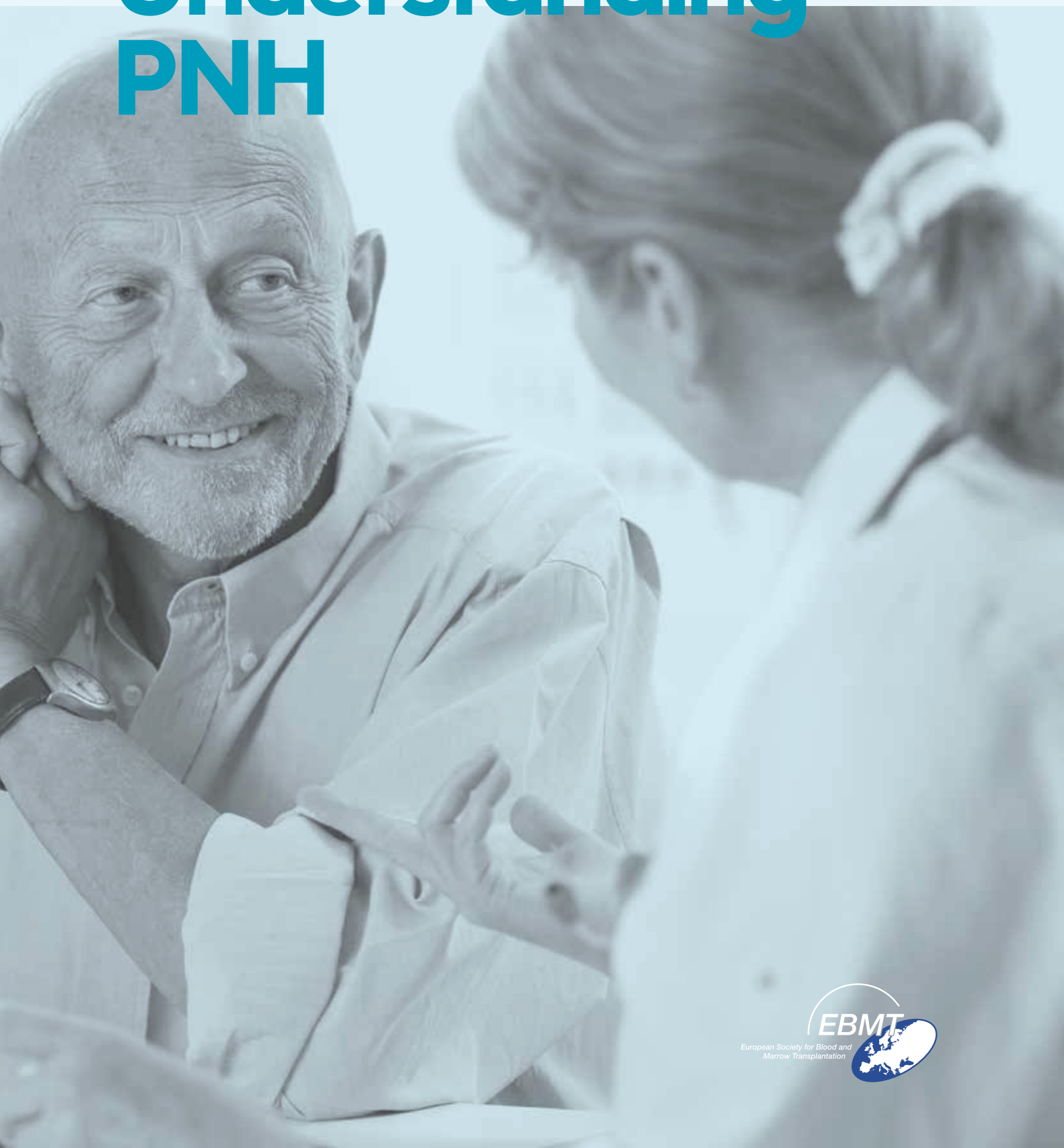
PNH

A practical guide for nurses and allied healthcare professionals

Understanding PNH



EBMT
European Society for Blood and Marrow Transplantation

The Nurses Group of the European Society for Blood and Marrow Transplantation (EBMT NG) gratefully acknowledges the following individuals for their critical review and contributions to this brochure:

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Contributors would like to extend a special thanks to Lars Ritzal, Germany, for his invaluable input to this brochure from the perspective of a patient with PNH.

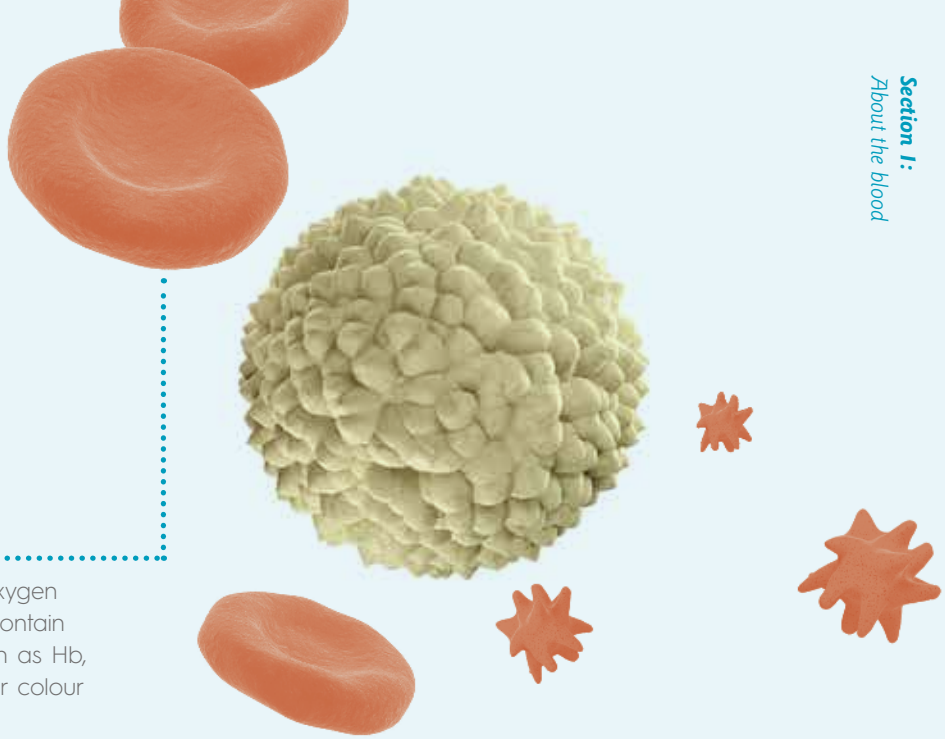
The aim of this brochure is to provide an overview of the causes, signs and symptoms, diagnosis and management of patients with paroxysmal nocturnal haemoglobinuria (PNH). The key role of nurses in the care of PNH patients is discussed and topics relating to the practical side of nursing care are addressed.

Terms that have been underlined are defined in the Glossary at the end of the brochure.

About the blood

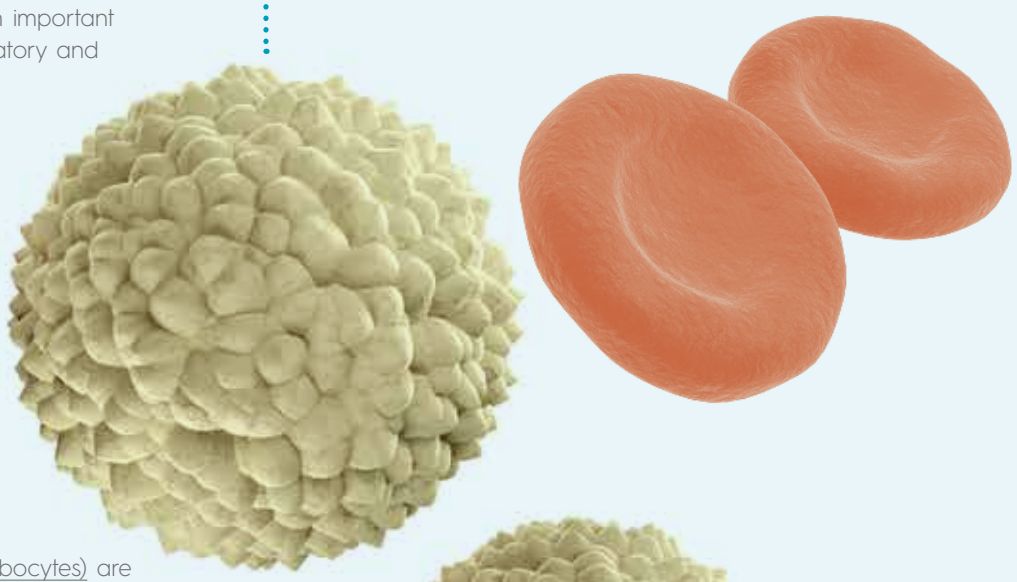
Blood is constantly circulated around the body by the pumping action of the heart, delivering nutrients to cells and removing waste. Approximately 50% of blood is plasma and the remaining 50% is made up of cells.[1]

