Acquired Aplastic Anaemia (AA) & Paroxysmal Nocturnal Hemoglobinuria (PNH) – Where is the link?

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AA and PNH

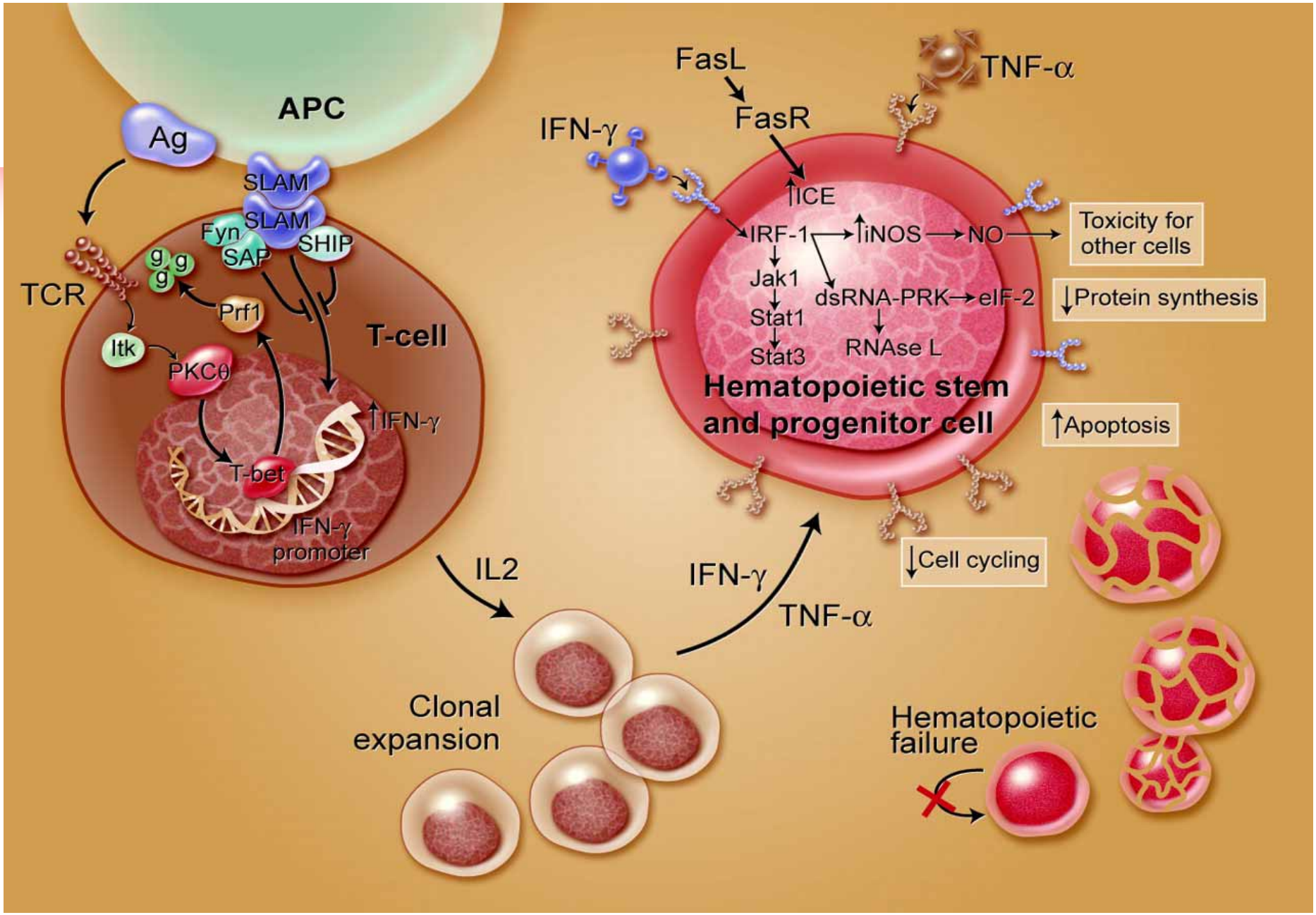
- What is AA?
- What is PNH?
- Is there a common link between AA and PNH?
- Treatment Options

What is AA?

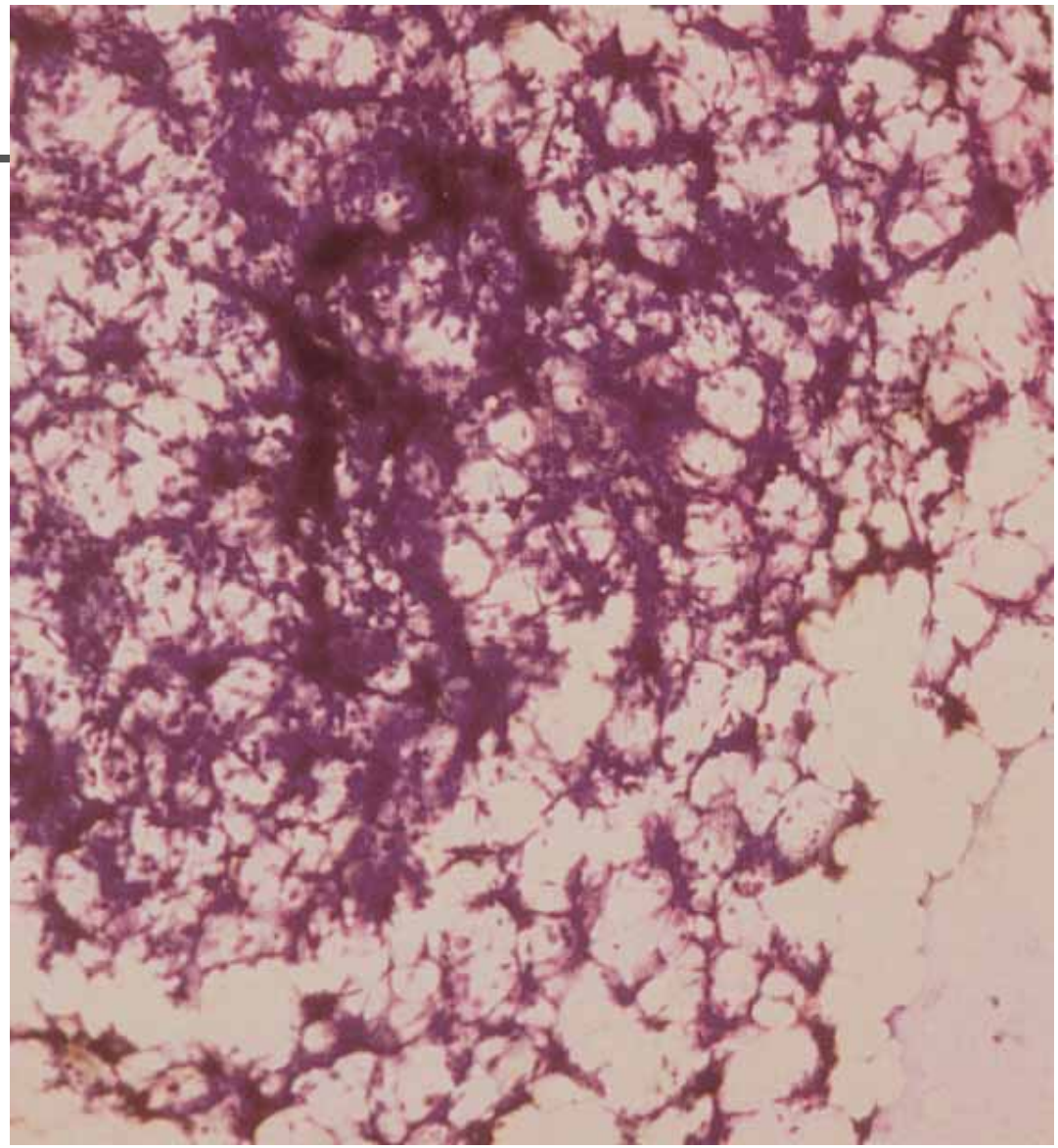
- Bone marrow failure
- Decreased / absent production of normal blood cells
- Manifests as
  - Decreased red cells — Anemia
  - White blood cells — Infections
  - Platelets — Bleeding complications

