A Critical Appraisal of Clinical Practice Guidelines for Pharmacological Treatments of Paroxysmal Nocturnal Hemoglobinuria

ABSTRACT

Aims: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare chronic disease characterized by complement-mediated hemolysis, thrombosis, and bone marrow failure. This study aims to identify methodological limitations in Clinical Practice Guidelines (CPG) for the treatment of PNH. Thus, we critically evaluate the guidelines, highlighting relevant recommendations supported by high-quality evidence to improve healthcare strategies.
Methodology: A systematic search was carried out in PubMed/MEDLINE, Scopus, Embase, COCHRANE, and TRIP databases. From 1995 initially identified references, 1649 articles underwent title and abstract screening. Twenty-three references were selected for full-text screening. Ultimately, 12 CPGs were included. Four independent reviewers assessed the CPGs' methodological quality using the instruments "Appraisal of Guidelines for Research and Evaluation II" (AGREE II) and "Recommendation Excellence" (AGREE-REX). Their characteristics, as well as any differences in recommendations, were summarized and compared.
Results: Twelve guidelines published from 2011 to 2022 by Spain, Brazil, Mexico, Israel, Canada, Turkey, Scotland, and the United Kingdom were included. The UK's and Brazil's CPGs received the highest scores. Overall, the CPGs scored strongly in the domains of "Scope and Purpose" and "Clarity of Presentation" since they addressed fundamental aspects, such as aim, specific health questions, target population, and language. All guidelines presented deficiencies in the"Editorial Independence" in AGREE II, and "Values and Preferences" in AGREE-REX, demonstrating the need for a careful revision and improvement of future versions.
Conclusion: We found disparities in the methodological quality of the available CPGs. Despite being extremely important, recommendations on adapting treatment to local policies and further updates that include newly approved medications were absent. Approaches that prioritize the engagement of methodologists and multidisciplinary collaborators may also lead to higher quality CPGs for treating PNH.

KEYWORDS: Paroxysmal nocturnal hemoglobinuria; Practice guideline; Monoclonal antibody; Immunobiological treatment.

1. INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem cell disorder. It is characterized by the clonal expansion of hematopoietic stem cells with a deficiency of glycosylphosphatidylinositol (GPI) anchored surface protein.It occurs due to mutations in phosphatidylinositol glycan class A (PIG-A), a gene involved in the GPI anchor

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biosynthesis.The absence of CD55 and CD59 leads to complement-mediated erythrocyte lysis. The glycoprotein CD59 interacts with the membrane attack complex (MAC) to prevent the formation of pores that disrupt the cell membrane, while CD55 accelerates the destruction of membrane-bound C3 convertase. The activity of C3 convertases on PNH erythrocytes initiates intravascular hemolysis [1, 2].

PNH signs and symptoms may include smooth muscle dystonia, anemia, hemoglobinuria, severe fatigue, renal impairment, and pulmonary hypertension. In addition to being at risk of thrombosis, PNH patients may also experience the consequences of nitric oxide depletion, due to the toxic effects of freely circulating hemoglobin [3].

Managing PNH patients may be complex, and often requires different strategies to address thrombosis, hemolytic anemia, and bone marrow failure. Currently, hematopoietic stem cell transplants and anti-complement drugs stand out as the optimal choice for thetreatment of PNH. The complement inhibitors are effective in reducing or eliminating the need for blood transfusions, the incidence of thromboembolic events, as well as improving anemia in a substantial number of patients. Complement inhibition, when coupled with patient and physician education, can potentially prevent the morbidity and mortality associated with the disorder [2-4].

Eculizumab, the first monoclonal anti-C5 antibody, was approved for the treatment of PNH by the Food and Drug Administration (FDA) in 2007. Later in 2018, the FDA also approved Ravulizumab. Both drugs operate by binding to C5, thereby inhibiting its cleavage into C5a and C5b,preventing the subsequent formation of the MAC, and the lysis of erythrocytes[5, 6]. Thus, the C5 inhibition compensates for the loss of CD59 and prevents intravascular hemolysis [1].Pegcetacoplan, a drug approved for treating PNH in 2021, is also highly effective, as it operates at the C3 level to block complement activation [7].

