Graft Failure
Graft Versus Host Disease
Graft Versus Leukemia

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Objectives
- Define graft failure
- Describe Graft vs. Leukemia effect
- Review pathophysiology and risk factors for Graft vs. Host Disease (GVHD)
- Describe signs and symptoms of GVHD
- Describe nursing interventions for skin, gut and liver GVHD
- Review disease prophylaxis and first line management
- Discuss therapies for the treatment of steroid refractory GVHD

“Graft” Definitions
- Engraftment: When the patient begins creating blood cells from the repopulated marrow.
- Graft Failure: When engraftment does not occur or occurs and subsequently is not sustained.
  - Primary Graft Failure
  - Secondary Graft Failure

What is Graft Vs Host Disease?

“Graft” Definitions
- Acute Graft vs Host Disease (aGVHD): An immunologic reaction to the transplanted HSCs classically occurring in the first 100 days post HSCT involving the skin, liver, and gut.

“Graft” Definitions
- Chronic Graft vs Host Disease (cGVHD): An immunologic reaction resembling an auto-immune disorder (scleroderma, Sjogren’s syndrome) potentially involving many of the organs and structures of the body without features of aGVHD.
- Graft vs Leukemia (or Tumor) Effect (GVL or GVT): The beneficial effect that aGVHD and cGVHD have on reducing relapse.
**Graft vs. Leukemia Effect (GVL)**

- There is an increased incidence of disease relapse in T-cell depleted, autologous and syngeneic transplants where there is less GVHD and decreased incidence of disease relapse in patients with GVHD.
- Immunologic mechanisms mediated by the donor immune cells contained in or derived from the stem cell graft assist in the eradication of malignant cells after allogeneic HSCT.

**GVL and Type of Malignancy**

- All malignancies were not created equally when it comes to GVL.
  - GVL has been documented in most leukemias, multiple myeloma and MDS.

**Manipulating GVL: Current Methods**

- Pre-emptive;
  - Goals for GVL designed into GVHD prophylaxis.
- Discontinuation of immunosuppressive therapy if relapse post-HSCT occurs.
- Donor Lymphocyte Infusions (post-HSCT).
- Interleukin-2 administration (post-HSCT).
- Non-myeloablative HSCT.

**Questions about GVL?**

**Significance of GVHD**

- GVHD is one of the most frequent complications after HSCT.
- Incidence 30-70% in matched transplants.
- Major cause of morbidity and mortality after HSCT.
- Mortality (direct or indirect) can reach 50%.

**Acute Graft Versus Host Disease**
Immunology Review

**Hematopoiesis**

**Adaptive**

- Lymphocytes

**Innate**

- Granulocytes
  - Eosinophil
  - Neutrophil
  - Basophil
- Monocyte and Macrophage
- Platelet
- Erythrocyte

**T Cells “Generals and Assassins”**

- Type of Lymphocyte
- T-Cells are produced in marrow and mature in the Thymus (T)
- Many sub-types
  - Helper T Cells “Generals”
  - Cytotoxic T Cells “Assassins”
  - Memory
  - Regulatory
  - Natural Killer

**Antigen Presenting Cells (APCs)**

- Cells that internalize pathogens (phagocitosis) and display a small piece of protein from that pathogen on its surface
- T Cells have receptors that receive this protein and the ability to recognize or not
- Examples of APCs are:
  - Macrophages
  - Neutrophils
  - B Cells

**T Cells “Generals and Assassins”**

- Helper T Cells (CD4)
  - Mature B cells
  - Stimulate cytotoxic T cells
  - Stimulate macrophages
- Cytotoxic T Cells (CD8)
  - Destroy virally infected and tumor cells
  - Recognize self from not self

T Cells have receptors that receive this protein and the ability to recognize or not.
### Cytokines
- Chemical/hormonal messengers that allow immune cells to communicate to each other.
- Immune cells need to:
  - Produce them
  - Release them
  - Receive messages (receptors)
  - React to them
- Examples of Cytokines:
  - Interferon
  - Interleukin
  - Tumor necrosis factor

