Hematopoietic Stem Cell Transplantation

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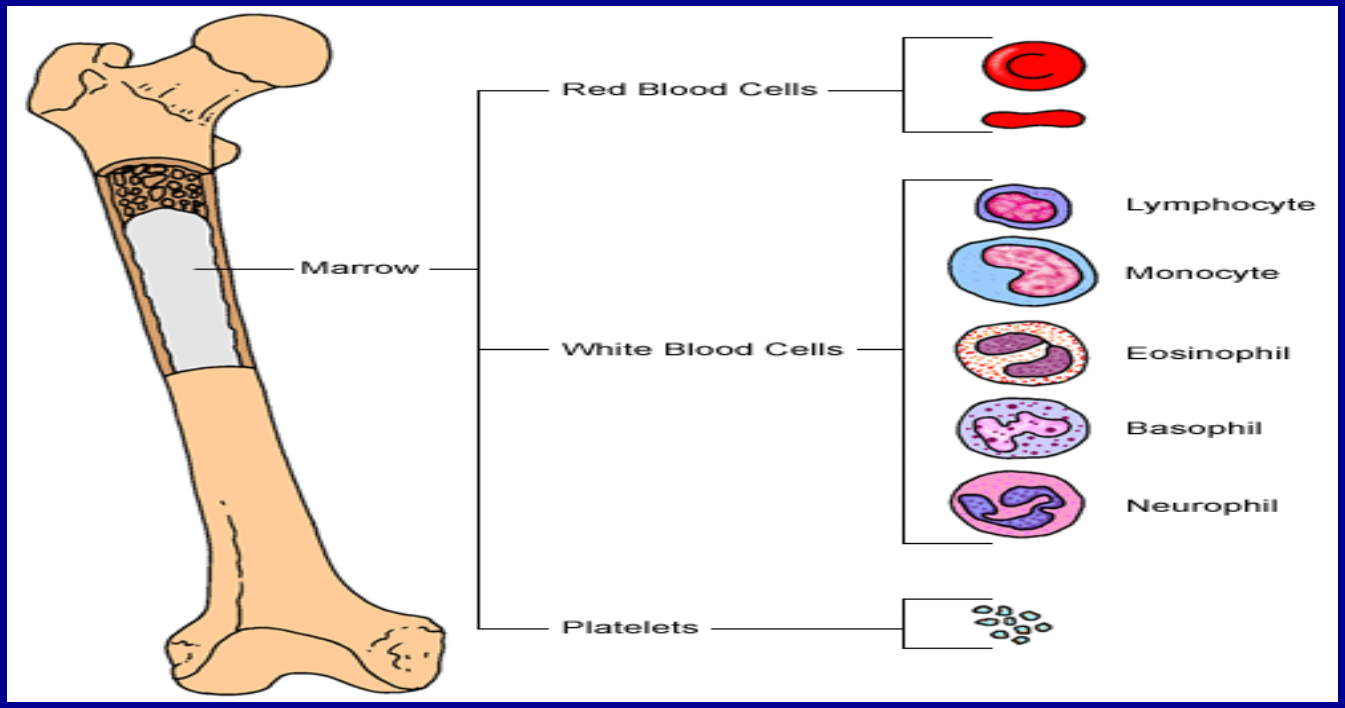
Term-IV 2020, Ankara

What is the Bone Marrow ?

- Bone Marrow is the soft spongy tissue that fills the cores of larger bones.
- It serves an active function in the body by producing all three types of blood cells, as well as lymphocytes, which support the immune system.



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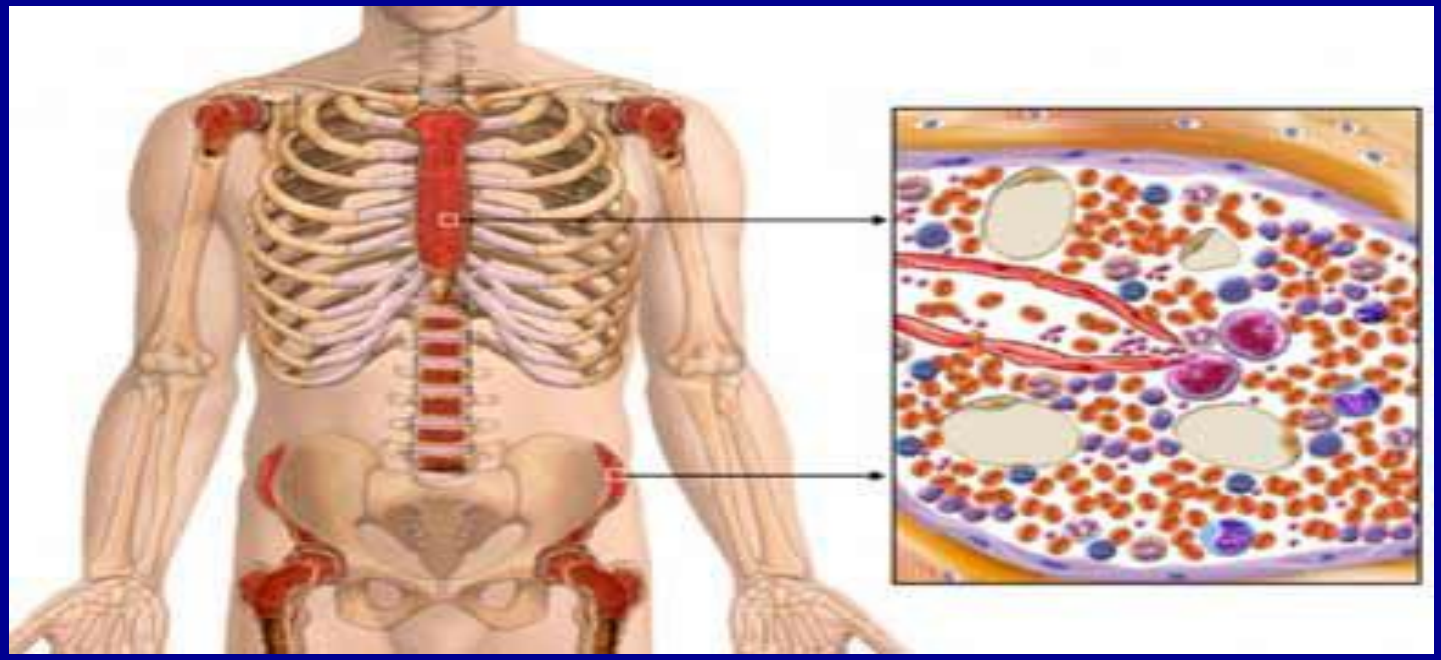
What is the BMT?

- Bone Marrow transplant is a procedure used to treat patients with life-threatening blood, immune or genetic disorders, This includes leukemia and bone marrow cancers.
- A bone Marrow transplant replaces the unhealthy blood-forming cells with healthy ones.
- Healthy bone marrow stem cells are harvested from matching bone marrow donors.



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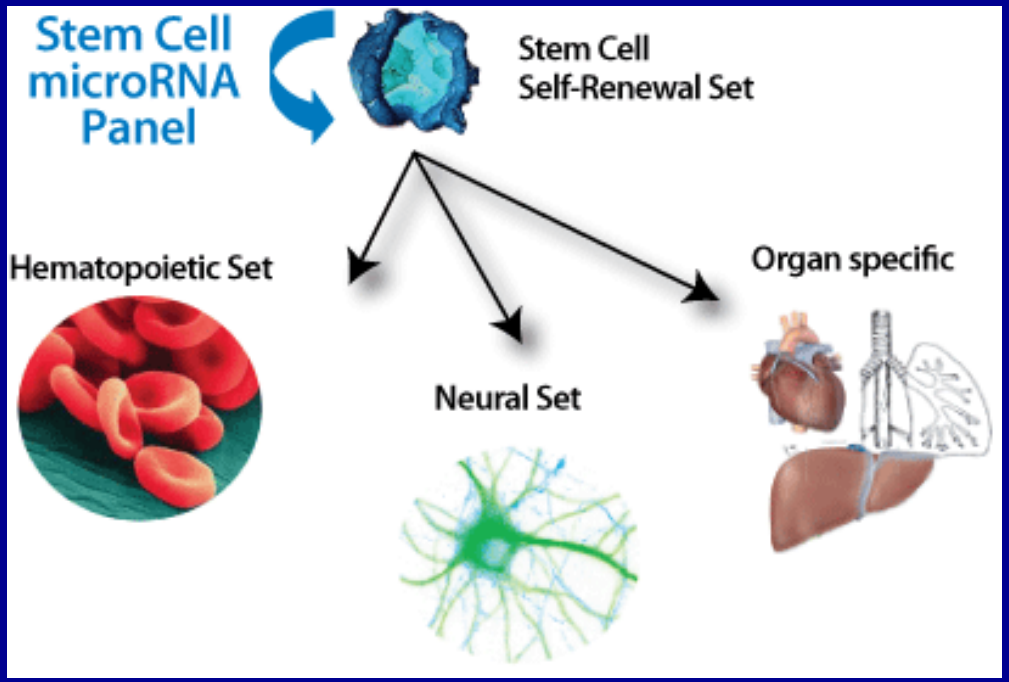
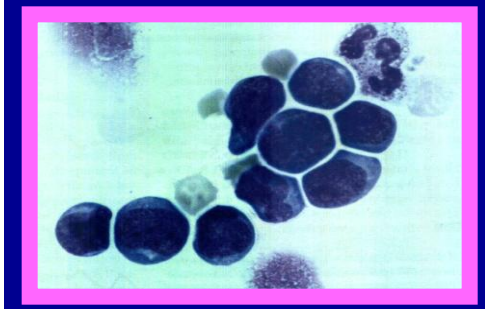
What are stem cells?

Stem cells are immature cells in the bone marrow that give rise to all your blood cells.





