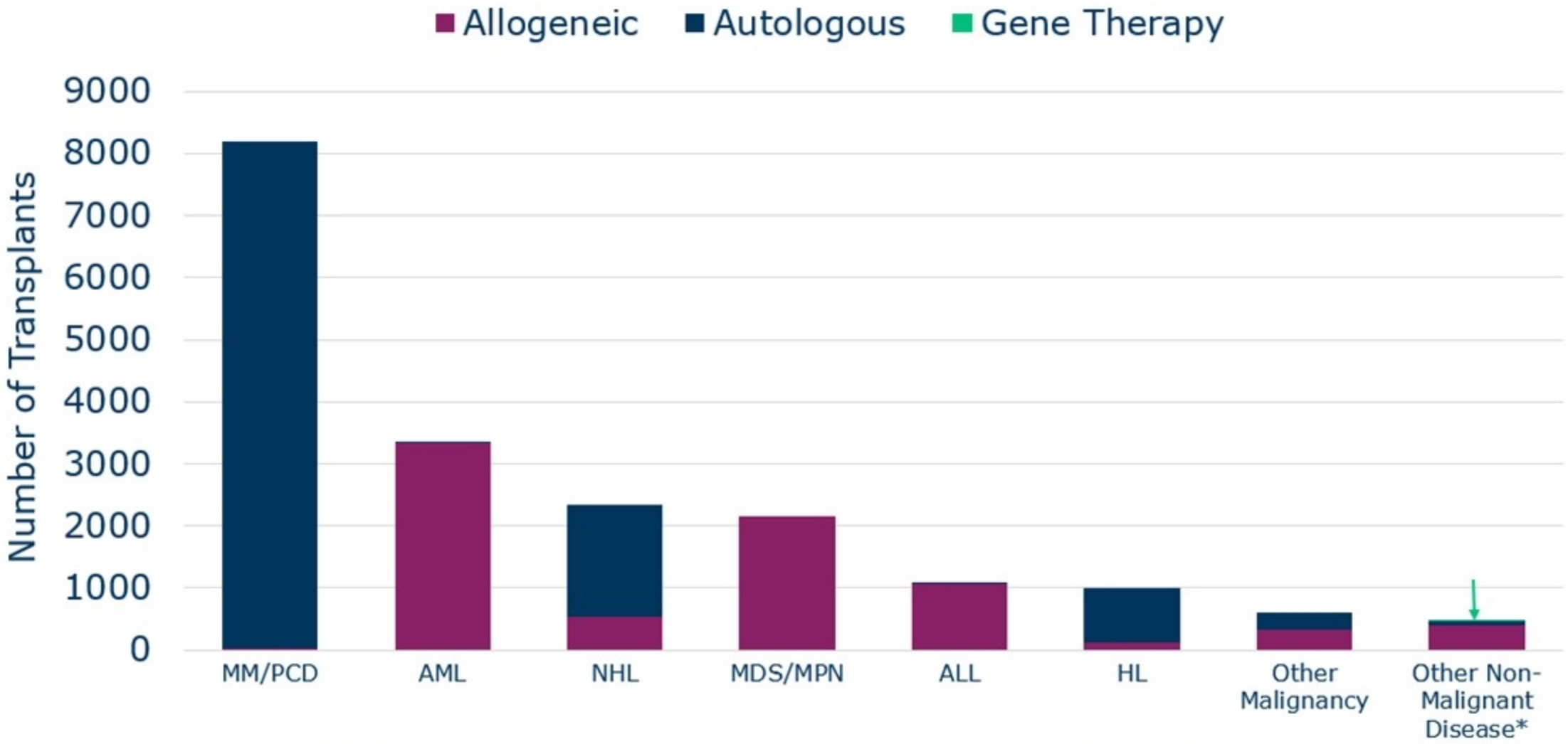
Hematopoietic Stem Cell Transplantation

Naveed Ali MD
Assistant Professor, Clinical Research Division
Fred Hutchinson Cancer Center
University of Washington
October 10, 2025
Email: nali2@fredhutch.org

Disclosure

- No relevant financial interest to disclose.
- This review will not focus on investigational therapies.

Number of HCTs by Indications in the US, 2023, Adult



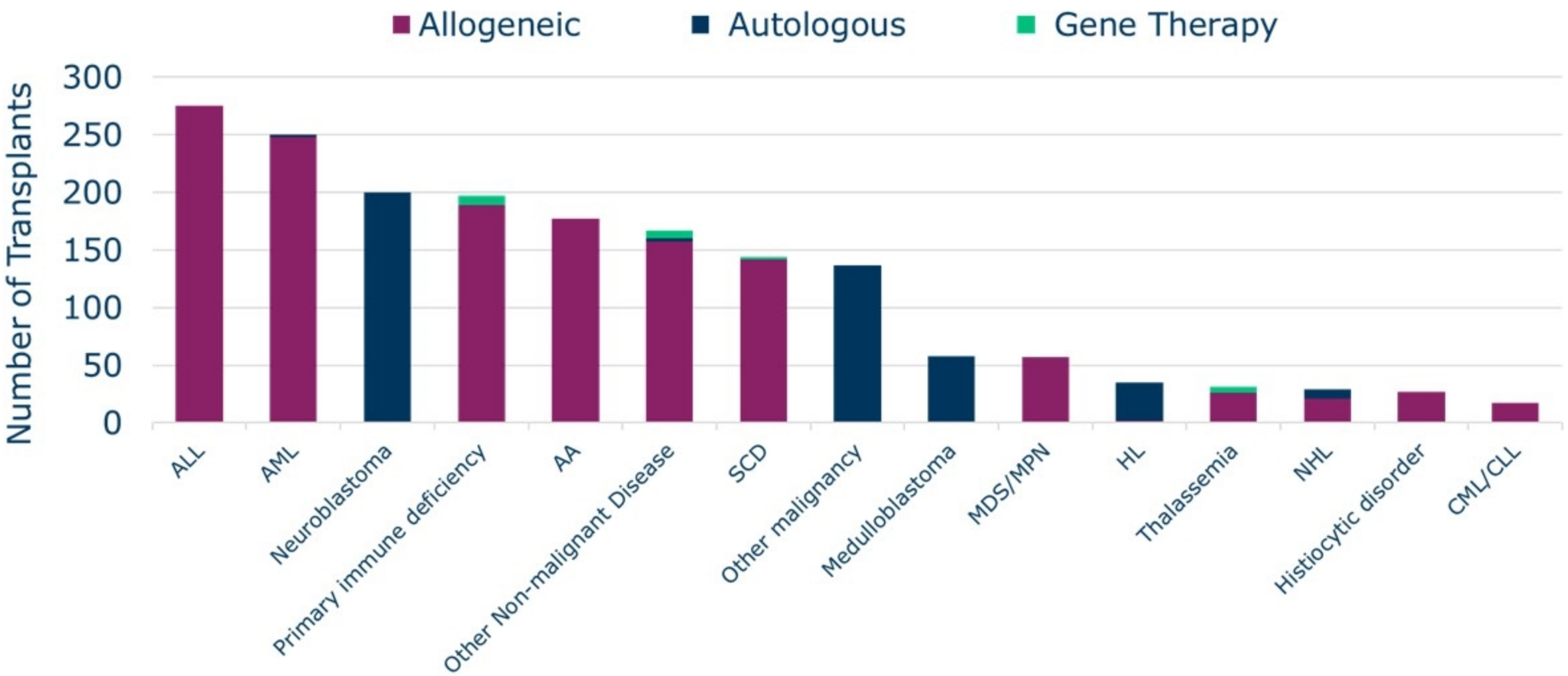
*Includes 22 limited gene therapy events

Abbreviations:
ALL, acute lymphoblastic leukemia;
AML, acute myeloid leukemia;
CLL, chronic lymphocytic leukemia;
HL, Hodgkin lymphoma;
MDS, myelodysplastic syndromes;
MM, multiple myeloma;
MPN, myeloproliferative neoplasms;
NHL, non-Hodgkin lymphoma;
PCD, plasma cell disorders.

CIBMTR®
A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

Spellman SR, et al. Transplant Cell Ther. 2025 Aug;31(8):505-532

Number of HCTs by Indications in the US, 2023, Pediatrics



CIBMTR®
A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

*Includes limited gene therapy events
Abbreviations:
ALL, acute lymphoblastic leukemia;
AML, acute myeloid leukemia;
AA, aplastic anemia;
CLL, chronic lymphocytic leukemia;
CML, chronic myeloid leukemia;
HL, Hodgkin lymphoma;
MDS, myelodysplastic syndromes;
MPN, myeloproliferative neoplasms;
NHL, non-Hodgkin lymphoma;
SCD, sickle cell disease.

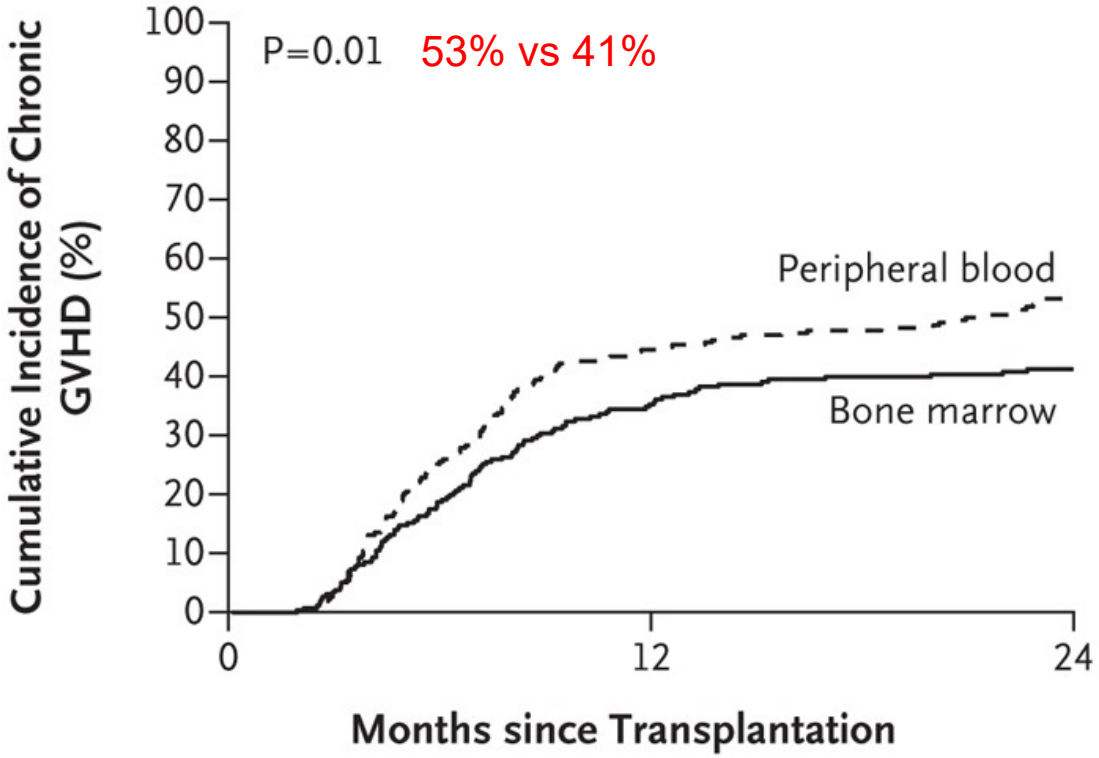
Spellman SR, et al. Transplant Cell Ther. 2025 Aug;31(8):505-532

Stem Cell Sources

	Peripheral blood	Bone marrow	Umbilical cord blood
Clinical use	Most common source in adults	- Common in pediatrics - Non-malignant disorders	- Common in pediatrics - Use in adults is decreasing
Time to engraftment	Fast (2 weeks)	Slow (~3 weeks)	Slowest (3- 4 weeks)
Chronic GVHD	High	Low	**Low** to high
Relapse	Lowest	High	Low
Infection	Low	High	Highest
Transplant related mortality	Moderate to high	Low	Highest
Logistics	- Less invasive - Outpatient	Need for general anesthesia	Expensive

Mobilized PBSC vs BM

- BMT CTN 0201 RCT compared PB and BM grafts
  - MUD
  - MAC conditioning
  - CNI + methotrexate
- Neutrophil engraftment occurred 5 days early in PB graft
- More graft failure with BM graft (9% vs 3%)
- Higher chronic GVHD with PB graft
- No difference in overall survival or relapse



Anasetti C, et al. N Engl J Med. 2012;367:1487-96
Stem Cell Trialists' Collaborative Group. J Clin Oncol. 2005;23:5074-87

