Hematopoietic Stem Cell Transplantation & CAR T-cell Therapy

AN OVERVIEW

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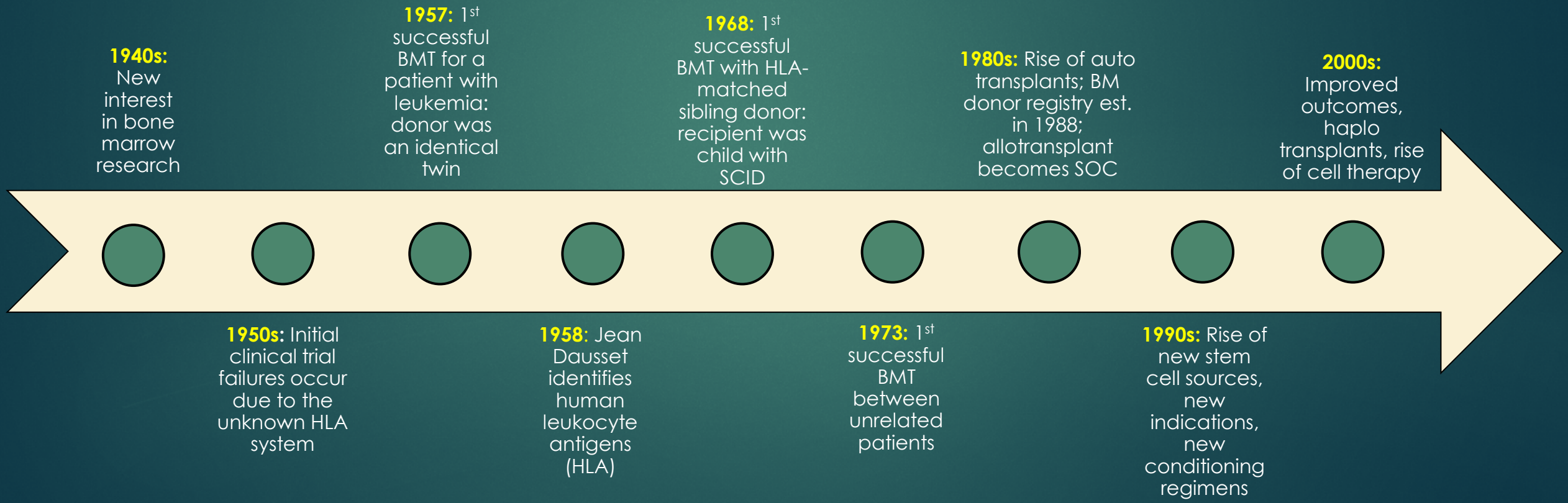
BRIEF HISTORY of HSCT

1940s: Marrow injury was a potentially lethal side effect of radiation exposure from the atomic bomb and industrial accidents. Given concern about the spread of nuclear technology, the US Atomic Energy Commission and the military propelled studies of bone marrow transplantation.



Allogeneic Stem Cell Transplant: Why Does it Work?

- **Allotransplantation** involves utilizing the healthy immune and blood system of a donor to treat or cure a patient's underlying disorder. The disorder may include any of the following:
  - A malignancy refractory to chemotherapy and radiation (AML, ALL)
  - A dysfunctional immune system (PID)
  - A dysfunctional blood system (Sickle cell, Aplastic Anemia)
- A main therapeutic component is the **graft-versus-tumor effect** mediated by T-cells in the allograft. Donor T-cells can eliminate residual malignant cells. Additionally, the **graft-versus-marrow effect** occurs when donor stem cells "take over" the marrow and subsequently eliminate the defective immune or blood system.

Autologous stem cell transplant: Why Does it Work?

- **Autotransplantation** involves harvesting a patient's own stem cells for storage before giving high dose chemotherapy or radiation to treat his/her disease. The stored stem cells are then infused back into the patient. This "stem cell rescue" restores the patient's immune system following the bone marrow damaging effects of the treatment.
- The underlying disease must be chemo-responsive in order for the transplant to be effective, and the disease may return over time.

Indications For Transplant

Autologous HSCT	Allogeneic HSCT
Multiple Myeloma (most common)	Acute myeloid leukemia (most common)
Non-Hodgkin lymphoma	Acute lymphoblastic leukemia
Hodgkin disease	Chronic myeloid leukemia
Acute myeloid leukemia	Chronic lymphocytic leukemia
Neuroblastoma	Myeloproliferative disorders
Germ cell tumors	Myelodysplastic syndromes
Autoimmune disorders	Multiple Myeloma
	Non-Hodgkin lymphoma
	Hodgkin disease
	Aplastic anemia
	Sickle Cell Disease
	Primary Immune Deficiencies

Standard of Care Considerations

	Disease	Auto-HSCT	Allo-HSCT
Hematologic malignancy	Acute myeloid leukemia	S	S
	Acute lymphoblastic leukemia	CO	S
	Chronic myeloid leukemia	S	CO
	Myelodysplastic syndrome	GNR	S
	Non-Hodgkin's lymphoma	S	CO
	Hodgkin's lymphoma	S	CO
Bone marrow failure	Acquired aplastic anemia	GNR	S
	Diamond-Blackfan anemia	GNR	S
	Dyskeratosis congenita	GNR	S
	Fanconi anemia	GNR	S
	Constitutional monocytopenia	GNR	S
Immunodeficiencies	Severe combined immunodeficiency	GNR	S
	Chediak–Higashi syndrome	GNR	S
	Wiskott–Aldrich syndrome	GNR	S
	Chronic granulomatous disease	GNR	S
	Leukocyte adhesion deficiency	GNR	S
	X-linked lymphoproliferaltive syndrome	GNR	S
	Leukocyte adhesion deficiency	GNR	S
Hemoglobinopathies	Thalassemia	GNR	S
	Sickle cell disease	GNR	S
Solid tumor	Neuroblastoma	S	CO
	Medulloblastoma	S	GNR
	Ewing's sarcoma	S	GNR
	Wilms tumor	CO	GNR
	Germ cell tumor	CO	GNR
	Soft tissue sarcoma	CO	GNR
	Brain tumors	CO	GNR
Metabolic disease	Mucopolissacaridose	GNR	S
	Mannosidosis sphingolipidosis	GNR	CO
	Adrenoleukodystrophy	GNR	CO

S standard of care, *CO* clinical option after careful assessment of risks and benefits, *GNR* generally not recommended

Witkowska, et al. Archivum immunologiae et therapiae experimentalis. 2014; 62, 319–327.

Donor Selection

Human Leukocyte Antigen Considerations:

Higher degree of HLA mismatching associated with ↑ rates of GVHD and graft failure

Donor and recipients are matched at 6-12 loci, including:

HLA class I (-A, -B, and -C) and

class II (-DRB1, -DQB1, -DPB1)

Matching out of 6: (-A, -B, -DRB1)

Out of 8: (-A, -B, -C, -DRB1)

Out of 10: (-A, -B, -C, -DRB1, -DQB1)

Other Donor Factors:

Must determine if donor is available, suitable, eligible, and willing to donate to the recipient

Donor age 18–32 associated with ↑ chance of overall survival

CMV (+) donors preferred for CMV (+) patients

Male donors preferred for male patients

Avoid multiparous female donors

ABO match affects stem cell dose in BM transplants

Major/Minor ABO incompatibilities must be managed during infusion and after transplant

Donor medical hx is an important consideration

Potential Stem Cell Sources

Autologous: Marrow or PBSC

Allogeneic: Marrow, PBSC, Umbilical Cord Blood

Allo transplant sources may include:

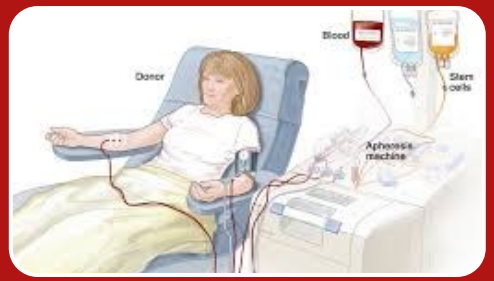
HLA Matched Related Donor (MRD), 8/8 Matched Unrelated Donor (MUD)

