Paroxysmal nocturnal hemoglobinuria prevalence in patients with idiopathic pulmonary arterial hypertension (IPAH) and chronic thromboembolic pulmonary hypertension (CTEPH)

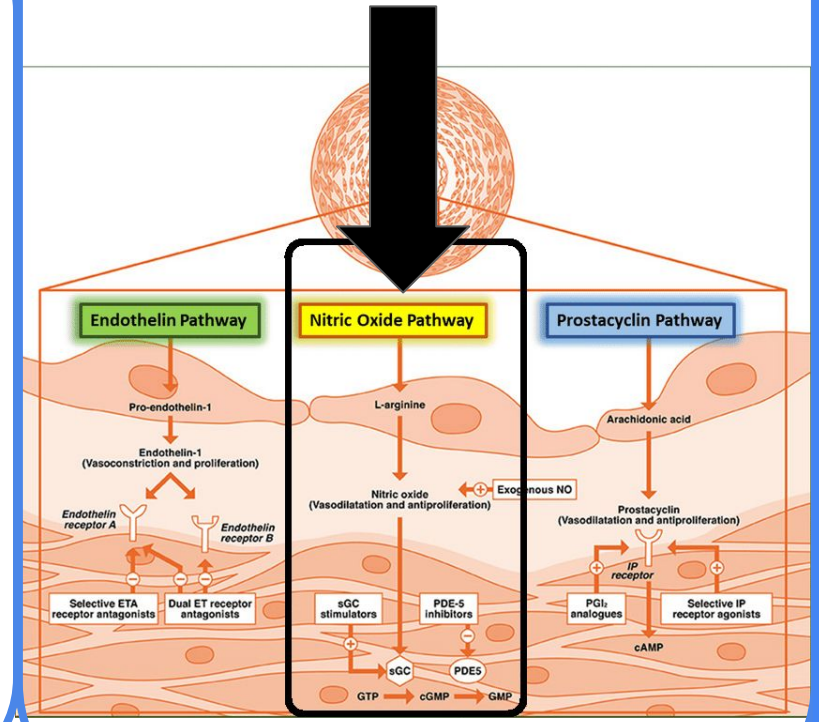
V. Ankudovich,..., A. Skride.

Hemolyisis - induced pulmonary hypertension - is a specific PH subgroup, that is associated with intravascular hemolysis. The main pathogenetic mechanism is binding of NO by free hemoglobin with resultant NO shortage and increased PVR. Those include:

- **Sickle cell disease**
- **Thalassemia syndromes**
- **Paroxysmal Nocturnal hemoglobinuria**
- **Malaria**
- **Hereditary spherocytosis**
- **Autoimmune hemolytic anemia**

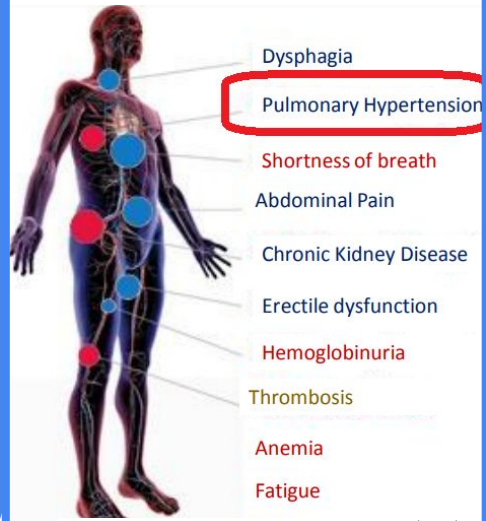
Wahl, S., & Vichinsky, E. (2010). Pulmonary hypertension in hemolytic anemias. *F1000 medicine reports*, *2*, 10.

NO pathway is impeded by hemolysis



Vazquez, Z. G. S., & Klinger, J. R. (2020). Guidelines for the Treatment of Pulmonary Arterial Hypertension. *Lung*, *198*(4), 581–596.

Paroxysmal nocturnal hemoglobinuria - is a rare disease in which blood cells are destroyed by immune system (namely complement system) that leads to chronic and acute hymolysis, thromboses and many other life changing manifestations, including pulmonary hypertension with resultant heart failure and dyspnea.



Hill, A., DeZern, A. E., Kinoshita, T., & Brodsky, R. A. (2017). Paroxysmal nocturnal haemoglobinuria. *Nature reviews. Disease primers*, *3*, 17028.

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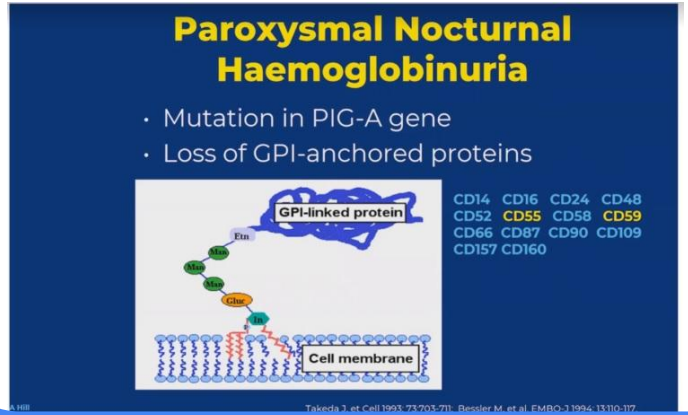
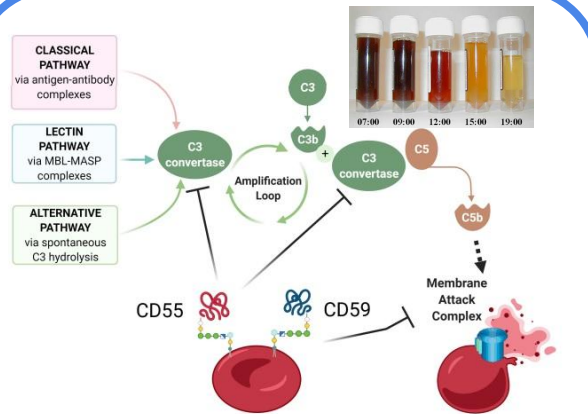
Table 1
Clinical Indications for PNH Testing

