Hematopoietic Cell Transplantation for Myelodysplastic Syndrome

September 9, 2023

MDS Foundation Forum

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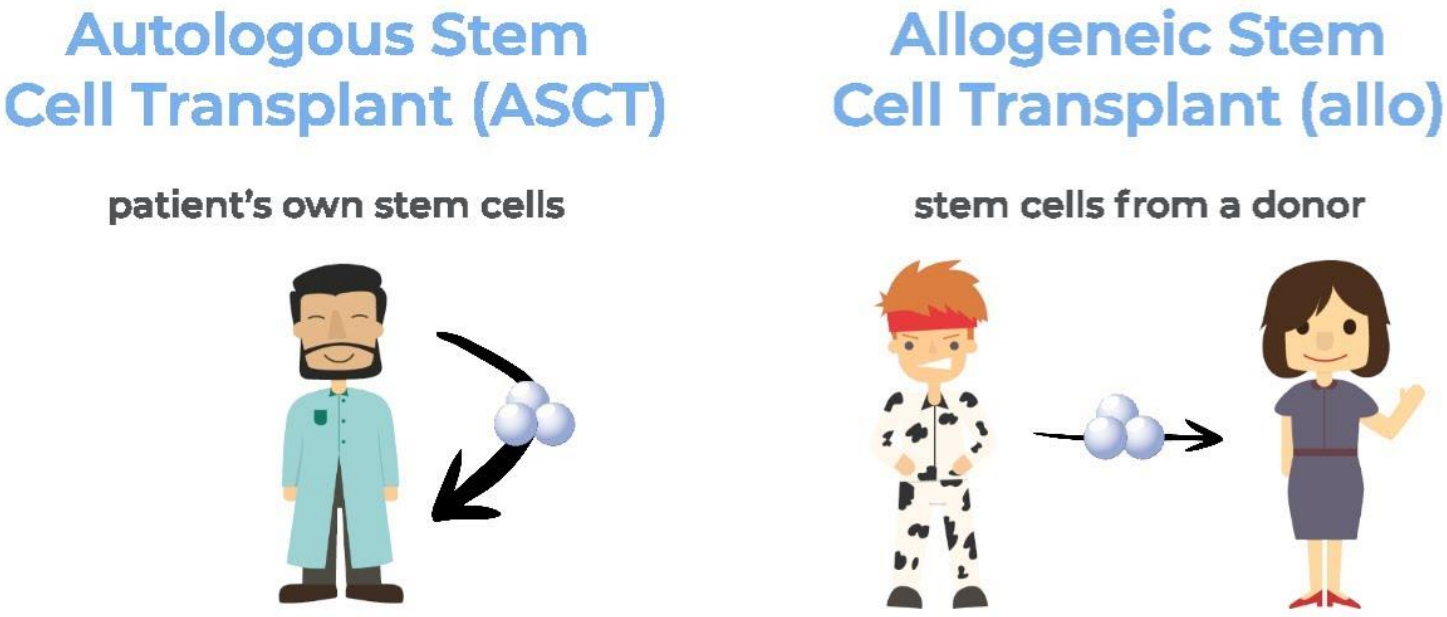
Disclosures

None

Outline

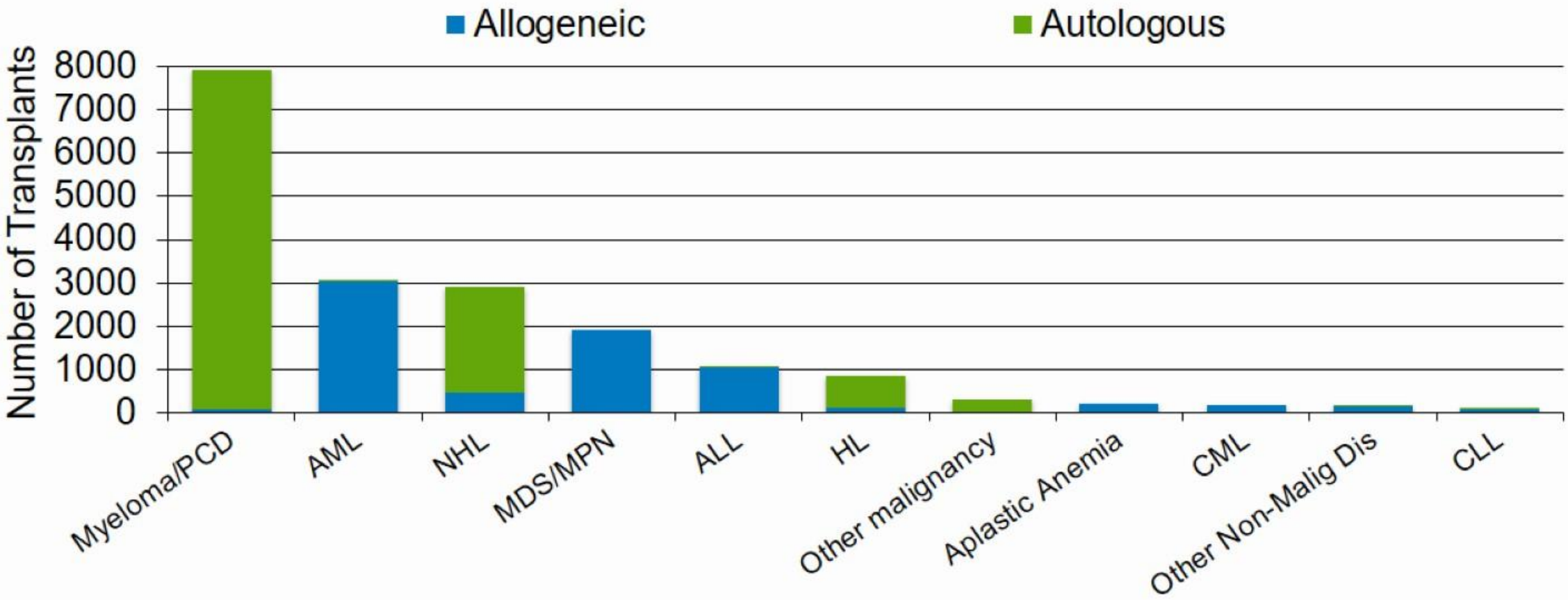
- What is Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)
- Transplant Outcomes in MDS
- Selecting a Donor
- HSCT Process
- Risks and Complications of HSCT

Allogeneic vs Autologous Stem Cell Transplant



Bone Marrow Transplant = Stem Cell Transplant = Hematopoietic Cell Transplant

Number of HCTs by Indications in the U.S., Adult, 2021



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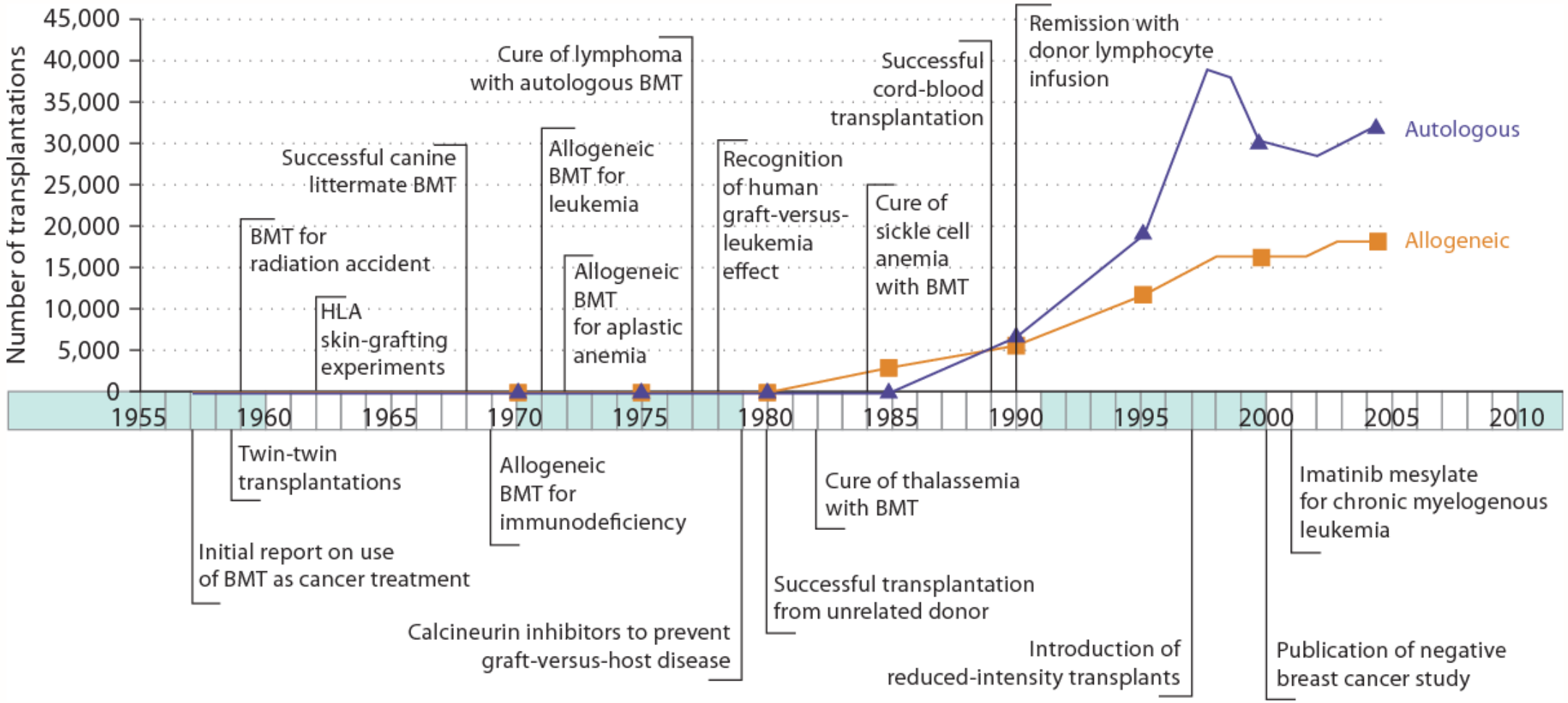
Abbreviations –
PCDs: Plasma Cell Disorders;
AML: Acute Myeloid Leukemia;
NHL: Non-Hodgkin Lymphoma;
MDS: Myelodysplastic Syndromes;
MPN: Myeloproliferative Neoplasms;
ALL: Acute Lymphoblastic Leukemia;
HL: Hodgkin Lymphoma;
CML: Chronic Myeloid Leukemia;
CLL: Chronic Lymphocytic Leukemia.
Non-malignant disease excludes Aplastic Anemia. Adult: ≥18 years

