Paroxysmal Nocturnal Hemoglobinuria: Understanding your Disease and Treatments Options

AA·MDS INTERNATIONAL FOUNDATION

Conference Agenda
Living with Aplastic Anemia, MDS, or PNH
March 24, 2018 • Rockville, MD

Antonio M. Risitano, M.D., Ph.D.
Head of Bone Marrow Transplantation Unit
Federico II University of Naples

CONFLICT OF INTEREST DISCLOSURE

Art. 3.3 sul Conflitto di Interessi, Reg. Applicativo dell'Accordo Stato-Regione (5/11/09)

Antonio M. Risitano

Company	*Type of conflict*
Alexion	Research funding, member of AB, lecture fee
Alnylam	Research funding
Novartis	Research funding, lecture fee, consultant
RA Pharma	Research funding
Pfizer	Lecture fee
Amyndas	Consultant
Jazz	Lecture fee

PNH association and patients' days

The Italian experience

AIEPN-ONLUS
ASSOCIAZIONE
ITALIANA
EMOGLOBINURIA
PAROSSISTICA
NOTTURNA

Napoli,27 giugno 2009

GIORNATA PAZIENTI EPN

L'EPN: come si manifesta, come si cura

Dr. Antonio M. Risitano
Ematologia Università Federico II

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Epidemiology

Rare disease

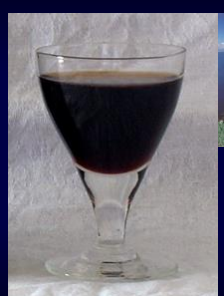
- Based on EU definition: prevalence (number of affected patients within the population) <5/10,000

Paroxysmal nocturnal hemoglobinuria

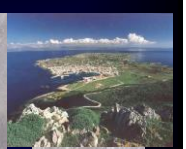
- Large population studies are lacking
- Prevalence estimated around 2-10 cases per million
  - Wordlwide distribution, with possible increased rates in Asia (overlapping with increased rates of aplastic anemia)
  - No gender difference
- Incidence (number of new cases within the population) estimated around 1-2 new cases per million per year
  - No age restriction, even if pediatric cases are rare and the highest incidence is seen in 3rd and 4th decades

Hemoglobinuria: about drinks…

Marchiafava and Micheli, 1928



Marsala: a regional wine from Sicily, fortified wine similar to Porto



PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

??? WHAT A STRANGE NAME???

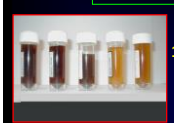
- ✓ **Paroxysmal:** a condition characterized by an unpredictable clinical course, with some recurrent events (the so-called «**crisis**»)
- ✓ **Nocturnal:** these events appear to be particularly frequents in the early morning
- ✓ **Hemoglobinuria:** the typical event is the change in urine appearance, with a light red-to-black typical color

Hemoglobinuria

- ✓ **Hemoglobinuria is not hematuria (in the urine you find only hemoglobin rather than intact blood cells)**
- ✓ **It gives the name to the disease, since it is one of he most evident manifestations (quite impressive especially in old era)**

THE CLINICAL TRIAD OF PNH

EPIDEMIOLOGY: rare disease (1-5 per million/year)

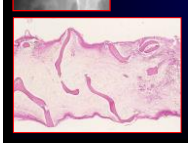


1. Chronic hemolytic anemia with paroxistic crises

Intravascular hemolysis, complement mediated

2. Propensity to thromboembolisms

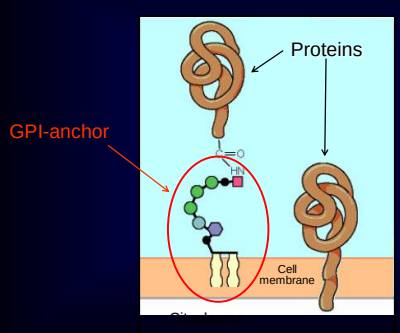
Often at unusual site, especially veins (cerebral veins, hepatic veins, splenic vein)



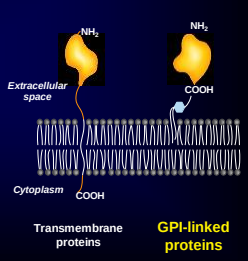
3. Variable cytopenia

Stigmata of marrow failure, possible overlapping with aplastic anemia (AA/PNH)

Mechanism of protein binding to cell surface



PATHOPHYSIOLOGY OF PNH



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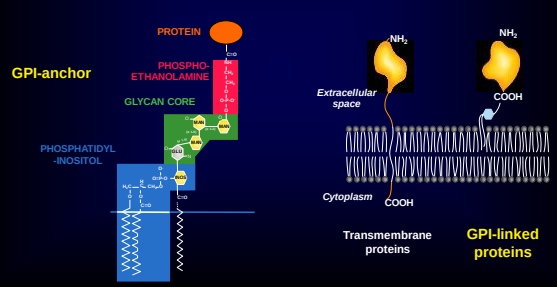
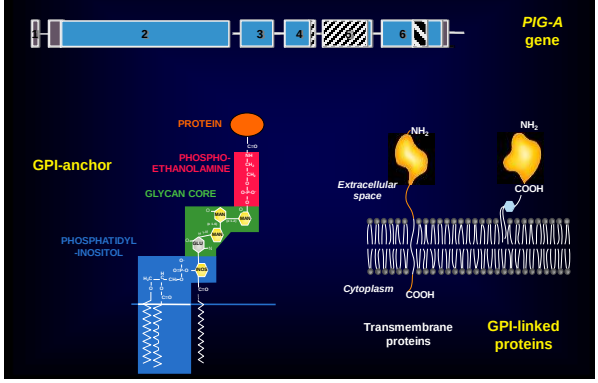
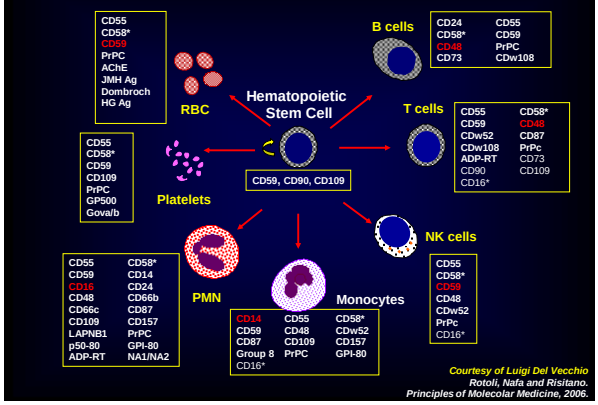


PATHOPHYSIOLOGY OF PNH



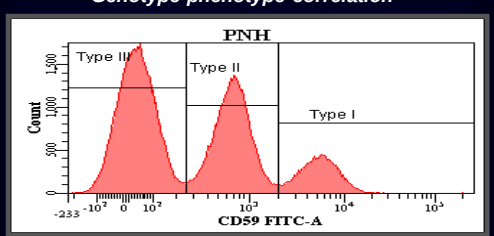
Proteins Deficient on PNH Blood Cells



Courtesy of Luigi Del Vecchio
Rotoli, Nafa and Risitano.
Principles of Molecolar Medicine, 2006.

THE PIG-A gene

Genotype-phenotype correlation



RBC are labelled with anti CD59 FITC.

