FRED HUTCHINSON CANCER RESEARCH CENTER/ SEATTLE CANCER CARE ALLIANCE

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LONG-TERM FOLLOW-UP AFTER HEMATOPOIETIC STEM CELL TRANSPLANT

GENERAL GUIDELINES FOR REFERRING PHYSICIANS

These guidelines describe generally accepted practices for medical care after hematopoietic stem cell transplantation. Care has been taken to assure that the information in these guidelines is current and accurate based on the available literature and the experience of physicians and patients at FHCRC / SCCA. Recommendations in these guidelines must be implemented in a medically reasonable way that accounts for the specific situation of the individual patient. Recommendations for patients who are enrolled in specific protocols may differ from the recommendations in these guidelines and will be communicated separately. Questions concerning the recommendations in these guidelines or their application to particular patients should be directed to the LTFU office. See Section I of the guidelines for information on how to contact the LTFU office.

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I. HOW TO CONTACT THE LONG-TERM FOLLOW-UP OFFICE AT THE FRED HUTCHINSON CANCER RESEARCH CENTER AND SEATTLE CANCER CARE ALLIANCE

We offer telephone consultation to all physicians caring for patients who have been transplanted at the Fred Hutchinson Cancer Research Center (FHCRC) and Seattle Cancer Care Alliance (SCCA). We have developed a Consultation FAX form (Appendix A) in order to facilitate communication between your office and the LTFU office. This form can be filed in your medical records and sent to 1-800-376-8197 (toll-free, USA and Canada) whenever you need assistance. All efforts will be made to respond within 48 hours on regular workdays. For urgent questions from 8:00 a.m. to 4:00pm Pacific Time on workdays, you can call (206) 667-4415. For urgent questions after hours and on weekend and holidays, please call (206) 288-7600 and ask for the transplant charge nurse. The nurse will triage the call and page the appropriate physician to assist you. For non-urgent inquiries, you may also contact our LTFU Office at LTFU@seattlecca.org. Please include the patient identification and your phone number to contact you back.

Information about LTFU services can be accessed on our website at; http://www.fhcrc.org/science/clinical/ltfu/contact.html .

You can also find us on **Google** by typing **FHCRC.LTFU**, then clicking in the *"Information for Physician"* in the left hand navigation column.

We also request that you notify us immediately after certain types of events. We have developed an LTFU Alert FAX form in order to facilitate the notification from your office to the LTFU office (Appendix B). This form can be filed in your medical records and sent to 1-800-376-8197 (toll-free, USA and Canada) to report the following events:

1. Death of the patient
2. Diagnosis or change in therapy of chronic GVHD
3. Recurrent malignancy
4. Diagnosis of myelodysplasia or secondary malignancy
5. Surgery or biopsy planned for evaluation of suspected secondary malignancy
6. Change of M.D.
7. Change of M.D. office address
8. Change of patient name or address
9. Requests from patients that we refrain from contacting them

II. FREQUENCY OF OFFICE VISITS

After returning home, hematopoietic transplant patients should be followed with weekly office visits for one month. The interval time between visits can be extended to 2 weeks for 2 months and then monthly for 6-12 months if the patient's medical condition remains stable. Vital signs and body weight should be monitored at each clinic visit. Weight and height should be recorded at monthly intervals for assessment of growth and development in pediatric patients. Patients who have had an allogeneic hematopoietic stem cell transplant should be monitored for development of chronic graft-versus-host disease (GVHD). Helpful tips on how to assess and score chronic GVHD can be found at http://www.fhcrc.org/ltfu by clicking on "Information for Physicians" in the left hand navigation column. Then click on the right blue "GVHD Tips & Forms" button. Here you will find the Chronic GVHD Assessment and Scoring form (Appendix D), Range of Motion Assessment form (Appendix F), Skin Thickness Assessment form/ Rodnan Score for patients with sclerosis or fasciitis (Appendix E) and other helpful information. More detailed information about chronic GVHD is outlined in Section X.

If manifestations of chronic GVHD develop or worsen, please contact the LTFU office (Appendix A).

III. LABORATORY TESTS

A. Complete blood cell counts (CBC), differential and platelet counts should be measured at each office visit. Patients receiving ganciclovir (or ValGANCiclovir), daily Trimethoprim/Sulfamethoxazole (TMP/SMX), Cellcept (mycophenolate mofetil), and other myelosuppressive medication should have a CBC at weekly intervals or more often when counts are low.

B. Liver function tests (LFT's) (alkaline phosphatase, ALT, AST, LDH and total bilirubin) should be measured at each office visit. Patients receiving immunosuppressive medications or other hepatotoxic drugs such as itraconazole, voriconazole, INH, should have LFT's measured at two-week intervals or more often when abnormalities are present. If drug toxicity suspected, blood levels should be checked if available.

C. Renal function tests (serum creatinine, BUN, and magnesium) should be measured at each office visit. Patients receiving cyclosporine, tacrolimus (formerly known as FK506), amphotericin or other nephrotoxic drugs should have renal function monitored at weekly intervals or more often when abnormalities are present. Dose adjustment may be needed for medications such as cyclosporine, tacrolimus, ganciclovir, valacyclovir, acyclovir, among others.

D. Drug levels:

Cyclosporine or tacrolimus (FK506) blood levels should be monitored at least twice monthly until levels remain stable within the therapeutic range. Sirolimus (rapamycin) should be monitored weekly until levels remain stable within levels maintained no higher than 10 ng/dL). Sirolimus, cyclosporine or tacrolimus (FK506) levels should be checked more frequently when toxicity is suspected (i.e., new onset of thrombocytopenia, worsening anemia, abnormal renal function, abnormal LFT's, development of tremors or other neurological symptoms), when blood levels are outside the therapeutic range or when manifestations of GVHD is not under control.

Itraconazole blood levels should be monitored at monthly intervals until levels remain stable within the therapeutic range. Itraconazole levels should be checked more frequently when results are outside the therapeutic range and when results of LFT's are abnormal. **Voriconazole, posaconazole and the other azoles should be used with caution during treatment with sirolimus. If treatment with azoles is warranted please contact the LTFU office to discuss sirolimus dose adjustment.**

E. Fasting lipids profile is recommended periodically due to increased risk of cardiovascular disease and increased risk of metabolic syndrome in transplant survivors. In patients receiving sirolimus, tacrolimus or cyclosporine, monthly fasting lipids profile is recommended until acceptable values are achieved, thereafter, monitoring may be decreased to every 3 to 6 months, or more often if clinically indicated.

F. **Thyroid function in blood** should be monitored yearly due to increased thyroid disease after transplant. For patients who received radiolabeled iodine antibody therapy, thyroid function should be checked sooner at 3 and 6 months within the first year after transplant, and other times as clinically indicated.

G. **Blood cultures** should be drawn whenever clinically indicated. For high risk patients (i.e., treatment with prednisone at a dose of more than 1 mg/kg/day), weekly surveillance blood cultures may be beneficial.

H. **CMV monitoring** in blood should be instituted for all patients who are at risk of CMV disease after transplant. CMV **seropositive recipients** of <u>non-cord blood</u> allogeneic transplants or CD34 selected autologous transplants should have CMV monitored in blood *weekly until day 100* after transplant. CMV **seropositive cord blood recipients** should have CMV monitored *twice weekly until day 100* after transplant. CMV **seronegative recipients of cord blood** should have CMV monitored *weekly until day 100 days* after transplant. CMV **seronegative non-cord blood transplant recipients** should be monitored *weekly until day 60* after transplant.

After day 100 posttransplant, CMV monitoring in blood continued, initially *weekly,* until 1 year after transplant for *allogeneic* recipients at risk of late CMV disease which include:

- CMV-seropositive recipients receiving steroids for chronic GVHD
- Patients who were treated for CMV early after transplant.
- Cord blood transplant recipients

The frequency of CMV blood surveillance after day 100 posttransplant may be decreased for non-cord transplant recipients. In patients receiving treatment with <1mg/kg/day of corticosteroids and who have had three consecutive negative surveillance tests after day 100, *every other weekly* CMV monitoring may be sufficient. If treatment with corticosteroid is increased or additional systemic immunosuppressive treatment for chronic GVHD is added, *weekly CMV monitoring* should be resumed as long as clinically indicated.

Cord blood transplant recipients have increased risk of CMV infections and thus are recommended to receive prophylactic treatment in addition to CMV blood surveillance (see section IV, D).

<u>CMV surveillance tests:</u> CMV monitoring can be performed using CMV DNA by PCR or hybrid capture, pp67 mRNA, or pp65 antigenemia (culture based assays are not appropriate for monitoring.) PCR is recommended over pp65 antigenemia for patients who have samples shipped to the FHCRC or to other laboratories requiring overnight shipping.

I. CMV, EBV and Adenovirus Monitoring After Treatment with Anti-Human Thymocyte Globulin (ATG) (ATGAM or Thymoglobulin) Unless Specified Differently per Protocol

Weekly blood monitoring by PCR for EBV, adenovirus, and CMV is recommended for at least 6 months after last dose of ATG or absolute lymphocyte count >300 cells/mm^3, whichever is later for recipients at increase risk for viral disease which include:

- Patients receiving ATG for the treatment of steroids refractory GVHD
- Haplo identical, cord blood or CD 34+ selected transplants recipients who received ATG as part of conditioning

J. Disease Monitoring of Blood and Bone marrow.

Bone Marrow:

Bone marrow should be evaluated at one year after transplant. Testing should include evaluation of morphology and immunophenotyping, cytogenetics and molecular testing as applicable. Subsequent bone marrow evaluations should be done as clinically indicated such as:

- The CBC or platelet count shows any abnormalities
- If the most recent marrow evaluation or other testing showed any evidence of persistent malignancy
- If the patient has a disease for which maintenance treatment would be indicated if disease were discovered after a previous evaluation with no evidence of malignant cells.

Blood:

Patients transplanted for chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphocytic leukemia (Ph-positive ALL) should have blood tested for BCR/abl transcripts at 6 month intervals for the first 2 years after transplant and then at yearly intervals. When BCR/abl transcripts are detected in the blood, a marrow aspirate should be evaluated by cytogenetic testing, morphology and molecular testing.

If recurrent malignancy occurs, please contact the LTFU office for consultation for specific treatment and follow-up recommendations (Appendix A).

IV. INFECTIONS PROPHYLAXIS, PREEMPTIVE THERAPY AND INTRAVENOUS IMMUNOGLOBULIN

All transplant recipients have some degree of immunodeficiency, especially during the first 6-12 months after the transplant. Bacterial, fungal and viral infections occur most frequently during this time interval. In the absence of GVHD, most patients have adequate immune reconstitution by one year after the transplant. Patients with chronic GVHD remain immunodeficient and have a high risk of infections.

A. Pneumocystis jiroveci pneumonia (PCP)

All patients should receive prophylaxis against PCP for at least 6 months after the transplant or until all immunosuppressive medications have been discontinued, whichever occur later. The preferred drug is trimethoprim-sulfamethoxazole administered according to the following regimen:

- Adults: 1 double strength tablet p.o. b.i.d. on 2 consecutive days weekly
- Children $\geq$ 20 kg: 1 single strength tablet p.o. b.i.d. on 2 consecutive days weekly
- Children $\leq$ 20 kg: and 5 mg/kg/day of trimethoprim component in two divided doses on 2 consecutive days weekly.

Patients who are allergic to sulfa should be desensitized whenever possible. If desensitization is not feasible, Dapsone should be administered at a dose of 50 mg p.o. b.i.d. daily for adults and 1 mg/kg/day in two divided doses (up to 100 mg/day) for children. Before starting treatment with Dapsone, patients must be tested to rule out G-6-PD deficiency. Other alternative PCP prophylaxis regimens have been less effective in preventing PCP in stem cell transplant recipients. Please contact the LTFU office (Appendix A) for consultation regarding other alternative PCP prophylaxis regimens if needed.

B. Varicella-zoster virus

All VZV-seropositive patients and those with a history of VZV infection after the transplant should receive prophylaxis with acyclovir or valacyclovir throughout the first year after the transplant or until 6 months after systemic immunosuppressive for control of GVHD ends.

Acyclovir should be administered according to the following regimen (assuming adequate renal function):

- Weight $\geq$ 40 kg, receiving < 0.5 mg/kg/day of corticosteroids: 800 mg P.O. B.I.D.*
- Weight < 40kg, receiving < 0.5 mg/kg/day of corticosteroids: 600 mg/ m^2 P.O. B.I.D.

Alternatively, valacyclovir should be administered according to the following regimen:

- Weight $\geq$ 40 kg, receiving > 0.5 mg/kg/day of corticosteroids: 500 mg P.O. B.I.D*.
- Weight < 40 kg, receiving $\geq$ 0.5 mg/kg/day of corticosteroids: 250 mg P.O. B.I.D.

*Note: In VZV seropositive/HSV seronegative, patients $\geq$ 40 kg, lower doses of prophylaxis are sufficient, 800 mg/day of acyclovir or 500 mg/day of valacyclovir. For patients < 40 kg, the dose of acyclovir should be 300 mg/m^2 (maximum 400 mg) P.O. B.I.D.

It is difficult to prevent VZV transmission to susceptible patients because infected individuals are contagious for 24-48 hours before the rash appears. The incubation period of VZV is 10-21 days. Individuals with VZV (chickenpox or shingles) remain contagious until all skin lesions have crusted.

All patients exposed to chickenpox or zoster during the first year after the transplant or during treatment with immunosuppressive medications should be evaluated. VZV-seronegative patients and those not receiving prophylactic acyclovir should be treated with valacyclovir from days 3 to 22 after exposure unless treatment with ganciclovir, foscarnet or cidofovir is being given for another reason. Valacyclovir should be given at a dose of 1gm p.o. t.i.d. for patients $\geq$ 40 kg and at a dose of 500 mg p.o. t.i.d. for patients < 40 kg. In adults and children without adequate oral intake, acyclovir can be administered at a dose of 500mg/m^2 IV every 8 hours if renal function is normal. In seronegative recipients, administration of VZIG within 96 hours of exposure should also be used, if available, in addition to valcyclovir as outlined above. Patients exposed to chickenpox or zoster during prophylaxis with acyclovir or valacyclovir must be followed closely for the development of VZV infection.

Vaccination against VZV should be delayed (See vaccination Section IX for details).

C. Encapsulated bacteria

Patients with chronic GvHD are highly susceptible to recurrent bacterial infections, especially with encapsulated bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis.* Susceptibility to these organisms may be due to persistent low levels of opsonizing antibodies, low CD4 counts, poor reticuloendothelial function, and long-term use of immunosuppressive therapy, especially corticosteroids, with their suppressive effects on phagocytosis. Long-term chemoprophylaxis is recommended in this setting due to unpredictable protection provided by vaccination, which is also recommended after transplant. Due to the emergence of penicillin resistance (and the concomitant need for PCP prophylaxis in these patients), trimethoprim-sulfamethoxazole (TMP-SMX) is recommended as first-line drug for chemoprophylaxis for infections with encapsulated bacteria. If TMP-SMX is not tolerated, the traditional penicillin-based prophylaxis should be substituted for encapsulated bacteria and dapsone also should be prescribed to provide PCP prophylaxis.

Other patient groups who should be considered for encapsulated organism prophylaxis include those who are:

- Without GVHD but are receiving glucocorticoid or other immunosuppressive medications.
- With persistent or recurrent manifestations of chronic GVHD without ongoing use of immunosuppressive medications
- Being treated for relapsed or progressive malignancy after transplant
- Surgically and/or functionally asplenic (see below for more details).
- Patients who are age$\geq$ 65 years old post-allogeneic stem cell transplantation.

Patients receiving systemic immunosuppressive therapy for chronic GVHD should receive antibiotic prophylaxis against infection with encapsulated bacteria for at least 6 months after discontinuation of all immunosuppressive medications. Double-strength (DS) trimethoprim-sulfamethoxazole (800mg sulfamethoxazole) given as a single dose daily is adequate for prevention of infection with both PCP and encapsulated bacteria in adults.

In patients with sulfa allergies, Penicillin VK (Pen-Vee-K) should be given for encapsulated bacteria prophylaxis (see Table below). Children $\leq$ 30 kg who do not tolerate daily trimethoprim-sulfamethoxazole (TMP/SMX) should receive Penicillin VK (See Table below).

Additional medication is required for PCP prophylaxis in patients who receive penicillin instead of daily trimethoprim-sulfamethoxazole (TMP/SMX). **(See Section IV.A)**

Table - Penicillin VK dosing for encapsulated bacterial prophylaxis:

Adults and Children ($\geq$ 60 kg)	750 mg PO BID
Adults (< 60 kg) and Children (40 to 60 kg)	500 mg PO BID
Children (20 to 40 kg)	250 mg PO BID
Children (< 20 kg)	125 mg PO BID or (50mg/kg/day)

For more information, see the Standard Practice Guideline section "Antibiotic Prophylaxis for Encapsulated Bacteria in Allogeneic Patients with Chronic GVHD Requiring Immunosuppressive Therapy"

Antimicrobial prophylaxis for asplenic patients
Patient education is paramount to prevent fatal infections in asplenic patients. Studies have shown that 11% to 50% of postsplenectomy patients remain unaware of their increased risk for serious infection or the appropriate health precautions that should be undertaken. Important education points include the following:

- Persons without a functioning spleen are more susceptible to certain infections.
- The risk of infection is life-long, but it is highest in the first year or two after the surgery.
- If unwell (particularly in case of fever associated with rigors**), patients should seek prompt medical attention**. Infections can be rapidly progressive and life-threatening in a matter of hours. The use of prophylactic or preemptive measures should never be allowed to engender a false sense of security.
- Travel-related infections (such as babesiosis and malaria) are particularly important; adherence to antimalarial prophylaxis cannot be overemphasized.
- All physicians caring for the patient should be informed of the condition, no matter how long after the splenectomy.

Antimicrobial regimens are the same as for prevention of encapsulated bacteria in patients with chronic GVHD, and include daily Trimethoprim/Sulfamethoxazole (TMP/SMX) or twice-daily Penicillin VK therapy. Penicillin VK provides no protection against PCP; thus dapsone or other PCP prophylaxis must be added.
The duration of antibiotic prophylaxis in the asplenic patient after transplant is dependent of the presence of chronic GVHD (See Table below).

Table - Duration of propylaxis for encapsualted organism in asplenic patients according to chronic GVHD	
HCT recipients with chronic GVHD	Until 6 months after immunosuppression d/c'd OR until age 6 OR 2 years after splenectomy (whichever occurs later)
All HCT receipients *without* chronic GVHD (allo, auto, syngenic)	1 year after BMT OR until age 6 OR 2 years after splenectomy (whichever occurs later)

Antimicrobial prophylaxis should also be considered for patients AT ANY TIME post-splenectomy during travel to sites where medical care will not be rapidly accessible.

Preemptive therapy for the post-splenectomy patient with fever and rigors
Another strategy that has been advocated is the provision of "standby" antipneumococcal antibiotics; this strategy may be particularly relevant for patients who are not receiving prophylaxis. Under this strategy, the patient retains a personal supply of antibiotics to be taken at the first sign of respiratory illness, fever, or rigors, particularly if there is likely to be a delay in medical evaluation. There is currently no evidence that such early self-treatment will lower the mortality associated with post splenectomy sepsis (PSS). In fact, the literature series with the lowest mortality reported to date emphasized patient education, close follow-up, and prompt physician intervention at the earliest sign of even minor infection. Thus, even if patients have their own supply of antibiotics, medical help should be sought immediately**,** at which time a physician should decide whether to continue antibiotic therapy.

Recommended antibiotics and doses that may be useful in preemptive approaches include the following:

- Adults: Amoxicillin 500 mg tablets; take 4 tablets (2 grams) and report immediately for medical attention
  Levofloxacin 500 mg tablets; take 1 tablet and report immediately for medical attention

- Children 20-40 kg: Amoxicillin 250 mg tablets; take 4 tablets (1 gram) and report immediately for medical attention

- Children < 20 kg: Amoxicillin 50 mg/kg administered as chewable tablets and report immediately for medical attention

For penicillin-allergic children, consider Bactrim or other drugs as clinically indicated.

