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CLINICAL SPECTRUM AND THERAPEUTIC ADVANCES IN PEDIATRIC PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

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ABSTRACT

Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired hematopoietic stem cell disorder driven by somatic PIGA mutations, leading to uncontrolled complement activation, intravascular hemolysis, and thrombotic risk. Pediatric PNH represents fewer than 10% of cases and demonstrates a distinct clinical phenotype that complicates diagnosis and management.
Methods: A comprehensive literature search of PubMed, Embase, Web of Science, and Scopus was conducted through July 2025 using predefined keywords related to PNH, pediatrics, bone marrow failure, and complement inhibitors. Eligible studies included clinical trials, registry data, systematic reviews, case series, and case reports. Relevant adult studies were also reviewed when mechanistic or therapeutic insights were applicable to pediatric disease. Data were synthesized narratively, focusing on pathophysiology, clinical spectrum, diagnostic approaches, and therapeutic advances.
Results: Pediatric PNH most often presents with bone marrow failure syndromes rather than classic hemolytic features. Hemoglobinuria is infrequent, while cytopenias predominate. Thrombosis, though less common than in adults, remains a serious complication. High-sensitivity flow cytometry enables early and accurate diagnosis, particularly for small clone sizes. Complement inhibitors—including eculizumab, ravulizumab, and crovalimab—have markedly improved survival and reduced morbidity, while emerging agents targeting proximal complement pathways (pegcetacoplan, iptacopan, danicopan) show promise. Hematopoietic cell transplantation remains the only curative option but is reserved for selected patients.
Conclusions: Pediatric PNH differs significantly from adult disease in presentation and management. Advances in complement inhibition have transformed prognosis, but further pediatric-specific research and inclusion in clinical trials are urgently needed to establish evidence-based guidelines and optimize long-term outcomes.

KEYWORDS

Paroxysmal Nocturnal Hemoglobinuria, Complement-Mediated Hemolysis, Thrombosis, Eculizumab, Bone Marrow Failure Syndromes

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1. Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, life-threatening hematopoietic stem cell disorder characterized by a debilitating clinical course and a median survival of approximately 10 years from diagnosis in untreated patients(Hillmen et al., 1995). A somatic, non-hereditary mutation in the PIGA gene underlies the disease's pathophysiology(Bessler et al., 1994). This mutation results in a clonal expansion of hematopoietic cells that are missing glycosylphosphatidylinositol-anchored proteins (GPI-APs), which include the crucial complement regulators, CD55 and CD59(Schmidt et al., 2016). The absence of these protective proteins allows the complement cascade, a crucial component of the innate immune system, to proceed without regulation, resulting in uncontrolled activation and the formation of the terminal membrane attack complex (MAC)(Holt et al., 2024). Uncontrolled complement activation, a consequence of the absence of these protective proteins, makes red blood cells susceptible and leads to a triad of clinical features: chronic hemolysis, bone marrow failure, and a high risk of thrombotic complications(Ware et al., 1991).

Although PNH can occur at any age, it typically has its onset during adulthood. Cases in pediatric and adolescent patients are exceedingly rare, representing less than 10% of total diagnosed cases(Urbano-Ispizua et al., 2017). The limited incidence of pediatric PNH has historically restricted its study to small case reports and series, which has made it difficult to form a complete understanding of the disease in this population(Urbano-Ispizua et al., 2017). While the underlying pathophysiology is shared, the clinical and hematological manifestations of PNH in pediatric and adolescent patients are markedly distinct from those

observed in adults. Due to a higher incidence of bone marrow failure at diagnosis and a unique symptom profile, recognizing the disease early is a challenge in the pediatric population(Curran et al., 2010).

This review provides a comprehensive summary of the current knowledge regarding pediatric PNH. It focuses on the disease's unique clinical spectrum and the latest therapeutic advancements that have transformed its management. By synthesizing data from key publications, we aim to highlight the distinguishing features of PNH in the pediatric population and evaluate the evolving therapeutic landscape, specifically the implications of emerging targeted complement inhibitors for future treatment paradigms.

2. Pathophysiology of pediatric PNH

PNH arises from a somatic mutation in the PIGA gene, a non-inherited event that affects a single hematopoietic stem cell or progenitor cell. The PIGA gene is located on the X chromosome, a crucial detail in the pathophysiology of this disease. This mutation results in a deficiency of GPI-APs on the surface of hematopoietic cells(Bessler et al., 1994). The mutation is a loss-of-function type, resulting in an inactive protein or no protein production at all(Johnston et al., 2012). Because of X-chromosome inactivation, a single inactivating mutation in the PIGA gene is sufficient to completely disrupt glycosylphosphatidylinositol(GPI) anchor synthesis. This leads to the absence of all GPI-APs from the cell surface. This unique chromosomal location means that a single genetic event can lead to the full disease phenotype, regardless of the patient's sex(Brodsky, 2014).

The product of the PIGA gene is essential for the first step of GPI-APs biosynthesis. Consequently, a mutation in the PIGA gene leads to a complete lack of this anchor's synthesis. The GPI anchor is crucial for attaching approximately 150 different proteins to the outer surface of the cell membrane(Colden et al., 2022; Kumar & Babushok, 2021). Although the mutation affects the absence of many proteins, the clinical phenotype of PNH is predominantly caused by the deficiency of two specific complement regulatory proteins: CD55 and CD59. The absence of these key proteins on the surface of hematopoietic cells, including erythrocytes, leukocytes, and platelets, is the direct cause of the pathological manifestations(DeZern & Brodsky, 2015).

The complement system, a crucial element of the innate immune response, defends the body by promoting the opsonization and lysis of pathogens. Its function relies on a proteolytic cascade that can be triggered by three primary routes: the classical, lectin, and alternative pathways(Walport, 2001a, 2001b). Under normal conditions, healthy cells have protective mechanisms to prevent self-aggression, including membrane regulatory proteins such as CD55 and CD59, anchored to the cell membrane via the GPI anchor(Medof et al., 1987).

Understanding the pathophysiology of PNH requires a detailed knowledge of the distinct roles of CD55 and CD59 in the complement cascade. CD55 acts early in the cascade. Its main function is to inhibit the formation and accelerate the breakdown of C3 and C5 convertases. By regulating these key enzymes, CD55 prevents the amplification of the complement cascade(Bharti et al., 2022). CD59, a terminal regulator of the complement cascade, prevents the formation of the MAC. It specifically achieves this by inhibiting the polymerization of C9 molecules and their subsequent integration into the cell membrane, thereby blocking the creation of a lytic pore(Couves et al., 2023).

