Early Complications of Allogeneic Stem Cell Transplantation

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Objectives

1. Briefly describe the process of allogeneic stem cell transplantation (alloHSCT)
2. Determine indications and conditioning regimens for alloHSCT
3. Manage and/or prevent complications following alloHSCT
    a. veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS),
    b. HSV/VZV,
    c. CMV,
    d. EBV,
    e. PJP,
    f. invasive fungal infections,
    g. graft-versus-host-disease (GvHD), and
    h. revaccination
4. Identify situations where non-hematology pharmacists can intervene and offer supportive care to patients who have undergone alloHSCT

Objectives

"Here's a little ditty about family, pollution, racism, friendship, war, sex, poverty, education, religion, love, bullying, homelessness, puppies, healthcare, the climate, parenting, inequality, hope, hunger, beauty, politics, the future, labor, justice, the Chicago Cubs, censorship, change, loneliness, and a longing so deeply profound that words cannot express it. And it goes a little something like this…"

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Q1: What does your practice/specialty look like?

1. Primarily inpatient **internal medicine**
2. Primarily inpatient **surgical care** (post-op unit)
3. Primarily inpatient **critical care** (including emergency)
4. Primarily **oncology care** (including inpatient or outpatient)
5. Primarily **ambulatory clinic** setting
6. Primarily **consult service** (eg infectious diseases, thrombosis, pharmacokinetics)
7. More than one from above (eg I **rotate** between multiple areas)
8. I'm a pharmacy **technician/assistant**
9. I'm a **learner** (student, intern, resident, postgrad, just starting career)
10. I'm a **manager** or higher
11. I'm **not an active** direct patient-care pharmacist
12. Other? Or TL/DR?

Not differentiating between **adult and pediatric** pharmacists
Pharmacy technicians that align with any specialty should select that specialty

Q2: Do you provide care for transplant patients of any kind?

1. I regularly provide care to **heart** transplant patients
2. I regularly provide care to **liver** transplant patients
3. I regularly provide care to **lung** transplant patients
4. I regularly provide care to **renal** transplant patients
5. I regularly provide care to **stem cell** transplant patients
6. I regularly provide care to **all sorts of** transplant patients
7. Not regularly, but I occasionally see a transplant patient come my way (~1-2/month)
8. No, I rarely am involved in the care of a transplant patient (~1-5/year)

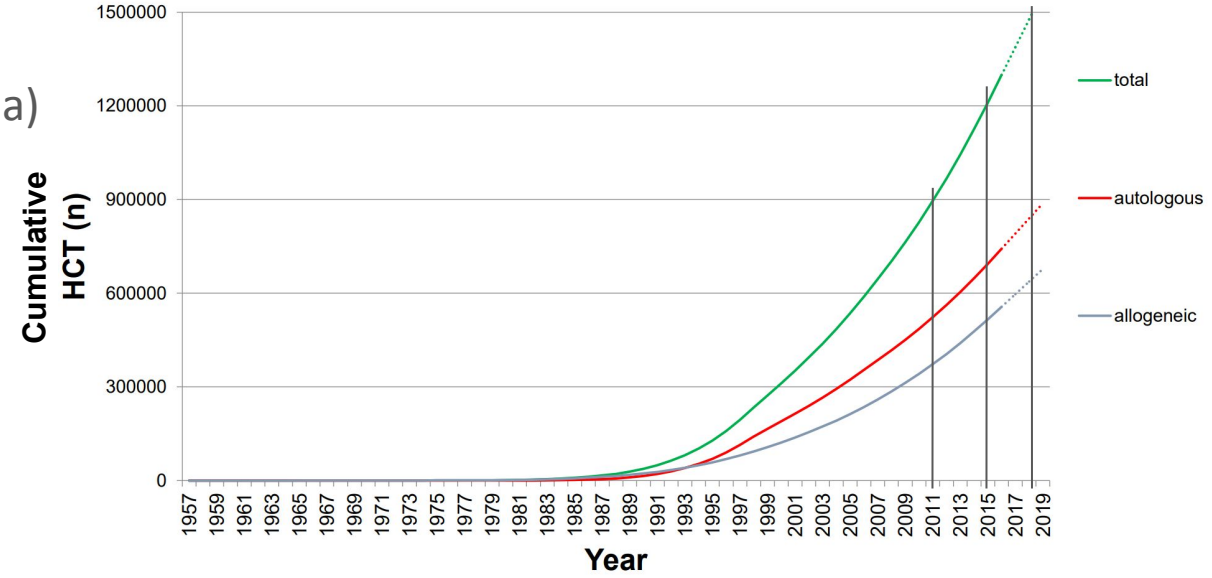
Stem Cell Transplantation in Numbers

Number of transplants: Waiting for Canadian/Ontario numbers from CTTC and CCO, but

~80,000-90,000 transplants/yr (world)

~20,000 transplants/yr (US)

~2,000 transplants/yr (Canada)



Niederwieser D *et al*. Haematologica 2022 May 1; 107 (5): 1045-1053

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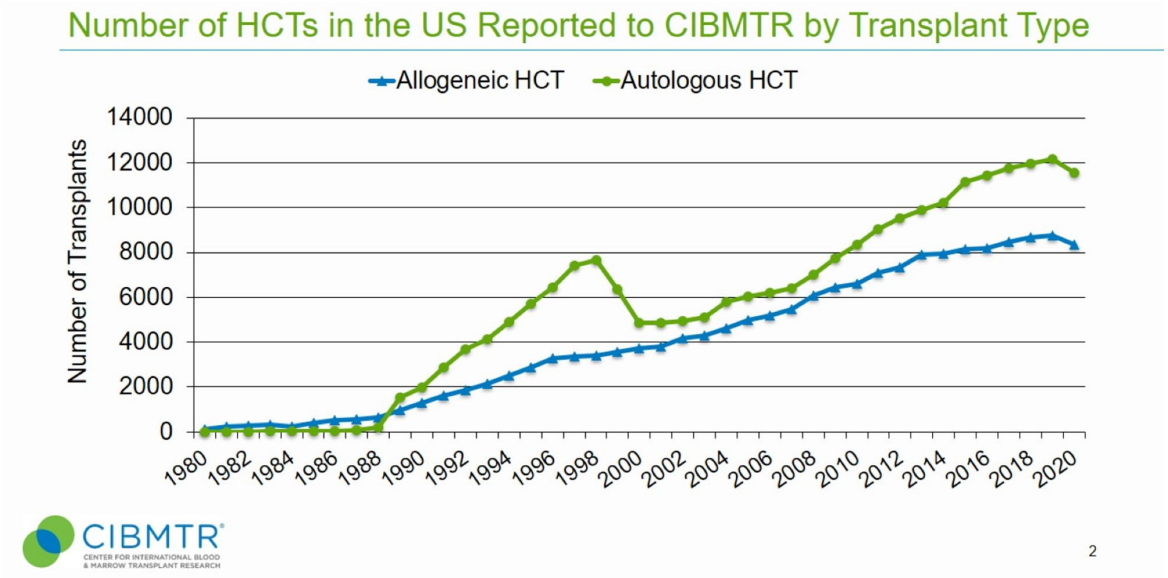

Auletta JJ *et al*. Center for International Blood and Marrow Transplant Research (CIBMTR) 2021 US summary slides

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Table 2: Transplants Performed within Ontario and Out of Country, Year-Over-Year Volumes

HCT Type	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
Transplants Performed within Ontario								
Autologous (including Day 1 transfers)*	405	383	394	478	505	538	590	632
Allogeneic-related	80	81	79	65	78	91	116	137
Allogeneic-unrelated	79	77	104	104	120	115	138	144
Total Ontario	564	541	577	647	703	744	844	913

Cancer Care Ontario. Complex Malignant Hematology Services in Ontario: Year in Review 2017 Jun

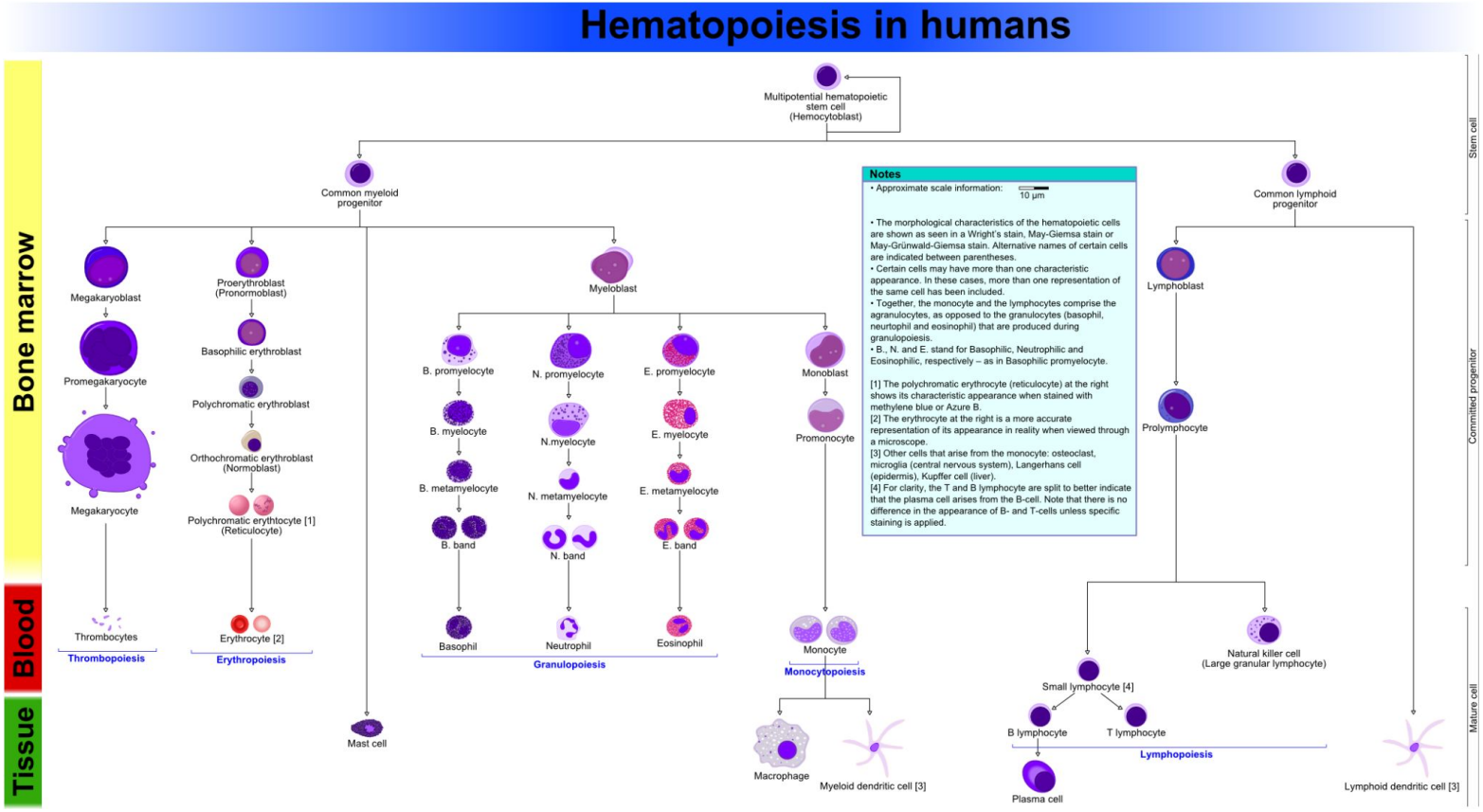
Types of Stem Cell Transplantation

BMT = bone marrow transplantation (now blood & marrow transplantation)

SCT = stem cell transplantation

HCT/HSCT = hematopoietic (stem) cell transplantation

Hematopoiesis

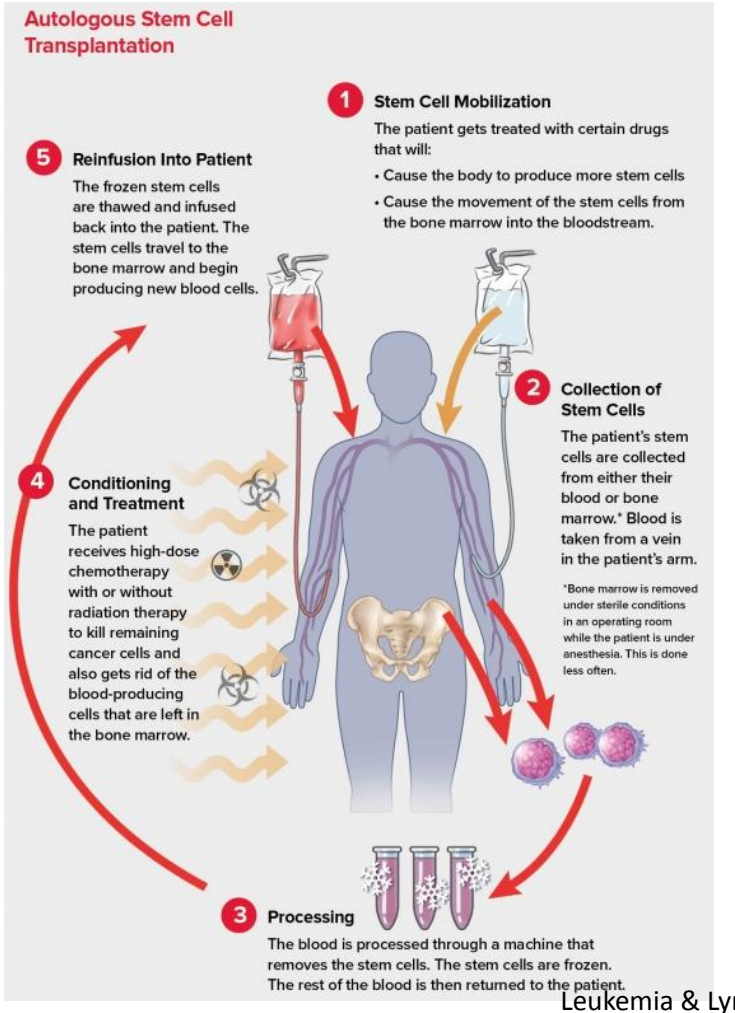


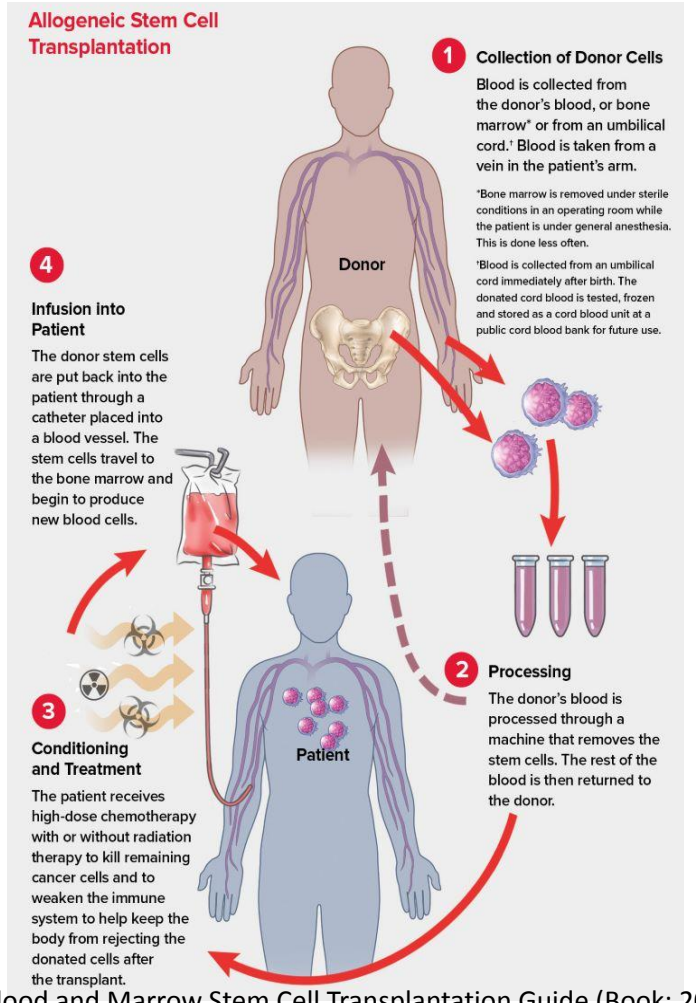
Types of Stem Cell Transplantation

Autologous (*auto-* = ‘self’)
derived from the **same individual**

Allogeneic (*allo-* = ‘different’ or ‘other’)
involving, derived from, or being individuals of the **same species that are sufficiently unlike genetically** to interact antigenically

