webinar

HEALTH PROFESSIONALS

Thursdays Webinars

Advancing Diagnostics and Therapeutic Strategies in Paroxysmal Nocturnal Hemoglobinuria: A Comprehensive Guide to Managing a Complex Disorder

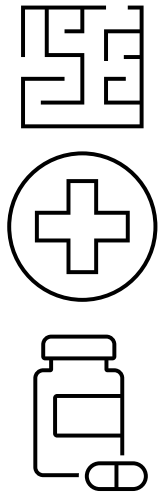
Jens PANSE
Universtity Hospital RWTH Aachen,
Center for Integrated Oncology Aachen, Bonn, Cologne, Düsseldorf, CIO-ABCD

19 February 2026

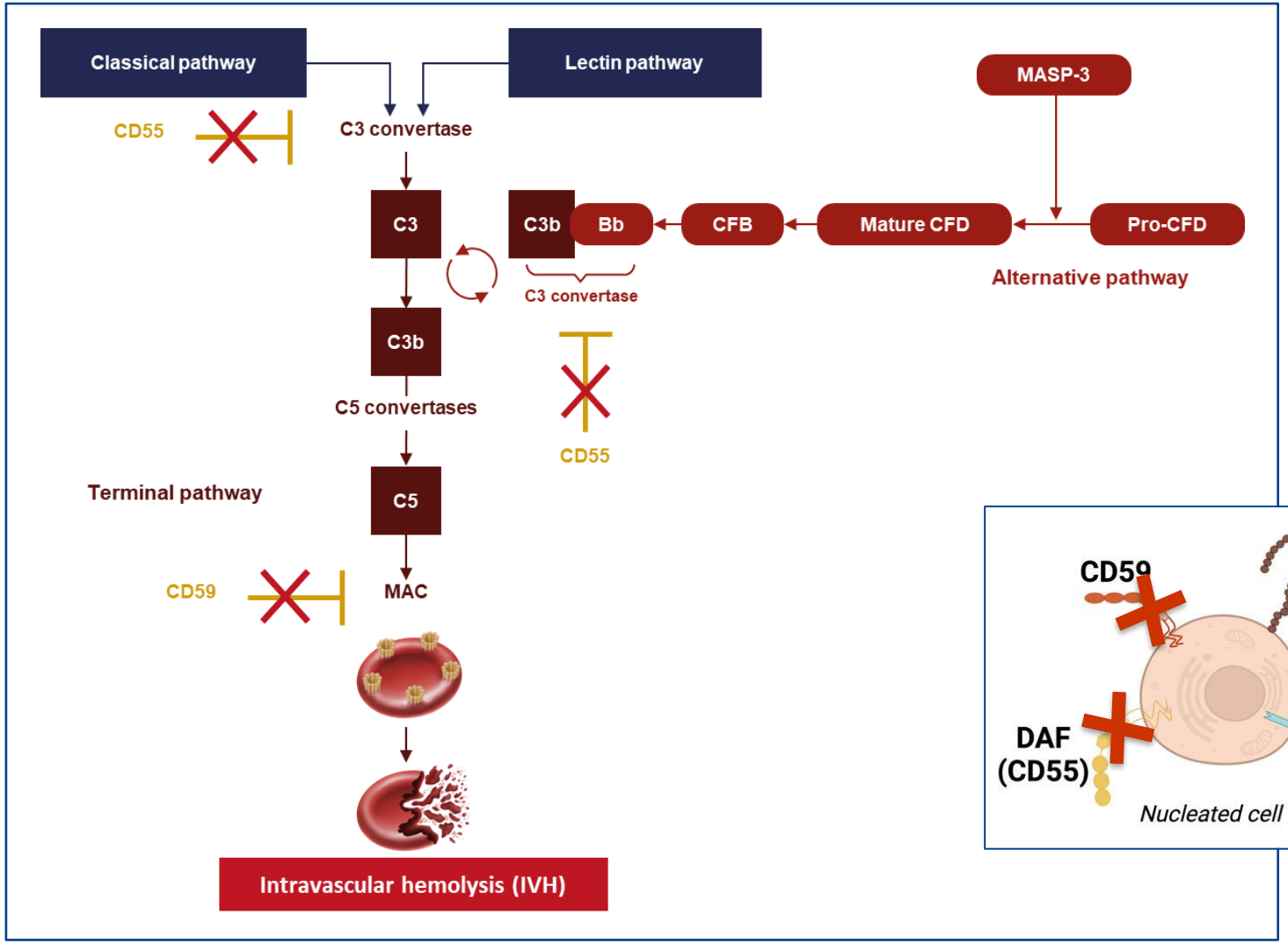
ERN | EuroBloodNet

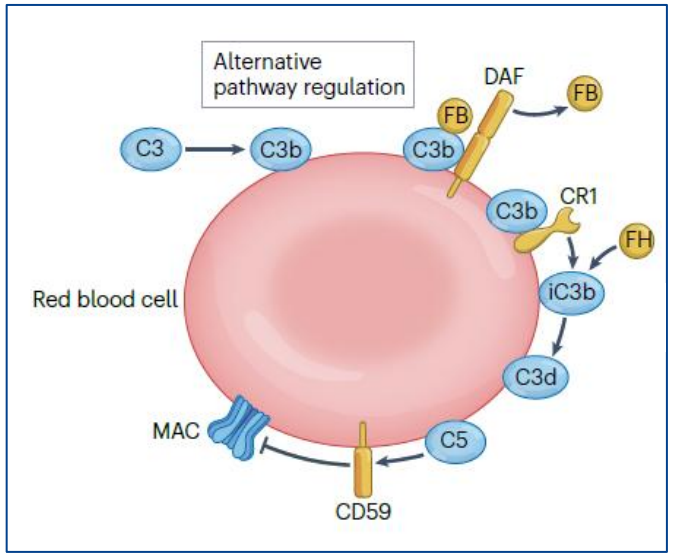
Advancing Diagnostics and Therapeutic Strategies in Paroxysmal Nocturnal Hemoglobinuria: A Comprehensive Guide to Managing a Complex Disorder

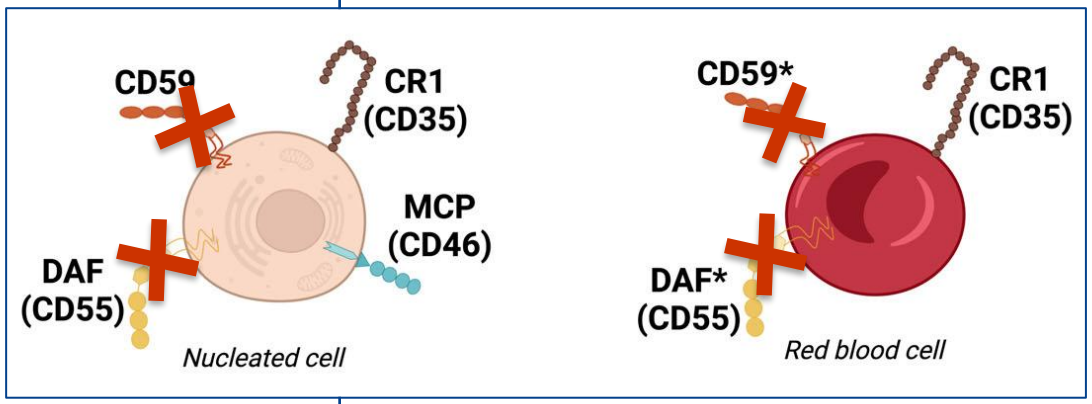
- Complex Disorder
- Diagnosis
- Management



Complex Disorder







adapted from Belcher JD *et al. Transl Res.* 2022;249:1–12; Duval A, Frémeaux-Bacchi V. Am J Hematol. 2023 May;98 Suppl 4:S5-S19
Mastellos DC, Hajishengallis G, Lambris JD. Nat Rev Immunol. 2024 Feb;24(2):118-141

GPI-Anchor mutation – flow-cytometry-based diagnosis

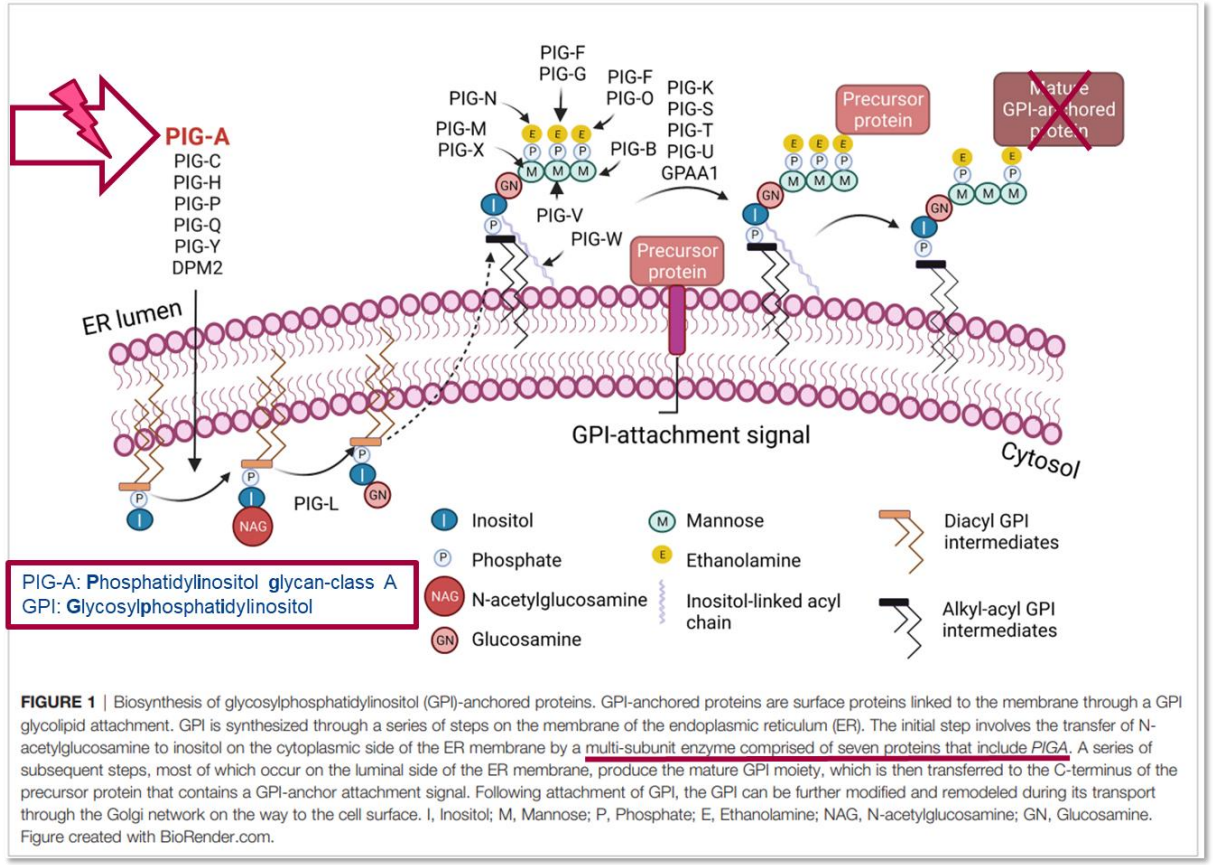
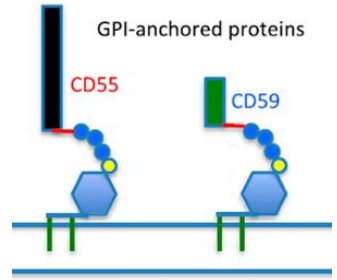
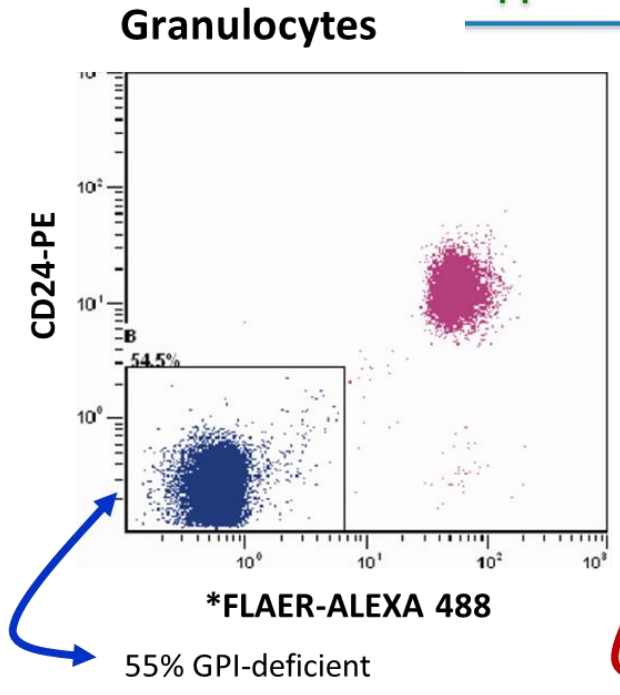
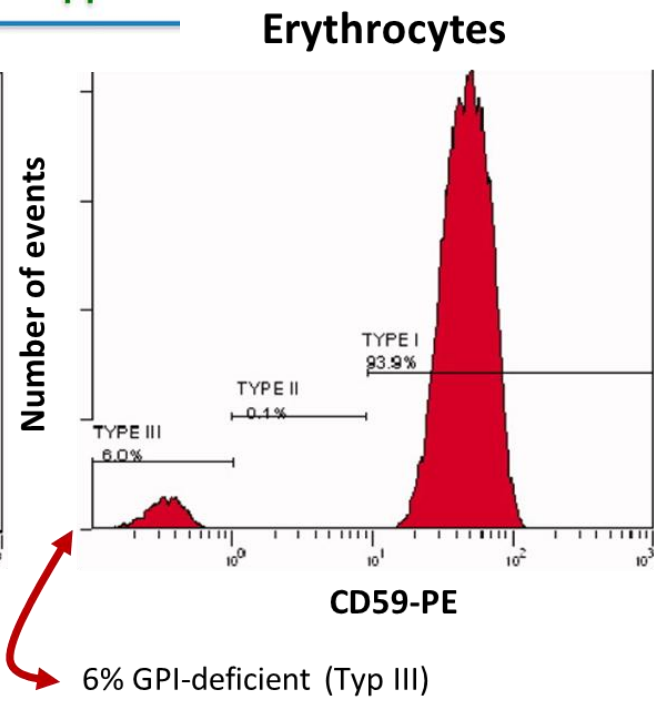


FIGURE 1 | Biosynthesis of glycosylphosphatidylinositol (GPI)-anchored proteins. GPI-anchored proteins are surface proteins linked to the membrane through a GPI glycolipid attachment. GPI is synthesized through a series of steps on the membrane of the endoplasmic reticulum (ER). The initial step involves the transfer of N-acetylglucosamine to inositol on the cytoplasmic side of the ER membrane by a multi-subunit enzyme comprised of seven proteins that include *PIGA*. A series of subsequent steps, most of which occur on the luminal side of the ER membrane, produce the mature GPI moiety, which is then transferred to the C-terminus of the precursor protein that contains a GPI-anchor attachment signal. Following attachment of GPI, the GPI can be further modified and remodeled during its transport through the Golgi network on the way to the cell surface. I, Inositol; M, Mannose; P, Phosphate; E, Ethanolamine; NAG, N-acetylglucosamine; GN, Glucosamine. Figure created with BioRender.com.







Borowitz, M.J. et al., Cytometry B Clin Cytom 2010;4:211-230; Parker CJ ASH Educ Program. 2016 Dec 2;2016(1):208-216, Colden MA, Kumar S, Munkhbileg B and Babushok DV (2022) Front. Immunol. 12:830172