The complement inhibitors lead to an impressive control of intravascular hemolysis and reduction of thrombosis rates, increasing thechances of survival. Patients who experienced clinically meaningful improvements have reported a substantial reduction in fatigue, better physical conditioning, and changes in hematological parameters [5, 8].

Clinical practice guidelines (CPGs) are a mainstay of evidence-informed medicine; they facilitate the delivery of appropriate health care and guide the decision-making process [9]. These documents often reflect synthesized opinions of expert groups, review the available scientific evidence, and/or include a formal assessment of the treatments' benefits and

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drawbacks. However, not all CPGs adhere to rigorous methodologies, and their development processes vary widely due to a lack of methodological guidance [10].

While CPGs can lead to improved health outcomes, strengthen healthcare systems, and contribute to evidence-based decision-making [11], global critical reviews have shown they are not sufficiently robust. To address this issue, validated tools such as the Appraisal of Guidelines for Research and Evaluation Instrument version 2 (AGREE II), can be employed to evaluate the methodological quality, rigor, and transparency of guidelines. The use of these tools not only helps toidentify areas for improvement,but also ensures that they are evidence-based and relevant to clinical practice [12]. The AGREE II stands out as the most widely used and prolifically cited tool in the literature. The AGREE-REX, in turn, is a newly developed tool that focuses on assessing CPGs' clinical credibility and Implementability [10, 13].

In PNH management, as the options remain limited, it is imperative that guidelines arestandardized for clinical practice. Thus, in this study, we critically appraise guidelines for the treatment of PNH using both the AGREE II and AGREE-REX instruments. Identifying strengths and weaknesses may guide the development of future guidelines for the treatment of PNH, as well as provide an evidence-based approach to the disorder's management.

2. METHODOLOGY

2.1Study Design

We conducted a systematic review of CPGs according to the Cochrane Collaboration recommendations [14] and based on the rigorous standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. The protocol for this review is registered in the International Prospective Register of Systematic Reviews under the code CRD42023388024.

2.2Literature Search and Eligibility Criteria

The systematic search was conducted in the PubMed/MEDLINE, Scopus, Embase, COCHRANE, and TRIP databases. The search strategies for each database are available in the Supplementary Material. Additionally, we searched specific websites,*i.e.* government websites that host guidelines inEnglish, Portuguese, or Spanish. The search strategy included manual searching and screening of reference lists. No filters regardingthe year of publication or country of study were applied to the search.

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In order to assess whether the references found were relevant, we established the following inclusion criteria: (a) Clinical practice guidelines, and Recommendations and Consensus authored by an authors' organization or specialized society; (b) Inclusion of pharmacological treatment of PNH; (c) Publications in Portuguese, English, and Spanish.

The exclusion criteria were: (a) CPGs solely focused on PNH detection, diagnosis, mapping, staging, imaging, scanning, or follow-up without treatment; (b) Unavailable papers, surveys, audits, editorials, letters to the editor, case reports, or notes; (c) Guidelines authored by individuals or groups not commissioned by professional associations or health ministries.

All potentially eligible studies were preselected using the Rayyan online tool. Two researchers screened the studies' titles and abstracts, independently and in parallel, to exclude unrelated papers. Subsequently, the two reviewers independently screened the full text of all studies identified as potentially relevant.

2.3Quality Assessment Strategy

Four reviewers independently evaluated the methodological rigor of PNH guidelines using the AGREE II tool. Since these assessment tools are subjective and the results could be influenced by the user's skill level, users must hold a rigorous academic attitude. Thus, to minimize performance bias, at least two independent reviewers should be involved in the process, ideally possessing epidemiological knowledge as well [16].

