Bone Marrow Transplant with Myelodysplastic Syndromes (MDS)

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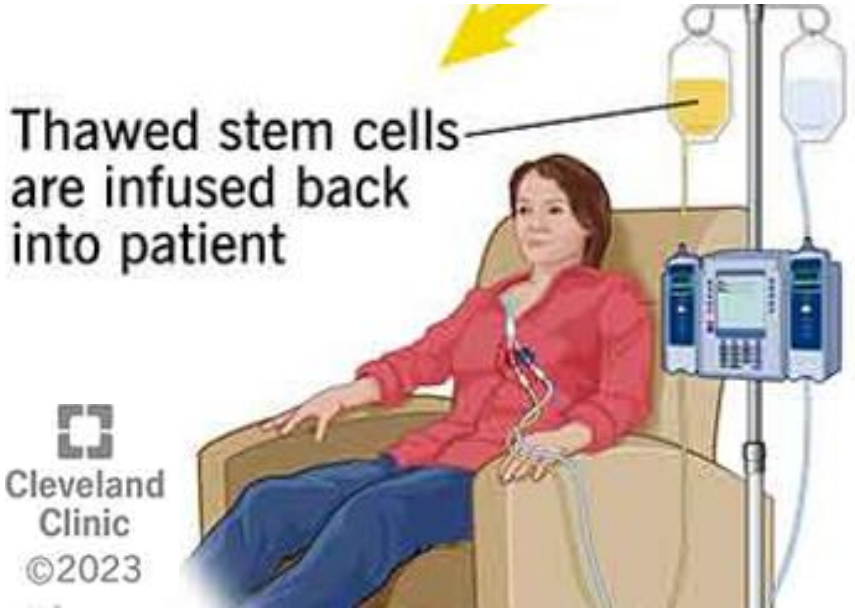
Disclosures

- Conflict of interest: None.
- Financial Disclosures: None.
- May contain disturbing graphics, viewer discretion is advised.

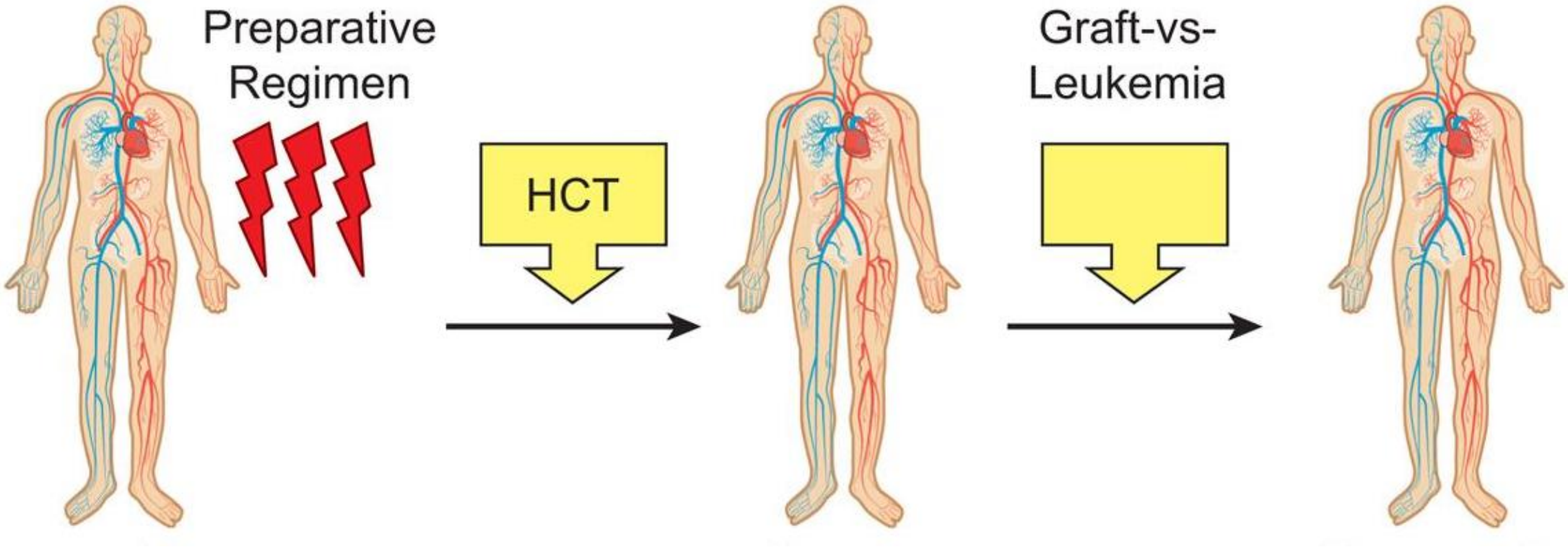
What is a Bone Marrow Transplant?

- **H**ematopoietic **C**ell **T**ransplant (HCT), sometimes referred to as bone marrow transplant, involves administering healthy hematopoietic stem cells to patients with dysfunctional or depleted bone marrow[1].



