Clinical Guidance
Breakthrough Hemolysis in Paroxysmal Nocturnal Hemoglobinuria

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WHAT IS PNH?

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired clonal blood disorder caused by genetic mutations in the *PIGA* gene in hematopoietic stem cells.[1] In PNH, mutations in the *PIGA* gene result in deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins, including CD55 and CD59. These complement regulators safeguard host cells from damage caused by the membrane attack complex (MAC) generated by the continuously active alternative complement pathway.[1-3]

WHAT IS BTH?

Breakthrough hemolysis (BTH) is the reappearance of intravascular hemolysis (IVH) in patients with paroxysmal nocturnal hemoglobinuria (PNH) who are receiving complement inhibitor therapy. BTH can be more pronounced in patients on proximal inhibitors due to a larger pool of surviving PNH red cells susceptible to hemolysis, and because incomplete proximal blockade may allow for upstream enzymatic amplification.[4]

CLINICAL DEFINITION OF BTH:[5]

Lactate dehydrogenase (LDH) >1.5x upper normal limit (ULN) and either:
1) Hemoglobin (Hb) drop ⩾ 20 g/L
2) Signs/symptoms of intravascular hemolysis (IVH) (e.g. hemoglobinuria, abdominal pain, dyspnea)
3) Thrombosis

WHO IS AT RISK OF BTH?

All treated patients with PNH, including those on C5 inhibitors and/or proximal inhibitors, are at risk of BTH.

