Paroxysmal Nocturnal Hemoglobinuria

CHI Formulary Development Project

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Council of Health Insurance

November 2023

Table of Contents

List of Tables

List of Figures

Abbreviations

AA	Aplastic Anemia
APC	Alternative Pathway
ASH	American Society of Hematology
BMD	Bone Marrow Deficiency
BMF	Bone Marrow Failure
BMT	Bone Marrow Transplant
C3	Complement 3
C5	Complement 5
DAT	Direct Antiglobulin Test
FLAER	Fluorescently Labelled inactive toxin Aerolysin
GPI	Glycosylphosphatidylinositol
GPI-Aps	GPI-Anchored proteins
HCT	Hematopoietic stem Cell Transplantation
LDH	Lactate Dehydrogenase
MAC	Membrane Attack Complex
MDS	Myelodysplastic Syndrome
PIGA	Phosphatidylinositol Glycan class A
PNH	Paroxysmal Nocturnal Hemoglobinuria
QoL	Quality of Life
RBC	Red Blood Cell
TE	Thromboembolism Events

Executive Summary

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disorder that leads to the premature death and impaired production of blood cells. The disorder affects erythrocytes, leukocytes, and thrombocytes[1]. It is characterized by intravascular hemolysis, thrombotic events, serious infections, and bone marrow failure[2]. Hemolysis in PNH is due to the action of the complement on abnormal red blood cells (RBCs)[2].

The **complement cascade** is a complex series of biochemical reactions in the immune system that helps defend the body against pathogens. It involves a cascade of proteins that enhance immune responses, including inflammation, opsonization (making pathogens more susceptible to phagocytosis), and cell lysis[3].

The cascade can be activated through various pathways, including the classical, alternative, and lectin pathways:

1. Classical pathway: this pathway is typically activated by antibodies bound to antigens, leading to the formation of complement 3 (C3) convertase.
2. Alternative pathway (APC): this pathway can be activated spontaneously and is also antibody independent. It begins with the hydrolysis of C3, leading to the formation of C3 convertase.
3. Lectin pathway: this pathway is initiated by the binding of mannose-binding lectin or other lectins to microbial carbohydrates, ultimately leading to the formation of C3 convertase.

All three pathways converge at the formation of C3 convertase, which is a key enzyme in the complement system.

Figure 1 below demonstrates the complement cascade and its regulatory mechanisms.

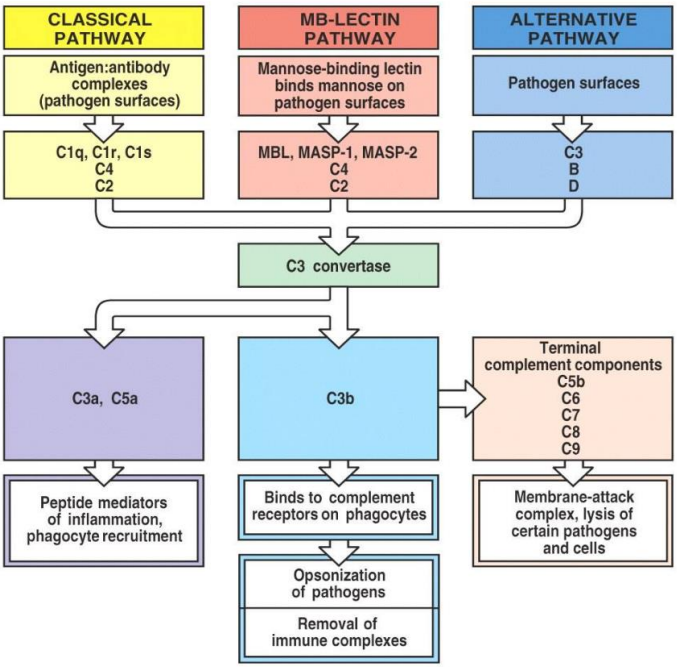

Figure 1. *Overview of Complement Activation and Function. Retrieved from https://www.bio.davidson.edu/courses/immunology/students/spring2006/finley/c3.html*

Glycosylphosphatidylinositol (GPI), a lipid anchor for numerous cell-surface proteins, is constructed through a sequence of enzymatic reactions on a phosphatidylinositol lipid within the endoplasmic reticulum. The process begins with the involvement of the phosphatidylinositol glycan class A (PIGA) gene, which plays a crucial role in the first step of GPI anchor biosynthesis[4].

Once formed, GPI establishes a covalent attachment to the carboxyl terminus of proteins, and the resulting complex GPI-protein is transported to the plasma membrane.

Figure 2 below demonstrates the GPI biosynthesis.

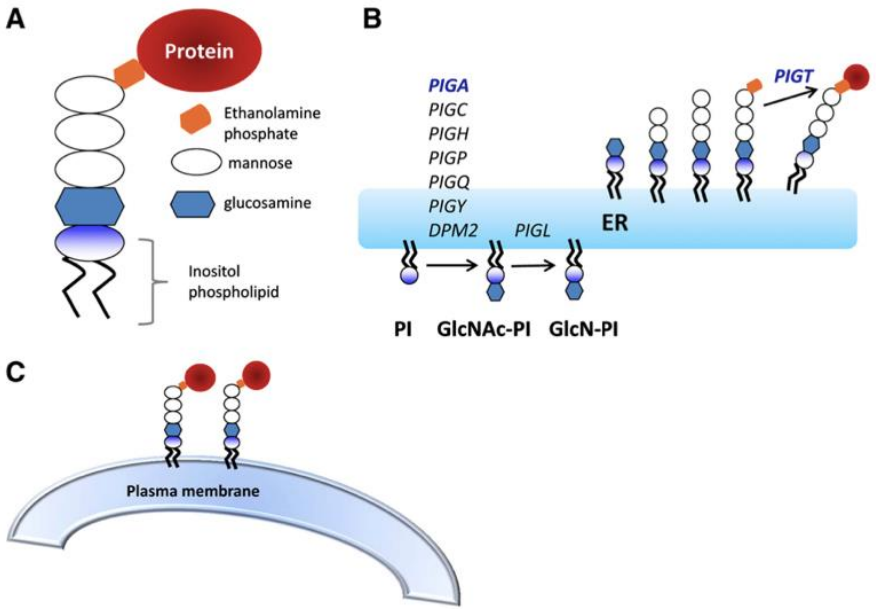

Figure 2. *Glycosylphosphatidylinositol (GPI) Anchor Biosynthesis. Retrieved from Brodsky RA. Paroxysmal Nocturnal Hemoglobinuria. Blood. 2014;124(18):2804-2811.*

More than 12 GPI-anchored proteins (GPI-APs) are found on hematopoietic cells, including blood group antigens, adhesion molecules, and complement regulatory proteins like **CD55** and **CD59:**

- CD59 is a glycoprotein that directly interacts with the membrane attack complex (MAC) to prevent lytic pore formation by blocking the aggregation of C9.
- CD55 glycoprotein functions to accelerate the rate of destruction of membrane bound C3 convertase, hereby decreasing the amount of C3 that is cleaved.

The proliferation of a hematopoietic stem cell with a significant shortage or absence of GPI due to somatic mutations in the PIGA gene is defined as **paroxysmal nocturnal hemoglobinuria (PNH).**

PNH is classified into three different categories illustrated in figure 3:

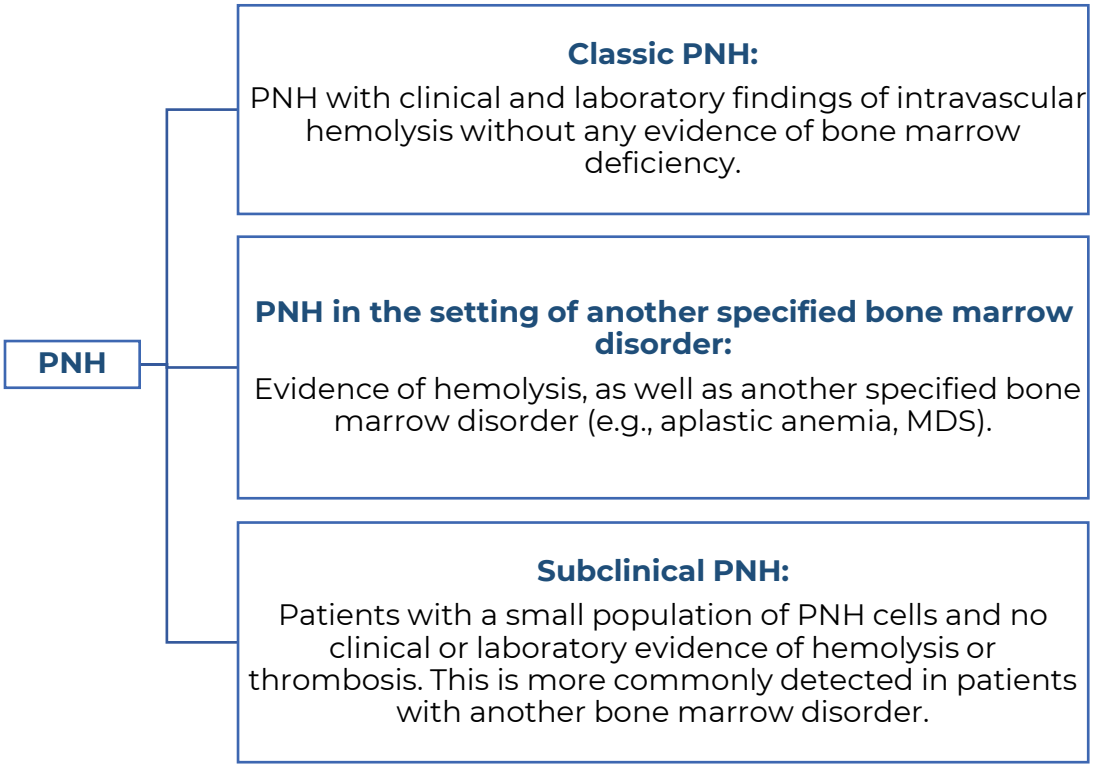

Figure 3. *Paroxysmal Nocturnal Hemoglobinuria (PNH) Classification*

The resulting deficiency of CD55 and CD59 on erythrocytes leads to symptoms such as bone marrow insufficiency, an increased risk of thrombosis and a complement-mediated lysis:

- Intravascular hemolysis begins with heightened C3 convertase activity on the surface of PNH erythrocytes due to the absence of CD55. This triggers the activation of C3, C5, and the final stage of the complement pathway, resulting in the formation of the MAC (normally regulated by CD59).
- Extravascular hemolysis in PNH begins with increased opsonization of PNH erythrocytes by complement fragments (mostly C3d). This is the result of the lack of CD55. Opsonized erythrocytes are cleared and destroyed by cells of the reticulo-endothelial system.

