Aplastic Anemia & PNH

Loree Larratt

Aplastic Anemia

- Misnomer "Aplastic Pancytopenia"
- Incidence: 2 – 4 / Million / year
- Young adults with second peak in 5^{th} or 6^{th} decade of life

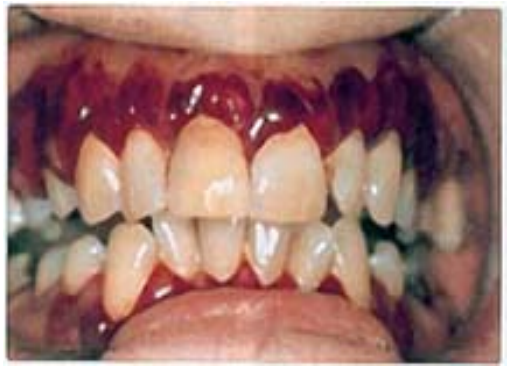
Presentation

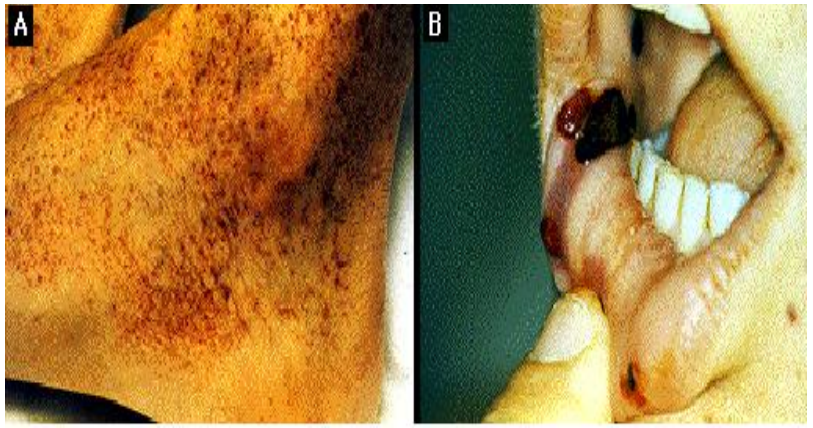
- Insidious onset
- Signs & Symptoms of cytopenias in all three blood lineages
- Splenomegaly (enlarged spleen) rare unless secondary

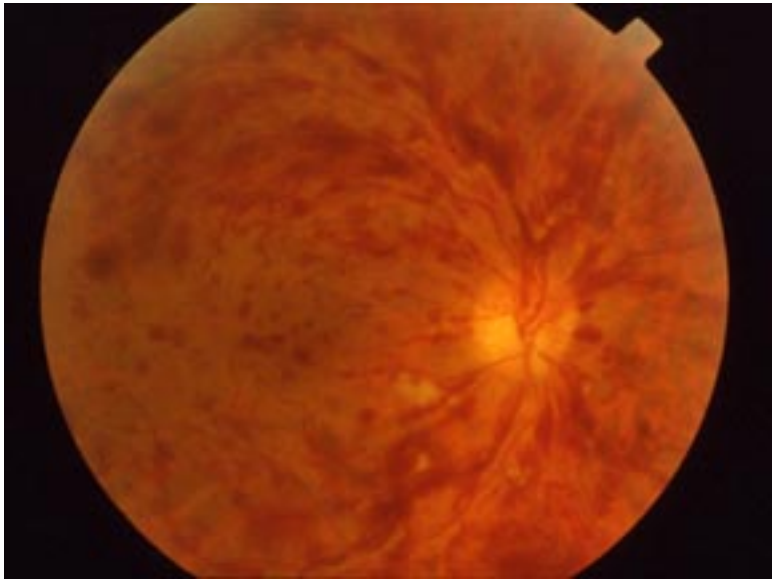
Presentation

- Cytopenia:
  - Anemia
    - Low red blood cell count
    - Fatigue, pallor, hear pulse in head
  - Thrombocytopenia
    - Low platelets
    - Bruise easily, petechiae (pinpoint red spots)
  - Neutropenia
    - Low white count
    - Impaired immune function, susceptible to infection, viruses

Thrombocytopenia







Aplastic Anemia History

- Ehrlich 1888:
  - rapidly fatal case of severe anemia and leucopenia with fever, ulcerated gums and menorrhagia
  - at autopsy, no active marrow
- Chauftard 1904: aplastic anemia
- 1934: distinct entity

Laboratory

- Red Blood Cell count (RBC) sl macrocytosis, low reticulocyte count
- White Blood Cell count (WBC) low PMN with no immature forms
- Thrombocytopenia
- Bleeding time prolonged depending on platelet count
- Coagulation studies normal
- No signs of hemolysis (unless PNH)
- Bone Marrow hypo / aplastic

