PNH: Current Thinking on the Disease, Diagnosis, and Treatment

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What is Paroxysmal Nocturnal Hemoglobinuria?

- What is a clone?
- What is complement?
- Why does a defect in complement regulation cause problems?
- What are the clinical problems
- What can be done about it?

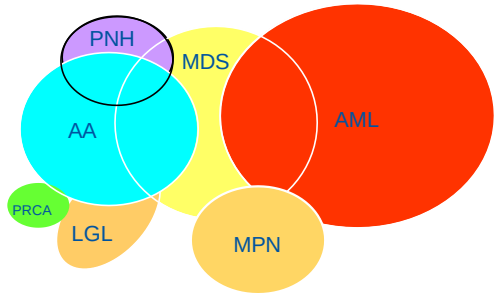
What is PNH?

- PNH is a disease of chronic complement-mediated cellular injury
- Due to the acquisition of a mutation in the PIG-A gene resulting in loss of the normal complement inhibitors (e.g. CD55 [DAF] and CD59 [MIRL]) on cell surfaces

PNH: What it is Not

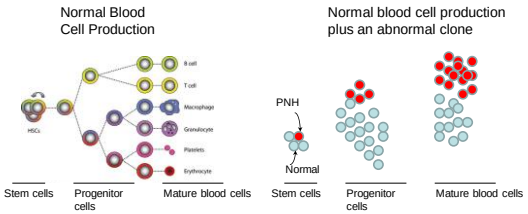
- It is not paroxysmal
- It is not usually nocturnal
- Hemoglobinuria is a less commonly seen complication

PNH Can CoExist with Other Blood Disorders



Young NS. *Ann Intern Med.* 2002 Apr 2;136(7):534-46

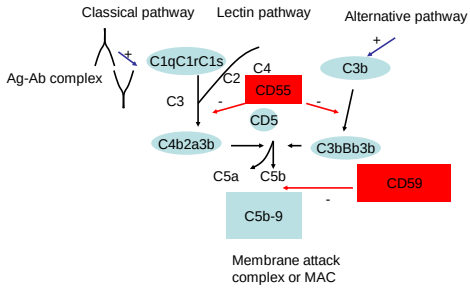
PNH Cells are Derived from a Single Mutated Stem Cell or Clone



Complement System: Always on, Amplified, Dependent on Natural Regulators

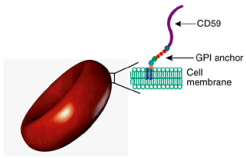
- The complement system is a vital component of the natural (innate) protective immune system
- Complement is activated by three mechanisms (classical, alternative, and lectin)
- Always 'on' to allow rapid immune response
  - Rapid amplification leads to powerful immune reactions
  - Natural inhibitors of complement keep amplification in check and prevent uncontrolled complement activation

Complement Cascade – Mechanism to Help Antibodies Kill Bacteria

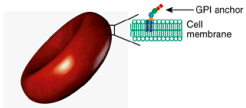


Complement Must be Regulated

- CD59 (Membrane activator of reactive lysis or MIRL)
- CD55 (Decay accelerating factor)
- These keep the complement system from getting out of control
- Particularly important in "tick-over" or nonspecific activation of complement
- Increase in complement activation in infection, trauma, surgery, inflammation

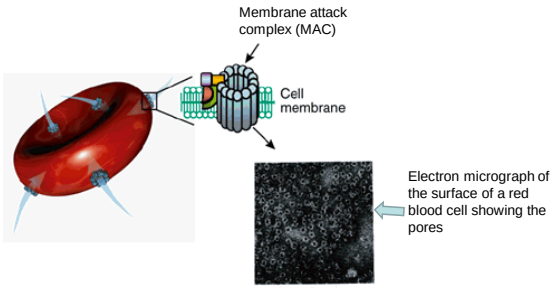


- CD55 and CD59 are responsible for maintaining the integrity of the membrane
- Attached via the GPI anchor. These proteins protect the cells from complement



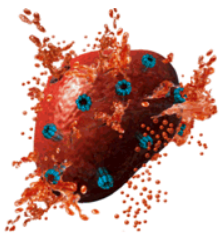
- If the GPI anchor does not form correctly, the protective proteins are lost and the cell becomes susceptible to complement
- This results from a mutation in a gene called PIG-A (phosphatidylinositol glycan class A)

Adapted from: Rother RP,. *Nature Biotechnol 2007*;**25:**1256-64



In PNH the loss of protection via CD55 and CD59 results in complement organizing itself into channels or pores that allow water to enter the cells

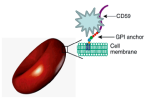
Rother RP (2007)



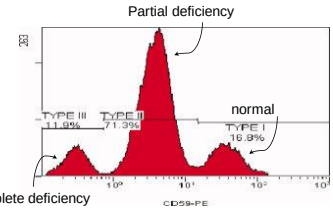
- Too much water enters the cell causing the cell to burst.
- This is called **intravascular hemolysis**
- Anemia due to hemolysis is a hemolytic anemia
- Hemoglobin is released into the plasma where it does not belong
- The urine may turn dark from the hemoglobin - hemoglobinuria