Although both proteins are absent in PNH, studies indicate that CD59 is the more critical molecule(Wilcox et al., 1991). Isolated CD55 deficiency can be compensated for, but the absence of CD59 alone is sufficient to induce hemolysis. This functional difference clarifies why the main therapeutic objective in PNH is to inhibit the terminal complement cascade(Telen & Green, 1989).

The absence of CD55 and CD59 removes the necessary regulators of the complement system. This leads to uncontrolled activation, which proceeds without inhibition on the surface of GPI deficient cells(Colden et al., 2022). This activation, even triggered by spontaneous alternative pathway activation or inflammatory states, leads to the rapid and uncontrolled formation of C3 and C5 convertases. As a result, there is a massive deposition of C3b on the cell surface and the cleavage of C5 into C5b(Brodsky, 2014).

In the absence of CD59, the terminal complement components C5b-C9 assemble freely, forming the MAC. The MAC perforates the erythrocyte membrane, leading to acute intravascular hemolysis, which is a hallmark of the disease(Bektas et al., 2020).

The pathophysiology of PNH involves not only hemolysis but also a hypercoagulable state. Research materials reveal a direct link between the coagulation and complement systems(Rother et al., 2005). Thrombin, a pivotal enzyme in the coagulation cascade, can directly cleave C5 into C5a. This action bypasses the conventional complement activation pathways, contributing to the inflammatory state and heightened thrombotic risk characteristic of PNH(Rittirsch et al., 2008). This explains why thrombosis in PNH is such a serious problem and why blocking the terminal complement cascade is effective not only in treating hemolysis but also in reducing the risk of thrombotic events(DeZern & Brodsky, 2015).

3. Clinical Spectrum and Diagnostic Challenges

3.1 Clinical Spectrum

The clinical manifestations of PNH vary significantly. In children, PNH is an extremely rare condition, and its presentation often deviates markedly from the classic adult phenotype. The non-specific nature of its symptoms and the frequent overlap with other childhood illnesses can lead to significant diagnostic delays, sometimes exceeding two years(M. Karwacki et al., 2019). This delayed diagnosis can have serious consequences, as the disease is associated with considerable morbidity and mortality if left untreated. A deep understanding of the unique clinical spectrum of pediatric PNH and the nuances of its diagnostic process is, therefore, essential for early and accurate intervention(Griesser et al., 2020).

In the pediatric population, PNH should be considered first and foremost a bone marrow failure syndrome(van den Heuvel-Eibrink, 2007). This is a critical distinction from the adult-predominant classic PNH, which is typically characterized by overt hemolytic symptoms. PNH clones are frequently found in patients with other severe bone marrow failure syndromes, particularly aplastic anemia (AA) and, to a lesser extent, myelodysplastic syndrome (MDS)(Narita et al., 2017). The coexistence of PNH with bone marrow failure is reported to be substantially higher in children, with some studies indicating a prevalence of up to 80%, compared to approximately 30% in adults(Krishnaprasadh et al., 2019). Data from a large international registry demonstrated that a history of aplastic or hypoplastic anemia was present in nearly 78% of children with PNH at the time of their enrollment, a significantly higher proportion than in the adult cohort. The underlying mechanism for this strong association is thought to be an autoimmune process where healthy hematopoietic stem cells are targeted and destroyed by the immune system(Urbano-Ispizua et al., 2017). The *PIGA*-mutated, GPI-deficient stem cells, which are not recognized by this misguided immune attack, gain a selective survival and proliferative advantage. This allows them to expand clonally and become the dominant source of blood cells, even while the overall bone marrow remains hypocellular and fails to produce sufficient healthy blood cells(Krishnaprasadh et al., 2019). This pathophysiology directly explains the common laboratory finding of severe cytopenia - including anemia, leukopenia, and thrombocytopenia - which is observed more frequently in children with PNH than in adults(Griesser et al., 2020).

While chronic intravascular hemolysis is a defining feature of PNH, its clinical expression in children is often less pronounced than in adults. Although the frequency of hemolysis itself is comparable between pediatric and adult cohorts, its severity is notably lower in children. This is evidenced by significantly lower levels of lactate dehydrogenase (LDH) and reticulocyte counts in children compared to adults with PNH(Urbano-Ispizua et al., 2017).

The most striking clinical consequence of this difference is the absence of overt hemoglobinuria, the symptom from which the disease derives its name. While approximately 50% of adult PNH patients present with hemoglobinuria, it is reported in only 10% to 20% of pediatric cases(Griesser et al., 2020). This lack of a hallmark symptom can easily lead to misdiagnosis, as the remaining signs of chronic hemolysis, such as fatigue, pallor, and dyspnea, are non-specific and common to many other childhood conditions. This phenomenon highlights the inherent challenge: clinicians looking for the classic signs of hemolysis may overlook the possibility of PNH in a child presenting with symptoms of bone marrow failure(Brodsky, 2014).

Thrombosis is a major cause of morbidity and the leading cause of death in patients with PNH. Although it is less common in children than in adults, it remains a serious and life-threatening complication that requires a high index of suspicion. The frequency of thrombotic events in pediatric PNH has been reported to range between 20% and 50% in the literature(Griesser et al., 2020). These events are particularly dangerous because they often occur at unusual, atypical sites, such as the cerebral and visceral veins(Hill et al., 2013).

Beyond the primary hematological manifestations, PNH can present with a variety of non-hematological symptoms that can act as a "diagnostic mask" and significantly delay diagnosis(M. W. Karwacki et al., 2019). These symptoms include dysphagia, esophageal spasms, and abdominal pain. They arise from the depletion of nitric oxide (NO) caused by chronic hemolysis. Free hemoglobin released during hemolysis binds and consumes NO, leading to smooth muscle dystonia in various organs(Pu & Brodsky, 2011).

A case study by Karwacki et al. illustrates this critical point, describing a 16-year-old boy who experienced a diagnostic delay of more than four years due to the disease's "abdominal mask" of recurrent abdominal pain. This recurring, non-specific symptom, while seemingly benign, is a direct consequence of the same underlying pathological process that makes patients susceptible to a major, life-threatening complication: thrombosis. The visceral pain caused by smooth muscle dystonia can be an early warning sign of impending or developing visceral venous thrombosis, the most common site for thrombosis in PNH. This interconnection

means that PNH must be considered in the differential diagnosis for any child with chronic, unexplained abdominal pain, especially in the presence of other subtle hematological abnormalities(M. Karwacki et al., 2019). The key differences in clinical presentation between pediatric and adult PNH patients are summarized in Table 1.

