

## The George L. Strike Bone Marrow Transplant Program Practice Guidelines

### Management: GVHD Post Solid Organ Transplant

Graft-versus-host disease (GvHD) following solid organ transplantation (SOT) is an uncommon complication but has high mortality and represents a major diagnostic challenge. GvHD occurs when immunocompetent donor lymphocytes originating from the transplanted organ undergo activation and clonal expansion, allowing them to mount a destructive cellular immune response against recipient tissues. Humoral GvHD is usually seen after an ABO-mismatched liver transplant, but cellular GVHD is directed against the major histocompatibility complex and often results in severe multisystem disease with high mortality.

The incidence was reported to be 0.1% by United Networks of Organ Sharing, however some clinical trials reported an incidence of up to 1%.<sup>1,3</sup> Skin rash, diarrhea and fever are the most frequent early signs, followed by leukopenia. The mortality rate of acute GvHD following SOT exceeds 75%.<sup>4</sup> In most cases, death results from overwhelming sepsis or gastrointestinal bleeding as a consequence of bone-marrow involvement. There are more than 80 cases reported post-liver transplant<sup>8</sup>.

A literature review demonstrated limited case study treatment options that included discontinuation of immunosuppression (6 patients) – the theoretical benefit of this approach was that by reducing or discontinuing immunosuppression, the host immune system may be able to reject the donor lymphocytes mediating the GvHD<sup>8</sup>. Extracorporeal Photopheresis (ECP) was used to treat two patients – both of which died<sup>6</sup>. This modality did show evidence that donor chimerism was decreased by treatment. Thus, further studies for ECP are needed. The final article describes the use of a CD34 selected haplo-identical stem cell transplant following failed IVIG and rabbit ATG<sup>11</sup>. Pancytopenia resolved as well as GvHD and liver graft functioned normally.

The essential requirements for the development of GvHD: first, the graft must contain immunologically competent cells; second, the recipient must be recognized as foreign by the graft; and, third, the recipient must be unable to reject the graft before it mounts an effective immune response. Pathophysiology: immunocompetent donor T cells transferred with the graft are activated by allo-antigens presented by host antigen presenting cells, resulting in an inflammatory response against host organs.

## Pathophysiology: aGVHD

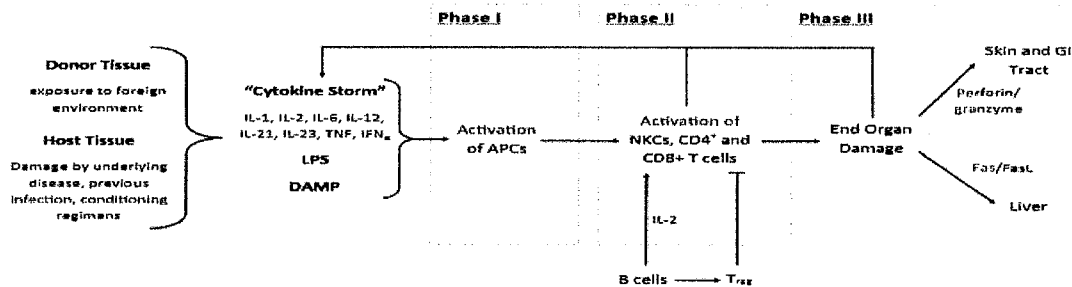


Fig. 1. The pathophysiology of aGVHD.

In many cases, the first manifestation of the immune reaction of donor lymphoid tissue against host tissue occurs in the skin. A maculopapular eruption can be a clue to the diagnosis and may facilitate early modification of the therapeutic strategy. Differential diagnosis of skin symptoms includes drug-induced eruptions and viral infections. An accurate diagnosis can be achieved by using specific histological and immuno-histochemical criteria. Histological changes include the following: in grade I, lymphocytic infiltrates in the upper dermis without epidermal changes; in grade II, vacuolization of basal cells; in grade III, subepidermal clefts through confluence of basal vacuolization; and, in grade IV, massive necrosis of keratinocytes resembling toxic epidermal necrolysis GVHD.

GvHD can also affect other organs systems such as lung, intestine and brain. Pancytopenia, which is uncommon in GVHD after stem-cell transplantation, manifests regularly in patients with GVHD after Liver Transplant.<sup>5</sup> GVHD after SOT occurs less frequently than it does after stem-cell transplantation, but mortality is markedly higher.

