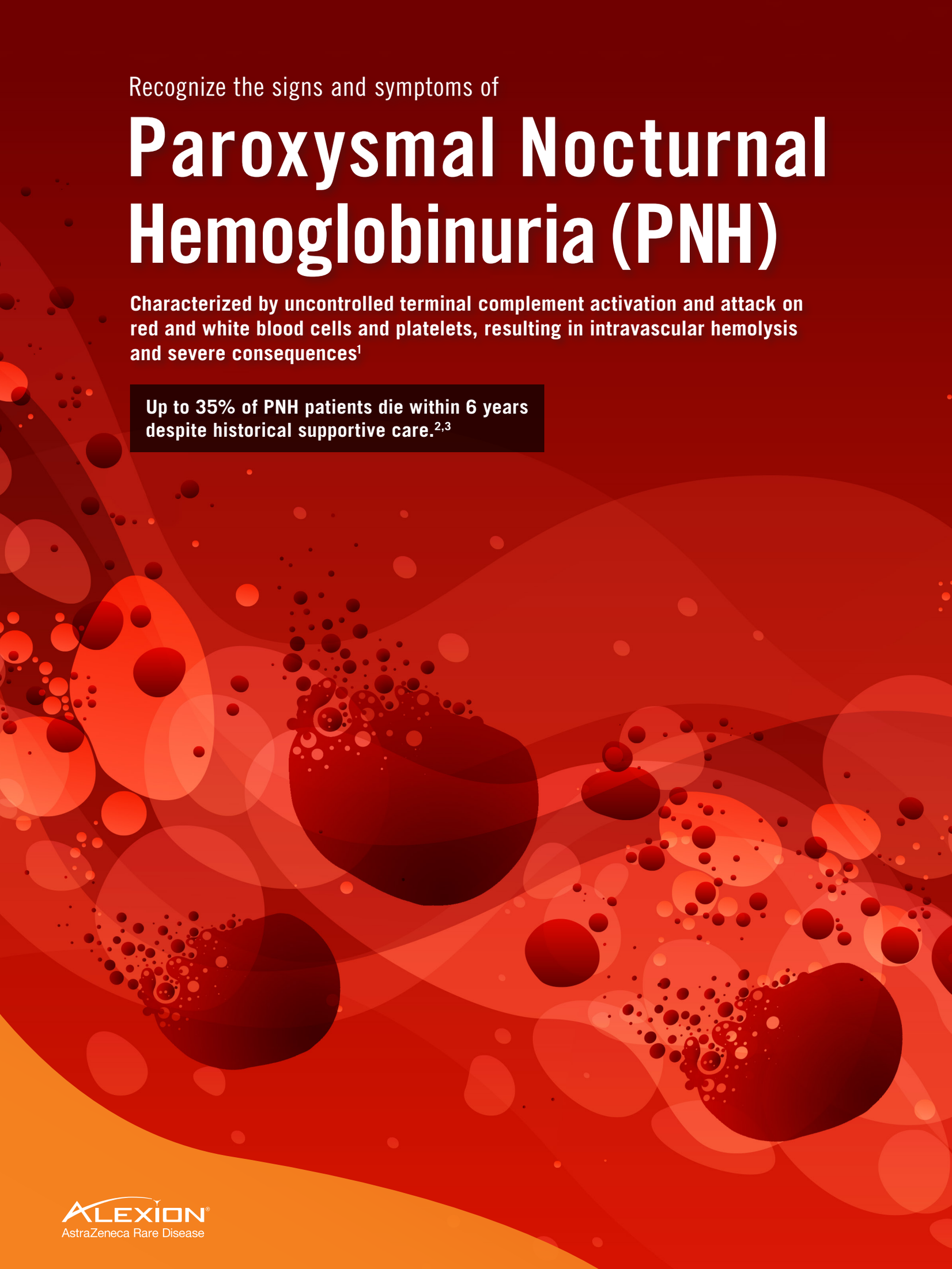
Recognize the signs and symptoms of

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Characterized by uncontrolled terminal complement activation and attack on red and white blood cells and platelets, resulting in intravascular hemolysis and severe consequences[1]

Up to 35% of PNH patients die within 6 years despite historical supportive care.[2,3]



ALEXION®
AstraZeneca Rare Disease

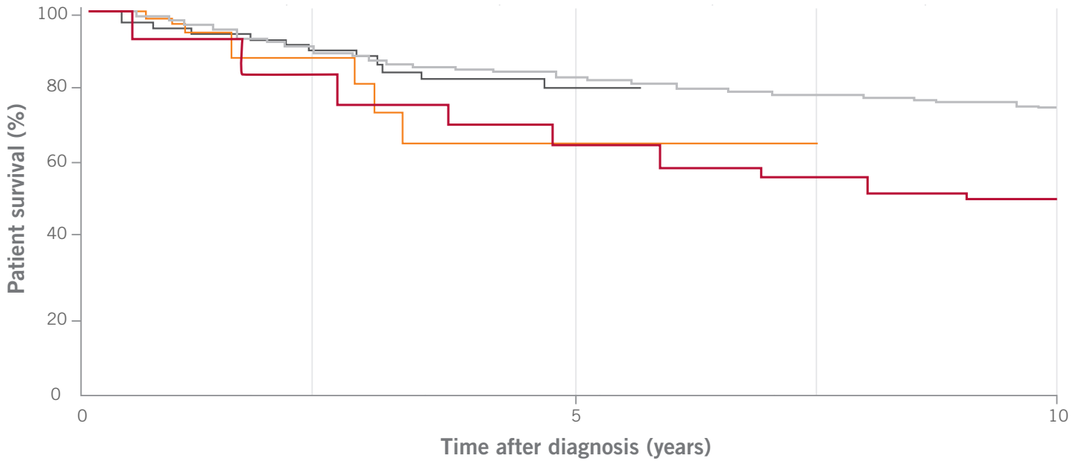
PNH is an acquired hemolytic disease caused by a genetic mutation in hematopoietic stem cells[4]

- PNH has **multifactorial symptoms** that result in many patients experiencing a lengthy and complex path to diagnosis, with high morbidity and early mortality.[5]
- Prevalence of PNH is estimated to be **~12-13 per million people** in the general population.[6]
- **24% of all PNH diagnoses can take 5 years or longer, while approximately 60% take longer than 1 year to diagnose.[7]**
- **Diagnostic delay** can be a source of distress and affect **patients' emotional well-being.[8]**
- **PNH is characterized by terminal complement–mediated intravascular hemolysis**, which can lead to the devastating and potentially life-threatening consequences of thrombosis, multi-organ failure, and early mortality.[1]
- PNH impacts both **children** and **adults** and is believed to affect males and females in equal numbers.[9,10]
- The **median age** at diagnosis is **during the 30s.[11,12]**
- **A majority of patients (80%) with PNH** report experiencing fatigue, which can result in decreased physical activity and quality of life.[13,14]

