Introduction to Graft-versus-Host Disease (GVHD)

Celebrating a Second Chance at Life
Survivorship Symposium

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LEARNING OBJECTIVES

- Differences between acute and chronic graft-versus-host disease
- Sites (Organs/tissues) typically affected by GVHD
- Incidence and typical onset of acute & chronic GVHD
- Therapies to prevent and treat acute & chronic GVHD
- Side effects of therapies used to treat GVHD
- Physical & Emotional challenges associated with GVHD

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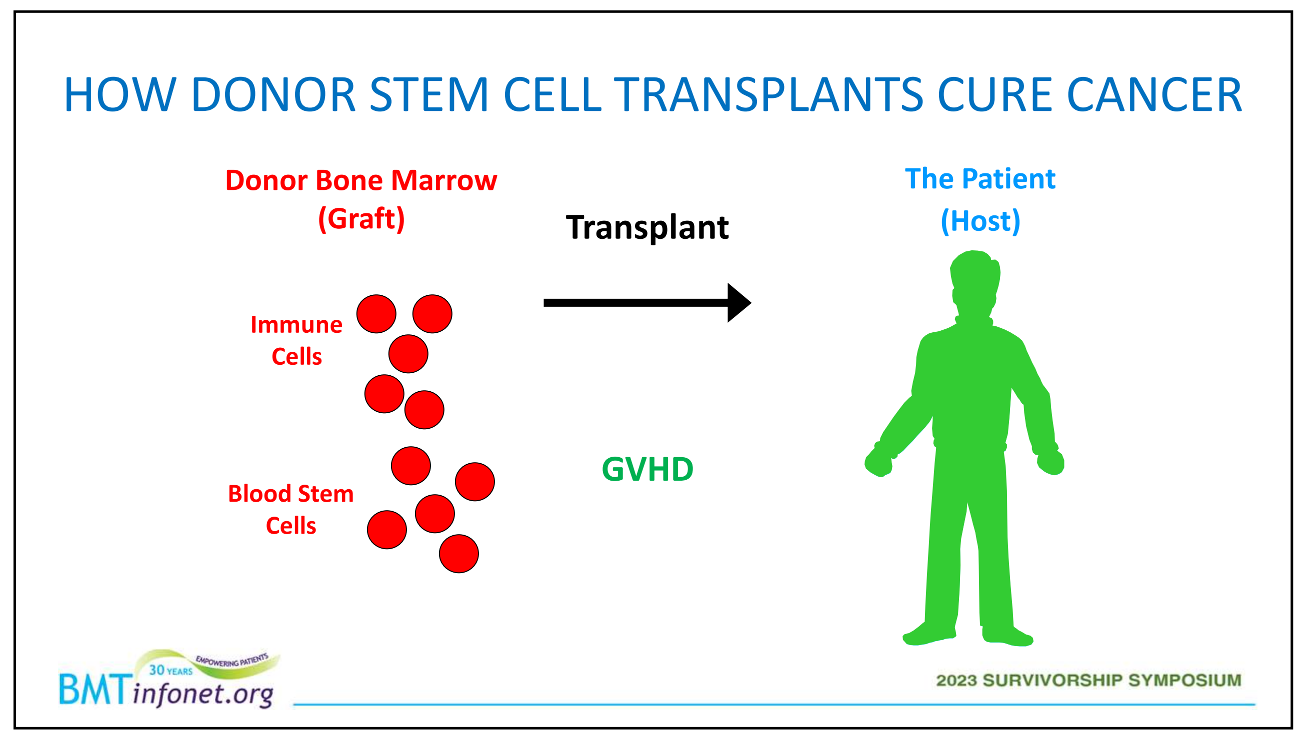

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THE TWO FORMS OF GRAFT-VERSUS-HOST DISEASE

- Acute Graft-versus-host disease
  - Typically occurs earlier after transplant
  - Primarily affects the skin, intestines and liver
  - Inflammatory Process
- Chronic Graft-versus-host disease
  - Typically does not occur until 2+ months after transplant
  - Can affect most parts of the body
  - Closely resembles autoimmune diseases

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GVHD PREVENTION: GRAFT MANIPULATION

Graft Manipulation (modifying the transplanted cells)

