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Vaccination in paroxysmal nocturnal hemoglobinuria patients treated with terminal and proximal complement inhibitors — Polish Expert Consensus

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Abstract

Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hematologic disorder characterized by uncontrolled complement activation that leads to hemolysis and thrombosis. Clinical outcomes have dramatically improved with administering terminal and proximal complement inhibitors (CIs). However, these treatments come at the cost of increasing the risk of severe infection, especially from encapsulated bacteria. This has created compulsory vaccination recommendations by regulatory authorities to patients with PNH on CIs treatment.

Material and methods: An adaptation of the Delphi consensus process involving a group of experts in the field of hematology, infectious diseases, and vaccinology was used to develop Polish vaccination recommendations for patients with PNH treated with CIs. The experts reviewed 16 proposed statements, rating each from 1 to 9 in 3 rounds (1–3 denoted as “disagree,” 4–6 as “neutral” and 7–9 as “agree”). A final decision on statements that were converged to strong or even moderate agreement was taken into practice.

Results: A Delphi process ended with convergence into consensus all 16 prepared statements. Recommendations include routine immunization against meningococcus (MenACWY, MenB) in patients on proximal and terminal CIs, extended immunization against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b in patients on proximal CIs, and the use of antibiotic prophylaxis against meningococcal infection in patients where the institution of CI therapy cannot be delayed until vaccines have been given. Annual immunizations against influenza and COVID-19 are also recommended.

Conclusions: These consensus guidelines emphasize the paramount importance of optimal immunization for PNH patients treated with CIs. Completing vaccination schedules and implementing prophylactic strategies may significantly reduce the risk of severe, potentially life-threatening infections, thus allowing for safer and more effective management of the disease.

Keywords: meningococcal vaccine, pneumococcal vaccine, haemophilus influenzae type b vaccine, complement-mediated hemolysis, infection prevention in PNH

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hematologic disorder caused by a somatic mutation in the *PIGA* gene in hematopoietic stem cells that results (among others) in a deficiency or lack of complement-regulating proteins CD55 and CD59 on the surface of red blood cells (RBCs) leading to intravascular hemolysis (IVH) via an uncontrolled complement system [1]. This condition affects approximately 16 people per million and can occur at any age, but is more commonly diagnosed in adults with a median age of 30 years [2]. The destruction of RBCs occurs spontaneously or is triggered by conditions activating the complement system, such as infections, vaccinations, surgical interventions or pregnancy. Intravascular hemolysis can, among other complications, lead to life-threatening venous and arterial thromboembolic (TE) episodes. Without targeted treatment, 35% of patients die within 5 years and 50% within 10 years of disease diagnosis, mainly due to thrombotic complications [3, 4].

Treatment of PNH is focused on the prevention of premature death, managing symptoms and complications, as well as improving patients' quality of life. Currently, the mainstay of treatment is complement inhibition, which can be achieved through monoclonal antibodies such as eculizumab and ravulizumab [5, 6]. These medications target the complement component 5 (C5) and inhibit the terminal complement pathway, reducing IVH, thromboses, and other complications associated with PNH. In patients in whom C5 inhibition is ineffective, mainly due to extravascular hemolysis (EVH) (clinically significant EVH may occur in patients with PNH under C5i treatment and a significant proportion of C5i treated patients have emergent EVH and residual IVH), the proximal complement inhibitors such as

pegcetacoplan (that blocks complement component 3 and 3b, C3/C3b), iptacopan (that blocks factor B, FB) or danicopan (that blocks factor D, FD) can be used [7–9].