HLA Mismatched Haplo Related Donor, 7/8 MMUD, 5/8 (or better) UCB

Pros and Cons of Graft Source

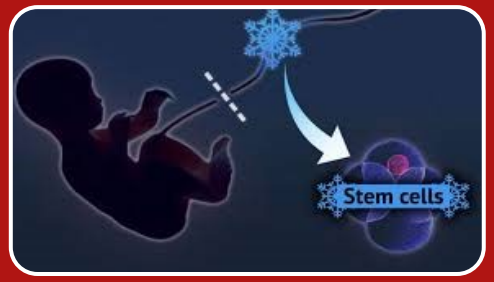
Bone Marrow

- P: ↓ T-cells in graft, ↓ cGVHD
- C: ↑ Donor morbidity, slower engraftment, OR required



Peripheral Blood

- P: Faster engraftment, ↓ Donor morbidity
- C: Must mobilize donor stem cells, ↑ T-cells in graft, ↑cGVHD



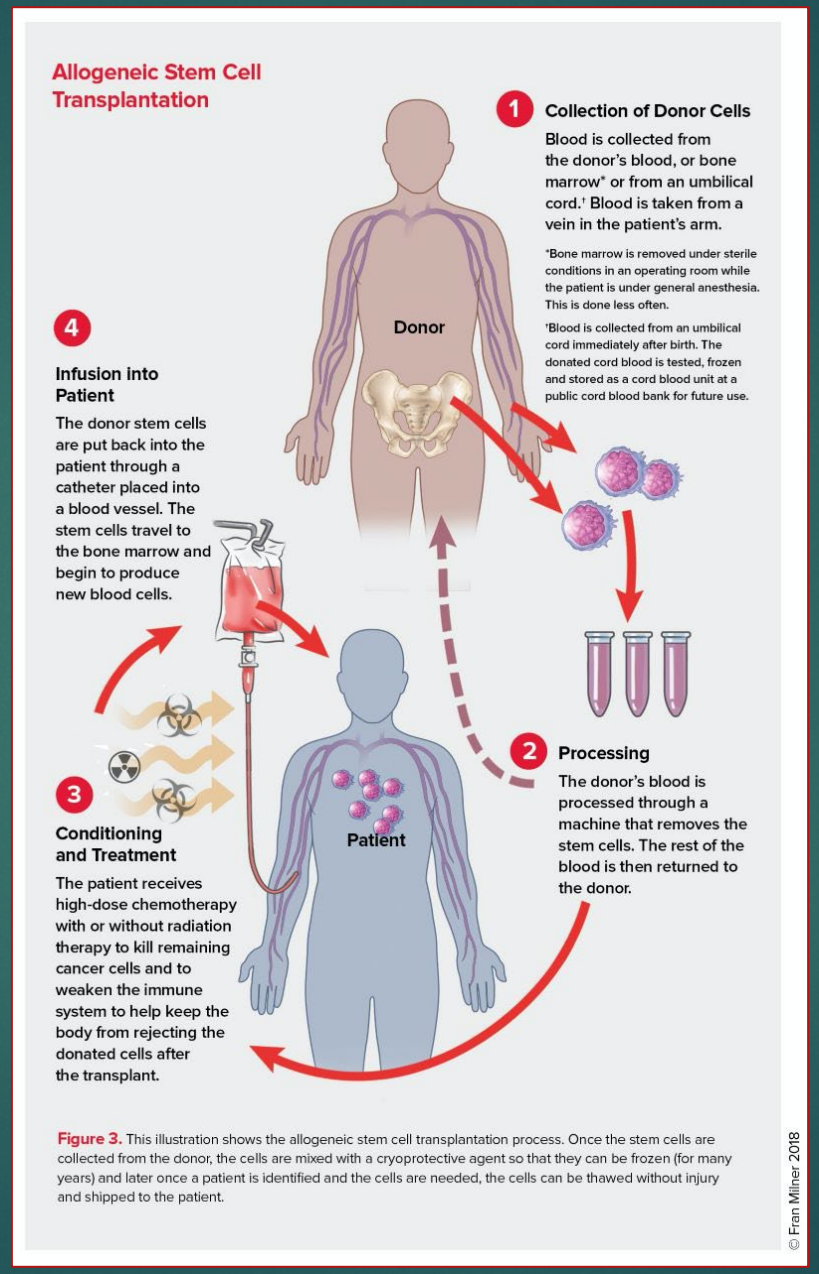
Cord Blood

- P: "Match" criteria less strict, ↓ alloreactive lymphocytes, ↓GVHD per mismatch
- C: Need high cell dose, slow engraftment, ↑ infections, no DLI available

How are the Stem Cells Selected?

***CD34*:** In vitro and surrogate in vivo assays have been used to isolate a population of hematopoietic stem cells capable of multilineage growth. Cells with these functions express the HSC antigen CD34 and are lineage negative. Clinical trials using highly purified populations of CD34+ cells have demonstrated that this cell population alone is capable of rapid and sustained hematopoietic engraftment. Using current technology of magnetic bead separation, CD34+ cells are isolated and purified with high efficiency.

Transplant Process:



Millner, Fran. "Allogeneic Stem Cell Transplantation." Leukemia & Lymphoma Society, https://www.lls.org.

Conditioning Regimens

The preparative (or conditioning) regimen is a critical element in the HSCT process, and the purpose is twofold:

- **To provide adequate immunosuppression to prevent rejection of the transplanted graft**
- **To eradicate the disease for which the transplant is being performed**

Myeloablative – A MAC regimen consists of a single agent or combination of agents expected to destroy the hematopoietic cells in the BM and thereby result in profound pancytopenia within 1–3 weeks. The resulting pancytopenia is long-lasting and irreversible unless hematopoiesis is restored by infusion of stem cells. Examples include total body irradiation ≥5 Gy in a single dose or busulfan >8mg/kg.

Reduced intensity – RIC regimens are an intermediate category of regimens that do not fit the definition of myeloablative or nonmyeloablative. Such regimens cause cytopenias that may be prolonged and may result in significant morbidity and mortality. They may require HSC support. Regimens generally considered RIC include ≤8 mg/kg of busulfan.

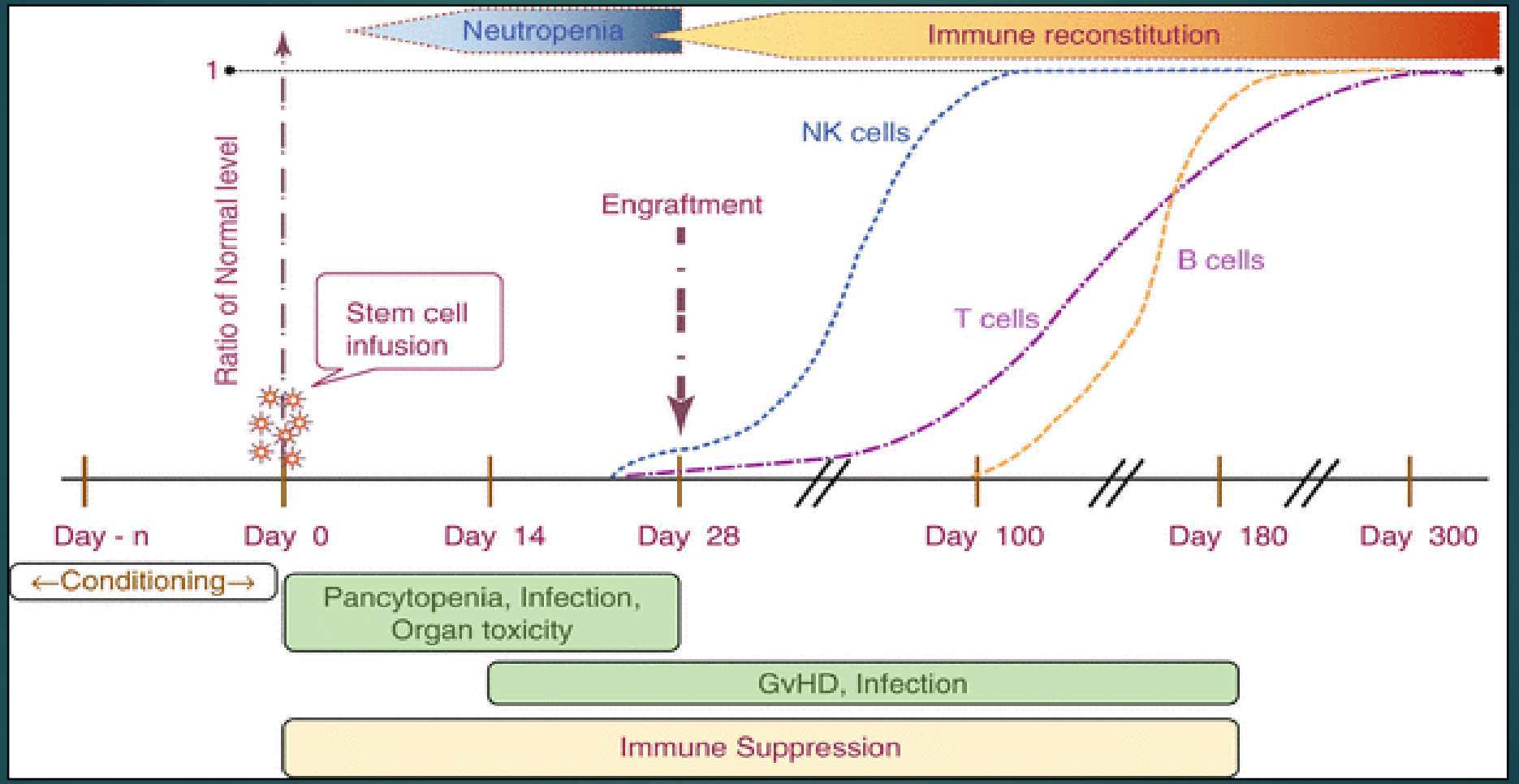
Nonmyeloablative – A NMA regimen is one that will cause minimal cytopenia and may not require stem cell support. Examples include fludarabine plus cyclophosphamide or total body irradiation ≤2 Gy. However, when given in this setting the HSCT usually becomes MAB because the engrafting donor T cells will eventually eliminate host hematopoietic cells and allow the establishment of donor hematopoiesis (graft-versus-marrow effect).