1. NIH StatPearls: Hematopoietic Stem Cell Transplantation. https://www.ncbi.nlm.nih.gov/books/NBK536951/. Accessed May 5, 2024.

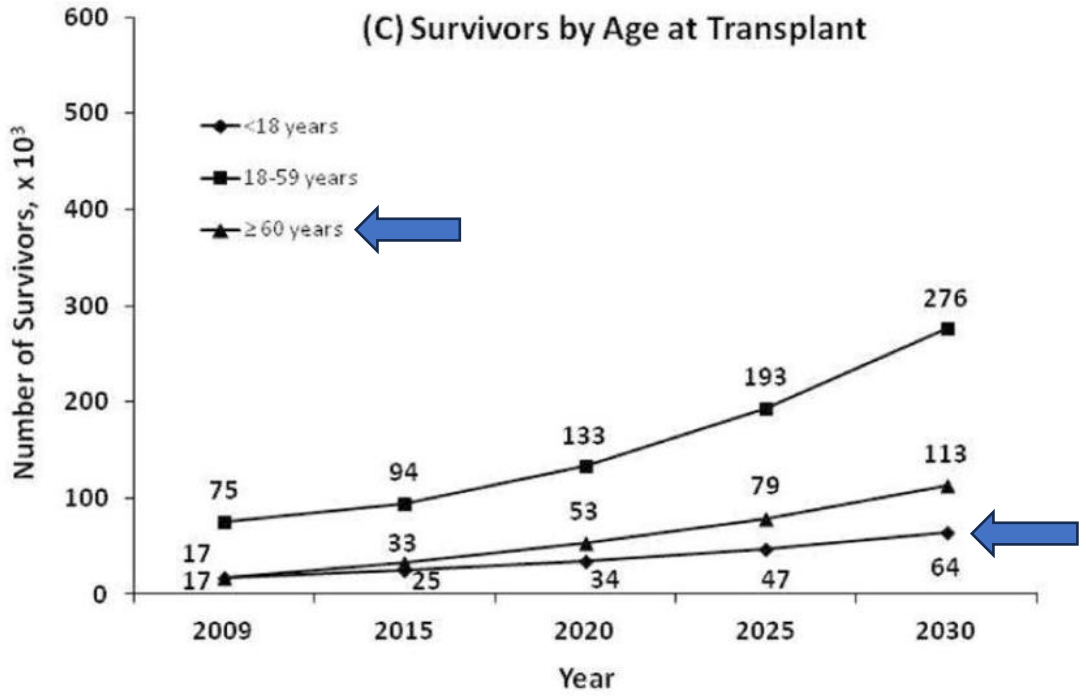
Bone Marrow Transplant Process Overview



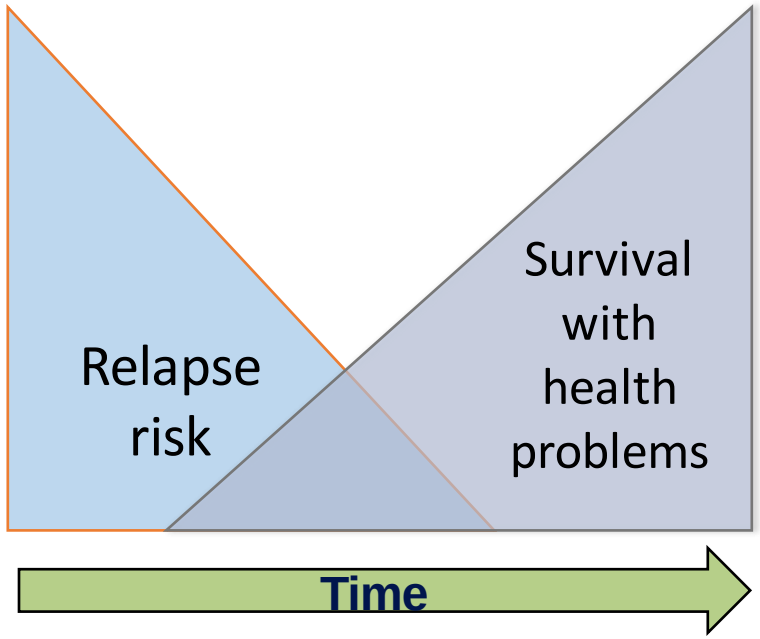
MD, Qaiser B. Manual of Hematopoietic Cell Transplantation and Cellular Therapies - E-Book. Available from: VitalSource Bookshelf, Elsevier Limited (UK), 2022.

Why don’t we take everyone to transplant?

- Treatment related mortality: toxicities, infections related to pancytopenia, post transplant immunodeficiencies.
- Risk viral, bacterial and fungal infections.
- Advances in transfusion medicine and medical pharmacology have improve outcomes.



Projected number of HPSCT survivors in the US by year 2030



Courtesy of S Bauer.

