA approved the orphan drug eculizumab (Soliris®) as a treatment for PNH
In 2018 FDA approved ravulizumab (Ultomiris®) for treatment of the hemolysis in PNH



Soliris

- Soliris was the first drug to be approved for PNH
- Soliris does not cure PNH, but halts the breakdown of red blood cells therefore reduces the risk of thrombosis and improves overall quality of life
- Soliris works by blocking the complement system of the body that destroys PNH red blood cells

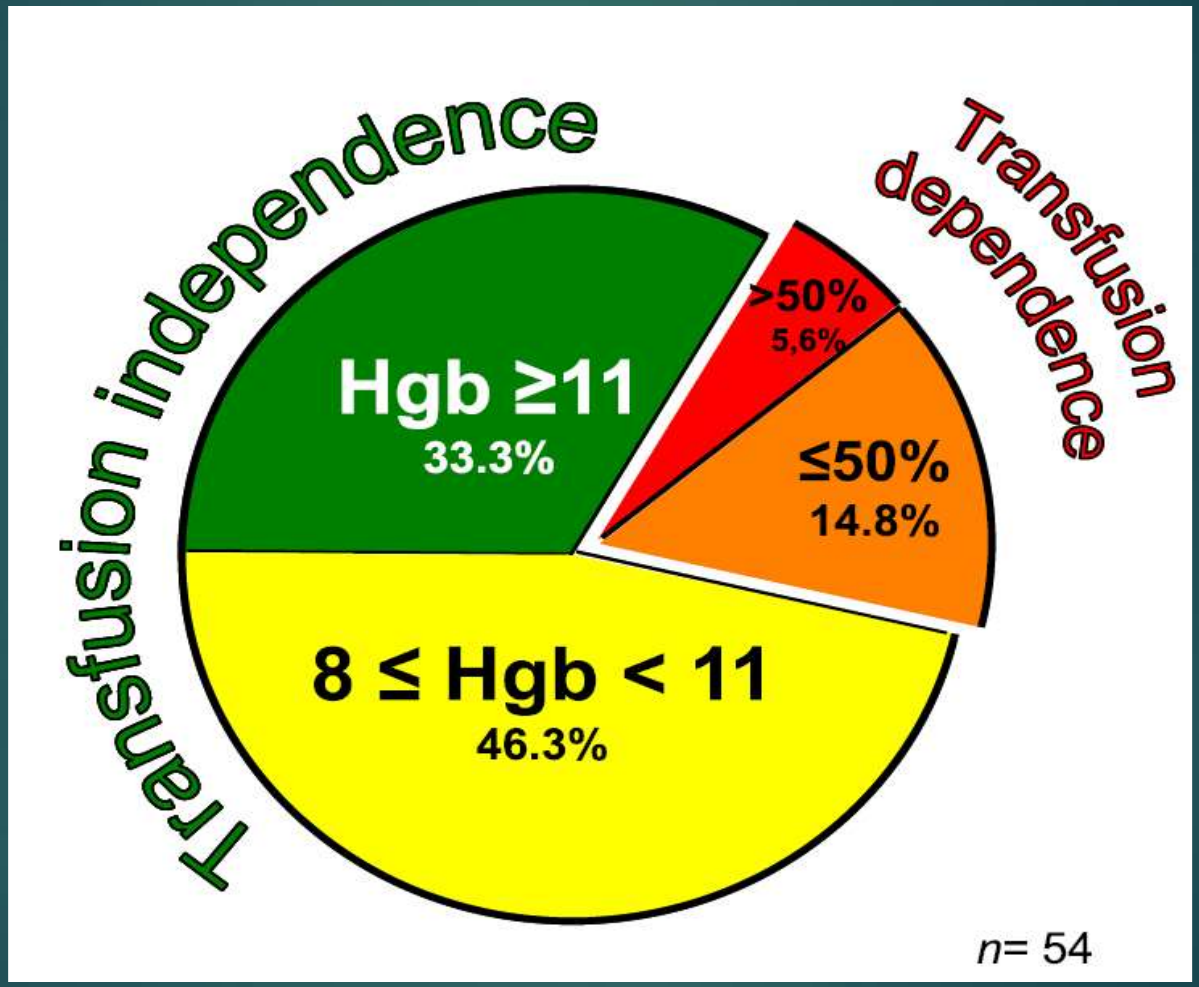
Soliris

- Because Soliris blocks the body's natural immune system, Soliris increases the risk of life-threatening meningitis(meningococcal infection)
- Therefore, patients must be vaccinated with a meningococcal vaccine at least two weeks prior to receiving the first dose of Soliris

