Thrombosis in PNH: Prevention and Therapy
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Disclosures:

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PICO questions and grading the evidence.

- *Population*: Patients with PNH
- *Intervention*: Anticoagulation
- *Comparison*: No anticoagulation
- *Outcome*: Thrombosis

GRADE Grading of Recommendation Assessment, Development and Evaluation

- **High**: very confident true effect close to estimated effect
- **Moderate**: true effect likely close to estimated effect
- **Low:** limited confidence that true effect lies close to estimated effect

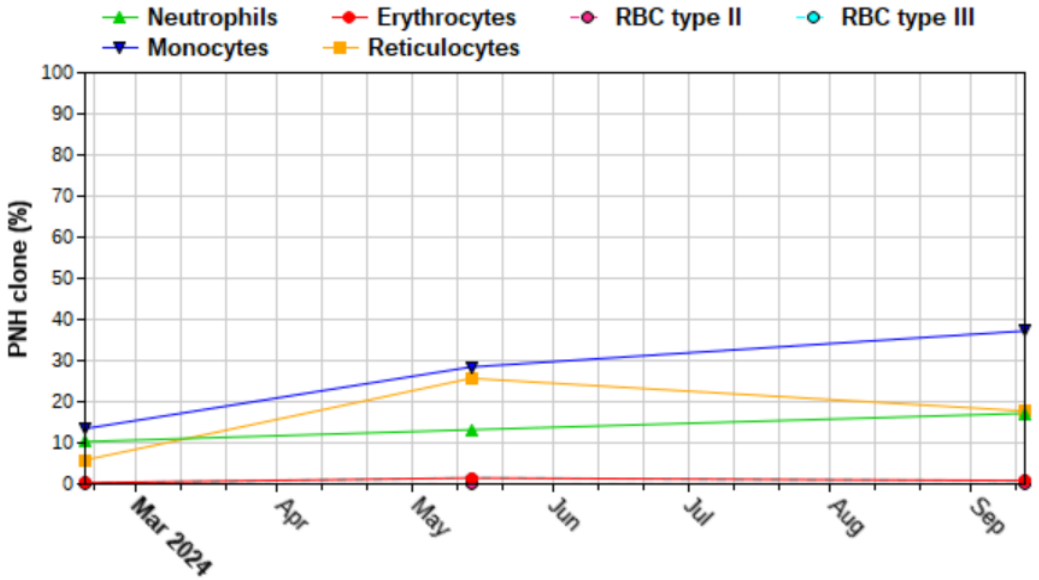
(Very low: true effect likely substantially different from estimated effect)

Prevention of thrombosis with anticoagulation (Vitamin K antagonist, LMWH, DOACS): yes or no?

Yes: if no contra -indication

- If history of PNH related-thrombosis.
- If granulocyte or monocyte clone >50% .
- In pregnancy even with a moderate clone.

GRADE Evidence ? moderate



09/09/2024: 17.17% PNH neutrophils, 37.21% PNH monocytes, 0.82% PNH erythrocytes and 17.74% PNH reticulocytes (0.57% type II and 17.27% type III cells).

Prevention: YES: Hall et al, Blood 2003; 102: 3587 – 3591.

Retrospective study: since 1997 warfarin targeting INR 2-3, if gran clone > 50% and plts>100x10.9/L. N=163 , med FU 6 yr (0.2 - 38 yrs).

Clone	**Patients**	**On anticoagulation**
>50%	97	32
≤50% / unknown	66	7

Clone > 50%:	Thrombosis (pat)	Pat yrs	Per 100 patient yrs
Before Warfarin	19	**511.5**	3.7
On Warfarin:	0	**117.8**	0

10 yr cumulative thrombosis incidence	**clone >50 *vs* < 50%**
All	34.5 : 5.3%
Not on anticoagulation	44.0 : 5.8%

EVIDENCE: Moderate

2 serious haemorrhages in 117.8 patient yrs on anti-coagulation .

Prevention: No anticoagulation in PNH

Incidence of thrombosis ? No anticoagulation??

All of France

- Socie G. et al Lancet 1996; 348: 573-577

220 patients 1950-1995: 8 yrs 28%

- Loschi *et al* AJH 2016; 91:366-370. 9.4 yrs 27%

Historical controls 191 PNH patients with indication for eculizumab before this was available.