Syngeneic (*syn-* = ‘identical’)
involving, derived from, or being **genetically identical or similar individuals** of the same species especially with respect to antigenic interaction





Leukemia & Lymphoma Society. Blood and Marrow Stem Cell Transplantation Guide (Book; 2019)

Autologous vs Allogeneic Stem Cell Transplantation

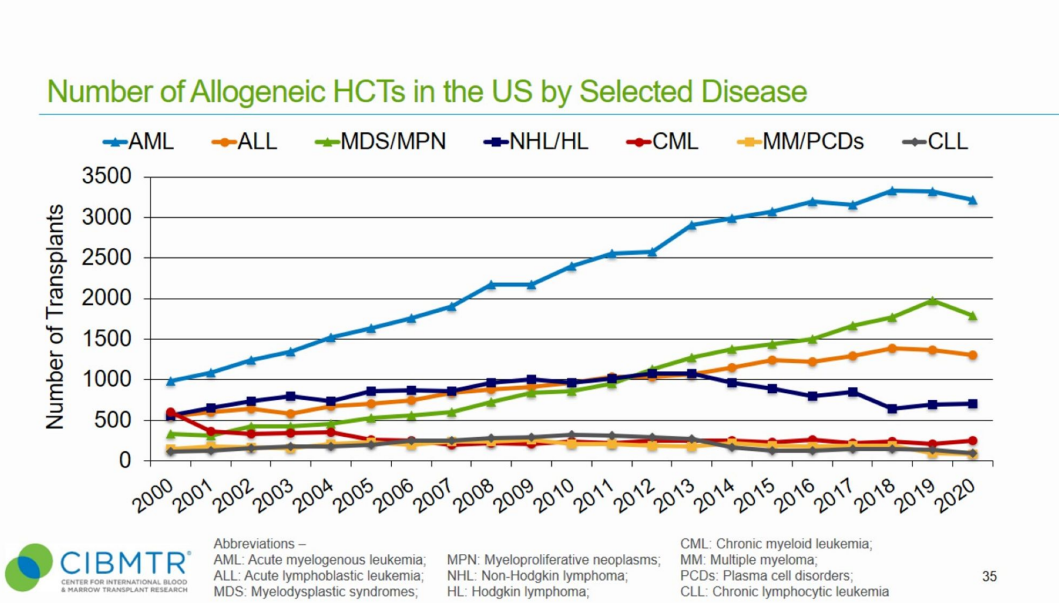
	Autologous Transplant	Allogeneic Transplant
Stem cell source	Patient	Healthy donor
Indications	Lymphoma, Myeloma	Leukemia, Lymphoma
Goal	Ability to deliver high doses of chemotherapy Assist recovery from chemotherapy with fresh stem cells	Replace malignant stem cells with healthy stem cells Create an immune response directed against remaining malignant cells
Complications	Infections (feb neutropenia) Chemotherapy toxicities	Same + more infections (viral, fungal) Graft-versus-host disease
Mortality (TRM)	<1-2%	25-40%

Allogeneic Stem Cell vs Solid Organ Transplantation

	Solid Organ Transplant	Allogeneic Stem Cell Transplant
Graft (transplanted 'organ')	Heart, kidney, liver, lung, etc	Hematopoietic stem cells
Immune system	From the patient	From the donor
Remaining organ systems	From the patient	From the patient
Complications	Graft rejection	Graft-versus-host disease
Immunosuppression	Lifelong?	Temporary!

Indications for Allogeneic Stem Cell Transplantation

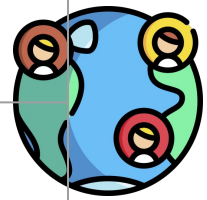
Acute lymphoblastic leukemia (ALL)
Acute myeloid leukemia (AML)
Aplastic anemia (AA)
Chronic lymphocytic leukemia (CLL)
Chronic myeloid leukemia (CML)
Hodgkin's lymphoma (HL)
Multiple myeloma (MM/PCD)
Myelodysplastic syndrome (MDS)
Myeloproliferative neoplasm (MPN)
Non-Hodgkin's lymphoma (NHL)



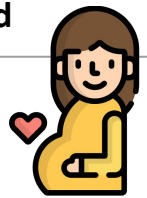
Auletta JJ *et al*. Center for International Blood and Marrow Transplant Research (CIBMTR) 2021 US summary slides

Source of allogeneic stem cells (Donor selection)

		Probability of a ‘match’
Matched related donor (MRD)	Sibling with identical HLA	25%
Matched unrelated donor (MUD)	Donor from international registry with identical HLA	25-80% (?)
Mismatched unrelated donor (MMUD)	Donor from international registry with near identical HLA	25-50% 65-97% (MUD or MMUD)
Haploidentical donor	Family member sharing ½ HLA	100%
Umbilical cord blood	Identical/near-identical HLA	



alternative donors

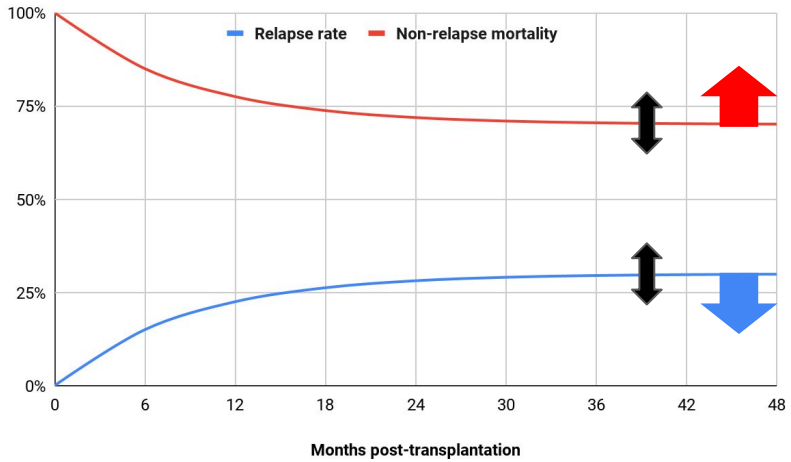


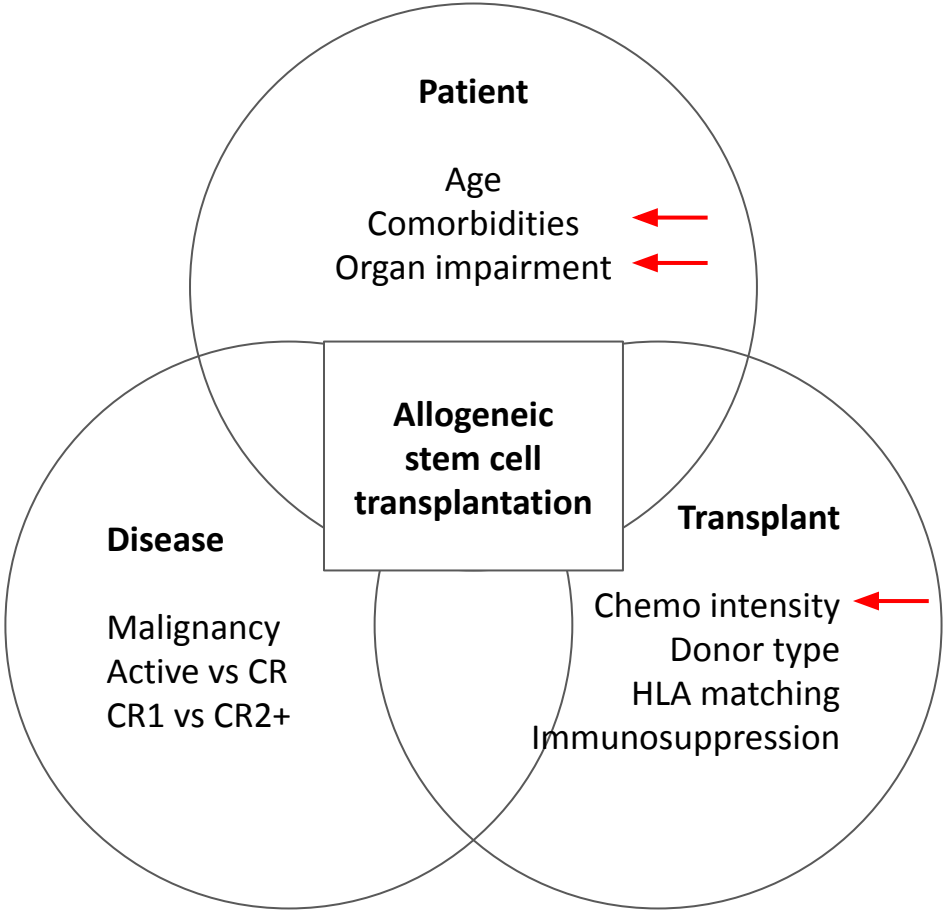
Risk factors prior to alloHSCT

Patient-related factors

Disease-related factors

Intervention- (transplant-) related factors

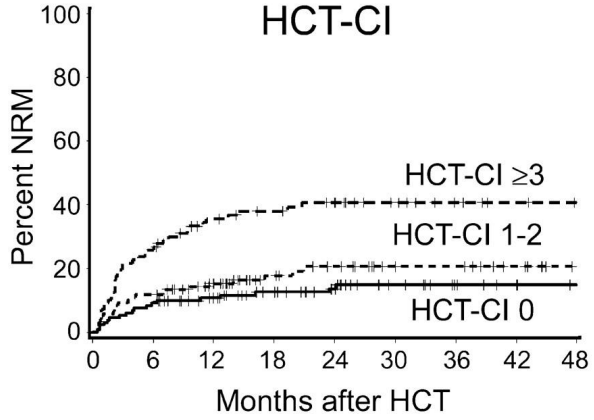


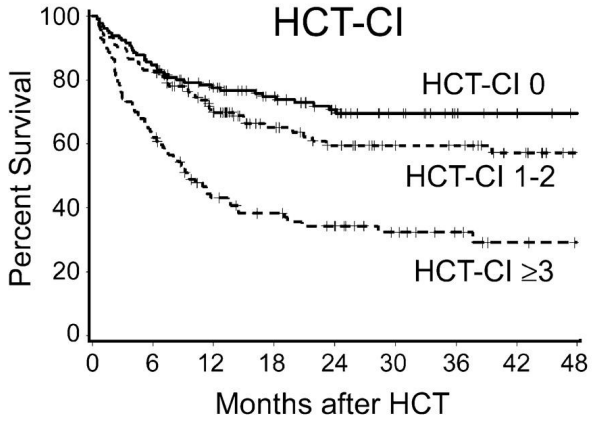


Comorbidities prior to alloHSCT

Table 1. HCT-CI

Comorbidities	HCT-CI scores
Arrhythmia	1
Cardiovascular comorbidity	1
Inflammatory bowel disease	1
Diabetes or steroid-induced hyperglycemia	1
Cerebrovascular disease	1
Psychiatric disorder	1
Mild hepatic comorbidity	1
Obesity	1
Infection	1
Rheumatologic comorbidity	2
Peptic ulcer	2
Renal comorbidity	2
Moderate pulmonary comorbidity	2
Prior malignancy	3
Heart valve disease	3
Moderate/severe hepatic comorbidity	3
Severe pulmonary comorbidity	3
	Total score = _____





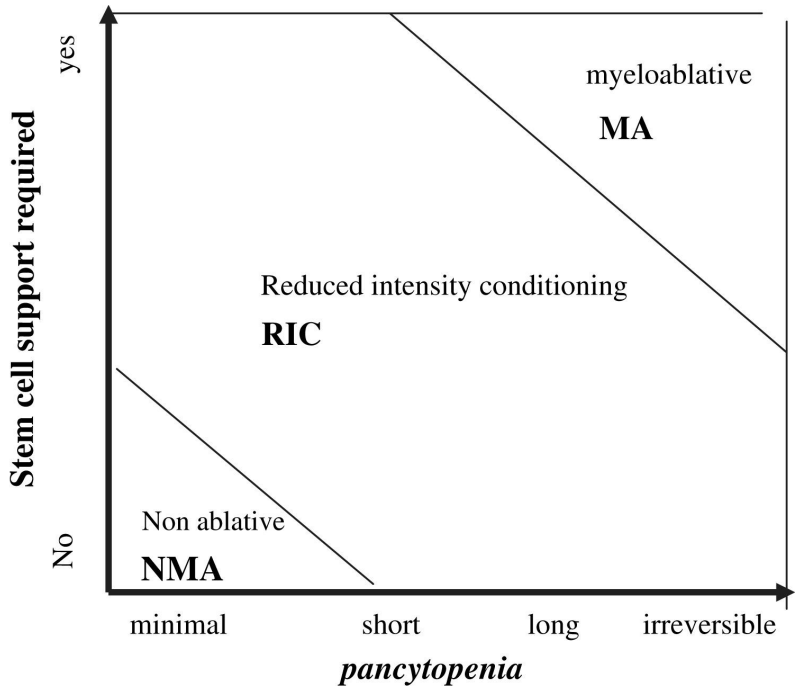
Sorror ML *et al*. Blood 2005 Oct 15; 106 (8): 2912-2919

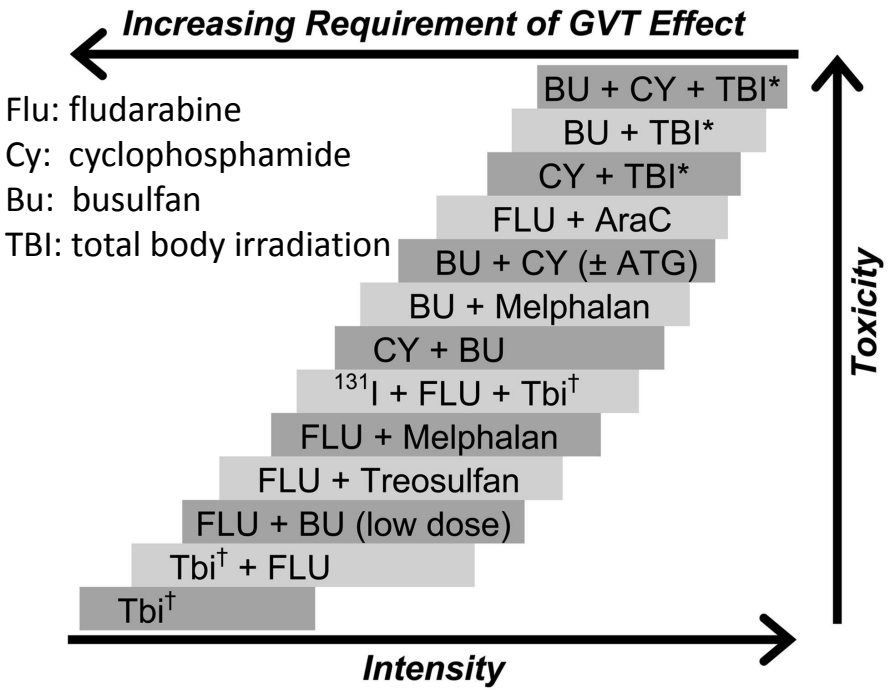
Table 4. Definitions of comorbidities included in the HCT-CI and HCT-CI scores compared with original CCI scores