PNH – clinical suspicion

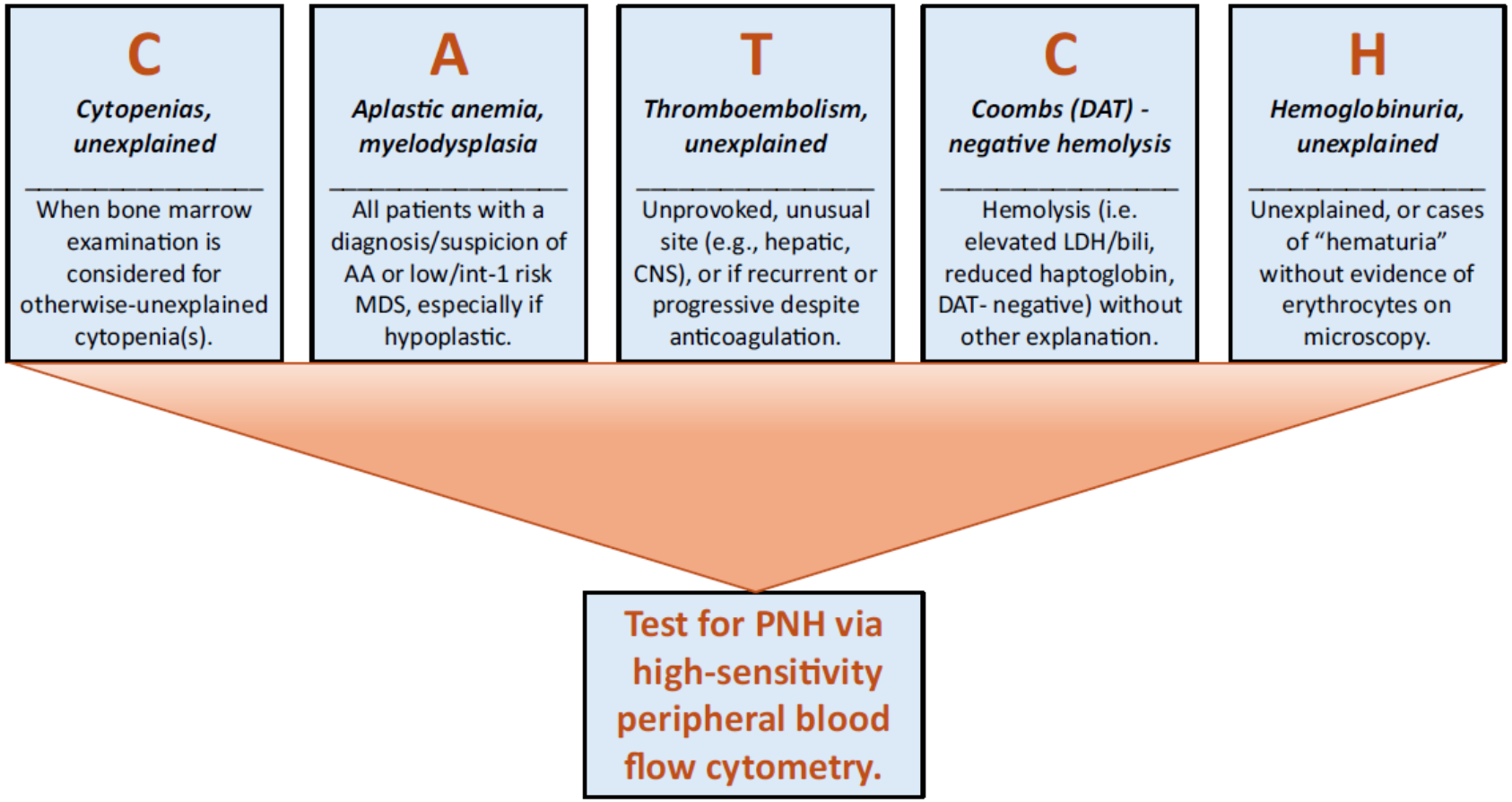
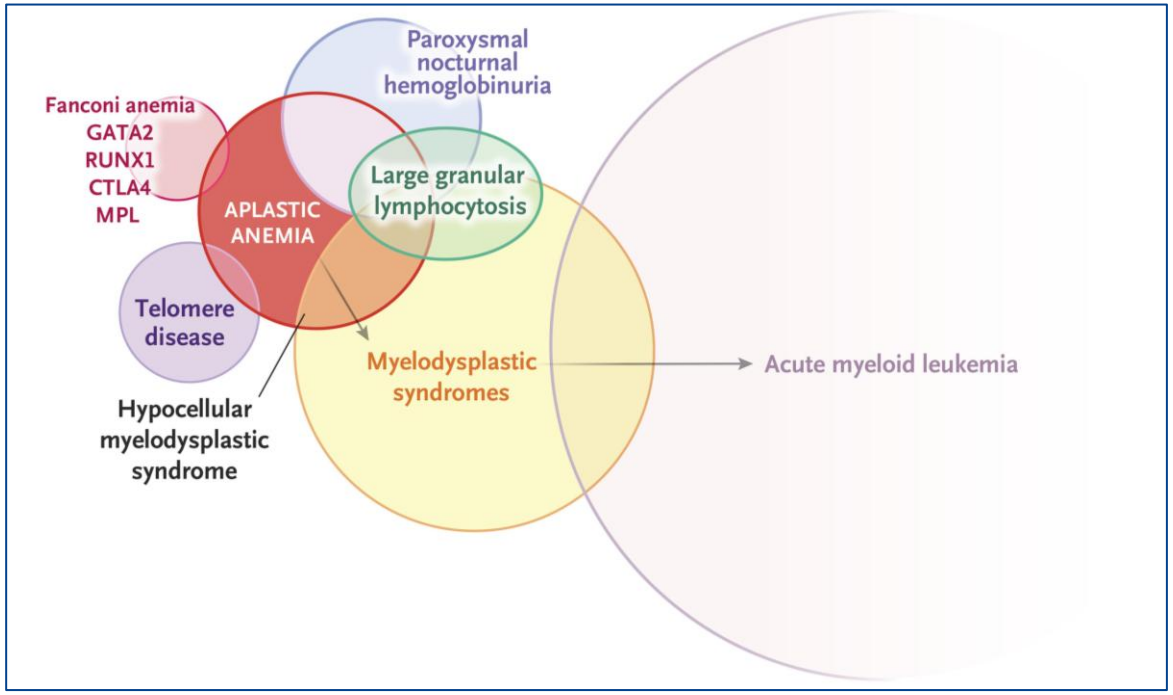


Figure 1. CATCH mnemonic for PNH recognition and diagnosis. The mnemonic is meant as a guide to identify higher-yield situations in which a diagnosis of PNH should be considered. It does not encompass all potential patient journeys to diagnosis.[7] AA, aplastic anemia; CNS, central nervous system; DAT, direct antiglobulin test, aka Coombs' test; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal hemoglobinuria.

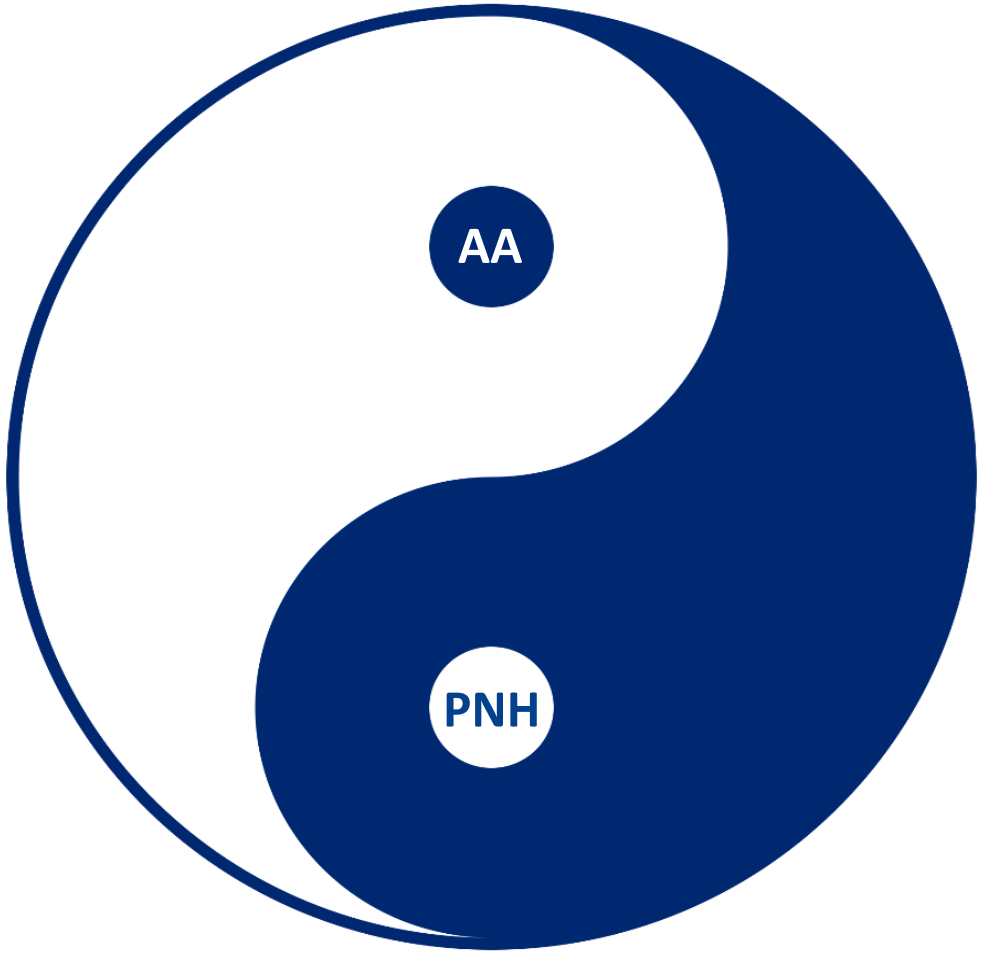
Bienz M, Patriquin CJ. Hematology Am Soc Hematol Educ Program. 2025 Dec 5;2025(1):154-163

Complexment Disorder & BMFS-Disorder

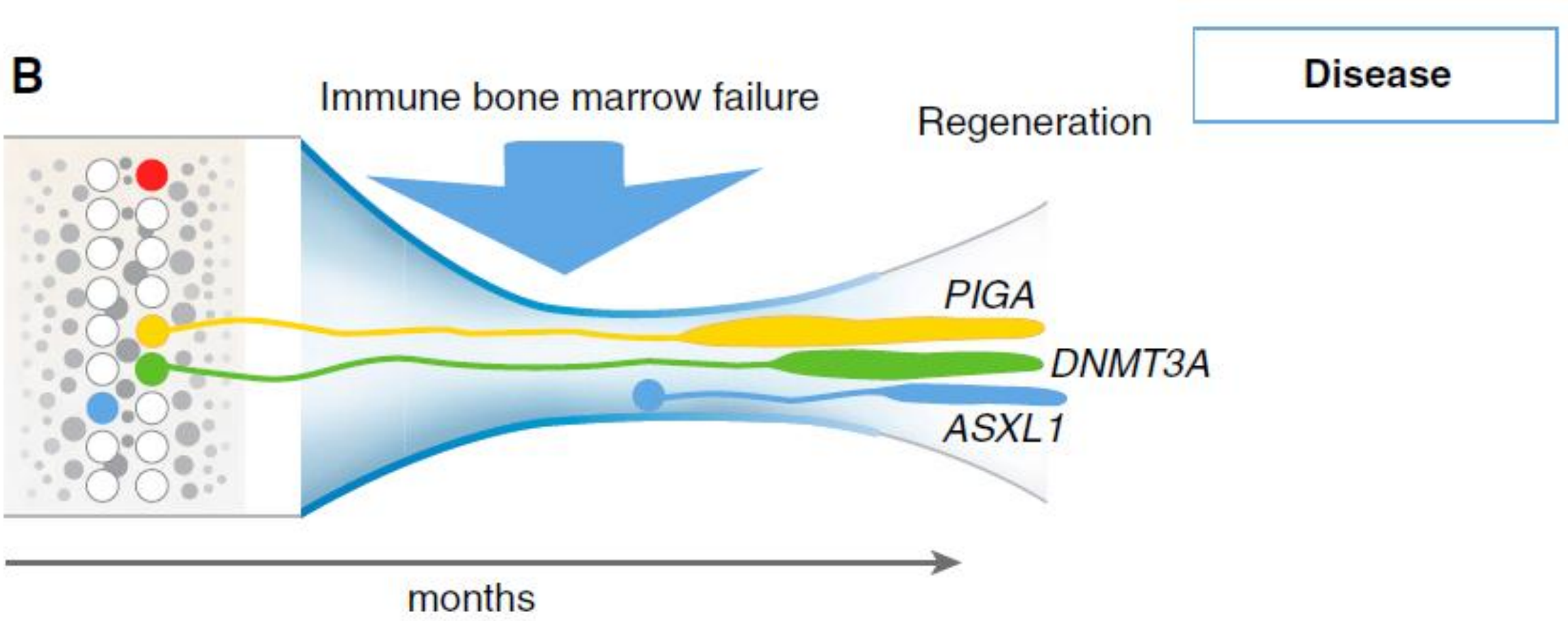
BMFS



Young NS. Aplastic Anemia. NEJM. 2018 Oct 25;379(17):1643-1656

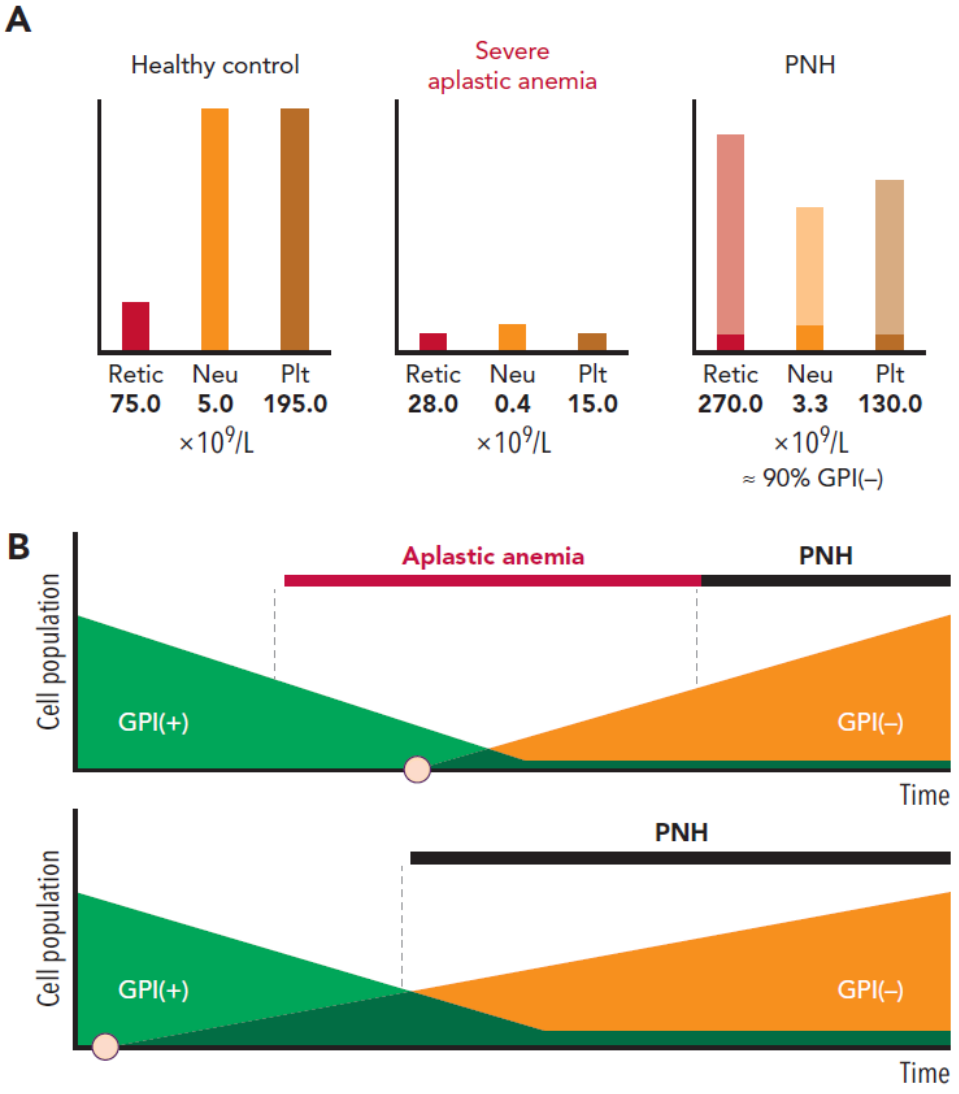


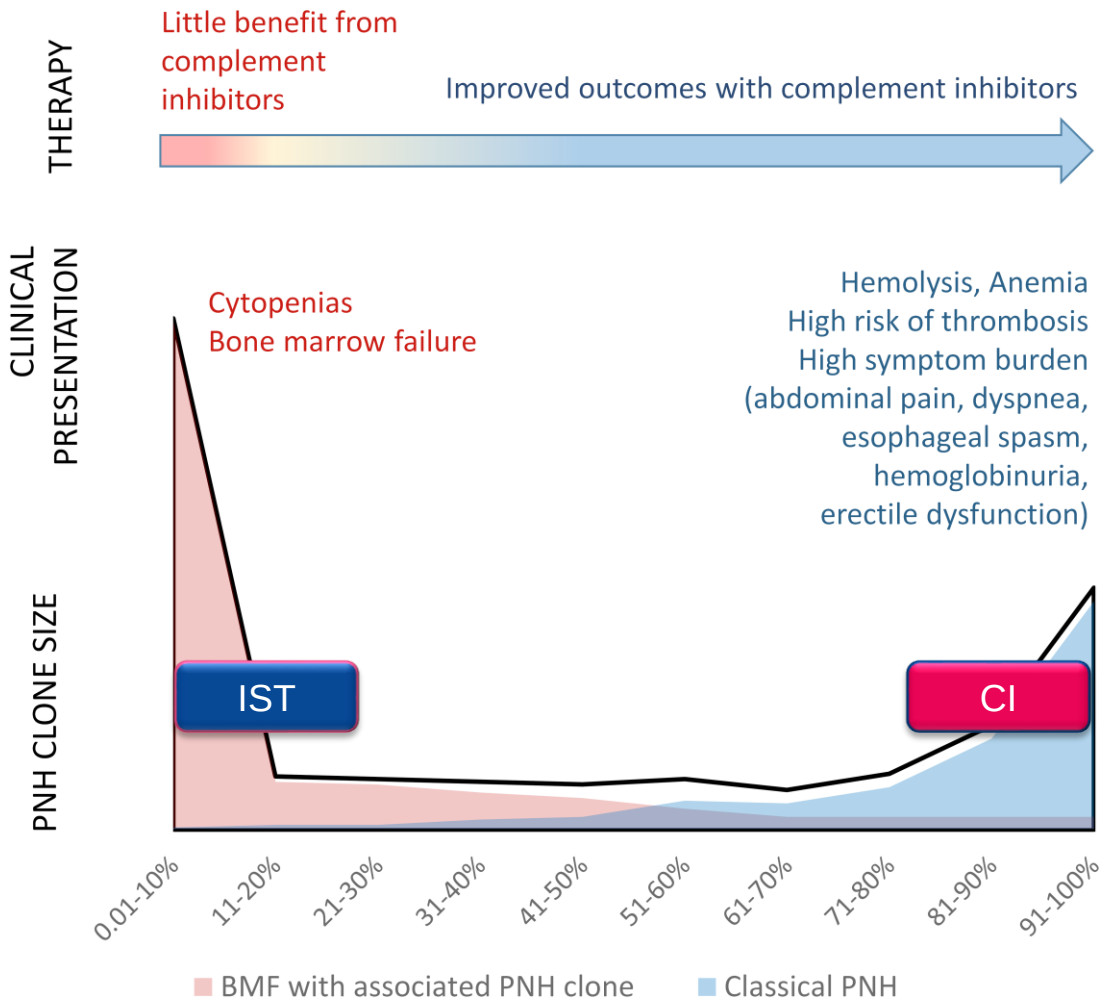
Complexment Disorder & BMFS-Disorder



Cooper JN, Young NS. Blood. 2017 Nov 30;130(22):2363-2372

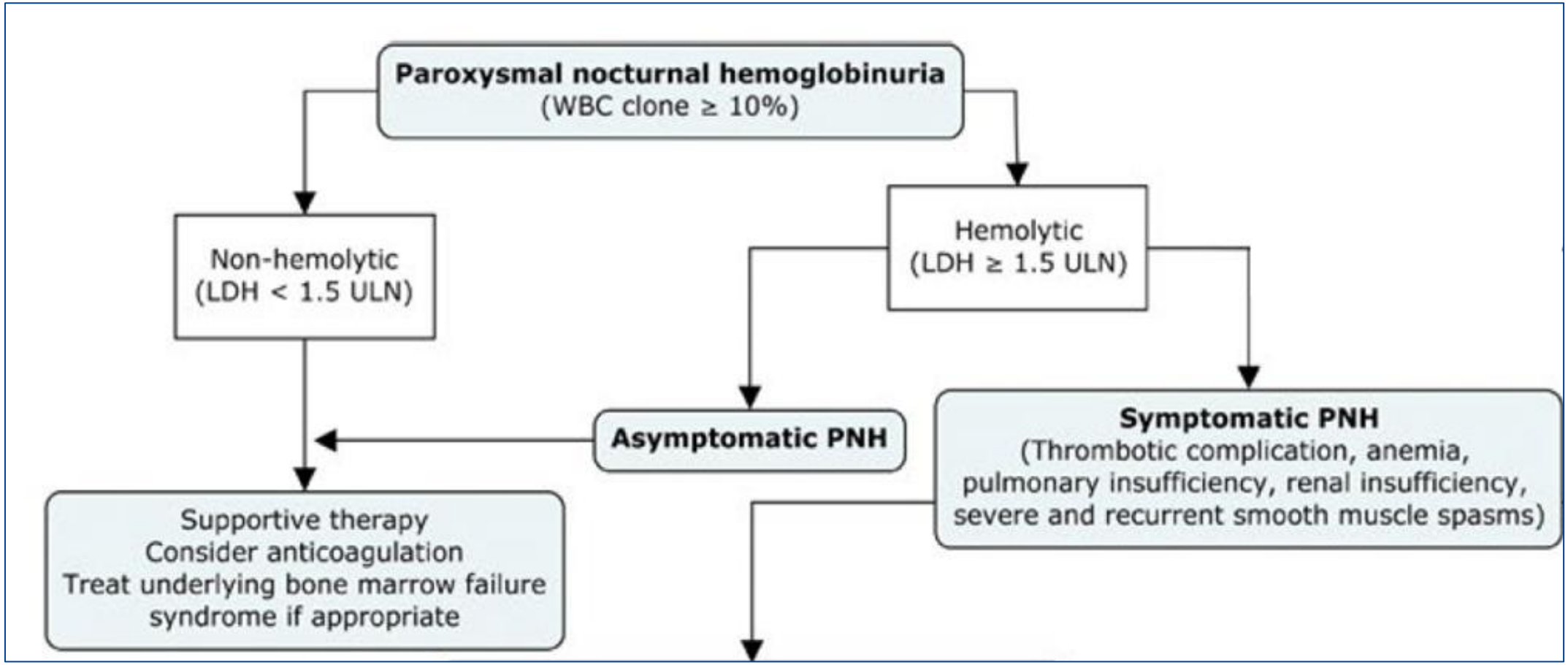
Complement Disorder & BMFS-Disorder





Luzzatto L, Nakao S. Blood. 2025 Jun 26;145(26):3077-3088; Babushok D Hematology 2021; 143-152, 2021