The AGREE II comprises six domains: Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity of Presentation, Applicability, and Editorial Independence. Appraisers also provide an overall assessment of the CPGs' quality and determine whether it will be recommended for use.

Moreover, the AGREE-REX tool was used to evaluate the clinical quality, credibility, and implementability of the recommendations. This instrument comprises three domains with nine items, including Clinical Applicability, Values and Preferences, and Implementability. Each item was scored using a seven-point Likert scale, which ranges from 1 (strongly disagree) to 7 (strongly agree). Domain scores were calculated based on the AGREE Manual [17]. Any score discrepancies among authors were resolved through group discussions. The minimum standard score for each domain is 0% and the maximum is 100%. Based on previous research and expert consensus, we established a cut-off score of at least 60% for AGREE-II and AGREE-REX domains as indicative of a high-quality guideline [18-20].

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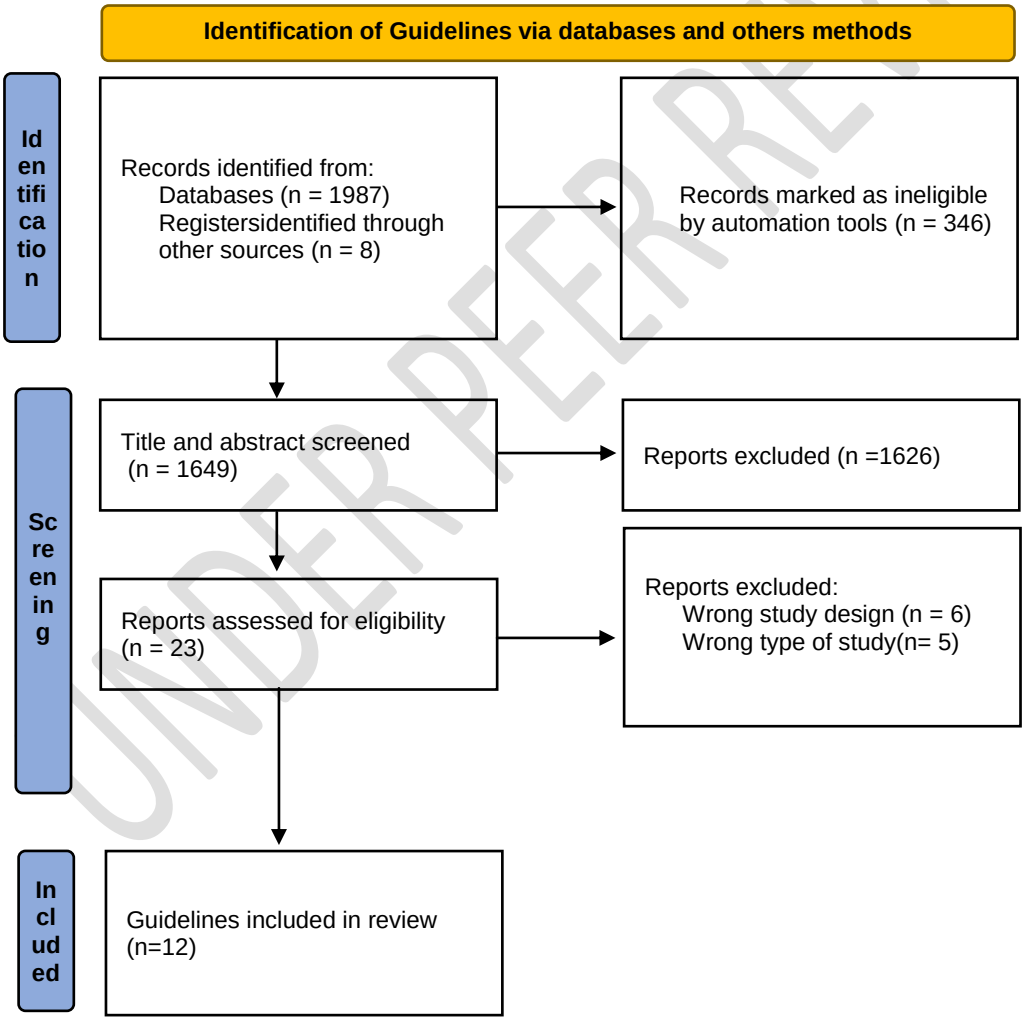
3. RESULTS

