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BLOOD & MARROW TRANSPLANT INFORMATION NETWORK

Introduction to Graft-versus-Host Disease

Celebrating a Second Chance at Life Survivorship Symposium

April 17- 23, 2021

Marcello Rotta MD
Colorado Blood Cancer Institute,
Presbyterian St. Luke's Hospital

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Introduction to

Graft Versus Host Disease

BMTinfonet.org - Symposium 2021
April 17th, 2021

Marcello Rotta, MD
Assistant Member
Leukemia Service Director
Long Term Follow Up Service Co-Director
Colorado Blood Cancer Institute
Presbyterian St. Luke's Hospital
Denver, CO

CBCI COLORADO BLOOD CANCER INSTITUTE

SARAH CANNON Cancer Institute at Presbyterian/St. Luke's Medical Center | HealthONE

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Introduction to Graft-versus-Host Disease (GVHD)

1. Donor cell transplant : a quick introduction
2. Mechanisms leading to GVHD
3. Incidence and risk factors for GVHD
4. Signs and symptoms of GVHD
5. Prevention of GVHD
6. GVHD treatment

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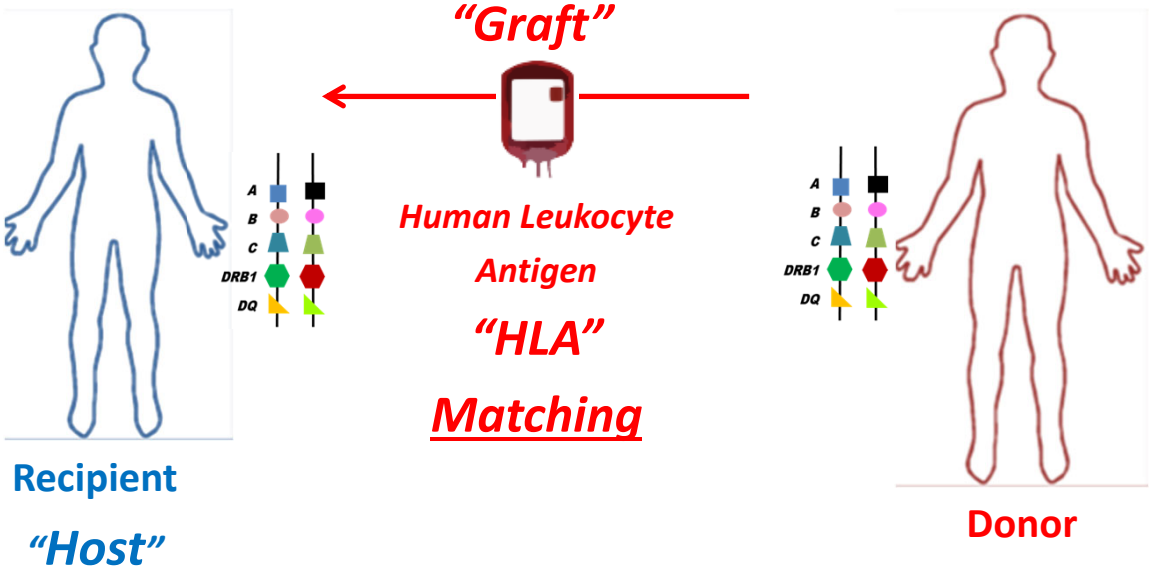
Donor cell transplant



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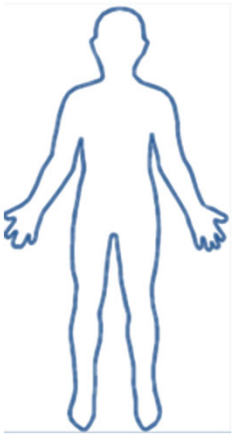
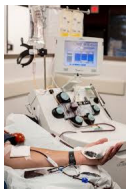
Source of cells for allogeneic stem cell transplant



Recipient

"Host"

Peripheral Blood Stem Cell



Bone Marrow Harvest

Cord Blood Unit

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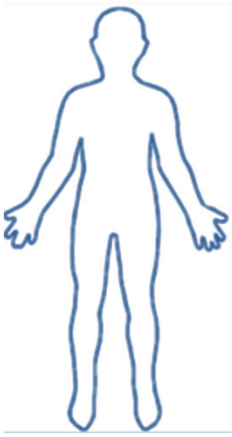
Potential donors for allogeneic stem cell transplant



Recipient

"Host"

<u>In the Family:</u>
Matched Sibling
Haploidentical

<u>Volunteers:</u>
Matched Unrelated
Cord Blood

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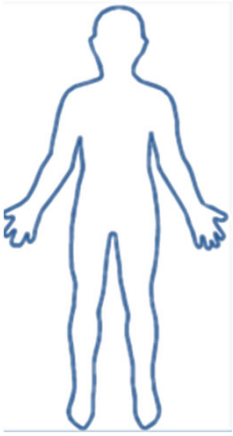
What is the donor really donating?