PNH is likely one of the most vicious acquired thrombophilic states known in medicine[15-17]

- Up to **35%** of PNH patients die within 6 years despite historical supportive care.[2,3,a]

Historical survival rates in patients with PNH[2,3,17,18,b]



- Peffault de Latour, et al. *Blood.* 2008. 10-year mortality (6.8 years median follow-up time) in patients diagnosed with PNH between 1950 and 2005 across France (N=454)[18,c]
- Loschi, et al. *Am J Hematol.* 2016. 6-year mortality in historical control patients diagnosed with PNH between 1985 and 2005 in France (N=100)[3]
- Kelly, et al. *Blood.* 2011. Mortality in patients diagnosed with PNH between 1997 and 2004 in Leeds, UK (N=30)[2]
- Hillmen, et al. *N Engl J Med.* 1995. 10-year mortality in patients diagnosed with PNH between 1940 and 1970 in London, UK (N=80)[19,d]

Terminal complement activation results in intravascular hemolysis and activation of white blood cells and platelets, leading to potentially devastating consequences in PNH[20]

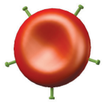
[a]Supportive care included blood transfusion, anticoagulation, immunosuppressive therapy, and bone marrow transplantation.[2,3] [b]These data reflect observations from multiple studies conducted under different conditions and in different patient populations, which may limit generalizability. [c]Patients in the Peffault de Latour 2008 study were followed up to 40 years.[18] [d]Patients in the Hillmen 1995 study were followed up to 25 years.[19]

PNH is an acquired hemolytic disease caused by an acquired mutation in hematopoietic stem cells and characterized by terminal complement–mediated intravascular hemolysis[4]

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.[4,21]

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.[4]

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

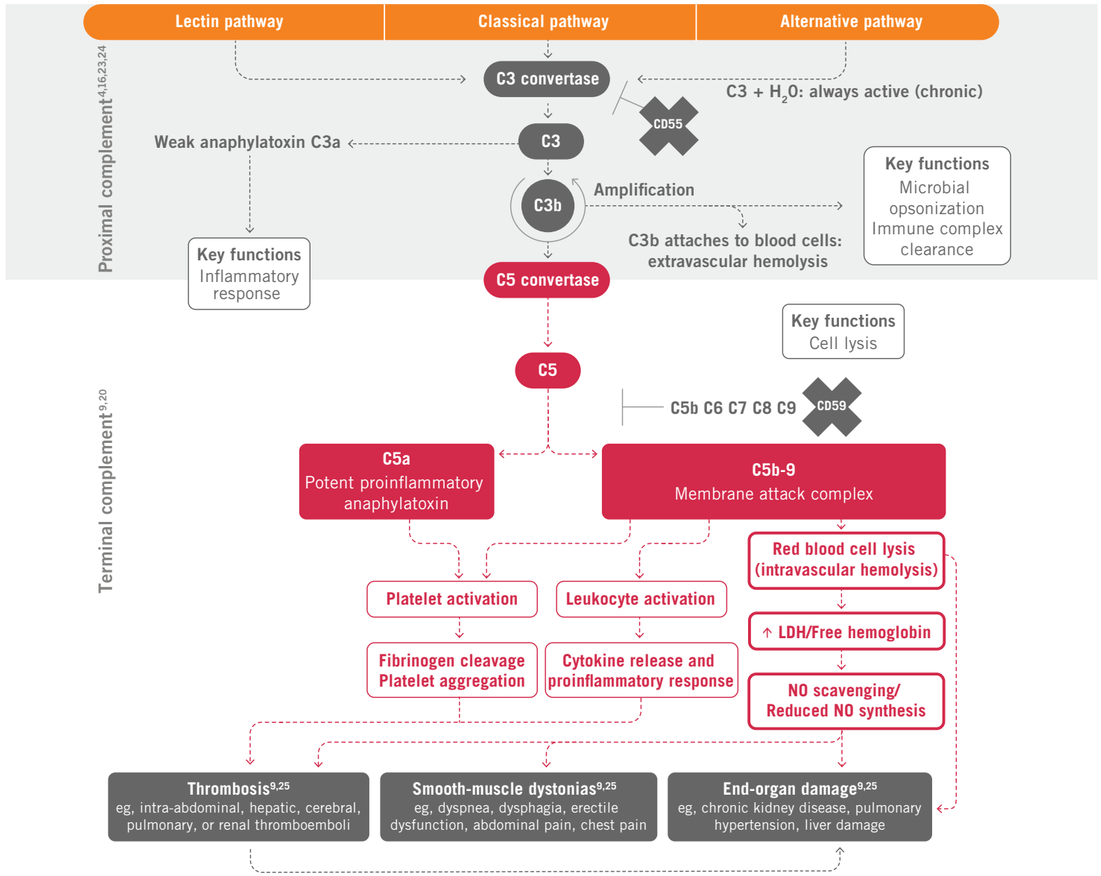
PNH blood cell

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.[4]

Clone size is the percentage (number) of blood cells that are affected by PNH. The percentage of cells that do not have GPI-anchored complement regulatory proteins is referred to as the PNH clone size.[22]

PNH is characterized by terminal complement–mediated attack on red blood cells, white blood cells, and platelets, 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.[4]

An intact complement system helps to protect against infections[26,27]

The pattern of infectious risk varies based on whether proximal or terminal complement activity is disrupted.[26,27]

Proximal complement (C3)

Deficiency of the C3 opsonic activities of proximal complement may lead to increased susceptibility to bacterial infection[26]

C3 convertase activity is an important defense against bacterial infections.[26]

Infections associated with proximal complement defects primarily include[28,29]:

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[29]

Deficiencies in terminal complement predispose the patient to infection with meningococcal and disseminated gonococcal infections.[29]

Infections associated with terminal complement defects primarily include[28,29]:

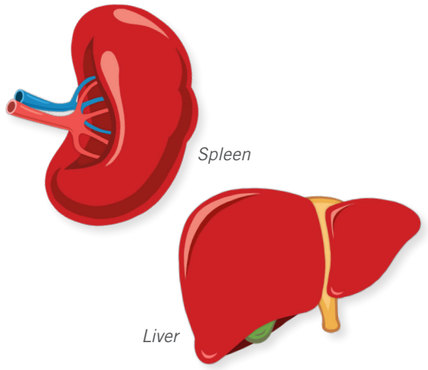
- Meningococcal infections
- Disseminated gonococcal infections