Majhail et al.Biol Blood Marrow Transplant. 2013 Oct;19(10):1498-501

Indications for Bone Marrow Transplant

- Malignant Conditions
  - MDS, Acute Leukemias, Multiple Myeloma, Lymphomas, Myelofibrosis, etc.
- Non-Malignant Conditions
  - Bone Marrow Failure Syndromes: i.e. Aplastic Anemia.
  - Immune Deficiencies: i.e Severe Combined Immune Deficiency Syndrome.
  - Hemoglobinopathies: i.e Sickle Cell Disease.

Types Bone Marrow Transplant

	Autologous Transplant	Allogenic Transplant
Matched Donor Stem Cells		✓
Patient Own Stem Cells	✓	
Complicated by Graft vs Host Disease (GVHD) effect		✓
Uses Myelosuppressive Therapy	✓	✓
High Risk for Complications		✓
High Risk for Transplant Failure		✓

Stem Cell Donors/Source for Allogeneic Transplants

Allogeneic Transplant

- Compatibility by matching donor and recipient by typing Human Leukocyte Antigens (HLA). Donor Specific Antibody Screen.

Related donors (family members):

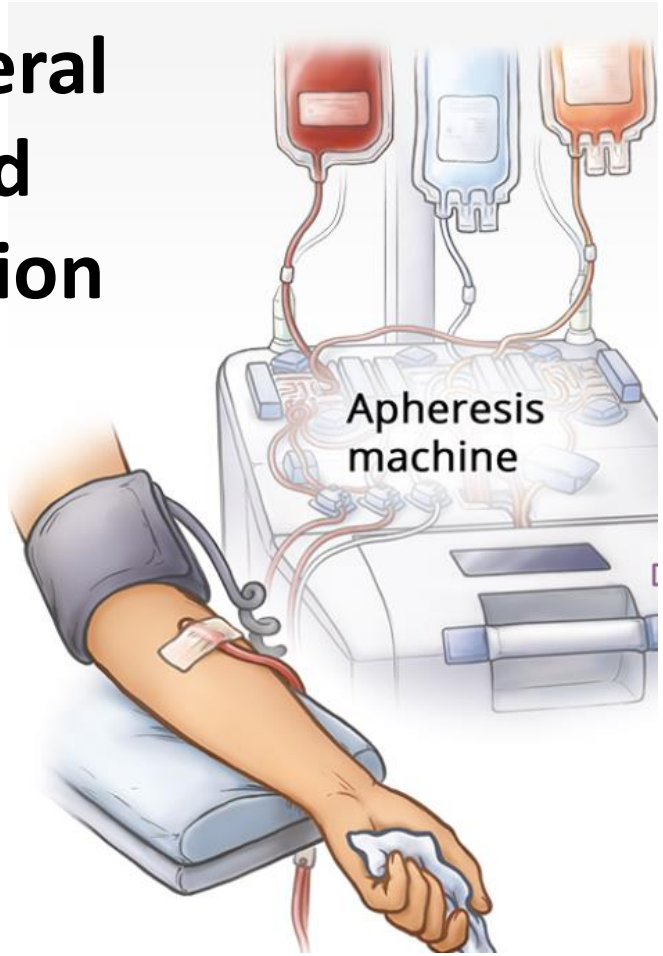
- Brother/sister (sibling)
- Parent or child: haploidentical donors

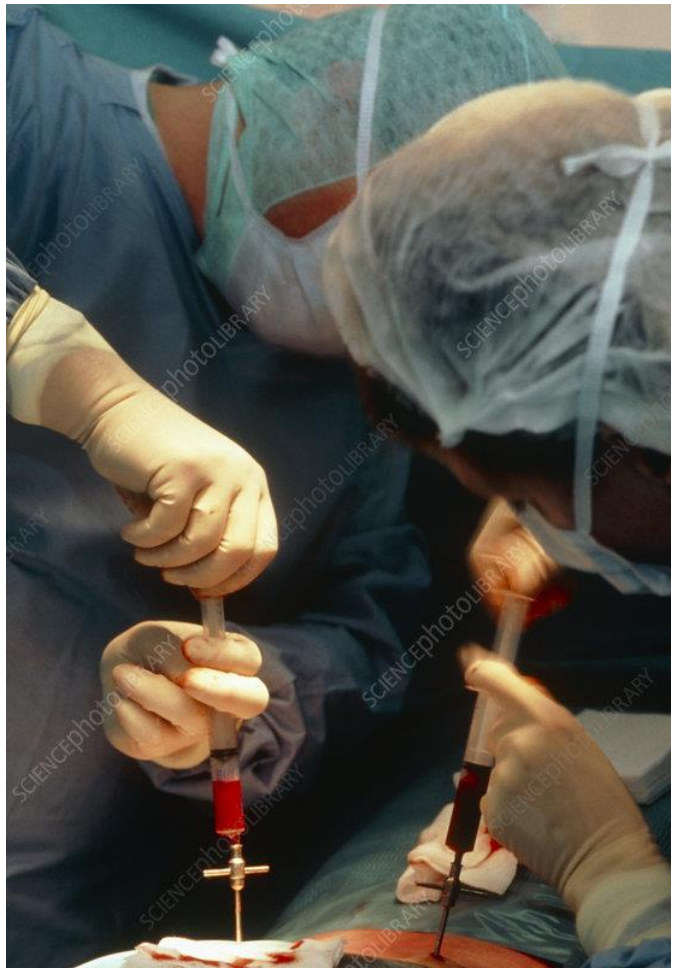
Unrelated donors:

- Match Unrelated Donors (MUD).
- Cord Blood: stems cells from donated umbilical cords-placentas after delivery. Limitation: limited amount of stem cells. Rarely used.