Engraftment

- Neutrophil engraftment occurs first and is generally observed 10–28 days after the stem cell infusion (may take longer for BM or cord blood). Other cell lines engraft subsequently over the next 6 months.
- An absolute neutrophil count of ≥500/mm3 for 3 consecutive days, a platelet count of ≥20,000/m3 for 3 consecutive days (without transfusions for 7 days), and a hematocrit ≥25% for at least 20 days (without transfusions) are criteria for engraftment in those cell lines.
- Multiple factors including underlying disease, pre-transplant therapy, conditioning regimen, graft quality, graft source, and post-transplant complications may affect engraftment.
- **Engraftment syndrome** is a constellation of signs and symptoms that may occur during this period. Signs include major criteria of fever, rash, or non-cardiogenic pulmonary edema and minor criteria of weight gain, hepatic dysfunction, renal dysfunction, encephalopathy, or diarrhea. Treatment includes diuretics and steroids.

Immune Reconstitution

Monocytes, Neutrophils, CD8 T cells, NK cells, Red cells, Platelets, CD4 T cells, B cells



Talekar and Olson. *Immune reconstitution after Hematopoietic Stem Cell Transplantation*, 2017.

Complications of Allo HSCT

Early Complications	Late Complications
Mucositis	cGVHD
Infection	Infection
aGVHD	Relapse
Bleeding	Gonadal Failure
Organ toxicity (Liver/VOD, Cardiac, GI, Renal, Pulmonary)	Secondary Malignancy
Graft Failure	Organ toxicity

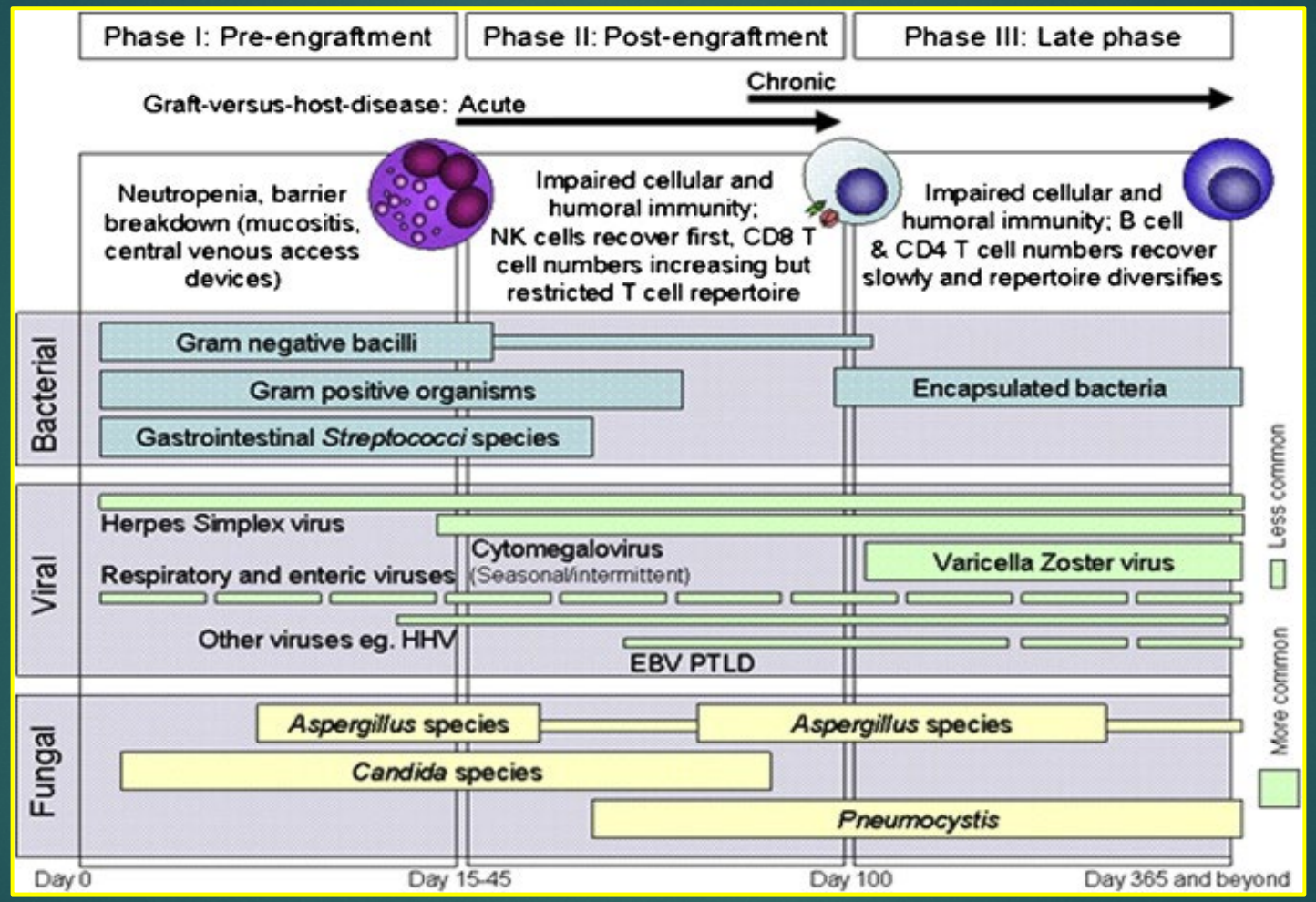
**** The most important factors affecting HSCT outcome include degree of HLA matching, performance status, recipient CMV serostatus, disease status, and graft cell dose.**

Prophylaxis

Infections are a significant cause of non-relapse mortality in HSCT recipients. Specific risk for infection is related to prior exposure history (e.g. relapse of latent infection), intensity of conditioning regimens or immunosuppression, and new exposures in the setting of an altered immune response. The following ppx is given during the transplant course:

Organism/Situation	Options
HSV/VZV	Acyclovir
CMV (if recipient is sero-positive)	Letermovir
Bacterial (febrile neutropenia)	Ceftazidime or Cefipime (at NIH)
Asplenia or cGVHD	Pen VK or Azithromycin
Fungal	Micafungin, Fluconazole, or Posaconazole
Pneumocystis jiroveci (PJP)	Bactrim, Pentamidine, Atovaquone
Toxoplamosis	Bactrim
HBV (if recipient is core Ab+)	Entecavir
Strongyloides (if from endemic area)	Ivermectin

Phases of Opportunistic Infections



Riches et al. *Journal of the ASBMT,* 2009.