- T-cell depletion/CD34+ Cell Selection
  - Removal of the immune cells that cause GVHD
  - Associated with increased infection risk, slow immune recovery
- αβ-T-cell and B-cell Depletion
  - Leaves γδ T-cells while removing other immune cells
  - Felt to improve risk for infections and relapse compared to T-cell depletion
- Newer strategies being investigated
  - Naïve T-cell depletion, ORCA-T grafts

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GVHD PREVENTION MEDICATIONS: CYCLOSPORINE AND TACROLIMUS

Tacrolimus (Prograf, FK-506), Cyclosporine (Neoral)

- Immunosuppressive medicines, also used for solid organ transplant
- Typically Started before day of transplant, continued for 2-6 months
- Must monitor drug levels
- Can be harmful to kidneys
- Can cause low magnesium levels
- Cyclosporine can cause gum thickening and excess hair growth

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GVHD PREVENTION MEDICATIONS: METHOTREXATE

- Chemotherapy agent used to treat cancer and autoimmune diseases
  - When used to prevent GVHD, given at autoimmune doses
  - Typically given on post-transplant days 1, 3, 6 ± 11
- Can worsen mouth sores from chemotherapy/radiation (mucositis)
- Cannot be given during time of liver injury
- Cannot be given if fluid collections (effusions or ascites) are present

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GVHD PREVENTION MEDICATIONS: MYCOPHENOLATE

Mycophenolate Mofetil (MMF, CellCept, Myfortic)

- Typically started around time of transplant, continued for 1 month
- Can cause lower blood counts
- Can cause gastrointestinal symptoms
  - Nausea, Vomiting, Diarrhea

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GVHD PREVENTION MEDICATIONS: SIROLIMUS

Sirolimus (Rapamycin)

- Can be used instead of Tacrolimus or Cyclosporine
- Also can be harmful to kidneys
- Drug levels must be monitored
- Can cause high triglyceride and cholesterol levels

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GVHD PREVENTION MEDICATIONS: CYCLOPHOSPHAMIDE

- Typically given on days +3 and +4 after transplant
- Can cause nausea and vomiting
- Can cause bladder irritation/bleeding
  - Prevented with IV hydration and Mesna (IV medicine)

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GVHD PREVENTION MEDICATIONS: ABATACEPT

- IV Medication given in 4 doses over 1st month of transplant
- Tends to be well tolerated
- May cause higher blood pressures

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GVHD PREVENTION: COMMON STRATEGIES

- Tacrolimus/Cyclosporine/Sirolimus with:
  - Methotrexate (most common with matched related and unrelated donor transplantation)
  - Mycophenolate (common with cord blood transplantation)
- Cyclophosphamide + Tacrolimus + Mycophenolate
  - Commonly used with haploidentical (half-matched) transplant
  - Being more widely used following unrelated donor transplant
- Abatacept + Tacrolimus + Methotrexate
  - Used following mismatched unrelated donor transplant
  - Being investigated following matched unrelated donor transplant

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ACUTE GVHD: INCIDENCE & TYPICAL ONSET

- Occurs in anywhere from 25-70% of patients depending on age, transplant type and risk factors
- Most often occurs between 2 weeks and 2 months post-transplant
- May occur later (6+ months after transplant)
- Can involve any combination of skin, intestinal and liver involvement

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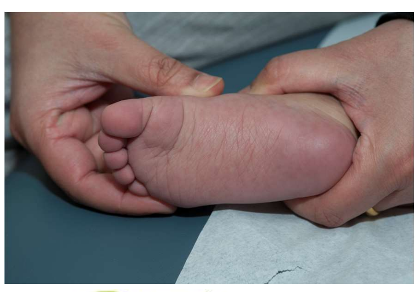
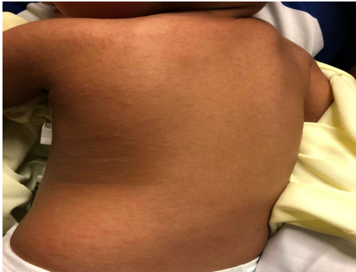
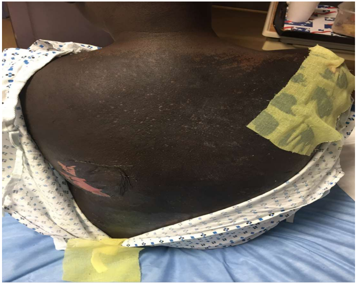
ACUTE GRAFT-VERSUS-HOST DISEASE: SKIN