Table 1. Differences in clinical presentation between pediatric and adult PNH patients

Parameter	Pediatric Patients	Adult Patients
PNH Clone Size	Predominantly small (<10%) in >50% of patients	Predominantly large (>50%) in ~40% of patients
Incidence of Bone Marrow Failure	Up to ~80% coexistence; severe cytopenia more frequent	~30% coexistence; severe cytopenia less frequent
Hemoglobinuria	Presenting symptom in ~10-20% of patients	Presenting symptom in ~50% of patients
Hemolysis Severity	Less severe (lower LDH, reticulocyte count)	More severe (higher LDH, reticulocyte count)
Thrombotic Events	Less frequent than in adults but still a serious risk	More frequent

3.2 Diagnostic Challenges

The average diagnostic delay for PNH is more than two years. This protracted period is not a result of a lack of diagnostic technology but rather a lack of initial clinical awareness. The rarity of the disease, combined with its non-specific symptoms and its significant overlap with more common childhood disorders like aplastic anemia and myelodysplasia, frequently leads to misdiagnosis or a prolonged diagnostic journey(Griesser et al., 2020). Many children with PNH are initially treated for aplastic anemia due to their predominant bone marrow failure phenotype. The core challenge lies in the fact that the subtle signs of hemolysis, such as elevated LDH or low haptoglobin, may be overlooked in the presence of more severe cytopenias. Therefore, a high index of suspicion is required to connect unexplained hemolysis, with or without bone marrow failure, to the possibility of PNH, thereby prompting the appropriate diagnostic testing(Urbano-Ispizua et al., 2017; van den Heuvel-Eibrink, 2007)

With the advent of high-sensitivity flow cytometry, the diagnostic landscape for PNH has been revolutionized. This technique has replaced older, less sensitive methods, such as the Ham and sucrose lysis tests, and is now considered the gold standard for definitive diagnosis(van den Heuvel-Eibrink, 2007). The assay's methodology is highly specific and sensitive, capable of detecting PNH clones comprising as little as 0.01% of the total cell population. The critical components of the assay involve the use of specific GPI-linked antibodies and fluorescein-labeled proaerolysin (FLAER), a reagent that binds directly and with high affinity to the GPI anchor itself. The importance of this approach lies in its ability to analyze multiple peripheral blood cell lineages - including granulocytes, monocytes, and red blood cells. A key reason for this multi-lineage analysis is that reliance on red blood cell analysis alone can lead to false-negative results or an underestimation of the true clone size. This is because ongoing hemolysis may destroy the GPI-deficient red blood cells, or a patient may have received a recent blood transfusion, diluting the PNH clone. Therefore, the analysis of white blood cells, which have a longer lifespan, is a more robust indicator of the true PNH clone size(Borowitz et al., 2010; Sutherland et al., 2014).

High-sensitivity flow cytometry provides a quantitative measure of the PNH clone size, which is the percentage of GPI-deficient cells. This measurement is crucial because the size of the clone directly correlates with the clinical phenotype. Patients with "classic PNH," characterized by dominant hemolytic symptoms, typically have large clone sizes exceeding 50%. Conversely, patients with PNH in the context of another bone marrow failure disorder usually have a smaller clone size, often less than 50%. This distinction is of paramount importance in pediatrics, where more than half of children with PNH have a small clone size of less than 10%. This finding underscores that the dominant pediatric phenotype is a bone marrow failure syndrome, with the PNH clone often being a small but clinically significant component. The development of high-sensitivity flow cytometry has fundamentally changed our understanding of pediatric PNH, revealing a previously underdiagnosed population of children who would have been missed by older, less sensitive tests(Borowitz et al., 2010; Sutherland et al., 2014).

4. Therapeutic Landscape

4.1 Complement Inhibitors

Since its approval in 2007 by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), eculizumab, a complement component 5 (C5) inhibitor, has served as the first-line therapy for PNH. In a Phase 3 clinical trial, eculizumab reduced hemolysis, as indicated by an 87% decrease in LDH levels, increased hemoglobin concentrations, and a 52% reduction in RBC transfusion rates, from a mean of 12.3 to 5.9 RBC units per patient. Additionally, 51% of patients remained transfusion-independent throughout a 52-week treatment period. The quality of life, as assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score, improved significantly after one week of therapy(Brodsky et al., 2008).

Pediatric assessments of eculizumab demonstrated comparable outcomes. Normal lactate dehydrogenase (LDH) levels, defined as less than 275 U/L, were achieved by week 2 of treatment, with a 65% reduction from baseline observed at week 12. Plasma free hemoglobin concentrations decreased from a mean of 17.7 mg/dL at baseline to 7.4 mg/dL at week 12(Reiss et al., 2014). Since transfusion rates were infrequent in the study group prior to treatment, the data do not permit conclusions regarding changes in transfusion requirements. However, several studies have reported cases in which patients did not require transfusions during eculizumab treatment(Reiss et al., 2014; Yen et al., 2012). The optimal pediatric dosing regimen of eculizumab for PNH has not been established due to the low incidence of the hemolytic variant in pediatric populations(van den Heuvel-Eibrink, 2007). Adult dosing consists of a 600 mg induction dose administered weekly for four weeks, followed by a 900 mg maintenance dose in week five, and then 900 mg every two weeks thereafter. The authors recommend this regimen for children over 30 kg(Reiss et al., 2014). To the best of our knowledge, eculizumab dosing has not been assessed in smaller children. Serum hemolytic activity is inhibited when eculizumab concentrations exceed 35 mg/mL(Hillmen et al., 2004). In pediatric patients, the median trough level at week 12 was 192.5 mg/mL, and the median peak level was 425.4 mg/mL(Reiss et al., 2014). These data indicate that adult dosing achieves therapeutically effective eculizumab concentrations in pediatric patients over 30 kg.