Three populations of RBC can be seen:

- **type I** cells with normal expression of CD59;
- **type II** cells with partial deficiency of CD59 (Ham test: 3-5 x more sensitive to complement than normal cells)
- **type III** cells with complete deficiency of CD59 (Ham test: 15-25 x more sensitive to complement than normal cells)

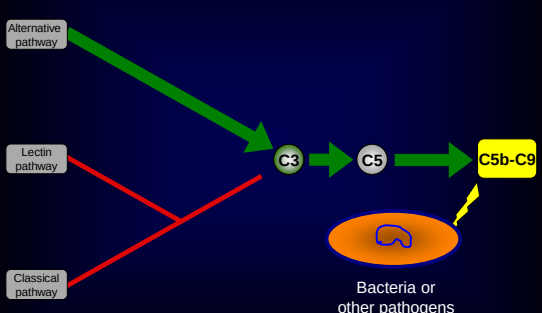
THE CLINICAL TRIAD OF PNH

EPIDEMIOLOGY: rare disease (1-5 per million/year)

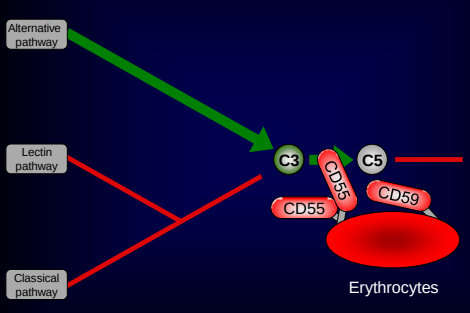
1. Chronic hemolytic anemia with paroxistic crises

Intravascular hemolysis, complement mediated

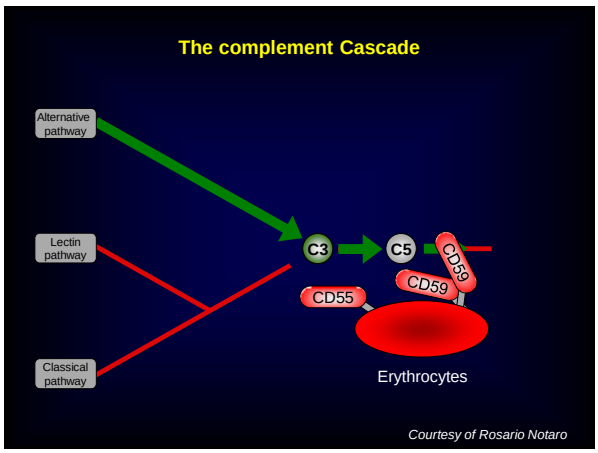
The complement Cascade

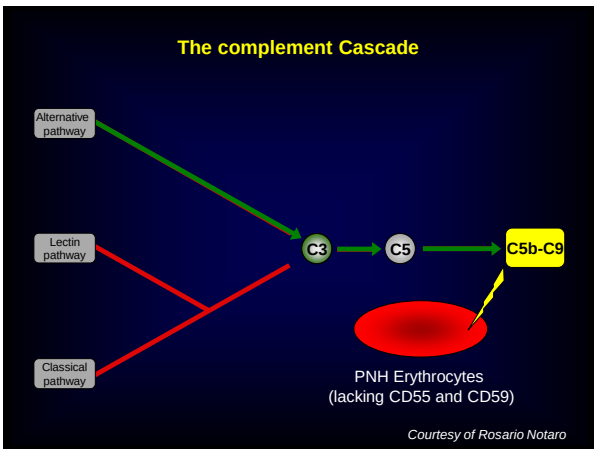


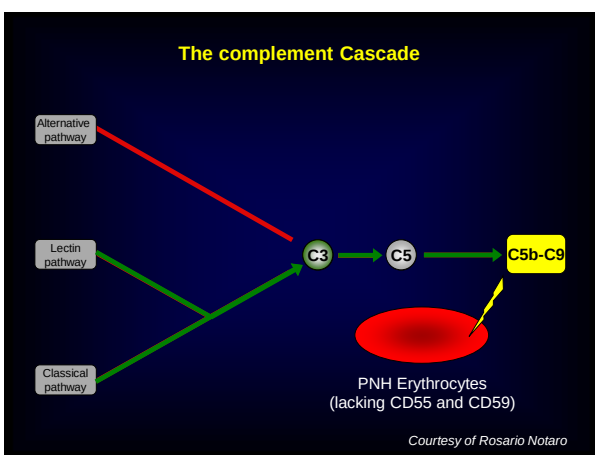
The complement Cascade



Courtesy of Rosario Notaro


The complement Cascade
Alternative pathway
Lectin pathway
Classical pathway
C3
C5
CD59
CD59
CD55
Erythrocytes
Courtesy of Rosario Notaro


The complement Cascade
Alternative pathway
Lectin pathway
Classical pathway
C3
C5
C5b-C9
PNH Erythrocytes
(lacking CD55 and CD59)
Courtesy of Rosario Notaro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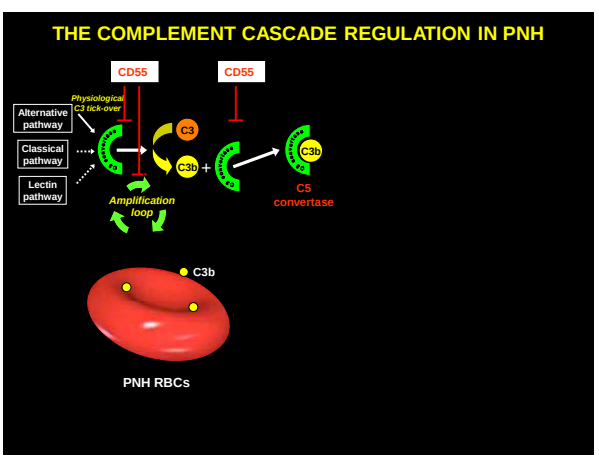
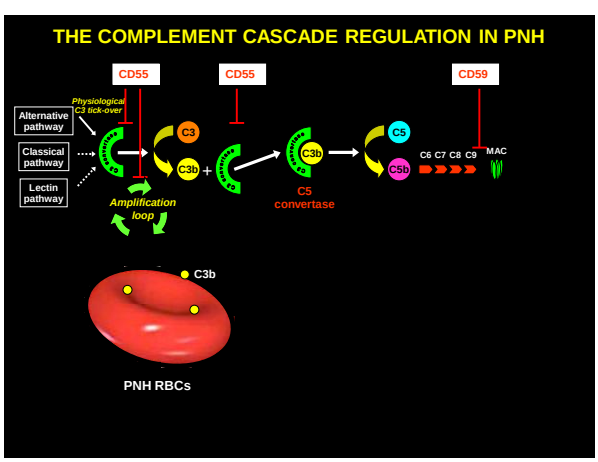

THE COMPLEMENT CASCADE REGULATION IN PNH
CD55
CD55
Physiological C3 tick-over
Alternative pathway
Classical pathway
Lectin pathway
C3
C3b
Amplification loop
C5 convertase
C3b
PNH RBCs


THE COMPLEMENT CASCADE REGULATION IN PNH
CD55
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Physiological C3 tick-over
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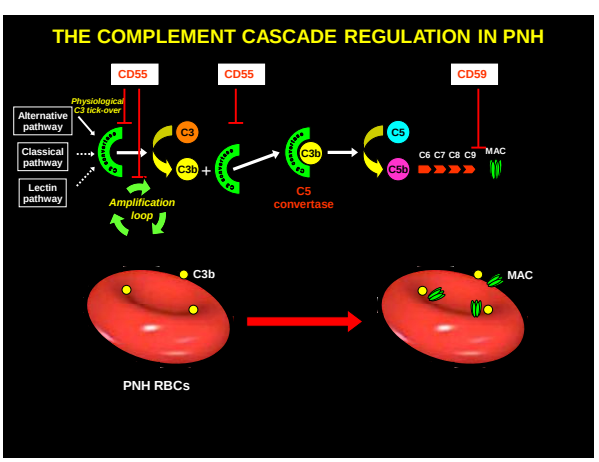
C3
C3b
Amplification loop
C5 convertase
C5
C5b
C6 C7 C8 C9
MAC
C3b
PNH RBCs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CD55
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Physiological C3 tick-over
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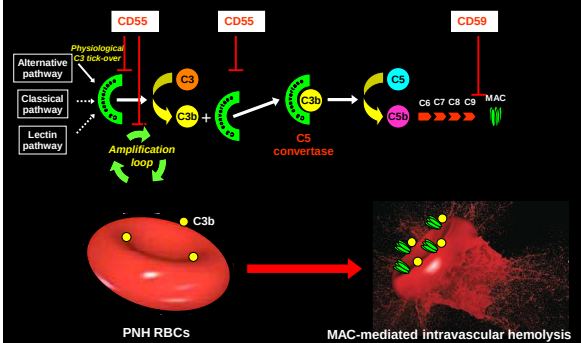
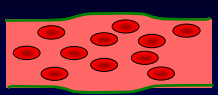
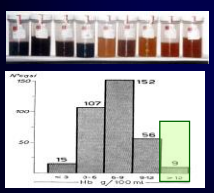
THE COMPLEMENT CASCADE REGULATION IN PNH



