What is graft-versus-host disease (GVHD)?

GVHD is a process in which donor T-cells "attack" the host cells, manifesting primarily in skin, liver and gastrointestinal complications. It is a frequent complication of allogeneic hematopoetic cell transplant (HCT), stem cell or bone marrow, though it has been reported rarely in syngeneic (from a twin donor) and autologous HCT. In addition, GVHD can be a rare complication of blood transfusion (irradiation of product prevents GVHD) or solid organ transplant.

GVHD is a significant cause of morbidity and mortality in allogeneic HCT; with a 30-50% incidence in HLA matched sibling donor transplants and 65-70% incidence with unrelated donors. GVHD has traditionally been defined as:

- Acute: occurring within the first 100 days after transplant
- Chronic: occurring after 100 days and can last months to years after

Recently, it is recognized that the timing of onset is insufficient to distinguish acute from chronic GVHD, and more attention is paid to clinical manifestations rather than temporal onset of symptoms. In addition, the use of reduced intensity and T cell depleted transplants has blurred this 100 day mark distinguishing acute from chronic, which we will discuss further.

Changes in protocols

Traditionally allogeneic transplant recipients always received myeloablative regimens. Now, almost half of all allogeneic transplants are of the "reduced intensity" variety, also known as "mini" transplants, which use less intense preparative regimens. These are based on the knowledge that much of the curative potential of allogeneic transplant is not due to the preparative regimen, but is a result of the graft versus tumor affect. This is the ability of the donor's T cells to attack and destroy stray tumor cells. Mini transplants have lower toxicity, therefore expanding patient eligibility, including older patients and those with co-morbidities.

Peripherally collected stem cells (PSC) are used in many cases instead of harvested bone marrow as the product for allogeneic transplant. This results in fewer complications for donors, but may increase the risk of chronic GVHD. The choice of PSC vs bone marrow as the graft source may depend on the underlying disease state and the donor. HLA matched or mismatched cord blood used for transplant appears to result in lower rates of GVHD but in adults is limited by slower rates of engraftment and delayed immunologic recovery.

Pathophysiology of GVHD

Acute GVHD is likely initiated during the preparative regimen and occurs over several steps: (see figure below)

- High dose conditioning regimen causes cell injury and inflammation in the host cells, leading to a release of cytokines (TNF alfa, IL-1). Cytokines are protein mediators that activate the immune system.
- Host Antigen Presenting Cells (APCs) cause activation of the donor T cells.
- Cell injury and death is induced by cytokines and donor T cells

The pathophysiology of chronic GVHD is not well understood.

Diagram of "cytokine storm" leading to acute GVHD:
Risk factors for GVHD

Several factors increase the risk of developing acute or chronic GVHD. These may be factors inherent to the patient or donor, or factors associated with the transplant protocol or product.

**Donor/recipient factors**

- Increased age
- Female donor (especially if multigravida or received multiple blood transfusions) and male recipient
- HLA mismatch and / or unrelated donor
- Advanced disease status at time of transplant
- Infection with CMV
- Higher risk for chronic GVHD if had acute GVHD.

**Protocol factors**

- More intense preparative regimen, higher intensity TBI
- Use of cord blood product (decreased risk)
- PSC grafts compared to BM grafts (increased chronic GVHD)
- Less aggressive use of prophylactic agents
- Use of donor T lymphocytes infusions after transplant in refractory or relapsed disease
- Withdraw of immunosuppressive medications to induce graft versus malignancy effect in relapsed or refractory disease

**Acute GVHD**

The onset of acute GVHD develops with conventional allogeneic transplant between 14-35 days after infusion (median 21-25 days), but typically can occur up to 100 days or longer. Reduced intensity transplant recipients can develop acute GVHD weeks to months after the transplant. T cell depleted grafts may also develop acute GVHD later. Donor lymphocyte infusions (DLI) may be given to stimulate a graft versus tumor effect after a relapse and this can stimulate acute GVHD as well.

Hyperacute GVHD typically occurs 1 week after transplant and can be rapidly fatal, but is rare with appropriate prophylaxis. It is manifested by high persistent fevers, diffuse erythroderm, and other organ toxicity and is more common with mismatched donors. Because of the various time frames for acute GVHD, some have proposed that the persistence, recurrence, or new onset of acute GVHD signs and symptoms should be labeled acute GVHD, regardless of the time after transplantation.

**Characteristics of acute GVHD (See grading table below)**

Acute GVHD is graded using one of two scales. The Glucksberg scale was developed over 30 years ago and is still used in many institutions. In recent years, there has been a push to use the International Bone Marrow Transplant Registry (IBMTR) interpretation of this scale, which appears to better correlate with outcomes.
Skin

- Skin GVHD is graded according to the percentage of body surface area involved. Maculopapular, erythematous rash, often starting on the palms and soles. This can progress to severe blistering and desquamation.
- May be pruritic or painful.
- Must differentiate from drug reaction, skin infection, Stevens Johnson syndrome, etc.
- Biopsy can help differentiate but is typically non-diagnostic early of SCT.