### Pathophysiology
- **Three Step Process**
  1. Tissue damage
  2. Donor T-cell activation and cytokine secretion
  3. Cellular and inflammatory effectors

### Step 1: Tissue Damage
- Prior to transplant, patient’s tissues are damaged by:
  - Underlying disease and its treatment
  - Infection
  - Drugs and radiation used in conditioning regimen

### Effects of Conditioning
- Chemotherapy and radiation therapy leads to tissue damage
- This damages causes:
  - Activation of host antigen presenting cells (APCs)
    - Cells that display a foreign antigen with HLA on its surface (recognized by T cells)
  - Lipopolysaccharides (LPS) to leak through the intestinal mucosa into the circulation
    - LPS stimulates the release of the inflammatory cytokines, tumor necrosis factor (TNFα), IL-1, and others
Step 2: Donor T-cell Activation and Cytokine Secretion

- Inflammatory cytokines and LPS help to activate donor T-cells
- Activated T-cells proliferate and secrete cytokines, including IL-2 and Interferon
- Secretion of cytokines activates phagocytes

Step 3: Cellular and Inflammatory Effectors

- Activated phagocytes, along with T cells, secrete inflammatory cytokines that cause target cell death (apoptosis) and tissue damage
- Damage to the GI tract, caused principally by inflammatory cytokines, amplifies LPS release and leads to "cytokine storm" and further tissue damage

Who is at greater risk for GVHD?

**Acute GVHD: Well Established Risk Factors**

*Increased Risk:*
- HLA-mismatch
- Older recipients
- Older donors
- High-dose TBI
- Sex mismatch (esp female to male)
- Unrelated donors

*Reduced Risk:*
- T cell depletion
- Cord blood

**GVHD Onset**

- GVHD will become evident in patients soon after engraftment
  - Median onset: Day +19
- Exceptions
  - Hyperacute GVHD: "Early" GVHD that occurs Day +7 to +14 before ANC returns which includes fever, generalized erythroderma and desquamation
  - GVHD in nonmyeloablative HSCT: "Late" GVHD that can occur 6-12 months after transplant
Manifestations of Acute GVHD
- Skin
- GI Tract
- Liver

Diagnosis and Staging

Diagnosis of GVHD
- May be clinical
- Liver enzymes
- Biopsy
  - Skin
  - Endoscopy (upper or lower)
- Biopsy result may be needed for some study enrollment, even if clinical findings are clear

Acute GVHD: Clinical Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin</th>
<th>Liver</th>
<th>Gut (Adults)</th>
<th>Gut (Peds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% BSA Rash</td>
<td>Bilirubin</td>
<td>Stool volume in mls/day</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>&lt;25</td>
<td>2-3</td>
<td>&lt;1000</td>
<td>&lt;10/kg</td>
</tr>
<tr>
<td>++</td>
<td>25-50</td>
<td>3-6</td>
<td>1000-1500</td>
<td>10-20/kg</td>
</tr>
<tr>
<td>+++</td>
<td>50-100</td>
<td>6-15</td>
<td>&gt;1500</td>
<td>20-30/kg</td>
</tr>
<tr>
<td>++++</td>
<td>Bullae</td>
<td>&gt;15</td>
<td>Severe pain</td>
<td>&gt;30/kg</td>
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Clinical Grading of aGVHD
Glucksberg Criteria

<table>
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<tr>
<th>Overall Grade</th>
<th>Skin</th>
<th>Stage GI</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (mild)</td>
<td>I to II</td>
<td>0</td>
<td>0</td>
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<td>2 (moderate)</td>
<td>I to III</td>
<td>I</td>
<td>I</td>
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<td>3 (severe)</td>
<td>II to III</td>
<td>II to III</td>
<td>II to IV</td>
</tr>
<tr>
<td>4 (life threatening)</td>
<td>II to IV</td>
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The Grade of AGVHD influences response to therapy and survival

