ANEMIA

General information

Definition of anemia

1. Reduction in the hemoglobin concentration in blood
2. Decreased total circulating red cell mass

Normal values for peripheral blood

		Female	Male
Erythrocytes	(per µl)	$4.8 \pm 0.6 \times 10^6$	$5.4 \pm 0.8 \times 10^6$
Hemoglobin	(g/dl)	14 ±2	16 ±2
Hematocrit	(%)	42 ±5	47 ±5
Reticulocytes	(%)	1	1

Mean corpuscular volume (MCV; μm^3)	82-92
Mean corpuscular hemoglobin (MCH; pg)	27-32
Mean corpuscular hemoglobin concentration (MCHC; %)	32-36

Etiologic classification of anemias

I. **Impaired red cell production**
   - A. Disturbance of proliferation and differentiation of stem cells
   - B. Disturbance of proliferation and maturation of erythrocytes

II. **Increased rate of destruction (hemolytic anemias)**
   - A. Intrinsic abnormalities
   - B. Extrinsic abnormalities

Etiologic classification of anemias (1)

I. Impaired red cell production

A. Disturbance of proliferation and differentiation of tem cells: aplastic anemia, pure red cell aplasia

B. Disturbance of proliferation and maturation of erythrocytes:

1. Defective DNA synthesis (megaloblastic anemias)
2. Defective Hb synthesis:
    a/ Deficient heme synthesis: iron deficiency
    b/ Deficient globin synthesis: thalassemia
3. Unknown or multiple mechanisms: anemia of chronic disease

Etiologic classification of anemias (2)

II. Increased rate of destruction (hemolytic anemias)

A. Intrinsic abnormalities

Hereditary

1. Red cell membrane defects: hereditary spherocytosis, eliptocytosis

2. Red cell enzyme deficiencies

a/ Glycolytic enzymes: pyruvate kinase, hexokinase

b/ Enzymes of hexose monophosphate shunt: G-6PD, glutathione synthetase

3. Disorders of globin synthesis

a/ Deficient globin synthesis: thalassemia

b/ Structurally abnormal globin synthesis: sickle cell anemia

Acquired

1. Membrane defect: paroxysmal nocturnal hemoglobinuria

Etiologic classification of anemias (3)

B. Extrinsic abnormalities

1. Antibody mediated
   a/ Autoantibodies (idiopathic, drug-associated, SLE, malignancies)
   b/ Isohemagglutinins (transfusion reactions, erythroblastosis fetalis)
2. Mechanical trauma of RBC
   a/ Microangiopathic hemolytic anemias (TTP, DIC)
   b/ Cardiac traumatic hemolytic anemia
3. Chemicals and microorganisms
4. Sequestration in mononuclear phagocytic system
   - hypersplenism

Classification of anemias (simplified)

1. Deficiency anemias
2. Aplastic anemia
3. Hemolytic anemias
4. Secondary anemias

Morphologic classification of anemias

Type	MCV	MCHC	Common cause
Macrocytic anemia	increased	normal	Vitamin B_{12} deficiency Folic acid deficiency
Microcytic anemia			
- hypochromic	decreased	decreased	Iron deficiency Thalassemia
- normochromic	decreased or normal	normal	Spherocytosis
Normocytic anemia	normal	normal	Aplastic anemia
- normochromic			Chronic renal failure Some hemolytic anemia