The systematic review process was carried out in January 2023. In total, 1995 potentially relevant references (n=1987) were identified from database searches: Pubmed/MEDLINE (n=128), Embase (n=64), COCHRANE (n=1714), TRIP (n=81), as well asfrom organization websites and manual search (n=8). After the duplicates were excluded, 1649 articles underwent title and abstract screening, and 23 references were selected for full-text screening. Ultimately, 12 CPGs were included in the review [21-32]. The PRISMA flowchart is reported in Figure 1.

Figure 1. Flow diagram of systematic review of PNH treatment guidelines



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3.1Study Characteristics

Table 1 provides an overview of the 12 included CPGs [21 - 32]. These range from 2011 to 2022. Among them, four (33.33%) were developed by researchers and clinicians in Spain, two (16.67%) in Brazil, and one (8.33%) in Mexico, Israel, Canada, Turkey, Scotland, and the United Kingdom.

Table 1. Characteristics of the Included PNH Treatment Guidelines

Year of Publication	Country	Guideline (Original title)
2011	Spain	Diagnóstico y Tratamiento de la Hemoglobinuria Paroxıstica Nocturna
2015	Spain	Informe de Posicionamiento Terapéutico de Eculizumab (Soliris®) en la Hemoglobinuria Paroxística Nocturna
2015	Mexico	Consenso mexicano para el tratamiento de la hemoglobinúria paroxística nocturna
2016	Spain	Consenso Español para el Diagnóstico y Tratamiento de la Hemoglobinuria Paroxística Nocturna
2016	Turkey	Pesg PNH diagnosis, follow-up and treatment guidelines
2018	Canada	How we treat paroxysmal nocturnal hemoglobinuria: A consensus statement of the Canadian PNH Network and review of the national registry
2019	Brazil	Protocolo Clínico e Diretrizes Terapêuticas Hemoglobinúria Paroxística Noturna
2020	Israel	PHYSICIAN'S GUIDE TO PRESCRIBING for patients with PNH
2021	Brazil	Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria
2021	Scotland	Ravulizumab 300mg/30mL concentrate for solution for infusion (Ultomiris®)
2021	United Kingdom	Ravulizumab for treating paroxysmal nocturnal haemoglobinuria
2022	Spain	Informe de Posicionamiento Terapéutico de ravulizumab

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	(Ultomiris®) en hemoglobinúria paroxística nocturna

3.2Assessment of CPGs Using the AGREE II Tool

The AGREE II domain scores for the CPGs are displayedin Table 2. In Domain 1, "Scope and Purpose", all guidelines presented high quality, with scores ranging from 62.50% to 100%. Five (46.67%) documents scored above 80% [23, 26, 27, 30, 31].