Blood cells are produced in the bone marrow and fall into three types: red blood cells, white blood cells and platelets.[1]

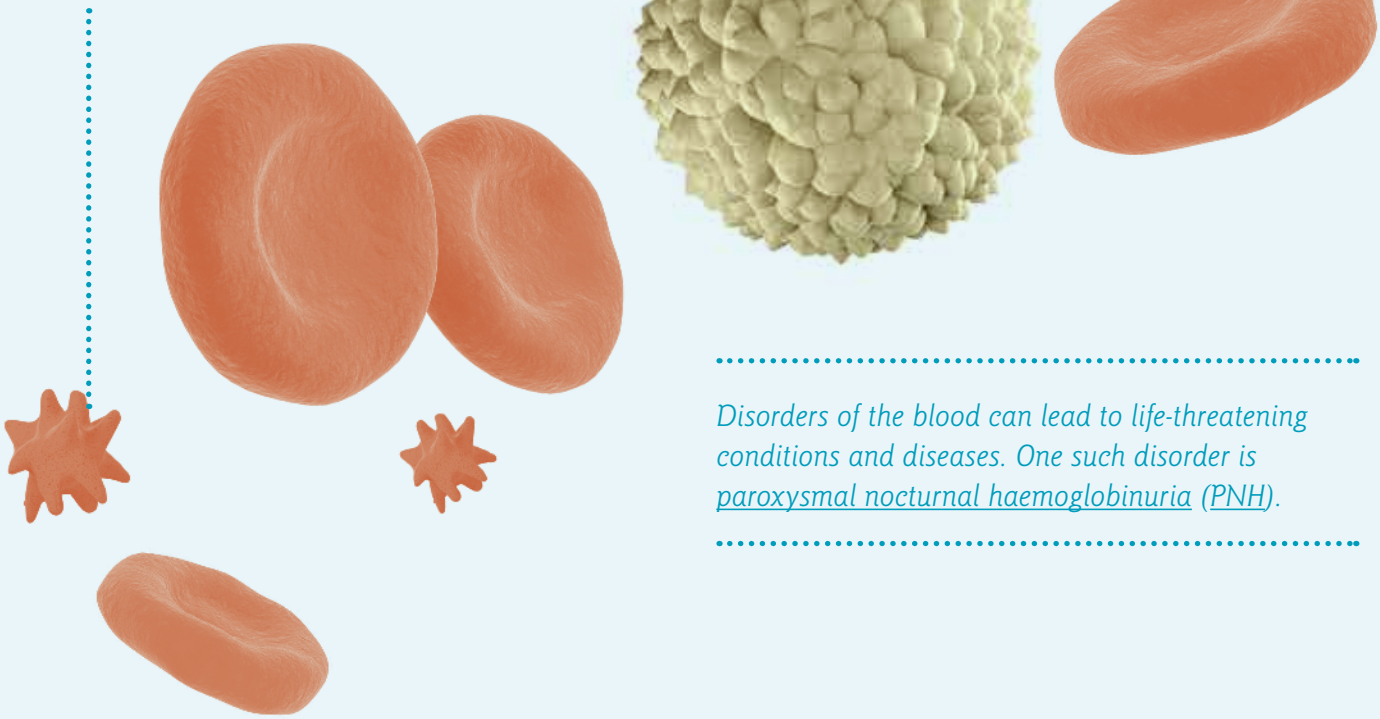


Red blood cells (erythrocytes) circulate oxygen around the body. They contain haemoglobin, also known as Hb, which gives red cells their colour

White blood cells (leukocytes) play an important role in the inflammatory and immune responses



Platelets (thrombocytes) are involved in the initial stages of thrombosis and stop bleeding



Disorders of the blood can lead to life-threatening conditions and diseases. One such disorder is paroxysmal nocturnal haemoglobinuria (PNH).

What is PNH?

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare chronic disease, which can have acute manifestations. It is a blood disorder in which chronic, uncontrolled activation of the complement system against red blood cells, white blood cells and platelets leads to a massively increased risk of thrombosis, which if untreated results in a significant increase in morbidity and mortality.[1-3] Part of this increase in thrombotic risk is due to red blood cell haemolysis and the toxic effects of free haemoglobin in circulation.[3]

PNH is a rare haemolytic blood disease. An absence of protective protein shields on the surface of the blood cells leaves them vulnerable to destruction by a part of the immune system called the complement system. The complement system can destroy the red blood cells leading to a chronic or acute loss of haemoglobin.[3-5] There is a great increase in thrombotic risk associated with this haemolytic process which can be potentially fatal.[3,4]

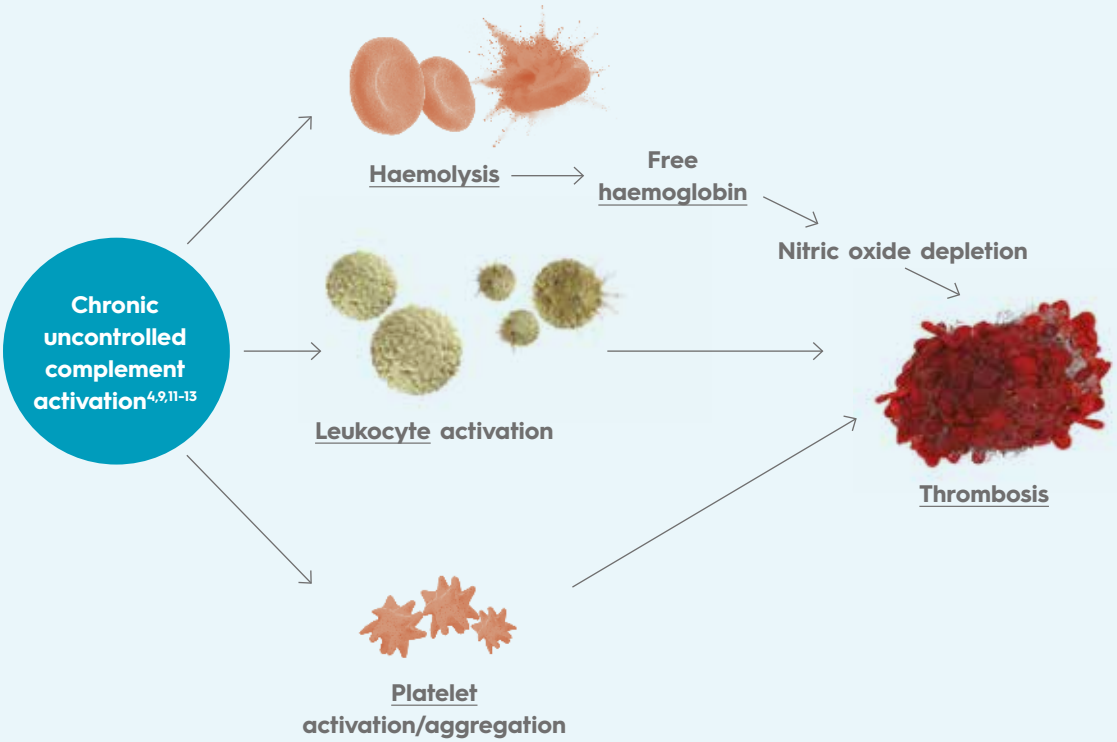
Some causes of PNH are well understood and some are still under examination. PNH often occurs in the setting of bone marrow failure (BMF) syndromes such as aplastic anaemia (AA) and myelodysplastic syndrome (MDS). However, this is not always the case and patients may have PNH in isolation also known as 'classical PNH'.[6]