<table>
<thead>
<tr>
<th>Grade</th>
<th>Response rate (%)</th>
<th>Survival at D100 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>NA</td>
<td>78-90</td>
</tr>
<tr>
<td>II</td>
<td>63-95</td>
<td>66-92</td>
</tr>
<tr>
<td>III</td>
<td>17-39</td>
<td>29-62</td>
</tr>
<tr>
<td>IV</td>
<td>0-6</td>
<td>23-25</td>
</tr>
</tbody>
</table>
GVHD Signs and Symptoms: Skin
- Organ most commonly affected by GVHD
- Initial presentation often involves the skin and may seem like a flush of the face, ears, palms, soles, and upper trunk
- Maculopapular rash may become generalized
- When severe, rash may progress to bulla formation and widespread desquamation

Nursing Interventions
- Assess skin frequently
  - Especially groin, axilla, skin folds
- Skin should be kept clean
  - Daily baths/shower with gentle cleansers
- Infection prophylaxis
- Use non-perfumed, heavy emollients frequently
- Avoid tape and other irritants

How to we care for patients with skin GVHD?

Nursing Interventions
- Pain control
- Treat as burn in severe cases
- Refer to Standard Practice or institutional guidelines of care
- Patient and family education

GI Tract
- GI manifestations highly variable and non-specific
- Diarrhea is most common symptom
- Anorexia, nausea, food intolerance, cramping, abdominal pain, bloody stools, mucosal sloughing, and ileus may also be present
How do we care for patients with GI GVHD?

Nursing Intervention
- Monitor intake, nausea and anti-emetic use/patterns
- Monitor, describe and test all emesis and stool
- R/O pathogens
- Strict I/Os
- Weight monitoring
- Stool replacement as needed

Nursing Intervention
- Peri-rectal care
- Gut rest for severe cases
- Alternate diets
  - Low fat, low fiber, low lactose
- TPN/Fluid and electrolyte management
- Patient and family education

Liver
- Jaundice and/or an increase in alkaline phosphatase and bilirubin are early signs of GVHD
- Obstructive hyperbilirubinemia is the primary hepatic manifestation
- Measurement of severity of liver involvement is based on total bilirubin level
- Liver biopsy helpful in discerning underlying etiology

Nursing Interventions
- Strict I/Os
- Management of symptoms
  - Pruritis and skin care
  - Nausea and vomiting
- Monitor for confusion/lethargy
- Fall precautions
  - Maintain safe environment
- Patient/family education

Autologous “Pseudo” Graft vs. Host Disease
- Stem cells collected from patient after mobilization may develop capacity to produce self-reactivity after autologous HSCT when the patient lacks immune regulation due to conditioning.
- Manifestations:
  - Maculopapular skin rash (can be histologically identical to aGVHD)
  - Nausea, vomiting and diarrhea
- Incidence: <8%
- Onset: Day +7 to +21
- Treatment: Steroids
Prevention of Acute GVHD

WHAT CAN WE DO BEFORE TRANSPLANT TO PREVENT GVHD?

Prophylaxis: Pre-Transplant

- Conditioning Regimen
  - Reduced Intensity Regimens
- T-cell Depletion

Reduced Intensity Regimens

- Reduced intensity conditioning regimens result in less severe GVHD, as a result of diminished cellular injury from reduced endotoxin exposure due to less mucosal injury
- Delayed onset of GVHD seen with reduced intensity conditioning regimens

Acute GVHD is delayed and is less frequent after Non-Ablative compared to Ablative transplants

T-Cell Depletion

- The number of T cells in donor stem cells is directly associated with severity of aGVHD
- T-cell depletion is one of the most effective forms of GVHD prophylaxis
- However, overall survival rates equivalent
What are the Pros and Cons of taking T-Cells out?

Advantages and Disadvantages of T-Cell Depletion

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>Low incidence of acute and chronic GVHD</td>
<td>Higher incidence of graft failure</td>
</tr>
<tr>
<td>Reduced or no requirement for post-transplantation immune suppression</td>
<td>Loss of GVL activity (higher incidence of disease relapse)</td>
</tr>
<tr>
<td>Decreased pulmonary and hepatic toxicity early after HSCT</td>
<td>Delayed immune reconstitution</td>
</tr>
<tr>
<td>Decreased early transplant-related mortality</td>
<td>Increased risk for post-transplantation EBv-LPDs</td>
</tr>
<tr>
<td>Reduced or no requirement for post-transplantation immune suppression</td>
<td>Higher incidence of CMV reactivation</td>
</tr>
<tr>
<td>Decreased pulmonary and hepatic toxicity early after HSCT</td>
<td>Overall survival not improved compared to non-TCD HSCT</td>
</tr>
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Drugs Commonly Used in GVHD Prophylaxis