Comorbidity	Definitions of comorbidities included in the new HCT-CI	HCT-CI weighted scores	Original CCI scores*
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1	0
Cardiac‡	Coronary artery disease,§ congestive heart failure, myocardial infarction, or EF $\leq$ 50%	1	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1	0
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1	1
Psychiatric disturbance†	Depression or anxiety requiring psychiatric consult or treatment	1	Not included
Hepatic, mild‡	Chronic hepatitis, bilirubin $>$ ULN to 1.5 $\times$ ULN, or AST/ALT $>$ ULN to 2.5 $\times$ ULN	1	1
Obesity†	Patients with a body mass index $>$ 35 kg/m^2	1	Not included
Infection†	Requiring continuation of antimicrobial treatment after day 0	1	Not included
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2	1
Peptic ulcer	Requiring treatment	2	1
Moderate/severe renal‡	Serum creatinine $>$ 2 mg/dL, on dialysis, or prior renal transplantation	2	2
Moderate pulmonary‡	DLco and/or FEV_1 66%-80% or dyspnea on slight activity	2	1
Prior solid tumor‡	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3	2
Heart valve disease	Except mitral valve prolapse	3	0
Severe pulmonary‡	DLco and/or $FEV_1 \leq$ 65% or dyspnea at rest or requiring oxygen	3	1
Moderate/severe hepatic‡	Liver cirrhosis, bilirubin $>$ 1.5 $\times$ ULN, or AST/ALT $>$ 2.5 $\times$ ULN	3	3

Sorror ML *et al*. Blood 2005 Oct 15; 106 (8): 2912-2919; Sorror ML. Blood 2013 Apr 11; 121 (15): 2854-2863

Intensity of conditioning chemotherapy regimens





Bacigalupo A *et al*. Biol Blood Marrow Transplant 2009 Dec; 15 (12): 1628-1633; Gyurkocza B & Sandmaier BM. Blood 2014 Jul 17; 124 (3): 344-353

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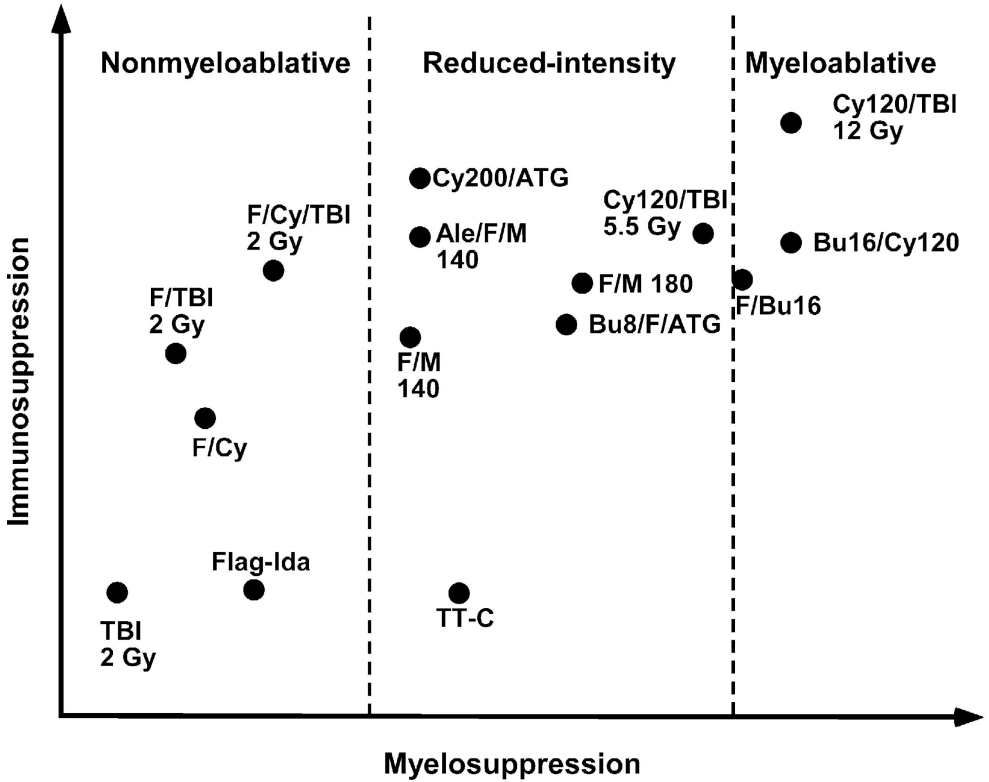


Increasing HLA mismatch

Increasing aggressiveness of malignancy

F: fludarabine
Cy: cyclophosphamide
Bu: busulfan
M: melphalan
TBI: total body irradiation

Baron F & Storb R. Mol Ther 2006 Jan; 13 (1): 26-41

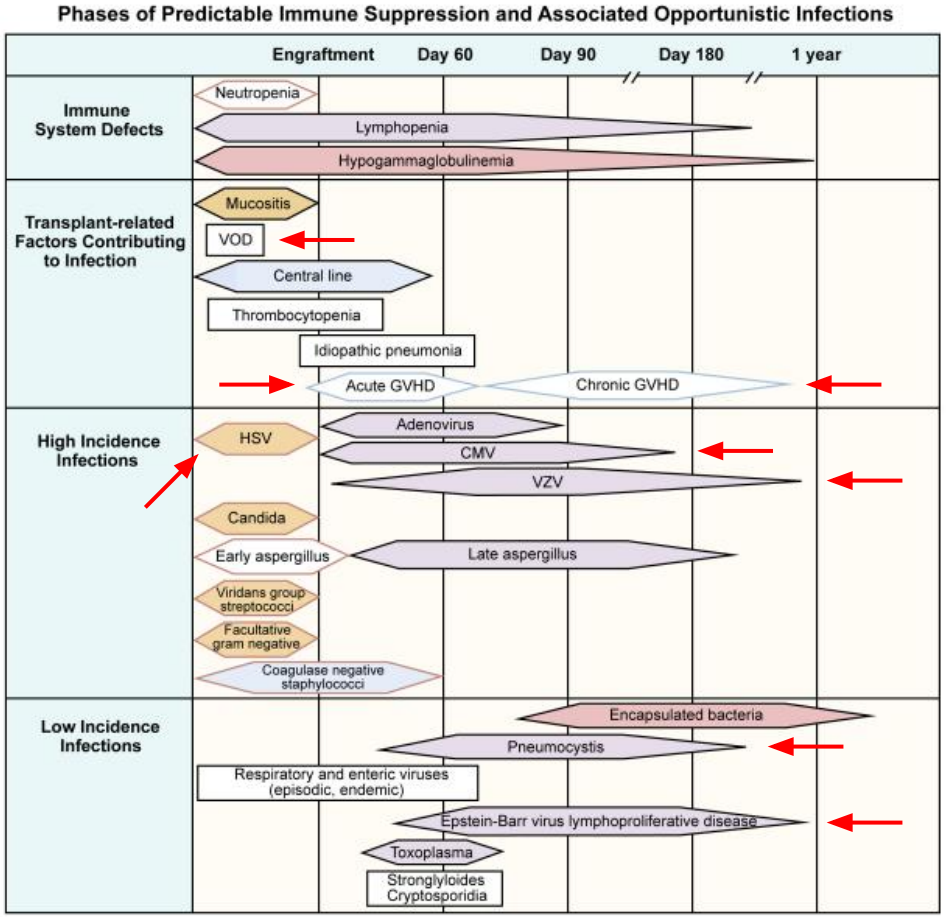
Complications of alloHSCT

Transient/temporary risks

Overlapping periods

"Management" includes:

- surveillance
- prophylaxis
- treatment



PDQ Pediatric Treatment Editorial Board. 2022 Feb 11. In: PDQ Cancer Information Summaries, National Cancer Institute
Available from: https://www.ncbi.nlm.nih.gov/books/NBK577669/

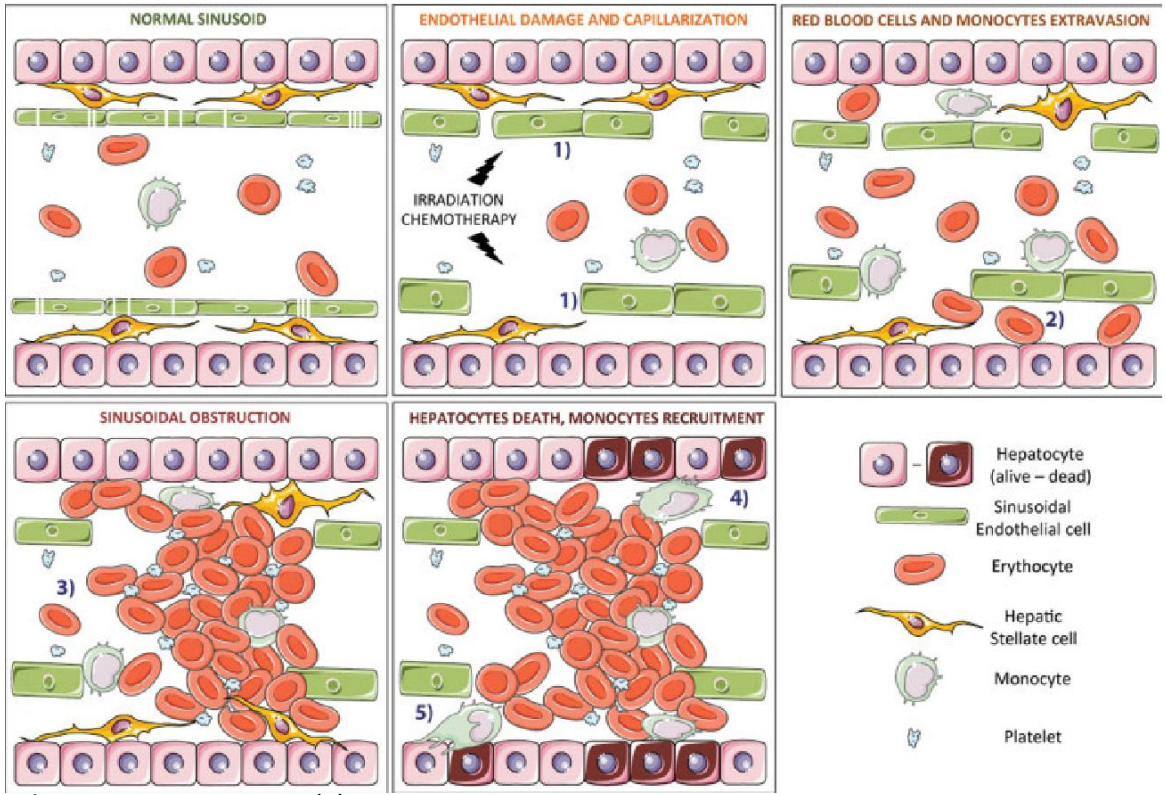
Veno-occlusive disease or Sinusoidal obstruction syndrome

Veno-occlusive disease or Sinusoidal obstruction syndrome

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS) is an early complication of allogeneic transplant conditioning regimens

May also occur with other intense/high-dose chemotherapy regimens (eg leukemia remission induction chemotherapy or autologous stem cell transplant)

Veno-occlusive disease or Sinusoidal obstruction syndrome



Vion AC *et al*. Semin Thromb Hemost 2015 Sep; 41 (6): 629-643

VOD/SOS risk factors

Table 1. Risk factors for SOS/VOD

Transplant-related factors
- Unrelated donor
- HLA-mismatched donor
- Non T-cell-depleted transplant
- Myeloablative-conditioning regimen
- Oral or high-dose busulfan-based regimen
- High-dose TBI-based regimen
- Second HCT

Patient and disease-related factors
- Older age
- Karnofsky score below 90%
- Metabolic syndrome
- Female receiving norethisterone
- Advanced disease (beyond second CR or relapse/refractory)
- Thalassemia
- Genetic factors (GSTM1 polymorphism, C282Y allele, *MTHFR* 677CC/1298CC haplotype)

Hepatic-related
- Transaminases >2.5 ULN
- Serum bilirubin >1.5 ULN
- Cirrhosis
- Active viral hepatitis
- Abdominal or hepatic irradiation
- Previous use of gemtuzumab ozogamicin or inotuzumab ozogamicin
- Hepatotoxic drugs
- Iron overload

Mohty M *et al*. Bone Marrow Transplant 2016 Jul; 51 (7): 906-912

VOD/SOS diagnostic criteria

Table 2. New EBMT criteria for SOS/VOD diagnosis in adults

Classical SOS/VOD In the first 21 days after HSCT	*Late onset SOS/VOD* >21 Days after HSCT
Bilirubin ⩾2 mg/dL and two of the following criteria must be present:	Classical VOD/SOS beyond day 21 OR
Painful hepatomegaly	Histologically proven SOS/VOD
Weight gain >5%	OR
Ascites	Two or more of the following criteria must be present: Bilirubin ⩾2 mg/dL (or 34 μmol/L) Painful hepatomegaly Weight gain >5% Ascites AND Hemodynamical or/and ultrasound evidence of SOS/VOD

Mohty M *et al*. Bone Marrow Transplant 2016 Jul; 51 (7): 906-912

VOD/SOS severity grading

Table 3. New EBMT criteria for severity grading of a suspected SOS/VOD in adults

	Mild[a]	*Moderate*[a]	*Severe*	*Very severe - MOD/MOF*[b]
Time since first clinical symptoms of SOS/VOD[c]	>7 Days	5–7 Days	⩽4 Days	Any time
Bilirubin (mg/dL) Bilirubin (μmol/L)	⩾2 and <3 ⩾34 and <51	⩾3 and <5 ⩾51 and <85	⩾5 and <8 ⩾85 and <136	⩾8 ⩾136
Bilirubin kinetics			Doubling within 48 h	
Transaminases	⩽2 × normal	> 2 and ⩽5 × normal	>5 and ⩽8 × normal	>8 × Normal
Weight increase	< 5%	⩾5% and <10%	⩾5% and <10%	⩾10%
Renal function	<1.2 × baseline at transplant	⩾1.2 and <1.5 × baseline at transplant	⩾1.5 and <2 × baseline at transplant	⩾2 × baseline at transplant or others signs of MOD/MOF

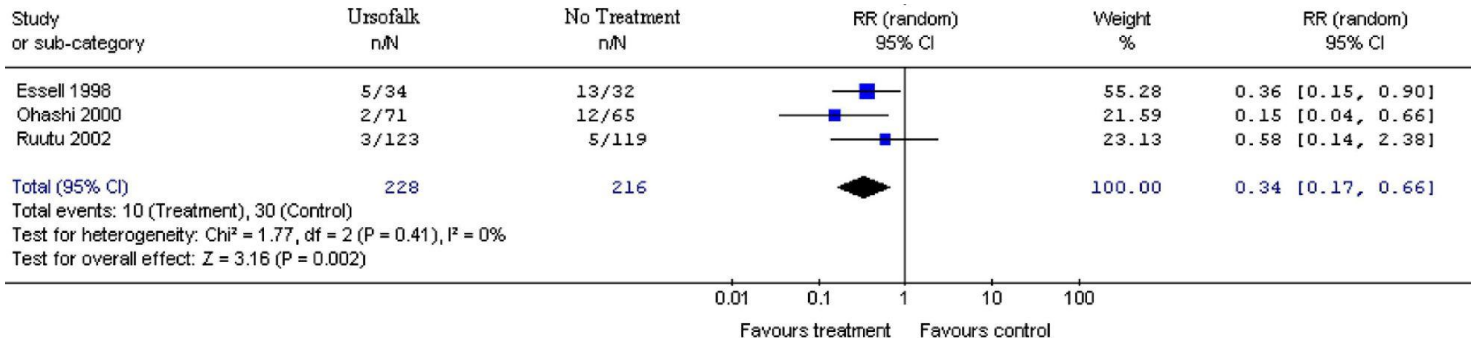
Important (maybe obvious):

Patient must meet diagnostic criteria for VOD/SOS prior to grading the severity!