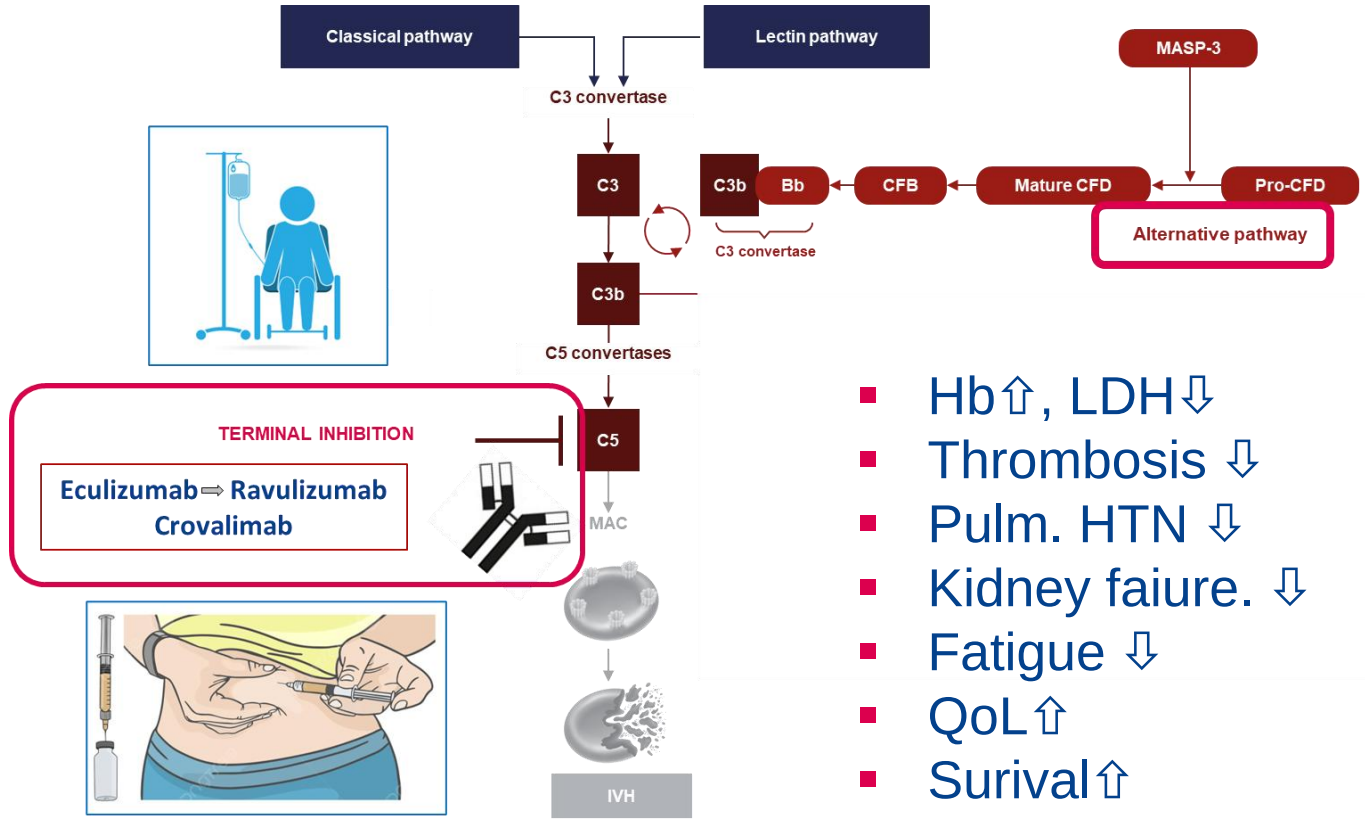
Management – hemolytic or non-hemolytic



Complement Inhibition [CI]

Bienz M, Patriquin CJ. Hematology Am Soc Hematol Educ Program. 2025 Dec 5;2025(1):154-163

Management – Complement Inhibition [CI] - terminal



- Hb⇧, LDH⇩
- Thrombosis ⇩
- Pulm. HTN ⇩
- Kidney faiure. ⇩
- Fatigue ⇩
- QoL⇧
- Surival⇧

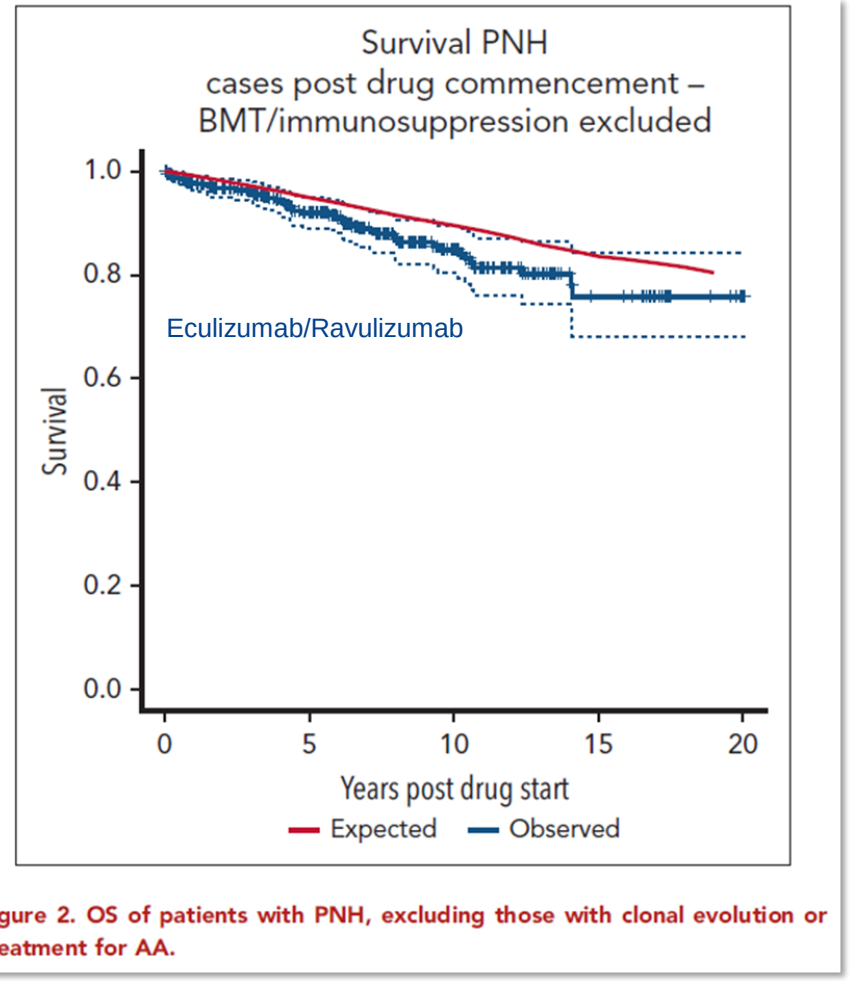
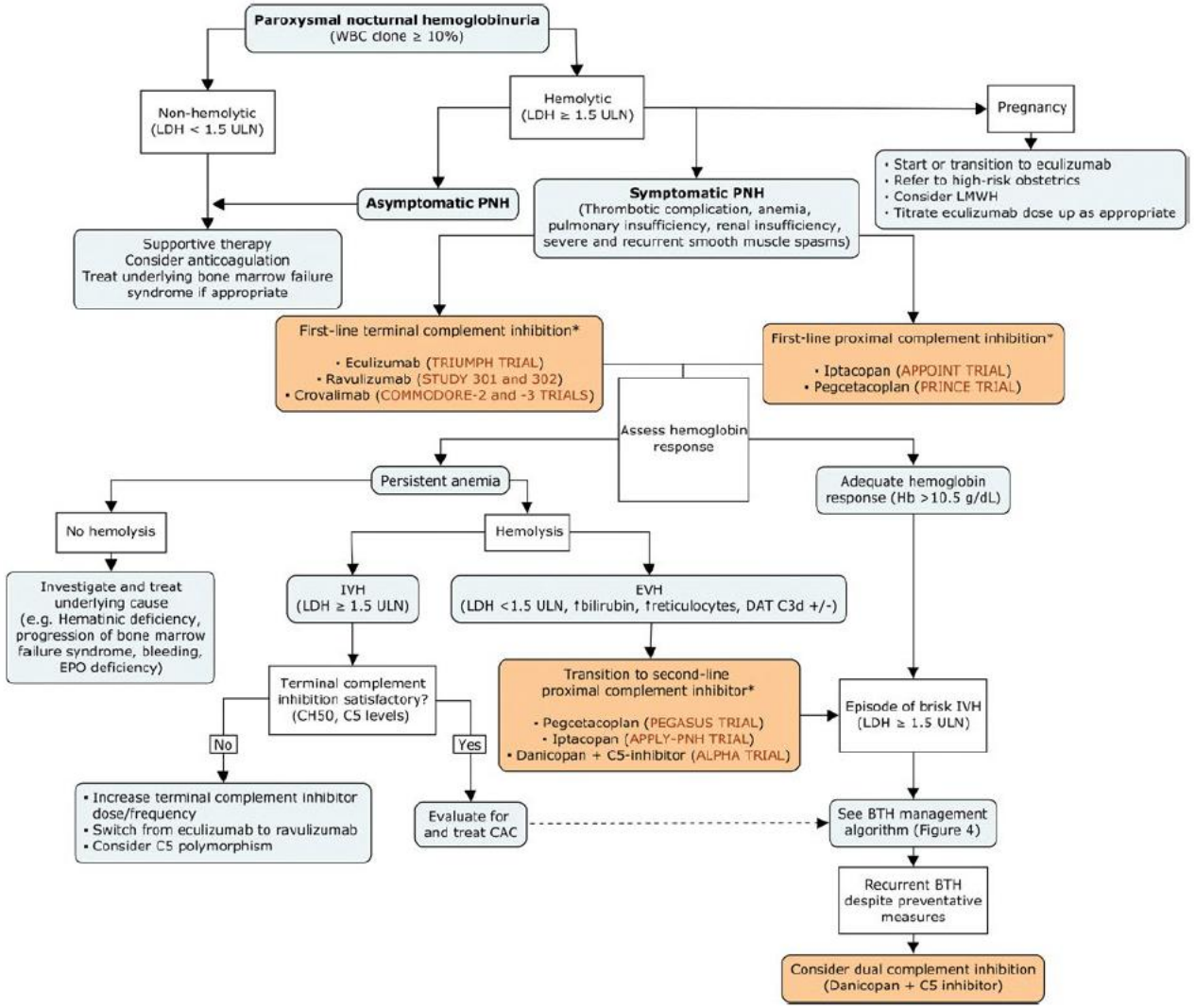


Figure 2. OS of patients with PNH, excluding those with clonal evolution or treatment for AA.

aiophtoz.com; id.pngtree.com; adapted from Belcher JD *et al. Transl Res.* 2022;249:1–12; Kelly RJ, et al: Blood. 2024;143(12):1157-1166.

Management – Complement Inhibition [CI] – there's more (complex…)



Bienz M, Patriquin CJ. Hematology Am Soc Hematol Educ Program. 2025 Dec 5;2025(1):154-163

Management – Complement Inhibition [CI] – there's more

- EVH [extravaxcular hemolysis]
- terminal CI – proximal CI
- BTH [break through hemolysis]
- small clone size / CI + IST
- pregnancy
- anticoagulation
- QoL

Management – Complement Inhibitors – approval date

- Eculizumab 2007 (+ Biosimilars 05/2023)

terminal KI

- Ravulizumab (07/2019)

terminal KI

- Pegcetacoplan (12/2021)

proximal KI

- Danicopan
  (plus Ravu/Ecu) (04/2024)

proximal KI

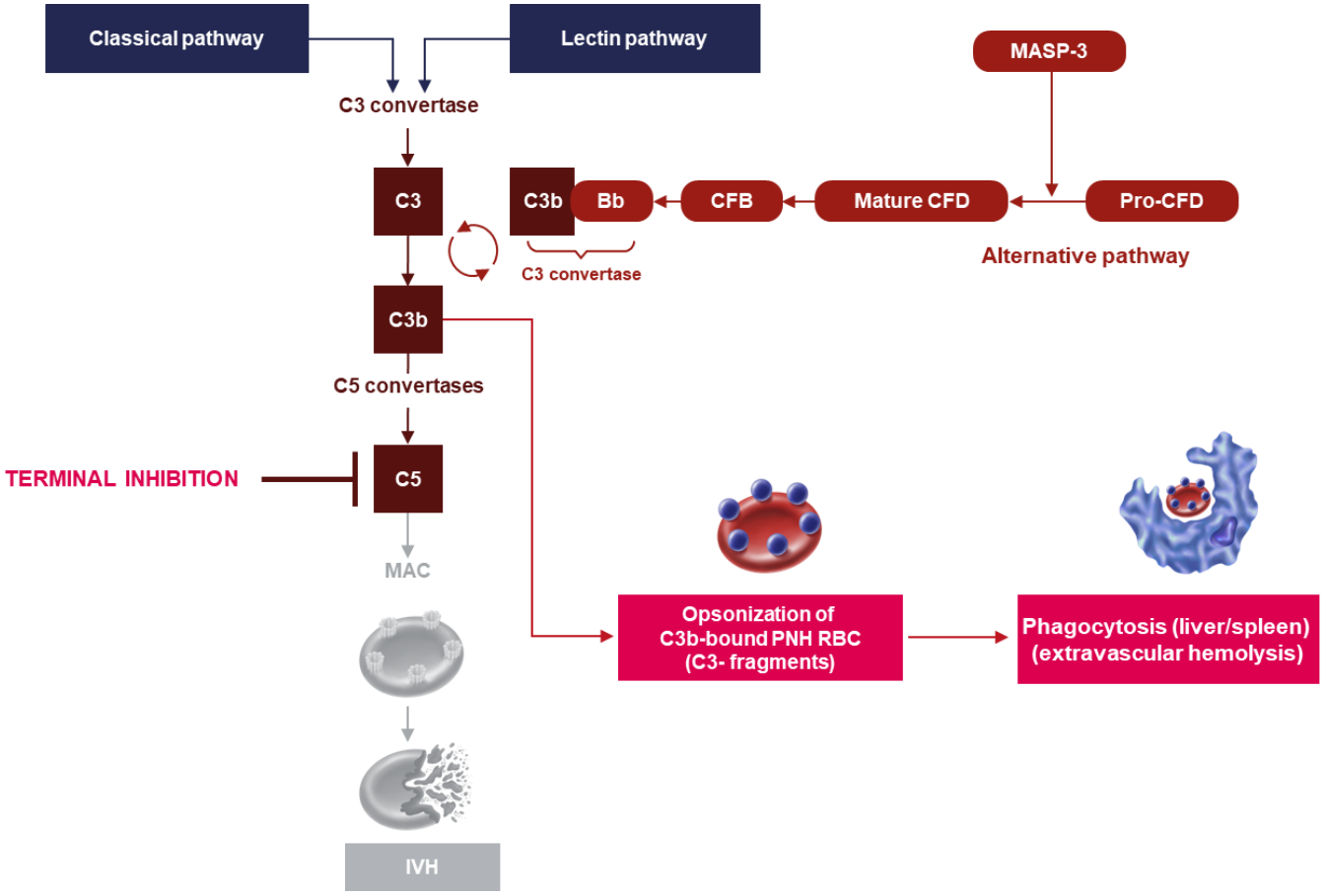
- Iptacopan (05/2024)