Pathophysiology of PNH

The complement system is a part of the body's immune system that consists of a group of approximately 25 proteins that work together to help antibodies to destroy bacteria, viruses and abnormal cells.[7] In normal blood cell lines, the action of the complement system is controlled by complement system regulatory proteins bound to the surfaces of cells by a glycolipid anchor called glycosylphosphatidylinositol (GPI).[1,3,8]

GPI is produced by the PIG-A enzyme. Patients with PNH have a mutation in the PIG-A enzyme gene. This causes affected red blood cells to be GPI anchor deficient, and leads to the deficiency of two key complement system regulatory proteins, CD55 and CD59.[9] In the absence of these regulatory proteins, the complement system becomes activated and forms a membrane attack complex. This membrane attack complex initiates the destructive process of haemolysis and activates other components of the blood such as leukocytes and platelets leading to an elevated risk of thrombosis.[4,5,10] It is important to note that the production of the complement system is upscaled during infective episodes, which can exacerbate PNH symptoms and lead to more acute presentation.[3]

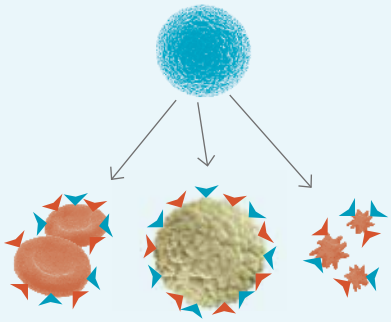
In some patients with PNH the bone marrow, which is responsible for producing healthy blood cells, does not function properly. Currently, the causes of BMF underlying PNH are poorly understood.[6]



Types of PNH cell

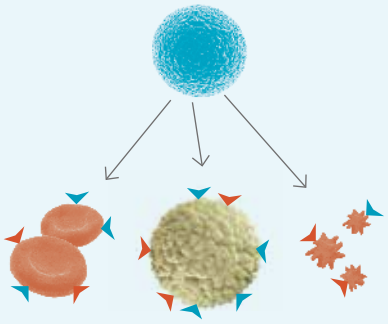
The blood cells of people with PNH are divided into three types:[14]

Normal (type I) stem cell



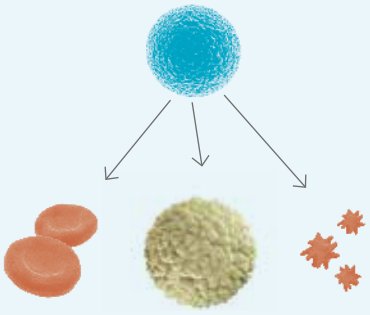
PNH I cells (also known as type I cells) are normal blood cells that have GPI anchors on their surface with complement system regulatory proteins (CD55 and CD59) attached.

PNH (type II) stem cell



PNH II cells (also known as type II cells) are missing some GPI anchors from their surface and therefore have a deficiency in CD55 and CD59 complement system regulatory proteins. This makes affected red blood cells more sensitive to destruction by the complement system and results in affected leukocytes and platelets being activated by the complement system.

PNH (type III) stem cell



PNH III cells (also known as type III cells) have no GPI anchors and hence no CD55 and CD59 complement system regulatory proteins on their surface. Affected red blood cells are more sensitive to destruction by the complement system, while affected leukocytes and platelets are activated by the complement system.

What are PNH clone cells and what does PNH clone size mean?

Blood cells that have been affected by PNH, e.g. PNH II and PNH III cells, are known as PNH clone cells. These cells are lacking GPI anchors and hence protective complement system regulatory proteins (CD55 and CD59) on their surface.[15]

The PNH clone size refers to the proportion of PNH-affected cells versus normal cells within the total cell population. For example, a patient who has complement system regulatory proteins on 40% of their cells and no complement system regulatory proteins on the remaining 60% of their cells has a PNH clone size of 60%.

PNH clone size can vary enormously, with some patients having very few PNH clone cells and others having almost all PNH clone cells. Furthermore, the PNH clone size can change over time and should be checked regularly as it can help give an understanding about the disease.[15] The granulocyte count is the most reliable result due to the longer life of the cell and the fact that red blood cells can be transfused.[15]

Who is affected by PNH?

PNH is a very rare acquired genetic disease (rather than an inherited disorder). The most reliable data on the incidence and prevalence of PNH is from work undertaken in Yorkshire, England. In this study, the prevalence of patients with PNH clone cells of any size is 15.9 per million and the incidence is 1.3 per million of the total population.[16] PNH cannot be passed down to children from their parents.[7] Men and women are equally affected by PNH and, although it occurs in all age groups (including children), it is mostly diagnosed in early- to mid-30s. PNH is associated with a variety of signs and symptoms that may appear unrelated to each other or common to those of other diseases, so it is not unusual for months or years to pass before the correct diagnosis is made.[17]

What is the prognosis for patients with PNH?

Haemolysis and the elevated risk of thrombosis (associated with haemolysis and the activation of platelets and leukocytes) are the central mechanisms underlying the morbidities and mortality associated with PNH.[3,9,18] However, with new medical advances, patients with PNH may now survive for decades, having a normal life expectancy and experiencing only minor symptoms.[19,20]

PNH signs and symptoms

PNH is a very serious disease that can cause many health problems and may have life-threatening consequences such as thrombosis,[1] however it can often go undiagnosed for years because it presents differently in each patient, and it has a variety of symptoms often associated with other conditions.[2]

Although there are some symptoms of PNH that patients can easily see or feel, such as abdominal pain, fatigue or dark-coloured urine, there are also signs that may go unnoticed. These signs and symptoms can all be linked with haemolysis and the elevated risk of thrombosis observed in patients with PNH.[3] Early detection of the disorder is vital to ensure that patients have the best opportunity to improve their outcomes.[1]

41%
Dysphagia

47%
Pulmonary hypertension

66%
Dyspnoea

64%
Chronic kidney disease (CKD)

57%
Abdominal pain

26%
Haemoglobinuria

47%
Erectile dysfunction

88%
Anaemia

96%
Fatigue, impaired quality of life

40%
Thrombosis

Frequency of a range of PNH signs and symptoms at presentation. Adapted from Dacie, 1972;[4] Hillmen, 1995;[5] Hillmen, 2010;[6] Hill, 2010;[7] Meyers, 2007;[8] Nishimura, 2004.[9]

Thrombosis

Thrombosis is the term used to describe the clotting of blood and normally takes place when vessels are damaged by trauma in order to stop blood loss and to begin the repair process.[10]

Abnormal thrombosis can occur in both venous and arterial vessels and can have devastating consequences on the patient. On the venous side, abnormal thrombosis most commonly occurs in the deep veins of the legs and pelvis (deep vein thrombosis or DVT) and this is also the case in PNH. Pieces of thrombi formed in the deep veins of the legs and pelvis can break off and travel in the bloodstream (thromboembolism) to the lungs (causing a pulmonary embolism), which can result in significant morbidity or sudden death.[10] PNH can also cause thrombosis in unusual veins such as the hepatic veins draining the liver (Budd-Chiari syndrome) and the superior sagittal sinus. Thromboembolism is the leading cause of death in people with PNH.[11]

Thrombosis can also occur in arteries and is most serious when affecting arteries in the heart (causing a heart attack or myocardial infarction) and the brain (causing a stroke).[12] About 15% of the thrombotic events (TEs) occurring in PNH occur in the arterial system.[13]

Haemolysis

Haemolysis is the destruction of red blood cells. In PNH, this occurs when the complement system attacks the PNH red blood cells (PNH II and III clone cells) and the cells burst.[14,15] The haemoglobin that is released during haemolysis directly causes some of the signs and symptoms that may be associated with PNH. However, the most important consequence of chronic haemolysis is that it is one of the factors contributing to the increased risk of major TEs in PNH patients.[5,9,15,16]

Haemolysis is best monitored by lactate dehydrogenase (LDH) rather than haemoglobin alone, and it is recommended to conduct this test whenever assessing the bloods of a PNH patient.[14,15]

Anaemia

Anaemia is a condition in which the blood is deficient in red blood cells, haemoglobin or in total volume. One of the characteristics of PNH is haemolytic anaemia. This is anaemia that occurs because of haemolysis. Poor bone marrow function can also contribute by not producing the normal amount of red blood cells and by not having the capacity to replace the cells that are lost through haemolysis.[9] Anaemia therefore may occur in varying degrees from person to person. Anaemia can affect the amount of oxygen that is delivered throughout the body. People with anaemia may experience fatigue, shortness of breath upon exertion, pallor, palpitations, dizziness and fainting.[17]