Stem Cell Collection

Peripheral Blood Collection





Bone Marrow Harvest

1. What Is Bone Marrow Transplant? (also called Stem Cell Transplant). https://together.stjude.org/basicsofblood/treatment/bone-marrow-transplant/what-is-bone-marrow-transplant.html. Accessed May 5, 2024.
2. Bone marrow transplant: harvesting bone marrow. https://www.sciencephoto.com/media/278909/view/bone-marrow-transplant-harvesting-bone-marrow. Accessed May 5, 2024.

Pretransplant Evaluation

JNCCN
National Comprehensive Cancer Network®
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Table 3. Suggested Patient and End-Organ Parameters for Allo-HCT Eligibility

Parameter	Myeloablative Allo-HCT	Reduced-Intensity Allo-HCT
Age limit, y	<55 to 65[a]	<75 to 80[a]
KPS	≥70	≥60 to 70
LVEF	≥45%	≥40% to 45%
Heart rhythm	No uncontrolled arrhythmias	No uncontrolled arrhythmias
Lung function tests		
FEV_1 (% of predicted value)	≥50% to 60%	≥50% to 60%
DLCO corrected for hemoglobin	≥40% to 45%	≥40% to 45%
Liver		
Liver function	No cirrhosis or Child-Pugh score A	No cirrhosis or Child-Pugh score A
Serum bilirubin (except Gilbert's syndrome), mg/dL	≤2	≤2
ALT/AST	≤2 × ULN	≤2 to 4 × ULN
Second active malignancy[b]	Must be absent	Must be absent
Pregnancy test	Negative	Negative
Creatinine		
Serum creatinine,[c] mg/dL	≤2	≤2 to 2.5
Creatinine clearance (Cockcroft-Gault method/24-hour urine), mL/min	>50 to 60	>50 to 60
Uncontrolled infections[d]	Must be absent	Must be absent
Psychosocial and financial	Adequate support	Adequate support

Eligibility Criteria for Patients Undergoing Allogeneic Hematopoietic Cell Transplantation. https://doi.org/10.6004/jnccn.2020.7559. Accessed May 8, 2024.

Preparation Regimens = Conditioning (Type and dose of chemotherapy before the transplant)

Myeloablative Conditioning	Reduce Intensity Conditioning/Nonmyeloablative Conditioning
High dose chemotherapy	**Lower dose** chemotherapy = Less toxic
Irreversible cytopenias without HCT	Enough suppression for donor engraftment
Goal to eradicate disease with chemotherapy	More reliance on graft vs malignancy
Ideally lower risk of relapse	Higher rates of failure
	More tolerable for elderly patients and patients with co-morbidities

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Transplant is a commitment to a long-term relationship

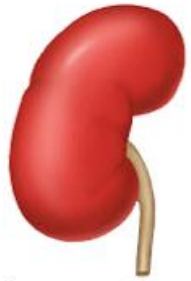
- Frequent medical appointments during first year.
- Multiple repeat bone marrow biopsies.
- Repeat vaccinations.
- This can be a lifestyle limiting intervention.

Early Complications: usually first year post transplant

- Infections: can be fatal.
  - Fungal: i.e. Oral Candida.
  - Bacterial: i.e. Pneumonia, hardware infections.
  - Viral: usually reactivation; herpes viruses, chickenpox/shingles, BK virus (hematuria), Cytomegalovirus, etc.
  - Antimicrobial prophylaxis.
- Sinusoidal Obstruction Syndrome or Veno-occlusive disease
  - Liver damage from conditioning chemotherapy.
- Graft Rejection or Failure: stem cell booster, second transplants, etc.
- Drug related toxicity: chemotherapy, radiation, immunosuppressive drugs, etc.
- Blood product transfusion support.

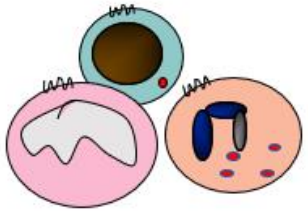
GVHD after Allogenic Transplant

Caused by the interaction between the transplanted immune system (graft) and recipient tissues (host)