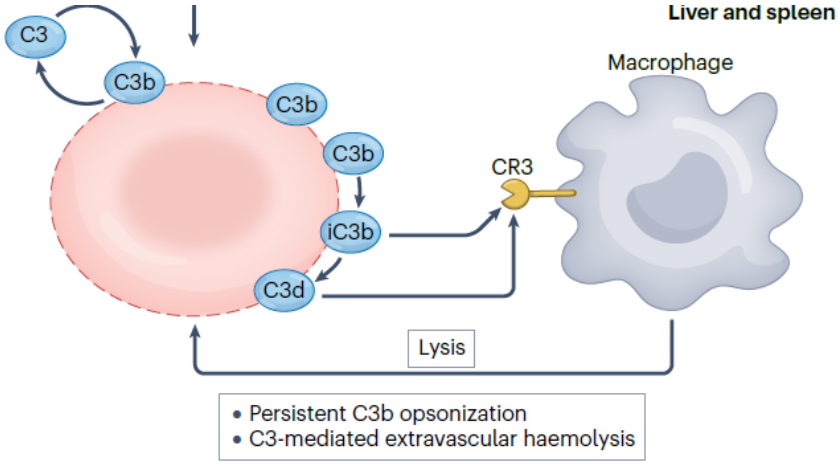
proximal KI

- Crovalimab (07/2024)

terminal KI

Management – terminal CI – EVH – proximal CI

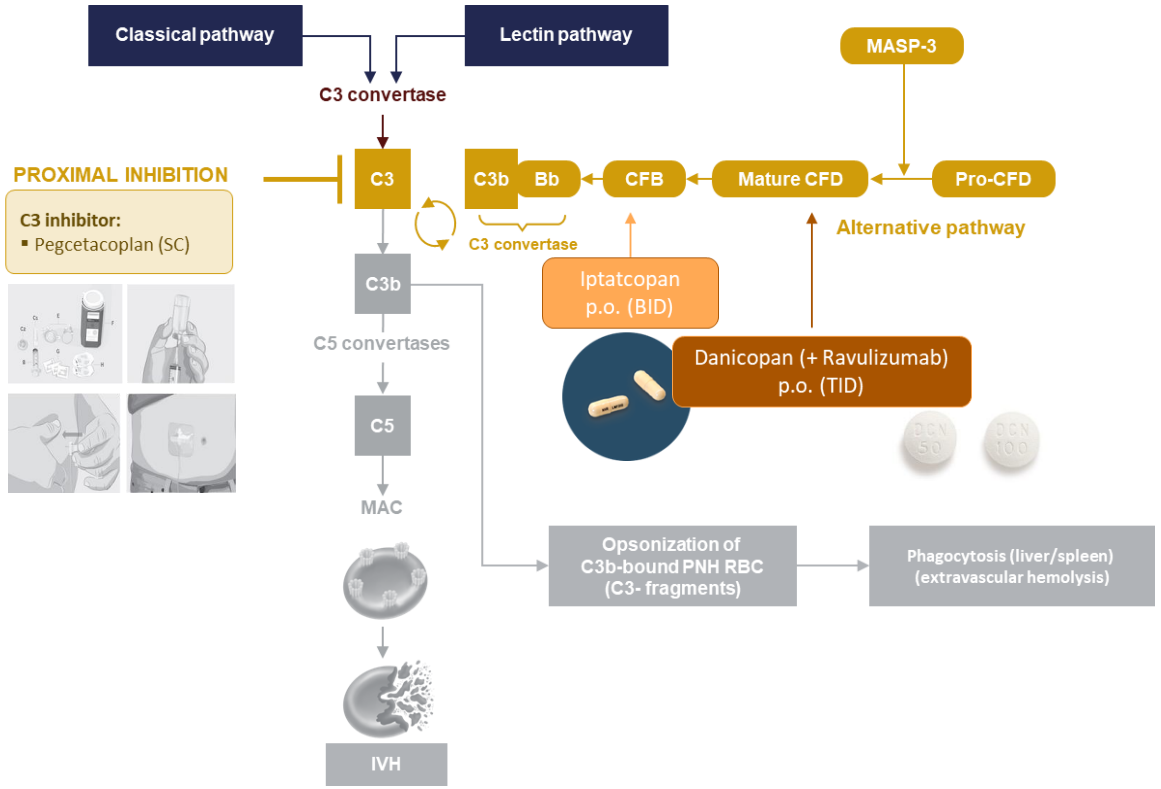


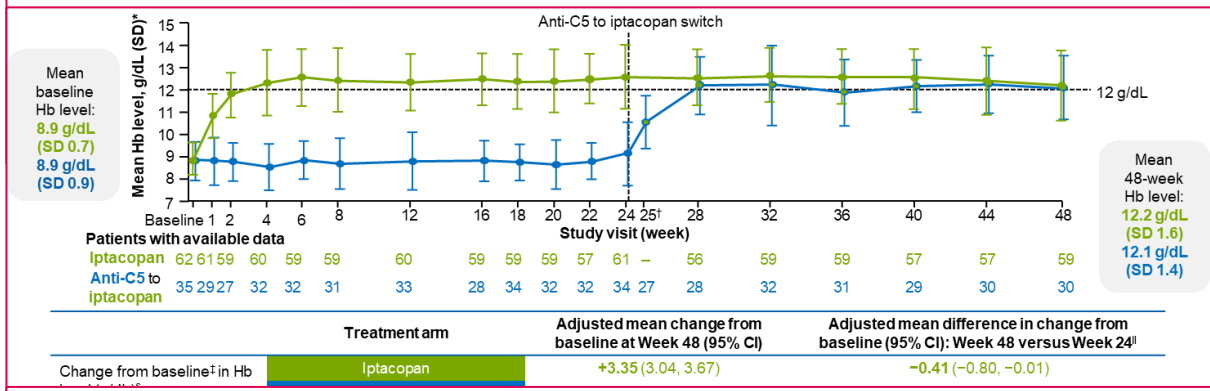


- Hb⇩
- ARC⇧
- LDH slightly⇧
- Bilirubin⇧
- Fatigue⇩
- C3d⇧ [DAT+]

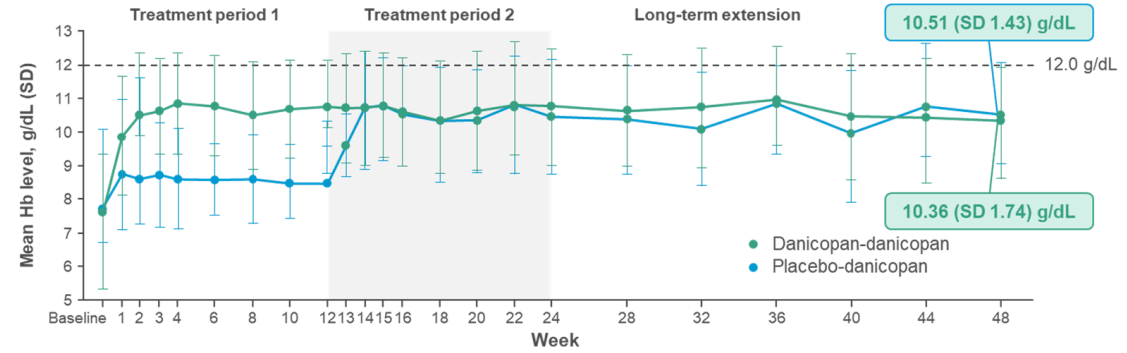
EVH

Management - proximal CI





	Treatment arm	Adjusted mean change from baseline at Week 48 (95% CI)	Adjusted mean difference in change from baseline (95% CI): Week 48 versus Week 24‖
Change from baseline‡ in Hb	Iptacopan	+3.35 (3.04, 3.67)	−0.41 (−0.80, −0.01)



LSM change in Hb level from baseline, g/dL (SE)	Week 12		Week 24	
	Placebo + eculizumab/ravulizumab	Danicopan + eculizumab/ravulizumab	Placebo to danicopan + eculizumab/ravulizumab	Danicopan + eculizumab/ravulizumab
	+0.50 (0.31)	+2.94 (0.21)	+2.26 (0.34)	+3.17 (0.30)

Figure adapted from Kulasekararaj AG *et al.* ASH. San Diego, CA, 9–12 December 2023;oral 508
LSM, least squares mean; SD, standard deviation; SE, standard error
1. Kulasekararaj AG *et al.* ASH. San Diego, CA, 9–12 December 2023;oral 508

adapted from Belcher JD *et al. Transl Res.* 2022;249:1–12, drugs.com, fabhalta.com, https://eu.lekovi.org/en/h/7513f842/aspaveli-v1.php

Proximal CI – Hb optimization, less fatigue

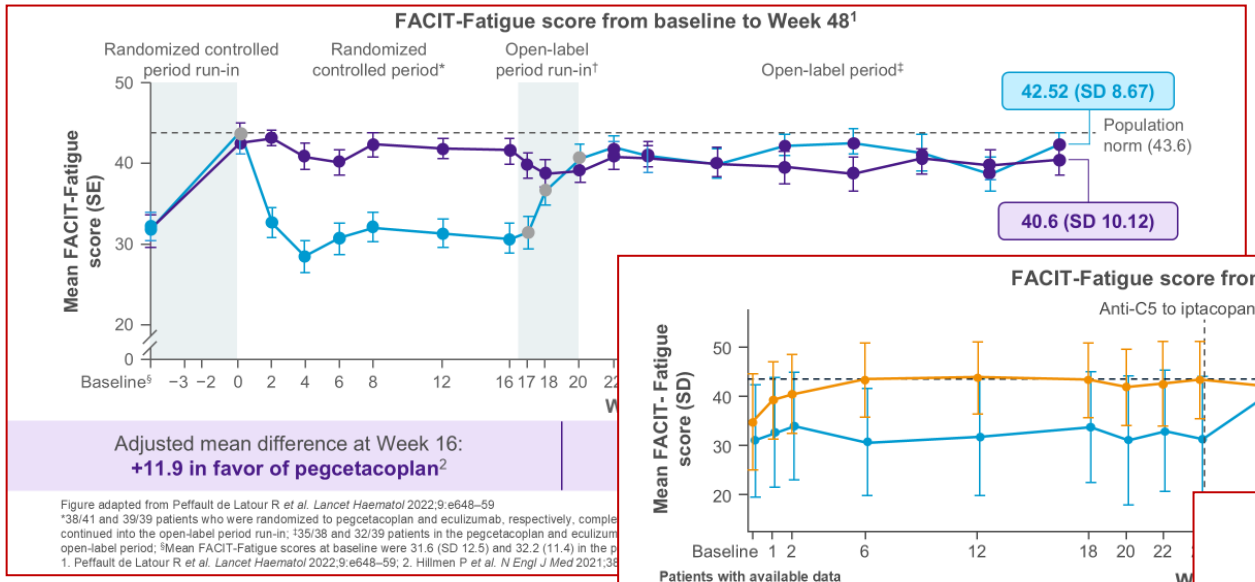


Figure adapted from Peffault de Latour R *et al. Lancet Haematol* 2022;9:e648–59
*38/41 and 39/39 patients who were randomized to pegcetacoplan and eculizumab, respectively, comple
continued into the open-label period run-in; †35/38 and 32/39 patients in the pegcetacoplan and eculizum
open-label period; §Mean FACIT-Fatigue scores at baseline were 31.6 (SD 12.5) and 32.2 (11.4) in the p
1. Peffault de Latour R *et al. Lancet Haematol* 2022;9:e648–59; 2. Hillmen P *et al. N Engl J Med* 2021;3

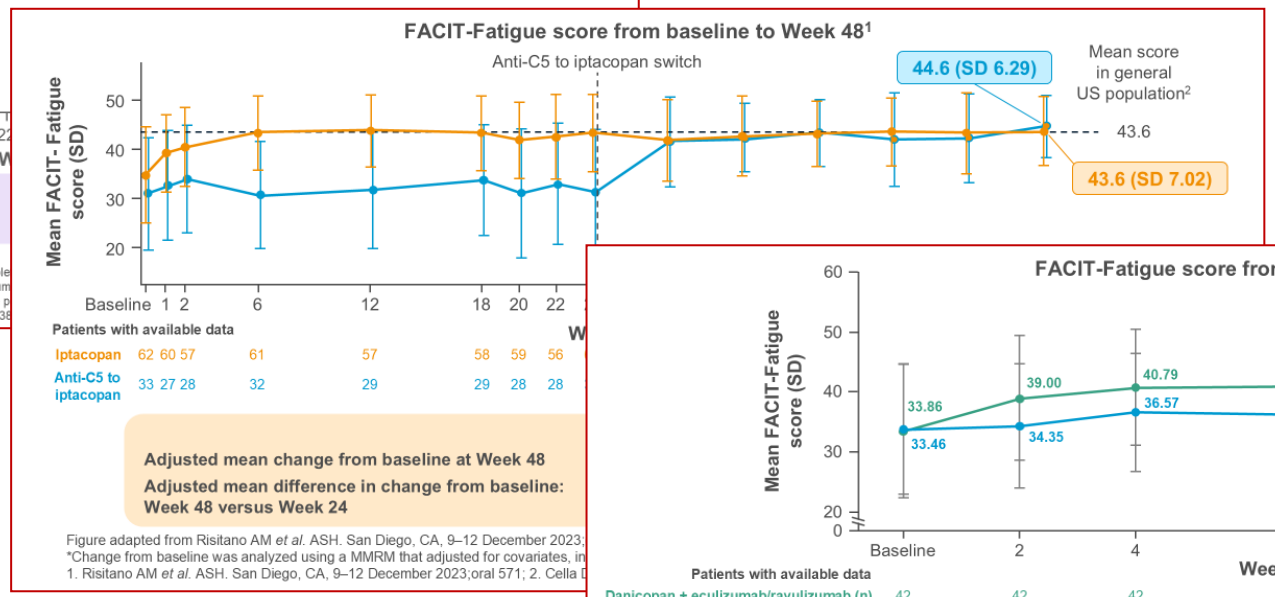


Figure adapted from Risitano AM *et al.* ASH. San Diego, CA, 9–12 December 2023;
*Change from baseline was analyzed using a MMRM that adjusted for covariates, in
1. Risitano AM *et al.* ASH. San Diego, CA, 9–12 December 2023;oral 571; 2. Cella

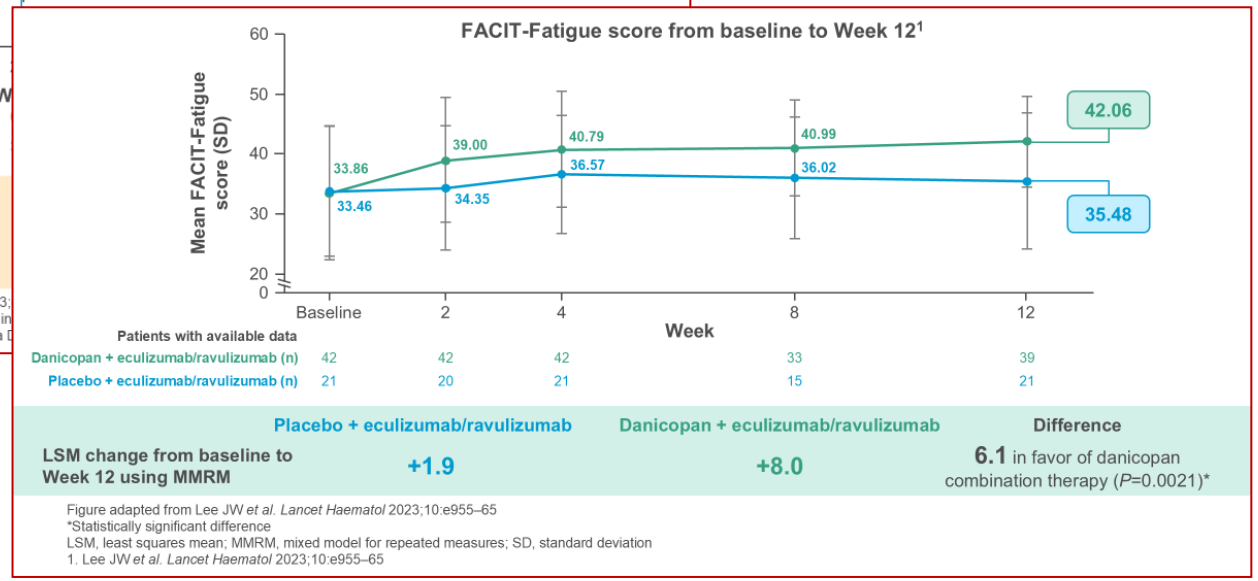
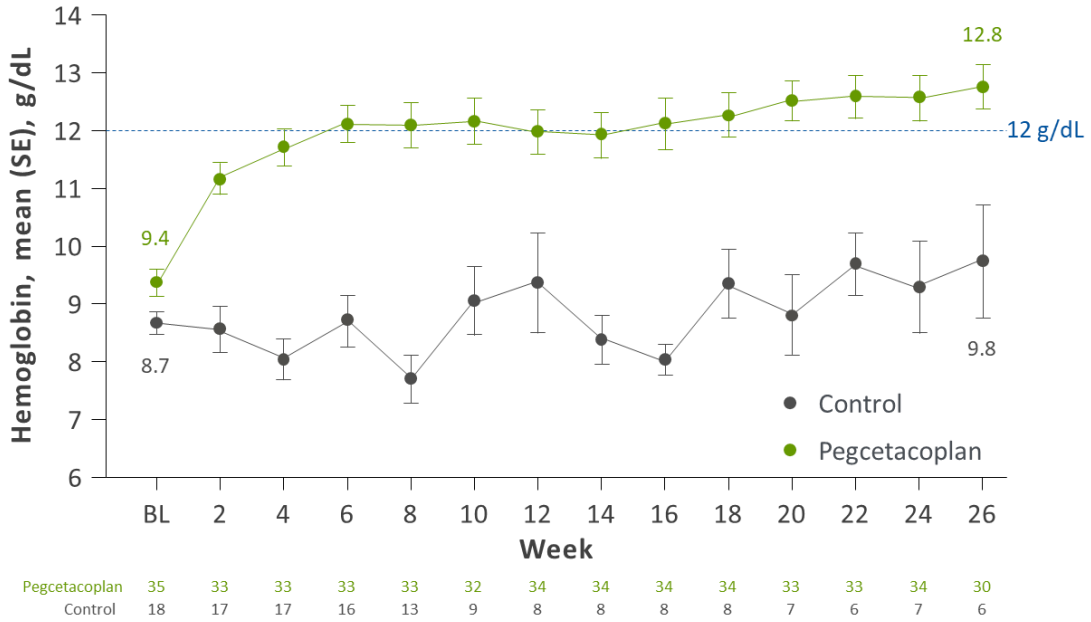
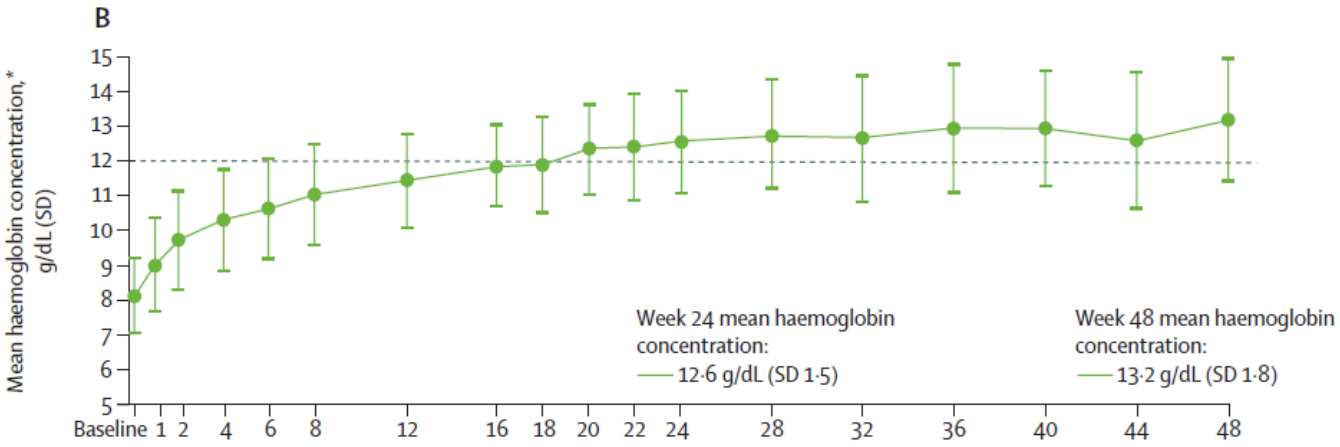