During treatment with complement-targeted therapeutics, the function of the complement system is suppressed, and the patients are at increased risk of bacterial infections [10]. The complement system is crucial in recognizing and eliminating encapsulated bacteria such as *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type b [11]. Terminal complement blockers mainly increase the risk of *Neisseria* infections, including meningococcal sepsis and meningitis. Therefore all patients on C5 inhibitors should be vaccinated against *N. meningitidis* [12]. Inhibition of the proximal complement pathway further increases the risk of encapsulated bacterial infections; thus, a more expanded vaccination scheme may be advised, including vaccinations against *S. pneumoniae,* and *H. influenzae* type b. It is worth noting that adequate vaccination of PNH patients is essential because infections can exacerbate the clinical course of PNH and lead to life-threatening episodes of breakthrough hemolysis (BTH) [13].

This paper aims to provide clinicians with practical guidance on mitigating the risk of severe infections in PNH patients receiving terminal and proximal complement inhibitors.

Material and methods

A modified Delphi consensus procedure was conducted to develop consensus recommendation.

Participants

The study involved seven experts in hematology, infectious diseases, and vaccinology. Four experts specialized in hematology (JeW, IH, AP, MH), while the other three specialized in vaccinology and infectious diseases (EK, LS, JaW). Experts were invited to participate in meetings to develop vaccine recommendations for patients with PNH treated with complement inhibitors.

The first meeting of Delphi panelists

Before the first meeting, all experts reviewed the literature on vaccination in patients with PNH. The meeting focused on three main topics: identifying the vaccines necessary for patients with PNH on CIs, establishing a vaccination schedule, and exploring alternative prevention strategies beyond vaccination. The experts' discussions were based on the available literature including existing vaccine recommendations and their own clinical experiences. After the first meeting, the experts compiled their initial vaccine recommendations for patients with PNH. These recommendations represented a crucial starting point for future deliberations.

The second meeting of Delphi panelists

During the second meeting, experts reviewed and refined the initial recommendations from the first meeting. After the second advisory board meeting, the panel's delegate (JeW) formulated the main statements of vaccine recommendations for patients with PNH treated with complement inhibitors. A list of 16 statements was generated and sent to all panelists.

Modified Delphi process

The modified RAND/UCLA Appropriateness Method (RAM) was implemented [15–17] during a Delphi process comprising three rounds. The evaluation framework involved experts assigning scores on a scale of 1–9, with responses of 1–3 denoted as "disagree," 4–6 as "neutral" and 7–9 as "agree." Using the methodology delineated by Duivon et al. [17], the evaluation of each statement was based on the median and range of experts' opinions, classified as follows:

- Strong agreement: median >6 [Range 7–9]
- Moderate agreement: median >6 [Range 5–9]
- Strong disagreement: median <4 [Range 1–3]
- Moderate disagreement: median <4 [Range 1–5]
- Uncertain, with lack of consensus: other cases

In the initial round, experts evaluated each statement on a 1–9 scale and had the opportunity to add comments. Recommendations categorized as “strong agreement” were endorsed, while those designated as “strong disagreement” were rejected.

During the second round, the experts’ delegate (JeW) scrutinized the results of the initial round, considering comments left by their peers. The second round concentrated on statements that lacked unequivocal consensus. The rating process mirrored that of the initial round. The statements not accepted in the second round were modified and reassessed in the final third round. Ultimately, statements with strong or moderate agreement ratings were assimilated into the recommendations.

Ethical considerations

The study followed ethical principles, and all experts agreed to participate in the meetings. The study did not involve human or animal subjects, and ethical approval was not required.

Results

After one round, a strong agreement was achieved for 13 statements, and the remaining three statements were classified as “uncertain, with lack of consensus.” The responses and comments were evaluated and utilized by the appointed delegate (JeW) to develop 3 modified statements for the second round of Delphi voting. After the second round, one statement achieved strong agreement and the remaining two achieved moderate agreement. Because some panelists made relevant comments on the latter two statements after modifications were made by the appointed delegate (JeW), the third round of Delphi voting was held. In this final round both statements achieved moderate agreement. All 16 statements, including the panelists’ comments made in the third round of Delphi voting are reported in Table I. Table II presents the immunization schedule for patients initiating treatment with C5 inhibitors, and Table III — for patients switching from C5i to C3 inhibitor (pegcetacoplan).