Classification

Severe AA

- ANC< 500/ul
- ARC< 40,000/ul
- Pl<20,000
- 2 out of 3 criteria

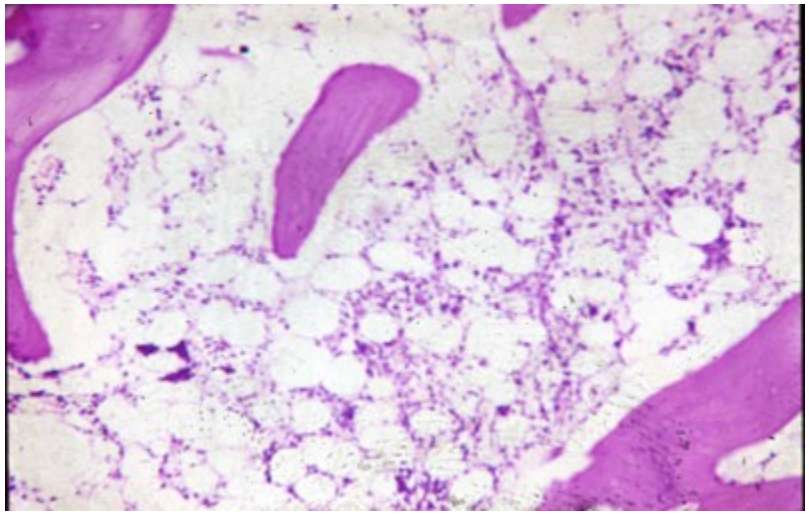
Very Severe AA

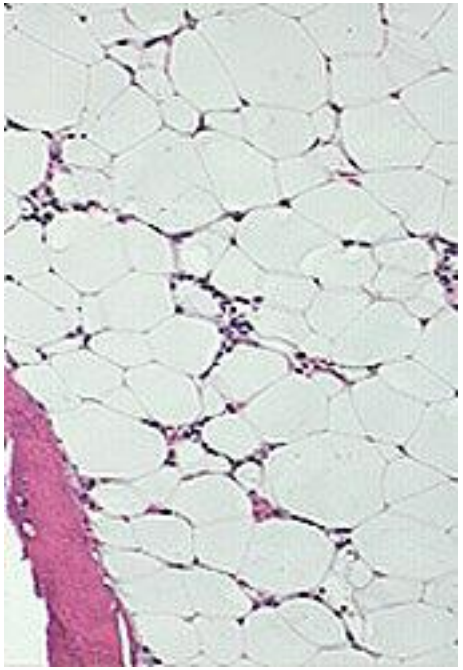
- ANC< 200/ul

Moderate AA

- Not fulfilling severity criteria
- Chronic needs > 3 months

Bone Marrow





Lab Ancillary tests

- Bone marrow biopsy to rule out hypoplastic MDS
- Cytogenetics to rule out MDS & congenital disorder Fanconi's Anemia
- Flow cytometry (CD55 & CD59) to rule out PNH
- Liver function tests
- Flow cytometry to rule out Large Granular Lymphocyte leukemia, Hairy Cell Leukemia
- HLA typing for BMT
  - increased DR15 in AA & PNH patients

Pathogenesis

- Primary defect or damage to stem cell or less commonly microenvironment
- Evidence for immune mechanism:
  - Autologous engraftment after allogeneic transplant
  - Failure of engraftment with syngeneic transplant
  - Response to immunosuppressive therapy

Etiology

- Idiopathic 40 – 70 %
- Constitutional
- Irradiation (> 7Gy Irreversible: >5Gy 50%)
- Drugs
- Toxins
- Infections (Hepatitis, Mono , Parvo)
- Pregnancy
- PNH

Other

Other disorders can result in aplastic anemia

- Fanconi's Anemia
- Dyskeratosis Congenita
- Schwachman Diamond Syndrome

Standard Immunosuppressive Therapy

- ATG/CyA
  - Anti-thymocyte globulin over 4 – 5 days with
  - cyclosporine for 6 – 12 months
- Initial steroids to reduce allergic reaction and serum sickness
- RR 70 – 80 % typically within 3 – 6 mo
- G-CSF does not impact survival
- Relapse 10 – 30 %
- Risk of developing clonal disease (MDS or PNH)

Treatment failure

- Exhaustion of stem cell reserves
  - Immune mediated AA
- Insufficient Immunosuppression
  - Persistent attack
- Misdiagnosis
- Hereditary Bone Marrow failure
  - Non-immune pathogenesis

Other Immunosuppressive Therapy

- Cell Cept (mycophenolate)
- Campath
- Cyclophosphamide
  - Time of response > 1year
- Eltrombopag (revolade) Off label use

Alternate agents

- Growth factors alone
  - Not advocated
  - Monosomy 7 with prolonged g-csf use reported
- Androgens
  - Ancillary and no longer primary therapy

BMT

- Only curative therapy
- Matched allogeneic
  - Donor available 25%
  - Survival 80 – 90 % decreasing with adv age
  - 30 – 35 year cut off
- MUD (matched unrelated donor)
  - 40 % < 20 ; 30% 21 – 40 y
  - Older patient IS > BMT