Chronic intracascular hemolysis with paroxysm

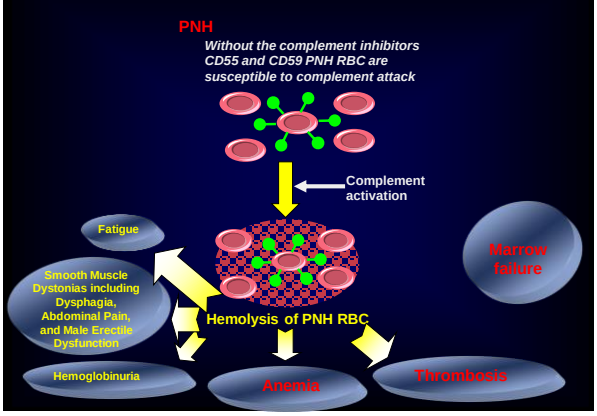




Hemoglobin

- Hemoglobinuria
- Anemia
- Abdominal pain
- Dysphagia
- Erectile dysfunction
- Fatigue

CLINICAL CONSEQUENCES OF HEMOLYSIS IN PNH



THE CLINICAL TRIAD OF PNH

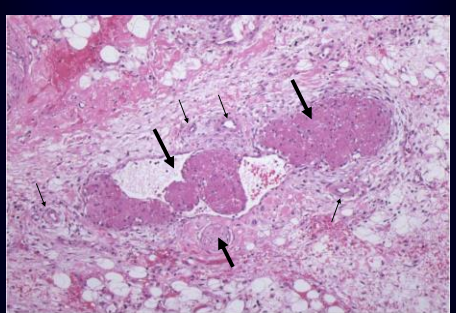
EPIDEMIOLOGY: rare disease (1-5 per million/year)

2. Propensity to thromboembolisms

Often at unusual site, especially veins (cerebral veins, hepatic veins, splenic vein)

Thromboembolism in PNH

Often multiple events, venous thrombosis, peculiar sites

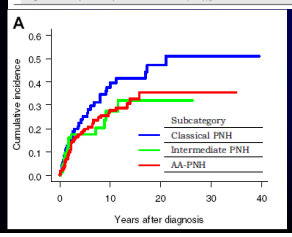


NATURAL HISTORY OF PNH

Impact of thrombosis on survival and relationship with disease category

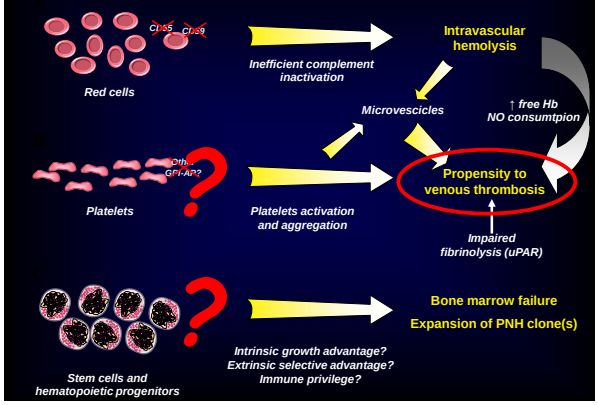
Table 4. Independent prognosis factors in the 3 subcategories of PNH

Factors	Classic PNH, n = 109	AA-PNH syndrome, n = 221	Intermediate PNH, n = 90
Period, 1985 or after	3.6 (1.3-10.3), .010	0.89 (0.74)†	4.1 (1.0-16.9), .045
Age at diagnosis			
Between 40 and 55 y	5.4 (1.9-15.7), <.001		
More than 40 y		1.7 (0.11)†	
More than 55 y	21.4 (6.6-68.7), <.001		5.7 (1.4-23.3), .020
Thrombocytopenia			0.16 (0.04-0.60), .007
Androgens/danazol	0.17 (0.03-0.88), .013		
Immunosuppressive treatment*		0.33 (0.11-0.99), .026	
Transfusions before 1996		2.7 (1.3-5.6), .007	
Evolution to*			
Bicytopenia or pancytopenia	7.3 (2.5-21.5), <.001	NA‡	2.5 (0.29)†
Thrombosis	7.8 (3.4-17.8), <.001	33.0 (14.3-76.2), <.001	17.6 (4.5-68.5), <.001
Malignant disease (MDS/AML)	2.2 (0.68)†	48.8 (16.9-140.6), <.001	38.6 (4.5-327.9), .003



De Latour et al, Blood 2008

PATHOPHYSIOLOGY OF THROMBOSIS IN PNH



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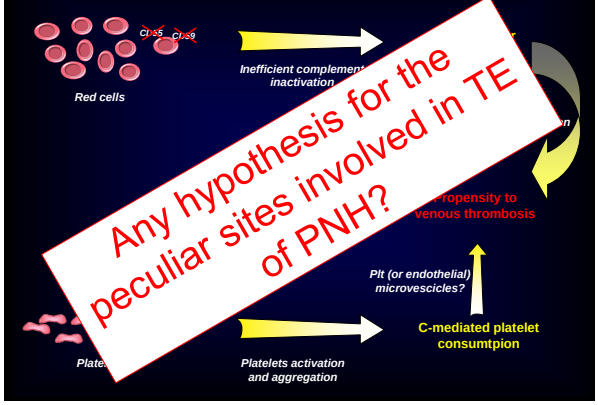
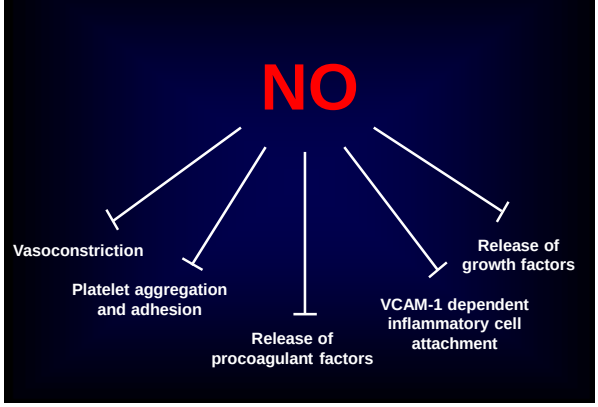
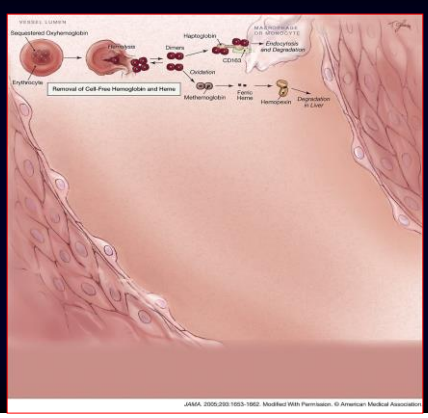