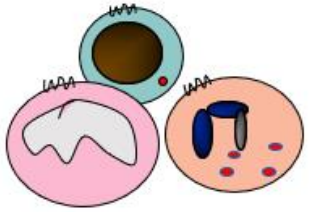


Transplanted organ

Rejection

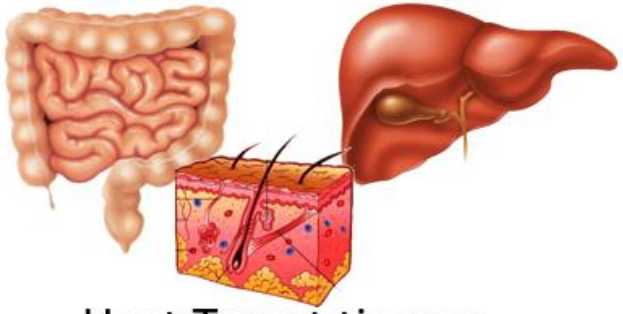


Host Immune system



Transplanted graft

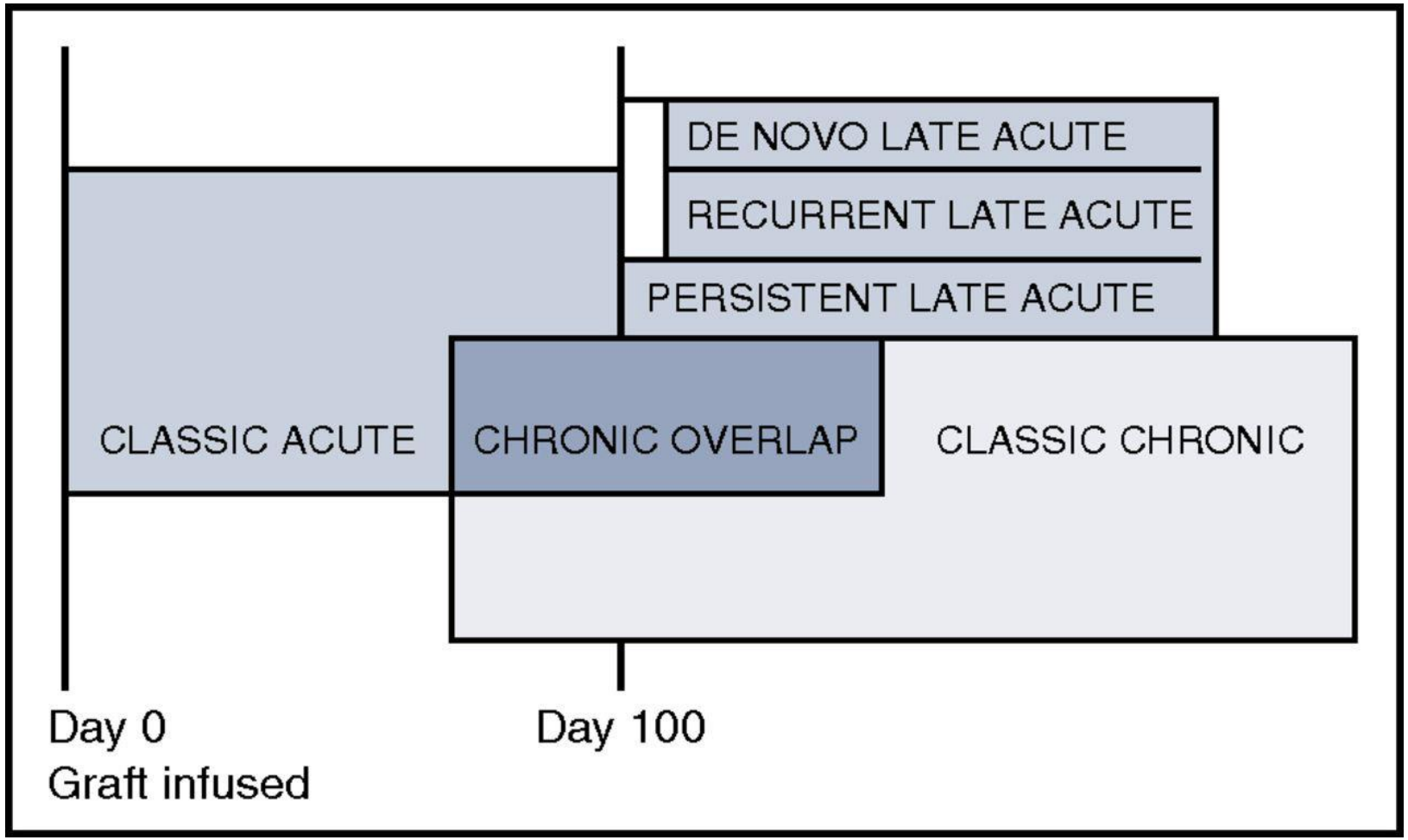
GvHD



Host Target tissues

Courtesy of JF DiPersio & I Pusic

Acute and Chronic GVHD



Courtesy of I Pusic

Acute GVHD

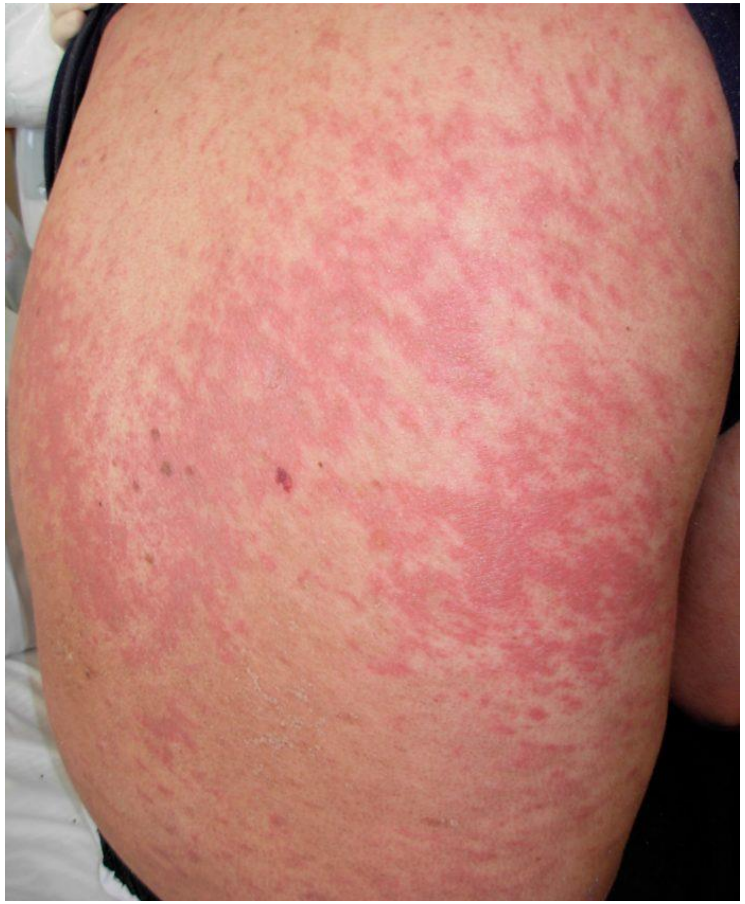
- < 100 days post transplant.
- One of the leading causes of death post transplant.
- Frequency of 30-50%.
- Some of the Risk Factors:
  - Advance age (donor and recipient).
  - Conditioning regiment, including PT-Cy.
  - HLA disparity.
  - Stem cell source.
  - Chimerism establishment speed.

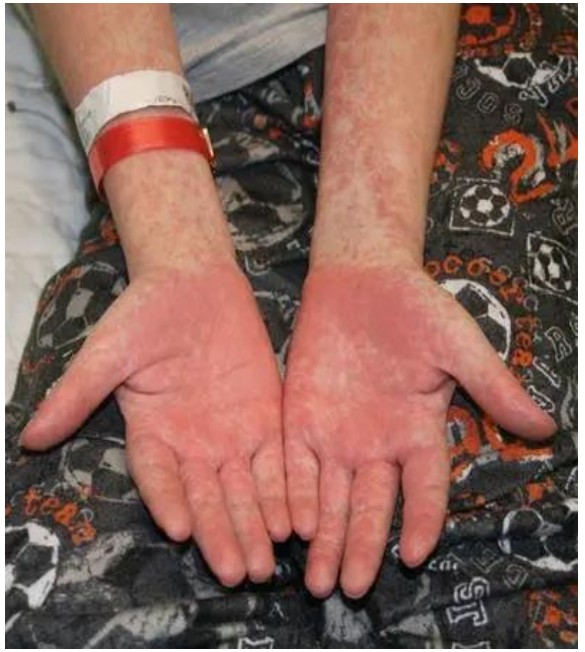
Acute GVHD: Manifestations

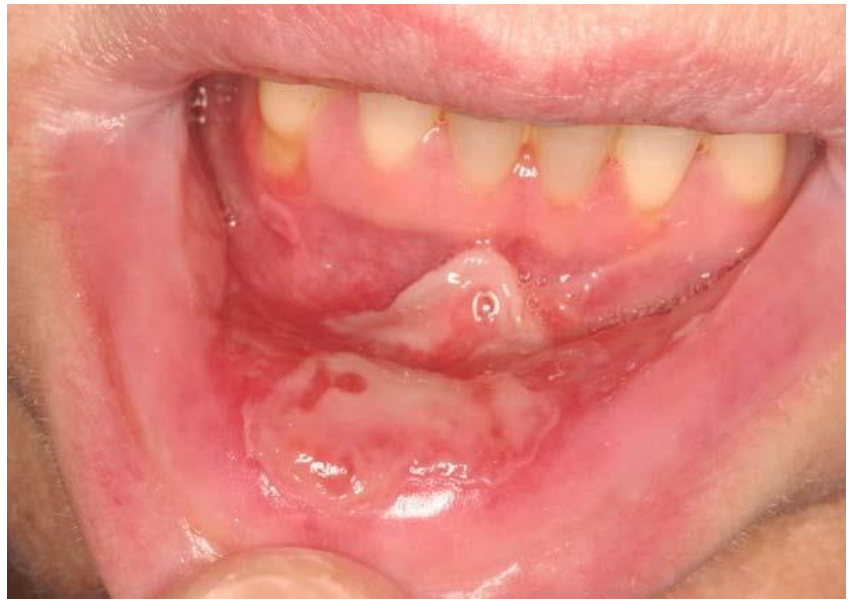
- Affects surface tissue that protects against pathogens.
  - Skin: rash (can be painful and pruritic), ulcerations, blisters, etc.
  - Gastrointestinal tract: diarrhea, nausea/vomiting, cramping, etc.
  - Liver: jaundice.