Causes of Acquired AA

- Idiopathic (75-80%)
- Drugs e.g NSAID, chloramphenicol
- Chemicals such as benzene
- Hepatitis kind of illness
- Viruses
- Pregnancy

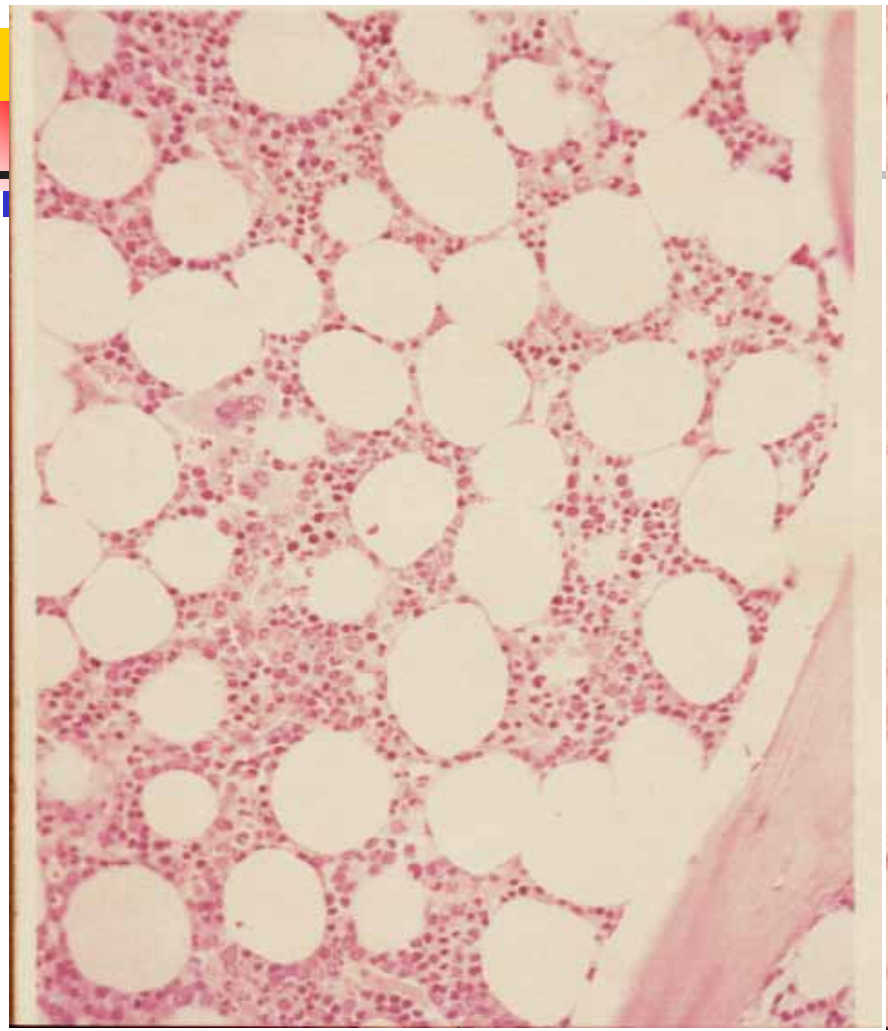

APC
Ag
SLAM
SLAM
Fyn
SAP
SHIP
TCR
g
g
g
Prf1
Itk
PKCθ
T-cell
IFN-γ
T-bet
IFN-γ promoter
IL2
Clonal expansion
IFN-γ
TNF-α
FasL
FasR
TNF-α
IFN-γ
ICE
IRF-1
iNOS
NO
Toxicity for other cells
Jak1
dsRNA-PRK
eIF-2
Protein synthesis
Stat1
Stat3
RNAse L
Hematopoietic stem and progenitor cell
Apoptosis
Cell cycling
Hematopoietic failure

