FABHALTA - Paroxysmal nocturnal haemoglobinuria (PNH) - Therapy Area
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# Paroxysmal nocturnal haemoglobinuria (PNH)

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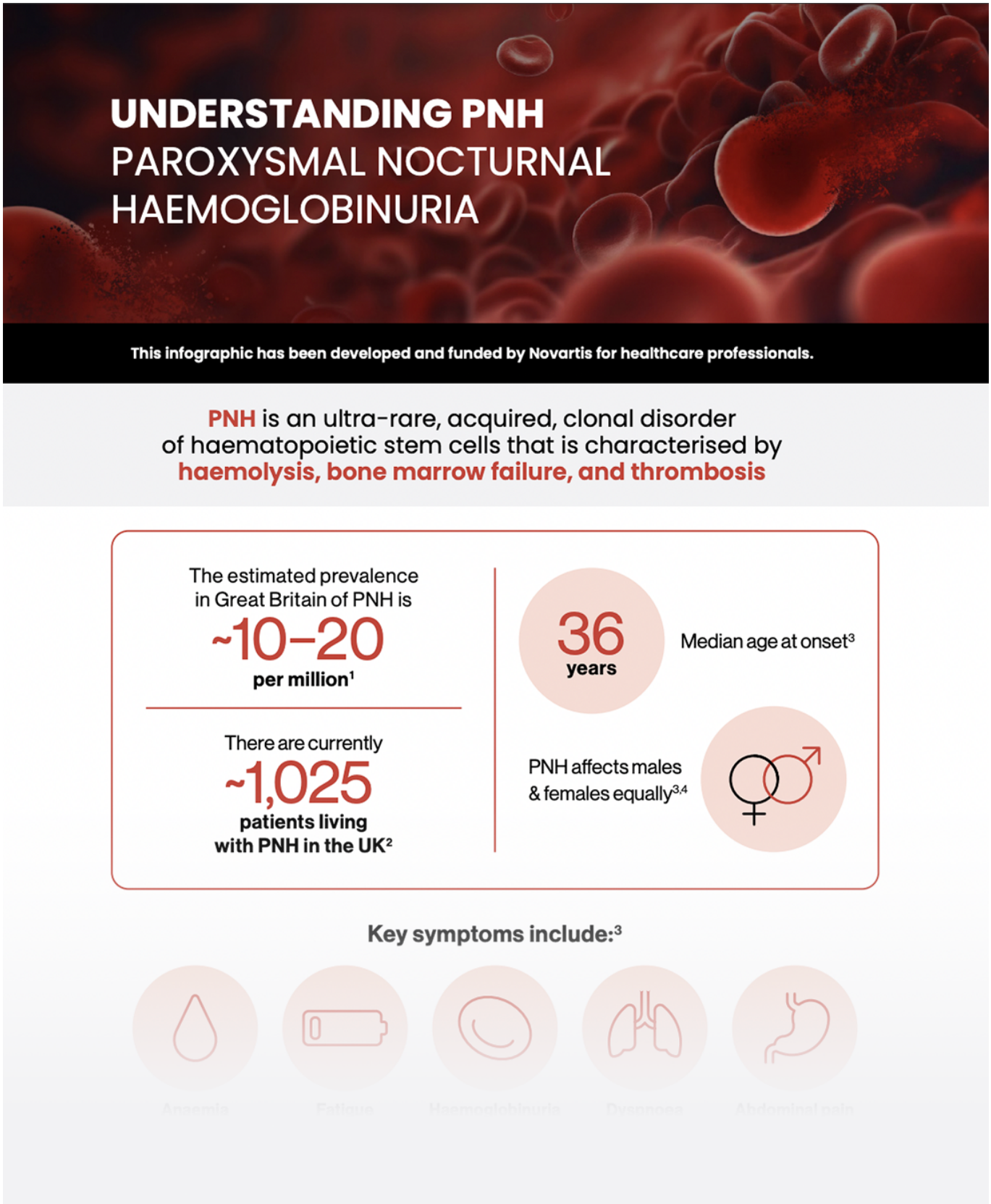


## Understanding PNH infographic

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## Understanding PNH

PNH is an ultra-rare, acquired, clonal disorder of haematopoietic stem cells that is

characterised by haemolysis, bone marrow failure, and thrombosis.

- Aetiology

- Epidemiology

- Clinical presentation

Paroxysmal nocturnal haemoglobinuria (PNH) is a chronic, life-threatening, ultra-rare blood disorder that often manifests with complement-mediated haemolysis, anaemia, and fatigue.[1] In PNH, red blood cells (RBCs) are destroyed prematurely by the complement system, leading to a range of potentially debilitating symptoms.