Figure adapted from Lee JW *et al. Lancet Haematol* 2023;10:e955–65
*Statistically significant difference
LSM, least squares mean; MMRM, mixed model for repeated measures; SD, standard deviation
1. Lee JW *et al. Lancet Haematol* 2023;10:e955–65

Proximal CI – CI naïve patients [pegcetacoplan/iptacopan]





Wong et al. *Blood Adv* 2023; Lancet Haematol 2025; 12: e414–30

Proximal CI

- Switch from terminal to proximal [or addition of proximal CI]
  - increase: hemoglobin
    PNH clone size
  - decrease: ARC
    fatigue
    LDH
- ID risk mitigation strategy
  - vaccination: meningococcus
    pneumococcus
    HiB

pill [antibiotic] in the pocket

- increase in hemoglobin also in pts. with Hb > 10 [12] g/dl
- proximal CI works well in CI naive patients

Management – Complement Inhibition [CI] – there's more (complex…)

- Eculizumab 2007 (+ Biosimilars 05/2023)

terminal KI

- Ravulizumab (07/2019)

terminal KI

- Pegcetacoplan (12/2021)

proximal KI

- Danicopan
  (plus Ravu/Ecu) (04/2024)

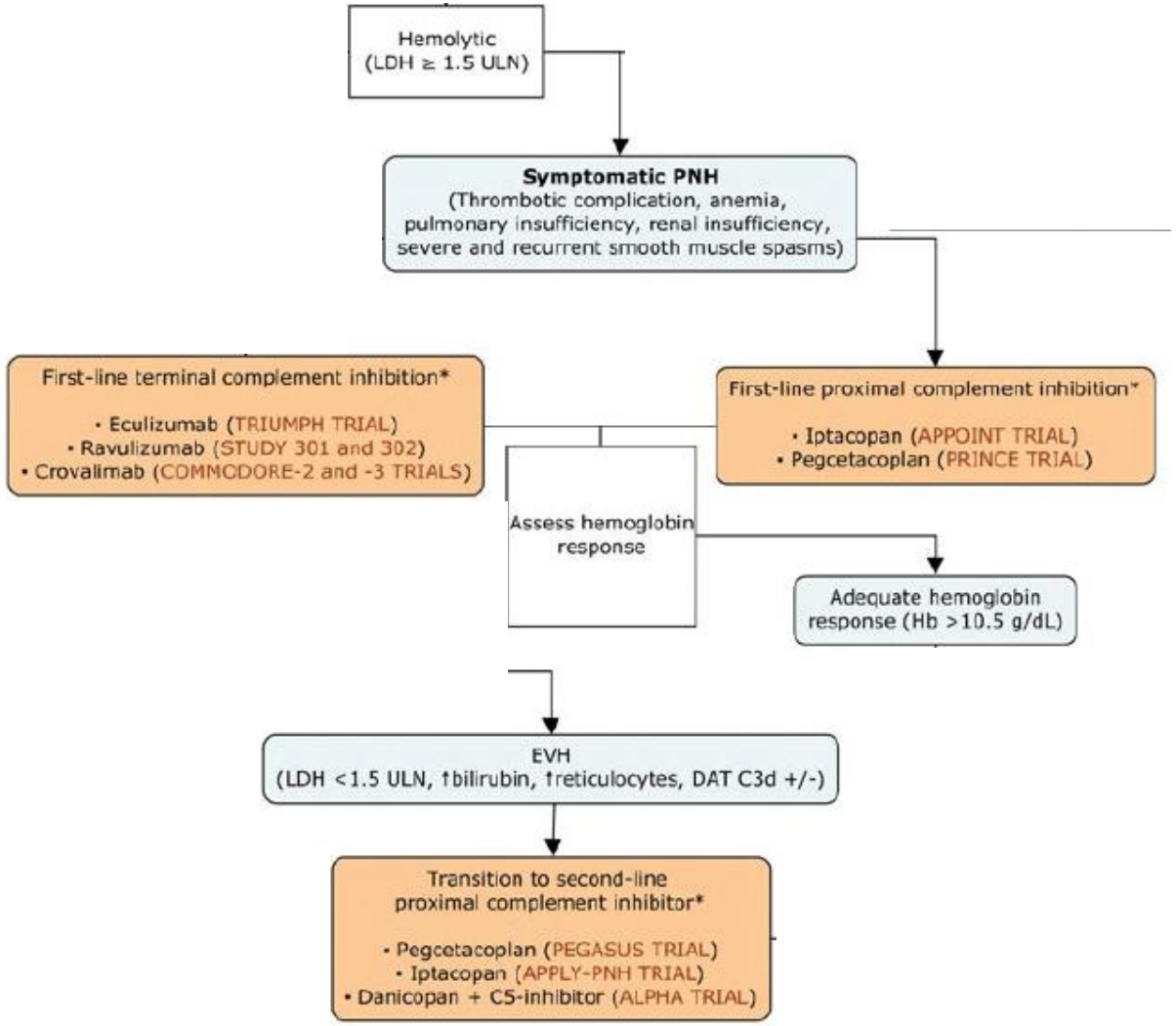
proximal KI

- Iptacopan (05/2024)

proximal KI

- Crovalimab (07/2024)

terminal KI



Bienz M, Patriquin CJ. Hematology Am Soc Hematol Educ Program. 2025 Dec 5;2025(1):154-163

Proximal CI – costs/availability

EXPERT REVIEW OF HEMATOLOGY
2025, VOL. 18, NO. 1, 5–9
https://doi.org/10.1080/17474086.2025.2449864

Taylor & Francis
Taylor & Francis Group

EDITORIAL

Check for updates

Proximal complement inhibitors in paroxysmal nocturnal hemoglobinuria: an abundance of options in a rare disease

Taylor S White[a], Justin R Arnall[b], Paul Christopher Parish[c], Jamie Tolerico[c], Thuy Tran[b] and Donald C Moore[a]

[a]Department of Pharmacy, Atrium Health, Levine Cancer Institute, Charlotte, NC, USA; [b]Department of Pharmacy, Atrium Health Specialty Pharmacy Service, Charlotte, NC, USA; [c]Department of Pharmacy, Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Winston-Salem, NC, USA

ARTICLE HISTORY Received 27 September 2024; Accepted 02 January 2025

KEYWORDS Paroxysmal nocturnal hemoglobinuria; complement inhibitor; danicopan; pegcetacoplan; iptacopan

Austria

Denmark

France

Germany

Italy

Switzerland

Differences in availability, reimbursement and treatment structures even within six countries within Western Europe

Table 2. Cost comparison of complement inhibitors approved for treatment of PNH.

Drug	Route of administration and dosing frequency	FDA approval	Cost*
Eculizumab	Intravenous Weekly x 4 weeks, then every 2 weeks	Monotherapy	$62,620.80 for first month; then ~$46.965.60 monthly thereafter
Ravulizumab	Intravenous load, week 2, then every 8 weeks	Monotherapy	$23,054.40–$69,1632.20**
Pegcetacoplan	Subcutaneous twice weekly	Monotherapy	$45,068.80
Iptacoplan	Oral twice daily	Monotherapy	$54,246.60
Danicopan	Oral three times daily	Add-on to C5 inhibitor	$4,957.20

*based on average wholesale price for 30-day supply.
**varies based on patient's weight.

CI - BTH

- Definition
- Pharmacodynamic vs. Pharmacokinetic BTH

TABLE 3 | Definition of clinical and subclinical *breakthrough* hemolysis during eculizumab treatment for PNH.

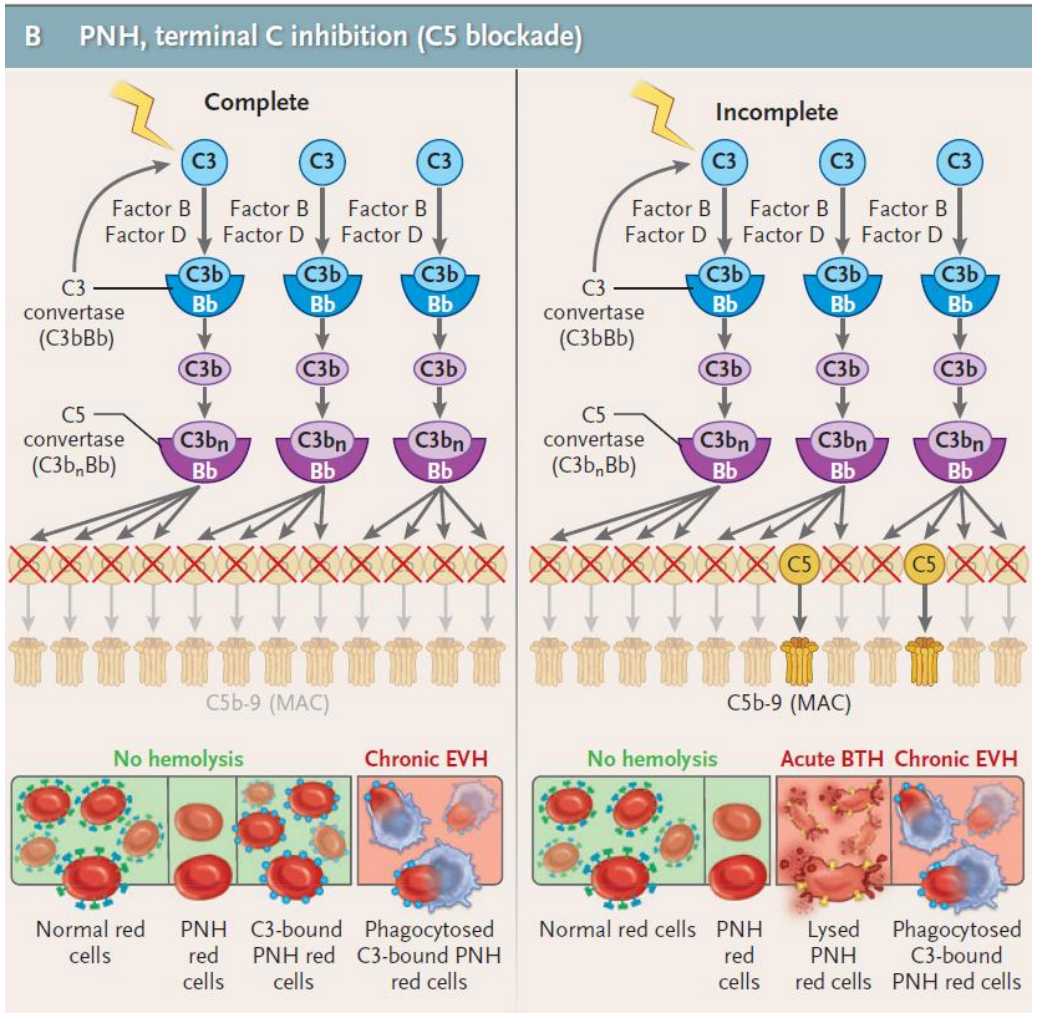
	Clinical criteria		Laboratory criteria
	Hemoglobin level	**Sign or symptoms**	**LDH level**
Clinical breakthrough*	Drop ≥2 g/dL (compared to the latest assessment, within 15 days)	Gross hemoglobinuria, painful crisis, dysphagia or any other significant clinical finding	>1.5x ULN (and increased as compared to the steady-state)
Subclinical breakthrough	Drop <2 g/dL (compared to previous assessment, within 15 days)	No clinical symptom or sign, except moderate hemoglobinuria	>1.5x ULN (and increased by at least 50% as compared to the steady-state)

*LDH, lactate dehydrogenase; ULN, upper limit of the normal. *The breakthrough is defined clinical if either one of the two clinical criteria is demonstrated, in presence of the laboratory evidence of intravascular hemolysis (LDH level).*

TABLE 4 | Definition of pharmacokinetic and pharmacodynamic *breakthrough* hemolysis during eculizumab treatment for PNH.

	Timing	Frequency	Concomitant conditions	Free C5	Eculizumab plasma level	Mechanism	Intervention
Pharmacokinetic breakthrough	>7–10 days from previous dosing	Recurrent	Usually none*	Always >0.5–1 μg/mL	Inadequate	Residual free C5 available for steady-state (normal) C5 convertase activity	Decrease interval of dosing (10-12 days) or increase dose of eculizumab (1,200 mg)
Pharmacodynamic breakthrough	Any time	Sporadic	Infectious events (both bacterial and viral, such as common seasonal viruses) or any event leading to inflammation (i.e., surgery, possible comorbidities)	Usually ≤0.5–1 μg/mL (but it may occur with any free C5 plasma level)	Adequate	Massive complement activation leading to excess C5 convertase activity, which might displace C5 from eculizumab	None (treat the underlying cause triggering complement activation)

**Events leading to pharmacodynamic breakthrough (i.e., triggers of complement activation) may eventually contribute also to pharmacokinetic breakthrough.*



Risitano AM et al; Front Immunol. 2019 Jun 14;10:1157, Notaro R, Luzzatto L. N Engl J Med. 2022 Jul 14;387(2):160-166.

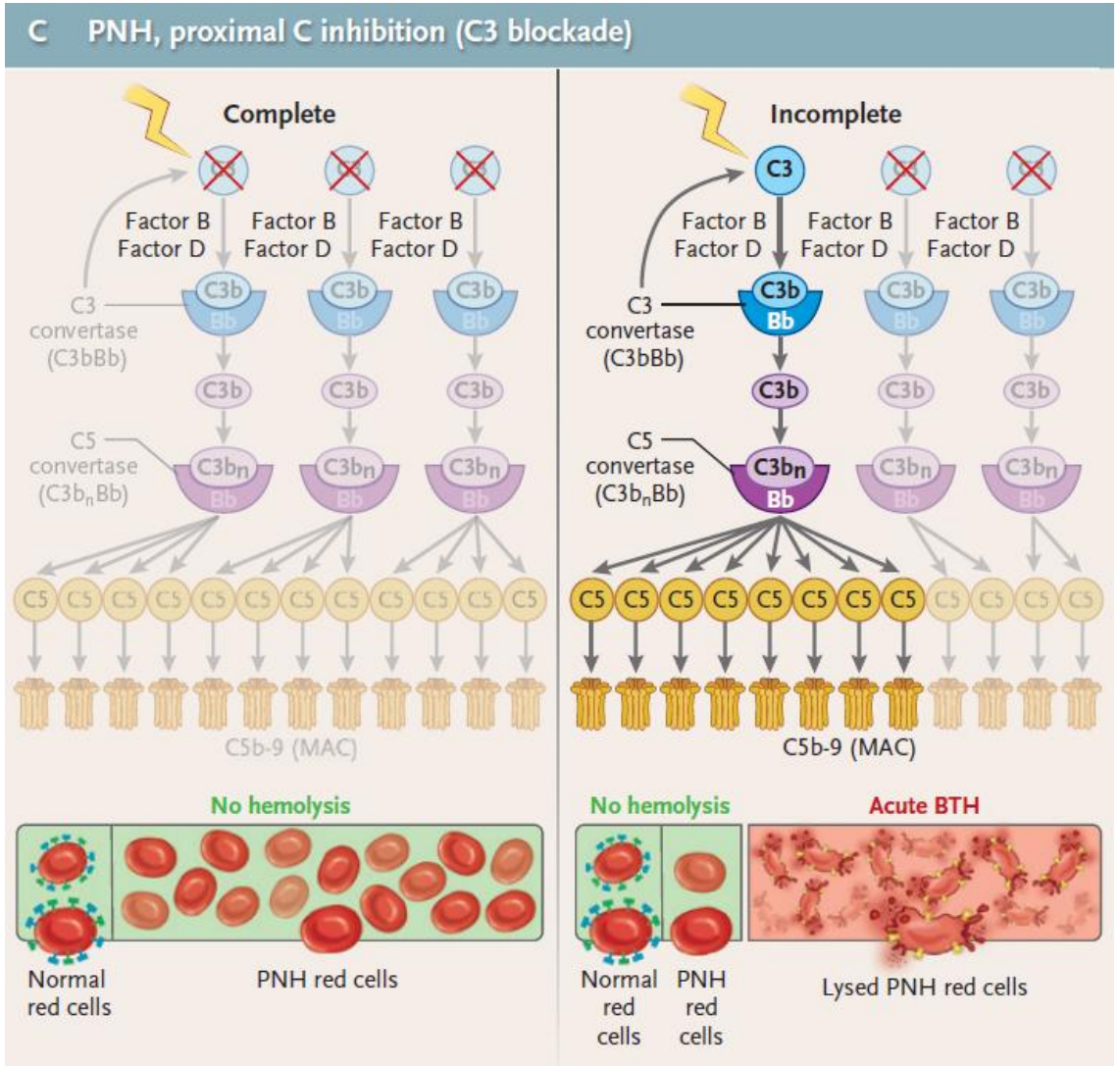
CI - BTH

Table 3. Expert consensus on severity classification of BTH events.

Hemoglobin decrease*	Symptom presentation	Severity classification
≥1.5–<2.5 g/dL	Asymptomatic	Mild
	Symptoms other than SOB, chest pain, abdominal pain†	Mild (if CAC is stabilizing/improving‡) Moderate (if CAC is worsening§)
	SOB, chest pain, abdominal pain¶	Moderate
≥2.5–4 g/dL	Symptoms other than SOB, chest pain, abdominal pain	Moderate
	SOB, chest pain, abdominal pain	Severe
≥4 g/dL	Any	Severe

Note: BTH: breakthrough hemolysis; CAC: complement amplifying condition; ICU: intensive care unit; LDH: lactate dehydrogenase; SOB: shortness of breath; ULN: upper limit of normal.
* In the presence of newly elevated LDH >1.5 × ULN, caused by a CAC (e.g. vaccination, infection, surgery).
† Such as SOB (dyspnea) only on exertion, fatigue, jaundice, or a single episode of hemoglobinuria.
‡ You believe the patient is stable or getting better (e.g. received a routine vaccination, is recovering as expected from a planned surgery).
§ You believe the patient is worsening (e.g. is early in a case of influenza, is in the ICU with COVID-19, has a post-surgical infection).
¶ Or other more severe symptoms such as thrombosis, dysphagia, erectile dysfunction, extreme fatigue, or persistent or recurrent episodes of hemoglobinuria.

- Definition
- BTH under terminal vs BTH under proximal



Dingli D et al; Hematology. 2024 Dec;29(1):2329030, Notaro R, Luzzatto L. N Engl J Med. 2022 Jul 14;387(2):160-166.