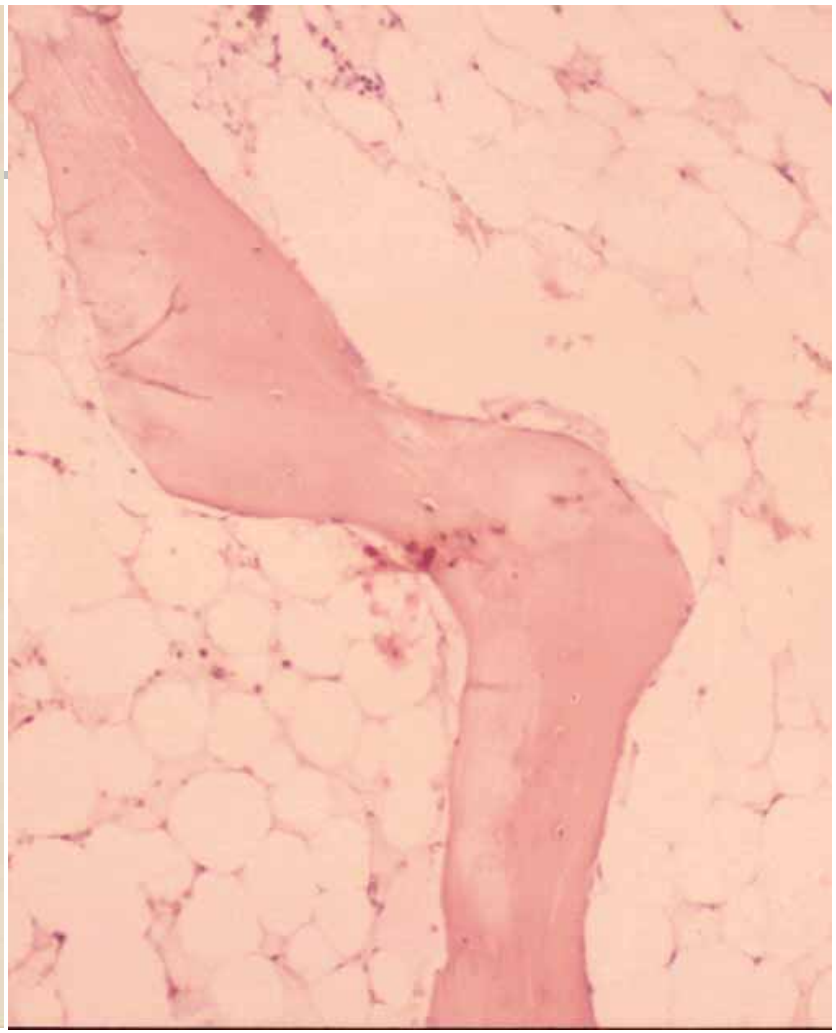
Aplastic anaemia bone marrow aspirate



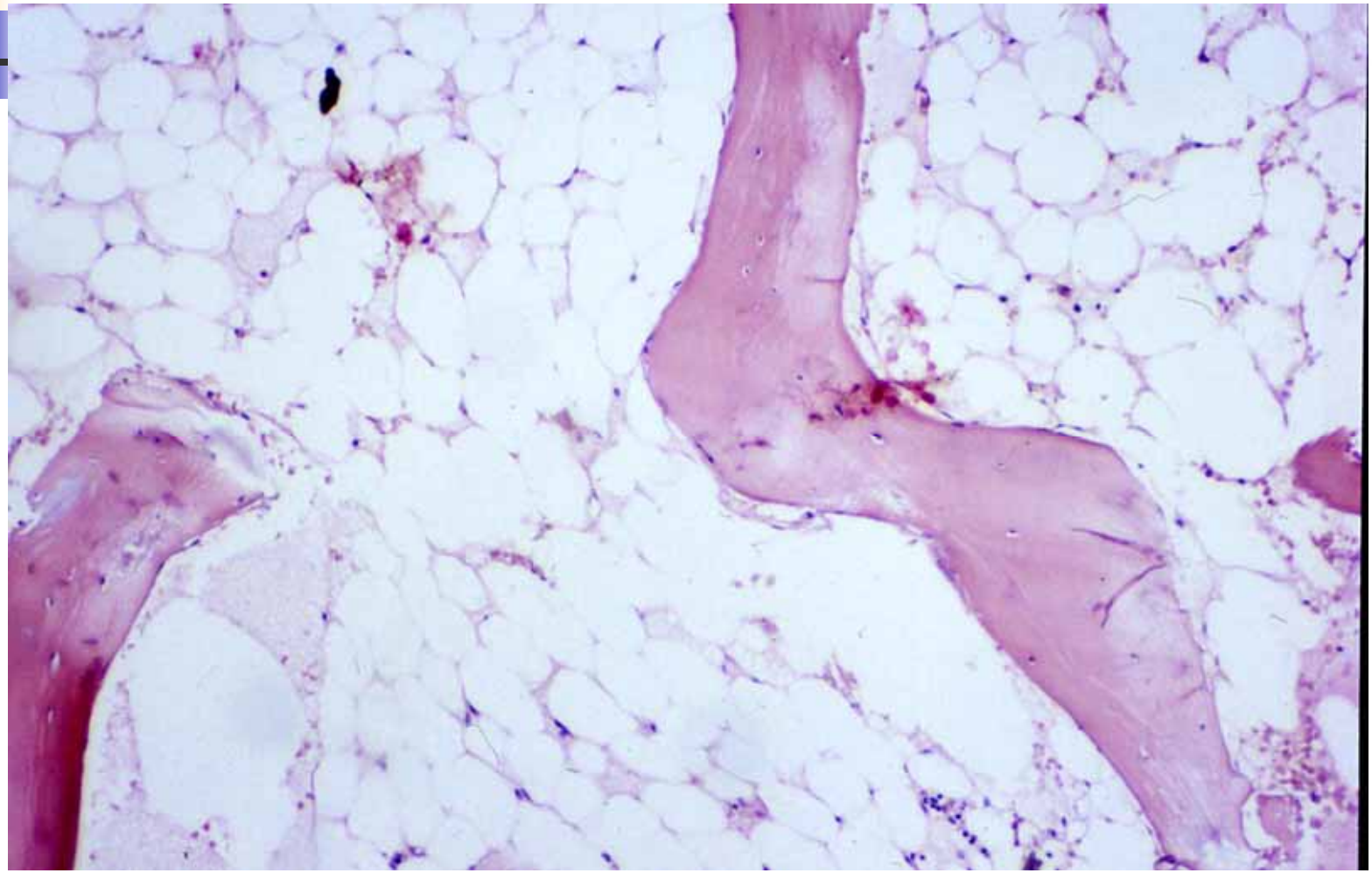
Normal

Severe aplastic anaemia





Aplastic anaemia

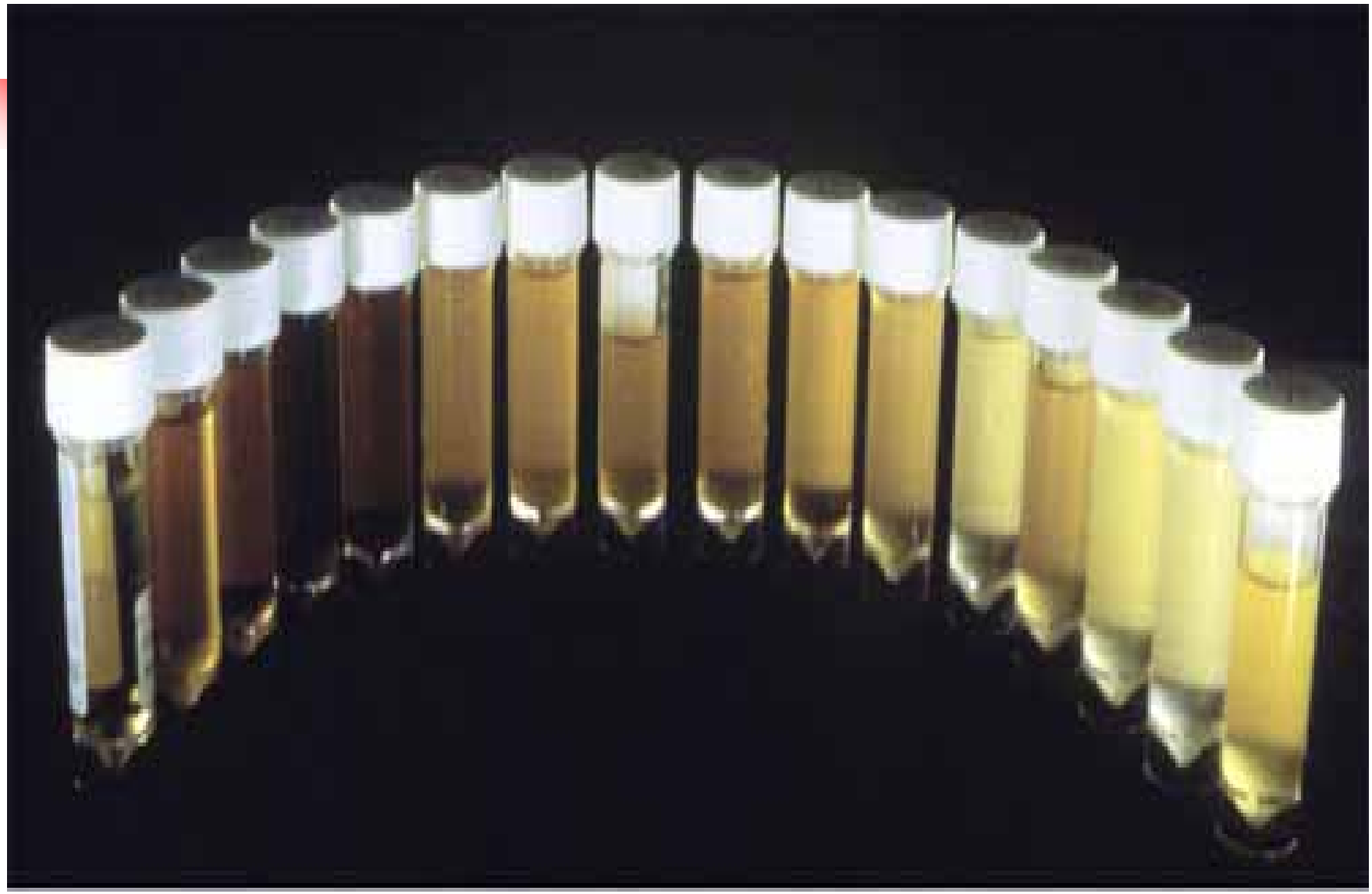


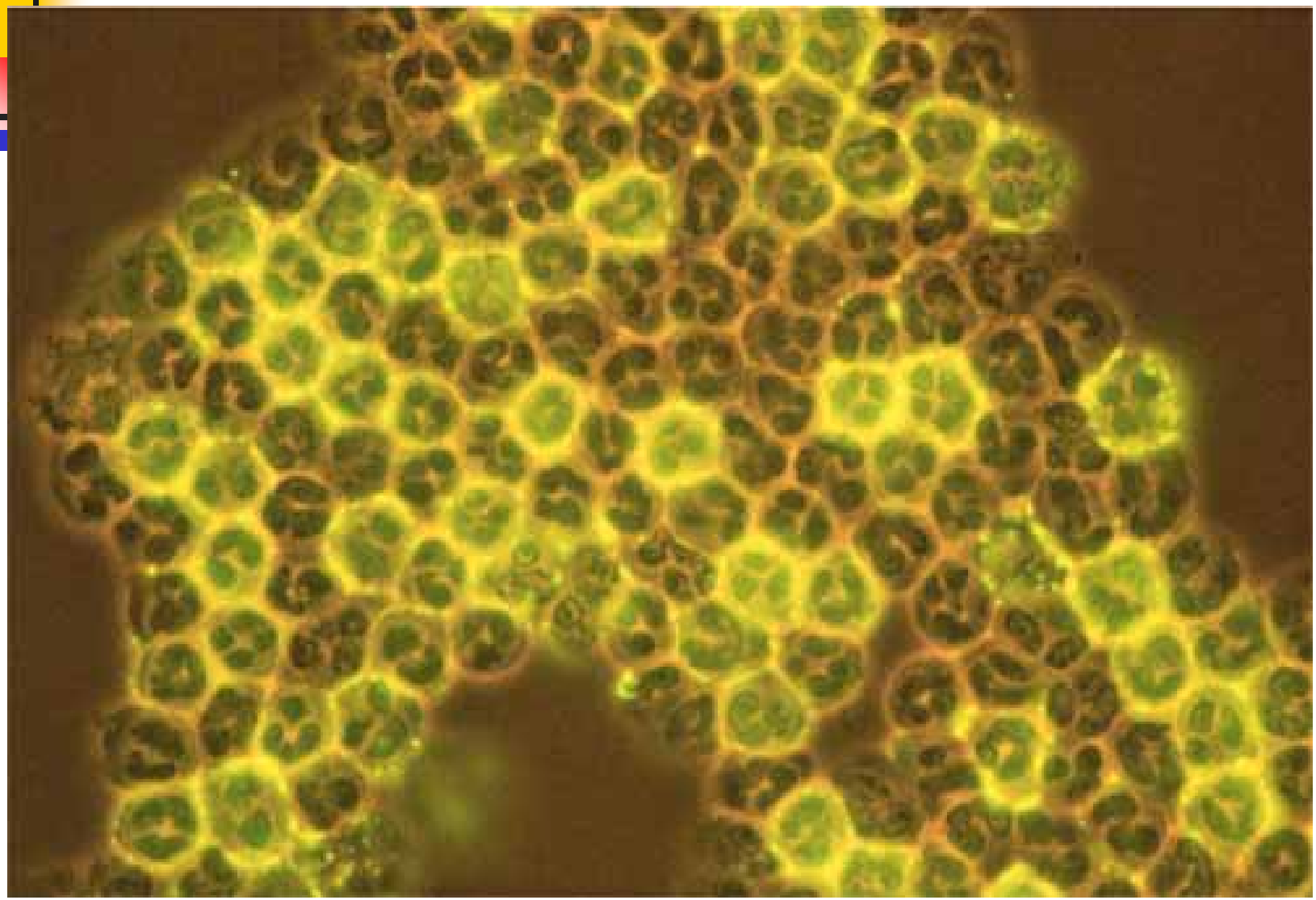
What is PNH?