Hammersmith Hospital London

- Hillmen *et al* 1995: 80 Pat.1940 - 1970 10 yrs 39%

Not enough info for GRADE evidence

Prevention

Cascade of thromboses progressing during sequentially fenprocoumon, nadroparine, danaparoid, aspirin, stopped with eculizumab.

Schutgens *et al* : Thrombosis and Haemostasis 2011; 106(2) 383-385

F age 43 :

- **PE** (1991) : NSAA and HAM +: PNH. Haemolysis since 1993.
  Anticoagulation 1993 - 1998. No other treatment.
- **DVT** (2003): LDH 7.5x ULN Hb 60 g/L, reticulocytes 247x10.9/L,
  90% PNH granulocytes. Anticoagulation. Transfusions 3x/yr.
- **Skin thrombosis** (2009): Complement activating event: Parvo B19 infection.

Cascade of thromboses, continued:

Day 1: Fever, arthralgia

Day 2: Purpura skin over wide expanding area, day 6 biopsy
LDH 4xULN, Hb 70 g/L, Plt 48x10.9/L

Day 14: ACS: distal occlusion right Coronary Art.

Percutaneous coronary intervention: stenting, acetyl salicylic acid, clopidrogel, aggrastat (GPIIb/IIIa receptor antagonist).

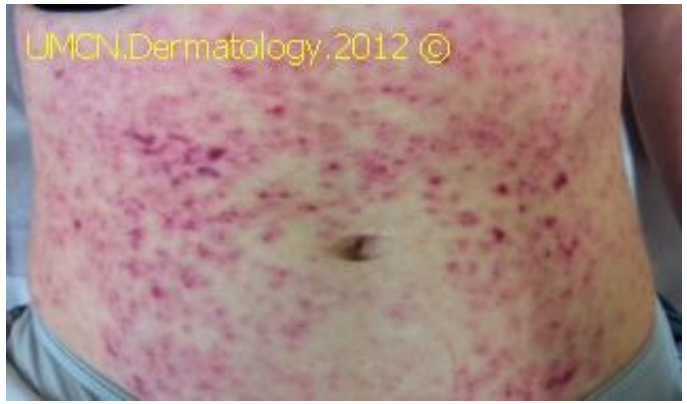
Day 18: ACS distal occlusion left Coronary Art and complete occlusion of the right Coronary Art (not in stent)

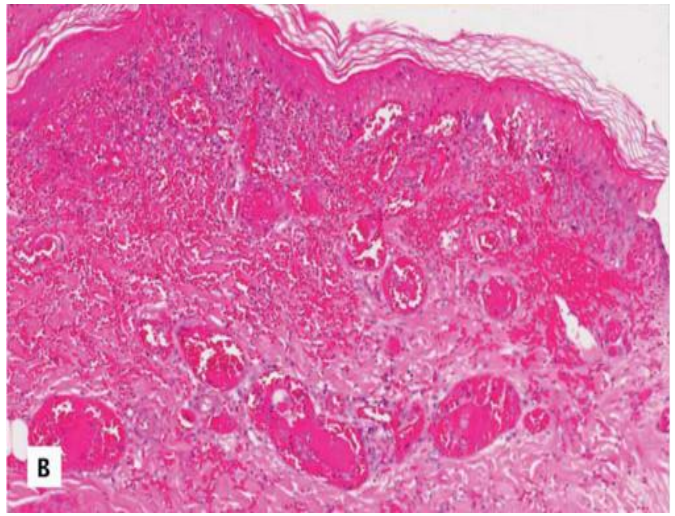
Inaccessible for intervention. GPIIb/IIIa receptor antagonist