Empiric therapy for post-splenectomy sepsis (PSS) or other serious infections
Early recognition of infection followed by aggressive intervention is the cornerstone of PSS management. Initial empiric antimicrobial therapy for the splenectomized patient with unexplained fever, rigors, and other systemic symptoms should always include a broad-spectrum antibiotic active against *S. pneumoniae, H. influenzae*, and *N. meningitidis* such as ceftriaxone. In areas with high-level penicillin-resistant pneumococci, vancomycin may be added empirically, particularly in cases with suspected or proven meningitis

D. Cytomegalovirus (Section III H and I for monitoring frequency).

1. Who Should Receive Pre-emptive Therapy for CMV

- Recipients of non-cord blood allogeneic transplants after day 100, ganciclovir should be given preemptively when CMV DNA is detected in the blood by PCR tests with ≥ 250 IU per mL (equivalent to ≥1000 numbers of copies per mL), or rising DNA levels (> 5x baseline within one month) or by an antigenemia test with any numbers of positive cells per slide. See Table 1

- Recipients of CD34 selected autologous transplants, ganciclovir should be given preemptively when CMV DNA is detected in the blood by PCR tests with ≥ 25 IU per mL (equivalent to ≥100 numbers of copies per mL) or by any level of antigenemia test before 100 days post transplant. See Table 1

Table 1. Pre-emptive Regimen for CMV Reactivation Among NON-Cord Blood Recipients with Adequate Renal Function After 100 days to 1 year After Transplant

INDUCTION		MAINTENANCE	
Preferred	**Alternative**	**Preferred**	**Alternative**
Ganciclovir 5 mg/kg IV Q 12hrs **OR** ValGANCiclovir (ONLY for patients with good oral intake, no active gut GVHD, no significant liver disease and no severe diarrhea): Adults and Peds ≥ 50 kg: 900 mg PO Q 12 hrs Peds ≥ 40 to < 50kg: 675 mg PO Q 12 hrs Peds ≥ 30 to < 40kg: 450 mg PO Q 12 hrs Peds ≥20 to <30 kg: 450 mg PO Q 12 hrs ***or*** Liquid 14 mg/kg Q 12 hrs Peds ≥ 15 to <20 kg: 225 mg PO Q12 hrs (= ½ pill) ***or*** Liquid 14 mg/kg Q12 hrs Peds ≥10 to < 15 kg: Liquid 14 mg/kg Q12 hrs	Foscarnet 90 mg/kg IV Q 12hrs	Ganciclovir 5 mg/kg IV Q DAY **OR** ValGANCiclovir (ONLY for patients with good oral intake, no active gut GVHD, no significant liver disease and no severe diarrhea): Adults and peds ≥ 50 kg: 900 mg PO Q Day Peds ≥ 40 to < 50 kg: 675 mg PO Q Day Peds ≥30 to < 40 kg: 450 mg PO Q Day Peds ≥20 to <30 kg: 450 mg PO Q Day ***or*** Liquid 14 mg/kg QD Peds ≥ 15 to <20 kg: 225 mg PO QD (= ½ pill) ***or*** Liquid 14 mg/kg QD Peds ≥10 to < 15kg: Liquid 14 mg/kg QD	Foscarnet 90 mg/kg IV Q DAY
Duration: Induction therapy should be given for 1 week or until a decrease of PCR or antigenemia levels have been documented, whichever is later.		Duration: Maintenance therapy should be given for at least 2 weeks after induction therapy has been completed.	
Preemptive therapy may be discontinued when the surveillance test is negative after a minimum of 3 weeks of therapy. Shorter courses may be appropriate for subsequent episodes of CMV reactivation. Please consult the LTFU office for questions (206-667-4415)			

- Recipients of cord blood transplant after day 100, ganciclovir should be given preemptively when CMV by PCR DNA testing is detected in ≥ 250 IU per mL (equivalent to ≥ 1000 copies per mL) or rising DNA levels (> 5x baseline within one month)**. See additional information for Cord Blood Transplant recipients**

including CMV prophylaxis after day 100 below. See Table 2

Table 2. Pre-emptive Regimen for CMV Reactivation Among Cord Blood Recipients with Adequate Renal Function After 100 Days to 1 Year After Transplant

INDUCTION		MAINTENANCE	
Preferred	**Alternative**	**Preferred**	**Alternative**
Ganciclovir 5 mg/kg IV Q 12hrs **OR** ValGANCiclovir*(ONLY for patients with good oral intake, no active gut GVHD, no significant liver disease and no severe diarrhea): Adults and Peds ≥ 50 kg: 900 mg PO Q 12 hrs Peds ≥ 40 to < 50kg: 675 mg PO Q 12 hrs Peds ≥ 30 to < 40kg: 450 mg PO Q 12 hrs Peds ≥20 to <30 kg: 450 mg PO Q 12 hrs ***or*** Liquid 14 mg/kg Q 12 hrs Peds ≥ 15 to <20 kg: 225 mg PO Q12 hrs (= ½ pill) ***or*** Liquid 14 mg/kg Q12 hrs Peds ≥10 to < 15 kg Liquid 14 mg/kg Q12 hrs	Foscarnet 90 mg/kg IV Q 12hrs	Ganciclovir 5 mg/kg IV Q DAY **OR** ValGANCiclovir* (ONLY for patients with good oral intake, no active gut GVHD, no significant liver disease and no severe diarrhea): Adults and Peds > 50 kg: 900 mg PO Q Day Peds ≥ 40 to < 50 kg: 675 mg PO Q Day Peds ≥ 30 to < 40 kg: 450 mg PO Q Day Peds ≥ 20 to <30 kg: 450 mg PO Q Day ***or*** Liquid 14 mg/kg QD Peds ≥ 15 to <20 kg: 225 mg PO QD (= ½ pill) ***or*** Liquid 14 mg/kg QD Peds ≥ 10 to < 15kg: Liquid 14 mg/kg QD	Foscarnet 90 mg/kg IV Q DAY
Duration: 1 week or until a decrease of PCR or antigenemia levels have been documented, whichever is later.		Duration: Maintenance therapy should be given for at least 2 weeks after induction therapy has been completed.	
Preemptive therapy may be discontinued when the surveillance test is negative after a minimum of 3 weeks of therapy. Shorter courses may be appropriate for subsequent episodes of CMV reactivation. *Please consult the LTFU office for questions (206-667-4415)* **Upon discontinuing pre-emptive therapy, resume prophylaxis for CMV (see Table 3)**			

***** Consider evaluation for CMV resistance in patients who develop CMV viremia on ValGANCiclovir maintenance, particularly in those with poor response to ganciclovir induction.

Monitoring during treatment:

- CBC and differential must be measured within 24 hours before initiating treatment.
- CBC and differential must be measured 2-3 times weekly during treatment with ganciclovir.
- Daily CBC is mandatory if the absolute neutrophil count (ANC) is <1,500/mm^3.
- If ANC <1,000/mm^3 before ganciclovir or ValGANCiclovir is started, alternative therapy is foscarnet.
- Renal function tests must be measured at least weekly.

Dose adjustment and other precautions during treatment:

- STOP ganciclovir or ValGANCiclovir if the ANC is below 1,000/mm^3 and consider foscarnet.
- AVOID using ganciclovir, ValGANCiclovir and foscarnet concurrently with acyclovir. Please contact the LTFU office (Appendix A) for consultation.
- Ganciclovir, ValGANCiclovir and foscarnet MUST be adjusted for renal dysfunction.

If quantitative CMV by PCR or antigenemia levels rises for more than 3 weeks on continuous ganciclovir/ValGANCiclovir or foscarnet treatment, antiviral drug resistance should be considered.. Testing for antiviral sensitivity or molecular screening for UL97 and UL54 mutations should be considered as well as changing to other drugs. Clinical management with the Fred Hutchinson Cancer Research Center Infectious Disease Service may be considered. Please contact the LTFU office (Appendix A).

2. CMV Prophylaxis After Day 100 in Seropositive Cord Blood Transplant Recipients

CMV seropositive cord blood transplant recipients remain at significantly increased risk for CMV reactivation after day 100 after transplant. Therefore, antiviral prophylaxis and continued close monitoring after day 100 (see Table 3 below) are recommended for all CMV seropositive cord blood transplant recipients.

Table 3: CMV Prophylaxis and Monitoring after Day 100 to 1 Year for CMV-seropositive Cord Blood Recipients with Prior Posttransplant CMV Reactivation

DOSING	PREFERRED		ALTERNATIVE	MONITORING BLOOD
	Able to tolerate PO	*Unable to tolerate PO*	*Able to tolerate PO*	
Adult or Pediatric ≥50 kg	**ValGANCiclovir**† 900mg PO QD	**Ganciclovir** 5 mg/kg IV Q DAY	**Valacyclovir*** 2 grams PO TID	Weekly: CMV PCR, Creatinine, CBC with Differential.
Pediatric ≥40 to <50 kg	**ValGANCiclovir**† 675 mg PO QD(=1½ pills)		**Valacyclovir*** 2 grams PO TID	
Pediatric ≥30 to <40 kg	**ValGANCiclovir**† 450 mg PO QD		**Valacyclovir*** 1 gram PO TID	
Pediatric ≥20 to < 30 kg	**ValGANCiclovir**† 450 mg PO QD) ***or*** Liquid 14 mg/kg QD		**Valacyclovir*** 1 gram PO TID	
Pediatric ≥15 to < 20 kg	**ValGANCiclovir**† 225 mg PO QD(= ½ pill) ***or*** Liquid 14 mg/kg QD		**Acyclovir*** 600 mg/m^2 PO QID	
Pediatric ≥10 to < 15 kg	**ValGANCiclovir**† Liquid 14 mg/kg QD		**Acyclovir*** 600 mg/m^2 PO QID	

† Absorption of ValGANCiclovir is significantly enhanced when taken with food; thus patients should be instructed to take ValGANCiclovir with food. Patients with poor oral intake, severe diarrhea/gut GVHD are NOT good candidates for ValGANCiclovir and should receive IV ganciclovir daily.

* Valacyclovir tablets should NOT be crushed. Oral acyclovir suspension has poor bioavailability and is not a preferred choice.

Table 4: CMV Prophylaxis and Monitoring after Day 100 for CMV-seropositive Cord Blood Recipients without Prior Posttransplant CMV Reactivation

DOSING	PREFERRED		ALTERNATIVE	MONITORING BLOOD
	Able to tolerate PO intake	Unable to tolerate PO intake		
Adult or Pediatric ≥50 kg	Valacyclovir* 2 grams PO TID	Acyclovir‡ 500 mg/m^2 IV Q 8 hr	Ganciclovir 5 mg/kg IV Q DAY	Weekly: CMV by PCR Creatinine and CBC with Differential
Pediatric ≥40 to <50 kg	Valacyclovir* 2 grams PO TID			
Pediatric ≥30 to <40 kg	Valacyclovir* 1 gram PO TID			
Pediatric ≥20 to < 30 kg	Valacyclovir* 1 gram PO TID			
Pediatric ≥15 to < 20 kg	Acyclovir 600 mg/m^2 PO QID			
Pediatric ≥10 to < 15 kg	Acyclovir 600 mg/m^2 PO QID			

* Oral Valacyclovir is the preferred agent and is available in tablets or compounded liquid formulation for children.
Crushing tablets is NOT recommended.

‡ If patients cannot tolerate oral tablets or liquid formulation, they should receive IV Acyclovir (adjusted to ideal body weight). Oral acyclovir suspension has poor bioavailability, thus not a preferred choice.

Dose adjustment and other precautions during treatment:

- STOP ganciclovir or ValGANCiclovir if the ANC is below 1,000/mm^3 and consider acyclovir, valacyclovir or foscarnet, as clinically indicated.
- AVOID using ganciclovir, ValGANCiclovir, foscarnet and valacyclovir concurrently with acyclovir. Please contact the LTFU office (Appendix A) for consultation.
- Ganciclovir, foscarnet, ValGANCiclovir, valacyclovir and acyclovir MUST be adjusted for renal dysfunction.

E. Fungal organisms

The current standard practice for antifungal prophylaxis is to administer fluconazole (400 mg/day) until day 75 after an allogeneic or CD34 selected autologous transplant or until engraftment and resolution of mucositis after an unselected autologous transplant. This strategy has been shown to reduce the incidence of candidemia and candidiasis-related mortality. Fluconazole does not prevent infection with Aspergillus and other mold species.

F. Intravenous immunoglobulin (IVIG) replacement and adjunctive therapy

This section addresses the use of IVIG after hematopoietic cell transplantation (HCT) when given after day 100 to 1 year. Reported IVIG studies are listed in the end of the LTFU general guidelines [1-8]. For information regarding IVIG administration before100 days after transplant see Standard Practice Committee guidelines.

1. Indication for prophylactic administration of IVIG after 100 days following HCT:

- Allogeneic patients transplanted for myeloma, low grade lymphoma or CLL and those with chronic GVHD with persistent severe hypogammaglobulinemia (IgG levels below 400 mg/dL).
- Patients transplanted for primary immunodeficiency disease.

2. Dosing and administration of prophylactic IVIG after 100 days following HCT:

a. For allogeneic patients transplanted for myeloma, low grade lymphoma or CLL and those with chronic GVHD with severe hypogammaglobulinemia:

Administer IVIG 400 mg/kg at monthly intervals to maintain serum IgG levels above 400 mg/dL for 10 months after transplant.
Beyond one year after HCT, a 6 month trial of monthly prophylactic IVIG may be beneficial for patients with recurrent sinopulmonary infections and persistent hypogammaglobulinemia, especially in those with chronic GVHD.

b. For primary immune deficiency disease (PID):

Pre-infusion IgG serum level [1] (mg/dL)	**IVIG dosing regimen [1,2]**
600 – 1000	Begin at 200 mg/kg/every 2 weeks and wean to 400 mg/kg/every 4 weeks if troughs remain satisfactory
< 600	300 mg/kg/every 2weeks up to 500 mg/kg every week[2]
≥1000	400 mg/kg/every 4 weeks until B cell function fully restored

[1] When low levels are attributable to increased losses (e.g. chronic diarrhea) both IVIG dose and frequency should be increased.
[2] For pediatric patients the maximum dose of IVIG is 40 grams.

For pediatric patients whose central line is only being used for IVIG prophylaxis, transition to subcutaneous human immunoglobulin preparation (Hizentra®) may be considered under the approval and guidance of Pediatric Immunology Service.

c. IVIG should be held two months before the annual posttransplant evaluation to assess immune reconstitution. (e.g. serum immunoglobulins levels and other immunological panel).

d. Select immunoglobulin product according to precautions to decrease adverse effects as applicable (see cautionary note below).

3. IVIG for treatment of CMV pneumonia:

There is no convincing efficacy data to add standard IVIG to antiviral therapy for CMV pneumonia after HCT. The overall benefit of CMV IgG combined with antiviral for treatment of CMV pneumonia has been reported by some but not all investigators. Due to high mortality associated with CMV pneumonia, some experts recommends antiviral therapy combine with CMV IgG as follows:

- CMV-IVIG may be administered at 150mg/kg every other day for 2 weeks (7 doses) followed by weekly administration for 4 additional weeks in combination with anti-CMV medication.
- When high titer CMV-IVIG product (CytoGam) is not available, some experts has recommended using standard IVIG at 500mg/kg given at the same schedule as described above for CMV IgG.

4. Premedications before IVIG administration:

Given the high incidence of side effects of IVIG infusion (i.e., fever, chills, nausea, emesis, headache, myalgias, rash and hypotension without anaphylaxis), premedication with acetoaminophen and anti-histaminices (i.e., diphenhydramine) is recommended.

5. Contraindication for IVIG:

1. Antibodies to IgA present
2. Anaphylaxis or severe prior reaction to immunoglobulin or serum therapy.

6. Cautionary note about IVIG:

IgA deficiency: IgA deficiency is considered a contraindication for IVIG use because patients may develop IgE antibodies to IgA which increases their risk of anaphylaxis if exposed to a product containing significant quantities of IgA. IVIG formulation products with the lowest IgA content available should be given to patients known to be deficient in IgA who require IVIG and who do not have detectable antibodies to IgA. All patients with absent pre-transplant serum IgA levels should be evaluated for the presence of anti-IgA antibodies. *(see table below)*

Renal insufficiency (creatinine clearance less than 60 ml/min):
Sucrose-free containing IVIG products should ONLY be used in the setting of renal insufficiency. *(see table below)*

IVIG Preparations

Preparation	Sugar Content	IgA Content
CMV IVIG		
Cytogam	5% Sucrose	?
IVIG		
Carimune	5% Sucrose	720mcg/ml
Panoglobulin	5% Sucrose	720mcg/ml
Gammar	5% Sucrose	?
Sandoglobulin	5% Sucrose	?
Octagam	10% Maltose	≤200 mcg/ml
Venoglobulin	5% Sorbitol	15-50mcg/ml
Flebogamma	5% Sorbitol	<50mcg/ml
Gammar	5% Glucose	<25 mcg/ml
Iveegam	5% Glucose	<10mcg/ml
Low IgA containing IVIG		
Polygam	2% Glucose	<3.7mcg/ml
Gammagard SD (powder)	2% Glucose	<1 mcg
Sugar Free IVIG		
Gamunex		45mcg/ml
Gammagard 10% (liquid)		37 mcg/ml
Privigen		<25mcg/ml
Gammaplex		?

V. FEVER OF UNKNOWN ETIOLOGY

Fever should be considered a sign of infection until proven otherwise. The following evaluation should be instituted promptly in all patients with fever.

1. Complete physical examination including the perineal and rectal area.
2. Blood culture
3. Urine culture
4. Cultures from any site suspicious for infection
5. Chest X-ray. CT of the chest should be obtained if respiratory symptoms are present even if the chest x-ray is negative.
6. Sinus CT scan should be obtained if respiratory symptoms are present.

Empiric treatment with antibiotics may be indicated after cultures have been obtained. Sudden, overwhelming sepsis syndrome with Pneumococcus or other encapsulated organisms can occur, especially in patients who have poor compliance with antibiotic prophylaxis. Organisms should be tested for antibiotic susceptibility. Please contact the LTFU office (Appendix A) for consultation or assistance regarding specific treatment and other evaluation as needed.

VI. EVALUATION OF RESPIRATORY PROBLEMS AND LUNG INFILTRATES

If the patient develops respiratory problems that do not resolve after initial diagnostic evaluation and treatment, we urge you to contact the LTFU office (Appendix A) to discuss further evaluation and management.

A. Diagnostic Evaluation

1. Chest x-ray PA and lateral
2. Lung CT scan if respiratory symptoms persist
3. Sinus CT scan if symptomatic or suspected sinus infection
4. Blood culture (always)
5. Nasopharynx culture for pertussis if clinically indicated
6. Bronchoalveolar Lavage (BAL) is recommended for patients with pulmonary symptoms or pulmonary infiltrates to rule out infectious complication.
7. Transbronchial or thoracoscopic biopsy if BAL is negative with persistent pulmonary infiltrates

B. Tests Recommended for BAL and Transbronchial Biopsy Specimens

See algorithm on the end of this section for overview.

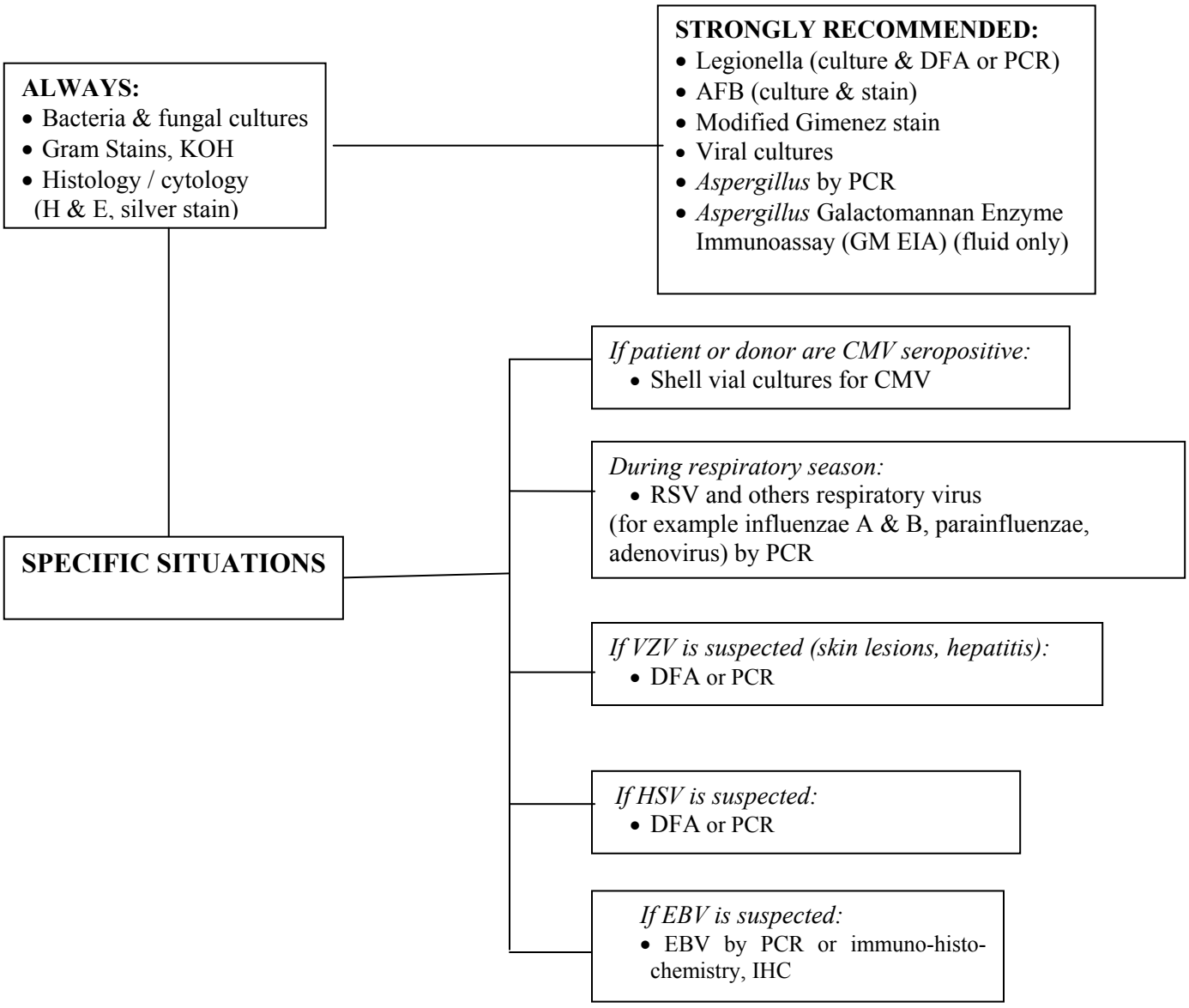
1. Bacterial, fungal, mycobacterial, and Legionella cultures
2. Stains specific for viral inclusions and general morphology to rule out malignancy (Papanicolaou, Wright-Giemsa, Hematoxylin & Eosin)
3. Methenamine silver, Kinyoun AFB, modified Gimenez and Gram stains, KOH
4. for BAL *Aspergillus* Galactomannan Enzyme Immunoassay (GM EIA) (fluid only) or aspergillus by PCR
5. CMV shell vial test
6. DFA (direct fluorescent antibody) staining for herpes viruses (HSV, VZV),
7. PCR for respiratory viruses (RSV, influenzae A and B, parainfluenzae, adenovirus)
8. DFA (direct fluorescent antibody) for Legionella or PCR for Legionella
9. If clinically indicated, PCR or IHC for EBV.