Pleiotropic role of nitric oxide in vascular homeostasis



PATHOPHYSIOLOGY OF THROMBOSIS IN PNH - II



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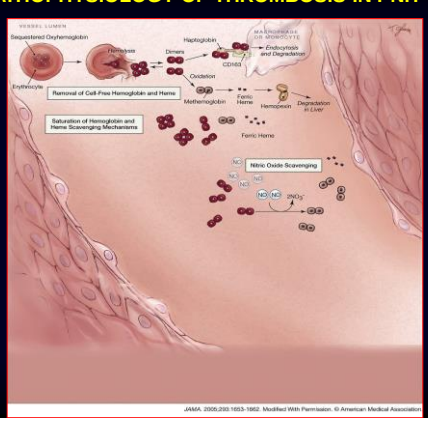

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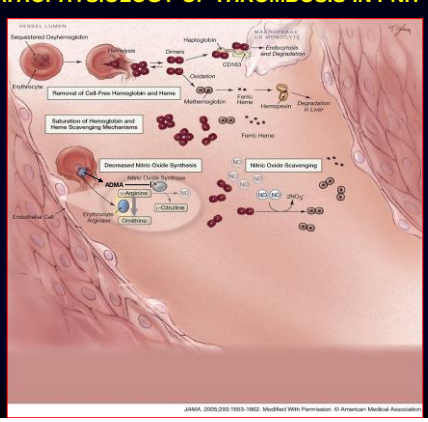

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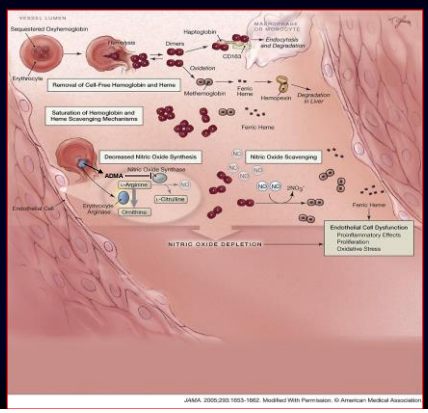

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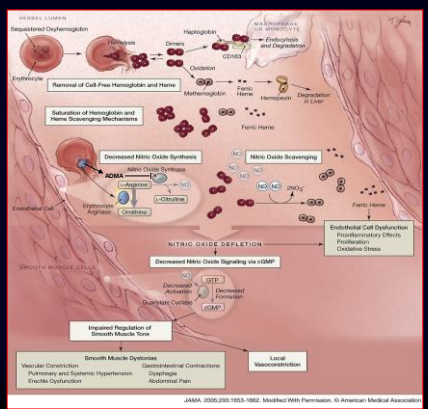

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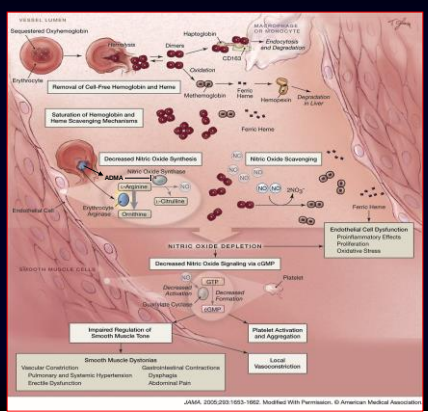

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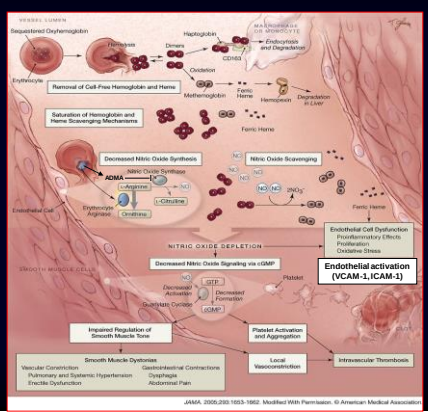
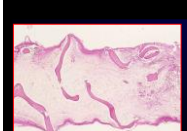


THE CLINICAL TRIAD OF PNH

EPIDEMIOLOGY: rare disease (1-5 per million/year)

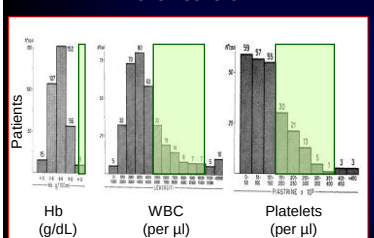


3. Variable cytopenia

Stigmata of marrow failure, possible overlapping with aplastic anemia (AA/PNH)

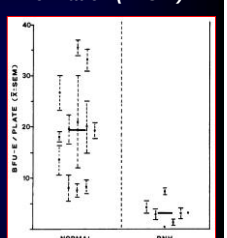
STIGMATA OF BONE MARROW FAILURE IN PNH

Frequent (pan)cytopenia, even severe



Centro Nazionale Ricerche, 1973

Reduced Erythroid Colony Formation (BFU-E)



Rotoli et al, Blood 1982

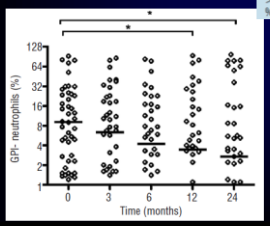
Paroxysmal nocturnal hemoglobinuria clones in severe aplastic anemia patients treated with horse anti-thymocyte globulin plus cyclosporine

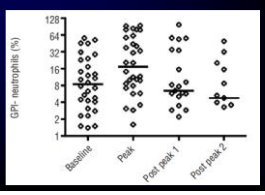
Phillip Scheinberg,[1] Michael Marte,[2] Olga Nunez,[1] and Neal S. Young[1]

Haematologica 2010

- ✓*A PNH population is present at diagnosis in about 40% of patients (usually <50%, without hemolysis)*
- ✓*Subsequent fluctations are common*
- ✓*Clinical PNH in 5-10%*

	N (%)	Median (IQR)
Total	207	
Age		30 (19-52)
Age < 18	45 (22)	14 (11-16)
Pre-treatment PNH (all ages) > 1%	83 (40)	
% clone size		9.7 (3.5-29)
Pre-treatment PNH (age < 18) > 1%	14 (31)	
% clone size		16 (4.3-40)





Bone Marrow Failure and PNH

Aplastic + PNH = Normal

PNH

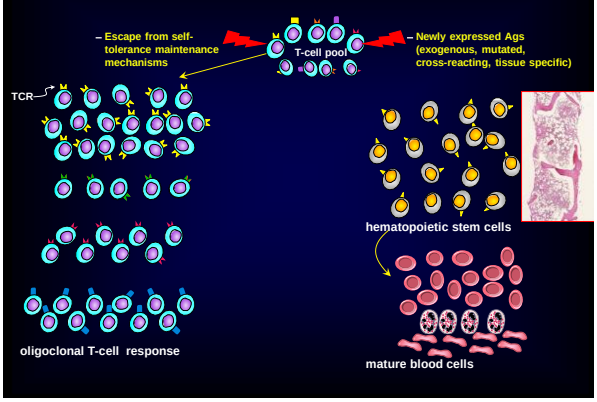
Hemolysis

Cytopenia

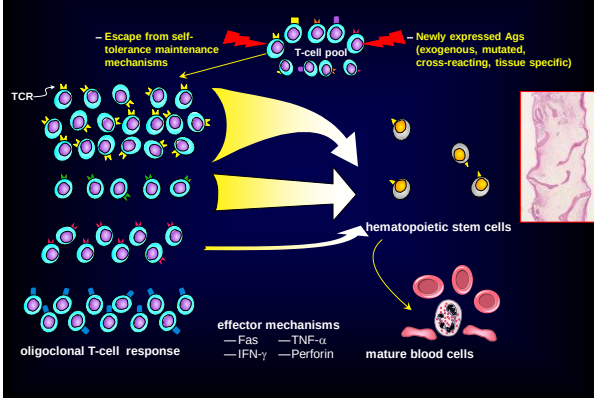
Aplastic Anemia

Aplastic

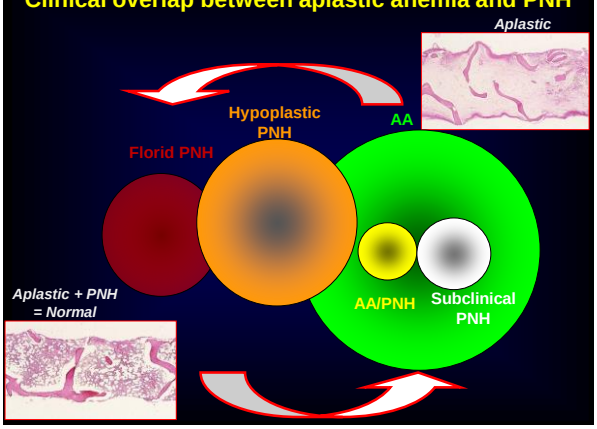
Immune pathophysiology of aplastic anemia



Immune pathophysiology of aplastic anemia



Clinical overlap between aplastic anemia and PNH



PNH is…

… still a puzzle!