Any deficiencies in the complement system can decrease the ability to fight infections and pathogens[26,27]

In PNH, the key consequences of clonal expansion of *PIG-A* mutant HSCs are intravascular hemolysis and thrombosis[17]

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[30]



- 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.[31]
- 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.[31]
- This process will stimulate new red blood cell production but may result in anemia if production cannot keep up with destruction.[31,32]

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[17,31,33]

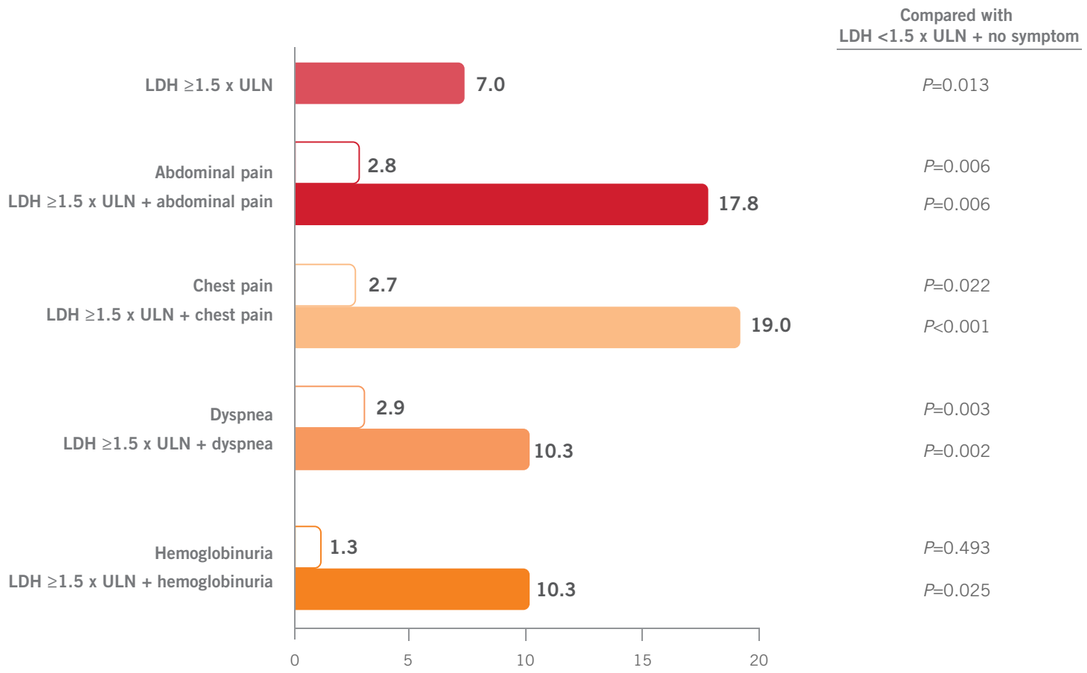
- Unlike extravascular hemolysis, there are limited mechanisms to process the cellular debris.[17,31]
- When contents of red blood cells spill out into the vessels, it causes multiple pathological consequences.[17,31]
- Intravascular hemolysis can result in marked increase in circulating free hemoglobin as well as enzymes such as LDH.[17,31]
- 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.[17,31]

In PNH, hemolysis can take place in two pathways: extravascular hemolysis and intravascular hemolysis. In some patients being managed for PNH, extravascular hemolysis may be the more prominent form of hemolysis[17,34,35]

LDH is an important clinical marker of terminal complement–mediated intravascular hemolysis and an important measure of the severity of PNH disease activity[13,36,37]

- 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.[36,37,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).[37,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.[36,37,a]

Hemolysis as measured by LDH and clinical symptoms are associated with increased risk of thrombosis in patients with PNH[36,b]



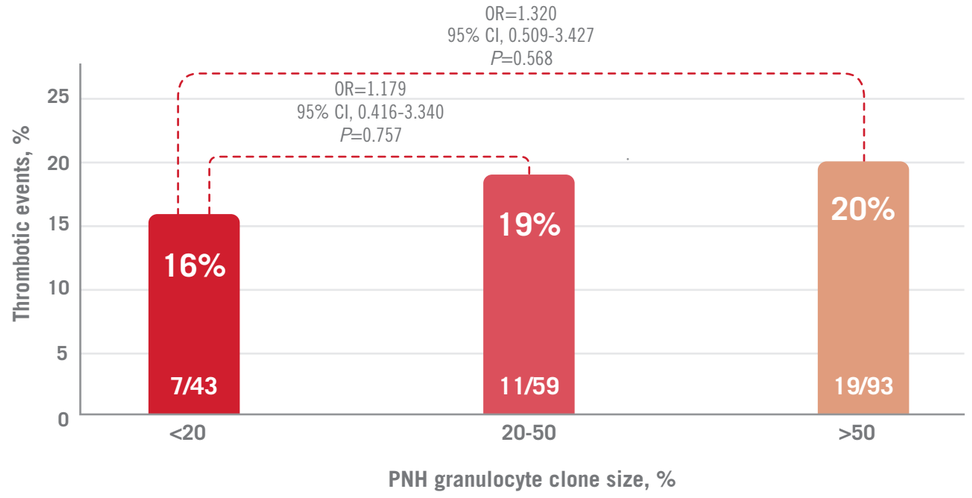
Regularly assess for labs indicating hemolysis along with clinical signs and symptoms to help diagnose PNH. Once positive for PNH, monitor LDH as it is an indicator of risk for thrombosis, organ damage, and early mortality in PNH[1,13,36,37]

[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.[37] [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.[36]

Patients with PNH are at risk of thrombosis regardless of PNH granulocyte clone size and bone marrow failure[36]

- Thrombosis leads to severe morbidity and is the most common cause of premature mortality in PNH.[15,36]
- Clone size is the percentage (number) of blood cells that are affected by PNH. The percentage of cells that do not have GPI-anchored complement regulatory proteins is referred to as the PNH clone size.[22]
- Even PNH clone sizes <20% are associated with a risk of thrombosis.[36]

Incidence of thrombosis in PNH granulocyte clone size categories[36,a]

