

## Treating PNH

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### How do we treat PNH?

- Hemolytic anemia
  - Iron, folic acid
  - Transfusion
  - Steroids
  - Eculizumab
- Thrombosis
  - Coumadin prophylaxis
  - Acute treatment with lytic agents (clot busters)
  - Anticoagulation therapy
  - Bone marrow transplantation
  - Eculizumab
- Bone marrow failure
  - Stimulating agents such as erythropoietin
  - Immunosuppressive agents (ATG, cyclosporine A)
  - Bone marrow transplantation

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## SOLIRIS™ (eculizumab)

**SOLIRIS is a complement inhibitor indicated for the treatment of patients with PNH to reduce hemolysis**

**SOLIRIS is the first FDA approved therapy for PNH**

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### What does Eculizumab do?

- Quickly and effectively blocks complement activation.
- Blocks hemolysis and related effects
- Stops hemoglobinuria
- Markedly reduces transfusion requirements
- Hemoglobin / hematocrit may not return to “normal”

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### Possible long term effects of Eculizumab

- Improve kidney function
- Improve hypertension
- Prevent pulmonary hypertension
- Increase survival

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### TRIUMPH: Results

All 1<sup>o</sup> and 2<sup>o</sup> endpoints met with statistical significance

Parameter	Placebo (n = 44)	Eculizumab (n = 43)
LDH levels at end of study, median (U/L) (range)	2,167 (1183 - 5643)	239* (142 - 2984)
Packed RBC units transfused per patient, median (range) †	10 (2 - 21)	0* (0 - 16)
Transfusion avoidance, %	0	51*
Patients with stabilized hemoglobin levels, †	0	49*
Free hemoglobin at end of study, median, (mg/dL) (range)	62 (0.7 - 386)	5* (3 - 194)

\*P < 0.001; † denotes co-primary endpoints

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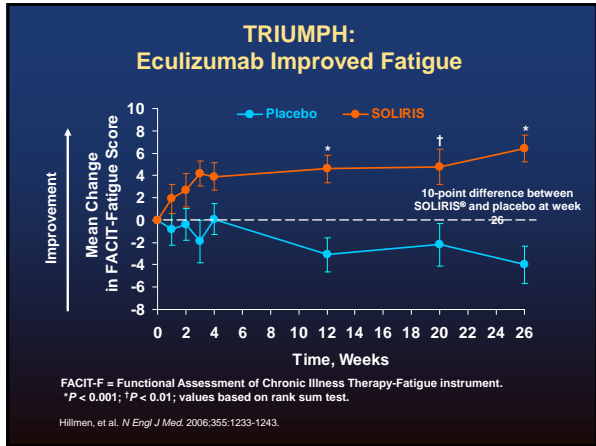
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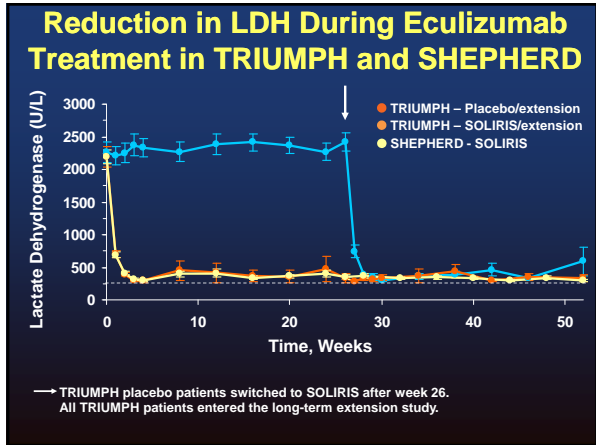
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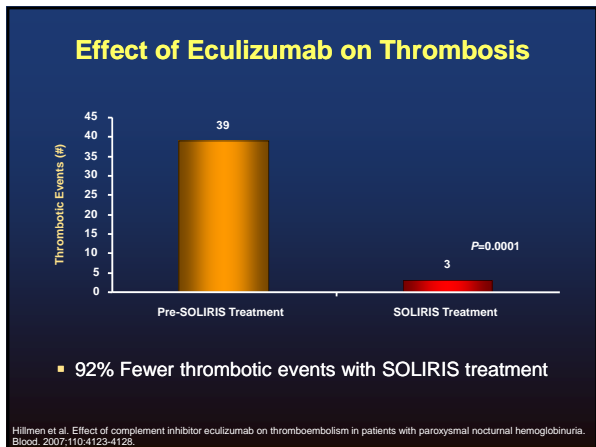
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### What Eculizumab Does Not Do

- Probably does not help bone marrow failure (improve other low blood counts)
- Completely correct anemia
  - Bone marrow failure (poor production)
  - Extravascular hemolysis
- Teach you how to play the violin if you have never played before

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### Who should receive Eculizumab?