Mohty M *et al*. Bone Marrow Transplant 2016 Jul; 51 (7): 906-912

Ursodiol for prophylaxis of VOD/SOS

Ursodeoxycholic acid (ursodiol) has been evaluated in 3 prospective randomized trials; two showed a decreased incidence of VOD/SOS and one did not. A meta-analysis of all three trials also showed a decreased incidence of VOD/SOS



In addition, ursodiol reduced incidence of severe aGvHD, liver and GI GVHD, and NRM

Tay J *et al*. Biol Blood Marrow Transplant 2007 Feb; 13 (2): 206-217

Defibrotide for treatment of VOD/SOS

Defibrotide is a salt of complex single-stranded oligodeoxyribonucleotides derived from porcine mucosal DNA

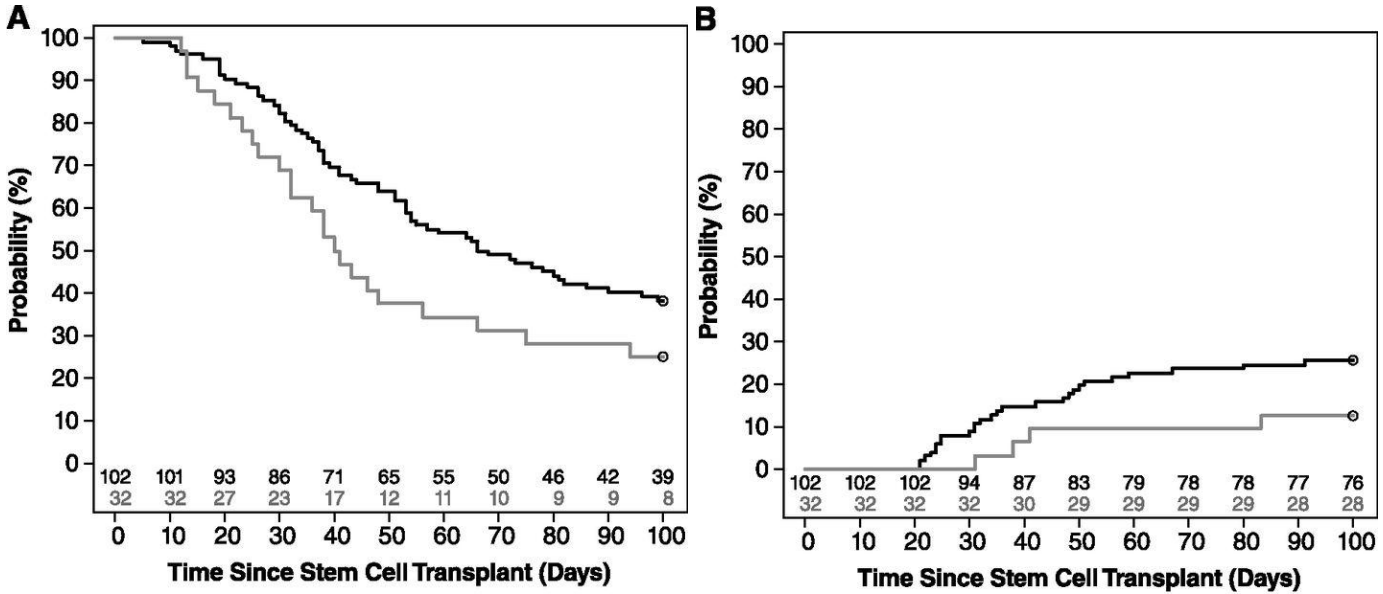
Defibrotide stabilizes endothelial cells by reducing endothelial cell activation and protecting them from further chemotherapy-induced damage, and also enhances fibrinolytic activity

Data leading to regulatory approval comes for a phase 3 study in patients with hepatic VOD/SOS and advanced multi-organ failure (MOF)

102 patients were prospectively enrolled and treated with defibrotide 25 mg/kg/day, and compared with 32 historical controls identified out of 6867 HSCT patient medical charts

Richardson PG *et al*. Blood 2016 Mar 31; 127 (13): 1656-1665

Defibrotide for treatment of VOD/SOS



Richardson PG *et al*. Blood 2016 Mar 31; 127 (13): 1656-1665

Ursodiol prophylaxis versus defibrotide treatment

	60kg patient	**100kg patient**	
Ursodiol prophylaxis	C$ 165 / 90 days	C$ 245 / 90 days	**~ 550x-650x**
Defibrotide treatment	C$ 97,000 / 21 days	C$ 161,000 / 21 days	

Q3: What do HSV, VZV, CMV and EBV all have in common?

1. Blood-borne transmission only
2. All sensitive to varying doses of acyclovir
3. Members of one family of viruses
4. Possibility of cross-species viral transmission
5. Apples and oranges (and grapes and bananas)

Cytomegalovirus

Cytomegalovirus (CMV)

CMV (or HCMV) is primarily transmitted through bodily fluids, including blood, urine, saliva, tears

Horizontal transmission (eg sexual intercourse) or vertical (eg childbirth or breast milk)

Outside of transplantation, most common form of infection is congenital

Exposure may occur throughout life, rarely causing any form of infection

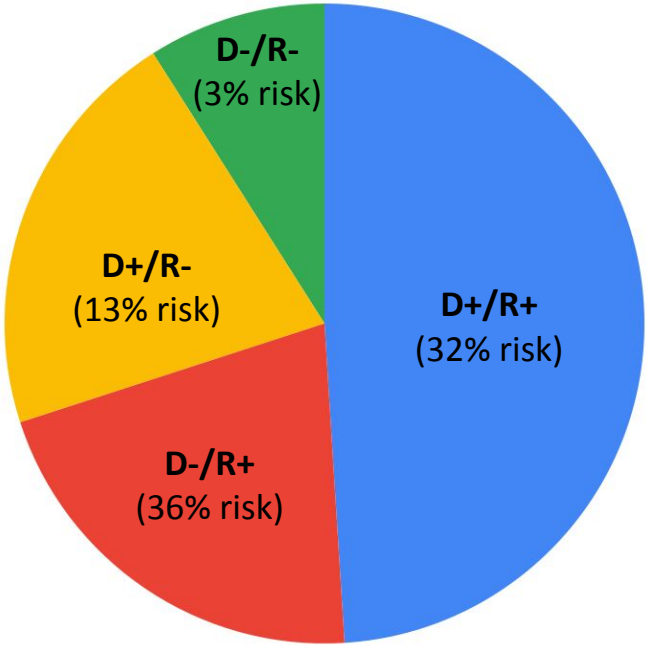
After transmission (with/without infection), lymphocytes continue to harbor latent CMV

Probability of previous exposure to CMV (IgG seroprevalence) varies by geographical area, and increases with age (approximately 60-80% in adults)

CMV serostatus and risk of reactivation

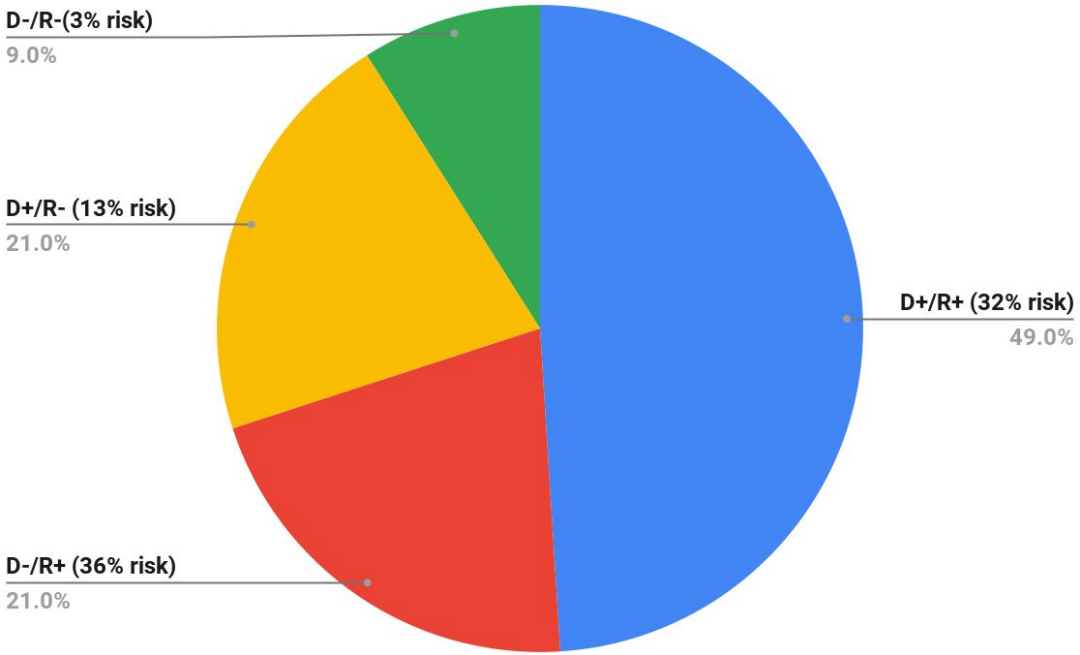
	Donor-seropositive (D+) 70%	Donor-seronegative (D-) 30%
Recipient-seropositive (R+) 70%	49%	21%
Recipient-seronegative (R-) 30%	21%	9%

	Donor-seropositive (D+) 70%	Donor-seronegative (D-) 30%
Recipient-seropositive (R+) 70%	32%	36%
Recipient-seronegative (R-) 30%	13%	3%



Styczynski. Infect Dis Ther 2018 Mar; 7 (1): 1-16

CMV serostatus and risk of reactivation

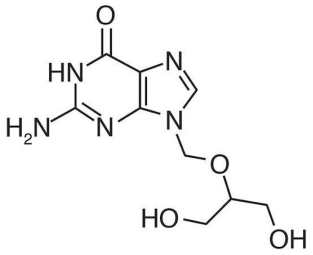


Styczynski. Infect Dis Ther 2018 Mar; 7 (1): 1-16

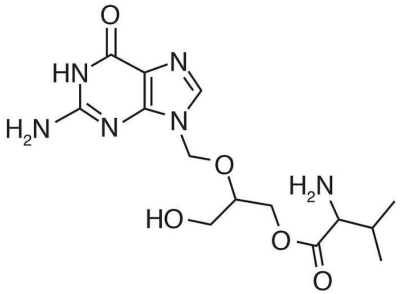
CMV-active antivirals

	Ganciclovir	Valganciclovir	Foscarnet	Cidofovir	Maribavir
Dosing/freq/route	5mg/kg IV q12h	900mg PO bid (60% bioavail)	60-90mg/kg IV q8-12h	5mg/kg IV qwk	400mg PO bid
Mechanism	inhibits DNA polymerase; incorporates into viral DNA	inhibits DNA polymerase; incorporates into viral DNA	inhibits DNA polymerase; inhibits pyrophosphate exchange	inhibits DNA polymerase; incorporates into viral DNA	inhibits protein kinase (protein phosphorylatn)
Myelosuppression	Yes	Yes	Some	Yes	(GI AEs)
Nephrotoxicity	Little	Little	Yes (and electrolyte abnormalities)	Yes	

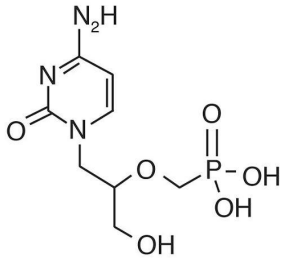
CMV-active antivirals



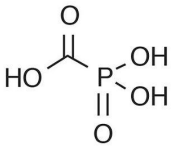
Ganciclovir



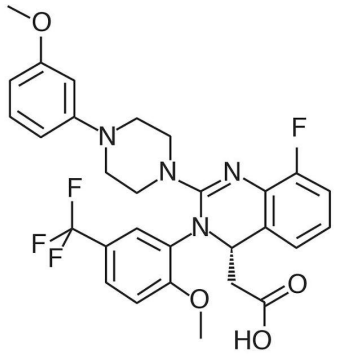
Valganciclovir



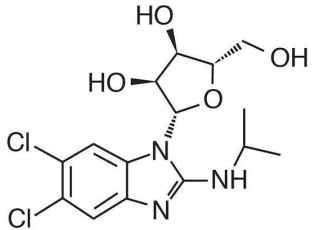
Cidofovir



Foscarnet



Letermovir



Maribavir

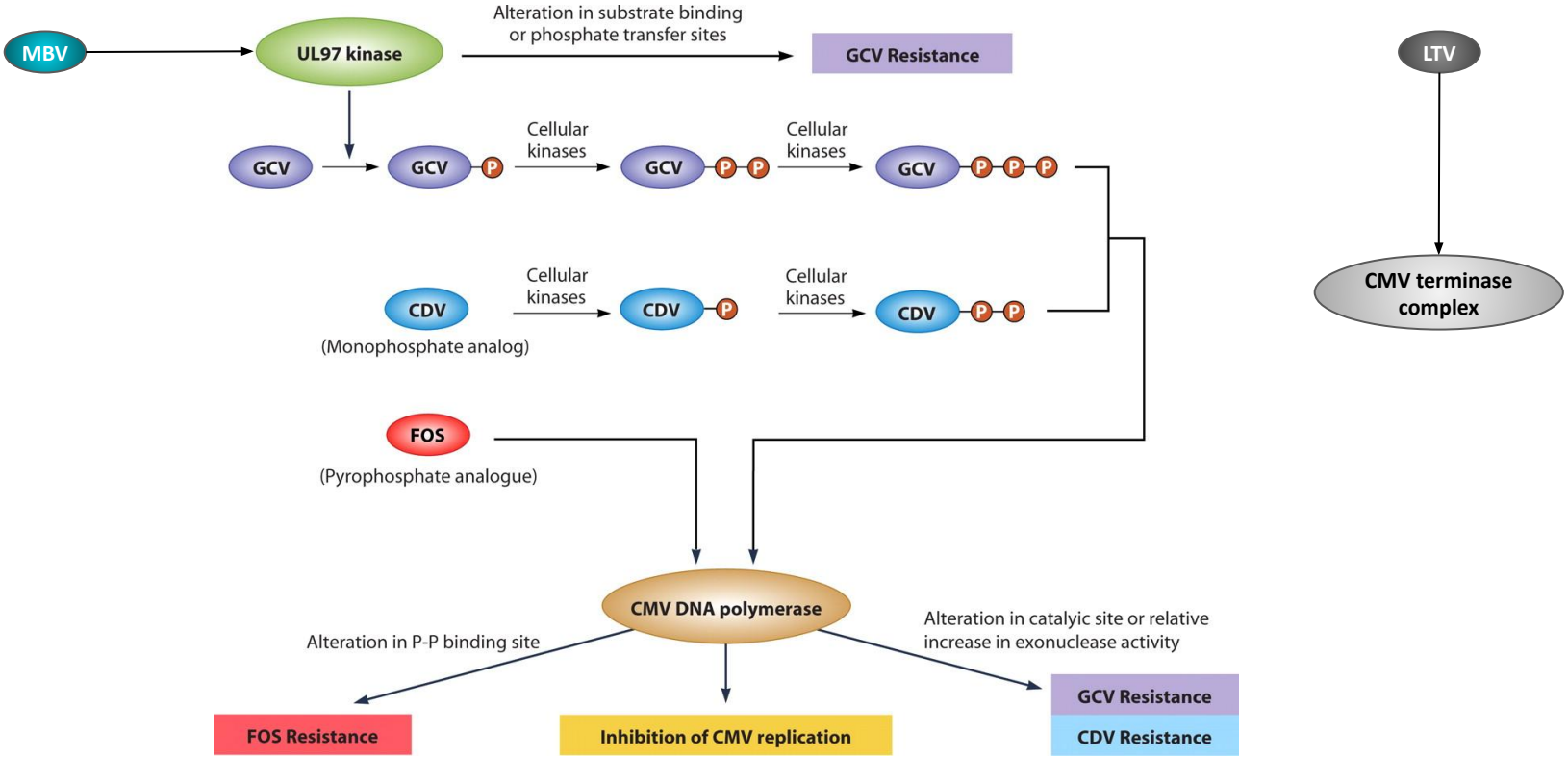
Lurain NS and Chou S. Clin Microbiol Rev 2010 Oct; 23 (4): 689-712

CMV-active antivirals

	Ganciclovir	Foscarnet
Severe neutropenia (ANC < 0.5)	**11%**	4%
Hematopoietic growth factor usage	**25%**	8%
Neutro/thrombocytopenia → discontinuation	**6%**	0%
Renal impairment	2%	**5%**
Electrolyte abnormalities (K, Ca, Mg, PO_4)	6, 4, 6, 0%	**17, 22, 18, 6%**