Soliris

- Soliris is given as an infusion over 35 minutes in adults and 1 to 4 hours in pediatric patients
- It is given at the dose of 600 mg weekly for 4 weeks, followed by 900 mg a week later, and then 900 mg every two weeks
- Treatment should be continued without any significant breaks otherwise PNH symptoms quickly return

Responses to Soliris



Ultomiris

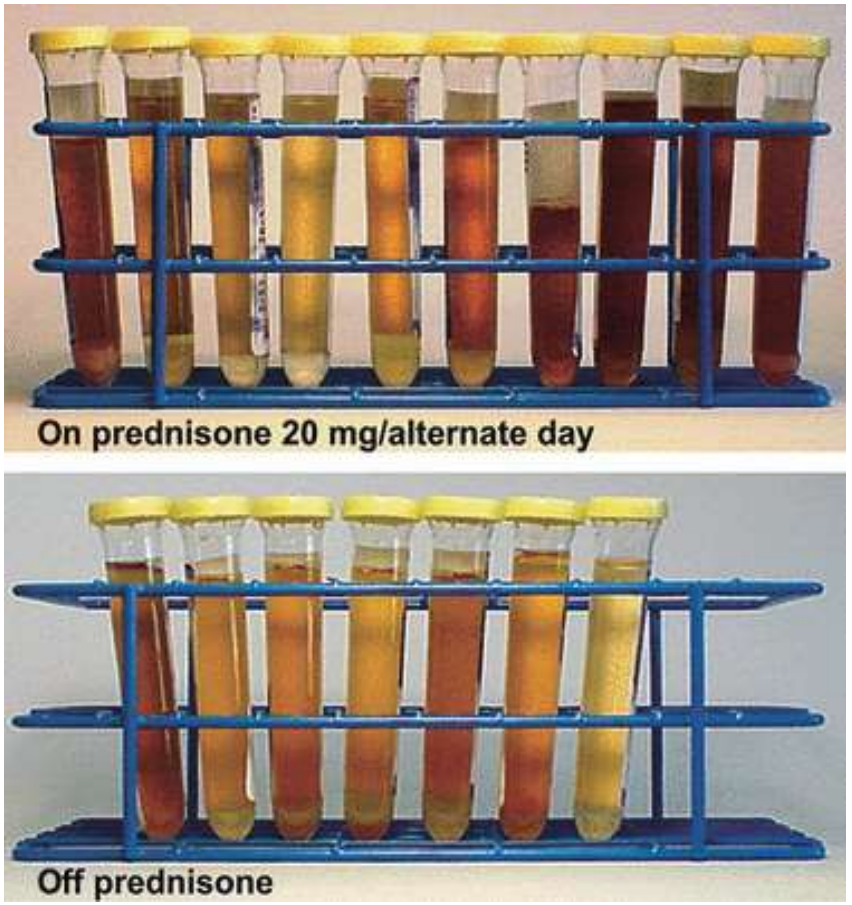
- Ultomiris has similar structure and works in a manner identical to Soliris
- Ultomiris was shown to be clinically as good as Soliris
- It stays in the system substantially longer then Soliris
- Therefore, Ultomiris can be given every eight weeks

Ultomiris

- Ultomiris dosing is weight based and consists of a loading dose followed by maintenance doses once every 8 weeks
- Infusion usually lasts over about 2 hours in adults and up to 4 hours in children
- Patients receiving Ultomiris also must be vaccinated with a meningococcal vaccine at least two weeks prior to receiving the first dose