Fatigue

In severe haemolysis, the destruction of red blood cells causes a quicker release of free haemoglobin and may cause excessive tiredness. Fatigue is a symptom of anaemia, but in PNH the tiredness experienced by a person can far outweigh that which would be expected in people with other types of anaemia and isn't necessarily improved by transfusions or improving the anaemia. This tiredness can be debilitating, and people with PNH may often have to change their lives and activities because of tiredness. Haemoglobin levels may not always reflect the levels of fatigue or impaired quality of life experienced by a person with PNH. Sometimes excessive tiredness may be misdiagnosed as depression.[18]

Pulmonary hypertension (PHT) and dyspnoea

Approximately half of people with PNH have evidence of pulmonary hypertension (PHT).[7,19] This is a condition in which the blood pressure of the pulmonary arteries is abnormally high. As PHT affects the lungs, shortness of breath and difficulty in breathing (dyspnoea) are common symptoms of this condition, which can also put extra strain on the heart. As well as affecting breathing and quality of life, PHT is associated with an increased risk of other serious health problems, such as TEs, and may be a very serious condition if left unaddressed.[19]

Arterial hypertension (AHT)

Arterial hypertension (meaning high blood pressure) is a medical condition in which the blood pressure in the arteries is elevated. Some patients report headaches, light-headedness, vertigo, tinnitus or altered vision. Usually hypertension does not cause symptoms initially, but sustained hypertension over time is a major risk factor for hypertensive heart disease, coronary artery disease, stroke, aortic aneurysm, peripheral artery disease and chronic kidney disease.[20]

Jaundice

Bilirubin is a yellow bile pigment released from the breakdown of red blood cells and the degradation of haemoglobin. Elevated levels of bilirubin can cause yellow discolouration of the eyes or skin known as jaundice, and this can occur in PNH as a result of excessive haemolysis.[21] Jaundice may also be accompanied by itchy skin.

Gallstones

Gallstones are hardened deposits of bile component that can form in the gall bladder. Gallstones can form if there are unusually high levels of bilirubin (a bi-product of the breakdown of haemoglobin) being excreted in the bile. They can cause a variety of medical problems such as cholecystitis (an inflammation of the gall bladder), biliary colic (pain due to obstruction of the bile duct) and, most seriously, pancreatitis (an inflamed pancreas due to blockage of the bile duct). Patients with PNH may also develop gall bladder 'sludge', which can lead to similar symptoms to gallstones. Removal of the gall bladder may be recommended to alleviate symptoms of gallstones and gall bladder 'sludge'.[22]

Abdominal pain and difficulty swallowing

Free haemoglobin released during haemolysis can bind with nitric oxide. A lack of nitric oxide can cause spasms in certain smooth muscle, such as the abdomen and the oesophagus, which may cause PNH patients to suffer episodic or ongoing pain in the stomach and abdominal region, as well as difficulty and pain on swallowing (dysphagia). This pain can be mild or very severe and may require treatment. The pain is often diffuse and can last several hours at a time. It is often unrelieved by analgesia, positioning or bowel movement. Pain can also occur in the lower back and cause headaches.[23]

Renal dysfunction and chronic kidney disease

One of the recognised complications of PNH is decreased kidney function, and a significant proportion of people with PNH have chronic kidney disease.[6] Chronic haemolysis is thought to be a root cause of kidney scarring, which in turn can impair kidney function and affect the ability of the kidneys to filter waste products from the blood. Over time, this process results in kidney failure, one of the leading causes of death in PNH.[6,9,24]

Erectile dysfunction

Men with PNH may experience problems getting and/or maintaining erections. This occurs because the free haemoglobin released into the blood during haemolysis binds to nitric oxide, reducing the levels of nitric oxide in the bloodstream. Nitric oxide is responsible for smooth muscle relaxation and is required for a man to get an erection.

Budd-Chiari syndrome

This is an extremely rare condition where the majority of patients present with abdominal pain, ascites, distension and hepatomegaly to varying degrees and intensities. Renal impairment and occasionally jaundice may also be seen. Some patients may however be asymptomatic and many centres regularly perform surveillance ultrasounds of patients' liver and hepatic veins and arteries to monitor for undetected thrombi. Further investigations are necessary to obtain a diagnosis such as blood tests and radiological imaging (including ultrasound scans, CT scans or MRI scans). Medical and in some cases surgical intervention may be indicated such as angioplasty or placement of a stent or shunt. Such procedures require patient preparation both physically and psychologically. The patient should be referred to a specialist liver team.[14,23,25]

Increased PNH disease activity

In patients with PNH, as the level of complement system activity affecting the blood cells increases, the disease activity increases and the risk of serious complications rises. The level of disease activity (and therefore risk) cannot be assumed from the level of anaemia or from the clone size. A better measure of disease activity is to combine an assessment of the amount of haemolysis taking place (measured by the LDH level in the blood) with the presence of one or more symptoms of the disease.[26,27]

The presence of one or more of the symptoms listed below in conjunction with an LDH level ≥1.5 times the upper limit of normal) indicates high disease activity.[28]

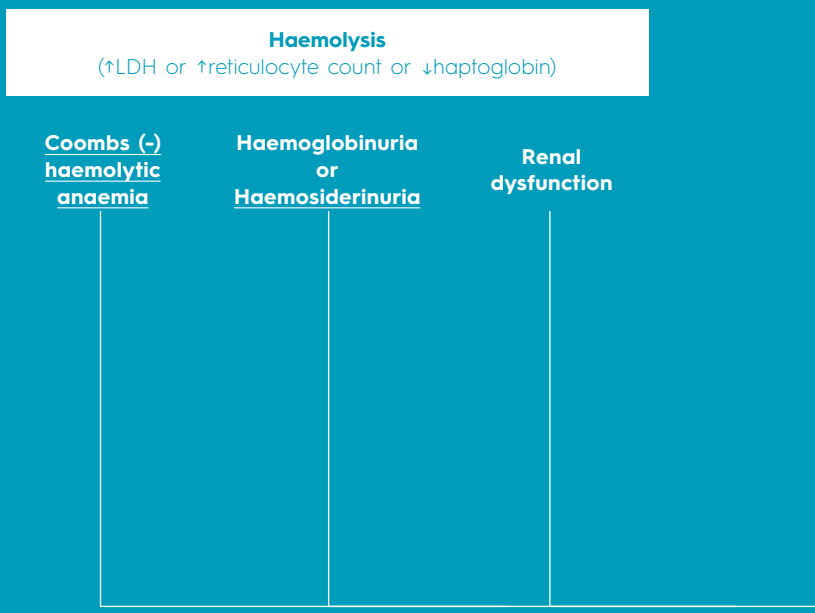
- Fatigue
- Haemoglobinuria
- Abdominal pain
- Dyspnoea
- Anaemia (haemoglobin <100 g/L)
- Major vascular event (including thrombosis)
- Dysphagia
- Erectile dysfunction