Dacie & Lewis. *Sem Haemat.* 1972
Rosse. 2000
Hillmen, et al. *New Engl J Med.* 1995

Clones are Detected by Flow Cytometry



A fluorescent antibody that recognizes CD59, CD55 or FLAER that recognizes GPI are bound to the cells

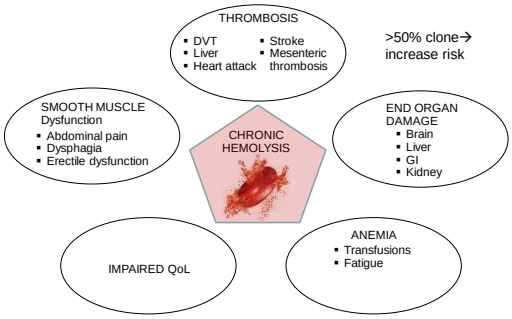


Borowitz MJ, et al. Cytometry B Clin Cytom. 2010l;78:211-30.

Epidemiology

- <2-5 cases per million in USA
- Female = male
- Median age – 30-40 yrs (6-82)
- Cause is unknown
  - Many healthy people have tiny clones that can only be detected experimentally
  - Immunologic inhibition of healthy stem cells may leave the PNH clones behind
- May be primary or may occur after immunosuppressive therapy for aplastic anemia
- Small clones are common in myelodysplastic syndrome

Symptoms of PNH



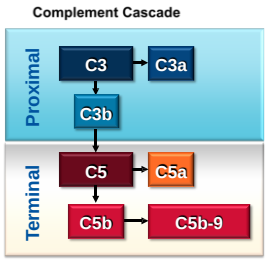
Major Complications of PNH

Clinical signs or symptoms	Incidence Rate (%)
Thrombosis	40%
Anemia	90%
Aplastic anemia	10-45%
Fatigue	96%
Hemoglobinuria	30%
Abdominal Pain	60%
Dysphagia	40%
Erectile Dysfunction	50%
Chronic Renal Insufficiency	30%

Management Options for PNH

- Depends on severity of symptoms and clone size
  - Not everyone needs to be treated
- Supplements
  - Folic acid
  - Iron
- Transfusions
- Anticoagulants
- Steroids/androgen hormones
- Eculizumab – anti-C5, prevents MAC complex
- Allogeneic bone marrow transplant

Eculizumab Blocks Terminal Complement



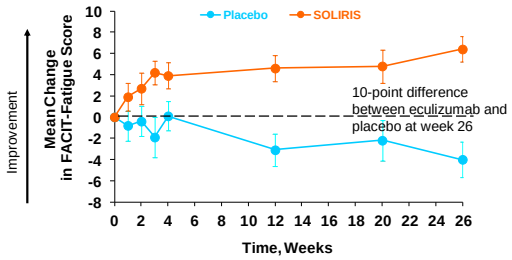
Soliris

- Eculizumab binds with high affinity to C5
- Terminal complement - C5a and C5b-9 formation blocked
- Proximal functions of complement remain intact

Eculizumab - Soliris

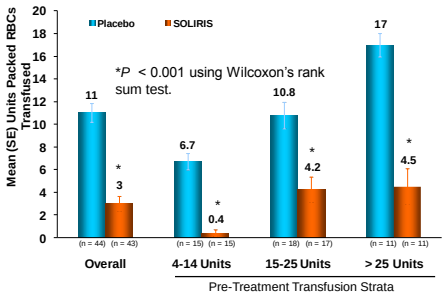
- Monoclonal antibody to C5
- Prevents the late steps of complement activation and thus the MAC complex
- Therefore there is less intravascular hemolysis
- However the complement system is inhibited and there is an increase risk of certain infections
  - Particularly meningococcus

Improvement in Fatigue

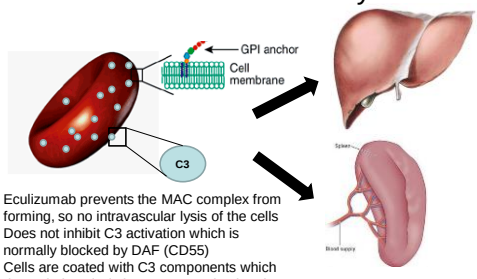


FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue instrument.

