Hematopoietic Stem Cell Transplantation

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Fellowship of Pediatric Hematopoietic Stem Cell Transplantation

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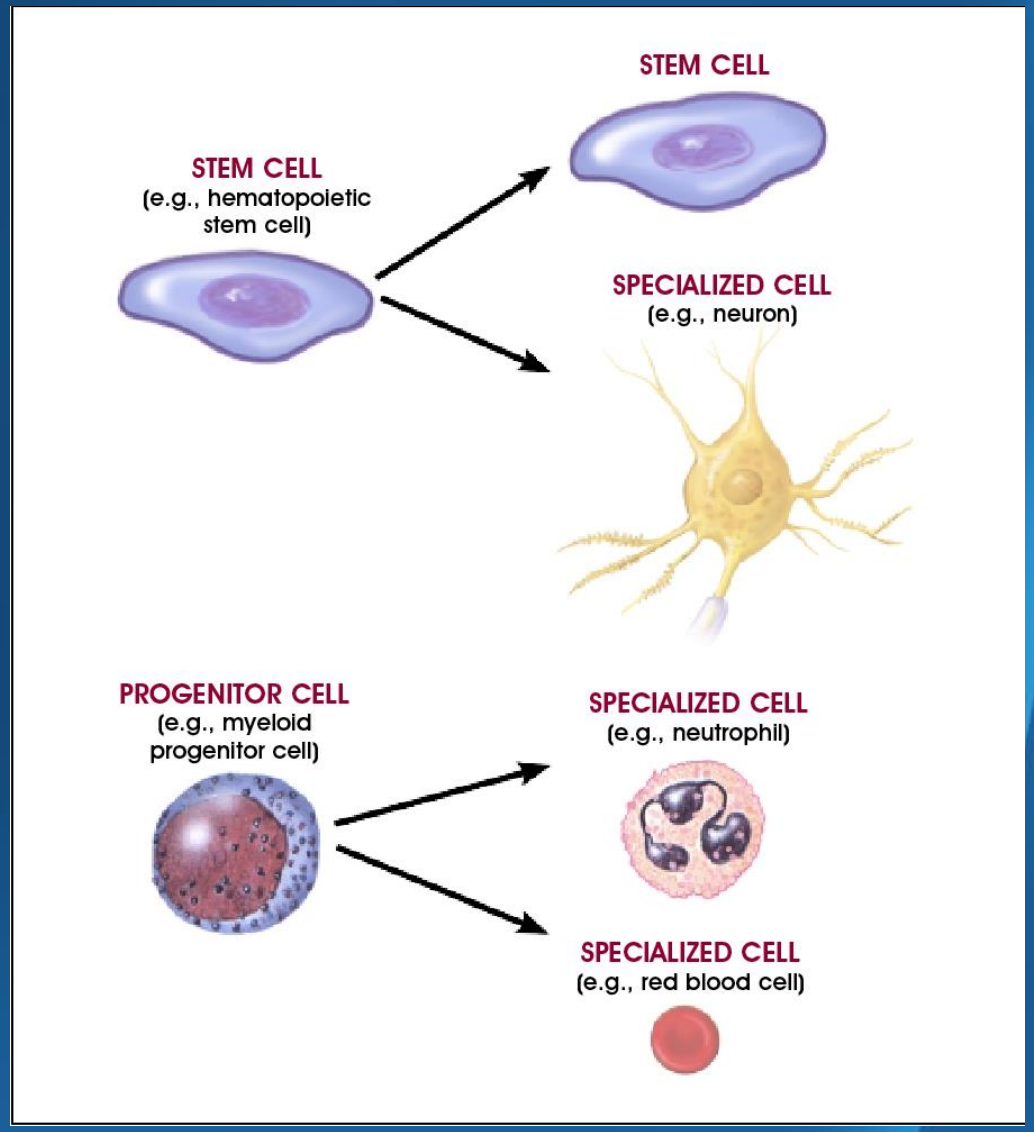
Questions to be answered

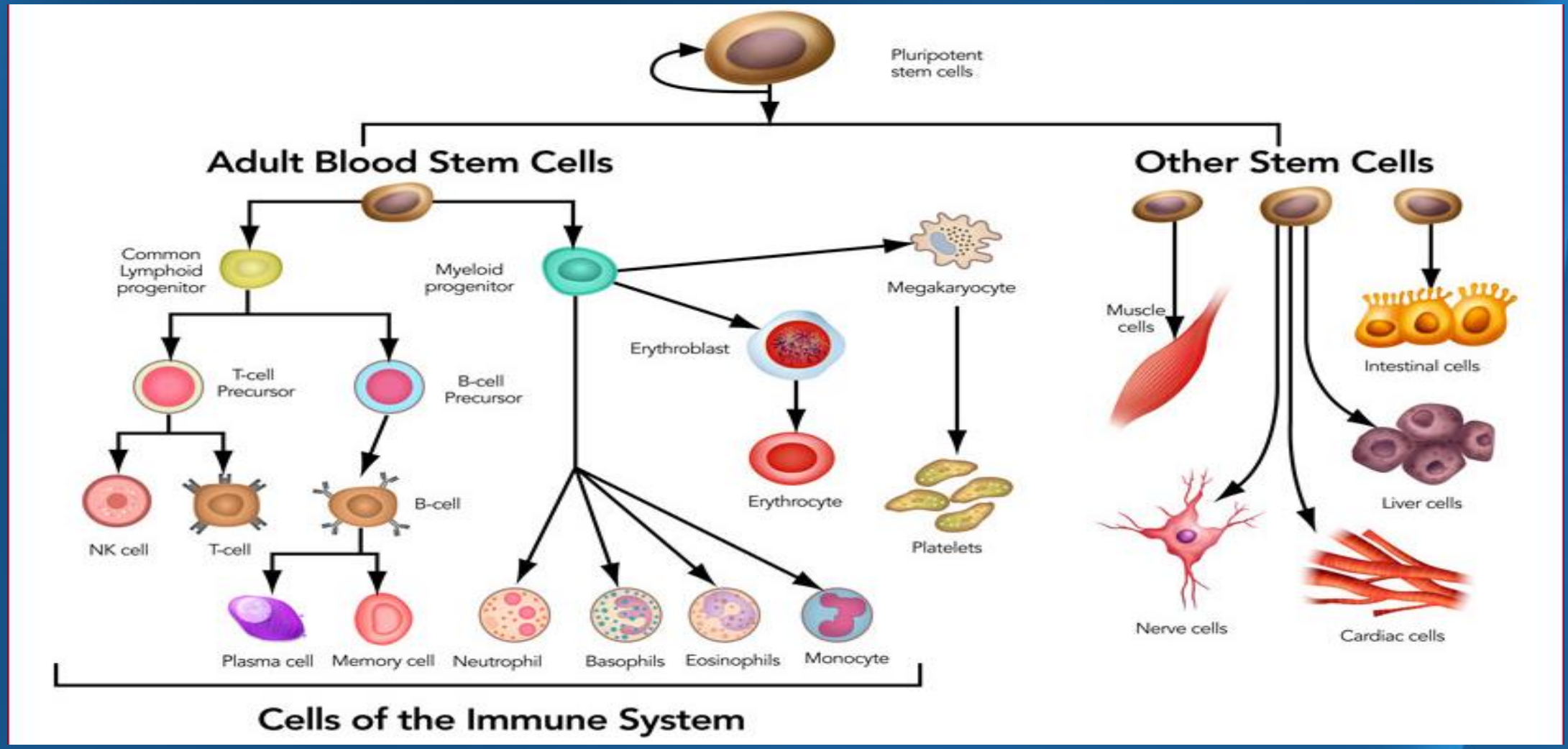
- What is a stem cell transplant?
- Where do stem cells come from?
- When does a patient need a transplant?
- Who can be a donor?
- How does all this happen?
- what problems can kids have after transplant?

What are Stem Cells?

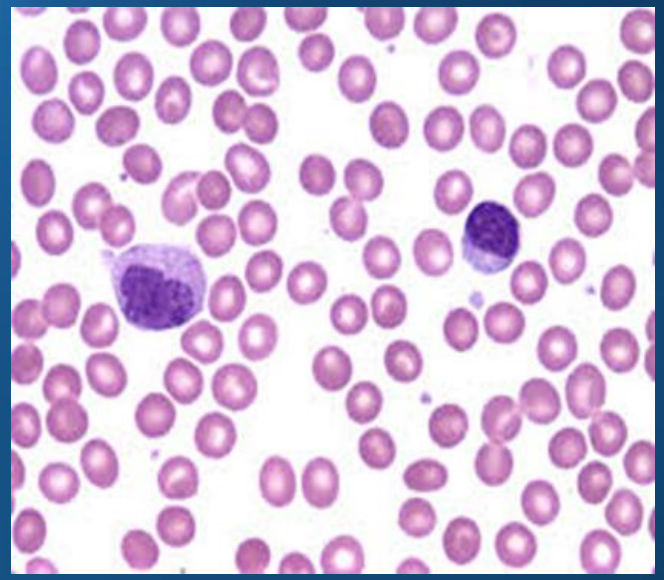
- Not characteristics of specific tissues
- Divide for the lifetime of the organism
- Can replenish themselves