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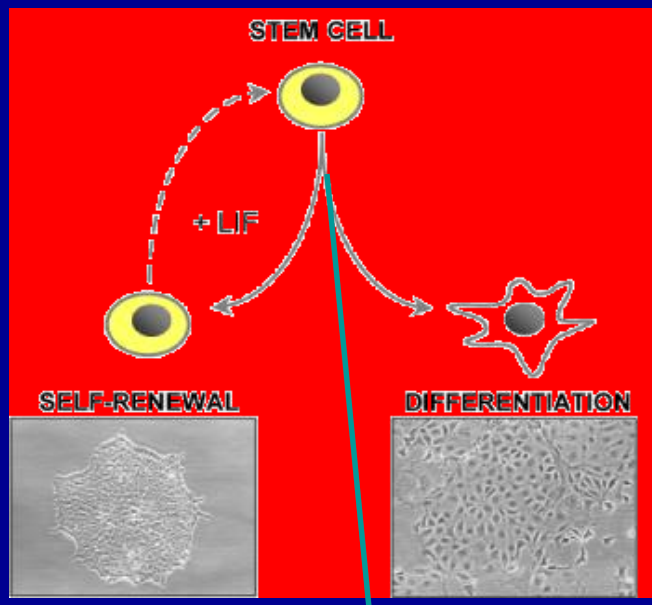
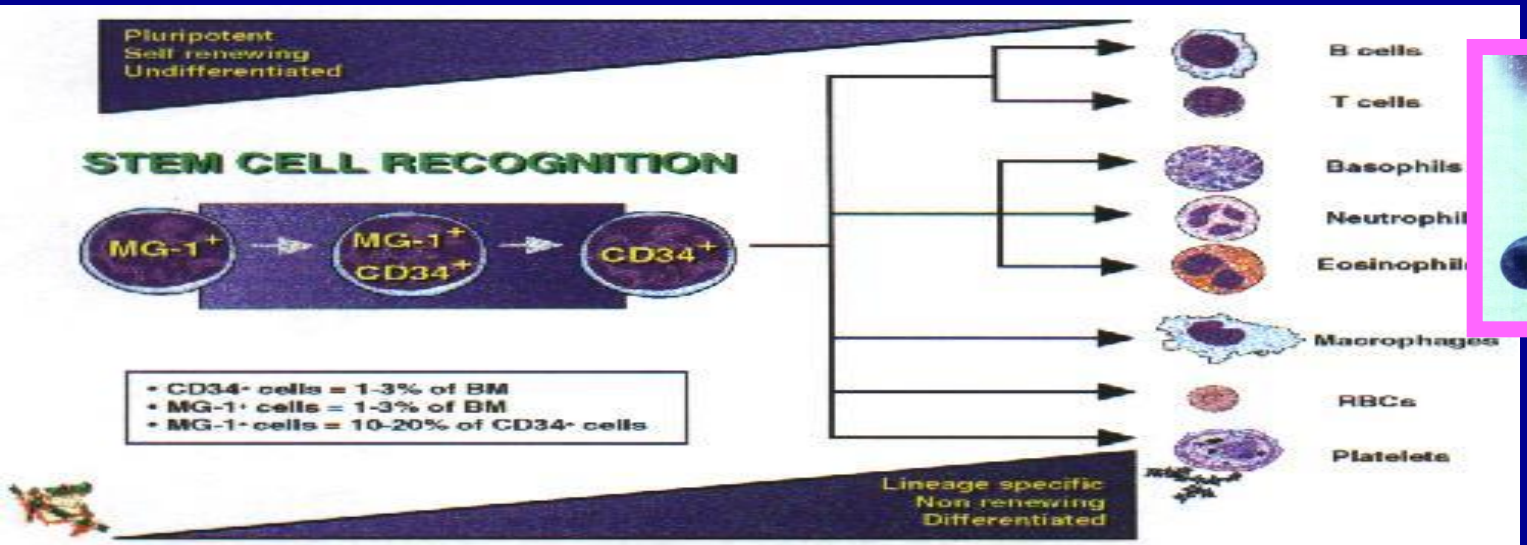
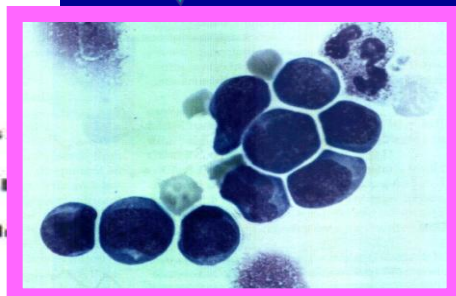
HEMATOPOETIC STEM CELL

Definition

- can renew itself (**Self-Renewal**).
- can differentiate to a variety of specialized cells (**Differentiation**).
- can mobilize into peripheral blood (**Mobilization**).
- **clonal** cells.







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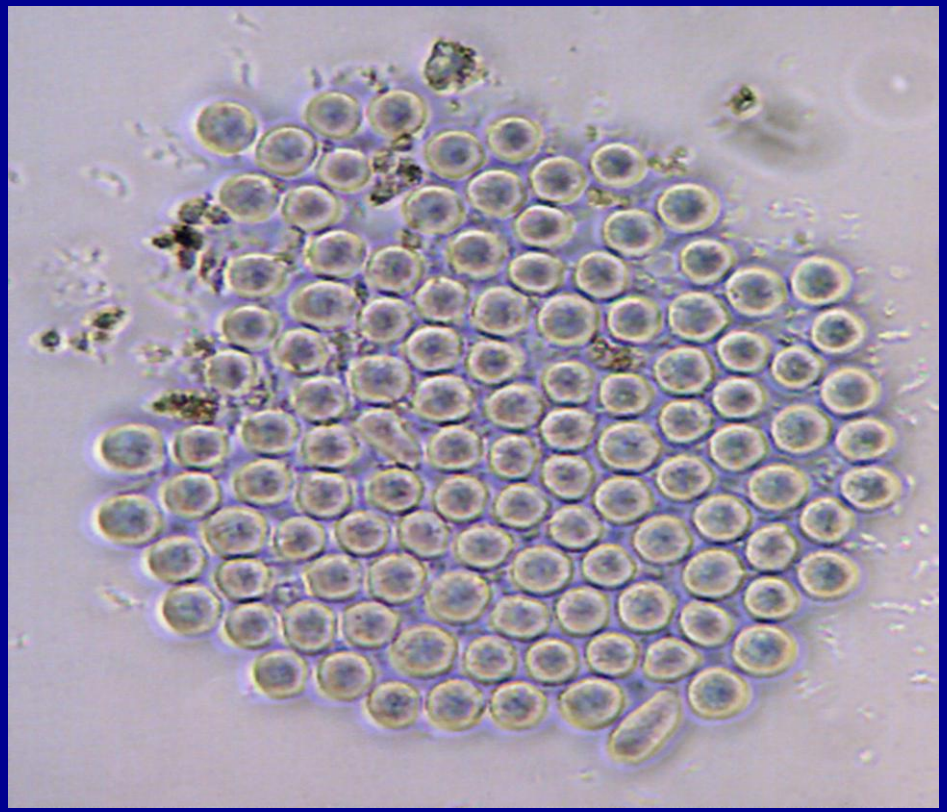
Hematopoietic stem cells- Markers

Hematopoietic stem cells

1 / 25 000 - 100 000 of bone marrow cells



Characteristic:

- **CD34**
- CD133
- Lin^-
- C-kit (CD117)
- BCRP

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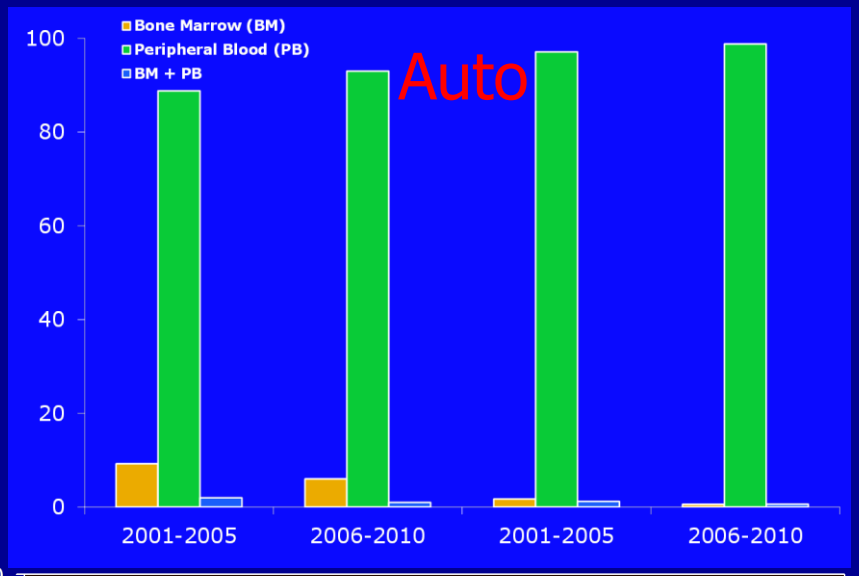
HEMATOPOETIC STEM CELL

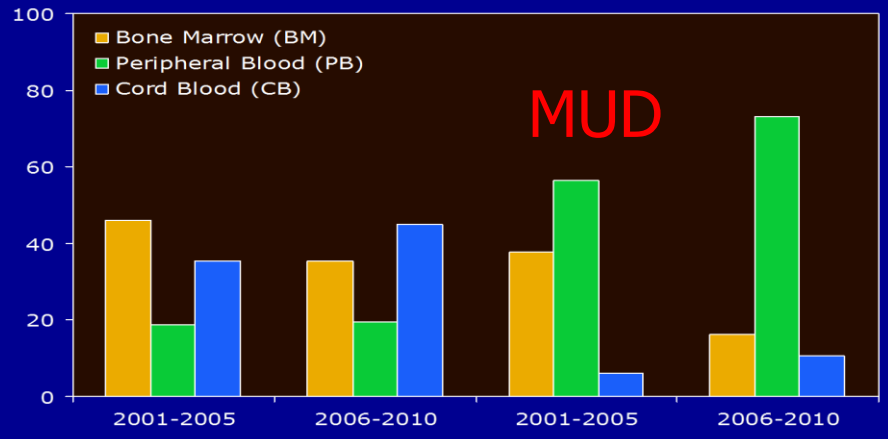
Source

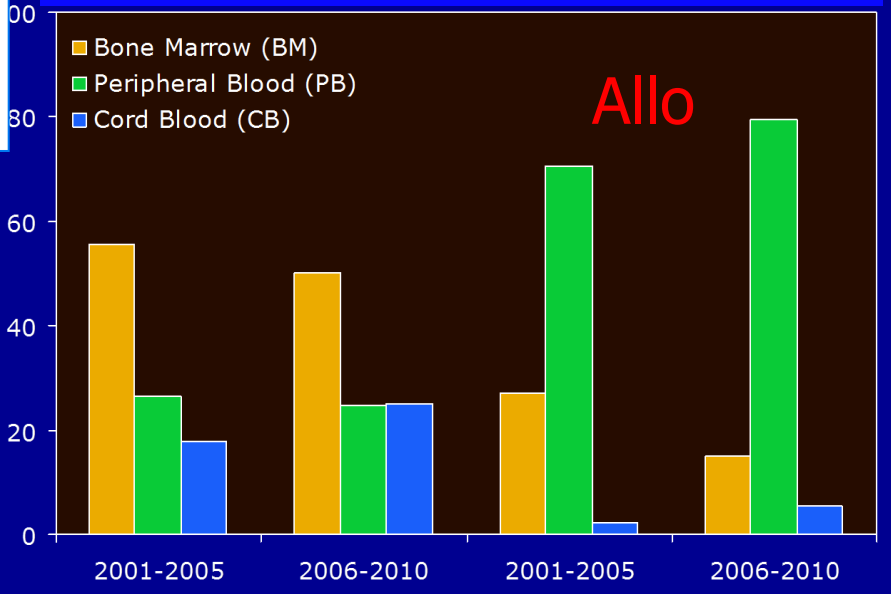
① **Bone marrow**

② **Peripheral Blood**

③ **Cord Blood**







What is the HSCT?

- **Definition**
  - any procedure where hematopoietic stem cells of any donor and any source are given to a recipient with intention of repopulating/replacing the hematopoietic system in total or in part.

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What is the type of HSCT?

- **AUTOLOGOUS TRANSPLANTS**
  - Patients receive their own stem cells.
- **ALLOGENEIC TRANSPLANTS**
  - Patients receive stem cells from someone other than the patient or an identical twin.
- **SYNGENEIC TRANSPLANTS**
  - Patients receive stem cells from their identical twin.