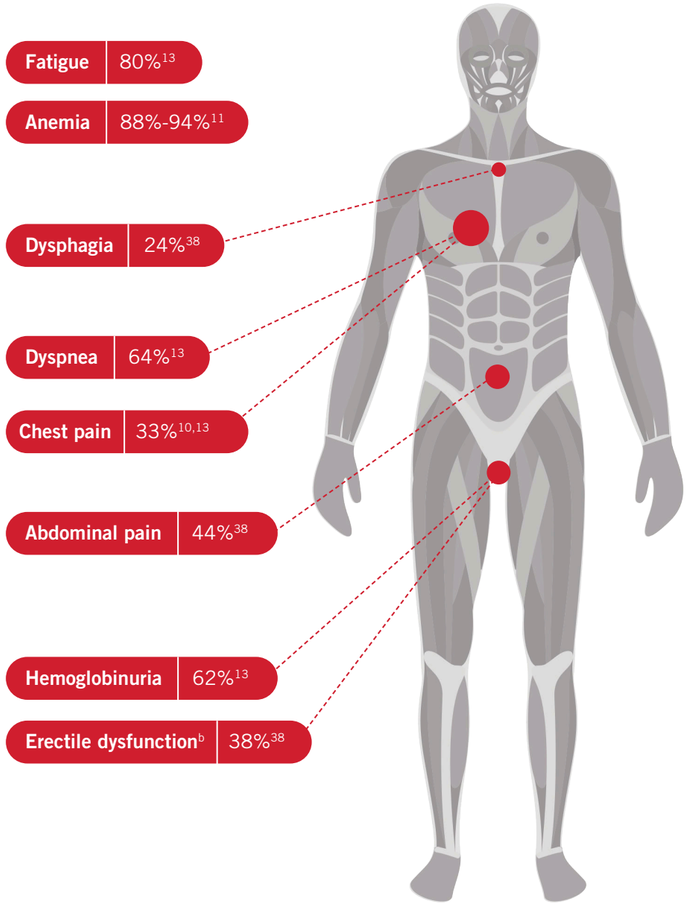


- In a retrospective study, the incidence of thromboembolic events in patients with PNH was ~18% (54/301).[36]
  - Thrombotic events reported in 37 patients were stratified by clone size; they occurred in 16% of the patients with a clone size of <20%, in 19% of the patients with a clone size of 20% to 50%, and in 20% of the patients with a clone size >50%.
  - The risk of experiencing thrombosis was not related to clone size (*P*=0.843).

Although clone size is not related to thrombosis, LDH is an indicator of disease activity, including thrombosis, organ damage, and early mortality in PNH[1,13,36,37]

[a]A retrospective analysis of medical charts of 301 patients with PNH in a South Korean registry to describe the burden of disease, the clinical characteristics of thrombosis, and the risk factors associated with thrombosis in PNH; N=number of PNH granulocyte clones.[36]

Signs and symptoms of PNH can include a wide range of unpredictable and potentially life-threatening complications[13,37,a]



Historically, approximately...

16% to 46%
of PNH deaths were due to venous or arterial **thrombosis**[3,18,38,c-e]

2% to 18%
of PNH deaths were associated with **renal failure**[11,38,d,f]

47%
of patients suffered from **pulmonary hypertension**[39,g]

Approximately 20% to 35% of patients with PNH die within 6 years of diagnosis despite historical supportive care[2,11,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.[13,38] [b]Male patients only (n=410).[38] [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).[3] [d]Retrospective chart review of patients diagnosed with PNH in South Korea (N=301).[37] [e]Retrospective study of patients diagnosed with PNH (N=465) between 1950 and 2005 in France.[18] [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).[11] [g]Data from patients with PNH enrolled in an international phase 3 randomized, placebo-controlled trial between October 2004 and June 2005 (N=87).[39] [h]Five-year survival in patients diagnosed with PNH between 1997 and 2004 in Leeds, UK (N=30).[2] [i]Supportive care included blood transfusion, anticoagulation, immunosuppressive therapy, corticosteroids, and bone marrow transplantation.[2,3]

Rapid recognition of the signs and symptoms of PNH and early diagnosis are important to patient management[22,40]

The International Clinical Cytometry Society and International PNH Interest Group recommend testing high-risk patients.[41-43]

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.[22,41,44,45]

Core signs and symptoms of PNH (any of the following)[5,22,41,43,46]

- **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[5,22,41,43,46,47]

Bone marrow dysfunction

Unprovoked[a] and unexplained thrombosis

Hemolysis
Any of: ↑LDH ↓haptoglobin ↑reticulocyte count ↑bilirubin

C A T C H

Unexplained cytopenia[b]
With any of the following:
- Any subtype[c] with evidence of hemolysis
- Refractory iron deficiency anemia
- Nonresponsive to therapy
- Thrombosis

Aplastic anemia

Myelodysplastic syndrome
With any of the following:
- Any subtype with evidence of hemolysis
- Hypoplastic
- Refractory cytopenia

Thrombosis venous or arterial
With any of the following:
- Evidence of hemolysis
- Usual and unusual sites[d]
- Any cytopenia
- Nonresponsive to anticoagulant

Coombs-negative hemolytic anemia

Hemoglobinuria or hemosiderinuria

With or without signs of: Renal dysfunction

Test for PNH with high-sensitivity flow cytometry with FLAER on peripheral blood, the gold-standard diagnostic test for PNH[5,22,44,e]

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

Frequency of cases showing PNH clone cells at diagnosis in high-risk conditions[48,f]

Hemolysis	Bone marrow failure	Unexplained thrombosis
• Coombs-negative hemolytic anemia: **18.6%** • Hemoglobinuria: **47.9%**	• Aplastic anemia: **44.9%** • Myelodysplastic syndrome: **9.8%** • Unexplained cytopenia: **8.8%**	• Thrombosis with nonhemolytic anemia and/or other cytopenias: **13.7%**

Establish a definitive diagnosis via high-sensitivity flow cytometry with FLAER on peripheral blood, the gold-standard diagnostic test for PNH[22,41-43,48]

[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.[5] [b]Unexplained persistent cytopenia in a patient in whom (minimal) diagnostic criteria for myelodysplastic syndrome are not fulfilled.[5] [c]Anemia, neutropenia, or thrombocytopenia.[50] [d]Unusual sites include hepatic veins (Budd-Chiari syndrome), other intra-abdominal veins (portal, splenic, splanchnic), cerebral sinuses, and dermal veins.[5] [e]Detects PNH cells down to a 0.01% clone size.[22] [f]A multicenter, prospective evaluation of diagnostic screening for PNH by flow cytometry in 3,938 peripheral blood samples tested in 24 laboratories in Spain (N=1,718) and a reference center in Brazil (N=2,220).[48]