### Differential Diagnosis:

The differential diagnosis of GvHD after liver transplant is frequently delayed because early symptoms are often non-specific. The differential diagnosis consists of (1) drug-induced skin reactions, including toxic epidermal necrolysis and mycophenolate mofetil toxicity (MMF); (2) viral exanthemas; (3) infectious enteritis, including CMV infection and *Clostridium difficile* colitis, and (4) organ rejection. Many of the clinical signs of GvHD may also be seen with CMV infection. The presence of CMV in a patient with GvHD may complicate the appropriate diagnosis and delay treatment. A significant association between acute GvHD and CMV after transplant has been documented and may be related to pancytopenia resulting from bone-marrow depletion by attacking donor lymphocytes. A rapid differential diagnosis and early implementation of treatment for GvHD following liver transplant are two factors that affect survival.

**DIAGNOSTIC WORK-UP:** High degree of suspicion in patients with small bowel & liver transplant presenting with rash, fever, diarrhea, hyperbilirubinemia and cytopenia.

- ◆ Complete viral work-up including CMV PCR, EBV PCR, HHV6, HHV8, Adenovirus, Parvovirus, HIV, & Hepatitis panel
- ◆ Donor Chimerism – send to HLA Lab at Hoxworth 513-558-1501
- ◆ Skin bx to rule out GvHD and BMBx – confirm pancytopenia and R/O viral etiology
- ◆ Upper & lower GI Scope with biopsies for GvHD, viral infection including CMV etiology
- ◆ C diff sampling
- ◆ HLA High resolution typing – patient to include DP and donor specific antibody screen (DSA).
- ◆ Consult Heme Malignancy BMT

#### **TREATMENT PLAN:**

##### **INITIAL**

1. If Viral and Bacterial work-up is negative, biopsy proven GvHD or high clinical suspicion, start methylprednisolone 1 mg/kg IV every 12 hours
2. Start G-CSF (example: filgrastim 5 mcg/kg subcutaneously) daily if ANC < 1000. **NOTE:** Heme Malignancy BMT Consult for clinical judgement
3. Consider patient evaluation of Stem Cell Transplant
  - a. Patient will need clearance as per BMT O-16.
  - b. Donor evaluation and clearance reference SOP BMT O-02 and Practice Guideline PG-205
4. Place Apheresis capable dual lumen catheter and begin Extracorporeal Photopheresis (ECP) 5 time a week. Refer to PG-233 for additional ECP guidelines.

##### **NO RESPONSE after DAY 3 Therapy**

1. Add Antithymocyte Globulin Rabbit (rATG) 1.5 mg/kg IV daily for 3 days.

##### **NO RESPONSE after DAY 7-10 Therapy**

1. If patient meets candidacy criteria for transplant & appropriate donor has been identified and cleared, begin transplant preparative regimen
  - a. Fludarabine 30mg/m<sup>2</sup>/ day x 3 days
  - b. rATG 1.5mg/kg/day x 3 days
  - c. TBI 2 GY if patient is not vented

##### **RESPONSE DEFINITION**

1. Improvement in GVHD (rash, diarrhea, liver enzymes and/or bilirubin)
2. ANC > 1000 cells/microliter
3. Platelets >20 10<sup>3</sup>/microliter

4. Chimerism of donor decreased to 20%

Treatment Algorithm	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7-10
<ul style="list-style-type: none"> <li>Viral &amp; Bacterial Work Up</li> <li>Biopsy proven GvHD or high suspicion</li> <li>Methylprednisolone 1 mg/kg IV every 12 hours</li> <li>G-CSF (example: filgrastim 5 mcg/kg) daily if ANC &lt;1000</li> <li>Initiate stem cell transplant evaluation and donor evaluation</li> <li>ECP 5 x a week</li> </ul>				X			
<ul style="list-style-type: none"> <li>Antithymocyte globulin rabbit (rATG) 1.5 mg/kg daily for 3 days</li> </ul>				X	X	X	
<ul style="list-style-type: none"> <li>Initiate hematopoietic stem cell transplant conditioning regimen followed by stem cell transplant</li> <li>If transplant is decided, stop G-CSF, methylprednisolone, calcineurin inhibitors, and ECP prior to preparative regimen</li> </ul>							X

Transplant Algorithm and Preparative Regimen	Day -4	Day -3	Day -2	Day -1	Day 0	Day +1
<b>Fludarabine</b> 30 mg/m <sup>2</sup> /day IV daily on day -4, -3, and -2	X	X	X			
<b>Thymoglobulin, r-ATG</b> 1.5 mg/kg IV daily on day -3, -2, and -1		X	X	X		
<b>TBI</b> 2 GY on day -1				X		
<b>Tacrolimus</b> 0.02 mg/kg/day IV continuous infusion over 24 hours starting on day -2			Titrate tacrolimus to goal range 5-10 ng/mL. Levels to be drawn Mondays, Wednesdays, and Friday.			
<b>CD34+ selected Product</b> Infusion Minimum 5 x 10 <sup>6</sup> /kg					X	
<b>Mycophenolate</b> 500 mg PO TID starting day +1 and continuing through day +30						X

1. Donor Mobilization – Refer to Practice Guideline PG-201

- Related donors will undergo stem cell mobilization using filgrastim (Neupogen) subcutaneously.