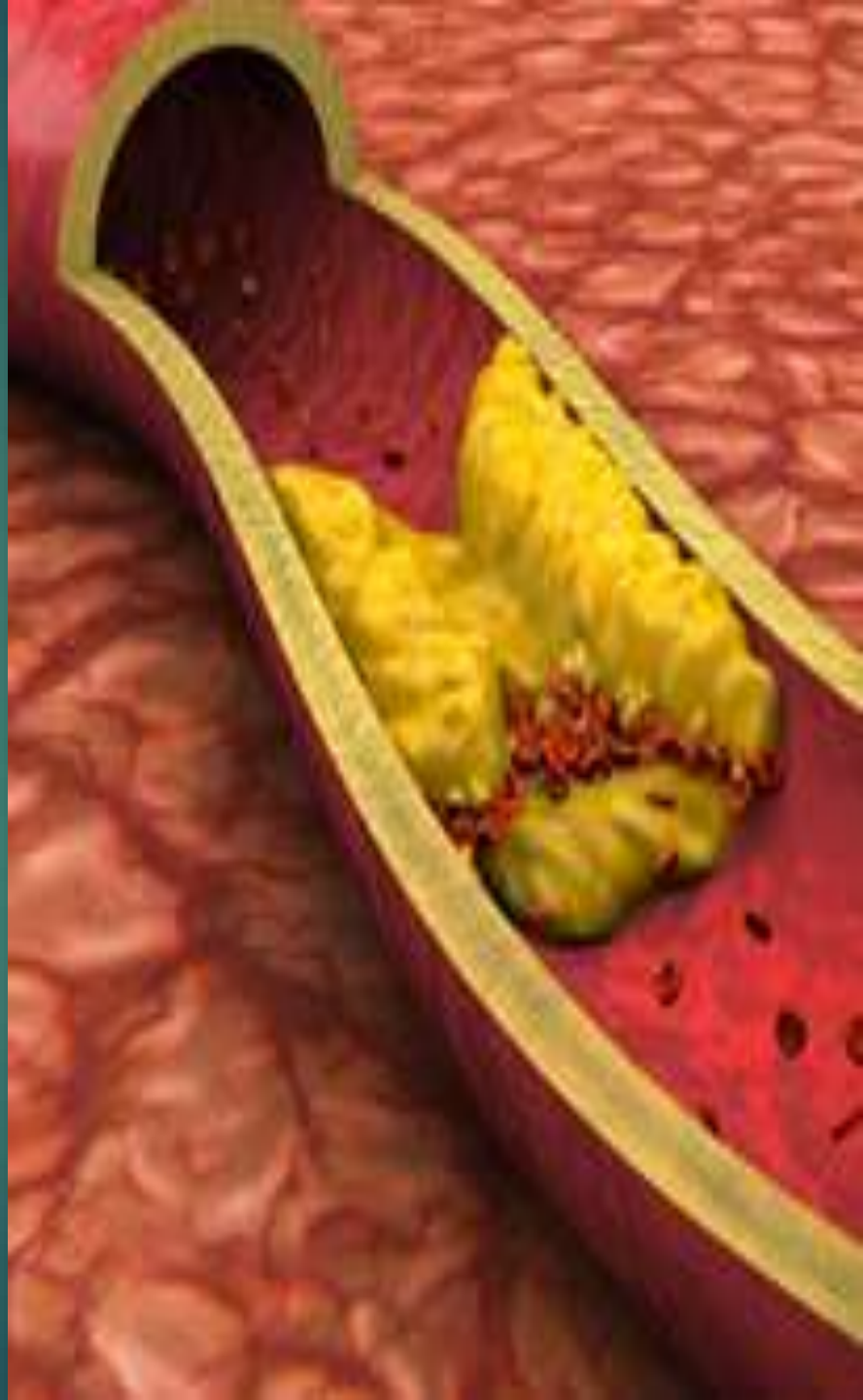
Supportive Treatment

- Steroids. Prednisone can reduce hemolysis
- Iron supplements are helpful in the case of significant hemolysis
- Folic acid supplementation for increased need of red cells turn over
- Blood transfusions as needed
- Androgenic hormones effective but mechanism unclear