What is allogeneic hematopoietic cell transplantation?

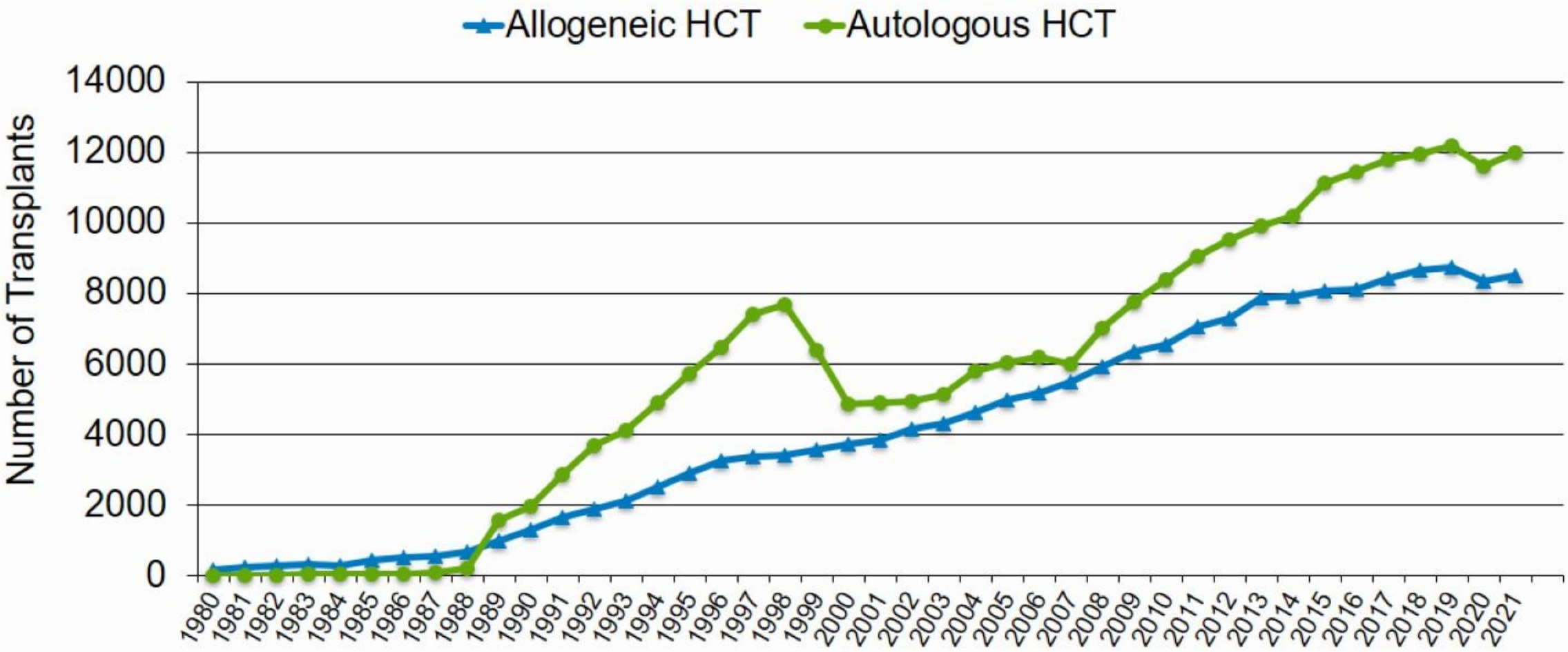
- A procedure in which bone marrow that is diseased or damaged is replaced with stem cells from another donor
- New (transplanted/donor) immune system attacks cancer cells that survived chemotherapy/radiation (graft-versus-tumor effect)

Historical Timeline



Gratwohl A, Niederwieser D. *Curr Probl Dermatol*. 2012;43:81-90.

Number of 1st HCTs reported to CIBMTR in the U.S.



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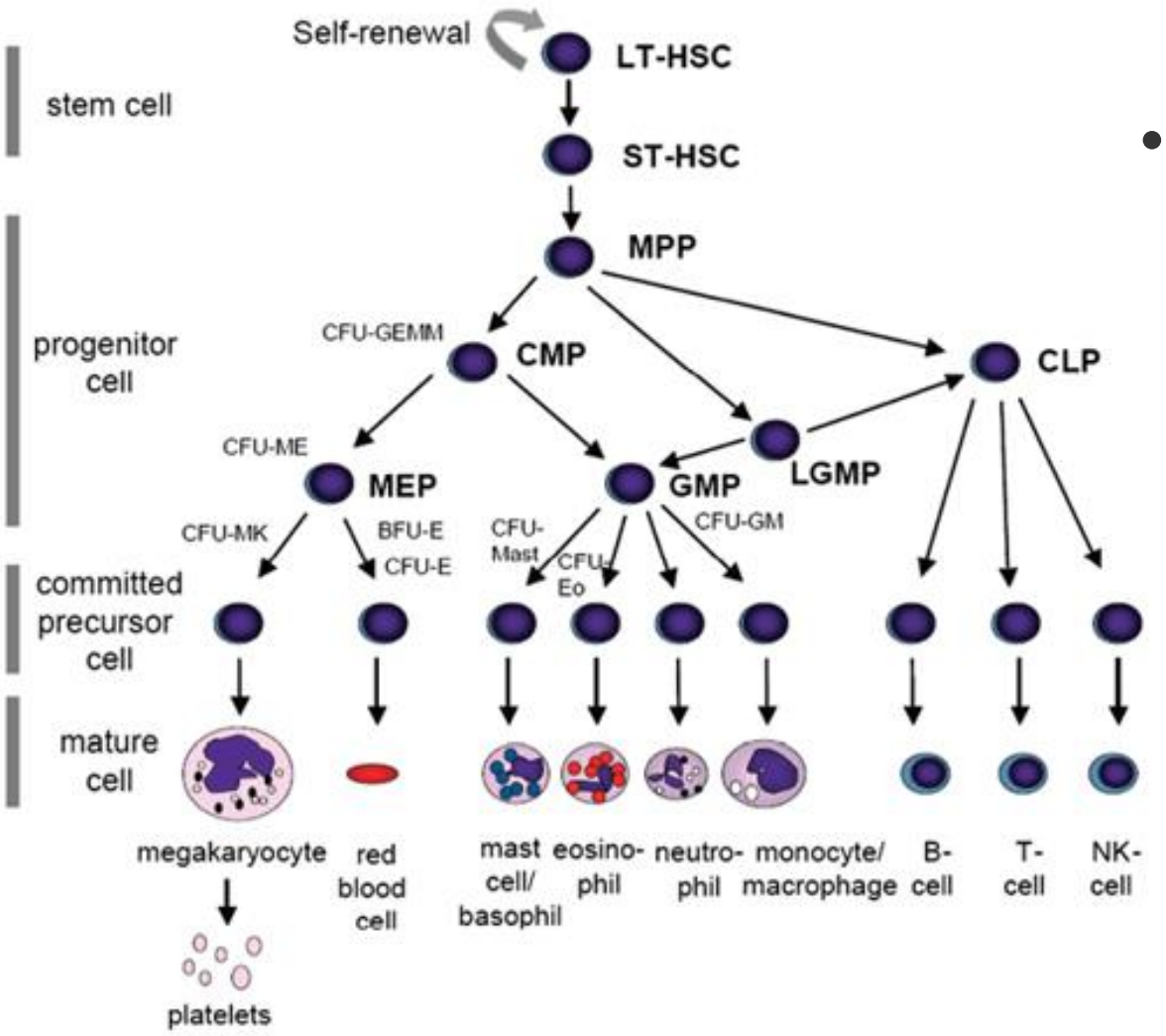
The Hematopoietic Stem Cell