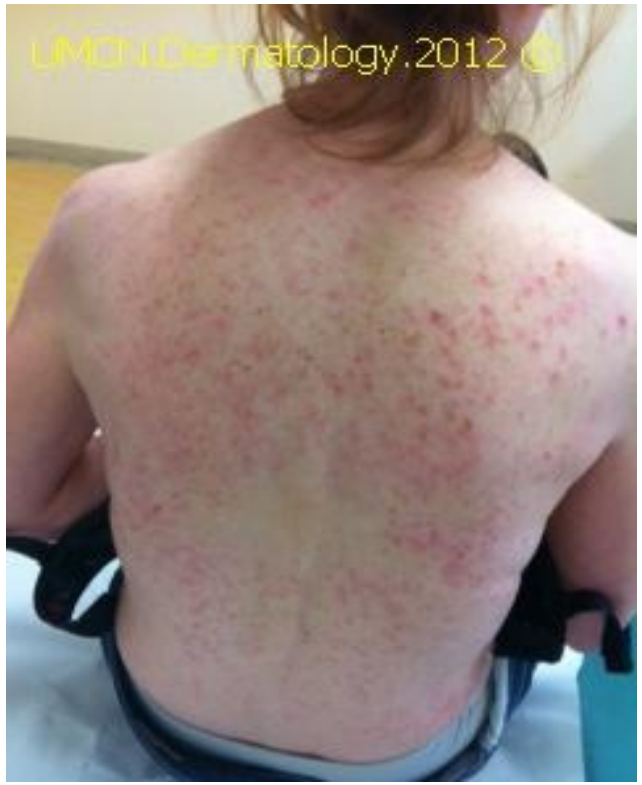
Day 19: commencement of eculizumab. End of thrombosis cascade. She is well since. Scars from deep skin thrombosis.

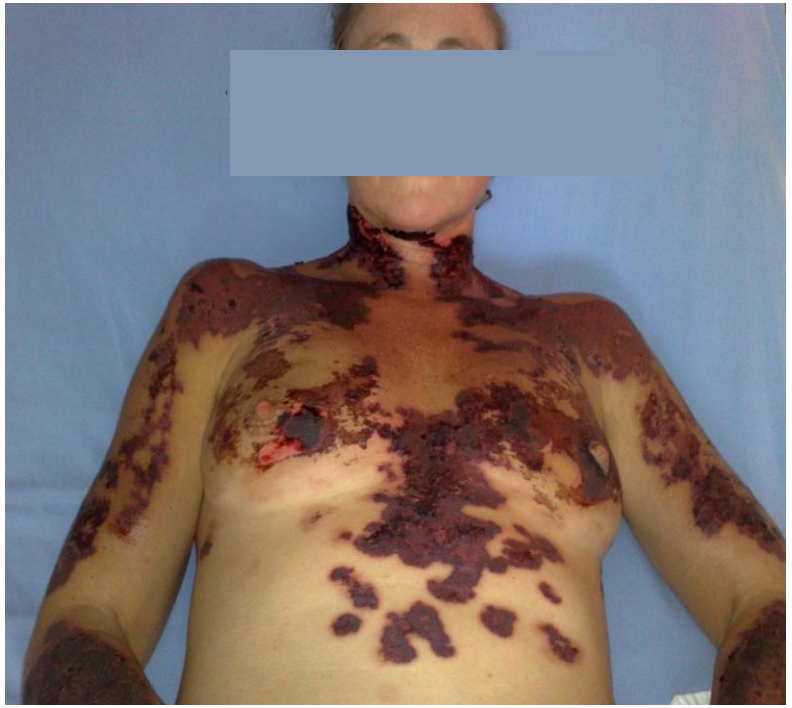
Rash since a few hrs in untreated PNH pat on vit K antagonist

Otters *et al*, Br J Dermatology, 2013









Prevention

Conclusion of PICO question: benefit from anticoagulation in untreated patients: maybe?

- Preventive anticoagulation did not prevent multiple thrombotic events.
- Multiple thromboses, both years apart and as a cascade within months in same patient.
- Parvo virus was the CAC leading to skin- and further thromboses
- C5 inhibition best option to stop thromboses

GRADE Evidence: **moderate at best**

Discussion:

More serious even if no anticoagulation?

Thrombosis different if single event *versus* cascade?

Prevention of thrombosis with eculizumab: yes or no

Yes

Loschi *et al* AJH 2016:91:366-370: 123 patients eculizumab vs 191 historical controls

No preventive anticoagulation used in France.

