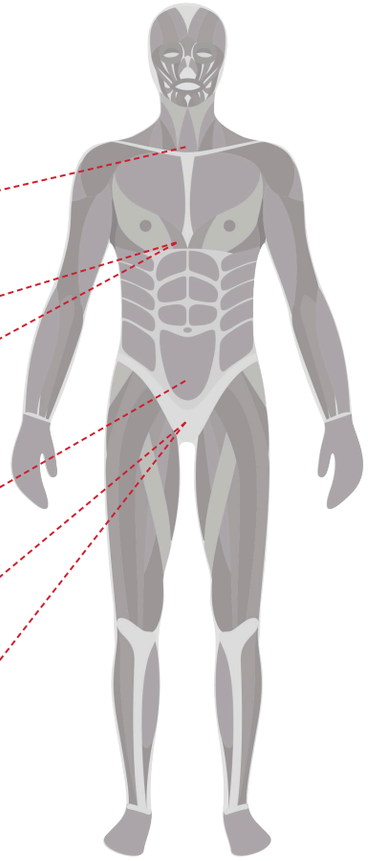
Paroxysmal Nocturnal Hemoglobinuria (PNH):

Pathophysiology

Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic, devastating, and potentially life-threatening disease characterized by uncontrolled terminal complement–mediated attack on white and red blood cells and platelets that can lead to severe consequences of thrombosis, organ damage, and early mortality.[1]

Signs and symptoms of PNH can include a wide range of unpredictable and potentially life-threatening complications[2,3,a]

- **Fatigue** 80%[2]
- **Anemia** 88%-94%[4]
- **Dysphagia** 24%[3]
- **Dyspnea** 64%[2]
- **Chest pain** 33%[2,3]
- **Abdominal pain** 44%[3]
- **Hemoglobinuria** 62%[2]
- **Erectile dysfunction**[b] 38%[3]



Historically, approximately...

16% to 46%
of PNH deaths were due to venous or arterial **thrombosis**[5-7,c,e]

2% to 18%
of PNH deaths were associated with **renal failure**[4,6,d,f]

47%
of patients suffered from **pulmonary hypertension**[8,g]

Approximately 20% to 35% of patients with PNH die within 6 years of diagnosis despite historical supportive care[4,9,c,h,i]

[a]The percentages for the signs and symptoms of PNH (with exception of anemia) are from Schrezenmeier 2014 and supplement: PNH Global registry with 856 patients self-reporting symptoms via a baseline questionnaire.[2,3] [b]Male patients only (n=410).[3] [c]Retrospective 6-year survival in historical control patients diagnosed with PNH between 1985 and 2005 in France (N=100). Retrospective thrombosis data presented are also from historical control group (N=44).[5] [d]Retrospective chart review of patients diagnosed with PNH in South Korea (N=301).[6] [e]Retrospective study of patients diagnosed with PNH (N=465) between 1950 and 2005 in France.[7] [f]Retrospective study comparing patients diagnosed with PNH since 1966 from the United States (N=176) to patients with PNH in a database registry in Japan (N=209).[4] [g]Data from patients with PNH enrolled in an international phase 3 randomized, placebo-controlled trial between October 2004 and June 2005 (N=87).[8] [h]Five-year survival in patients diagnosed with PNH between 1997 and 2004 in Leeds, UK (N=30).[9] [i]Supportive care included blood transfusion, anticoagulation, immunosuppressive therapy, corticosteroids, and bone marrow transplantation.[5,9]

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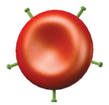
PNH is a hemolytic disease caused by an acquired mutation in hematopoietic stem cells and characterized by terminal complement–mediated intravascular hemolysis[10]

In patients with PNH, an acquired mutation in the *PIG-A* gene prevents the production of GPI anchors and results in the lack, or reduced expression, of GPI-anchored complement regulatory proteins, leading to dysregulation of the complement system.[10,11]

Hematopoietic stem cells in bone marrow

Normal hematopoietic stem cells



Normal red blood cell

GPI-anchored complement regulatory proteins

In healthy red blood cells, GPI-anchored complement regulatory proteins (CD55 and CD59)[a] defend against complement-mediated hemolysis.[10]