Table 2. AGREE II assessments of 12 included PNH CPGs

ORGANIZATION/AUTHORS	YEAR	D1	D2	D3	D4	D5	D6
Urbano-Ispizua et al	2011	62,50%	12,50%	14,58%	95,83%	25%	37,50%
Ministerio de Sanidad/Agencia Española de Medicamentos y Productos Sanitários	2015	72,22%	26,38%	16,67%	77,78%	17,71%	8,330%
Góngora-Biachi et al.	2015	80,55%	30,55%	20,83%	100%	26,04%	0
Sociedad Española De Hematología y Hemoterapia/Villegas et al.	2016	70%	33,33%	19,79%	100%	31,25%	31,25%
Sahin et al.	2016	70,83%	38,88%	14,06%	100%	27,08%	0
Patriquin et al.	2018	80,55%	44,44%	23,44%	94,44%	46,88%	0
Comissão Nacional de Incorporação de Tecnologias (CONITEC)	2019	100%	79,16%	76,56%	95,83%	75%	8,33%
Alexion Pharma Israel Ltd./The Israeli Ministry of Health (MOH)	2020	77,77%	23,61%	10,42%	90,28%	32,29%	0
Cançado et al.	2021	69,44%	22,22%	21,88%	90,28%	33,33%	8,33%
Scottish Medicines Consortium	2021	87,50%	38,88%	25%	87,50%	50%	4,17%
National Institute for Health and Care Excellence - NICE	2021	87,50%	68,05%	53,13%	91,67%	64,58%	22,92%
Ministerio de Sanidad/Agencia Española de Medicamentos y Productos Sanitários	2022	70,83%	11,11%	22,92%	84,72%	15,62%	2,08%

D1 – Domain 1 Scope and Purpose, D2 – Domain 2 Stakeholder Involvement, D3 – Domain 3 Rigor of Development, D4 – Domain 4 Clarity of Presentation, D5 – Domain 5 Applicability, D6 – Domain 6 Editorial Independence.

In Domain 2, "Stakeholder Involvement", only two guidelines (16%) scored above 60% [27,31], while the remaining ten guidelines exhibited scores ranging from 11.11% to 44.44% [21-26, 28-30, 32].

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In Domain 3, “Rigor of Development”, only one PNH Guideline scored higher than 60%, with a score of 76.56% [27], while the other 11 guidelines presented low quality in this aspect, with scores ranging from 10.42% to 53,13%. The authors neither completely describe the development process nor classify the strength of the recommendation (for example, risk of bias, inconsistency, indirectness, publication bias). The low score may reflect both the clinical and economic conditions in which the recommendations were formulated. Regarding Domain 4, “Clarity of Presentation”, all guidelines presented a high methodological quality score (84.72%–100%); of which, three scored 100% [23-25].

In Domain 5, “Application”, only the Brazilian [27] and British [31] guidelines scored above 60%. Finally, none of the guidelines included in this review scored ≥60% in Domain 6, “Editorial Independence”. All guidelines presented low scores, and four documents [23, 25, 26, 28] had a final score of 0% indicating that all reviewers scored 1 (the minimum score) for all items. Although some guidelines mentioned conflicts of interest, they failed to specify the interests, the identification process for conflicts, and how interests might have influenced how recommendations were developed and formulated. Declarations of interest were poorly described in the guidelines, lacking explicit statements that the funding source did not influence the guidelines’ content.

3.3Assessment of CPGs Using the AGREE-REX Tool

In Domain 1, “Clinical Applicability”, three guidelines scored >70%(75%–87.50%) [27, 30, 31]; four had scores ranging between 60% and 70% (62.58%–68.06%) [23, 26, 28, 32], and five guidelines presented lowerscores (44.44%–59.72%) [21, 22, 24, 25, 29]. In Domain 2, “Values and Preferences”, none of the CPGs’ recommendations for the treatment of PNH reached a sufficient score to be considered high or moderate, being evaluated as “low quality” (10.42%–57.29%) [21-32]. As for Domain 3, “Recommendations”, five (41.67%) guidelines scored>60% (60.42%–68.75%) [23, 26, 27, 30, 31]. The results of the AGREE-REX assessment and domain scores are shown in Table 3.