- PNH patients with symptomatic hemolytic anemia
- PNH patients with thrombosis

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### Downside of Eculizumab treatment

- Increased risk of meningococcal infections
  - All patients must be vaccinated
  - All patients educated on signs and symptoms of meningitis and what to do
  - All patients given cards describing this
- Cost
- Inconvenience
  - Must be given intravenously every 12-14 days

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## Summary of Clinical Efficacy

- In clinical trials, Eculizumab significantly reduced hemolysis the underlying cause of morbidity and mortality in PNH
  - 86% reduction in hemolysis (as measured by LDH)
  - 92% reduction in thrombotic events
  - 73% reduction in need for transfusions across all patient populations
  - 78% reduction in fatigue, significant improvement in a broad range of QoL measures
  - Adverse events with Eculizumab were similar to placebo
- Eculizumab does not treat the bone marrow failure associated with PNH.
- Eculizumab does not completely restore the hemoglobin to normal values.

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## CONTROVERSIAL MANAGEMENT PROBLEMS

- **Decision to start Soliris?**
  - Moderate anemia, no thrombotic events
  - Size of the PNH clone?
- **Decision to start anticoagulation?**
  - No history of thrombotic events but a large PNH clone
- **Decision to stop anticoagulation in patients who started Soliris?**
  - Antithrombotic value of Soliris
- **Who should be transplanted?**
  - Donor, age, severity, potential for cure vs. risk

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## Where are we going?

- Improve current therapy
  - Oral eculizumab
  - Increase treatment intervals
  - Understand extravascular hemolysis
- Find other ways to inhibit complement
- Understand how PNH cells take over the bone marrow so we can reverse this process (Restore normal stem cells)
- Improve our understanding of what leads to blood clots (and can prevent blood clots)
- Gene therapy
- Stem cell transplants

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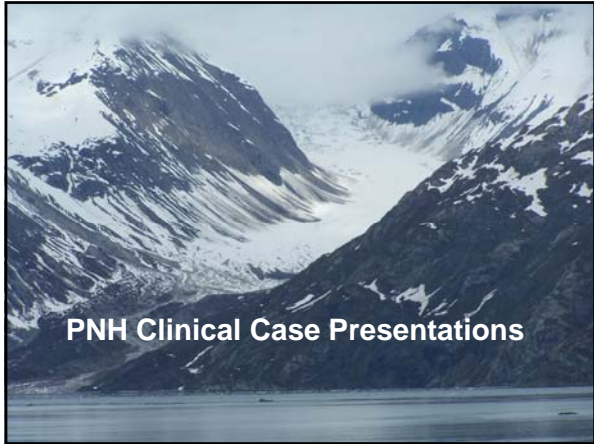
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**PNH Case Presentations  
Case 1**

- 41 y/o WF transferred to DUMC on 4/25/09 with pleural effusion, abdominal distention.
- Prior history of 4 miscarriages, "Crohn's disease"
- March 2006 develops HELLP syndrome during pregnancy, undergoes stat C-section.  
H = hemolysis  
EL = elevated liver enzymes  
LP = low platelets
- Post op course very complicated. Ultrasound shows heterogenous liver with reversal of portal venous flow. Develops DVT at PICC site. Treated with 6 months warfarin.
- As outpatient undergoes workup of hemolysis, no clear cause found.