Recipient
"Host"

Blood forming cells:
Replace host's stem cells

Immune Cells:
Destroy cancer cells in the recipient
"Graft versus Leukemia"

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Transplant: Unique way to treat blood cancers

- ❑ "4 MUST":
  1. Recipient disease status
  2. Recipient fitness status
  3. Donor availability
  4. Support system
- ❑ IMMUNOTHERAPY: Graft versus Leukemia → CURE
- ❑ LIFE CHANGING

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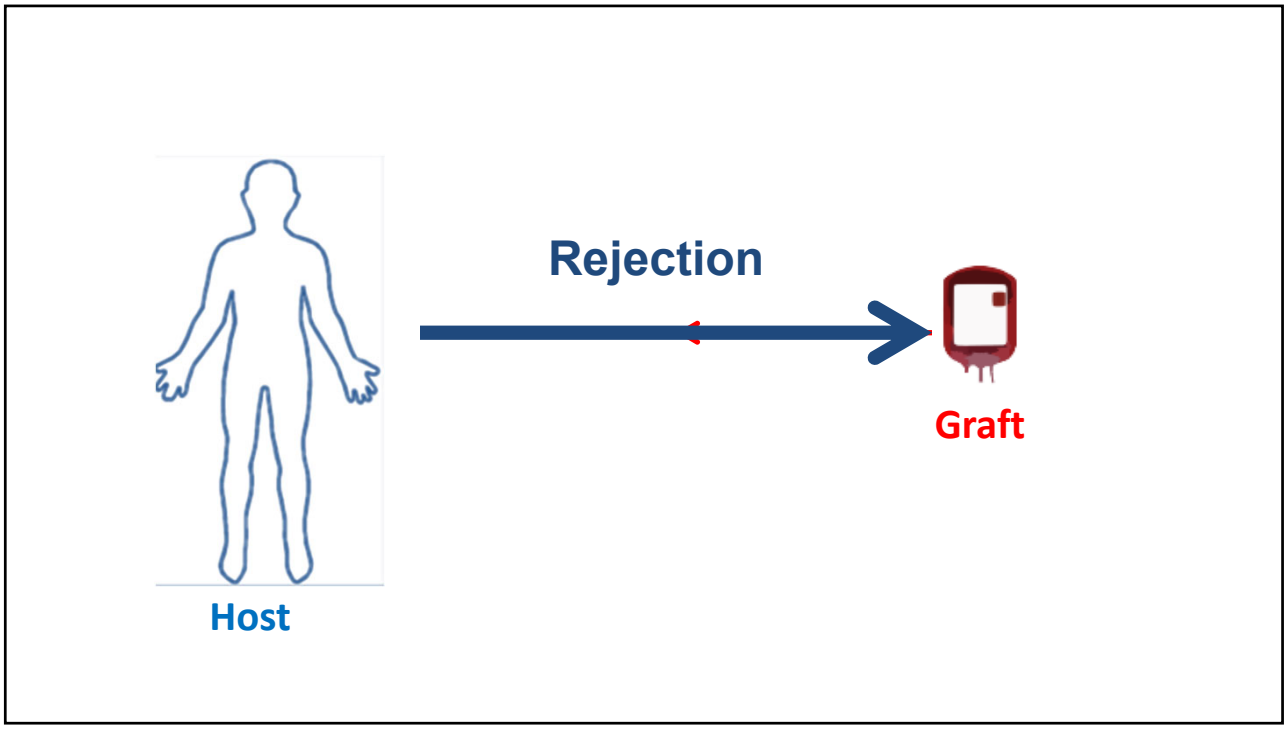
Rejection
Graft
Host