Bone marrow failure

Bone marrow failure

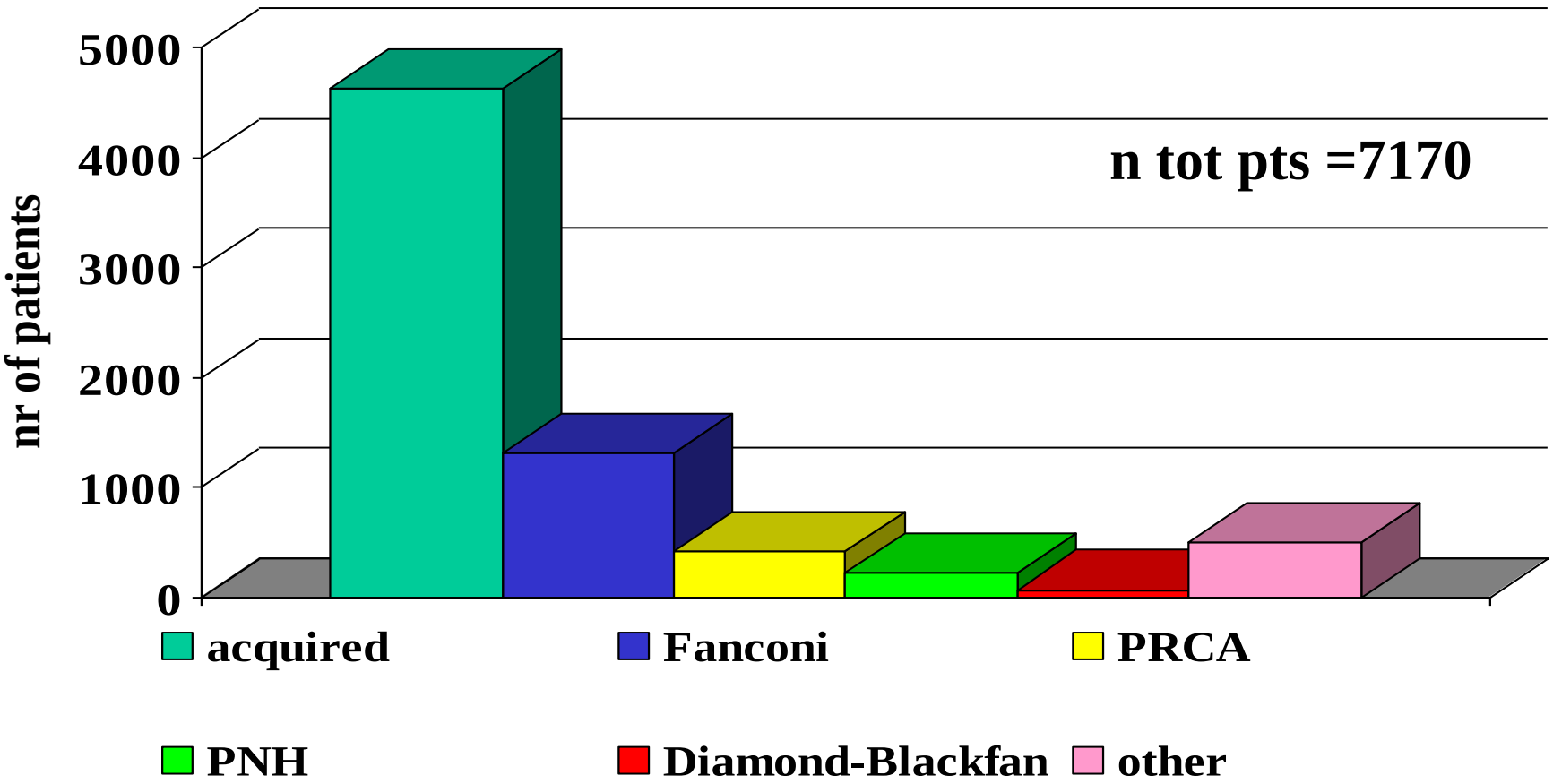
Aplastic anemia

Pure red cell aplasia

Congenital

Acquired

Diagnosis


nr of patients
5000
4000
3000
2000
1000
0
n tot pts =7170
acquired
Fanconi
PRCA
PNH
Diamond-Blackfan
other

Aplastic anemia (AA)

- **Definition**
  - **AA is characterized by pancytopenia with hypocellular marrow; hematopoietic tissue is replaced by fat cells, in absence of abnormal infiltrate or increase in reticulin**

- **Incidence (acquired)**
  - **2/1000000 (Europe, North America)**
  - **2-3 times higher in East Asia**
  - **rare < 1 year; peaks from 10 to 20 yrs; plateaus 20-60 yrs; increase > 60 yrs**

Causes of aplastic anemia (1)

I. Primary (idiopathic) 70-80%: immune-mediated disease

II. Secondary - drugs

1. Unpredictable (idiosyncratic reaction)
   - antiepileptic drugs (hydantoins)
   - oral antidiabetic agents (tolbutamide, chlorpropamide)
   - tranquillizers (chlorpromazine, chlordiazepoxide)
   - antirheumatic drugs (gold, indomethacin, phenylobutazone)
   - antibacterial agents (sulfonamides, isoniazid, streptomycin, tetracyclines, chloramphenicol)
2. Unpredictable hypersensitivity (immune reaction)
   - many drugs

Causes of aplastic anemia (2)

III. Associated diseases

1. viral hepatitis

2. CMV infection

3. EBV infection

4. Parvovirus B19

5. paroxysmal nocturnal hemoglobinuria

IV. Industrial and household chemicals: benzene, some organic solvents, trinitrotoluene, certain insecticides (DDT, chlordane, lindane)