Follow-up

- 4.5 (2.5 – 5.6) yrs for the eculizumab group 4% TE = 5 patients
- 9.4 (2.2 – 15.9) yrs for the control group 27% TE

Prevention of thrombosis with eculizumab, and with ravulizumab? yes

Major studies:	Thrombosis incidence
Ecu: Hillmen *et al*, 2007	1.07 vs 7.37 /100 pat yrs
Ecu: Hillmen et al, 2013	2.1 vs 7.37 /100 pat yrs
Rav: Kulasekararaj *et al*, 2022**	1.21/100 pat yrs
Ecu/Rav, 20 yrs: Kelly *et a*l, 2024	0.73/100 pat yrs
Ecu/Rav , Gumari *et al,* 2024	2.1 /100 pat yrs

Note: TE considered: TEAE. Better to study freedom of TE as endpoint.

GRADE evidence: high

Prevention of thrombosis with early inhibitor Pegcetacoplan? yes or no?

Kelly et al: Res Pract Thromb Haemost. 2024 May; 8(4): 102416.

Yes

Retrospective study all clinical trials and postmarketing experience
464 patients 619.4 pat yrs 7 thrombotic events in 6 patients,
5/7 in the trials and 2/7 post marketing.

TE: 1.13 per 100 patient yrs
Clinical trials 409.4 pat yrs : 1.22/100 pat yrs
Post marketing 210 pat yrs : 0.95/100 pat yrs

Note: Pegasus patients previously on C5 inhbitors and anticoagulation likely stopped then.

GRADE evidence moderate /high

Prevention of thrombosis in other early inhibitors: No studies.

Unknown:

- Crovalimab
- Iptacopan
- Danicopan
- Others.

Prevention

anticoagulation during C5 inhibition: yes or no

Yes: if no contra-indication

- Pregnancy and ≥ 3 months until end of breast feeding (eculizumab and LMWH) .
  GRADE evidence? HIGH

- Prior thrombosis. **GRADE evidence? MODERATE**

Pregnancies before eculizumab: despite LMWH

- Maternal mortality 8 and 20.8% by thrombo embolism, post-partum.
- Fetal mortality 4 and 9% due to premature births

De Guibert *et al: Haematologica* 2011;96:1276-1283

Prevention

LMWH + Eculizumab in pregnancy + 3 months /end breast feeding

R Kelly et al: NEJM 2015;373:1032-1039

- Retrospective study: 75 pregnancies in 61 women. Prior thrombosis: 8/61
- LMWH at doses:
  - therapeutic 27/66
  - intermed 7/66
  - prophylactic 32/66
- Eculizumab start before conception (n=46), or in 2nd or 3rd trimester (29).
- Outcome:
  - Thrombosis : None during pregnancy, 2 post-partum and 2 more after stopping eculizumab postpartum, one during ongoing LMWH anticoagulation.

But: 10 haemorhages in patients on LMWH in therapeutic (n=2) or prophylactic dose (n=7) or no anticoagulation.

Prevention

Primary anticoagulation during stable complement inhibition, yes or no?

No

• Eculizumab: Hillmen *et al*, 2007	1.07/100 pat yrs
• Ravulizumab: Kulasekararaj *et al*, 2022	1.21/100 pat yrs
• C5 inhibitors, 20 yrs: Kelly *et a*l, 2024	0.73/100 pat yrs
• C5 inhibitors, Gumari *et al,* 2024	2.1 /100 pat yrs
• Crovalimab 2024	?
• Pegcetacoplan: Kelly *et al*, 2024:	? 1.13/100 pat yrs
• Add on Danicopan	!

GRADE evidence : **high** for ecu/rav and likely add on danicopan

Moderate for pegcetacoplan

Unknown for Crovalimab, Iptacopan and others:

Re-commence anticoagulation during complement inhibition at Complement Amplifying Conditions (CAC) and/or Breakthrough Haemolysis: yes or no ?

From:

- Brodsky et al Haematologica 2021; 106 (1): 230-237: Substudy into causes of BTH in Phase III randomized studies of ravulizumab vs eculizumab (trials 301 and 302).
- Dingli et al Hematology 2024; 29: No1, 2329030 , expert consensus on pharmacodynamic BTH

Outcome unknown. No known studies.

Common practise: Treat the CAC and the BTH

Discussion: Would anticoagulation “make up” for insufficient inhibition of complement?

TREATMENT of Thrombosis

Role of thrombolysis /intervention in Thrombosis in PNH: yes or no.