C. Evaluation of Pulmonary Nodules or Persistent Infiltrates with a Negative BAL

1. Thoracoscopic biopsy or open lung biopsy is recommended for patients with nodular infiltrates to rule out fungal, malignancy, bronchiolitis obliterans with organizing pneumonia (BOOP) or other processes. Thoracoscopic lung biopsy generally causes less morbidity than open lung biopsy. Fresh tissue should be submitted for microbiologic and pathologic evaluation.
2. Tests recommended for lung tissue
   a) Fresh samples should be obtained for DFA and culture or PCR for Legionella.
   b) Imprints of the frozen section and permanent section should be made and evaluated for morphology and assessment of viral inclusions and possible malignancy by using Papanicolaou, Wright-Giemsa, hematoxylin and eosin stains. Specimens should be evaluated for Pneumocystis, fungi, mycobacteria, Legionella and other bacteria by using methenamine silver, Kinyoun AFB, modified Gimenez and tissue Gram stains. Warthin-Starry stain should be done if needed. When available, immunohistochemistry staining and in situ hybridization are recommended for detection of viral infection.
   c) Samples should be submitted for microbiologic evaluation to detect fungi, mycobacteria, and other bacterial organisms.
   d) *Aspergillus* by PCR
   e) Samples should be submitted for viral cultures, in addition:

-DFA staining for herpes viruses (HSV, VZV)
-PCR for respiratory viruses (RSV, influenzae A and B, parainfluenzae, adenovirus)
-Shell vial testing for CMV or PCR testing for CMV, VZV, HSV, EBV, HHV-6, depending on the level of clinical suspicion.

Tests Recommended for Bronchoalveolar Lavage Fluid or Lung Biopsy Specimens



- Keep material in the refrigerator / freezer until a definitive diagnosis is made.
- If any of the tests above is not available locally, please contact the LTFU office (Appendix A).

VII. EVALUATION OF DIARRHEA AND OTHER GI COMPLICATIONS

If the patient develops diarrhea or other gastrointestinal complications that do not resolve after initial diagnostic evaluation and treatment (see algorithm on the end of this section), we urge you to contact the LTFU office (Appendix A) to discuss further evaluation and management.

A. Diagnostic Evaluation and Initial Management

1. Diarrhea caused by oral magnesium supplementation should be ruled out. If necessary, patients should receive IV replacement of magnesium.
2. The clinical evaluation of diarrhea depends on its duration and volume, the presence of blood, and the occurrence of fever and other constitutional symptoms. Normal stool volume is <200 ml/day. Volumes >1000 ml/day indicate a small intestinal source (GVHD, magnesium effect, enteric virus, giardiasis or cryptosporidiosis). Bloody diarrhea suggests a bacterial enteric pathogen, GVHD or CMV enteritis. A more directed approach can be taken if there is a history of foreign travel or history of exposure to children from day-care setting. An algorithm for evaluation of diarrhea is summarized on the following page.
3. Patients should remain NPO for 24-48 hours and IV fluids should be given to prevent volume depletion. Special diets are recommended for patients with diarrhea caused by GVHD (Section XX).
4. Immunosuppressive medications should be given IV if the volume of diarrhea exceeds 1.5 liter/day in adults of if diarrhea persists for more than 3 days. Contact the LTFU office (Appendix A) for IV doses of immunosuppressive medications.
5. Monitor creatinine closely, and check the cyclosporine or tacrolimus (FK506) level weekly.
6. Avoid treatment with anti-diarrhea agents containing atropine-like drugs (e.g. Loperimide).
7. If the diarrhea does not resolve with these measures or recurs after the patient resumes oral medications, a search for enteric pathogens including, for example, norovirus, c. difficile, adenovirus and for children, rotavirus and endoscopy with biopsies is recommend. Adequate platelet count and coagulation parameters should exist to do biopsy safely.

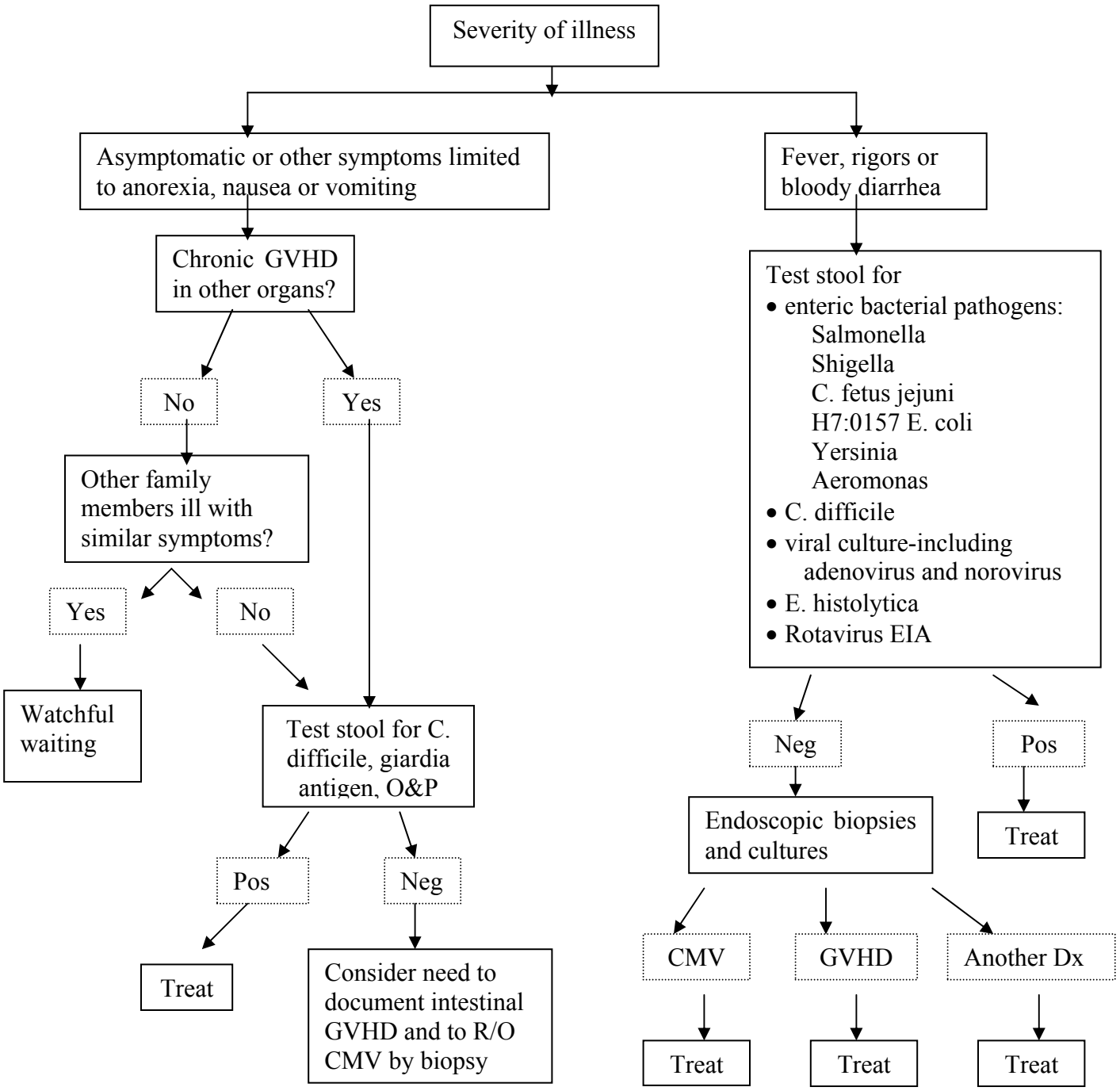
B. Procedures for Gastrointestinal Endoscopic Biopsies

1. Maintain platelet counts >50,000 before and for 3 - 4 days after the procedure.
2. Esophagogastroduodenoscopy should be carried out with multiple biopsies. Biopsy of any erosion or ulcerations is indicated. If there are no macroscopic abnormalities found, we suggest 6-8 biopsies of the gastric antrum. To minimize the risk of bleeding, avoid biopsies of the duodenum unless this is the only site of abnormalities.
3. When diarrhea is the major GI symptom in a patient without other manifestations of GVHD, either upper endoscopy or colonoscopy may be indicated to rule out CMV infection or occult GVHD. All infections other than CMV can be identified from stool samples. Biopsies obtained from the gastric antrum are usually sufficient to diagnose GVHD, even in cases where the major symptom is diarrhea.
4. Biopsies samples (n = 4) should be placed in fresh buffered formalin.
5. Fresh biopsy samples (gastric, rectal or colon) should be placed in viral transport medium and sent to a virology lab to perform rapid testing (shell vial) for CMV and Varicella zoster as well as HSV if there are esophageal lesions. The last stomach sample should be placed in CLO media to test for H. Pylori.

6. Please send slides and biopsy blocks to the address below if you wish our pathologists to review the specimen. Because GVHD may be found in one but not all sites, it is important to send as many slides or blocks as possible.
7. Please label the material with the patient's name, the date obtained and sites.
8. Send the material to the following address:

   Seattle Cancer Care Alliance / Fred Hutchinson Cancer Research Center
   825 Eastlake Ave. E. / Attn: LTFU G-1500
   PO Box 19023
   Seattle, WA 98109-1023
9. Please call (206) 667-4415 to notify our office when to expect the arrival of shipments.

C. Algorithm for Evaluation of Acute Onset Diarrhea in Transplant Survivors*



*In all patients with diarrhea, oral administration of Mg^{++} should be discontinued, and IV administration should be substituted.

VIII. TREATMENT OF SPECIFIC INFECTIONS

Please contact the LTFU office (Appendix A) to discuss the most appropriate therapy in patients developing any of the infections described below.

A. Cytomegalovirus (CMV)

Late onset CMV infections have become an increasingly difficult problem for patients who have had a hematopoietic stem cell transplant. Reconstitution of the T cells that respond to CMV is slow and may be delayed by prophylactic use of ganciclovir during the first 3 months after the transplant. Patients at risk of CMV infection should be monitored closely and should receive prophylactic antiviral treatment to prevent CMV disease. Note that some patients present with nausea and vomiting as initial manifestations of CMV infection, in the absence of CMV antigenemia. Prophylactic treatment is recommended when CMV is detected in blood or plasma by antigenemia assay (CMV pp65) or by PCR, in patients at risk as outlined in Section IV D. To obtain recommendations for treatment of patients who develop CMV pneumonia or other diseases caused by this virus, we urge you to contact the LTFU office (Appendix A).

B. Varicella zoster

Varicella zoster virus (VZV) infection occurs in 40-50% of patients during the first year after the transplant (peak risk 2-8 months) when prophylactic acyclovir is not given. In approximately 10% of patients, VZV infection presents with abdominal distension or pain in the abdomen or back, often accompanied by increased serum ALT, before the development of any skin lesions. Visceral VZV is frequently fatal if treatment is delayed. If prodromal zoster or documented VZV infection occurs during the first year after the transplant or at any time during continued treatment with immunosuppressive medications, parenteral treatment should be started immediately with high dose acyclovir, and blood should be sent to confirm the diagnosis by a VZV PCR test.

Patients should be treated according to the following recommendations.

1. Fluids should be administered at twice the daily maintenance level during treatment with high dose acyclovir.
2. Prophylactic treatment with acyclovir should be resumed after high–dose treatment has been completed.
3. Renal function tests must be followed closely during treatment with high dose acyclovir.
4. Doses of acyclovir must be decreased in patients with renal impairment.

Disseminated zoster:

IV acyclovir 500 mg/m^2 administered as a one hour IV infusion q 8 hr until there is no evidence of new lesions for 72 hours. Treatment may then be continued with valacyclovir 1 gm t.i.d. p.o. for patients $\geq$ 40 kg and 500 mg t.i.d. p.o. for patients < 40 kg to complete the course of treatment (generally 10-14 days).

Localized zoster:

IV acyclovir 500 mg/m^2 administered as a one hour IV infusion q 8 hr for three doses, then change to oral valacyclovir as outlined above to complete the course of treatment. Dose adjustment is necessary in patients with impaired renal function.

C. Pneumocystis Carinii Pneumonia (PCP)

All patients should receive trimethoprim-sulfamethoxazole prophylaxis (Section IV A). Patients who do not comply with the recommended prophylactic regimen may develop PCP and will require appropriate treatment. Trimethoprim-sulfamethoxazole should be given at a dose of 15-20 mg/kg/day of the trimethoprim component in divided doses every 6-8 hr for 14-21 days for treatment of PCP pneumonia.

IX. VACCINATIONS

Antibody titers to vaccine-preventable diseases (e.g. tetanus, polio, measles, mumps, rubella, and encapsulated organisms) decline between 1 and 4 years after allogeneic or autologous HCT if the recipient is not revaccinated. The clinical relevance of reduced antibody titers to these diseases is not readily apparent because only a limited number of vaccine-preventable diseases have been reported among HCT recipients. Nonetheless, vaccine-preventable diseases continue to pose risks to the population. Additionally, there is evidence that infections with encapsulated organisms, measles, varicella and influenzae can pose risk to HCT recipients. Therefore, HCT recipients should be routinely vaccinated after HCT so that they can experience immunity to the same vaccine-preventable diseases as others.

"Guidelines for Preventing Infectious Complications Among Hematopoietic Cell Transplant Recipients: A Global Perspective" have recently been updated by organizations that include: American Society for Blood and Marrow Transplantation (ASBMT), Center for International Blood and Marrow Transplant Research (CIBMTR), National Marrow Donor Program (NMDP), the European Group of Blood and Marrow Transplantation (EBMT), Infectious Diseases Society or America (IDSA), and the Centers for Disease Control and Prevention (CDC). The vaccination recommendations shown in the following schema were formulated based on review of the approaches taken by these organizations. The earliest time to start vaccinations is 6 months post transplant in Non-Primary Immune Deficiency patients and should be considered in conjunction with factors that significantly delay immune reconstitution.

See tables for recommendation for vaccinations for adult and pediatric patients:

IX.A1 Adult Vaccination Schema- Inactivated Vaccines: If eligible to begin vaccination before 12 months

IX.A2 Adult Vaccination Schema- Inactivated Vaccines: If patient not vaccinated before 12 months

IX.A3 - Adult Vaccination Schema- Live Vaccines

IX.P1 Pediatric Vaccination Schema: If eligible to begin vaccination before 12 months

IX.P2 Pediatric Vaccination Schema: If patient not vaccinated before 12 months

Table IX.A1: Adult Vaccination Schema-Inactivated Vaccines: If eligible to begin vaccination before 12 months [1, 6]

Vaccine	≥6m[1]	≥8m	≥10m	≥12m	≥14m	≥16m	≥18m	≥24m	≥60m	Minimal Time Interval Between Vaccinations
Influenzae (inactivated) (Sept –March)	**Flu**									
H. Influenzae type B	**HiB**	**HiB**	**HiB**	✓ titers				✓ titers		1-2 month
Meningococcal (Menactra, Menveo, MCV4)	**MCV4**									
Pneumococcal-conjugate (Prevnar 13™)	**PCV13**	**PCV13**	**PCV13**	✓ titers[2a]				✓ titers[2a]		1-2 month
Pneumococcal-polysaccharide (Pneumovax[2b])							**PCV13 or Pneumovax[2b]**			
Polio (inactivated)				**IPV**	**IPV**	**IPV**				
Hepatitis A[4]				**HAV**			**HAV**			6 month
Hepatitis B[4]				**HBV**	**HBV**		**HBV**	✓ titers[5]		2 month
HPV (Gardasil), 9-26 years				**HPV**	**HPV**		**HPV**			2 m after 1st; 4 m after 2nd dose
Acellular Pertussis-Tetanus-Diphtheria[4]				**Tdap**	**Td**	**Td**		✓ titers[3]		1-2 month

[1] For patients not markedly immunosuppressed (For adults transplanted for immunodeficiency disorders see following section, "Posttransplant Vaccination of Primary Immunodeficiency Disorders".)
[2a] Check titers for S. Pneumonia (IgG, 23 serotypes). If titer not done at 12 months, do it at 24 months.
[2b] In patients with CGVHD who are unlikely to respond to Pneumovax it is preferable to administer a 4th dose of Prevnar (PCV13)
[3] Check Anti-tetanus toxoid titer
[4] Combination vaccines may be available: ***Adacel*** = Tdap (age ≥ 11 y), ***Boostrix*** = Tdap (age ≥ 10 y), ***Twinrix*** = HBV/HAV (age ≥18 y)
[5] Only if not done at 20 months. Post-vaccination testing for antibody to hepatitis B surface antigen is recommended 1-2 months after the 3rd dose to ensure protection. Patients who do not respond to the primary vaccine series should receive a second 3 dose series. High dose (40mcg/dose) **hepatitis B** vaccination is recommended in immunocompromised or hemodialysis patients.
[6] For inactivated "dead" virus vaccine, vaccination should be at least 2 months post last dose of IVIG.

Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) recommend that vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated. If syncope develops, patients should be observed until the symptoms resolve.

Table IX.A2: Adult Vaccination Schema-Inactivated Vaccines: If patient not vaccinated before 12 months [1, 6]

Vaccine	≥12m	≥14m	≥16m	≥18m	≥22m	≥24m	≥60m	Minimal Time Interval Between Vaccinations
Influenzae (inactivated) (Sept –March)	**Flu**							
H. Influenzae type B	**HiB**	**HiB**	**HiB**			✓ titers		1-2 month
Meningococcal (Menactra, Menveo, MCV4)				**MCV4**				
Pneumococcal-conjugate (Prevnar 13™)	**PCV13**	**PCV13**	**PCV13**	✓ titers[2]		✓ titers[2]		1-2 month
Pneumococcal-polysaccharide (Pneumovax) See note[2]						**PCV13 or Pneumovax**[2]		
Polio (inactivated)	**IPV**	**IPV**	**IPV**					
Hepatitis A[4]	**HAV**			**HAV**				6 month
Hepatitis B[4]	**HBV**	**HBV**		**HBV**		✓ titers[5]		2 month
HPV (Gardasil), 9-26 years		**HPV**		**HPV**	**HPV**			2 m after 1st; 4 m after 2nd dose
Acellular Pertussis-Tetanus-Diphtheria[4]	**Tdap**	**Td**	**Td**			✓ titers[3]		1 -2 month

[1] For patients not markedly immunosuppressed (For adults transplanted for immunodeficiency disorders see following section, "Posttransplant Vaccination of Primary Immunodeficiency Disorders".)
[2] Check titers for S. Pneumonia (IgG, 23 serotypes). If titer not done at 18 months then do it at 24 months. In patients with CGVHD who are unlikely to respond to Pneumovax it is preferable to administer a 4th dose of Prevnar (PCV13)
[3] Check anti-tetanus toxoid titer.
[4] Combination vaccines may be available for certain age groups: ***Adacel*** = Tdap (age ≥ 11 y), ***Boostrix*** = Tdap (age ≥ 10 y), ***Twinrix*** = HBV/HAV (age ≥18 y)
[5] Titer at 24 month visit if not done at 20 months. Post-vaccination testing for antibody to hepatitis B surface antigen is recommended 1-2 months after the 3rd dose to ensure protection. Patients who do not respond to the primary vaccine series should receive a second 3 dose series. High dose (40mcg/dose) **hepatitis B** vaccination is recommended in immunocompromised or hemodialysis patients.
[6] For inactivated "dead" virus vaccine, vaccination should be at least 2 months post last dose of IVIG.

Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) recommend that vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated. If syncope develops, patients should be observed until the symptoms resolve.

Table IX.A3: Adult Vaccination Schema-Live Vaccines: Not to begin vaccination before 24 months [1]

Vaccine	<24m	≥24m	≥60m	Minimal Time Interval Between Vaccinations
Measles/Mumps/Rubella (MMR) ***"2-1-5 Rule"***[2]	***No Live Vaccines are given until at least 2 yr post-HCT and then only when certain other criteria are met as outlined in the left-hand column***	**MMR**[2]		
High-Titer Varicella-Zoster (Zostavax) ***Seropositive ONLY*** and ***Adults > 60 yr ONLY*** and ***"5-1-5 Rule"***[3]			**Zostavax**[3]	
Varicella-Zoster (Varivax) ***Seronegative ONLY*** and ***"2-1-5 Rule"***[2] First dose may be given with MMR		**VZV**[2]		Second dose given 1 month later[4]

[1] For live virus vaccine, vaccination should be at least 5 months post last dose of IVIG.
[2] ***2-1-5 Rule*** = Not until 2 years post HCT and > 1 year off all immunosuppressive therapy (IST) and at least 5 months since last dose of IVIG/VZIG or most recent plasma transfusion.
[3] ***5-1-5 Rule*** = Not until 5 years post HCT and > 1 year off all immunosuppressive therapy (IST) and at least 5 months since last dose of IVIG/VZIG or most recent plasma transfusion.
[4] Check varicella serology at least 1-2 months after second dose of Varivax to ensure seroconversion of the VZV seronegative patient.

Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) recommend that vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated. If syncope develops, patients should be observed until the symptoms resolve.

Table IX.P1: Pediatric Vaccination Schema: If eligible to begin vaccination before 12 months [1, 8]

Vaccine	≥6m[1]	≥8m	≥10m	≥12m	≥14m	≥16m	≥18m	≥24m	Minimal Time Interval Between Vaccinations
Influenzae (inactivated) < 9 years (September –March)	**Flu**	**Flu**							1 month
≥ 9 years	**Flu**								
H. Influenzae type B[5]	**HiB**	**HiB**	**HiB**	✓ titers				✓ titers	1-2 month
Meningococcal (Menactra, Menveo, MCV4)	**MCV4**								
Pneumococcal-conjugate (Prevnar 13™)	**PCV13**	**PCV13**	**PCV13**	✓ titers[2a]			**PCV13 or Pneumovax[2b]**	✓ titers[2a]	1-2 month
Pneumococcal-polysaccharide (Pneumovax)[2b]									
Polio (inactivated)[5]				**IPV**	**IPV**	**IPV**			
Hepatitis A[5]				**HAV**			**HAV**		6 month
Hepatitis B[5]				**HBV**	**HBV**		**HBV**	✓ titers [6]	2 month
HPV (Gardasil), 9-26 years				**HPV**	**HPV**		**HPV**		2 m after 1st; 4 m after 2nd dose
Acellular Pertussis-Tetanus-Diphtheria ≤ 7 years (DTaP[5])				**DTaP**	**DTaP**	**DTaP**		✓ titers[3]	1-2 month
> 7 years (Tdap)				**Tdap**	**Td**	**Td**			1-2 month
Measles/Mumps/Rubella (MMR) ***"2-1-5 Rule"[7]***	***No Live Vaccines are given until at least 2 yr post-HCT and then only when certain other criteria are met as outlined in the left-hand column***							**MMR[7]**	
Varicella-Zoster (Varivax) ***Seronegative ONLY*** and ***"2-1-5 Rule"[7]*** First dose may be given with MMR								**VZV[7]**	Second dose given 1 month later[4]

[1] For patients not markedly immunosuppressed (For children transplanted for immunodeficiency disorders see following section, "Posttransplant Vaccination of Primary Immunodeficiency Disorders".)

[2a] Check titers for S. Pneumonia (IgG, 23 serotypes). If titer not done at 12 months, do it at 24 months.

[2b] In patients with CGVHD who are unlikely to respond to Pneumovax it is preferable to administer a 4th dose of Prevnar (PCV13)

[3] Check anti-tetanus toxoid titers.

[4] Check varicella serology at least 1-2 months after second dose of Varivax to ensure seroconversion of the VZV seronegative patient

[5] Combination vaccines may be available for certain age groups: ***Infanrix, Daptacel*** = DTaP (age < 7 y), ***Pediarix*** = DTaP/HBV/IPV (age < 7 y), ***Pentacel*** = DTaP/HiB/IPV (age < 4 y), ***Adacel*** = Tdap (age ≥ 11 y), ***Boostrix*** = Tdap (age ≥ 10 y), ***Twinrix*** = HBV/HAV (age ≥18 y) Also, the Advisory Committee for Immunization Practices (ACIP) has recently recommended giving Tdap to patients ages 7-10.

[6] Titer at 24 month visit if not done at 20 months. Post-vaccination testing for antibody to hepatitis B surface antigen is recommended 1-2 months after the 3rd dose to ensure protection. Patients who do not respond to the primary vaccine series should receive a second 3 dose series.

[7] ***2-1-5 Rule*** = Not until 2 years post HCT and > 1 year off all immunosuppressive therapy (IST) and at least 5 months since last dose of IVIG/VZIG or most recent plasma transfusion

[8] For live virus vaccine, vaccination should be at least 5 months post last dose of IVIG. For inactivated "dead" virus vaccine, vaccination should be at least 2 months post last dose of IVIG.

Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) recommend that vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated. If syncope develops, patients should be observed until the symptoms resolve.

Table IX.P2: Pediatric Vaccination Schema: If patient not vaccinated before 12 months [1, 8]

Vaccine	≥12m	≥14m	≥16m	≥18m	≥22m	≥24m	Minimal Time Interval Between Vaccinations
Influenzae (inactivated) (September –March) < 9 years	**Flu**	**Flu**					1 month
Influenzae (inactivated) (September –March) ≥ 9 years	**Flu**						
H. Influenzae type B[5]	**HiB**	**HiB**	**HiB**			✓ titers	1-2 month
Meningococcal (Menactra, Menveo, MCV4)				**MCV4**			
Pneumococcal-conjugate (Prevnar 13™)	**PCV13**	**PCV13**	**PCV13**	✓ titers[2]		✓ titers[2]	1-2 month
Pneumococcal-polysaccharide (Pneumovax[2])						**PCV13 or Penumovax[2]**	
Polio (inactivated)[5]	**IPV**	**IPV**	**IPV**				
Hepatitis A[5]	**HAV**			**HAV**			6 month
Hepatitis B[5]	**HBV**	**HBV**		**HBV**		✓ titers[6]	2 month
HPV (Gardasil), 9-26 years		**HPV**		**HPV**	**HPV**		2 m after 1st; 4 m after 2nd dose
Acellular Pertussis-Tetanus-Diphtheria ≤ 7 years (DTaP[5])	**DTaP**	**DTaP**	**DTaP**			✓ titers[3]	1-2 month
Acellular Pertussis-Tetanus-Diphtheria > 7 years (Tdap)	**Tdap**	**Td**	**Td**				1-2 month
Measles/Mumps/Rubella (MMR) ***"2-1-5 Rule[7]***	***No Live Vaccines are given until at least 2 yr post-HCT and then only when certain other criteria are met as outlined in the left-hand column***					**MMR[7]**	
Varicella-Zoster (Varivax) ***Seronegative ONLY*** and ***"2-1-5 Rule"[7]*** First dose may be given with MMR						**VZV[7]**	Second dose given 1 month later[4]

[1] For patients not profoundly immunosuppressed (For children transplanted for immunodeficiency disorders see following section, "Posttransplant Vaccination of Primary Immunodeficiency Disorders".)

[2] Check titers for S. Pneumonia (IgG, 23 serotypes). If titer not done at 18 months, do it at 24 months. In patients with CGVHD who are unlikely to respond to Pneumovax it is preferable to administer a 4th dose of Prevnar (PCV13)

[3] Check anti-tetanus toxoid titer

[4] Check varicella serology at least 1-2 months after second dose of Varivax to ensure seroconversion of the VZV seronegative patient

[5] Combination vaccines may be available for certain age groups: ***Infanrix, Daptacel*** = DTaP (age < 7 y), ***Pediarix*** = DTaP/HBV/IPV (age < 7 y), ***Pentacel*** = DTaP/HiB/IPV (age < 4 y), ***Adacel*** = Tdap (age ≥ 11 y), ***Boostrix*** = Tdap (age ≥ 10 y), ***Twinrix*** = HBV/HAV (age ≥18 y) Also, the Advisory Committee for Immunization Practices (ACIP) has recently recommended giving Tdap to patients ages 7-10.

[6] Titer at 24 month visit if not done at 20 months. Post-vaccination testing for antibody to hepatitis B surface antigen is recommended 1-2 months after the 3rd dose to ensure protection. Patients who do not respond to the primary vaccine series should receive a second 3 dose series.

[7] ***2-1-5 Rule*** = Not until 2 years post HCT and > 1 year off all immunosuppressive therapy (IST) and at least 5 months since last dose of IVIG/VZIG or most recent plasma transfusion

[8] For live virus vaccine, vaccination should be at least 5 months post last dose of IVIG. For inactivated "dead" virus vaccine, vaccination should be at least 2 months post last dose of IVIG

Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) recommend that vaccine providers should strongly consider observing patients for 15 minutes after they are vaccinated. If syncope develops, patients should be observed until the symptoms resolve.

- Please keep records of all vaccinations (dates and types of all vaccines) given to the patient after the transplant and report any toxicity to the LTFU.

Posttransplant Vaccination of Primary Immunodeficiency Disorders (PID):

- From a practical standpoint, patients with primary immunodeficiency disorders (PID) are not candidates for the Standard Practice early vaccination policy that begins at 6 months after transplant.
- Bacteriophage testing will be offered to all PID patients when they have discontinued all immunosuppressive therapy with few exceptions (e.g. history of anti-CD20 antibody therapy or PID with poor donor B cell engraftment) but will not be the main arbiter to determine when a PID patient is eligible to receive vaccines.
- PID patients will first be considered as candidates for vaccination at 1 year after transplant if they satisfy the following criteria:

A. It is reasonable to attempt a 3 month trial off IVIG replacement therapy based on a negative history of patient infections in the past 6 months ***and***

B. The prevalence of community infections with influenza, RSV, metapneumovirus, or parainfluenza during the planned trial off IVIG therapy is low ***and***

C. ***All*** of the following laboratory criteria:

Criteria	Comment
1. Trough IgG > 600 mg/dL on standard IVIG dosing	Suggests numeric IgG reconstitution
2. Detectable serum IgA (> 6 mg/dL)	A detectable IgA level indicates potential ability to "class switch"
3. ***Donor***[a] B cell count > 200 per microliter	Arbitrarily set at 1-log higher than our standard practice for those transplanted for malignancy
4. ***Donor***[b] CD4 T cell count > 200 per microliter	Same as our standard practice for those transplanted for malignancy

[a] as determined by donor B cell chimerism times total absolute B cell count
[b] as determined by donor CD4 cell chimerism times total absolute CD4 T cell count

Standard Protocol for Re-vaccination with Killed Vaccines after HCT for PID:

1. If patient satisfies criteria A and B above, then obtain results of **trough** IgG, IgA and IgM levels, CD19 or CD20 B cell count per microliter and B cell chimerism (% donor), CD4 T cell count per microliter. If patient visit is not timed with the expected trough following last dose of IVIG, then defer quantitative immunoglobulin testing until trough levels are expected.
2. If the results of (1) indicate that the patient now satisfies criteria A, B and C then:
    - Plan to hold IVIG therapy for the next 12 weeks
    - **Week 0**: Give one dose each of: Prevnar, HiB, DTaP (or Tdap) and HBV (combination vaccines are preferred to limit the number of shots).
    - **Wks 6-8**: Repeat the series given at Week 0
    - **Week 12**: Check antibody response titers including :

      Hib, 23-pneumococcal serotypes, tetanus toxoid, and hepatitis B surface antibody

3. Pediatric LTFU Attendings will decide whether patient's responses to tetanus, HiB and Prevnar are sufficient for the patient to remain off immunoglobulin therapy and to proceed with vaccination against pneumococcus, hemophilus influenza Type B, tetanus, diphtheria, pertussis, and hepatitis B, as well as to begin a standard series of conjugated meningococcal, hepatitis A and inactivated polio vaccines. Alternatively, if vaccine response is inadequate then patient will resume IVIG therapy and further vaccination will be deferred.

Standard Protocol for Re-vaccination with Live Vaccines after HCT for PID:

1. If patient has responded adequately to killed vaccines the patient may be considered for the live attenuated measles, mumps and rubella vaccine, and the varicella-zoster vaccine (in VZV seronegative patients only) assuming the following additional criteria are met:
    a. At least 2 years posttransplant
    b. At least 1 year off all systemic immunosuppressive therapy
    c. At least 5 months after last dose of gammaglobulin therapy

Posttranslant Vaccination of All Other Patients (NON-PID)

Clinically relevant, 2-4 fold rises in specific antibody levels, or a rise from undetectable to a level considered protective, require at lease partial reconstitution of adaptive (T and B cell) immunity. Therefore, factors that might influence a decision to delay a series of vaccinations include:

Table IX.1

Delay of T cell recovery	Delay of B cell recovery
• CD4 T cells < 200/μL	• CD19 or CD20 B cells < 20/μL
• Active GVHD	• Anti-CD20 antibody < 6 months
• IVIG therapy < 2 months ago	• Moderate to severe GVHD
• Receiving chemotherapy or biological therapeutic agents	• Receiving chemotherapy or biological therapeutic agents

General Recommendations:

- Vaccination for *S. pneumoniae* and *H. influenzae* is recommended for all transplant recipients, but does not supplant chemoprophylaxis due to variable serologic responses.

- Inactivated vaccine injections should be used for family members who need vaccinations against polio. Isolation is necessary if live (oral) polio vaccine is administered to family members or other persons in close contact with the patient during the first year after the transplant or at any time during treatment with immunosuppressive medications. The virus can be shed for 8 to 12 weeks after vaccination.

- **Influenzae** vaccination: Live attenuated influenzae vaccine is not recommended.

- **Smallpox vaccine** is comprised of live vaccinia virus. **Smallpox vaccination is contraindicated in HSCT recipients** because it may result in development of generalized vaccinia or inadvertent inoculation at other sites such as the face, eyelid, nose, mouth, genitalia, and rectum. Smallpox vaccine should not be administered to any family members or other persons who share living space with the patient during the first year after transplant and beyond one year if the patient continues on treatment with immunosuppressive medications. If smallpox vaccination is administered to these close contacts, then these individuals should be prevented from having close contact with the immunocompromised HSCT recipient. See the CDC website for further detailed information http://www.bt.cdc.gov.

- **Other live vaccines (i.e., BCG, oral polio, yellow fever, typhoid)** should not be administered in patients with active manifestation of GVHD or receiving immunosuppressive therapy.

- **Anthrax vaccine** is an inactivated, cell-free filtrate vaccine (e.g., no dead or live bacteria in the preparation). Currently, anthrax vaccination is not routinely recommended for anyone except certain high-risk groups such as persons working directly with the organism in the laboratory or certain military personnel. Recommendations for HSCT recipients would be the same as for other at-risk individuals. Detailed information is available at the CDC website http://www.bt.cdc.gov

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X. CHRONIC GRAFT-VERSUS-HOST DISEASE (GVHD)

Chronic GVHD is a major complication of allogeneic hematopoietic cell transplantation. The incidence of chronic GVHD varies between 20 to 85% and depends on many factors such as the transplant source (blood stem cell vs. marrow vs. umbilical cord), donor type and other characteristics (previous pregnant female versus male donor), age (older vs. younger) and others factors. Chronic GVHD syndrome has features resembling autoimmune and other immunologic disorders such as scleroderma, Sjogren's syndrome, primary biliary cirrhosis, wasting syndrome, bronchiolitis obliterans, immune cytopenias, and chronic immunodeficiency. Symptoms usually present within three years after allogeneic HCT and are often preceded by a history of acute GVHD. Approximately 50% of patients who develop chronic GVHD are diagnosed by 6 months after transplant.

Features of chronic GVHD can begin before day 100 after the transplant and manifestations that are typical or "classical" of acute GVHD can develop or persist long after day 100. Moreover, chronic and acute GVHD features may present simultaneously [1,2]. For this reason, the differential diagnosis between acute and chronic GVHD cannot be made solely according to the time interval from transplant [3,4]. Criteria to categorize acute and chronic GVHD by the chronic GVHD NIH consensus working group is outlined in Table 1 [4]. Helpful tips on how to assess and score chronic GVHD can be found at **http://www.fhcrc.org/ltfu** by clicking on "*Information for Physicians*" in the left hand navigation column. Then click on the right blue "*GVHD Tips & Forms*" button. Here you will find the Chronic GVHD Assessment and Scoring form (Appendix D), Range of Motion Assessment form (Appendix F), Skin Thickness Assessment form/ Rodnan Score for patients with sclerosis or fasciitis (Appendix E) and other helpful information.

A. Table 1. Categories of acute and chronic GVHD [4]

Category	Time of symptoms after HCT or DLI †	Presence of Acute GVHD Features	Presence of Chronic GVHD Features*
Acute GVHD			
Classic acute GVHD	≤ 100 days	Yes	No
Persistent, recurrent or late onset acute GVHD	> 100 days	Yes	No
Chronic GVHD			
Classic chronic GVHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

† DLI (donor lymphocyte infusion)

* See Table 2 below

B. Table 2. Signs and Symptoms of chronic GVHD [4]

ORGAN OR SITE	*DIAGNOSTIC* *(Sufficient to establish the diagnosis of chronic GVHD)*	*DISTINCTIVE* *(Seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)*	*OTHER FEATURES**	*COMMON* *(Seen with both acute and chronic GVHD)*
Skin	• Poikiloderma • Lichen planus-like features • Sclerotic features • Morphea-like features • Lichen sclerosus-like features	• Depigmentation	• Sweat impairment • Ichthyosis • Keratosis pilaris • Hypopigmentation • Hyperpigmentation	• Erythema • Maculopapular rash • Pruritus
Nails		• Dystrophy • Longitudinal ridging, splitting or brittle features • Onycholysis • Pterygium unguis • Nail loss** (usually symmetric, affects most nails)		
Scalp and Body Hair		• New onset of scarring or non-scarring scalp alopecia, (after recovery from chemoradiotherapy) • Scaling, papulosquamous lesions	• Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes), • Premature gray hair	
Mouth	• Lichen-type features • Hyperkeratotic plaques • Restriction of mouth opening from sclerosis	• Xerostomia • Mucocele • Mucosal Atrophy • Pseudomembranes** • Ulcers**		• Gingivitis • Mucositis • Erythema • Pain
Eyes‡		• New onset dry, gritty, or painful eyes† • Cicatricial conjunctivitis • Keratoconjunctivitis sicca† • Confluent areas of punctate keratopathy	• Photophobia • Periorbital hyperpigmentation • Blepharitis (erythema of the eye lids with edema)	
Genitalia	• Lichen planus-like features • Vaginal scarring or stenosis	• Erosions** • Fissures** • Ulcers**		
GI Tract	• Esophageal web • Strictures or stenosis in the upper to mid third of the esophagus**		• Exocrine pancreatic insufficiency	• Anorexia • Nausea • Vomiting • Diarrhea • Weight loss • Failure to thrive (infants and children

(continued) Table 2 - Signs and Symptoms of chronic GVHD [4]

ORGAN OR SITE	*DIAGNOSTIC* *(Sufficient to establish the diagnosis of chronic GVHD)*	*DISTINCTIVE* *(Seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)*	*OTHER FEATURES**	*COMMON* *(Seen with both acute and chronic GVHD)*
Liver				• Total bilirubin, alkaline phosphatase > 2 x upper limit of normal† • ALT or AST > 2x upper limit of normal†
Lung	• Bronchiolitis obliterans diagnosed with lung biopsy	• Bronchiolitis obliterans diagnosed with PFTs and radiology†		• BOOP
Muscles, Fascia, Joints	• Fasciitis • Joint stiffness or contractures secondary to sclerosis	• Myositis or polymyositis †	• Edema • Muscle cramps • Arthralgia or arthritis	
Hematopoietic and Immune			• Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulinemia • Autoantibodies (AIHA, ITP)	
Other			• Pericardial or pleural effusions • Ascites • Peripheral neuropathy • Nephrotic syndrome • Myasthenia gravis • Cardiac conduction abnormality or cardiomyopathy	

* Can be acknowledged as part of the chronic GVHD symptomatology if diagnosis is confirmed

** In all cases, infection, drug effect, malignancy or other causes must be excluded.

† Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Ophthalmology exam for eyes).

‡ Schirmer's test with a mean value $\leq$ 5 mm (average of both eyes) at 5 minutes, or values of 6-10 mm in patients who have sicca symptoms, or keratitis detected by slit lamp examination are used for the diagnosis of chronic GVHD or the eyes (again other causes of dry eyes need to be ruled out (e.g., drug effect).

Abbreviations: GVHD (graft versus host disease); ALT (alanine aminotransferase); AST (aspartate aminotransferase); BOOP (bronchiolitis obliterans organizing pneumonia); PFTs (pulmonary function tests); AIHA (autoimmune hemolytic anemia); ITP (idiopathic thrombocytopenic purpura).

C. How to diagnosis chronic GVHD

Signs and symptoms of chronic GVHD have been reviewed and reported by the NIH consensus Working Group to standardize criteria for diagnosis and classification of chronic GVHD for the purpose of clinical trials (Table 2) [4]. The diagnosis of chronic GVHD has no time limit and requires the presence of at least one *diagnostic* clinical sign of chronic GVHD (e.g. poikiloderma or esophageal web) or the presence of at least one *distinctive* manifestation (e.g. keratoconjunctivitis sicca) confirmed by pertinent biopsy or other relevant tests in the same or another organ (Table 2)

The criteria for the diagnosis of chronic GVHD include:

i. *Distinction from acute GVHD (Table 1)*
ii. *Presence of at least one diagnostic clinical manifestation OR at least one distinct manifestation confirmed by pertinent biopsy or other relevant tests (Table 2)*
iii. *Exclusion of other possible diagnosis for the clinical manifestation (e.g., infection, drug effect, others)*

D. How to score each organ/site severity with chronic GVHD (Appendix D)

The new scoring system (0-3) has been developed to describe the severity of chronic GVHD for each organ or site taking functional impact into account [4]. Appendix D is a modified chronic GVHD Scoring and Assessment form to help physicians to evaluate their patients with chronic GVHD. Appendix E is another tool developed to help physicians to assess skin thickness in patients with sclerotic features or fasciitis related to chronic GVHD.

