

PNH: Long-Term and Post-Treatment Issues

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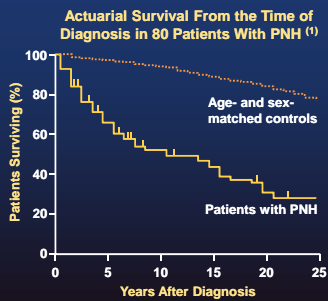
PNH: Long-Term and Post-Treatment Issues

- What are the long-term complications of PNH?
- What are the known complications of different PNH therapies?
- What are some special situations for PNH patients?
 - Pregnancy
 - Surgery
 - Vaccinations

PNH – Long-term outcomes

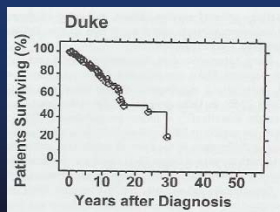


Paroxysmal Nocturnal Hemoglobinuria: Long term outcomes



(1) Hillmen P et al. NEJM 1995; 333:1253-8;

Paroxysmal Nocturnal Hemoglobinuria: Long term outcomes



Kaplan-Meier Survival Curve of patients with PNH from Duke University (n=173). Average survival was 19.4 years.

Nishimura et al. Medicine 83: 193-207, 2004.

PNH – What do patients die from?

Cause of death	Duke	Japan
Thrombosis	16 (42%)	3 (8%)
Abd site	8	1
Other site	7	0
Arterial	3	2
Hemorrhage	4 (10.5%)	9 (24%)
Severe Infection	14 (36.5%)	14 (36.8%)
MDS/AML	3 (8%)	6 (16%)
Renal failure	3 (8%)	7 (18%)
Other malignancy	2 (5%)	2 (5%)
Unknown	2 (5%)	0

Nishimura et al. Medicine 83: 193-207, 2004.

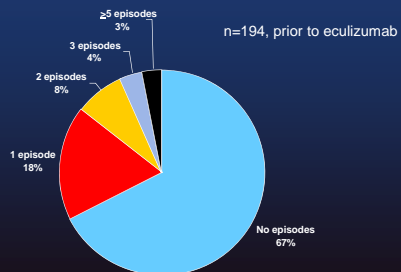
PNH - Thrombosis

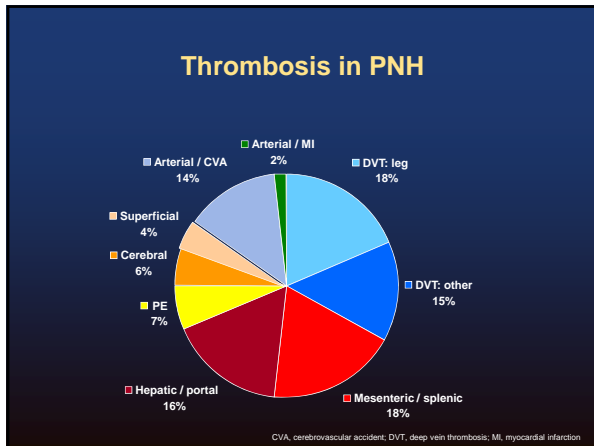


Thrombosis in PNH

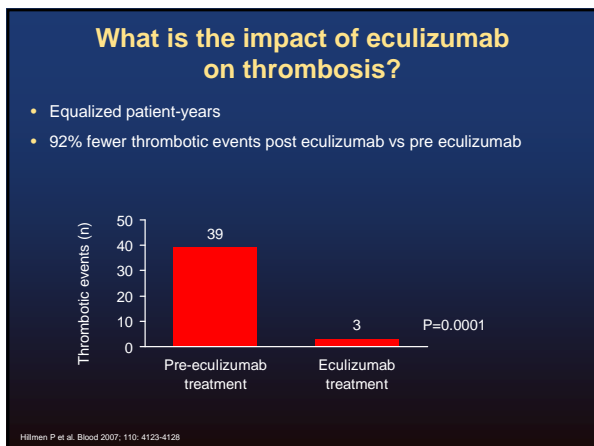
- Recognized early as a problem
- Occurs in ~40% of European-descended populations
 - much less in East Asian populations
- Is the worst prognostic indicator
- Is the leading cause of death
- Once a thrombosis occurs, no clear evidence that any anticoagulant will prevent further clots

Incidence of thrombosis in PNH



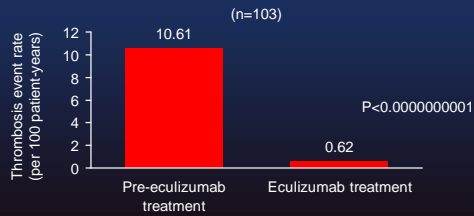


- ### Peculiarities of thrombosis in PNH
- Incidence may be much higher
 - small, undetectable thromboses
 - D-dimer data
 - Once established, tends to recur and continue
 - inexorable course of hepatic vein thrombosis
 - Incidence much lower in East Asian populations
 - includes Mexican population
 - Role of surgery and pregnancy in initiating thrombosis



Effect of eculizumab on thromboembolic event rate: concomitant antithrombotics

- Pre-eculizumab event rate elevated despite use of antithrombotics
- 91% reduction in event rate with eculizumab



Hilmen P et al. Blood 2007; 110: 4123-4128

Will Eculizumab affect survival by lowering the incidence of thrombosis?