The disease severity is graded according to the clone size and level of deficiency in the proteins as type I (normal expression), type II (partial deficiency) or type III (complete deficiency).

Due to its rarity, the precise prevalence and incidence of PNH remain uncertain. In the United States, PNH is estimated to occur at a rate 5 to 10 times less frequent than aplastic anemia, which affects approximately 0.6 to 6.1 cases per million individuals. The estimated prevalence ranges from 12 to 13 cases per 1 000 000 people. On a

global scale, PNH affects 15.9 individuals per 1 million, with an annual incidence rate of around 5 to 6 cases per 1 million people[5].

The prevalence of PNH in Middle Eastern countries, including Saudi Arabia, has not been extensively studied in terms of the epidemiological figures and clinical patterns. To address this gap, a systematic review focusing on PNH in Saudi Arabia was conducted. The aim of the study was to assess the incidence and characteristics of patients diagnosed with PNH in the King Faisal Specialist Hospital and research center. The rarity of PNH in the Saudi Arabian population and its predominant presentation as aplastic anemia or thrombosis were confirmed[6].

The primary objective in treating patients with PNH is to effectively control hemolysis, improve symptoms, and prevent complications associated with the disease. This is typically achieved through the comprehension of the disease classification, whether it's classical PNH, subclinical PNH, or PNH in the setting of another bone marrow failure syndrome.

→ In the case of classical PNH, where patients experience both hemolysis and thrombotic events, the advent of targeted therapies like **eculizumab** and **ravulizumab** has revolutionized treatment outcomes. By targeting the C5 protein, these therapies prevent the formation of the membrane attack complex, thereby reducing damage to red blood cells and significantly improving the quality of life for individuals with classical PNH.

Pegcetacoplan is another promising therapy for PNH. It is a targeted C3 inhibitor, which works by blocking the complement cascade at the C3 level. It has shown efficacy in controlling hemolysis and improving outcomes in PNH patients, including those who have not responded adequately to eculizumab.

Additionally, novel therapies like danicopan (a Factor D inhibitor) and iptacopan (a Factor B inhibitor) are being explored as add-on treatments to further enhance symptom control.

Management also involves supportive care and regular monitoring for potential complications, including thrombosis. Overall, advancements in PNH treatment have significantly improved outcomes and quality of life for affected individuals.

→ For patients with PNH concurrent with another bone marrow failure syndrome, a multifaceted treatment strategy is imperative. It involves not only addressing the PNH-related symptoms but also managing the underlying marrow disorder, which could be aplastic anemia or myelodysplastic syndrome.

→ Subclinical PNH, characterized by small PNH clones without evident clinical or laboratory signs of hemolysis or thrombosis, necessitates a more conservative approach. Monitoring any signs of progression is crucial and providing supportive care as needed forms the cornerstone of management.

In addition to targeted therapies, such as eculizumab, a vital aspect of care involves vigilant monitoring and management of associated conditions. This encompasses proactive measures to address issues like bone marrow failure and thrombosis, which can significantly impact the overall well-being of PNH patients.

This report compiles all clinical and economic evidence related to PNH according to the relevant sources. The ultimate objective of issuing PNH guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to PNH patients in Saudi Arabia. The main focus of the review was on Saudi, American, European and International guidelines issued within the last five years.

Several classes and drugs can be used for the management of PNH and are summarized in the table below.

Table 1. Summary of SFDA-Registered Drugs for the Management of PNH

Drug	Indication	Dose	HTA recommendations
Complement C5 Inhibitor			
Ravulizumab	In patients with classic PNH symptoms (hemolysis) indicating high disease activity, regardless of transfusion history. In adults and children with PNH who are stable after 6 months of eculizumab treatment, with a longer half-life and 8-week dosing intervals.	**IV:** ***Weight 20 kg to <30 kg:*** Loading dose: IV: 900 mg as a single dose. Maintenance dose: IV: 2,100 mg once every 8 weeks starting 2 weeks after the loading dose. ***Weight 30 kg to <40 kg:*** Loading dose: IV: 1,200 mg as a single dose. Maintenance dose: IV: 2,700 mg once every 8 weeks starting 2 weeks after the loading dose. ***Weight 40 kg to <60 kg:*** Loading dose: IV: 2,400 mg as a single dose. Maintenance dose: IV: 3,000 mg once every 8 weeks	**Positive recommendations from NICE, CADTH, PBAC, IQWIG and HAS:** Ravulizumab is equally effective and safe as eculizumab, requires less frequent administration, improving quality of life and is more cost-effective due to reduced dosing frequency.

		starting 2 weeks after the loading dose. ***Weight 60 kg to <100 kg:*** Loading dose: IV: 2,700 mg as a single dose. Maintenance dose: IV: 3,300 mg once every 8 weeks starting 2 weeks after the loading dose. ***Weight ≥100 kg:*** Loading dose: IV: 3,000 mg as a single dose. Maintenance dose: IV: 3,600 mg once every 8 weeks starting 2 weeks after the loading dose. **SUBQ:** *Weight ≥40 kg:* Maintenance dose: 490 mg once weekly starting 2 weeks after weight based IV loading dose.	
Complement C3 Inhibitor			
Pegcetacoplan	In PNH patients who do not respond adequately to or cannot tolerate eculizumab or ravulizumab therapy. As an option for treating PNH adults who have anemia after at least 3 months of treatment with a C5 inhibitor.	**SUBQ:** 1,080 mg twice weekly.	**Positive recommendations from NICE, PBAS, CADTH:** Pegcetacoplan is a more cost-effective option than ravulizumab and eculizumab while providing enhanced effectiveness for adults experiencing anemia alongside C5 inhibitor treatment. **HAS and IQWIG**: not available

Non SFDA registered drugs:

- **Eculizumab**, a C5 inhibitor, is an approved drug by the EMA for use in PNH patients who experienced both hemolysis and thrombotic events and in cases of "PNH in the setting of another bone marrow failure syndrome" experiencing PNH-related complications. The recommended dose is 900 mg every 2 weeks ± 2 days.
- **Iptacopan**, a factor B inhibitor, reduces extravascular hemolysis while maintaining control of intravascular hemolysis in patients treated with a c5 inhibitor.
- **Danicopan**, a factor D inhibitor, is an add-on treatment used to control the signs and symptoms of extravascular hemolysis in patients receiving a C5 inhibitor.
- Late-stage clinical development for PNH includes phase 3 trials of three anti-C5 monoclonal antibodies, eculizumab biosimilars, a phase 2/3 investigation of rVA576 (Coversin) for eculizumab-resistant patients, a subcutaneously administered RNA interference therapy targeting the C5 component (Cemdisiran/ALN-CC5), and Phase 2/3 trials of two oral Factor D inhibitors (BCX9930 and vemircopan).

It is important to emphasize that these treatment approaches serve as general recommendations. The appropriate treatment plan for each patient should be determined based on the specific type of PNH, as well as their overall health status. To provide a concise overview, the report will feature in section 3 a synthesis of key recommendations, focusing on the relevant drugs that align with these guidelines.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

1.1 KSA Guidelines

1.1.1 Flow Cytometry Screening for Paroxysmal Nocturnal Hemoglobinuria, A Single-Center Experience in Saudi Arabia (2015)

To date, specific guidelines for managing NPH in KSA have not been published. However, PNH, including flow cytometry screening, was discussed in an article published in 2015 based on a single-center experience in Saudi Arabia[6].

PNH is a rare, acquired disorder of clonal hematopoietic stem cells, characterized by a deficiency of GPI, which normally anchors proteins in cell membranes. It can manifest with symptoms such as hemoglobinuria, thrombosis, or bone marrow failure.

Flow cytometry has emerged as the preferred method for diagnosing PNH, widely recognized in the medical community. This study analyzes PNH cases diagnosed through flow cytometry assays, aiming to assess the prevalence of PNH within a sample population from Saudi Arabia.

All samples demonstrated type II and III GPI-deficient clones, with a median clone size of 15% in red blood cells (RBCs) (ranging from 0.7% to 56%) and 63% in WBCs (monocytes and granulocytes) (ranging from 3.8% to 100%). The study found a low incidence of PNH (4%) among the samples analyzed. In the study group, 73% had aplastic anemia (AA), with two of these patients also experiencing thrombosis. Additionally, one patient (9%) presented with thrombosis alone (Budd-Chiari syndrome) without AA. This highlights thrombosis as the second most common presentation after AA, underscoring the importance of screening for PNH in patients with thrombosis, especially in atypical sites like portal vein thrombosis.

The current approved treatment, eculizumab, a humanized monoclonal antibody targeting the terminal complement protein C5, has led to significant improvements in the quality of life for individuals with hemolytic PNH, reducing hemolysis, thrombosis, and transfusion requirements. However, for this treatment to be effective, screening of appropriate patients and accurate diagnosis are essential.

Further research is warranted to comprehend the clinical significance of clone size variation between granulocytes and monocytes and its potential impact on the disease's course.

1.2 European Guidelines

1.2.1 Complement Inhibition in Paroxysmal Nocturnal Hemoglobinuria (PNH): A Systematic Review and Expert Opinion from Central Europe on Special Patient Populations (2023)

There is growing evidence supporting the use of terminal and proximal complement inhibition in PNH, but determining when and in which specific patient groups to use anti-C5 or -C3 agents remains unclear. To address this need, an international Delphi effort involving 11 PNH experts from 9 Central European countries was conducted[7]. The effort aimed to develop consensus recommendations on when to transition from a C5 inhibitor to a C3 inhibitor for special patient populations, such as those commonly encountered in real-world clinical practice but not included in pivotal trials. Due to the ultra-rare nature of PNH, there is limited data available regarding treatment response and Quality of Life (QoL).