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Graft Sources

- Autologous Transplant
  - Tumor with dose response curve
  - Tumor sensitive to myelosuppressive agents
  - No evidence of disease in the blood or bone marrow
  - Transplant related mortality (TRM) lowest with autos (<5%)
  - Relapse rates are higher depending on the disease
  - Absence of graft versus tumor effects

Lazarus HM. Autologous and allogeneic transplantation procedures for hematologic malignancies. Manual of Clinical Hematology, 3rd edition 2002:399-409

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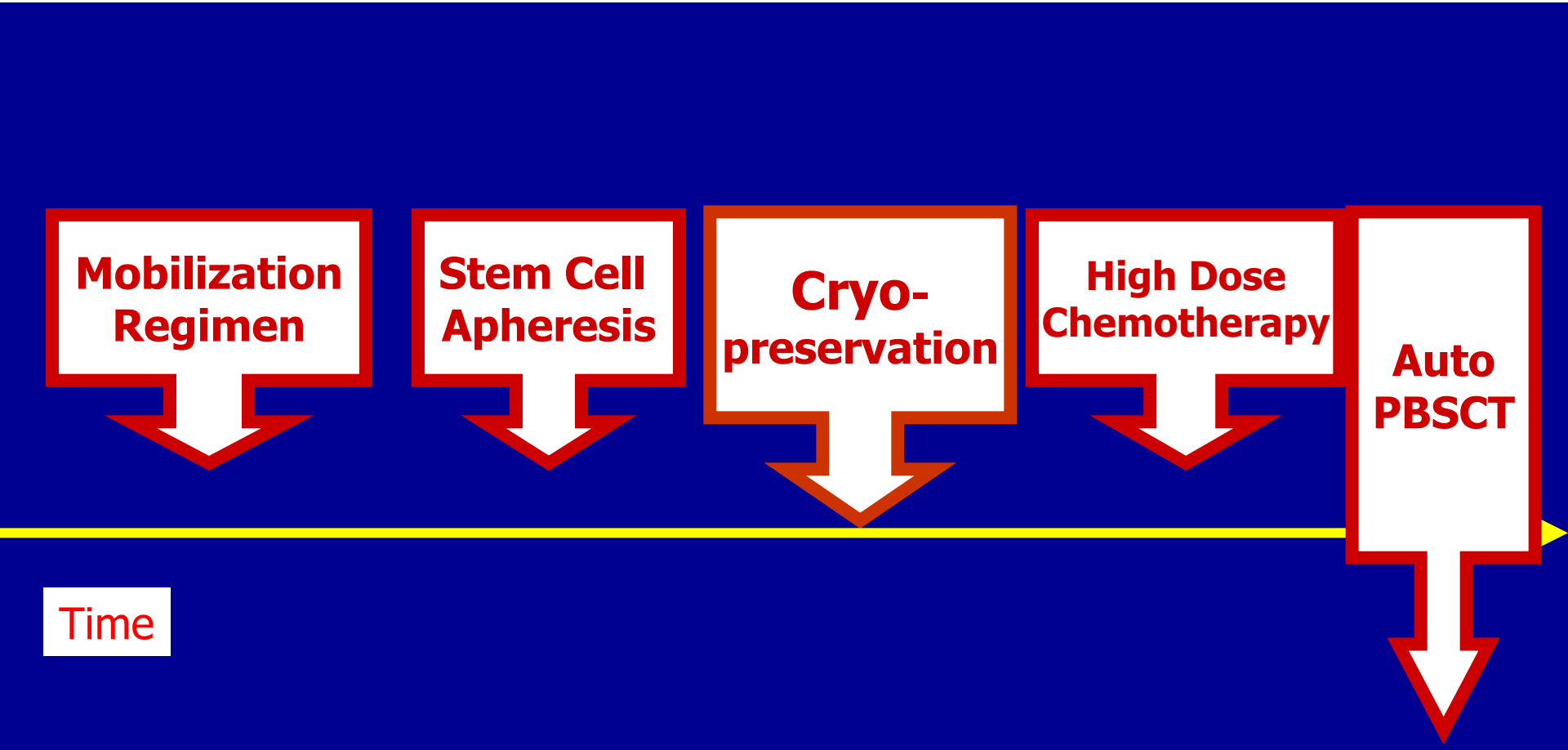
AUTOLOGOUS STEM CELL TRANSPLANTATION



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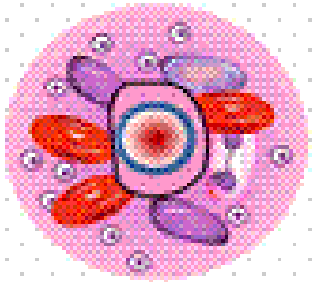
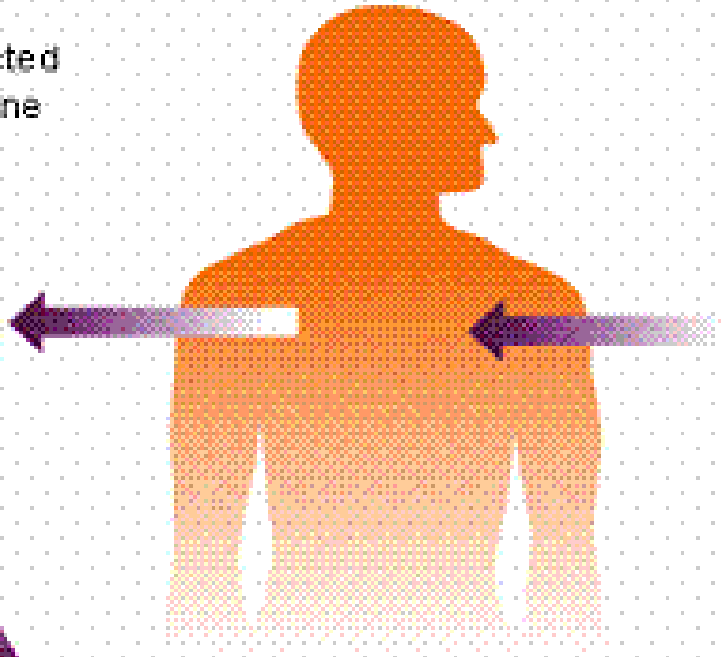
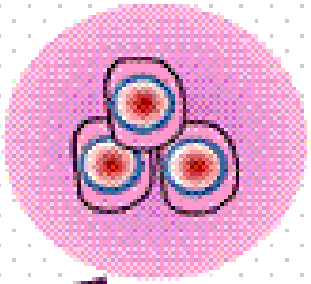
The Autologous Transplant Process

1. Collection
Stem cells are collected from the patient's bone marrow or blood.

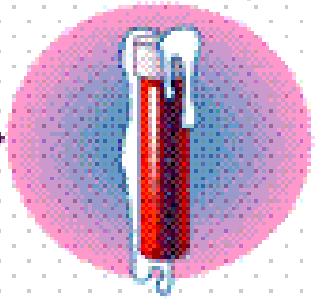








2. Processing
Blood or bone marrow is processed in the laboratory to purify and concentrate the stem cells.



3. Cryopreservation
Blood or bone marrow is frozen to preserve it.



4. Chemotherapy
High dose chemotherapy and/or radiation therapy is given to the patient.

5. Reinfusion
Thawed stem cells are reinfused into the patient.

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Graft Sources

- Allogeneic Transplants
  - High TRM (30-50%)
  - Lower relapse rates due to graft versus tumor effects
  - Graft versus host effects
- Matched Related Donor (siblings)
  - 25% chance a sibling will be a match
  - The more siblings a patient has the better chance for a match

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Allogeneic Hematopoietic Stem Cell Transplantation

Old Paradigm

The allograft is a rescue product to replace the defective stem cells following ablation with cytotoxic therapy.

New Paradigm

Main therapeutic component of an allogeneic stem cell transplant is the "graft *vs.* leukemia" effect mediated by T-cells in the allograft.

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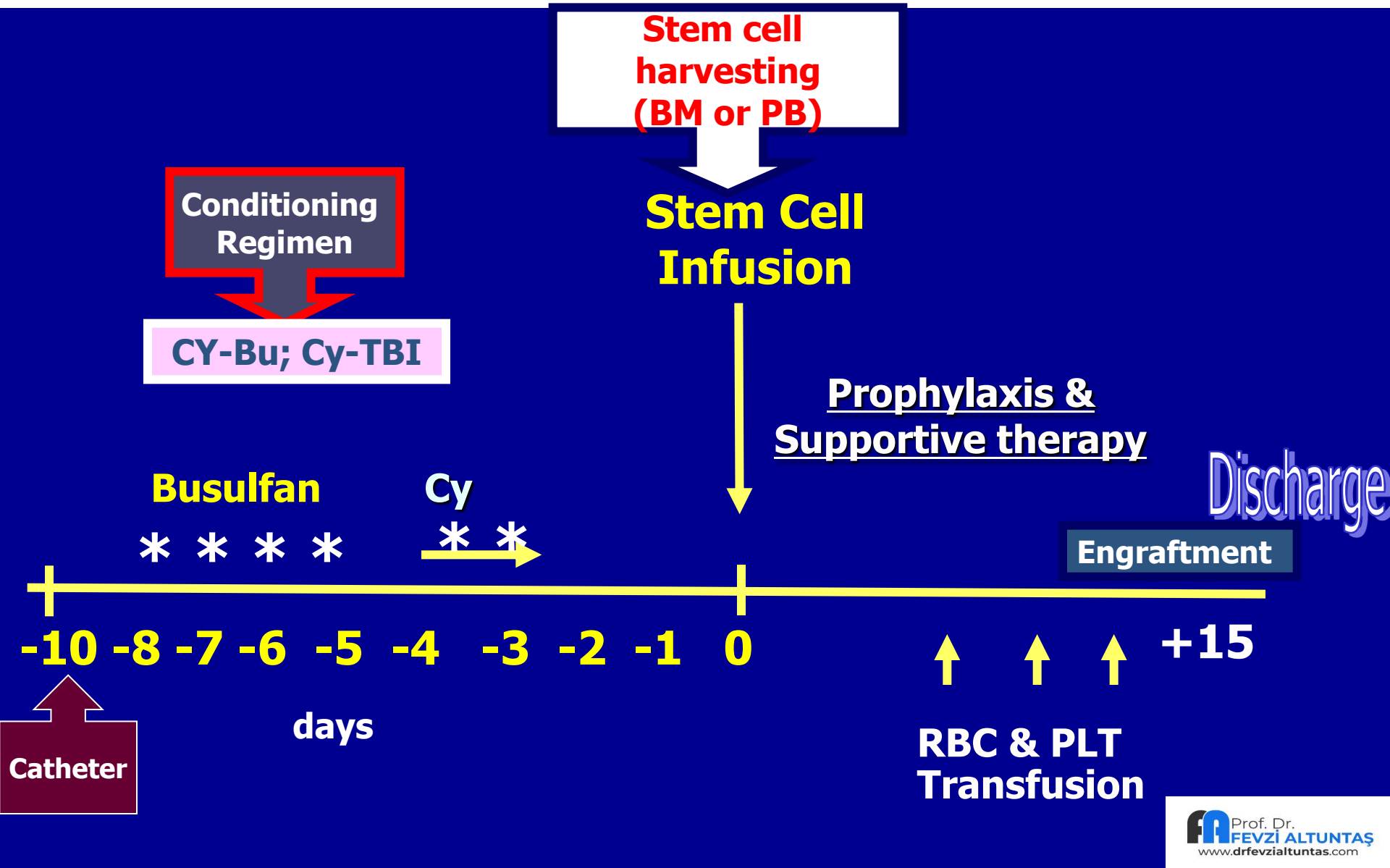
ALLOGENEIC STEM CELL TRANSPLANTATION



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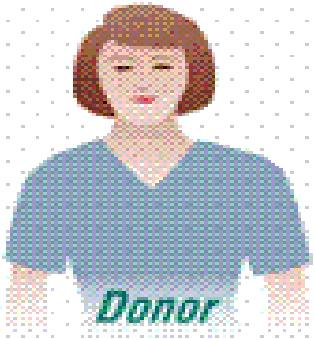
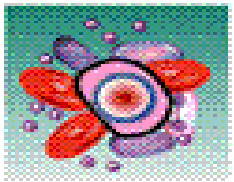
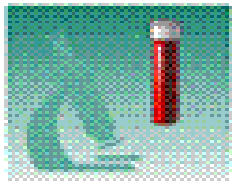
The Allogeneic Transplant Process





1 Collection

Stem cells are collected from the patients bone marrow or blood.



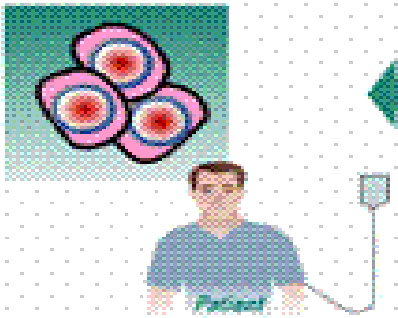
2 Processing

Bone marrow or periferal blood is taken to the processing laboratory where the stem cells are concentrated and prepared for the freezing process.



3 Cryopreservation

Bone marrow or blood is preserved by freezing (cryopreservation) to keep stem cells alive until they are infused into the patient's bloodstream.