- First description “voided dark urine only in the morning”
- Why it happens?
  - Expansion of one or several clones which can grow in BM environment where normal BM cells have difficulty in growing
  - Blood cells derived from PNH clone are deficient in proteins which use Glycophosphotidyl Inositol (GPI) for attachment to cell surface

PNH

- Some of these proteins such as CD55 and CD59 protect the red cells against attack by component of immune system called complement
- PNH blood cells lack these proteins
- Complement can attack and punch a hole in red blood cells
- Bursting red blood cells release Hb, which is passed in the urine
- Term PNH a “misnomer”





What are other symptoms of PNH?

- Dark color urine
- Abdominal pain
- Headache
- Esophageal spasm
- Anemia
- Fatigue
- Impotence
- Increased tendency to develop blood clots

Case Study

- 26F diagnosed with AA in Jan 2004, no treatment received as patient was pregnant
- July 2006 – sent to PMH for second opinion regarding treatment allogeneic BMT versus immunosuppression
- Very heavily transfused
  - Had received 50 pRBC and 20 platelet transfusions to date
- Had Matched sibling donor
- Repeated work up - PNH screen sent during initial assessment

Case Study

- PNH screen:
  - Granulocytes — 90% FLAER negative
  - Monocytes — 83% FLAER negative
  - RBCs — >95% Type I
    <0.01 Type II
    0.01 Type III
  - Technologist noted recent pRBC transfusion
  - **Aplastic anemia with large PNH clone**
- Decision: proceed with alloBMT

Case Study

- August 2006: Presents with severe abdominal pain
  - CT scan: multiple thrombi of hepatic veins
  - Platelet count = 20
- Tinzaparin (blood thinner) started
- Transplant postponed until resolution of thrombi

Case Study

- Subsequently, thrombosis resolved
- Received transplant in Dec 2006
- Transplant
  - Restoration of normal blood counts
  - PNH clone disappeared
  - Now 21 months post transplant and doing well

Case Summary

- A young patient with aplastic anemia developed expansion of PNH clone and later on developed life threatening complications in form blood clot
- Question?
  - Why do AA patients develop PNH?

We all have a little PNH in us

- Healthy controls have 22 GPI-AP-deficient granulocytes per 10^6 cells
- But why do we not progress to PNH?

AA and PNH – the link

- Immune attack needs GPI anchored protein
- PNH cells lack GPI anchor protein, therefore spared from immune attack
- These cells can expand in patients with AA whose marrow is empty
- Expansion of clone can cause symptoms of disease either as hemolysis or thrombosis

PNH clones in AA and MDS

- 30-40% of aplastic anemia have PNH clones
  - 5% of untreated patients will exhibit PNH clone expansion, and progress to clinical PNH
- 10-20% of MDS have PNH clones

Treatment Options for AA

- Bone Marrow Transplantation
- Immunosuppressive therapy

HLA identical sibling BMT

Initial treatment of choice if :

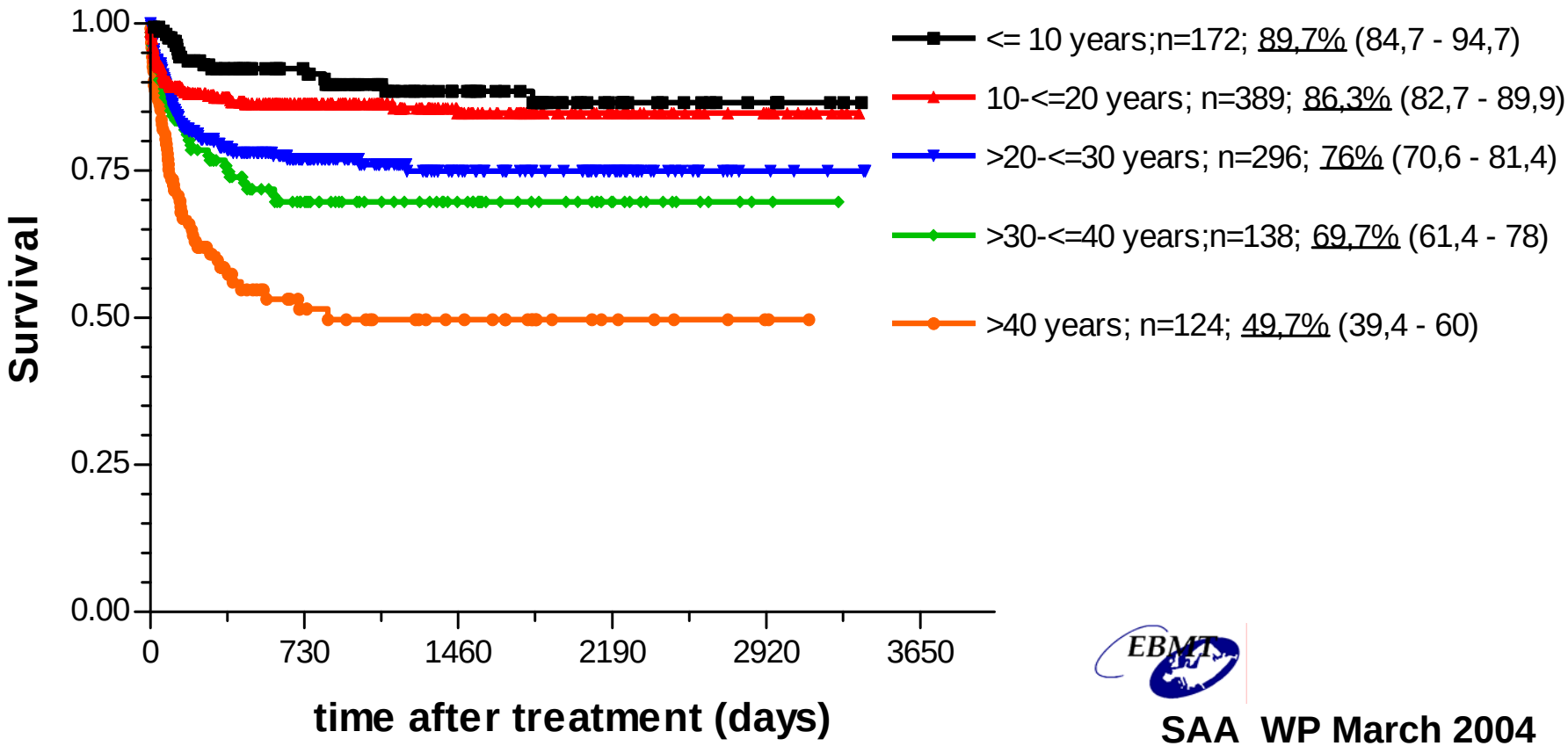
- severe or very severe aplastic anaemia
- HLA identical sibling
- age <40 yr