Intravascular hemolysis as evidenced by hemoglobinuria or elevated plasma hemoglobin
Evidence of unexplained hemolysis with accompanying:
Iron-deficiency, OR
Abdominal pain or esophageal spasm, OR
Thrombosis (see below), OR
Granulocytopenia and/or thrombocytopenia
Other acquired Coombs'-negative, non-schistocytic, non-infectious hemolytic anemia
Thrombosis with unusual features:
Unusual sites
Hepatic veins (Budd-Chiari syndrome)
Other intra-abdominal veins (portal, splenic, splanchnic)
Cerebral sinuses
Dermal veins
With signs of accompanying hemolytic anemia (see above)
With unexplained cytopenia
Evidence of bone marrow failure:
Suspected or proven aplastic or hypoplastic anemia
Refractory cytopenia with unilineage dysplasia
Other cytopenias of unknown etiology after adequate workup

Borowitz, M. J., Craig, F. E., Digiuseppe, J. A., Illingworth, A. J., Rosse, W., Sutherland, D. R., Wittwer, C. T., Richards, S. J., & Clinical Cytometry Society (2010). Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. *Cytometry. Part B, Clinical cytometry*, *78*(4), 211–230.



- Acquired mutation in PIG-A gene.
- Loss of GPI proteins.
- CD 55/59 are the most significant ones.
- Absence of CD 55/59 predisposes blood cells to hemolysis.



Risitano, A. M., & Rotoli, B. (2008). Paroxysmal nocturnal hemoglobinuria: pathophysiology, natural history and treatment options in the era of biological agents. *Biologics : targets & therapy*, *2*(2), 205–222.

- Due to the absence of CD 55/59 blood cells cannot protect themselves from complement system.
- Cells deficient in CD 55/59 are destroyed by complement system.
- Blood cell destruction leads to anemia, thromboses and many other signs and symptoms.

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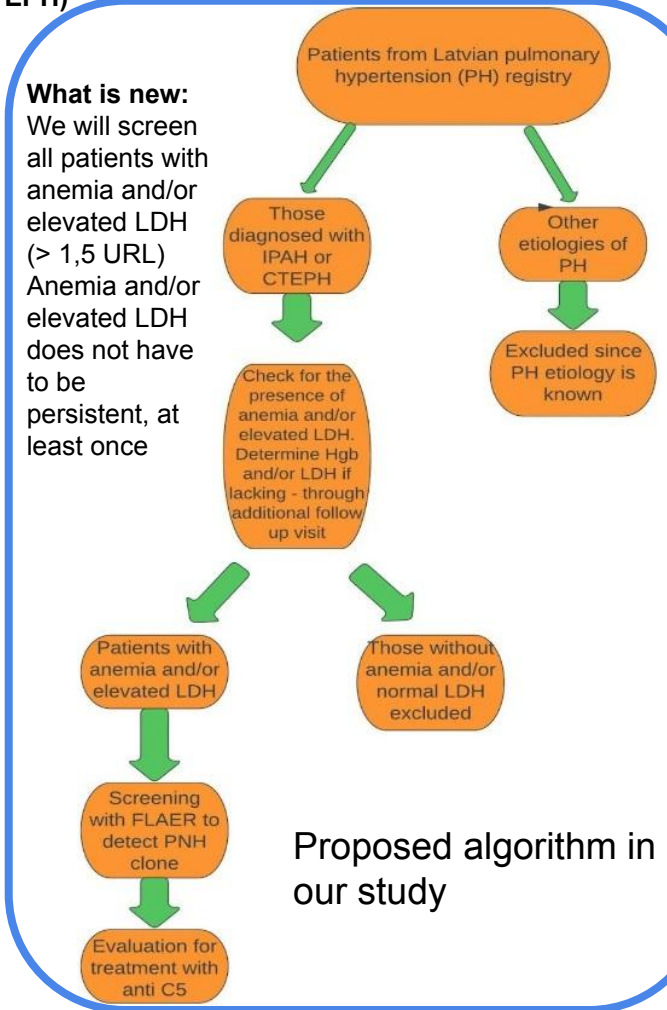
Aim of the study - to determine prevalence of PNH clone in pulmonary hypertension patients, namely idiopathic pulmonary hypertension (IPAH) and chronic thromboembolic pulmonary hypertension. We decided to conduct this study because PNH is known to cause PH, but so far in Latvia only two cases of PNH were diagnosed. Through this study we hope to find additional cases.

Methods:

1) Patients with IPAH and CTEPH - other ethiologes will be excluded
2) Select those with anemia and/or elevated LDH
3) Screen those selected for PNH clone using FLAER assay
4) Evaluate PNH clone positive patients for treatment with complement inhibitors (like eculizumab)

What is new:
We will screen all patients with anemia and/or elevated LDH (> 1,5 URL) Anemia and/or elevated LDH does not have to be persistent, at least once



Proposed algorithm in our study

Why it is so important:

- PNH is treatable
- Treatment improves outcomes
- Treatment reduces risks of complications

Conclusions:
Through this study we possibly will be able to find PNH cases and improve prognosis by starting appropriate treatment