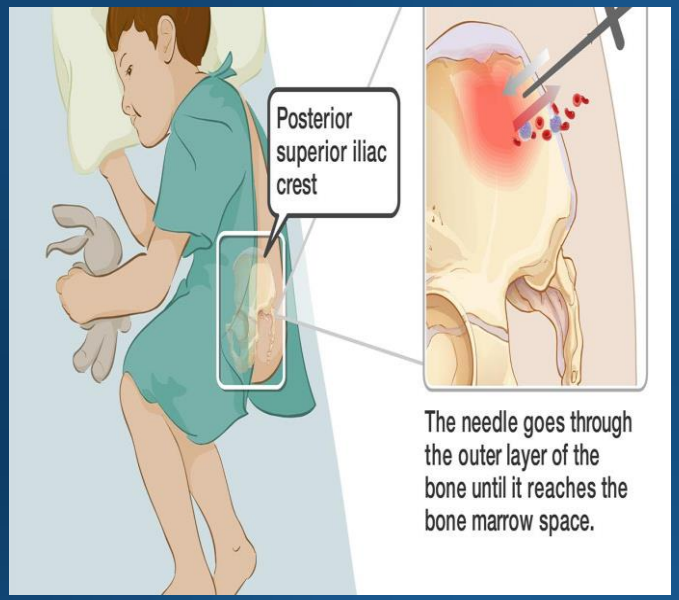
Stem Cell


Pluripotent stem cells
Adult Blood Stem Cells
Other Stem Cells
Common Lymphoid progenitor
Myeloid progenitor
Megakaryocyte
Erythroblast
T-cell Precursor
B-cell Precursor
Muscle cells
Intestinal cells
Liver cells
Erythrocyte
Platelets
B-cell
NK cell
T-cell
Nerve cells
Cardiac cells
Plasma cell
Memory cell
Neutrophil
Basophils
Eosinophils
Monocyte
Cells of the Immune System

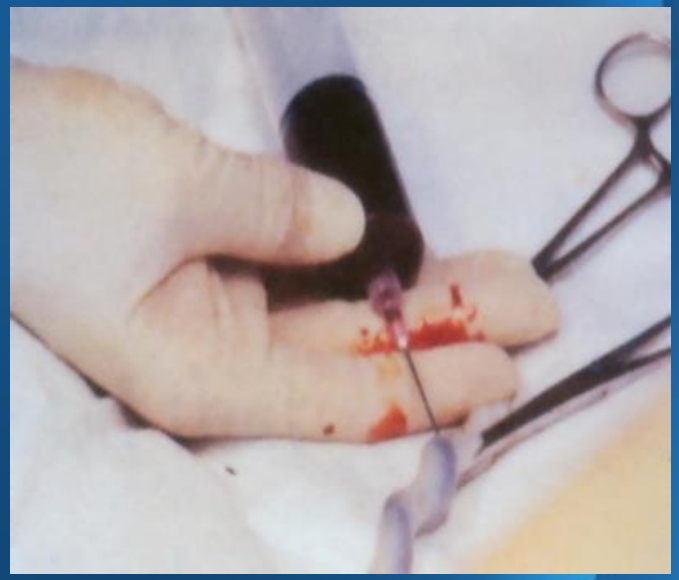
Sources of Stem Cells



Peripheral Blood



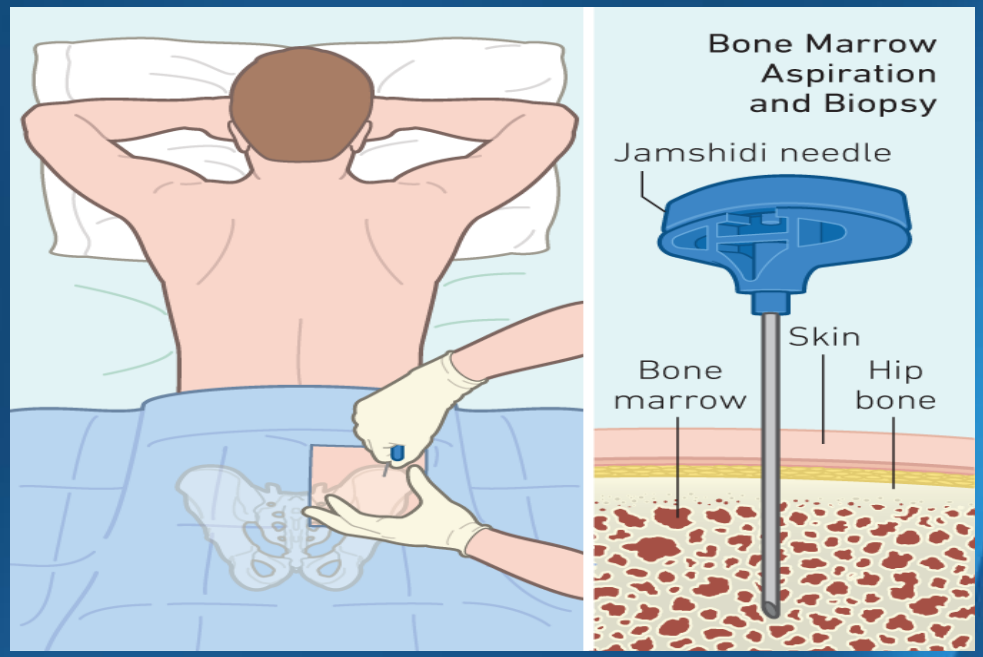
Bone Marrow



Cord blood

Collection of HSCs

- Bone marrow

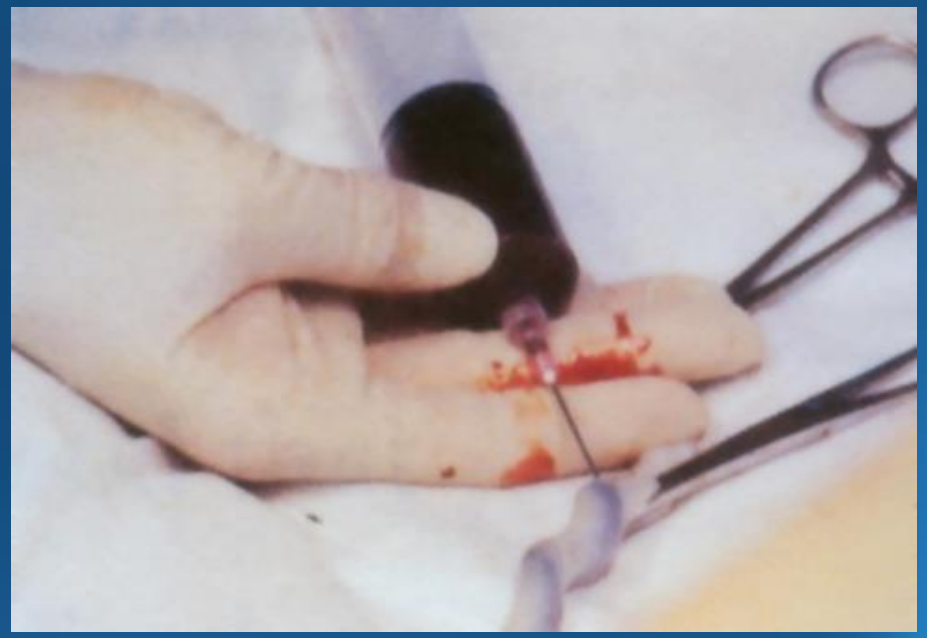


Collection of HSCs

- Peripheral blood
  - **Using cytokine stimulation (G-CSF injections)**
  - **BM releases large number CD34 stem cells into circulation**
  - **Stem cells harvested via peripheral line using apheresis**
  - **(cell separator machine)**