Stem Cell Mobilization and Collection

- Mobilization is done with chemotherapy, G-CSF and CXCR4 inhibitor plerixafor
- Plerixafor is a reversible CXCR4 antagonist that prevents interaction with stromal cell-derived factor 1 (SDF-1)
- 3-5 fold higher CD34+ cell release into peripheral circulation
- Peak effect in 8-10 hours
- Phase 3 RCTs show significantly higher CD34+ cell yield with less failure rate with G-CSF plus plerixafor compared to G-CSF alone
- Side effects: Gastrointestinal (mainly diarrhea)

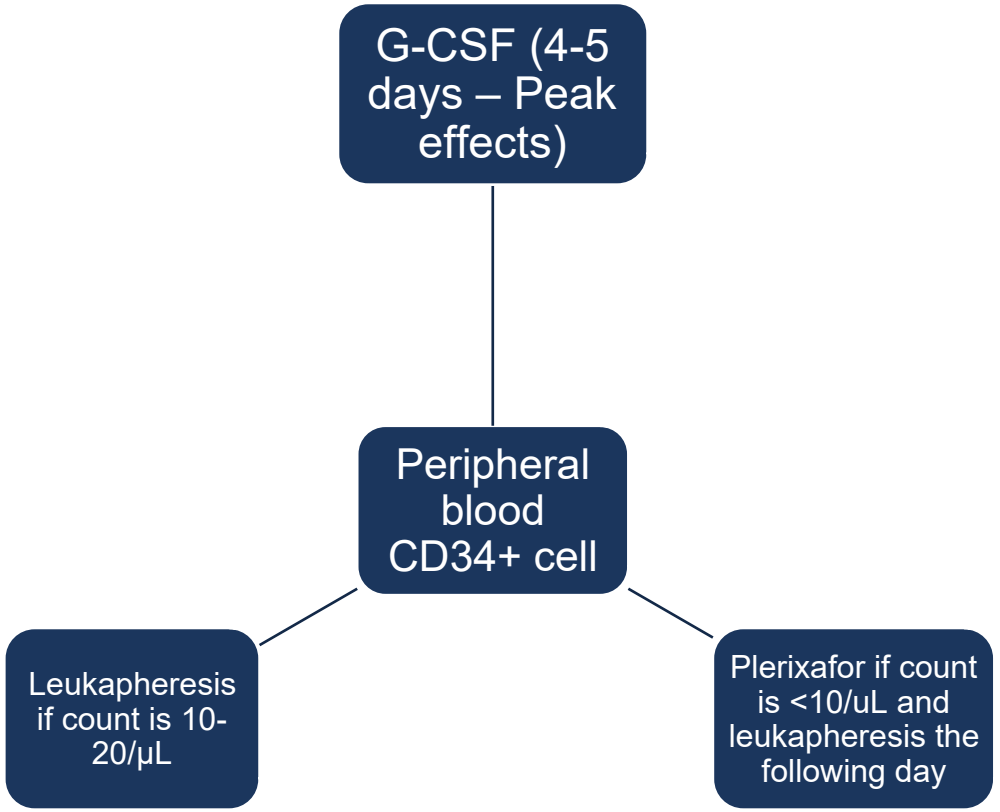
DiPersio JF, et al. J Clin Oncol. 2009;27(28):4767-73

DiPersio JF, et al. Blood. 2009;113(23):5720-6

Stem Cell Mobilization and Collection

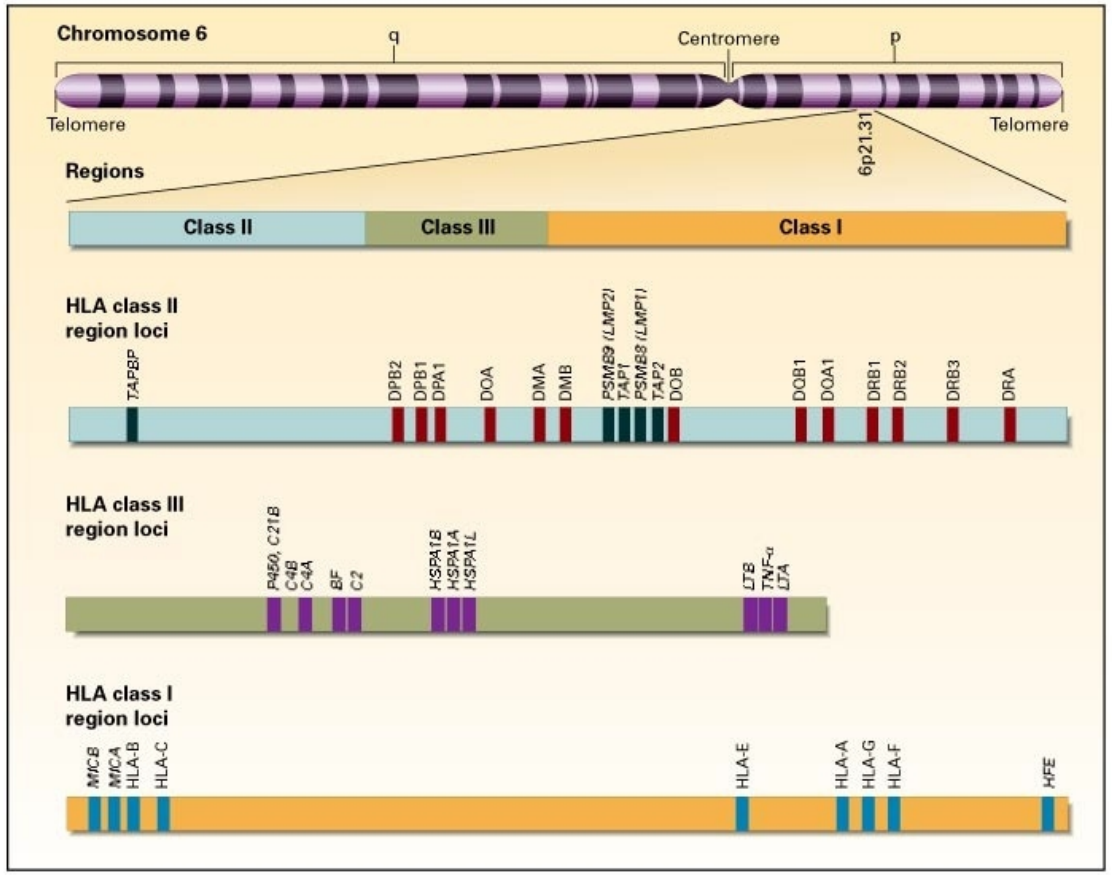
- Autologous:
  - G-CSF alone
  - Chemotherapy plus G-CSF
  - G-CSF plus plerixafor (on-demand) – most common method

- Allogeneic:
  - 4-5 days of G-CSF followed by leukapheresis



The HLA System

- Highly polymorphic gene system
- Short arm of chromosome 6
- Class I antigens are HLA-A, -B and -C
  - Expressed on all somatic cells
- Class II antigens are HLA-DR, -DQ and -DP
  - Expressed on B cells, activated T cells, macrophages, dendritic cells, and thymic epithelial cells
- HLA typing is done using PCR/ NGS based methods



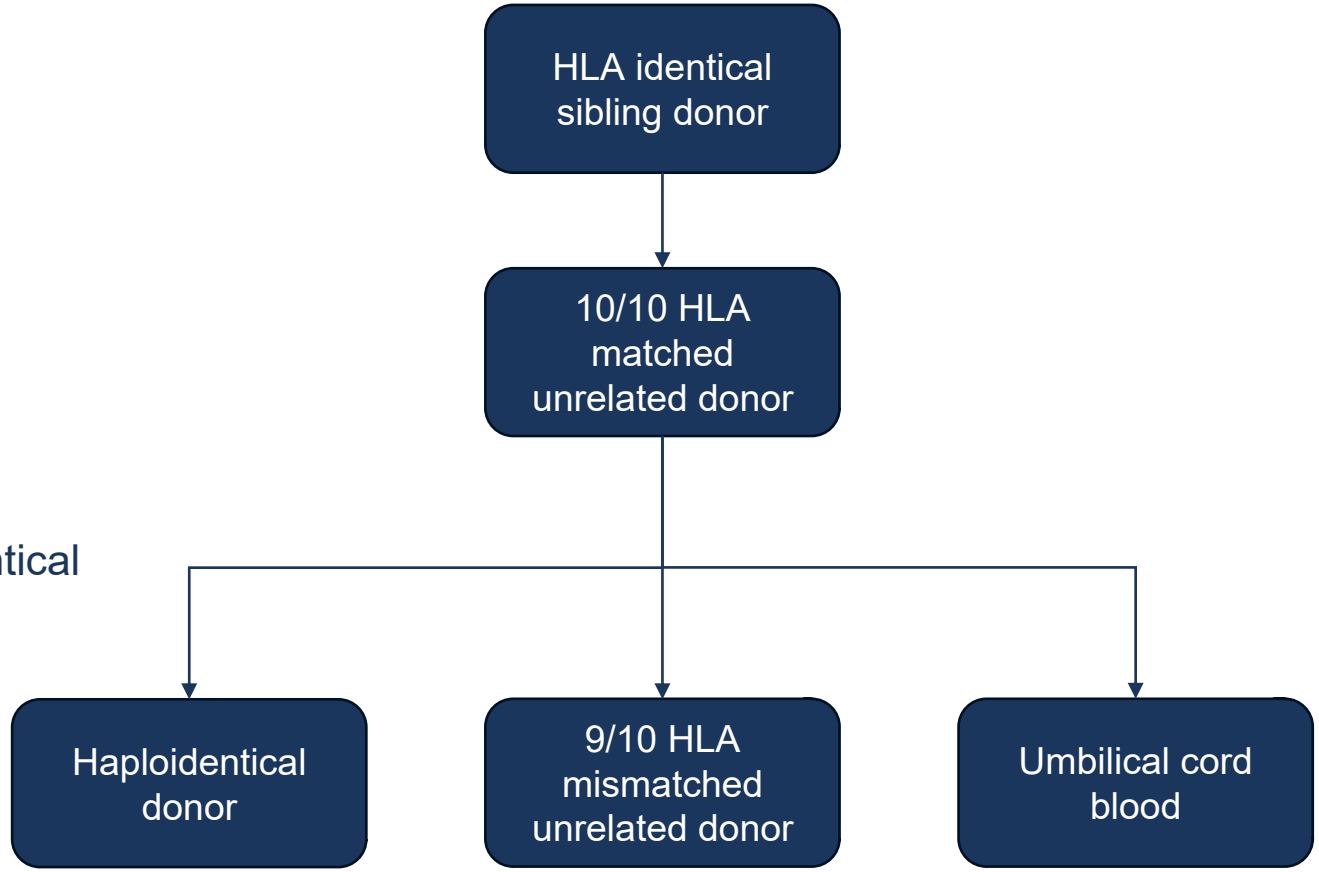
Klein J, Sato A. N Engl J Med. 2000;343(10):702-9

Donor Selection Criteria

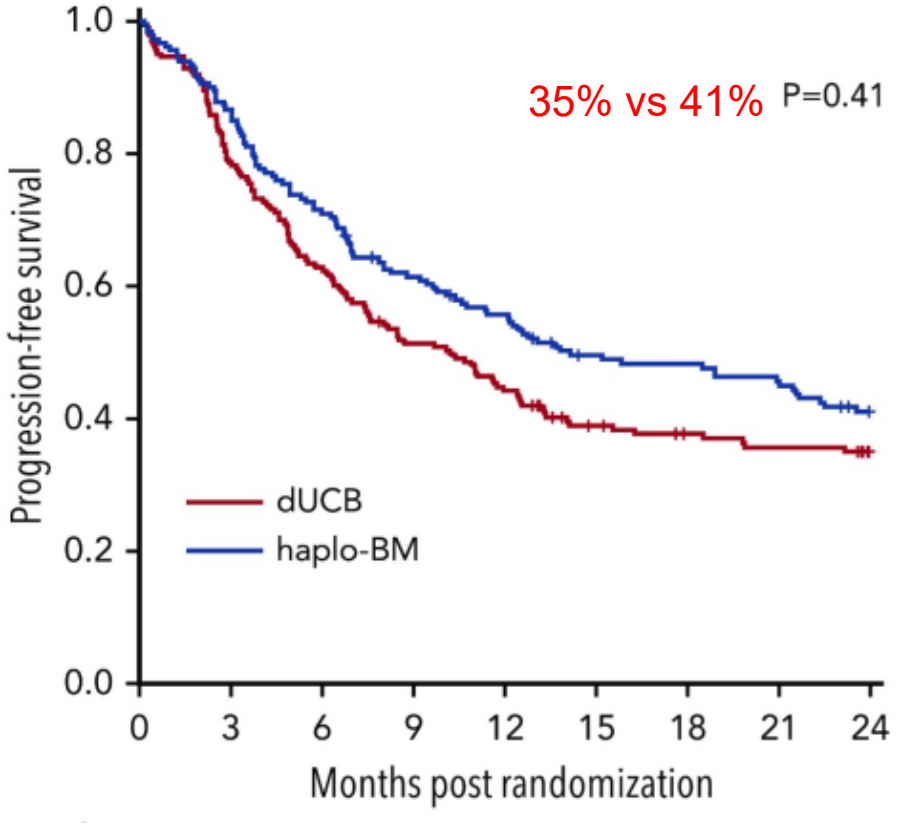
- HLA match – most important, matching at HLA-A, -B, -C, -DR, DQ
- Donor age – younger donors preferred
- CMV serostatus
  - CMV negative donor for CMV negative recipient
  - CMV positive (preferred) or negative donor for CMV positive recipient
- ABO compatibility – Not required
- Donor specific antibodies (DSA):
  - Preformed antibodies against donor HLA antigens
  - Pregnancy, blood products, previous organ or stem cell transplantation
  - Can lead to graft rejection if high titers, especially haploidentical donors