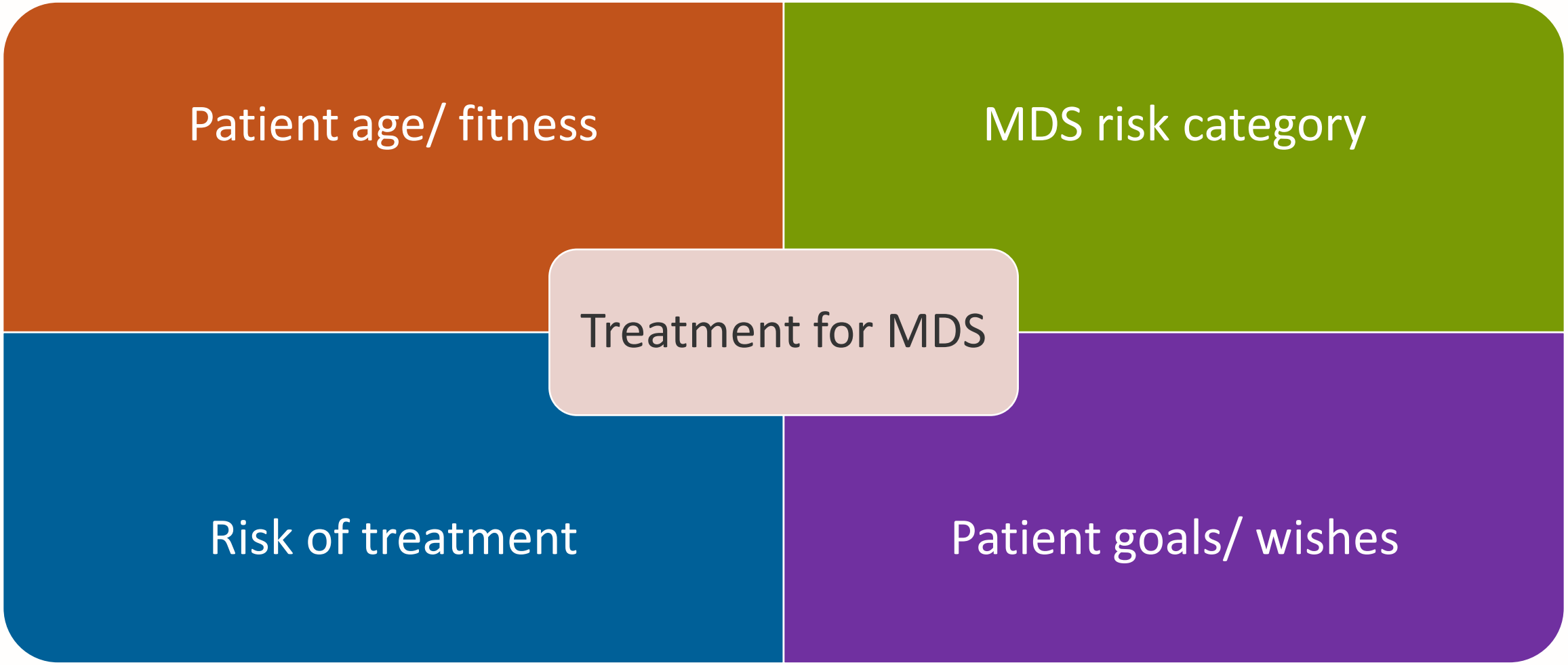


- Stem cells:
  - develop into mature white blood cells, red blood cells, or platelets
  - found in
    - bone marrow, especially in the pelvis, femur, and sternum
    - umbilical cord blood
    - in small numbers, in blood

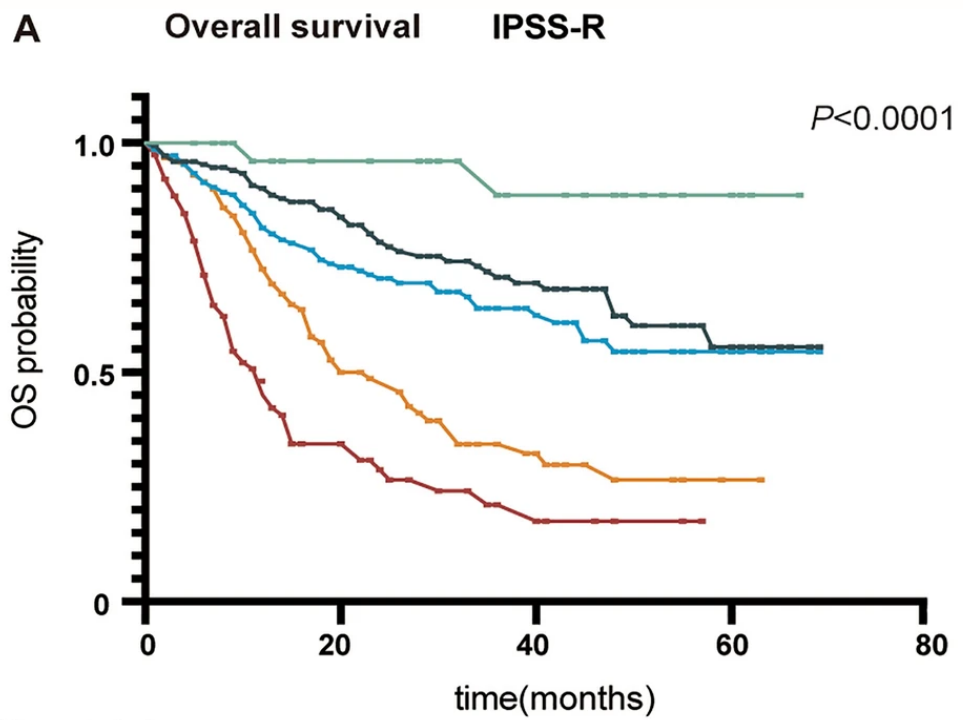
How do we treat MDS?

- Supportive care:
  - transfusions, growth factors, minimal medical interventions
- Disease Modifying treatments:
  - treatments that may change the natural history of the MDS but don't "cure" it
- Curative therapy:
  - HCT-hematopoietic cell transplantation

How do we decide which treatment approach is best?

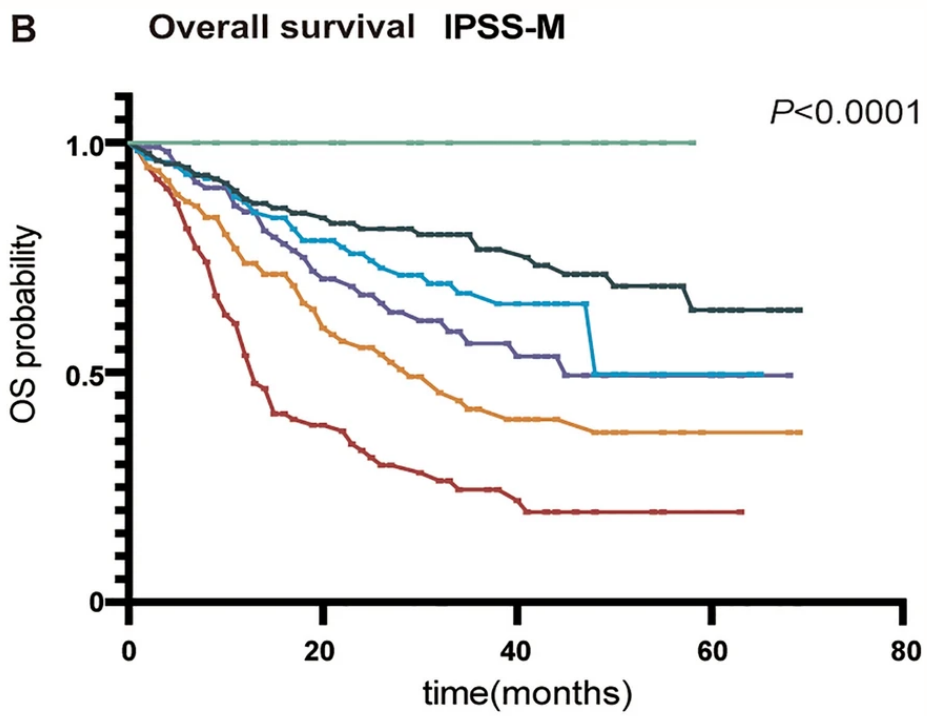


MDS Risk Stratification



No. at risk

VL	28	18	11	4
Low	171	103	54	11
Inter	220	92	39	8
High	155	43	18	1
VH	113	21	6	0



No. at risk

VL	21	14	8	0
Low	130	80	44	12
ML	116	59	28	5
MH	102	45	20	4
High	150	47	18	2
VH	167	31	10	1

Wu J, Zhang Y, Qin T, et al. IPSS-M has greater survival predictive accuracy compared with IPSS-R in persons ≥ 60 years with myelodysplastic syndromes. *Exp Hematol Oncol*. 2022;11(1):73. Published 2022 Oct 17.