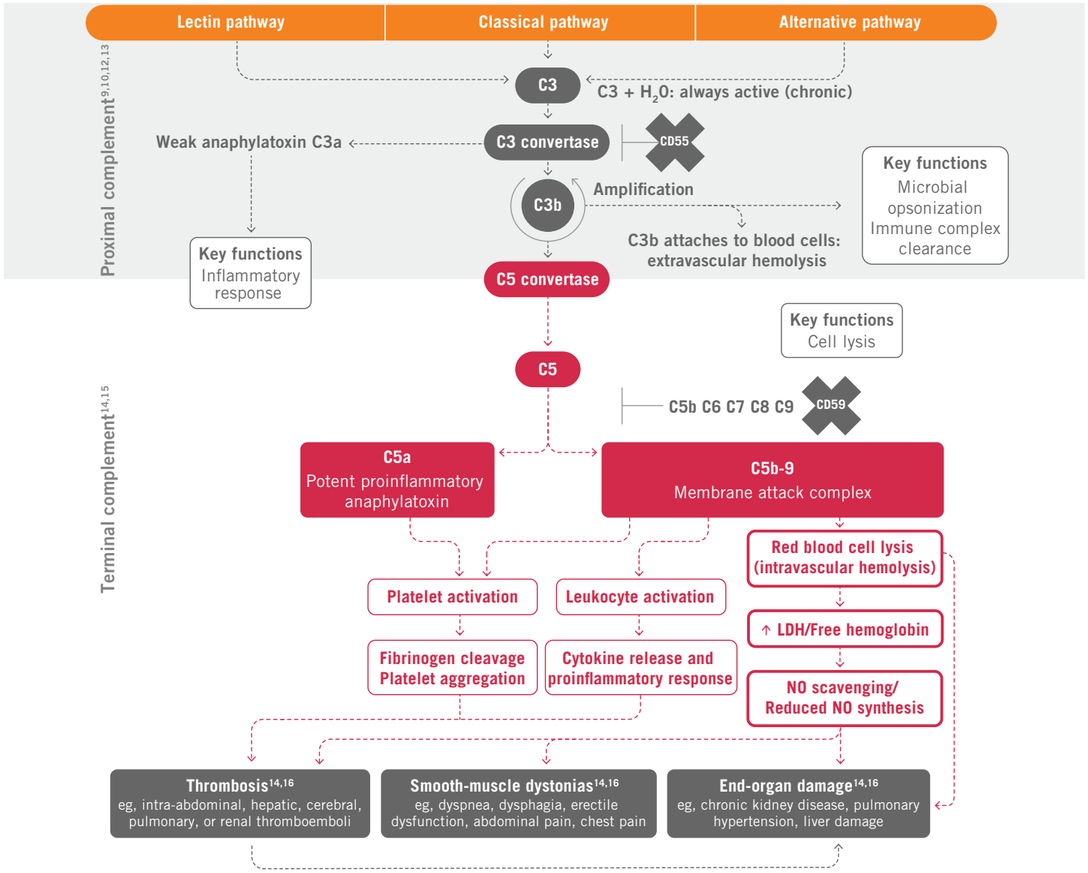
Hematopoietic stem cells with acquired mutation in *PIG-A* gene

PNH blood cell

No GPI-anchored complement regulatory proteins

In PNH, an acquired *PIG-A* mutation can lead to the complete or partial absence of GPI-anchored complement regulatory proteins. Red blood cells lacking surface expression of GPI-anchored complement regulatory proteins have increased sensitivity to complement attack. White blood cells and platelets without the GPI-anchored complement regulatory proteins are activated by complement attack.[10]

PNH is characterized by terminal complement–mediated attack, leading to severe consequences of thrombosis, organ damage, and early mortality[1]



[a]Complement-inhibiting proteins CD55 (decay-accelerating factor) and CD59 (membrane inhibitor of reactive lysis) defend red blood cells against complement-mediated lysis by regulating the formation and stability of the C3 convertase and blocking the assembly of the membrane attack complex, respectively.[10]

An intact complement system helps to protect against infections. Any deficiencies in the complement system can decrease the ability to fight infections and pathogens[17,18]

The pattern of infectious risk varies based on whether proximal or terminal complement activity is disrupted.[17,18]

Proximal complement (C3)