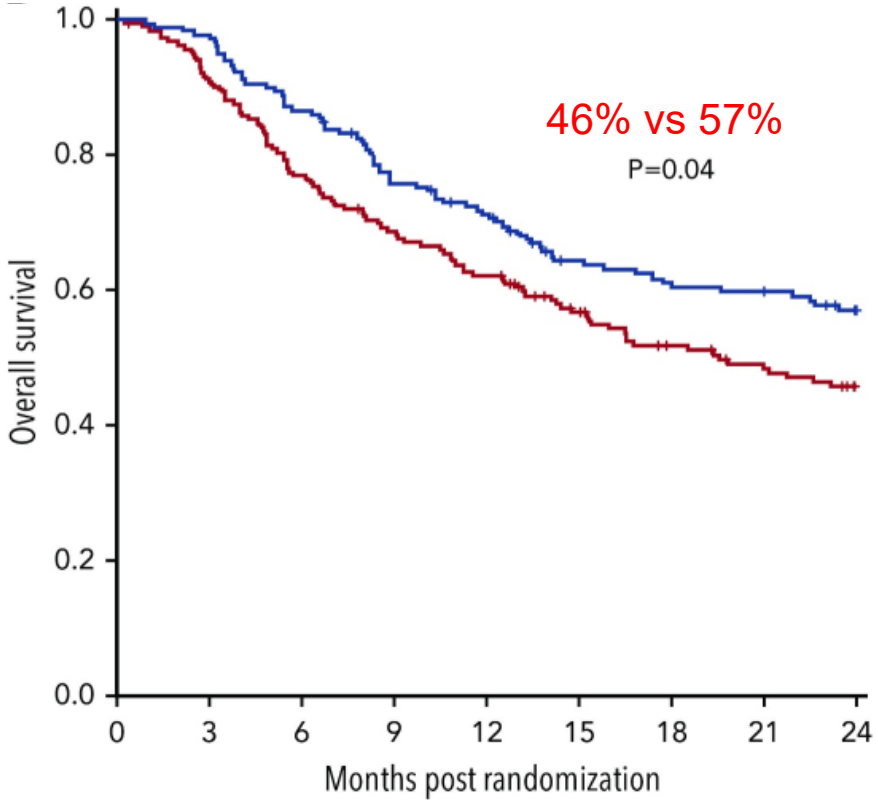
Donor Choices and Selection

- Sibling donors
  - ~25% chance of being HLA identical
- Unrelated donors
  - 10/10 HLA match
  - National and international donor registries
- Haploidentical donors
  - Share a haplotype with recipient
  - Parents and children are haploidentical
  - Siblings have 50% chance of being haploidentical
- Umbilical cord blood units (single or double)
  - Allows higher degree of HLA disparity
  - HLA-A, -B and -DR alleles
  - 4/6 HLA match allowed



Haploidentical vs Cord Blood Transplant





Fuchs EJ, et al. Blood. 2021 Jan 21;137(3):420-428

Conditioning Regimens

- Chemotherapy or chemotherapy and radiation
- Depends on disease, donor type and graft source
- Prior to autologous or allogeneic stem cell transplant
- Eradicate malignancy (autologous and allogeneic)
- Suppress recipient immune system to prevent graft rejection (allogeneic)

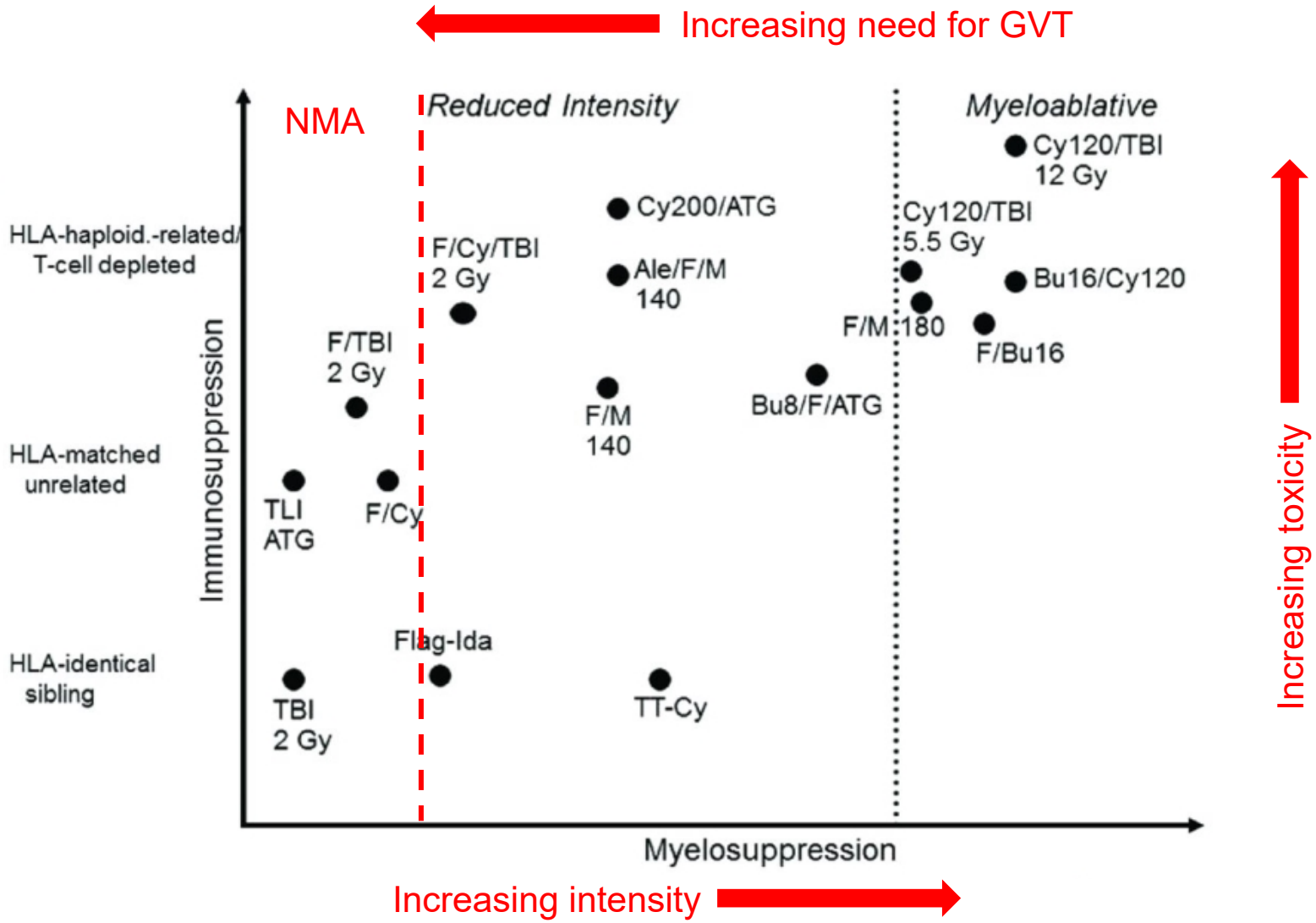
Conditioning Intensity

- Myeloablative Conditioning (MAC):
  - Irreversible myelosuppression without stem cell support
  - Provides direct anti-tumor effect as well as graft vs tumor effect

- Reduced Intensity Conditioning (RIC):
  - Not considered MAC or NMA
  - Potentially require stem cell support and result in prolonged cytopenia
  - Relies mainly on graft vs tumor effect

- Non-myeloablative (NMA):
  - Reversible myelosuppression without stem cell support
  - Relies heavily on graft vs tumor effect

Gyurkocza B, Sandmaier BM. Blood. 2014;124(3):344-53



Storb R, Sandmaier BM. Haematologica. 2016 May;101(5):521-30.

Gyurkocza B, Sandmaier BM. Blood. 2014 Jul 17;124(3):344-53.

Conditioning Regimens by Diseases

Disease	Conditioning regimen
AML/ MDS/ MPN	MAC: Flu/Bu4, Bu/Cy, Cy/HD-TBI RIC: Flu/Mel, Flu/Bu2 NMA: Flu/TBI (2-3 Gy)
ALL	TBI based regimens e.g., Cy/HD-TBI
Multiple myeloma	Melphalan 200 mg/m^2 or 140 mg/m^2 (elderly or comorbidity)
Lymphoma (NHL and HL)	BEAM (BCNU, etoposide, Ara-C, melphalan)
CNS lymphoma	Thiotepa based regimens (Bu/Cy/TT or BCNU/TT for age >60)
Germ cell tumor	TEC-TIC, CE (carboplatin, etoposide)
Aplastic anemia	Cy/ATG, Flu/Cy/ATG ± TBI

Hematopoietic Recovery after HSCT

- Engraftment – first of 3 days of absolute neutrophil count > 500/µl

- Delayed with bone marrow or cord blood graft

- Can be accelerated – WBC growth factors (G-CSF)
- Autologous:
  - Early engraftment by 2-4 days in autologous transplant
  - Strong recommendation to administer per ASCO guidelines
  - No overall survival benefit
- Allogeneic:
  - Weak recommendation per ASCO guidelines
  - Routinely used following cord blood graft

Smith TJ, et al. J Clin Oncol. 2015;33(28):3199-212

Dekker A, et al. J Clin Oncol. 2006;24:5207-5215

Engraftment Syndrome

- Characterized by:
  - Fever
  - Maculopapular rash
  - Hypoxemia
  - Weight gain
  - Pulmonary edema
- Within a week of neutrophil engraftment
- Corticosteroids (usually 0.5-1 mg/kg for 3-5 days)

ABO Incompatibility

- Major – recipient has ABO antibodies against donor antigens
- Minor – donor has ABO antibodies against recipient antigens
- Bidirectional – both recipient and donor have ABO antibodies

- Can cause hemolytic reactions
- Delayed erythroid engraftment
- Pure red cell aplasia

	Recipient ABO	Donor ABO
Major mismatch	O A B	A, B, AB AB AB
Minor mismatch	A B AB	O O A, B, O
Bidirectional mismatch	A B	B A

Booth GS, et al. Biol Blood Marrow Transplant. 2013;19(8):1152-8

Transfusion Support

- Transfusion thresholds are variable per institutional guidelines
  - RBC transfusion: 7-8 g/dl
  - Platelet transfusion: 10,000 /µl
- Leukocyte reduced blood products minimize HLA alloimmunization
- Gamma irradiated blood products prevent transfusion - associated GVHD and CMV transmission

Gajewski JL, et al. Blood. 2008;112(8):3036-47

Complications of HSCT

- Non-infectious complications
- Infectious complications
- Acute graft vs host disease
- Chronic graft vs host disease
- Late complications

Gastrointestinal Toxicity – Oral Mucositis

- Common after autologous and allogeneic HSCT
- Disruption of mucosal integrity from direct effect of chemotherapy and radiation
- Risk factors are poor oral hygiene, TBI based and more intense conditioning regimens
- Prophylaxis:
  - Pre-HSCT dental evaluation
  - Good oral hygiene, oral saline rinses
  - Oral cryotherapy (high dose melphalan), ice 30 minutes before and for 4-6 hours after melphalan infusion, RCT (74% vs 14%)
  - Palifermin (recombinant human keratinocyte growth factor) for intense regimens