- Most commonly involved site of acute GVHD
- Presents as a red rash
- Can be splotchy or more widespread
- When most severe (rare), can cause blisters or sloughing of skin







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ACUTE GRAFT-VERSUS-HOST DISEASE: INTESTINES

- Acute Gastrointestinal GVHD: Divided into upper and lower GI GVHD
- Upper gastrointestinal acute GVHD
  - Constant nausea
  - Frequent vomiting
  - Loss of appetite with associated weight loss
- Lower Gastrointestinal acute GVHD
  - Watery diarrhea (typically 3+ episodes per day)
  - May have associated crampy pain
  - Severe pain and/or bloody stool at most severe

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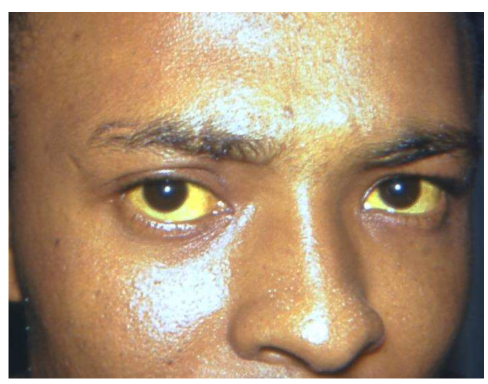
ACUTE GRAFT-VERSUS-HOST DISEASE: LIVER

- Least commonly involved site
- Presents with increased bilirubin on blood tests
- Clinically presents with jaundice
  - Yellowing of eyes and skin, darker urine
  - Typically is painless



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ACUTE GVHD: TREAMTENT

- For mild skin GVHD (<50% body coverage)
  - Topical steroids
- For upper gastrointestinal GVHD
  - Can consider nonabsorbable oral steroids (budesonide and/or beclomethasone)
- For all others, systemic (Oral or Intravenous) steroids
  - Current clinical trials may add a second agent

Treatment is over weeks to months!

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ACUTE GVHD TREATMENT: STEROIDS

- Typically started at twice daily dosing for 1+ week
  - If GVHD is improving, decrease dose fairly rapidly
- Side Effects
  - Weight gain (including “moon facies”)
  - Mood swings
  - High blood sugars
  - High blood pressures
  - Risk for infections
  - Bone health concerns (long-term effect)

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ACUTE GVHD MEDICATIONS: SECOND LINE TREATMENT

- Ruxolitinib (Jakafi)
  - Oral medication given twice daily
  - Can cause low blood counts
- Extracorporeal Photopheresis (ECP)
  - Treatment procedure involving UV light therapy to collected immune cells
  - Typically given 2+ times per week initially, then spaced out
- Many clinical trials of other therapies underway
  - Mesenchymal Stem Cells, Hormones, New Medicines

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CHRONIC GVHD: INCIDENCE AND TYPICAL ONSET

- Occurs in anywhere from 15-40% of patients depending on transplant type and risk factors
- Most often occurs between 4 months and 2 years post-transplant
- May occur sooner (2 months after transplant) or later
- Can involve any almost any body site and any combination of sites