Ravulizumab, another C5 inhibitor, is a therapeutic agent used in PNH that demonstrated non-inferiority to eculizumab in two adult Phase 3 clinical trials. The primary endpoints in these studies included hemolysis, assessed by LDH levels, and avoidance of blood transfusion. Ravulizumab also demonstrated non-inferiority in secondary endpoints, including the incidence of breakthrough hemolysis, FACIT-Fatigue score, stabilization of hemoglobin concentration, and the total number of RBC units transfused(Kulasekararaj et al., 2019; Lee et al., 2019). In 2021, the FDA approved ravulizumab for the treatment of PNH in patients aged one month and older. Similarly, the EMA approved ravulizumab in patients weighing at least 10 kg. A Phase 3 clinical trial evaluated the safety and efficacy of ravulizumab in pediatric patients. The study population consisted of both patients who had not previously received eculizumab and those with prior exposure to eculizumab. Mean hemolytic activity remained below 20% following the initial infusion. At study completion, mean hemolytic activity was 21.9% in eculizumab-naive patients and 31.9% in eculizumab-experienced patients. These results indicate complete inhibition of C5(Chonat et al., 2024). The eculizumab-naive group achieved secondary endpoints, including significant reductions in LDH levels. Specifically, LDH decreased by 55.52% on day 15, 47.91% on day 183, and 60.15% on day 911. In contrast, eculizumab-experienced patients did not show additional LDH reduction because their LDH levels were already within the normal range at the start of ravulizumab therapy. During the primary 26-week evaluation period, 80% of eculizumab-naive patients and 100% of eculizumab-experienced patients were able to avoid transfusions. Over the subsequent four-year period, 80% of eculizumab-naive and 87% of eculizumab-experienced patients continued to avoid transfusions(Chonat et al., 2024). Ravulizumab dosing in adults is based on patient body weight, with an initial dose of 2400 to 3000 mg. The first maintenance dose is administered two weeks after the initial dose is given. Subsequent maintenance doses are given every eight weeks. Additionally, ravulizumab therapy can be initiated two weeks following the final eculizumab dose(Lee & Kulasekararaj, 2020). Compared to eculizumab, ravulizumab requires less frequent administration. Eculizumab is administered every two weeks, whereas ravulizumab is administered every four or eight weeks, depending on pediatric patient weight(Chonat et al., 2024). Reduced dosing frequency may enhance quality of life in pediatric patients. Table 2 presents pediatric dosing of ravulizumab as studied in a Phase 3 clinical trial. Children weighing less than 20 kg received maintenance doses every four weeks(Chonat et al., 2024). In contrast, children over 40 kg received the same dosing regimen as adults, with an eight-week interval.

Table 2. Pediatric dosing of ravulizumab(Chonat et al., 2024)

Patient body weight (kg)	Initial dose (mg)	Maintenance dose (mg)
≥5 to <10	600	300 (every 4 weeks)
≥10 to <20	600	600 (every 4 weeks)
≥20 to <30	900	2100
≥30 to <40	1200	2700
≥40 to <60	2400	3000
≥60 to <100	2700	3300
≥100	3000	3600

Crovalimab, a recently approved therapeutic agent, has received authorization from both the FDA and the EMA for the treatment of PNH in patients aged 12 years and older and 13 years and older, respectively. Both regulatory agencies have established a minimum weight requirement of 40 kilograms for crovalimab administration. The COMMODORE 2 trial demonstrated that crovalimab is non-inferior to eculizumab in terms of hemolysis control, transfusion avoidance, prevention of breakthrough hemolysis, and maintenance of stable hemoglobin levels. Furthermore, crovalimab is administered subcutaneously and is suitable for self-administration at four-week intervals(Roth et al., 2024).

4.2 Hematopoietic Cell Transplantation (HCT)

Complement inhibitors represent the standard therapy for PNH. However, allogenic hematopoietic cell transplantation (allo-HCT) remains the only curative treatment and is generally reserved for patients with bone marrow failure, patients who do not respond to complement inhibitor therapy, or when such therapy is unavailable. Bone marrow transplantation is preferred to peripheral blood progenitor cell transplantation due to the non-malignant nature of PNH(Ussowicz et al., 2024).

Allo-HCT is infrequently performed in pediatric patients with PNH due to the low incidence of the disease in this population. The majority of published data on pediatric PNH cases consist of individual case reports. In 2019, Andolina et al. summarized 22 pediatric cases of allo-HCT, with 18 patients surviving and all survivors remaining disease-free. Among these 22 children, ten received myeloablative conditioning, five received non-myeloablative conditioning, one received no conditioning, and the conditioning regimen was not reported in six cases(Andolina et al., 2018).

Reduced-toxicity transplant conditioning should be considered for patients undergoing allo-HCT for PNH. Immunoablative protocols remain appropriate for those with aplastic anemia or severe aplastic anemia. Patients with classic PNH may benefit from reduced-intensity conditioning(Ussowicz et al., 2024). Although pediatric data are limited, several successful cases of allo-HCT with reduced conditioning have been reported(Andolina et al., 2018). Allo-HCT carries significant risks, including life-threatening complications such as graft-versus-host disease. A thorough evaluation of potential benefits and risks is essential before proceeding.

4.3 Supportive Care

The introduction of complement inhibitors has reduced the reliance on supportive treatments for PNH. Iron and folate supplementation, previously considered essential(Parker et al., 2005), are now infrequently documented in recent literature. RBC transfusions remain necessary for patients with anemia. However, the reduction in transfusion rates due to the use of complement inhibitors has been suggested as early as 2011(Curran et al., 2012) and is now well-documented(Hillmen et al., 2004).

Thrombosis represents the leading cause of mortality among individuals diagnosed with PNH. Thrombotic events frequently develop in atypical sites, including the mesenteric, cerebral, and cutaneous veins(Ali et al., 2024). Adult patients presenting with acute thrombotic events should receive unfractionated heparin or low-molecular-weight heparin combined with a complement inhibitor. Patients already receiving eculizumab should receive an additional dose in conjunction with therapeutic anticoagulation(Kokoris et al., 2024). The duration of subsequent anticoagulation therapy, typically with a vitamin K antagonist, depends on clinical factors including risk of recurrence and bleeding, and requires individualized assessment. Evidence regarding the safety and efficacy of direct oral anticoagulants (DOACs) in PNH remains limited; further studies are warranted(Ali et al., 2024).

Pediatric patients diagnosed with PNH have also developed thrombosis in uncommon locations, including the portal, hepatic, renal, and mesenteric veins as well as the cerebral sinuses(Curran et al., 2012). Complement inhibitors are the primary recommended treatment(Kokoris et al., 2024). Additionally, heparin, low-molecular weight heparin, and vitamin K antagonists have been utilized as adjunct therapies following thrombosis(Curran et al., 2012; Griesser et al., 2020).