The Delphi method is widely accepted for developing consensus recommendations based on expert opinions when limited evidence-based literature is available. A significant advantage of the Delphi method is its systematic, anonymous process that encourages the open exchange of opinions and treats all expert opinions equally, reducing the influence of biased individuals. However, there are notable limitations to the treatment recommendations. Some recommendations were reached by consensus and lack support from prospective, randomized data. Due to the rarity of PNH, there is a scarcity of clinical studies supporting the switch from C5 inhibition to C3 inhibition in specific PNH patient populations. Despite an extensive literature search, the evidence mainly comprises case reports, retrospective/prospective case series, and real-world observational studies with short follow-up periods, potentially subject to publication bias. No formal assessment of bias or quality control was conducted for the studies included in the review.

The European Medicines Agency (EMA) has approved three complement inhibitors for use in treating PNH: **eculizumab** and **ravulizumab**, both of which are humanized monoclonal antibodies targeting the same C5 epitope, with approvals in 2007 and 2019, respectively. Additionally, there is the more recently approved cyclic peptide, **pegcetacoplan**, which acts as a C3 inhibitor in 2021.

1.2.1.1 Treatment Options for PNH

a) C5 Inhibitors (Eculizumab and Ravulizumab)

- Eculizumab, a humanized monoclonal antibody targeting C5, is approved for treating PNH in patients with high disease activity, regardless of transfusion history. Approval of eculizumab was based on the TRIUMPH study published in the *New England Journal of Medicine* in September 2006, which demonstrated its effectiveness in reducing hemolysis, transfusion requirements, and fatigue in PNH patients[8]. The SHEPHERD study (*Blood*, February 2008) also confirmed the benefits of eculizumab, including those with thrombocytopenia and minimal transfusion needs[9]. An open-label extension of these studies showed a significant reduction in thromboembolism events (TE) with eculizumab[10].
- Ravulizumab is indicated for adults and children with PNH who are stable after six months of eculizumab treatment, with a longer half-life and 8-week dosing intervals. Studies demonstrated that ravulizumab is non-inferior to eculizumab in terms of efficacy and safety.
- Eculizumab and ravulizumab are recommended for classic PNH symptoms indicating high disease activity, regardless of transfusion history. Consequently, patients with a significant PNH clone (> 50% PNH granulocytes), intravascular hemolysis (LDH ≥ 1.5 ULN), and robust bone marrow reserves (high reticulocyte count) are likely to benefit from C5 inhibitors.
- In rare cases, patients with AA and extensive PNH clonal expansion undergoing immunosuppressive therapy may experience worsening PNH symptoms similar to classic PNH patients. They should be treated accordingly.
- Patients with bone marrow failure, active hemolysis, and an indication for hematopoietic stem cell transplantation (allo-HCT) should receive anti-C5 treatment before HCT to reduce transplant-related mortality.
- Use of complement inhibitors in asymptomatic subclinical PNH patients is not recommended. Close monitoring (every 6 to 12 months) is essential to detect PNH clone expansion and hemolysis symptoms.
- Switching from eculizumab to ravulizumab:
    - Patients with PNH can safely switch from eculizumab (administered every 2 weeks) to ravulizumab (administered every 8 weeks) at the discretion of their treating physician. Meningococcal vaccination status should be verified per national guidelines.

- Ravulizumab maintains disease control with stable hematologic and renal parameters while reducing treatment frequency. Patients experiencing regular pharmacokinetic breakthrough hemolysis on eculizumab may benefit from switching to ravulizumab. Ravulizumab's less frequent administration schedule reduces the treatment burden for patients and their families compared to eculizumab.

- Other Considerations:
    - Preclinical data has shown that complement activation plays a role in severe acute respiratory syndrome coronavirus-mediated disease. Eculizumab is currently used off-label to treat COVID-19, but its effectiveness in this context is still unproven. Recent data suggest that PNH patients receiving eculizumab may exhibit mild COVID-19 symptoms, but more research is needed to confirm these findings.
    - Patients with PNH who have a history of thrombosis or other thrombophilic markers should receive secondary thromboprophylaxis while on C5 inhibition therapy, regardless of their COVID-19 status.
    - No randomized clinical trials have assessed eculizumab or ravulizumab use during pregnancy. Pregnant PNH patients not previously treated with a C5 inhibitor should be individually assessed and strongly considered for eculizumab to prevent TE complications. C5 inhibitors should be continued post-birth to reduce the risk of thrombotic complications.
    - Patients receiving either eculizumab or ravulizumab should be vaccinated against meningococcal infections before starting therapy.

b) C3 Inhibitors (Pegcetacoplan)

- Pegcetacoplan is the first and only licensed C3 inhibitor in Europe. It regulates C3b-mediated extravascular hemolysis and prevents terminal intravascular hemolysis by blocking the complement cascade proximally.
- Approved for subcutaneous use in adult PNH patients who are anemic after receiving C5 inhibitor treatment for at least 3 months.
- Pegcetacoplan's approval was based on results from the PEGASUS phase 3 clinical trial conducted by Hillmen et al. and published in the New England Journal of Medicine in March 2021[11]:
    - The trial compared the efficacy and safety of pegcetacoplan with eculizumab in PNH patients with hemoglobin levels below 10.5 g/dL despite eculizumab therapy.

    - Pegcetacoplan demonstrated superiority over eculizumab in improving hemoglobin and noninferiority in other clinical and hematologic outcomes.
    - In the open-label period of the PEGASUS study, pegcetacoplan showed significant improvement in hemoglobin levels compared to eculizumab, with 85% of pegcetacoplan-treated patients being transfusion-free over 16 weeks. Meaningful improvements were observed in key disease markers and patient-reported outcomes.
- A post hoc analysis of the phase 3 PEGASUS trial revealed that:
    - Patients receiving pegcetacoplan, as well as those who switched to pegcetacoplan after 16 weeks on eculizumab, experienced significant improvements in Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue) scores.
    - These improvements were accompanied by enhanced hemoglobin levels and reduced fatigue levels.
    - The recommendation to consider transitioning to pegcetacoplan in PNH patients experiencing severe fatigue and impaired QoL after at least 3 months of C5 inhibitor treatment was the only recommendation that did not achieve unanimous consensus among experts.
    - Potential reasons for differing expert opinions include limited clinical data in this specific patient group, the absence of objective criteria for assessing fatigue, the unavailability of C3 inhibition in some countries, and a lack of personal experience with agent switching.
    - It is important to note that evaluating the need for C3 inhibitors cannot rely solely on a QoL scoring system. However, the presence of persistent anemia, linked to hemolysis or bone marrow failure, may serve as an objective criterion.
- The phase 3 PRINCE study (*Blood*, 2021) compared pegcetacoplan to standard-of-care (excluding complement inhibitors) in treatment-naïve PNH patients. Pegcetacoplan demonstrated statistical superiority in hemoglobin stabilization and LDH reduction at week 26. QoL improvements were noted, with significant reductions in fatigue symptoms and improved QoL scores in pegcetacoplan-treated patients[12].
- Prior to pegcetacoplan treatment, patients must be vaccinated against Neisseria meningitidis, Streptococcus pneumoniae, and Hemophilus influenzae.

c) Switching from C5 to C3 Inhibitors

The Central European expert group identified real-world situations that pose challenges in managing PNH patients who do not fit the criteria of clinical trials. These situations are pertinent not only to Central European countries but also to most countries globally and call for specific treatment guidance. The experts have identified five distinct patient populations where transitioning from a C5 to a C3 inhibitor is highly relevant. Recommendations and consensus percentages for these five special patient groups are summarized below:

1) Patients with breakthrough intravascular hemolysis during regular C5 inhibitor treatment for ≥ 3 months (Occurs in 11.0–27.0% patients with PNH on C5 inhibitor): 100 % of the consensus

- If a clinical trial is an option, it should be considered.
- In cases of recurrent pharmacokinetic breakthrough hemolysis (these occur regularly with an interval of more than 7 to 10 days between doses due to inadequate drug dosing), you can either opt for a clinical trial or adjust the eculizumab dose to 1200 mg or shorten the dosing interval to 10 days.
- Another option is to switch to ravulizumab.
- Alternatively, switching to pegcetacoplan is also a possibility.
- For sporadic pharmacodynamic breakthrough hemolysis (these sporadically happen at any time and are associated with conditions that amplify complement activity, such as pregnancy, infections, and major surgeries), it's advisable not to change the therapy. Instead, focus on treating the underlying triggering condition.

2) Patients with clinically relevant C3-mediated extravascular hemolysis on C5 inhibitor treatment for ≥ 3 months (100.0% of patients treated with eculizumab show some degree of extravascular hemolysis): 100 % of the consensus

- If a clinical trial is an option, it should be considered.
- Alternatively, switching to pegcetacoplan is also a possibility.

3) Patients with unprovoked TE while on C5 inhibitor for ≥ 3 months (The rate of both venous and arterial TE during Eculizumab treatment is 1.1 events per 100 patient-years): 100 % of the consensus

- If a clinical trial is an option, it should be considered.
- Explore secondary thrombo-prophylaxis with anticoagulants, unless there are contraindications.

- As an alternative, consider switching to pegcetacoplan and combine it with anticoagulant therapy. It's highly recommended to consider this switch if a TE event occurs during thrombo-prophylaxis. Note that all patients should undergo an evaluation for additional thrombophilic markers.

4) Patients with severe fatigue and impaired QoL despite ≥ 3 months of C5 inhibitor treatment: 72 % of the consensus

- If a clinical trial is an option, it should be taken into account.
- Assess indicators of hemolysis and contemplate transitioning to pegcetacoplan. Note that it is essential to evaluate all patients regarding their hemoglobin levels.

5) Patients with PNH and rare C5 polymorphisms non-responsive to C5 inhibition (A rare C5 polymorphism is found in 3.0% of the Japanese population which prevents C5 inhibitors from binding to C5): 100% of the consensus

- Consider a clinical trial if available.
- Alternatively, switching to pegcetacoplan is also a possibility.