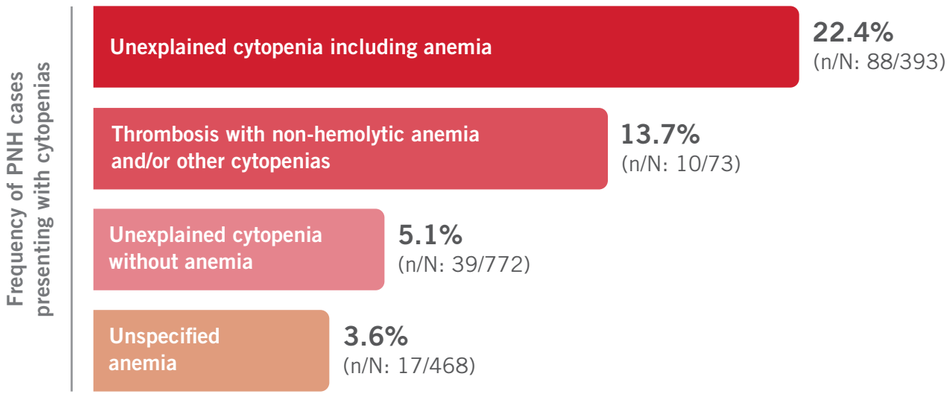
CATCH

Patients with unexplained cytopenias are at high risk for PNH[22,48]

About 1 of 11 patients with unexplained cytopenias have PNH clones[18]

- The International Clinical Cytometry Society recommends PNH testing in patients with unexplained cytopenias and hemolysis or thrombosis.[22,41,43,48]
- Cytopenias can be suggestive of numerous conditions; therefore, it is important to rule out PNH in patients with unexplained cytopenias.[5]

Patients with PNH and concomitant cytopenias[48,a]



International Clinical Cytometry Society Guidelines recommend testing patients with cytopenias and hemolysis or thrombosis, or patients with cytopenias that remain unexplained after a thorough workup[22]

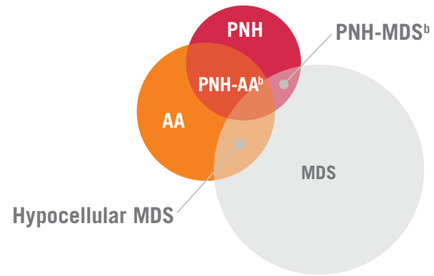
[a]A multicenter, prospective evaluation of diagnostic screening for PNH by high-sensitivity flow cytometry in 3,938 peripheral blood samples tested in 24 laboratories in Spain (N=1,718) and a reference center in Brazil (N=2,220).[48]

CATCH

Patients with PNH may have complex and diverse presentations due to concomitant bone marrow failure syndromes, such as aplastic anemia and myelodysplastic syndrome[22,48]

- International Clinical Cytometry Society Guidelines recommend regularly testing these patients for PNH with flow cytometry with FLAER performed on peripheral blood.[22,44]
- Patients with PNH and aplastic anemia are also at risk of thrombosis.[18,51]

Overlap of PNH and bone marrow failure syndromes[52,a]

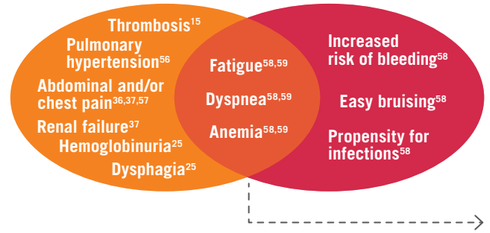


Patients with PNH may exhibit some of the same signs and symptoms as patients with other types of bone marrow failure syndromes, such as aplastic anemia[52]

[a]Overlapping circles indicate difficulties in diagnostic discrimination and shared underlying mechanisms. Circles are not drawn to scale by relative incidence of disease. The incidences of aplastic anemia, PNH, and myelodysplastic syndrome are estimated to be 2.3, 5.7, and between 53 and 131 cases/million/year, respectively.[6,52-54] [b]In a multicenter, prospective study of 3,938 peripheral blood samples submitted for diagnostic screening of PNH by high-sensitivity flow cytometry, 44.9% (243 of 541) of the patients with aplastic anemia and 9.8% (26 of 266) of the patients with low-grade myelodysplastic syndrome had a detectable PNH clone (>0.01% in ≥2 different white blood cell lineages).[48]

Although PNH and aplastic anemia may have overlapping symptoms, each condition can progress independently and the predominant clinical features can evolve over time[55]

PNH[25]
Clinical manifestations predominantly result from uncontrolled complement activation and terminal complement–mediated intravascular hemolysis



Aplastic anemia[58]
Clinical manifestations predominantly result from inadequate hematopoiesis

Patients with PNH and concomitant bone marrow failure may have decreased hemoglobin as well as a need for transfusions due to production issues[60]

- In a retrospective study,[c] the 10-year cumulative incidence of thrombosis was not significantly different between PNH and PNH + aplastic anemia (37.9% vs 27.8%, respectively; *P*=0.095).[18]

[c]A retrospective study of 460 French patients diagnosed with PNH between 1950 and 2005 that evaluated the epidemiology of classic PNH and PNH-aplastic anemia syndrome and risk factors for thrombosis.[18]

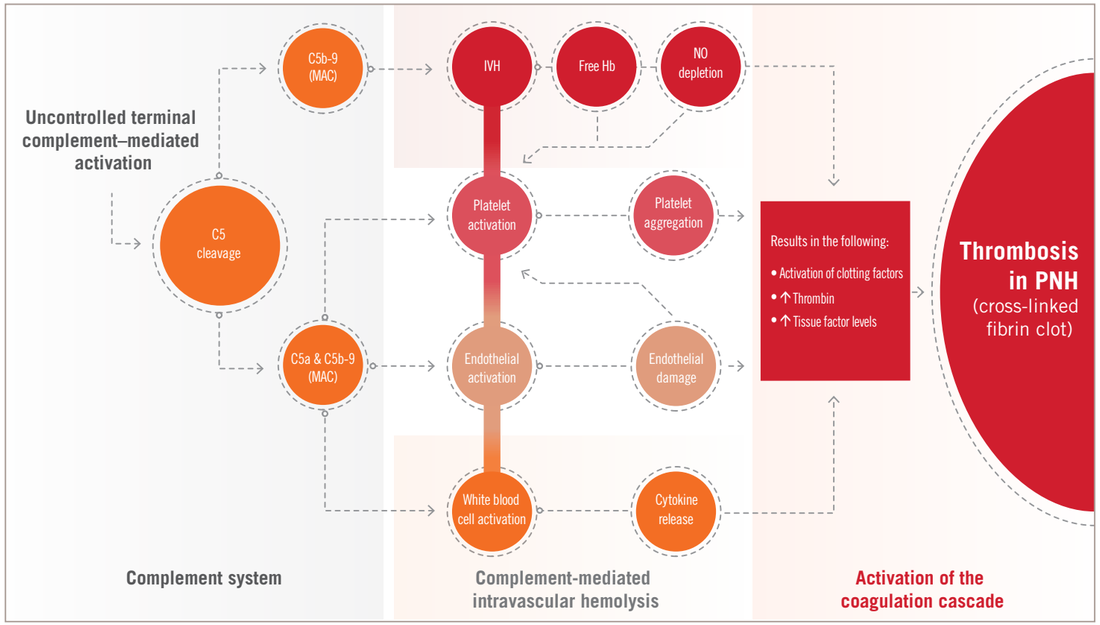
Investigate other potential causes of persistent transfusion dependence among patients with PNH, such as an underlying bone marrow dysfunction (eg, aplastic anemia or myelodysplastic syndrome)[4]