Deficiency of the C3 opsonic activities of proximal complement may lead to increased susceptibility to bacterial infection[17]

C3 convertase activity is an important defense against bacterial infections.[17]

Infections associated with proximal complement defects primarily include[19,20]:

Streptococcus pneumoniae	*Neisseria meningitidis*	*Enterococcal* species
Staphylococcus aureus	*Streptococcus agalactiae*	Certain fungal organisms
Escherichia coli	*Kingella kingae*	
Haemophilus influenzae	*Stenotrophomonas maltophilia*	

Terminal complement (C5)

Deficiency in components of terminal complement (eg, C5, C6, C7, C8, or C9) may impact the formation of the membrane attack complex, such as C5b-9, and its ability to lyse certain bacteria[20]

Deficiencies in terminal complement predispose the patient to infection with meningococcal and disseminated gonococcal infections.[20]

Infections associated with terminal complement defects primarily include[19]:

- Meningococcal infections
- Disseminated gonococcal infections

Abbreviations: FLAER=fluorescent aerolysin; **GPI**=glycosylphosphatidylinositol; **HSC**=hematopoietic stem cell; **LDH**=lactate dehydrogenase; ***PIG-A***=phosphatidylinositol glycan complementation class A; **PNH**=paroxysmal nocturnal hemoglobinuria.

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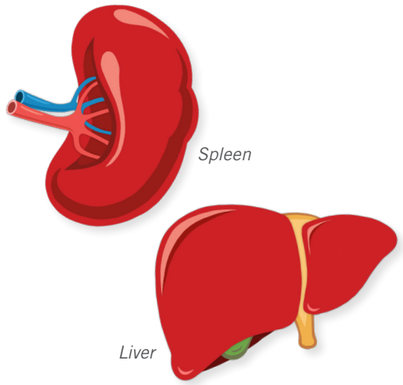
In PNH, the key consequences of clonal expansion of *PIG-A* mutant HSCs are intravascular hemolysis and thrombosis[21]

Proximal complement–mediated extravascular hemolysis

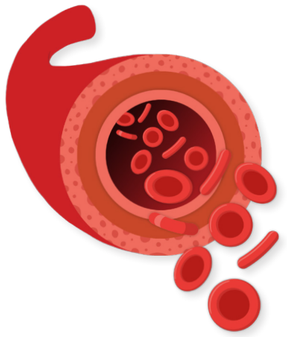
Proximal complement–mediated extravascular hemolysis means the lysis of red blood cells occurs outside of the vascular system and in organs—specifically in the spleen and liver[22]



- Extravascular hemolysis is caused by C3b being deposited on the surface of defective red blood cells and tagging those cells for removal by macrophages, which results in the destruction of those red blood cells in the liver and spleen.[23]
- This is similar to how old or damaged red blood cells are removed from circulation, but in extravascular hemolysis, the process in PNH is premature.[23]
- This process will stimulate new red blood cell production but may result in anemia if production cannot keep up with destruction.[23,24]

Terminal complement–mediated intravascular hemolysis

Terminal complement–mediated intravascular hemolysis is the destruction of red blood cells within the blood vessels as a result of defective red blood cells (as in PNH), complement activation, drugs, or infection[21,23,25]