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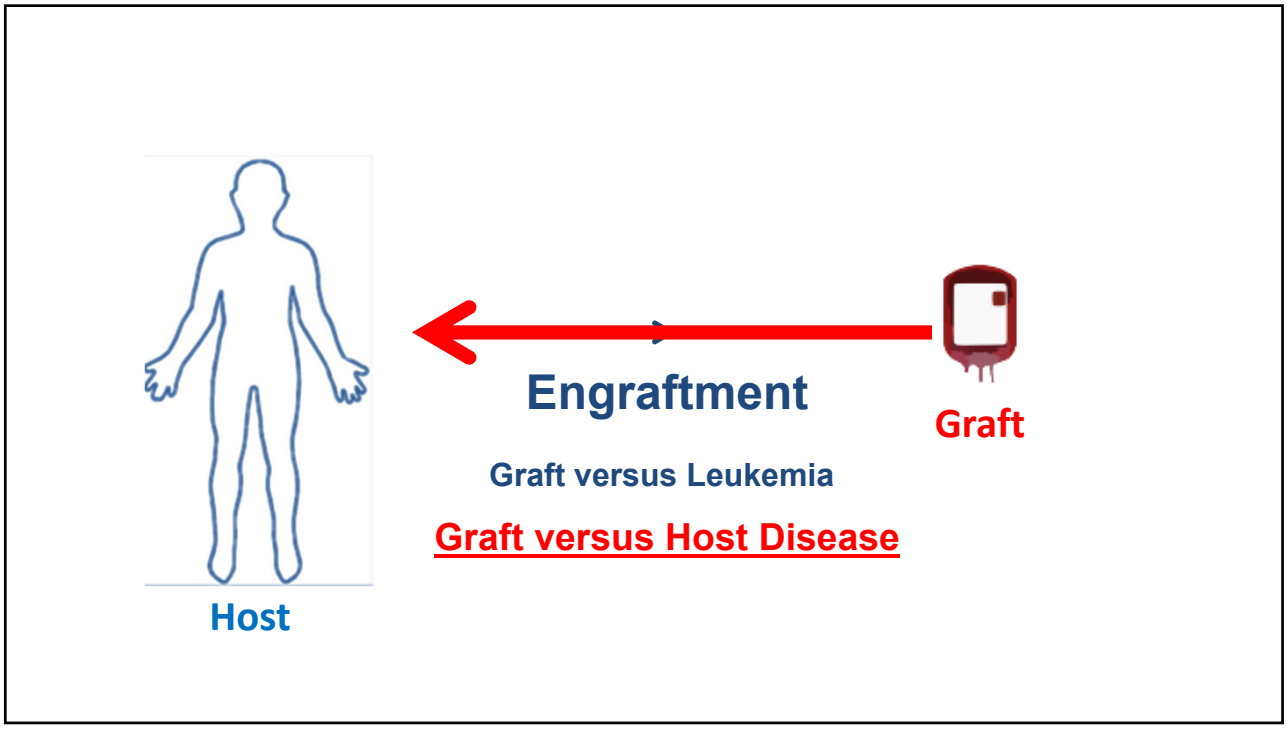
Engraftment
Graft
Graft versus Leukemia
Graft versus Host Disease
Host

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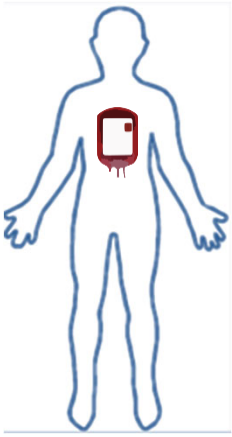
Allogeneic transplant: How to define success



Tolerance

- ❑ Engraftment
- ❑ Cure the leukemia
- ❑ NO Graft versus Host Disease
- ❑ Provide immunity lifelong

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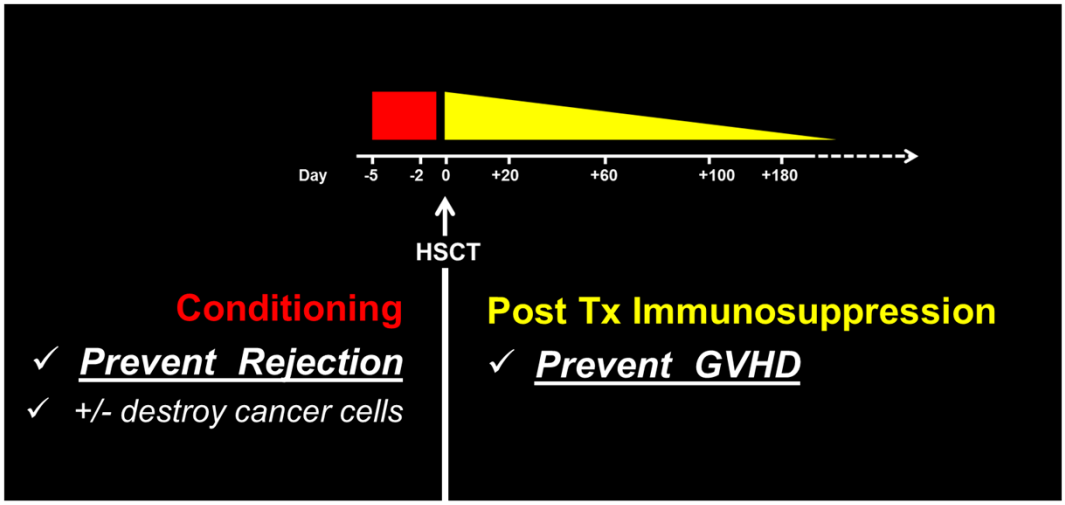
Allogeneic transplant: General Schema



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What is Graft-versus-Host Disease (GVHD)?