Lilleby K, et al. Bone Marrow Transplant. 2006;37(11):1031-5

Hensley ML, et al. J Clin Oncol. 2009;27:127-45

Oral Mucositis

- Management:
  - Mild (Grade I-II) – saline oral rinses, good oral hygiene
  - Moderate (Grade III) – topical analgesics, opioid pain medication (PCA), total parenteral nutrition
  - Severe (Grade IV) – preventative intubation, total parenteral nutrition

- Tends to resolve after neutrophil recovery

VOD/ SOS

- Potentially fatal liver complication
- Occurs during the first 3 weeks after HSCT, less common after 3 weeks
- Risk factors:
  - Older age
  - Pre transplant therapy (inotuzumab ozogamicin, gemtuzumab ozogamicin, other hepatotoxic drugs)
  - Conditioning regimen (12 Gy TBI, high dose cyclophosphamide, busulfan)
  - GVHD prophylaxis (sirolimus, methotrexate)
  - Liver disease (hepatic steatosis, iron overload, high ferritin level)

VOD/ SOS

- Baltimore criteria – Bilirubin ≥ 2 mg/dl within 21 days of transplant plus 2 of the following criteria:
  - Painful hepatomegaly
  - Weight gain > 5% from baseline
  - Ascites
- Modified Seattle criteria – 2 of the following criteria within 20 days of transplant:
  - Bilirubin ≥ 2 mg/dl
  - Painful hepatomegaly
  - Weight gain more than 2% from baseline
- Liver US with Doppler – hepatomegaly, ascites and reversal of portal venous flow
- Hepatic venous wedge pressure gradient > 10 mmHg

McDonald GB, et al. Hepatology. 1984;4:116

Jones RJ et al. Transplantation. 1987;44:778

VOD/ SOS

- Prophylaxis:
  - Tailor conditioning regimen according to risk factors
  - Targeted busulfan dosing based on pharmacokinetics
  - Ursodeoxycholic acid (ursodiol) – starts before conditioning regimen and continues for 3 months post-HSCT
  - Defibrotide has no role in prevention

- Treatment:
  - Mild to moderate – Supportive
  - Severe (multiorgan system involvement) – Defibrotide (early initiation improves OS)
  - No benefit of heparin

Richardson PG, et al. Blood. 2016;127:1656

Pulmonary Complications

- Common after HSCT
- Infectious pneumonias
- Idiopathic pneumonia syndrome (IPS)
- Diffuse Alveolar hemorrhage (DAH)
- Cryptogenic organizing pneumonia (COP)
- Bronchiolitis obliterans (BOS)

Idiopathic Pneumonia Syndrome (IPS)

- First few weeks post-HSCT
- Incidence 7-10%, median time to onset 21 days
- Risk factors: TBI, BCNU, prior bleomycin exposure
- High morbidity and mortality
- Imaging shows multilocular infiltrates
- Diagnosis of exclusion, bronchoalveolar lavage should be negative for infectious cause and hemorrhage
- Treatment:
  - Corticosteroids (1-2 mg/kg per day)
  - TNF-α inhibitor etanercept

Diffuse Alveolar Hemorrhage (DAH)

- Early post-transplant period after engraftment
- Incidence: 1-2%
- Risk factors: older age, MAC (high dose TBI), thrombocytopenia, coagulopathy, pulmonary disease
- Imaging shows bilateral alveolar opacities
- Bronchioalveolar lavage – progressively bloody return (diagnostic)
- Hemosiderin laden macrophages (>20%) if onset 2-3 days
- Infectious workup negative
- High dose corticosteroid (1 g methylprednisolone for 3-5 days and slow taper over 1-3 months)

Cryptogenic Organizing Pneumonia (COP)

- Weeks to months after transplant
- Presentation includes dry cough, dyspnea, hypoxemia and fever
- Patchy consolidative or ground glass infiltrates on imaging
- Prolonged corticosteroids course (starting dose usually 1 mg/kg)
- Usually reversible

Bronchiolitis Obliterans (BOS)

- Occurs months after transplant
- Manifestation of chronic GVHD (6-10%)
- Insidious onset of dry cough and dyspnea
- PFTs show obstructive pattern (FEV1/FVC <70 or 10% decrease in FEV1, increase in TLC)
- High resolution CT scan shows bronchial dilation, mosaic pattern attenuation and air trapping
- Therapy:
  - Treatment of chronic GVHD
  - FAM regimen (inhaled fluticasone, azithromycin and montelukast)

Transplant Associated Thrombotic Microangiopathy (TA-TMA)

- Microangiopathic hemolytic anemia following allogeneic transplant
- Risk factors – CNI (tacrolimus, cyclosporine), sirolimus, TBI, unrelated donor, GVHD, infections/ sepsis
- Diagnosis:
  - New or worsening anemia and thrombocytopenia
  - Hemolysis (schistocytes, elevated LDH, low haptoglobin, indirect hyperbilirubinemia)
  - Elevated serum creatinine
  - Proteinuria
  - Hypertension
  - Elevated terminal complement (sC5b-9)
- Management:
  - Discontinue CNI/ sirolimus if possible
  - Eculizumab

GVHD Prophylaxis

- Depends on donor type and conditioning intensity
- MAC:
  - Post-transplant cyclophosphamide (PTCy)-based regimens – becoming the new standard
  - CNI (cyclosporine or tacrolimus) + methotrexate for unrelated or related – previous standard
  - PTCy for haploidentical
  - CNI + Mycophenolate mofetil (MMF) for umbilical cord blood transplant
- RIC:
  - **PTCy + CNI + MMF** – Standard for RIC regimens
  - CNI + sirolimus + MMF is superior to CNI + MMF
  - PTCy + CNI + sirolimus is superior to CNI + sirolimus + MMF
- Abatacept - **only FDA approved drug** for GVHD prophylaxis in combination with CNI/methotrexate
- T cell depletion or CD34 selection
- Role of ATG is controversial, some studies have shown reduced acute and chronic GVHD

Nash RA, et al. Blood. 2019;6:e409-e418

Kroger N, et al. Blood. 2009;114:5264-70

Sandmaier BM, et al. Lancet Haematol. 2019;6:e409-e418

Kroger N, et al. NEJM 2016;374:43-53

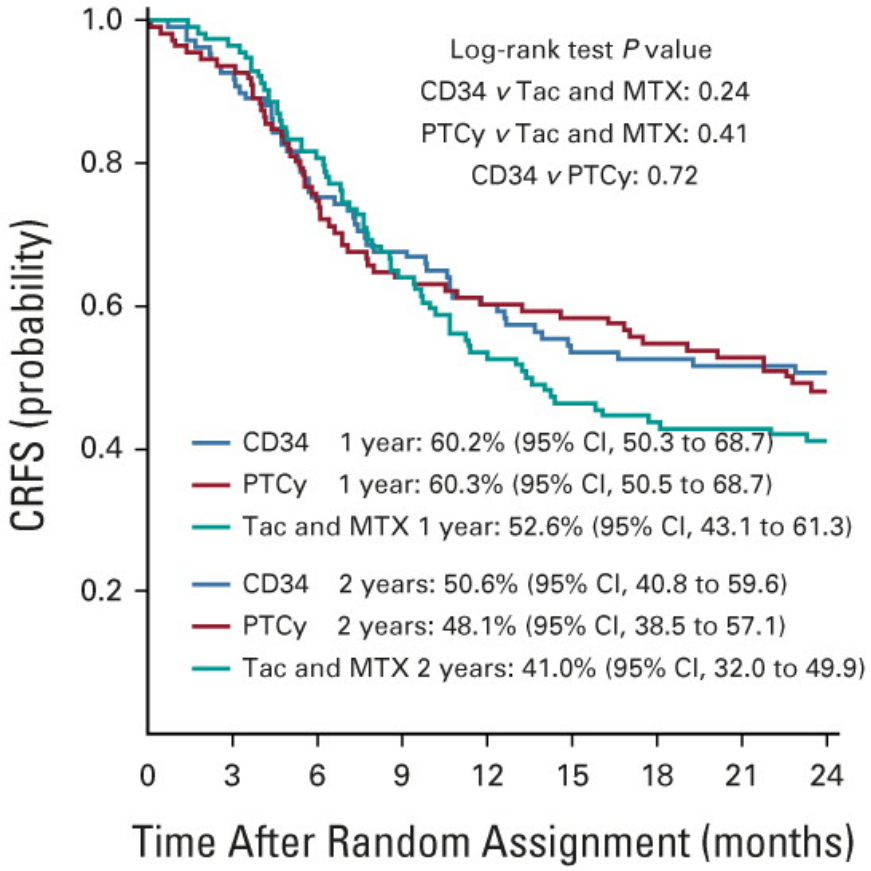
Watkins B, et al. J Clin Oncol 39, 1865-1877(2021)

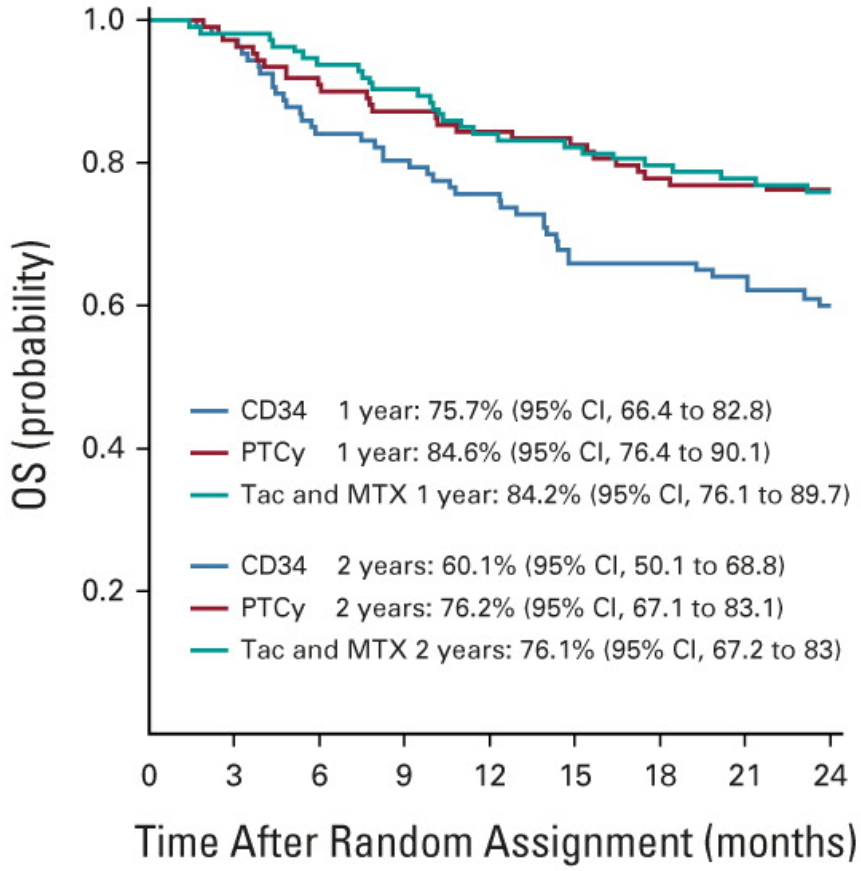
Bolaños-Meade J, et al. N Engl J Med. 2023;388(25):2338-2348