Providing general recommendations on the order and duration of these treatment options is challenging because different countries have varying regulations that may favor one treatment agent over another. In general, we consider all three choices equally acceptable. The duration of treatment will also be influenced by the patient's response. As a guideline, the consensus views a trial period of five doses of eculizumab, three doses of ravulizumab, or three weeks of pegcetacoplan as reasonable. If the patient does not respond adequately, switching to another option is recommended.

When patients transition from a C5 inhibitor to pegcetacoplan, during the initial 4 weeks, pegcetacoplan is administered twice weekly at a dose of 1080 mg alongside the patient's ongoing C5 inhibitor treatment. This approach minimizes the risk of hemolysis associated with abruptly discontinuing C5 inhibitor treatment. After the initial 4 weeks, the patient should discontinue the C5 inhibitor and continue with pegcetacoplan monotherapy.

d) Allo-HCT

- Potentially curative but not recommended as initial therapy, except for PNH associated with bone marrow failure.
- Not recommended for PNH patients with thrombotic complications.
- Should be considered selectively, primarily in cases resistant to thromboprophylaxis and C5 inhibitor therapy, and in patients with PNH/AA and PNH/MDS with significant BMD.

1.3 American Guidelines

1.3.1 Update on the Diagnosis and Management of Paroxysmal Nocturnal Hemoglobinuria (2016)

In 2016, the American Society of Hematology (ASH) released a consolidated set of clinical guidelines for the diagnosis and treatment of patients with PNH[13]. This publication served as an update to the previous ASH guideline issued in 2014. Recommendations are synthesized in the following section.

1.3.1.1 Diagnosis and Classification of PNH

Traditionally, Ham test (acidified serum lysis) and sucrose lysis test performed on a patient's blood sample were used to detect lysis of red blood cells exposed to activated complement. These tests are labor intensive and have poor sensitivity due to the short half-life of circulating PNH red blood cells. Nowadays, flow cytometry analysis with fluorescently labelled inactive toxin aerolysin (FLAER) and cell surface markers on blood cells is the method of choice for diagnosis and monitoring PNH patients.

Once suspected based on clinical and laboratory data (cytopenia, elevated lactate dehydrogenase LDH, elevated indirect bilirubin, low haptoglobin), diagnosing PNH is straightforward because deficiency of GPI-Aps on peripheral blood cells is readily demonstrated by flow cytometry.

In addition to flow cytometric analysis, the initial assessment of a patient with PNH should encompass a complete blood count and reticulocyte count to evaluate the impact of the disease on the production of leukocytes, platelets, and erythrocytes. Biochemical markers indicating hemolysis (serum LDH concentration, fractionated bilirubin, and haptoglobin levels), iron store determination, and examinations including bone marrow aspirate, biopsy, and cytogenetics should also be conducted.

These diagnostic procedures will enable the classification of patients into three groups in accordance with the recommendations of the International PNH Interest Group:

Table 2. Classification of Paroxysmal Nocturnal Hemoglobinuria (PNH)

Category	Rate of intravascular hemolysis	Bone marrow	Flow cytometry	Benefit from eculizumab
Classic	Florid (markedly abnormal LDH often with episodic macroscopic hemoglobinuria)	Cellular marrow from erythroid hyperplasia and normal or near-normal morphology	Large population (>50%) of GPI-AP–deficient PMNs	Yes
PNH in the setting of another bone marrow failure syndrome	Mild (Often with minimal abnormalities of biochemical markers of hemolysis)	Evidence of a concomitant bone marrow failure syndrome	Although variable, the percentage of GPI-AP–deficient PMNs is usually relatively small (<50%)	Typically, no, but some patients have relatively large clones and clinically significant hemolysis and may benefit from treatment
Subclinical	No clinical or biochemical evidence of intravascular hemolysis	Evidence of a concomitant bone marrow failure syndrome	Small (<10%) population of GPI-AP–deficient PMNs	No

1.3.1.2 Clinical Manifestations and Their Management

- **Anemia** in PNH is multifactorial, arising from a combination of both intravascular hemolysis and bone marrow failure (BMF). An elevated reticulocyte count and up to a 10-fold increase in LDH are also common. Patients with subclinical PNH are asymptomatic with normal or near normal blood counts and few PNH granulocytes.
- **Thrombosis** leads to severe morbidity and is the primary cause of mortality in PNH. Thrombotic events can occur at various locations, though venous thrombosis is more frequently observed than arterial. Notably, common sites of occurrence include veins within the intraabdominal region (such as hepatic, portal, mesenteric, and splenic veins) and cerebral veins (particularly sagittal and cavernous sinuses). Among these, hepatic vein thrombosis (known as Budd-Chiari syndrome) stands out as the most prevalent site of thrombosis in PNH. Unless there is a clear and absolute contraindication, such as hemorrhagic

infarction in the central nervous system, immediate anticoagulation with heparin is necessary for acute thrombotic events. For PNH patients who have a prior history of thromboembolic complications, a vitamin K antagonist may be used. Whether low-molecular-weight heparins or novel oral anticoagulants such as direct thrombin inhibitors and factor Xa inhibitors are more, less, or equally efficacious has not been determined.

- **Thrombocytopenia** often complicates PNH, and this issue must be addressed when formulating an anticoagulation management plan. Transfusions should be given to maintain the platelet count in a safe range rather than withholding therapy.
- **Smooth muscle dystonia**: Abdominal pain, dysphagia, esophageal spasm, and erectile dysfunction are common symptoms associated with classical PNH and are a direct consequence of intravascular hemolysis, the release of free hemoglobin and NO depletion.
- **Hemoglobinuria:** Patients with NPH present dark urine due to the destruction of red blood cells (hemolysis) by complement. Chronic intravascular hemoglobinuria may lead to iron deficiency that should be treated.
- **Increased risk of chronic kidney disease**.

1.3.1.3 Treatment of PNH

Completing the comprehensive diagnostic assessment as outlined in table 2 above will facilitate the development of a structured treatment strategy based on disease classification.

a) Classical PNH:

- The MAC is composed of complement components C5b, C6, C7, C8, and multiple C9 molecules (figure 1). Blocking its formation can inhibit the complement-mediated intravascular hemolysis in PNH.
- Eculizumab is a humanized monoclonal antibody that binds to complement C5, preventing its activation to C5b by the APC C5 convertase and thus inhibiting MAC formation. Its use is recommended in classic PNH.
- The recommended dose of eculizumab is fixed at 900 mg every 2 weeks ± 2 days.
- Some patients may exhibit signs of breakthrough intravascular hemolysis, characterized by an increase in LDH levels and the emergence of constitutional symptoms, near the end of a 14-day treatment cycle. To address this, shortening the treatment cycle to either 13 or 12 days is recommended. Additionally, in some cases, it may be necessary to increase the maintenance dose of eculizumab or to undergo a bone marrow transplant (BMT).

- In extravascular hemolysis, splenectomy or corticosteroids may ameliorate the hemolysis in symptomatic or transfusion-dependent patients by removing or inhibiting the function of phagocytic cells.
- Eculizumab seems to lower the risk of thromboembolic complications. For patients on eculizumab without a history of such complications, prophylactic anticoagulation may not be required. However, for those who experienced a thromboembolic event before starting eculizumab, continuing anticoagulation is recommended.

b) PNH in the setting of another bone marrow failure syndrome (patients with a bone marrow failure syndrome along with a PNH clone exhibiting clinical or biochemical signs of hemolysis):

- In these cases, the primary clinical concern revolves around bone marrow failure, while hemolysis is primarily an incidental discovery. Most individuals with PNH/aplastic anemia (AA) and PNH/myelodysplastic syndromes (MDS) typically possess relatively modest PNH clones. Consequently, specific PNH therapy is generally unnecessary.
- Instead, treatment should be centered on addressing the underlying bone marrow failure syndrome.
- For patients presenting with clinical PNH in the context of bone marrow failure, approximately 50% of cases necessitate the management of PNH-related complications (utilizing eculizumab for hemolysis and anticoagulation for thrombosis).

c) Subclinical PNH

Patients who present with subclinical PNH do not typically progress to clinical PNH. Specific PNH therapy is not recommended. Some studies suggest a favorable response to immunosuppressive therapy.

1.4 International Guidelines

1.4.1 Brazilian Association of Hematology, Hemotherapy and Cell Therapy: Consensus Statement for Diagnosis and Treatment of Paroxysmal Nocturnal Hemoglobinuria (2020)

The recommendations issued by the Brazilian Association of Hematology, Hemotherapy and Cell Therapy and summarized below reflect expert opinions and are grounded in the most up-to-date evidence and international guidelines, with the aim of assessing the diagnosis and treatment of patients with PNH, as well as the early identification of its systemic complications[2].

1.4.1.1 Screening

Screening for PNH should be considered for patients experiencing one or more of the symptoms listed below:

- Patients with chronic intravascular hemolysis characterized by:
    - LDH levels ≥1.5 times the upper limit of normal
    - Low haptoglobin levels
    - Negative Direct Antiglobulin Test (DAT)
    - Hemoglobinuria or renal dysfunction
- Unexplained thrombosis (venous or arterial), especially when occurring in unusual locations and in young patients displaying signs of hemolytic anemia and/or cytopenia.
- Symptoms such as dysphagia, abdominal pain, or erectile dysfunction of unknown origin, accompanied by evidence of hemolysis.
- Patients with iron deficiency of unknown cause and signs of hemolysis.
- Suspected or confirmed diagnoses of aplastic anemia, MDS, particularly those with hypoplastic MDS.
- Persistent unexplained cytopenia without an identified cause.