Graft-Versus-Host-Disease (GVHD)

GVHD occurs when the donor's T cells (the graft) view the patient's healthy tissues (the host) as foreign, and attack and damage them. Graft-versus-host disease can be mild, moderate or severe. In some cases, It can be life-threatening.

GVHD Prophylaxis:

- Methotrexate (Trexall®)
- Cyclosporine
- Tacrolimus (Prograf®)
- Mycophenolate mofetil (CellCept®)
- Sirolimus (Rapamune®)
- Corticosteroids (methylprednisolone or prednisone)
- Antithymocyte globulin (ATG)
- Alemtuzumab (Campath®)
- Cyclophosphamide (Cytoxan®)

ACUTE GVHD

Usually develops within the first 100 days after transplantation, but can occur later. Affects the skin, the GI tract, or the liver.

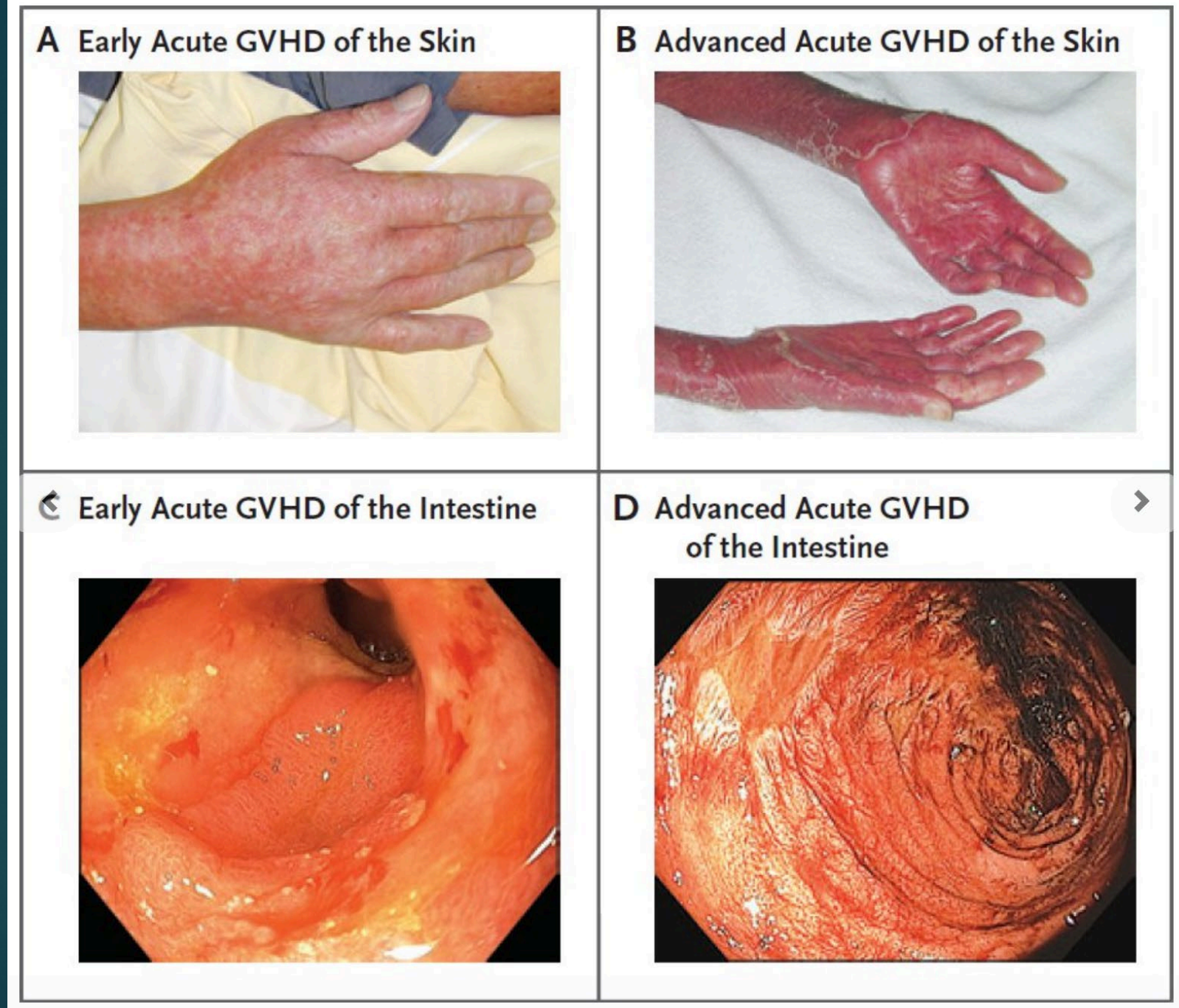
- **SKIN:** A rash, with burning and redness of the skin. This may erupt on the patient's palms or the soles of the feet, and often involves the trunk and other extremities as well. The skin may blister or flake off in severe cases.
- **GI tract:** Nausea, vomiting, abdominal cramps, loss of appetite and diarrhea.
- **LIVER:** Jaundice, abnormal LFTs

Treatment: High dose IV steroids (may harm graft). No standard 2nd line therapy: may use CNI, MMF, sirolimus, infliximab, daclizumab, ECP, etanercept, tocilizumab, pentostatin, or Campath. Mortality associated with steroid-refractory GVHD is > 50%. Most deaths are related to infectious complications.

Acute GVHD Scoring

GVHD Staging			
Stage	Skin	Liver (total bilirubin)	GI tract (diarrhea output/day)
0	No GVHD rash	<2 mg/dl	Adult: <500 ml/d *Child: <10 ml/kg/d
1	Maculopapular rash <25% body surface area	2-3 mg/dl	Adult: 500-999 ml/d Child: 10-19.9 ml/kg/d -or- persistent nausea, vomiting, or anorexia with a positive upper GI biopsy
2	Maculopapular rash 25-50% BSA	3.1-6 mg/d	Adult: 1000-1500ml/d Child: 20-30 ml/kg/d
3	Maculopapular rash >50% BSA	6.1-15 mg/dl	Adult: >1500ml/d Child: >30 ml/kg/d
4	Generalized erythroderma (>50% BSA) plus bullous formation or desquamation >5% BSA	>15 mg/dl	Severe abdominal pain with or without ileus, or grossly bloody diarrhea
*Use adult values for patients ≥ 50 kg			
Overall Clinical Grade: Grade 0: No GVHD of any organ Grade 1: Stage 1-2 skin and no liver OR GI tract involvement Grade2: Stage 3 skin and/or stage 1 liver and/or stage 1 GI tract Grade 3: Stage 0-3 skin with stage 2-3 liver and/or stage 2-3 GI tract Grade 4: Stage 4 skin, liver, and/or GI tract			

Glucksberg et al. *Transplantation,* 1974.



Zeiser, et al. *N Engl J Med,* 2017.

CHRONIC GVHD

A **syndrome** that may involve a single organ or several organs. Occurs anywhere from 3 months to a year following allo HSCT. Occurs in approximately 30-70% of patients receiving an allo transplant and is a leading cause of medical problems or death after transplant.

- **Mouth:** dryness, sensitivity to foods, painful ulcers, gum disease/tooth decay
- **Skin/Nails:** rash, dry/itchy skin, thickening/tightness of skin w/ joint restriction (scleroderma), brittle nails, hair or nail loss
- **GI Tract:** loss of appetite, weight loss, N/V/D, abdominal pain
- **Lungs:** SOB, dyspnea, chronic cough, wheezing
- **Liver:** abdominal distension, jaundice, transaminitis
- **Muscles/Joints:** muscle weakness and cramps, joint stiffness
- **Genitalia:** vaginal dryness/itching/pain, vaginal/penile/scrotal ulcerations and scarring, dyspareunia, narrowing of vagina or urethra

Treatment: systemic steroids, calcineurin inhibitors, sirolimus, MMF, methotrexate, rituximab, ruloxitinib, ECP, imatinib, ibrutinib, and pomalidomide.