- **Biological consequence** of the transfer of a donor immune system into the recipient
- Immunosuppressive medications **to prevent GVHD is necessary**
- GVHD can be eliminated by **removing immune cells (T-cells) from the donor collection**

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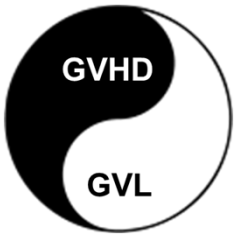
Graft-versus-host disease (GVHD)

- **GVHD** is associated with **graft-versus-leukemia (GVL) effect**
- **Remove the donor T cells** from transplant = increase risk of disease relapse



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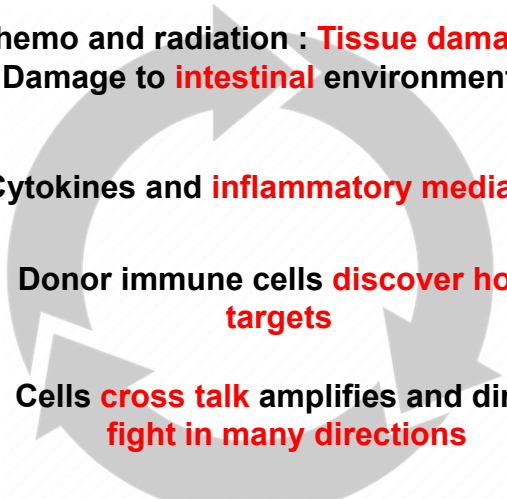
GVHD: How does it happen?



Chemo and radiation : Tissue damage
Damage to intestinal environment

Cytokines and inflammatory mediators

Donor immune cells discover host targets

Cells cross talk amplifies and direct fight in many directions

Issues in *control* and *education* the immune cells

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Acute GVHD: three-step model

(1) INITIATION Phase:
- Chemo and radiation→ inflammation
- Release of inflammatory substances

(2) ACTIVATION Phase:
Donor Immune cells
- "recognize" non self environment
- expand in number

(3) EFFECTOR Phase:
Donor immune cells ***attack tissues***

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Chronic GVHD: It gets complicated

- **Tissue damage → Inflammation**
- Damage to small vessels
- Donor B and T cells expand into an **"aggressive subtype"**
- Immune cells **escape regulation**: attack recipient organs
- **Inflammation persists**
- **Activation of cells macrophages and fibroblast → Fibrosis**
- Overproduction of **antibodies** that target body and deposit into organs

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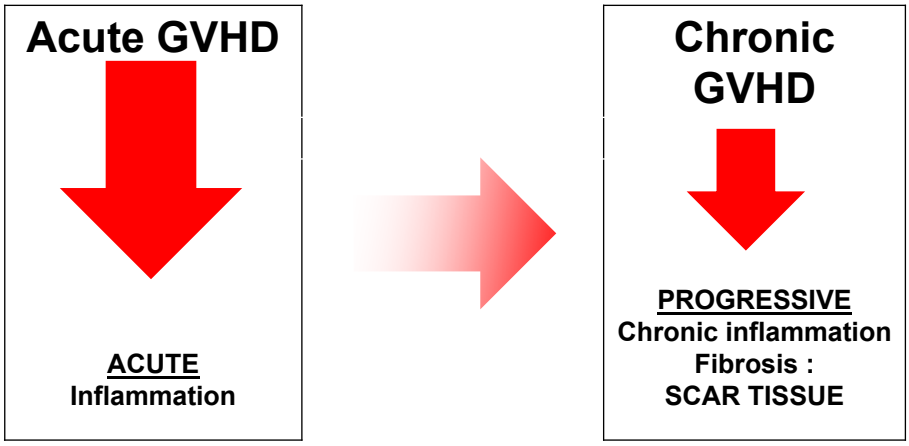
GVHD: Acute and Chronic



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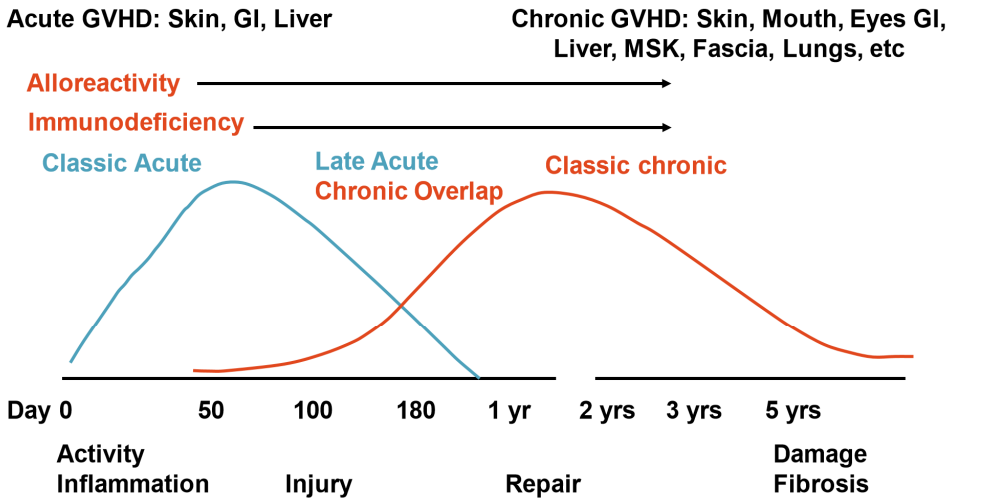
GVHD: Acute and Chronic



Cutler BMTinfo 2020

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Acute GVHD:

- About 70% of patients get it
- Most commonly early after transplant (2-6 weeks), but can happen later too (past 3 months)
- Bad or life threatening in 10-15% of patients
- When happens the first treatment does not work in 30-40% of cases
- Leading cause of early post transplant death

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Acute GVHD: Risk factors

Donor factors	HLA Mismatched
	Unrelated donor
	Sex mismatch {Woman → Man}
	If donor is a woman: number of pregnancies
	Older donor
Transplantation factors	Stem cell source {Blood > Bone marrow > cord blood}
	High cell dose
	Pre-transplant chemo or radiation {more >less intense}
	Post- transplant immunosuppression combo

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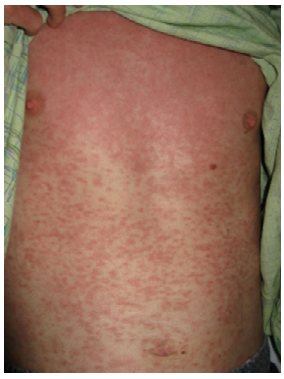
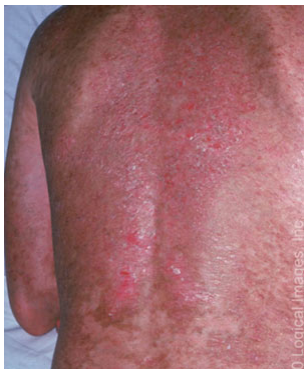
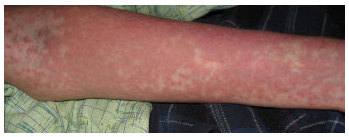
Organs affected by acute GVHD

Skin	Rash
GI	Diarrhea No appetite Nausea vomiting Rapid weight loss
Liver	Increased labs







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Chronic GVHD

- Most serious and common long-term complication of transplant
- Occurs in 30% (young, sibling donors) to 70% (older, unrelated donors)
- Median time to development is 4-6 months after Transplant
- 50% of patients have 3 or more involved organs/tissues
- On average needs treatment for 2-3 years; 15% require therapy >7 years

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Chronic GVHD: Risk factors

Previous history of severe acute GVHD

Same as acute GVHD

Donor factors

Transplant factors

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Chronic GVHD: Organ Involvement

608 FLOWERS and MARTIN BLOOD, 22 JANUARY 2015 • VOLUME 125, NUMBER 4

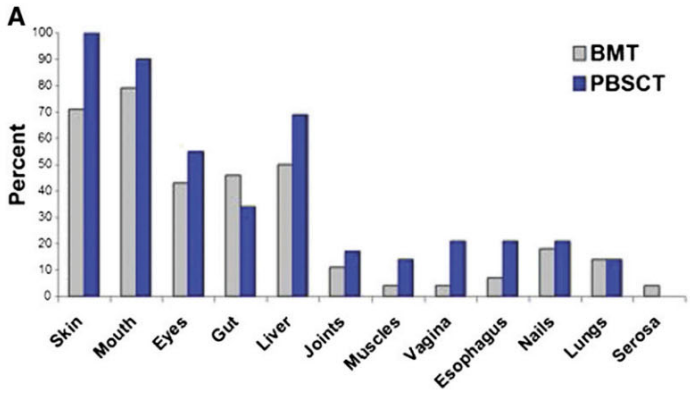

Figure 1. The frequency of involvement by chronic GVHD varies across organs and sites and is higher after HCT with mobilized blood cells as compared with marrow. (A) The most frequently involved organs and sites are the skin, mouth, eyes, gastrointestinal tract, and liver.[3] (B) Chronic GVHD can affect all layers of the skin. Photographs of each manifestation in italic may be found in the supplemental Data, available on the *Blood* Web site. Artwork by Delilah Cohn, MFA, CMI, used with permission.

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Chronic GVHD: Review of symptoms

- **Skin feels tight or hard**, increased dryness, pruritus, or looks different (ie, new rash, papules, discoloration, shining scar-like, scaly)
- **Sweat glands:** Inability to sweat or to keep body warm
- **Loss of hair** (scalp or body including bows or lashes), or nail changes (ridges, brittle, loss)
- **Stiffness** or pain in the wrists, fingers, or other joints
- **Eye** dryness, sensitivity to wind or dry environments, pain

Adapted, Flowers & Martin Blood 2015

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Chronic GVHD: Review of symptoms

- **Oral dryness**, taste alterations, sensitivities (spicy/carbonated drinks, toothpaste), ulcers/sores, pain
- **Foods or pills gets stuck** upon swallowing
- **Cough, dyspnea** (on exertion or rest) or wheezes
- **Vaginal dryness,** pain, dyspareunia (female); pain or dysuria due to stenosis of urethra (male)
- **Unexplained weight loss** or inability to gain weight