Collection of HSCs

- Cord Blood



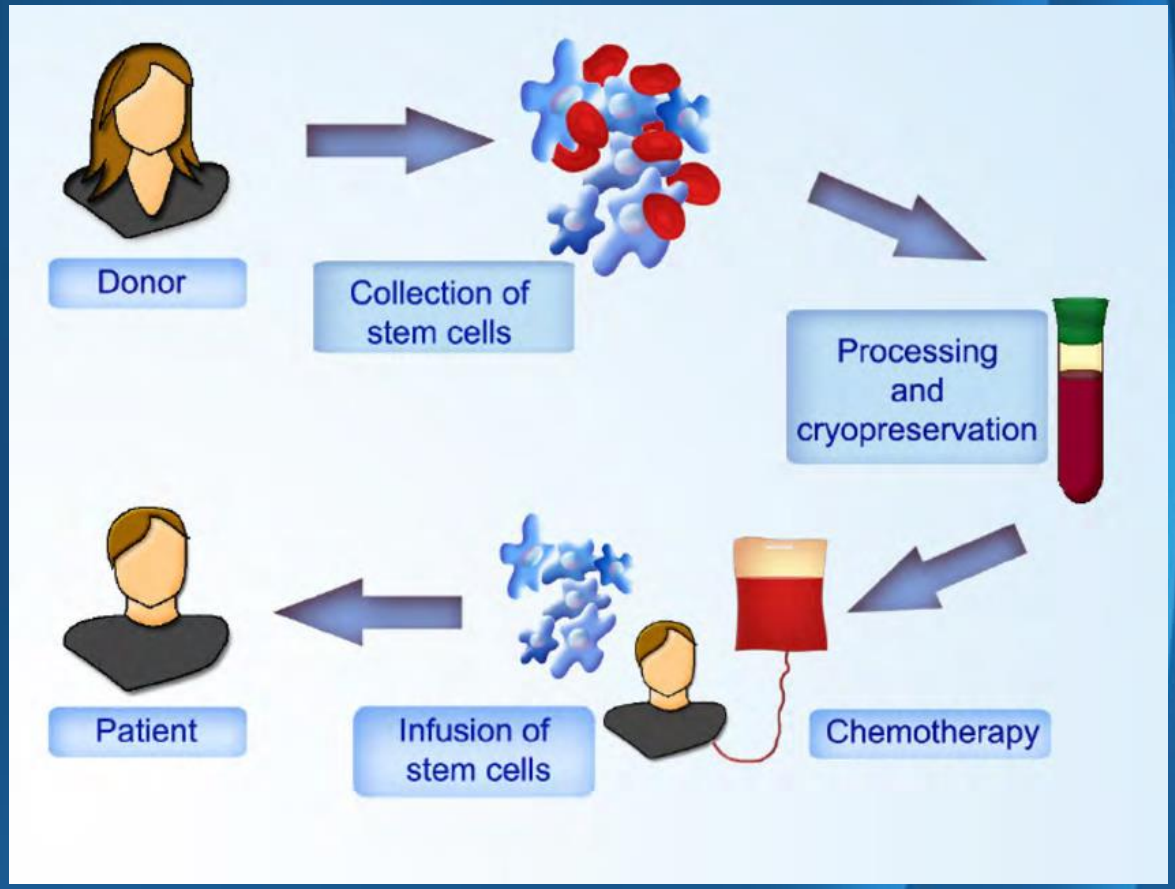
Collection of HSCs

Bone Marrow vs Peripheral Blood

Bone Marrow	Peripheral Blood	Cord Blood
1-2 nights in hospital	Outpatient procedure takes 4-5 hours	-
Advantages:		
- No G-CSF injections	- Less invasive - No general anesthetic - more rapid hematopoietic recovery	- Collection has no risks - Tolerance of greater degree of HLA mismatch - More quickly available
Disadvantages:		
- Requires general anesthetic - Side effects: - Side effects of anesthesia - Pain, infections or bleeding at harvest site	- G-CSF injections required Side effects - Headaches, bone or joint pains - Citrate toxicity - Electrolyte imbalances	- Low cell dosages may limit to small recipients - Longer time to engraftment→ increased costs - No additional cells if first transplant does not take - No medical history of donor - Small volume makes transplant into adults difficult

Type of HSCT

- Allogeneic transplant:
  - uses stem cells from another person
- Autologous transplant:
  - uses stem cells taken from the patient

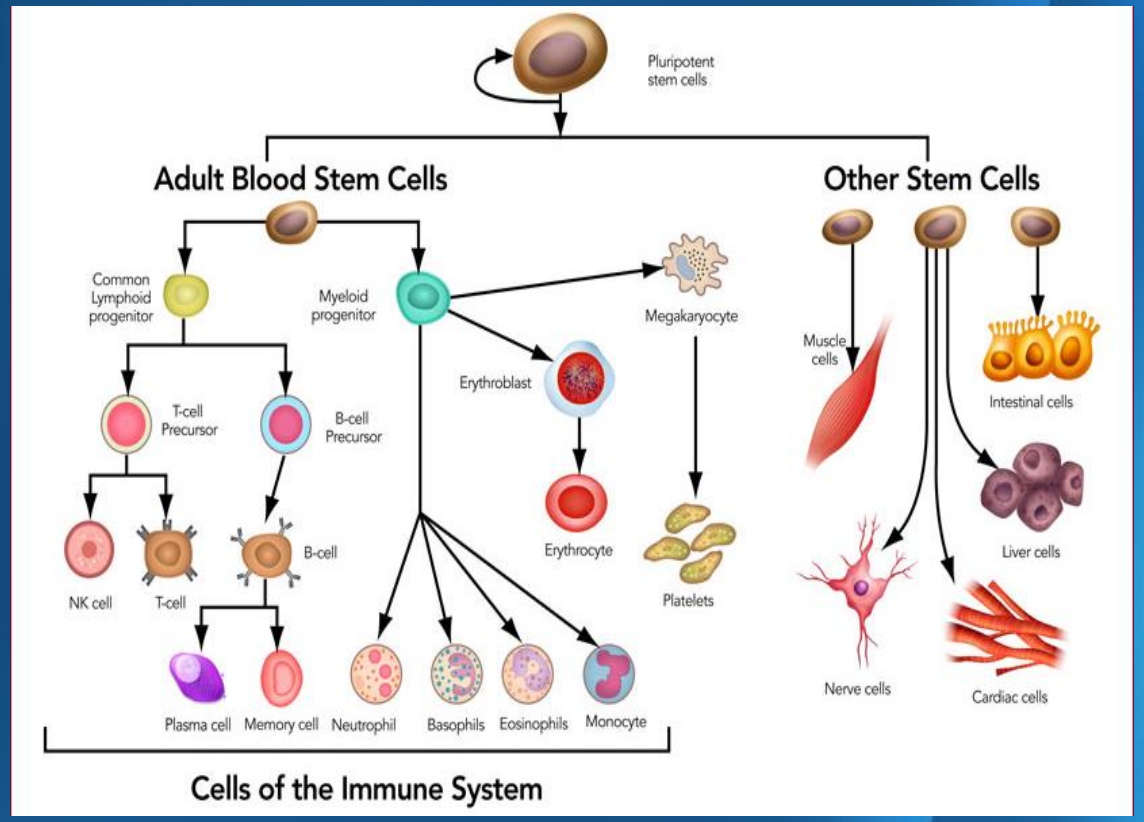


Rationale for HSCT

- Autologous HSCT:
  - Allows delivery of supra-lethal doses of chemotherapy (transplant given as rescue)
- Allogenic HSCT:
  - Donor cells may directly attack cancer cells (anti-cancer effect)
  - Correct congenital defects in bone marrow (replaces defective marrow)
  - Corrects congenital immunodeficiencies (replaces immune system)

HSCT indications

- Malignancies
  - Leukemia, Lymphoma, solid tumors, …
- Immunodeficiencies
  - SCID, CGD, SCN, …
- Metabolic disorders
  - MPS, osteopetrosis,…
- Hematologic disorders
  - Thalassemia, …



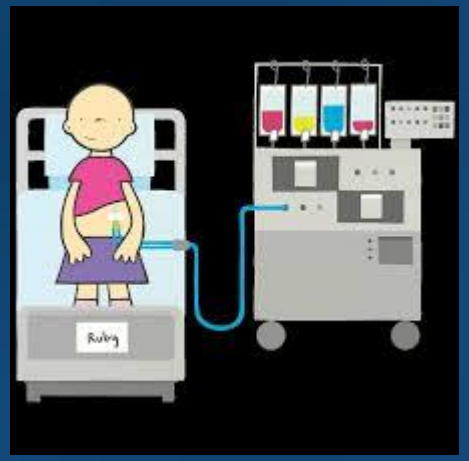
Rationale for HSCT

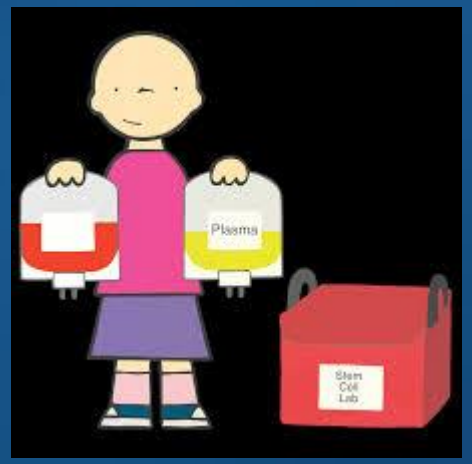
- Choice of graft is based on
  - disease type
  - patient condition
  - donor compatibility and health