We don't know but we certainly hope so.

Please enroll in the International PNH registry.

PNH – Renal Failure



Background Renal Damage in PNH

- Chronic hemolysis and cell-free plasma hemoglobin lead to chronic kidney disease in PNH ^(1,2)
- Renal damage in PNH may be due to repetitive exposure of tissue to cell-free hemoglobin ^(3,4)
- 64% of patients with PNH have stage 1-5 chronic kidney disease ⁽⁵⁾
- Renal failure has been identified as the cause of death in approximately 8 – 18% of PNH patients ^(6,7)

(1) Parker C et al. Blood 2005;106:3699-3709; (2) Rother RP et al. JAMA 2005;293:1653-1662; (3) Clark DA et al. Blood 1981;57:83-9; (4) Hillmen P et al. NEJM 1995; 333:1253-8; (5) Hillmen P et al. Blood 2007;110(11):3678; Poster at American Society of Hematology 49th Annual Meeting; (6) Nishimura JI et al. Medicine 2004;83:193-207; (7) Rosse and Nishimura. Int J Hematol 2003;77:113-20.

Evidence of renal sequelae by MRI in PNH

- MRI studies show virtually all PNH patients with low-intensity signal in renal cortex, including PNH patients with:
 - low levels of hemolysis
 - aplastic anemia
 - MDS
 - no hemoglobinuria
 - smaller PNH clones
- MRI findings are typical of intravascular hemolysis and are not typically found with extravascular hemolysis

Mathieu D et al. Blood 1995; 85: 3283-3288;
Rimola J et al. Br J Radiol 2004; 77: 953-956;
Hakim F et al. Blood 1996; 88: 4725-4729;
Suzukawa K et al. Intern Med 1993; 32: 686-690

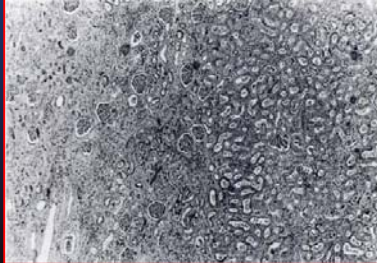
Autopsy and functional findings in PNH

- 8–18% of mortality in PNH
- Autopsy or biopsy findings with:
 - heavy hemosiderin accumulation in the proximal tubules
 - hemoglobin tubular casts
 - signs of chronic interstitial nephritis and fibrosis
- Functional tubular defects are commonly found with:
 - impaired ability to concentrate urine
 - medullary microinfarction or inability of tubular epithelium to sustain maximum osmotic gradient
 - renal tubular acidosis
 - decreased reabsorption of phosphate
 - aminoaciduria

Nishimura J et al. Medicine 2004; 83: 193-207; Mulopulos GP et al. AJR Am J Radiol 1986; 146: 51-52; Nguyen JS et al. N Engl J Med 2006; 355: 1048-1052;
Clark DA et al. Blood 1981; 57: 83-89; Riley AL et al. Am J Med 1977; 62: 125-129; Zachée P et al. Clin Nephrol 1993; 39: 28-31;
Naim K et al. Kidney Int 2001; 60: 106-117

Renal pathology in PNH

Micrograph of a renal biopsy from a PNH patient, indicative of vascular damage



Interstitial scarring on the left

Normal tissue on the right

Clark DA et al. Blood 1981; 57: 83-89

CKD stages

- Stage 5 GFR <15 mL/min/1.73 m²
- Stage 4 GFR 15–30 mL/min/1.73 m²
- Stage 3 GFR 30–60 mL/min/1.73 m²
- Stage 2 GFR 60–90 mL/min/1.73 m² and evidence of kidney damage, which may include spot urinalysis with proteinuria or by abnormal imaging findings
- Stage 1 GFR >90 mL/min/1.73 m² and evidence of kidney damage, which may include spot urinalysis with proteinuria or by abnormal imaging findings

Renal Function in PNH: Conclusions

- Changes in renal function are common in PNH (65% of PNH patients; 6.6-fold more common than in the general population)¹
- Severe CKD is observed in 21% of PNH patients and appears to be under-diagnosed in this patient population
- 21% of patients with CKD prior to eculizumab were no longer classified with CKD during eculizumab treatment
- Administration of eculizumab to patients with more mild baseline kidney disease was associated with the greatest likelihood of improvement and prevention of worsening in kidney function
- Long-term eculizumab treatment resulted in a significant improvement and prevention of worsening in CKD at all initial stages of renal disease

1. Stevens, LA, et al., *N Engl J Med*. 2006;354:2473-83.
Hillman et al. *Blood*. 2007 Abstract 3678; High Incidence of Progression to Chronic Renal Insufficiency in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH).