Chronic GVHD Scoring

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	Symptomatic, ambulatory, capable of self-care, >50% of waking hours of bed (ECOG 2, KPS or LPS 60-70%)	Symptomatic, limited self-care, >50% of walking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN † ☐ **SCORE % BSA** *GVHD features to be scored by BSA:* **Check all that apply:** Maculopapular rash/erythema; Lichen planus-like features; Sclerotic features; Papulosquamous lesions or ichthyosis; Keratosis pilaris-like GVHD	No BSA involved	1-18% BSA	19-50% BSA	>50% BSA
SKIN FEATURES SCORE:	No sclerotic features		Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** Deep sclerotic features "Hidebound" (unable to pinch); Impaired mobility; Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** Hyperpigmentation; Hypopigmentation; Poikiloderma; Severe or generalized pruritus; Hair involvement; Nail involvement; *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* **Yes** **No**	No symptoms	Mild symptoms **with** disease signs but not limiting oral intake significantly	Moderate symptoms with disease signs **with** partial limitation of oral intake	Severe symptoms with disease signs on examination **with** major limitation of oral intake
*Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Jagasia, et al. "*Biol Blood Marrow Transplant,* 2015.

cGVHD Scoring, cont'd

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS** **Symptom score**:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **%** FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

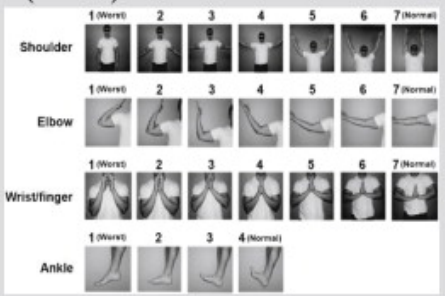
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ___ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

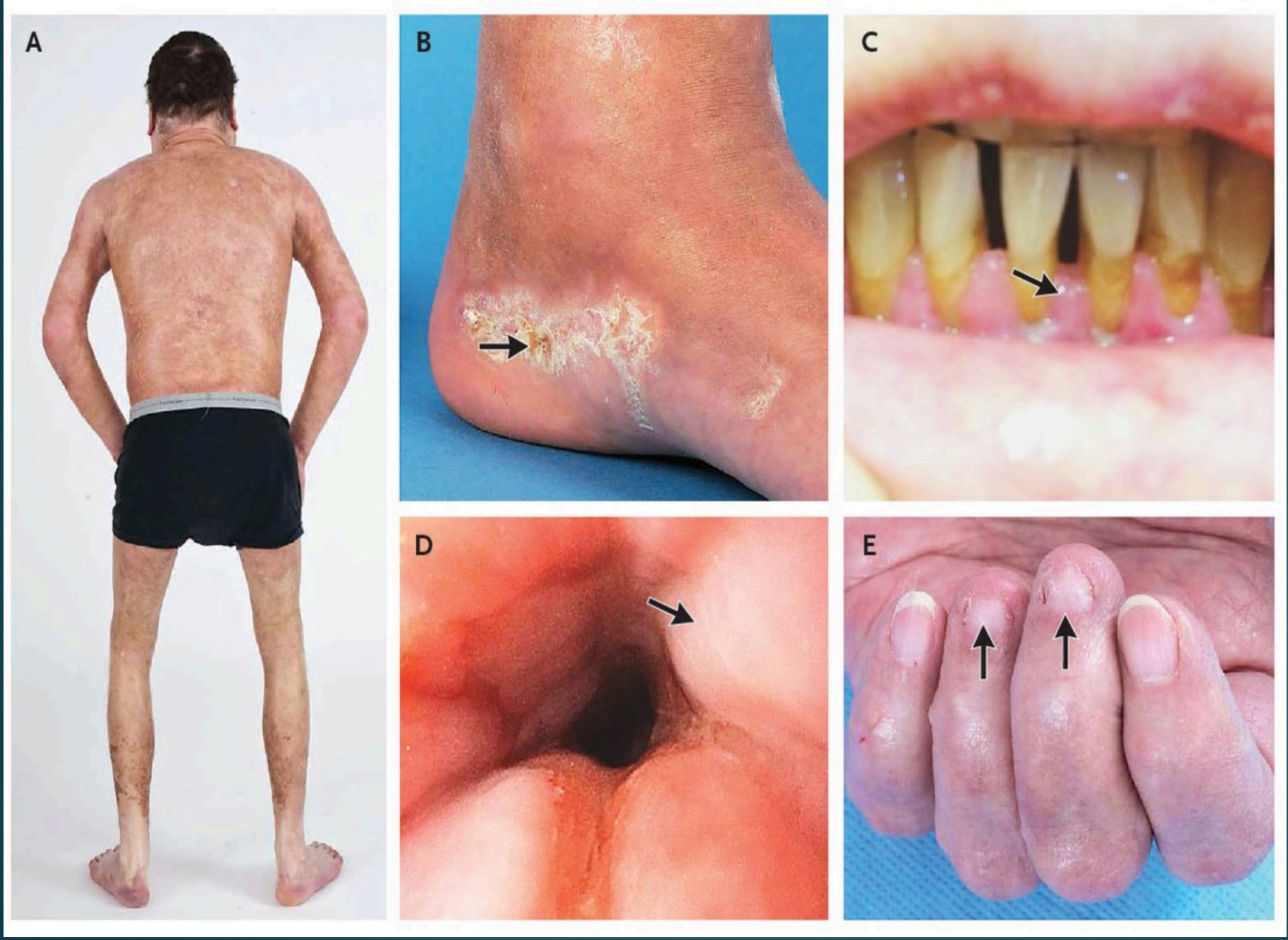
Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ❑ **No GVHD** ❑ **Mild** ❑ **Moderate** ❑ **Severe**

Photographic Range of Motion (P-ROM)





Zeiser, et al. *N Engl J Med,* 2017.

How do we know whose cells have engrafted?

WBC Chimerism: a laboratory study that relies on pre-transplant samples to identify unique DNA fragments in both the donor and the recipient. The post-transplant sample is assessed for the presence of these unique identifiers. Chimerism is usually expressed as a percentage, and a 100% chimerism reflects that all hematopoietic cell lines in the recipient are of donor origin. Chimerism usually improves over time due to the **"graft versus marrow"** effect.

Long Term Follow Up Care

- Frequent follow up is necessary through day 100 to evaluate for GVHD and other complications. Disease reassessment occurs at different intervals post-transplant.
- Immune suppression: (GVHD ppx) should be tapered gradually post-transplant in a step-wise, linear fashion.
- Vaccines: auto and allo transplant patients should be treated as though they have never been vaccinated. Live vaccines (Varicella, MMR) should be avoided for at least 2 yrs post HSCT and for as long as the patient is on immunosuppressive therapy.
- DEXA: patients are at high risk of developing osteoporosis post HSCT. They should be screened with a DEXA scan after a year and started on calcium/vitamin D prn.
- Endocrine: patients should be screened for endocrine abnormalities (thyroid studies, testosterone, estrogen, FSH, LH). Hormone replacement may be necessary.
- Skin care and diet: patients should wear sun protection as skin is more sensitive following chemo exposure. They should also maintain a low bacteria diet following transplant to prevent food-borne illnesses.

Future Indications/Studies

Solid Tumor Indications for Allo HSCT:

- Initial reports have demonstrated that GvT effect may occur against some solid tumors, including breast cancer, ovarian cancer, renal cell carcinoma, and others. Currently, HSCT may be a clinical option (after careful assessment of risks and benefits) for relapsed/resistant renal cancer. It remains a developmental therapy (further trials are needed) for breast and ovarian cancer.

Additional Studies at NIH on which I am a contributor:

- Use of HSCT for primary immune deficiencies
- Use of HSCT for disorders of T-cell proliferation and/or dysregulation
- Optimizing dose and timing of post transplant cyclophosphamide (used to prevent GVHD)

Case #1

- 28 yo male with AML in CR admitted for matched related donor BMT using a fludarabine/busulfan myeloablative conditioning regimen.
- Day +10 post transplant experienced 20% weight gain since admission, sharp decrease in urinary output, and painful hepatomegaly.
- Day +15 developed respiratory distress with labs significant for serum creatinine of 2.5 and total bilirubin of 4.