Causes of marrow aplasia

1. **Ionizing radiation**
2. **Antineoplastic drugs:**
   - **folic acid antagonists,**
   - **alkylating agents,**
   - **anthracyclines,**
   - **nitrosoureas**
   - **purine and pyrimidine analogous**

Pathogenesis of AA

- Quantitative or qualitative abnormalities of pluripotent stem cell
- Abnormal humoral or cellular control of hematopoiesis
- Abnormal hematopoietic microenvironment
- Immunologic suppression of hematopoiesis

Diagnosis of aplastic anemia

1. Personal medical history; family history
2. Physical examination
3. Clinical symptoms:
   - infections
   - bleeding
   - symptoms of anemia
4. Laboratory findings:
   - anemia, neutropenia, thrombocytopenia
   - bone marrow: hypocellular with fatty changes

Diagnosis of AA

1. FBC and reticulocyte count
2. Blood film examination
3. HbF% in children
4. Bone marrow aspirate and trephine biopsy, including cytogenetics
5. Peripheral blood chromosomal breakage analysis to exclude Fanconi anaemia if <50 years
6. Flow cytometry for GPI-anchored proteins (see note below concerning Ham test)*
7. Urine haemosiderin if Ham test positive or GPI-anchored protein deficiency
8. Vitamin B12 and folate
9. Liver function tests
10. Viral studies: Hepatits A, B and C, EBV, HIV (CMV, see page 5)
11. Anti-nuclear antibody and anti-dsDNA
12. Chest X-ray
13. Abdominal ultrasound scan and echocardiogram
14. Peripheral blood gene mutation analysis for dyskeratosis congenita *DKC1*, *TERC*, *?TERT*) if clinical features or lack of response to immunosuppressive therapy

Criteria for diagnosis of AA

1. Cytopenia	-	Hb	<10 g/dL
	-	ANC	<1,5 G/L
	-	PLT	<100 G/L

2. Bone marrow histology and cytology
   - decreased marrow cellularity (< 30%)
   - increased fat cells component
   - no extensive fibrosis
   - no malignancy or storage disease
3. No preceding treatment with X-ray or antyproliferative drugs
4. No lymphadenopathy or hepatosplenomegaly
5. No deficiencies or metabolic diseases
6. No evidence of extramedullary hematopoiesis

Classification of aplastic anemia

Severe AA (Camitta *et al*, 1975)	BM cellularity <25%, or 25–50% with <30% residual haemopoietic cells* 2/3 of the following: Neutrophil count $<0{\cdot}5 \times 10^9$/l Platelet count $<20 \times 10^9$/l Reticulocyte count $<20 \times 10^9$/l
Very severe AA (Bacigalupo *et al*, 1988)	As for severe AA but neutrophils $<0{\cdot}2 \times 10^9$/l
Non-severe AA	Patients not fulfilling the criteria for severe or very severe aplastic anaemia