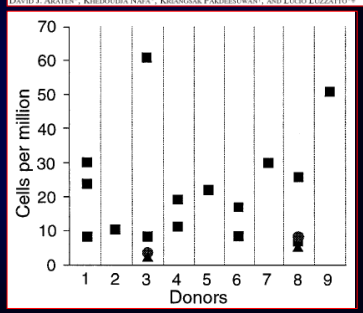
GPI(–) cells are Found in Normal People

Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 5209–5214, April 1999
Medical Sciences

Clonal populations of hematopoietic cells with paroxysmal nocturnal hemoglobinuria genotype and phenotype are present in normal individuals

David J. Araten*, Khedoudia Nafa*, Kriangsak Pakdeesuwan†, and Lucio Luzzatto*‡

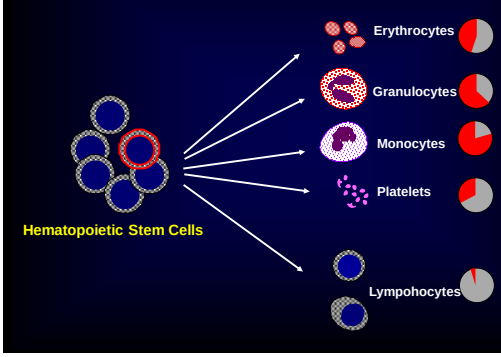
Number of GPI-granulocytes in healthy donors ranges between 1 and 50 per million



PIG-A mutation is not sufficient for developing PNH

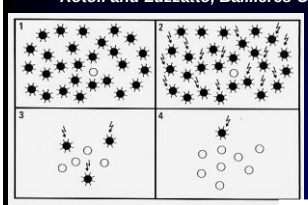
PNH is related to the expansion of mutated HSCs

Why PNH HSCs overcome normal hematopoiesis?



THE DUAL PATHOPHYSIOLOGY OF PNH

Rotoli and Luzzatto, Baillieres Clin Haematol 1989; Cell, 1997



Bruno Rotoli 1937-2009

Cell, Vol. 88, 1–4, January 10, 1997, Copyright ©1997 by Cell Press

Somatic Mutations in Paroxysmal Nocturnal Hemoglobinuria: A Blessing in Disguise?

Lucio Luzzatto, Monica Bessler, and Bruno Rotoli*

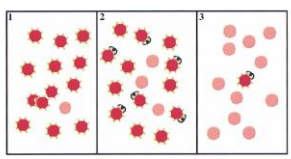
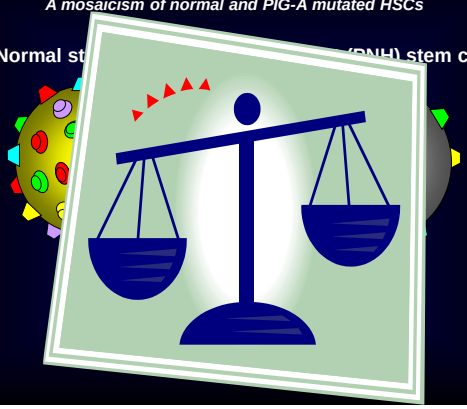


Figure 2. A Model for the Pathogenesis of PNH

HEMATOPOIESIS IN PNH

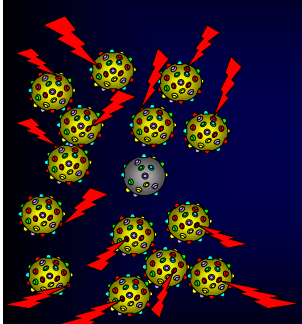
A mosaicism of normal and PIG-A mutated HSCs

Normal st (PNH) stem cells



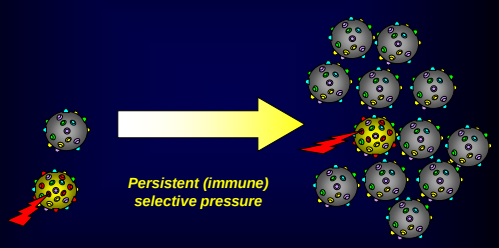
PATHOPHYSIOLOGY OF PNH

The relative advantage/immune escape theory



PATHOPHYSIOLOGY OF PNH

The relative advantage/immune escape theory



Persistent (immune) selective pressure

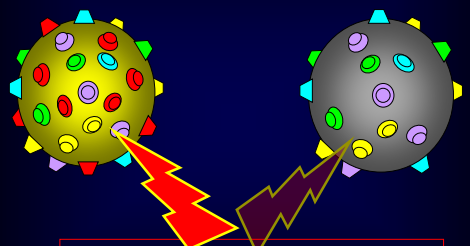
Progressive expansion of PNH hematopoiesis

PATHOPHYSIOLOGY OF PNH

The dual step hypothesis

Normal stem cells

GPI-deficient (PNH) stem cells



The second step
(a "permissive environment"):
an attack of hematopoiesis
sparing PNH HSCs?

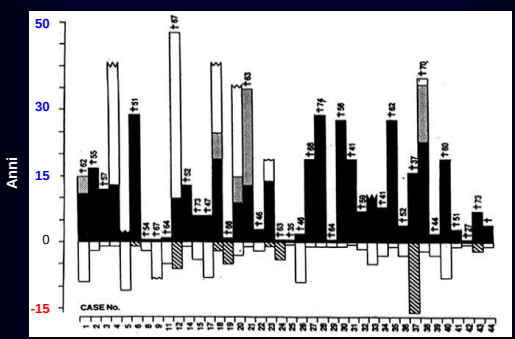
Multiple dimensions of PNH

More than a complement-mediated disease

PNH is…

- ✓ … a genetic, not inherited, disorder
  - *Inactivating mutations of the PIG-A gene, disabling the synthesis of the GPI-anchor*
- ✓ … a clonal, not malignant, disorder
  - *Abnormal (PIG-A mutated) blood cells derive from an ancestral hematopoietic stem cell which replaces normal hematopoiesis*
- ✓ … an immune-mediated disease, through the adaptive immunity
  - *T cell mediated bone marrow failure, accounting for selection of PNH hematopoiesis and possible concomitant aplastic anemia*
- ✓ … an immune-mediated disease, through the innate immunity
  - *Complement-mediated hemolytic anemia, with associated thrombophilia*
- ✓ … a chronic, life-threatening, heterogeneous disease requiring different therapeutic strategies

PNH is a chronic disease (even in the past)