Reduced Transfusions Due to Intravascular but not Extravascular Hemolysis



Eculizumab Does Not Prevent Extravascular Hemolysis



- Eculizumab prevents the MAC complex from forming, so no intravascular lysis of the cells
- Does not inhibit C3 activation which is normally blocked by DAF (CD55)
- Cells are coated with C3 components which do not induce lysis but are recognized and removed from the circulation by liver and spleen – extravascular hemolysis

Eculizumab Treatment Expectations

- 1 week
  - Reduction in hemolysis and fatigue
- 2-3 weeks
  - Improvement in shortness of breath
- 2-6 months
  - Reduction in transfusion frequency
- More than 6 months
  - Stabilization with improved quality of life

Adverse Reactions Reported in ≥ 5% of Eculizumab Treated Patients in TRIUMPH

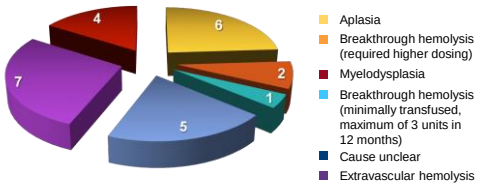
Reaction	Patients, n (%)	
	Soliris (n=43)	Placebo (n=44)
Headache	19 (44)	12 (27)
Nasopharyngitis	10 (23)	8 (18)
Back pain	8 (19)	4 (9)
Nausea	7 (16)	5 (11)
Fatigue	5 (12)	1 (2)
Cough	5 (12)	4 (9)
Herpes simplex virus infections	3 (7)	0
Sinusitis	3 (7)	0
Respiratory tract infection	3 (7)	1 (2)
Constipation	3 (7)	2 (5)
Myalgia	3 (7)	1 (2)
Pain in extremity	3 (7)	1 (2)
Influenza-like illness	2 (5)	1 (2)

Hillmen P, et al. *NEJM.* 2006;355:1233-1243.

Summary of Clinical Efficacy

- 86% sustained reduction in hemolysis as measured by LDH
- 92% reduction in thrombotic events
- 73% reduction in transfusion requirements across all patient populations
- 78% clinically meaningful improvement in fatigue
- Improved dyspnea

Reasons for Transfusion in 25 Patients in Leeds Not Transfusion Independent

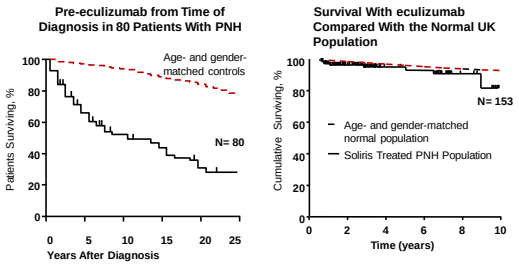


25 patients still requiring transfusions:

The mean number of transfusions fell significantly from 24.6 units (range 4-44) to 11.4 units (range 2-45), *P*=0.0002

Hill A. ASH 2012.

Paroxysmal Nocturnal Hemoglobinuria:



Despite best supportive care - 5 year mortality: 35%[1]

Hillmen P et al. *N Engl J Med.* 1995;333:1253-1258.
Kelly RJ et al. *Blood.* 2011;117:6786-6792 3.
Hillmen et al. *Br Jnl Haematol.* 2013;162:62-73

Eculizumab

Benefits

- Reduces intravascular hemolysis
- Reduces transfusion requirement
- Improves symptoms
- Reduces the risk of thrombosis. Unclear if anticoagulation is required
- Reduces mortality

Limitations

- Does not prevent extravascular hemolysis
- Does not treat aplastic anemia
- Frequent infusions
- Risk of meningococcal meningitis
- Intrinsic resistance to eculizumab due to altered C5 found n 3.5% of Japanese patients and occasional others

Meningitis Vaccines

- Meningitis ACYW135 (Quadrivalent Vaccines)
  - MenHibrix (Hib-Men CY-TT) BIVALENT children 6 weeks-18 mos
  - Menveo (Men ACWY-CRM) 2 months-55 years of age
  - Menactra (Men ACWY-D) 9 months-55 years of age
  - Menomune (MPSV4) polysaccharide
    - allergic reactions
    - Older than 55
    - No mucosal immunity
    - Duration of immunity less than 3 years—no memory T cells
- **Meningitis B**
  - Bexsero (Novartis) 10-25 years of age
    - 2 dose series (0 and 1-6 months)
  - Trumenba (Pfizer) 10-25 years of age
    - 3 dose series (0,2, and 6 months)

Stem Cell Transplantation

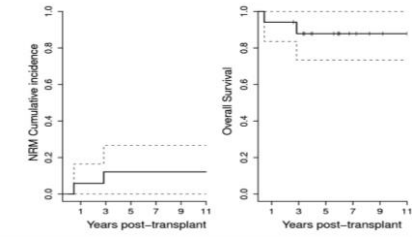
Benefits

- The only curative therapy
- No further infusions
- Less expensive

Limitations

- Donor availability
- Transplantation related complications
  - Graft rejection
  - Graft-vs-Host disease
  - Infection
- Susceptibility to infection results in limited ability to be in public for about 1 year

Stem Cell Transplantation is Curative for PNH



Pantin, et al. BBMT 2014;20:1435-9

Summary

- Acquired loss of complement regulatory components
- Anemia, thrombosis, risk of renal and pulmonary injury
- Associated with aplastic anemia and MDS
- Controlled with eculizumab
- Cured with marrow transplantation