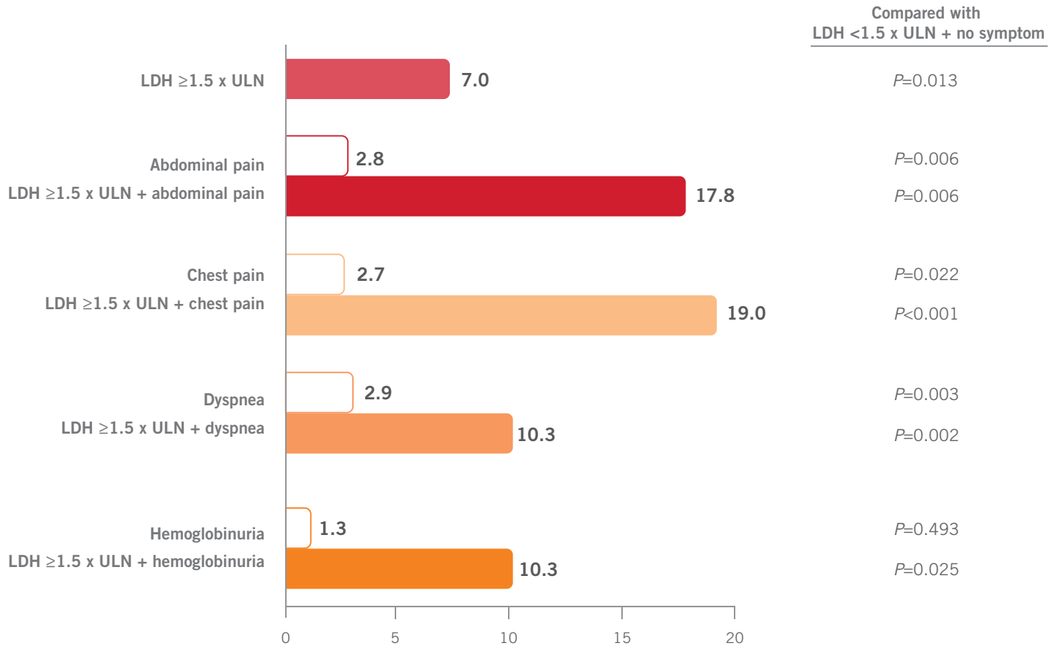
- Unlike extravascular hemolysis, there are limited mechanisms to process the cellular debris.[21,23]
- When contents of red blood cells spill out into the vessels, it causes multiple pathological consequences.[21,23]
- Intravascular hemolysis can result in marked increase in circulating free hemoglobin as well as enzymes such as LDH.[21,23]
- Patients can often manifest acute, significant anemia in the setting of intravascular hemolysis with evidence of end-organ damage, particularly within the renal system, attributable to terminal complement fixation.[21,23]

Intravascular hemolysis represents ~10 times more red blood cell destruction than in extravascular hemolysis. Available evidence indicates that extravascular hemolysis does not contribute to reduced survival[21,26,27]

LDH is an important clinical marker of terminal complement–mediated intravascular hemolysis and an important measure of the severity of PNH disease activity[2,6,28]

- LDH ≥1.5 x ULN has been shown to significantly increase the risk for thrombosis and be a predictor of premature mortality in patients with PNH.[6,28,a,b]
  - Patients with PNH and LDH ≥1.5 x ULN had a 4.8-fold higher mortality rate compared with the age- and sex-matched general population (*P*<0.001).[28,a]
  - LDH ≥1.5 x ULN alone or in combination with chest or abdominal pain has been reported to increase the risk of thrombosis and premature mortality in patients with PNH.[6,28,a,b]

Hemolysis as measured by LDH and clinical symptoms are associated with increased risk of thrombosis in patients with PNH[28,b]



Regularly assess for labs indicating hemolysis along with clinical signs and symptoms to help diagnose PNH. Once positive for PNH, monitor LDH as it is an indicator of risk for thrombosis, organ damage, and early mortality in PNH[1,2,6,28]

[a]A retrospective chart review of 301 patients with PNH, enrolled into the South Korean PNH registry, assessed the clinical signs and symptoms predictive of mortality using a standardized mortality ratio compared with an age- and sex-matched general Korean population.[6] [b]A retrospective analysis of 301 patients from the South Korean PNH registry evaluated risk factors for thrombosis using a multivariate analysis matched for age, sex, and bone marrow failure. Data are presented as odds ratios comparing patients with LDH ≥1.5 x ULN with specified symptoms to patients with LDH <1.5 x ULN and no symptoms.[28]

Rapid recognition of the signs and symptoms of PNH and early diagnosis are important to patient management[29,30]