Table I. Consensus statements

No	Statement	Classification of consensus
1	PNH patients must receive mandatory vaccinations against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* type b at least	Strong agreement Median 9 (range 7–

	two weeks before initiation of treatment with complement C3 inhibitor (pegcetacoplan)	9)
2	PNH patients must receive mandatory vaccinations against *N. meningitidis* at least two weeks before initiating treatment with complement C5 inhibitor. However, vaccinations against *S. pneumoniae* and *H. influenzae* type b should also be considered	Strong agreement Median 9 (range 7–9)
3	If due to emergency there is a need to commence the complement inhibition (CI) immediately, the mandatory vaccines can be given after CI treatment has started provided pharmacologic prophylaxis with antibiotics is given	Strong agreement Median 9 (range 7–9)
4	Prophylaxis of infections with antibiotics [e.g., penicillins (PCN), or, in case of allergy to PCN, macrolides] should be commenced with the first dose of CI therapy and continued until two weeks from the last dose after mandatory vaccine administration Remark: we suggest using preferable beta-lactams, e.g., penicillin V potassium (PCN VK) 250 mg orally twice daily or amoxicillin 500 mg orally twice daily. In case of serious PCN allergy, we suggest using azithromycin 250 mg orally once daily Comment from two panelists: Fluoroquinolones should be included as an option	Moderate agreement Median 8.5 (range 6–9)
5	Patients with PNH should receive two types of vaccine against *N. meningitidis*: quadrivalent against serogroups A, C, W, and Y (Men-ACWY), and the other against serogroup B (Men-B)*	Strong agreement Median 9 (only 9)
6	The second dose of Men-ACWY should be administered 8 weeks after the first dose, and the second and third dose of Men-B – 1–2, and 6 months after the first dose, respectively*	Strong agreement Median 9 (range 7–9)
7	A booster dose of Men-B is recommended one year after the primary vaccination scheme is completed and subsequently every 3 years*	Strong agreement Median 9 (range 8–9)
8	A booster dose of Men-ACWY is recommended every 5 years	Strong agreement Median 9 (range 8–

		9)
9	Determination of antibody titer against *N. meningitidis*, *S. pneumoniae*, or *H. influenzae* to establish the need for vaccination is not recommended	Strong agreement Median 9 (range 8–9)
10	Pneumococcal vaccination consists of the administration of either: 1) a single dose of 20-valent pneumococcal conjugate vaccine (a single dose of PCV20 is the complete vaccination course) or 2) a single dose of 13- or 15-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide vaccine at least 8 weeks later. These patients should additionally receive a single booster dose of 23-valent pneumococcal polysaccharide vaccine or 20-valent pneumococcal conjugate vaccine 5 years later	Strong agreement Median 9 (range 8–9)
11	Vaccination against *H. influenzae* type b comprises the administration of one single dose of conjugate Hib vaccine regardless of previous vaccination history	Strong agreement Median 9 (only 9)
12	In case of concerns about the adverse effects of vaccines, one vaccine can be administered at a time during a single visit; however, it is permissible to give >1 vaccine during a visit Comments from two panelists: Panelist 1: it is admissible to give >1 vaccine during one visit but only in patients with a low risk of hemolysis exacerbation; Panelist 2: it is admissible to give >1 vaccine during one visit in patients with a low risk of IVH exacerbation, e.g., in a patient with a small PNH clone or well-controlled IVH on C5 inhibitors	Moderate agreement Median 8.5 (range 6–9)
13	In patients already on CI therapy, scheduled subsequent vaccines should be administered when the concentration of complement inhibitor in the patient's blood is high (i.e., in the first days following the last dose of CI). This recommendation is based on the assumption that the risk of vaccine-triggered hemolysis is highest when the complement inhibitor blood concentration is low	Strong agreement Median 9 (range 8–9)
14	All patients with PNH on CI therapy should be instructed to evaluate infectious signs and to take appropriate antibiotics	Strong agreement Median 9 (range 9–

	early	9)
15	In case of infection, the CI therapy must not be discontinued	Strong agreement Median 8 (range 7–9)
16	Vaccination for COVID-19 and annual vaccination for influenza are recommended in all PNH patients on CI treatment	Strong agreement Median 9 (only 9)