Late Complications of BMT

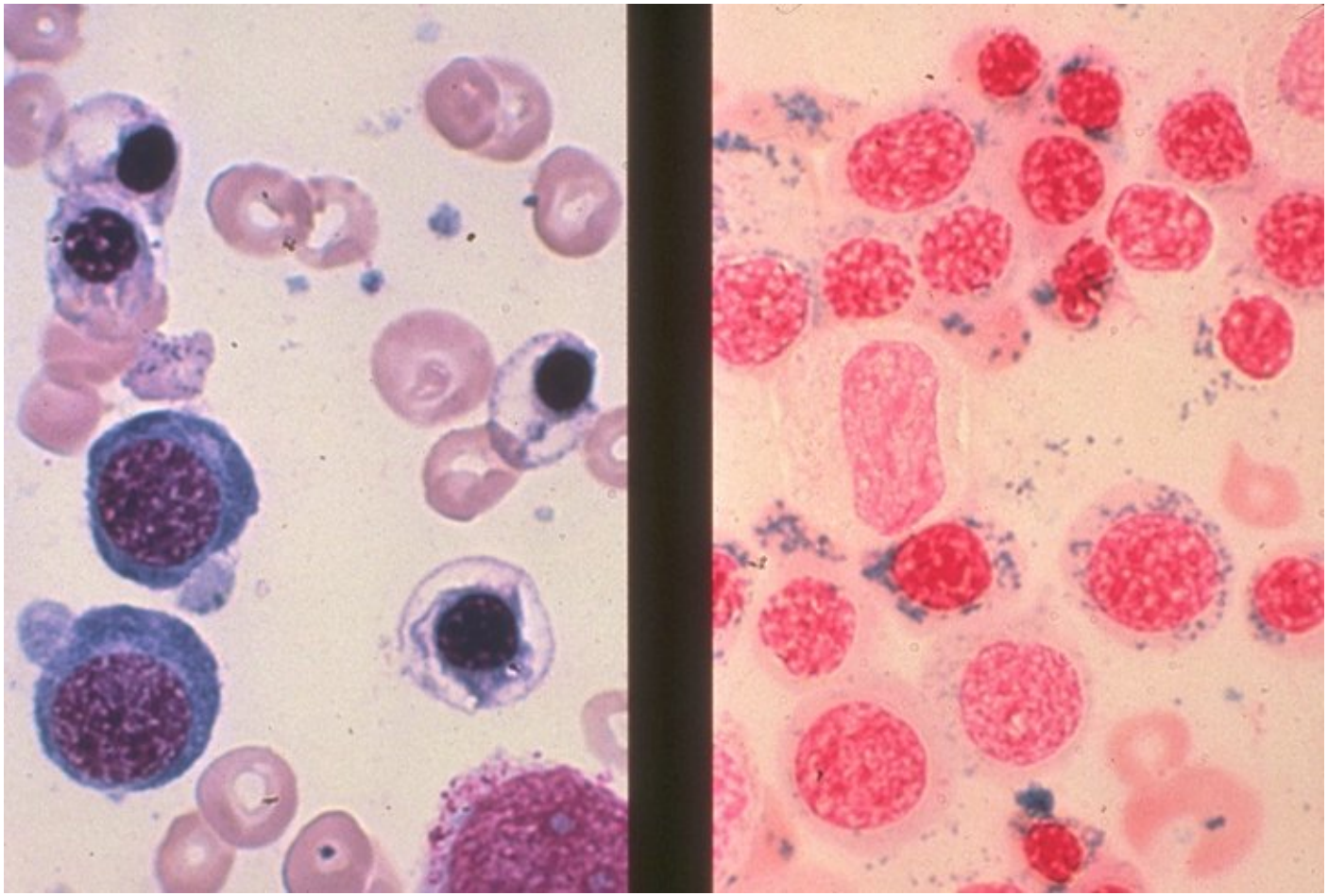
- Chronic Graft vs Host Disease (GVHD)
- Solid Tumors
- Lung Disease
- Cataracts
- Infertility
- Graft Failure
- etc

Late Complications of IS

- MDS
  - Variable risk
  - Clonal evolution and progression to leukemia
  - Complex and monosomy 7 bad
  - Trisomy 8 & 13q may respond to IS
  - Concern AA vs Hypoplastic MDS

  - Dr Zhu presentation

MDS



Late Complications of IS

- Paroxysmal Nocturnal Hemoglobinuria
  - May occur at aplastic diagnosis or late as a complication of IS therapy (up to 20%)
  - Disease characterized by Hemolysis, Thrombosis and marrow failure

Paroxysmal Nocturnal Hemoglobinuria

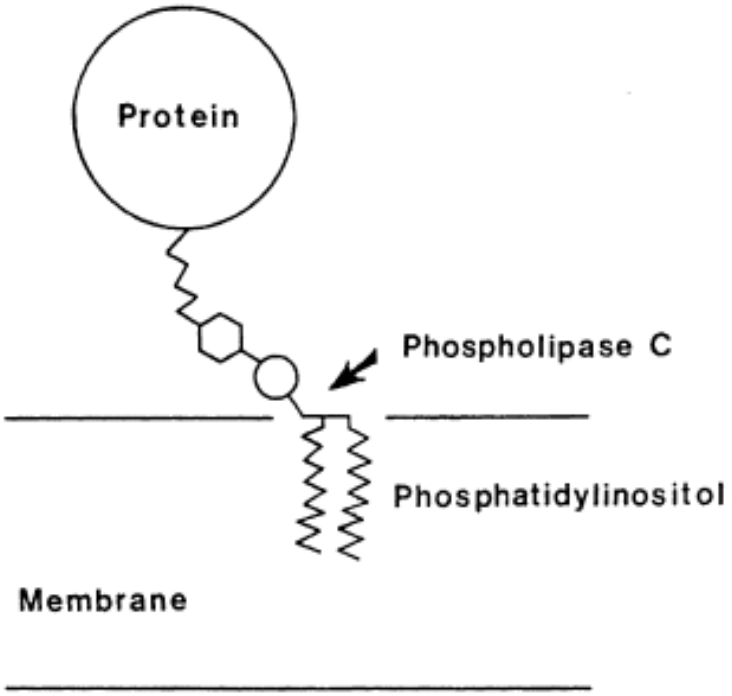
- Paroxysmal - episodic
- Misleading "Nocturnal"
- Hemoglobinuria – hemoglobin in the urine
- Incidence:
  - unknown, believe that there are 8000 – 10000 cases in North America & Western Europe
  - More common in southeast Asia
  - Global PNH Registry underway
- M=F
- Median age of diagnosis is 42 years but range is 2-83 years

PNH History

- 1866: William Gull describes first patient nocturnal hemoglobinuria
- First definitive description: Paul Strubing, 1882
  - 29-year old male “voided dark urine only in the morning”
  - Gradual intravascular hemolysis
  - Distinct from march and cold hemoglobinuria
- 1993: Kinoshita discovers mutant gene

PNH

- Disorder characterized by a defect in the GPI Anchor due to an abnormality in the PIG-A gene.



PNH

- Leads to a partial or complete absence of GPI-linked proteins – CD59 (membrane inhibitor of reactive lysis) and CD55 (decay accelerating factor)
- Lack of these proteins leads to the clinical picture allowing excessive sensitization of the rbc to complement mediated hemolysis
- PNH patients deficient in both CD55 & CD59 and to varying degrees in individual patients

WHAT DOES COMPLEMENT HAVE TO DO WITH PNH?