E. How to assess overall severity of chronic GVHD - Global Assessment

Manifestations of chronic GVHD may be restricted to a single organ or tissue or may be widespread. Historically, chronic GVHD was classified as "limited" or "extensive" based on a small cohort patients reported more than two decades ago [5]. Because of inadequacies of the original classification (e.g., difficulty to apply the historical criteria in patients transplanted with newer HCT approaches and progress in our understanding of chronic GVHD), overtime, this widely adopted chronic GVHD classification has proved to have limitation [3,4]. *The new global assessment of chronic GVHD severity* **(mild, moderate or severe)** is based on numbers of organs/sites involved and the degree of involvement in affected organs/sites (Table 3) [4]. This new global assessment of chronic GVHD severity has been developed to replace the historical "extensive/limited" classification.

Table 3. Global assessment of chronic GVHD severity

Global severity	No. organs/sites affected	Maximum score in all affected organ/site*
Mild	One or two (except lungs‡)	1‡
Moderate	Three or more **or** One or more	1‡ 2‡‡
Severe	Any	3

* See Appendix D.
‡A lung score of 1 is considered moderate.
‡‡ A lung score of 2 or greater is considered severe.

F. Other laboratory testing and diagnostic indicators used in chronic GVHD

Biopsy	(Skin, lip and other tissues). Histological confirmation is necessary in the absence of diagnostic clinical features or distinctive features confirmed by other pertinent test (Table 2). Nonetheless, diagnostic histological features of chronic GVHD are uncommon.
Lung	New obstructve lung defect often represent lung involvement if: infectious process, asthma or recurrent aspiration from the sinuses or from gastroesophageal reflux have been ruled out (Table 2 and Appendix D). In the absence of chronic GVHD in any other organ, the diagnosis of bronchiolitis obliterans (BO) requires negative microbiological tests from bronchoalveolar lavage, evidence of air trapping by high resolution end-expiratory and end-inspiratory CAT scan of the lungs, or confirmation by thoracoscopic biopsy. Pulmonary scoring (Appendix D) should be performed using both the symptom and pulmonary function testing (PFT) scale whenever possible. When discrepancy exists between pulmonary symptom or PFT scores the higher value should be used for final scoring. Scoring using the Lung Function Score (LFS) is preferred, but if DLCO (carbon monoxide diffusion capacity corrected for hemoglobin) is not available, grading using FEV1 (forced expiratory volume) should be used. The LFS is a global assessment of lung function after the diagnosis of bronchiolitis obliterans has already been established.[28] The percent predicted FEV1 and DLCO (adjusted for hematocrit but not alveolar volume) should be converted to a numeric score as follows: > 80% = 1; 70-79% = 2; 60-69% = 3; 50-59% = 4; 40-49% = 5; < 40% = 6. The LFS = FEV1 score + DLCO score, with a possible range of 2-12.
Esophagus	Esophageal web formation, stricture or dysmotility demonstrated by barium swallow, endoscopy or manometry.
Muscle	Elevated CPK or aldolase, EMG findings consistent with myositis with biopsy revealing no other etiological process.
Blood	Thrombocytopenia (usually 20,000-100,000/microliter), eosinophilia ($\geq$ 500/microliter), hypogammaglobulinemia. Hypergammaglobulinemia and autoantibodies occur in some cases.

G. Monitoring and other chronic GVHD information

Karnofsky or Lansky Clinical Performance scores <60%, $\geq$15% weight loss, and recurrent infections are usually signs of poorly controlled chronic GVHD. Chronic GVHD can lead to debilitating consequences, e.g., joint contractures, loss of sight, end-stage lung disease, or mortality resulting from profound chronic immune suppression leading to recurrent or life-threatening infections. Close monitoring is recommended after allogeneic HCT or donor lymphocyte infusion so that appropriate treatment and supportive care can be instituted promptly to prevent serious outcome.

H. Guidelines for treatment of chronic GVHD

We strongly recommend that you consult the LTFU office (Appendix A) before beginning treatment and before making changes in immunosuppressive treatment for patients with chronic GVHD. ***Clinical trials should always be considered because current standard therapies are associated with high morbidity and decreased survival for patients with high risk chronic GVHD (Section X.A. 2).***

Appendix D is a modified chronic GVHD Scoring and Assessment form to help physicians to evaluate patients for chronic GVHD. Appendix E is another tool developed to help physicians to assess skin thickness in patients with sclerotic features or fasciitis related to chronic GVHD. Appendix C provides a cartoon with body area surface to help calculating the percentage of skin involved by GVHD.

Table 4 outlines the criteria currently used for indication of systemic therapy in patients diagnosed with chronic GVHD according to global severity (Table 3) and risk factors.

Table 4. Indication for systemic treatment for chronic GVHD

Global severity‡	High risk*	Prolonged systemic therapy
Mild	No	No
Mild	Yes	Yes‡‡
Moderate	Yes or No	Yes‡‡
Severe	Yes or No	Yes

‡ See Table 3

* Patients with either thrombocytopenia (<100,000/microliter) or receiving glucocorticoids at time of diagnosis of chronic GVHD.

‡‡ The benefits of graft-versus-tumor effect and the risk of chronic GVHD require careful consideration especially in patients transplanted for malignancy with high risk of relapse.

Standard treatment of chronic GVHD usually begins with administration of glucocorticoids (1mg/kg/day) followed by taper to eventually reach an alternate-day regimen, with or without daily cyclosporine or tacrolimus (FK506). Other medications used for glucocorticoid-resistant or dependent chronic GVHD or in combination are displayed on Table 5. Telephone consultation with the LTFU medical team is available to you, seven days a week, to discuss appropriate treatment and provide other follow up recommendations (Appendix A).

The duration of systemic immunosuppressive treatment of chronic GVHD varies but requires at least one year of therapy. Approximately 80% of patients require systemic immunosuppressive for 2 years and 40% of them requires therapy for at least 4 years.

I. Table 5. List of medications other than glucocorticoids used in chronic GVHD

GENERIC NAME	TRADE NAME	DRUG LEVEL	MAJOR TOXICITIES
Cyclosporine (CSP)	Sandimmune Neoral (or equivalents)	Range*120-240 ng/ml [††] by LC-MS/MS	RENAL: increased creatinine, decreased magnesium; GI: nausea, vomiting, increased serum bilirubin or transaminase levels; pancreatitis NEUROLOGIC: tremor, paresthesias, visual disorder, headache, seizures, anxiety, disorientation, depression; VASCULAR: hypertension, hemolytic-uremic syndrome, thromboembolism OTHER: hyperglycemia, hypertrichosis, rash, gingival hypertrophy, gynecomastia
Tacrolimus (FK506)	Prograf Note: generic medication used in SCCA system	Range*5-15 ng/ml[†] by immunoassay in whole blood [IMX, Abbot]	Similar to Cyclosporin toxicities
Mycophenolate mofetil (MMF)	Cellcept	Clinical correlation not yet established	GI: vomiting, diarrhea HEMATOLOGIC: neutropenia, anemia.
Rapamycin	Rapamune Sirolimus	Range* 5-10 ng/mL [by HPLC assay]	HEMATOLOGIC: neutropenia, thrombocytopenia; METABOLIC: hyperlipidemia VASCULAR: hemolytic-uremic syndrome (HUS)
Thalidomide	Thalomid	Clinical correlation not yet established	TERATOGENIC (birth defects) NEUROLOGIC: sedation, sleepiness, peripheral neuropathy (dysesthesias, clumsiness, weakness) GI: constipation HEMATOLOGIC: neutropenia
Azathioprine	Imuran	Clinical correlation not yet established	HEMATOLOGIC: neutropenia, thrombocytopenia GI: constipation, cholestasis, venocclusive disease
Clofamizine	Lamprene	Clinical correlation not yet established	SKIN: discoloration, pruritis EYES: corneal discoloration GI: abdominal and epigastric pain, diarrhea nausea, vomiting, hepatitis
Acitretin	Soriatane	Clinical correlation not yet established	MUCOCUTANEOUS: cheilosis, rash, rhinitis hyperesthesia, paronychia EYES: xerophthalmia HEMATOLOGIC: reticulocytosis METABOLIC: hyperlipidemia, hyperglycemia, increased transaminase levels and CPK OTHER: arthralgia, rigors, occult blood in the stool

*Dose adjustment should be based on evaluation of toxicity and GVHD activity, as well as drug levels.
[†]In patients also taking sirolimus, it is generally recommended that tacrolimus levels not exceed 10 nanograms/mL
[††] In patients also taking sirolimus, it is generally recommended that cyclosporine levels not exceed 200 nanograms/mL

XI. GENERAL GUIDELINES FOR PREVENTION OF OSTEOPOROSIS AND GLUCOCORTICOSTEROID INDUCED OSTEOPOROSIS

Treatment with high-dose glucocorticoids has been recognized as the primary risk factor for development of osteoporosis after stem cell transplantation. Areas of loss include the femoral neck, vertebrae, ribs. Glucocorticoid myopathy and muscle weakness may contribute to osteoporosis by removing the normal forces on bone that are produced by muscle contraction. In hematopoietic transplant recipients, other factors that may contribute to osteoporosis include electrolyte imbalances, inactivity, significant weight loss, and endocrine deficiencies.

Two degrees of bone loss can be described. Osteopenia is defined as bone mineral density less than -1 standard deviation but above –2.5 standard deviations below the peak mean of young normal controls [T-score]. A T-score of < -2.5 is defined as osteoporosis.

A. Patient monitoring

Women: Baseline and annual measurement of FSH and estradiol for ages > 10 and < 61 years

Men: Baseline and annual measurement of
LH, FSH and free testosterone for ages < 60 years,
Free testosterone and FSH for ages ≥ 60 years
Baseline and followup prostate exam, measurements of PSA and lipid profile in men who are being treated with testosterone

All patients:

- Height: twice yearly
- Weight: monthly.
- DEXA SCANS:
  a) for allogeneic patients on steroid therapy, Dexa scan annually during steroid therapy
  b) for all other allogeneic patients ≥ 40 years of age, Dexa scan at one year post transplant
  c) for all autologous lymphoma and myeloma transplant patients, Dexa scan at one year post transplant.
  d) for all pediatric patients not on steroid therapy, Dexa scan at one year post transplant only if Dexa scan at Discharge from SCCA system was abnormal

- Urinary N-telopeptide (NTx): baseline and at three months from starting treatment with bisphosphonates, or as clinically indicated. NTx test (Osteomark) is used to assess treatment response of bisphosphonate. It measures urinary excretion of the cross-linked N-telopeptide of type I collagen which is a marker of bone resorption. A decrease of 30% or greater in urinary NTx is clinically significant (Eastell R et al.: Biological variability of serum and urinary N-telopeptides of type I collagen in postmenopausal women. *J Bone Miner Res.* 2000; 15: 594-8.

- **Vitamin D blood level**
  - Vitamin D (25 Hydroxy) blood level should be checked between 80-100 days post transplant for all patients.
  - Vitamin D (25 Hydroxy) levels are generally rechecked 2-3 months after beginning therapy and the target level is ≥30 ng/mL.

- **Patients treated with bisphosphonate:** liver function tests, calcium, magnesium, creatinine and electrolytes should be measured at baseline and at least monthly thereafter

B. Elemental Calcium requirement between diet and supplement

The Medical Nutrition Therapy staff educates patients to consume the following amounts of calcium during steroid therapy:

Age 7-12 months 600 mg/day
Age 1-3 years: 1000 mg/day
Age 4-8 years: 1200 mg/day
Age ≥ 9 years: 1500 mg/day

The nutritionist recommends appropriate levels of calcium supplementation for patients unable to meet daily requirements with diet. *Calcium citrate* is the preferred formulation.

Calcium requirement for patients not on steroid therapy:

Age	Daily Minimal Calcium requirements (milligrams)
Children 7-12 months	250
Children 1-3 years	700
Children 4-8 years	1000
Children 9-18 years	1300
Adult Males	1000-1200
Adult Females	
On hormone therapy	1000-1200
Not on hormone therapy	1500

C. Vitamin D requirement

Currently there is not substantive benefit by choosing Vitamin D2 or vitamin D3 over the other with regard to correcting Vitamin D (25 Hydroxy) levels. The more important decision is prescribing enough. Dose frequency appears to be less important than cumulative amount so that 2000 IU daily for 50 days is approximately equivalent to giving 50,000 IU monthly for 2 months.

Table 1: Vitamin D3 (or D2) Supplementation

	Adults (>18 yrs)	Children (≤18 yrs)
Prevention of Deficiency / Treatment of Insufficiency [Vitamin D (25 Hydroxy) levels 20-30 ng/mL] [2]		
▪ Routine	▪ 1000 IU per day	▪ Age < 1 yr: — 400 IU daily (800 IU in dark skinned) ▪ Age 1-8 yr: — 600 IU daily ▪ Age 9-18 yr: — 800 IU daily
▪ Malabsorption syndromes[1]	▪ 50,000 IU per week	▪ Age < 1 yr: — Consult Endocrinology ▪ Age 1-18 yr: — 50,000 IU per week ***or*** — 5000 IU daily
▪ Chronic Renal Disease	▪ Consult Nephrology	▪ Consult Nephrology
Treatment of Deficiency [Vitamin D (25 Hydroxy) level <20 ng/mL][2]		
▪ Uncomplicated	▪ 50,000 IU per wk x 8 (Repeat if Vitamin D (25 Hydroxy) level < 30 ng/mL otherwise treat as for insufficiency above)	▪ Age 1-12 months: — 1000-2000 IU daily x 8 wks ▪ Age 1-18 yr: — 1000-5000 IU daily x 8 wks ***or*** — 50,000 IU weekly x 8 (Repeat if Vitamin D (25 Hydroxy) level < 30 ng/mL otherwise treat as for insufficiency above)
▪ Malabsorption syndromes[1]	▪ 10,000-50,000 IU daily or every other day ▪ UVB irradiation in patients also with skin GVHD	▪ Age < 1 yr: — Consult Endocrinology ▪ Age 1-18 yr: — 50,000 IU per week
▪ Chronic Renal Disease	▪ Consult Nephrology	▪ Consult Nephrology

[1] Patients who remain deficient or insufficient after adequate therapy are generally treated with hydroxylated vitamin D metabolites which are more readily absorbed or, if feasible, with sun or sunlamp exposure. While 25-OH vitamin D (Calcidiol) is the most logical choice of activated vitamin D for patients with liver disease, calcidiol is not readily available in the U.S. The 1,25-OH activated formulation of vitamin D (Calcitriol) is used most commonly in chronic renal disease when there is secondary hyperparathyroidism. Calcitriol can also be used in patients with liver disease or severe malabsorption when there is a lack of the 25-OH vitamin D substrate to be converted to 1,25-OH vitamin D by the kidney.

[2] Vitamin D (25 Hydroxy) levels are generally rechecked 2-3 months after beginning therapy and the target level is ≥30 ng/mL.

D. Magnesium

Hypomagnesemia may result in hypocalcemia, peripheral vitamin D resistance and resistance to parathyroid hormone. Normal serum magnesium levels are necessary to prevent osteopenia and bone fragility. Patients taking cyclosporine or tacrolimus should receive adequate magnesium supplementation to maintain normal concentrations of serum magnesium (see Section XX)

E. Exercise

A combination of weight bearing and resistive exercise is recommended for 30-60 minutes daily to promote cardiovascular function, minimize bone loss, strengthen skeletal muscles and improve balance, helping to prevent falls.

Appropriate forms of exercise include swimming, biking (on a stationary bike if the patient has poor balance), Nordic tracking, rowing, low impact aerobic dancing. Duration should be gradually increased to 30-60 minutes daily. Excessive stress to joints caused by high impact exercise (running, jumping, etc.) should be avoided.

F. Gonadal hormone replacement

Females: Women who are not on hormonal therapy with estrogen can be treated with biphosphonates.

Males: Free testosterone, FSH and LH serum levels should be evaluated as follows:
LH, FSH and free testosterone for ages < 60 years,
Free testosterone and FSH for ages ≥ 60 years
Testosterone replacement should be prescribed as appropriate. Testosterone replacement should be given to men if the serum testosterone level is low, unless contraindicated.

G. Bisphosphonates

Therapy with anti-resorptive agents to prevent bone loss may be considered for T-score less than -1 for HCT recipients with a prior significant history of corticosteroid exposure and those with GVHD anticipated to remain on long term corticosteroids. In low risk patients with a T-score between -1 and -2.5 (osteopenia), we encourage assessment of fracture risk (eg, using the FRAX score)(www.shef.ac.uk/FRAX/). Anti-resorptive therapy can be considered in patients who are at high risk for subsequent fractures. All patients with osteoporosis (T-score < -2.5) or bone loss-associated fractures should be offered therapy. (*McClune, Navneet S Majhail, and Mary E.D. Flowers Bone Loss and Avascular Necrosis of Bone After Hematopoietic Cell Transplantation. Semin Hematol 49:59-65, January 2012*)

Bisphosphonates are effective for prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis. Because the risks and benefits of bisphosphonates during the early posttransplant period are unclear, consideration of bisphosphonate therapy is not recommended for osteoporosis until at approximately 3 months posttransplant.

Bisphosphonates (Continued)

Adults with hip or vertebral fractures, or documented osteoporosis (DEXA T score < -2.5) may receive either oral or intravenous bisphosphonate therapy. Therapy is also advised for posttransplant patients with ostoepenia (T-score -1.0 to -2.5) who are not receiving hormone replacement therapy and who are to receive prolonged glucocorticoid therapy. For postmenopausal women, and men age 50 and over, the widely used FRAX® WHO Fracture Risk Assessment Tool (www.shef.ac.uk/FRAX/) can be used to help guide which patients with osteopenia might benefit from bisphosphonate therapy based on their estimated 10-year hip fracture probability being ≥ 3% or their 10-year major osteoporosis related fracture probability being ≥ 20%.

Therapy is usually continued until glucocorticoid therapy has been discontinued and the T-score enters the normal range (-1.0 to +1.0) or the risk for fractures based on the FRAX® tool is no longer increased.

In patients taking alendronate for 5 years or more, post-marketing reports have recently highlighted the occurrence of atypical hip fractures. (Watts NB and Diab DL. Long-term use of bisphosphonates in osteoporosis. J Clin Endocrinol Metab 95: 1555-1565, 2010.)

Secondary analyses of the results from 3 large randomized bisphosphonate trials showed that rates of subtrochanteric or diaphyseal femoral fractures were very low (1 to 6 cases per 10,000 patient years). While these analyses did not demonstrate an increase in risk associated with bisphosphonate use, the study was underpowered for definitive conclusions. (Black DM et al. Bisphosphonates and fractures of the subtronchanteric or diaphyseal femur. N Engl J Med 362: 1761-1771, 2010.)

One approach to consider for patients at mild risk for fracture is to stop bisphosphonate therapy after 5 years and remain off as long as bone mineral density is stable and no fractures occur. Higher risk patients may be treated for 10 years, and then consider having a bisphosphonate holiday for 1-2 years, with nonbisphosphonate therapy during that time. (Watts NB and Diab DL. Long-term use of bisphosphonates in osteoporosis. J Clin Endocrinol Metab 95: 1555-1565, 2010.

Children with documented osteoporosis based on Z-score, or at risk for reduced BMD may be considered for bisphosphonate therapy after discussion with the Pediatrician. If it is determined that bisophosphonate therapy is appropriate, the specific bisphosphonate regimen will be decided by the Pediatrician, often in collaboration with a consulting Pediatric Endocrinologist.

Cautionary Notes about Bisphosphonates:

- Intravenous bisphosphonates are not recommended for patients with creatinine clearance <35 ml/minute.

- Oral bisphosphonates can cause esophageal ulceration (pill esophagitis). Oral administration should be discontinued if patients develop esophageal symptoms.

Drugs:

i. Alendronate (Fosamax®)
Osteoporosis treatment: Administer alendronate as a single dose of 70 mg weekly (or 35 mg twice weekly).

ii. Risedronate (Actonel®)
Osteoporosis treatment: Administer risedronate as a single dose of 35 mg weekly (or 150 mg monthly).

iii. Zoledronate (Reclast®)
Zoledronate may be given as a single 5 mg intravenous dose once a year.

iv. Forteo and Prolia are newer drugs but to date there has not been much experience in their use in the posttransplant setting.

H. Calcitonin as secondary therapy for osteoporosis

Calcitonin (100-200 International Units nasal spray daily) may be given to adults if the measures described above are not adequate.

I. Low Sodium Diet

Sodium increases urinary calcium loss. A reduced sodium diet (<4 grams daily) is encouraged during steroid therapy.

J. Endocrinology

Refer for endocrinology consult if clinically indicated.

XII. HYPERLIPIDEMIA

Hyperlipidemia, especially chronic elevation of serum low-density lipoprotein cholesterol (LDL-C), is an established risk factor for premature (<55 years) coronary heart disease (CHD) in the general population. It is also important to recognize that survivors of hematopoietic cell transplantation (HCT) have been shown to experience increased cardiovascular death compared to a randomly selected matched control population.[1] Increased cumulative incidence of CHD, cardiomyopathy, heart failure, stroke, vascular diseases, rhythm disorders, hypertension, dyslipidemia and diabetes was also shown among these HCT survivors. The latter three conditions are also relevant because together with abdominal obesity, insulin resistance and prothrombotic/inflammatory states, they constitute a cluster of risk factors for premature CHD known as the *metabolic syndrome*. Recipients of allogeneic HCT did not differ from their autologous counterparts aside from having a higher rate of hypertension. A 49% prevalence rate (95% CI: 38%-60%) for metabolic syndrome has been noted among long-term survivors of HCT, or a 2.2-fold increase (95% CI, 1.3–3.6, P = 0.002) compared with controls in one cross-sectional study.[2] Taking all these observations together it follows that effective management of hyperlipidemia be considered for patients who have undergone HCT.