CI — complement inhibition; Hib — *H. influenzae* type b; IVH — intravascular hemolysis; Men-ACWY — a quadrivalent vaccine against serogroups A, C, W and Y of *N. meningitidis*; Men-B — vaccine against serogroup B of *N. meningitidis*; PCV13 — 13-valent pneumococcal conjugate vaccine; PCV15 — 15-valent pneumococcal conjugate vaccine; PCV20 — 20-valent pneumococcal conjugate vaccine; PNH — paroxysmal nocturnal hemoglobinuria; PPSV23 — 23-valent pneumococcal polysaccharide vaccine

*At the time of writing this manuscript Food and Drug Administration changed the label for the meningococcal serogroup B MenB-4C vaccine (Bexsero) from a 2-dose schedule (0 and ≥1 month) to a 2-dose schedule (0 and 6 months) and added a 3-dose schedule (0, 1-2 and 6 months) for persons aged ≥10 years at increased risk (e.g., persons using a complement inhibitor) [43]

Table II. Immunization schedule for patients initiating treatment with C5 inhibitors

Vaccine	Schedule	Notes
Men-ACWY	1. The first dose should be administered at least two weeks before initiating C5 inhibitor therapy 2. The second dose should be administered eight weeks after the first dose 3. A booster dose should be administered every 5 years	1. The initial dose of Men-B should be administered at least two weeks after the first dose of Men-ACWY
Men-B*	1. The first dose should be administered after the start of treatment with a C5 inhibitor 2. The second and third dose should be administered 1–2, and 6 months after the first dose, respectively 3. A booster dose should be administered a year after the primary vaccination scheme is completed and subsequently every 3 years.	

C5 — complement component 5; Men-ACWY — a quadrivalent vaccine against serogroups A, C, W and Y of *N. meningitidis*; Men-B — vaccine against serogroup B of *N. meningitidis*

*At the time of writing this manuscript Food and Drug Administration changed the label for the meningococcal serogroup B MenB-4C vaccine (Bexsero) from a 2-dose schedule (0 and ≥1 month) to a 2-dose schedule (0 and 6 months) and added a 3-dose schedule (0, 1–2 and 6 months) for persons aged ≥10 years at increased risk (e.g., persons using a complement inhibitor) [43]

Table III. Immunization schedule for patients switching from C5 to C3 inhibitor (pegcetacoplan)

Vaccine	Schedule	Notes
Men-ACWY	1. A booster dose should be administered every five years.	1. This schedule presupposes that the patient has received adequate Men-ACWY and Men-B vaccinations during prior C5 inhibitor treatment. 2. Determination of antibody titer against *N. meningitidis*, *S. pneumoniae*, or *H. influenzae* in order to establish the need for vaccination is not recommended.
Men-B	1. A booster dose should be administered a year after completion of the primary vaccination scheme and subsequently every 3 years.	
PCV	1. A single dose is recommended when using PCV20. 2. If PCV13 or PCV15 is used, it is necessary to administer one dose of PPSV23 with a minimum interval of at least eight weeks. a. These patients should receive a single booster dose of 23-valent pneumococcal polysaccharide vaccine or PCV20 5 years later.	
Hib	1. A single dose is all that is necessary.	

C3 — complement component 3; C5 — complement component 5; Hib — *H. influenzae* type b; Men-ACWY — a quadrivalent vaccine against serogroups A, C, W and Y of *N. meningitidis*; Men-B — vaccine against serogroup B of *N. meningitidis*; PCV13 — 13-valent pneumococcal conjugate vaccine; PCV15 — 15-valent pneumococcal conjugate vaccine; PCV20 — 20-valent pneumococcal conjugate vaccine; PPSV23 — 23-valent pneumococcal polysaccharide vaccine.