4 Chemotherapy

High dose chemotherapy and/or radiation therapy is given to the patient.



5 Infusion

Thawed stem cells are infused into the patient.

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HUMAN LEUKOCYTE-ASSOCIATED (HLA) ANTIGENS

- A set of proteins on the surface of their cells.
- A set of HLA proteins are inherited equally from parents.
- Chances of having a full match are ~ 1 in 3.
- The higher the number of matching HLA antigens, the greater the chance that the patient's body will accept the donor's stem cells.

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HLA Matching

- 6/6, 8/8, or 10/10
  - HLA loci on chromosome 6
  - HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, HLA-DP
- ABO incompatibility is not an exclusion

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Stem Cell Source

	Allogeneic	Autologous
Donor Availability	Limited	Majority
Tumor Content	None	Possible
GVHD/GVL	Possible	None
Tx-related Mortality	10-40%	0-10%

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Bone Marrow

- Standard source of hematopoietic cells for more than 30 years.
- Transplant physicians may select marrow because:
  - Extensive clinical data are available about marrow transplant outcomes
  - Extensive information is available about the marrow donation experience

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Collection of Stem Cells

- Bone Marrow Harvest
  - General anesthesia
  - Equivalent of 50-100 bone marrow biopsies
  - Used much less often
  - 2 deaths in 8000 collections



Copelan EA. Hematopoietic stem-cell transplantation. NEJM 2006;354:1813-1826.

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Peripheral Stem Cell Mobilization

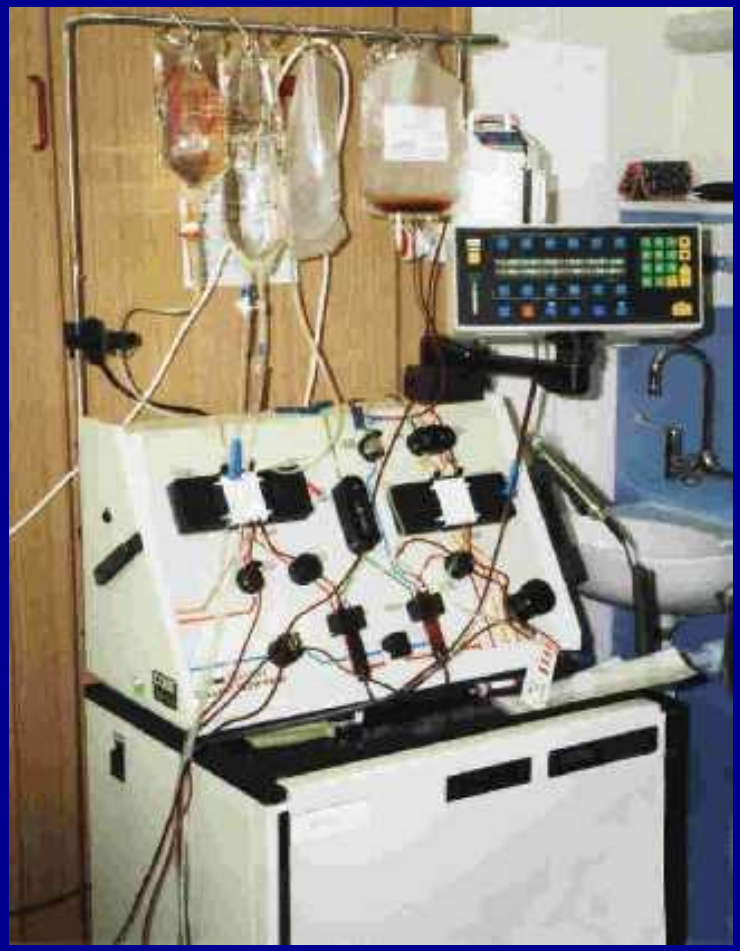
- The concentrations of HSCs are 10-100 times greater in the BM compared to the PB.
  - 0.1% of PB mononuclear cells
  - 1-4% bone marrow cells
- Therefore, methods to increase the circulating concentrations of HSCs are necessary to ensure adequate and successful collections.
- Agents used to mobilize HSCs include the administration of cytokines with or without chemotherapy prior to scheduled collection periods.





Collection of Stem Cells

- Stem cells circulate in the blood
- Identified by CD34+ by flow cytometry
- Filgrastim, sargramostim, AMD 3100
- Stem cells are collected through an apheresis catheter
- More cells are collected
- Higher chronic GVHD than bone marrow harvest
- More rapid marrow recovery



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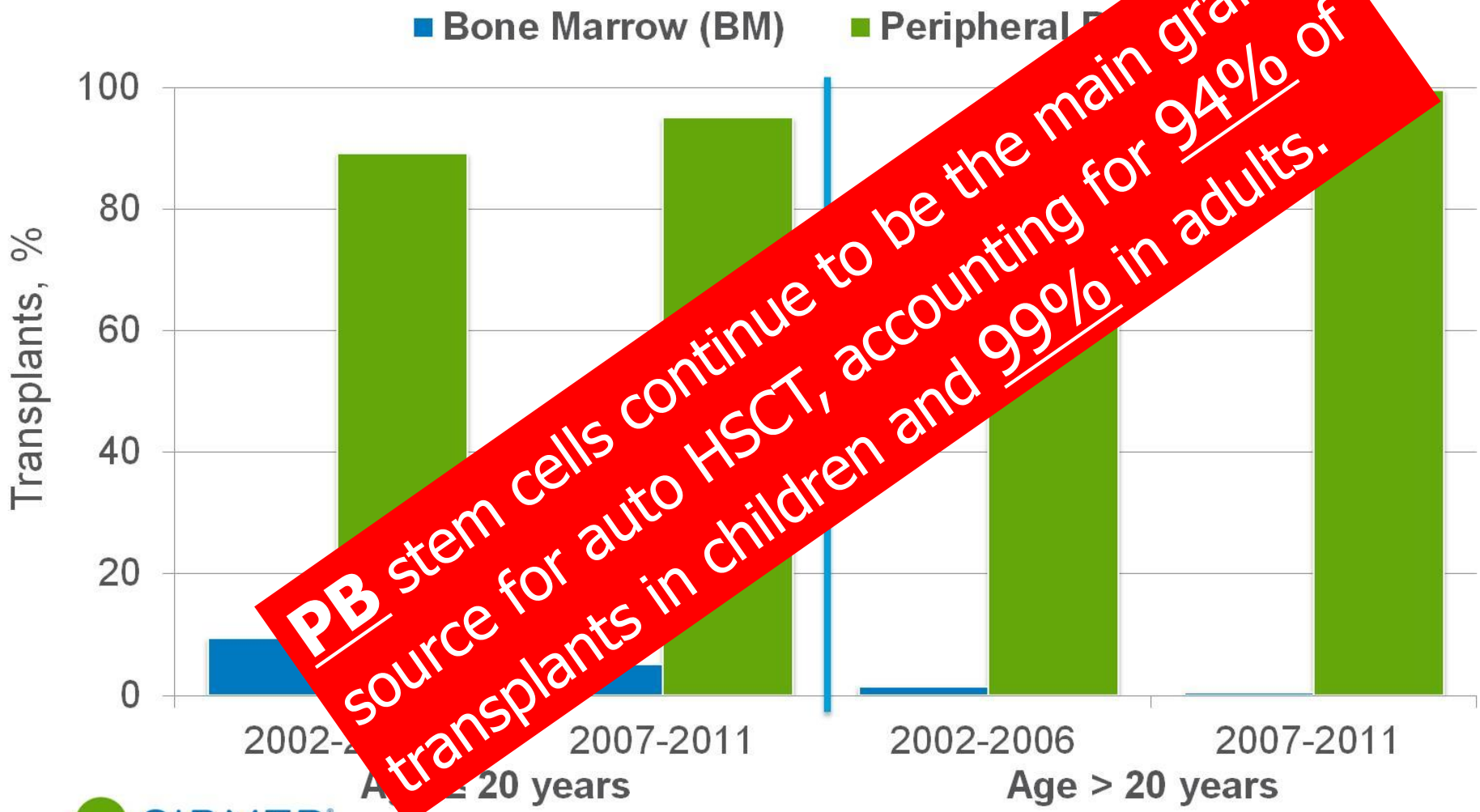
Autologous Stem Cell Sources by Recipient Age



PB stem cells continue to be the main graft source for auto HSCT, accounting for 94% of transplants in children and 99% in adults.

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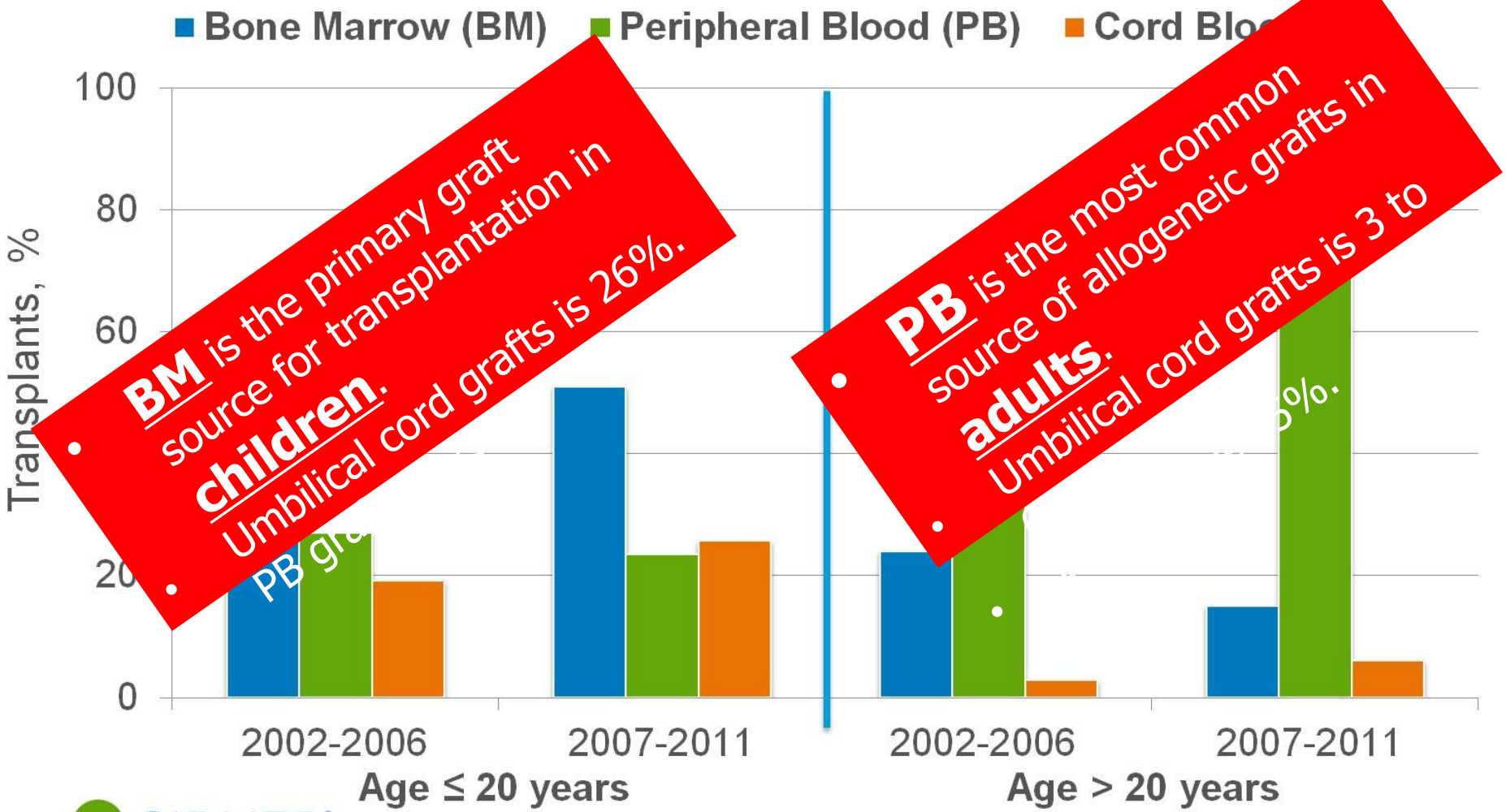
Allogeneic Stem Cell Sources by Recipient Age



- **BM** is the primary graft source for transplantation in **children**.
- Umbilical cord grafts is 26%.