Controversy over upper age limit

WP AA Registry: Survival for aplastic anaemia

HLA identical sibling donors (1994 – 2003)

stratified by age at transplant (years)



EBMT

SAA WP March 2004

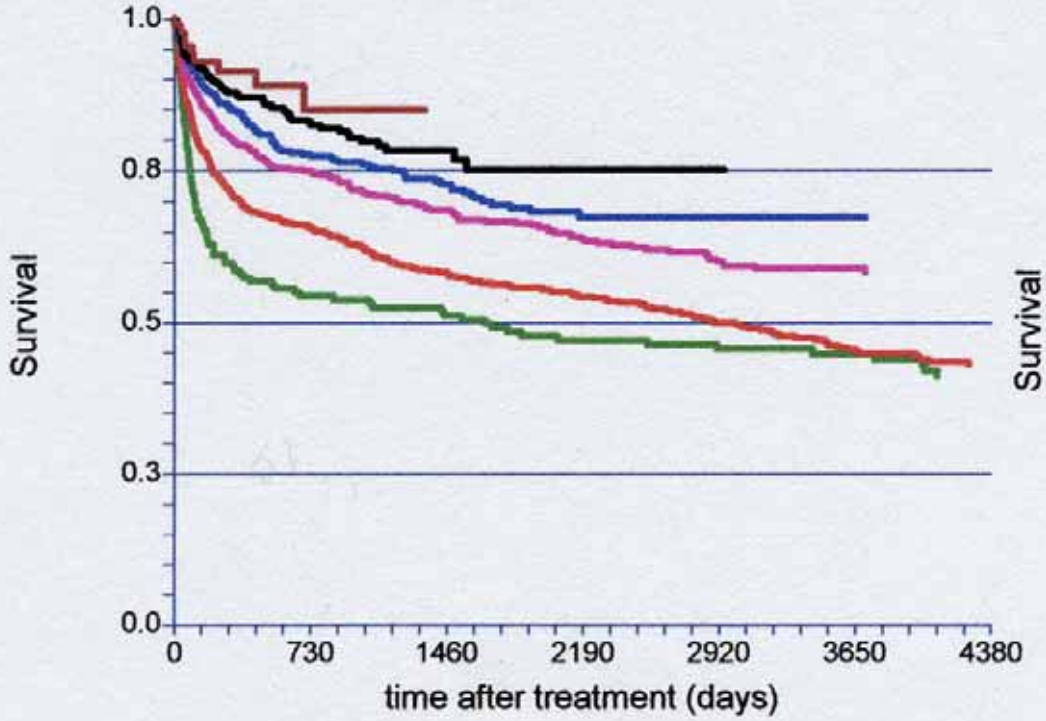
Indications for immunosuppressive therapy (IST)

Severe or very severe AA >40y of age

Non-severe AA and transfusion dependent

Severe or very severe AA <40 y with no compatible sibling donor

Immunosuppression



	Time period	*IS, survival at 3 years*
1	< 1980	52% (45%-60%)
2	1980-1985	61% (57%-65%)
3	1986-1989	71% (67%-75%)
4	1990-1993	75% (71%-80%)
5	1994-1997	80% (75%-84%)
6	1998-2001	85% (74%-95%)

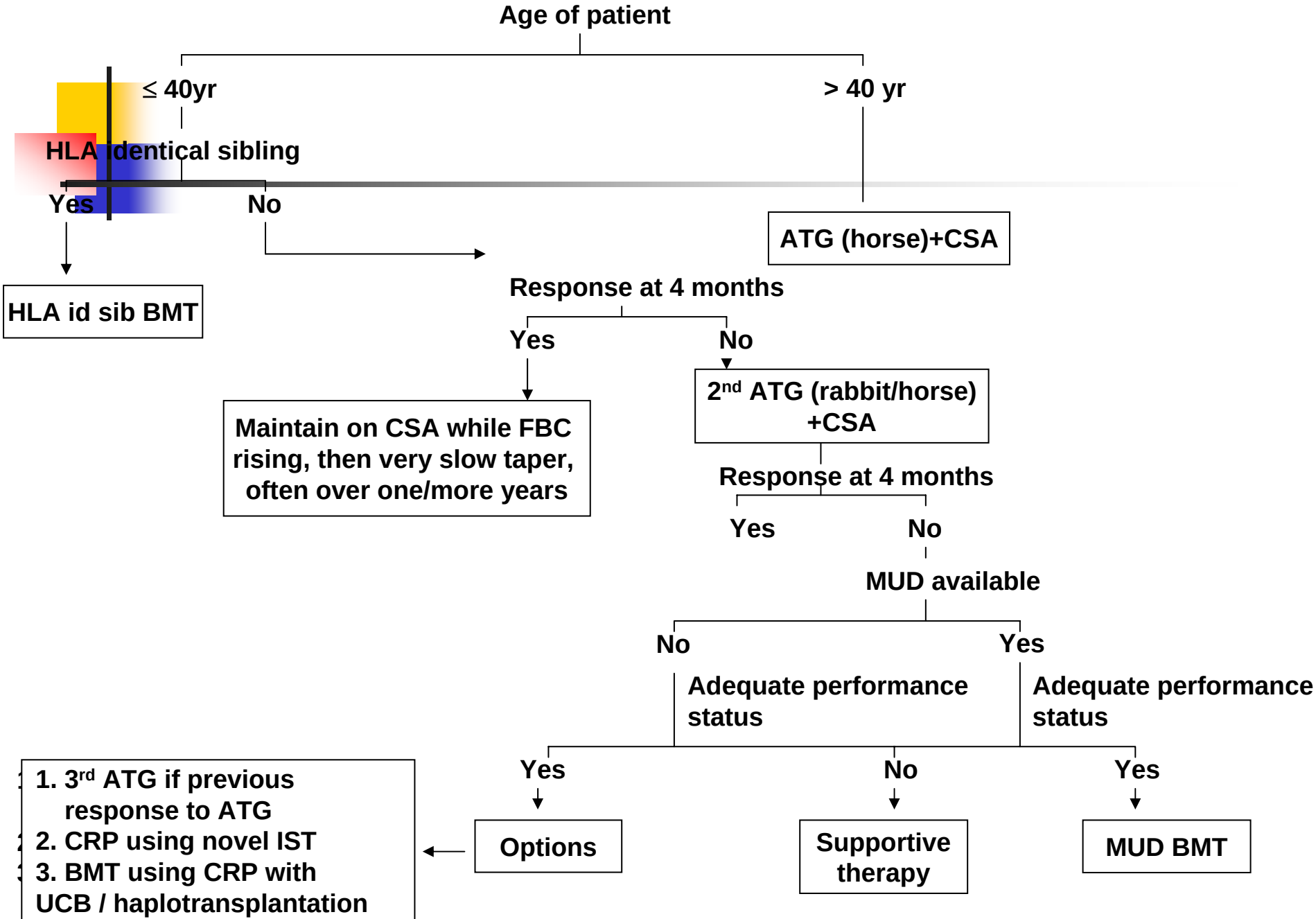
What is the optimum Immunosuppressive therapy (IST)

- Randomized studies have shown the combination of ATG and CSA is superior to either drug alone
- Therefore, ATG and CSA is considered the current standard of care
- No additional benefit of adding GCSF

Immunosuppressive therapy (IST)

- ATG + CSA is current standard of care of IST and is an effective treatment but
  - 65-70% respond
  - Delayed response
  - One third of responders relapse
  - secondary complications occur
    - Risk of clonal disorders such as MDS/AML,PNH
    - Cytogenetic evolution
    - Solid tumors