Hepatic Sinusoidal Obstruction Syndrome (Veno-occlusive disease)

VOD is characterized by injury to the hepatic venous endothelium following transplant, causing widespread zonal liver disruption and centrilobular hemorrhagic necrosis. Occurs in approximately 14% of transplant patients (incidence varies). Pre-existing liver disease, use of MAB conditioning, and drugs like Busulfan or Sirolimus are risk factors. Usually occurs within 21 days of HCT.

** Baltimore diagnostic criteria include bili >2 and two of the following: hepatomegaly, ascites, weight gain >5%.

Management:

- Consider Defibrotide
- Trend weight closely, restrict fluids, diurese to restore euvolemia
- Consider paracentesis when ascites does not respond to medical management (sodium restriction, diuretics).
- Infuse albumin to correct hypoalbuminemia following paracentesis.
- Consider thoracentesis if effusion contributes to poor oxygenation.

Case #2

- 18 yo male with ALL admitted for haplo PBSCT. Received RIC regimen.
- Day +21 developed diffuse diarrhea (>3 liters per day). Viral cultures and stool studies were negative.
- Day +27 experienced continued increase in stool output with grossly bloody stools and significant drop in Hgb. A colonoscopy showed diffuse erythema and biopsy revealed apoptotic bodies.

Acute GVHD

- A leading cause of morbidity and mortality following allo HSCT.
- Up to 50% of allogeneic HCT patients develop grade II – IV GVHD.
- Steroid-refractory GVHD has a very poor survival rate of less than 30%
- Risk factors include extent of HLA disparity, age of both the recipient and the donor, gender disparity, multiparous female donors, ineffective GVHD prophylaxis, transplant conditioning regimen and source of graft.

GVHD Management

- Maintain therapeutic CNI levels
- 1st line treatment: high-dose steroids
- 2nd line treatment options: CNI, MMF, sirolimus, infliximab, daclizumab, ECP, etanercept, tocilizumab, pentostatin, or Campath.
- Supportive care: emollients, octreotide for diarrhea, pain management

Case #3

- 54 yo F with T cell lymphoma admitted for MUD PBSCT. Of note, the patient had prolonged neutropenia prior to admission.
- On day +5 after transplant, her CBC showed a WBC of <0.1/µL. She developed a fever to 39°C, chills, and a BP of 60/30.
- She received two 1L NS boluses with no improvement in her BP.

Sepsis

- A leading causes of ICU admission in HSCT
- Transplant patients have a 4-fold increased risk of mortality with severe sepsis
- Transplant patients admitted to the ICU for sepsis are more likely to require renal replacement therapy, corticosteroids, insulin, and blood products.
- HSCT recipients have increased risk of multidrug resistant organisms
- Gram negative (esp enteric) and gram positive cocci (esp strep viridans) bacteria are most common causative agents during early post transplant period, followed by viral infections.

Sepsis Management

- Empirical antibacterial therapy should include broad-spectrum β-lactam antibiotics such as ceftazidime, cefepime, piperacillin/tazobactam, or carbapenem
- Consider steroids
- Maintain glucose control below upper limit of normal (150-180) with an insulin sliding scale regimen.

Resuscitation Goals:

- Achieve central venous pressure (CVP) of > 8 mm Hg
- Achieve central venous oxygen saturation (ScvO2) of > 70%
- Achieve MAP > 65 mmHg and a urine output of > 0.5 ml/kg/h

Bone Marrow Registry

https://bethematch.org

Chimeric Antigen Receptor = CAR

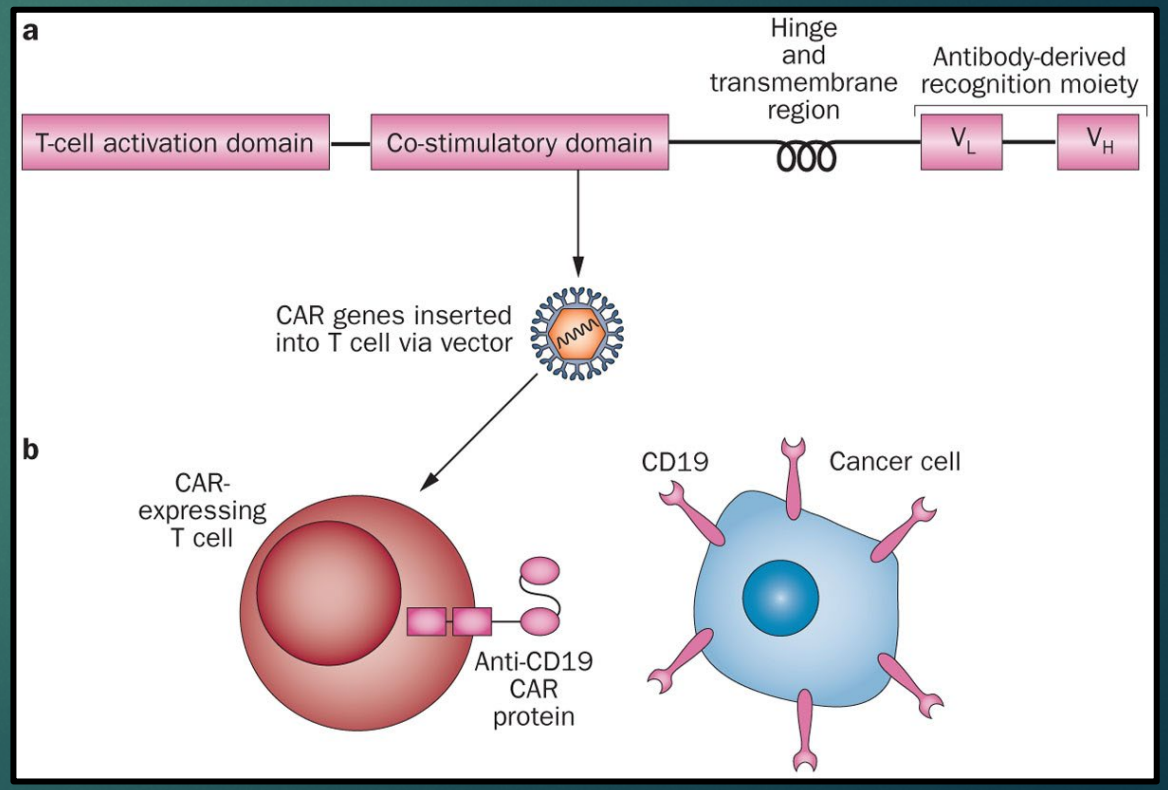
- For years, the foundations of cancer treatment were surgery, chemotherapy, and radiation therapy.
- In recent years, **immunotherapy** has emerged as the most important new field in cancer treatment. It involves harnessing the power of the patient's own immune system to target cancer cells. Examples include monoclonal antibodies, tumor vaccines, and checkpoint inhibitors.

One rapidly evolving immunotherapy approach is **adoptive cell transfer (ACT),** which involves collecting and manipulating immune cells and "transferring" them into a patient to attack cancer. HSCT and TILS are older examples of ACT, while newer examples include TCRs and **CAR T-cells.**