A. Principles and special considerations for lipid lowering therapy after HCT

The approach outlined here follows the guidance of the National Heart Lung and Blood Institute (NHLBI) Adult Treatment Panel III (ATP III) and includes interventions with ***therapeutic lifestyle changes*** and drug therapy that are calibrated primarily to LDL goals as determined by CHD risk category (see **http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm**):

- Therapeutic lifestyle changes (TLC) include:
  - Dietary saturated fat < 7% of calories, transfat < 1% of calories, cholesterol < 200 mg/day
  - Dietary increased soluble fiber 10-25 g/day
  - Omega-3-fatty acid supplements may improve triglyceride and LDL-C levels but most are not regulated and are of variable content. Therefore, consuming a diet rich in omege-3-fatty acids is the preferable method of supplementation (major sources include flaxseed oil, canola oil, walnut oil, wheat germ, soybeans, mackerel, herring, salmon, sardines in oil, and swordfish).
  - Weight management
  - Increased physical activity on a regular basis/ regular exercise regimen
- Management of hyperlipidemia in the general population begins and always includes TLC. However, after hematopoietic cell transplantation TLC are not always possible due to transplant-related complications or concerns.
- ATPIII drug therapy first focuses on achieving goal LDL levels using HMG-CoA reductase inhibitors (statins) because they protect against premature CHD and improve survival among those with elevated cholesterol levels in the general population.

- Statins also protect against premature CHD and improve survival in solid organ transplant recipients.[4-12] Additional roles for statins in mediating improved renal function, control of hypertension, osteopenia, avascular necrosis, and even GVHD have been suggested.[14-20]
- While statins may offer similar benefits for Blood or Bone Marrow Transplant (BMT) survivors with hyperlipidemia the safety of statins has not been established in this group and extra caution is advised due to the potential for important drug interactions in the BMT setting.

B. Algorithm for Evaluation and Management of Hyperlipidemia in BMT Survivors

Step 1: Exclude untreated hypothyroidism, nephrotic syndrome and obstructive liver disease.

Step 2: Identify presence of clinical atherosclerotic disease (CHD or "CHD risk equivalents" which include symptomatic carotid artery disease, peripheral vascular disease and abdominal aortic aneurysm) and if present the 10-year risk is > 20% ("High-risk") and then skip to Step 4.

Step 3: Consider major risk factors other than LDL, CHD or CHD risk equivalents (ie. Cigarette smoking, hypertension, low HDL, premature CHD in a 1st degree relative, age) and categorize as "Moderate" or "Low" 10-year risk using the Framingham tables or online risk calculator available at: **http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof**.

Step 4: Establish the LDL goal of therapy and determine the need for TLC and drug therapy:

Simplified Fasting Level Target Goals for BMT patients adapted from ATPIII

Risk Category	**LDL Goal** (mg/dL)	**LDL level to begin TLC** (mg/dL)	**LDL level to consider drug therapy** (mg/dL)
High 10-yr risk > 20%: CHD or CHD risk equivalents	<100	≥100	≥130
Moderate 2+ risk factors	<130	≥130	≥130 if 10-yr risk 10-20% ***or*** ≥160 if 10-yr risk <10%
Low 10-yr risk ≤ 10% 0-1 risk factors	<160	≥160	≥190

Step 5: If clinically feasible in a post-transplant survivor initiate TLC if LDL is above goal.

Step 6: Consider adding drug therapy with TLC for High-risk (CHD/CHD-equivalents). For other risk categories, if clinically feasible allow a 3-month trial of TLC before adding drug therapy

Suggested Medication Options for High LDL-C in Adults* after BMT

Drug	Daily Dose[a] mg	Class Effects	Precautions and Monitoring
Statins (HMG-CoA reductase inhibitors)	*Start at lowest doses and rarely exceed middle of the dose range when taking concomitantly calcineurin inhibitors.*	LDL ↓18-55% HDL ↑5-15% TG ↓7-30%	• Contraindicated in liver disease • Counsel patient to report muscle pain, weakness, dark or cola-colored urine, especially when accompanied by fever and malaise. • Routinely monitor liver functions at baseline, 2 & 4 weeks and then monthly on therapy. • If myopathy or rhabdomyolysis is suspected, or if AST/ALT are significantly elevated stop therapy and check CK and creatinine. • Toxicities may occur weeks to many months after starting therapy. • ***Toxicities are potentially enhanced by CYP3A4 inhibitors***[b] like cyclosporine, tacrolimus, macrolide antibiotics, sirolimus and triazole antifungals, non-dihydropyridine calcium channel blockers (verapamil, diltiazem). • **Consider reduction of statin dose when adding a calcineurin inhibitor or other drug that can increase toxicities**
• Atorvastatin (Lipitor)	10-80		
• Fluvastatin (Lescol)	20-80		
• Lovastatin (Mevacor)	10-80		
• Pravastatin (Pravachol)	10-40		
• Simvastatin (Zocor)	5-40 (80[c])		
Rosuvastatin (Crestor)	5-40		

[a] Consult Pharmacy for pediatric dosing of statins.
[b] Adverse interactions with CYP3A4 inhibitors may be less for statins metabolized by other pathways: pravastatin (non-CYP), fluvastatin (CYP2C9) and rosuvostatin (CYP2C9 & CYP2C19), however, toxicities have been reported for all statins.
[c] Patients on 80 mg for more than 1 year can continue (Check manufacturer black box warning)

Step 7: Risk benefit ratio of drug therapy for management of hyperlipidemia should always be considered and medical intervention individualized in BMT recipients.

Step 8: Identify metabolic syndrome based on presence of ***any three*** of the following:

Abdominal obesity: – Men – Women	Waist circumference: >102 cm (>40 inches) >88 cm (>35 inches)
Hypertriglyceridemia	≥ 150 mg/dL
Low HDL cholesterol – Men -Women	 <40 mg/dL <50 mg/dL
Hypertension	Per JNC7 http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf
Fasting hyperglycemia	≥ 150 mg/dL

Treat any underlying causes:

- Intensify weight management
- Increase physical activity on a regular basis/ regular exercise regimen
- Treat lipid and non-lipid risk factors if they persist despite TLC:
- Treat hypertension (See hypertension section of LTFU guidelines)
- Consider aspirin for CHD patients to reduce prothrombotic state if not contraindicated
- Treat elevated triglycerides and/or low HDL (Step 9)

Step 9: Treat elevated triglycerides:

- Primary aim of therapy is to reach LDL goal
- Intensify weight management
- Increase physical activity on a regular basis/ regular exercise regimen
- If triglycerides are 200 mg/dL after LDL goal is reached, set secondary goal for non-HDL-C (total – HDL) 30 mg/dL higher than LDL goal (see Table below):

Non-HDL goals for HCT survivors

Risk Category	**Non-HDL Goal** (mg/dL)
High": 10-yr risk > 20%: CHD or CHD risk equivalents	<130
Moderate: 10-yr risk ≤ 20% 2+ risk factors	<160
Low: 10-yr risk ≤ 20% 0-1 risk factors	<190

Therapies for Hyperlipidemia for Adult Patients

Drug	Daily Dose mg	Class Effects	Precautions and Monitoring
Omega-3-Acid Ethyl Esters[a] • Lovaza ®	2000 BID	LDL may ↑ HDL ↑ 9% TG ↓45% VLDL↓40%	• Generally minimal side effects, eructation, dyspepsia • *May potentiate INR if on warfarin* • Avoid if fish/shellfish allergic • Monitor AST/ALT periodically • Has been combined with simvastatin for mixed hyperlipidemia
Fibric Acids • Fenofibrate (Tricor) • Gemfibrozil (Lopid)	*Start at lowest doses and rarely exceed middle of the dose range when taking concomitantly calcineurin inhibitors*. 48-145 600-1200	LDL ↓5-20% HDL ↑10-20% TG ↓20-50%	• Contraindicated in severe liver or renal disease • May cause myopathy especially when combined with statins, and in setting of impaired renal function in patients receiving cyclosporine or other drugs that interact with statins • May cause cholelithiasis and GI symptoms • May cause reversible increase in serum creatinine • Fenofibrate-statin combination may be better that gemofribrozil-statin therapy because gemfibrozil can increase statin levels by 2-6 fold • Counsel patient to report muscle pain, weakness, dark or cola-colored urine, especially when accompanied by fever and malaise. • Routinely monitor liver functions (including AST/ALT) at baseline, 2 & 4 weeks and then monthly on therapy. • If myopathy or rhabdomyolysis is suspected, or if AST/ALT are significantly elevated stop therapy and check CK and creatinine. • Toxicities may occur weeks to many months after starting therapy. • ***Toxicities are potentially enhanced by CYP3A4 inhibitors***[b] like cyclosporine, tacrolimus, macrolide antibiotics, sirolimus and triazole antifungals, non-dihydropyridine calcium channel blockers (verapamil, diltiazem).

[a] Note over the counter omega-3-acid ethyl esters are generally insufficient to significantly lower triglycerides and VLDLs. Only Lovaza® has been approved for this indication.

Consult Pharmacy for pediatric dosing of Lovaza® or fibric acids.

— If triglycerides 200-499 mg/dL after LDL goal is reached consider intensifying therapy with LDL-lowering drug, or add fibrate or Lovaza® to further lower VLDL. ***If statin fails to lower both LDL and TG it is very reasonable to consider referral to consultant cardiologist, endocrinologist, or other expert on high risk patients with mixed hyperlipidemia.***

— If triglycerides ≥ 500 mg/dL, first lower triglycerides to prevent pancreatitis:
- Add fibrate unless counterindicated
  Or Lovaza® if patient is unable to take fibrates
- Very low-fat diet
- Weight management and physical activity

XIII. HYPERTENSION

New onset or aggravation of hypertension occurs frequently after hematopoietic cell transplantation (HCT) with the most common cause of hypertension after allogeneic HCT being due to treatment with glucorticoids and tacrolimus or cyclosporine. It is important to recognize also that HCT survivors have a high prevalence metabolic syndrome which represents a cluster of risk conditions associated with premature coronary heart disease (CHD).[1] Components of the metabolic syndrome including hypertension, dyslipidemia, and diabetes occurred with higher cumulative incidence among HCT survivors compared to a randomly selected matched control.[2] Thus, adequate control of hypertension is strongly recommended in HCT recipients to minimize target organ damage and most importantly in the brain, heart and kidneys.

A. Key Points about Hypertension and its treatment

- In uncomplicated hypertension, without diabetes mellitus, renal dysfunction or cardiac dysfunction the blood pressure (BP) goals are indicated in the table below

Age (y)	Male	Female
≥18	140/90	140/90
17	132/82	125/80
16	130/80	124/80
15	127/79	123/79
14	125/78	122/78
13	122/77	121/77
12	120/76	119/76
11	117/76	117/75
10	115/75	115/74
9	114/75	113/73
8	112/73	111/72
7	111/72	109/71
6	110/70	108/70
5	108/68	106/68
4	107/65	104/66
3	105/61	103/63
2	102/57	101/59
1	99/52	100/54

Pediatric data based on 90th percentile limits for blood pressure at The 50th percentile for height (1999-2000 NHANES)

- If an adult patient has a diagnosis of diabetes and/or renal dysfunction, the BP goal is < 130/80 mm HG. If an adult patient has more than 1 gm of proteinuria, the BP goal is < 125/75 mm HG.

B. Other key points about control of hypertension and treatment:

- Reductions in myocardial infarctions, stroke incidence and heart failure with BP lowering below 140/90 mm HG are approximately 25%, 35%, and 50%, respectively.
- Patients with SBP > 160 mm HG and/or DBP > 100 mm HG tend to need two different agents and it is recommended that two agents are begun at the same time.

- Caffeine intake and nicotine use an hour before blood pressure monitoring may give falsely elevated readings.
- ***Referral to a hypertension specialist is advised for patients with poorly controlled blood pressure.***
- In the general population, thiazide diuretics should be used in drug treatment for most patients with uncomplicated hypertension, alone or combined with drugs from other classes but the potential of thiazides to aggravate pre-renal azotemia and other electrolyte abnormalities often limit their use in HCT.
- No single class of drugs has emerged as the standard of care for management of hypertension in patients receiving calcineurin inhibitors (CNI). Other agents may be indicated for patients with other co-morbidities (see Table 1).

Table 1 - Antihypertensive Medications According to Clinical Setting

Clinical Setting	Anti-Hypertensive Therapy	Monitoring
Uncomplicated Hypertension	Options include CCB, beta-blockers, thiazide diuretics, ACE-I or ARBs	• ***If not on a CNI or at risk for volume depletion, thiazide diuretics are the treatment of choice***. If used with CNI, limit dose to 12.5-25 mg per day to limit most metabolic side effects. • Calcium Channel Blockers (CCB) can affect CNI levels (cyclosporine and tacrolimus). Check CNI levels with K and Cr 7-10 days after starting CCB. • Non-dihydropyridine CCBs (e.g. verapamil, diltiazem) may potentiate the toxicity of CNI, statins and fibrates • CCB may worsen proteinuria • Beta-blockers may diminish sympathetic activity including CNI induced headaches/migraines and tachyarrhythmias.
Chronic kidney disease*, history of AKI, ***presence of proteinuria or microalbuminuria*** (see Table 2)	• ACE-I/ARB,	• Possibly in combination with CCB if still on CNI. • Avoid CCB alone due to further increase in proteinuria • *Consider holding during persistent diarrhea, vomiting or poor fluid intake* • *Check serum K and Cr 7-10 days after adding*
Diabetes With or without proteinuria	Angiotensin converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs)	• No known interactions with CNI. • May aggravate hyperkalemia and prerenal azotemia; avoid in patients with or at risk for volume depletion. *Consider holding during persistent diarrhea, vomiting or poor fluid intake* • *Check serum K and Cr 7-10 days after adding*
Heart Failure	• Diuretics • ACE-I or ARBs • Beta-blockers	• Careful to avoid pre-renal azotemia with potent loop diuretics. • Consider adding spironolactone or eplerenone if no hyperkalemia but *monitor for subsequent hyperkalemia*. • Carvedilol and metoprolol are beta-blockers of choice • For those unable to tolerate ACE-I and ARB's, therapy with hydralazine plus isosorbide may be beneficial, particularly in African Americans

Table 1 - Antihypertensive Medications According to Clinical Setting (continued)

Clinical Setting	Anti-Hypertensive Therapy	Monitoring
High-risk for Coronary Artery Disease	• ACE-I, ARBs, calcium channel blockers and beta-blockers.	• Diuretic may also be indicated based on risk/benefits profile • Calcium Channel Blockers (CCB) can affect CNI levels (cyclosporine and tacrolimus). Check CNI levels with K and Cr 7-10 days after starting CCB.
Ischemic Heart Disease	• Beta blockers	• Carvedilol and metoprolol are the beta-blockers of choice
History of Myocardial Infarction	• ACE-I, aldosterone antagonists and the beta-blockers carvedilol or metoprolol are indicated.	• Consider adding spironolactone or eplerenone if hyperkalemia is not present
History of Strokes	• Calcium channel blockers, thiazides or ARB.	• Calcium Channel Blockers (CCB) can affect CNI levels (cyclosporine and tacrolimus). Check CNI levels with K and Cr 7-10 days after starting CCB.
Hypertensive Urgency not requiring hospitalization	• Clonidine • Labetatlol • Hydralazine • ***Preferred option is to consult a hypertension expert***	• Clonidine has rapid onset of action, can cause dry mouth and somnolence; avoid for general use • Hydralazine can cause edema and tachycardia • Evaluate patient every 1-3 days to assess response to therapy

CCB; calcium channel blockers,

* Definition of chronic kidney disease (CKD) criteria

1. Kidney damage for $\geq$ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either:
    - Pathological abnormalities; or
    - Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2. GFR < 60 mL/min/1.73 m^2 for $\geq$ 3 months, with or without kidney damage

C. Evaluation for microalbuminuria and additional recommendations

Screening for microalbuminuria before and after transplant is helpful for early diagnosis of proteinuria and to guide treatment. Microalbuminuria is determined by measuring the albumin and creatinine ratio in an urine sample.

Table 2. Recommendations based on albumin/creatinine ratio and hypertension

Spot Urine Albumin/creatinine ratio (U_{ACR})	Interpretation	Recommendations
Less 30 mg/g	Normal	– Repeat U_{ACR} in 1 year
30-300 mg/g without hypertension and not on hypertensive medications	Abnormal	– Repeat U_{ACR} in 3-6 months
30-300 mg/g with hypertension and on hypertensive medications	Abnormal	– If not already on, consider change to ACE-I or ARB therapy – Repeat U_{ACR} in 3-6 months
Greater than 300 mg/g on hypertensive medications	Abnormal	– If not already on, consider treating with ACE-I or ARB therapy – Quantify 24-hr total urine protein – If proteinuria (>1 gram) confirmed, refer to nephrologist – Monitor spot U_{ACR} in 3 months

XIV. RECURRENT MALIGNANCY

In most cases recurrent malignancy occurs within the first 2 years after the transplant, with few occurring more than 5 years after the transplant.

For patients who had leukemia or other hematological malignancies, peripheral blood counts should be monitored at least monthly for the first year. Monitoring for minimal residual disease and recurrent malignancy will vary according to the specific disease and enrollment in specific protocols. Chimerism testing in blood or bone marrow may be needed to help establish the diagnosis of recurrent malignancy and to assess options for treatment (adoptive immunotherapy, biologic response modifiers, gene therapy among others).

If recurrent malignancy is suspected or confirmed, please contact the LTFU office (Appendix A) promptly to discuss additional diagnostic tests and treatment options.

XV. SECONDARY MALIGNANCIES

Recipients of hematopoietic stem cell transplant have an increased risk of developing secondary malignancies, including skin cancers, solid tumors, myelodysplastic syndromes, leukemias and post-transplant lymphoproliferative disorder (PTLD). Solid tumors that occur at increased frequency include skin cancers (squamous cell, basal cell, malignant melanoma) and cancers of the buccal cavity, followed by liver, central nervous system, thyroid, bone, and connective tissue. PTLD generally occurs within the first year after the transplant, predominantly in patients who received T cell-depleted grafts and in patients treated with intensive immunosuppressive regimens to control GVHD.

All transplant recipients should have oncologic screening evaluations at annual intervals throughout life. We recommend the following general guidelines for oncologic screening.

1. Skin exam with the complete physical and history
2. Pap smears & mammogram (women $\geq$ 35 years) & education to reinforce self breast exams
3. Prostate exam and PSA (men $\geq$ 45 years)
4. Occult blood in stool ($\geq$ 40 years)
5. Colonoscopy (baseline at age 50 years and as clinically indicated thereafter)
6. Oral exam by the dentist at 6 month intervals
7. Complete blood counts, thyroid function, and other tests as applicable

All patients should use sunblocking creams ($\geq$ 30 SPF – sun protection factor) when outdoors to prevent skin cancers and to prevent activation of chronic GVHD.

Please contact the LTFU office (Appendix A) if you are planning surgery or a biopsy for evaluation of suspected secondary malignancy or if secondary malignancy has been diagnosed.

XVI. OTHER COMPLICATIONS

A. GONADAL HORMONE INSUFFICIENCY

Gonadal hormone insufficiency is related to the age of the patient and the intensity of the transplant preparative regimen.

MALES: Prepubertal boys may require treatment with gradually escalated doses of testosterone to promote sexual maturation. (Hormonal replacement in prepubertal boys should be done in collaboration with a pediatric endocrinologist.) Men who were past puberty at the time of transplant may develop primary gonadal failure. Testosterone replacement should also be considered in men who are receiving corticosteroids for long-term treatment of chronic GVHD (see Section XI). Men who receive testosterone replacement therapy should have a baseline prostate exam and measurement of prostate specific antigen (PSA), liver enzymes and serum lipids. Follow-up monitoring of these parameters may be appropriate.

FEMALES: Women often develop primary ovarian failure and have symptoms of premature menopause. They are also at risk for development of osteoporosis. Permanent ovarian failure invariably occurs in all female patients who receive busulfan and cyclophosphamide (BU/CY). Recovery of ovarian function has been observed after transplant in 54% of younger patients (less than 26 years) conditioned with cyclophosphamide alone. The probability of ovarian function recovery after fractionated TBI is at least 10% by 6 years after transplant.

Premature (<40 years) or early (40 – 50 years) onset of menopausal symptoms and osteoporosis can significantly affect the quality of life of women after a hematopoietic cell transplant (HCT). During the past 30 years, replacement therapy with estrogen alone (for patients without a uterus) or combined with progestin (for patients with a uterus) has been used to prevent or treat menopausal symptoms and to prevent bone loss. In children, hormonal replacement therapy (HRT) is needed after transplant to promote the development of secondary sexual characteristics.