- **PB** is the most common source of allogeneic grafts in **adults**.
- Umbilical cord grafts is 3 to

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Umbilical Cord Blood

- Umbilical Cord Blood
  - Cryopreserved
  - Small number of stem cells
  - Higher incidence of engraftment failure
    - Using more than one unit in adults
  - Lower risk of GVHD
  - Degree of matching not as stringent

Chao NJ, Emerson SG, Weinberg KI. Stem cell transplantation (Cord Blood Transplants). Am Soc Hematol Ed Book. 2004:354-371.

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Umbilical Cord Blood

- 1st UCB transplant 16 years ago
  - Child with Fanconi's anemia
- Cell dose is given per recipient weight
  - Lower patient weights the high the cell dose
  - 2 x 10^7 nucleated cells/kg
  - 1.7 x 10^7 CD 34+ cells/kg
- 4/6 match UCB with sufficient cells has a similar outcome to a matched or one antigen mismatched MUD

Chao NJ, Emerson SG, Weinberg KI. Stem cell transplantation (Cord Blood Transplants). Am Soc Hematol Ed Book. 2004:354-371.

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Cord Blood Transplantation

Advantages

- Waste product of normal deliveries
- Readily available
- Increased availability for minorities
- Decreased transmission of viruses (e.g. CMV)

Disadvantages

- One unit rescues one patient/no DLI
- Theoretical risk of genetic disease transmission
- Theoretical risk of maternal cell contamination (GVHD)
- Efficacy in adults unknown

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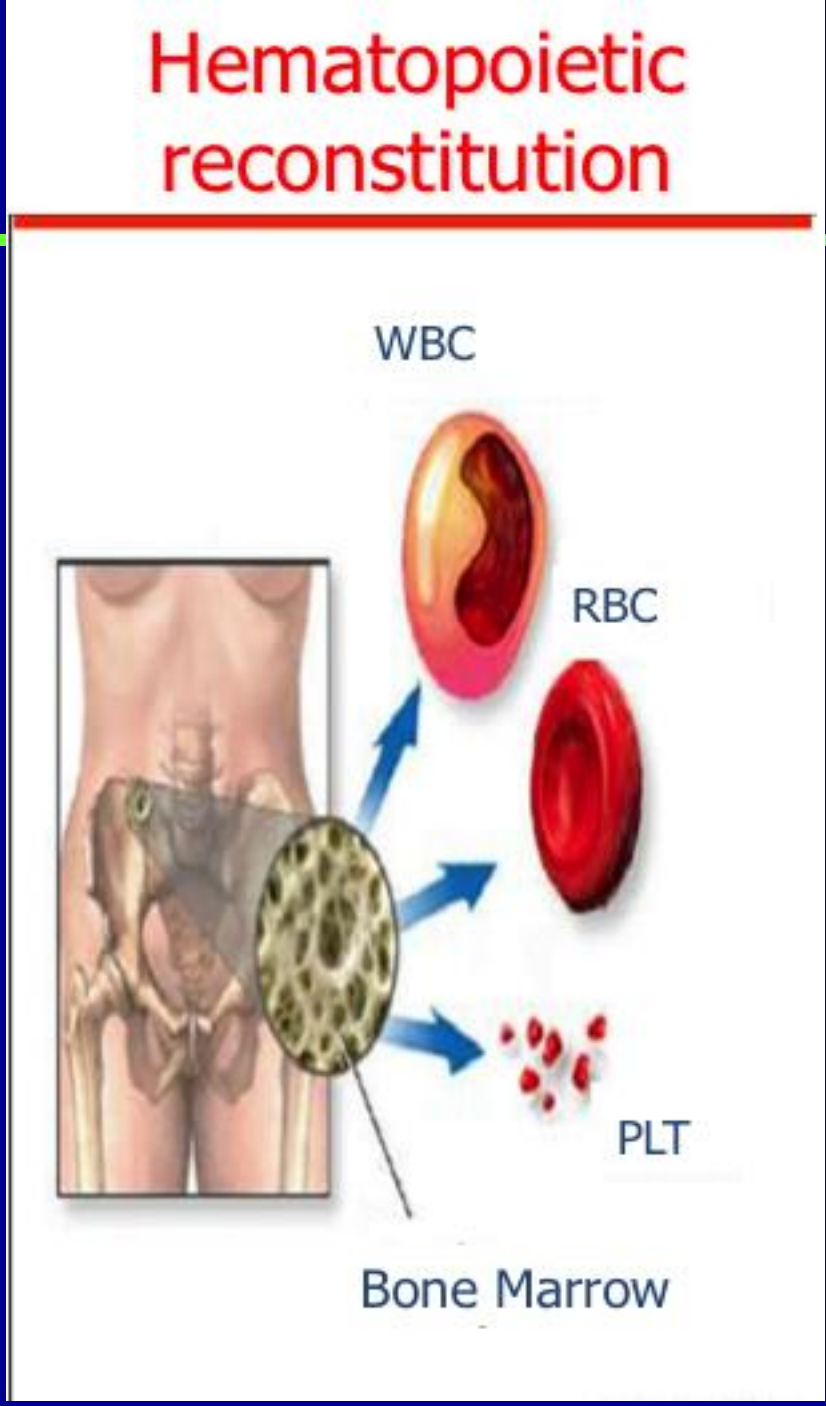
Dose of CD34

- Auto SCT
  - **> 2 x10^6 CD34+ cell/kg**
- Allogeneic SCT
  - **> 5 X10^6 CD34+ cell/kg**
- Cord blood SCT
  - **> 2 x10^6 CD34+ cell/kg**



Hematopoietic Stem Cell transplantation Types

- **Source**
  - Bone Marrow
  - Peripheral blood
  - Cord Blood
- **Donor**
  - Allogeneic
    - Sibling
    - Unrelated
  - Autologous
  - Singeneic
- **Conditioning**
  - Myeloablative
  - RIC
  - Nonmyeloablative

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Indication for HSCT

I. Neoplastic disorders

1) Hematological malignancies
   a) Lymphomas (Hodgkin and Non-Hodgkin)
   b) Leukemias (acute and chronic)
   c) Multiple myeloma
   d) MDS
2) Solid tumors

II. Non-neoplastic disorders

1) Aplastic anemia
2) Hemoglobinopathies
3) Autoimmune diseases
4) Immunodeficiency
5) Inborn errors of metabolism

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Indications for Autologous Transplant

- Multiple myeloma
- NHL
- Hodgkin's disease
- AML
- Neuroblastoma
- Ovarian cancer
- Germ-cell tumors
- Autoimmune disorders
- Amyloidosis

Copelan EA. Hematopoietic stem-cell transplantation. NEJM 2006;354:1813-1826.

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Indications for Allogeneic Transplant

- AML
- ALL
- CML
- MDS
- MPD
- NHL
- Hodgkin's Disease
- CLL
- Multiple myeloma
- Juvenile CML
- Aplastic anemia
- PNH
- Fanconi's anemia
- Blackfan-Diamond
- Thalessemia major
- Sickle cell anemia
- SCID
- Wiskott-Aldrich
- Inborn errors of metabolism

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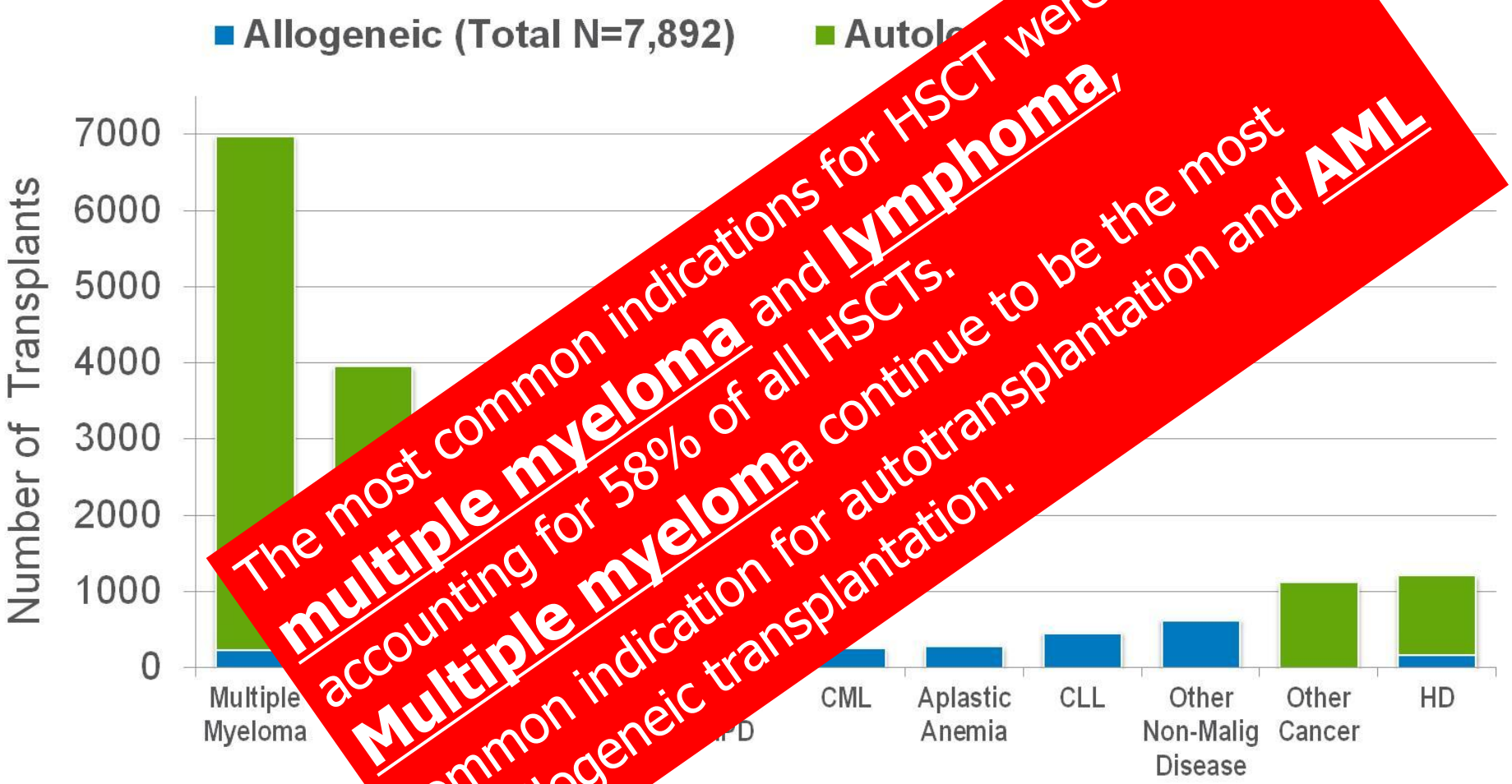
Indications for Hematopoietic Stem Cell Transplants in the US, 2011



The most common indications for HSCT were **multiple myeloma** and **lymphoma**, accounting for 58% of all HSCTs. **Multiple myeloma** continue to be the most common indication for autotransplantation and **AML** for allogeneic transplantation.

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Transplant

- Patient's bone marrow stem cells are replaced with healthy cells
- Existing bone marrow and abnormal leukocytes killed
- Chemotherapy and radiation
- Next bone marrow containing healthy stem cells re-infused

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Transplant Process (5 steps)

(1) Conditioning

(2) Stem cell infusion

(3) Neutropenic phase

(4) Engraftment phase

(5) Post-engraftment period.