Limitations of Allogeneic HSCT

- Scarcity of suitable donors
- Graft versus Host Disease
- Infections

HSCT-definition

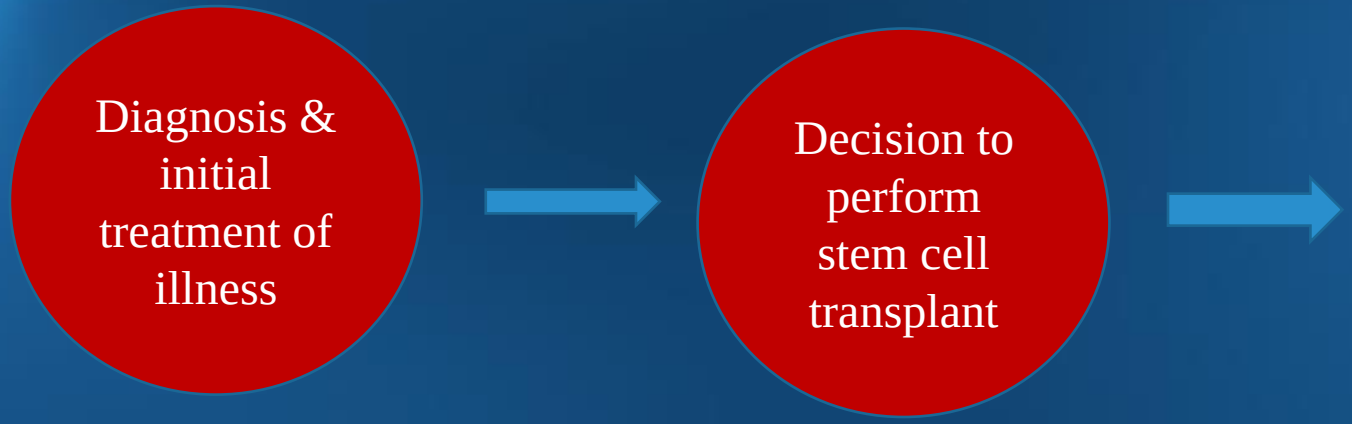




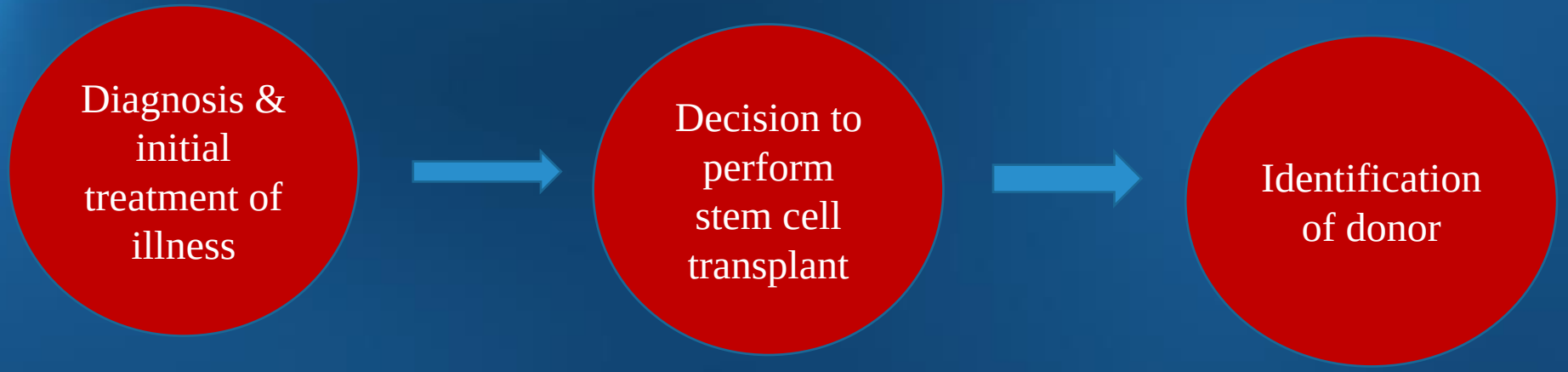
Stem Cell Transplant Procedure

Diagnosis & initial treatment of illness

Stem Cell Transplant Procedure



Stem Cell Transplant Procedure



Identification of Donor
HLA Typing

- HLA are proteins found on short arm of chromosome 6
- Antigens important in HSCT
  - HLA-A
  - HLA-B
  - HLA-C
  - HLA-DRB1
  - HLA-DQB1

  one set of 3 from each parent
- Brings to a total of 10 antigens to match
- A full match is “10/10”
- ABO incompatibility is not an exclusion

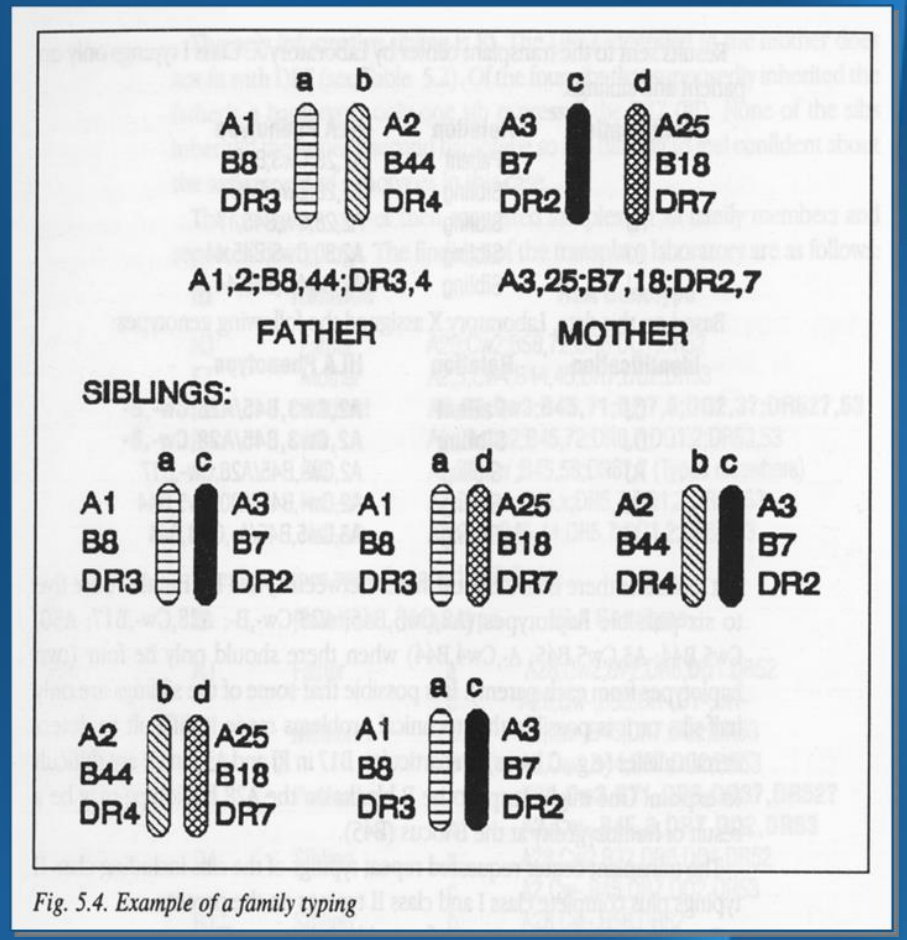
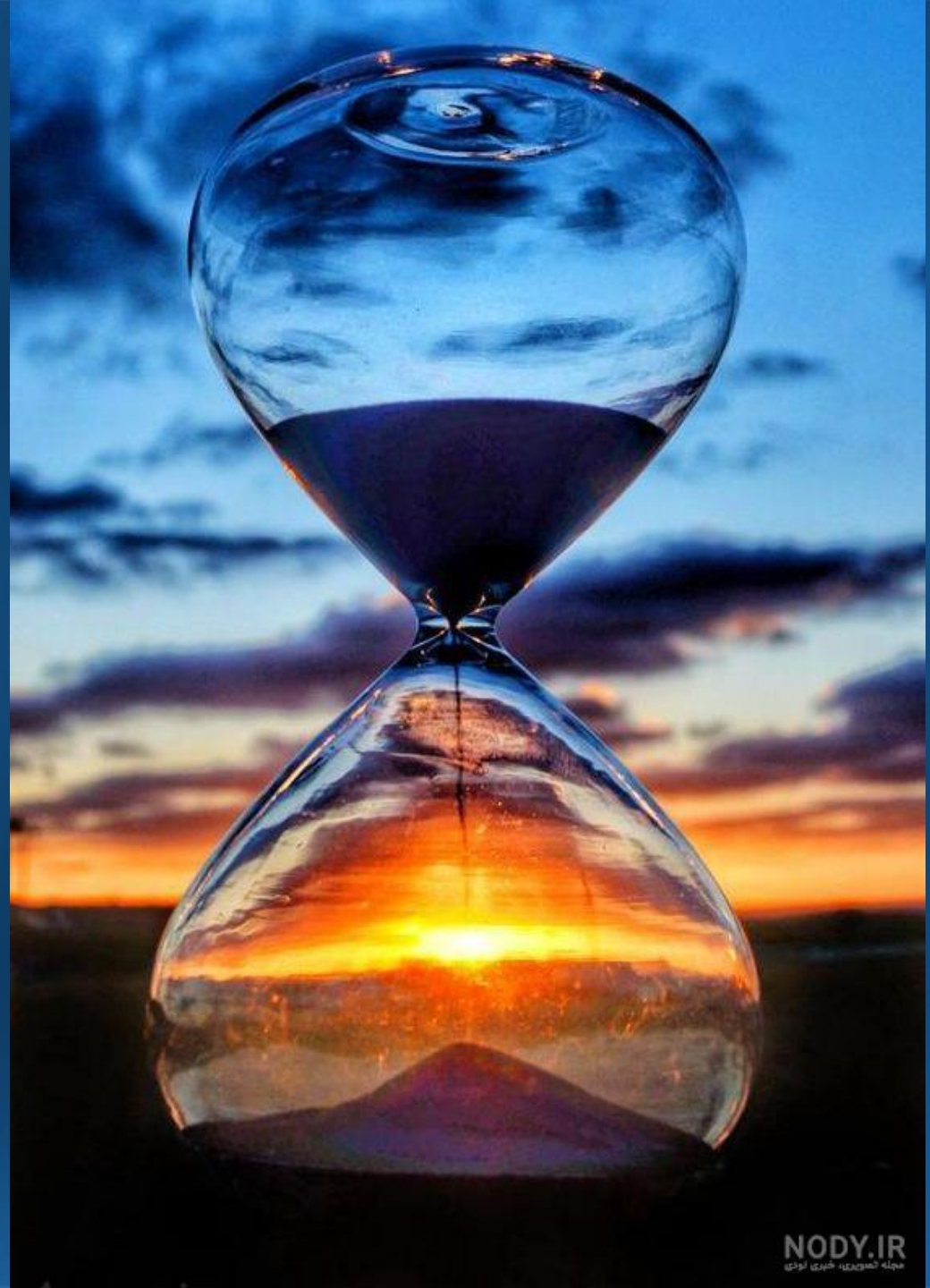