BMT CTN 1102 Study Design:
Multicenter, biologic assignment study

Enrollment

Matched related or unrelated donor search for up to 90 days

Donor arm: transplant using lower intensity regimen within 6 months

No Donor arm: hypomethylating agent or best supportive care

Inclusion criteria

- high risk MDS
- 50-75 years
- Any prior therapy
- No prior unrelated donor search
- Eligible for reduced intensity alloHCT from a matched related or unrelated donor

Primary endpoint:

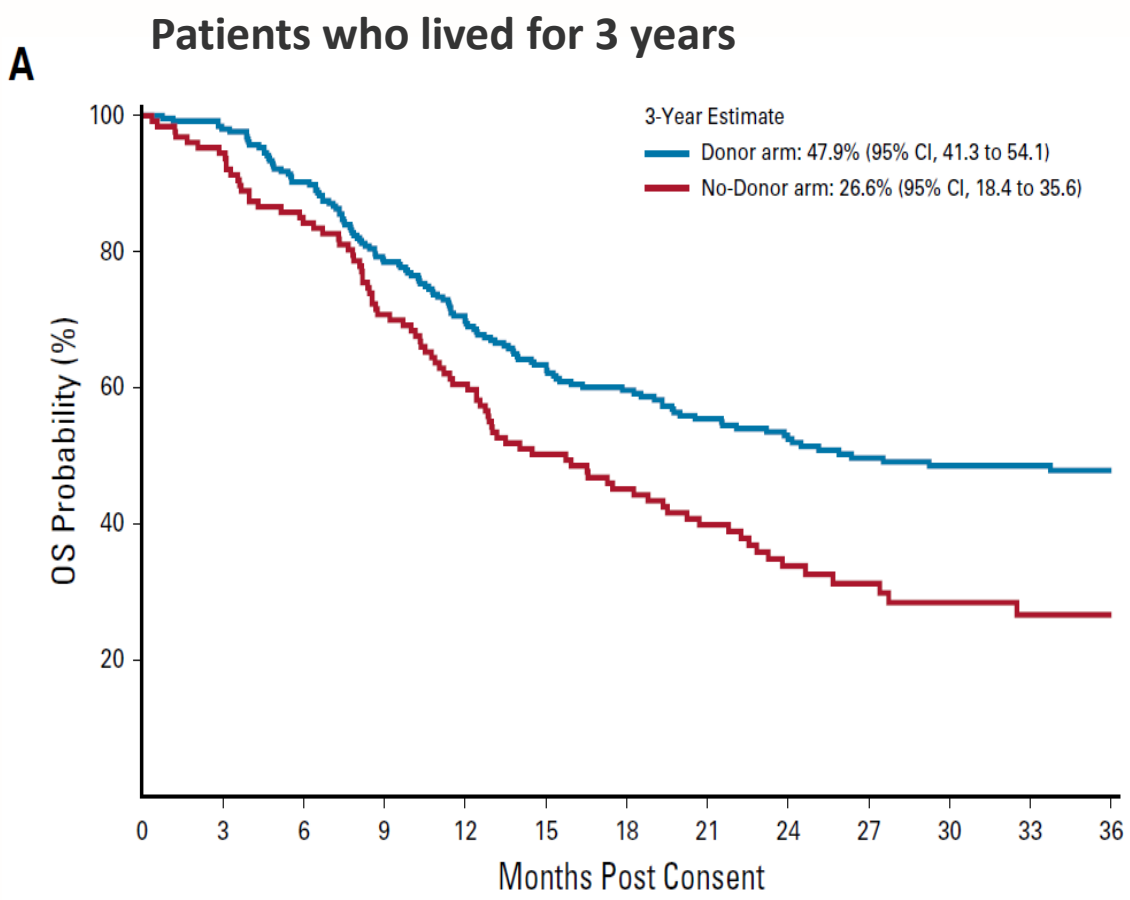
❖ Lived for 3 years

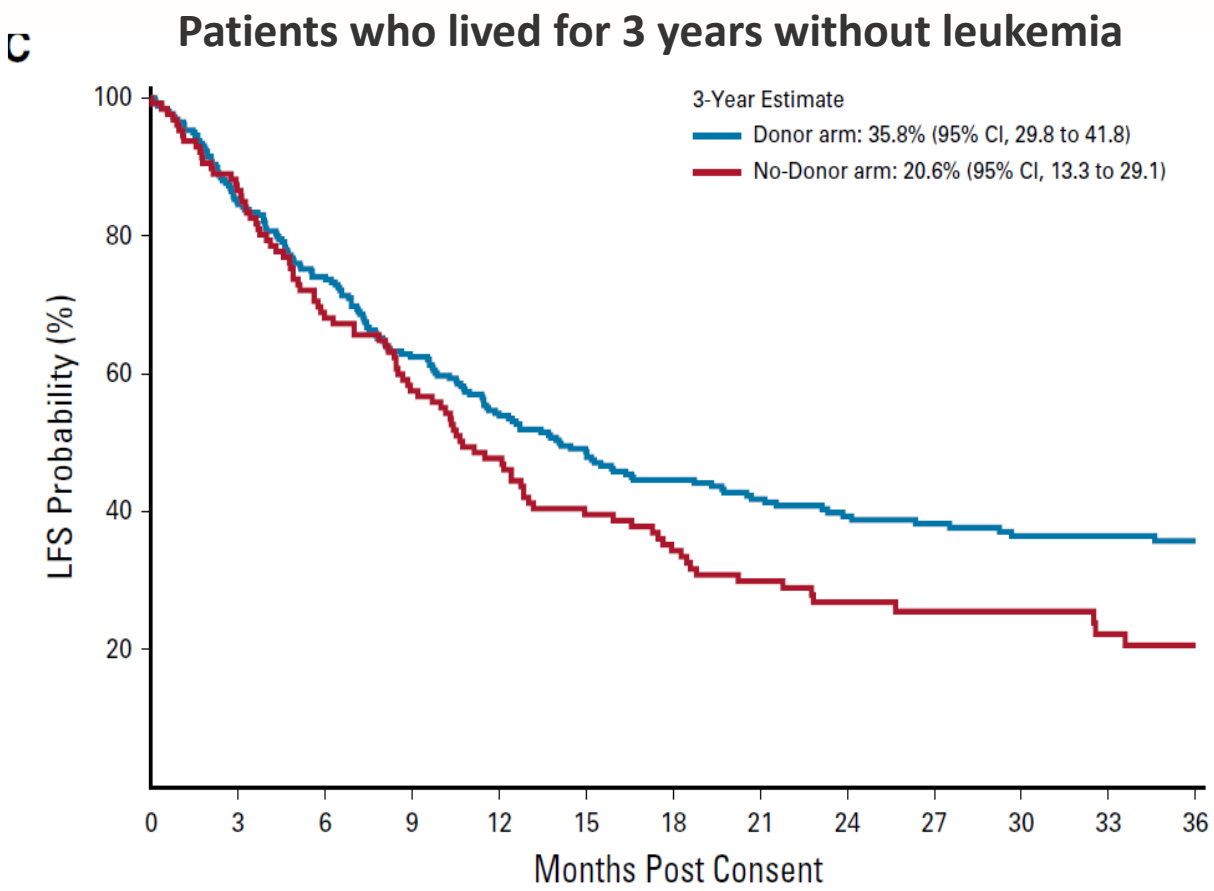
Secondary endpoints:

❖ Lived for 3 years without leukemia
❖ Quality of life (QoL)
❖ Cost effectiveness

Nakamura et al. JCO 2021

Clinical outcomes
(Donor arm=260 and No donor arm=124 patients)





Risks and Benefits of Transplant

High risk of complications from transplant
- -infections
- -GVHD
- -organ toxicity