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Conditioning Phase

- The conditioning period typically lasts 7-10 days.
- The purposes are (by delivery of chemotherapy and/or radiation)
  - to eliminate malignancy
  - to provide immune suppression to prevent rejection of new stem cells
  - create space for the new cells
- Radiation and chemotherapy agents differ in their abilities to achieve these goals.

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Conditioning regimens

- **Principles**
  - "space-making" (controversial)
  - immunosuppression
  - disease eradication
- **Strategy**
  - Ablative therapy
    - radio/chemo
  - Reduced intensity therapy
    - radio/chemo
  - Non-myloablative therapy
    - radio/chemo

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Conditioning regimens

- Myeloablative
  - High doses of chemotherapy +/- radiation
  - 3 goals
    - Eliminate malignancy
    - Immunosuppression to allow engraftment
    - Decrease graft versus host effects

- Copelan EA. Hematopoietic stem-cell transplantation. NEJM 2006;354:1813-1826.
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Myeloablative Regimens

- Myeloablative Regimens
  - Most common regimens
    - Cyclophosphamide/TBI
    - Busulfan/Cyclophosphamide
- Stem cells are essential to restore marrow function

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Myeloablative Regimens

- Therapy is based on disease
- Other drugs
  - Etoposide, BCNU, cytarabine, melphalan
- Graft versus leukemia effects in allogeneic donors

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Conditioning regimens

- Nonmyeloablative (Mini-allo)
  - Sufficient immunosuppression to allow donor cell engraftment
  - Injury to organs less, fewer infections, fewer transfusions
  - Higher relapse rates
  - May have mixed chimerism
  - Graft versus tumor effects

Lazarus HM. Autologous and allogeneic transplantation procedures for hematologic malignancies. Manual of Clinical Hematology, 3rd edition 2002:399-409

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Non-myeloablative Conditioning

- Alternative to conventional myeloablative regimens
- Older patients or patients with comorbid conditions
- Therapeutic graft versus tumor effect
  - Mediated by allogeneic T-cells
  - Donor T-cells eradicate the host's malignant cells

Georges GE, Storb R. Review of "minitransplantation": nonmyeloablative allogeneic hematopoietic stem cell transplantation. Int J Hematol. 2003;77:3-14.

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Non-myeloablative Regimens

- Nonmyeloablative Regimens
  - Usually fludarabine based
  - ATG is added
  - May be combined with other drugs
    - Busulfan, cyclophosphamide, melphalan

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Non-myeloablative Regimens

- Better for slow growing cancers
  - CLL, NHL
- Graft eradicates the cancer not the chemo
- High relapse rates

Copelan EA. Hematopoietic stem-cell transplantation. NEJM 2006;354:1813-1826.

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Reduced Intensity Conditioning Regimens

- Advantages
  - Reduction in mortality
  - Reduction in non-relapse mortality
  - Reduced PRBC and platelet transfusions
  - Duration of neutropenia reduced
  - Reduced numbers of bacteremias
  - Able to give to heavily pretreated patients

Sandmaier BM, Mackinnon S, Childs RW. Reduced intensity conditioning for allogeneic hematopoietic stem cell transplanation: Current perspectives. Biol Blood Marrow Transplant. 2007;13:87-97.

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Reduced Intensity Conditioning Regimens

- Reduced GVHD compared to myeloablative
- Late onset acute GVHD occurring beyond day 100

Sandmaier BM, Mackinnon S, Childs RW. Reduced intensity conditioning for allogeneic hematopoietic stem cell transplanation: Current perspectives. Biol Blood Marrow Transplant. 2007;13:87-97.

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Stem cell processing and infusion

- Infusion - 20 minutes to an hour, varies depending on the volume infused.
- The stem cells may be processed before infusion, if indicated.
- Depletion of T cells can be performed to decrease GVHD.
- Premedication with acetaminophen and diphenhydramine to prevent reaction.

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Stem cell processing and infusion

- Infused through a CVL, much like a blood transfusion.
- Anaphylaxis, volume overload, and a (rare) transient GVHD are the major potential complications involved.
- Stem cell products that have been cryopreserved contain dimethyl sulfoxide (DMSO) as a preservative and potentially can cause renal failure, in addition to the unpleasant smell and taste.

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Infusion of Stem Cells

- Stem cells may be infused fresh within a few hours of collection
- May be frozen using DMSO
  - Creamed corn or garlic smell
- Umbilical cord blood is obtained from one of the umbilical cord veins and frozen with an anticoagulant and nutrient media

Lazarus HM. Autologous and allogeneic transplantation procedures for hematologic malignancies. Manual of Clinical Hematology, 3rd edition 2002:399-409

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Stem Cell Manipulation

- ABO incompatible
  - Removal of isoagglutinins or RBCs
- T-cell depletion
  - Reduce incidence of GVHD
  - Increased graft failure
  - Increased relapse rates
- In vitro purging
  - Removal of tumor cells
  - Positive selection of CD34+ cells

Lazarus HM. Autologous and allogeneic transplantation procedures for hematologic malignancies. Manual of Clinical Hematology, 3rd edition 2002:399-409

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Neutropenic Phase

- During this period (2-4 wk), the patient essentially has no effective immune system.
- Healing is poor, and the patient is very susceptible to infection.
- Supportive care and empiric antibiotic therapy are the mainstays of successful passage through this phase.

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Engraftment Phase

- During this period (several weeks), the healing process begins with resolution of mucositis and other lesions acquired.
- In addition, fever begins to subside, and infections often begin to clear.
- The greatest challenges at this time are management of GVHD and prevention of viral infections (especially CMV).

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Recovering from the transplant

- Recovery of normal levels cells is called engraftment
- Day 8 - 12
- Neutrophil engraftment important (GCSF) may be given to accelerate the process
- Platelets are the next to return with red cells last.
- Commonly patients require transfusion of red cells and platelets following a transplant.
- Discharge upon neutrophil & platelet engraftment

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POST-BONE MARROW TRANSPLANTATION CARE

- A two- to four-week waiting period follows the marrow transplant before its success can begin to be judged.
- The marrow recipient is kept in isolation during this time to minimize potential infections.
- The recipient also receives intravenous antibiotic, antiviral, and antifungal medications, as well as blood and platelet transfusions to help fight off infection and prevent excessive bleeding.
- Blood tests are performed
- daily to monitor the patient's kidney and liver function, as well as nutritional status.
- Other tests are performed as necessary.
- Further side effects, such as nausea and vomiting, can be treated with other medications.

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Post-engraftment Phase

- This period lasts for months to years. Hallmarks of this phase include the gradual development of tolerance, weaning off of immunosuppression, management of chronic GVHD, and documentation of immune reconstitution.

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Factors influencing the outcome of HSCT

- **Disease factors**
  - Stage
- **Patient - related factors**
  - Age
- **Donor - related factors**
  - Histocompatibility (HLA)
  - Sex
  - Viral status (CMV positivity)
- **Peri-transplant factors**
  - Conditioning
  - GVHD prevention
  - Stem cell source and content
- **Post-transplant factors**
  - GVHD

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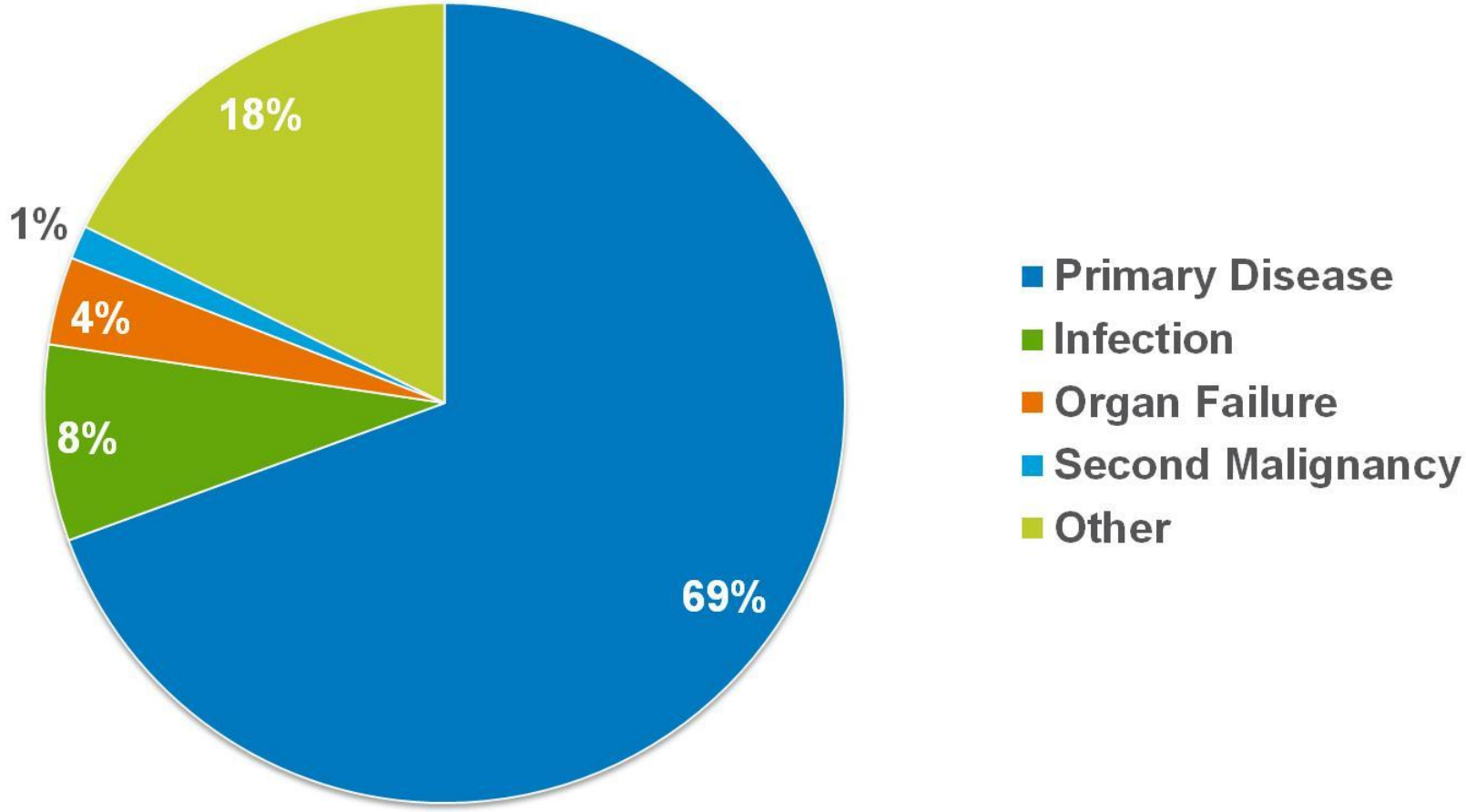
Causes of Death after Autologous Transplants done in 2010-2011