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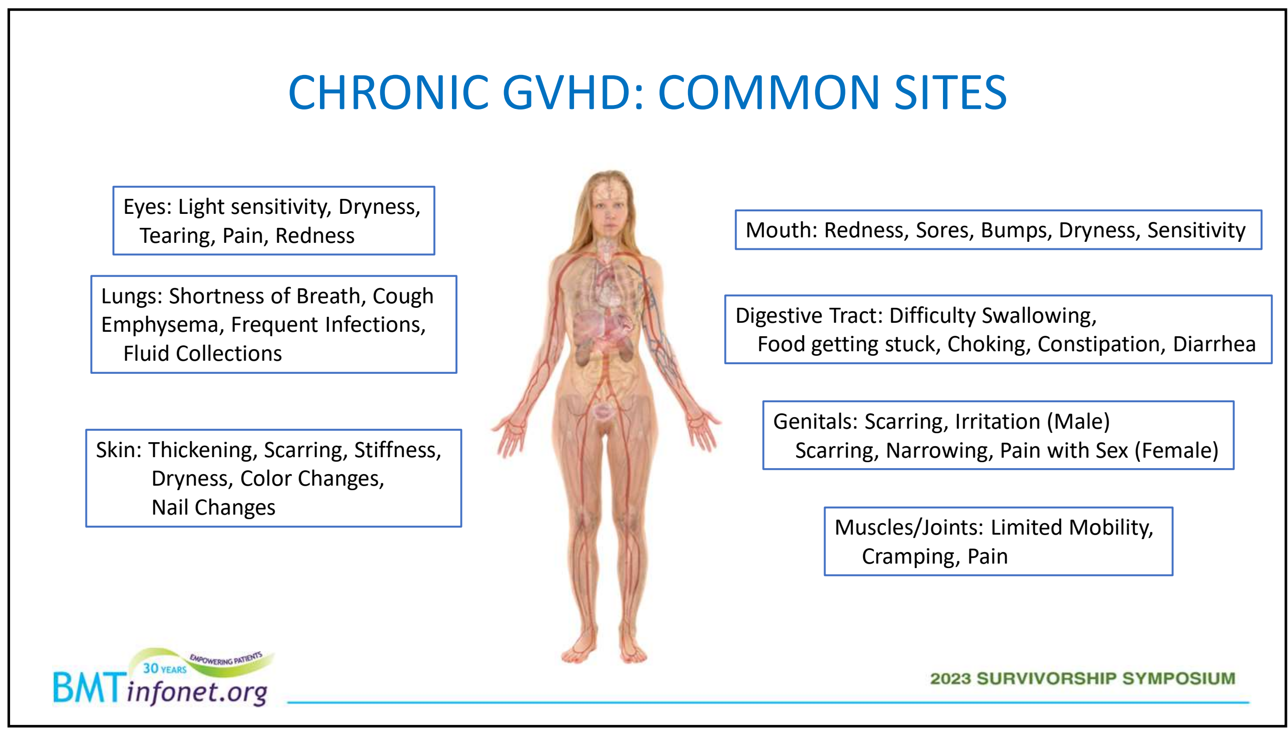

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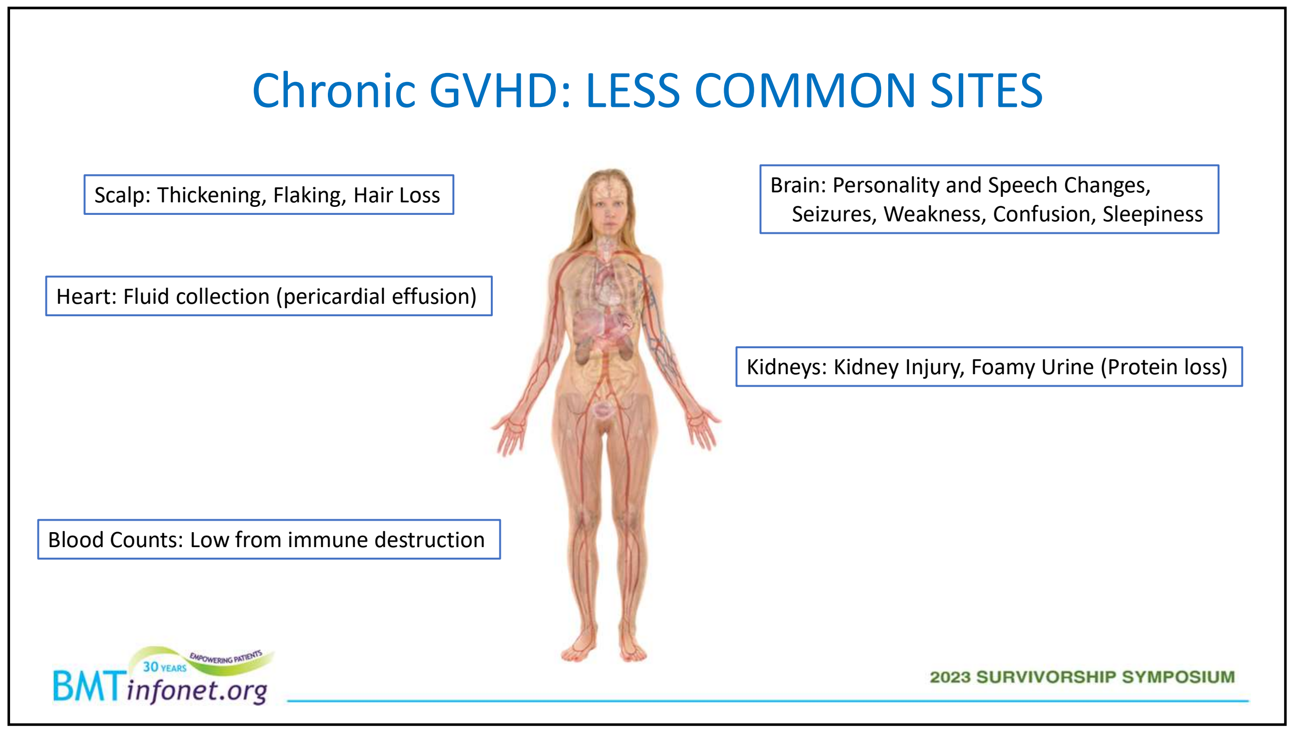