Curtis DJ, et al. N Engl J Med 2025;393:243-254

Ueda Oshima M, et al. J Clin Oncol 0, JCO-25-01238

GVHD Prophylaxis – MAC with MRD/MUD

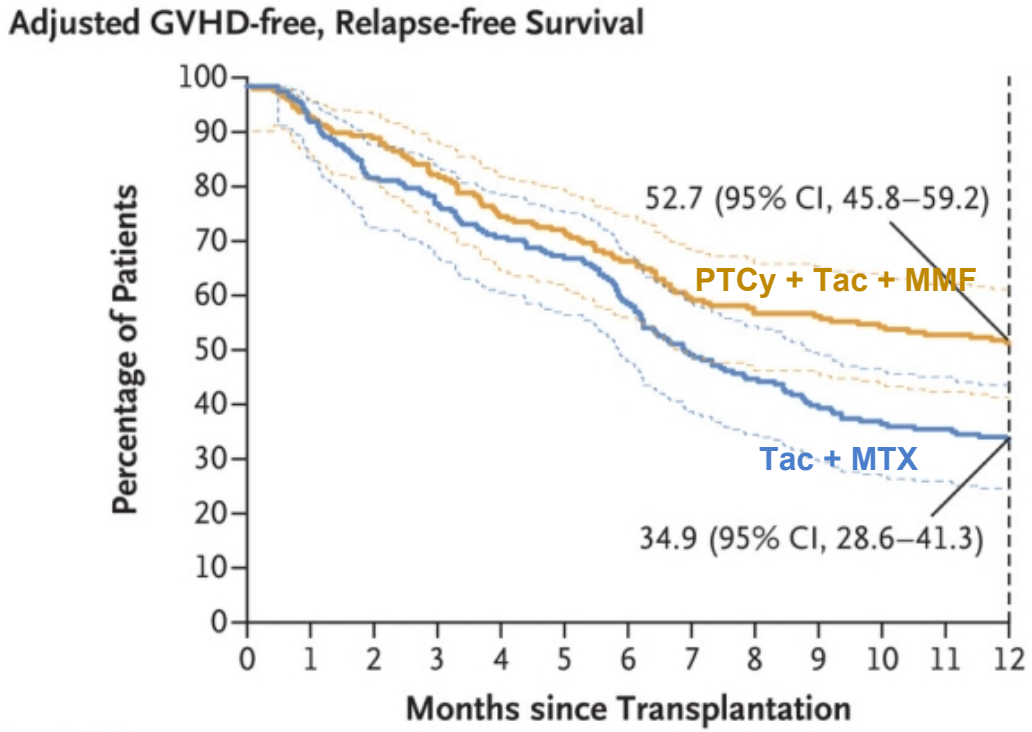




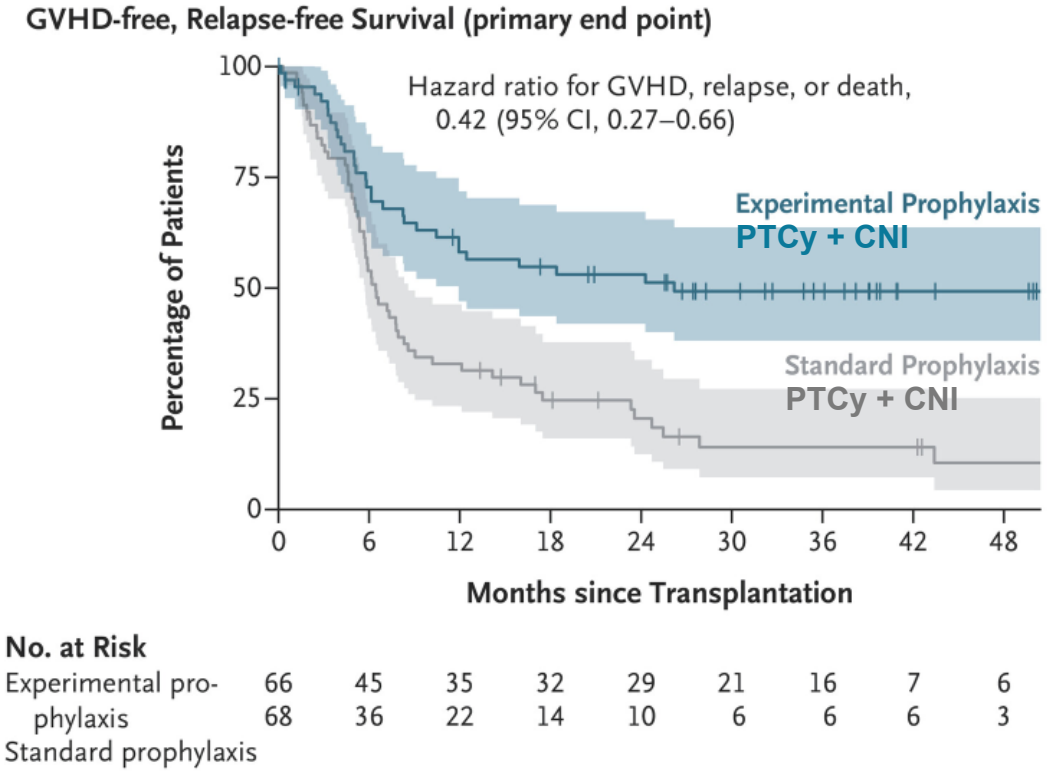
Luznik L, et al. J Clin Oncol. 2022;40:356-368

GVHD prophylaxis

RIC using MRD/MUD/MMUD



MAC/RIC using MRD



No. at Risk									
Experimental prophylaxis	66	45	35	32	29	21	16	7	6
Standard prophylaxis	68	36	22	14	10	6	6	6	3

Bolaños-Meade J. N Engl J Med. 2023;388(25):2338-2348

Curtis DJ, et al. N Engl J Med 2025;393:243-254

GVHD Prophylaxis Side Effects – Calcineurin Inhibitors

- Tacrolimus/ cyclosporine:
  - Renal insufficiency (acute and chronic)
  - Hypertension
  - Hyperglycemia
  - Electrolyte abnormalities (Hypomagnesaemia, hyper-/ hypokalemia)
  - Transplant associated-TMA
  - Remember interaction with azoles and statins (increase drug levels)
  - Progressive reversible encephalopathy syndrome (PRES)
    - Headache, confusion, visual disturbances, hypertension, seizures
    - MRI brain shows T2 white matter enhancement in occipital lobe
    - Withdrawal of CNI
  - Gingival hyperplasia (cyclosporine)
  - Hirsutism (cyclosporine)

GVHD Prophylaxis Side Effects – Others

- Sirolimus:
  - Hypertension, peripheral edema
  - Hypertriglyceridemia, hypercholesterolemia
  - Risk of TA-TMA and VOD/ SOS
- Mycophenolate mofetil (MMF):
  - GI symptoms, mucosal ulceration
  - Pancytopenia
  - Viral infections
- Methotrexate
  - Mucositis
  - Abnormal liver function
- Post-transplant cyclophosphamide
  - Hemorrhagic cystitis
  - Cardiovascular (including arrythmia)
  - Delayed immune reconstitution (infections)

GVHD

- Acute GVHD
  - Occurs before day 100
- Late onset acute GVHD
  - Occurs after day 100
  - Absence of chronic GVHD features
- Chronic GVHD
  - Presents any time after HSCT, usually after day 100
- Overlap syndrome:
  - Features of both acute and chronic GVHD
- Timing is less important than clinical features

Acute GVHD

- 30-70% of allogeneic transplant
- Sibling donors have less risk
- Risk factors:
  - HLA disparity
  - GVHD prophylaxis
  - Mobilized peripheral blood stem cells
  - Multiparous female donor
  - Conditioning regimen intensity
- Involves skin (rash), liver (hyperbilirubinemia and liver enzyme elevation) and gut (upper and lower GI symptoms)
- Pathology: Apoptotic bodies, perivascular lymphocytic infiltration, cryptic abscess

Acute GVHD

Modified Glucksberg Grading			
	Skin (BSA)	**Liver (bilirubin)**	**Gut (stool volume)**
Stage			
1	<25%	2-3 mg/dl	500-1000 ml/24 hours or persistent nausea, vomiting or anorexia
2	25-50%	3.1-6 mg/dl	1000-1500 ml/24 hours
3	>50%	6.1-15 mg/dl	1500-2000 ml/24 hours
4	Generalized erythroderma with bullous formation	>15 mg/dl	Severe abdominal pain with or without ileus
Grade			
I	Stage 1–2	None	None
II	Stage 3	Stage 1	Stage 1
III	--	Stage 2-3	Stage 2-4
IV	Stage 4	Stage 4	--

Acute GVHD – Treatment

- Grade I:
  - Topical corticosteroid, UV light therapy
- Grade II-IV
  - Upper GI: 0.5-1 mg/kg/day methylprednisolone (or equivalent prednisone)
  - Skin/Lower GI/ Liver: 1-2 mg/kg/day methylprednisolone (or equivalent prednisone), topical steroids
  - Budesonide and beclomethasone may be added for GI GVHD
- Ruxolitinib is the only FDA approved drug (2019)

Suggested Systemic Agents for Steroid-Refractory GVHD[a]

Acute GVHD[1]

The following agents are often used in conjunction with the original immunosuppressive agent.

FDA-approved category 1 agents

- **Ruxolitinib (category 1)[c,2]**

Alternative agents (listed in alphabetical order)

- **Alemtuzumab[3,4]**
- **Alpha-1 antitrypsin[5]**
- **ATG[6]**
- **Basiliximab[7]**
- **Calcineurin inhibitors (CNIs) (eg, tacrolimus, cyclosporine)**
- **Etanercept[8]**
- **Extracorporeal photopheresis (ECP)[d,9]**
- **Infliximab[10]**
- **mTOR inhibitors (eg, sirolimus)[11,12]**
- **Mycophenolate mofetil[13,14]**
- **Pentostatin[15-17]**
- **Tocilizumab[18-21]**
- **Urinary-derived human chorionic gonadotropin/ epidermal growth factor (uhCG/EGF)[22]**
- **Vedolizumab[23]**

NCCN guidelines. Hematopoietic cell transplantation

Chronic GVHD

- 20-50% of allogeneic transplant, 10-15% with PTCy-based prophylaxis

- Risk factors:
  - HLA disparity
  - GVHD prophylaxis
  - Mobilized peripheral blood stem cells
  - Multiparous female donor
  - Conditioning regimen intensity
  - Prior acute GVHD

Chronic GVHD – Clinical Manifestations

Panel 2: Chronic GVHD symptoms

Skin
Dyspigmentation, new-onset alopecia, poikiloderma, lichen planus-like eruptions, or sclerotic features

Nails
Nail dystrophy or loss

Mouth
Xerostomia, ulcers, lichen-type features, restrictions of mouth opening from sclerosis

Eyes
Dry eyes, sicca syndrome, cicatricial conjunctivitis

Muscles, fascia, joints
Fasciitis, myositis, or joint stiffness from contractures

Female genitalia
Vaginal sclerosis, ulcerations

Gastrointestinal tract
Anorexia, weight loss, oesophageal web or strictures

Liver
Jaundice, transaminitis

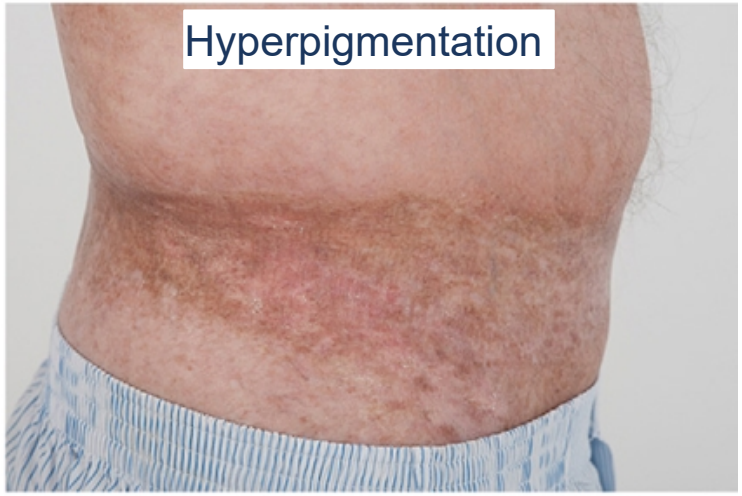
Lungs
Restrictive or obstructive defects on pulmonary function tests, bronchiolitis obliterans, pleural effusions

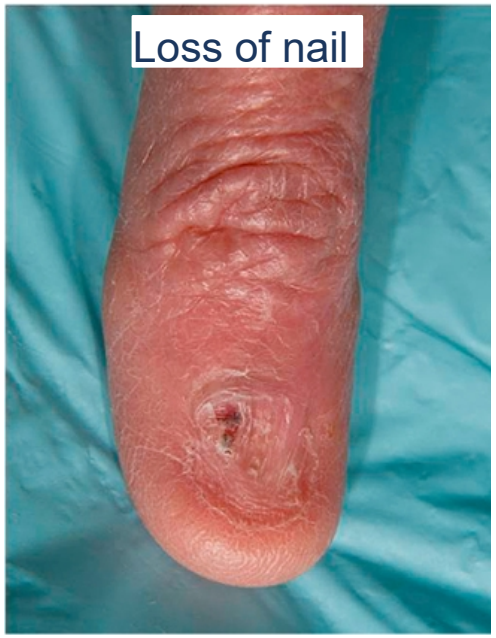
Kidneys
Nephrotic syndrome (rare)