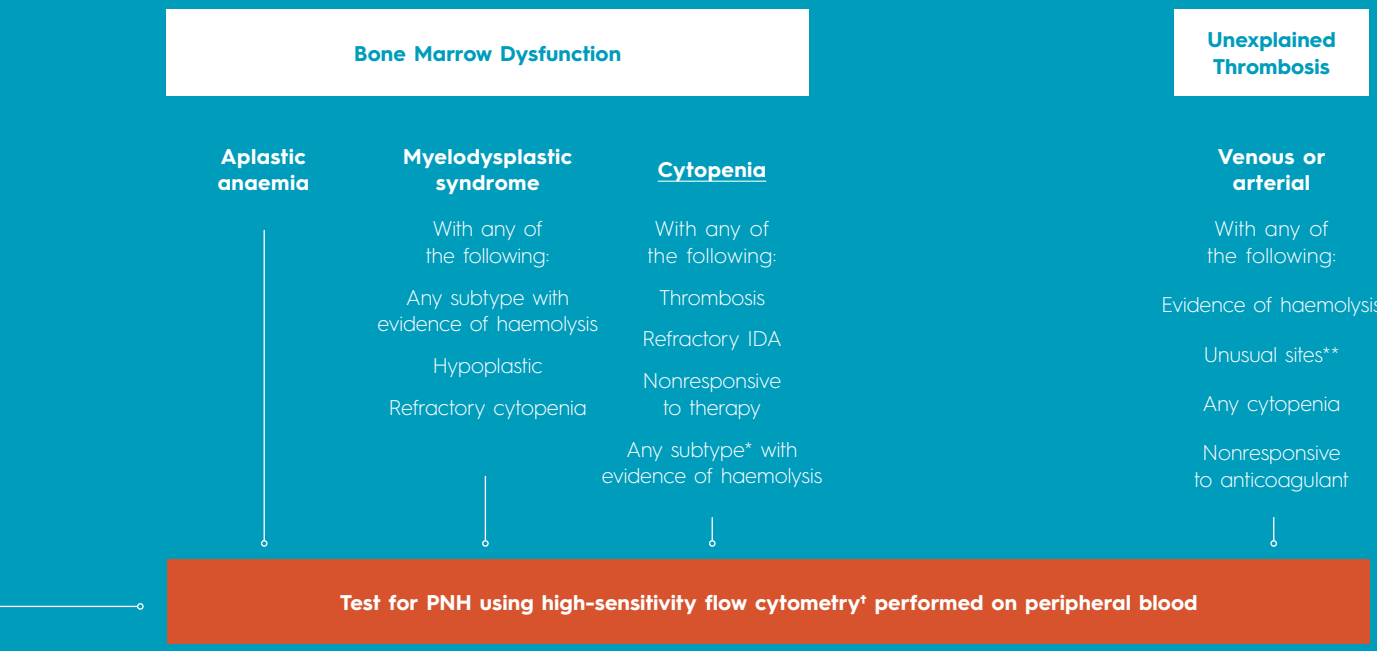
Assessment and diagnosis

Who should be tested for PNH?

Early diagnosis is essential for improved patient management and prognosis. In high-risk populations of patients with unexplained thrombosis, haemolysis and BMF, the high prevalence of positive PNH clone cells supports screening these patients for PNH.[1]

Certain groups are at higher risk of having PNH clones, and should be identified early[2-10]





High sensitivity flow cytometry (HSFC) of GPI-linked proteins: International Clinical Cytometry Society (ICCS) recommendations

The gold standard diagnostic test for PNH is routine or high-sensitivity flow cytometry (HSFC) performed on the peripheral blood. Flow cytometry tests are non-invasive and count the number of cells affected by PNH (the clone size) for each type of blood cell.[2]

PNH red blood cells are identified by looking at the proportion of GPI-anchored complement system regulatory CD59 proteins on the cell surface. Type II PNH red blood cells have a partial CD59 protein deficiency on their surface while type III cells have a complete CD59 deficiency. PNH white blood cells (monocytes and granulocytes) are identified by quantifying the presence of GPI on the cell surface using fluorescent Aerolysin (FLAER), a reagent that binds specifically to the GPI anchor or a GPI-linked marker such as CD24 or CD14.[2]

Consideration of red blood cells alone is not adequate for the evaluation of PNH patients as haemolysis and the dilution effects of transfusions may underestimate clone size. White blood cells give the most accurate estimate of PNH clone size. A low red blood cell clone size compared to white blood cell clone size is indicative of intravascular haemolysis.[3,11]

IDA = Iron deficiency anaemia. *Anaemia, neutropenia, thrombocytopenia or pancytopenia. **Unusual sites include hepatic virus (Budd-Chiari syndrome), other intra-abdominal veins (portal, splenic, splanchnic), cerebral sinuses and dermal veins. †Detects PNH cells down to 0.01% clone size.

Flow cytometry for PNH testing

Flow cytometry is the gold standard for PNH testing: rapid, accurate and highly reliable[2-4,12,13]

1

Prepare your sample

Specimen source	Peripheral blood (not bone marrow)
Sample volume	1 – 3 mL
Maximum sample age	Within 48 hrs of collection
Sample storage	4°C after 24 hrs
Anticoagulant	EDTA, heparin or anticoagulant citrate dextrose (ACD)
Cell lineages	White blood cell test most accurately reflects PNH clone size

2

Request a clear reporting

- **It is essential for appropriate clinical decisions**
- **When ordering a PNH flow cytometry, request:**
  - Clear terminology: 'Negative result' vs 'Negative PNH cells'
  - Clone size for each cell lineage tested and proportion of type II and III PNH clones
  - Sensitivity level used
  - Previous flow results in order to monitor clonal expansion

3

Monitor your PNH patients

- **Clone size increased in 40% (10/25) of patients with PNH clone size between 0.11% and 10%**
- **International PNH Interest Group (IPIG) recommends routine monitoring every 6 to 12 months of patients who have an identified clone**
- **International Clinical Cytometry Society guidelines, consensus guidelines and the IPIG recommend continued monitoring of patients at higher risk for PNH**

Bone marrow biopsy and aspiration

Some patients with PNH will have their bone marrow studied to get a full understanding of how well the bone marrow is functioning because PNH is often found in the presence of an underlying bone marrow disorder, such as AA, MDS, or myelofibrosis.[3] A biopsy is a sample of the solid bone marrow tissue, whereas aspiration is the process of taking a sample of the liquid part of the bone marrow, normally from the hip bone.

Laboratory testing

Although signs and symptoms tell part of the patient's PNH story, they do not always convey what is happening inside the body.

That is why laboratory test results are important to reveal the full picture; even patients with low levels of PNH-affected cells (small clone sizes) can experience severe PNH-related health problems.[14] In addition, a patient's clone size may change over time, so patients must receive continuous monitoring.[2,15]

Blood tests that can be used to aid in the diagnosis and management of PNH include:*

Test	Description
LDH level	LDH is an enzyme found in various tissues that is abundant in red blood cells. In PNH when red blood cells are destroyed, LDH is released into the bloodstream. Therefore, the level of LDH in a person with PNH can indicate the amount of haemolysis that is occurring. An LDH level ≥1.5 times the upper limit of normal (normal range = 105–333 IU/L) indicates an elevated level of haemolysis.
Reticulocyte count	This test measures how fast red blood cells made by the bone marrow (reticulocytes) are released into the blood. The reticulocyte count rises when red blood cells are destroyed prematurely, for example during haemolysis. A reticulocyte level >1.5% indicates elevated haemolysis, or additional bone marrow dysfunction.
Haemoglobin level	Patients with PNH often, or in many cases, have a low haemoglobin level (<12.1 g/dL in females and <13.8 g/dL in males).
Haptoglobin levels	Haptoglobin is a protein that binds to haemoglobin. Haptoglobin levels <41 mg/dL provide evidence of elevated intravascular haemolysis in patients with PNH.
Tests of kidney function	As PNH can cause kidney problems, people with PNH should have their kidney function measured by blood tests. A low estimated glomerular filtration rate (<90 mL/min/1.73m^2) and elevated levels of serum creatinine (>1.1 mg/dL in females and >1.3 mg/dL in males) are indicators of impaired renal function. This is especially true during haemolytic crisis due to the risk of acute renal failure.
Bilirubin level	Bilirubin is a waste product of the breakdown of red blood cells. Levels of bilirubin can be elevated in PNH due to increased haemolysis. Direct and total levels of bilirubin that indicate elevated haemolysis are >0.3 mg/dL and >1.9 mg/dL, respectively.
Serum ferritin test	Ferritin is a protein that stores iron within cells. In PNH, due to the destruction of red blood cells, the levels of ferritin can be higher than normal. In patients with haemolytic PNH without complement inhibition and without an accompanying bone marrow failure syndromes, patients usually present with low iron levels. If there is a shift to extravascular haemolysis or additional bone marrow failure syndromes, an iron overload can occur.
Low platelet count	In PNH, activation of the complement system results in platelet activation which in turn leads to platelet aggregation and possibly thrombosis.[16] Therefore, in patients with PNH, platelet levels are lower than normal (<150 x 10^9/L).
NT-proBNP level	N-terminal pro-brain natriuretic peptide (NT-proBNP) is a marker of pulmonary vascular resistance and right ventricular function, both of which are indicators for PHT. Almost half of patients with PNH have elevated levels of NT-proBNP.[17]
D-dimer level	A D-dimer is a protein fragment produced during the degradation of a thrombus. Elevated D-dimer levels (>250 ng/mL) are a sign of thrombosis.
Folate and vitamin B12	Measuring levels of folate and vitamin B12 can help to diagnose anaemia. Folate levels <4.5 nmol/L and vitamin B12 levels <200 pg/mL are indicative of anaemia.