Estrogen can treat hot flashes, vaginal and vulvar symptoms, prevent bone loss and improve the quality of life for HCT recipients who are postmenopausal or who have premature ovarian failure. The positive effect on cognitive function claimed by many women taking estrogen remains to be confirmed. In young girls, estrogen replacement therapy is often critical for the development of secondary sexual characteristics and for the attainment of peak bone mass in early adulthood.

a) Special Considerations:

- It is unclear if estrogen alone or combined with progesterone replacement will add to the already increased risk of secondary breast cancer in posttransplant women (Friedman et al.Blood;2008;111:939-944). Among patients who survived for more than 10 years posttransplant the observed/expected risk ratio is 3.2 for breast cancer (Rizzo et al, Blood 2009; 113: 1175-1193). Radiation has been identified as the primary risk factor associated generally with the development of solid tumors after a stem cell transplant.

b) Hormonal Replacement Guidelines for Girls:

In young girls, estrogen replacement therapy is often critical for the development of secondary sexual characteristics during the transitional from adolescence to adulthood and for the attainment of peak bone mass in early adulthood. Hormonal replacement in prepubertal girls should be done in collaboration with a pediatric endocrinologist**.**

c) Hormonal Replacement Guidelines for Women:

Temporary relief of menopausal symptoms:

Unless medically contraindicated, a finite course of estrogen alone (women without uterous) or combined with progesterone (women with uterous) may be prescribed for the temporary relief of menopausal symptoms, provided that patients are frequently reassessed by their physician to determine the appropriate duration of therapy.

General considerations for posttransplant Gonadal Hormonal Therapy (HRT) include:

- Management of ovarian failure should be tailored according to a patient's particular clinical manifestations and individual risks for side effects of HRT such as:

  a) history (or family history) of breast cancer
  b) history of deep venous thrombosis, stroke or hypercoaguable state
  c) history (or family history of colorectal cancer
  d) severe osteoporosis with vertebral crush fractures
  e) presence of absence of a uterus

- Overall benefits and risks of long-term HRT should be discussed with each patient.

- Information about non-hormonal alternatives for management of ovarian failure manifestations should be discussed with all patients.

- A patient and her physician should be able to clearly state the indication (s) for which the patient is to start (or continue) posttransplant HRT.

- HRT should be prescribed at the lowest effective dose.

- Annual gynecological follow-up evaluation is recommended for all women.

- Monthly self-breast examination is recommended for all women.

- Baseline mammography is recommended for all women from 35-40 years of age. Annual follow-up is also recommended.

- Yearly re-evaluation of a patient's ovarian failure management plan is recommended to determine if it remains the most appropriate plan for that patient.

Specific Contraindications to HRT:

- Systemic estrogen alone or combined with progesterone should not be prescribed for patients with a history of thromboembolic diseases (i.e., venous thrombosis, pulmonary embolism, strokes, etc.), hypercoagulation disorders, breast cancer or active liver disease.

Alternatives to HRT:

- Diet, exercise and other non-hormonal strategies are available for management of hot flashes, insomnia and mood disturbances.
- Topical estrogen alone may relieve local vaginal/vulva symptoms caused by gonadal insufficiency.
- Osteoporosis can alternatively be treated with bisphosphonates in combination with adequate calcium and vitamin D intake (See Standard Practice Osteoporosis document).
- Difficulties such as decreased libido and/or dyspareunia may be multifactorial in etiology and may often be managed without the use of systemic conjugated equine estrogen and medroxyprogesterone.

B. Endocrine Abnormalities

Compensated or overt hypothyroidism, thyroiditis and thyroid neoplasms may develop in patients who received radiation. The incidence of compensated hypothyroidism after fractionated total body irradiation (TBI) before transplant ranges between 15-25%. Patients should be evaluated yearly with physical examination and thyroid function tests.

Growth hormone (GH) deficiency and growth failure (decreased growth rate/year) occurs in 70-80% of children who received total body irradiation or ≥1800 cGy cranial irradiation. The onset of GH deficiency and growth failure varies with the age of the child at the time of irradiation. The onset of these problems appears to occur later in younger children than in peri-pubertal children. All children should have height monitored at least annually, and those <14 years of age should have annual GH testing until they either develop GH deficiency or are >14 years of age, whichever occurs first.

Among pre-pubertal children, treatment with total body irradiation, busulfan or ≥2400 cGy testicular irradiation may delay subsequent pubertal development. Children who received busulfan appear to have the highest risk of delayed or absent pubertal development. Approximately half of the very young children treated with total body irradiation progress through pubertal development at an appropriate age, while older children treated with total body irradiation have a higher risk of delayed pubertal development. Treatment with cyclophosphamide alone does not delay pubertal development.

Beginning at age 10, all children should have Tanner development scores determined as part of an annual physical examination. Children who are Tanner Stage I or II by age 12 years should be referred to a pediatric endocrinologist to evaluate the need for hormonal supplementation.

C. Ocular complications

An annual eye exam with slit lamp examination is recommended for all patients who have had an allogeneic transplant and for those who are at risk of cataracts. The risk of cataracts after transplant is high for patients who received fractionated TBI (30 – 50%) and for patients treated with corticosteroids after the transplant (45%). In patients who received neither TBI or prior cranial irradiation, the incidence for cataract is approximately 15% and, is primarily due to corticosteroids. The median time to develop cataracts after transplant ranges from 2 to 5 years. Cataract extraction can be performed safely even when ocular sicca is present. Unanticipated complications after placement of an intraocular lens have not been reported. Other late complications involving the eyes are related to chronic GVHD as described in Section X A and B.

D. Oral complications and guidelines for dental care

The new development of oral pain or dryness beyond day 100 after the transplant suggests the development of chronic GVHD involving salivary glands or the mucosal surface. Cultures for candida albicans and DFA or rapid cultures for herpes simplex virus should always be obtained to rule out concomitant infections. A dental/oral medicine consultation should be strongly considered in all patients with oral complications.

General guidelines for dental care in hematopoietic transplant recipients include:

- Routine (non-urgent/non-emergency) dental care especially in patients with chronic GVHD should be delayed for at least the first year after transplant due to increase risk of bacteremia because patients are still immunocompromised.
- Routine dental health examinations (with radiographs as needed) are recommended to monitor for tooth decay and oral hygiene effectiveness/gingivitis/periodontitis. Patients should be encouraged to carry out focused and effective oral hygiene (brushing, flossing, etc.).
- Patients with dry mouth should be placed on a regimen of daily brush-on fluoride gel to reduce the risk of dental decay.
- Complete blood cell counts with differential and platelet count should be checked before any dental procedure to assess the risk of bleeding and infection.
- When urgent or emergency dental treatment is required efforts should be taken to minimize bacteremia including prophylactic antibiotics and reduce the risk of aspiration of aerosolized bacteria and debris (i.e., perform procedures under a rubber dam, use high volume suction, reduce air spray during procedures, etc.). For short non-surgical/non invasive surgical procedures, we recommend following the American Heart Association (AHA) prophylactic antibiotic recommendations. Antibiotic administration should be extended if there is significant local dental infection and risk of subsequent spread of infection (local or disseminated).
- In lieu of evidence based guidelines, prophylactic antibiotics (AHA guidelines for low-moderate endocarditis risk) should be used for all dental procedures in patients who have indwelling central venous catheters.

E. Renal insufficiency

Nephrotoxic drugs are the most common cause of impaired renal function after a stem cell transplant. Monitoring renal function and drug levels is recommended for all patients who are at risk of renal insufficiency (Section III C & D).

F. Neurological Complications

Peripheral neuropathy and central nervous system complications may develop after transplantation. Neurological complications may be caused by drugs used to control GVHD (cyclosporine, tacrolimus) (Section X), electrolyte abnormalities, infection (HHV-6, HSV, VZV, fungal organisms, toxoplasma, among others), prior cranial irradiation, intrathecal chemotherapy, GVHD and malignancy. The following evaluation is recommended:

1) Perform neurological examination including mini-mental state exam.
2) Consider
   - **Medications (CSA, FK506, opiods, benzodiazepines, high-dose steroids, voriconazole, etc) and check CSA/FK506 levels**
   - Metabolic abnormalities (hypo/hypernatremia, hypercalcemia, hypercapnia, hyperosmolarity, renal or hepatic failure, hypothyroidism, adrenal insufficiency, hypoglycemia, etc.)
   - Non-CNS infection such as UTI, pneumonia, etc.
   - Unremitting pain or insomnia
   - Intracranial hemorrhage
   - Hypovolemia – due to bleeding or other cause
   - Head trauma
   - CNS malignancy
   - CNS infection

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When available, refer to institutional policies on the management of patients with delirium.

If medication/metabolic/endocrine/pain effect/sleep deprivation are felt to be unlikely etiologies OR if symptoms persist for >24-48 hours despite efforts to correct what's felt to be underlying cause:

1) Brain Imaging (MRI preferred)
2) Lumbar puncture
   Standard: cell count, protein, glucose, cytology, gram stain, bacterial/fungal cultures, HHV-6 PCR (viremia should not be assumed to be a marker for HHV-6 detection in the CSF), additional CSF saved for future studies
   Additional testing for malignancy of infection (see table below) may be considered as clinically indicated:
3) Consider ID consult for evaluation of infectious etiologies of delirium
4) Consider Neurology consult for evaluation of neurological etiologies of delirium
5) Consider psychiatry consult for evaluation and treatment of delirium

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Depending on the clinical scenario, the following additional tests for infectious etiologies may be considered:

Pathogen	Relative Frequency	Clinical Setting	Recommended Initial Evaluation
Viruses			
HHV-6	Frequent	• Early after transplant • Temporal lobe contrast-enhancing lesions • Memory loss characterizing delirium	CSF: HHV-6 PCR
HSV	Occasional	• Temporal lobe contrast-enhancing lesions • Seropositive and not on ACV/GCV	CSF: HSV PCR
VZV	Occasional	• Seropositive or following significant exposure and not on ACV/GCV	CSF: VZV PCR
CMV	Rare	• Donor or recipient seropositive and late after transplant	CSF: CMV PCR
EBV	Occasional	• T-cell depleted, including CD 34+ selected • Receipt of anti-T cell antibodies	CSF: EBV PCR
Enterovirus	Occasional	• Child • Summer/fall	CSF: Enterovirus PCR
West Nile Virus*	Occasional	• Donor is from endemic state • Significant mosquito exposure • Neuromuscular weakness as component of meningoencephalitis	CSF: WNV PCR (low sensitivity), IgM (MAC-ELISA) Serum: IgM (MAC-ELISA) Contact Public Health
JC virus	Rare	• Brain imaging: non-enhancing white matter lesions • other work-up negative	CSF: JCV PCR Brain biopsy
Parasites			
Toxoplasma	Occasional	• Ring-enhancing lesions • Seropositive pretransplant and not on prophylaxis – TMP/SMX, dapsone, etc.	CSF: PCR (low sensitivity) Plasma: PCR
Fungi			
Aspergillus and other molds	Frequent	• Enhancing brain lesion (s) consistent with abscess • Concurrent pulmonary lesions (nodules) • High degree of immunosuppression, or neutropenia	CSF: PCR and galactomannan (unknown sensitivity/specificity), fungal culture Plasma: galactomannan
Cryptococcus	Rare	• High degree of immunosuppression, or neutropenia • +/- enhancing meningitis or nodule or hydrocephalus	CSF: cryptococcal antigen, fungal culture Serum: cryptococcal antigen
Bacteria			
Usual bacterial pathogens: *S. pneumoniae*, Listeria, GNR, Nocardia, etc.	Frequent	• Meningitis • Enhancing brain lesion (s) consistent with abscess	No additional testing recommended as these pathogens should be identified by standard bacterial culture.
Syphilis	Rare	• Positive pre-transplant serology • Significant exposure	CSF: VDRL, FTA, or TPPA; IgM immunoblotting: intrathecal T. pallium antibody (ITPA) index, PCR,
Tuberculosis**	Rare	• Meningitis (basilar or diffuse) or ring-enhancing lesion(s) • Recipient from endemic area • Positive PPD pretransplant • Significant exposure	CSF: AFB stain and culture, PCR (both, low sensitivity)

* If concerned about other arboviruses, please discuss with Infectious Diseases.

** If concerned about non-tuberculous mycobacteria, please discuss with Infectious Diseases.

If the appropriate test is not locally available, arrangements should be made to send the specimen to another laboratory. Please contact the LTFU office (see Appendix A)

Some children, especially those given cranial irradiation before the transplant, may have learning disabilities (particularly in mathematics and abstract thinking). These abnormalities typically begin to appear 24-42 months after the transplant. When recognized as a problem, refer for psychological testing. Special educational instruction should be considered for these children. Short-term memory deficit can occur in adults, and psychometric testing should be performed as clinically indicated.

Total body irradiation can delay the onset of developmental landmarks in very young children. These effects are most severe throughout the first year after transplant, and affected children benefit from occupational therapy to assist their normal development. After they have achieved appropriate developmental landmarks, further development appears to proceed normally. IQ and ability to succeed in school do not appear to be affected by total body irradiation.

G. Bone Complications (see Section XI)

Osteoporosis, fractures and avascular necrosis (AVN) are common complications after transplantation. Long-term treatment with corticosteroids is the primary risk factor for these complications, while gonadal failure, electrolyte imbalances, physical inactivity and treatment with cyclosporine play an additional contributory role. Approximately 50% of patients receiving long-term corticosteroid therapy will eventually develop bone fractures. Increased osteoclast-mediated bone resorption and decreased osteoblast-mediated bone formation cause trabecular bone loss. In allogeneic HCT recipients, evaluation for bone loss and osteoporosis includes a careful assessment of risk factors (www.shef.ac.uk/FRAX/) and exposures in addition to BMD measurement. (see References, section XXV, Other Complications, Bone Complications)

Bone loss can be minimized by minimizing glucocorticoid dose, optimizing calcium and vitamin D intake, participating in weight-bearing exercise, and by hormone replacement therapy. Section XI provides detailed guidelines for preventing and monitoring osteoporosis in patients who are being treated with corticosteroids. Section XX describes vitamins and other minerals requirements. Section XXI outlines diet for patients treated with corticosteroids. Section XI outlines hormone replacement therapy.

H. Chronic Pulmonary Complications

Some reports have shown that the FEV_1/FVC is less than 70% in 15% of patients by one year after the transplant and in 30% of patients by three years after an allogeneic transplant. Among patients with chronic GVHD, 5-10% will develop severe obstructive airway disease that resembles obliterative bronchiolitis. Pulmonary function tests (PFTs) with measurement of total lung capacity and DLCO should be evaluated at 1 and 5 years after transplant and yearly or more often in patients with chronic GVHD (Section X B). *If new abnormalities are noted in PFTs please contact the LTFU office to discuss further recommendations (Appendix A).*

Children who received total body irradiation are at risk of delayed onset pulmonary restrictive disease 5-20 years after the transplant. All patients who were in the pediatric age group at the time of transplant should have annual pulmonary function tests.

I. Hepatobiliary Complications

(see References, section XXV, Liver)

Elevations of serum ALT, alkaline phosphatase or bilirubin may occur after day 100, even in patients who had no indication of liver problems earlier. The presentations fall into four clinical categories.

- **Acute hepatitis.** Elevations of serum ALT after day 100 are most commonly caused by drug-induced liver injury (an azole antifungal or trimethoprim-sulfamethoxazole are the most common causes of Drug Induced Liver Injury (DILI) in this setting), chronic GVHD, an exacerbation of hepatitis B or C, or a herpesvirus hepatitis (VZV, HSV).

  Three clinical situations demand immediate diagnosis and treatment.
  1) Rapidly rising ALT accompanied by anorexia, abdominal distension or pain in the abdomen or back can be signs of visceral VZV infection (Section VIII B).
  2) Patients who have indications of hepatitis B before transplant (HBsAg-positive or anti-HBc-positive) or who had a donor who was infected with hepatitis B are at risk of fulminant hepatitis B after the transplant if they did not receive antiviral prophylaxis..
  3) Chronic GHVD can present as an acute hepatitis, usually after tapering or discontinuation of immunosuppressive medications, particularly cyclosporine or tacrolimus, or after DLI.

  Patients with a rapidly rising ALT and those with ALT values >500 u/L should be given IV acyclovir until VZV hepatitis is ruled out. An urgent PCR for VZV DNA in serum is needed to establish the diagnosis. Contact the LTFU office (Appendix A) for guidance in difficult cases.

- **Chronic hepatitis.** Chronic fluctuations in serum ALT levels without a discrete episode of acute hepatitis may represent DILI, hepatitis B or C virus infection (Section XVII), iron overload (Section XVIII) or cGVHD (Section X).

- **Jaundice or signs of cholestasis.** Elevated serum bilirubin and elevated alkaline phosphatase can be caused by chronic GVHD (Section X), drug-induced cholestasis, acute hepatitis (see above), or biliary obstruction. An ultrasound should be obtained to evaluate whether the common bile duct is dilated. Liver biopsy might not be needed in patients who have cholestasis with biopsy-documented chronic GVHD in other organs. Some patients have liver involvement as the dominant manifestation of chronic GVHD, and liver biopsy might be needed in

order to establish the diagnosis when other manifestations of chronic GVHD are absent.

- **Hepatomegaly or right upper quadrant pain.** The sudden onset of hepatomegaly suggests acute hepatitis, Epstein-Barr virus-induced lymphoproliferative disorder involving the liver, or rarely, Budd-Chiari syndrome. More indolent hepatomegaly can occur with metastatic tumor, leukemia infiltration or rarely, constrictive pericarditis or mycobacterial infection. Right upper quadrant pain can be caused by acute cholecystitis, biliary obstruction with cholangitis, biliary sludge syndrome, or rarely, fungal liver abscess. Liver imaging with helical CT X-ray or ultrasound is needed to resolve the diagnosis.

Suggestions for liver biopsy and handling of liver tissue. The technique of liver biopsy depends on the clinical situation (diffuse process vs. focal lesion) and the platelet count. A percutaneous biopsy is preferred if platelet counts are >100,000/mm^3 and the risk of bleeding is small (including normal PT/PTT) but transvenous biopsy through either the femoral or jugular route is satisfactory for diagnosis of any diffuse hepatitis or GVHD. Tissue should be cultured for viruses and fungi and should be fixed in freshly-prepared neutral buffered formalin.

J. Gastrointestinal Complications:

(see References, section XXV, Liver)

GVHD is the most common cause of anorexia, nausea, vomiting and diarrhea after an allogeneic transplant. However, each of these symptoms has a narrow differential diagnosis that requires careful evaluation before concluding that GVHD is the sole cause. Anorexia, nausea and vomiting can be caused by HSV, VZV, and CMV infections and by certain medications such as trimethoprim-sulfamethoxazole, voriconazole, itraconazole, mycophenolate mofetil, cyclosporine or tacrolimus. Abdominal pain can be caused by visceral VZV infection, biliary sludge syndrome, acute cholecystitis, or rarely, Epstein-Barr virus-induced lymphoproliferative disease. Diarrhea occurring more than 3 months after transplant is commonly caused by magnesium – containing medications, unresolved GVHD, or less commonly by an infection (giardiasis, cryptosporidiosis, C. difficile, or CMV). Section VII provides guidelines for evaluation of diarrhea and endoscopy.

XVII. BLOOD PRODUCT TRANSFUSIONS

All Red Blood Cells and Platelets be irradiated (2,500 cGy) to prevent transfusion related GVHD. Red blood cells and platelets will also be leukocyte reduced to prevent HLA alloimmunization and reduce the risk of CMV transmission. Leukocyte reduced blood components are accepted as "CMV safe" for CMV seronegative patients. Granulocytes are never leukoreduced.

If the donor and recipient had ABO blood group incompatibility, low-grade hemolysis can delay erythroid recovery for many months after the transplant. Hemagglutinin titers and reticulocyte counts should be followed to monitor the change from recipient to donor ABO type. Type O red cells should be used for patients who have isoagglutinins against donor red blood cell antigens until the donor blood group type is fully established in the recipient. Treatment with erythropoietin can be beneficial in some patients. Donor-type platelets should be used for transfusions.

XVIII. VIRAL HEPATITIS in long term transplant survivors

(see References, section XXV, Liver)

Compared to hepatitis C, hepatitis B is more likely to result in severe clinical hepatitis and death from post-transplant liver disease, although these outcomes occur only in the minority of HBV-infected patients. One exception: patients infected by HCV who are receiving MMF for GVHD prophylaxis may develop a more severe, potentially fatal form of liver disease called fibrosing cholestatic hepatitis C. In this setting, it should be assessed whether MMF may be discontinued. Antiviral treatment should be considered for HBV-and HCV-infected transplant recipients unless contraindications are present. Liver test abnormalities post-transplant may be caused by hepatic GVHD, HBV, HCV, a herpes virus infection (VZV, CMV, HSV), adenovirus, or drug-induced injury (Sections I, X and XV). In this situation, liver biopsy should be performed to determine the dominant pathologic process.

A. Hepatitis B

Even in patients with very low levels of viral replication before transplantation and relatively normal liver function and histology, impaired cellular immunity can permit reactivation of HBV. Serological patterns of HBV infection may be atypical in transplant survivors, likely as a consequence of immunosuppression. Patients with HBV requiring systemic immunosuppressive medications for control of chronic GVHD remain at risk for acute exacerbation of hepatitis whenever immunosuppression is tapered or ceased. Such flares may result in hepatic failure and death. Cirrhosis due to chronic HBV has not emerged as a major problem after transplantation.