- Needs engraftment to develop GVHD.
- Can mimic drug toxicity and infections.

Acute GVHD: Manifestations (cont)







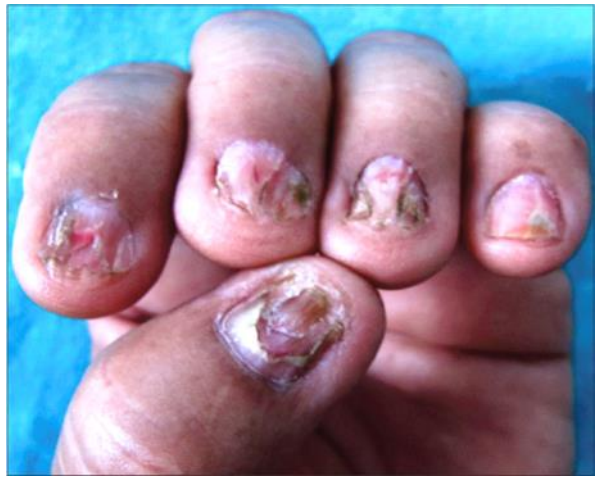
Acute GVHD: Interventions

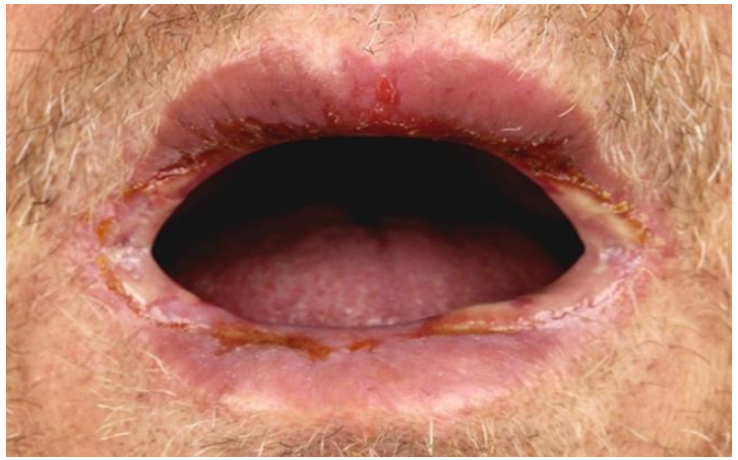
- Prophylaxis:
  - Post-transplant cyclophosphamide (PT-Cy).
  - Immunosuppression: mycophenolate, tacrolimus, cyclosporine, methotrexate.
  - Side effects: liver and renal damage, mucositis, marrow suppression, neurotoxicity, etc.
- Treatment:
  - 1st line: Systemic Steroids: hyperglycemia, insomnia, etc.
  - 1st line: Topical steroids.
  - 2nd line: depending on the organ: Ruxolitinib, different immunosuppressors/immunobiological, clinical trials.