Adapted, Flowers & Martin Blood 2015

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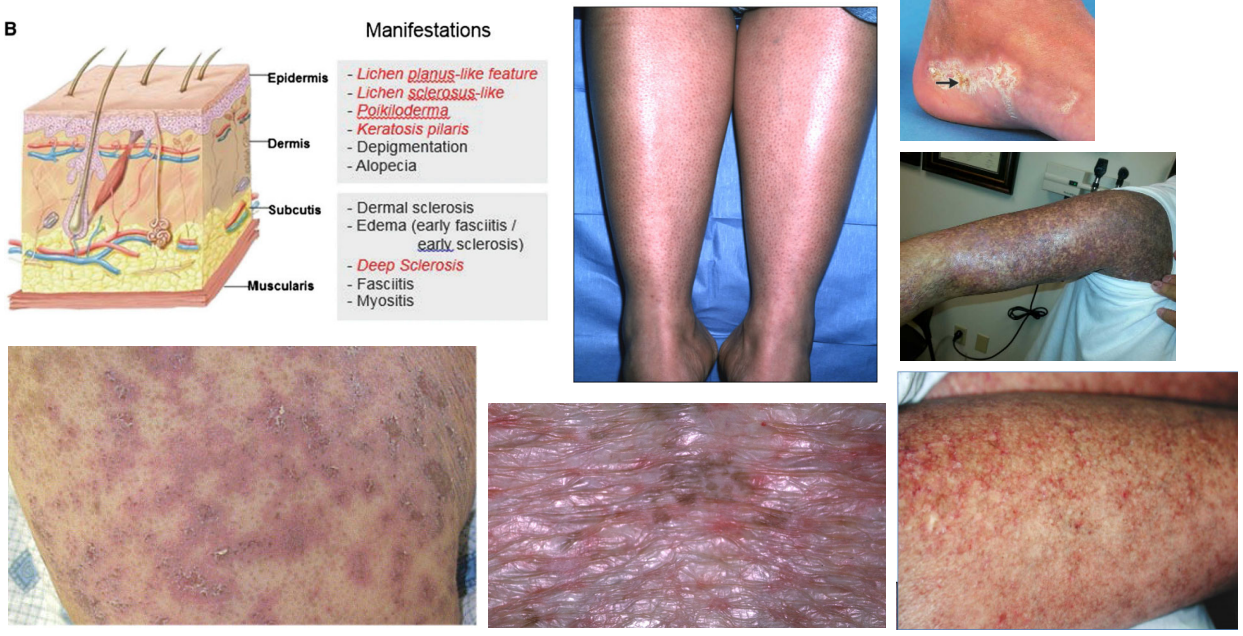
cGVHD: Skin and deep tissues



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cGVHD: Skin and deep tissues

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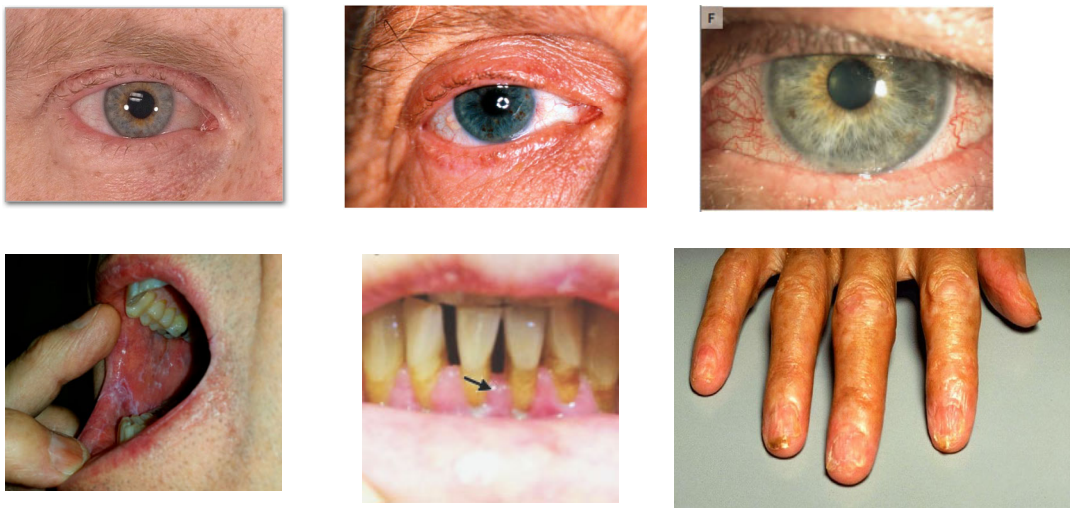
cGVHD: Eye, mouth, nails



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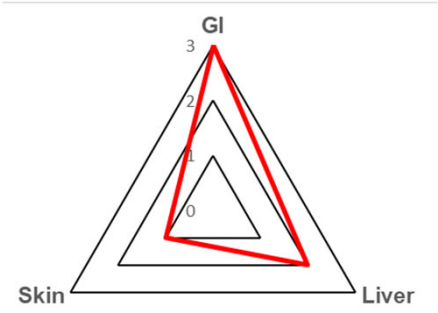
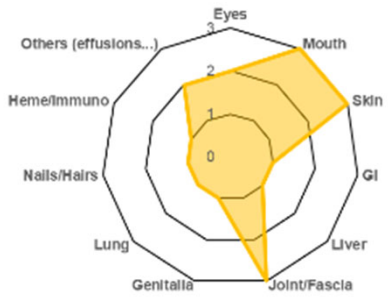
GVHD: Multiorgan disease

aGVHD



cGVHD



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Chronic GVHD: Graded based on disability