5. Future Directions and Emerging Therapies

5.1 New Complement Inhibitors

Pegcetacoplan, a complement component 3 (C3) inhibitor, has been approved by the FDA and later by the EMA for the treatment of adults with PNH. In the PRINCE study, compared to supportive care only, pegcetacoplan demonstrated superior hemoglobin stabilization and a greater change from baseline in LDH levels. Notably, more than 90% of patients in the pegcetacoplan group remained transfusion-free throughout the study duration, compared to less than 6% in the supportive care group. Furthermore, no serious adverse effects associated with pegcetacoplan were observed(Wong et al., 2023). Pegcetacoplan resulted in a greater increase in hemoglobin levels from baseline compared to eculizumab, demonstrating the superiority of pegcetacoplan. Additionally, 85% of patients receiving pegcetacoplan remained transfusion-free, whereas only 15% of those receiving eculizumab achieved this outcome. Pegcetacoplan was also non-inferior to eculizumab in terms of changes in LDH levels from baseline(Hillmen et al., 2021). Currently, pegcetacoplan is undergoing a Phase 2 clinical trial in pediatric patients with PNH (NCT04901936).

Iptacopan is the first oral medication for PNH to receive approval from both the FDA and the EMA for use in adult patients with PNH. It functions as a proximal complement inhibitor targeting factor B in the alternative complement pathway(Peffault de Latour et al., 2024). Iptacopan is administered orally, twice a day(Perry et al., 2025). In the APPLY-PNH trial, iptacopan demonstrated superiority over anti-C5 therapy in increasing hemoglobin levels and achieving a hemoglobin concentration of 12 g/dL without the need for red blood cell transfusions or meeting transfusion criteria. Participants in the APPOINT-PNH study were complement inhibitor-naive. Ninety-two percent achieved the primary endpoint, defined as an increase in hemoglobin of at least 2 g/dL. Sixty-three percent reached a hemoglobin concentration of 12 g/dL without requiring red blood cell transfusions(Peffault de Latour et al., 2024). A phase 3 clinical trial (NCT06934967) investigating iptacopan for the treatment of pediatric PNH has recently begun.

Danicopan is an oral factor D inhibitor, approved by both the FDA and EMA for the treatment of PNH in adult patients. Danicopan is administered orally three times a day, with an initial dose of 150 mg, which can be escalated to 200 mg if necessary. In the Phase 3 ALPHA trial, danicopan was administered in combination with either eculizumab or ravulizumab. After 12 weeks, this combination resulted in a significant increase in hemoglobin levels compared to the placebo group that received eculizumab or ravulizumab alone(Lee et al., 2023). In the subsequent phase, participants initially assigned to a placebo were switched to danicopan. These participants achieved hemoglobin levels comparable to those in the original danicopan group by week 14 and maintained these levels through week 72(Kulasekararaj et al., 2025). Danicopan is currently undergoing a Phase 3 study (NCT06449001) as an add-on treatment to eculizumab or ravulizumab in pediatric patients with PNH who have clinically significant extravascular hemolysis.

5.2 Gene Therapy

Gene therapy has potential utility in PNH because mutations in the PIGA gene are a primary cause of the disease. Restoration of normal PIGA gene function could address the underlying pathophysiology. Although some authors have referenced conference materials reporting successful gene therapy outcomes(Perry et al., 2025), there is currently no published evidence to suggest that this treatment has been utilized or investigated specifically in pediatric patients.

5.3 Considerations for Developing Pediatric Clinical Guidelines.

PNH is a rare disease that typically presents in adults(Ware et al., 1991), making pediatric cases particularly uncommon. Further research involving pediatric populations is necessary to inform the development of evidence-based clinical management guidelines, determine optimal dosing regimens, and refine strategies for managing adverse effects in this population. Additionally, clinical trials of emerging therapies should include pediatric cohorts to address the distinct physiological and therapeutic needs of children.

6. Conclusions

Pediatric paroxysmal nocturnal hemoglobinuria (PNH) is a uniquely challenging entity within the spectrum of rare hematologic disorders. Although it shares the same PIGA-driven molecular basis as adult PNH, its clinical profile is distinct - dominated by bone marrow failure and cytopenias rather than overt hemolysis. These atypical features, coupled with the rarity of the disease, contribute to frequent diagnostic delays and under-recognition. High-sensitivity flow cytometry has revolutionized diagnostic accuracy, particularly by detecting small clones that characterize pediatric cases.

Therapeutic advances have markedly improved outcomes. The introduction of C5 inhibitors, particularly eculizumab and ravulizumab, has transformed prognosis by effectively controlling hemolysis, reducing transfusion dependence, and lowering the risk of life-threatening thrombosis. Newer agents - including crovalimab, pegcetacoplan, iptacopan, and danicopan - expand the therapeutic arsenal, offering more convenient routes of administration, extended dosing intervals, and the potential for more comprehensive complement blockade. Allogeneic hematopoietic cell transplantation remains the only curative approach but is reserved for selected cases, given its risks.

Future directions lie in integrating emerging complement inhibitors, exploring gene therapy as a potential definitive cure, and ensuring that pediatric populations are systematically included in clinical trials. Given the rarity of the disease in children, collaborative international registries and multicenter studies will be essential to generate the evidence base needed for standardized pediatric guidelines.

Ultimately, the evolution of PNH management - from supportive care and transfusions to targeted complement inhibition - represents one of the most striking therapeutic successes in rare hematology. Extending these advances to pediatric patients requires heightened clinical suspicion, earlier diagnosis, and tailored therapeutic strategies that account for the unique clinical spectrum of this population.