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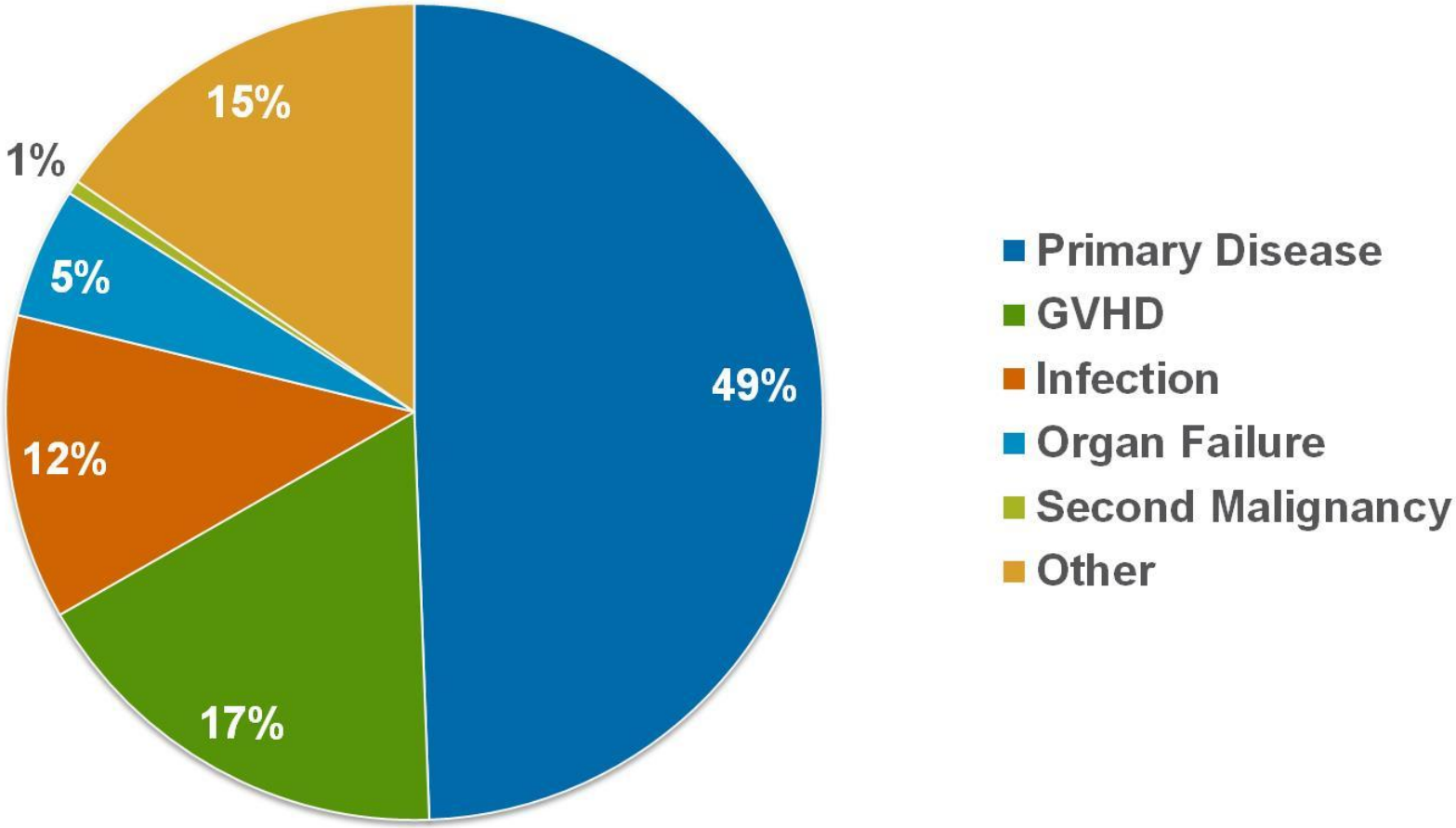
Causes of Death after HLA-identical Sibling Transplants done in 2010-2011



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Complication

- **Allogeneic**
  - **Early**
    - infection
    - aGVHD
    - bleeding
    - toxicity
    - graft failure
  - **Late**
    - chGVHD
    - infection
    - relapse
    - gonadal failure
    - secondary malignancy
    - toxicity
- **Autologous**
  - **Early**
    - infection
    - bleeding
    - toxicity
  - **Late**
    - relapse
    - infection
    - gonadal failure
    - secondary malignacy
    - toxicity

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Graft versus Host Disease (GVHD)

- If donor cells see the host cells as foreign, the donor cells will attack the host.

- Skin, gut, and liver most likely to be affected.
  - Acute < 100 days after the transplant
  - Chronic > 100 days

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Graft versus Host Disease (GVHD)

- What are risk factors for GVHD?
  - HLA match / mismatch
  - Lymphocytes in graft
  - Inadequate immune suppression
  - Other

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AlloHSCT - graft versus host disease

- **GVHD**
  - Acute (1- 4°)
  - Chronic (limited, extensive)
- **Prophylaxis**
  - Cyclospirine
  - Metotrexate
- **Treatment**
  - Cyclosporine
  - Steroid
  - Mycofenolate mofetil
  - Antithymocytic globuline
  - Anti-TNF alfa, anti-IL 2

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Graft versus Host Disease (GVHD)





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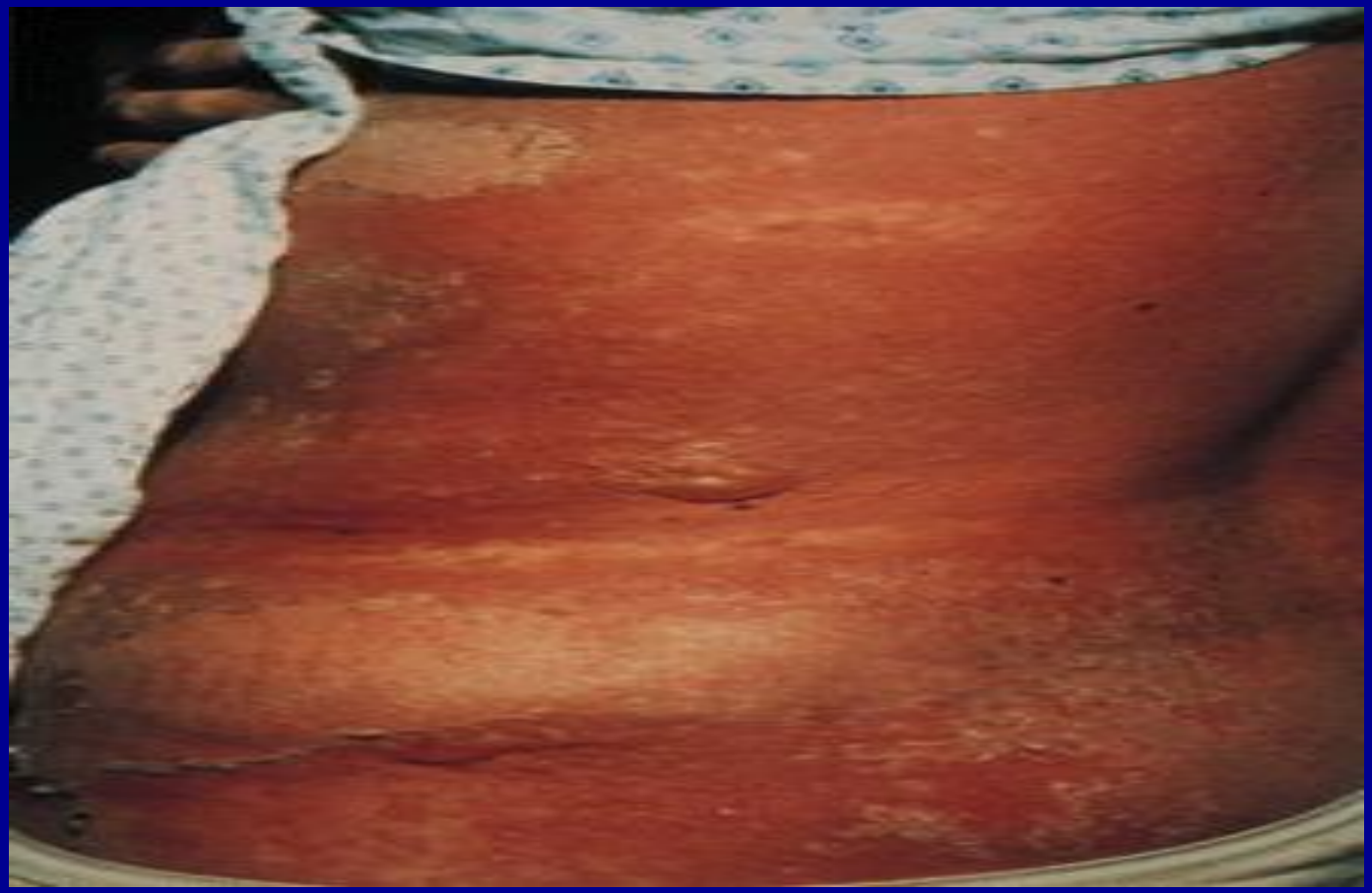
Acute Graft versus Host Disease of Skin



Graft Versus Host Disease of the Skin: Grade IV

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Chronic Extensive Graft versus Host Disease