Grading in each organ/system:

0 No clinical manifestations/ symptoms

1 Clinical manifestations with **mild disability**

2 Clinical manifestations with **moderate disability**

3 Clinical manifestations with **severe disability**

Mild	• 1 or 2 organs or sites (except lung) with score 1
	  • Mild oral symptoms, no decrease in oral intake
	  • Mild dry eyes, lubricant eyedrops ≤ 3x/day

Moderate	• 3 or more organs with score 1
	• At least 1 organ or site with score 2
	  • 19-50% body surface area involved or superficial sclerosis
	  • Moderate dry eyes, eyedrops > 3x/day or punctal plugs
	• Lung score 1 (FEV1 60-79% or dyspnea with stairs)

Severe	• At least 1 organ or site with score 3
	  • > 50% body surface area involved
	  • Deep sclerosis, impaired mobility or ulceration
	  • Severe oral symptoms with major limitation in oral intake
	  • Severe dry eyes affecting ADL
	• Lung score 2 (FEV1 40-59% or dyspnea walking on flat ground)

2014 NIH Consensus

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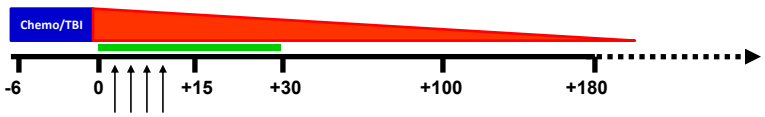
GVHD prophylaxis: planned immunosuppression



Tacrolimus OR Cyclosporine +/- Sirolimus (rapamicyn)
+
Methotrexate OR MMF

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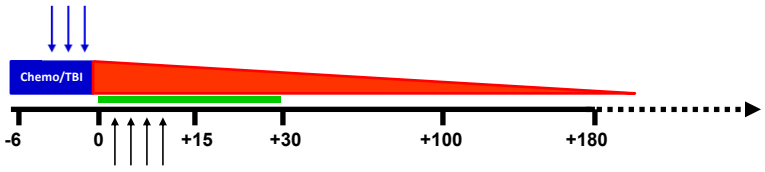
GVHD prophylaxis: Planned immunosuppression

ATG
(Rabbit) antibodies vs T cells



Tacrolimus OR Cyclosporine +/- Sirolimus (rapamicyn)
+
Methotrexate OR MMF

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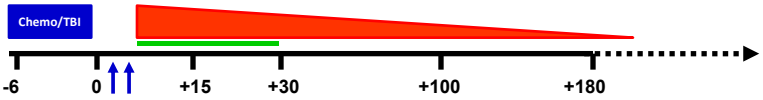
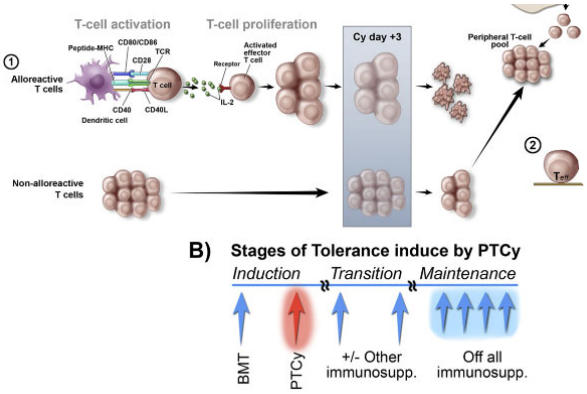
GVHD prophylaxis: Planned immunosuppression



Tacrolimus+MMF

Cyclophosphamide (PTCY)



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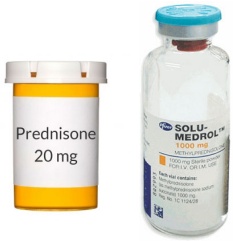
GVHD treatment: principles

1. **Start treatment EARLY, LOCAL:**
   - supportive treatment + nonabsorbable steroids
   - Get a specialist involved

2. **Steroids: mainstay of Systemic Treatment**
   - Acute: 40-60% responds < 5 days
   - Chronic**: needed long course, combo not better**



3. **Steroids don't work: always an issue**
   - Bad: always predict poor outcome
   - Good: **new drugs**

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Organ specific treatment

- **Skin: topical steroid, Tac, CSA, PUVA/UVB**
- **Oral: topical steroid, Tac, CSA**
- **Eye: ear drops, CSA eye drops, punctal occlusions, contact lenses, scleral lenses**
- **Lung: FAM**
- **Liver: Ursodiol**
- **GI: non absorbable steroids**
- **GU: topical steroid, Tac, CSA**