CATCH

Multiple terminal complement–mediated actions are implicated in the creation of a prothrombotic state in PNH[15,23,25]

All cell lineages are involved in terminal complement–mediated attack that independently leads to increased risk for thrombosis and combined lead to multifactorial prothrombotic events.[15,23,25]

Multifactorial prothrombotic mechanism in PNH[15]



Anticoagulation therapy does not address the underlying cause of terminal complement–mediated intravascular hemolysis and attack on platelets, white blood cells, and endothelial cells and the associated morbidities and early mortality in PNH[1,15,61]

- First thrombosis can be fatal.[37,a]
  - A nearly 14-fold higher mortality rate from thrombosis has been observed in patients with PNH compared with the general population.[37,b]
- After the first thrombotic event occurs, patients with PNH have a greater risk of recurrent thrombosis and a 5- to 10-fold increase in risk of mortality.[11,61,c,d]

International Clinical Cytometry Society Guidelines recommend testing patients with unexplained or unprovoked thrombosis or with unexplained cytopenias for PNH. The risk of thrombosis in PNH is based on terminal complement–mediated attack that leads to the multifactorial prothrombotic risk in PNH[1,22,41,48]

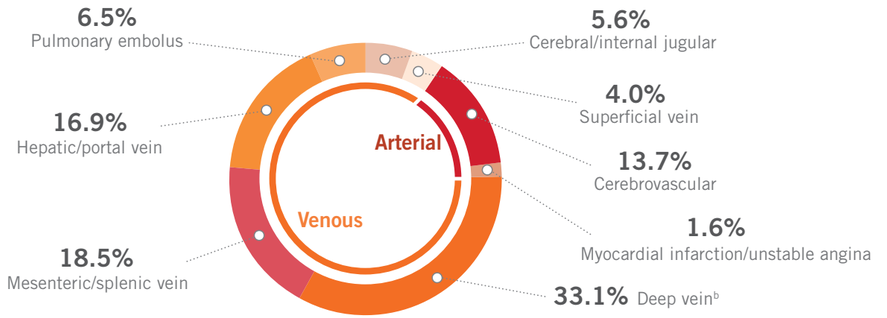
[a]Data from a retrospective chart review of 301 patients with PNH, enrolled into the South Korean PNH registry, to assess the clinical signs and symptoms predictive of mortality using standard mortality ratio compared with an age- and sex-matched general South Korean population.[37] [b](SMR, 13.92 [95% CI, 8.23-19.61]; *P*<0.001). [c]Retrospective data from a French cohort of 454 patients with PNH, diagnosed between 1950 and 1995, to evaluate long-term outcomes of PNH and to search for prognostic factors that affect survival.[62] [d]Retrospective data from 2 large cohorts of patients with PNH from Duke University (N=176) and Japanese institutions (N=209) to determine and directly compare the clinical course of disease in White and Asian populations.[11]

CATCH

Thrombosis in PNH can be life-threatening and can occur at any site[15]

- Multiple sites may be involved in more than one-fifth of cases.[15]

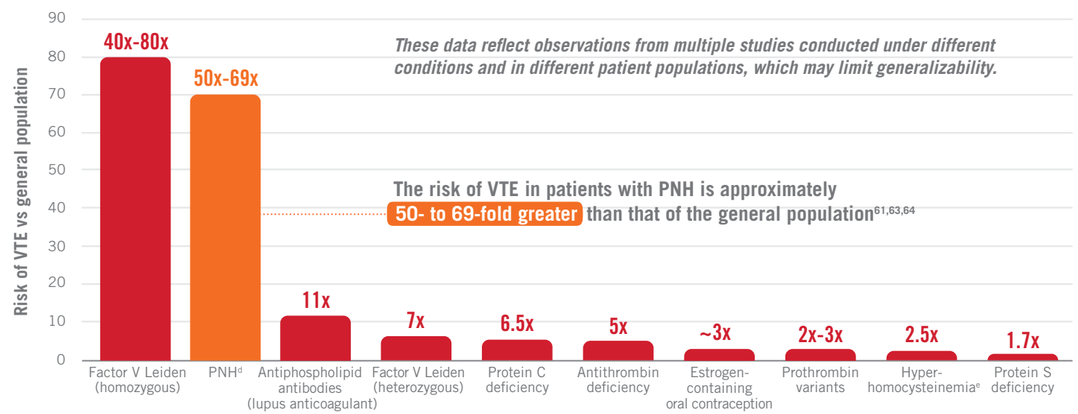
Sites of thrombosis in patients with PNH[61,a,b]



[a]Data pooled from examining the medical histories of patients with PNH (N=195) from 3 independent studies. Thrombotic events occurred in 63 patients: 1 event in 35 patients, 2 events in 15 patients, 3 events in 7 patients, and ≥5 events in 6 patients.[61] [b]Includes events in lower extremity (n=23) and other locations (n=18; including inferior vena cava, bilateral lower extremity, pelvic, ureter, axillary, subclavian, and brachiocephalic veins).[61]

- Venous thromboembolism is approximately 50x to 69x more likely in patients with PNH vs the general population.[61,63,64]

Approximated risk of developing venous thromboembolism in PNH and other inherited hypercoagulable conditions based on data from multiple studies[61,63-66,c]