1.4.1.2 Diagnosis

- Laboratory findings in PNH demonstrate characteristics of non-antibody-mediated intravascular hemolysis, including: Anemia, elevated reticulocyte count, increased levels of LDH and bilirubin, reduced haptoglobin levels, presence of free serum hemoglobin causing pink/red serum, hemoglobinuria leading to pink/red urine, positive dipstick test for heme and negative sediment for red blood cells, negative DAT or coombs, loss of GPI-anchored proteins, findings associated with organ damage resulting from hemolysis and/or thrombosis.
- Flow cytometry is the primary and widely accepted method for confirming a PNH diagnosis. Some clinicians use annual flow cytometry to screen patients with underlying bone marrow disorders. Flow cytometry involves incubating the patient's peripheral blood cells with fluorescently labeled monoclonal antibodies targeting GPI-anchored proteins.
- PNH diagnosis is confirmed when ≥2 blood cell lineages (preferably granulocytes and monocytes) show reduced or absent GPI-linked proteins. Assayed proteins include CD59, CD55, CD14, CD15, CD16, CD24, CD45, CD64, and FLAER, a reagent derived from the bacterial toxin aerolysin, which directly

binds to the GPI anchor. Proaerolysin, the inactive precursor of aerolysin, also binds to GPI.

- It's crucial to classify PNH based on flow cytometry results for reticulocyte count, serum LDH concentration, and bone marrow analysis:
    - Subclinical PNH: No specific PNH therapy required. Focus on addressing BMF syndrome.
    - PNH/BMF Syndrome: Prioritize treatment for BMF. Patients with significant PNH clones may benefit from eculizumab.
    - Classic PNH: Eculizumab therapy is recommended.

1.4.1.3 Treatment

Treatment options for PNH include supportive care, allogeneic HCT, and Complement blockade using the anti-C5 monoclonal antibody eculizumab.

a) Supportive care

- Oral Iron and Supplements:
    - Oral iron may be needed to replace significant urinary losses.
    - Folate and vitamin B12 supplementation are typically recommended.
- RBC Transfusion:
    - RBC transfusion might become necessary if the above measures fail to maintain adequate hemoglobin levels.
- Antibiotic Treatment:
    - Prompt antibiotic treatment is essential for bacterial infections in PNH patients to prevent exacerbation of hemolytic crises.
- Use of Glucocorticoids:
    - Glucocorticoids are commonly used, but their effectiveness is empirical with no clear benefits, as no randomized studies support their use.
    - Steroid therapy may be considered in specific situations and for a limited duration to reduce the severity and duration of hemolytic crises.
- Thromboprophylaxis and Eculizumab:
    - Primary prophylaxis should be considered in patients without eculizumab and with high PNH clone size (>50% granulocyte clone),

elevated D-dimer levels, during pregnancy, perioperative conditions, and other thrombophilic risk factors.

- Secondary prevention with eculizumab is appropriate for patients who have already experienced thromboembolic events related to PNH.

- Immunosuppressive Treatment:
  - Immunosuppressive treatment should be considered for PNH patients with AA and BMD.
  - It is not recommended to use immunosuppressive treatment to address hemolysis crises or activity.

b) Allogeneic hematopoietic stem cell transplantation (HCT)

- Allogeneic HCT is a potentially curative treatment for PNH.
- However, it is typically reserved for the most severely affected patients due to significant associated morbidities and mortality risks.
- Suitable candidates for HCT usually include individuals with life-threatening PNH-related conditions, such as: Severe AA who have access to an HLA-matched donor, some high-risk cases of MDS, PNH complications that do not respond to eculizumab or when eculizumab is not available.

c) C5 Inhibitors: Eculizumab

- Eculizumab (Soliris®) is a humanized anti-C5 antibody. It is the only FDA and EMA-approved treatment for PNH, also approved by ANVISA in Brazil.
- Eculizumab binds to C5, inhibiting the formation of C5a and C5b-9, which reduces uncontrolled complement activation.
- Evidence supporting eculizumab's efficacy and safety comes from randomized trials and observational studies. Prolonged use of eculizumab improves quality of life, reduces thrombotic events and hemolysis compared to a placebo.
- Candidates eligible for Eculizumab: Hemolysis (LDH ≥ 1.5 ULN) and symptomatic patients with any of the following:
  - Hb < 7 g/dL or Hb < 10 g/dL in cardiac symptom cases
  - Thrombosis related to PNH
  - Complications associated with hemolysis: renal dysfunction and pulmonary hypertension
  - Symptoms like abdominal pain, dysphagia, or erectile dysfunction
  - Pregnancy, especially in cases with prior gestational complications

- Eculizumab should not be considered for patients with:
    - Mild or no hemolysis-related symptoms.
    - Small granulocyte clone size (<30%) with no hemolysis or normal blood counts.
- Eculizumab doesn't address the underlying hematopoietic stem cell defect causing PNH. It's not a curative treatment and is not proven beneficial for PNH without hemolysis or thrombosis, especially in AA or MDS cases. Its use is limited in these cases due to high costs and the importance of other therapies for underlying AA or MDS.
- Discontinuation of Treatment: Consider discontinuing eculizumab treatment when there is no clinical benefit and one or more of the following associated clinical or laboratory features are present:
    - If the need for RBC transfusions decreases by less than 30% six months after the initial eculizumab dose.
    - When significant hemolysis continues despite minimal improvement in baseline hemoglobin levels after the first eculizumab dose.
    - In cases where the disease goes into remission without the need for eculizumab.
    - If a patient develops severe BMF syndrome.
    - When the patient decides to stop treatment or fails to adhere to treatment and clinical monitoring procedures.
- Pregnancy and Eculizumab: Treatment with eculizumab can help prevent complications for both the mother and the baby. Therefore, pregnant patients on eculizumab should not discontinue the medication during pregnancy and breastfeeding. In some cases, preventive prophylaxis with warfarin might be considered.

d) Next-generation anti-complement drugs

In addition to eculizumab, there are several other approaches under development for blocking complement activation. These include monoclonal antibodies and various anti-complement proteins such as peptide inhibitors, small molecule inhibitors, and decoy receptors. One promising example is ravulizumab, a novel monoclonal antibody that, like eculizumab, targets C5 to prevent its cleavage by C5 convertases. What sets ravulizumab apart is its longer half-life, allowing for administration every eight weeks, potentially offering similar efficacy and safety benefits.

Section 2.0 Drug Therapy

2.1 Complement C5 Inhibitor

2.1.1 Ravulizumab

Information on Ravulizumab is detailed in the table below[14].

Table 3. Ravulizumab Drug Information

SCIENTIFIC NAME RAVULIZUMAB	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes, December 2018
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	D59.5
Drug Class	Complement inhibitors
Drug Sub-class	Complement C5 Inhibitor
ATC Code	L04AA43
Pharmacological Class (ASHP)	Monoclonal Antibodies
DRUG INFORMATION	
Dosage Form	Solution for infusion
Route of Administration	IV, SUBQ
Dose (Adult) [DDD]	**IV:** ***Weight 20 kg to <30 kg:*** Loading dose: IV: 900 mg as a single dose. Maintenance dose: IV: 2,100 mg once every 8 weeks starting 2 weeks after the loading dose. ***Weight 30 kg to <40 kg:*** Loading dose: IV: 1,200 mg as a single dose. Maintenance dose: IV: 2,700 mg once every 8 weeks starting 2 weeks after the loading dose.

	Weight 40 kg to <60 kg: Loading dose: IV: 2,400 mg as a single dose. Maintenance dose: IV: 3,000 mg once every 8 weeks starting 2 weeks after the loading dose. ***Weight 60 kg to <100 kg:*** Loading dose: IV: 2,700 mg as a single dose. Maintenance dose: IV: 3,300 mg once every 8 weeks starting 2 weeks after the loading dose. ***Weight ≥100 kg:*** Loading dose: IV: 3,000 mg as a single dose. Maintenance dose: IV: 3,600 mg once every 8 weeks starting 2 weeks after the loading dose. **SUBQ:** *Weight ≥40 kg:* Maintenance dose: 490 mg once weekly starting 2 weeks after weight-based IV loading dose.
Maximum Daily Dose Adults	N/A
Dose (pediatrics)	Dose is based on weight at time of treatment for that dose.
Maximum Daily Dose Pediatrics	N/A
Adjustment	**Adjustment for Toxicity: Adult** Adverse reaction during infusion: May slow or stop infusion. Interrupt infusion and begin appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.
Prescribing edits	MD, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Ravulizumab must be administered by a healthcare professional and under the supervision of a physician

	experienced in the management of patients with hematological disorders.
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Ravulizumab is recommended as an option for treating PNH in adults whose disease is clinically stable after having eculizumab for at least 6 months.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**>10%:** Gastrointestinal: Diarrhea Local: Injection-site reaction Nervous system: Headache Respiratory: Upper respiratory tract infection **1% to 10%:** Genitourinary: Urinary tract infection Hypersensitivity: Infusion-related reaction Neuromuscular & skeletal: Arthralgia, back pain, limb pain
Drug Interactions	Category X: • Tofacitinib • Upadacitinib • Tacrolimus (Topical)
Special Population	N/A
Pregnancy	Ravulizumab is a humanized monoclonal antibody (IgG2). The transfer of human IgG through the placenta depends on factors like IgG subclass, maternal serum levels, birth weight, and gestational age, generally increasing as pregnancy progresses. The period of organogenesis is likely to have the lowest exposure.
Lactation	The presence of ravulizumab in breast milk is currently not understood.