- **Calcineurin Inhibitors**
  - **Cyclosporine or Tacrolimus**
    - Calcineurin inhibitors; decrease production of IL-2 and affect the receptor for IL-2 on T cells; result is decreased ability of resting T cells to be stimulated to become active

Prophylaxis - Gold Standard

- **Tacrolimus** increasingly being used in place of CSP
  - Continuous infusions preferred over bolus dosing for decrease in toxicities and constancy in serum levels
  - Usually starts 24-36 hours pre-transplant
Calcineurin Inhibitors

- **Dose**
  - Adjust according to blood levels
  - Taper varies depending on protocol
  - CSP; Oral Neoral® dose = 2.5X the IV dose
  - Tac; Oral Prograf® dose = 4X the IV dose
  - Usually given as 23.5hr continuous infusion
  - May be given Q12 IV/PO

Calcineurin Inhibitors; Considerations

- Do not give with beverages containing bergamottin (grapefruit juice, Sunny Delight, Fresca and Squirt)
- If patient vomits within one hour of oral dose, repeat dose
- Patients should receive 3 bolus doses or 24 hours of continuous infusion before receiving stem cells
- Serum levels drawn from opposite lumen
  - Based on target level range
  - Steady levels not achieved for 48-72 hours after dose adjustment

Calcineurin Inhibitors; Side Effects

- Hypertension
- Tremor
- Headache
- Hirsutism (CSP)
- N/V
- Diarrhea
- Infection
- Hyperlipidemia
- Hyperkalemia
- Hypomagnesemia
- Elevated BUN/Cr
- Infusion related effects: flushing, erythema, hand & foot paresthesias (CSP)
- Hemolysis
- Abdominal discomfort
- Hyperbilirubinemia
- Elevated transaminases
- Hyperglycemia
- Acne
- Delirium

What are some side effects from Cyclosporine and Tacrolimus?

- Anorexia
- Rash
- Diarrhea
- N/V
- Increased mucositis
- Myelosuppression
- Increased LFTs

Prophylaxis - Gold Standard

- **Methotrexate**
  - Usually given day +1, 3, 6, 11
  - Allogeneic fully myeloablative transplants
  - Folate inhibitor that blocks production of reduced folates which are necessary for DNA synthesis; this effect is not specific to T cells

Methotrexate

- Side Effects
  - Anorexia
  - Rash
  - Diarrhea
  - N/V
  - Increased mucositis
  - Myelosuppression
  - Increased LFTs
- NOTE; dose is ordered on day of administration and may be held if SOS or third spacing present
Mycophenolate Mofetil (MMF)

- Minis and cords
- Decreases lymphocyte proliferation
- Given Q8 or Q12 IV/PO
  - IV dose equal to PO dose
- Side Effects
  - Constipation
  - Diarrhea
  - N/V
  - Confusion
  - Tremor
  - Gastrointestinal bleeding
  - Hypertension
  - Peripherial edema
  - Cough
  - Myelosuppression
  - Infection

Immunosuppressive Medications used to Prevent GVHD Based on Transplant Type
(Seattle Cancer Care Alliance)

<table>
<thead>
<tr>
<th>GVHD Prophylaxis</th>
<th>Allogeneic Transplants</th>
<th>Cord Blood Transplants</th>
<th>Non-myeloablative Transplants</th>
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<tr>
<td>Tacrolimus &amp; Methotrexate</td>
<td>Cyclosprine &amp; Mycophenolate</td>
<td>Tacrolimus or Cyclosprine &amp; Mycophenolate</td>
<td></td>
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Alternate Prophylaxis – Post HSCT

- **Ursodial** (Ursodeoxycholic acid)
  - A bile acid that comprises, in part of bear bile
  - Stabilizes hepatocyte cell membranes
  - Reduces the release and expression of inflammatory cytokines
  - Used for Sinusoidal Obstructive Syndrome (SOS) prophylaxis
    - also affecting liver, skin and gut GVHD!