Fig. 5.4. Example of a family typing

Type of Donor

- **Allogeneic transplant:**
  - **from sibling/related donor**
  - **from unrelated donor: found using a donor registry**
  - **Haploidentical: half-matched family member**

- **Autologous transplant:**
  - **Affected Patient (Self)**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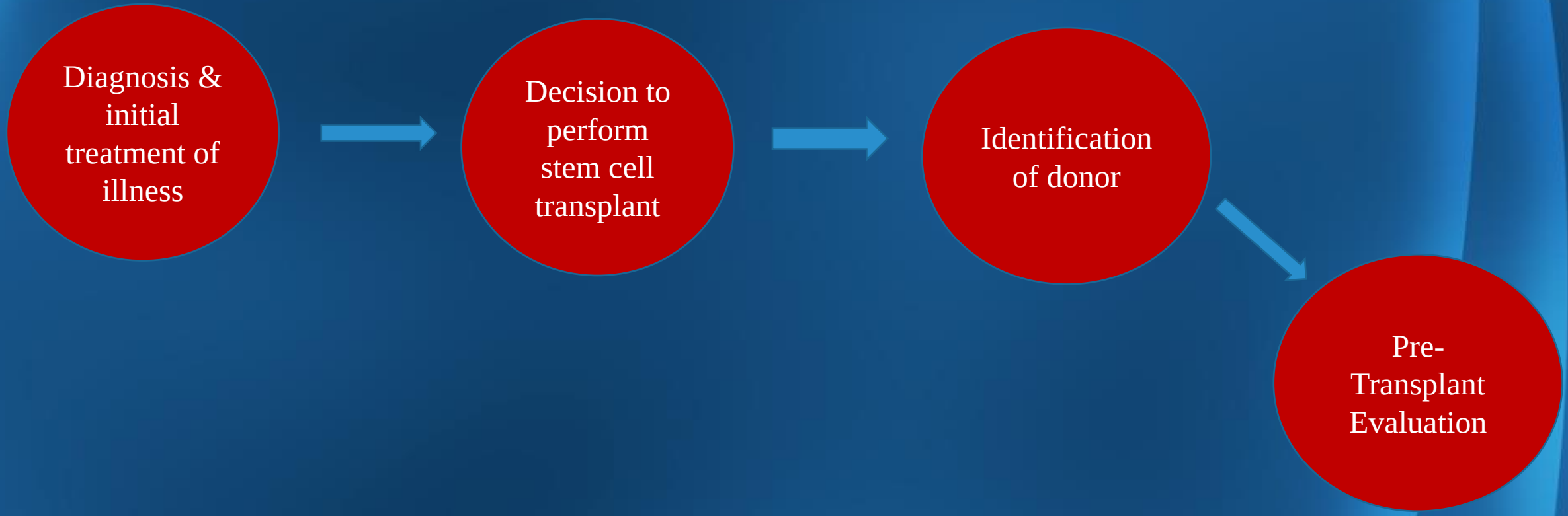
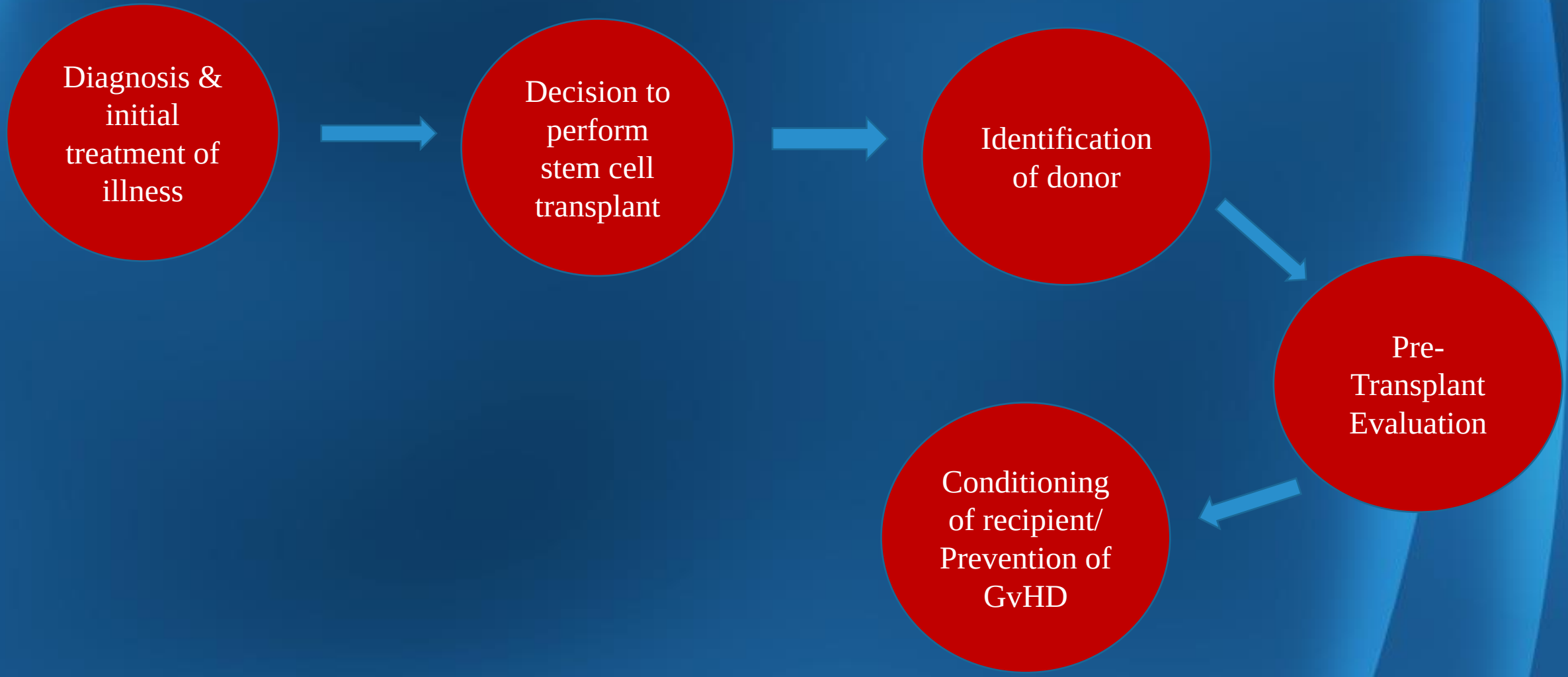
Stem Cell Transplant Procedure



Pre-Transplant Evaluation

Rationale	Investigation
To assess disease status	PET / CT scans; Bone marrow aspirate. etc …
To assess cardiac function	Echocardiogram
To assess pulmonary function	Lung function tests
To assess suitability for HSCT	Blood tests: FBS, ABO, Urine analysis, clotting screen, syphilis, Viral screen – CMV, TOXO, EBV,HSV, VZV, HIV, Hep B&C, HTLV 1& 2 etc..

Stem Cell Transplant Procedure



Conditioning Regimens

- The first stage of the transplant
  - May be given in one dose or over several days.
- 2 arms:
  - Myeloablative & Immunosuppressive
- Necessary for:
  - Suppressing the patient's immune system
  - Destroying remaining cancer cells
  - Creating room in the bone marrow for the transplanted stem cells

Conditioning Regimens

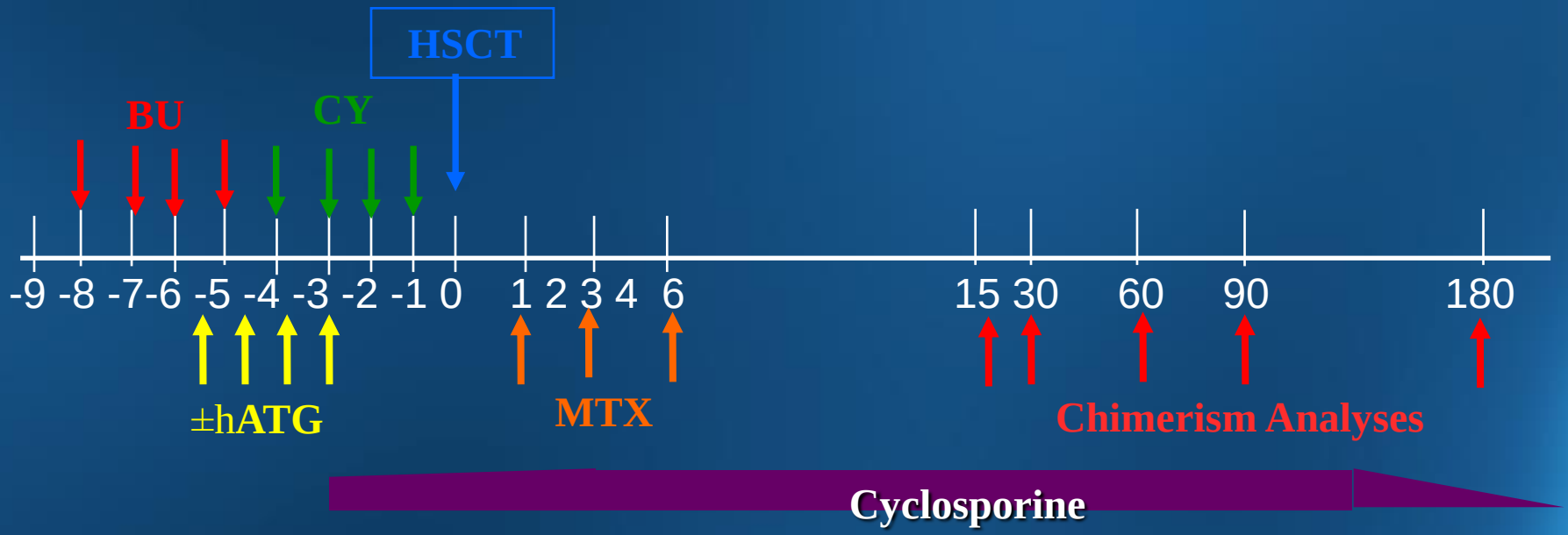
- Conditioning regimen is dependent on
  - the type of disease
  - the type of transplant
  - co-morbidities and age
  - given 3-10 days before transplant