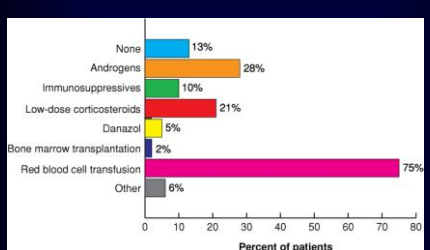


Hillmen *et al*, *N Engl J Med* 1995

Treatment of PNH

Paroxysmal Nocturnal Hemoglobinuria

Therapeutic options before 2007



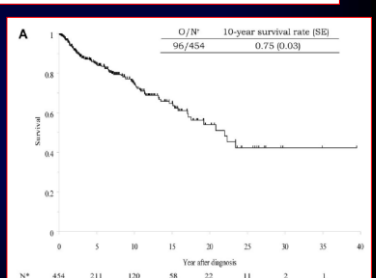
NATURAL HISTORY OF PNH

Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories

Régis Peffault de Latour,[1] Jean Yves Mary,[2] Célia Salanoubat,[3] Louis Terriou,[4] Gabriel Etienne,[5] Mohamad Mohty,[6] Sophie Roth,[7] Sophie de Guibert,[8] Sebastien Maury,[9] Jean Yves Cahn,[10] and Gerard Socié,[1] on behalf of the French Society of Hematology and of the French Association of Young Hematologists

Increased mortality due to:

- **Thromboembolism**
- **Severe marrow failure**
- ***(Clonal evolution to MDS/leukemia?)***



De Latour et al, Blood 2008

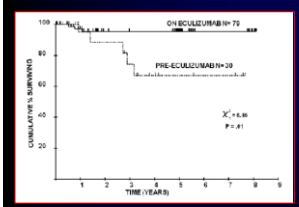
ECULIZUMAB AND PNH: EFFECTS ON SURVIVAL

blood

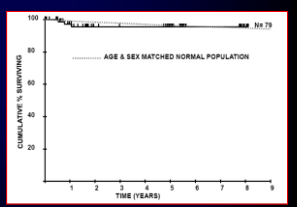
Long term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival

Richard J Kelly, Anita Hill, Louise M Arnold, Gemma L Brooksbank, Stephen J Richards, Matthew Cullen, Lindsay D Mitchell, Dena R Cohen, Walter M Gregory and Peter Hillmen

Untreated vs Ecu-treated PNH



Treated PNH vs normal population



Hill et al, Blood 2011

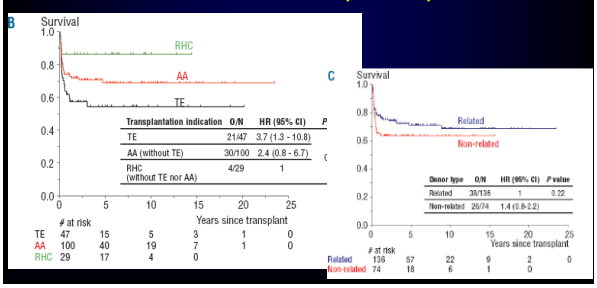
Is there any cure for PNH?

PNH: an EBMT retrospective study

Allogeneic stem cell transplantation in paroxysmal nocturnal hemoglobinuria

by Régis Peffault de Latour, Hubert Schrezenmeier, Andrea Bacigalupo, Didier Blaise, Carmino A. de Souza, Stephane Vigouroux, Roelf Willemze, Louis Terriou, Andre Tichelli, Mohamad Mohty, Sophie de Guibert, Judith Marsh, Jakob Passweg, Jean Yves Mary, and Gerard Socie

211 SCT for PNH from the EBMT database (1978-2007)

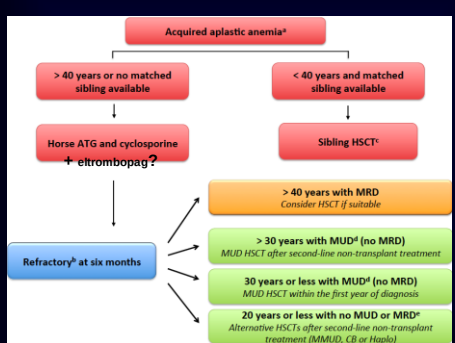


How to manage… …bone marrow failure in PNH?

PNH patients with AA should receive the same therapy of non-PNH AA patients

Treatment algorithm of aplastic anemia

Updated to 2017

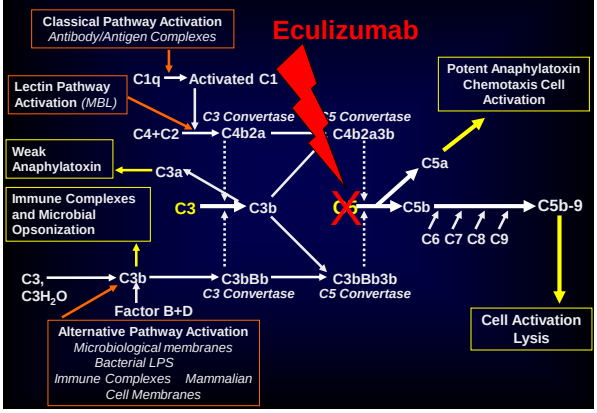


Peffault De Latour, ASH Educational 2016

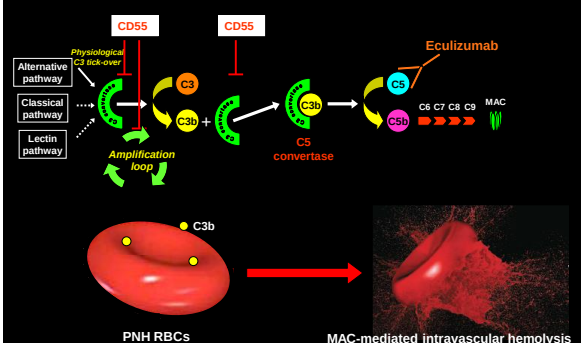
How to manage…

…hemolytic anemia in PNH?

Targeting Complement Inhibitors



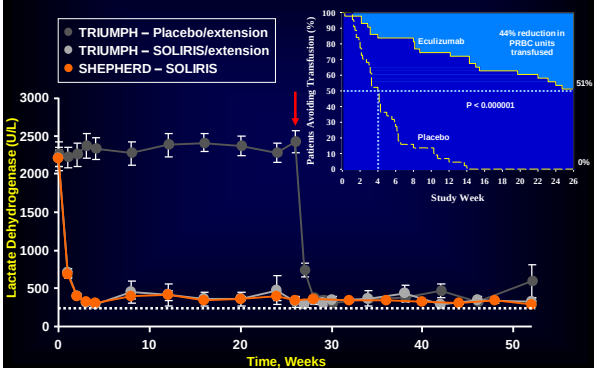
THE COMPLEMENT CASCADE REGULATION IN PNH



Risitano et al, Blood 2009

EFFECT OF ECULIZUMAB ON HEMOLYSIS

Lactate dehydrogenase (LDH) and transfusion independency



ECULIZUMAB AND PNH

Conclusions from all studies (and more)

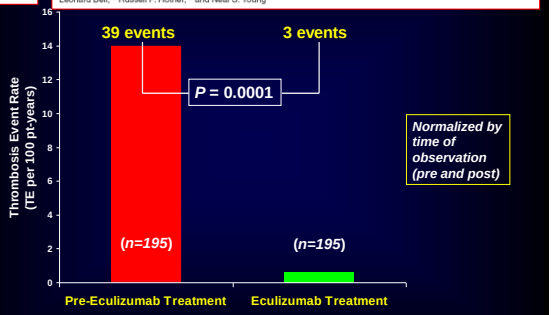
- ✓ Soliris™ is the first and only approved therapy for the treatment of PNH (USA March 2007, Europe June 2007)
- ✓ Terrific efficacy and excellent safety profile *(anti-meningococcal vaccination)*
  - ✓ Robust control of intravascular hemolysis (even if hematological benefit is heterogeneous)
  - ✓ Remarkable effect on thrombophilic risk
  - ✓ Anticipated effect on survival (to be confirmed with longer follow up)
- ✓ Eculizumab is the first choice treatment for all PNH patients to manage both hemolysis and thromboembolic risk of PNH
- ✓ Eculizumab has been reported extremely useful in allowing safe pregnancies in PNH women (Kelly et al, NEJM 2015)

How to manage…

…thromboembolism in PNH?

Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria

Peter Hillmen,[1] Petra Muus,[2] Ulrich Dührsen,[3] Antonio M. Risitano,[4] Jörg Schubert,[5] Lucio Luzzatto,[6] Hubert Schrezenmeier,[7] Jeffrey Szer,[8] Robert A. Brodsky,[9] Anita Hill,[1] Gerard Socié,[10] Monica Bessler,[11] Scott A. Rollins,[12] Leonard Bell,[12] Russell P. Rother,[12] and Neal S. Young[13]



- 92% reduction in event rate with eculizumab

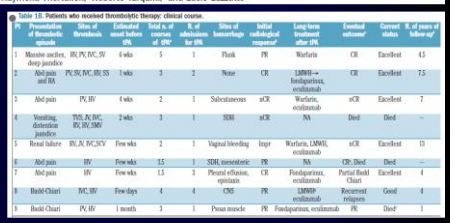
Hillmen et al., Blood 2007

Thrombolytic Therapy with tPA in PNH

Haematologica | 2010; 95(4)

Thrombolytic therapy is effective in paroxysmal nocturnal hemoglobinuria: a series of nine patients and a review of the literature

David J. Araten,[1] Rosario Notaro,[2] Howard T Thaler,[1] Nancy Kernan,[1] Farid Boulad,[1] Hugo Castro-Malaspina,[1] Trudy Small,[1] Andromachi Scaradavou,[1] Heather Magnan,[1] Susan Prockop,[1] Sara Chaffee,[1] Jason Gonsky,[1] Raymond Thertulien,[1] Roberto Tarquini,[2] and Lucio Luzzatto[2]



N=41

✓9 eligible (recent events)

✓15 procedures

✓Beneficial in all cases (4 CR, 4 PR, 1 impr)

✓Risk of relapse (multiple sites)

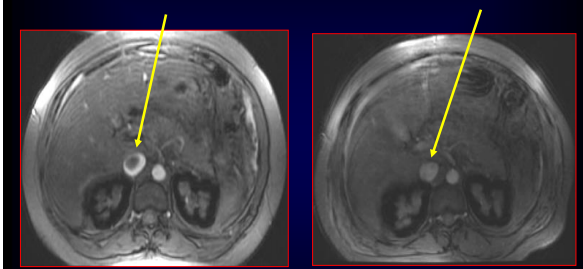
✓20% hemorrhagic complications (1 fatal)

✓HITT???

Thrombolysis by systemic tPA should be considered in all PNH patients developing life-threatening TE refractory (by adequate imaging techniques) to standard anti-coagulation

Thrombolytic Therapy with tPA in PNH

CT scan

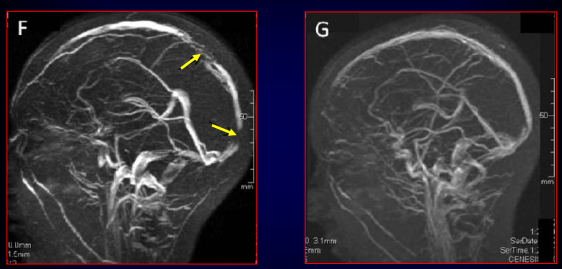


before tPA treatment | after tPA treatment

Courtesy of Prof. Lucio Luzzatto

Thrombolytic Therapy with tPA in PNH

Magnetic Resonance Venogram



before tPA treatment | after tPA treatment

Araten et al, Haematologica 2012

MANAGEMENT OF THROMBOEMBOLISM IN PNH

Secondary prophylaxis

- Once experienced one thromboembolic event, PNH patients are at very high risk of further thromboembolism
  - No absolute contraindication in case of thrombocytopenia
    - Platelet transfusion if required
- Guidelines: all PNH patients experiencing thrombosis should receive indefinite secondary antithrombotic prophylaxis
  - No consensus on the best strategy
    - Low molecular weight heparin
    - High-dose warfarin (INR 3-4)
    - Low-dose warfarin (INR 1,5-3)
    - Anti-platelets agents?
  - Lack of prospective studies
- Complications
  - Recurrency and/or relapse
  - Risk of hemorrhages, especially in patients with thrombocytopenia

MANAGEMENT OF THROMBOEMBOLISM IN PNH

Primary prophylaxis

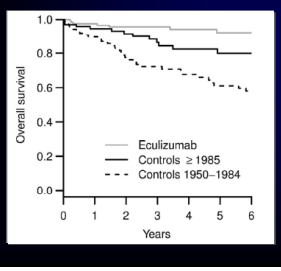
- No consensus on primary prophylaxis
  - Thromboembolic risk may differ according to ethnicity, genetic predisposition and other disease related features (i.e., PNH WBC clone size)
- Lack of prospective randomized studies
  - International PNH registry project
    - Retrieve retrospective data
    - Possibly design prospective studies
- Strategies of prophylaxis
  - Low dose warfarin (INR 1,5-3)
  - Low molecular weight heparin
  - Anti-platelets agents (Aspirin)?
  - Novel oral anti-thrombin inhibitors
- Complications
  - Risk of hemorrhage, especially in patients with thrombocytopenia

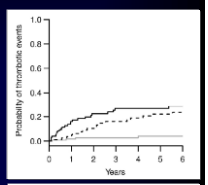
Long-term effect of eculizumab treatment in PNH

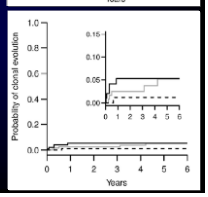
A retrospective comparison (Loschi et al, AJH 2016)

PNH patients with indication to eculizumab (clinically meaningful hemolysis and/or thrombosis)

- Eculizumab: n=123 (>2005)
- Non-eculizumab: n=191







PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

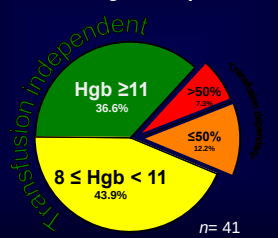
Future goals

✓ Any room for improvement?
✓ If yes, how we can do it?

THE CLINICAL RESPONSE TO ECULIZUMAB

The Italian experience

Hematological response

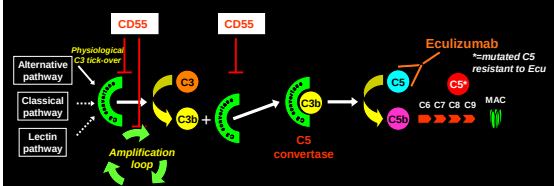


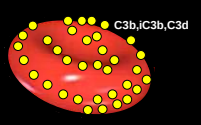
n= 41

- Normal or almost-normal LDH level in all patients
- Persistent reticulocytosis in almost all patients