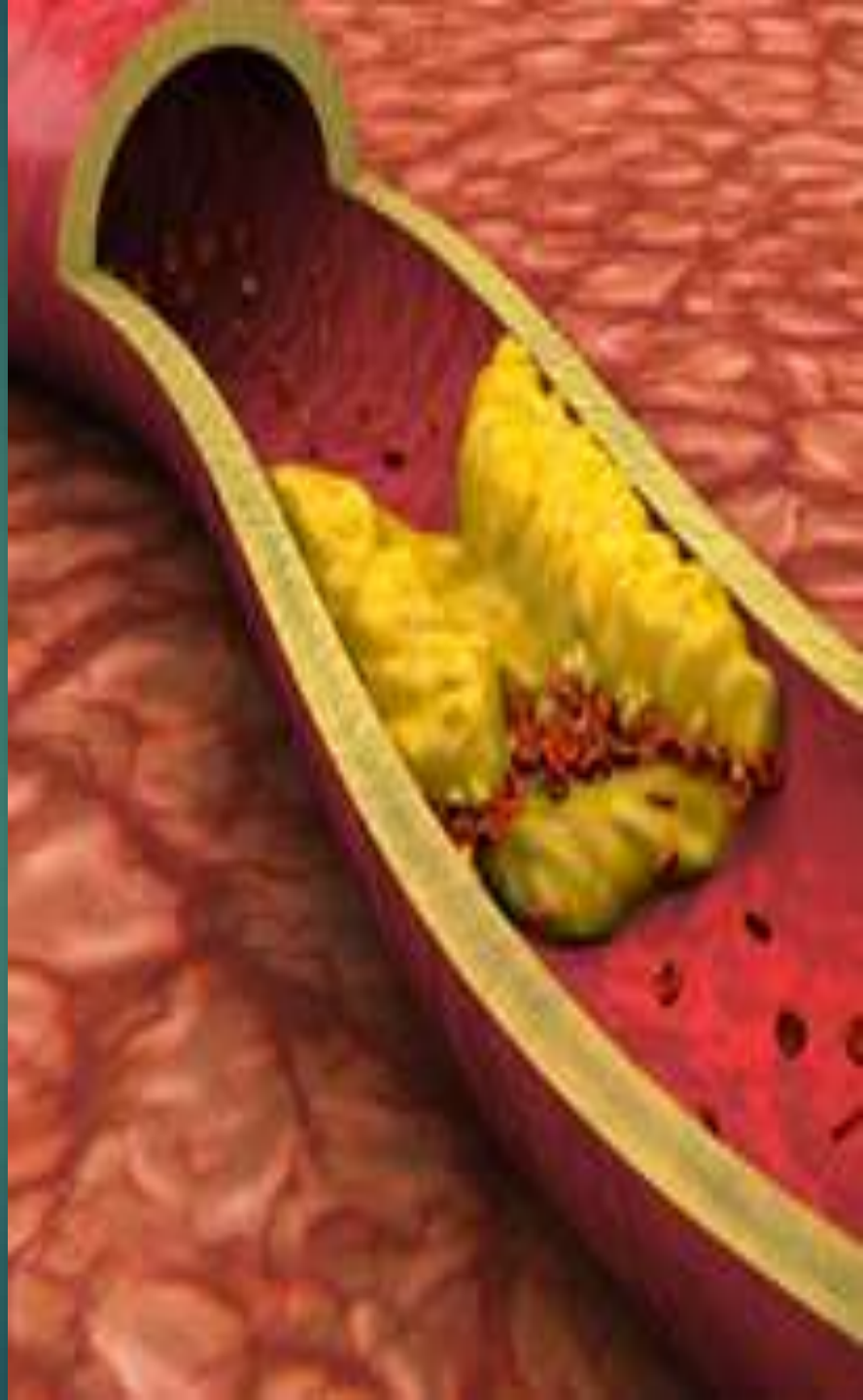
Treatment of acute blood clots

- First episode – blood thinners such as warfarin (Coumadin) or heparin (Lovenox) for at least 3 months
- Recurrent episodes – lifetime blood thinners
- Coumadin is preferred drug. Lovenox can be used as well
- No data about the efficacy of new oral blood thinners such as Eliquis, Pradaxa or Xarelto