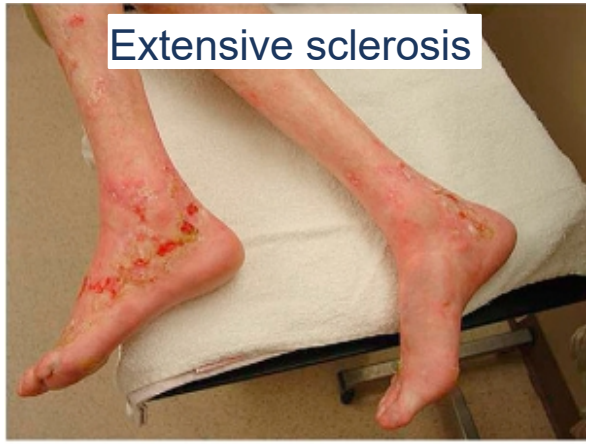
Heart
Pericarditis

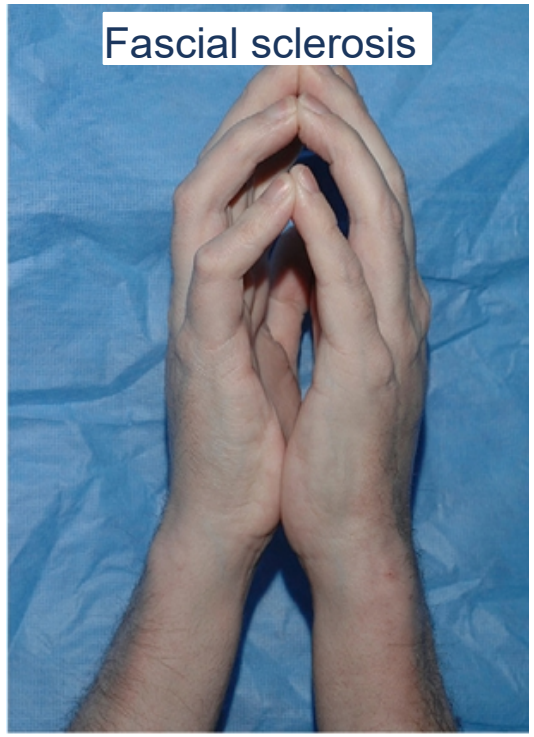
Marrow
Thrombocytopenia, anaemia, neutropenia

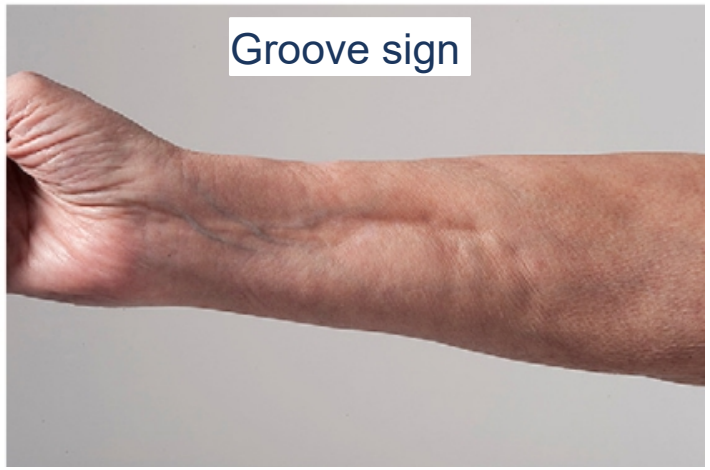
Ferrara et al, Lancet. 2009;373:1550-61

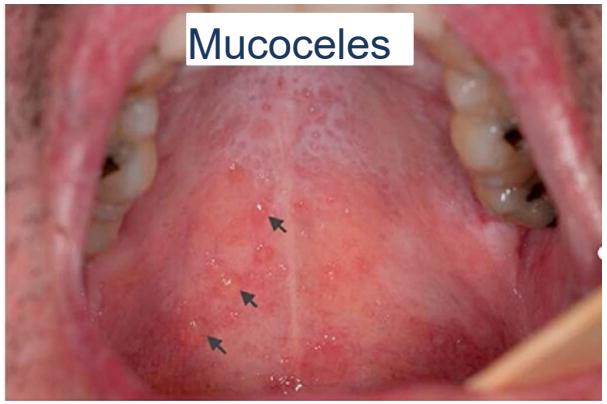


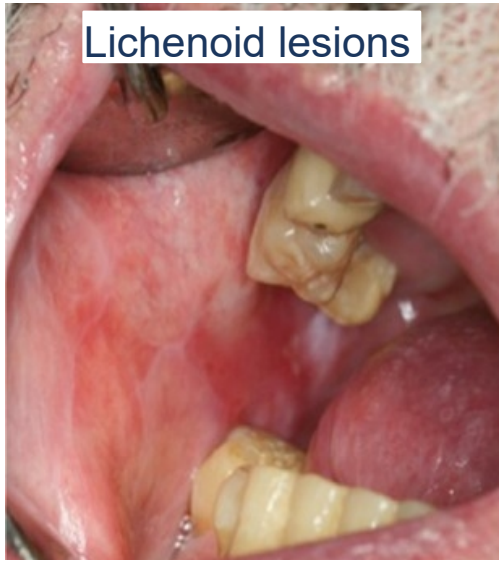








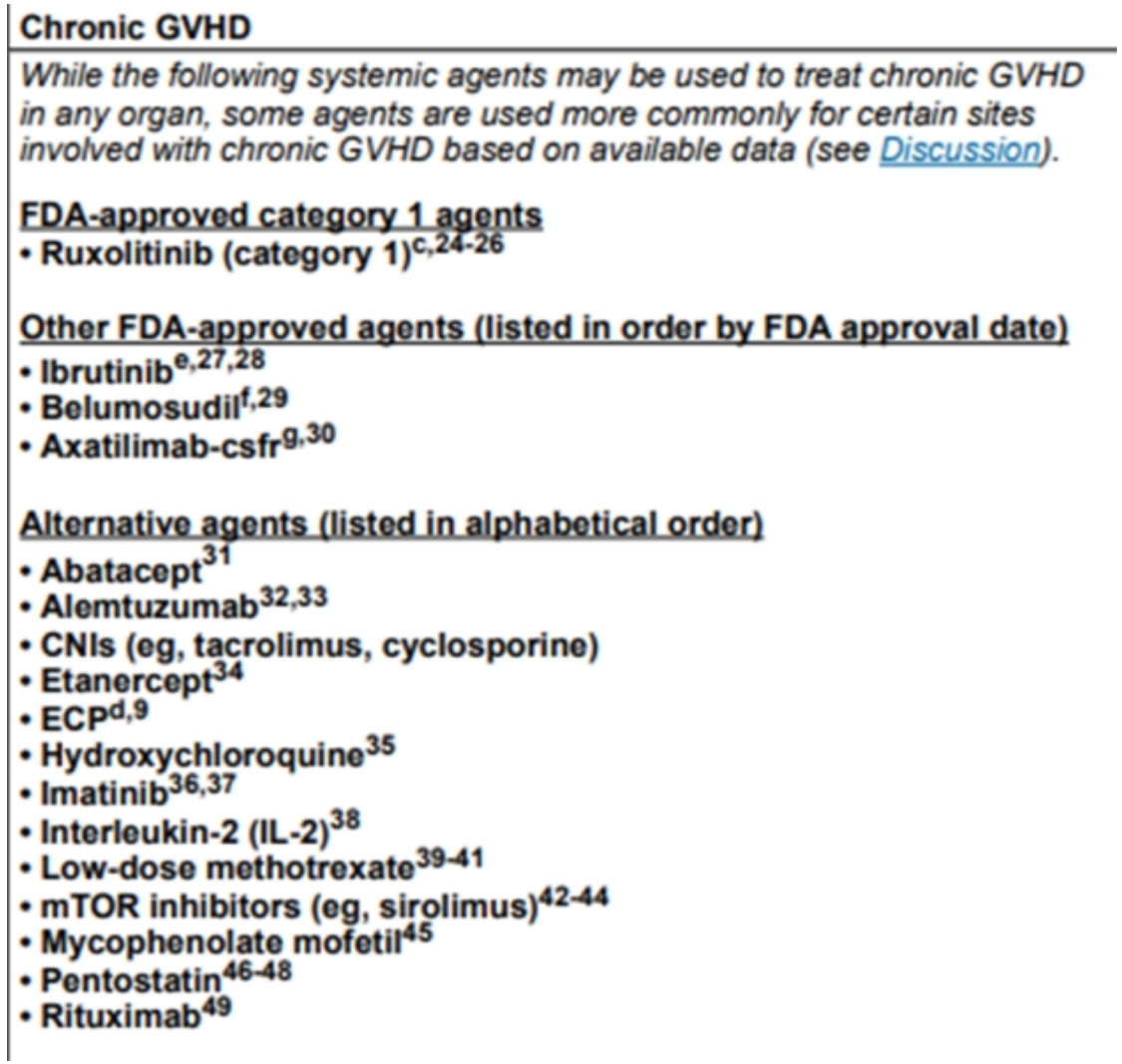




Hymes SR, et al. J Am Acad Dermatol. 2012;66:515.e1-18
Margaix-Muñoz M, et al. J Clin Exp Dent. 2015;7:e138-45

Chronic GVHD - Treatment

- Treatment is based on individual organ involvement and severity
- Oral cavity: Dexamethasone swishes
- Eyes: artificial tears, Restasis (cyclosporin) drops
- BOS: FAM
- Moderate to severe chronic GVHD
  - Systemic corticosteroids 0.5–1 mg/kg/day methylprednisolone (or equivalent prednisone dose)
- FDA approved:
  - Ibrutinib (2017)
  - Ruxolitinib (2021)
  - Belumosudil (2021)
  - Axatilimab (2024)



Chronic GVHD

While the following systemic agents may be used to treat chronic GVHD in any organ, some agents are used more commonly for certain sites involved with chronic GVHD based on available data (see Discussion).

FDA-approved category 1 agents

- Ruxolitinib (category 1)[c,24-26]

Other FDA-approved agents (listed in order by FDA approval date)

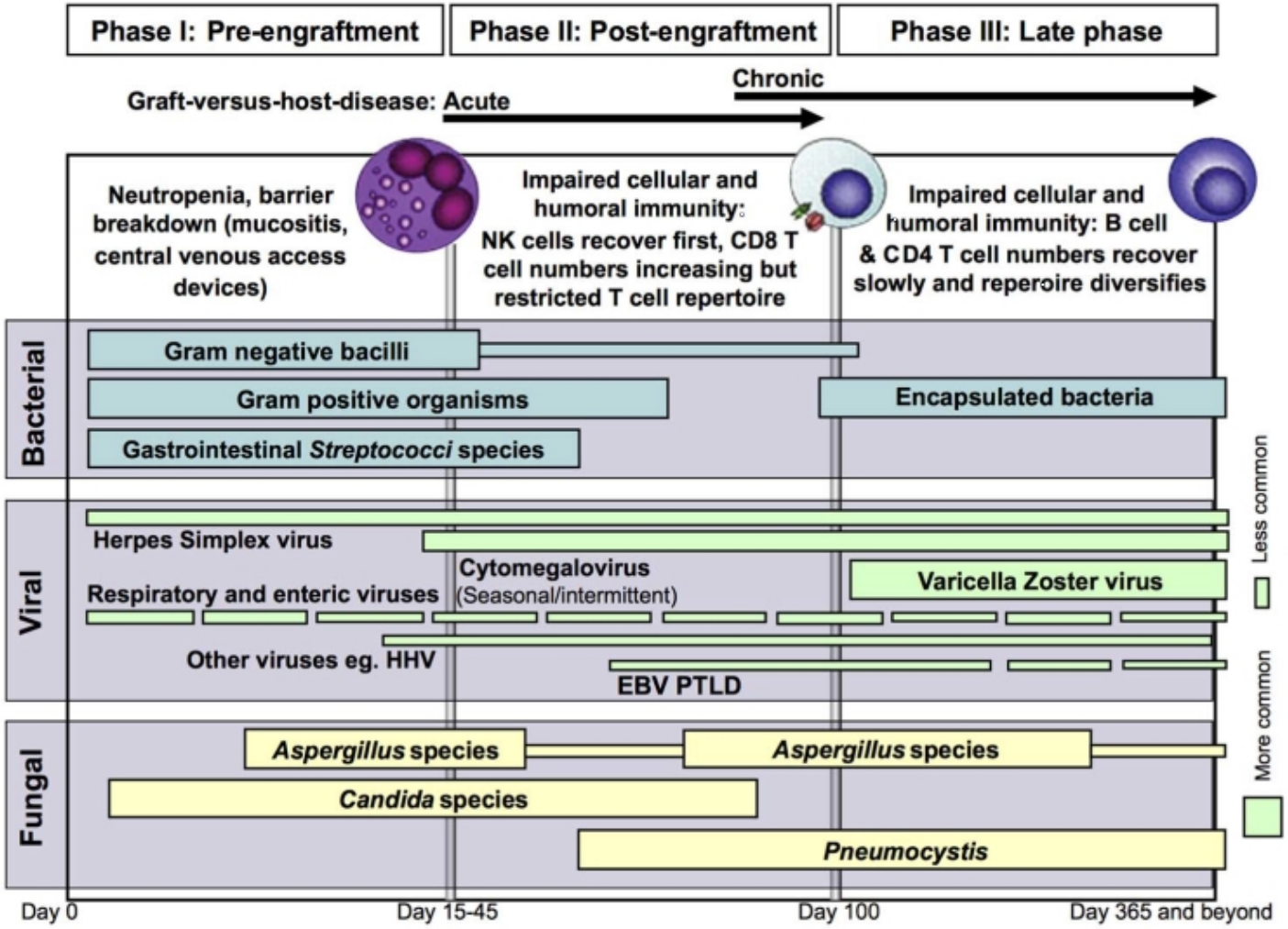
- Ibrutinib[e,27,28]
- Belumosudil[f,29]
- Axatilimab-csfr[g,30]