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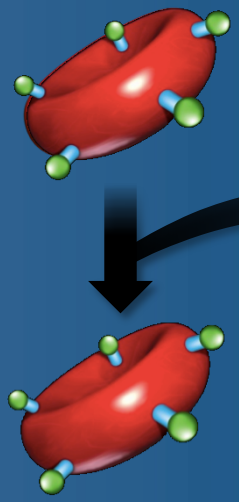
Normal RBCs are protected from complement attack by a shield of terminal complement inhibitors (GPI-anchored proteins – most important are CD55 and CD59)

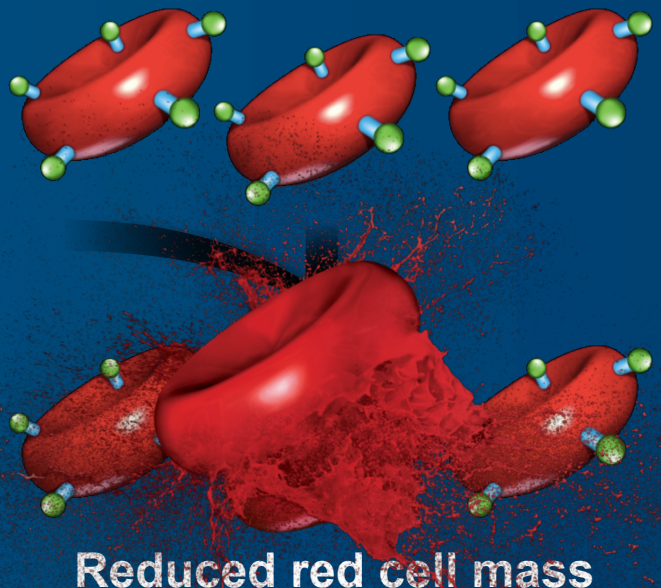


Intact RBC

Complement activation

Lack of bound CD55 and CD59 leads to uncontrolled complement activation

Without this protective complement inhibitor shield, PNH RBCs are destroyed



Reduced red cell mass

Free hemoglobin

GPI = glycosylphosphoinositol.

1. Parker C et al., 2005.; 2. Brodsky R *in* Hoffman R et al., eds. 2005.; 3. Rother RP et al., 2005.; 4. Socié G et al., 1996.; 5. Hill A et al., 2007.

CHRONIC UNCONTROLLED COMPLEMENT ACTIVATION LEADS TO DEVASTATING CONSEQUENCES

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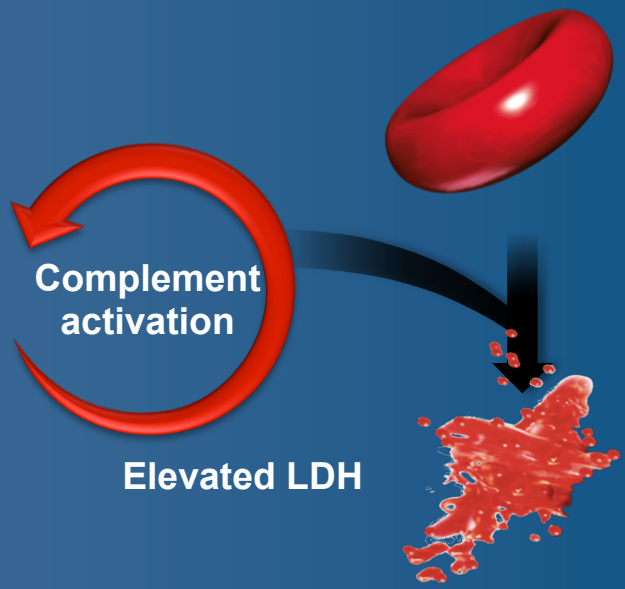


- Thrombosis
- Renal failure
- Pulmonary hypertension
- Abdominal pain
- Chest pain
- Dyspnea