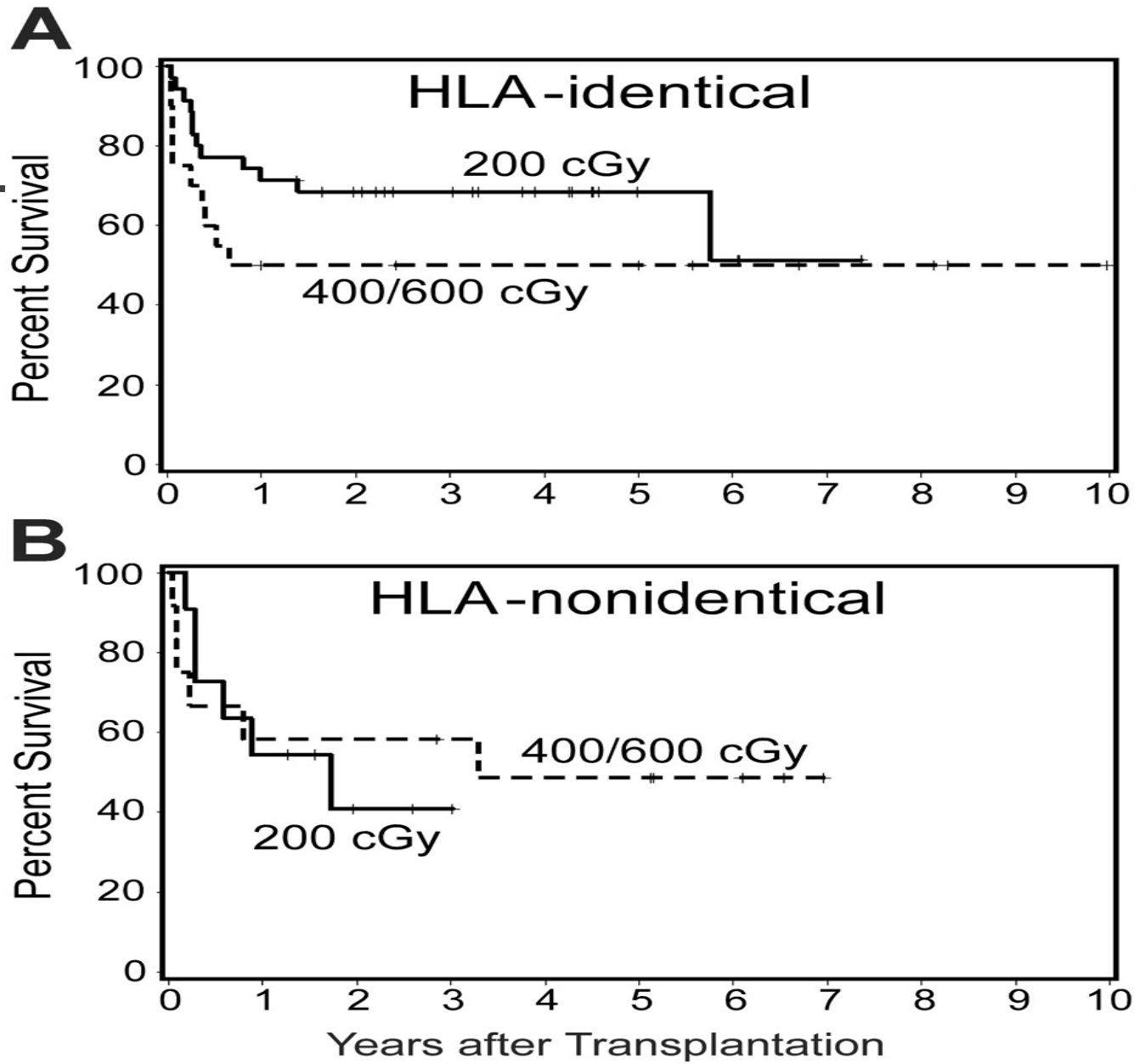
Treatment strategies for newly diagnosed patient with Severe Aplastic Anaemia (Gupta and Marsh, 2008)



How these treatment algorithm may change?

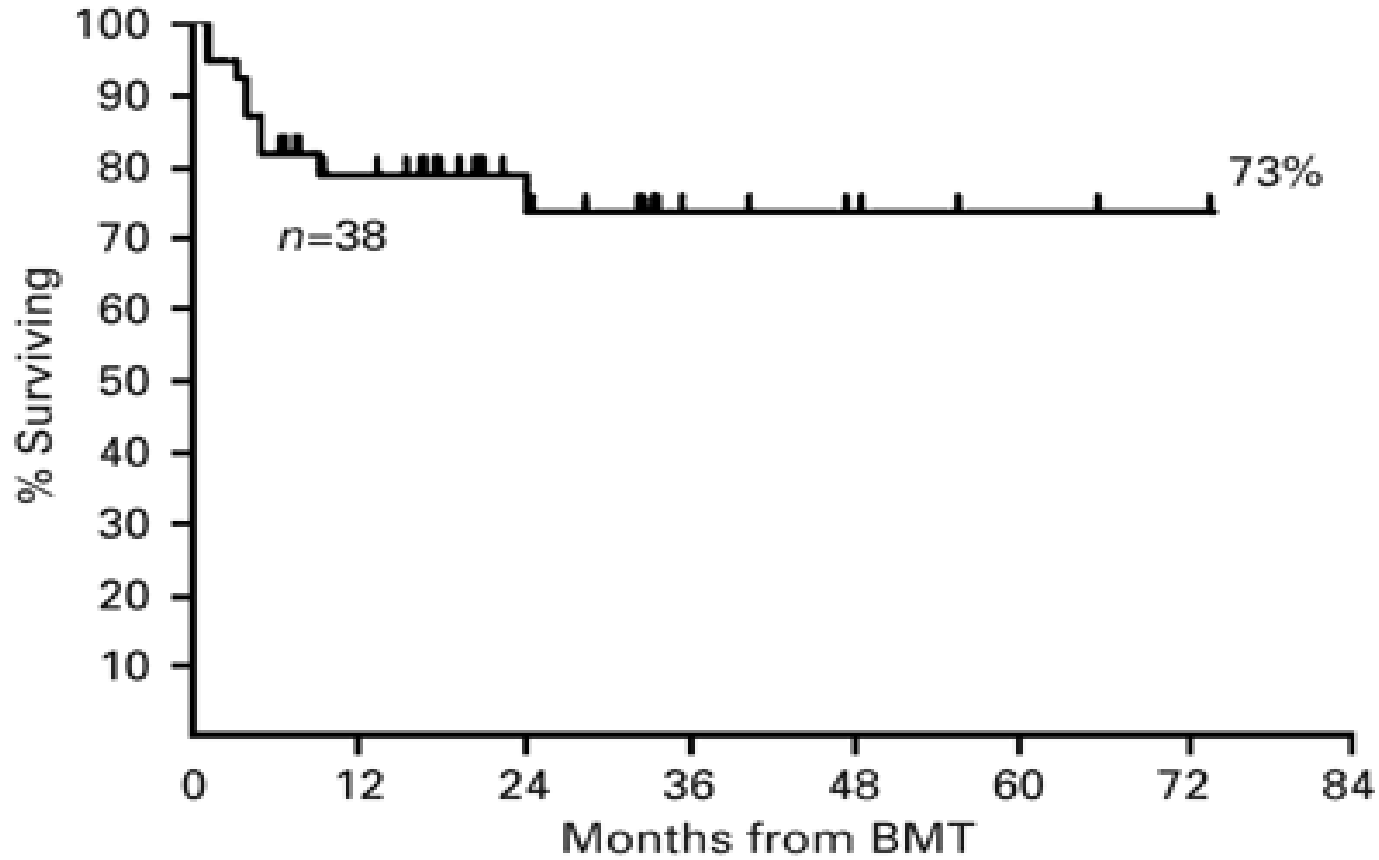
- Increased use of alternative donor transplants
- Results of unrelated donor transplants also appears to have improved recently
  - Better HLA matching techniques
  - Better supportive care

Unrelated donor tx for AA (Deeg et al. Blood 2006)



Low-Dose Cyclophosphamide, Fludarabine and ATG as preparative regimen for aplastic anaemia from alternative donors

(Bacigalupo et al, BMT, 2005)



Treatment Options for PNH

- Best treatment strategy “Learn to live with PNH”

  Lucio Lazatto, ASH 2000

- Has this changed?