*Values for this chart were defined by the upper or lower limits of normal, as assessed by either MedlinePlus, Medscape, or the Mayo Foundation.

Monitoring

There is no single sign, symptom, or lab result that defines PNH. At times, patients may feel better, but the lab results may not show any improvement, or vice versa. This is why it is important to monitor signs and symptoms, as well as lab results closely and track them over time.

Data shows that in PNH-positive patients with small PNH clones, monitoring is essential because clone size can rapidly increase over a period of several months.[13]

Due to the life-threatening and progressive nature of PNH, these high-risk patients should be tested and continually monitored with the highest quality diagnostic test as recommended by international guidelines: high-sensitivity flow cytometry, performed on peripheral blood (not bone marrow).[2,3]

It is useful to ask patients to keep a record of their symptoms and bring it to their appointments. A patient diary and symptom tracker exists as a separate resource for you to give to your patients.

Management options and treatment of PNH

There are several management and treatment options available to help people to cope with the symptoms of PNH.

It is important to remember that symptoms of PNH may vary from patient to patient, and a plan to manage PNH may work for some but may not work for others. This is why it is so important for each patient to receive a management plan that is tailored to their needs.

Furthermore, it should be noted that the severity of the symptoms experienced by an individual will not always be related to clone size and clone size alone should not indicate treatment.[1]

The following management and treatment approaches are most commonly used in PNH:

Blood transfusions

Transfusions are recommended during times of severe haemoglobin depletion when the body cannot generate enough new cells to make up for those lost to haemolysis. They may be used on a periodic basis when the haemoglobin level is steadily decreasing.

Anticoagulants

Thromboembolic disease is a major cause of morbidity and mortality in patients with PNH and therefore anticoagulants are commonly prescribed. However, anticoagulation does not reverse all thrombotic risk.[2] Furthermore, the use of anticoagulants in patients with PNH can be risky because of the increased bleeding risk which could be problematic in PNH patients with BMF whose red blood cell count is already low. Therefore, anticoagulants can only be used in some patients with PNH who have certain risk factors.[3]

Vitamin and mineral supplements

Vitamin and mineral supplements, such as iron, vitamin B12 and folic acid, may be given to aid red blood cell formation.[4]

Erythropoietin

Some people with PNH will require erythropoietin, which is a growth factor that encourages the bone marrow to make red blood cells. Erythropoietin can reduce the need for blood transfusions; however, in some cases it can make symptoms worse by exacerbating haemolysis and increasing the production of red blood cells that are deficient in GPI-anchored complement system regulatory proteins,[4] so it is not always suitable.

Complement inhibitors

Complement system inhibitors, such as eculizumab, are drugs that bind to targeted components of the complement system. Their role is to suppress or reduce the activity of the complement system. Complement system inhibition has been studied in clinical trials in adults, children and adolescent patients (aged 11 years to <18 years) with PNH.[5]

In all patients with PNH, treatment with complement system inhibition improved overall function and reduced the occurrence of TEs and haemolysis, resulting in a decreased need for blood transfusions and improved quality of life and life expectancy.[5]

Eculizumab (Soliris) belongs to a group of medications called monoclonal antibodies, however, unlike other drugs in this family it is 'inert' and reactions to the drug are rare. It is administered at regular intervals, commonly fortnightly by intravenous infusion, and should be given indefinitely. Patients are required to be vaccinated against meningitis prior to commencement of treatment and many physicians also prescribe prophylactic antibiotics to provide additional protection against meningococcal bacterial infection.[5]

Bone marrow transplantation (BMT)

Allogeneic bone marrow transplantation (BMT) is the only known treatment that may cure PNH. It involves replacing the body's defective blood stem cells with new healthy ones from a donor.

However, BMT is associated with significant morbidity and mortality resulting from complications such as graft failure and graft versus host disease. Furthermore, it has been shown that in PNH patients with thromboembolism, transplantation is associated with a worse outcome compared with no transplantation.[6]

With the recent development of complement system inhibitors, such as eculizumab, which reduce intravascular haemolysis and the risk of thrombosis, allogeneic BMT may no longer be the best option for PNH patients with TEs.[6]

General advice for PNH patients and carers

Living with PNH can be difficult for patients, but there are lifestyle tips that can help to make day-to-day life easier.

Support following a PNH diagnosis

Different people react differently to being diagnosed with PNH, some may feel upset, anxious or angry, whilst others may feel relieved at finally receiving a diagnosis. This diversity of emotions may affect not only the person diagnosed with PNH but also their loved ones. Following a PNH diagnosis it is important that all people affected feel that they are supported and have someone to talk to whether that be another family member or friend, a member of the healthcare team, counsellor or psychotherapist.

For advice on communicating with family, friends, carers and children about PNH please direct patients to the patient brochure 'Understanding PNH: brochure and diary for patients'.

Adapting to life with PNH

The signs and symptoms of PNH are very diverse. Some people will have very few symptoms and feel well enough to carry on a normal life despite having PNH, whilst others can be very unwell, experiencing severe symptoms and needing to make changes to their daily routine. In the latter instance it is important that patients rationalise their priorities and think about what can be managed each day.

Patients can find tips for making day-to-day life easier and advice on managing work and family life in the patient brochure.

Managing symptoms and side effects of treatment

Patients can positively contribute to the management of their disease by keeping their healthcare team informed of any disease symptoms or treatment side effects that they may be experiencing. Patients should be advised to keep a note of this information in the patient diary found in the patient brochure.

PNH and pregnancy

Women with PNH who are hoping to become pregnant should be advised to speak to their specialist PNH team and an obstetrician who specialises in high-risk births prior to conception.

For women with PNH, pregnancy can be risky for both the mother and the child. During pregnancy, a woman with PNH has a higher risk of experiencing thrombosis and developing pre-eclampsia, a dangerous condition that causes high blood pressure and can put both mother and baby at risk. Babies who are born to a mother with PNH are more likely to be born prematurely, to die *in utero*, to have a low birth weight, and to have delayed growth and development.[1]

Despite this, many babies whose mothers have PNH do not face any of these problems, particularly if the condition is well managed.[1]

Treatment with eculizumab (Soliris) and additional anticoagulation with low molecular weight heparin peri-pregnancy is strongly recommended.[2]

Patients should be encouraged to discuss these issues with their healthcare team.

Contraception

For people with PNH, the safest methods of contraception are either the progesterone-implanted coil, condoms or femidoms, or sterilisation or vasectomy. The combined oral contraceptive pill should be avoided because it can result in an increased risk of developing a blood clot. Patients should be encouraged to discuss contraception with their healthcare team.

Surgery

Surgery can pose a number of risks for people with PNH. It can increase activity of the complement system, which causes haemolysis. It can also increase the risk of thrombosis and can cause serious bleeding in people with a low platelet count (which can occur in PNH).[1] People with PNH who require surgery should be advised to speak to their specialist PNH doctor to ensure that any special measures can be put in place, for example anticoagulation or antibiotic cover.

Complementary therapies

Some patients with PNH may benefit from complementary therapies, such as counselling, aromatherapy, massage therapy, meditation and visualisation techniques, to promote physical and emotional wellbeing, help to improve quality of life, reduce stress and anxiety, improve sleep patterns and relieve some symptoms.

PNH and travel

Patients wishing to travel should discuss this with their healthcare team first. When looking to obtain travel insurance patients should be well informed about their disease and treatment as insurers will often ask for details of travellers' ages, destination of travel and any pre-existing medical conditions, including PNH.

A list of useful websites with additional information and advice for patients with PNH is provided at the end of the patient brochure.

The key role of nurses in PNH patient care

Nurses play a key role in the care of patients with PNH and their carers. As frontline healthcare professionals they provide support across the trajectory of PNH management – from investigations and diagnosis, through to treatment and palliative care.

Nursing role in caring for patients with PNH

The clinical nursing management of a patient with PNH depends greatly on the symptoms/complications that the patient has, and the setting in which nursing care is being delivered.