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**Case 1**

- October 2008 develops marked abdominal pain. CT scan of abdomen shows "liver inflammation, ascites, splenomegaly."
- November 2008 undergoes liver biopsy complicated by subcapsular hematoma. Path suggests sinusoidal dilatation raising the possibility of outflow tract obstruction. Ultrasound with doppler show no evidence of clot within hepatic veins.
- Evaluated by Duke Hepatology Jan 09. WBC 5.2, Hgb 8.9, plt 76K, T bili 2.1

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### Case 1

- 4/09 develops progressive shortness of breath, pleural effusion requiring chest tube, abdominal distension with ascites.
- Transferred to DUMC 4/25/09. WBC 9.9, HCT 30, plt 44K, reticulocyte 3.38%, T bili 4.8, alk phos 160, AST 44, ALT 31
- Ultrasound with doppler show thrombus in IVC, right portal vein, and reversal of flow in main portal vein.
- PNH screen 4/27/09 – consistent with PNH
- MRI abdomen – Budd-Chiari syndrome, splenic infarction, and decreased renal cortical signal consistent with hemosiderin deposition.

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### Case 1 Points of discussion

- Delay and difficulty in diagnosis (common)
- Thrombosis (blood clots) in PNH
- Treatment of thrombosis in PNH

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### Delays in diagnosing PNH – Educating the medical community

When you hear hoofbeats, ...



When you don't find the horse,  
learn how to spot the zebra



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**Case 1  
Follow up**

- Started on Eculizumab by end of May.
- Seen back in my clinic on 6/29/09 (after 5<sup>th</sup> dose)
- Doing very well. Abdominal swelling much better. Still having some pain and discomfort. WBC 3.0, Hgb 8.9, plt 63K
- Will patients liver get better?

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**IMMUNOSUPPRESSIVE THERAPY AND  
PNH  
Case 2**

Which patients are likely to benefit from immunosuppression and what are the therapeutic choices?

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## CASE PRESENTATION #2

- I.D.
  - 56 y. o. male
- Presentation
  - Low counts picked up on a routine physical 5 months ago
    - Moderate cytopenia involving all hematopoietic lineages
- Symptoms
  - Increased fatigue at the time of evaluation
- Past medical history
  - Normal counts recorded 5 years ago
  - Not contributory
- Subsequent course
  - RBC transfusion on one occasion
  - Gum bleeding and petechiae
  - GI bleed which required platelet transfusion
  - Further decline in counts
  - Dark urine noticed, yellow sclerae

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## LABORATORY EVALUATION

- Blood counts
  - WBC 2100/uL
  - Hg 8.9g/dL
  - Pti 27 000/uL
  - Retic 62 000/uL
  - ANC 620/uL
- Chemistries
  - Indirect Bili 2.8 mg/dL
  - AST 48U/L
  - LDH 680 U/L
  - Ferritin 10 ng/mL
- Bone marrow
  - Hypercellular
  - No dysplasia
  - Megakaryocytes present
  - Erythroid predominance
  - Normal karyotype
- PNH flow cytometry
  - 10% CD55-CD59- red cells
  - 65% CD59-CD66b- granulocytes

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## THERAPEUTIC CONSIDERATIONS

- Established Standard/Experimental evidence
  - severe AA, AA/PNH syndrome with severe cytopenia
    - ATG/CsA
- Therapeutic options, scientifically established standard does not exist
  - moderate AA
    - CsA alone
    - ATG, ATG/CsA
    - Observation
  - PNH
    - Immunosuppressive therapy less established
    - Standard supportive care
    - Androgens

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### FURTHER COURSE

- Further decline in Ptl count
- Patient started on CsA
  - Increase in Ptl count to 100 000/uL
  - Persistent anemia with high reticulocyte count
  - Ongoing hemolysis without need for transfusions
  - Stable ANC

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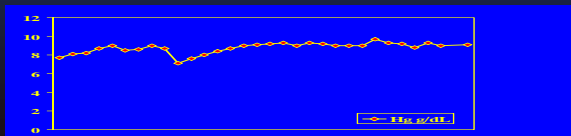
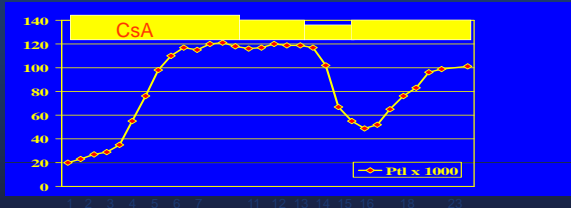
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### Therapy