	Because there is a risk of significant adverse effects in the infant being breastfed, the manufacturer advises against breastfeeding during the treatment period and for a duration of 8 months following the last dose of ravulizumab.
Contraindications	Unresolved *Neisseria meningitidis* infection; patients not currently vaccinated against *N. meningitidis*, unless the risks of delaying ravulizumab treatment outweigh the risks of developing a meningococcal infection.
Monitoring Requirements	Before starting treatment with ravulizumab, assess the patient's immunization history. Be vigilant for early signs of meningococcal infection, and promptly evaluate any suspected infection. If administering ravulizumab to patients with active systemic infections, closely monitor for signs of infection worsening. For patients receiving SUBQ injections of ravulizumab, monitor them for at least one hour after the injection to watch for infusion reactions. After discontinuing ravulizumab treatment, closely monitor the patient for at least 16 weeks to detect hemolysis and other reactions. Keep an eye out for signs and symptoms of hemolysis, such as an increase in LDH levels along with a sudden decrease in PNH clone size or hemoglobin, or the reappearance of symptoms like fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea)...
Precautions	**Concerns related to adverse effects:**

	• Infection: Vaccinate for S. pneumoniae and Hib according to the Advisory Committee on Immunization Practices (ACIP) recommendations. • Infusion reactions: If signs of cardiovascular instability or respiratory compromise occur, interrupt infusion, and manage supportively. • Meningococcal infection: If urgent ravulizumab therapy is indicated in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible and provide at least 2 weeks of antibacterial prophylaxis. To reduce the risk for meningococcal disease, consider antimicrobial prophylaxis with oral antibiotics (penicillin, or macrolides if penicillin-allergic) for the duration of ravulizumab therapy. **Concurrent drug therapy issues:** Anticoagulation: Treatment with ravulizumab should not alter anticoagulation management; the effect of anticoagulant therapy withdrawal is unknown. **Other warnings/precautions:** • Discontinuation in atypical hemolytic uremic syndrome: If thrombotic microangiopathy complications occur after discontinuation, consider restarting ravulizumab treatment or appropriate organ-specific supportive measures. • Discontinuation in PNH: If hemolysis signs/symptoms (including elevated LDH) occur after discontinuation,

	consider restarting ravulizumab treatment.
Black Box Warning	**Serious Meningococcal Infection:** Life-threatening meningococcal infections and sepsis have occurred in patients treated with ravulizumab. Patients should receive meningococcal vaccines at least 2 weeks before their first ravulizumab dose, unless delaying ravulizumab therapy carries a greater risk of harm than the potential for a meningococcal infection. Regularly monitor patients for early signs of such infections and seek immediate evaluation if infection is suspected.
REMS	Counsel patients about the risk of meningococcal infection/sepsis; provide REMS educational materials to patients, and ensure patients are vaccinated with meningococcal vaccines.

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of PNH treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. The recommendations below are for Ravulizumab.

Table 4. Ravulizumab HTA Analysis

MEDICATION	AGENCY	HTA RECOMMENDATION
Ravulizumab	NICE[15]	19 May 2021: Ravulizumab is **recommended**, within its marketing authorization, as an option for treating PNH in adults: • With hemolysis with clinical symptoms suggesting high disease activity, **or** • Whose disease is clinically stable after having eculizumab for at least 6 months, **and**

		• The company provides it according to the commercial arrangement. Currently, eculizumab infusions every 2 weeks are the standard treatment. Ravulizumab, as an alternative treatment, is a cost-effective use of NHS resources for PNH: • Clinical trial evidence indicates that ravulizumab is equally effective and safe as eculizumab. • Ravulizumab requires less frequent administration, improving quality of life (reduced infusion frequency with ravulizumab leads to fewer nurse visits, enabling other activities) • It may also be more cost-effective due to reduced dosing frequency.
	CADTH[16]	February 11, 2022: • Ultomiris (ravulizumab for injection) is approved for treating adult patients with PNH. • **Reimbursement** for Ultomiris is subject to specific clinical **criteria and conditions**. • Ultomiris coverage is restricted to patients who meet the existing reimbursement criteria established for a similar drug, eculizumab, used in PNH treatment. • Furthermore, the cost of Ultomiris treatment should not exceed the cost of eculizumab treatment. • Patients who initially respond inadequately or have experienced treatment failure with eculizumab at the recommended Health Canada dosage are not eligible for ravulizumab reimbursement.
	HAS[17]	May 2021: Approval for reimbursement in the treatment of PNH in adult patients: • Who have hemolysis with clinical symptoms indicating high disease activity. • Who are clinically stable after treatment with eculizumab for at least the last 6 months.
	IQWIG[18]	August 2019:

		The Objective of the report was to evaluate the additional advantages of ravulizumab when compared to eculizumab, which serves as the appropriate comparator therapy, in two specific patient groups: • Adult patients with PNH experiencing hemolysis along with clinical symptoms indicating high disease activity. • Adult PNH patients who have achieved clinical stability after receiving eculizumab treatment for a minimum of the last 6 months. It is important to note that the report did not establish evidence of added benefit in either of these patient populations.
	PBAC[19]	July 2021 recommended: • The PBAC recommended an Authority Required (non-immediate assessment) listing for ravulizumab in PNH treatment, stipulating that it should be available only under special arrangements in the Section 100 “Highly Specialized Drugs Program”. • The PBAC's decision was based on the belief that ravulizumab's safety and effectiveness were likely comparable to eculizumab. • The PBAC considered the submission for ravulizumab as an opportunity to reevaluate the cost-effectiveness of eculizumab for inclusion in the PBS. • While clinical data suggested a survival advantage for eculizumab compared to best supportive care, the exact magnitude of this benefit in PNH remained uncertain, and the cost-effectiveness was deemed very high. • Nevertheless, the PBAC recommended that eculizumab be included in the PBS at a reduced price. • Ravulizumab's listing was advised based on cost-minimization compared to eculizumab.

CONCLUSION STATEMENT – Ravulizumab

Currently, eculizumab infusions every 2 weeks are the standard treatment. Ravulizumab, as an alternative treatment, is a cost-effective use for PNH. It is recommended as an option for treating PNH in adults:

- With hemolysis with clinical symptoms suggesting high disease activity.
- Whose disease is clinically stable after having eculizumab for at least 6 months.

Ravulizumab may transfer through the placenta, with exposure likely lowest during the period of organogenesis. The presence of ravulizumab in breast milk is not well understood, and breastfeeding is discouraged during treatment and for 8 months after the last dose due to potential adverse effects on the infant.

Patients treated with ravulizumab have experienced life-threatening meningococcal infections and sepsis. To mitigate this risk, patients should receive meningococcal vaccines at least 2 weeks prior to their initial ravulizumab dose unless delaying ravulizumab treatment poses a greater danger than the risk of a meningococcal infection. Continuous vigilance for early signs of these infections is crucial, and prompt evaluation should be sought if an infection is suspected.

2.2 Complement C3 Inhibitor

2.2.1 Pegcetacoplan

Information on Pegcetacoplan is detailed in the table below[20].

Table 5. Pegcetacoplan Drug Information

SCIENTIFIC NAME PEGCETACOPLAN	
SFDA Classification	Prescription
SFDA	Yes
US FDA	N/A
EMA	Yes, 2021
MHRA	Yes
PMDA	Yes March 2023
Indication (ICD-10)	D59.5
Drug Class	Complement inhibitors
Drug Sub-class	Complement C3 Inhibitor
ATC Code	L04AA54

Pharmacological Class (ASHP)	Monoclonal Antibodies
DRUG INFORMATION	
Dosage Form	Solution for infusion
Route of Administration	SUBQ
Dose (Adult) [DDD]	**SUBQ:** 1,080 mg twice weekly. *Conversion from C5 inhibitors:* • *Conversion from eculizumab:* When converting from eculizumab to pegcetacoplan, initiate pegcetacoplan while continuing eculizumab at its current dose. After 4 weeks, discontinue eculizumab and continue pegcetacoplan monotherapy. • *Conversion from ravulizumab:* Initiate pegcetacoplan no more than 4 weeks after the last ravulizumab dose.
Maximum Daily Dose Adults	N/A
Dose (pediatrics)	No data are available, therefore, there is no indication for pediatric use.
Maximum Daily Dose Pediatrics	N/A
Adjustment	**For LDH >2 times upper limit normal:** Adjust pegcetacoplan dosing regimen to 1,080 mg every 3 days. Monitor LDH twice weekly for at least 4 weeks after a dose increase.
Prescribing edits	MD, ST
AGE (Age Edit):	N/A
CU (Concurrent Use Edit):	N/A
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Pegcetacoplan should be prescribed by or in consultation with a hematologist experienced in managing PNH.
PA (Prior Authorization):	N/A
QL (Quantity Limit):	N/A
ST (Step Therapy):	Indicated for the treatment of adult patients with PNH who have an

	inadequate response to, or are intolerant of, a C5 inhibitor.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**>10%:** Gastrointestinal: Abdominal pain, diarrhea Infection: Respiratory tract infection, viral infection Local: Injection site reaction Nervous system: Fatigue **1% to 10%:** Cardiovascular: Chest pain, hypertension Nervous system: Headache Neuromuscular and skeletal: Back pain Respiratory: Hypersensitivity pneumonitis
Drug Interactions	Category X: • Pimecrolimus • Natalizumab • Tofacitinib • Upadacitinib:
Special Population	N/A
Pregnancy	Patients at risk of pregnancy should employ reliable contraception methods throughout the treatment period and continue for 40 days after their final pegcetacoplan dose. Based on findings from animal studies, exposure to pegcetacoplan during pregnancy may result in harm to the fetus.
Lactation	The presence of pegcetacoplan in breast milk has not been established. The manufacturer advises against breastfeeding during treatment and for 40 days following the last pegcetacoplan dose due to the

	potential for severe adverse effects in the nursing infant.
Contraindications	• Hypersensitivity to pegcetacoplan or any component of the formulation. • Patients who are not currently vaccinated against certain encapsulated bacteria, unless the risks of delaying pegcetacoplan treatment outweigh the risks of developing a bacterial infection with an encapsulated organism. • Unresolved serious infection caused by encapsulated bacteria including *S. pneumoniae*, *N. meningitidis*, and *H. influenzae*.
Monitoring Requirements	• Assess immunization status before starting treatment. • Monitor LDH levels at baseline, periodically during treatment, and twice weekly for at least 4 weeks after a dose increase. • Evaluate the pregnancy status of patients who may become pregnant before initiating treatment. • Keep vigilant for signs and symptoms of serious infections and serious hypersensitivity reactions, including anaphylaxis, facial swelling, rash, and urticaria. • Continuously monitor for signs and symptoms of hemolysis for a minimum of 8 weeks after discontinuing pegcetacoplan.
Precautions	In cases of discontinuation in PNH, if there are indications or symptoms of hemolysis (including an increase in LDH), it should be contemplated to restart pegcetacoplan therapy.
Black Box Warning	**Serious infections caused by encapsulated bacteria:**

	Meningococcal infections can occur in individuals receiving pegcetacoplan treatment and pose a rapid, potentially life-threatening, or fatal risk if not promptly identified and treated. Pegcetacoplan use may increase susceptibility to severe infections, particularly those caused by encapsulated bacteria like Streptococcus pneumoniae, Neisseria meningitidis (serogroups A, C, W, Y, and B), and Haemophilus influenzae type B.
REMS	Pegcetacoplan is available only through a restricted program under a REMS. Under the pegcetacoplan REMS, prescribers must enroll in the program. Enrollment in the pegcetacoplan REMS program and additional information are available by telephone: 1-888-343-7073 or at https://www.empavelirems.com.