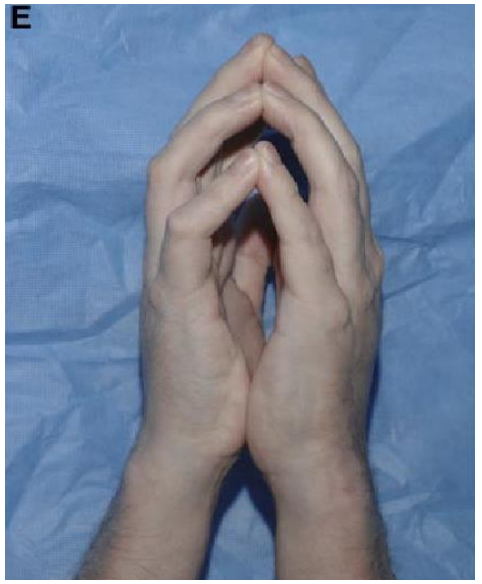
Chronic GVHD

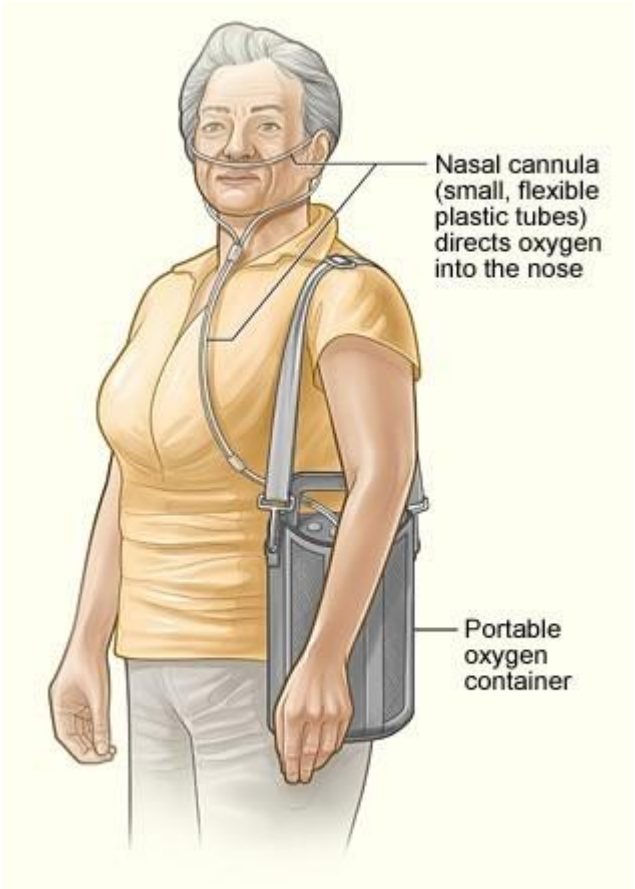
- >100 days post transplant.
- Major cause of late nonrelapse morbidity and mortality.
- Can significantly affect quality of life.
- Can affect multiple organs.
- Different degree of severity.
- Chronic inflammation leading to fibrosis.

Chronic GVHD: Manifestations





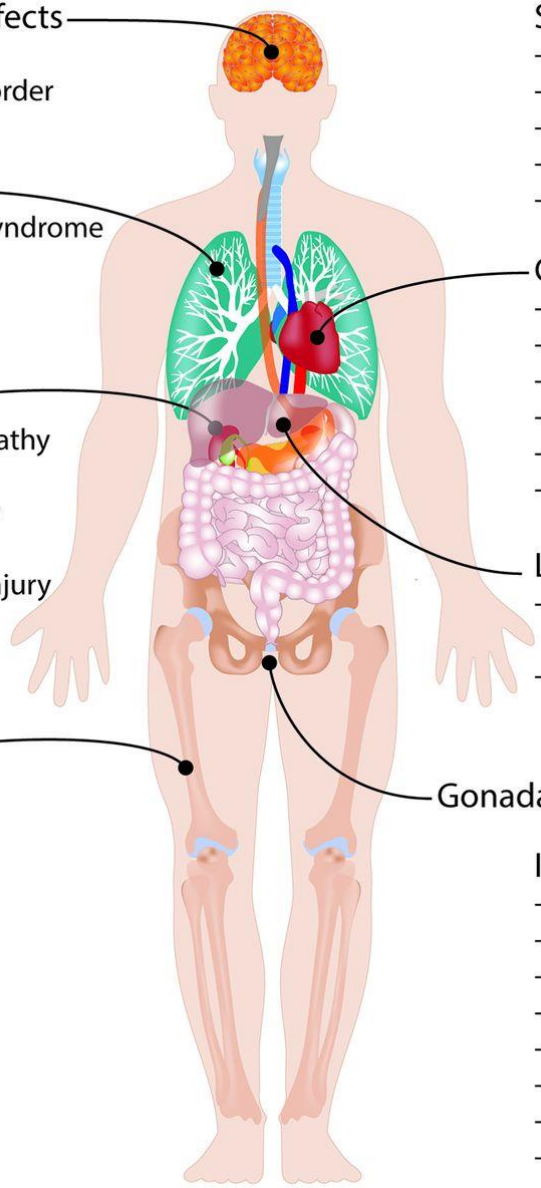




Chronic GVHD: Interventions

- Mild: target therapies.
- Moderate to severe: systemic immunosuppression and therapies.
    - Balance between symptoms and treatment complications.
    - Prevent progression.
    - Maintain anti-tumor effect.
- Clinical trials.

Late effects of blood and marrow transplantation



Neuropsychological effects
- Depression, anxiety
- Post-traumatic stress disorder
- Neurocognitive deficits

Pulmonary diseases
- Bronchiolitis obliterans syndrome
- Cryptogenic organizing pneumonia
- Pulmonary hypertension

Kidney diseases
- Thrombotic microangiopathy
- Nephrotic syndrome
- Idiopathic chronic kidney disease
- Persistent acute kidney injury
- BK virus nephropathy

Iron overload

Bone diseases
- Osteopenia
- Osteoporosis
- Avascular necrosis

Endocrine diseases
- Thyroid dysfunction
- Gonadal dysfunction
- Diabetes
- Dyslipidemia
- Metabolic syndrome
- Adrenal insufficiency

Solid cancer
- Oral cavity
- Skin
- Breast
- Thyroid
- Other sites

Cardiovascular diseases
- Cardiomyopathy
- Congestive heart failure
- Valvar dysfunction
- Arrhythmia
- Pericarditis
- Coronary artery disease

Liver diseases
- Hepatitis B, Hepatitis C, liver cirrhosis
- Nodular regenerative/focal nodular hyperplasia

Gonadal dysfunction/infertility

Infectious diseases
- *Pneumocystis jirovecci*
- Encapsulated bacteria
- Fungi
- Varicella-zoster virus
- Cytomegalovirus
- Respiratory syncytial virus
- Influenza virus
- Parainfluenza virus

Inamoto and Lee Haematologica 2017;102:614-625