Pulmonary Hypertension in PNH



Hemolysis-associated pulmonary hypertension

- An important complication in hereditary hemolytic anemias such as thalassemia, stomatocytosis, and spherocytosis
- A common morbidity in sickle cell disease
- Linked to intravascular hemolysis, leading to the term 'hemolysis-associated pulmonary hypertension' (PHT)
- An independent risk factor for death in sickle cell disease

Gladwin MT et al. N Engl J Med 2004; 350: 886-895

Brain natriuretic peptide

- Elevated levels of BNP:
 - released from stretched right heart chambers
 - reflect cardiac chamber volume and pressure overload
 - indicate increased PHT and right ventricular dysfunction
- In patients with hemolytic syndrome, NT-proBNP ≥ 160 pg/mL:¹
 - is a highly positive predictive value for diagnosis of PHT
 - is an independent predictor of mortality
- TRIUMPH study: 47% of PNH patients had baseline levels of NT-proBNP ≥ 160 pg/mL²
- Suggestive of PHT

¹Machado RF et al. JAMA 2006; 296: 310-318;
²Hillmen P et al. N Engl J Med 2006; 355: 1233-1243

BNP, brain natriuretic peptide

Pulmonary Hypertension - Summary

- PHT is a serious and life-threatening complication of hemolytic disorders
- PHT and PNH symptoms are common in patients with hemolytic PNH
- PHT may be under-diagnosed clinically in patients with PNH
- Hemoglobinemia, NO consumption, and disruption of vasomotor tone contribute to PHT in patients with PNH
- Eculizumab treatment significantly reduces PHT, as measured by BNP, and PHT-related symptoms in patients with PNH
- Eculizumab treatment dramatically reduces hemolysis, hemoglobinemia, and NO consumption in patients with PNH

Complications of PNH Therapy



Complications of PNH Therapy

- Eculizumab
 - Neisseria infection
 - Cost and convenience
- ATG/Cyclosporine
 - Hospitalization
 - Anaphylactic reactions
 - Serum sickness
 - Immunosuppression / Infection
- Bone marrow transplantation
 - Allogeneic bone marrow transplant
 - Prolonged hospitalization
 - Up to 44% mortality at 2 yrs with HLA-matched sibling donor
 - Acute GVHD in 34%; chronic GVHD in 33%
 - GVHD-free survival in 14% of patients

Special Situations in PNH

- Vaccinations
 - May activate complement
 - Role for Eculizumab
- Surgery
 - May activate complement
 - May lead to thrombosis
 - Role for Eculizumab
- Pregnancy



PNH and Pregnancy

PNH is a known hypercoagulable state

Pregnancy is a hypercoagulable state

High estrogen levels

Compression of abdominal and pelvic veins by the enlarging uterus

PNH and Pregnancy

De Gramond et al., Lancet 1987;1:868

23 women: 19 with PNH, 4 with AA/PNH

38 pregnancies

11 miscarriages

Pregnancy: 6 hemolysis, 6 hemorrhage

Labor: 5 hemolysis, 3 hemorrhage

1 thrombosis, 1 sepsis

No maternal deaths

Uncomplicated in one-third of pregnancies

Women with PNH Effects on Pregnancy

Ray et al., Haemostasis 2000; 30: 103-117

Thrombosis: 5 women

- 2 with previous clots (Budd-Chiari syndrome, pulmonary embolus)
- 1 during pregnancy (phlebitis)
- 2 post-partum (hepatic, intracranial)

Hemolysis: 24 pregnancies (73%)

20 required PRBC transfusions

Thrombocytopenia: 9 cases

Obstetrical complications: 4 women

Hypertension, pre-eclampsia, eclampsia

Women with PNH Effects on Infants

Ray et al., Haemostasis 2000; 30: 103-117

Perinatal outcomes of 33 pregnancies

45% of the babies were pre-term

Average birthweight 2800g

Three infant deaths

Two had hemolytic disease of the newborn, not related to PNH

No infant thrombosis

PNH and Pregnancy Summary

Pregnancy is possible for women with PNH, with or without aplastic anemia, but is potentially hazardous for mother and infant.

Pregnancy leads to complications in up to 50% of women: worse cytopenia, transfusion dependency, thrombosis, and the need for anticoagulation or immunosuppressants

Pregnancy for women with PNH is risky, and should be planned carefully with an experienced hematologist and high-risk OB.

There is emerging data on the use of Eculizumab in pregnancy.