Nursing evaluation of patients with suspected or diagnosed PNH (in an inpatient setting, or when a patient is unwell) includes monitoring of:

- Vital signs (e.g. blood pressure, pulse, respiratory frequency, respiratory rate, oxygen saturations)
- Daily weight measurements – particularly relevant if there are concerns regarding fluid build-up such as ascities
- Recording fluid intake and output (recording on a fluid balance sheet) – as above, particularly relevant if there are concerns regarding fluid build-up
- Dietary intake – this is influenced by problems with swallowing, especially in the morning.
- Pain (intensity and site) and level of pain management
- Urine – testing for haemoglobinuria and recording the colour
- Fatigue (and changes in the ability to perform activities of daily living)
- Respiratory symptoms – including dyspnoea or cough
- Signs of bleeding
- Skin changes – discolouration/swelling/integrity etc.
- Signs of a TE – including leg pain or swelling/chest pain/shortness of breath/headache/abdominal discomfort etc.

All abnormalities should be reported to the medical team immediately to ensure appropriate and timely intervention.

More specific nursing interventions may be necessary in certain clinical situations:

- **Blood and urine testing** – Section 4 describes laboratory tests that may be important for the diagnosis and management of PNH – it is often the role of the nurse to ensure that these samples are collected on time and according to local practice guidelines in order to facilitate patient monitoring, and to report colour of the urine.
- **Renal dysfunction** may be chronic or acute in relation to PNH. As well as blood tests to monitor biochemistry, urea and creatinine levels, urine testing (PCR) and fluid balance monitoring, an electrocardiogram (ECG) may be required if hyperkalaemia is present. In some cases, it may be necessary to follow a diet limiting fluids, reducing protein and restricting salt, potassium, phosphorous and other electrolytes.[1] If this is indicated by the medical team, support from a dietician should be sought to help the patient with dietary planning.
- **Pulmonary hypertension** – similarly, blood tests to monitor biochemistry, urea and creatinine levels. Diuretics may be indicated, requiring strict fluid balance monitoring. Where anticoagulants are prescribed, blood monitoring is required to ensure an appropriate therapeutic range. Evaluation of cardiac function may be recommended as well as the initiation or modification of medication. Administration of oxygen therapy and monitoring of oxygen saturation levels is sometimes necessary.[2]

  It is important to note that both renal dysfunction (acute or chronic) and pulmonary hypertension warrant the commencement of treatment with a complement system inhibiting drug, for example eculizumab.[3,4]
- **Meningococcal infection in patients treated with eculizumab (Soliris)** – The eculizumab (Soliris) antibody inhibits the complement system and therefore increases a patient's susceptibility to meningococcal infection (*Neisseria meningitidis*). This is an uncommon but serious and potentially fatal side effect. To reduce the risk of infection, patients should receive vaccination against meningococcus at least 2 weeks prior to starting eculizumab.[5] Alternatively, many centres vaccinate on the day of treatment to avoid delay and to reduce the thrombotic risk associated with vaccination, and provide additional cover for meningococcal risk with stronger antibiotics, such as ciprofloxacin, for two weeks.[5] Subsequently, they continue to provide long-term prophylactic antibiotics such as penicillin.

  Patients should be monitored for early signs of meningococcal infection such as fever, headache and stiff neck.[5] Additional symptoms also include nausea, vomiting, photophobia, confusion, rigors, pain, tachypnoea, diarrhoea and cold hands/feet. Any fever that occurs in these patients must always raise the suspicion of meningococcus infection and medical evaluation should be sought urgently. Emergency blood cultures should be performed and a lumbar puncture if there is any doubt. Meningococcal infection can be treated with a number of effective antibiotics.

  Patients are asked to carry a card alerting them to the signs and symptoms of meningitis which they should familiarise themselves with and carry on their person should they need to attend hospital with suspicion of infection.

Nurses also have a key role in the delivery and administration of supportive treatments. This may include administration of blood products, analgesia, electrolyte and fluid administration, and other pharmacological therapies as prescribed (i.e. diuretics, anticoagulants, vitamin and mineral supplements, hormone therapies, erythrocyte or granulocyte growth factors and complement therapy). Nurses should have appropriate training and knowledge to be able to administer prescribed medications as well as understanding the potential effects of treatment and necessary patient monitoring. Providing education in relation to supportive and pharmacological therapies is an important part of nursing care, as is ensuring patients are made aware of self-care requirements, medication adherence and follow-up after discharge.

Patient education

In order to provide information and educate patients, nurses must be up to date with the latest disease information and management strategies, and know where to access resources to support their patients.

Encouraging patients to report variations in their condition

Encouraging patients to take an active role in their care is both empowering and important for successful disease management. Early detection of signs and symptoms can aid the healthcare team to provide optimal care in a timely manner to avoid more serious complications.

Patients should be encouraged to report:

- Fatigue
- Abdominal pain or distension
- Urine colour (haemoglobinuria)
- Shortness of breath
- Chest pain
- Trouble swallowing
- Erectile dysfunction
- Leg pain or swelling
- Weakness
- Headaches
- Difficulty performing everyday tasks

Adverse event reporting

You should contact your national medicines regulatory authority for advice on how to report side effects of medicines. National authorities have put various methods in place to facilitate the reporting of suspected side effects, and healthcare professionals, including nurses, play a critical role in monitoring the safe use of medicines.

Helping patients to deal with common symptoms related to PNH and its treatments

Managing symptoms related to PNH and side effects of treatment can improve the quality of life of patients. Nurses can provide information and support to ease symptoms and promote wellbeing in this patient group.

Pain

Pain is a subjective experience; however, its presence and severity should not be underestimated as it may be an indicator of a serious complication. Severe abdominal pain in patients with PNH may be a sign of Budd-Chiari syndrome or haemolytic crisis. Patients should be educated to report pain and seek review by a healthcare professional. Analgesics may be prescribed for pain relief and monitoring the efficacy of therapy is important.[6]

Fatigue

The inability to perform normal daily activities because of severe tiredness can be psychologically challenging. Organising the daily routine may help in ensuring that patients use their time to do the things they want. Suggestions may include spreading housework throughout the week rather than all in one day, asking for help with shopping or shopping online, being able to do activities whilst sitting down, and taking a bath rather than a shower where possible. Encourage patients to ask for help with activities – often patients do not want to ask for help so as not to overburden others, but providing help can be a positive experience for family members or carers.

Encouraging patients to eat well and drink plenty of fluids can increase energy. Physical activity should be encouraged for both physical and mental wellbeing. This can range from light passive exercises, light house work and gentle walks to more intensive activities such as cycling or running. Stress can also contribute to feelings of tiredness so encouraging patients to take time to relax and to use relaxation techniques may help in this situation.

Sleep is also important in fatigue management. Anxiety, worry and fear about the future can also impact on sleep. Sleeping should be avoided during the day, and patients should keep to regular sleeping patterns. Avoiding caffeine-containing drinks and alcohol, or taking a warm bath before bed may also help. If getting to sleep is an issue, it can help to get out of bed and go into another room, or to relax by reading or listening to music.

Itching and jaundice

The cause of the jaundice must be promptly ascertained and may warrant urgent treatment with a complement blocking medication such as eculizumab. Where patients are experiencing itching due to jaundice, antihistamines may be given to relieve symptoms.

Sexuality and sexual functioning

The fatigue, anxiety and changing emotions due to PNH can impact upon interest in sex. In addition, PNH can cause problems getting or keeping an erection in males. This is a sensitive subject which can be difficult to talk about. A proactive approach should be adopted where healthcare professionals should encourage open discussions with the team to address any concerns that patients may have. Patients should be encouraged to talk openly with a partner as this can help to remove the tension of a sensitive subject by explaining that a lack of interest in sex does not mean that there is any change in the level of affection for that person, and intimacy can also be expressed by touching, holding hands, kissing and hugging. Referral should be available for patients (and their partners) to trained counsellors who can help further. Erectile dysfunction can be medically supported and appropriate referral to a general practitioner or urologist may be sought.

Providing social support: Work and family life

Work and family life can be challenging even when feeling well. Trying to cope with the symptoms and emotions that result from PNH can make it even more difficult for patients. It is important for people with PNH to rationalise their priorities and think about what can be managed each day; planning time and saving energy for the things that are most important. Work is important to most people, and patients should discuss with their employers the challenges that the disease presents. Patients on treatment may need to negotiate hours to allow them to have their infusions.