Conditioning Regimen Intensity

- Decrease toxicities
- Reduction mortality
- Increased risk of non-engraftment

- Increase toxicities
- Increased level of disease control
- Quicker engraftment

Treatment Protocol DBA

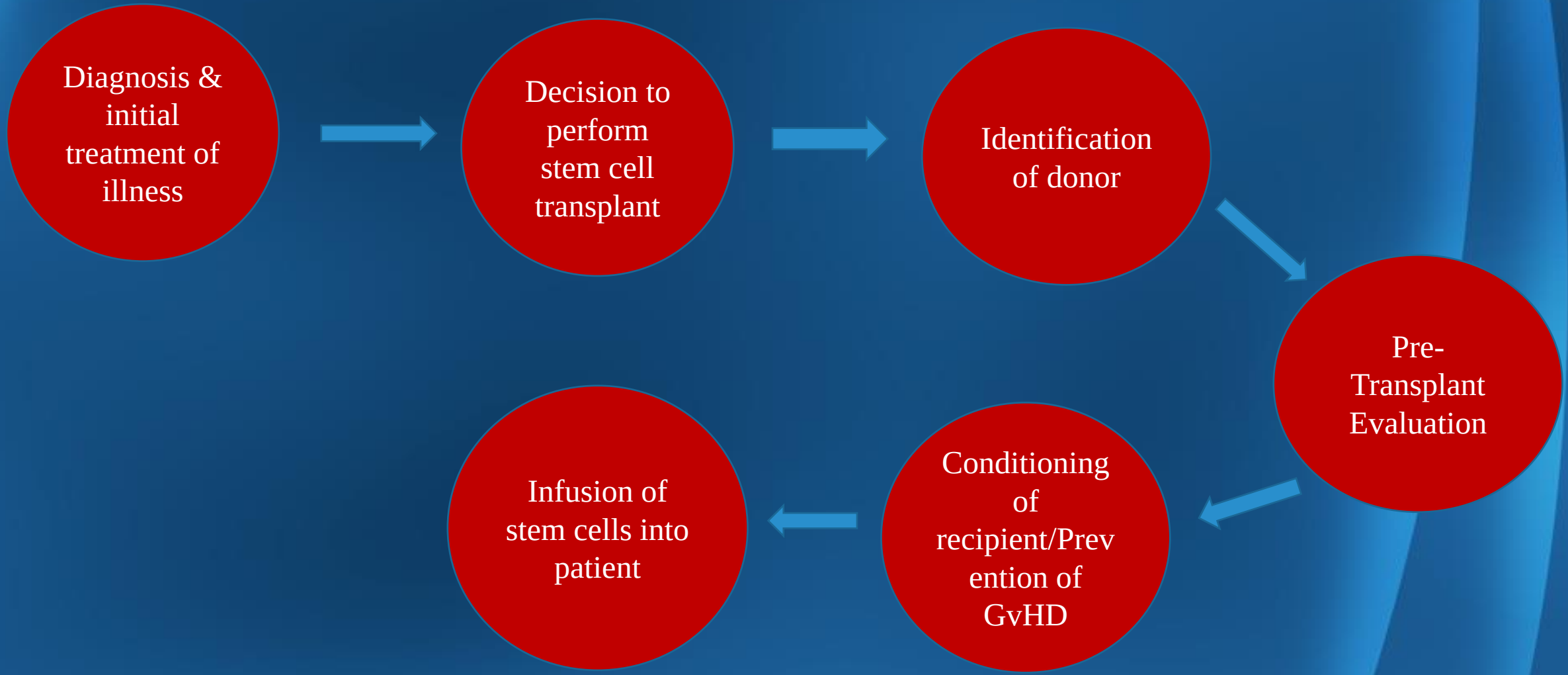


Prevention of GvHD

- Donor selection: HLA matching
- Reduced intensity conditioning regimens
- T cell depletion
- Use of immunosuppressive drugs
  - Cyclosporin
  - Methotrexate
  - Mycophenolate mofetil
  - Tacrolimus

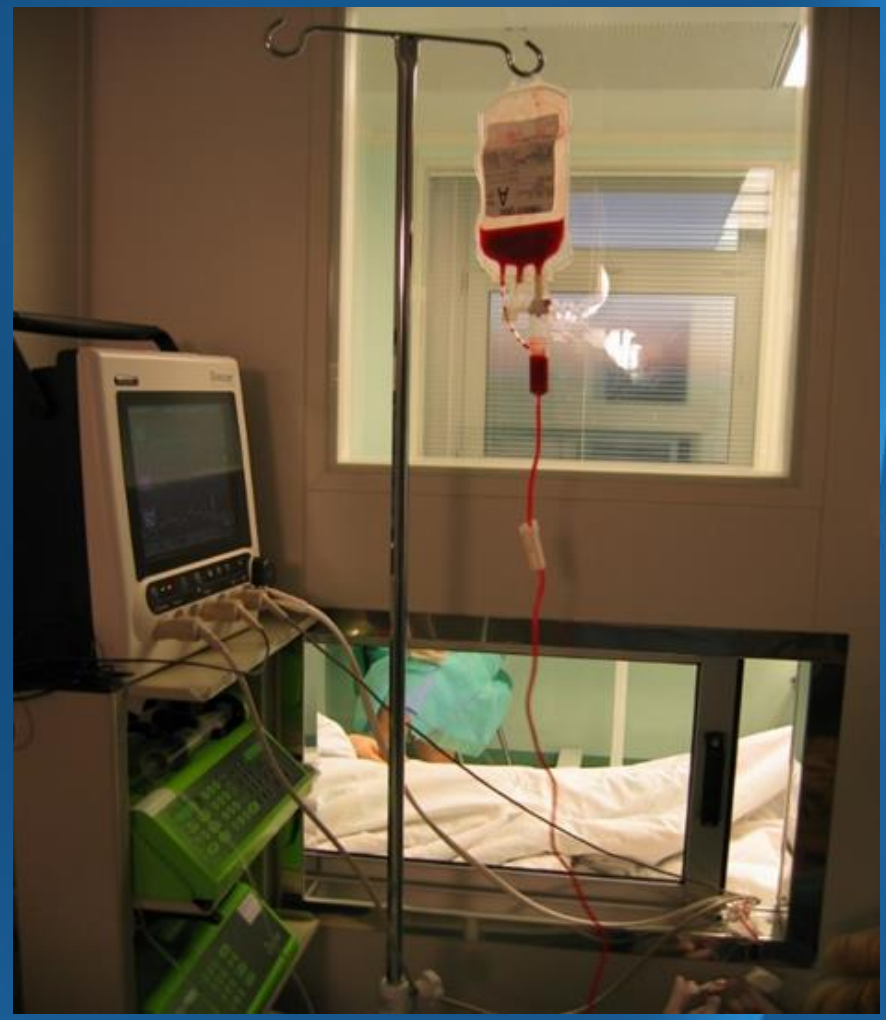
(Single agent NOT considered standard of care)

Stem Cell Transplant Procedure



Stem Cell infusion

- At least 24 hour after the conditioning
- will be given on Day 0.
- These are generally given through a central line and takes approximately 30 minutes.
- Infused like a blood product
- We do NOT do the surgery!



Stem Cell infusion

Stem cells are either cryopreserved or fresh.