REFERENCES

1. Ali, E. A., Al-Sadi, A., Ali, S., Rozi, W., Idriss, M., Jain, M., Mohamed, A., & Yassin, M. A. (2024, Dec). Direct Oral Anticoagulants and Paroxysmal Nocturnal Hemoglobinuria: A Systematic Review and Update on Evidence. *Cureus, 16*(12), e76702. https://doi.org/10.7759/cureus.76702
2. Andolina, J. R., Reinish, A. L., Akhtar, R., Noronha, S., Shand, J. C., Girvin, A., Korones, D. N., Bruckner, L. B., Mullen, C. A., Curran, K. J., & Boulad, F. (2018, Aug). Successful reduced-intensity conditioning hematopoietic stem cell transplantation for paroxysmal nocturnal hemoglobinuria with aplastic anemia in two children. *Pediatric Blood & Cancer, 65*(8), e27218. https://doi.org/10.1002/pbc.27218
3. Bektas, M., Copley-Merriman, C., Khan, S., Sarda, S. P., & Shammo, J. M. (2020, Dec). Paroxysmal nocturnal hemoglobinuria: role of the complement system, pathogenesis, and pathophysiology. *J Manag Care Spec Pharm, 26*(12-b Suppl), S3-s8. https://doi.org/10.18553/jmcp.2020.26.12-b.s3
4. Bessler, M., Mason, P. J., Hillmen, P., Miyata, T., Yamada, N., Takeda, J., Luzzatto, L., & Kinoshita, T. (1994, Jan 1). Paroxysmal nocturnal haemoglobinuria (PNH) is caused by somatic mutations in the PIG-A gene. *Embo j, 13*(1), 110-117. https://doi.org/10.1002/j.1460-2075.1994.tb06240.x
5. Bharti, R., Dey, G., Lin, F., Lathia, J., & Reizes, O. (2022, Dec 28). CD55 in cancer: Complementing functions in a non-canonical manner. *Cancer Lett, 551*, 215935. https://doi.org/10.1016/j.canlet.2022.215935
6. Borowitz, M. J., Craig, F. E., Digiuseppe, J. A., Illingworth, A. J., Rosse, W., Sutherland, D. R., Wittwer, C. T., Richards, S. J., & Clinical Cytometry, S. (2010, Jul). Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. *Cytometry. Part B: Clinical Cytometry, 78*(4), 211-230. https://doi.org/10.1002/cyto.b.20525
7. Brodsky, R. A. (2014, Oct 30). Paroxysmal nocturnal hemoglobinuria. *Blood, 124*(18), 2804-2811. https://doi.org/10.1182/blood-2014-02-522128
8. Brodsky, R. A., Young, N. S., Antonioli, E., Risitano, A. M., Schrezenmeier, H., Schubert, J., Gaya, A., Coyle, L., de Castro, C., Fu, C. L., Maciejewski, J. P., Bessler, M., Kroon, H. A., Rother, R. P., & Hillmen, P. (2008, Feb 15). Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. *Blood, 111*(4), 1840-1847. https://doi.org/10.1182/blood-2007-06-094136
9. Chonat, S., Kulagin, A., Maschan, A., Bartels, M., Buechner, J., Punzalan, R., Richards, M., Ogawa, M., Hicks, E., Yu, J., Baruchel, A., & Kulasekararaj, A. G. (2024, Jun 11). Pharmacokinetics, pharmacodynamics, efficacy, and safety of ravulizumab in pediatric paroxysmal nocturnal hemoglobinuria. *Blood Adv, 8*(11), 2813-2824. https://doi.org/10.1182/bloodadvances.2023012267
10. Colden, M. A., Kumar, S., Munkhbileg, B., & Babushok, D. V. (2022, 2022-January-28). Insights Into the Emergence of Paroxysmal Nocturnal Hemoglobinuria [Review]. *Frontiers in Immunology, Volume 12 - 2021*. https://doi.org/10.3389/fimmu.2021.830172

11. Couves, E. C., Gardner, S., Voisin, T. B., Bickel, J. K., Stansfeld, P. J., Tate, E. W., & Bubeck, D. (2023, Feb 16). Structural basis for membrane attack complex inhibition by CD59. *Nat Commun, 14*(1), 890. https://doi.org/10.1038/s41467-023-36441-z
12. Curran, K. J., Kernan, N. A., Prockop, S. E., Scaradavou, A., Small, T. N., Castro-Malaspina, H., Araten, D., DiMichele, D., O'Reilly, R. J., & Boulad, F. (2010). Paroxysmal Nocturnal Hemoglobinuria (PNH) In Pediatric Patients: Review of a Single Center Series. *Blood, 116*(21), 2231-2231. https://doi.org/10.1182/blood.V116.21.2231.2231
13. Curran, K. J., Kernan, N. A., Prockop, S. E., Scaradavou, A., Small, T. N., Kobos, R., Castro-Malaspina, H., Araten, D., DiMichele, D., O'Reilly, R. J., & Boulad, F. (2012, Sep). Paroxysmal nocturnal hemoglobinuria in pediatric patients. *Pediatric Blood & Cancer, 59*(3), 525-529. https://doi.org/10.1002/pbc.23410
14. DeZern, A. E., & Brodsky, R. A. (2015, Jun). Paroxysmal nocturnal hemoglobinuria: a complement-mediated hemolytic anemia. *Hematol Oncol Clin North Am, 29*(3), 479-494. https://doi.org/10.1016/j.hoc.2015.01.005
15. Griesser, C., Myskiw, M., & Streif, W. (2020, Jan). Paroxysmal Nocturnal Hemoglobinuria: An Underestimated Cause of Pediatric Thromboembolism. *TH Open, 4*(1), e36-e39. https://doi.org/10.1055/s-0040-1702155
16. Hill, A., Kelly, R. J., & Hillmen, P. (2013, Jun 20). Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood, 121*(25), 4985-4996; quiz 5105. https://doi.org/10.1182/blood-2012-09-311381
17. Hillmen, P., Hall, C., Marsh, J. C., Elebute, M., Bombara, M. P., Petro, B. E., Cullen, M. J., Richards, S. J., Rollins, S. A., Mojcik, C. F., & Rother, R. P. (2004, Feb 5). Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. *New England Journal of Medicine, 350*(6), 552-559. https://doi.org/10.1056/NEJMoa031688
18. Hillmen, P., Lewis, S. M., Bessler, M., Luzzatto, L., & Dacie, J. V. (1995, Nov 9). Natural history of paroxysmal nocturnal hemoglobinuria. *N Engl J Med, 333*(19), 1253-1258. https://doi.org/10.1056/nejm199511093331904
19. Hillmen, P., Szer, J., Weitz, I., Roth, A., Hochsmann, B., Panse, J., Usuki, K., Griffin, M., Kiladjian, J. J., de Castro, C., Nishimori, H., Tan, L., Hamdani, M., Deschatelets, P., Francois, C., Grossi, F., Ajayi, T., Risitano, A., & Peffault de Latour, R. (2021, Mar 18). Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria. *New England Journal of Medicine, 384*(11), 1028-1037. https://doi.org/10.1056/NEJMoa2029073
20. Holt, M., Newton, D. J., Griffin, M., Schmidt, C. Q., & Kelly, R. J. (2024). A review of the pathophysiology of paroxysmal nocturnal hemoglobinuria. *Annals of Blood, 9*. https://aob.amegroups.org/article/view/10256
21. Johnston, J. J., Gropman, A. L., Sapp, J. C., Teer, J. K., Martin, J. M., Liu, C. F., Yuan, X., Ye, Z., Cheng, L., Brodsky, R. A., & Biesecker, L. G. (2012, Feb 10). The phenotype of a germline mutation in PIGA: the gene somatically mutated in paroxysmal nocturnal hemoglobinuria. *Am J Hum Genet, 90*(2), 295-300. https://doi.org/10.1016/j.ajhg.2011.11.031
22. Karwacki, M., Adamowicz-Salach, A., & Matysiak, M. (2019). Pb1864 More Than 2 Years Delay in Diagnosis of Pnh Due to Gastrointestinal Mask of Bone Marrow Insufficiency. *HemaSphere, 3*(S1). https://doi.org/10.1097/01.HS9.0000565960.75002.be
23. Karwacki, M. W., Adamowicz-Salach, A., Matysiak, M., & Pankiewicz, A. (2019). Nocna napadowa hemoglobinuria u dzieci jako przykład rzadkich schorzeń ukrywających się pod różnymi maskami rozpoznań klinicznych. Dylematy kliniczne, etyczne i społeczne rozpoznawania chorób ultrarzadkich na kanwie przypadku. *Nowa Pediatria, 23*(1). https://doi.org/10.25121/np.2019.23.1.51
24. Kokoris, S., Polyviou, A., Evangelidis, P., Grouzi, E., Valsami, S., Tragiannidis, K., Gialeraki, A., Tsakiris, D. A., & Gavriilaki, E. (2024, Nov 11). Thrombosis in Paroxysmal Nocturnal Hemoglobinuria (PNH): From Pathogenesis to Treatment. *International Journal of Molecular Sciences, 25*(22). https://doi.org/10.3390/ijms252212104
25. Krishnaprasadh, D., Kaminecki, I., Sechser Perl, A., & Teitelbaum, J. (2019). Paroxysmal Nocturnal Hemoglobinuria: Diagnostic Challenges in Pediatric Patient. *Case Rep Pediatr, 2019*, 4930494. https://doi.org/10.1155/2019/4930494
26. Kulasekararaj, A., Griffin, M., Piatek, C., Shammo, J., Nishimura, J. I., Patriquin, C., Schrezenmeier, H., Barcellini, W., Panse, J., Gaya, A., Patel, Y., Liu, P., Filippov, G., Sicre de Fontbrune, F., Risitano, A., & Lee, J. W. (2025, Feb 20). Long-term efficacy and safety of danicopan as add-on therapy to ravulizumab or eculizumab in PNH with significant EVH. *Blood, 145*(8), 811-822. https://doi.org/10.1182/blood.2024026299
27. Kulasekararaj, A. G., Hill, A., Rottinghaus, S. T., Langemeijer, S., Wells, R., Gonzalez-Fernandez, F. A., Gaya, A., Lee, J. W., Gutierrez, E. O., Piatek, C. I., Szer, J., Risitano, A., Nakao, S., Bachman, E., Shafner, L., Damokosh, A. I., Ortiz, S., Roth, A., & Peffault de Latour, R. (2019, Feb 7). Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood, 133*(6), 540-549. https://doi.org/10.1182/blood-2018-09-876805
28. Kumar, S., & Babushok, D. V. (2021, Dec). Analysis of evolutionary conservation of GPI-anchored proteins between humans and mice. *Blood Cells Mol Dis, 92*, 102622. https://doi.org/10.1016/j.bcmd.2021.102622