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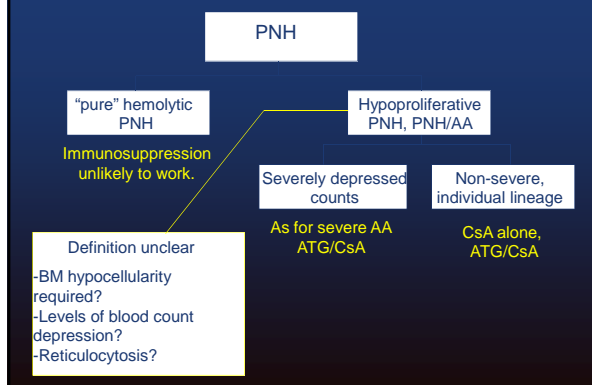
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### RATIONAL DECISION-MAKING PROCESS




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**Case 3**

- 36 y/o WF with PMH significant for
  - congenital pulmonary valve stenosis, S/P valve surgery in 1974, Hancock valve replacment in 5/02
  - Scoliosis, S/P spinal fusion surgery 1984
- Now referred for anemia in the setting of being 3 months pregnant

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**Case 3**

**Onset of PNH While Pregnant**

- Seen by her local hematologist. Prior CBC had shown normal Hct, WBC and platelet and low end of normal.
- Now has Hgb 7, MCV 102, LDH 1978, T bili 2.6, reticulocyte count 4.6%, negative DAT
- No evidence of schistocytes or red cell fragments.
- Bone marrow biopsy – normal with no storage iron
- “Hemolysis” due her valve, starts Fe.

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### Case 3

- No response to iron, Cardiology feels that valve hemolysis is highly unlikely.
- Refers her to Duke hematology.
- Only complaint is fatigue. Only medication is oral iron.
- Physical exam unremarkable.
- WBC 2.8, Hgb 7.8, MCV121, platelet 70K.
- Retic ct. elevated 5.4%, DAT negative.
- Peripheral blood shows polychromasia.

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### Case 3

- PNH screen shows 15.7% type III cells consistent with PNH.
- Started on folate and continued iron supplementation, heparin prophylaxis.
- At 35 weeks develops pre-eclampsia, undergoes unsuccessful induction followed by C-section.
- Post-operatively maintained on lovenox, platelet count 30K, requires transfusion of PRBC for some bleeding.
- Bone marrow biopsy –normocellular, normal morphology.

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### Case 3

- 2007 – increasing episodes of hemolysis, dark urine, usually associated with menses. Episodes associated with pain under rib cage. Unable to taper prednisone.
- PNH screen on granulocytes show 96% have absent CD59
- 10/5/07 starts eculizumab.
- No further episodes of hemolysis, prednisone tapered off.

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### Case 3

- Referred 4 weeks after discharge (Sept 2006)
- She and daughter doing well.
- WBC 2.8, Hgb 11.6, Hct 36, plt 59K, Retic 2.7%, LDH 2908
- Lovenox stopped.
- Iron, folate continued.
- Started on prednisone 20 mg q.o.d.
- 11/06- complains of occasional abd pain
- WBC 3.2, Hgb 9.8, Hct 32, plt 147K  
PNH screen – 63% Type III cells (RBC).

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### Case 3 Points for discussion

- Causes of hemolysis
- Treatment of PNH hemolytic anemia
- Eculizumab therapy
- Pregnancy and PNH (briefly)

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We like things to be black and white ...



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**Case 4 (de Castro)**

- Presented in July of 1999 with vague abdominal pain. Found to have mild pancytopenia with evidence of hemolytic anemia.
- Sucrose test positive, flow cytometry confirms PNH in Aug.
- Treated with folic acid, iron, and prednisone 20 mg every other day.
- Doing fairly well. Has episodes of hematuria and abdominal pain about every 2-3 months.

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**Case E**

- What should Mr. E do?
  - Continue current therapy
  - Start Eculizumab

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## Case E

- Everything we do in medicine is based on balancing the benefits of treatment versus the risks or side effects of treatment.
- For the most part, Mr. E is feeling well and relatively asymptomatic.
- There are long term consequences of chronic hemolysis
  - Renal
  - Pulmonary
  - Risk of thrombosis
- There are down sides to using Eculizumab
  - Neisseria infection (meningitis)
  - Cost
  - Convenience
  - Insurance and job issues

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## Questions?

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