Thromboembolism is the most common cause of mortality in patients with PNH and accounts for approximately 40% to 67% of PNH-related deaths of which the cause is known. Further, 29% to 44% of patients with PNH have been reported to have at least 1 thromboembolic event during the course of their disease[15]

[c]Data for hypercoagulable conditions based on observations from case control studies (with exception of antiphospholipid antibodies [lupus anticoagulant] and estrogen-containing oral contraception).[64] [d]Venous thromboembolism event rate (no. per 1,000 patient-years) is based on 105 events in 1,683.4 patient-years occurring in patients from the pretreatment periods of 3 clinical studies and a phase 3 extension study.[61] Venous thromboembolism rate in the general population based on a retrospective study using linked administrative healthcare databases to identify a cohort of Québec residents (74,297,764 person-years) with an incident event of venous thromboembolism from January 1, 2000, to December 31, 2009. The incidence rate of definite venous thrombosis (n=67,354) in this study was 0.91 (95% CI, 0.90-0.91) per 1,000 patient-years and the rate of probable venous thrombosis (n=91,761) was 1.24 (95% CI, 1.23-1.24) per 1,000 patient-years.[63] [e]Levels above the 95th percentile of the normal values as an arbitrary cutoff for mild hyperhomocysteinemia.[64]

CATCH

PNH is much more than a disease of hemolysis and anemia, having broad multisystem effects, including severe and potentially life-threatening consequences[1]

Test the following patients for PNH[5,22,44]

All patients with hemolysis but not necessarily renal dysfunction or Coombs-negative hemolytic anemia[17,41]

Signs of renal dysfunction
Proteinuria[1] ***and/or***
Hematuria[5,a] ***and/or***
Increased serum creatinine or reduced eGFR[1]

Evidence of hemolysis without obvious cause[5,b]
Elevated LDH ***and/or***
Low haptoglobin levels ***and/or***
Iron deficiency ***and/or***
Elevated bilirubin ***and/or***
Elevated reticulocytes

Perform routine PNH screening for patients with Coombs-negative hemolytic anemia, particularly if characteristic cellular abnormalities (spherocytes, sickle cells, schistocytes, etc) are not present[5,22]

- Hemolysis in PNH is due to complement-mediated attack on red blood cells.[67]
- Hemolysis with a negative Coombs test or direct antiglobulin test, based on International Clinical Cytometry Society Guidelines, warrants high-sensitivity flow cytometry with FLAER on peripheral blood to rule out PNH.[22,68]
- 18.6% (71/382) of patients with hemolytic anemia have been shown to test positive for a PNH clone.[48]
- The direct Coombs test in PNH is negative as the hemolysis of PNH is not caused by antibodies.[69]
- Patients with Coombs-negative hemolytic anemia and concomitant iron deficiency are more likely to present with a PNH clone.[22]

Patients with hemoglobinuria are at high risk for PNH[48]

- Proteinuria, hematuria, hemoglobinuria, or reduced estimated glomerular filtration rate, in conjunction with any evidence of hemolysis, should raise the index of suspicion for PNH.[25,46,57,70,71,b]
- 47.9% (35/73) of patients with hemoglobinuria have been shown to test positive for a PNH clone.[48]
- Hemoglobinuria, characterized by dark-colored urine, is a sign of terminal complement–mediated intravascular hemolysis.[41,72]

The International Clinical Cytometry Society and the International PNH Interest Group recommend testing patients with Coombs-negative hemolytic anemia and/or hemoglobinuria for PNH[22,72]

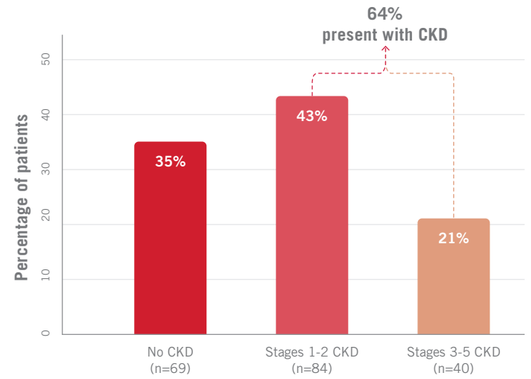
The information on this page is intended as educational information for healthcare providers. It does not replace a healthcare professional's judgment or clinical diagnosis.
[a]Failure to distinguish hemoglobinuria from hematuria is a principal cause of delay in diagnosis of PNH, often leading to an extensive urological evaluation before the distinction is made.[17,73] [b]Obvious causes of hemolysis include mechanical blood processing during surgery, infection, drug-induced hemolysis, and sickle cell disease.[17,73,74]

CATCH

Chronic terminal complement–mediated hemolysis causes progressive renal damage and early mortality in patients with PNH[1,46]

- Renal failure is the second leading cause of death in patients with PNH.[11,75]
- Evidence of renal damage has been shown in nearly all PNH patients via biopsy, imaging techniques, or postmortem examination.[46,71,76-82]

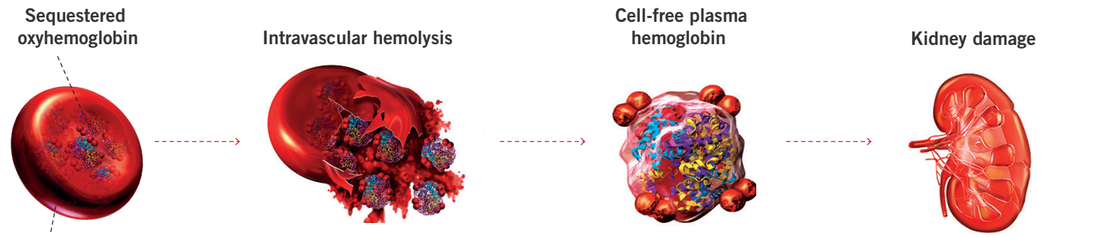
Prevalence of chronic kidney disease at screening[46,a,b]



Adapted from: Hillmen P, et al. *Am J Hematol.* 2010.

[a]A clinical study of 195 patients with PNH showing evidence of renal dysfunction or damage as evidenced by spot urinalysis with proteinuria or by abnormal imaging findings. CKD stages as defined by the Kidney Disease Outcomes Quality Initiative: Stage 1 (GFR >90 mL/min/1.73 m^2); Stage 2 (GFR 60-90 mL/min/1.73 m^2); Stage 3 (GFR 30-60 mL/min/1.73 m^2); Stage 4 (GFR 15-30 mL/min/1.73 m^2); Stage 5 (GFR <15 mL/min/1.73 m^2).[46] [b]National Kidney Foundation criteria applied at initial screening visit.