Table 3. AGREE-REX assessments of 12 included PNH CPGs

ORGANIZATION/SOCIETY/AUTHORS	YEAR	D1	D2	D3
Urbano-Ispizua et al	2011	44,44%	10,42%	35,42%
Ministerio de Sanidad/Agencia Española de Medicamentos y Productos Sanitários	2015	59,72%	14,58%	47,92%

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Góngora-Biachi et al.	2015	63,89%	20,83%	60,42%
Sociedad Española de Hematología y Hemoterapia/Villegas et al.	2016	52,78%	18,75%	43,75%
Sahin et al.	2016	59,72%	16,67%	43,75%
Patriquin et al.	2018	68,06%	17,70%	62,50%
Comissão Nacional de Incorporação de Tecnologias (CONITEC)	2019	87,50%	48,96%	64,58%
Alexion Pharma Israel Ltd./The Israeli Ministry of Health (MOH)	2020	62,50%	19,79%	50%
Cançado et al.	2021	48,61%	16,67%	52,08%
Scottish Medicines Consortium	2021	80,56%	40,62%	62,50%
National Institute For Health And Care Excellence - NICE	2021	75,00%	57,29%	68,75%
Ministerio de Sanidad/Agencia Española de Medicamentos y Productos Sanitários	2022	65,28%	13,54%	33,33%

D1 – Domain 1 "Clinical Applicability", D2 – Domain 2 "Values and Preferences", D3 – Domain 3 "Recommendations"

4. DISCUSSION

This paper assessed the methodological quality of CPGs for the treatment of PNH. Recognizing the subjectivity of methodological quality appraisal, AGREE II and AGREE-REX do not have predefined thresholds that differentiate between high and low-quality guidelines. Therefore, we adopted cut-off scores based on previous studies.

CPGs from Brazil [27] and the United Kingdom [31] obtained the highest AGREE II scores, exceeding 60% in at least four domains; therefore, based on this evaluation they are strongly recommended [33]. These guidelines notably excelled in the "Scope and Purpose" and "Clarity of Presentation" domains, which address fundamental aspects of recommendations, including the overall aim, specific health questions, target population, and language [34].

The British CPG [31] highlights the patients' perspective and raises social and personal issues that can affect the care process. For example, considering the frequency of Eculizumab infusions, it is difficult to work and socialize. It is also challenging to schedule the infusions, and the frequent cannulations can lead to scarring of the veins. Thus, NICE recommends Ravulizumab infusions every 8 weeks, and highlights the need for a new drug option to

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reduce the frequencyof administration. This CPG can be implemented in daily practice, and Ravulizumab is a cost-effective use of NHS resources in England.

Among the strengths of the Brazilian guideline [27], we can highlight the development of a treatment flowchart, the public consultation, and the consideration of the cost for implementation. This Protocol contains diagnostic criteria, and inclusion and exclusion criteria for the population receiving the treatment by the public health system, and they bring mechanisms for regulation, control, and evaluation. They recommend Eculizumab and its health benefits, side effects, and risks were considered in formulating the document.

"Values and Preferences" was the domain with the lowest scores in AGREE-REX; this observation aligns with previous research that had indicated consistently lower scores in this domain. Evidence- based medicine should include users' values and expectations, individual clinical expertise, and the best available clinical evidence. By providing information that supports patient involvement in decision-making, CPGs would be more implementable [35, 36].

When domains present low scores, they usually stem from insufficient discussions on guideline applicability or planning to update such documents, which includes a limited range of stakeholders [37]. Authors often overlook local resources and fail to accommodate local adaptations during CPGs' development.

Domain 2 of the AGREE II tool highlights the extent to which the guideline represents the views of stakeholders and target users. Ideally, documents should include expert members from various disciplines and professions, as well as guideline users and target groups. This domain primarily reflects the extent to which the guideline incorporates the views and availability of the target population, including patients and healthcare professionals [38, 39].

Improving the development of CPGs for the treatment of PNH would benefit from a multidisciplinary team, encompassing patients, caregivers, and different professional groups such as clinical pharmacy, nursing, and public health from multiple universities and locations [40]. Furthermore, including a methodologist on the team is essential to define methodological parameters, guide evidence evaluation, and facilitate discussions on the incorporation of evidence into the recommendations, thereby ensuring the CPGs' quality [41]. Moreover, guidelines should avoid biased evidence. The review process is usually labor-intensive, requiring financial resources and methodological expertise [42].