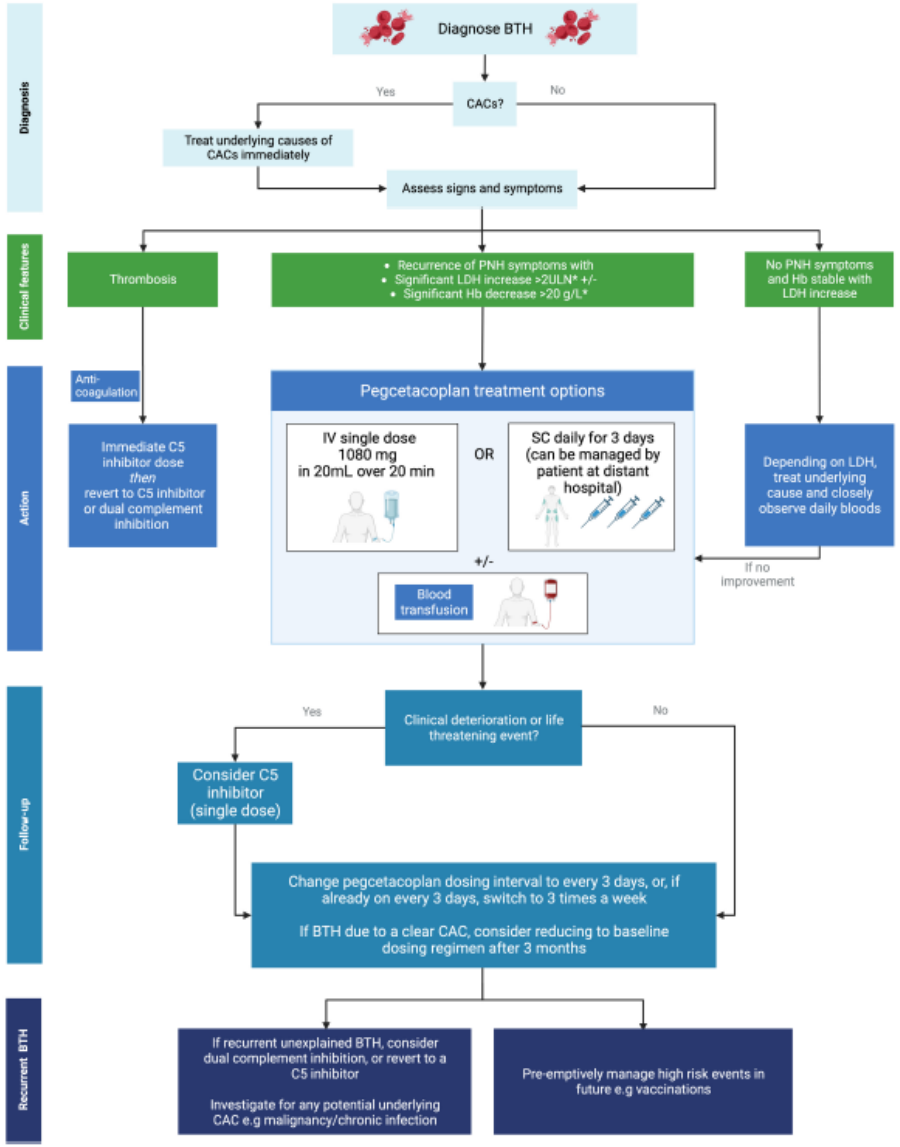
CI - BTH

- Definition
- BTH under terminal vs BTH under proximal
- BTH through EVH
- Management (dose intensity of CI, transfuion, CAC-treatment, anticoagulation, …)

Received: 15 August 2024 | Revised: 26 September 2024 | Accepted: 3 October 2024
DOI: 10.1002/ajh.27502

CORRESPONDENCE

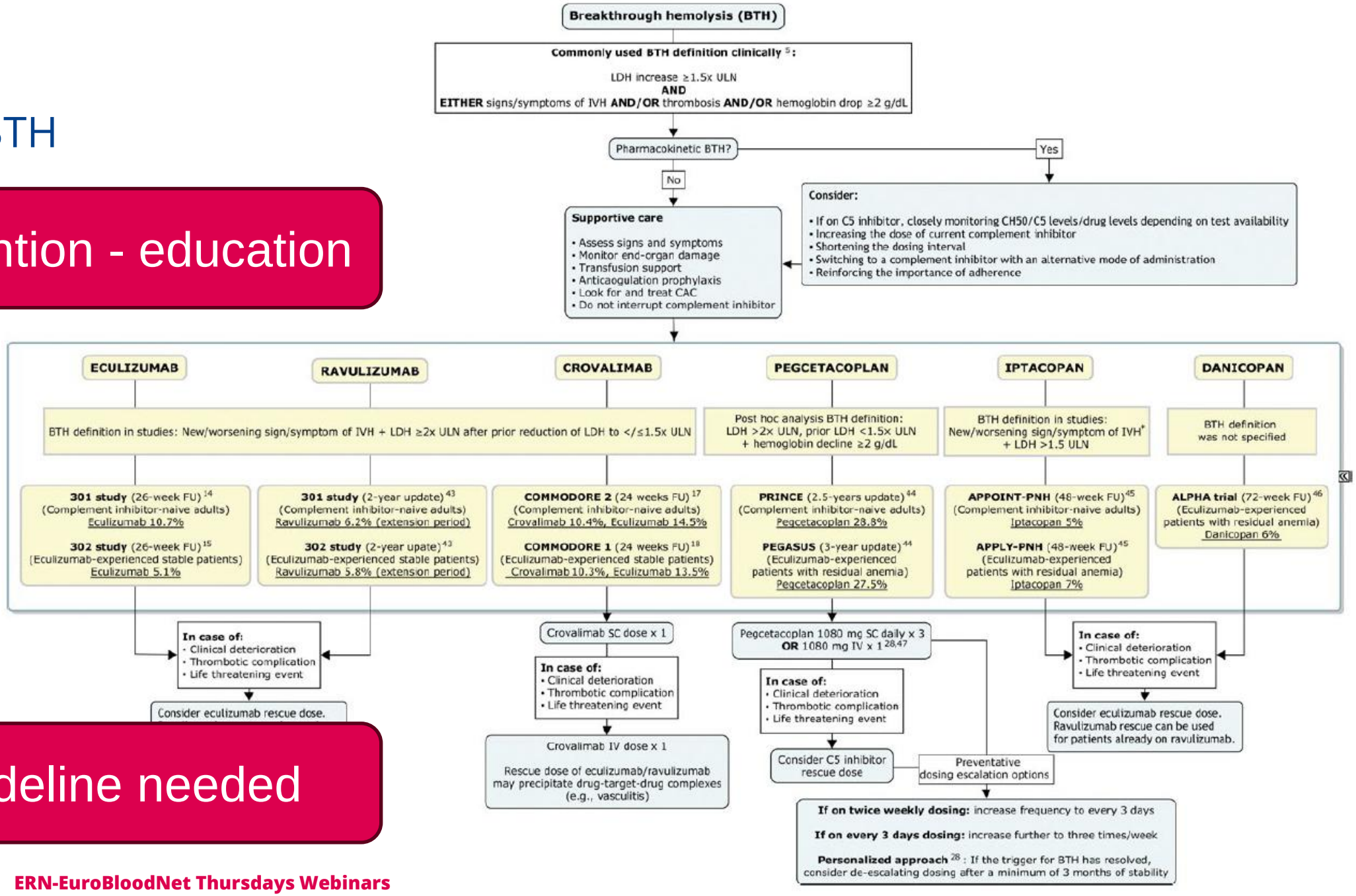
Massive hemolysis in paroxysmal nocturnal hemoglobinuria after switching from proximal complement inhibitor to anti-C5 therapy: A lesson not to be forgotten



Griffin M det al; Am J Hematol. 2024 May;99(5):816-823; Risitano AM et al; Am J Hematol. 2025 Jan;100(1):163-167

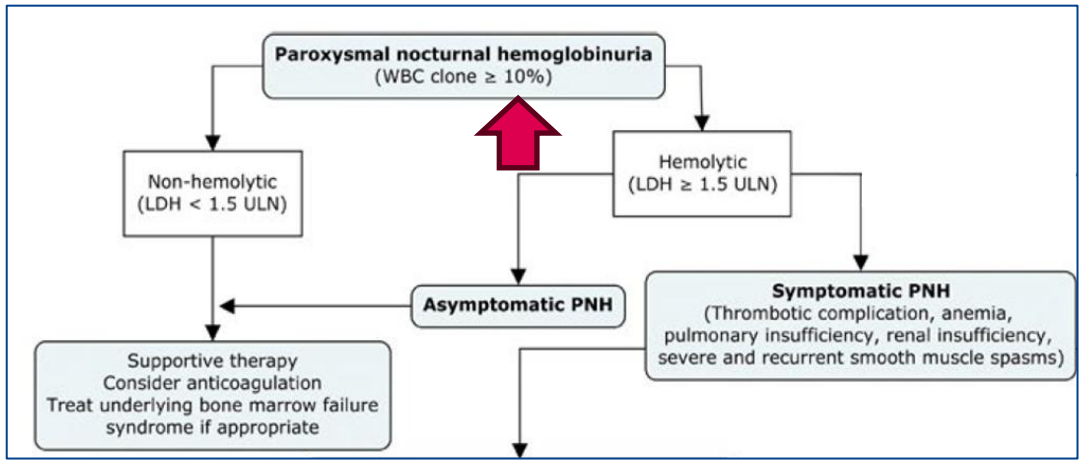
CI - BTH

prevention - education

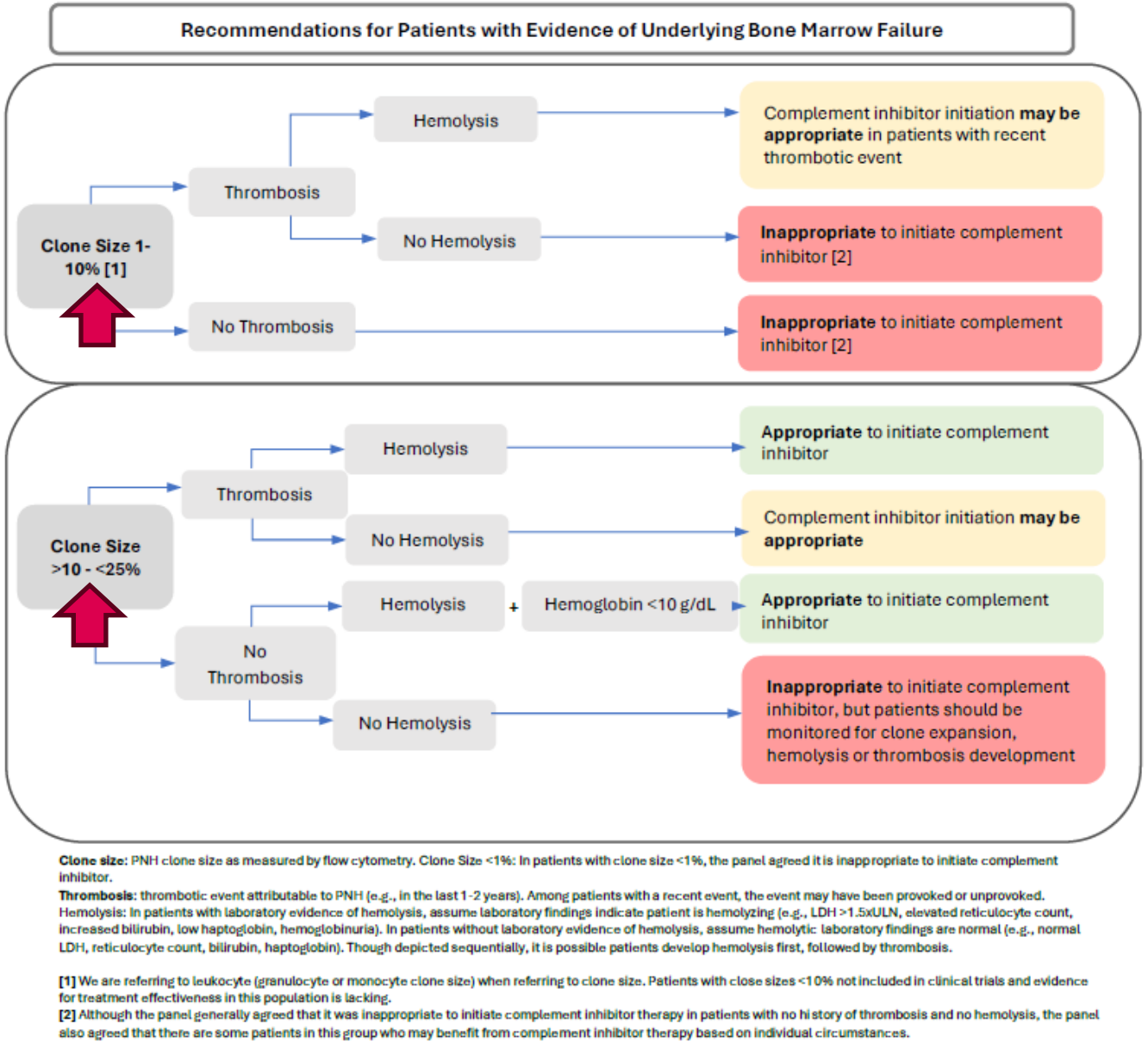


Guideline needed

Management – small clone size



different opinions about anticoagulation

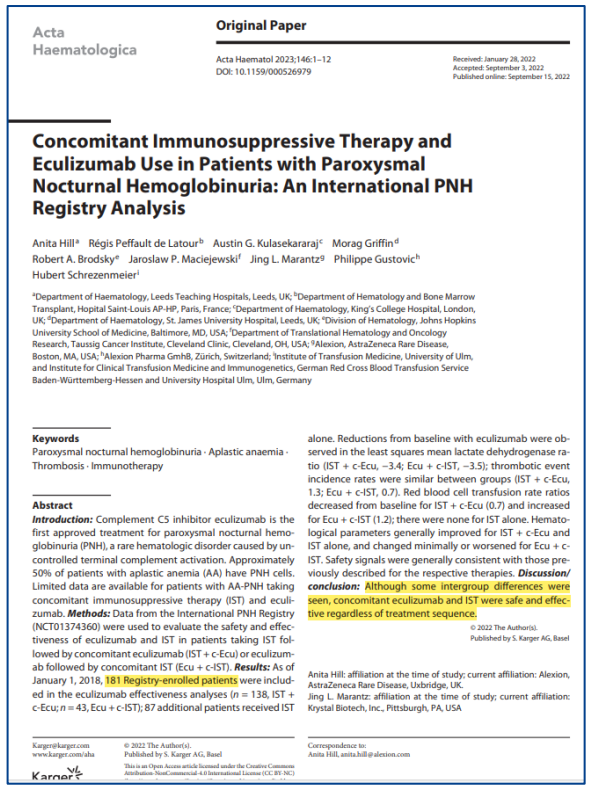


Clone size: PNH clone size as measured by flow cytometry. Clone Size <1%: In patients with clone size <1%, the panel agreed it is inappropriate to initiate complement inhibitor.
Thrombosis: thrombotic event attributable to PNH (e.g., in the last 1-2 years). Among patients with a recent event, the event may have been provoked or unprovoked.
Hemolysis: In patients with laboratory evidence of hemolysis, assume laboratory findings indicate patient is hemolyzing (e.g., LDH >1.5xULN, elevated reticulocyte count, increased bilirubin, low haptoglobin, hemoglobinuria). In patients without laboratory evidence of hemolysis, assume hemolytic laboratory findings are normal (e.g., normal LDH, reticulocyte count, bilirubin, haptoglobin). Though depicted sequentially, it is possible patients develop hemolysis first, followed by thrombosis.

[1] We are referring to leukocyte (granulocyte or monocyte clone size) when referring to clone size. Patients with clone sizes <10% not included in clinical trials and evidence for treatment effectiveness in this population is lacking.
[2] Although the panel generally agreed that it was inappropriate to initiate complement inhibitor therapy in patients with no history of thrombosis and no hemolysis, the panel also agreed that there are some patients in this group who may benefit from complement inhibitor therapy based on individual circumstances.

Bienz M, Patriquin CJ. Hematology Am Soc Hematol Educ Program. 2025 Dec 5;2025(1):154-163
Pullarkat V., Babushok DV., de Castro CM., et al.; Expert consensus on when to screen, monitor, and initiate complement inhibition treatment for paroxysmal nocturnal hemoglobinuria, submitted

Management – PNH/AA – CI + IST is feasible



Acta Haematologica

Original Paper

Acta Haematol 2023;146:1–12
DOI: 10.1159/000526979

Received: January 28, 2022
Accepted: September 3, 2022
Published online: September 15, 2022

Concomitant Immunosuppressive Therapy and Eculizumab Use in Patients with Paroxysmal Nocturnal Hemoglobinuria: An International PNH Registry Analysis

Anita Hill[a] Régis Peffault de Latour[b] Austin G. Kulasekararaj[c] Morag Griffin[d] Robert A. Brodsky[e] Jaroslaw P. Maciejewski[f] Jing L. Marantz[g] Philippe Gustovic[h] Hubert Schrezenmeier[i]

[a]Department of Haematology, Leeds Teaching Hospitals, Leeds, UK; [b]Department of Hematology and Bone Marrow Transplant, Hopital Saint-Louis AP-HP, Paris, France; [c]Department of Haematology, King's College Hospital, London, UK; [d]Department of Haematology, St. James University Hospital, Leeds, UK; [e]Division of Hematology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [f]Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA; [g]Alexion, AstraZeneca Rare Disease, Boston, MA, USA; [h]Alexion Pharma GmbH, Zürich, Switzerland; [i]Institute of Transfusion Medicine, University of Ulm, and Institute for Clinical Transfusion Medicine and Immunogenetics, German Red Cross Blood Transfusion Service Baden-Württemberg-Hessen and University Hospital Ulm, Ulm, Germany

Keywords
Paroxysmal nocturnal hemoglobinuria · Aplastic anaemia · Thrombosis · Immunotherapy

Abstract

Introduction: Complement C5 inhibitor eculizumab is the first approved treatment for paroxysmal nocturnal hemoglobinuria (PNH), a rare hematologic disorder caused by uncontrolled terminal complement activation. Approximately 50% of patients with aplastic anemia (AA) have PNH cells. Limited data are available for patients with AA-PNH taking concomitant immunosuppressive therapy (IST) and eculizumab. ***Methods:*** Data from the International PNH Registry (NCT01374360) were used to evaluate the safety and effectiveness of eculizumab and IST in patients taking IST followed by concomitant eculizumab (IST + c-Ecu) or eculizumab followed by concomitant IST (Ecu + c-IST). ***Results:*** As of January 1, 2018, 181 Registry-enrolled patients were included in the eculizumab effectiveness analyses (n = 138, IST + c-Ecu; n = 43, Ecu + c-IST); 87 additional patients received IST alone. Reductions from baseline with eculizumab were observed in the least squares mean lactate dehydrogenase ratio (IST + c-Ecu, −3.4; Ecu + c-IST, −3.5); thrombotic event incidence rates were similar between groups (IST + c-Ecu, 1.3; Ecu + c-IST, 0.7). Red blood cell transfusion rate ratios decreased from baseline for IST + c-Ecu (0.7) and increased for Ecu + c-IST (1.2); there were none for IST alone. Hematological parameters generally improved for IST + c-Ecu and IST alone, and changed minimally or worsened for Ecu + c-IST. Safety signals were generally consistent with those previously described for the respective therapies. ***Discussion/conclusion:*** Although some intergroup differences were seen, concomitant eculizumab and IST were safe and effective regardless of treatment sequence.