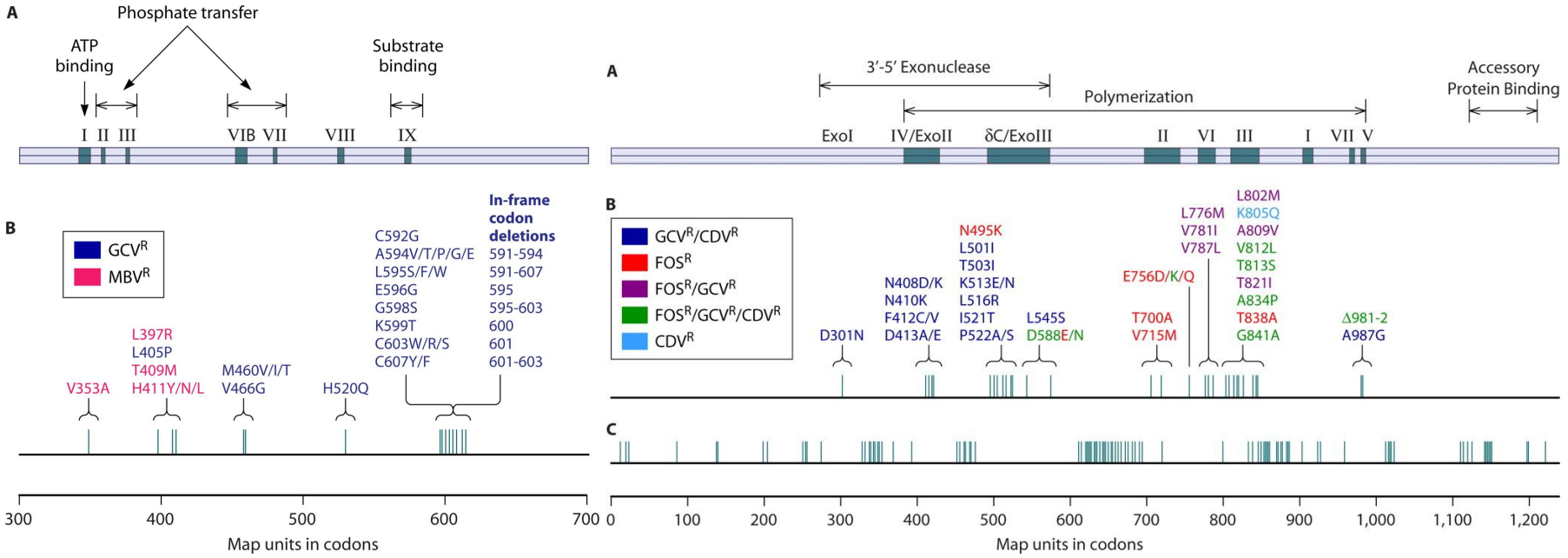
Reusser *et al*. Blood 2002 Feb 15; 99 (4): 1159-1164

CMV-active antivirals



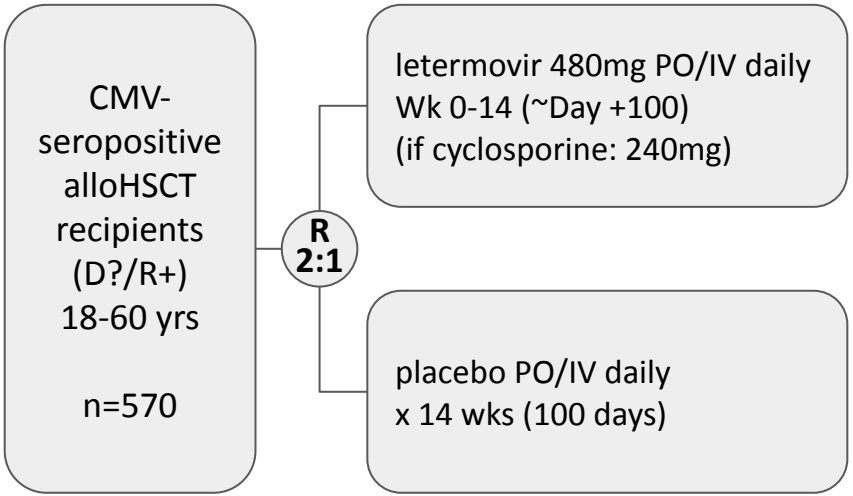
Lurain NS and Chou S. Clin Microbiol Rev 2010 Oct; 23 (4): 689-712

CMV mutations associated with antiviral resistance



Lurain NS and Chou S. Clin Microbiol Rev 2010 Oct; 23 (4): 689-712

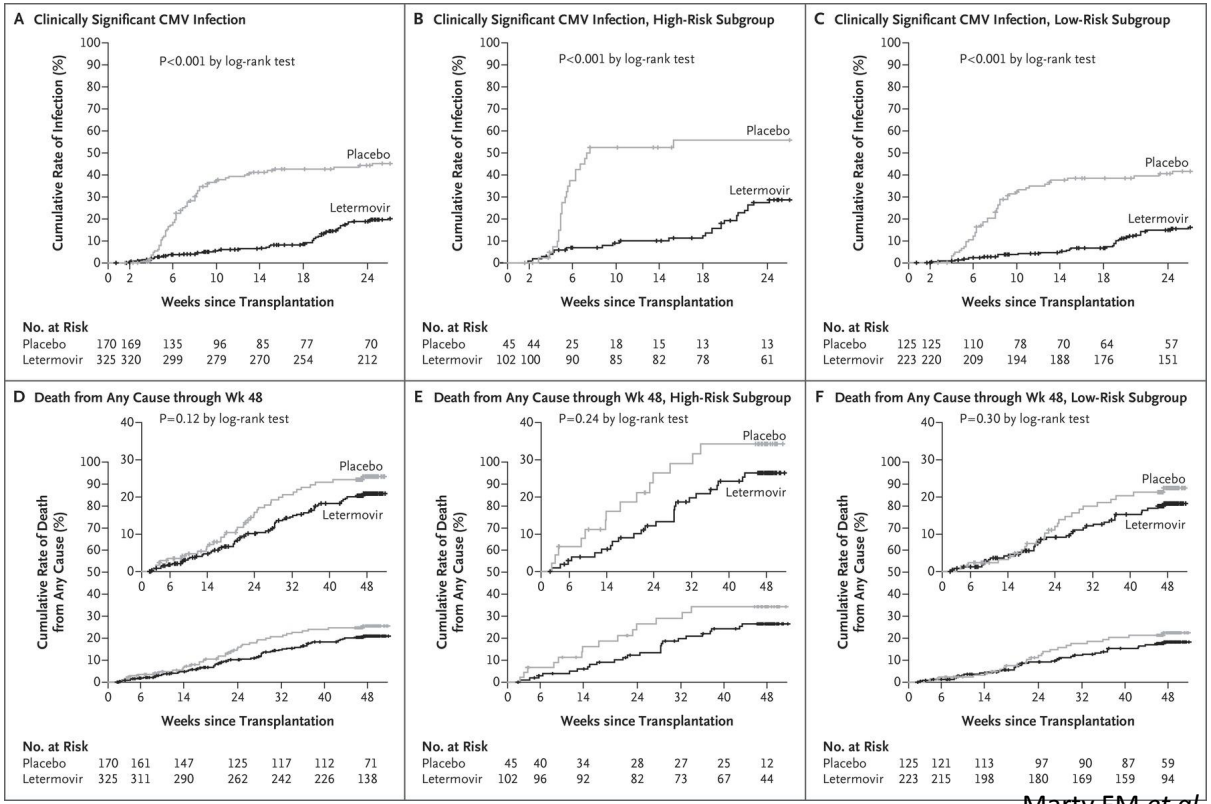
Letermovir for CMV prophylaxis post-allogeneic HSCT



Primary endpoint: % patients with csCMVi through week 24
Secondary endpoints: % patients with csCMVi through week 14, and time to csCMVi
csCMVi (clinically significant CMV infection) = CMV disease or CMV viremia leading to preemptive treatment

Marty FM *et al*. N Engl J Med 2017 Dec 21; 377 (25): 2433-2444

Letermovir for CMV prophylaxis post-allogeneic HSCT



High risk:

- related or unrelated donor with at least one HLA mismatch
- haploidentical donor
- umbilical cord blood as SC source
- *ex vivo* T-cell-depleted grafts
- GvHD (grade 2+) requiring ≥1 mg/kg/d prednisone (or equiv)

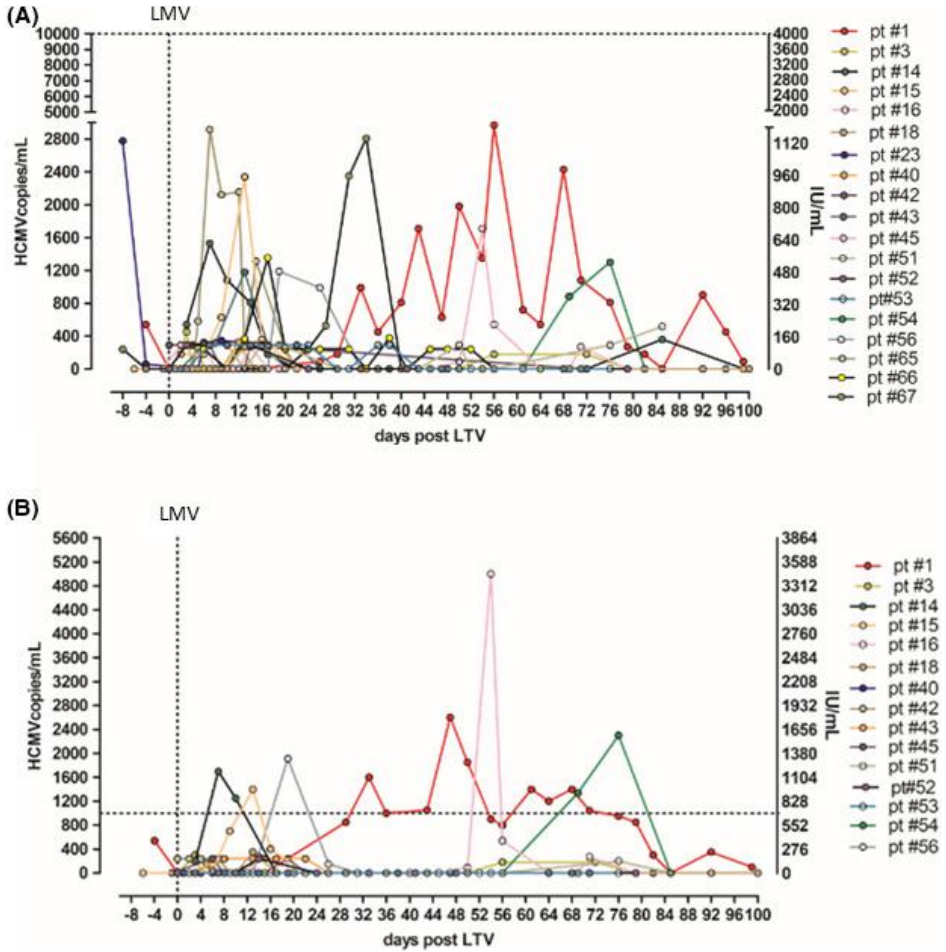
Marty FM *et al*. N Engl J Med 2017 Dec 21; 377 (25): 2433-2444

CMV viremia on letermovir

Detectable CMV viremia may occur during letermovir prophylaxis, and may not be associated with ‘viable’ CMV reactivation

28-35% of patients on LMV prophylaxis

None were treated with pre-emptive (val-)ganciclovir therapy



Cassaniti I *et al*. Am J Transplant 2021 Apr; 21 (4): 1622-1628

Epstein-Barr virus

Epstein-Barr virus (EBV)

EBV is primarily transmitted horizontally through bodily fluids, commonly saliva and genital secretions

EBV preferentially infects and establishes latency in B-lymphocytes

Outside of ‘reactivation’, most common form of infection is infectious mononucleosis

Exposure usually occurs through early life, rarely causing any form of infection

EBV IgG seroprevalence is approximately 90% in adults

Epstein-Barr virus lymphoproliferative disease (EBV-LPD)

EBV-positive non-Hodgkin's lymphoma
(includes Burkitt's lymphoma, diffuse large B-cell lymphoma (DLBCL), primary effusion lymphoma, HIV/AIDS-associated lymphoma)

EBV-positive Hodgkin's lymphoma

EBV-positive peripheral T-cell lymphoma

EBV-positive extranodal NK/T-cell lymphoma

EBV post-transplant lymphoproliferative disease (EBV-PTLD)

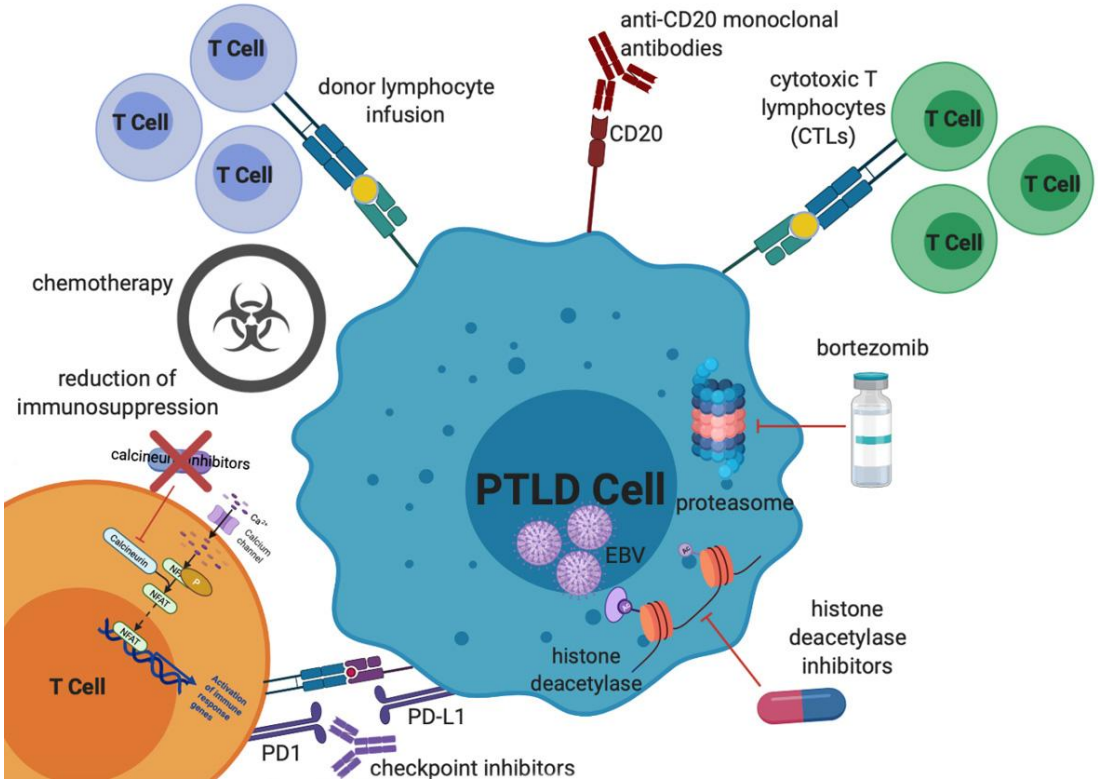
In the context of intensive (early) and prolonged immunosuppression, and lack of (or delayed reconstitution of) T-cell-mediated immunity,

EBV reactivation occurs in the form of uncontrolled proliferation of virus-harboring B-cells

If not identified and managed appropriately and in a timely manner, this proliferation results in post-transplantation lymphoproliferative disorder (PTLD)