Discussion

Currently, the standard of care therapy for hemolytic and thrombotic PNH is complement inhibitors. At the time of writing this manuscript, in Poland, as in many other countries, the first-line treatment is C5 inhibition with eculizumab or ravulizumab. Recently, the C3 inhibitor, pegcetacoplan, has also been given first-line indication (among others in the

European Union), yet to the best of our knowledge, pegcetacoplan is still mostly used as a second-line therapy in those PNH patients in whom the response to C5 inhibitors is unsatisfactory due to EVH. Three complement inhibitors have been recently licensed in the EU, i.e., crovalimab (C5 inhibitor), danicopan (FD inhibitor), and iptacopan (FB inhibitor), and two of them (crovalimab and danicopan) are being reimbursed in Poland since October 2025.

All patients receiving terminal inhibitors require meningococcal vaccination with both quadrivalent (MenACWY) and serogroup B (MenB) formulations following the schedule presented in Table II. Similarly to the other group of experts [14], for long-term protection, we recommend providing boosters for MenACWY every 5 years, and for MenB every 3 years without determining the antibody titer against *N. meningitidis*. MenB vaccine may cause a post-vaccination fever, therefore prophylactic use of paracetamol can be considered [18].

Patients switching from C5 to proximal inhibitors require additional protection against *S. pneumoniae* and *H. influenzae* type b and, therefore, they must receive adequate vaccinations, as shown in Table III. For vaccinating against *S. pneumoniae*, a 20-valent conjugated vaccine is recommended because of its broad serotype coverage and the requirement for only one dose [19]. Some doubts remain regarding the duration and quality of protection provided by the PCV20 vaccine since no studies analyze its immunogenicity in immunocompromised adults [20]. If PCV13 or PCV15 is used, at least eight weeks later an additional dose of PPSV23 should be administered to achieve complete protection against *S. pneumoniae*. Additionally, these patients should additionally receive a single booster dose of 23-valent pneumococcal polysaccharide vaccine or 20-valent pneumococcal conjugate vaccine five years later [20, 21]. The Hib vaccine provides protection only for a few years, so PNH patients treated with the proximal inhibitors who were vaccinated against *H. influenzae* type b during childhood should be re-vaccinated with one single dose of this vaccine [22]. Vaccination against *H. influenzae* type b requires written consent from adult PNH patients, as the Hib vaccine is licensed exclusively for pediatric patients under 5 years. However, it is noteworthy that this vaccine has been in routine use in adults with an absent or dysfunctional spleen and in adults undergoing hematopoietic stem cell transplantation for many years [23, 24].

One should realize that the above-mentioned vaccinations do not grant absolute immunity against diseases originating from encapsulated bacteria. There are reports of severe meningococcal infections in patients treated with C5 inhibitors despite vaccinations against

the microbe [25–28]. In one of the most recent studies, which included 509 adequately vaccinated PNH patients receiving long-term (between 2002 and 2022) C5 inhibition, the observed meningococcal infection rate was 0.35 events per 100 patients-years (11 patients developed meningococcal sepsis, one patient died) [25]. On the other hand, in another recently published study on 464 adequately vaccinated PNH patients receiving long-term (619.4 patient-years) treatment with pegcetacoplan, no infections with meningococcal bacteria were reported [29].

General guidelines for vaccination accept the co-administration of multiple vaccines at a time [30]. However, one should remember that vaccines can amplify complement activity and lead to severe hemolysis in PNH patients [14, 31–33]. To reduce the potential risk of vaccine-triggered hemolysis, some PNH experts believe that only one vaccine should be administered at a time in any PNH patient [14]. Our 12th recommendation allows for administering more than one vaccine at a time, provided the patient has a low risk of hemolysis exacerbation (small PNH clone and/or well-controlled IVH while on complement inhibitors). In patients already on CI therapy, the subsequent vaccines should be administered when the concentration of complement inhibitor in the patient's blood is high (i.e., in the first days following the last dose of CI) since the risk of vaccine-triggered hemolysis is highest when the complement inhibitor blood concentration is low.