Treatment Options for PNH

- Anemia
- Thrombosis
- Allogeneic BMT
- Novel therapeutic strategies

Anemia

- PRBC transfusion
- Iron supplement
- Folic acid
- Prednisone
- Androgenic hormones
- Recombinant monoclonal antibody (Eculizumab)

Thrombosis

- **Acute thrombosis treated with anticoagulation**
  - Lifelong anticoagulant treatment may be indicated
  - Prednisone ***may*** reduce complement activation

Thromboprophylaxis

- Warfarin (INR 2-3) for patients with granulocyte clone > 50%, PLT > 100
  - Retrospective study: at 10 years, 0% of prophylaxed patients had clots and 36.5% of non-prophylaxed had clots
  - 2 serious bleeds per 100 patient-years

Allogeneic stem cell Transplantation

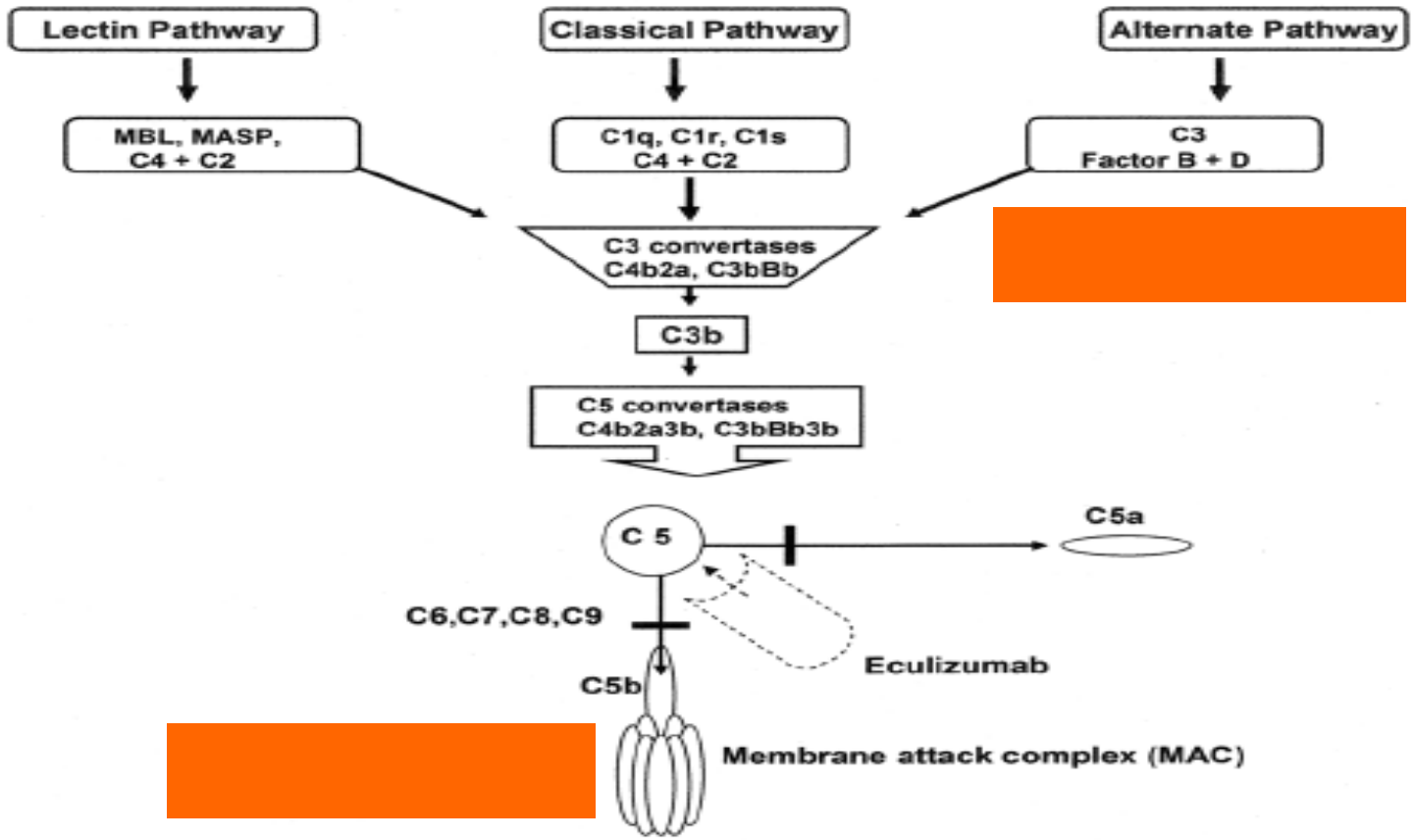
- **The only curative strategy**
- Carries considerable risk of mortality
- Mortality appears to be decreasing with reduced intensity transplants
- No consensus
  - Ideal timing of transplant? – Early versus late

Indications for consideration of transplantation

- Bone marrow failure.

- Major complication of PNH
  - Recurrent, life threatening thromboembolic events
  - Refractory, transfusion dependent hemolytic anemia

Can We Block Complement?



Eculizumab

- A recombinant humanized monoclonal antibody that binds to the C5 component of complement, inhibiting its cleavage into C5a & C5b
- Inhibits terminal complement activation
- Reported 1st in an open-label pilot study employing 11 transfusion- dependent patients with PNH

(Hillmen *et al*, Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. *NEJM 2004 Feb)*

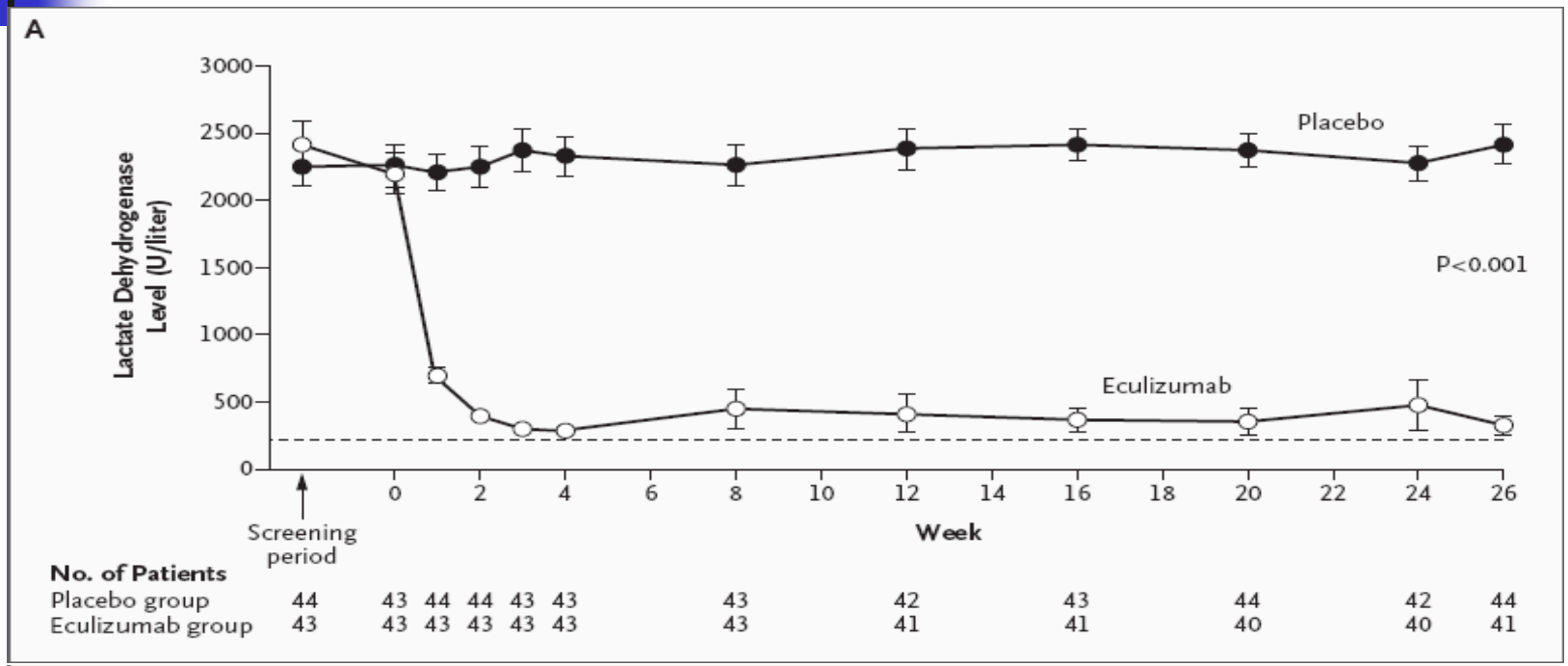
TRIUMPH study - 2006

- Phase 3 Transfusion Reduction Efficacy and Safety Clinical Investigation,a Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