In PNH, terminal complement–mediated attack on red blood cells leads to free hemoglobin and hemosiderin deposits that contribute to chronic kidney disease in PNH[23,25,46,83]



Experts recommend evaluation of renal function to detect signs of chronic kidney disease, which was observed in 64% of patients with PNH[46]

Comprehensive and routine clinical assessment is critical in identifying patients with PNH at risk of morbidities and early mortality[39,41,43,84]

Has your patient presented with any of the following laboratory values or symptoms?[a]

Evidence of elevated hemolysis[43,85]

- **LDH ≥1.5x ULN** (range of normal=105-333 IU/L)[86] _____ IU/L
- **Elevated reticulocyte count** (>1.5%)[87] _____ %
- **Low hemoglobin levels** (female: <12.1 g/dL; male: <13.8 g/dL)[88] _____ g/dL
- **Low haptoglobin levels**[b] (<41 mg/dL)[89] _____ mg/dL
- **Elevated bilirubin** (direct: >0.3 mg/dL; total: >1.2 mg/dL)[90] _____ mg/dL
- **Hemoglobinuria** Yes ☐ No ☐

Signs of impaired renal function[43,46]

- **Low eGFR** (<90 mL/min/1.73 m^2)[91] _____ mL/min/1.73 m^2
- **Elevated serum creatinine** (female: >1.1 mg/dL; male: >1.3 mg/dL)[92] _____ mg/dL

Signs and symptoms of thrombosis[15,43,84]

- **Elevated D-dimers** (>250 ng/mL)[93] _____ ng/mL
- **Low platelet count** (<150 x 10^9/L)[94] _____ x 10^9/L
- **Abdominal pain** Yes ☐ No ☐
- **Chest pain** Yes ☐ No ☐
- **Dyspnea** Yes ☐ No ☐
- **Dysphagia** Yes ☐ No ☐
- **Neurological symptoms** Yes ☐ No ☐

Quality of life factors[43,84]

- **Fatigue** Yes ☐ No ☐
- **Pain** Yes ☐ No ☐

Other evidence of disease progression[22,56]

- **Increasing clone size** Yes ☐ No ☐
- **Elevated NT-proBNP** (normal ranges vary with both gender and age) _____ pg/mL
- **History of thromboembolism** Yes ☐ No ☐

[a]Normal laboratory values may vary slightly among different laboratories and also among individuals. Elevated values for this chart were defined by the upper limit, and low levels by the lower limit, of normal ranges identified by either MedlinePlus, Medscape, or the Mayo Foundation. [b]Low haptoglobin is indicative of excess plasma hemoglobin released from hemolyzed red blood cells.[95]

Abbreviations: AA=aplastic anemia; **ANC**=absolute neutrophil count; **CI**=confidence interval; **CKD**=chronic kidney disease; **eGFR**=estimated glomerular filtration rate; **FLAER**=fluorescent aerolysin; **GPI**=glycosylphosphatidylinositol; **Hb**=hemoglobin; **HSC**=hematopoietic stem cell; **IVH**=intravascular hemolysis; **LDH**=lactate dehydrogenase; **MAC**=membrane attack complex; **MDS**=myelodysplastic syndrome; **NO**=nitric oxide; **NT-proBNP**=N-terminal prohormone brain natriuretic peptide; **OR**=odds ratio; ***PIG-A***=phosphatidylinositol glycan complementation class A; **PNH**=paroxysmal nocturnal hemoglobinuria; **RBC**=red blood cell; **ULN**=upper limit of normal; **VTE**=venous thromboembolism.

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Notes

Notes

Rapid recognition of the signs and symptoms of PNH and early diagnosis are important to patient management[22,40]

International Clinical Cytometry Society Guidelines and multiple experts have identified groups of patients at risk for PNH[5,22,40-42]

Core signs and symptoms of PNH (any of the following)[5,22,41,43,46]

- **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[5,22,41,43,46,47]

- **Bone marrow dysfunction**
- **Unprovoked[a] and unexplained thrombosis**
- **Hemolysis** Any of: ↑LDH ↓haptoglobin ↑reticulocyte count ↑bilirubin

C A T C H

- **Unexplained cytopenia[b]**
  - With any of the following:
    - Any subtype[c] with evidence of hemolysis
    - Refractory iron deficiency anemia
    - Nonresponsive to therapy
    - Thrombosis
- **Aplastic anemia**
- **Myelodysplastic syndrome**
  - With any of the following:
    - Any subtype with evidence of hemolysis
    - Hypoplastic
    - Refractory cytopenia
- **Thrombosis venous or arterial**
  - With any of the following:
    - Evidence of hemolysis
    - Usual and unusual sites[d]
    - Any cytopenia
    - Nonresponsive to anticoagulant
- **Coombs-negative hemolytic anemia**
- **Hemoglobinuria or hemosiderinuria**
- With or without signs of: Renal dysfunction

Test for PNH with high-sensitivity flow cytometry with FLAER on peripheral blood, the gold-standard diagnostic test for PNH[5,22,44,e]

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

[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.[5] [b]Unexplained persistent cytopenia in a patient in whom (minimal) diagnostic criteria for myelodysplastic syndrome are not fulfilled.[6] [c]Anemia, neutropenia, or thrombocytopenia.[50] [d]Unusual sites include hepatic veins (Budd-Chiari syndrome), other intra-abdominal veins (portal, splenic, splanchnic), cerebral sinuses, and dermal veins.[5] [e]Detects PNH cells down to a 0.01% clone size.[22]

- PNH is a chronic, devastating, and potentially life-threatening disease characterized by terminal complement–mediated attack on red blood cells, white blood cells, and platelets that can lead to the severe consequences of thrombosis, organ damage, and early mortality.[1]
- Terminal complement–mediated intravascular hemolysis, the clinical hallmark of patients with PNH, causes a wide range of unpredictable and potentially life-threatening complications.[13,18,25,37,38]
- Up to 35% of PNH patients die within 6 years despite historical supportive care. So early diagnosis is crucial.[2,3,11]
- Thrombotic events in PNH are caused by uncontrolled terminal complement activation leading to intravascular hemolysis, white blood cell activation, platelet activation, and aggregation.[25,46]
- LDH is an important clinical biomarker for terminal complement–mediated intravascular hemolysis and an important measure of PNH disease activity.[36]
- Establish a definitive diagnosis via high-sensitivity flow cytometry with FLAER performed on peripheral blood, the gold-standard diagnostic test for PNH.[22]

ALEXION® AstraZeneca Rare Disease