Frailty/ poor functional status

Donor availability

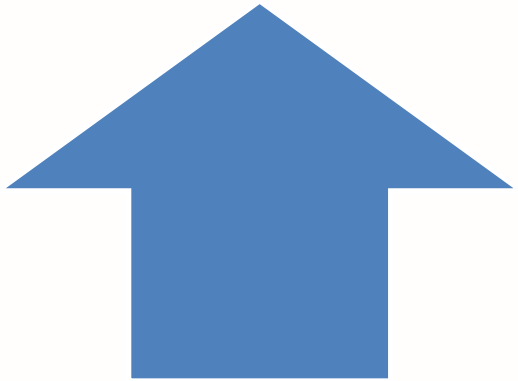
Insurance coverage

High risk MDS

Poor risk genetic mutations

No response to non-transplant treatments

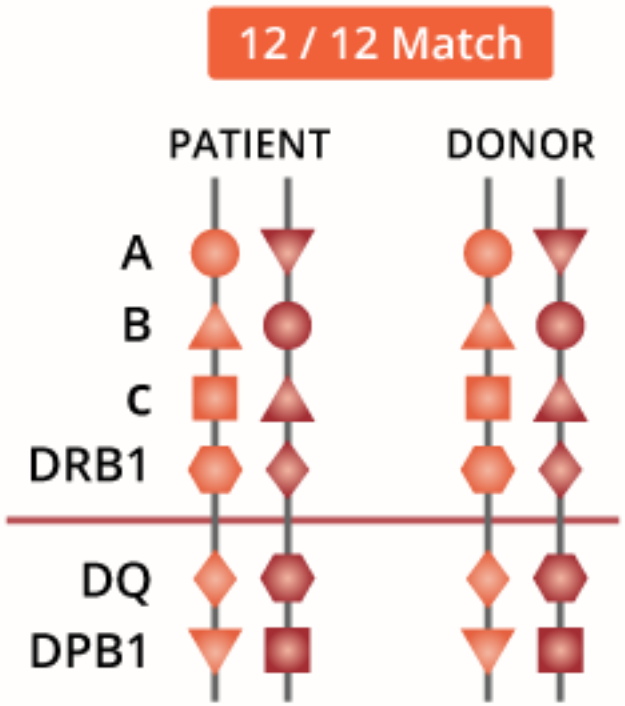
Potential cure

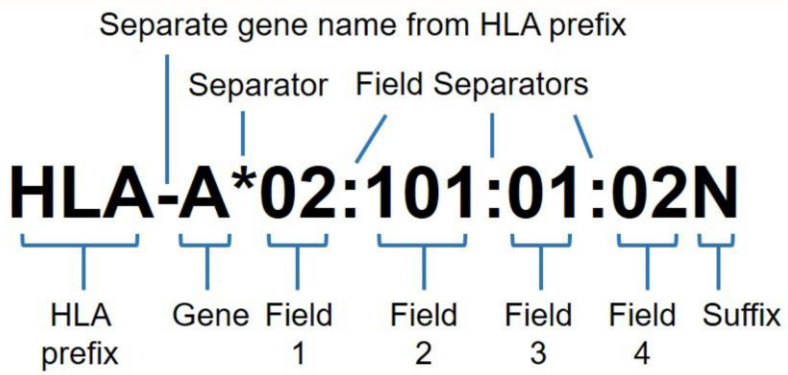


Donor Types

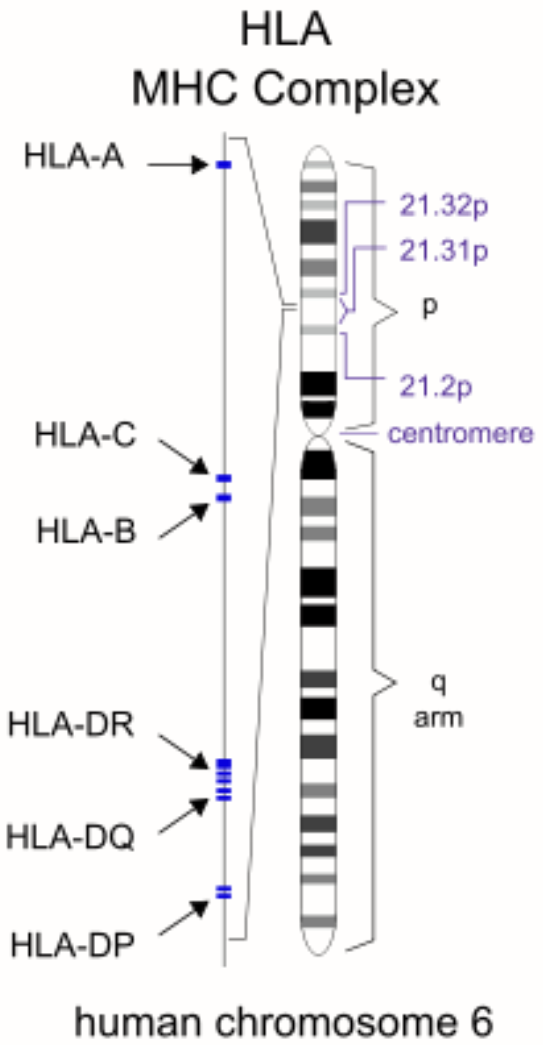
- HLA-Matched Related/Sibling Donor
- Matched Unrelated Donor
- Mis-Matched Unrelated Donor
- Haploidentical Donor
- Umbilical Cord Blood

HLA Typing

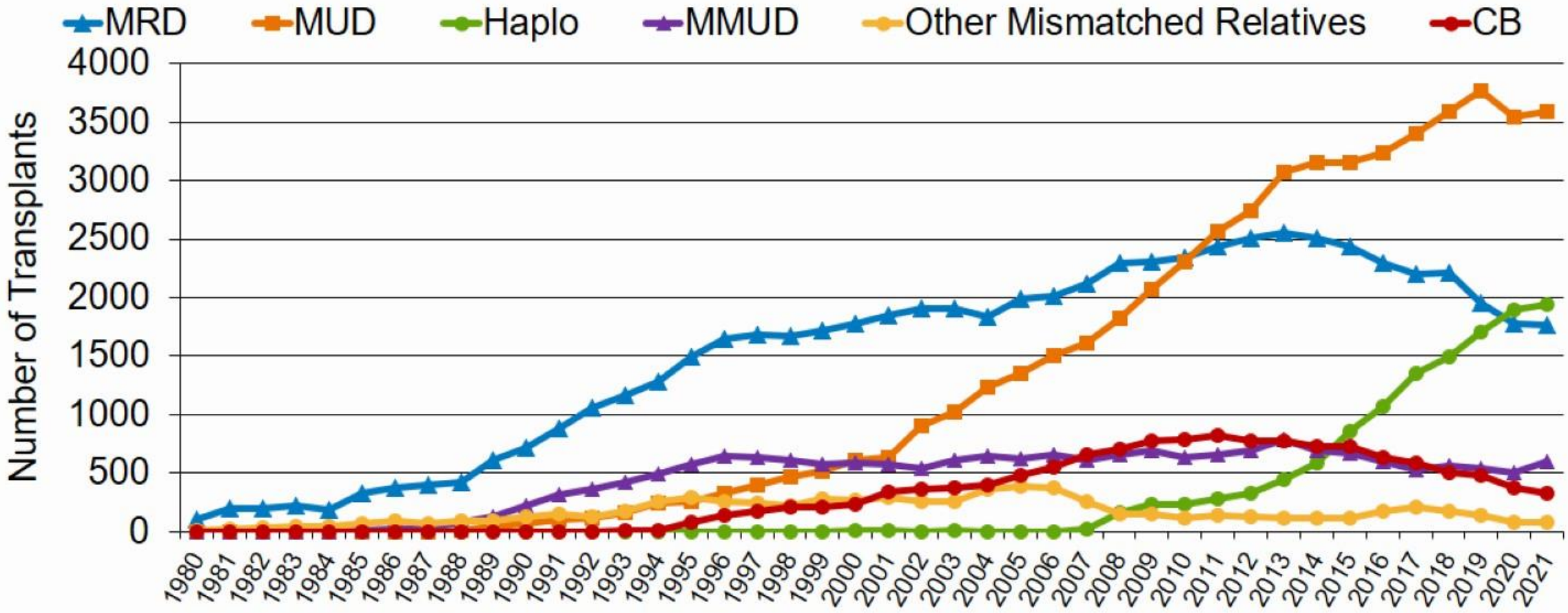




Field 1: Allele group
Field 2: Specific HLA protein
Field 3: Synonymous DNA substitution in coding region
Field 4: Changes in non-coding region
Suffix: Denoted changes in expression



Number of Allogeneic HCTs in the U.S. by Donor Type



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Abbreviations - MRD: Matched related donor; MUD: Matched unrelated donor; Haplo: ≥2 HLA antigen mismatch; MMUD: Mismatched unrelated donor ≤7/8 HLA allele match; CB: Cord blood

Bone Marrow vs Mobilized Peripheral Blood

- Stem cells should be collected prior to exposure to an alkylating agent, as these agents are stem cell toxic
- Collection may be done by bone marrow harvesting or peripheral blood stem cell apheresis following treatment with G-CSF
- Harvested cells are cryopreserved until time of transplant
- Peripheral blood preferred since development of colony stimulating factors and CXC4 inhibitor
- Daily measurement of peripheral CD34 count
- BMT CTN 0201
  - GVHD BM vs PB (41% vs 53%)
  - BM higher incidence of graft failure (9% vs 3%)
  - Donor preference (30% declined BM)
  - No difference in relapse, DFS, OS

Conditioning Regimens

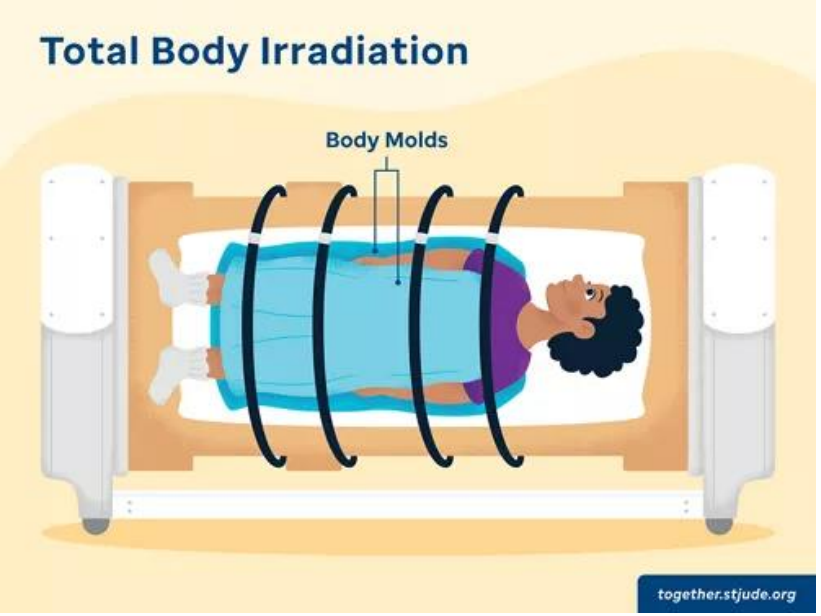
Objective of using a conditioning regimen for hematopoietic stem cell transplantation