Alternative agents (listed in alphabetical order)

- Abatacept[31]
- Alemtuzumab[32,33]
- CNIs (eg, tacrolimus, cyclosporine)
- Etanercept[34]
- ECP[d,9]
- Hydroxychloroquine[35]
- Imatinib[36,37]
- Interleukin-2 (IL-2)[38]
- Low-dose methotrexate[39-41]
- mTOR inhibitors (eg, sirolimus)[42-44]
- Mycophenolate mofetil[45]
- Pentostatin[46-48]
- Rituximab[49]

NCCN guidelines. Hematopoietic cell transplantation

Infectious Complications



Tomblyn M, et al. Biol Blood Marrow Transplant. 2009;15:1143-238

Bacterial Infections

- Risk factors: mucosal injury, old age, intense conditioning regimens, iron overload

- Bacterial prophylaxis for severe neutropenia (ANC <500/μL)
  - Fluoroquinolones
  - Pen VK or Bactrim for encapsulated bacterial infection (chronic GVHD, eculizumab, splenectomy)

- Neutropenic fever
  - 20-30% with documented source or bacteremia
  - Empiric treatment with anti-pseudomonal antibiotics (cefepime, ceftazidime, piperacillin-tazobactam, imipenem, meropenem)
  - Add vancomycin for gram positive coverage if indicated

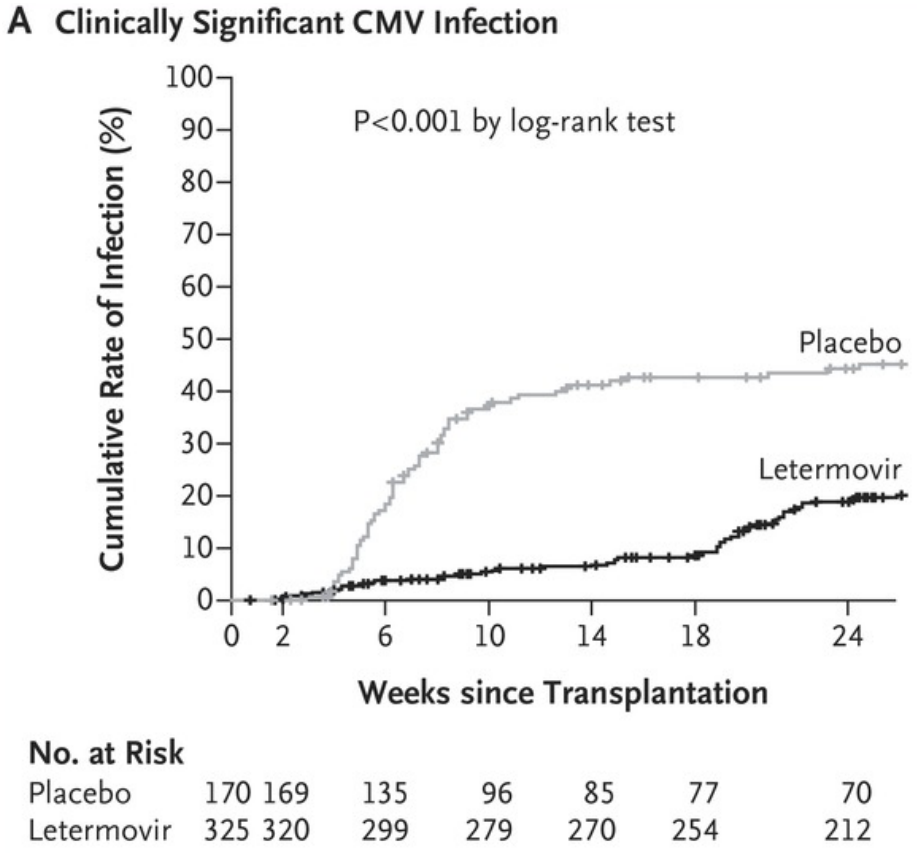
Cytomegalovirus (CMV)

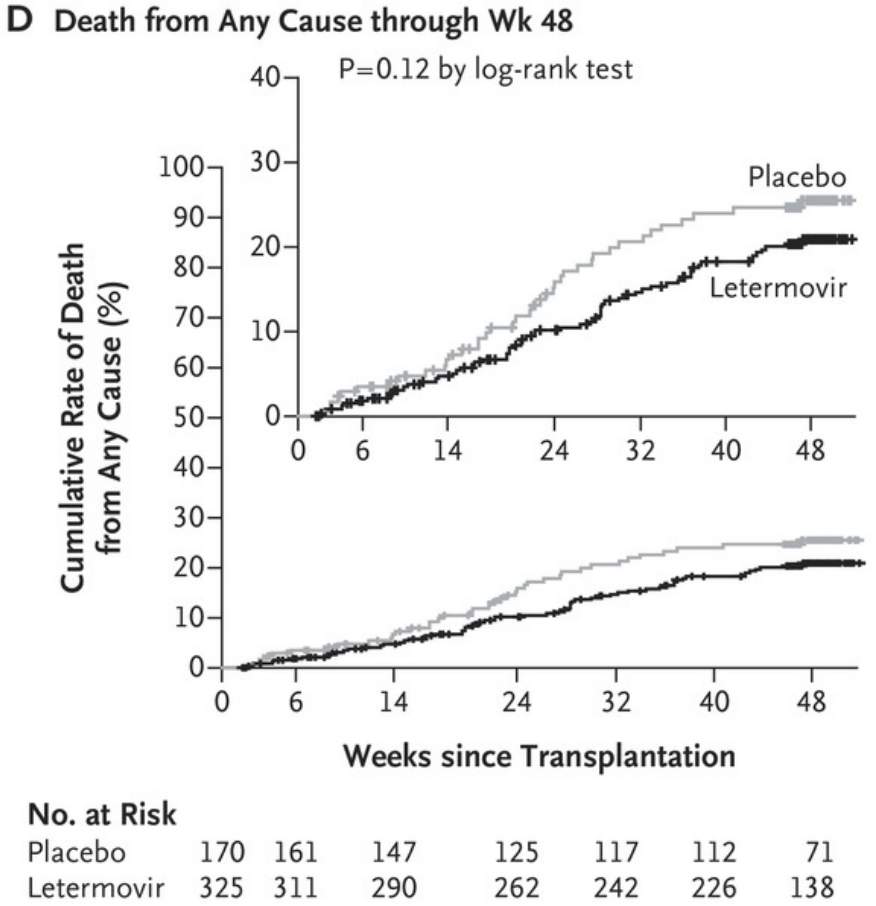
- Incidence: 40-60% allogeneic, <5% autologous
- CMV seropositive recipients – highest risk
- Asymptomatic viremia or invasive infections (pneumonia, colitis, hepatitis, retinitis)
- CMV viral load monitoring using PCR

- Prophylaxis/ prevention:
  - Letermovir (FDA approval for CMV seropositive recipient)
  - Leukocyte reduced blood products .

- CMV viremia:
  - Ganciclovir or valganciclovir (myelosuppression)
  - Foscarnet (electrolyte abnormalities, renal insufficiency)

CMV Prophylaxis





Marty FM, et al. N Engl J Med. 2017;377(25):2433-2444

Other Viral Infections

- HSV and VZV prophylaxis and treatment:
  - Acyclovir or valacyclovir
- HHV6 syndrome (encephalitis, hepatitis, skin rash, myelosuppression)
- BK virus – hemorrhagic cystitis
- Adenovirus
  - Hepatitis, gastroenteritis, pneumonitis
  - Cidofovir – nephrotoxicity, cytopenia
- RSV – Ribavirin
- Rhinovirus, influenza and parainfluenza viruses also common

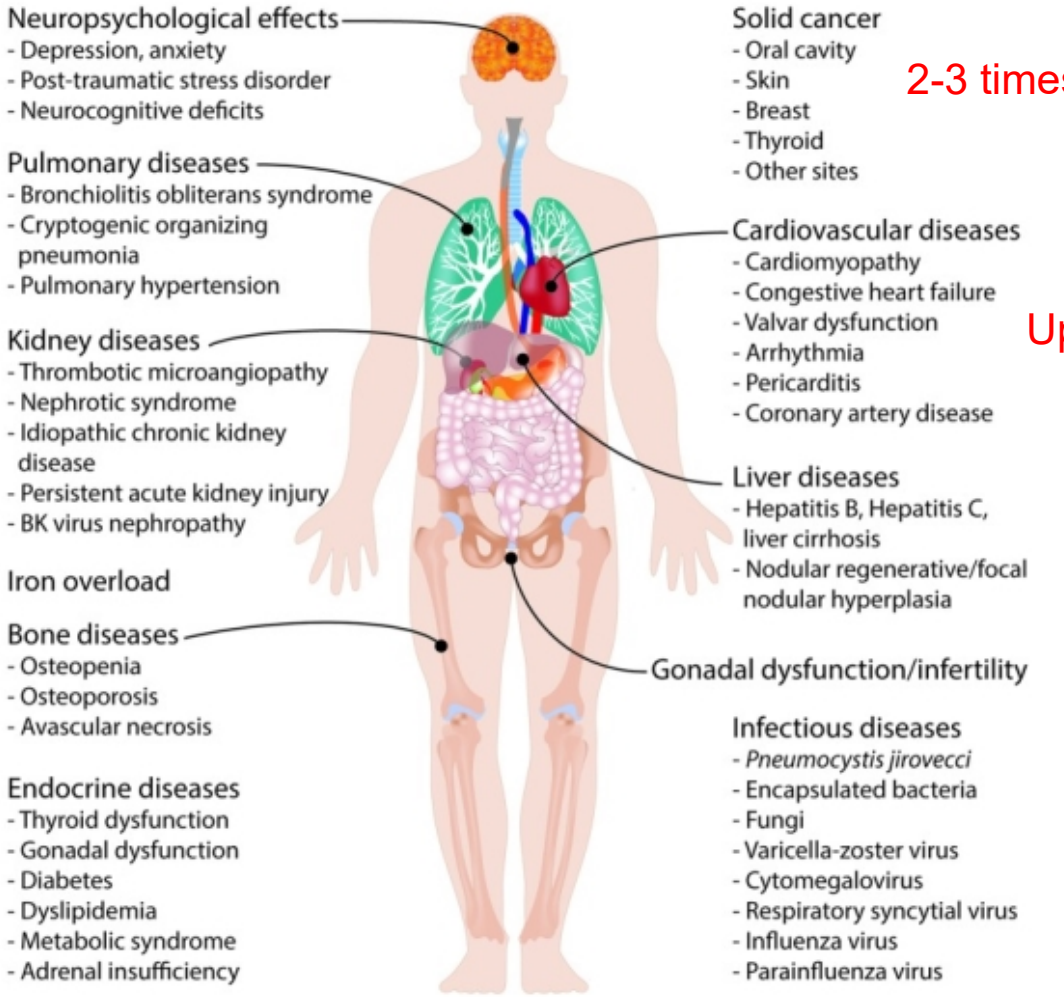
Fungal Infections (Yeast and Mold)

- Prophylaxis
  - Fluconazole
  - Posaconazole, voriconazole or isavuconazole (prolonged neutropenia, prior fungal infection, pulmonary nodules, high dose corticosteroid use)
- Invasive candidiasis
  - Neutropenia, indwelling catheter and TPN are risk factors
  - Echinocandins
- Invasive aspergillosis
  - Diagnosis based on imaging, galactomannan antigen and PCR testing
  - Posaconazole, voriconazole or isavuconazole
- Mucormycosis:
  - Amphotericin B, surgical debridement (sinus), lobectomy (lungs)
  - High mortality

Pneumocystis jirovecii (PCP)

- Bactrim
  - Preferred agent
  - Prevents toxoplasmosis
- Dapsone
  - Check G6PD before starting
  - Does not prevent toxoplasmosis
- Atovaquone
- IV or aerosolized pentamidine
  - Does not prevent toxoplasmosis