- AIM:

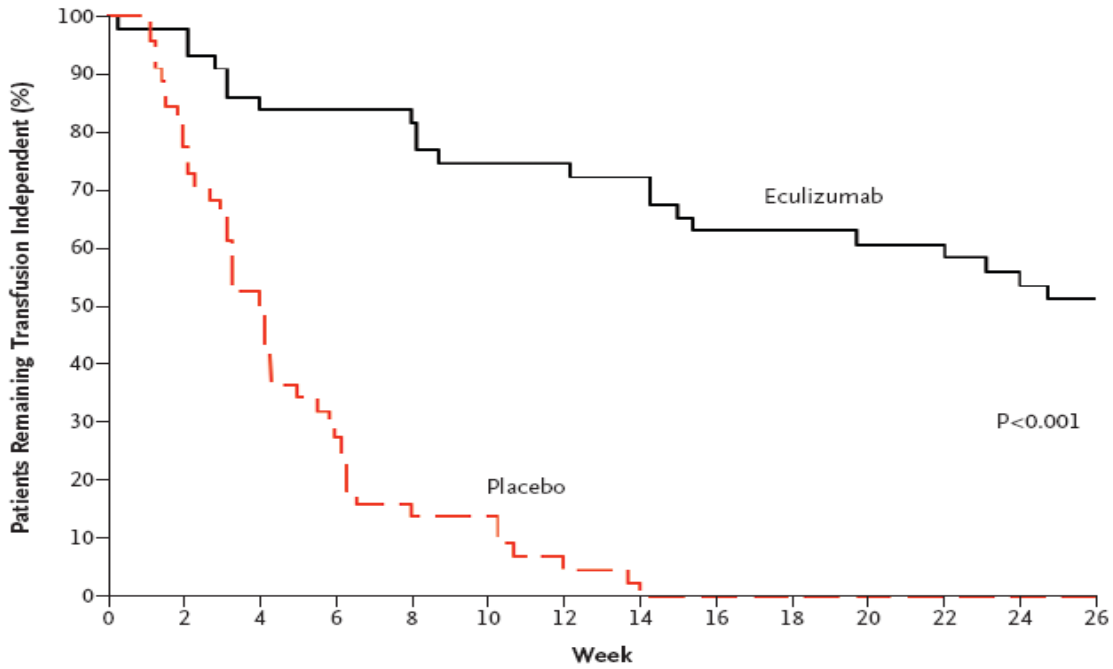
- safety & efficacy of Eculizumab in patients with PNH
- stabilized hemoglobin levels and reduced transfusion requirements in 87 transfusion-dependent patients with PNH during 6 months of treatment.

Effect on Hemolysis



Panel A shows the degree of intravascular hemolysis according to the mean levels of lactate dehydrogenase from baseline (week 0) to week 26 in the two study groups. The dashed line indicates the upper limit of the normal range for lactate dehydrogenase (normal range, 103 to 223 U per liter). In the eculizumab group the mean level of lactate dehydrogenase was reduced to just above the upper limit of the normal range at week 26; of 41 patients in this group who completed the study, 15 had levels within the normal range. In the placebo group, all patients had levels at least five times above the upper limit of normal at week 26.

Time to the first transfusion (Primary endpoints)

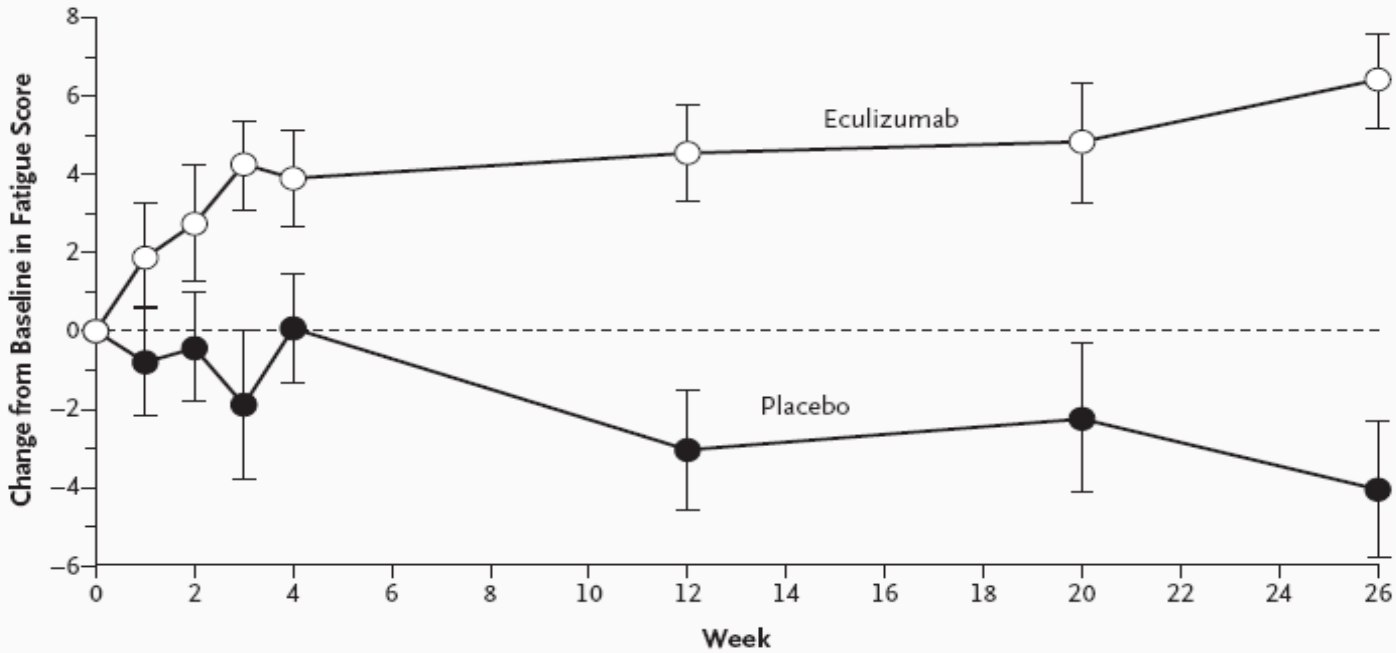


No. at Risk

Placebo group	44	44	36	30	23	13	7	6	3	1	0	0	0	0	0	0
Eculizumab group	43	41	41	39	37	36	36	32	32	31	27	27	26	26	24	22

Figure 2. Kaplan–Meier Curves for the Time to the First Transfusion during Treatment.
The P value for the comparison of times to the first transfusion between the two groups was calculated by the log-rank test.

Quality of Life



No. of Patients													
Placebo group	41	39	41	41	40			40			36		39
Eculizumab group	43	41	43	43	43			42			36		41

Figure 3. Change in Fatigue Scores from Baseline to Week 26.

Week 0 (baseline) represents the end of the observation period, within 10 days after the patient's receipt of the qualifying blood transfusion. Fatigue scores are therefore higher (indicating less fatigue) at week 0 than at the initial screening visits (data not shown). Values for the change from baseline (dashed line) represent means. A positive change from baseline indicates an improvement in fatigue and a negative change from baseline indicates a worsening in fatigue. I bars indicate the standard error.

Eculizumab

- Reduces intravascular hemolysis
- Reduces or eliminates need for transfusion
- Improves anemia, fatigue, and quality of life
- A recent case controlled study also showed significant decrease in thrombotic complications

Eculizumab

- Treatment with Eculizumab is chronic treatment
  - Does not fix the underlying problem
- Patient require long-term treatment every 2 weeks in form of IV infusions
- Toxicity of Eculizumab
  - Virtually none BUT>>>>>>

Toxicity of Eculizumab

- ONLY TOXICITY
  - FINANCIAL
- Available through SAP in Canada
- However, no Government funding mechanism established yet in Canada

Conclusion

- In the last decade, our understanding of the pathophysiology of AA and PNH have advanced significantly
- For patients with AA, there has been significant improvements in the results of marrow transplantation for related and unrelated donors
- Advances in immunotherapy and BMT have given us a hope of changing the natural history of PNH