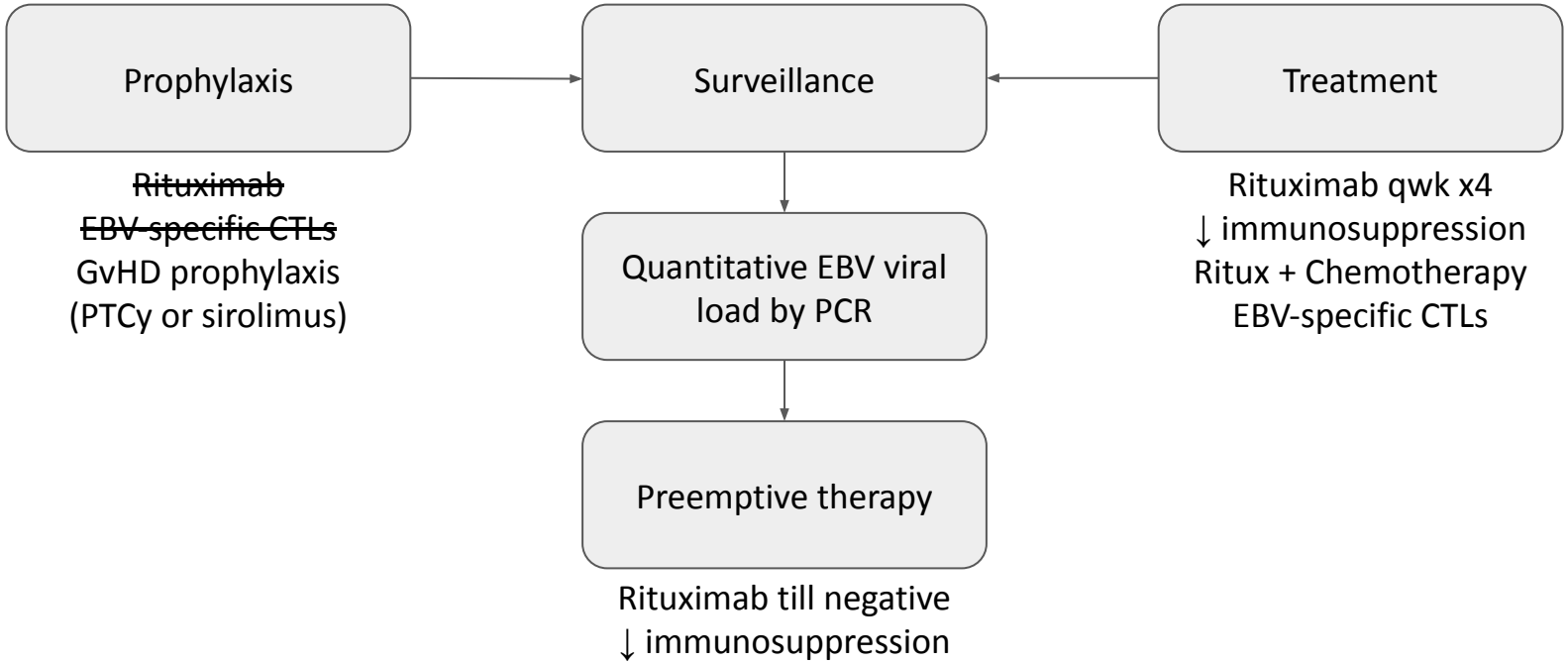
EBV-PTLD can be very aggressive in nature:
Prior to current approach of surveillance and preemptive therapy, the mortality rate due to EBV-PTLD is reported at approx 85%

Strategies for management of EBV-PTLD



Shahid S & Prockop SE. Cancer Drug Resist 2021; 4 (3): 646-664

Strategies for management of EBV-PTLD



Styczynski J *et al*. Haematologica 2016 Jul; 101 (7): 803-811

Preemptive therapy for DNAemia vs treatment of PTLD

Cumulative results of various therapeutic approaches in preemptive therapy and therapy of PTLD

Therapeutic approach	Cumulative number of treated patients	Cumulative number of patients with cure or improvement	Comments
Rituximab in preemptive therapy	341	306 (89.7%)	Administration of rituximab was often combined with other therapeutic approaches. Some reports deal both with preemptive and PTLD therapy
Rituximab in therapy of PTLD	146	92 (63%)	

Styczynski J *et al*. Transpl Infect Dis 2009 Oct; 11 (5): 383-392

Graft-versus-host-disease

Graft-versus-host-disease (GvHD)

In solid organ transplant, the recipient's immune system recognizes the donor's transplanted organ as 'foreign', and attacks the organ in an attempt to eliminate it (graft rejection)

While in allogeneic stem cell transplant, it is the immune system derived from (and in part adoptively transferred with) the donor's stem cells that recognizes the rest of the recipient's organs and tissues as 'foreign'

The immune response that results is termed graft-versus-host-disease (GvHD)

Graft-versus-host-disease (GvHD)

Although a severe and potentially fatal complication of transplant, graft-versus-host-disease (GvHD) shares the same (patho-)physiology as graft-versus-tumor (GvT, GvL), which is the purpose of allogeneic stem cell transplant

GvHD is more common and severe with increasing degree of HLA mismatch

However, HLA proteins are encoded by genes in the major histocompatibility complex (MHC). Another group of proteins called minor histocompatibility antigens (MiHA) are ‘presented’ on the cell surface by MHC proteins, and together identifies the cell as ‘self’

Therefore even in fully HLA-matched transplants, these MiHA mismatches may be responsible for development of GvHD

Graft-versus-host-disease (GvHD)

Allogeneic stem cell transplanters use some of the same immunosuppressent drugs and approaches as solid organ transplanters to minimize the incidence (prophylaxis) or the symptoms (treatment) graft-versus-host-disease and graft rejection, respectively

Prophylaxis/prevention of graft-versus-host-disease (GvHD)

Methotrexate (low doses 10-15mg/m^2 intermittently over the first two weeks)

Cyclosporine A (CySA) and then tacrolimus These are both calcineurin inhibitors

Mycophenolate (mofetil; MMF)

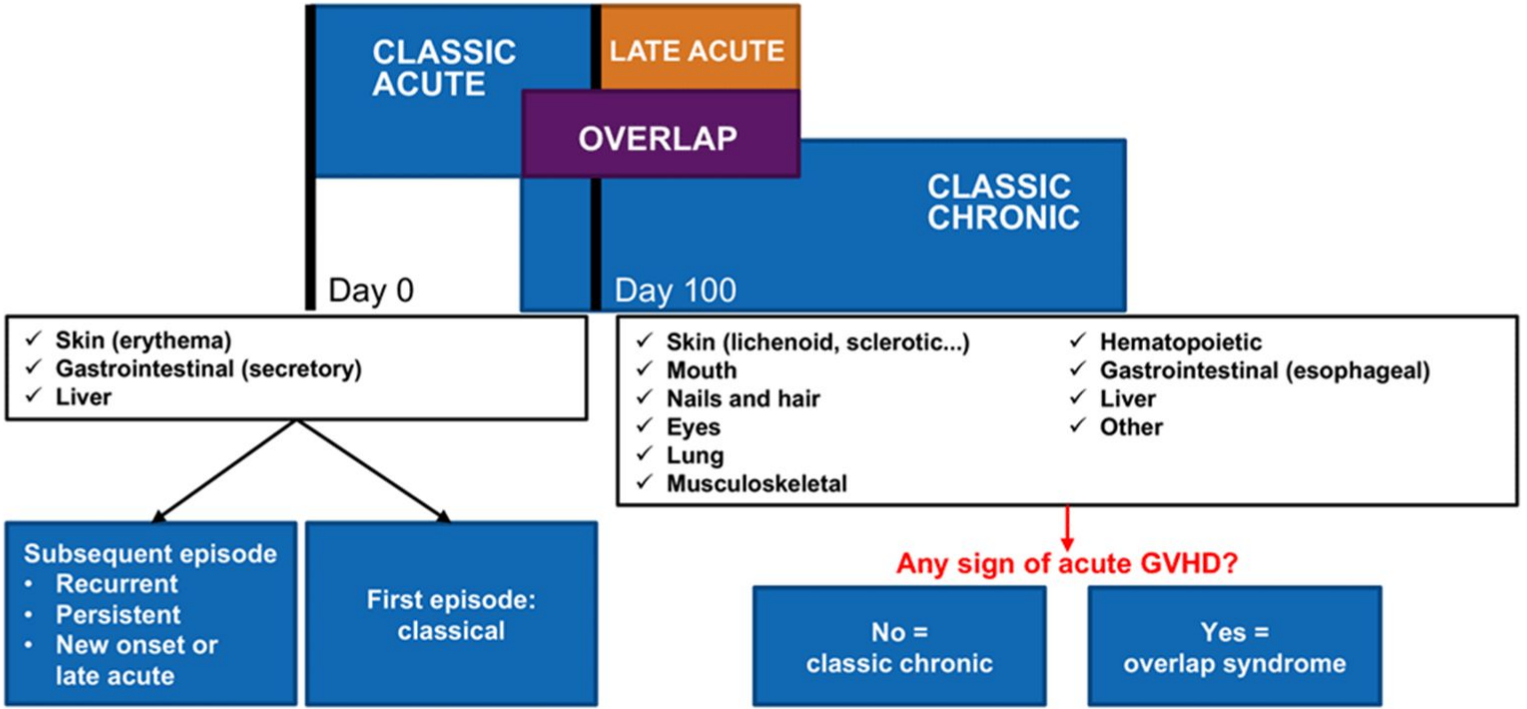
Anti-thymocyte globulin (ATG)

Post-transplant cyclophosphamide (PTCy)

Alemtuzumab (CD52-directed antibody)

Abatacept (CTLA-4 immunoglobulin)

Acute vs chronic graft-vs-host-disease



Lee SJ. Blood 2017 Jan 5; 129 (1): 30-37

Acute Graft-vs-Host-Disease (aGVHD)

aGVHD is the most common life-threatening complication of allogeneic HSCT, and the largest driver of non-relapse mortality (NRM)

Occurs when immune cells derived from the donor stem cells (the “graft”) recognize the cells of the recipient’s tissue (the “host”) as foreign, resulting in an immune response to attack and eliminate these perceived “foreign” cells

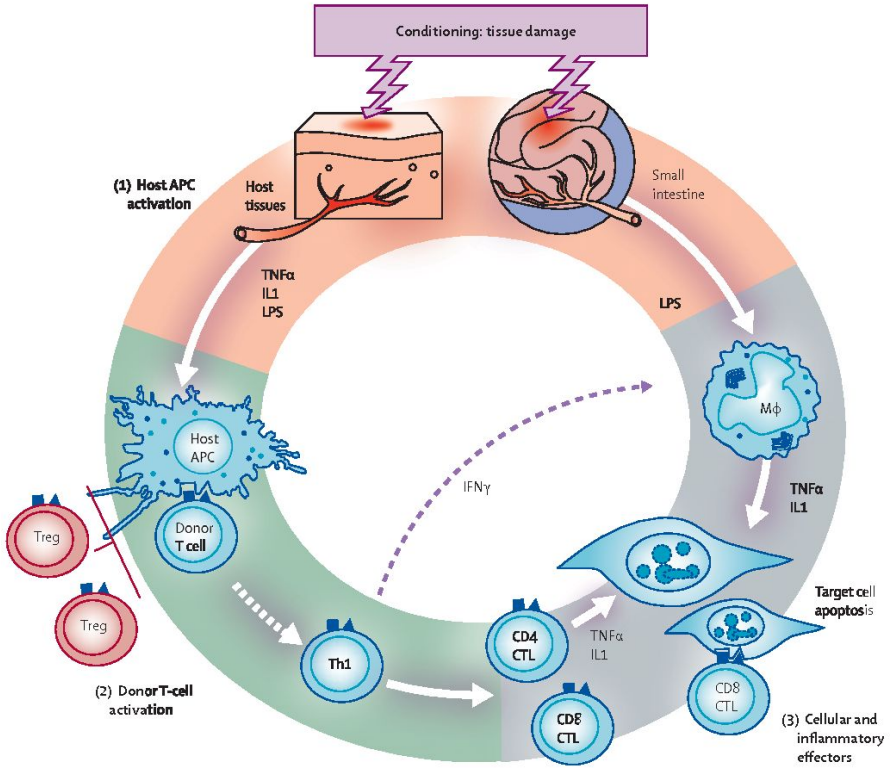
Occurs primarily in the first 100 days post-transplantation (“classic aGVHD”); however, “late onset aGVHD” or “recurrent aGVHD” may occur after Day +100, and is clinically distinct from chronic GVHD

Acute Graft-vs-Host-Disease (aGVHD)

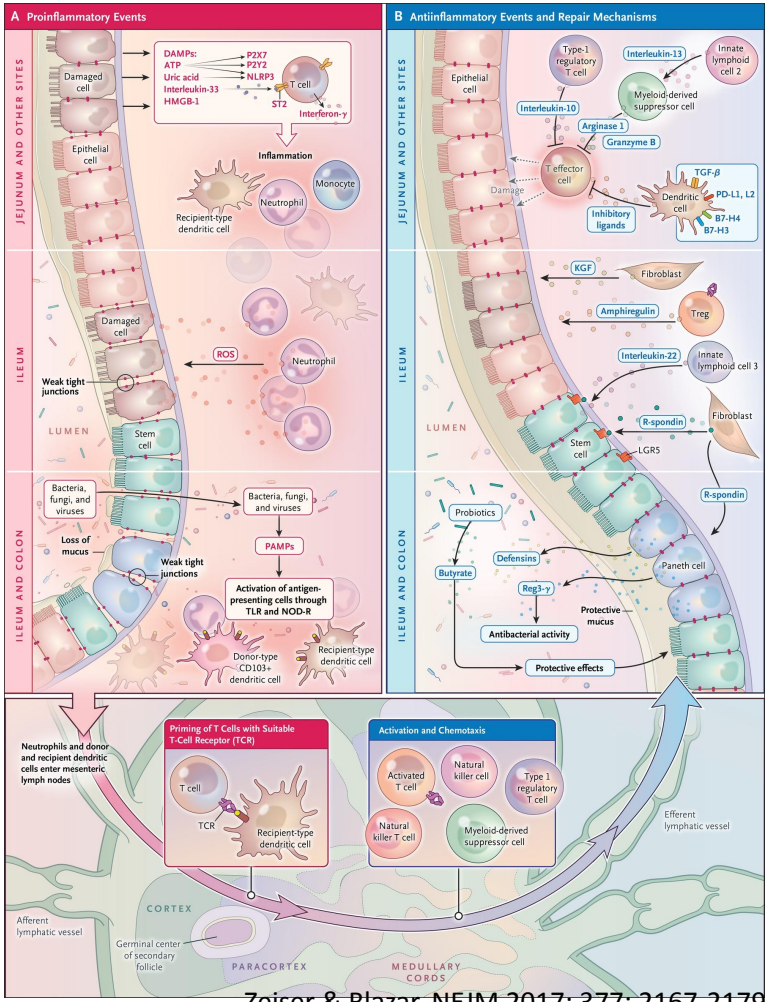
Occurs in approximately 30-75% of alloHSCT recipients (less frequently in related-donor transplants, and more frequently in unrelated-donor transplants)

Fun fact: aGVHD has also been described in SOT and autologous SCT in rare case reports

Pathophysiology of aGVHD



Ferrara et al. Lancet 2009; 373: 1550-1561



Zeiser & Blazar. NEJM 2017; 377: 2167-2179

Manifestations of aGVHD

Skin: maculopapular rash

Liver: hyperbilirubinemia □ jaundice □ cholestasis

Upper GI tract: nausea, vomiting and/or anorexia

Lower GI tract: watery or bloody diarrhea and abdominal pain

Manifestations of aGVHD	Differential Diagnoses?
Skin: maculopapular rash	Drug rash? Viral infection?
Liver: hyperbilirubinemia □ jaundice □ cholestasis	VOD/SOS? Drug-induced?
Upper GI tract: nausea, vomiting and/or anorexia	Toxicity? Infection? Drug AE?
Lower GI tract: watery or bloody diarrhea and abdominal pain	Infection?