Alternate Prophylaxis – Post HSCT

- **Cytoxan**
  - 2 doses given between day +2/4
  - Studies show decrease in GVHD and mucusitis
  - Protocol 2270 now open!

Treatment of GVHD

How to we usually TREAT GVHD?
1st Line Treatment - Corticosteroids

- Steroids, steroids, steroids!
  - May be given
    - Orally (Prednisone)
    - Intravenously (Methylprednisolone)
    - Topically (Beclomethasone)
  - Many effects...
    - Decrease proliferation of T cells by decreasing production of IL-1 and IL-2
  - Can be highly effective
  - Goal is to control acute manifestations and then to taper as soon as possible

Corticosteroids

- Problems with short and long term side effects and dependency
- Prolonged use of high-dose glucocorticoids for aGVHD is associated with increased risk for:
  - Infection
  - Relapse
  - Death

Treatment - Steroids

- Systemic steroids
  - Usually started at 1-2mg/kg/day
  - Tapers vary by
    - Response to treatment
    - Dose given
    - Length of time on steroids
    - SCCA Standard Tapers

Steroid Side Effects

- Euphoria
- Depression
- Abdominal discomfort
- Hypertension
- Sodium and fluid retention
- Impaired skin healing
- Infection
- Osteoporosis
- Avascular necrosis
- Skin atrophy
- Cataracts
- Glaucoma
- Muscle weakness
- Hyperglycemia
- Cushing’s syndrome
- Attention deficit
- Insomnia

Topical Steroids

- Taken orally to "coat" the gut, and decrease inflammatory response locally
- “B&B”
  - Beclomethasone Dipropionate (orBec®)
    - Immediate release used for upper GI tract GVHD
  - Budesonide
    - Extended release form of Beclomethasone used for lower GI tract GVHD
  - Little absorption systemically
  - Given in combination with systemic steroids
    - Can enable more rapid weaning
  - Studies open, using B&B as GVHD prophylaxis

orBec stops at D50
Prednisone taper
Prednisone taper with OrBec

Standard prednisone taper
### SCCA Treatment; Mild vs More than Mild

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### Steroid-Refractory GVHD

**Definition:**
- Experience return of symptoms when weaning attempted
- Have progressive or unstable disease on maximum steroid therapy
- 82% of patients with severe (grade III-IV) aGVHD will be steroid refractory
- Steroid refractory GVHD is associated with 20% survival past day 200

**What happens next?**
- No standard therapy/algorithm
- Depends on:
  - Body system involved
  - Patient’s health
  - Studies available
  - Physician and institutional preference

**Options**
- Alternate immuno-suppressive medications
  - MMF
  - Rapamycin
  - Pentostatin
  - Topical steroids
  - ATG
- Monoclonal antibodies
  - For example;
    - Visilizumab
    - Dacluzimab
    - Alemtuzumab
    - Infliximab
- Ultraviolet light therapy
  - Extra-corporeal photopheresis (ECP)
  - Psoralen Ultra Violet A therapy (PUVA)
- Future Directions
  - Mesenchymal Stem Cells
  - Fusion Proteins

### Alternate Immuno-Suppressive Medications

- **Sirolimus** (Rapamycin)
  - Blocks ability of IL-2 to stimulate progression of a T cell through it’s cell cycle, reducing T cell proliferation
  - Usually given for cGVHD
  - Do not give within 4 hours of CSP
Monoclonal Antibodies (MABs)

- Development of very specific antibodies through hybridoma technology
- Several MABs in use/being studied for GVHD

Monoclonal Antibodies (MABs)

- MAB action in GVHD therapy
  - Targets and "tags" a specific antigen which will then be destroyed
    - May be a certain type of T cell or cytokine
  - Blocks receptors (usually IL-2) on the surface of T cells, therefore blocking their ability to be activated

Monoclonal Antibodies (MABs)