- Cryopreserved
  - usually for autologous transplants
- Fresh
  - Usually for allogeneic transplants

Complications of Stem Cell infusions

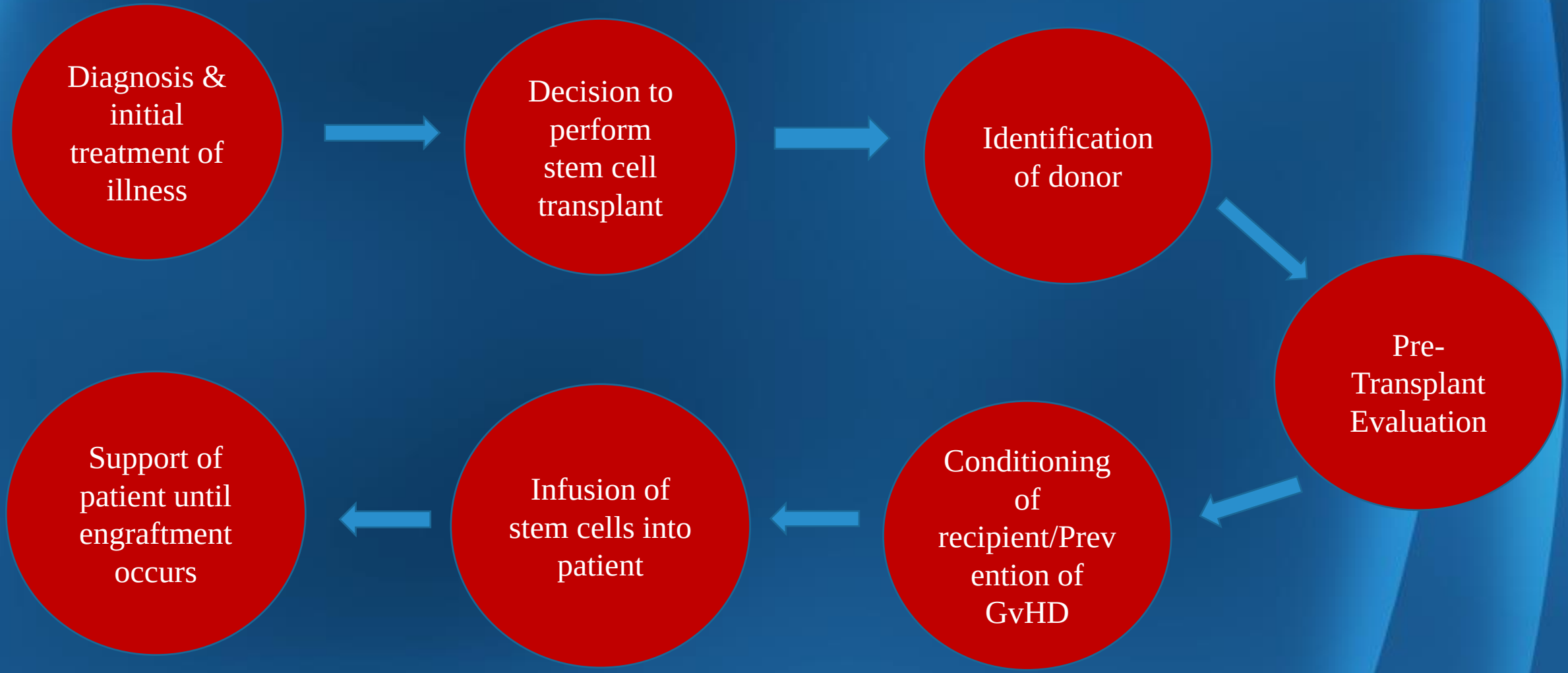
Immunologic complications

- **Immediate**
  - Acute Hemolytic Reaction
  - Anaphylactic reactions
  - Transfusion-related acute lung injury
- **Delayed**
  - Delayed hemolytic reactions

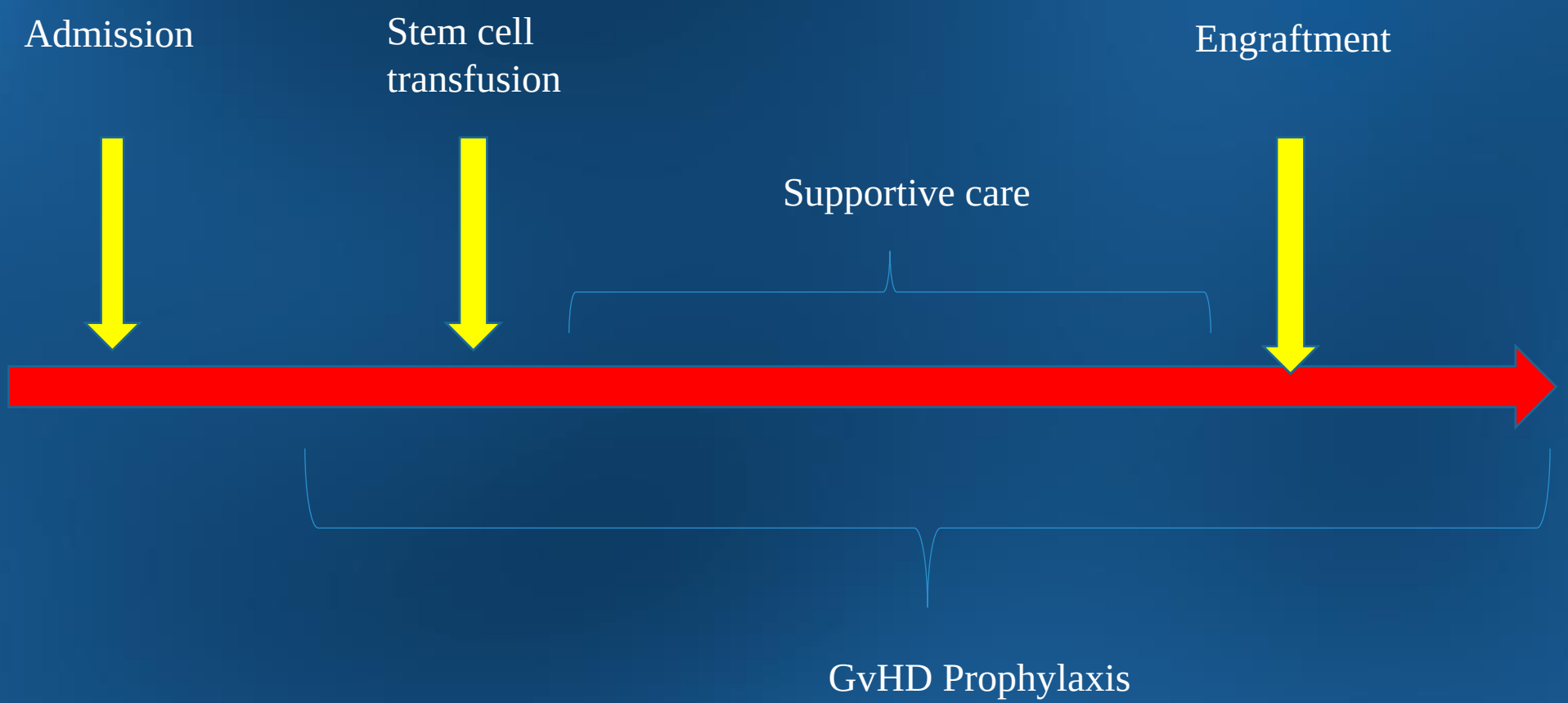
Non-immunologic complications

- DMSO Toxicity
- Septic infusion reaction
- Fat emboli
- Bleeding due to excessive anticoagulation
- Circulatory overload
- Hypothermia

Stem Cell Transplant Procedure



Stem Cell Transplant Procedure



- Success
- Reject
- GvHD
- death

Engraftment

- Engraftment is defined when:
  - the ANC ≥ 500 cells/mm3
  - platelets ≥ 20 x 109
- Time of engraftment:
  - Peripheral blood stem cells; day +10-14
  - Bone marrow; day +14-21
  - Umbilical cord blood; day +17-28
- Chimerism

Chimerism

- The presence of donor hematopoietic cell lines in the recipient of an allogeneic transplant
- FISH or STR Methods
- Check chimerism in 15, 30, 60, 90, 180, 360 days after HSCT, annually till 5 years

Rational for HSCT

- Non-engraftment
  - Booster
- Mixed chimerism
  - DLI

Supportive Care

- In solid organ transplantation, the main relevant immunologic process is graft rejection

- In marrow transplantation, a novel immunologic condition arises due to the immunologic competence of the graft itself.
  - Rejection is bi-directional
    - Graft rejection
    - Graft-vs.-host disease (GVHD)
  - Tolerance develops, immunosuppression not lifelong

HSCT Process:
Kill the Disease, Injure the Patient

Patient supported with

- ✓ Antibiotics,
- ✓ Blood transfusions,
- ✓ Treatment for other side-effects
- ✓ Total parenteral nutrition
- ✓ Antiemetics

Complications of HSCT

Early	Delayed
➢ Mucositis	➢ Chronic GvHD
➢ Infections	➢ Secondary tumors
➢ Pancytopenia	➢ Late infections
➢ Organ dysfunction	➢ Need to repeat vaccinations
➢ Graft rejection	➢ Endocrine
➢ Acute GvHD	

Complications of HSCT

Early

- Mucositis

Complications of HSCT

Early

- Transplant related infections
  - Damage to mouth, gut and skin
  - Prolonged neutropenia

Complications of HSCT

Early

- Sinusoidal obstructive syndrome (VOD)
- life threatening complication within the first 35- 40 days following myeloablative preparation regimen.
- present with a painful hepatomegaly, weight gain due to fluid retention and elevated serum bilirubin levels.