- Filgrastim 10 mcg/kg/day for 4 consecutive days and the morning prior to each apheresis session
- Apheresis will be started on day 5 and continued daily until at least  $5 \times 10^6$  CD34+ cells/recipient kg are collected.

## 2. Cell Selection – IRB approved Protocol – Refer to IRB documents

- Selection of mobilized CD34<sup>+</sup> cells was performed by positive immunomagnetic procedures (CliniMACS, Miltenyi Biotec, Bergisch Gladbach, Germany) to obtain a final product with be a minimum of  $5 \times 10^6$  CD34<sup>+</sup> cells/kg and  $<1 \times 10^4$  CD3<sup>+</sup> cells/kg of recipient body weight.
- Remaining CD34+ cells will be cryopreserved for use at a later point in time
- The negative fraction will be frozen as donor lymphocytes in doses of  $1 \times 10^7$ /kg of recipient weight.

## REFERENCES:

1. Taylor AL, Gibbs P, Bradley A. Acute graft versus host disease following liver transplantation: the enemy within. *Am J Transplant.* 2004; 4:466–74.
2. Burdick JF, Vogelsang GB, Smith WJ, Farmer ER, Bias WB, Kaufmann SH, et al. Severe graft-versus-host disease in a liver-transplant recipient. *N Engl J Med.* 1988; 318:689–91.
3. Smith DM, Agura E, Netto G, Collins R, Levy M, Goldstein R, et al. Liver transplant-associated graft-versus-host disease. *Transplantation.* 2003; 75:118–26. 10.1097/00007890-200301150-00022
4. Taylor AL, Gibbs P, Sudhindran S, Key T, Goodman RS, Morgan CH, et al. Monitoring systemic donor lymphocyte macrochimerism to aid the diagnosis of graft-versus-host disease after liver transplantation. *Transplantation.* 2004; 77:441–6. 10.1097/01.TP.0000103721.29729.
5. Romagnuolo J, Jewell LD, Kneteman NM, Bain VG. Graft-versus-host disease after liver transplantation complicated by systemic aspergillosis with pancarditis. 2000; 14:637. *Can J Gastroenterol.*
6. Houston, B.L., Yan, M., Tinckam, K., Kamel-Reid, S., Chang, H., Kuo, K., Tsien, C., Seftel, M.D., Avitzur, Y., Grant, D. & Cserti-Gazdewich, C.M. 2016. Extracorporeal photopheresis in solid organ transplant associated acute graft versus host disease. *Transfusion*, 56: 962–969.
7. Green T, Hind J. 2016. Graft-versus-host disease in paediatric solid organ transplantation: A review of the literature. *Pediatr Transplant*, 20: 607–618.

8. Kohler S, Pascher A, Junge G, Sauer IM, Nagy M, Schönemann C, Koch M, Neumann U, Pratschke J, & Neuhaus P. 2008. Graft versus host disease after liver transplantation - a single center experience and review of literature. *Transpl Int*; 21(5):441-51.
9. Perri, R., Assi, M., Talwalkar, J., Heimbach, J., Hogan, W., Moore, S. B. and Rosen, C. B. (2007), Graft vs. host disease after liver transplantation: A new approach is needed. *Liver Transpl*, 13: 1092–1099.
10. Taylor, A. L., Gibbs, P. and Bradley, J. A. (2004), Acute Graft Versus Host Disease Following Liver Transplantation: The Enemy Within. *American Journal of Transplantation*, 4: 466–474.
11. Akbulut, S., Yilmaz, M., & Yilmaz, S. (2012). Graft-versus-host disease after liver transplantation: A comprehensive literature review. *World Journal of Gastroenterology: WJG*, 18(37), 5240–5248.
12. Fryer J, Mehta J, Levitsky J. (2011) Haploidentical hematopoietic stem cell transplantation for graft-versus-host disease after liver transplantation. *Blood*. 118 (12): 448-3449.
13. Mandac Rogulj I, Deeg J, Lee S. (2012). Acute graft versus host disease after orthotopic liver transplantation. *Journal of Hematology & Oncology* 5 (50):1-6.
14. Gyurkocza B, Cao T, Storb R, et al. (2009) Salvage Allogeneic Hematopoietic Cell Transplantation with Fludarabine and Low-Dose Total Body Irradiation after Rejection of First Allografts. *Biol Blood Marrow Transplant*. 15: 1314-1322.

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