Prognosis of SAA with supportive therapy only

The overall mortality is 65-75% and the median survival 3 months

Management of severe aplastic anemia

1. Hematopoietic stem cell transplantation

2. Immunosuppressive treatment

- cyclosporine
- antilymphocyte/antityhymocyte globulin,
- methylprednisolone

3. Androgens

4. Supportive therapy

Hematopoietic stem cell transplatation in severe aplastic anemia

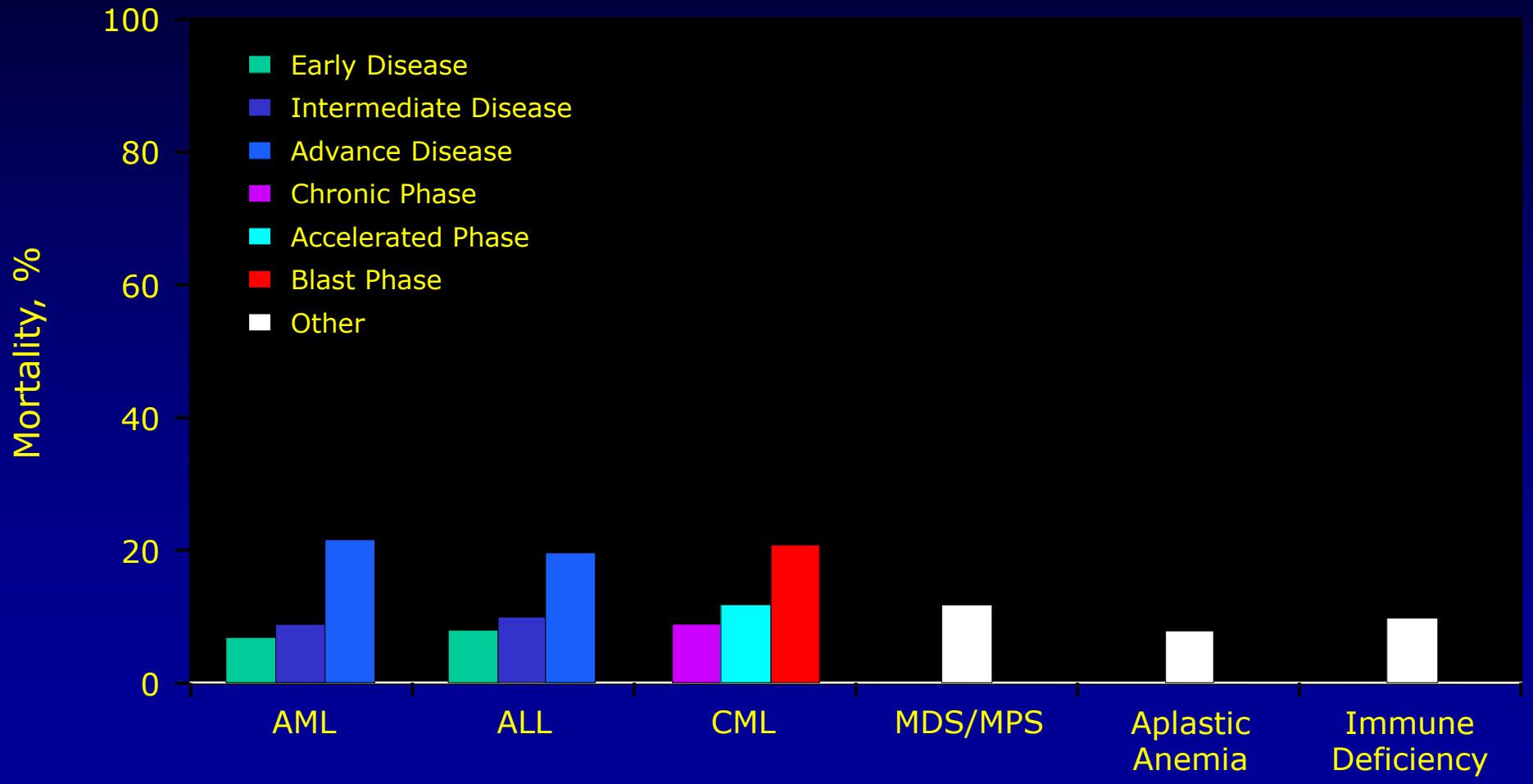
1. Advantages

- correction of hematopoietic defect
- long-term survival: 75% - 90% (HLA-matched sibling donor)
- majority of the patients appear to be cured