Staging & Grading of aGVHD (Organ Staging)

Stage	Skin	Liver	Upper GI	Lower GI
0	No rash	Bilirubin <34µmol/L	No/intermittent nausea, vomiting or anorexia	Diarrhea <500mL/day or <3 episodes/day
1	Maculopapular rash <25% BSA	Bilirubin 34-50µmol/L	Persistent nausea, vomiting or anorexia	Diarrhea >500mL/day or 3-4 episodes/day
2	Maculopapular rash 25-50% BSA	Bilirubin 51-102µmol/L		Diarrhea >1000mL/day or 5-7 episodes/day
3	Maculopapular rash >50% BSA	Bilirubin 103-255µmol/L		Diarrhea >1500mL/day or >7 episodes/day
4	Generalized erythroderma + bullous formation and desquamation > 5% BSA	Bilirubin >255µmol/L		Severe abdominal pain with or without ileus or grossly bloody stools

Harris AC *et al*. Biol Blood Marrow Transplant 2016 Jan; 22 (1): 4-10

Staging & Grading of aGVHD (Overall Grading)

Grade	Skin	Liver	Upper GI	Lower GI
I or **A**	Stage 1-2	None	None	None
II or **B**	Stage 3	Stage 1	Stage 1	Stage 1
III or **C**		Stage 2-3		Stage 2-3
IV or **D**	Stage 4	Stage 4		Stage 4

Harris AC *et al*. Biol Blood Marrow Transplant 2016 Jan; 22 (1): 4-10

First-Line Treatment of aGVHD

High-dose corticosteroids are the cornerstone of therapy for aGVHD

Dosing: prednisone 2-2.5mg/kg/day OR methylprednisolone 2mg/kg/day

Exception: for upper GI aGVHD, prednisone 1mg/kg/day

AE: hyperglycemia, hypertension, mood changes, fluid retention, weight gain, infections, myopathy, AVN

Steroid Dosing

Steroid Dosing

Mielcarek (2015): Phase III trial of 162 pts with ND aGVHD

Cohort A: upper GI symptoms OR diarrhea <1L/day OR rash <50% BSA (NO LIVER)
received prednisone either 0.5mg/kg/day (n=49) or 1mg/kg/day (n=53)

Cohort B: bilirubin >34µmol/L OR diarrhea ≥1L/day OR rash ≥50% BSA
received prednisone either 1mg/kg/day (n=30) or 2mg/kg/day (n=30)

Mielcarek M *et al*. Haematologica 2015 Jun; 100 (6): 842-848

Steroid Dosing

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Harris *et al*. BBMT 2016; 22: 4-10

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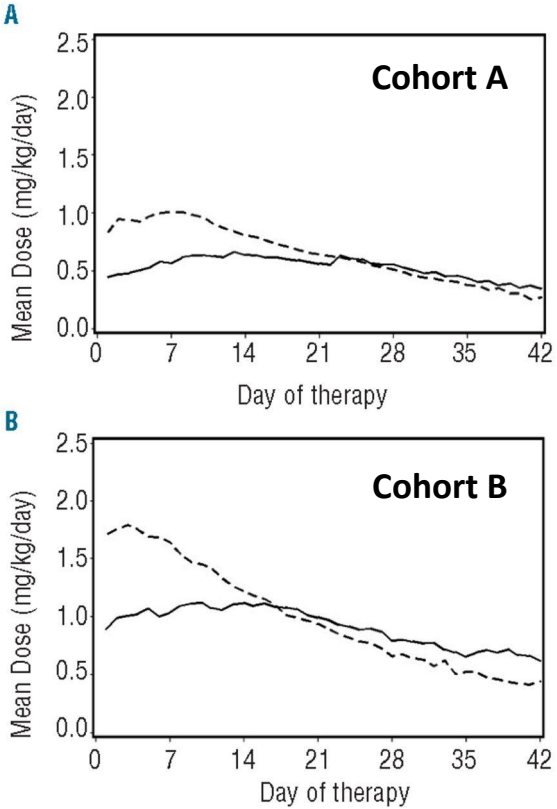
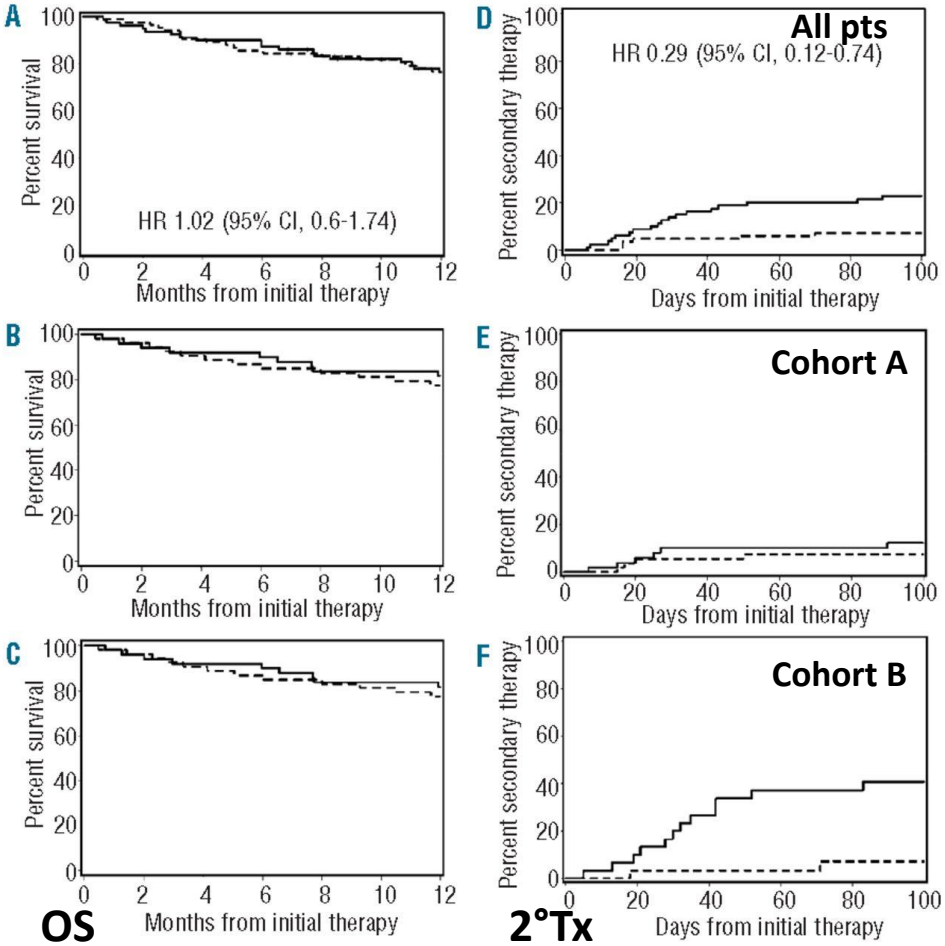
Mielcarek M *et al*. Haematologica 2015 Jun; 100 (6): 842-848

Steroid Dosing





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4	Generalized erythroderma + bullous formation and desquamation > 5% BSA	Bilirubin >255µmol/L	**2-2.5 mg/kg**	Severe abdominal pain with or without ileus or grossly bloody stools

(0.5-)1 mg/kg

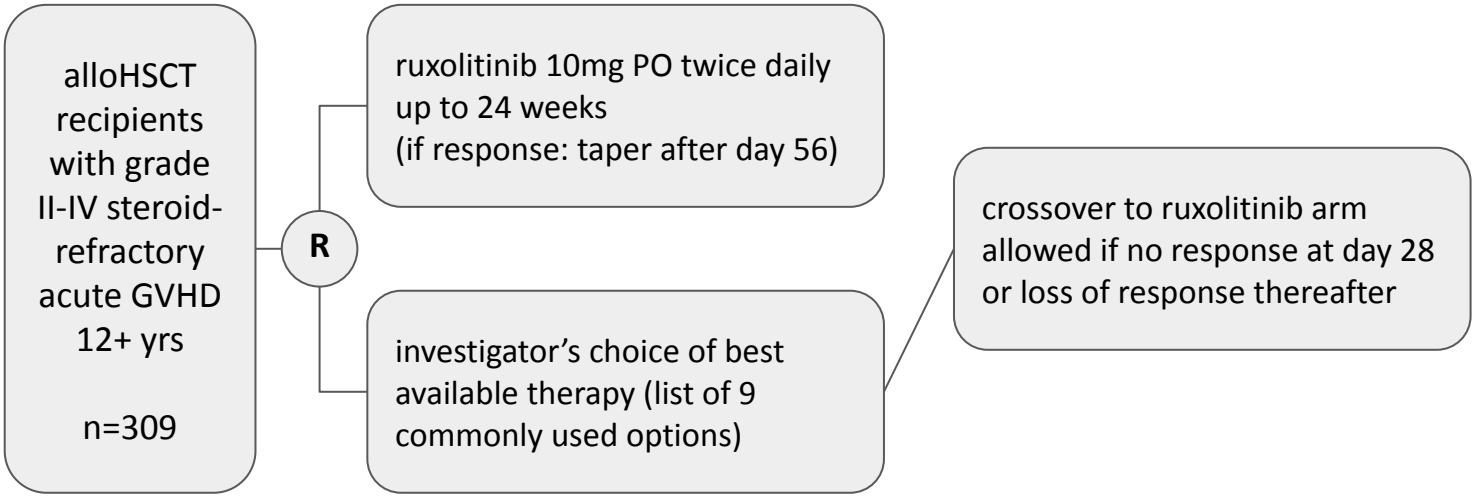
Harris AC *et al*. Biol Blood Marrow Transplant 2016 Jan; 22 (1): 4-10

Steroid-refractory acute graft-vs-host-disease (aGVHD)

Systemic corticosteroids are the usual first-line of therapy, however response rates with corticosteroids are approximately 50%

Mortality of SR aGVHD is significantly higher, with overall 6-month survival dropping from 65% to 50% for aGVHD patients requiring second-line therapy

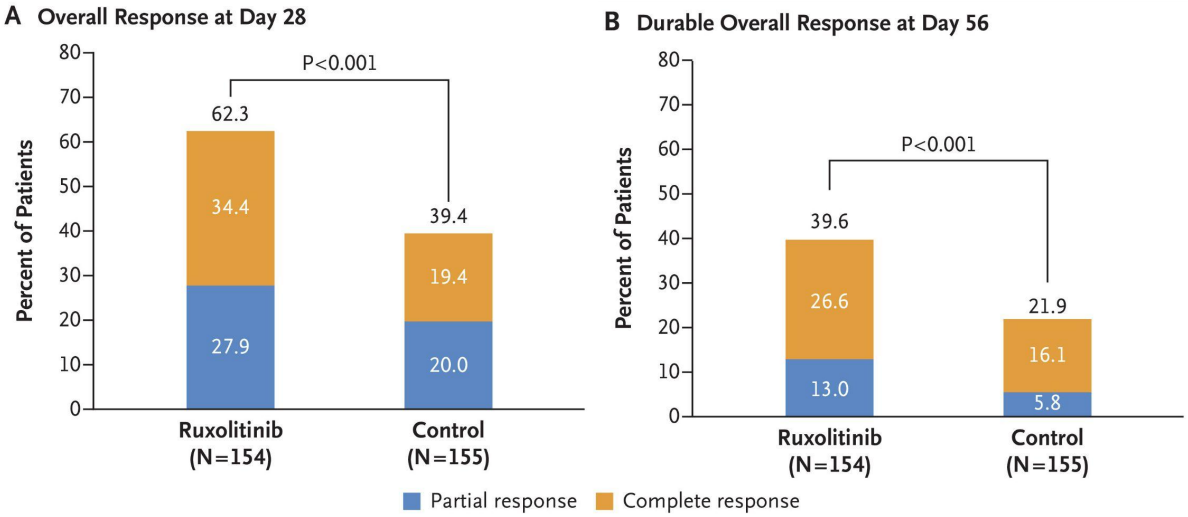
Ruxolitinib for treatment of steroid-refractory acute GvHD

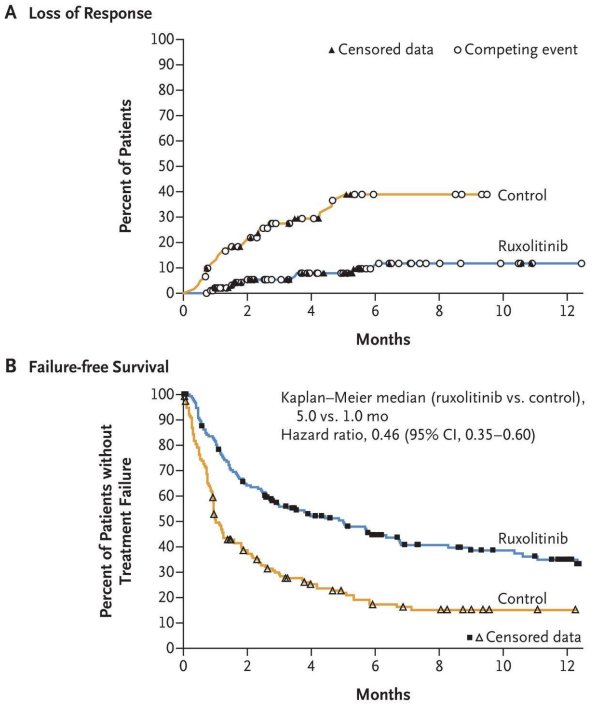


Primary endpoint: overall response (OR) at day 28 (% patients with complete or partial response)
Secondary endpoints: durable overall maintained at day 56, duration of response, best overall response, failure-free survival, overall survival, and cumulative glucocorticoid use until day 56

Zeiser R *et al*. N Engl J Med 2020 May 7; 382 (19): 1800-1810

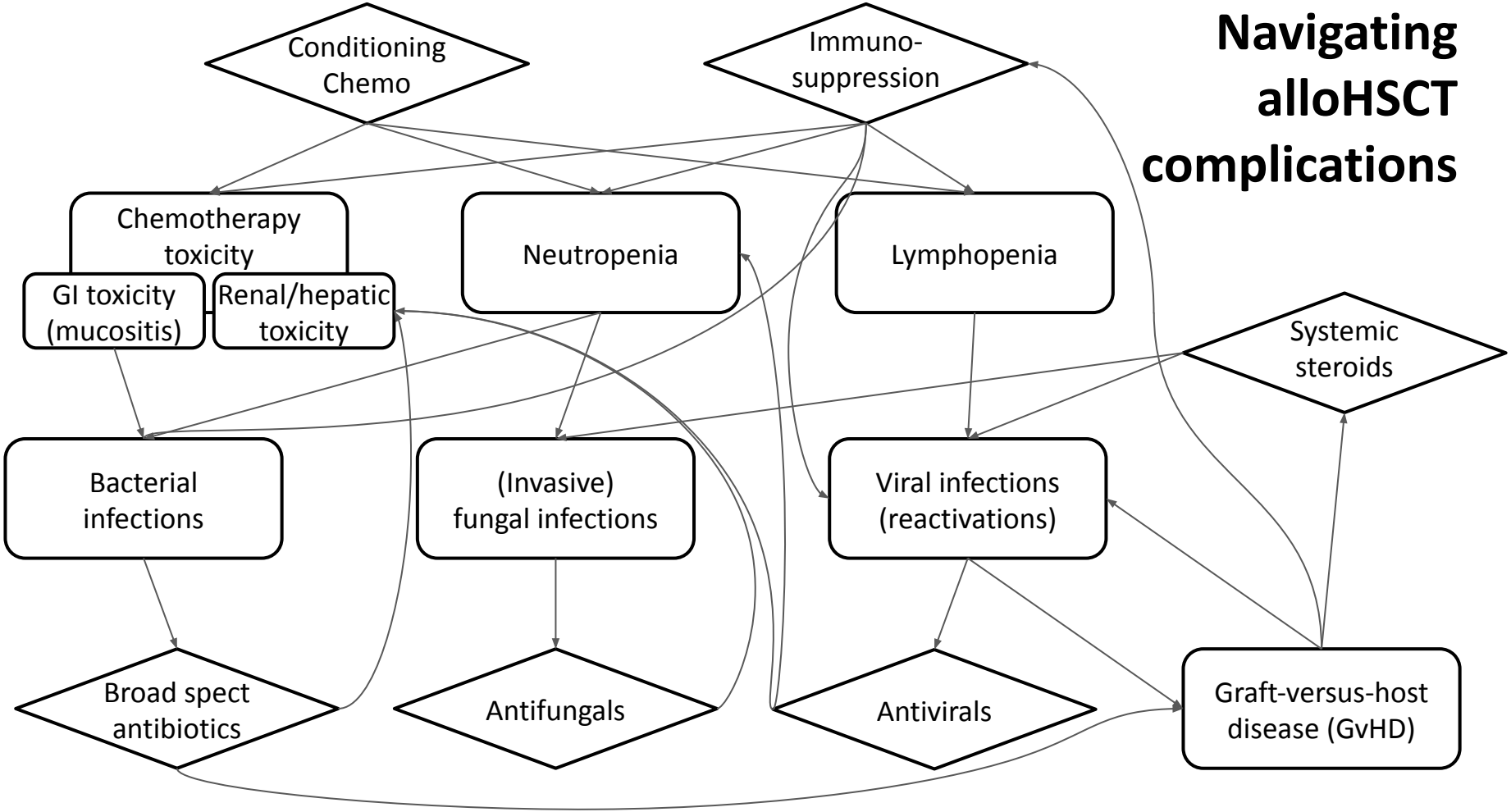
Ruxolitinib for treatment of steroid-refractory acute GvHD