Complications of HSCT

Early

- Pancytopenia
  - PRBC and platelet transfusions
  - Broad spectrum antimicrobials
  - Antifungals if prolonged fevers 3-5 days
- Graft Rejection
  - Host versus graft
  - Drug injury to marrow
  - Viral infections: CMV, HHV-6 & 8

Complications of HSCT

Early

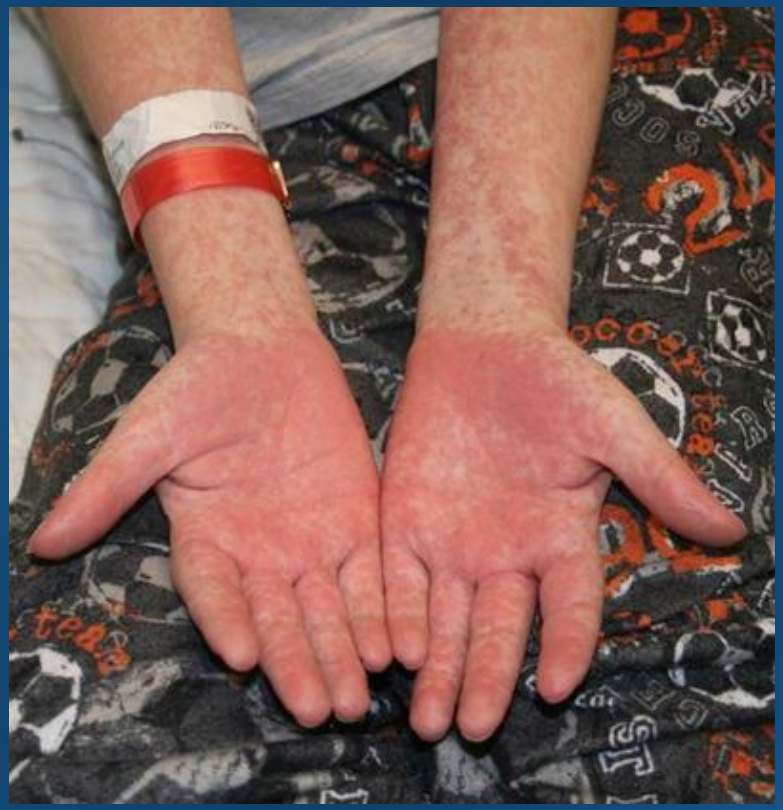
- Interstitial Pneumonitis
  - Diffuse alveolar hemorrhage
  - ARDS often caused by CMV

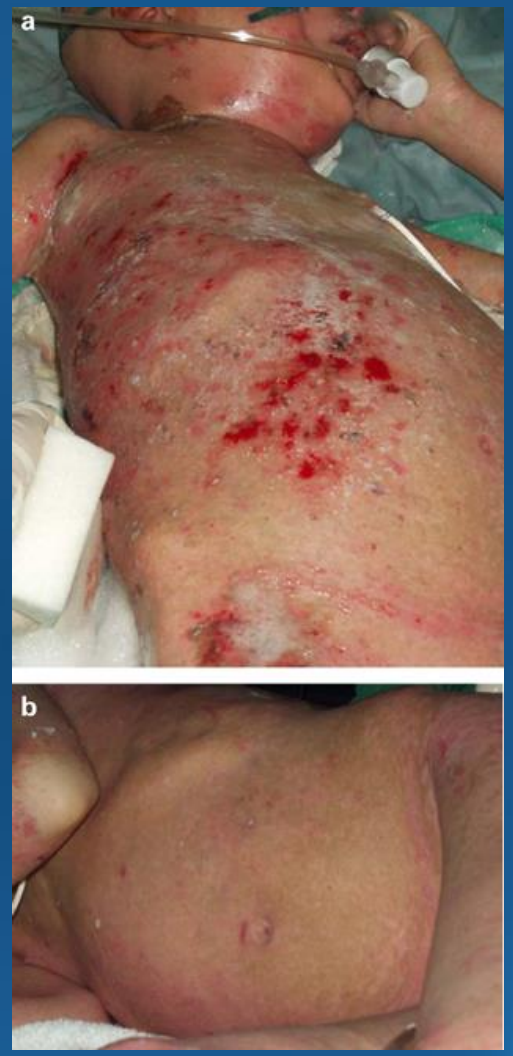
Complications of HSCT

Early

- Graft Versus Host Disease
  - Donor T cell response against recipient tissue cells
  - Up to Day +100
  - Target organ:
    - Skin,
    - GI
    - obstructive Liver dysfunction

Skin GvHD





Complications of HSCT

Delayed

- Chronic GVHD
  - After Day +100
  - manifestations of Skin especially, as well as Gut, Liver and Lung
  - 30-40% develop

Complications of HSCT

Delayed

- Secondary Tumors
  - Acute leukemias, solid tumors, MDS
  - Months to years after transplant
  - increased incidence with TBI

Complications of HSCT

Delayed

- Late Infections
  - Bacterial, viral fungal
  - Months after transplant
  - Associated with GVHD
- Need repeat vaccinations
  - Pneumovax, Hep B, Hemophilus influenza b, poliovirus, diphtheria/tetanus, flu

Complications of HSCT

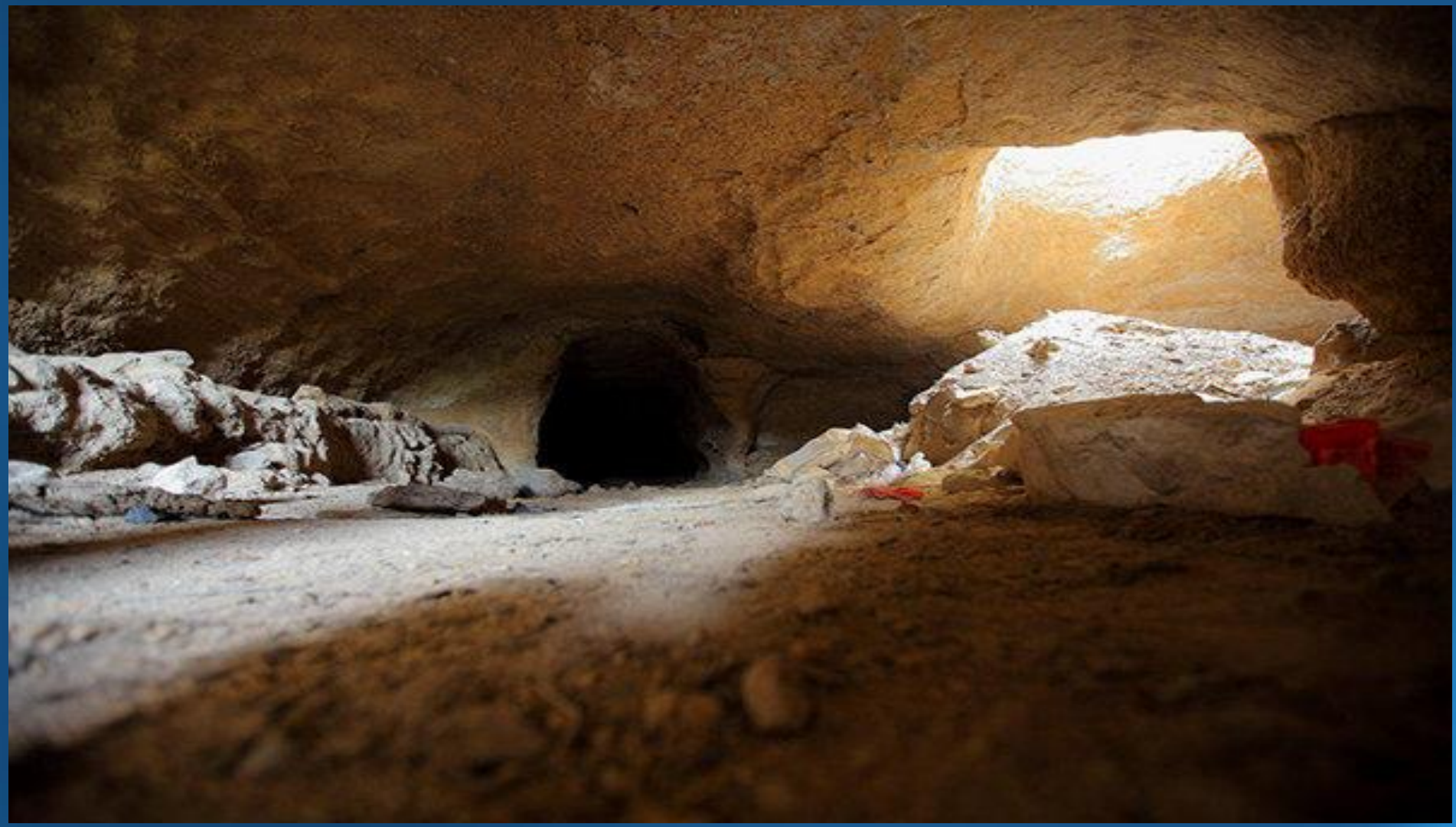
Delayed

- Short stature
- Hypothyroidism
- Gonadal failure
- Sterility
- Cataracts
- Learning disabilities
- Secondary malignancies

Complications of HSCT

Cost of BMT

- Variable due to several factors:
  - Indication: AML<CML<NHL<AA
  - Complications: hospital days, blood products most $$
  - Stem cell source: PBSC<Marrow (faster engraftment)
  - Preparative regimen: TBI expensive
  - Unrelated>>Allogeneic>Autologous




THANK YOU!