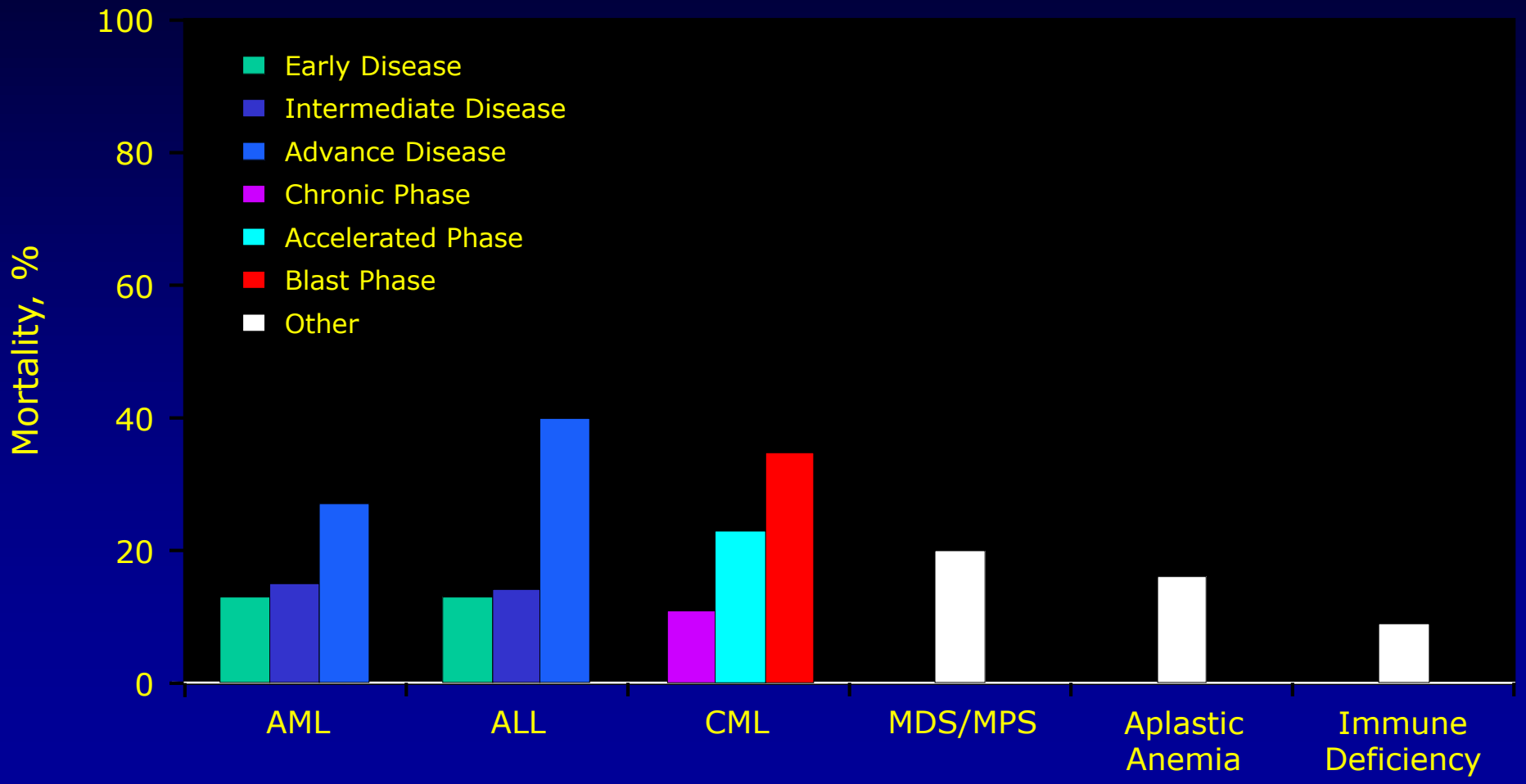
2. Restrictions

- age
- suitable donor (sibling vs unrelated)
- 12-30% risk of acute and 30-40% risk of chronic GVHD
- 4-14% risk of graft failure in multitransfused patients
- solid tumors (12%)