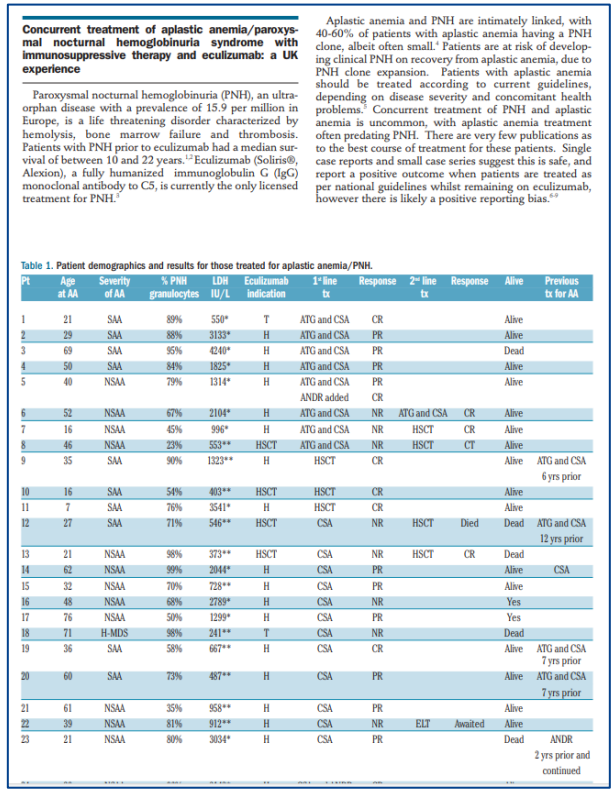
Anita Hill: affiliation at the time of study; current affiliation: Alexion, AstraZeneca Rare Disease, Uxbridge, UK.
Jing L. Marantz: affiliation at the time of study; current affiliation: Krystal Biotech, Inc., Pittsburgh, PA, USA

Karger@karger.com
www.karger.com/aha

© 2022 The Author(s).
Published by S. Karger AG, Basel

This is an Open Access article licensed under the Creative Commons Attribution-NonCommercial-4.0 International License (CC BY-NC)

Correspondence to:
Anita Hill, anita.hill@alexion.com



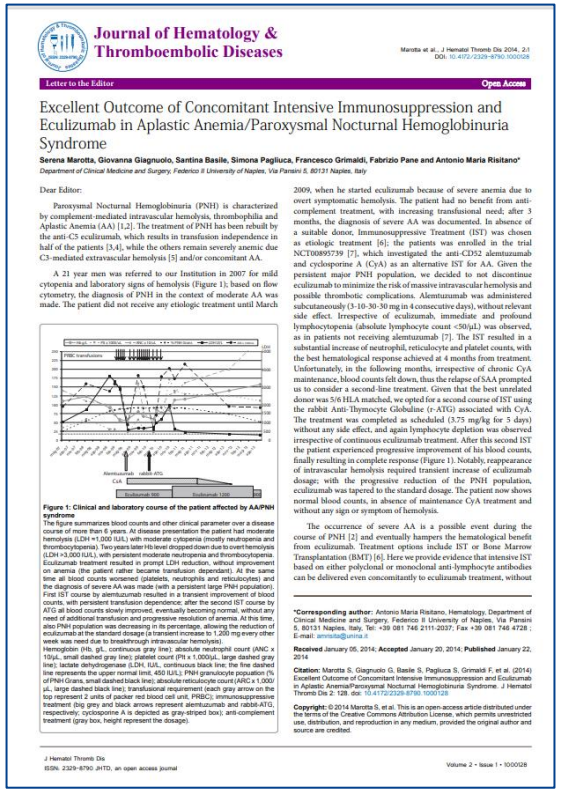
Concurrent treatment of aplastic anemia/paroxysmal nocturnal hemoglobinuria syndrome with immunosuppressive therapy and eculizumab: a UK experience

Paroxysmal nocturnal hemoglobinuria (PNH), an ultra-orphan disease with a prevalence of 15.9 per million in Europe, is a life threatening disorder characterized by hemolysis, bone marrow failure and thrombosis. Patients with PNH prior to eculizumab had a median survival of between 10 and 22 years.[1,2] Eculizumab (Soliris®, Alexion), a fully humanized immunoglobulin G (IgG) monoclonal antibody to C5, is currently the only licensed treatment for PNH.[3]

Aplastic anemia and PNH are intimately linked, with 40-60% of patients with aplastic anemia having a PNH clone, albeit often small.[4] Patients are at risk of developing clinical PNH on recovery from aplastic anemia, due to PNH clone expansion. Patients with aplastic anemia should be treated according to current guidelines, depending on disease severity and concomitant health problems.[5] Concurrent treatment of PNH and aplastic anemia is uncommon, with aplastic anemia treatment often predating PNH. There are very few publications as to the best course of treatment for these patients. Single case reports and small case series suggest this is safe, and report a positive outcome when patients are treated as per national guidelines whilst remaining on eculizumab, however there is likely a positive reporting bias.[6-9]

Table 1. Patient demographics and results for those treated for aplastic anemia/PNH.

Pt	Age at AA	Severity of AA	% PNH granulocytes	LDH IU/L	Eculizumab indication	1st line tx	Response	2nd line tx	Response	Alive	Previous tx for AA
1	21	SAA	89%	550*	T	ATG and CSA	CR			Alive	
2	29	SAA	88%	3133*	H	ATG and CSA	PR			Alive	
3	69	SAA	95%	4240*	H	ATG and CSA	PR			Dead	
4	50	SAA	84%	1825*	H	ATG and CSA	PR			Alive	
5	40	NSAA	79%	1314*	H	ATG and CSA	PR			Alive	
						ANDR added	CR				
6	52	NSAA	67%	2104*	H	ATG and CSA	NR	ATG and CSA	CR	Alive	
7	16	NSAA	45%	996*	H	ATG and CSA	NR	HSCT	CR	Alive	
8	46	NSAA	23%	553**	HSCT	ATG and CSA	NR	HSCT	CT	Alive	
9	35	SAA	90%	1323**	H	HSCT	CR			Alive	ATG and CSA 6 yrs prior
10	16	SAA	54%	403**	HSCT	HSCT	CR			Alive	
11	7	SAA	76%	3541*	H	HSCT	CR			Alive	
12	27	SAA	71%	546**	HSCT	CSA	NR	HSCT	Died	Dead	ATG and CSA 12 yrs prior
13	21	NSAA	98%	373**	HSCT	CSA	NR	HSCT	CR	Dead	
14	62	NSAA	99%	2044*	H	CSA	PR			Alive	CSA
15	32	NSAA	70%	728**	H	CSA	PR			Alive	
16	48	NSAA	68%	2789*	H	CSA	NR			Yes	
17	76	NSAA	50%	1299*	H	CSA	PR			Yes	
18	71	H-MDS	98%	241**	T	CSA	NR			Dead	
19	36	SAA	58%	667**	H	CSA	CR			Alive	ATG and CSA 7 yrs prior
20	60	SAA	73%	487**	H	CSA	PR			Alive	ATG and CSA 7 yrs prior
21	61	NSAA	35%	958**	H	CSA	PR			Alive	
22	39	NSAA	81%	912**	H	CSA	NR	ELT	Awaited	Alive	
23	21	NSAA	80%	3034*	H	CSA	PR			Dead	ANDR 2 yrs prior and continued



Journal of Hematology & Thromboembolic Diseases

Marotta et al., J Hematol Thromb Dis 2014, 2:1
DOI: 10.4172/2329-8790.1000128

Letter to the Editor — Open Access

Excellent Outcome of Concomitant Intensive Immunosuppression and Eculizumab in Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria Syndrome

Serena Marotta, Giovanna Giagnuolo, Santina Basile, Simona Pagliuca, Francesco Grimaldi, Fabrizio Pane and Antonio Maria Risitano*
Department of Clinical Medicine and Surgery, Federico II University of Naples, Via Pansini 5, 80131 Naples, Italy

Dear Editor:

Paroxysmal Nocturnal Hemoglobinuria (PNH) is characterized by complement-mediated intravascular hemolysis, thrombophilia and Aplastic Anemia (AA) [1,2]. The treatment of PNH has been rebuilt by the anti-C5 eculizumab, which results in transfusion independence in half of the patients [3,4], while the others remain severely anemic due C3-mediated extravascular hemolysis [5] and/or concomitant AA.

A 21 year men was referred to our Institution in 2007 for mild cytopenia and laboratory signs of hemolysis (Figure 1); based on flow cytometry, the diagnosis of PNH in the context of moderate AA was made. The patient did not receive any etiologic treatment until March 2009, when he started eculizumab because of severe anemia due to overt symptomatic hemolysis. The patient had no benefit from anti-complement treatment, with increasing transfusional need; after 3 months, the diagnosis of severe AA was documented. In absence of a suitable donor, Immunosuppressive Treatment (IST) was chosen as etiologic treatment [6]; the patients was enrolled in the trial NCT00895739 [7], which investigated the anti-CD52 alemtuzumab and cyclosporine A (CyA) as an alternative IST for AA. Given the persistent major PNH population, we decided to not discontinue eculizumab to minimize the risk of massive intravascular hemolysis and possible thrombotic complications. Alemtuzumab was administered subcutaneously (3-10-30-30 mg in 4 consecutive days), without relevant side effect. Irrespective of eculizumab, immediate and profound lymphocytopenia (absolute lymphocyte count <50/μL) was observed, as in patients not receiving alemtuzumab [7]. The IST resulted in a substantial increase of neutrophil, reticulocyte and platelet counts, with the best hematological response achieved at 4 months from treatment. Unfortunately, in the following months, irrespective of chronic CyA maintenance, blood counts felt down, thus the relapse of SAA prompted us to consider a second-line treatment. Given that the best unrelated donor was 5/6 HLA matched, we opted for a second course of IST using the rabbit Anti-Thymocyte Globuline (r-ATG) associated with CyA. The treatment was completed as scheduled (3.75 mg/kg for 5 days) without any side effect, and again lymphocyte depletion was observed irrespective of continuous eculizumab treatment. After this second IST the patient experienced progressive improvement of his blood counts, finally resulting in complete response (Figure 1). Notably, reappearance of intravascular hemolysis required transient increase of eculizumab dosage; with the progressive reduction of the PNH population, eculizumab was tapered to the standard dosage. The patient now shows normal blood counts, in absence of maintenance CyA treatment and without any sign or symptom of hemolysis.

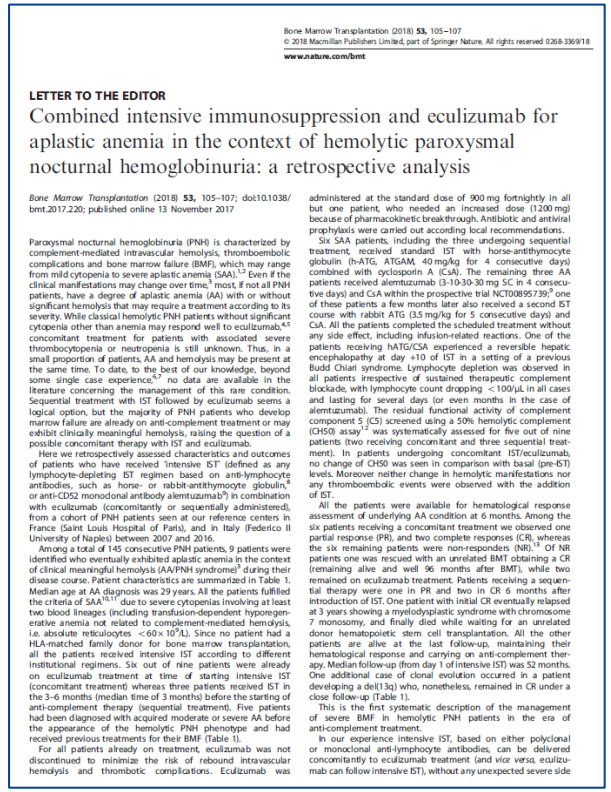
The occurrence of severe AA is a possible event during the course of PNH [2] and eventually hampers the hematological benefit from eculizumab. Treatment options include IST or Bone Marrow Transplantation (BMT) [6]. Here we provide evidence that intensive IST based on either polyclonal or monoclonal anti-lymphocyte antibodies can be delivered even concomitantly to eculizumab treatment, without

Figure 1: Clinical and laboratory course of the patient affected by AA/PNH syndrome
The figure summarizes blood counts and other clinical parameter over a disease course of more than 6 years. At disease presentation the patient had moderate hemolysis (LDH >1,000 IU/L) with moderate cytopenia (mostly neutropenia and thrombocytopenia). Two years later Hb level dropped down due to overt hemolysis (LDH >3,000 IU/L, with persistent moderate neutropenia and thrombocytopenia. Eculizumab treatment resulted in prompt LDH reduction, without improvement on anemia (the patient rather became transfusion dependant). At the same time all blood counts worsened (platelets, neutrophils and reticulocytes) and the diagnosis of severe AA was made (with a persistent large PNH population). First IST course by alemtuzumab resulted in a transient improvement of blood counts, with persistent transfusion dependence; after the second IST course by ATG all blood counts slowly improved, eventually becoming normal, without any need of additional transfusion and progressive resolution of anemia. At this time, also PNH population was decreasing in its percentage, allowing the reduction of eculizumab at the standard dosage (a transient increase to 1,200 mg every other week was need due to breakthrough intravascular hemolysis).
Hemoglobin (Hb; g/L, continuous gray line); absolute neutrophil count (ANC; x 10/μL, small dashed gray line); platelet count (Plt x 1.000/μL, large dashed gray line); lactate dehydrogenase (LDH, IU/L, continuous black line; the fine dashed line represents the upper normal limit, 450 IU/L); PNH granulocyte population (% of PNH Grans, small dashed black line); absolute reticulocyte count (ARC x 1.000/μL, large dashed black line); transfusional requirement (each gray arrow on the top represent 2 units of packer red blood cell unit, PRBC); immunosuppressive treatment (big grey and black arrows represent alemtuzumab and rabbit-ATG, respectively; cyclosporine A is depicted as gray-striped box); anti-complement treatment (gray box, height represent the dosage).

*Corresponding author: Antonio Maria Risitano, Hematology, Department of Clinical Medicine and Surgery, Federico II University of Naples, Via Pansini 5, 80131 Naples, Italy, Tel: +39 081 746 2111-2037; Fax +39 081 746 4728; E-mail: amrisita@unina.it

Received January 05, 2014; Accepted January 20, 2014; Published January 22, 2014

Citation: Marotta S, Giagnuolo G, Basile S, Pagliuca S, Grimaldi F, et al. (2014) Excellent Outcome of Concomitant Intensive Immunosuppression and Eculizumab in Aplastic Anemia/Paroxysmal Nocturnal Hemoglobinuria Syndrome. J Hematol Thromb Dis 2: 128. doi: 10.4172/2329-8790.1000128



Bone Marrow Transplantation (2018) 53, 105–107

www.nature.com/bmt

LETTER TO THE EDITOR

Combined intensive immunosuppression and eculizumab for aplastic anemia in the context of hemolytic paroxysmal nocturnal hemoglobinuria: a retrospective analysis

Bone Marrow Transplantation (2018) **53,** 105–107; doi:10.1038/bmt.2017.220; published online 13 November 2017

Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by complement-mediated intravascular hemolysis, thromboembolic complications and bone marrow failure (BMF), which may range from mild cytopenia to severe aplastic anemia (SAA).[1,2] Even if the clinical manifestations may change over time,[3] most, if not all PNH patients, have a degree of aplastic anemia (AA) with or without significant hemolysis that may require a treatment according to its severity. While classical hemolytic PNH patients without significant cytopenia other than anemia may respond well to eculizumab,[4,5] concomitant treatment for patients with associated severe thrombocytopenia or neutropenia is still unknown. Thus, in a small proportion of patients, AA and hemolysis may be present at the same time. To date, to the best of our knowledge, beyond some single case experience,[6,7] no data are available in the literature concerning the management of this rare condition. Sequential treatment with IST followed by eculizumab seems a logical option, but the majority of PNH patients who develop marrow failure are already on anti-complement treatment or may exhibit clinically meaningful hemolysis, raising the question of a possible concomitant therapy with IST and eculizumab.

Here we retrospectively assessed characteristics and outcomes of patients who have received 'intensive IST' (defined as any lymphocyte-depleting IST regimen based on anti-lymphocyte antibodies, such as horse- or rabbit-antithymocyte globulin,[8] or anti-CD52 monoclonal antibody alemtuzumab[9]) in combination with eculizumab (concomitantly or sequentially administered), from a cohort of PNH patients seen at our reference centers in France (Saint Louis Hospital of Paris), and in Italy (Federico II University of Naples) between 2007 and 2016.

Among a total of 145 consecutive PNH patients, 9 patients were identified who eventually exhibited aplastic anemia in the context of clinical meaningful hemolysis (AA/PNH syndrome)[3] during their disease course. Patient characteristics are summarized in Table 1. Median age at AA diagnosis was 29 years. All the patients fulfilled the criteria of SAA[10,11] due to severe cytopenias involving at least two blood lineages (including transfusion-dependent hyporegenerative anemia not related to complement-mediated hemolysis, i.e. absolute reticulocytes $<60\times10^9$/L). Since no patient had a HLA-matched family donor for bone marrow transplantation, all the patients received intensive IST according to different institutional regimens. Six out of nine patients were already on eculizumab treatment at time of starting intensive IST (concomitant treatment) whereas three patients received IST in the 3–6 months (median time of 3 months) before the starting of anti-complement therapy (sequential treatment). Five patients had been diagnosed with acquired moderate or severe AA before the appearance of the hemolytic PNH phenotype and had received previous treatments for their BMF (Table 1).

For all patients already on treatment, eculizumab was not discontinued to minimize the risk of rebound intravascular hemolysis and thrombotic complications. Eculizumab was administered at the standard dose of 900 mg fortnightly in all but one patient, who needed an increased dose (1200 mg) because of pharmacokinetic breakthrough. Antibiotic and antiviral prophylaxis were carried out according local recommendations.