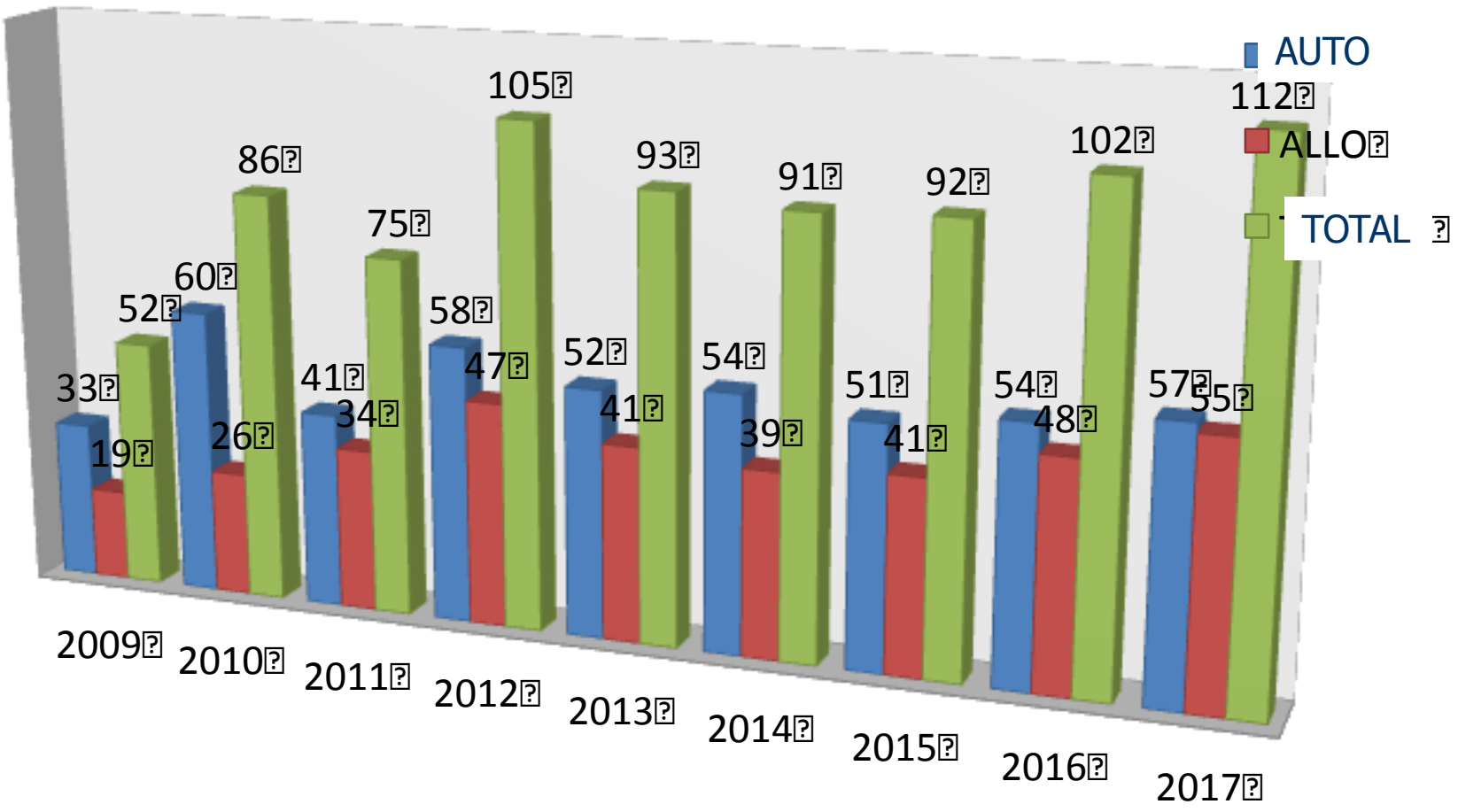




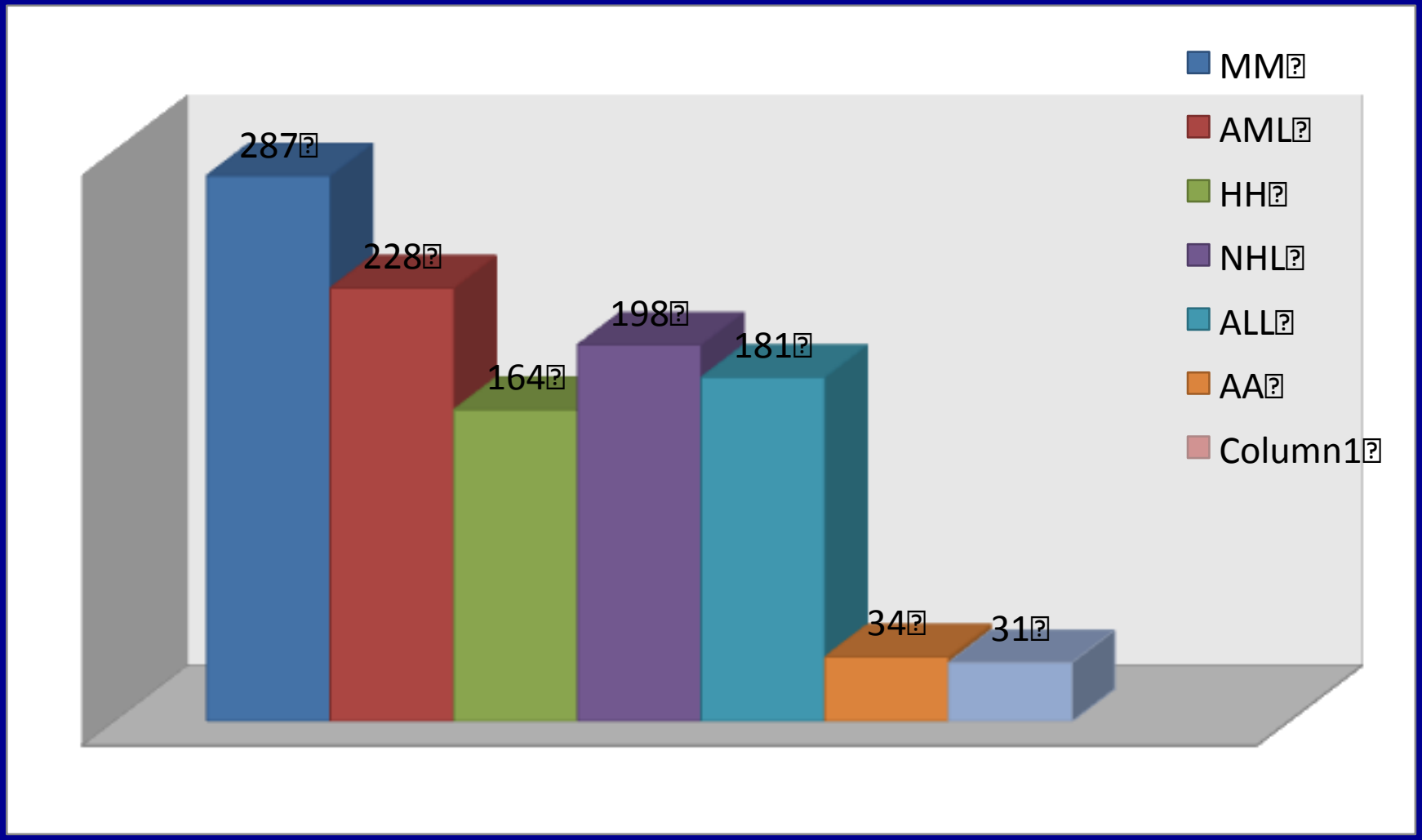
Ankara Oncology Education and Research Hospital

Hematopoietic stem cell transplantation applications

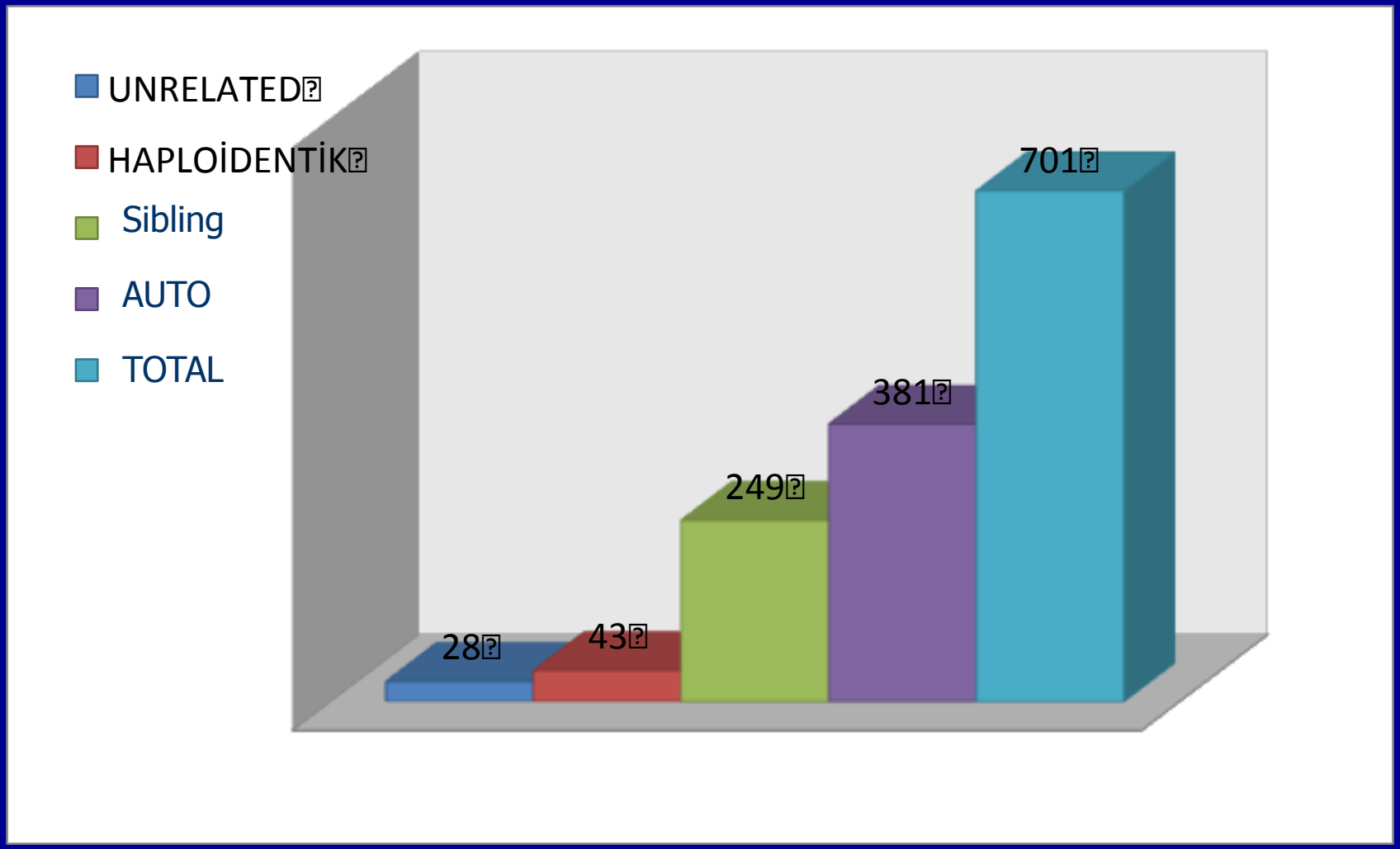
HSCT 2009 - 2017



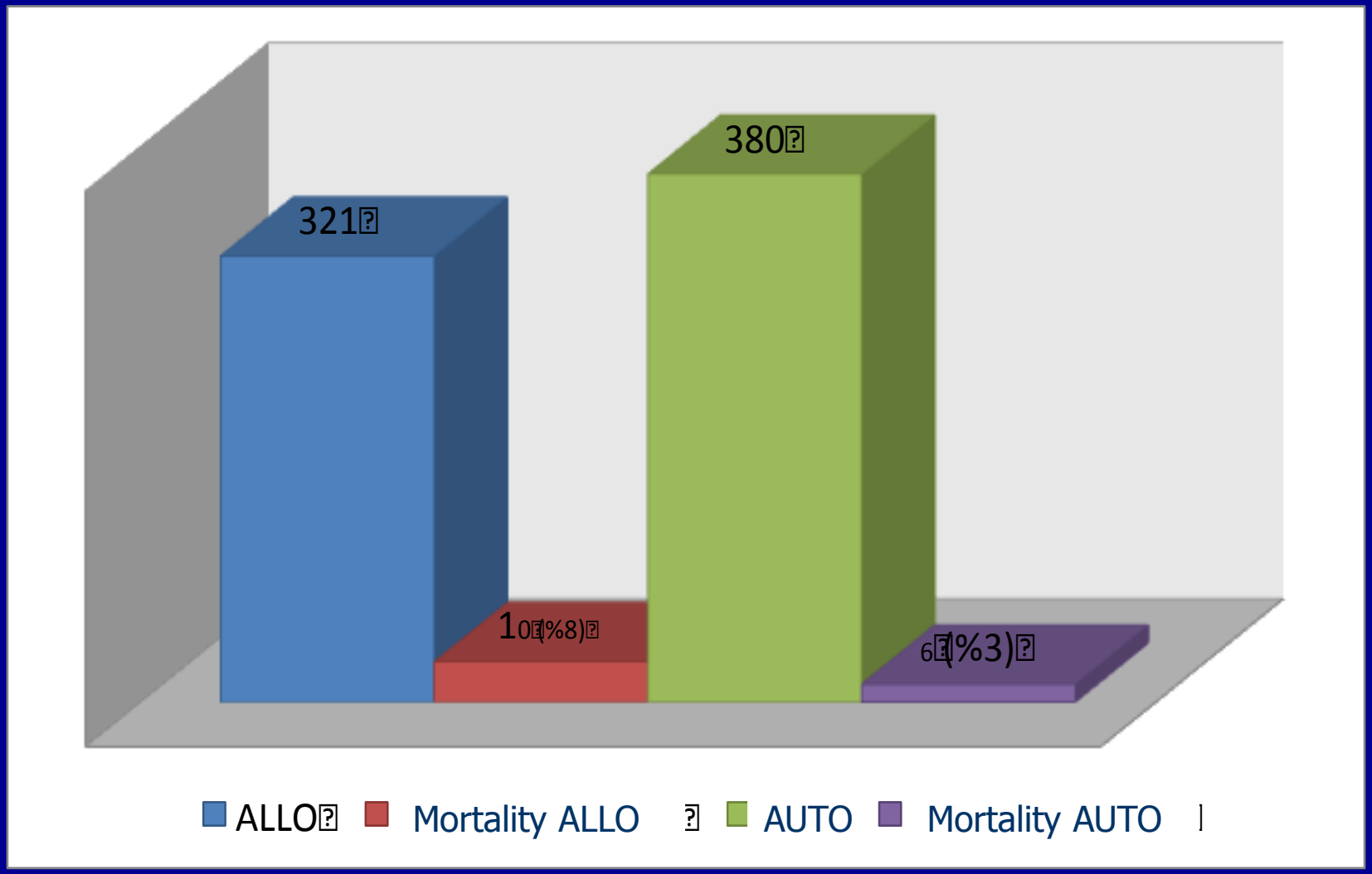
HSCT according to disease type



HSCT Types in 2017



TRM (D+100)



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