Providing psychological and emotional support

Patients tend to experience a variety of feelings after being diagnosed with PNH. Some may feel upset, anxious, angry or ask themselves 'why me?', whilst others may feel relieved at finally getting a diagnosis. This diversity of emotions can affect not only the person diagnosed with PNH, but also the people they care for. Therefore support may be necessary not only for the people diagnosed with PNH, but also for their friends and family. A PNH diagnosis means close monitoring of the condition and of treatment, which may have an impact upon daily activities, leading some people to feel a loss of control over their lives. Furthermore, due to the rarity and chronic ongoing nature of the disease, patients may feel very alone when dealing with day-to-day life with PNH. Being informed about the condition and involved in decision making can help to promote a sense of control in a new situation.

Emotions can affect physical health as well as mental wellbeing. It is common for people with PNH to feel stressed or anxious about their condition and the treatments they are receiving, which can cause physical symptoms. It can sometimes be difficult to identify the cause of these physical symptoms.

Partners, family and friends can be a great source of help and support. Having open discussions about concerns and worries enables people to share their feelings and often helps to manage everyday issues before they get out of hand. Patients and carers should be offered access to psychological support and counsellors if this is necessary.

Talking about PNH to patients and carers

It is important for the person with PNH and their carers to fully understand how PNH might affect them in order to help successfully manage the disease.

When talking to patients and their carers about PNH, it is important to understand how they are feeling – what their needs and concerns are and what they want to know. Information should be given based on an individual's needs and is often given on and over several occasions. A useful starting point would be to speak to the patient and their carers about the following:

- What is PNH?
- What is the underlying cause of PNH?
- What are the symptoms of PNH?
- How is PNH diagnosed?
- How is PNH monitored/what do you look for?
- What are the treatment options for PNH and why is treatment compliance important in the long term?

The patient brochure 'Understanding PNH: brochure and diary for patients' contains useful information about PNH, as well as a diary to help patients to track their symptoms. You may find it useful to use this brochure as a starting point when discussing PNH with patients and loved ones.

List of resources

A patient brochure, entitled 'Understanding PNH: brochure and diary for patients' is available for you to give to your patients. It contains useful information about PNH, as well as a diary to help them track their symptoms.

The following websites contain information and advice surrounding PNH and other rare diseases.

PNH Alliance:
www.pnh-alliance.org.uk

Asociación HPN:
www.hpne.org

ORPHANET:
www.orpha.net

EURORDIS:
www.eurordis.org

HEMATOSLIFE:
www.hematoslife.org

AIEPN:
www.aiepn.it

STEM ONLUS:
www.astem.it

ISS:
www.iss.it/cnmr/index.php?lang=1

PNH National Service (UK):
www.pnhleeds.co.uk

PNH UK:
www.pnhuk.org

PNH I Aplastische Anämie e.V.:
http://www.aplastische-anaemie.de/

Stiftung Lichterzellen:
http://www.lichterzellen.org/

Facebook: PNH Foundation Group:
https://www.facebook.com/PNHFoundation?fref=ts

DGHO (English):
https://www.onkopedia-guidelines.info/en/onkopedia/guidelines/paroxysmal-nocturnal-hemoglobinuria-pnh/@@view/html/index.html

DGHO (German):
https://www.onkopedia.com/de/onkopedia/guidelines/paroxysmale-naechtliche-haemoglobinurie-pnh/@@view/html/index.html

European Society for Blood and Marrow Transplantation (EBMT):
www.ebmt.org

Glossary

A

Anaemia: A decrease in the amount of red blood cells or haemoglobin in the blood.

Anticoagulants: A class of drugs that work to prevent the coagulation (clotting) of blood.

Aplastic anaemia (AA): A disorder in which the bone marrow decreases or stops blood cell production.

B

Bone marrow failure (BMF): When bone marrow is unable to produce sufficient amounts of blood cells to supply the needs of the body.

Bone marrow transplantation (BMT): Is the transplantation of the substance found inside the cavities of bones (bone marrow [stem cells]) and may be autologous (the patient's own stem cells are used) or allogeneic (the stem cells come from a donor).

Budd-Chiari syndrome: A rare problem that is caused by thrombotic or nonthrombotic obstruction of the hepatic veins, leading to hepatomegaly, ascites and abdominal pain.

C

Clone size (referring to PNH): The percentage of blood cells in the body that are affected by PNH. Often referred to as small/large clone.

Cluster of Differentiation (CD55 and CD59) cell membrane molecules: Cell membrane molecules that are used to classify cells.

Complement system: A part of the body's immune system; a group of ~25 proteins that work together to help the antibodies and phagocytes destroy bacteria.

Coombes test: A test for autoimmune haemolytic anaemia.

Cytopenia: A reduction in the number of blood cells.

D

Direct and total levels of bilirubin: Bilirubin travels through the body in two ways. Bilirubin that moves freely in the blood is called direct bilirubin, while bilirubin that is attached to a protein is called indirect bilirubin. The total level of bilirubin accounts for both direct and indirect bilirubin.

Dysphagia: Difficulty or discomfort in swallowing, as a symptom of disease.

Dyspnoea: Difficulty in breathing.

E

Erythrocyte: A red blood cell that contains haemoglobin and transports oxygen to the tissues.

F

Flow cytometry: A technique for counting and examining microscopic particles, such as cells and chromosomes.

G

Glomerular filtration rate: A measure of how much blood passes through the glomeruli each minute.

Glycosylphosphatidylinositol (GPI) anchors: GPI anchors tether proteins to the outer edge of the cell membrane.

H

Haptoglobin: A blood protein made by the liver.

Haemoglobin: The substance in red blood cells that carries oxygen in the blood.

Haemoglobinuria: A condition in which the substance in red blood cells that carries oxygen in the blood, haemoglobin, is found in abnormally high concentrations in the urine.

Haemolysis: The destruction of red blood cells by complement, a part of the body's natural defence system. Haemolysis is the main cause of the signs, symptoms and serious health problems in PNH, including some that are life-threatening.

Haemolytic anaemia: An anaemia cause by the premature destruction of red blood cells.

Haemosiderinuria: The presence of a yellow/brown pigment (haemosiderin, which is a product of haemolysis), in the urine.

I

Intravascular haemolysis: The destruction of red blood cells in the circulation with the release of cell contents into the plasma.

L

Lactate dehydrogenase (LDH): An enzyme found in red blood cells that is released during haemolysis. Testing for LDH can help show how much haemolysis is happening in the patient.

Leukocyte: A type of white blood cell that helps to protect the body against infection.

M

Mutation: A change in genetic material.

Myelodysplastic syndrome (MDS): MDS is a blood-related condition that occurs as a result of ineffective production of blood cells. People with MDS can develop severe anaemia and require blood transfusions. In some cases, the disease can worsen and the person can develop low blood counts caused by progressive bone marrow failure.

Myelofibrosis: A chronic blood cancer in which excessive scar tissue forms in the bone marrow and impairs its ability to produce normal blood cells.

P

Paroxysmal nocturnal haemoglobinuria (PNH): A disease where red blood cells are created with varying amounts of or no protective protein. This causes them to burst (a process called haemolysis) and can result in serious health problems and life-threatening complications.

Platelets/thrombocytes: Are a component of blood whose function is to stop bleeding by clumping and clogging blood vessel injuries.

PNH clones: Cells that have been affected by PNH. PNH clones are lacking a protein type called GPI anchor proteins.

R

Reticulocyte: Reticulocytes are immature red blood cells that are produced in the bone marrow. They eventually enter the bloodstream and become mature red blood cells.

T

Thrombocytes/platelets: Are a component of blood whose function is to stop bleeding by clumping and clogging blood vessel injuries.

Thrombus (plural: thrombi): A blood clot.

Thrombosis: The formation or presence of a blood clot in a blood vessel. Blood clots form when parts of the blood in the body clump together, potentially blocking veins and arteries. Blood clots can be fatal as they may cause heart attack, stroke and organ damage, among other problems.

Thrombotic events (TEs): Events relating to the formation of blood clots in places that may cause obstruction to the blood flow.

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Produced by the Nurses Group of the European Society for Blood and Marrow Transplantation (EBMT NG), this brochure was made possible by financial support received from Alexion Pharmaceuticals.

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Date of update: October 2015