Late Effects of Transplant



2-3 times higher risk

Up to 3 times higher risk

20% HCT survivors can develop osteoporosis

Inamoto Y and Lee SJ. Haematologica 2017;102:614-625

Secondary Malignancies

- 2-3 fold increased risk of solid malignancies

- Risk factors:
  - Age
  - Underlying diagnosis
  - Previous autologous transplant (high risk of therapy related MDS and AML)
  - Lenalidomide maintenance (high risk of therapy related MDS and AML, ~5-10%)
  - Higher does of TBI and chemotherapy (alkylating agents)
  - Chronic GVHD

- Screening: annual pap smear, annual skin evaluation, annual mammogram starting age 40, colorectal cancer screening starting age 50

Post-Transplant Lymphoproliferative Disorder (PTLD)

- Associated with EBV
- High risk with T-cell depleted grafts but occurs in other types too
- Decreasing immune suppression
- First line: Rituximab
- Refractory: chemotherapy (e.g., CHOP)

Donor Lymphocyte Infusion (DLI)

- Lymphocytes from donor; fresh or previously cryopreserved
- Not an option in case of cord blood transplant
- Indications:
  - Relapse of disease (overt or MRD) to improved GVT
    - Responses are variable, higher with MRD relapse
    - CML (60-80%)
    - AML/ MDS/ ALL (20-30%)
  - Declining donor chimerism (graft failure)
- Complications:
  - Acute GVHD (50-60%)
  - Bone marrow aplasia (3-4 weeks post-DLI)

Early Complications of CAR T-Cell Therapy

- Cytokine release syndrome (CRS)
  - 2-7 days, up to 3 weeks
  - High tumor burden
  - DIC
- Immune effector cell associated neurotoxicity syndrome (ICANS)
  - Median time to onset 4 days, can last 5-17 days
  - Delayed onset – Parkinson-like symptoms (anti-BCMA CAR T-cell therapy)
- Hemophagocytic lymphohistiocytosis (HLH)
- Cytopenia

CRS Management

ASTCT consensus grade	Management
Grade 1 - Fever ≥ 38°C - No hypotension - No hypoxia	- IV hydration - Supportive care - Empiric antibiotics
Grade 2 - Fever ≥ 38°C, *and* - Hypotension without vasopressor requirement, *and/or* - Hypoxia (≤ 6 L/minute)	- As grade 1 - Tocilizumab - Dexamethasone
Grade 3 - Fever ≥ 38°C, *and* - Hypotension requiring 1 vasopressor, *and/or* - Hypoxia (≥ 6 L/minute)	- As grade 2 - Transfer to ICU - Vasopressors
Grade 4 - Fever ≥ 38°C, *and* - Hypotension requiring multiple vasopressors, *and/or* - Positive pressure ventilation	- As grade 3 - Intubation and mechanical ventilation - Pulse dose methylprednisolone

Santomasso, et al. J Clin Oncol 39, 3978-3992(2021)

ICANS Management

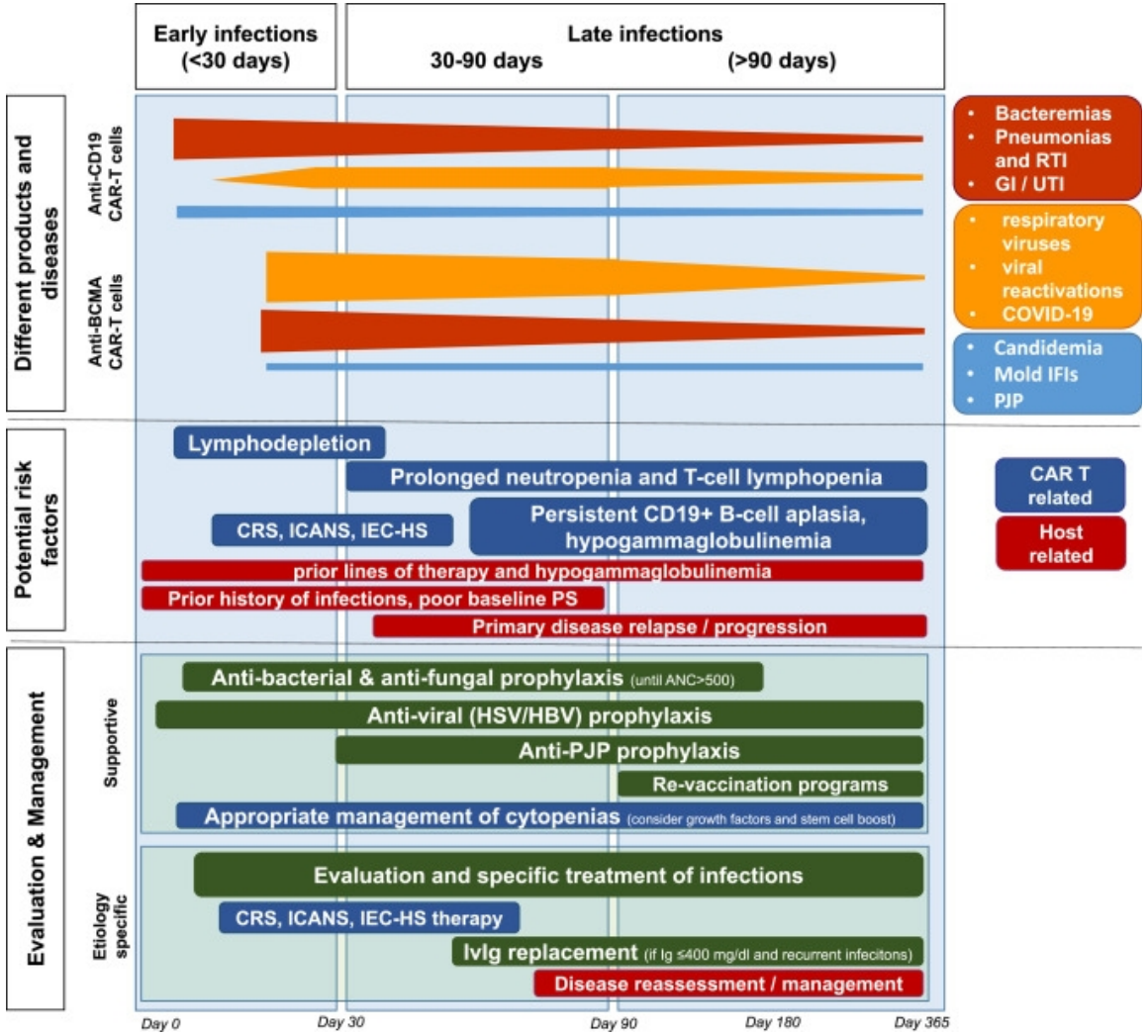
- Grading according to immune effector cell associated encephalopathy (ICE)
  - Mild – mild disorientation, inattentiveness, no depressed level of consciousness
  - Moderate – somnolence, slow to respond, disorientation to time and space
  - Severe – significant language dysfunction, mutism, severe impairment of consciousness, coma, seizures, focal neurological deficits, cerebral edema

- Treatment:
  - Tocilizumab
  - Dexamethasone, high dose methylprednisolone (severe cases)
  - Anakinra (refractory cases)
  - Seizure prophylaxis
  - ICU, mechanical ventilation

Santomasso, et al. J Clin Oncol 39, 3978-3992(2021)

CAR T-Cell Therapy – Infectious Prophylaxis

- Influenza and COVID vaccination
- Antiviral and PCP prophylaxis for 6-12 months
- Antifungal prophylaxis – corticosteroids for CRS or ICANS
- B-cell aplasia – hypogammaglobulinemia
  - Replete for IgG < 400 if frequent infections



Shahid S, et al. Transplant Cell Ther. 2024 Oct;30(10):955-969

Question 1

A 25-year-old male is an HLA-match for his brother who requires an allogeneic transplant for acute myeloid leukemia. The donor is nervous about going to the operating room and wonders if he might elect to donate peripheral blood instead. His consenting physician tells him which of the following is an advantage to using bone marrow over peripheral blood for allogeneic hematopoietic cell transplantation?

A. Patients receiving bone marrow engraft faster since there are more stem cells in the bone marrow product than in peripheral blood.
B. Patients receiving bone marrow have a lower incidence of graft rejection because they receive a higher stem cell dose.
C. Patients receiving bone marrow have less chronic graft versus host disease due to decreased numbers of lymphocytes in the bone marrow product.
D. Donors providing bone marrow recover significantly faster because they are not exposed to G-CSF.

Answer

C. Patients receiving bone marrow have less chronic graft versus host disease due to decreased numbers of lymphocytes in the bone marrow product.

Due to increased T-lymphocytes in the peripheral blood stem cell product, patients receiving peripheral blood stem cell transplants have a higher risk of chronic GVHD than those receiving bone marrow. Patients receiving peripheral blood stem cells engraft up to 1 week faster than bone marrow recipients. Because peripheral blood has a higher stem cell dose, there is a lower risk of graft rejection. There is no data to show that donors providing bone marrow recover faster than those receiving GCSF.

Question 2

A 45-year-old female with newly diagnosed AML with monosomy 7 who achieved complete remission following daunorubicin and cytarabine (3 + 7) induction. She then received high dose cytarabine consolidation prior to proceeding to a fully HLA matched sibling (brother) donor allogeneic transplant. Her conditioning regimen was myeloablative busulfan and cyclophosphamide. For graft vs host disease prophylaxis, she started on tacrolimus and received 4 doses of methotrexate on days 1, 3, 6 and 11. Currently, she is day 14 and has been complaining of right upper quadrant abdominal pain for the past 24 hours. She has not engrafted yet but her absolute neutrophil count is 0.3. Her total bilirubin is 3.1 mg/dl. Liver enzymes are normal. Her serum creatinine is 1.7 mg/dl. Tacrolimus level is 8.2 ng/ml (therapeutic). Abdominal US showed normal gall bladder, liver measuring 14 cm and ascites. She had been taking ursodiol. What is the next best management?

A. Start corticosteroids for acute liver GVHD
B. Start Defibrotide for VOD
C. Start corticosteroids for engraftment syndrome
D. Closely observe, this is methotrexate induced liver toxicity
E. Reduce tacrolimus dose as this is tacrolimus induced nephrotoxicity

Answer

B. Start Defibrotide for VOD

She meets the criteria for diagnosis of VOD (onset within 21 days, hyperbilirubinemia, painful hepatomegaly and ascites). In addition, she has renal dysfunction in the setting of VOD which should be treated with defibrotide. Early initiation of defibrotide reduces mortality. GVHD is unlikely prior to engraftment. Engraftment syndrome generally presents with fever, skin rash and evidence of fluid overload, and therefore unlikely to be the cause in her case. Methotrexate can cause liver dysfunction but her constellation of symptoms fit VOD. Tacrolimus level is therapeutic, so tacrolimus induced nephrotoxicity is less likely. Moreover, hyperbilirubinemia would not be explained by tacrolimus.

Question 3

A 67-year-old male is 42 days status post HLA matched unrelated donor peripheral blood stem cell transplant for high-risk B-ALL. His conditioning regimen was cyclophosphamide and 12 Gy TBI. His graft vs host disease prophylaxis was tacrolimus and methotrexate. He achieved neutrophil engraftment and largely recovered from gastrointestinal regimen related toxicities. He now presents to the clinic with 2-day history of new onset large volume diarrhea 7-8 times per day. He is admitted to the hospital where infectious workup is negative. A flexible sigmoidoscopy is performed which shows moderate to severe GVHD of the colon with many apoptotic cells and cryptic abscess. His stool volume is recorded at 1700 ml in 24 hours. He does not report nausea, vomiting or poor appetite. He does not have any skin rash and liver function is normal. What would be the next step in management of his acute GVHD?

A. Start 0.5 mg/kg/day methylprednisolone
B. Start ruxolitinib 10 mg twice daily
C. Start 2 mg/kg/day methylprednisolone
D. Start budesonide and hold systemic corticosteroids
E. Start loperamide

Answer

C. Start 2 mg/kg/day methylprednisolone

He has grade III acute GVHD of the lower GI tract. The standard treatment for grade III acute GVHD is 2 mg/kg/day methylprednisolone. Lower methylprednisolone dose (0.5-1 mg/kg/day) are used for grade I and II GVHD. Ruxolitinib was proven to be effective in REACH2 clinical trial as a treatment for steroid refractory acute GVHD and is FDA approved for this indication. Ruxolitinib would not be indicted for frontline therapy for acute GVHD. Budesonide is usually added to systemic steroids not as standalone treatment for grade III acute GVHD. Loperamide will not treat GVHD.

Fred Hutch Cancer Center

Thank you