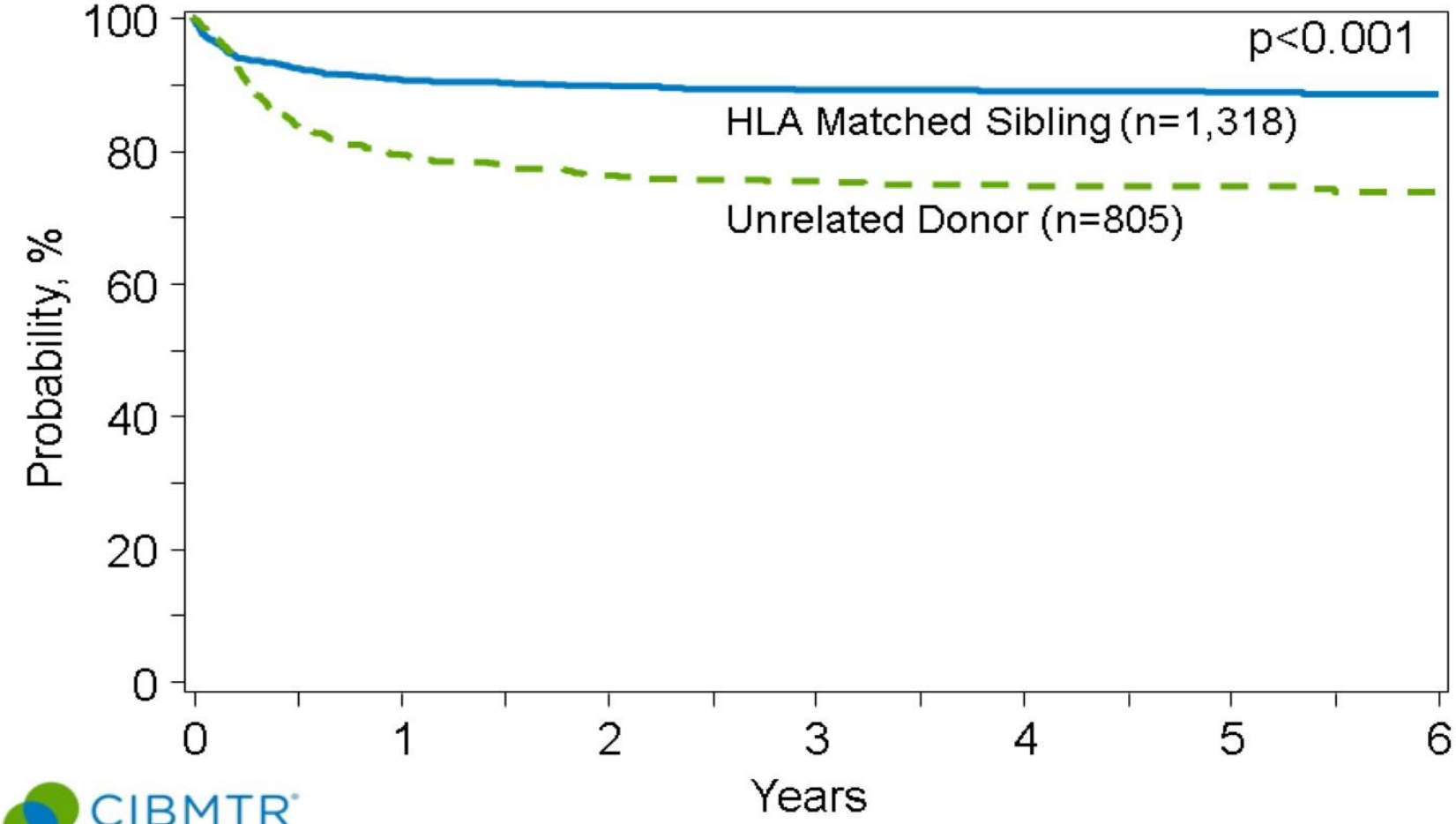
100-day mortality after HLA-identical sibling transplantation



100-day mortality after unrelated donor transplantation



Survival after Allogeneic Transplants for Severe Aplastic Anemia, <20 Years, 2003-2013



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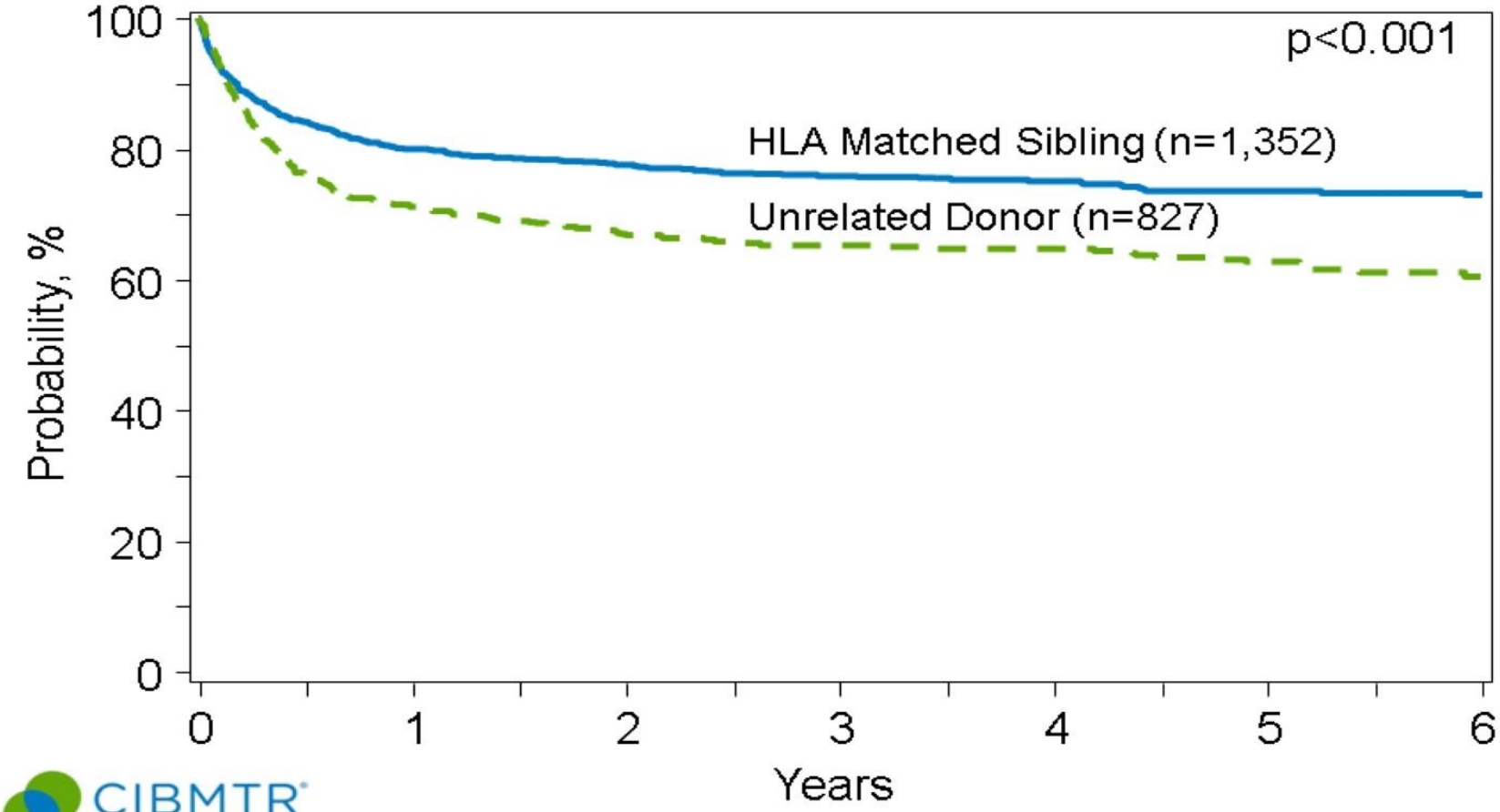
By Donor Type