A previous systematic review showed that although most institutions suggest incorporating patients and their views into the CPG's development process, the steps to

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achieve this are scarcely described in the literature. Thus, CPGs may not consistently incorporate patients' viewpoints [43].Previous studies suggest that guidelines developed without taking into account the users' and patients' values and preferences may not be relevant or applicable to their needs, which can lead to low adherence and poor results [12]. In addition, some recommendations are consensus-based and lack support from prospective, randomized data. Due to the rarity of the disease, clinical studies that examine these guidelines are still rare [3].

CPGs often score low in Domain 5 of AGREE II [44]. However, two guidelines (Brazil and Nice, United Kingdom) stood out for explicitly linking their recommendations to specific evidence, encompassing clinical trials, cost efficiency, time, and resource-intensiveness. Numerous factors can influence a guideline's "Applicability and Implementability". Some of these factors are intrinsic to individual characteristics of healthcare professionals, and the organizational capacity of health services to adapt and apply evidence.

Adapting guidelines to local contexts, implementing tailored interventions to promote guideline uptake, and monitoring the sustainability of recommendations are crucial. Thus, detailed instructions are needed for guideline implementation [45, 46]. These aspects also include barriers and facilitators to said implementation, along with advice and/or tools for a clinical practice experience. Most guidelines fall short in discussing the implementation aspects, neglecting to describe potential resource implications and criteria for monitoring the application of the recommendations [44].

Treatment options for PNH often include supportive care, allogeneic hematopoietic stem cell transplant, and complement inhibitors. The FDA has approved three complement inhibitors to treat PNH in recent years: Eculizumab, in 2007; Ravulizumab, in 2018; and Pegcetacoplan, in 2021. Studies have shown that Ravulizumab and Pegcetacoplan are non-inferior drugs compared to the first standardized treatment in efficacy and safety profile [47]. However, Pegcetacoplan is often overlooked in available CPGs, possibly due to its recent approval and the higher amount of evidence for Eculizumab and Ravulizumab.

The advancements in antibody engineering have allowed the development of safer therapeutic monoclonal antibodies with a lower risk of side effects [48]. Before the availability of Eculizumab in 2007, PNH patients had a median survival of between 10 and 22 years. In countries without access to monoclonal antibodies, long-term therapeutic anticoagulation is recommended [2]. However, the analyzed guidelines do not describe

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alternatives considering local needs, leaving PNH patients at risk of thrombotic extension and death. Thus, the standards of care and well-being of PNH patients are directly influenced by healthcare infrastructure, which can vary between countries. Recommendations should explicitly outline how to adapt services to attend to local demands and improve healthcare efficiency [3].

Health technology assessment must evaluate evidence considering efficacy, effectiveness, safety, and treatment costs. The political aspects related to the viability, acceptability, and sustainability of the health system must also be considered in the decision-making process; so, therefore continuous investment in scientific rigor, transparency, and editorial independence has to be made to achieve such goals [49, 50].

5. CONCLUSION

Developing credible and implementable recommendations for the pharmacological treatment of PNH is urgent. Currently, there are disparities in the methodological quality of available guidelines. Two exemplary CPGs, developed in Brazil and the United Kingdom, stand out for their high quality and are strongly recommended for daily practice. However, adapting them to local policies and incorporating newly approved medications is essential. The CPGs still do not mention Pegcetacoplan, a new drug approved in 2021. The complement inhibitors Eculizumab and Ravulizumab are the main options to treat PNH.

Nevertheless, the levels of evidence used in PNH guidelines remain low. Approaches that prioritize the engagement of methodologists and multidisciplinary collaborators may lead to the production of high-quality CPGs for PNH treatment.

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