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of PNH treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. The recommendations below are for Pegcetacoplan.

Table 6. Pegcetacoplan HTA Analysis

MEDICATION	AGENCY	HTA RECOMMENDATION
Pegcetacoplan	NICE[21]	March 2022: Pegcetacoplan is recommended, within its marketing authorization, as an option for treating PNH in adults who have anemia after at least 3 months of treatment with a C5 inhibitor: • Clinical trial data indicates that pegcetacoplan improves both hemoglobin levels and hematological PNH symptoms in patients who

		experience anemia while on eculizumab treatment. • Pegcetacoplan is a more cost-effective option than ravulizumab and eculizumab while providing enhanced effectiveness for adults experiencing anemia alongside C5 inhibitor treatment. As a result, it is recommended as a treatment choice. The committee considers pegcetacoplan innovative as it addresses both intravascular and extravascular hemolysis by targeting the complement cascade earlier than C5 inhibitors, and recognizes that pegcetacoplan, administered as a subcutaneous infusion that can be self-administered, may offer benefits over current treatments for some individuals.
	CADTH[22]	March 20, 2023: Indicated for the treatment of adult patients with PNH who have an inadequate response to, or are intolerant of, a C5 inhibitor. **Reimbursement conditions**: 1. To qualify for treatment with pegcetacoplan, patients must have a confirmed diagnosis of PNH and meet specific criteria: • Patients should have previously met public drug plan reimbursement criteria for initiating C5 inhibitor treatment. • Patients must either exhibit persistent anemia with hemoglobin levels below 10.5 g/dL despite undergoing a suitable trial of C5 inhibitor treatment, with causes other than extravascular hemolysis ruled out, or have experienced intolerable adverse events from C5 inhibitor treatment. 2. Renewal of pegcetacoplan treatment should follow a similar process as for other complement inhibitors already reimbursed for PNH patient treatment.

		3. Pegcetacoplan discontinuation should mirror the approach used for other complement inhibitors currently reimbursed for PNH patient treatment. 4. Pegcetacoplan should be prescribed by a hematologist with expertise in managing PNH or in consultation with one. 5. Pegcetacoplan should not be used concurrently with other complement inhibitors, except during the initial 4 weeks of treatment. 6. Price Reduction: CADTH's evaluation of health economic evidence suggests that, at the current public list price, Empaveli does not offer good value to the healthcare system. A price reduction is therefore necessary. Based on public list prices, Empaveli is estimated to generate cost savings of approximately $863,569 for public drug plans over the next 3 years when used to treat adult PNH patients with inadequate responses to or intolerance of C5 inhibitors. However, if public funding for eculizumab up-dosing is not available, Empaveli may increase public drug plan budgets.
	HAS	N/A
	IQWIG	N/A
	PBAC[23]	JULY 2022, recommended: The PBAC proposed the inclusion of pegcetacoplan in the Section 100 “Highly Specialized Drugs Program”, subject to authority requirements, for the treatment of adult patients with PNH who do not respond adequately to or cannot tolerate eculizumab or ravulizumab therapy. This recommendation was driven, in part, by the PBAC's assessment that pegcetacoplan would be cost-effective if its cost were minimized in comparison to ravulizumab. Additionally, the PBAC suggested potential changes to PBS restrictions for eculizumab to facilitate

		switching from PBS-subsidized pegcetacoplan during pregnancy and for eculizumab and ravulizumab to permit the return of patients who exhibit intolerance or resistance to pegcetacoplan.

CONCLUSION STATEMENT- Pegcetacoplan

Pegcetacoplan is recommended as an option for treating PNH in adults who have anemia after at least 3 months of treatment with a C5 inhibitor (eculizumab, ravulizumab).

Patients should use effective contraception during treatment and for 40 days after the last pegcetacoplan dose due to potential fetal harm based on animal studies. Breastfeeding is not recommended during pegcetacoplan treatment and for 40 days after the final dose due to uncertain presence in breast milk and potential severe adverse effects on nursing infants.

Serious infections, including meningococcal infections, are a potential risk with pegcetacoplan treatment and can be life-threatening if not promptly addressed. Pegcetacoplan use may heighten vulnerability to severe infections, particularly those caused by encapsulated bacteria such as Streptococcus pneumoniae, Neisseria meningitidis (serogroups A, C, W, Y, and B), and Haemophilus influenzae type B.

2.3 Other Drugs

2.3.1 Eculizumab[8,24–26]

- Eculizumab (Soliris®) is a humanized anti-C5 antibody. It is the only FDA and EMA-approved treatment for PNH, also approved by ANVISA in Brazil.
- Eculizumab is a humanized monoclonal antibody targeting C5, approved for treating PNH in patients with high disease activity, regardless of transfusion history.
- Approval of eculizumab was based on the TRIUMPH study, which demonstrated its effectiveness in reducing hemolysis, transfusion requirements, and fatigue in PNH patients. The SHEPHERD study also confirmed the benefits of eculizumab, including those with thrombocytopenia and minimal transfusion needs. An open-label extension of these studies showed a significant reduction in TE with eculizumab.
- Eculizumab is recommended for classic PNH symptoms indicating high disease activity, regardless of transfusion history. Consequently, patients with a significant PNH clone (>50% PNH granulocytes), intravascular hemolysis

(LDH ≥ 1.5 ULN), and robust bone marrow reserves (high reticulocyte count) are likely to benefit from C5 inhibitors.

- In rare cases, patients with AA and extensive PNH clonal expansion undergoing immunosuppressive therapy may experience worsening PNH symptoms similar to classic PNH patients. They should be treated accordingly.
- Patients with bone marrow failure, active hemolysis, and an indication for allo-HCT should receive anti-C5 treatment before HCT to reduce transplant-related mortality.
- Use of eculizumab in Subclinical PNH: Asymptomatic subclinical PNH patients do not require anti-complement treatment. Close monitoring (every 6 to 12 months) is essential to detect PNH clone expansion and hemolysis symptoms.
- IV: Induction: 600 mg weekly for 4 doses; Maintenance: 900 mg at week 5; then 900 mg every 2 weeks thereafter.
- Adverse Events (>10%): Cardiovascular: Hypertension, tachycardia; Central nervous system: Headache, insomnia, fatigue, dizziness; Dermatologic: Skin rash, pruritus; Gastrointestinal: Diarrhea, vomiting, abdominal pain; Hematologic & oncologic: Anemia, leukopenia.
- Patients receiving eculizumab should be vaccinated against meningococcal infections before starting therapy.
- Treatment with eculizumab can help prevent complications for both the mother and the baby. Therefore, pregnant patients on eculizumab should not discontinue the medication during pregnancy and breastfeeding.

2.3.2 Iptacopan[27]

- Iptacopan is a first-in-class oral Factor B inhibitor that can reduce extravascular hemolysis while maintaining control of intravascular hemolysis in patients treated with a C5 inhibitor.
- Not recommended for patients with a history of medication non-adherence due to the risk of missed doses, especially during conditions that amplify complement activity (e.g., infections) or with excessive alcohol consumption.
- Iptacopan has received FDA breakthrough therapy designation for PNH and orphan drug designations from both the FDA and EMA.

2.3.3 Danicopan[28,29]

- Danicopan is a pioneering oral inhibitor of complement Factor D, a component of the alternative complement pathway.

- It can effectively control signs and symptoms of extravascular hemolysis when used as an add-on treatment for patients receiving a C5 inhibitor.
- Preliminary results from a phase 3 trial show that for patients experiencing clinically significant extravascular hemolysis while on ravulizumab or eculizumab, the addition of danicopan was superior to adding a placebo. It resulted in reduced transfusions, increased hemoglobin levels, minimal toxicity, and continued intravascular hemolysis control.
- Danicopan has been granted breakthrough therapy designation by the FDA and PRIME (priority medicine) status by the EMA.

2.3.4 Novel Therapies in Late-Stage Clinical Development[26]

- Ongoing Phase 3 clinical trials are evaluating promising novel agents for PNH patients. These include three fully human anti-C5 monoclonal antibodies: crovalimab, LFG316, and pozelimab/REN3918.
- There are also several eculizumab biosimilars in development.
- A small protein complement C5 inhibitor, rVA576 (Coversin), is being investigated in Phase 2/3 trials, including for PNH patients resistant to eculizumab due to C5 polymorphisms.
- Cemdisiran (ALN-CC5) is a subcutaneously administered RNA interference (RNAi) therapeutic targeting the C5 component of the complement pathway.
- Two other oral, selective small molecule inhibitors of Factor D, BCX9930 and vemircopan, are also in Phase 2/3 PNH trials.

Section 3.0 Key Recommendations Synthesis

PNH is a rare condition characterized by complement-mediated hemolytic anemia, often accompanied by thrombosis, pain, and organ dysfunction due to the deficiency of complement inhibitor proteins on hematopoietic cells. PNH can co-occur with AA or MDS. Baseline evaluation should involve flow cytometry to estimate the size of the PNH clone and a bone marrow examination to assess for AA or MDS. Management of PNH depends on the PNH category and the severity of symptoms:

Classical PNH

C5 complement inhibitors are favored as initial therapy for symptom relief and thrombosis prevention, owing to their proven efficacy, low toxicity, convenience, and established track record.

Currently, eculizumab infusions every 2 weeks are the standard treatment. For patients receiving eculizumab without a history of such complications, prophylactic anticoagulation may not be necessary. However, for those who experienced a TE before starting eculizumab, it is recommended to continue anticoagulation.

Ravulizumab is suggested as an initial treatment due to comparable efficacy with eculizumab but with greater convenience, lower overall cost, and fewer cases of pharmacokinetic breakthrough hemolysis. It is recommended as an option for treating PNH in adults:

- With hemolysis with clinical symptoms suggesting high disease activity.
- Whose disease is clinically stable after having eculizumab for at least 6 months.