29. Lee, J. W., Griffin, M., Kim, J. S., Lee Lee, L. W., Piatek, C., Nishimura, J. I., Carrillo Infante, C., Jain, D., Liu, P., Filippov, G., Sicre de Fontbrune, F., Risitano, A., Kulasekararaj, A. G., & Investigators, A.-P.-. (2023, Dec). Addition of danicopan to ravulizumab or eculizumab in patients with paroxysmal nocturnal haemoglobinuria and clinically significant extravascular haemolysis (ALPHA): a double-blind, randomised, phase 3 trial. *Lancet Haematol, 10*(12), e955-e965. https://doi.org/10.1016/S2352-3026(23)00315-0
30. Lee, J. W., & Kulasekararaj, A. G. (2020, Mar). Ravulizumab for the treatment of paroxysmal nocturnal hemoglobinuria. *Expert Opinion on Biological Therapy, 20*(3), 227-237. https://doi.org/10.1080/14712598.2020.1725468
31. Lee, J. W., Sicre de Fontbrune, F., Wong Lee Lee, L., Pessoa, V., Gualandro, S., Fureder, W., Ptushkin, V., Rottinghaus, S. T., Volles, L., Shafner, L., Aguzzi, R., Pradhan, R., Schrezenmeier, H., & Hill, A. (2019, Feb 7). Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood, 133*(6), 530-539. https://doi.org/10.1182/blood-2018-09-876136
32. Medof, M. E., Gottlieb, A., Kinoshita, T., Hall, S., Silber, R., Nussenzweig, V., & Rosse, W. F. (1987, Jul). Relationship between decay accelerating factor deficiency, diminished acetylcholinesterase activity, and defective terminal complement pathway restriction in paroxysmal nocturnal hemoglobinuria erythrocytes. *J Clin Invest, 80*(1), 165-174. https://doi.org/10.1172/jci113043
33. Narita, A., Muramatsu, H., Okuno, Y., Sekiya, Y., Suzuki, K., Hamada, M., Kataoka, S., Ichikawa, D., Taniguchi, R., Murakami, N., Kojima, D., Nishikawa, E., Kawashima, N., Nishio, N., Hama, A., Takahashi, Y., & Kojima, S. (2017, Sep). Development of clinical paroxysmal nocturnal haemoglobinuria in children with aplastic anaemia. *British Journal of Haematology, 178*(6), 954-958. https://doi.org/10.1111/bjh.14790
34. Parker, C., Omine, M., Richards, S., Nishimura, J., Bessler, M., Ware, R., Hillmen, P., Luzzatto, L., Young, N., Kinoshita, T., Rosse, W., Socie, G., & International, P. N. H. I. G. (2005, Dec 1). Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood, 106*(12), 3699-3709. https://doi.org/10.1182/blood-2005-04-1717
35. Peffault de Latour, R., Roth, A., Kulasekararaj, A. G., Han, B., Scheinberg, P., Maciejewski, J. P., Ueda, Y., de Castro, C. M., Di Bona, E., Fu, R., Zhang, L., Griffin, M., Langemeijer, S. M. C., Panse, J., Schrezenmeier, H., Barcellini, W., Mauad, V. A. Q., Schafhausen, P., Tavitian, S., Beggiato, E., Chew, L. P., Gaya, A., Huang, W. H., Jang, J. H., Kitawaki, T., Kutlar, A., Notaro, R., Pullarkat, V., Schubert, J., Terriou, L., Uchiyama, M., Wong Lee Lee, L., Yap, E. S., Sicre de Fontbrune, F., Marano, L., Alashkar, F., Gandhi, S., Trikha, R., Yang, C., Liu, H., Kelly, R. J., Hochsmann, B., Kerloeguen, C., Banerjee, P., Levitch, R., Kumar, R., Wang, Z., Thorburn, C., Maitra, S., Li, S., Verles, A., Dahlke, M., & Risitano, A. M. (2024, Mar 14). Oral Iptacopan Monotherapy in Paroxysmal Nocturnal Hemoglobinuria. *New England Journal of Medicine, 390*(11), 994-1008. https://doi.org/10.1056/NEJMoa2308695
36. Perry, C., Von Buttlar, X., & Thota, S. (2025, May 22). The Advancing Landscape of Paroxysmal Nocturnal Hemoglobinuria Treatment. *Turk J Haematol, 42*(2), 74-81. https://doi.org/10.4274/tjh.galenos.2025.2025.0054
37. Pu, J. J., & Brodsky, R. A. (2011, Jun). Paroxysmal nocturnal hemoglobinuria from bench to bedside. *Clinical and Translational Science, 4*(3), 219-224. https://doi.org/10.1111/j.1752-8062.2011.00262.x
38. Reiss, U. M., Schwartz, J., Sakamoto, K. M., Puthenveetil, G., Ogawa, M., Bedrosian, C. L., & Ware, R. E. (2014, Sep). Efficacy and safety of eculizumab in children and adolescents with paroxysmal nocturnal hemoglobinuria. *Pediatric Blood & Cancer, 61*(9), 1544-1550. https://doi.org/10.1002/pbc.25068
39. Rittirsch, D., Flierl, M. A., & Ward, P. A. (2008, Oct). Harmful molecular mechanisms in sepsis. *Nat Rev Immunol, 8*(10), 776-787. https://doi.org/10.1038/nri2402
40. Roth, A., He, G., Tong, H., Lin, Z., Wang, X., Chai-Adisaksopha, C., Lee, J. H., Brodsky, A., Hantaweepant, C., Dumagay, T. E., Demichelis-Gomez, R., Rojnuckarin, P., Sun, J., Hoglund, M., Jang, J. H., Gaya, A., Silva, F., Obara, N., Kelly, R. J., Beveridge, L., Buatois, S., Chebon, S., Gentile, B., Lundberg, P., Sreckovic, S., Nishimura, J. I., Risitano, A., & Han, B. (2024, Sep). Phase 3 randomized COMMODORE 2 trial: Crovalimab versus eculizumab in patients with paroxysmal nocturnal hemoglobinuria naive to complement inhibition. *American Journal of Hematology, 99*(9), 1768-1777. https://doi.org/10.1002/ajh.27412
41. Rother, R. P., Bell, L., Hillmen, P., & Gladwin, M. T. (2005). The Clinical Sequelae of Intravascular Hemolysis and Extracellular Plasma HemoglobinA Novel Mechanism of Human Disease. *JAMA, 293*(13), 1653-1662. https://doi.org/10.1001/jama.293.13.1653
42. Schmidt, C. Q., Lambris, J. D., & Ricklin, D. (2016, Nov). Protection of host cells by complement regulators. *Immunol Rev, 274*(1), 152-171. https://doi.org/10.1111/imr.12475
43. Sutherland, D. R., Acton, E., Keeney, M., Davis, B. H., & Illingworth, A. (2014, Jan). Use of CD157 in FLAER-based assays for high-sensitivity PNH granulocyte and PNH monocyte detection. *Cytometry. Part B: Clinical Cytometry, 86*(1), 44-55. https://doi.org/10.1002/cyto.b.21111
44. Telen, M. J., & Green, A. M. (1989, Jul). The Inab phenotype: characterization of the membrane protein and complement regulatory defect. *Blood, 74*(1), 437-441.
45. Urbano-Ispizua, Á., Muus, P., Schrezenmeier, H., Almeida, A. M., Wilson, A., & Ware, R. E. (2017, Mar). Different clinical characteristics of paroxysmal nocturnal hemoglobinuria in pediatric and adult patients. *Haematologica, 102*(3), e76-e79. https://doi.org/10.3324/haematol.2016.151852