Significant impact on survival

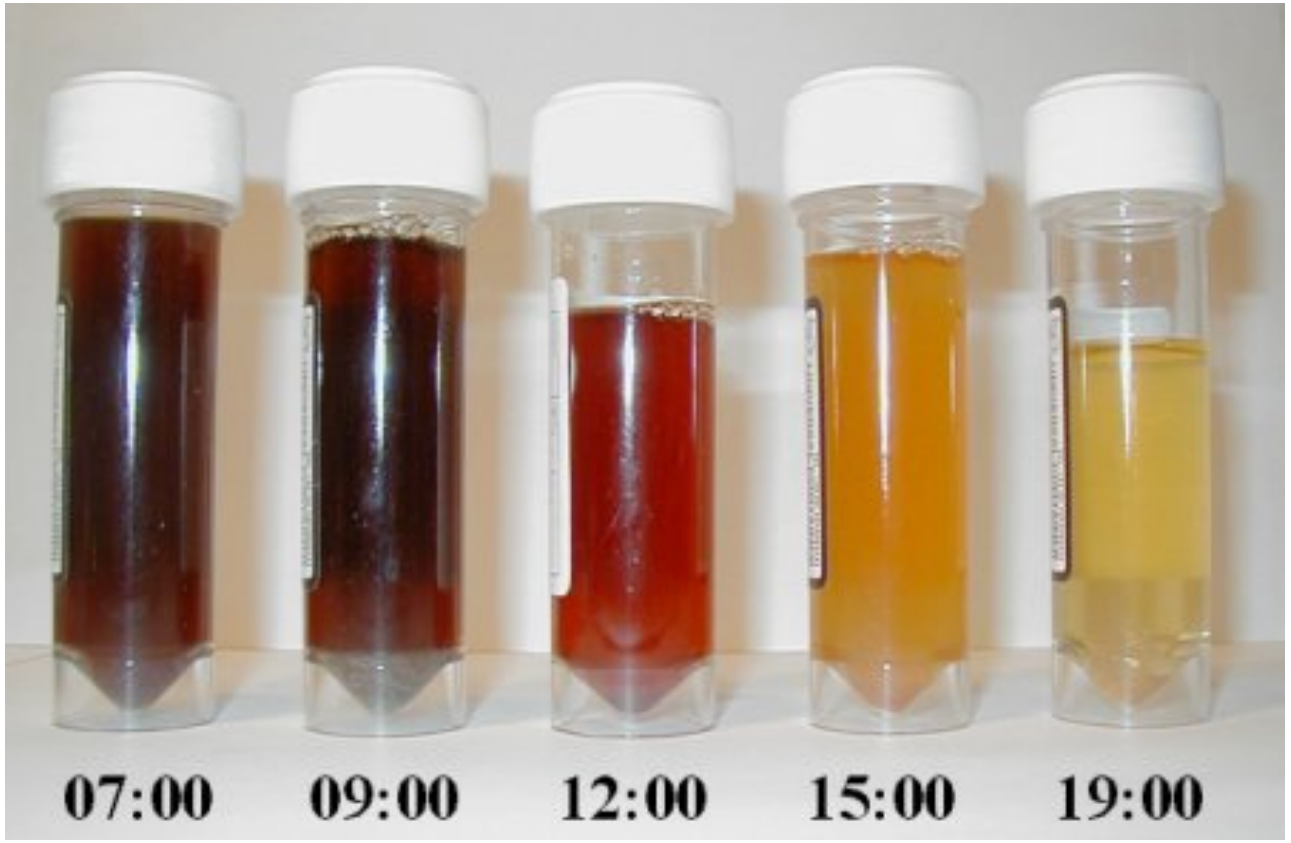
- Dysphagia
- Fatigue
- Hemoglobinuria
- Erectile dysfunction

Significant impact on morbidity

LDH = lactate dehydrogenase.

1. Parker C et al., 2005.; 2. Brodsky R *in* Hoffman R et al., eds. 2005.; 3. Rother RP et al., 2005.; 4. Socié G et al., 1996.; 5. Hill A et al., 2007.; 6. Lee JW et al., 2010 .; 7. Hill A et al., 2010.; 8. Hillmen P et al., 2010.

Clinical Manifestations
Intravascular Hemolysis



Clinical Manifestations
Venous Thrombosis

- Correlates with % PNH Granulocytes and D-dimers
- Higher incidence in whites than Asians
- Conventional and unusual sites
- Classic Budd Chiari
- Cerebral Veins
- ? Thrombosis enhanced With complement activation, More micro particle production, more tissue factor all contributors

Thrombosis

- 40% of PNH patients experience clinical TE
- Leading cause of death
  - Accounts for 40–67% of deaths
  - First TE can be fatal
  - Median time to TE was 2.3 years from diagnosis
- First TE increases risk for death 5- to 10-fold

THROMBOTIC EVENTS OCCUR IN A RANGE OF SITES, BOTH USUAL AND UNUSUAL

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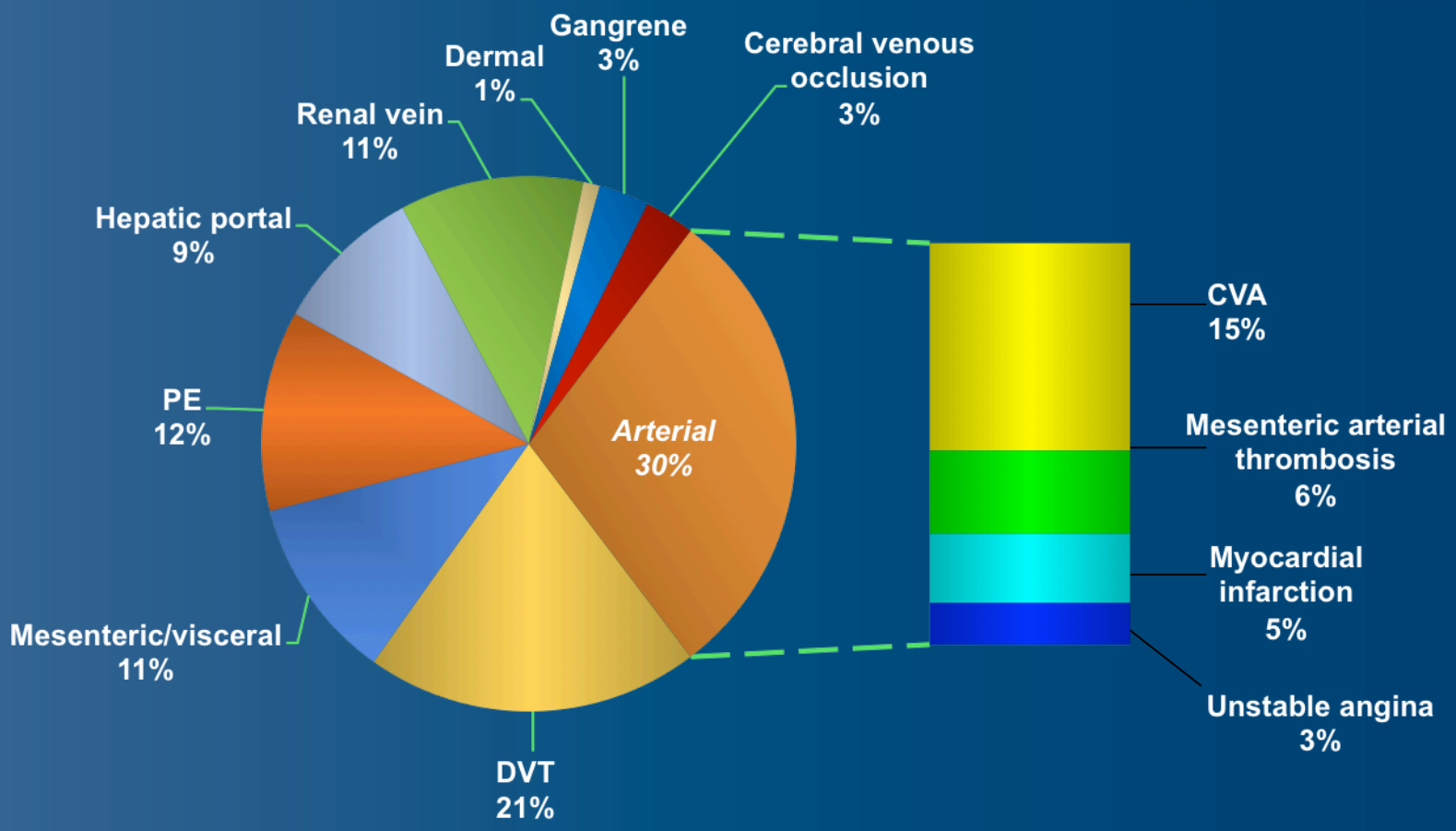