In cases of breakthrough hemolysis while on a C5 inhibitor, treatment with pegcetacoplan (or iptacopan or danicopan when available) is recommended instead of continuing with the C5 inhibitor. The Central European expert group identified five specific patient groups where transitioning from a C5 to a C3 inhibitor is highly relevant:

1. Patients with breakthrough intravascular hemolysis during regular C5 inhibitor treatment for ≥ 3 months: Consensus recommends considering a clinical trial, adjusting the eculizumab dose or dosing interval, switching to ravulizumab, or pegcetacoplan, and focusing on treating underlying conditions for sporadic breakthrough hemolysis (100% of the consensus).
2. Patients with clinically relevant C3-mediated extravascular hemolysis on C5 inhibitor treatment for ≥ 3 months: Consensus suggests considering a clinical trial or switching to pegcetacoplan (100% of the consensus).

3. Patients with unprovoked TE while on C5 inhibitor for ≥ 3 months: Consensus advises considering a clinical trial, exploring anticoagulant therapy, or switching to pegcetacoplan in combination with anticoagulants (100% of the consensus).
4. Patients with severe fatigue and impaired QoL despite ≥ 3 months of C5 inhibitor treatment: Clinical trial consideration is recommended, along with evaluating indicators of hemolysis and contemplating transitioning to pegcetacoplan (72 % of the consensus).
5. Patients with rare C5 polymorphisms non-responsive to C5 inhibition: Consensus suggests considering a clinical trial if available or switching to pegcetacoplan (100% of the consensus).

All patients receiving complement inhibitors should undergo vaccination and oral antibiotic prophylaxis to mitigate infectious risks.

PNH in the setting of another BMF syndrome *(patients with a BMF syndrome along with a PNH clone exhibiting clinical or biochemical signs of hemolysis).*

In these scenarios, the main clinical concern revolves around BMF, with hemolysis being primarily an incidental finding. Most individuals with PNH/AA and PNH/MDS typically have relatively small PNH clone sizes. As a result, specific PNH therapy is generally not required.

In the case of patients diagnosed with PNH accompanied by BMF (severe AA or higher-risk MDS), and who are considered medically suitable for transplantation, the recommendation is to opt for allo-HCT rather than relying solely on supportive care or a complement inhibitor. Patients with BMF, active hemolysis, and an indication for allo-HCT should receive anti-C5 treatment before HCT to reduce transplant-related mortality.

Subclinical PNH

Patients who exhibit subclinical PNH generally do not tend to advance to clinical PNH. Therefore, specific PNH treatment is not advisable. Some studies indicate a positive response to immunosuppressive therapy in these cases.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of PNH.

These recommendations should be used to support and not supplant decisions in individual patient management.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

Appendix B. PubMed Search Methodology Terms

Query	Filters	Search Details	Results
((((((((((((hemoglobinuria, nocturnal paroxysmal[MeSH Terms]) OR (Paroxysmal Hemoglobinuria[Title/Abstract])) OR (Paroxysmal Cold Hemoglobinuria[Title/Abstract])) OR (Hemoglobinuria, Paroxysmal Cold[Title/Abstract])) OR (Paroxysmal Hemoglobinuria, Cold[Title/Abstract])) OR (Cold Paroxysmal Hemoglobinuria[Title/Abstract])) OR (Hemoglobinuria, Cold Paroxysmal[Title/Abstract])) OR (Paroxysmal Nocturnal Hemoglobinuria[Title/Abstract])) OR (Hemoglobinuria, Paroxysmal Nocturnal[Title/Abstract])) OR (Marchiafava-Micheli Syndrome[Title/Abstract])) OR (Marchiafava Micheli Syndrome[Title/Abstract])) OR (Syndrome, Marchiafava-Micheli[Title/Abstract])) OR (Paroxysmal Hemoglobinuria, Nocturnal[Title/Abstract])) OR (Hemoglobinuria, Nocturnal Paroxysmal[Title/Abstract])) NOT (Nocturnal Paroxysmal Hemoglobinuria[Title/Abstract])	In the last 5 years	(("hemoglobinuria, paroxysmal"[MeSH Terms] OR "paroxysmal hemoglobinuria"[Title/Abstract] OR "paroxysmal cold hemoglobinuria"[Title/Abstract] OR "hemoglobinuria paroxysmal cold"[Title/Abstract] OR (("paroxysm"[All Fields] OR "Paroxysmal"[All Fields] OR "paroxysmally"[All Fields] OR "paroxysms"[All Fields]) AND "hemoglobinuria cold"[Title/Abstract]) OR "cold paroxysmal hemoglobinuria"[Title/Abstract] OR (("haemoglobinuria"[All Fields] OR "Hemoglobinuria"[MeSH Terms] OR "Hemoglobinuria"[All Fields]) AND "cold paroxysmal"[Title/Abstract]) OR "paroxysmal nocturnal hemoglobinuria"[Title/Abstract] OR "hemoglobinuria paroxysmal nocturnal"[Title/Abstract] OR "marchiafava micheli syndrome"[Title/Abstract] OR "marchiafava micheli syndrome"[Title/Abstract] OR (("syndrom"[All Fields] OR "syndromal"[All Fields] OR "syndromally"[All Fields] OR "Syndrome"[MeSH Terms] OR "Syndrome"[All Fields] OR "syndromes"[All Fields] OR "syndrome s"[All Fields] OR "syndromic"[All Fields] OR "syndroms"[All Fields]) AND "Marchiafava-Micheli"[Title/Abstract]) OR "paroxysmal hemoglobinuria	688

		nocturnal"[Title/Abstract] OR (("haemoglobinuria"[All Fields] OR "Hemoglobinuria"[MeSH Terms] OR "Hemoglobinuria"[All Fields]) AND "nocturnal paroxysmal"[Title/Abstract])) NOT "nocturnal paroxysmal hemoglobinuria"[Title/Abstract]) AND (y_5[Filter])	

Appendix C. Treatment Algorithm for PNH

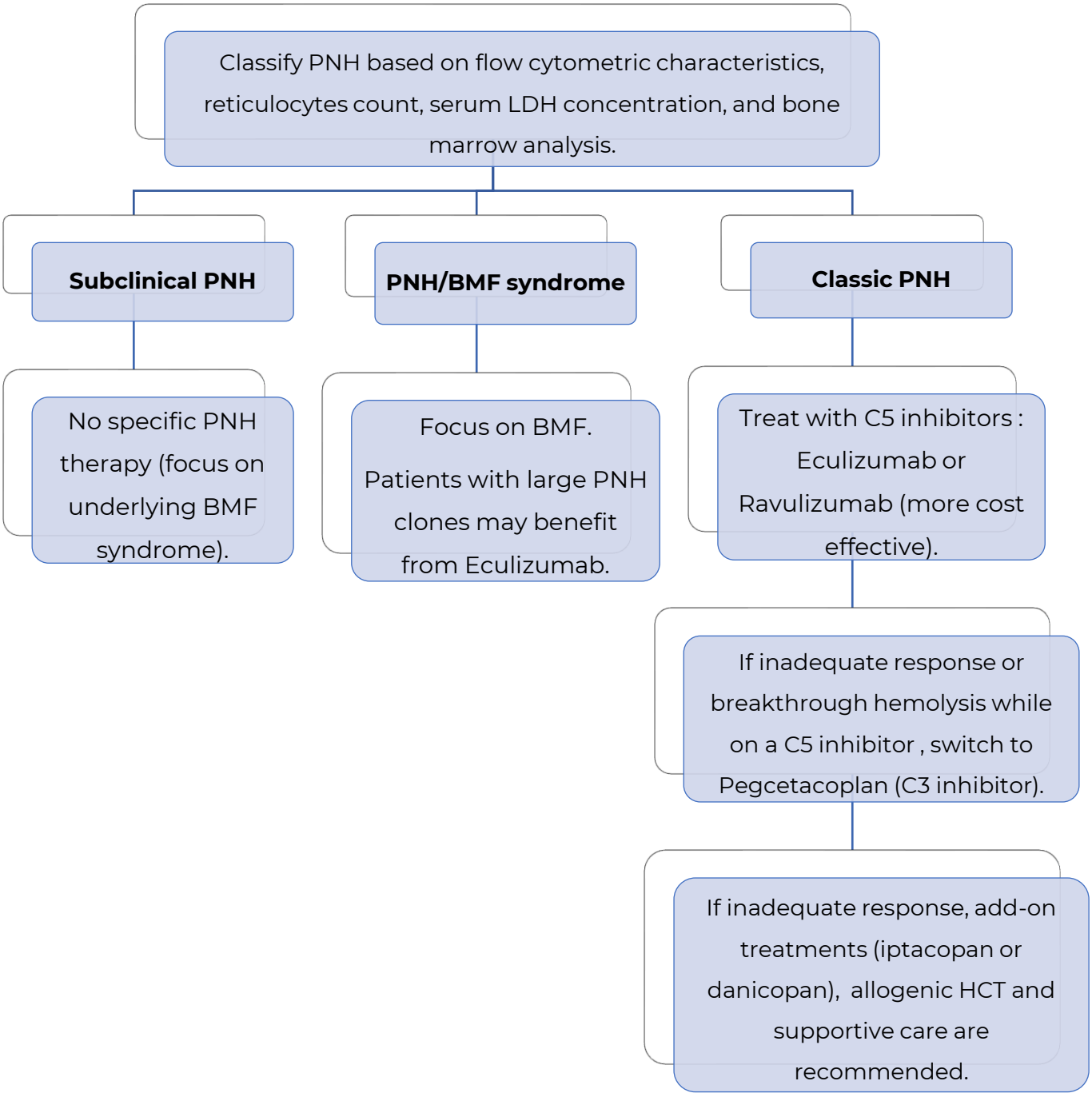

Figure 4. *Treatment Algorithm of Paroxysmal Nocturnal Hemoglobinuria*

Abbreviations: BMF: Bone marrow failure; HCT: Hematopoietic stem Cell Transplantation; PNH: Paroxysmal nocturnal hemoglobinuria.