- To reduce the bulk of malignant cells
- To decrease the risk of graft rejection via general host immune suppression
- To improve the engraftment of donor HSCs by providing profound immunosuppression of the host

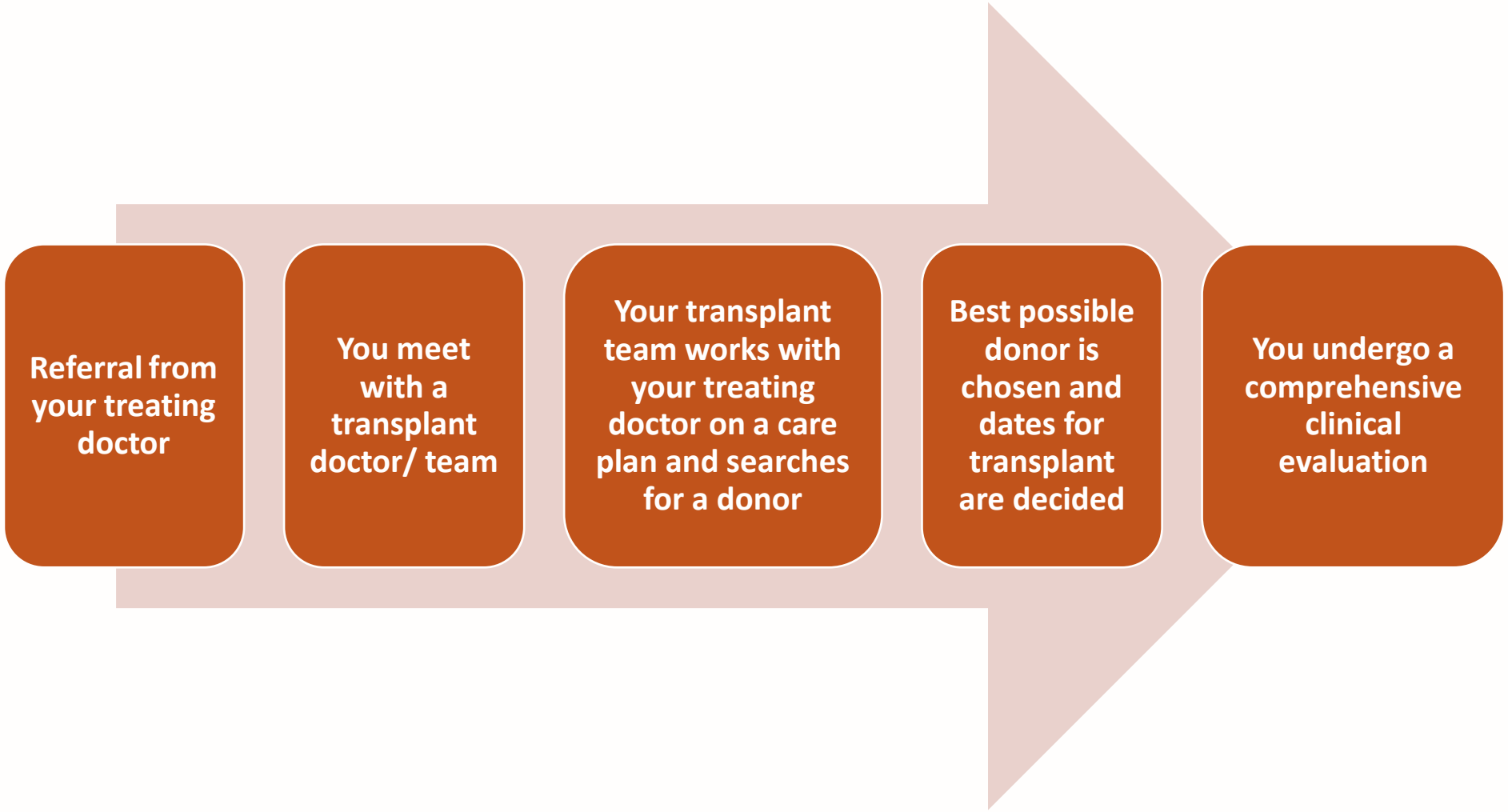
Conditioning Regimens

Intensity classified as

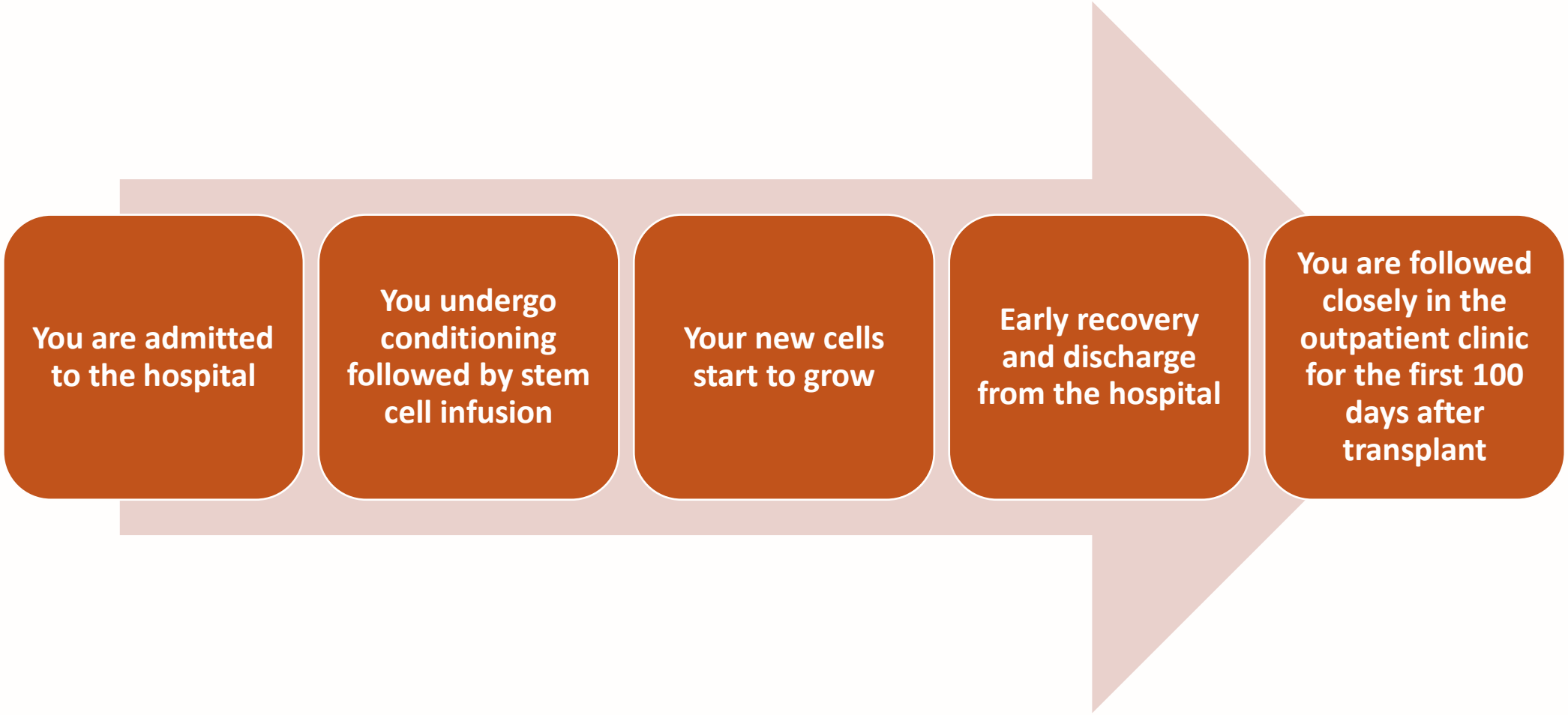
- Myeloablative (MA)
- Reduced intensity (RIC)
- Nonmyeloablative (NMA)