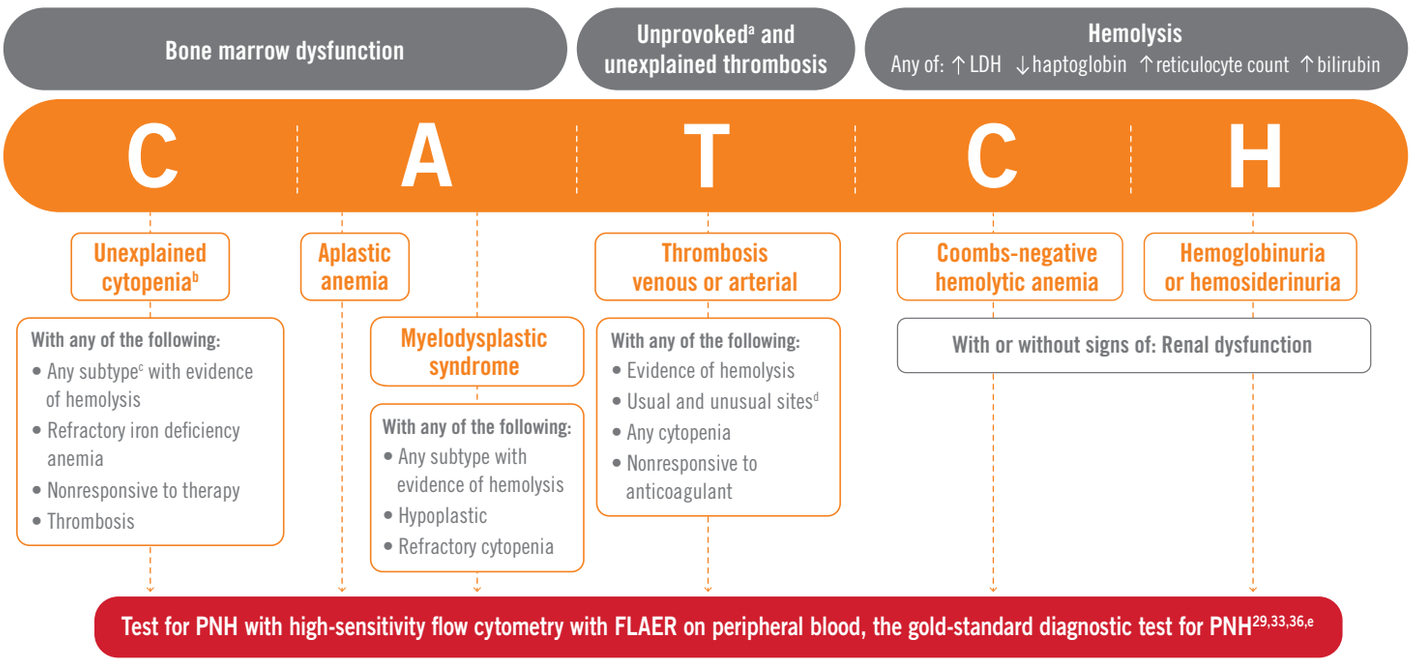
The International Clinical Cytometry Society and International PNH Interest Group recommend testing high-risk patients.[30-32] Patients who meet the criteria within any of the high-risk groups for PNH should be tested for PNH with high-sensitivity flow cytometry with FLAER on peripheral blood, the standard diagnostic test for PNH.[29,31,33,34]

Core signs and symptoms of PNH (any of the following)[29,31,35-37]

- **Symptoms of anemia** (eg, fatigue, tachycardia, shortness of breath, headache)
- **Thrombosis**
- **Dark-colored urine**
- **Intermittent abdominal pain**
- **Esophageal spasms**
- **Dysphagia**

in association with 1 of the following or if the patient exhibits 1 of the following (in the absence of an above symptom)

High-risk groups associated with PNH[29,31,35-38]



This algorithm is intended as educational information for healthcare providers. It does not replace a healthcare provider's professional judgment or clinical diagnosis.

Establish a definitive diagnosis via high-sensitivity flow cytometry with FLAER on peripheral blood, the gold-standard diagnostic test for PNH[29,32,33,35,39]

[a]Deep vein thrombosis and/or pulmonary embolism in a patient with no antecedent major clinical risk factor for venous thromboembolism that is not provoked by surgery, trauma, immobilization, hormonal therapy (oral contraceptive or hormone replacement therapy), or active cancer.[36] [b]Unexplained persistent cytopenia in a patient in whom (minimal) diagnostic criteria for myelodysplastic syndrome are not fulfilled.[36] [c]Anemia, neutropenia, or thrombocytopenia.[40] [d]Unusual sites include hepatic veins (Budd-Chiari syndrome), other intra-abdominal veins (portal, splenic, splanchnic), cerebral sinuses, and dermal veins.[36] [e]Detects PNH cells down to a 0.01% clone size.[29]

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