Survival after Allogeneic Transplants for Severe Aplastic Anemia, ≥20 Years, 2003-2013



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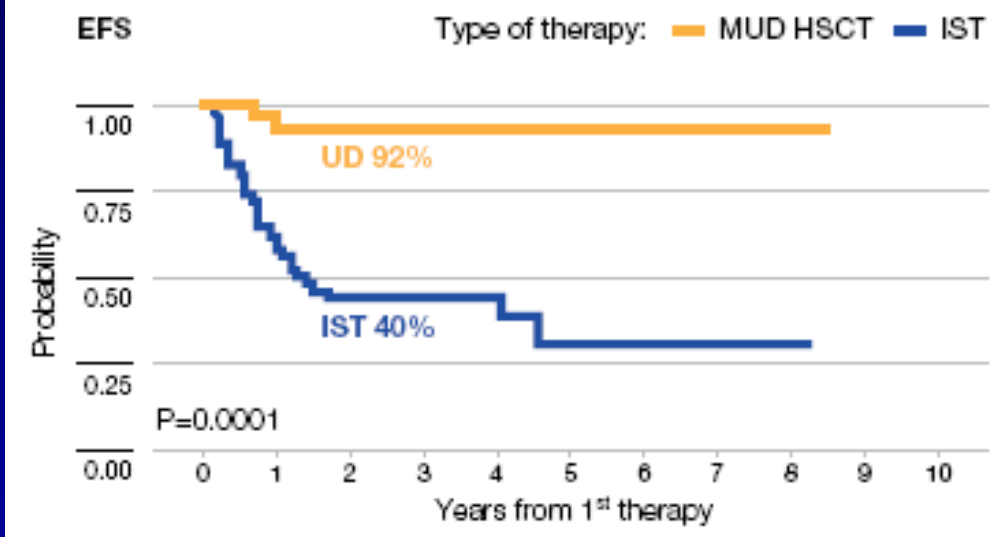
By Donor Type