Liver

- Liver GVHD is graded according to the bilirubin level.
- Typically presents with elevated total bilirubin and/or alkaline phosphatase.
- Diagnosis is a clinical judgment, as no definitive blood or radiology test exists. When possible, liver biopsy can clarify.
- Must differentiate from hepatic veno-occlusive disease, infection, drug induced, cholelithiasis or other liver problems.

Gut

- Gut GVHD is graded according to the volume of stool daily.
- Typically presents as nausea, anorexia, abdominal pain and/or watery, secretory diarrhea, which can be liters per day.
- Severe cases can have bloody diarrhea and/or ileus.
- The combination of fluid loss, via damaged skin, and diarrhea, along with decreased liver function, can result in severe electrolyte abnormalities. Patients require meticulous attention to monitoring and managing electrolytes and intake and output.
- If there is concern of other gastrointestinal toxicities, such as infection, or mucosal damage from conditioning regimen; biopsy of GI tissue can confirm GVHD and allow appropriate treatment.
- GI GVHD can also affect the gastric of esophageal tissue, causing unexplained nausea and vomiting.

Other Organs

- Some feel that GVHD can also affect the lung, causing problems such as alveolar hemorrhage, interstitial pneumonitis, bronchiolitis obliterator and other lung conditions.
- This remains somewhat controversial and unproven, particularly given the many possible causes of lung toxicity (infection, engraftment syndrome, radiation pneumonitis and chemotherapy toxicity).

Classification of Patients with Acute GVHD

<table>
<thead>
<tr>
<th>Level of Organ Injury</th>
<th>Skin</th>
<th>Liver Bilirubin (mg/dl)</th>
<th>Intestinal Tract (ml diarrhea/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Maculopapular rash &lt;25% of body surface</td>
<td>2-3 mg/dl</td>
<td>&gt;500 ml</td>
</tr>
<tr>
<td>2</td>
<td>Maculopapular rash 25-50% of body</td>
<td>3-6 mg/dl</td>
<td>&gt;1000 ml</td>
</tr>
<tr>
<td>3</td>
<td>Generalized erythroderma</td>
<td>6-15 mg/dl</td>
<td>&gt;1500 ml</td>
</tr>
<tr>
<td>4</td>
<td>Generalized erythroderma with bullous formation and desquamation</td>
<td>&gt;15 mg/dl</td>
<td>Severe abdominal pain with or without ileus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Grading</th>
<th>Skin</th>
<th>Liver</th>
<th>Intestine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucksberg Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Level 1-2</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>II</td>
<td>Level 1-3</td>
<td>Level 1</td>
<td>Level 1</td>
</tr>
<tr>
<td>III</td>
<td>Level 2-3</td>
<td>Level 2-3</td>
<td>Level 2-3</td>
</tr>
</tbody>
</table>
Chronic GVHD typically occurs 60-400 days after transplant and can last from months to years after. The median time to develop chronic GVHD with an unrelated donor is 133 days and 201 days for an HLA matched sibling donor. But, the timing is not particularly important to the diagnosis, rather the presence of chronic GVHD characteristics is imperative for diagnosis. Chronic GVHD can coexist with; occur after, or in the absence of acute GVHD, further complicating the diagnosis. In addition, the pathophysiology of chronic GVHD is not well understood.

**Characteristics (See grading scale below)**

Chronic GVHD resembles autoimmune disorders, such as lupus, Sjogren’s syndrome and scleroderma. The skin, oral mucosa, liver and lacrimal glands are the most frequently involved areas. Areas less frequently involved include: cardiac, CNS, GI tract and lungs.

**Skin**
- Skin changes can vary greatly, ranging from erythematous or purple papular rash and scaling to pigmentation changes and fibrosis.
- Skin can become fibrotic, immobile and fixed to tissue below it. Fibrosis over joints may result in limited range of motion.
- Hair may become brittle, thin or fall out; nails can develop ridges and become fragile.
- Sweat glands can be damaged, resulting in an inability to sweat and poor heat tolerance.

**Eyes**
- Chronic GVHD causes fibrosis of the lacrimal glands, resulting in decreased tear production.
- Patients report dry or burning eyes, photophobia or a sensation of something under the eyelid.
- Schirmer’s test can confirm decreased tear production.

**Oral**
- Damage to salivary glands results in decreased saliva production, dry mouth, irritation and dental decay.
- Erythema, ulceration and white plaques can develop in the oral mucosa.
- Must monitor for secondary infections, such as herpes simplex, candida and cytomegalovirus.

**Liver**
- Damages bile duct epithelium and can cause cholestasis.
- Elevations in bilirubin, alkaline phosphatase and GGT are common.