Arterial TEs were common in a large retrospective analysis

CVA = cerebrovascular accident; PE = pulmonary embolism.

South Korean National Registry.
Lee JW et al., 2013.

Clinical Manifestations
Bone Marrow Failure

- Complex relationship with AA
- PNH stem cell may have a survival advantage expanding post IS rx for AA
- Stem Cells may reduced proliferative ability
- Often complex with rbc hyperplasia and reduced wbc activity

Clinical Manifestations
Misc

- Esophageal Spasm
- Impotence
- Abdominal Pain

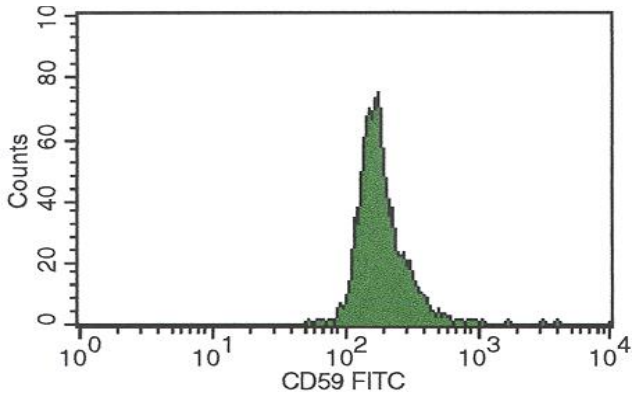
- ? Related to absence of Nitrous Oxide which is nb for smooth muscle relaxation

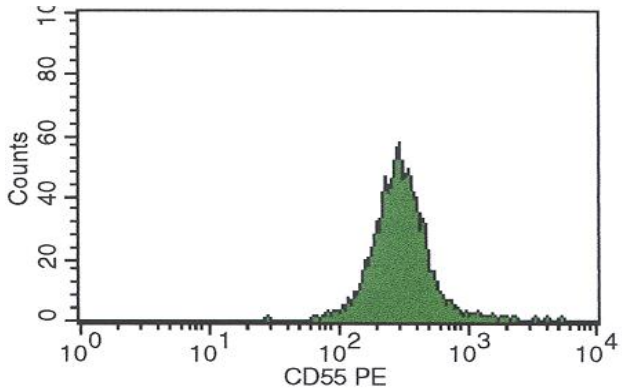
Laboratory Tests

- CBC and differential
- Markers of Hemolysis
- LAP Score historical
- Sucrose Lysis Test historical
- Ham's Acidified Serum Test historical
- Flow Cytometry gold standard

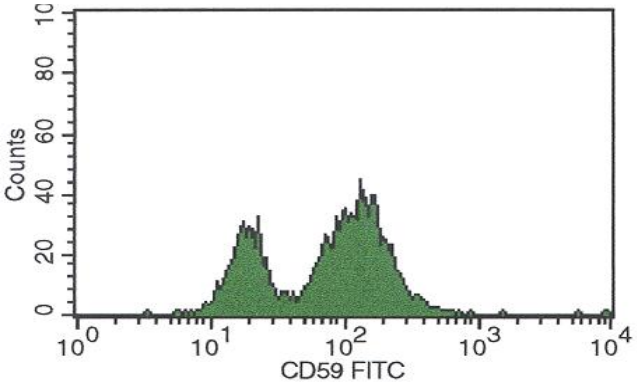
Laboratory Tests – Flow Cytometry

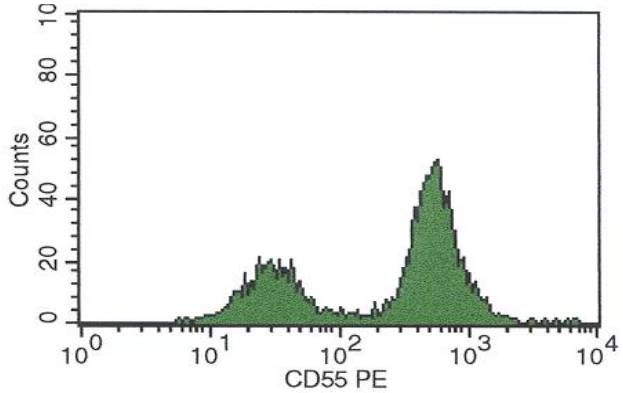
Healthy Control





Patient





Treatment (Hemolysis)