Patients with PNH who require immediate CI treatment before completion of the mandatory vaccination regimen must receive anti-Men pharmacologic prophylaxis with antibiotics. We recommend using penicillins (PCN) or macrolides in case of PCN allergy from the first dose of CI therapy until two weeks after the last doses of mandatory vaccine administration. The use of amoxicillin for infection prophylaxis in adult asplenic patients is well established [34]. Two panelists indicated fluoroquinolones as a possible option in this clinical situation (Tab. I).

In addition, all PNH patients treated with CIs should receive annual vaccinations against COVID-19 and influenza. Although there is no direct evidence of an increased risk of COVID-19 or influenza infections in PNH patients, it is well-established that infectious diseases can exacerbate the hemolytic symptoms of PNH due to increased complement activity [13, 35, 36]. However, one should not forget that hemolysis cases have also been reported in PNH patients treated with CIs after taking COVID-19 vaccines [31, 32].

Before initiating treatment with complement inhibitors, it is essential to ensure that the patient is fully informed about the increased risk of encapsulated bacterial infections and its

consequences. The individual must be educated about the possible symptoms of these infections and advised of the appropriate actions to take if symptoms occur. As a precautionary measure, patients should keep a supply of an antibiotic ("pill in pocket"), preferably amoxicillin/clavulanic acid or levofloxacin at home to take it immediately in case of infection symptoms (e.g., fever) and proceed to the closest emergency department [37]. One should remember that such infections are rare in the general adult population and therefore do not receive significant public attention [38]. Consequently, recognizing rapidly invasive infections caused by encapsulated bacteria can be challenging for general practitioners or internal medicine specialists, given their limited experience with such diseases [39]. Providing patients with a safety card detailing their increased risk of encapsulated bacterial infections is essential to address this problem. Such a card would be a convenient reference for sharing critical information with healthcare professionals [40].

Notably, the only absolute contraindication to vaccination is a severe allergic reaction to any vaccine component [41]. In such a rare event, the only solution in a patient with PNH requiring CI treatment seems to be long-term antibiotic prophylaxis [42]. Based on the published data, life-long antibiotic prophylaxis is feasible, yet its efficacy has not been proved in this setting [14, 42].

Conclusions

These recommendations highlight the importance of vaccinating PNH patients against *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* before initiating treatment with drugs inhibiting the complement system. Physicians must consider that full immunization of previously unvaccinated patients will take at least six weeks. In the event of an urgent need to start treatment, patients should receive antibiotic prophylaxis until at least two weeks after completion of the vaccination regimen. In addition, the recommendations stress the importance of COVID-19 and influenza vaccinations, as any infection can exacerbate the clinical course of PNH. By following these guidelines, healthcare providers can effectively manage and prevent infections in PNH patients, ultimately improving their quality of life.

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Conflict of interest

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AP — speaker fees or participation in advisory boards for: Alexion, Amgen, Astellas, AstraZeneca, Celgene/ Bristol Myers Squibb, Novartis, MSD, Pfizer, Sobi, Santen; support in conference participation: Alexion, AstraZeneca, Novartis, Pierre Fabre Médicament, Roche, Sanofi.
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JaW — speaker fees or participation in advisory boards for GSK, Pfizer, Sanofi, AstraZeneca, MSD.
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Data availability statement

Data available upon request from the authors.

Authors' contributions

All authors contributed to the methodology development, data processing, validation, analysis, investigation, data curation, reviewing, and editing of the manuscript. Jerzy Windyga supervised the study, prepared visualizations, and drafted the manuscript.

Supplementary material

Not applicable.

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