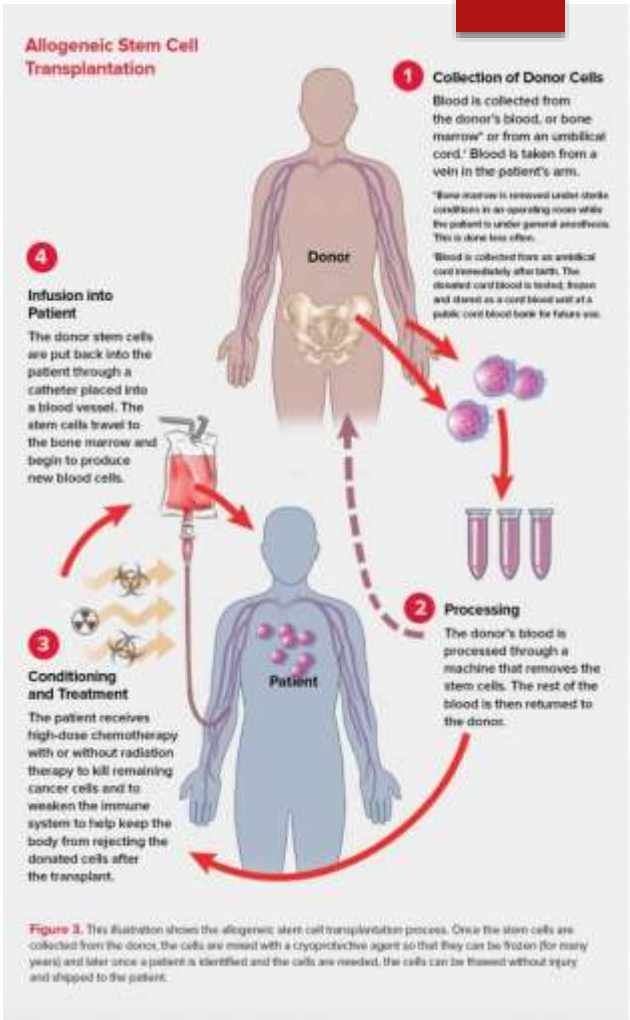
Prevention of blood clots

- Blood thinners are typically not indicated (risks higher than benefits)
- Treatment may be considered in PNH if PNH clone size is >50%
- Should be considered when risk of blood clots is high such as during surgery, immobilization or with use of indwelling intravenous catheters
- Heparin should be considered in 1st trimester of pregnancy until 4-6 weeks post-partum



Bone marrow(stem cell) transplantation

- The only curative therapy for individuals with PNH is bone marrow transplantation
- However, this procedure is associated with high risk of morbidity and mortality
- Typically it is reserved for individuals with serious complications such as severe bone marrow failure or repeated, life-threatening blood clots or for very young adults/children



Current clinical research

- No potentially breakthrough studies
- Very few trials are open in the U.S.
- Ongoing trials mostly focused on variety of newer complement inhibitors
- A Phase III, Randomized, Multi-Center, Open-Label, Active-Comparator Controlled Study to Evaluate the Efficacy and Safety of APL-2 in Patients With Paroxysmal Nocturnal Hemoglobinuria (PNH). APL-2 Complement (C3) Inhibitor administered subcutaneously twice weekly or every three days is open in the U.S.
- Other trials using following complement inhibitors rVA576 LNP023, REGN3918 rVA576 and ABP 959 are open outside the U.S.
- There is proposed eculizumab biosimilar called SB12 is being studied outside the U.S.
- Several trials are focused on improved outcomes after stem cell (bone marrow)transplant

Future therapies

- Protein transfer – Transfer of normal GPI-linked proteins
- Gene Therapy – Cloning of PIG-A gene
- Targeting the bone marrow environment