- Consider role of marrow failure in anemia
- Corticosteroids:
  - No trials but may help in acute episodes
  - No role in long term management
- Androgens
  - Possible role in both for acute and long term care
- Iron and folate replacement
- Transfusions for support

Treatment (Hemolysis)

- Complement inhibitor:
  - Monoclonal antibody against complement C5 (eculizumab) in Phase 3 trials
  - Phase 2 trials showed improved control of the signs and symptoms of hemolysis and better quality of life
  - Q14 day regimen
  - Approved in Canada with rigid criteria
  - Cost +++

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: COMPELLING LONG-TERM CLINICAL BENEFITS IN PNH PATIENTS

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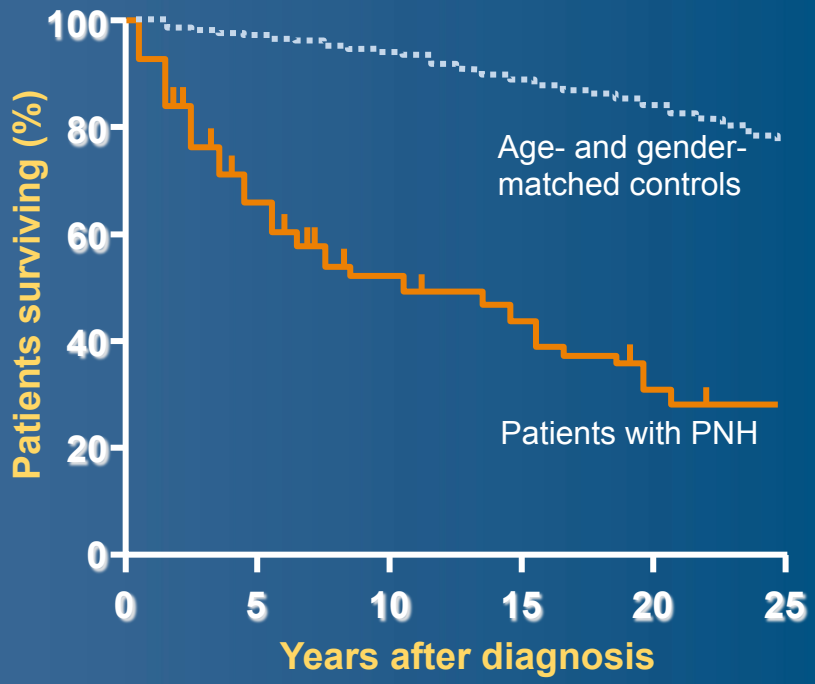
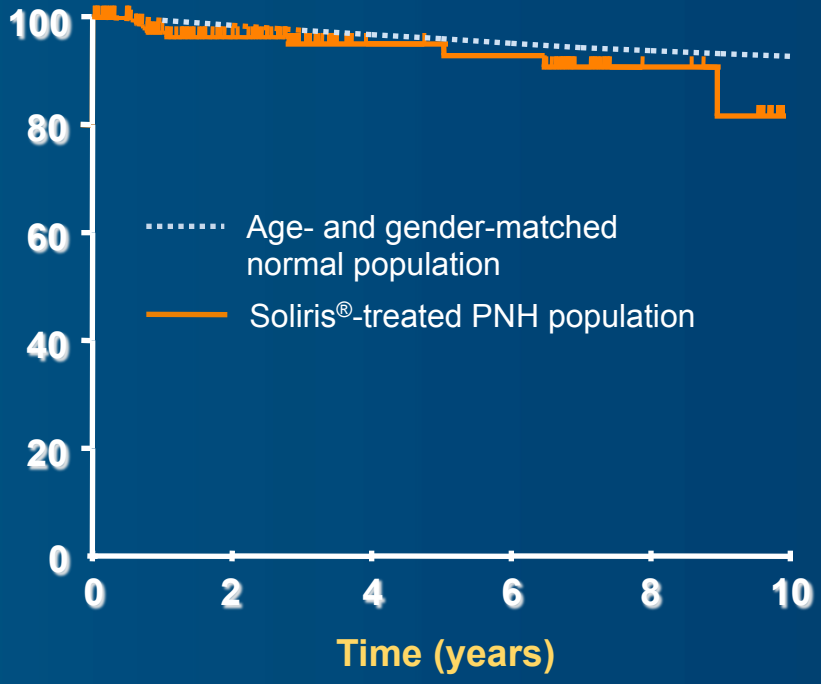
Pre-Soliris® from time of diagnosis in 80 patients with PNH[1]



- Despite best supportive care, 5-year mortality rate was 35%[1]

PNH patients on Soliris® compared with age- and gender-matched controls[2*]



- Hazard ratio = 2.24 (p = 0.013)

*Survival after 10 years is slightly inferior to controls with causes of death related to bone marrow failure and not hemolysis or thrombosis.

1. Hillmen P et al., 1995.; 2. Hill A et al., 2012.; 3. Soliris® (eculizumab) Product Monograph, 2013.

Treatment (Thrombosis)

- Primary Prophylaxis:
  - PNH WBC clones >50% 10 year thrombosis risk 44% vs 5.8% with smaller clones
  - Surgery, pregnancy
- Treatment of thromboembolic episodes:
  - Need immediate anticoagulation and then oral anticoagulation indefinitely
  - May require thrombolysis

Treatment

- Stem Cell Transplant
  - Patient with life threatening disease
  - Marrow failure
  - ? Children
  - Severe thrombotic events

BONE MARROW TRANSPLANTATION FOR MANAGEMENT OF PNH

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Bone marrow transplantation (BMT) is the only curative therapy

- BMT is associated with significant morbidity and mortality
- International Bone Marrow Transplant Registry (IBMTR)
  - 56% 2-year survival (n=48 HLA-identical sibling transplants)
  - 14% 5-year survival of allogeneic transplants
  - 33% chronic graft vs. host disease (1999)
- The European Blood and Marrow Transplant (2008)
  - N=141 (64% HLA-identical sibling donors)
  - 70% 5-year survival rate
  - 32% chronic graft vs. host disease
- Allogeneic BMT is only recommended for PNH patients with life-threatening cytopenias, or possibly the rare patient with disabling hemolysis or thrombosis not controlled with eculizumab

HLA = human leukocyte antigen.