Pre-transplant Process



Transplant Process

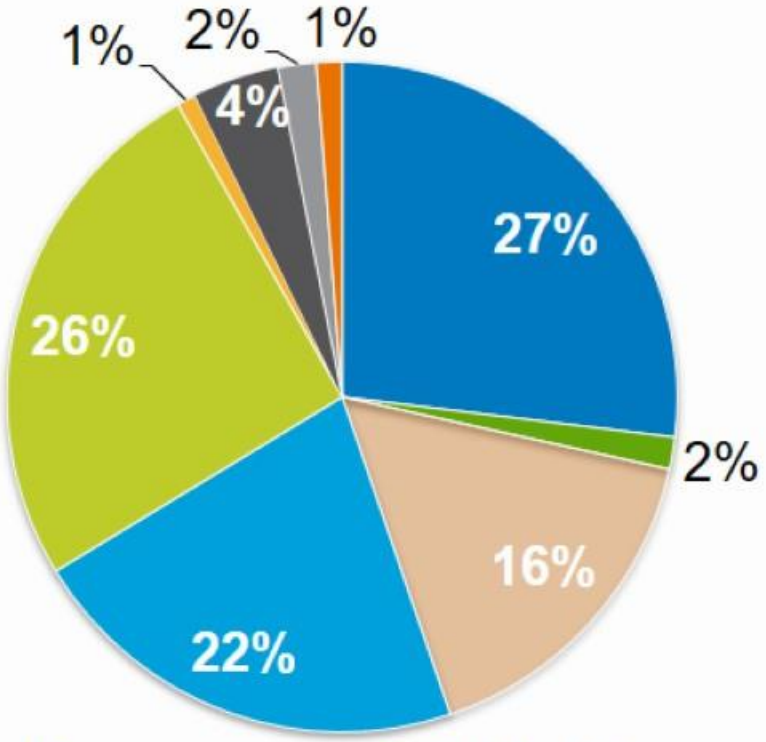


Stem Cell Transplant Phases

- Phase I: chemotherapy phase
  - Ends with the infusion of stem cells (Day 0)
- Phase II: cytopenic phase (+1 to engraftment, usually +14-21)
- Phase III: early recovery phase (+14 to +30)
  - Neutrophil recovery, engraftment syndrome, GVHD can begin to manifest
- Phase IV: early convalescence phase (+30 to +6-12 months)
  - Persistent immune-deficiency despite normal peripheral blood counts
  - Antibiotic, antiviral, and antifungal prophylaxis
- Phase V: late convalescence phase (+12 months)
  - Near full recovery of immune system
  - Last complications such as organ dysfunction or relapse

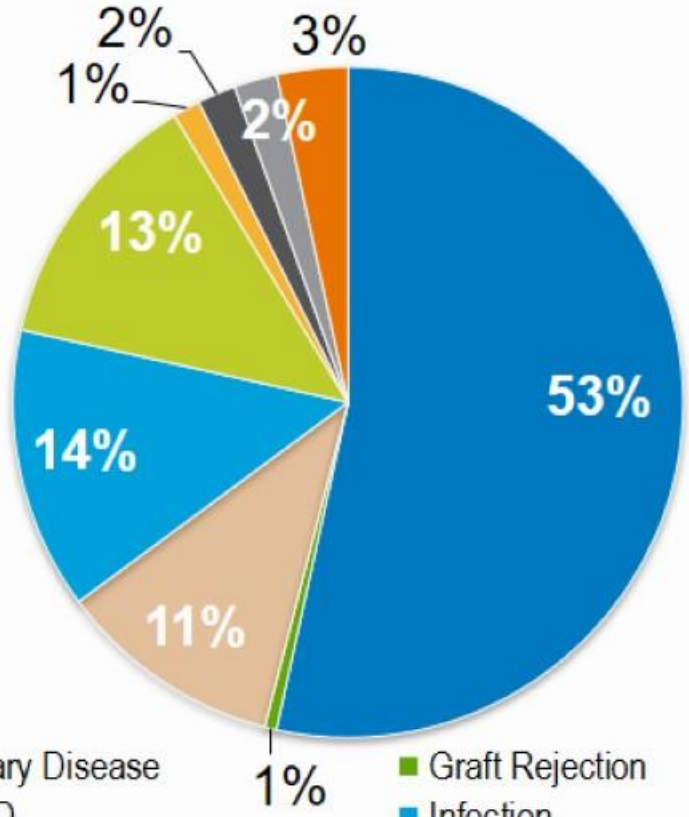
Causes of Death after Adult (age ≥18) Unrelated Donor HCT in the US, 2017-2018

Died within 100 days post-transplant



- Primary Disease
- Graft Rejection
- GVHD
- Infection
- Organ Failure
- Malignancy Subsequent to HCT
- Hemorrhage
- Other
- Unknown

Died at or beyond 100 days post-transplant*



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*Data reflects 3-year mortality

Transplant Complications and Outcomes

- Infection
  - PJP, fungal, CMV, VZV, HSV, EBV
- Myelosuppression
- Graft failure
- Hepatic Sinusoidal Obstruction Syndrome (SOS), previously VOD
  - Severe liver injury can result from cellular injury and obstruction in hepatic vein sinuses, results in elevated levels of bilirubin, hepatomegaly, fluid retention
  - Treatment: anticoagulants/defibrotide may reduce severity of hepatic SOS
  - Ursodiol can prevent SOS
- Pulmonary toxicities
  - Idiopathic pneumonia syndrome
  - Diffuse alveolar hemorrhage
- Thrombotic microangiopathy

Transplant Complications and Outcomes

- Mucositis
  - Injury to oropharyngeal mucosa commonly associated with conditioning regimen
  - Treatment: pain medications and IVF/TPN
- Engraftment syndrome
  - Rash, fever, capillary leak, pulmonary edema, renal failure
- GVHD
  - Rare occurrence post autologous transplant
  - Usually mild and self-limiting
- Secondary malignancies
  - Increased incidence of skin cancer, other solid tumors, acute leukemieas, MPNs
  - Increased risk in TBI based preparations
  - Post-HSCT oropharyngeal cancer may have more aggressive behavior with poorer prognosis

Engraftment and Graft Failure

Chimerism Analysis: STR-PCR: CD3, CD33
Primary Graft Failure: >95% recipient CD3 or CD34 after engraftment
Secondary Graft failure: loss of previously functioning graft by at least two cytopenic lines

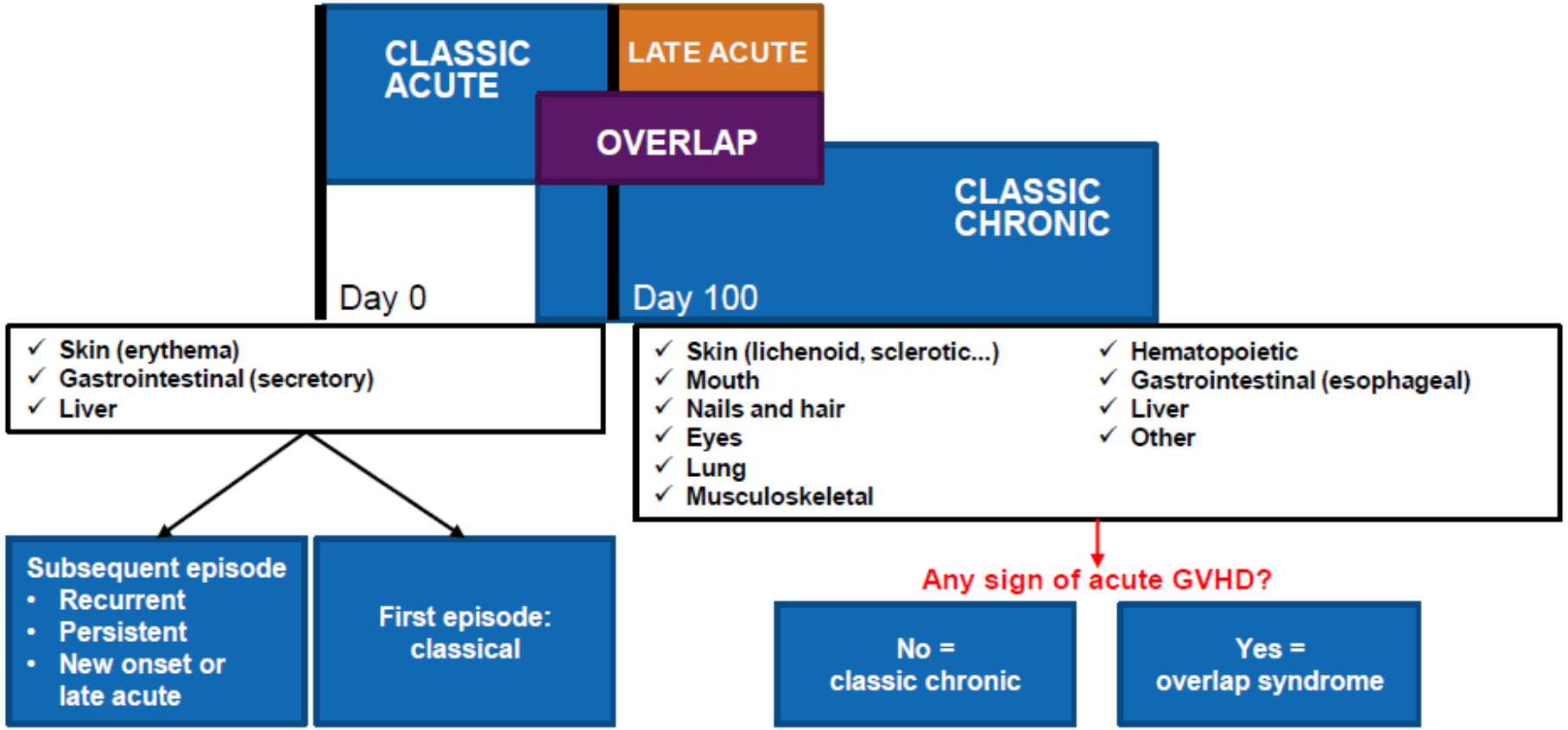
Factors associated with Graft Failure

- Quantitative progenitor issues
- Immunologic issues
- Viral infections
- Others (Drugs)