PNH occurs due to an acquired mutation in the body's haematopoietic stem cells, which makes the RBCs more susceptible to haemolysis by the complement immune system.[2,3]

- Aetiology

- Epidemiology

- Clinical presentation

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The estimated prevalence in Great Britain of PNH is **~10 to 20 per million**[4] Currently ~1,025 patients are living with PNH in the UK[5]

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median age at onset:
**36 years**[6]

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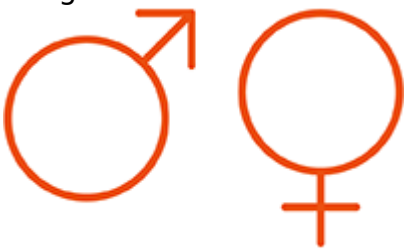

PNH equally affects
**males and females**[6,7]

- Aetiology

- Epidemiology

- Clinical presentation

PNH varies in presentation and is often associated with other clinical conditions, such as aplastic anaemia and myelodysplastic syndrome.[7]

Although the name of the condition refers to nocturnal haemoglobinuria, resulting in the production of classically dark urine during the night and in the morning, this symptom is intermittent and usually only present in approximately 25% of patients.[4]

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## Key signs and symptoms[6]

Signs and symptoms observed in the international PNH Registry, an ongoing, prospective, multicentre, global, observational study. Current analysis includes patients enrolled in the Registry who had data available as of July 17, 2017.[6]

**Anaemia**
**9.8 g/dL**
Median haemoglobin level

**Fatigue**
**81%**
(n=2684/3318)

**Haemoglobinuria**
**45%**
(n=1492/3313)

**Dyspnoea**
**45%**
(n=1501/3315)

**Abdominal pain**
**35%**
(n=1167/3314)

**Erectile dysfunction**
**24%**
(n=344/1422 males)

**Dysphagia**
**17%**
(n=547/3311)

**Thrombosis**
**13%**
(n=544/4134)

## Symptom burden typically results in patients with PNH having lower quality of life (QoL) compared with the general population[6]

## Complications[6]

Image

**19%**

of patients have a history of major adverse vascular events

Image

**61%**
have a history of RBC transfusions

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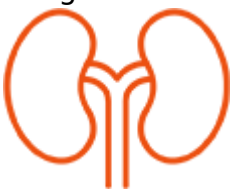

**43%**
show some level of renal impairment

## Thrombotic events are the leading cause of mortality in PNH, accounting for up to 67% of deaths with a known cause[8]

In its most severe form, PNH may lead to chronic anaemia, which can result in patients becoming transfusion-dependent, requiring patients to adapt their lives around scheduling treatment. Iron overload can also be a complication of chronic transfusions and can increase morbidity and mortality.[9]

Patients can also suffer from the direct effects of intravascular haemolysis leading to the absorption of nitric oxide. Nitric oxide is a major regulator of vascular physiology and many clinical symptoms seen in PNH are caused by depletion of nitric oxide, such as thrombosis, fatigue, abdominal pain, oesophageal spasm, and male erectile dysfunction.[8,10]

## Diagnosis

A diagnosis of PNH may be suspected in individuals who have signs of intravascular haemolysis (e.g., haemoglobinuria, abnormally high serum LDH concentration) with no known cause.[4,7]

A diagnosis may be made based upon a thorough clinical evaluation, a detailed patient history and a variety of specialised tests, including:[11,12]

- **Abdominal ultrasound**
- **Bone marrow examination**

- **CT scan**
- **D-dimer**
- **Echocardiogram**
- **Full blood count**
- **Kidney function test**
- **Lactate dehydrogenase (LDH)**
- **Reticulocyte count**
- **Bilirubin levels**

## Diagnosis of PNH is confirmed by flow cytometry, which is regarded as the gold standard test for diagnosis[7]

Flow cytometry is used to detect GPI-linked antigen deficiency in red cells, monocytes and granulocytes.[7]

## Mechanism of disease

- PNH develops due to a mutation in the PIG-A gene, which is necessary for the creation of glycosylphosphatidylinositol (GPI) anchors on the cell surface that attach proteins, including CD55 and CD59[4,13]
- CD55 and CD59 normally prevent the complement system from destroying normal cells, and in PNH, loss of the GPI anchor results in the lack of CD55 and CD59 on cells[13]
- This leads to complement-mediated haemolysis[4,13]

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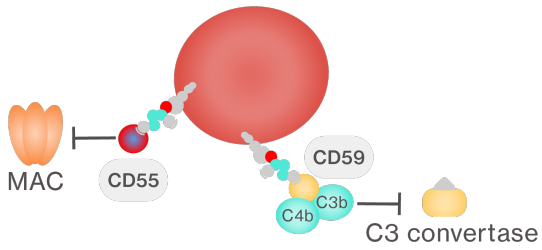
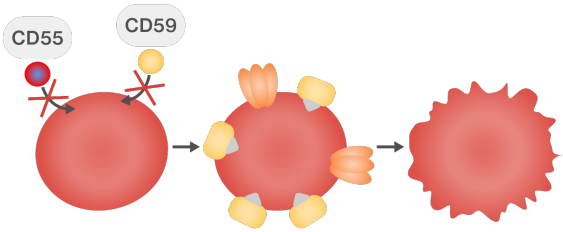



**Normal haematopoietic cells**




**PNH haematopoietic cells**

## Management goals

PNH treatment aims to address specific symptoms that are present in each individual and includes a variety of different therapeutic options.[7]

Approved therapies are not curative, but work to inhibit components of the complement system, halting the destruction of RBCs and can reduce the risk of thrombosis.[7]

The only curative therapy for individuals with PNH is bone marrow transplantation. However, because of the risk of morbidity and mortality, this is reserved for individuals with serious complications such as severe bone marrow failure or repeated, life-threatening blood clot formation.[7]

Additional treatment for PNH is symptomatic and supportive and varies depending upon the individual's age, general health, presence of associated disorders, severity of PNH and degree of underlying bone marrow failure.[7]

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**Find out about the National PNH Service & how to refer**

MAC, membrane attack complex; PIG-A, phosphatidylinositol glycan, class A.

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