YES

- Araten *et al,* 2012, Haematologica: Thrombolysis 9 pat cases + lit rev.

  Severe cases up to 6 weeks after first symptoms and worsening despite anticoagulation.

- Percutaneous transluminal angioplasty or TIPS when patient presents with Splanchnic Vein Thrombosis (SVT). Elkrief et al, 2023, vol 5 100667. review .

- Stroke or Myocardial infarction: BMJ trial comparing intra thrombus thrombolysis and aspiration thrombectomy: ongoing. MBJ Open 2023 13(11) e076476.

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GRADE evidence: Moderate

D Araten et al, Haematologica 2012. 2012;97(3): 344-352
Pat 2, 8 and 9 on anticoagulation prior to thrombotic event.
1985-2009: reported 15 pat: tPA (6),Urokinase (6), Streptokinase (3)

Table 1B

Patients who received thrombolytic therapy: clinical course.

Pt	Presentation of thrombotic episode	Sites of thrombosis	Estimated onset before tPA	Total n. of courses of tPA[a]	N. of admissions for tPA	Sites of hemorrhage	Initial radiological response[b]	Long-term treatment after tPA	Eventual outcome[c]	Current status	N. of years follow
1	Massive ascites, deep jaundice	HV, PV, IVC, SV	6 wks	5	1	Flank	PR	Warfarin	CR	Excellent	4.5
2	Abd pain and HA	PV, SV, IVC, HV, SS	1 wks	3	2	None	CR	LMWH→ fondaparinux, eculizumab	CR	Excellent	7.5
3	Abd pain	PV, HV	4 wks	2	1	Subcutaneous	nCR	Warfarin, eculizumab	nCR	Excellent	7
4	Vomiting, distention jaundice	TVS, JV, IVC, RV, HV, SMV	2 wks	3	1	SDH	nCR	NA	Died	Died	--
5	Renal failure	RV, JV, IVC,SCV	Few wks	2	1	Vaginal bleeding	Impr	Warfarin, LMWH, eculizumab	nCR	Excellent	13
6	Abd pain	HV	Few wks	3.5	1	SDH, mesenteric	PR	NA	CR[e], Died	Died	--
7	Abd pain	HV	Few wks	1.5	3	Pleural effusion, epistaxis	CR	Fondaparinux, eculizumab	Partial Budd Chiari	Excellent	4
8	Budd-Chiari	IVC, HV	Few days	4	4	CNS	PR	LMWH[g] eculizumab	Recurrent relapses	Good	4
9	Budd-Chiari	PV, HV	1 month	3	1	Psoas muscle	PR	Fondaparinux, eculizumab	PR	Died[f]	1

Abd: abdominal; wks: weeks; HV: hepatic vein; PV: portal vein; SV: splenic vein; JV: jugular vein; SMV: superior mesenteric vein; RV: renal vein; TVS: transverse sinus; SS: sagittal sinus; SCV: subclavian vein; CR: complete resolution; PR: partial resolution; nCR: near complete resolution; Impr: improvement; SDH: subdural hematoma; LMWH: low molecular weight heparin; HA: headache. [a]Total number of 24 h infusions administered during initial presentation; [b]initial response during first hospitalization; [c]eventual radiologic outcome of initial thrombosis; [d]years of clinical follow-up after the initial tPA infusion; [e]patent on post- mortem examination [f]elevated WBC, progression to chronic neutrophilic leukemia associated with acquired JAK2 mutation, treatment with decitabine, iron overload; [g]LMWH was discontinued after his bleeding complications, and he has been stable on eculizumab since then.

Treatment of thrombosis:

Prompt eculizumab: yes or no

- **Yes**: **GRADE evidence: high**

Discussion: prompt= same or next day, or within n weeks.

Discussion

- Same day commencement eculizumab if thrombosis
- If C5 inhibitor is available, could suction /thrombolyse/stenting be omitted in MI, Splanchnic Vein Thrombosis or Stroke
- Continue anticoagulation in stable early complement inhibition / newer C5 inhibition.
- How to study “freedom of thrombosis” as an “endpoint” in complement inhibitor studies.
- Cascade of thromboses and isolated thrombosis: different pathophysiology?