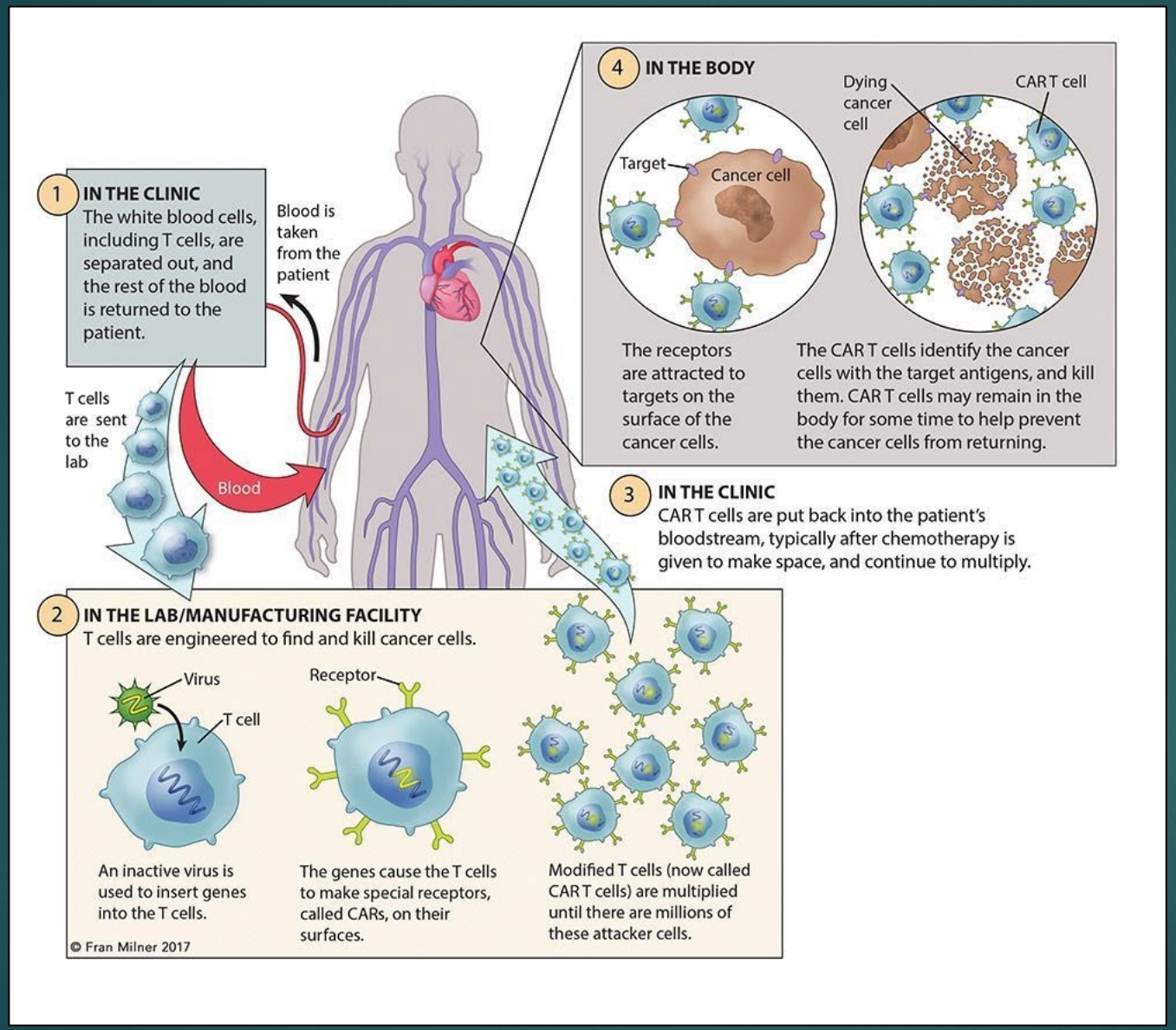
How are CAR T-cells made?

- Patient undergoes apheresis to remove WBCs and separate T-cells
- T-cells are transfected using lentiviruses or retroviruses to express a CAR
- The CAR is a recombinant receptor construct that includes:
  - An extracellular targeting domain derived from a monoclonal antibody that recognizes a specific antigen
  - Transmembrane domain
  - Co-stimulatory domain
  - T-cell activation domain

- **CAR-T cells become activated after binding a specific antigen on tumor cells.**
- **They kill tumor cells via secretion of perforin & granzyme or activation of death receptor signaling.**



Kochenderfer and Rosenberg. *Nature Reviews,* 2013.



Lymphodepleting chemotherapy is given prior to cell infusion to "make room" for the CAR T-cells.

Millner, Fran. "CAR T-Cell Therapy: How it Works." Leukemia & Lymphoma Society, https://www.lls.org.

Advantages of CAR T-cells

- HLA-independent antigen recognition that enables universal application
- Short treatment time (typical admission is 2 weeks)
- Rapid recovery following resolution of cytokine release syndrome
- Activity in both CD4+ and CD8+ T cells
- Action as a "living drug" with the potential to persist for years

FDA Approved CAR T-cell Therapies

Kymriah (tisagenlecleucel)

- **CD19 targeted, autologous**
- FDA approved August 30, 2017 to treat patients < 25 yo with refractory or 2nd relapsed pre-B ALL
- FDA-approved May 1, 2018 to treat patients >18 yo with relapsed, refractory large B-cell lymphoma after 2 lines of therapy

Yescarta (axicabtagene ciloleucel)

- **CD19 targeted, autologous**
- FDA approved October 19, 2017 to treat relapsed or refractory large B-cell lymphomas (including DLBCL)

** Cost of single cell infusion is around $373,000

CAR T-cell Therapy for ALL

- Pediatric and young adults with ALL have a 5 year survival of 78-91%
  - 2-3% will have refractory disease
  - 10-15% of patients will relapse
- Prognosis for R/R ALL is poor
  - Estimated 10 year survival in children ages 0-18 is 31%
- For patients whose cancers returned after chemotherapy or a stem cell transplant, the treatment options were limited
- ELIANA was the global, phase 2 trial that led to FDA approval of tisagenlecleucel for relapsed, refractory ALL
- Will CAR T-cells eventually replace HSCT in ALL?
  - Might be preferable for patients who are MRD+, have poor donor options, are ↑ risk for toxicities with HSCT, or have post-HSCT recurrence

CAR T-cell Therapy for DLBCL

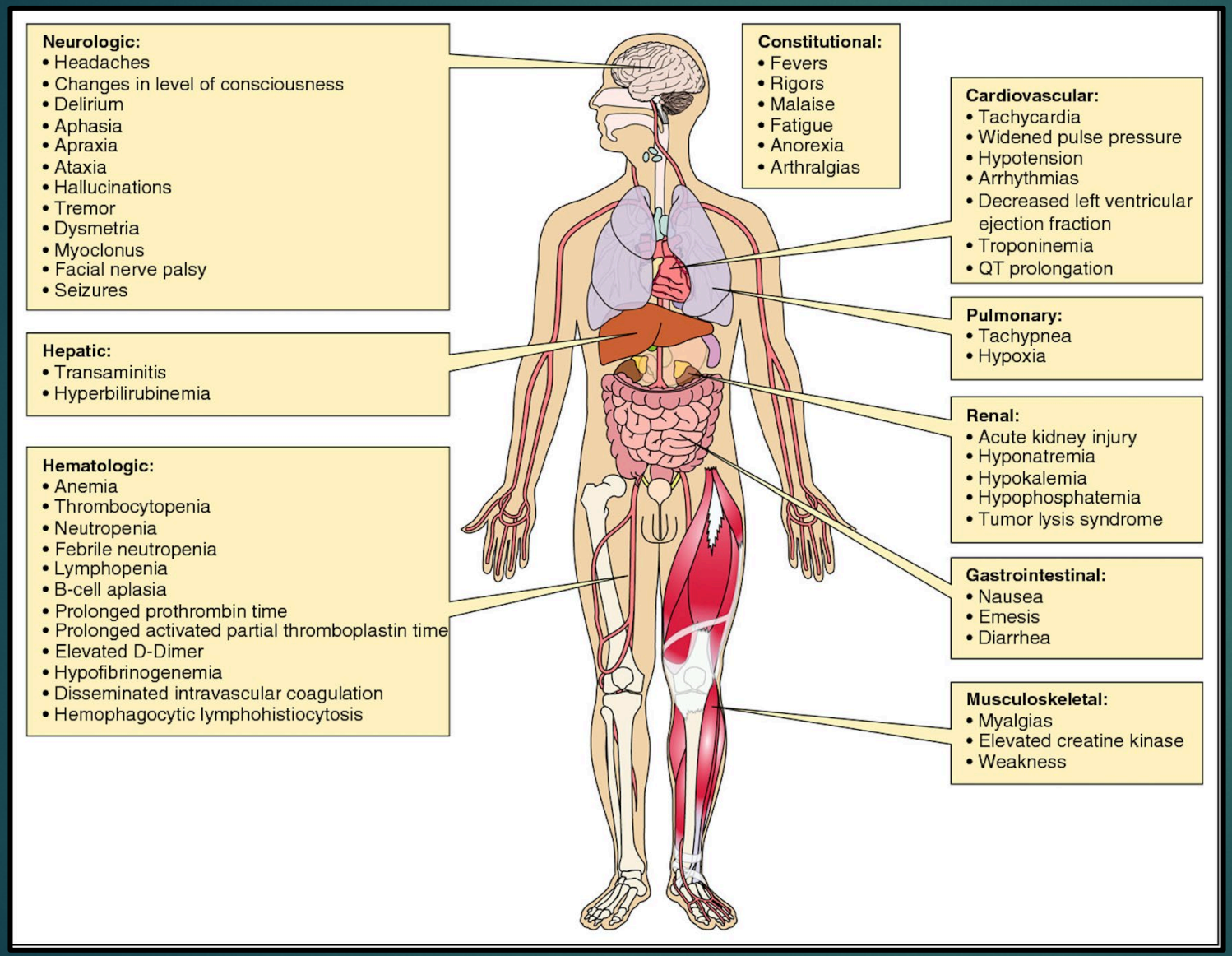
- Most common type of non-Hodgkin's lymphoma
- Chemoimmunotherapy can be curative
  - 30-40% of patients will relapse
  - 10% of patients will have refractory disease
- Poor prognosis for relapsed patients who are ineligible for auto HSCT or have failed 2nd line therapy
- Treatment options include additional chemotherapy or allo-HSCT
- ZUMA-1 was the global, phase 2 trial that led to FDA approval of Yescarta
- JULIET was the global, phase 2 trial that led to FDA approval of Kymriah

Are CAR T-cells Effective?