Future directions

- New complement inhibitors
- Gene Therapy
  - Correction of the PIG-A gene
- Protein Transfer
  - Transfer of GPI-proteins with microvesicles or lipoproteins

PNH

- Survival
  - Median 10-15 years but many live >25 years
  - Death primarily due to thrombotic events or bleeding
  - Occasional spontaneous recovery

Canadian PNH Network: Vision and mission

- Our Vision:
- "Patients in Canada must receive world-leading care that extends over case recognition, diagnosis and treatment follow-up."

- Our Mission:

1. To maintain the highest standard of clinical practice in the diagnosis and management of PNH

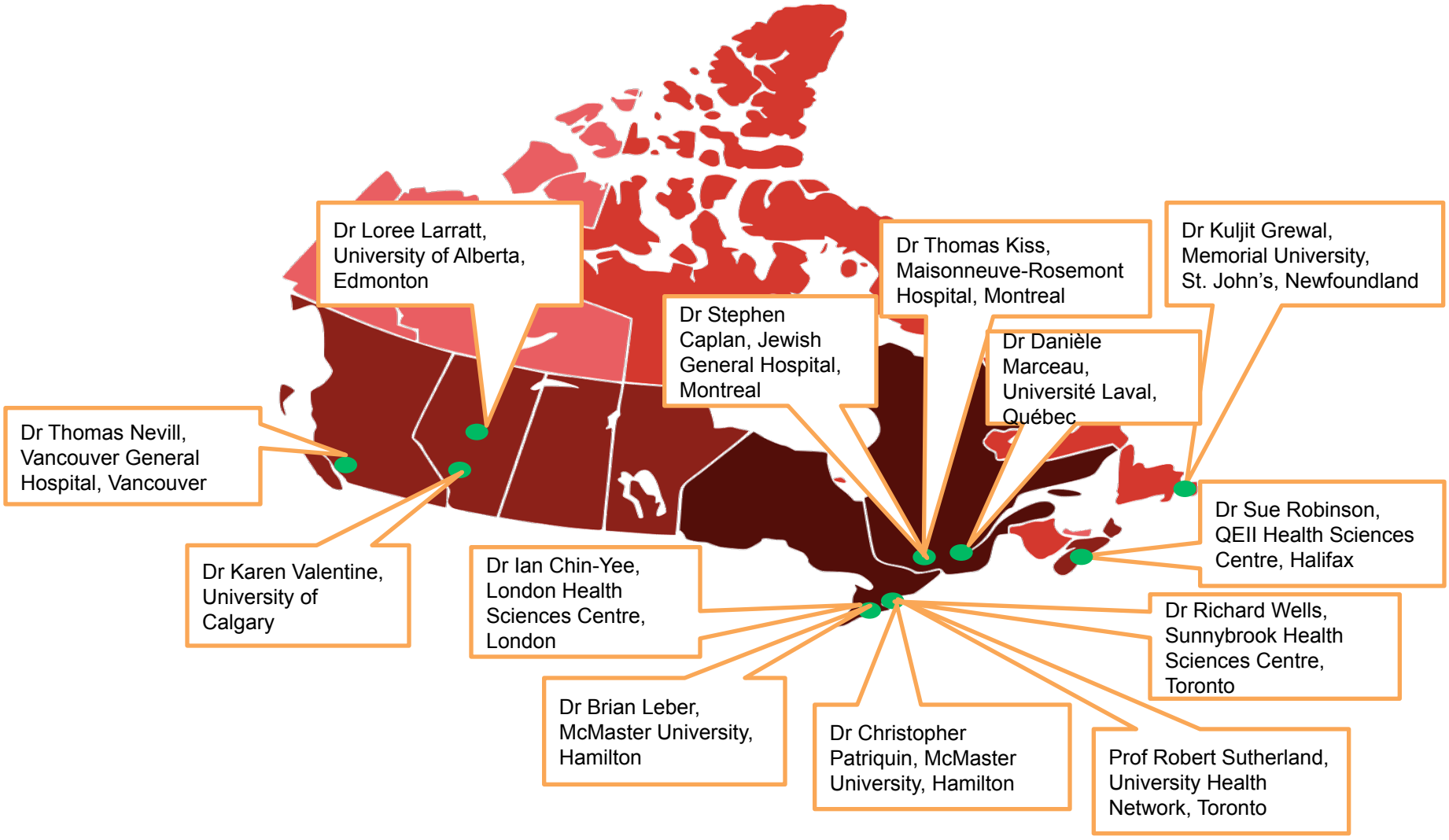
2. To provide continuing health education on the evolving management of PNH patients

3. To participate in the PNH registry to gain further understanding of the natural history of PNH

Canadian PNH Network: Goals

- To improve outcomes for patients with PNH by raising awareness of the disease, facilitating timely and accurate laboratory diagnosis, and helping to initiate the proper treatment strategy through a variety of research, education, and clinical initiatives. This will be achieved by:
  - Creating a globally recognized expert physician group in Canada
  - Improving patient care and access
  - Deploying nation-wide state-of-the-art flow cytometric assays to detect PNH
  - Advancing disease knowledge
  - Publishing uniquely Canadian data

Canadian PNH Network: Centres of Expertise



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- Questions?