da HPN varia conforme o grau de deficiência da âncora GPI, sendo mais intensa em células tipo III. Fatores como infecções, inflamação e cirurgias podem acentuar a ativação do complemento e a hemólise. A inflamação sistêmica e o risco trombótico reforçam a importância de terapias que inibem o complemento, como os bloqueadores de C5. A HPN é um modelo clássico de doença decorrente da falha na regulação do complemento, ocasionada pela mutação no gene PIGA e ausência de CD55/CD59. A compreensão dos mecanismos desse desequilíbrio fisiopatológico, que apresenta implicações clínicas e imunológicas, reforça o uso de terapias-alvo específicas.

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## FROM CLONAL SELECTION TO COMPLEMENT BLOCKADE: EVOLVING CONCEPTS IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

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**Background:** Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired clonal disorder of hematopoietic stem cells caused by somatic mutations in the X-linked PIGA gene. These mutations impair glycosylphosphatidylinositol (GPI) anchor biosynthesis, leading to the absence of GPI-anchored complement regulators such as CD55 and CD59 on blood cells, which become highly susceptible to complement-mediated destruction. The clinical spectrum ranges from subclinical clones to severe hemolytic disease with thrombosis and/or bone marrow failure. Clonal expansion of PIGA-mutant cells may occur via extrinsic immune selection—frequently associated with aplastic anaemia—or intrinsic clonal evolution involving additional genetic alterations. **Objectives:** To perform a comprehensive review of paroxysmal nocturnal hemoglobinuria (PNH) by integrating a narrative synthesis of the literature with a retrospective analysis of 180 patients diagnosed and followed at a single reference center. The study aims to describe clinical and laboratory features, clonal distribution, classification subtypes, treatment patterns, and outcomes, while contextualizing real-world cohort data within current knowledge on PNH pathophysiology, clonal dynamics, diagnostic strategies, and therapeutic advances in complement inhibition. **Material e methods:** We conducted a narrative review of the literature, incorporating historical and contemporary studies on PNH pathophysiology, clonal dynamics, diagnosis, and treatment. Key topics included immune-mediated mechanisms of clonal selection, disease classification systems, diagnostic approaches using high-sensitivity flow cytometry, and the evolving landscape of complement inhibition therapies. In parallel, we retrospectively reviewed the medical records of 180 consecutive patients with confirmed PNH diagnosed between 2000 and 2025 at Hospital de Clínicas da Universidade Federal do Paraná, collecting demographic, clinical, laboratory, and therapeutic data. Clonal distribution, disease subtype classification, treatment patterns, and outcomes were analysed, with particular focus on associations between clonal size, clinical presentation, and prognosis. Flow cytometry with monoclonal antibodies and/or FLAER remains the gold standard for PNH diagnosis, allowing high-sensitivity detection of GPI- deficient cells across hematopoietic lineages. Complement inhibition with eculizumab and ravulizumab, both C5 monoclonal antibodies, has markedly reduced intravascular hemolysis, thrombotic risk, and improved quality of life, although residual extravascular hemolysis from C3-mediated opsonization persists. Novel proximal complement inhibitors—such as pegcetacoplan (C3 inhibitor) and oral alternative pathway inhibitors targeting factor B (Iptacopan) or factor D (Danicopan)—offer broader complement blockade and more flexible dosing options. Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative therapy but is limited by high treatment-related risks. Despite these advances, access to complement inhibitors remains uneven worldwide. **Discussion and conclusion:** PNH exemplifies the link between clonal hematopoiesis, immune-mediated bone marrow failure, and complement dysregulation. Understanding its biology is essential for early diagnosis, risk stratification, and personalized care. New complement inhibitors may lessen disease burden. Continued research is needed to optimize therapeutic sequencing, improve accessibility, and clarify the molecular drivers of clonal evolution.

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## GENETIC VARIANTS AND LEVELS OF INFLAMMATORY CYTOKINES FROM SICKLE CELL ANEMIA PATIENTS FROM MANAUS, AMAZONAS, BRAZIL

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