Disease	Complete Remission	Overall Response Rate	
ALL, peds	66-90%		
ALL, adults	88%		
NHL	53%	80%	
CLL	22%	57%	

Adapted from "CAR 101" by Dr. Jennifer Brudno, NCI.

Severe Toxicities Can Occur



Toxicity risk factors include: disease type (ALL ↑ risk), higher percentage of BM involvement, higher disease burden, type of chemo, higher cell dose, structure of CAR.

Brudno and Kochenderfer. *Blood,* 2016.

Cytokine Release Syndrome (CRS)

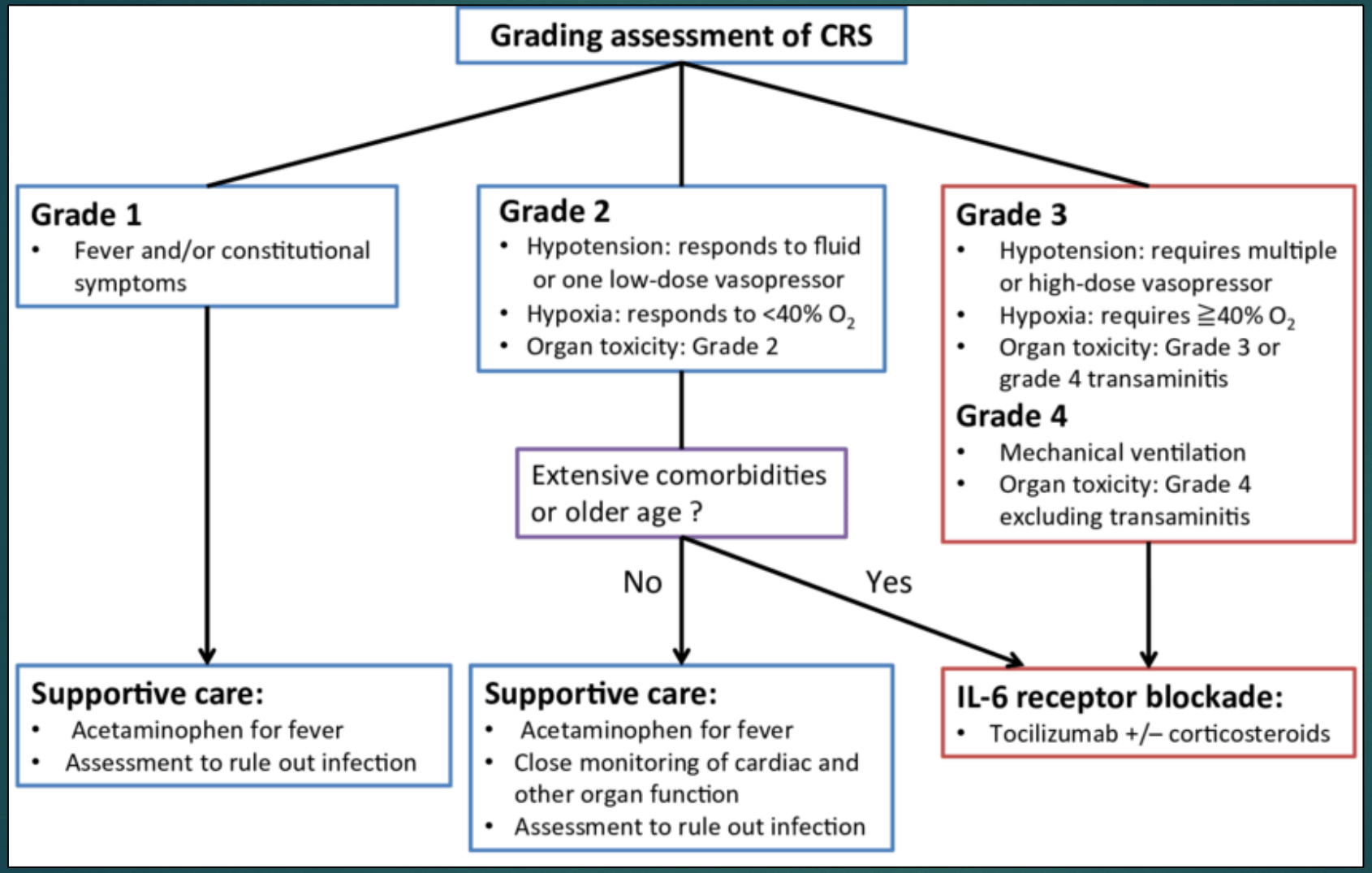
An immune activation resulting in elevated inflammatory cytokines like Interferon-gamma, IL6, and IL-10.

Most common adverse event! (occurs in 80-90% of patients)

- Median time to onset is 2-3 days (onset ranges from 1-22 days)
- Median duration is 7-8 days
- Presentation is similar to sepsis

- Degree of severity depends most on tumor burden
- Development of CRS does not necessarily correlate with response

CRS Grading & Management:



Tobinai et al. *Cancer Science*, 2017.

** Corticosteroids may be required in severe cases, but they can impair the CAR-T cells and correlate with less tumor responsiveness.

Neurologic Toxicity

- Cytokine-mediated endothelial activation causes coagulopathy, capillary leak, and blood brain barrier disruption
- Usually occurs within 8 weeks of cell infusion and is typically transient
- Signs/symptoms include HA, delirium, anxiety, confusion, agitation, tremor, altered consciousness, seizures, aphasia
- May be concurrent with CRS or may occur later following resolution of CRS
- May require corticosteroid intervention (tocilizumab can't cross BBB)

Other Potential Side Effects

- **Tumor Lysis Syndrome** (use allopurinol for prophylaxis)
- **Anaphylaxis**
- **On-target, Off-tumor Toxicity** (must choose target very carefully)
- **B-cell Aplasia** (often requires IVIG)

Current NCI CAR T-cell Trials

Target	Disease
BCMA	Multiple Myeloma
SLAMF7	Multiple Myeloma
CD30	Hodgkin Lymphoma
CD19	Non Hodgkin Lymphoma (follow-up only

Can They Stop Working?

CAR T-cells have activity against chemo refractory diseases, and cancer remissions can be durable. Some reasons patients may relapse over time include:

- Changes in tumor microenvironment or the effects of neighboring cells may cause 'CAR T cell exhaustion' and result in decreased proliferation and efficacy.
- Elevated expression of inhibitory signals around the CAR T cells may suppress them.
- Cancer cells may evolve and stop expressing the target protein.

The Future of CAR T-cells

- **Combination with checkpoint inhibitors**
- **Dual antigen targeting**
- **Armored CARs:** express additional pro-inflammatory cytokines to increase proliferation, cytolysis, and persistence
- **Expansion of potential targets in malignant disease:** CD125, CD133, EGFR, HER2, CEA, PSMA, L1-CAM, MUC1, mesothelin

Will CAR T-cells ever be effective against solid tumors like breast and colorectal cancer?

- Efforts to identify unique antigens on the surface of solid tumors have thus far been largely unsuccessful, but new ideas and innovations are constantly being developed.

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THANK YOU!

ANY QUESTIONS?

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