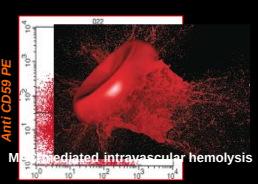
Risitano *et al*, *Blood* 2009

THE COMPLEMENT CASCADE REGULATION IN PNH





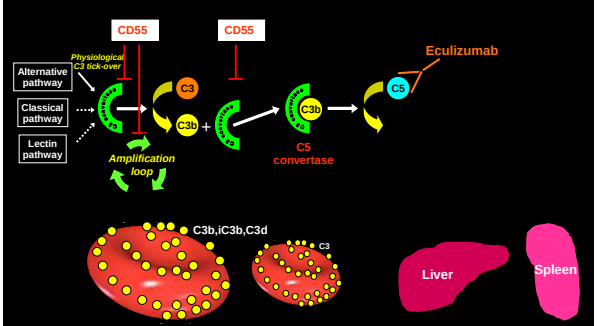
PNH RBCs



M[illegible]mediated intravascular hemolysis

Risitano et al, Blood 2009

THE COMPLEMENT CASCADE REGULATION IN PNH



C3-mediated extravascular hemolysis

Risitano et al, Blood 2009

Unmet clinical needs in anti-complement therapy

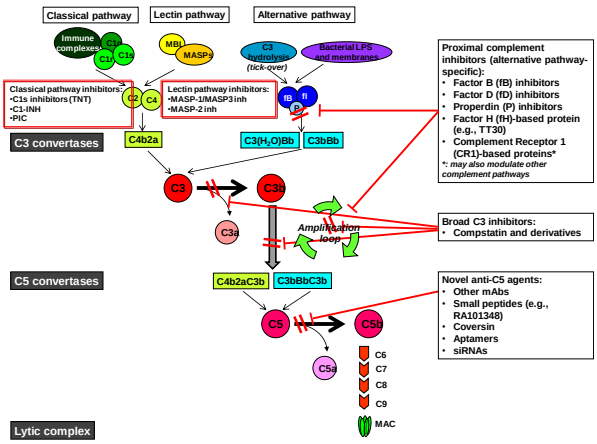
1. Rare intrinsic (genetic) resistance
2. Suboptimal hematological benefit
   - Underlying bone marrow failure
   - Breakthrough (pharmacokinetic and pharmacodynamics)
   - C3-mediated extravascular hemolysis
3. Patient perspective: i.v. therapy, bi-monthly infusion, (hospitalization)
4. Limited access (worldwide) and costs

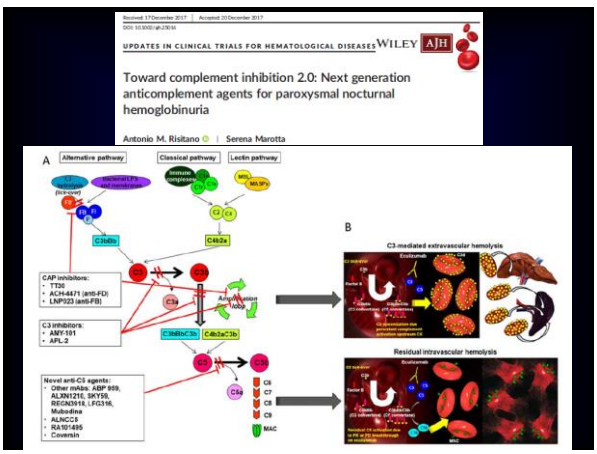
The perfect complement inhibitor for PNH

1. As safe as first-generation inhibitors (eculizumab)
2. Similar control of intravascular hemolysis, as compared with eculizumab
3. Possible effect on C3-mediated extravascular hemolysis
4. Effective in rare genotypes?
5. Possibly better in terms of patients compliance (administration route, frequency): no hospitalization?
6. Cost: a cheap treatment for everybody, worldwide

"Answers are better than questions"

Neapolitan phylosopher, 1973-.....about 2100





Second generation complement inhibitors for PNH

Take home messages

1. **Alternative anti-C5 agents (or terminal complement inhibitors) may result in limited benefit**
   - ✓ Possible improvement of treatment compliance: administration route and intervals (reduced/abolished hospitalization?)
   - ✓ Reduced costs?
   - ✓ Likely no clinical benefit over eculizumab (except for C5 mutations)
2. **Second-generation inhibitors must target early complement activation**
   - ✓ C3-mediated extravascular hemolysis is the main unmet clinical need in PNH

   i. **C3 inhibitors: compstatin**
   - ✓ Optimal strategy for PNH, due to deranged regulation along all the three pathways
   - ✓ Initial data in PNH very encouraging (mostly add-on therapy)
   - ✓ Subcutaneous availability, but need of s.c. INFUSIONS

   ii. **Alternative pathway inhibitors: anti-FB and anti-FD**
   - ✓ Preliminary data in PNH (anti-FD only) very promising (add-on therapy)
   - ✓ Orally available
   - ✓ short half-life; risk concerning "missing doses"

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Gerard Socié
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Ghulam Mufti
Judith Marsh
Austin Kulasekararaj

Sao Paolo University
Rodrigo Calado
Phillip Scheinberg

NIH, NHLBI
Neal S. Young

Cleveland, Cleveland Clinic
Jaroslaw Maciejewski

EMOGLOBINURIA PAROSSISTICA NOTTURNA

Cos'è

- ✓ Thanks to charities!
- ✓ Also in Italy patient association and patients' day
- ✓ What is the disease: definition starting with the name
- ✓ Clinical presentations
- ✓ Pathogenesis
- ✓ Prognosis
- ✓ Therapies
  - ✓ Curative
  - ✓ Supportive
  - ✓ Etiologic, disease-changing
- ✓ Perspective

AIEPN-ONLUS ASSOCIAZIONE ITALIANA EMOGLOBINURIA PAROSSISTICA NOTTURNA

MANAGEMENT OF THROMBOEMBOLISM IN PNH

Secondary prophylaxis

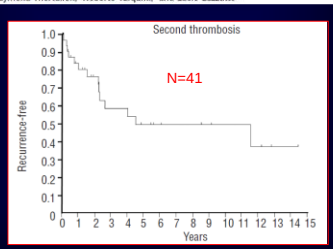
- Once experienced one thromboembolic event, PNH patients are at very high risk of further thromboembolism
  - No absolute contraindication in case of thrombocytopenia
    - Platelet transfusion if required
- Guidelines: all PNH patients experiencing thrombosis should receive indefinite secondary antithrombotic prophylaxis
  - No consensus on the best strategy
    - Low molecular weight heparin
    - High-dose warfarin (INR 3-4)
    - Low-dose warfarin (INR 1,5-3)
    - Anti-platelets agents?
  - Lack of prospective studies
- Complications
  - Recurrency and/or relapse
  - Risk of hemorrhages, especially in patients with thrombocytopenia

Thrombolytic Therapy with tPA in PNH

Haematologica
haematologica | 2010; 95(4)

Thrombolytic therapy is effective in paroxysmal nocturnal hemoglobinuria: a series of nine patients and a review of the literature

David J. Araten,[1] Rosario Notaro,[2] Howard T Thaler,[1] Nancy Kernan,[1] Farid Boulad,[1] Hugo Castro-Malaspina,[1] Trudy Small,[1] Andromachi Scaradavou,[1] Heather Magnan,[1] Susan Prockop,[1] Sara Chaffee,[1] Jason Gonsky,[1] Raymond Thertulien,[1] Roberto Tarquini,[1] and Lucio Luzzatto[2]



Recurrencies of TE are frequent and standard anticoagulant therapies are largely ineffective in preventing further TE episodes

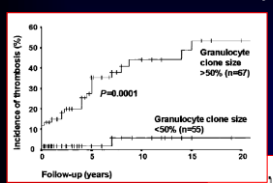
MANAGEMENT OF THROMBOEMBOLISM IN PNH

Primary prophylaxis

- No consensus on primary prophylaxis
  - Thromboembolic risk may differ according to ethnicity, genetic predisposition and other disease related features (i.e., PNH WBC clone size)
- Lack of prospective randomized studies
  - International PNH registry project
    - Retrieve retrospective data
    - Possibly design prospective studies
- Strategies of prophylaxis
  - Low dose warfarin (INR 1,5-3)
  - Low molecular weight heparin
  - Anti-platelets agents (Aspirin)?
  - Novel oral anti-thrombin inhibitors
- Complications
  - Risk of hemorrhage, especially in patients with thrombocytopenia

MANAGEMENT OF THROMBOEMBOLISM IN PNH

Primary prophylaxis



Hall et al, Blood 2003