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Managing Chronic GVHD

- Goal: relieve symptoms; avoid progression to sclerosis, ***get LIFE BACK***
- Therapy required for 2-3 years; 15% still require therapy >7 years

Extended GVHD Team

Subspecialists
- Oral medicine
- Ophthalmologist
- Dermatologist
- Gynecolologist

Supportive staff
- Physical therapist
- Occupational therapist
- Nutritionist

Psychosocial support (patient and caregiver)
- Mental health counselors
- Back-to-work or job retraining resources

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Managing Chronic GVHD

Systemic treatment

Once steroids fail or are not enough there is ***no optimal treatment choice***

Treatment choices are based on:

- Cost and duration
- Logistics
- Toxicity
- Physician experience
- Available **clinical trial**

Table 6. Agents used for secondary treatment of chronic GVHD*

Treatment	% Overall response*	Survival
ECP (Photopheresis)	65-70	70%-78% at 1 y
Rituximab	66-86	72% at 1 y
Imatinib	22-79	75%-84% at 1.5 y
Pentostatin	53-56	34%-60% at 1-3 y
Mesenchymal stem cells	50-74	78% at 2 y
Mycophenolate mofetil	26-64	67%-96% at 1 y
mTOR inhibitor	76	72% at 3 y
Interleukin-2	52	Not reported
Other therapies summarized in other reviews**		
Calcineurin inhibitor		
High-dose methylprednisolone		
Methotrexate		
Thalidomide		
Hydroxychloroquine		
Clofazimine		
Thoracoabdominal irradiation		
Alefacept		
Infliximab		
Etanercept[70]		

Adapted, Flowers & Martin Blood 2015

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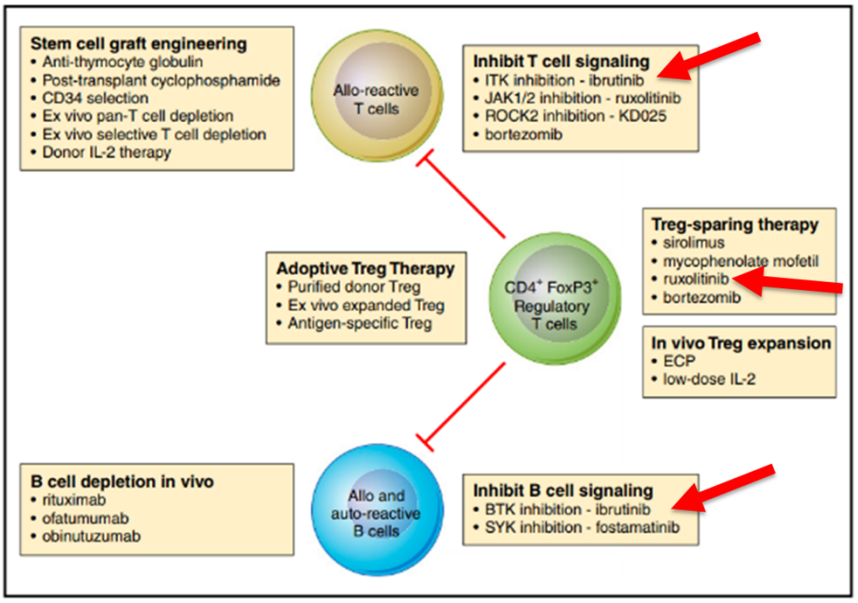
Mechanistic approach to manage GVHD



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New Drugs for Steroid Failure GVHD

		N patients	Overall Response Rate	FDA approved
Ibrutinib (Imbruvica)	*Chronic*	42	67% > 5 month lasting response	8/2017*
Ruxolitinib (Jakafi)	*Acute*	49	57%	5/2019*
Ruxolitinib (Jakafi)	*Chronic*	165	50% compared to 25.6%	Granted priority review
Belomosudil	*Chronic*	132	75% Median duration of response 50 weeks	Granted priority review

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GVHD: Challenges

- ❑ Wide spectrum of manifestation and severity: **diagnosis may be difficult**
- ❑ No **treatment fit all patients**
- ❑ No idea of **who will respond** to steroid, concern for under- or overtreatment
- ❑ Largely inefficient 1st line treatments, no standard 2nd line measures
- ❑ **Treatment is toxic, immunosuppressive, might be *lifelong***
- ❑ **Impact on quality of life, return to family life, relationships, work**

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GVHD: New Hope

- We understand this disease better and better
- Improved strategies for prevention
- Lots of work on biomarkers to diagnose and treat correctly and early
- New promising treatments are HERE, more on the horizon
- Improved culture of supportive care, Long Term Follow up, multidisciplinary team

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Thank you !!!

My Patients!
My Nurses
My colleagues

BMT*Infonet*

Pharmacists
Transplant coordinators
Case managers
Social workers
Administrative staff

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Questions?

Celebrating a Second Chance at Life Survivorship Symposium 2021

bmtinfonet.org ✦ help@bmtinfonet.org ✦ 847- 433-3313

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