Aplastic anemia - SCT

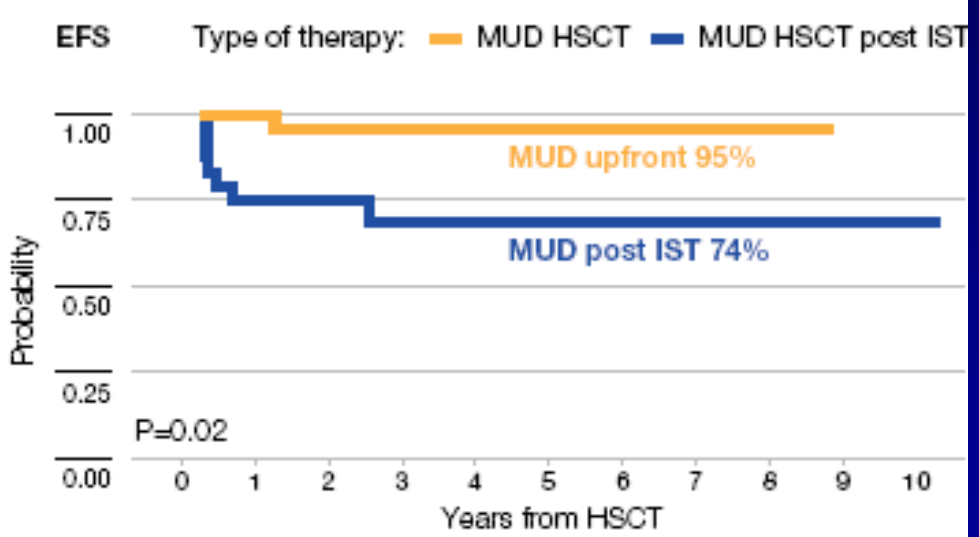
UD *vs* IST front-line

EFS of UD HSCT upfront is far better than IST front-line



MUD *vs* MUD post-failed IST

EFS of MUD HSCT upfront is better than MUD HSCT post failed IST



Immunosuppressive therapy in SAA

- **Immunosuppresive therapy**
  - Non-severe aplastic anemia
  - Severe aplastic anemia
    - > 40-50 yrs old
    - No HLA identical donor
- **Combination therapy** **60-80%**
  - Antithymocyte globulin
  - Cyclosporin
  - methylprednisolone

Complication of immunosuppressive therapy

1. **Failure of therapy and relapse of AA**
   a) exhaustion of stem cell reserves
   b) insufficient immunosuppression
   c) misdiagnosis (MDS)
   d) hereditary bone marrow failure (non-immune pathogenesis)
2. **Relapse of AA**
3. **Hematopoietic clonal disease**
   a) acute myelogenous leukemia
   b) myelodysplastic syndrom
   c) paroxysmal nocturnal hemoglobinuria

Other agents in treatment of AA (immunosuppresive, immunomodulators)

1. **Mycofenolate mofetil (Cellcept)**
2. **Anti-Il-2 receptor monoclonal antibody (daclizumab; Zenapax)**
3. **Anti CD52 monoclonal antibody (alemtuzumab; Campath)**
4. **Rapamycin**
5. **Anti-TNF alfa monoclonal antibody (etanercept; Enbrel)**

Therapy of non-severe aplastic anemia

1. „Watch and wait”
2. Androgens (?)
3. Supportive care
   - blood and platelet transfusion
   - antibiotics
   - growth factors
   - iron chelation therapy
4. Immunosuppressive treatment in selected patients

Androgens in the treatment of AA

1. Severe aplastic anemia
   - no effect when applied as a single agent
   - improve the results if in combination with ATG and cyclosporine
2. Non-severe aplastic anemia
   - effective in 20-30% of patients

Causes of pancytopenia

1.Failure of production of blood cells

a) bone marrow infiltration

- acute leukemias
- hairy cell leukemia
- multiple myeloma
- lymphoma
- myelofibrosis
- metastatic carcinoma

b) aplastic anemia

c) vit.B12 and folate deficiency

2. **Ineffective hematopoesis**

- myelodysplastic syndrome

3. **Increased destruction of blood cells**

- hipersplenism
- autoimmune disorders
- paroxysmal nocturnal hemoglobinuria

4. **Myelosuppression after irradiation or antiproliferative drugs**

Case report 1

- P.W. 18-years-old student
  - January 2002 : appendectomy
  - April 2002 : hepatitis B
  - June 2002 : progressive pancytopenia
  - July 2002 : SAA
  - September 2002 : BMT from sibling donor
  - alive and healthy

Case report 2

- P.S. 16-years-old girl
  - February 2000 : non-severe aplastic anemia
    - blood transfusion
  - November 2001 : immunosuppresive treatment
    - without improvement
  - May 2002 : BMT from sibling donor
    - complete recovery before +30 day
  - June 2002 : died because of TTP

Case report 3

- M.R. 25-years-old woman
  - June 2006 : severe aplastic anemia
    - no sibling donor
  - July 2006 : immunosuppressive treatment
    - without improvement
  - December 2006 : immunosuppressive treatment
    - improvement (without blood and platelet transfusion)
  - November 2007 : relapse of SAA
  - September 2008 : PBSCT from unrelated donor
  - alive and healthy