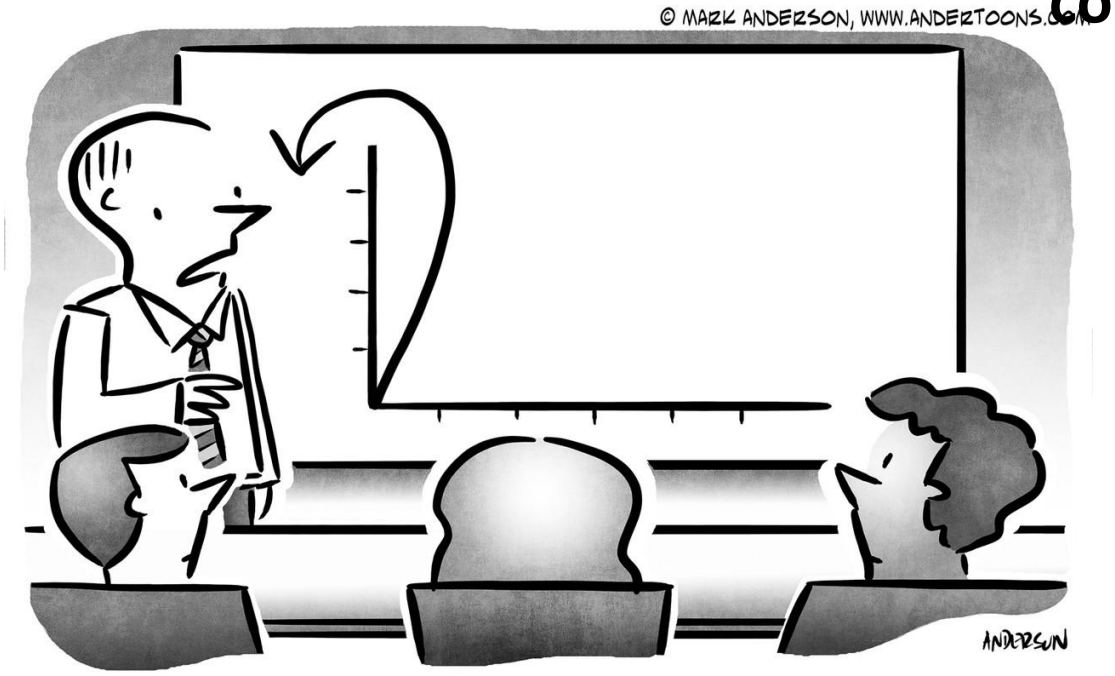


Zeiser R *et al*. N Engl J Med 2020 May 7; 382 (19): 1800-1810

Navigating alloHSCT complications



Navigating alloHSCT complications



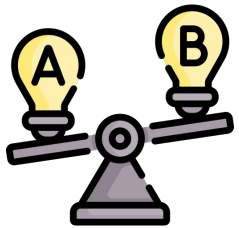
"I'm gonna be honest with you; I have no idea what the hell is happening here."

Balancing acts

Graft-vs-tumor

Immunosuppression

Intensive therapy



Graft-vs-host

Infections

Toxicities

Balancing acts

"It's a delicate balance between being good enough that you still get your presents, but not so good that you can't bug your sister."

Balancing acts

Vaccination schedule post-allogeneic transplant

Vaccination schedule post-allogeneic stem cell transplant

Vaccine	Post-transplantation	Comments
Inactivated vaccines		
Cholera and travellers' diarrhea (inactivated)	Use if indicated	Beginning 6 months post-HSCT
COVID-19	Recommended: 3 doses and booster(s)	Beginning 3 to 6 months post-HSCT
Diphtheria	Recommended: 3 doses	Beginning 6 to 12 months post-HSCT
Haemophilus influenzae type b (Hib)	Recommended: 3 doses	Beginning 6 to 12 months post-HSCT
Hepatitis A	Use if indicated	Beginning 6 months post-HSCT Pre-exposure prophylaxis for travel: consider Ig with hepatitis A vaccine unless receiving routine IG replacement therapy Post-exposure prophylaxis: Ig recommended along with hepatitis A vaccine unless receiving routine IG replacement therapy
Hepatitis B	Recommended: 3 or 4 doses. Use double the routine dose if already immunocompromised	Beginning 6 to 12 months post-HSCT Double the routine dose; 3 or 4 dose schedule recommended Post-immunization monitoring of anti-HBs titres recommended with booster dose if titre less than 10 IU/L
Herpes zoster (recombinant inactivated)	Consider if indicated by age	
HPV	Recommended if indicated by age: 3 doses	Beginning 6 to 12 months post-HSCT; 3 dose schedule

Public Health Agency of Canada (PHAC). Canadian Immunization Guide (dated 2021 Dec 23)

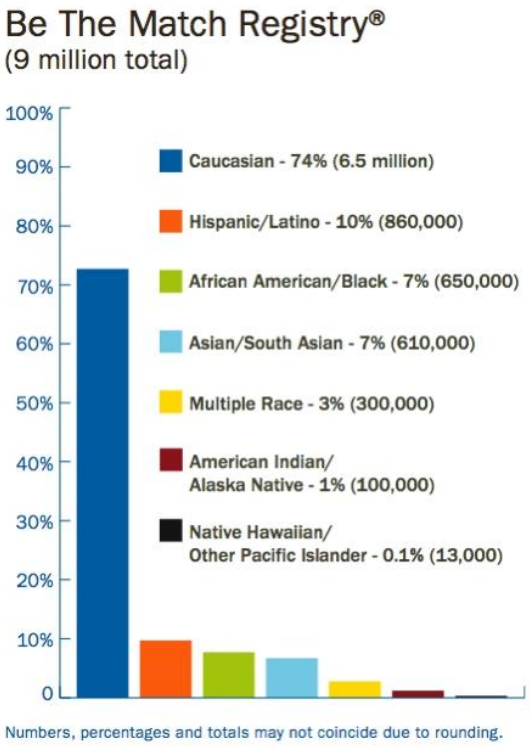
Vaccination schedule post-allogeneic stem cell transplant

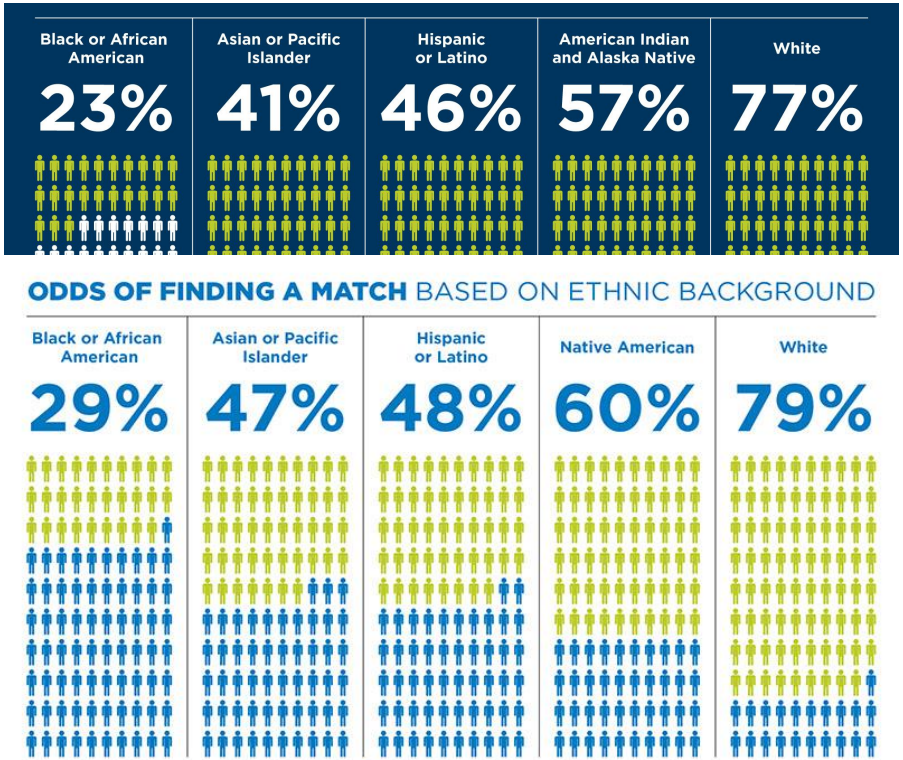
Vaccine	Post-transplantation	Comments
Inactivated vaccines		
Influenza (inactivated)	Recommended annually (2 doses the first year post transplant if less than 9 years old)	Beginning 4 to 6 months post-HSCT
Japanese encephalitis	Use if indicated	Beginning 6 months post-HSCT
Meningococcal conjugate	Routine use. Use quadrivalent conjugate meningococcal vaccine if indicated by risk factors for invasive meningococcal disease (e.g., functional hyposplenia)	Beginning 6 months post-HSCT
Meningococcal B	Should be considered if indicated by risk factors for invasive meningococcal disease (e.g., functional hyposplenia)	Beginning 6 months post-HSCT
Pertussis	Recommended: 3 doses for children and adolescents up to age 18 1 dose for adults 18 years of age and older	Beginning 6 to 12 months post-HSCT
Pneumococcal conjugate 13-valent (Pneu-C-13)	Recommended: 3 doses, regardless of age	Beginning 3 to 6 months post-HSCT 3 doses of Pneu-C-13 vaccine at least 4 weeks apart
Pneumococcal polysaccharide (Pneu-P-23)	Recommended: 1 dose	Give 12 to 18 months post-HSCT if no GVHD (6 to 12 months after the last dose of Pneu-C-13) If GVHD, give 4th dose of Pneu-C-13 and delay polysaccharide until GVHD resolved Consider re-immunization after 1 year
Polio (inactivated)	Recommended: 3 doses	Beginning 6 to 12 months post-HSCT

Vaccination schedule post-allogeneic stem cell transplant

Vaccine	Post-transplantation	Comments
Inactivated vaccines		
Rabies	Use if indicated	Do not use intradermally Give as needed for post-exposure management Use 5 dose schedule for post-exposure prophylaxis Beginning 6 to 12 months post-HSCT for pre-exposure prophylaxis Post-immunization serology recommended
Tetanus	Recommended: 3 doses	Beginning 6 to 12 months post-HSCT
Typhoid (inactivated)	Use if indicated	Beginning 6 months post-HSCT
Live vaccines		
Bacille Calmette-Guérin (BCG)	Contraindicated	
Herpes zoster (live)	Contraindicated. Use inactivated vaccine	
Influenza (live)	Not recommended - use inactivated vaccine	
Measles-mumps-rubella	Recommended: 2 doses	Beginning 24 months post-HSCT Serology recommended after 2nd dose
MMRV	Contraindicated	
Rotavirus	Contraindicated	
Smallpox	Contraindicated	
Typhoid (live)	Contraindicated - if indicated use inactivated	
Varicella (univalent)	Recommended: 2 doses	Beginning 24 months post-HSCT Serology recommended after 2nd dose
Yellow fever	May be given if indicated	Beginning 24 months post-HSCT

Racial and Ethnic Disparities in Donor Registries





Be the Match Registry

Racial and Ethnic Disparities in Donor Registries

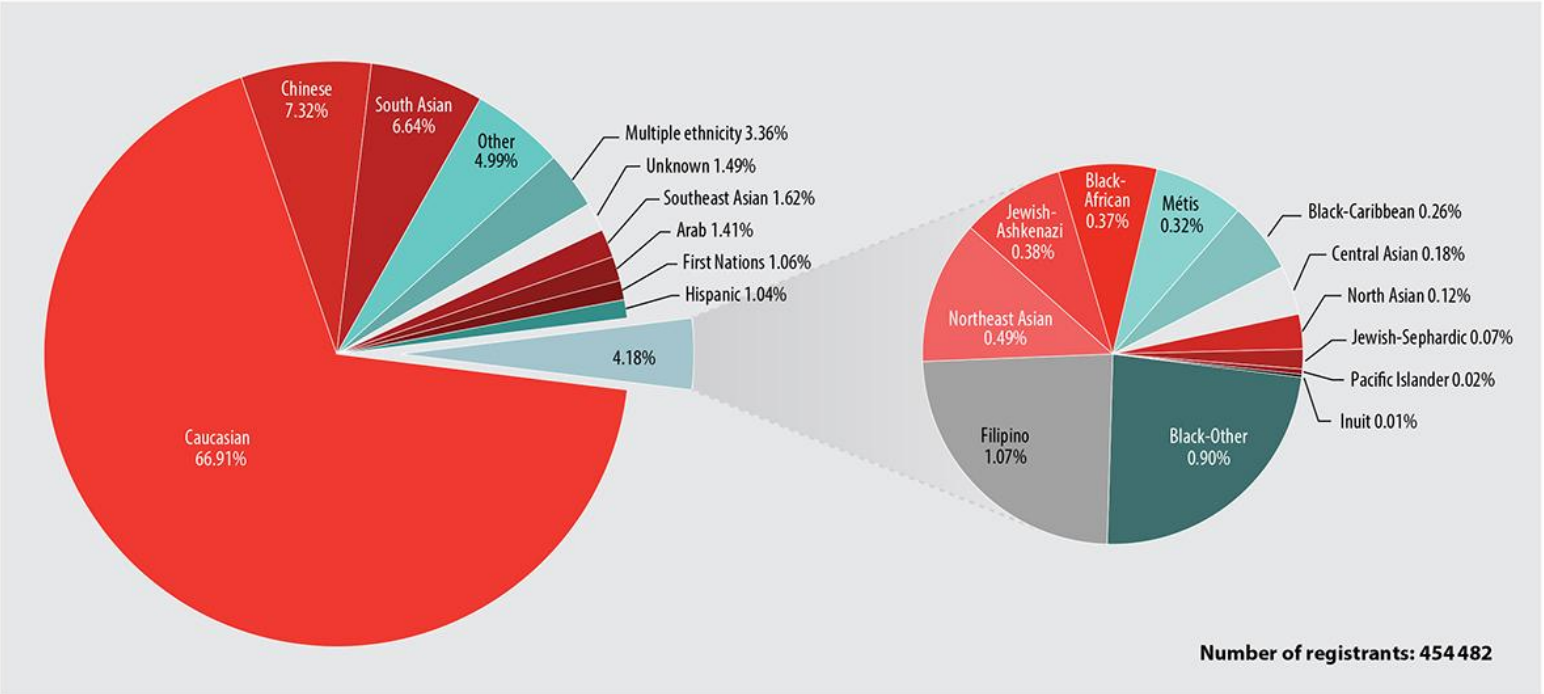


FIGURE 1. Ethnic composition of adult stem cell registry (provided by Canadian Blood Services, September 2019).

Wong EM. British Columbia Med J 2020 Mar; 62 (2): 62-64

Final plug

Canadian stem cell registry ethnic composition should reflect the highly ethnic and multicultural composition of the Canadian population

Only 20-30% of unrelated transplants in Canada are from Canadian donors

So…

Are you between the ages of 17 and 35?

No? You **must** know someone who is, though!

Final plug

give.blood.ca/goto/Rami

#GetSwabbed

Canadian Blood Services

BLOOD
PLASMA
STEM CELLS
ORGANS
& TISSUES

Thank you!

Questions?

Final plug

give.blood.ca/goto/Rami

#GetSwabbed

Canadian Blood Services

BLOOD
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& TISSUES