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CHRONIC GVHD: TOPICAL TREATMENTS

- SKIN
  - Topical steroid creams/ointments
  - Moisturizers
  - Other prescription creams/ointments (immunosuppressants, others)
  - UV Therapy
- Mouth
  - Steroid mouthwash
  - Light therapy (under investigation)
- Eyes
  - Artificial Tears
  - Other Prescription drops (steroids, immunosuppressant, others)

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CHRONIC GVHD: LUNG TREATMENTS

- FAM Therapy:
  - Inhaled steroids (e.g. Fluticasone, Budesonide)
  - Azithromycin – One pill three days per week
  - Montelukast (Singulair®) – Daily pill (Allergy/Asthma Medicine)

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CHRONIC GVHD: SYSTEMIC TREATMENT

- Always use Local/Topical therapies for affected sites
- First line treatment: Steroids (typically by mouth)
  - Lower starting dose than acute GVHD – 1-2 times daily
  - Treatment typically over several months
  - Same side effect risks as when used for acute GVHD

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CHRONIC GVHD TREATMENT: BEYOND STEROIDS

- 3 Approved Medications for Chronic GVHD failing steroids
- Ibrutinib (Imbruvica®)
  - Approved for adults and children at least 1 year old
  - Once daily Pill/Liquid
  - Common Side Effects:
    - Nausea/Diarrhea
    - Fatigue
    - Bruising
    - Muscle spasms
    - Infections (e.g. Pneumonia)

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BEYOND STEROIDS: RUXOLITINIB

- 3 Approved Medications for Chronic GVHD failing steroids
- Ruxolitinib (Jakafi®)
  - Approved for adults and children at least 12 years old
  - Twice daily pill
  - Common Side Effects:
    - Low Blood Counts
    - Infections

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BEYOND STEROIDS: BELUMOSUDIL

- 3 Approved Medications for Chronic GVHD failing steroids
- Belumosudil (Rezurock®)
  - Approved for adults and children at least 12 years old
  - Once/Twice Daily Pill
  - Common Side Effects:
    - Nausea/Diarrhea
    - Fatigue
    - Liver irritation
    - Infections (e.g. viral respiratory infections)

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BEYOND STEROIDS: OTHER TREATMENTS

- Extracorporeal Photopheresis (ECP)
  - Blood immune cell collection by machine
  - Treatment of immune cells with UV light
  - Cells given back by IV
  - Also used for acute GVHD
- Upcoming and experimental therapies
  - Axatilimab (clinical trial completed, promising results)
    - Given Intravenously every 2 weeks
  - Several other experimental treatments under investigation

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GVHD: PHYSICAL CHALLENGES

- Medication Side Effects
  - Steroids (Weakness, Weight Gain)
- Chronic GVHD
  - Limited Mobility (Joint/Skin Tightness)
  - Fatigue
  - Limitations in Activity (Lung involvement)

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GVHD: EMOTIONAL CHALLENGES

- Medication Side Effects
  - Steroids (Mood swings, sleep disruption)
- Body Image Issues
  - Hair Loss
  - Scarring/Rashes
  - Weight Gain/Acne from Steroids
- Limitations on work/school participation
- Chronic GVHD: Long Term Treatment
- Sexual Health

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QUESTIONS?

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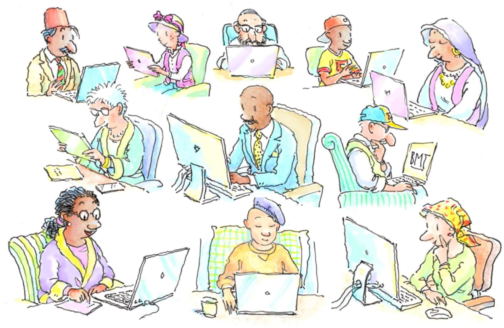
Let Us Know How We Can Help You!



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