MECHANISM OF BTH

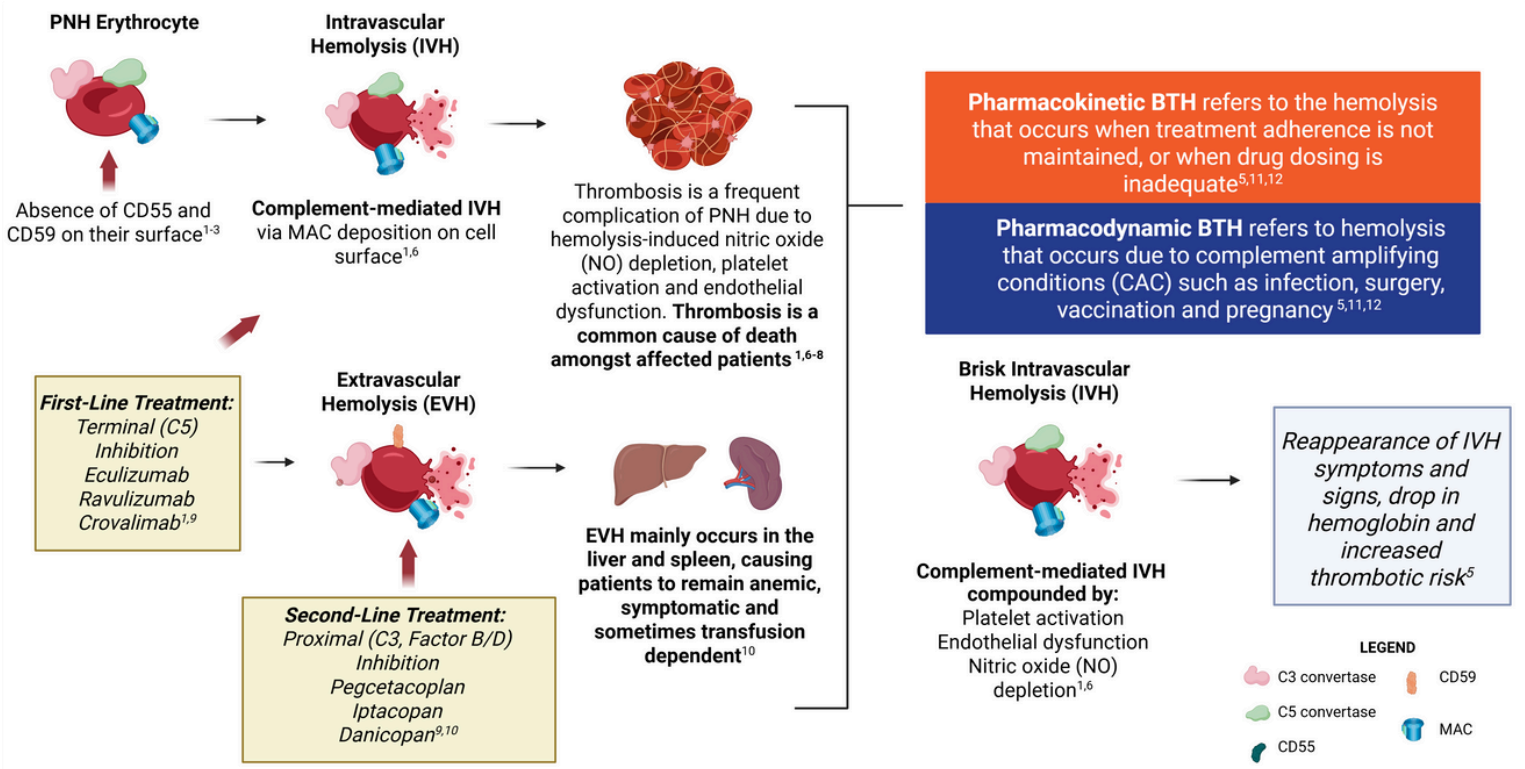

Figure 1: Mechanism of IVH, EVH and BTH in PNH[13]

Authors: Benjamin Chin-Yee, MD, PhD, FRCPC; Marc Bienz, MD, MSc, FRCPC, DRCPSC; Hafsa Omer, MSc (Myelin & Associates Inc.)

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MANAGEMENT OF BTH

Management of BTH has five key components:

Adequate Monitoring

Ensuring the patient is adequately monitored: Most cases require admission, but some milder cases may be managed in an outpatient setting with frequent blood test monitoring.

a) Consult hematology
b) Evaluate degree of hemolysis: CBC, reticulocytes, haptoglobin, LDH, bilirubin, urinalysis

Underlying Cause

Identifying the underlying cause:

a) Symptom-guided cultures and work-up for infectious CAC. Start broad spectrum antimicrobial therapy with central nervous system penetrance. Even in presence of infectious signs/ symptoms, do not stop the complement inhibitor
b) Review of other possible triggers: sick contacts, recent travel, vaccination history, recent surgical intervention, pregnancy
c) Review of complement inhibitor adherence
d) If on C5 inhibitor, assess terminal complement inhibition if testing is available (CH50, C5 levels, eculizumab levels, ravulizumab levels)

Complications

Managing and preventing complications of BTH:[14]

a) Monitor for end-organ damage: Creatinine, urine protein, troponin, D-dimer, symptom-guided work-up for thrombosis
b) If in an in-patient setting, administer prophylactic anticoagulation[5]
c) Supportive transfusions[5]
d) In case of severe hemolysis, clinical deterioration, thrombotic complication, or life-threatening event, administer an additional dose of the complement inhibitor appropriate to the patient's current therapy
   i. Eculizumab/Ravulizumab/ Iptacopan/Danicopan: Administer a rescue dose of eculizumab
   ii. Crovalimab: Administer a rescue dose of crovalimab
   iii. Pegcetacoplan: Administer three daily doses of pegcetacoplan.[12] In case of thrombotic complication or life-threatening event: Administer a rescue dose of eculizumab

Effective Inhibition

Re-establishing effective complement inhibition:

a) Importance to maintain adherence: This holds especially true for self-administered subcutaneous or oral complement inhibitors[5]
b) If eculizumab/ravulizumab levels were underdosed, dosage can be increased with close out-patient monitoring
c) Pegcetacoplan dosing can be increased from twice weekly to every 3 days and up to three times per week

Patient Education

Supporting accurate and comprehensive patient education:

a) Recognition of CAC and importance of seeking medical advice early
b) Recognition of signs and symptoms of IVH

To view references, scan QR code below:

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