- Example
  - Alemtuxumab (Campath®)
    - Targets CD52
    - Expressed on many cells involved in GVHD
      - Mature T and B lymphocytes
      - Natural killer cells
      - Most monocytes
      - Macrophages
      - Some dendritic cells
    - Linked to increased risk of opportunistic infections
      - Especially Cytomegalovirus (CMV)

Ultra-Violet Light Therapy

- 8-Methoxypsoralen (Psoralen®) is a plant-derived photo-sensitizer given prior to UV light exposure
- Exposure to Psoralen and long wavelength ultra violet light causes
  - DNA strand breaks, leading to poor repair and cell death
  - Depletion of cell surface markers
**Ultra-Violet Light Therapy - PUVA**

- Psoralen and ultraviolet light (PUVA) has been used in the treatment of many skin disorders such as Psoriasis, and more recently acute and chronic skin GVHD

- Treatment usually lasts 10 seconds - 10 minutes, given 2-3 times/wk

**Ultra-Violet Light Therapy – ECP**

- Extra-corporeal photopheresis (ECP) is a process of
  - Collecting T cells by apheresis
  - Adding Psoralen to cells
  - Exposing T cells to UVA
  - Returning cells to the patient

- Usually given on 2 consecutive days every week or other week
- Takes time to work; treatment can last weeks to months
- Effective salvage therapy for steroid resistant GVHD:
  - Most effective on skin
  - Greatest benefit may be steroid-sparing effect

**Future Directions …**

**Fusion Proteins**

- Proteins created by fusing genes
- Ontak® (Denileukin Diftitox)
  - Fusion protein combining IL-2 and Diptheria toxin
  - Binds to cells with IL-2 receptors and introduces the diptheria toxin into the cell, killing it
  - Ontak works best on cells with "high affinity" IL-2 receptors; Some leukemia and lymphoma cells and cytotoxic T cells
  - This not only kills the cell, but stops the growth, differentiation and survival of activated T cells

**Mesenchymal Stem Cells**

- Mesenchymal stem cells (MSCs) are undifferentiated, pluripotent cells that give rise to mesodermal tissue, including
  - Bone
  - Cartilage
  - Muscle
  - Tendon
  - Fat

- MSCs constitute the supportive stroma within the bone marrow that provides the microenvironment for HSCs

**Properties of Mesenchymal Stem Cells**

- The immune-regulatory properties of MSCs may be useful in preventing and treating GVHD
  - Modify the response of inflammatory immune cells
  - Assist with tissue repair, especially in the gut and liver
  - Suppress lymphocyte proliferation and inflammation
Properties of Mesenchymal Stem Cells

- MSCs might enhance engraftment
  - After conditioning, marrow stroma is damaged and slow to reconstitute
  - MSC infusion in animals have been shown to help reconstitution of stroma and enhance engraftment
  - MSCs produce important cytokines that promote expansion and differentiation of HSCs

Current Studies Open at SCCA for aGVHD

- UVADEX® and ECP for the Treatment of Pediatric Patients With Steroid Refractory Acute Graft Versus Host Disease
  - Single-Arm Study to Assess the Efficacy of UVADEX® (methoxsalen) Sterile Solution in Conjunction with THERAKOS® CELLEX® Photopheresis Systems in Pediatric Patients With Steroid-Refractory Acute Graft Versus Host Disease (aGVHD)

- A Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease (REACH1)
  - A Single-Cohort, Phase 3 Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease
  - Age 12+

- Selective Depletion of CD45RA+ T Cells From Allogeneic Peripheral Blood Stem Cell Grafts From HLA-Matched Related and Unrelated Donors in Preventing GVHD
  - A Phase II Study Evaluating Selective Depletion of CD45RA+ T Cells From Allogeneic Peripheral Blood Stem Cell Grafts From HLA-Matched Related and Unrelated Donors for Prevention of GVHD
  - Age 14+

Conclusions

- Severe and steroid-refractory GVHD is a major, life threatening complication of HSCT

- Advances in HLA typing, reduced intensity conditioning regimens, and T cell selection have the potential to decrease the incidence and severity of GVHD

- Continued development of targeted and alternative therapies will improve treatment of GVHD and steroid-refractory GVHD, morbidity, and mortality

Thank You!