Six SAA patients, including the three undergoing sequential treatment, received standard IST with horse-antithymocyte globulin (h-ATG, ATGAM, 40 mg/kg for 4 consecutive days) combined with cyclosporin A (CsA). The remaining three AA patients received alemtuzumab (3-10-30-30 mg SC in 4 consecutive days) and CsA within the prospective trial NCT00895739;[9] one of these patients a few months later also received a second IST course with rabbit ATG (3.5 mg/kg for 5 consecutive days) and CsA. All the patients completed the scheduled treatment without any side effect, including infusion-related reactions. One of the patients receiving hATG/CSA experienced a reversible hepatic encephalopathy at day +10 of IST in a setting of a previous Budd Chiari syndrome. Lymphocyte depletion was observed in all patients irrespective of sustained therapeutic complement blockade, with lymphocyte count dropping $<100/\mu L$ in all cases and lasting for several days (or even months in the case of alemtuzumab). The residual functional activity of complement component 5 (C5) screened using a 50% hemolytic complement (CH50) assay[12] was systematically assessed for five out of nine patients (two receiving concomitant and three sequential treatment). In patients undergoing concomitant IST/eculizumab, no change of CH50 was seen in comparison with basal (pre-IST) levels. Moreover neither change in hemolytic manifestations nor any thromboembolic events were observed with the addition of IST.

All the patients were available for hematological response assessment of underlying AA condition at 6 months. Among the six patients receiving a concomitant treatment we observed one partial response (PR), and two complete responses (CR), whereas the six remaining patients were non-responders (NR).[13] Of NR patients one was rescued with an unrelated BMT obtaining a CR (remaining alive and well 96 months after BMT), while two remained on eculizumab treatment. Patients receiving a sequential therapy were one in PR and two in CR 6 months after introduction of IST. One patient with initial CR eventually relapsed at 3 years showing a myelodysplastic syndrome with chromosome 7 monosomy, and finally died while waiting for an unrelated donor hematopoietic stem cell transplantation. All the other patients are alive at the last follow-up, maintaining their hematological response and carrying on anti-complement therapy. Median follow-up (from day 1 of intensive IST) was 52 months. One additional case of clonal evolution occurred in a patient developing a del(13q) who, nonetheless, remained in CR under a close follow-up (Table 1).

This is the first systematic description of the management of severe BMF in hemolytic PNH patients in the era of anti-complement treatment.

In our experience intensive IST, based on either polyclonal or monoclonal anti-lymphocyte antibodies, can be delivered concomitantly to eculizumab treatment (and *vice versa*, eculizumab can follow intensive IST), without any unexpected severe side

Hill A, et al.; Acta Haematol. 2023;146(1):1-13; Griffin M, et al2018 Aug;103(8):e345-e347; Pagliuca, S., et al; Bone Marrow Transplant 53, 105–107 (2018) Marotta S, Giagnuolo G, Basile S, Pagliuca S, Grimaldi F, Pane F, Risitano A.M. et al; J Hematol Thromb Dis. (2014) .

Management – Pregnancy

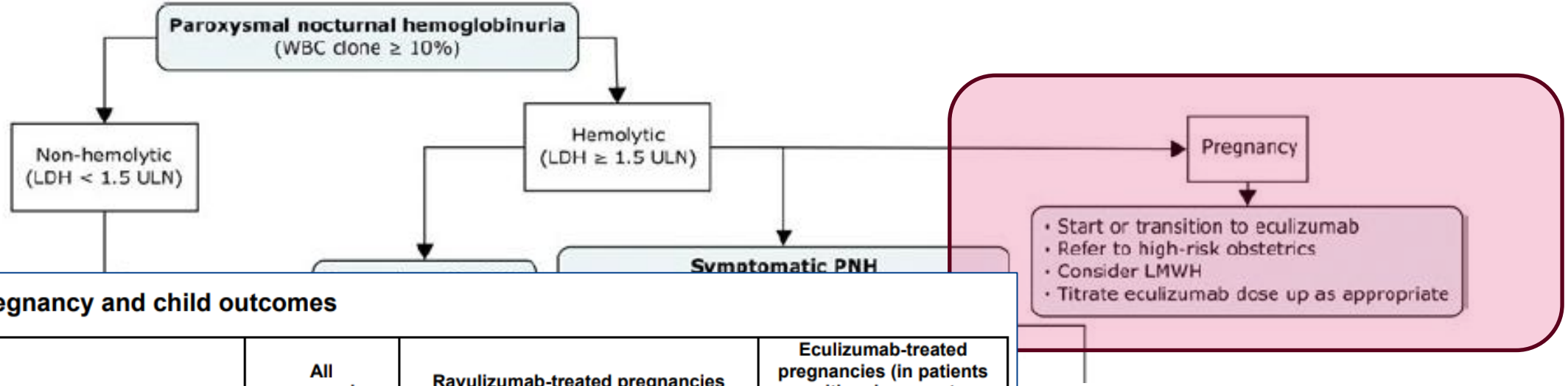


Table 2: Pregnancy and child outcomes

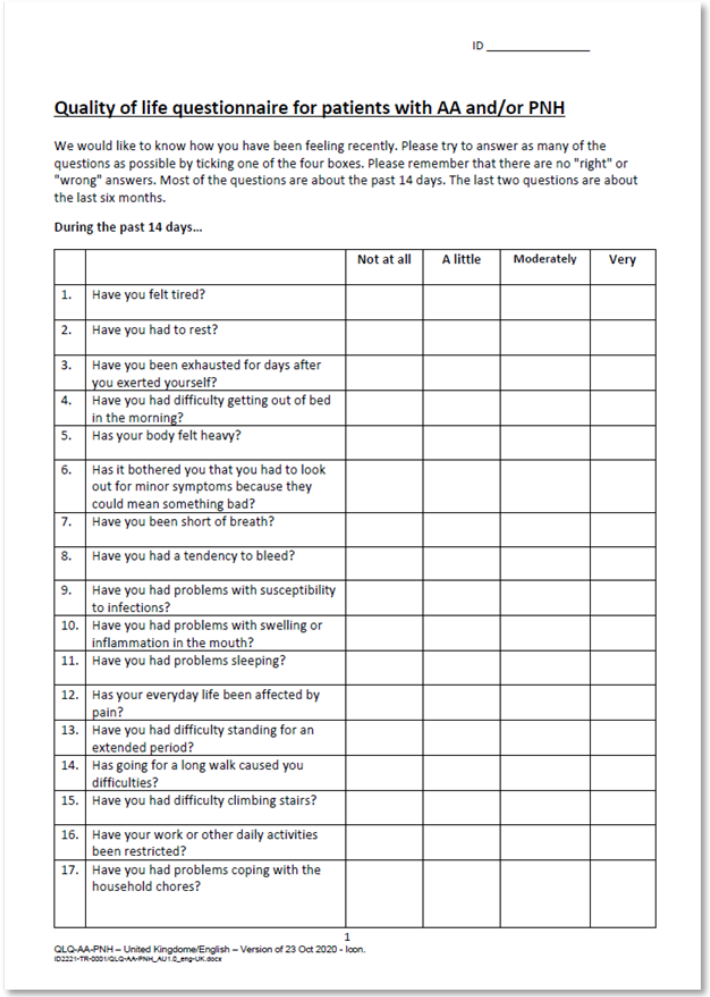
	All pregnancies (n=27)[1]	Ravulizumab-treated pregnancies (n=19)[1]	Eculizumab-treated pregnancies (in patients with subsequent Ravulizumab-treated pregnancies (n=8)
Summary of all pregnancies			
Miscarriages, number (% of pregnancies)	3 (11.1%)	0 (0%)	3 (37.5%)
Preterm delivery of nonviable infant, number (% of pregnancies)^	1 (3.6%)	0 (0%)	1 (12.5%)
Premature births, number (% of pregnancies)	3 (10.7%)	3 (15.8%)	0 (0%)
Emergency C-section, number (%)^	1 (3.7%)	1 (5.0%)	0
Scheduled C-section, number (%)	2 (7.4%)	2 (10.0%)	0
Live (viable) births, n (% of pregnancies)*	24 (85.7%)	20 (100%)*	4 (50.0%)
Summary of Live Births	**Total children (n=24)**	**Children from ravulizumab-treated pregnancies (n=20*)**	**Children from eculizumab treated pregnancies (n=4)**

Bienz M, Patriquin CJ. Hematology Am Soc Hematol Educ Program. 2025 Dec 5;2025(1):154-163

blood advances
American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

Ravulizumab for Treatment of Paroxysmal Nocturnal Hemoglobinuria During Pregnancy

Management – QoL



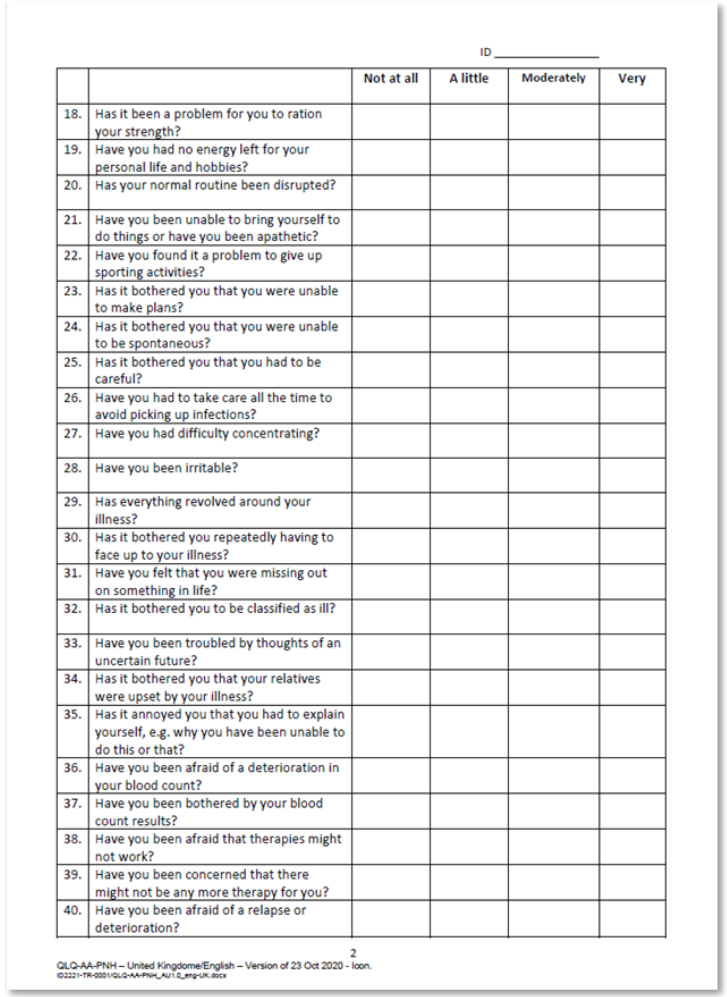
ID _____

Quality of life questionnaire for patients with AA and/or PNH

We would like to know how you have been feeling recently. Please try to answer as many of the questions as possible by ticking one of the four boxes. Please remember that there are no "right" or "wrong" answers. Most of the questions are about the past 14 days. The last two questions are about the last six months.

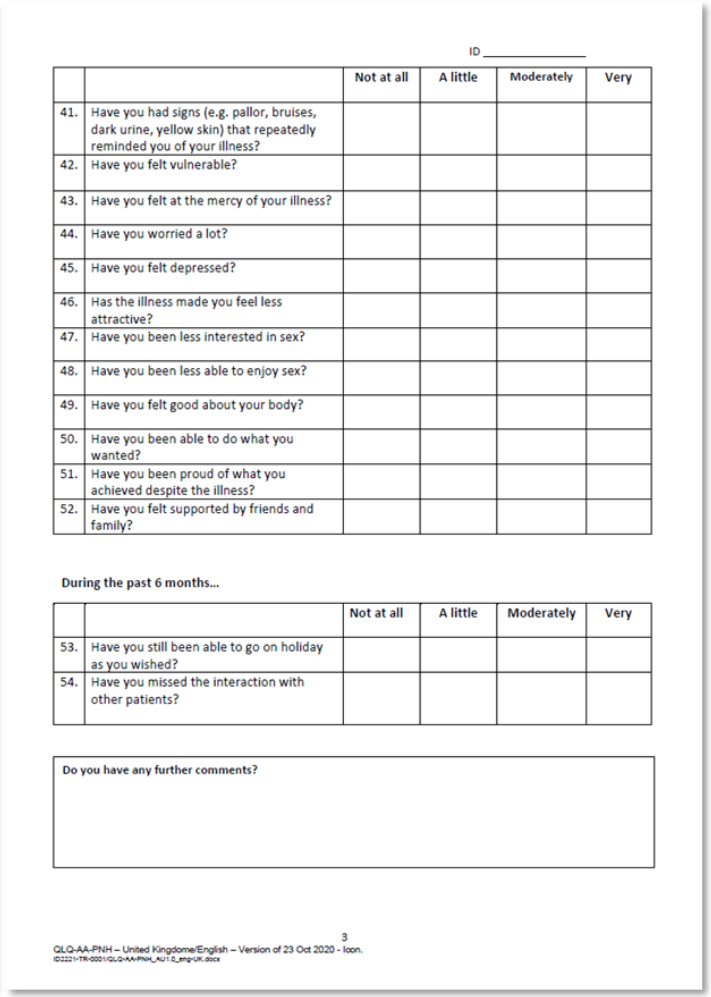
During the past 14 days…

		Not at all	A little	Moderately	Very
1.	Have you felt tired?				
2.	Have you had to rest?				
3.	Have you been exhausted for days after you exerted yourself?				
4.	Have you had difficulty getting out of bed in the morning?				
5.	Has your body felt heavy?				
6.	Has it bothered you that you had to look out for minor symptoms because they could mean something bad?				
7.	Have you been short of breath?				
8.	Have you had a tendency to bleed?				
9.	Have you had problems with susceptibility to infections?				
10.	Have you had problems with swelling or inflammation in the mouth?				
11.	Have you had problems sleeping?				
12.	Has your everyday life been affected by pain?				
13.	Have you had difficulty standing for an extended period?				
14.	Has going for a long walk caused you difficulties?				
15.	Have you had difficulty climbing stairs?				
16.	Have your work or other daily activities been restricted?				
17.	Have you had problems coping with the household chores?				



ID _____

		Not at all	A little	Moderately	Very
18.	Has it been a problem for you to ration your strength?				
19.	Have you had no energy left for your personal life and hobbies?				
20.	Has your normal routine been disrupted?				
21.	Have you been unable to bring yourself to do things or have you been apathetic?				
22.	Have you found it a problem to give up sporting activities?				
23.	Has it bothered you that you were unable to make plans?				
24.	Has it bothered you that you were unable to be spontaneous?				
25.	Has it bothered you that you had to be careful?				
26.	Have you had to take care all the time to avoid picking up infections?				
27.	Have you had difficulty concentrating?				
28.	Have you been irritable?				
29.	Has everything revolved around your illness?				
30.	Has it bothered you repeatedly having to face up to your illness?				
31.	Have you felt that you were missing out on something in life?				
32.	Has it bothered you to be classified as ill?				
33.	Have you been troubled by thoughts of an uncertain future?				
34.	Has it bothered you that your relatives were upset by your illness?				
35.	Has it annoyed you that you had to explain yourself, e.g. why you have been unable to do this or that?				
36.	Have you been afraid of a deterioration in your blood count?				
37.	Have you been bothered by your blood count results?				
38.	Have you been afraid that therapies might not work?				
39.	Have you been concerned that there might not be any more therapy for you?				
40.	Have you been afraid of a relapse or deterioration?				



ID _____

		Not at all	A little	Moderately	Very
41.	Have you had signs (e.g. pallor, bruises, dark urine, yellow skin) that repeatedly reminded you of your illness?				
42.	Have you felt vulnerable?				
43.	Have you felt at the mercy of your illness?				
44.	Have you worried a lot?				
45.	Have you felt depressed?				
46.	Has the illness made you feel less attractive?				
47.	Have you been less interested in sex?				
48.	Have you been less able to enjoy sex?				
49.	Have you felt good about your body?				
50.	Have you been able to do what you wanted?				
51.	Have you been proud of what you achieved despite the illness?				
52.	Have you felt supported by friends and family?				

During the past 6 months…

		Not at all	A little	Moderately	Very
53.	Have you still been able to go on holiday as you wished?				
54.	Have you missed the interaction with other patients?				

Do you have any further comments?

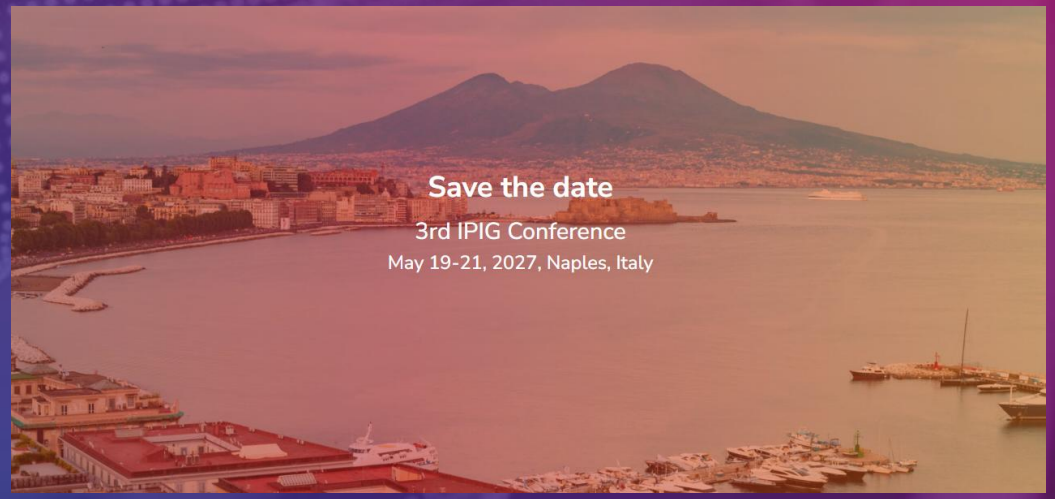
Groth M et al., Ann Hematol. 2017 Feb;96(2):171-181; Niedeggen C et al; Ann Hematol. 2019 Jul;98(7):1547-1559

Paroxysmal Nocturnal Hemoglobinuria:

COMPLEMENT AND BMFS DISCORDER
PROXIMAL AND TERMINAL CI
NEW THERAPIES – NEW DISEASE – NEW COMPLICATIONS
DIFFERENCES IN AVAILIBILITY; REIMBURSEMENT; TREATMENT STRUCTURES

CASES CAN BE PRESENTED/DISCUSSED ONLINE VIA TEAMS EVERY LAST THURSDAY/MONTH –
jschifflers@ukaachen.de; jpanse@ukaachen.de

IPIG guidelines



THANK YOU for your time

webinar

www.eurobloodnet.eu

@ERNEuroBloodNet

eurobloodnet-european-reference-network-on-rare-hematological-diseases

Eurobloodnet - European Reference Network on Rare Hematological Diseases

ERN-EuroBloodNet's EDUcational Youtube channel

Funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or European Health and Digital Executive Agency (HaDEA). Neither the European Union nor the granting authority can be held responsible for them.

Funded by the European Union