46. Ussowicz, M., Przystupski, D., Mensah-Glanowska, P., & Piekarska, A. (2024). Current status and perspectives of hematopoietic cell transplantation in patients with paroxysmal nocturnal hemoglobinuria. *Frontiers in Immunology, 15*, 1521484. https://doi.org/10.3389/fimmu.2024.1521484
47. van den Heuvel-Eibrink, M. M. (2007). Paroxysmal nocturnal hemoglobinuria in children. *Paediatr Drugs, 9*(1), 11-16. https://doi.org/10.2165/00148581-200709010-00002
48. Walport, M. J. (2001a, Apr 5). Complement. First of two parts. *N Engl J Med, 344*(14), 1058-1066. https://doi.org/10.1056/nejm200104053441406
49. Walport, M. J. (2001b, Apr 12). Complement. Second of two parts. *N Engl J Med, 344*(15), 1140-1144. https://doi.org/10.1056/nejm200104123441506
50. Ware, R. E., Hall, S. E., & Rosse, W. F. (1991, Oct 3). Paroxysmal nocturnal hemoglobinuria with onset in childhood and adolescence. *N Engl J Med, 325*(14), 991-996. https://doi.org/10.1056/nejm199110033251403
51. Wilcox, L. A., Ezzell, J. L., Bernshaw, N. J., & Parker, C. J. (1991, Aug 1). Molecular basis of the enhanced susceptibility of the erythrocytes of paroxysmal nocturnal hemoglobinuria to hemolysis in acidified serum. *Blood, 78*(3), 820-829.
52. Wong, R. S. M., Navarro-Cabrera, J. R., Comia, N. S., Goh, Y. T., Idrobo, H., Kongkabpan, D., Gomez-Almaguer, D., Al-Adhami, M., Ajayi, T., Alvarenga, P., Savage, J., Deschatelets, P., Francois, C., Grossi, F., & Dumagay, T. (2023, Jun 13). Pegcetacoplan controls hemolysis in complement inhibitor-naive patients with paroxysmal nocturnal hemoglobinuria. *Blood Adv, 7*(11), 2468-2478. https://doi.org/10.1182/bloodadvances.2022009129
53. Yen, T. A., Lu, M. Y., Kuo, M. F., Huang, C. C., Chen, J. S., & Yang, Y. L. (2012, Jul 15). Eculizumab treatment of paroxysmal nocturnal hemoglobinuria presenting as moyamoya syndrome in a 9-year-old male. *Pediatric Blood & Cancer, 59*(1), 203-204. https://doi.org/10.1002/pbc.24070