**Other Sites**
- GI tract: esophageal fibrosis causing poor motility, intestinal malabsorption and diarrhea.
- Lungs: lung disease presenting as cough, wheezing and dyspnea on exertion.
- Immune suppression, bone marrow suppression and cytopenias are not uncommon.
- Musculoskeletal, vulvar and vaginal, cardiac and kidney changes can occur.
### Chronic GVHD grading criteria

<table>
<thead>
<tr>
<th>Limited (Generally not requiring treatment)</th>
<th>Localized skin involvement and/or evidence of hepatic dysfunction.</th>
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<tbody>
<tr>
<td>Extensive (Requiring treatment)</td>
<td>Either generalized skin involvement, or localized skin involvement or hepatic dysfunction plus at least one of the following:</td>
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<tr>
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<td>- Liver histology showing chronic progressive hepatitis, bridging necrosis, or cirrhosis</td>
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<td>- Involvement of the eye (Schirmer’s test with less than 5 mm wetting)</td>
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<td>- Involvement of minor salivary glands or oral mucosa (as demonstrated on labial or mucosal biopsy specimen)</td>
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<td></td>
<td>- Involvement of any other target organ</td>
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### Nursing Considerations

#### Skin
- Topical steroid creams may be used
- Maintain skin integrity with lotions, creams and/or moisture barriers
- Repositioning and air mattress for wound prevention with decreased mobility
- Wound care for blistering or open areas
- Burn care for severe cutaneous involvement
- Education about sun exposure activating chronic GVHD, need for limiting exposure and using sun block.

#### Liver
- Education about liver biopsy (if needed)
- Cautious use of hepatotoxic medications
- Control pruritis with benadryl or atarax

#### Gut
- Strict monitoring of intake & output, particularly stool volumes, daily weight and serum electrolytes
- Possible NPO diet and hyperalimentation
- Rectal care consisting of cleansing after each bowel movement and use moisture barrier cream
- Mucosal sloughing may be present in stool
- Monitor for GI bleeding, test emesis and stool for occult blood
- Monitor hemoglobin, hematocrit and platelet counts
- Management of fecal incontinence to prevent skin breakdown
- Psychosocial support for self esteem issues related to incontinence, appearance and coping with complications of transplant that are potentially life threatening

### Prophylaxis and treatment medications & procedures

- **Corticosteroids**: considered first line therapy for acute and chronic GVHD. Destroys T cells and suppresses cytokine production via anti-inflammatory effects. They have a high side effect profile with prolonged use, including fluid retention, hyperglycemia, increased risk of infection, steroid myopathy and avascular necrosis.
- **Cyclosporine**: Non-specific T cell immunosuppressive action. Must monitor blood levels of the drug. Blood levels drawn from central line may be falsely elevated if drawn from the same line that drug is infused through. Toxicities include renal dysfunction, CNS, nausea & vomiting and hypertension. Used in prophylaxis regimens and when treating acute and chronic GVHD.
- **Tacrolimus (FK506)**: Also a non-specific T cell immunosuppressive agent requiring monitoring similar to cyclosporine.
Neurotoxicity, ranging from headaches to blindness and abrupt increases in blood pressure have been reported. Used in prophylaxis regimens and when treating acute and chronic GVHD.

- **Methotrexate**: Chemotherapy agent, often given day 1, 3, 6 & 11 to cause an anti-inflammatory effect for prophylaxis. Mucositis is often the dose limiting toxicity.

- **Anti-thymocyte globulin (Atgam, ATG, Thymoglobulin)**: Purified from horse serum, which may lead to infusion reactions or serum sickness. Requires monitoring during infusion. Works by suppressing cellular and humoral immune responses. In clinical studies, Atgam has been shown to improve GVHD symptoms, but not to extend survival.

- **IL-2 Receptor Antibodies (denileukin diftitox, basiliximab, daclizumab, inolimomab)**: Infection is a major concern with these agents. Studies looking at using these agents earlier in treatment, as these agents have been used for treatment of GVHD that was refractory to other treatments.

- **Mycophenolate (CellCept)**: Immunosuppressive agent, used as prophylaxis and in chronic GVHD. Side effects include opportunistic infections and abdominal cramps.

- **Sirolimus**: Used in acute and chronic GVHD, prophylaxis regimens and treatment. Toxicities include: renal dysfunction, hyperlipidemia, cytopenia and infection.

- **Extracorporeal Photopheresis**: Procedure used for treatment of chronic GVHD, involves giving patients a photosensitizing agent, removing peripheral mononuclear cells via pheresis, exposing these cells to ultraviolet light and reinfusing them. Appears to work by inhibiting alloreactive T cells, without suppressing the patient's immune function.

- **Other agents**: pentostatin, rituximab, topical steroids, hydroxychloroquine, azathioprine and thalidomide, alemtuzumab (Campath), cyclophosphamide.

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