Graft versus host disease (GVHD)

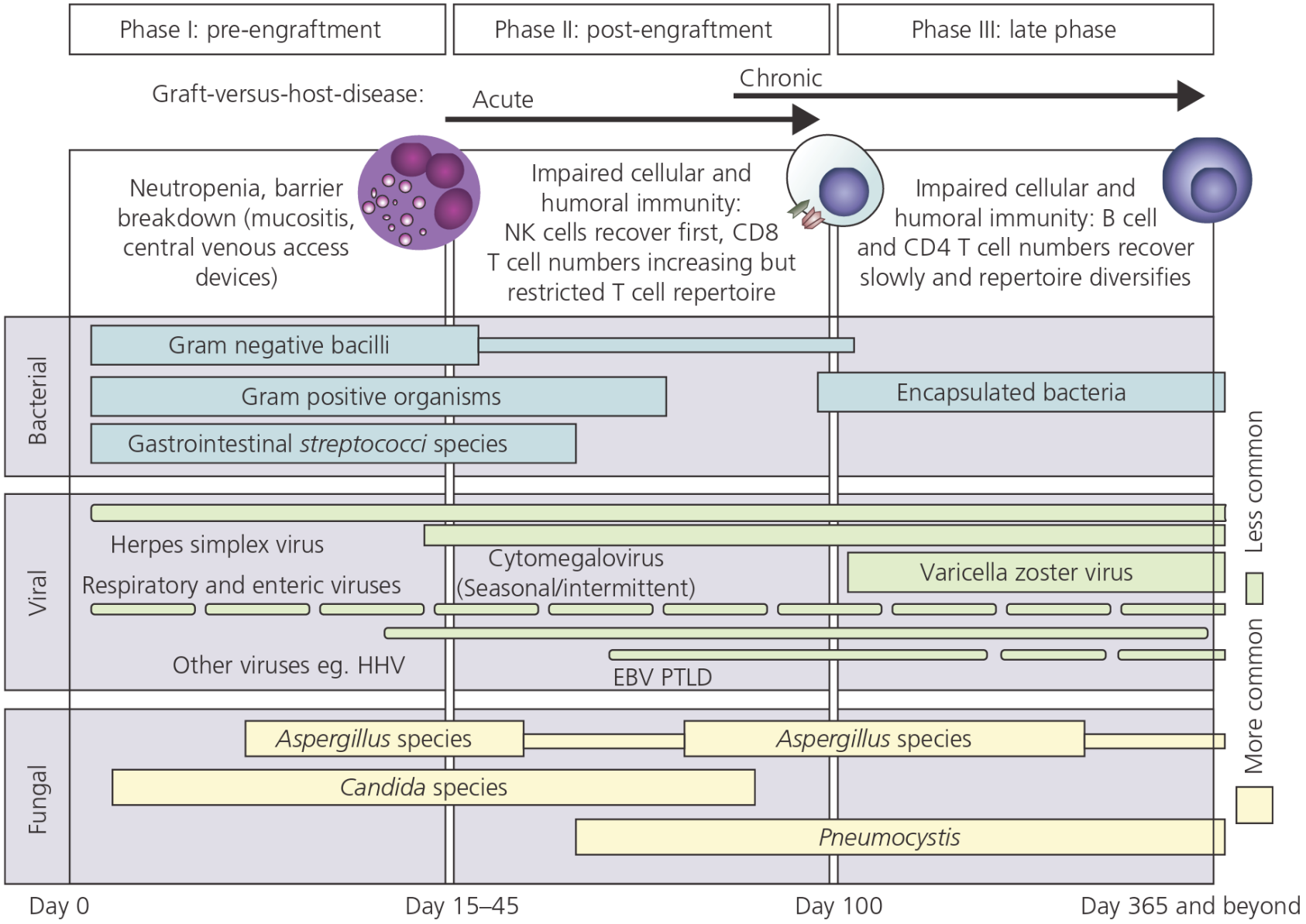
- Occurs because of differences between the cells of your body and the donor cells
- Severity ranges from mild to life-threatening
- Two types:
  - Acute:
    - Develops in the first 100 days after transplant but can occur later
    - usually involves skin rash, nausea/diarrhea or liver issues
  - Chronic GVHD:
    - Usually develops 3-6 months after transplant, but can appear earlier or later
    - Can involve most organ systems like skin, eyes, lungs, joints etc
    - Adversely impacts long term quality of life

Acute GVHD (aGVHD) and Chronic GVHD (cGVHD)[1,2]



1. Lee SJ. *Blood*. 2017;129:30-37. 2. Socié G, Ritz J. *Blood*. 2014;124:374-384.

PeerView.com


Phase I: pre-engraftment
Phase II: post-engraftment
Phase III: late phase
Graft-versus-host-disease:
Acute
Chronic
Neutropenia, barrier breakdown (mucositis, central venous access devices)
Impaired cellular and humoral immunity: NK cells recover first, CD8 T cell numbers increasing but restricted T cell repertoire
Impaired cellular and humoral immunity: B cell and CD4 T cell numbers recover slowly and repertoire diversifies
Bacterial
Gram negative bacilli
Gram positive organisms
Gastrointestinal streptococci species
Encapsulated bacteria
Viral
Herpes simplex virus
Respiratory and enteric viruses
Cytomegalovirus (Seasonal/intermittent)
Varicella zoster virus
Other viruses eg. HHV
EBV PTLD
Fungal
Aspergillus species
Aspergillus species
Candida species
Pneumocystis
Less common
More common
Day 0
Day 15–45
Day 100
Day 365 and beyond

Post-Transplant Vaccinations

- Non-live vaccinations begin at 1 year
- Non-live influenza vaccine can be given after Day +60
- Live vaccines administered after 2 years if off immunosuppression
- Can monitor CD4 and/or CD19 as surrogate for lymphocyte recovery

Vaccine Type[a]	Time after Transplant (months) ≥6	≥8	≥10	≥12	≥14	≥18	≥24	≥30	≥60	Minimal Time Interval Between Vaccines (Months)
Influenza[b]	Life long, seasonal. Start pre-HCT and continue starting at 6 months post-HCT.									
Pneumococcal 13-valent	Vaccination	Vaccination	Vaccination	Titer			Titer			1–2
Pneumococcal 23-valent				Vaccination	Vaccination					2 post-PCV13
DTaP[c]				Vaccination	Vaccination	Vaccination	Vaccination			1–2
Hib conjugate	Vaccination	Vaccination	Vaccination	Titer			Titer			1
IPV				Vaccination	Vaccination	Vaccination	Vaccination			2
Hep A[d]				Vaccination		Vaccination	Vaccination			2
Hep B				Vaccination	Vaccination	Vaccination	Titer			2 after 1st; 4 after 2nd
Meningococcal	Vaccination									
MMR [e,f]							Vaccination	Titer		1 if 2nd dose indicated
Low dose VZV [f,g]							Vaccination	Titer		2nd dose given 1 m later
High-dose VZV [h,i]									Titer	
HPV [j]				Vaccination	Vaccination	Vaccination	Vaccination			

Vaccination

Titer

Clinical manual of blood and bone marrow transplantation. Abutalib, Syed A., editor.; Hari, Parameswaran, editor.Hoboken, NJ : John Wiley & Sons Inc.; 2017

What determines the success of transplants?

- In general, transplants are most successful if:
  - MDS is in remission at the time of transplant and has not transformed to leukemia
  - Good organ function
  - Optimum functional status
  - No major uncontrolled infections
  - Good psychosocial support

How to prepare for transplant and improve chances of a successful outcome

- Get information about risks and benefits of transplant
- Explore non-transplant options such as clinical trials
- Select a transplant center
  - Live within about an hour of transplant center for at least 100 days after allogeneic HCT
- Continue to optimize your functional status and nutrition
- Select/decide about caregiver plan
- Plan your finances

What can I do as a potential transplant caregiver?

- 3 main areas of support:
  - Medical –gather information, talk to doctors and help care for the patient
  - Financial –talk to the insurance company and help manage transplant costs and daily household finances
  - Emotional and social –listen and support the patient
- Taking care of yourself while caring for your loved one
  - Many resources available for supporting caregivers

Potential challenges for transplant as treatment plan

- Patient perceived
  - Perceptions about high risks of transplantation
  - Social barriers
  - Need for transportation and lodging benefits
  - Lack of caregiver
  - Lack of insurance/ undocumented patients
  - Lack of optimal donors
- Provider perceived
  - Lack of awareness of the process of transplant among community hematologists/ oncologists
  - Potential revenue loss
  - Lack of care coordination
  - Financial barriers to HCT/need for in-network insurance
  - Lack of clarity on post-transplant care

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