The risk of fatal HBV liver disease among patients who are persistently HBsAg-positive after transplant and who are not receiving lamivudine or entecavir is approximately 12%. In hematopoietic cell transplant recipients who are anti-HBc and anti-HBs-positive, but HBsAg-negative, reactivation of latent infection can occur and may lead to fulminant hepatic failure, particularly if nucleotide substitutions in the precore region of the genome interfere with production of HBcAg. Because these patients remain HBcAg-negative despite high levels of viral replication, monitoring of HBV DNA levels is necessary in these HBsAg-positive patients.

Posttransplant HBV infection may result from

- Active HBV infection before transplant
- Reactivation of latent HBV infection
- New infection during the transplantation process
    - Infected hematopoietic cell product from an infected donor
    - Infected blood products (risk estimated in U.S. to be 1 in 500, 000 units).

1) Monitoring of Patients at Risk for HBV Infection

Moderate and high risk for HBV infections include patients who were HB_SAg-positive, HBeAg-positive or HBV DNA by PCR pretransplant OR patients who received hematopoietic cells from a donor who was HB_SAg-positive, HBeAg-positive, anti-HBc

positive or HBV DNA-positive by PCR. In addition, patients with markers of latent HBV infection (anti-HBc-positive) are at risk for HBV reactivation after transplant.

Careful monitoring of the patients described above is recommended and includes:

- **Serum ALT** weekly for three months post transplant, thereafter at least twice monthly until 1 year after HSCT and

HBV DNA by PCR should be tested:

A) For patients who were hepatitis B positive pre transplant: anytime at the onset of abnormal or worsening serum ALT.

B) For patients who were hepatitis B negative pre transplant and receiving donor cells that were hepatitis B DNA or surface antigen positive: Monitor serum ALT and HBV DNA by PCR at monthly intervals to 6 months post transplant. Thereafter HBV DNA by PCR anytime at onset of abnormal or worsening serum ALT.

2) Treatment

For patients at risk for HBV infection after transplant who are NOT receiving antiviral prophylaxis, we recommend initiation of antiviral treatment with entecavir when HBV DNA is first detected after transplant. The aim of antiviral treatment is to suppress viral replication completely, thereby minimizing the risk of viral mutation. Patients should be treated for 12 months or 6 months after discontinuation of systemic immunosuppressive treatment, whichever is longer.

3) Other considerations

-Clearance of antigenemia is commonly observed and is particularly likely if the hematopoietic cell donor was anti-HBs-positive.

- Based on CDC guidelines, vaccination with HAV is considered particularly important and is strongly recommended for any patient with evidence of infection with HBV to prevent the development of fulminant liver failure secondary to hepatitis A infection. (See section IX Vaccinations)

B. Hepatitis C

Infection with HCV virus is more frequent in patients who received blood product transfusions before 1991 when HCV testing was unavailable than with transfusions given after 1991. The prevalence of chronic hepatitis C in long-term HCT survivors ranges from 5% to 70%, depending on the endemic prevalence. Long-term survivors with HCV infection commonly have fluctuating levels of AST and ALT. During the first 10 years after infection, hepatitis C has little impact in morbidity or mortality—with the exception possibly of HCV-infected patients who are receiving MMF. The frequency of cirrhosis and end-stage liver disease caused by Hepatitis C in 40-year survivors of hematopoietic cell transplant is about 33%.

Regardless of whether HCV infection occurred before or after the transplant, clinical or biochemical evidence of hepatitis usually coincides with the return of cellular immunity and the tapering of immunosuppressive drugs used for GVHD prophylaxis. During this time, it is difficult to differentiate the hepatitic variant of GVHD of the liver from an exacerbation of HCV. The presence of hepatitis C viremia, even in high titer, is insufficient to make the distinction between these two disorders. The absence of hepatitis C viremia, however,

means that HCV is not a cause of ALT elevations. Unless there is evidence of active GVHD in other organs, a liver biopsy may be required before a therapeutic decision is made.

Pathologic distinction between hepatitis C and GVHD may be difficult, since both processes may be associated with portal lymphoid infiltration and bile duct injury. Marked bile duct injury with epithelial cell dropout and loss of interlobular bile ducts is more typical of GVHD. A flare of hepatitis C and hepatic GVHD may occur simultaneously. If the liver biopsy suggests both processes, immunosuppressive therapy should be administered, since ongoing lymphocytic attack leading to loss of interlobular bile ducts may result in severe and progressive cholestasis.

Fulminant immune-rebound hepatitis C has been reported only rarely after withdrawal of immunosuppression. Patients infected by HCV who are receiving MMF may be at risk to develop fatal fibrosing cholestatic hepatitis C. The role of antiviral agents, especially new polymerase and protease inhibitors specific for HCV, has not been defined in this circumstance. After the initial flare of hepatitis during immune reconstitution, the serum ALT levels may again return to normal, but laboratory abnormalities often settle into the pattern of chronic hepatitis seen in other patients with HCV infection. Anti-viral therapy for chronic HCV infection should be considered after the patient has discontinued all immunosuppressive drugs and has no evidence of active GVHD. Current studies are examining the use of combination antiviral drugs therapy for chronic HCV infection that do not include interferons as part of therapy; these regimens could be potentially useful for patients with chronic GVHD plus HCV infection, in whom avoidance of interferon therapy would be desirable. (see References, section XXV, Liver)

Monitoring:

- Liver function tests at least weekly to day 100, then bimonthly until 1 year
- HCV RNA should be checked around day 50 post transplant in those rare patients who were HCV antibody positive but HCV RNA negative pretransplant or whose donor was HCV RNA positive.
- Repeated testing for HCV RNA is not necessary once the diagnosis of HCV infection has been established.
- Patients known to have HCV should be referred to a hepatologist to assess three major issues: 1) Has the virus infection caused any damage to the liver yet? 2) Are there other causes of liver damage (i.e., alcohol, medications, chronic GVHD, hemosiderosis or the hepatitis B virus? 3) Should medications for HCV be instituted?

Therapy

Antiviral therapy should be considered in any long-term HCT survivor with chronic hepatitis C infection. Interferon-alfa and ribavirin can be administered to patients who have discontinued treatment with all immunosuppressive agents and have no evidence of GVHD or myelosuppression. Treatment with these agents may cause thrombocytopenia, neutropenia and exacerbation of GVHD. While experience is limited, response rates to interferon-alfa and ribavirin appear to be no different from those of other patients with hepatitis C. However, newer antiviral drugs active against HCV are in development, and

it is likely that combination antiviral drug therapy will be much more effective than older interferon/ribavirin regimens. (see References, section XXV, Liver)`

In patients with concomitant iron overload, phlebotomy or chelation therapy may be indicated to reduce hepatic iron stores (Section XVIII) before interferon therapy; mobilization of liver iron may increase the chance of response. The mobilization of iron after transplant largely depends on the iron burden, especially cardiac iron. A review of this topic has been published. (see References, section XXV, Liver)

Other Considerations:

- Based on CDC guidelines, vaccination against HAV and HBV are considered particularly important and are strongly recommended for any patient with evidence of infection with HCV to prevent the development of fulminant liver failure secondary to infection with other hepatitis viruses.
(See section IX Vaccinations)

XIX. IRON OVERLOAD

Iron overload occurs frequently after the transplant, often caused by ineffective erythropoiesis with associated intestinal hyperabsorption, in addition to red cell transfusions and, in some patients, genetic hemochromatosis. Relatively little is known about the effects of iron overload in HSC transplant patients other than those with hemoglobinopathies. Other patients with hepatic iron overload in the range of 3200 to 7000 μg/g dry weight have normal life expectancy. Extreme tissue iron overload (> 15,000 μg/g dry weight) has been associated with extensive organ toxicity in the posttransplant survivors of thalassemia. Principal organs at risk include the heart, liver, pancreas and pituitary gland, resulting in dysrhythmias and cardiac failure, portal fibrosis and cirrhosis, insulin-dependent diabetes mellitus and other endocrine insufficiencies. In patients with chronic hepatitis C, iron overload may accelerate the development of cirrhosis. Once transplant has restored normal hematopoieses and red cell transfusions are no longer required, body iron stores decline over several years [Angelucci, Lancet 1993]. Mobilization of iron in heavily overloaded patients improves cardiac function, normalizes serum ALT levels, and results in improved liver histology [Angelucci, Blood 1997; Mariotti, BJH, 1998].

Liver or marrow iron content correlates poorly with number of transfused red blood cell units. Marrow and hepatic iron content has been determined by spectrophotometry among 10 consecutive autopsied patients who were transplanted for hematological malignancy. The median hepatic iron content (HIC) at 50 to 100 days posttransplant was 4307 μg/g dry weight (range 1832-13120; normal 530-900) and the median marrow iron content was 1999 μ/g dry weight (range 932-3942). Marrow iron content can also be measured by morphometry based on digital photomicrographs of a Prussian blue-stained marrow biopsy. Because of correlation between morphometric and spectrophotometric analyses of marrow iron content ($r = 0.8$, $P= 0.006$) and hepatic iron index ($r = 0.82$, $P = 0.004$) morphometric analysis of marrow iron content is an acceptable alternative for quantifying tissue iron stores [Strasser, BMT 1998]. Earlier work also demonstated a close relationship between biochemical concentration and histologic grading of marrow iron [Gale et al 1963] although histological grading is subject to variation between and within observers [Cavill 1982].

Because the carrier frequency for homozygous HFE gene mutations is relatively high (0.3 to 0.5%) among individuals of northern and western European extraction, the possibility of genetic hemochromatosis contributing to posttransplant iron overload needs to be considered in relevant individuals. Two point mutations, C282Y (Cys282Tyr) and H63D (His63Asp), have been described within the HFE gene. Homozygosity for C282Y is associated with haemochromatosis; the effect of compound heterozygosity (C282Y/H63D)) on iron status in HCT recipients is variable [Grigg et al, 2001].

Individuals Particularly at risk for Iron Overload

- Hemoglobinopathies (Sickle Cell Disease, Thalassemia major)
- Congenital Anemia (e.g., Diamond-Blackfan)
- Hereditary Hemochromatosis
- Chronic Anemia with transfusional overload and ineffective erythropoiesis
- Hepatitis C may accelerate siderosis-induced hepatic damage

A. Evaluation of Iron Overload after HSC Transplant

1. Bone Marrow
    - Measurement of marrow iron by morphometry or spectrophotometry is appropriate to assess iron stores in most cases.

2. Serum Iron Studies and Liver function tests if $\geq$ 2 in grade in Bone Marrow, at 80-100 days post transplant, 1 year post transplant or at increased risk for iron overload.
    - Transferrin Saturation (TS)
    - Serum ALT and AST
    - Serum Iron, Total Iron-binding Capacity (TIBC)
    - Serum Ferritin
    - HFE genotype should be considered in patients with a family member with HC and in patients with Transferrin Saturation (TS) > 45% in patients of Northern or Western European ethnicity.

3. Assessment of Iron Stores in Tissues
    - **Indications**
      Assessment of Iron Stores is indicated in patients with Transferrin Saturation (TS) > 45% and HFE $^{C282y/C282y}$ or HFE $^{C282y/H63D}$ with either a ferritin level > 1000 or abnormal ALT and in patients with TS > 45% with HFE $^{wild\ type}$ with either ferritin levels > 2500 or abnormal ALT.
    - Measurement of hepatic iron by spectrophotometry of liver biopsy is the gold standard for testing and is preferred for patients with markedly elevated serum ferritin and ALT (especially if HFE homozygous or compound heterozygous). In addition, these samples should be reviewed for liver pathology (e.g., portal fibrosis, cirrhosis, or hepatitis).
    - While measurement of liver iron concentration is the gold standard, an iron-specific magnetic resonance imaging test (Ferriscan) is highly accurate in measuring liver iron and is an alternative to liver biopsy for the measurement of hepatic iron content.

4. Indication for Iron Mobilization Therapy According to Tissue Iron Content

Hepatic Iron Content (μg/g dry weight)	**Marrow Iron Content**	**Mobilization of Iron**
>15000	Very high ++++	Phlebotomy + Desferoxamine
7000 – 15000	Moderately high ++ to +++	1st choice: Phlebotomy 2nd choice: Desferoxamine or Desferasirox (especially if HCV+)
<7000	Not increased or mildly increased +	1) HFE^{wildtype}: observe 2) HFE$^{C282Y/C282Y\ or\ C282Y/H63D}$: Phlebotomy

B. Phlebotomy after Transplant

- If indicated, phlebotomy is likely to be the safest and most cost-effective approach for the mobilization of tissue iron.

- Regular phlebotomy requires normal hematopoiesis or hematopoiesis that can respond satisfactorily to weekly or every-other-week erythropoietic stimulating agents.

- Phlebotomy Regimen:

Phlebotomy volume	5 mL/kg as tolerated
Frequency	every 3-4 weeks as tolerated
Monitoring monthly	ferritin, iron and % iron saturation
Discontinue Phlebotomy	ferritin falls below 500-1000 ng/mL

- Erythropoietic Stimulating Agents may be administered subcutaneously to facilitate regular phlebotomy. The smallest number of whole vials should be prescribed per dose:

Body Weight (kg)	Erythropoietin[1] (Units weekly)	Darbepoetin[2] (micrograms every-other-week)
10-14	6000 to 8000	25 to 60
15-20	10000	60
21-24	10000 to 14000	60 to 100
25-29	14000	100
30-39	20000	100
40-60	40,000	200
≥60	Use darpopoetin	200

[1] Erythropoeitin (Epogen) vial sizes (2000, 4000, 10000, 20000, 40000 units)
[2] Darbepoetin (Aranesp) vial sizes (25, 60, 100, 150, 200, 300 micrograms)

C. Chelation Therapy

- If phlebotomy cannot be performed despite the use of erythropoietic stimulating agents within 3 - 6 months after transplantation, and if treatment to mobilize iron stores is indicated, iron chelation therapy with desferoxamine (Desferal) or deferasirox (Exjade) should be initiated.

1. Desferoxamine (Desferal)

- Iron overload increases the susceptibility of patients to Yersinia enterocolic and Yersinia pseudotubera infections. In rare cases, treatment with desferoxamine has enhanced this susceptibility, resulting in generalized infections by providing this bacteria with a siderophore otherwise missing. Rare infections with mucormycosis have also been reported in association with desferoxamine .
- Desferoxamine can be administered by continuous subcutaneous or intravenous infusion. Desferoxamine causes less toxicity if administered subcutaneously.
- The daily dose of deferoxamine (Desferal) should be 20 to 40 mg/kg subcutaneously, administered at least five days per week. The dose should not exceed 50 mg/kg and the infusion rate should not exceed 15 mg/kg/hour in order to avoid hypotension.

Desferoxamine is administered parenterally by continuous overnight infusion with ambulatory pumps. Plasma concentrations reach a plateau at 12 hours.

- Most of the toxicity caused by desferoxamine occurs when the dose exceeds 50 mg/kg or when the iron burden is not high.
- Toxic effects caused by desferoxamine include ocular and auditory abnormalities, sensorimotor, neurotoxicity, renal insufficiency, pulmonary toxicity, and failure of linear growth.
- Toxicity can be avoided by regular assessment of the body iron stores. Patients receiving desferoxamine should have annual measurement of total body iron (liver biopsy or another suitable measure). In general, direct assessment of body iron stores should also follow when desferoxamine toxicity occurs.
- If hepatic iron content is $\leq$3000 mcg/gm dry liver weight, or marrow iron content is not increased or only mildly increased, treatment with desferoxamine should be discontinued for six months. Thereafter, the dose of desferoxamine should be adjusted to maintain hepatic iron content between 3000 and 7000 mcg/gm dry liver weight.

Suggested monitoring of desferoxamine-related toxicity is shown below.

Toxicity	Tests	Frequency	Alteration In Rx
High frequency sensorineural hearing loss	Audiogram	Annually; if symptomatic, check immediately	Stop desferoxamine; repeat audiogram at 3 month intervals until normal or stable
Retinopathy (pigmentairy degenaration); cataracts; corneal opacities; visual impairment	Eye exam including visual acuity, slit-lamp and fundoscopy	Annually; if symptomatic, check immediately	Stop desferoxamine if retinopathy or hearing impairment
Metaphyseal/Spinal	Plain x-ray of wrists, knees, spine; bone age in children	Annually	Reduce desferoxamine to 25 mg/kg/day
Growth retardation	Sitting and standing height	Every 6 months	Reduce desferoxamine to 25 mg/kg/day; reassess every 6 months

2. Deferasirox (Exjade)

- Deferasirox is an oral medication for iron chelation. It is available in 125mg, 250mg, and 500mg tablets.
- The starting dose of deferasirox is 20mg/kg/day. The dose of deferasirox may be adjusted in 5-10mg/kg/day increments every 3-6 months if necessary depending on serum ferritin trends. Doses of deferasirox should not exceed 30mg/kg/day. Therapy should be temporarily discontinued if the serum ferritin level falls below 500mcg/L.
- Deferasirox should be taken once daily on an empty stomach (at least 30 min prior to eating). Tablets should be completely dispersed by stirring in water, orange juice, or apple juice until there is a fine suspension. Doses <1 gram should be dispersed in 3.5 ounces of liquid, and doses ≥1 gram should be dispersed in 7 ounces of liquid. After swallowing, any residue

should be resuspended in a small volume of liquid and swallowed. Doses should be separated by 2 hours from aluminum containing antacids.

- Dosing of deferasirox should be reduced for renal dysfunction. If the serum creatinine level increases more than 33% over the course of two consecutive visits, the dose of deferasirox should be reduced by 10mg/kg. For pediatric patients, the dose should be reduced by 10mg/kg if the serum creatinine is greater than the upper limit of normal on 2 consecutive visits.
- Toxicities of deferasirox include GI symptoms (diarrhea, vomiting, nausea, abdominal pain), headaches, pyrexia, skin rash, increases in serum creatinine, intermittent proteinuria, cytopenias (including agranulocytosis, neutropenia, and thrombocytopenia), hepatic dysfunction, auditory disturbances, and ophthalmic disturbances. Post marketing surveillance has shown cases of acute renal failure or cytopenias with fatal outcomes in patients taking deferasirox. The relation to deferasirox in these cases is uncertain.
- Serum ferritin levels should be monitored every month while on deferasirox. Serum creatinine, urine protein levels, CBCs, and liver function tests should be checked at baseline and at least monthly while on therapy. Patients with pre-existing renal dysfunction or other risk factors should be monitored with weekly serum creatinine levels for at least the first month, and then monthly thereafter. Baseline auditory and ophthalmic testing are recommended with regular follow up assessments every 12 months.

XX. VITAMINS AND OTHER MINERAL SUPPLEMENTS

It is recommended that all allogeneic patients have iron-free multiple vitamin/mineral supplementation for one year or until all immunosuppressive therapy is discontinued after the transplant. Autologous patients should continue supplementation for one year if dietary intake does not meet daily requirements. Iron supplementation should not be used routinely in any patient unless iron deficiency is clearly documented. Most patients have iron-overload because of red cell transfusions and increased absorption of iron in the GI tract (see Section XIX).

A. Calcium and Vitamin D daily intake requirements

Adequate calcium and vitamin D intake are necessary in order to decrease the risk of bone complications after transplant. Women with ovarian failure and patients who require long-term treatment with corticosteroids have a high risk of osteoporosis, and pediatric patients can have poor bone development after chemotherapy and radiation. Avoidance of sunlight and the use of sunscreen to block UV radiation can contribute to vitamin D deficiency.

Patients who cannot consume adequate calcium or vitamin D from foods should receive supplements to meet their daily requirements. Supplemental calcium should be given in divided doses, preferably as calcium citrate. Some "natural" calcium supplements do not contain enough bioavailable calcium to prevent osteopenia. The maximum amount that can be absorbed with each dose is 500 mg. See Section XI for prevention of osteoporosis in patients who are being treated with glucocorticoids.

	Daily requirements	
Age (years)	**Elemental Ca^{++}**	**Vitamin D**
1 - 5	800 mg	400 International Units
6 - 8	1200 mg	400 International Units
9 - 18	1500 mg	400 - 800 International Units
>18	1500 mg	800 International Units

B. Magnesium supplementation

Cyclosporine and tacrolimus (FK-506) increase urinary excretion of magnesium, resulting in low serum magnesium levels. Hypomagnesemia has been associated with seizures in patients treated with cyclosporine or tacrolimus (FK506). All patients receiving these immunosuppressive drugs require magnesium supplementation and monitoring serum magnesium levels monthly, or more often as indicated. Oral magnesium with protein (133 mg/tablet) is better tolerated than magnesium oxide. The magnesium requirements range from 6 to 20 or more tablets daily for adults and 1 to 9 or more tablets daily for children. Some patients may require intravenous supplementation (magnesium sulfate) if oral administration causes diarrhea.

XXI. DIETS AND OTHER NUTRITIONAL GUIDELINES

A. Diet for immunosuppressed patients after transplant

Patients after hematopoietic transplant or after high dose chemotherapy are at increased risk of developing food-related infections. It is recommended that all transplant recipients follow the nutrition guidelines for discharge home, including the Diet for Immunosuppressed Patients. These guidelines can be found at *www.seattlecca.org* under *patientsandfamilies/nutrition/nutritionDietsguidelines/ osteoporosisNutritionguidelines.* The duration of immunosuppressed patient diet depends on the immunocompromised status of the patient and the type of transplant, as described below:

- *Allogeneic* transplant recipients should follow the immunosuppressed patient diet guidelines until all immunosuppressive treatments are discontinued.

- *Autologous* transplant recipients should follow the immunosuppressed patient diet guidelines until one month after discontinuation of corticosteroids or three months after chemotherapy or transplant (whichever occurs later) and as long as there are no GI symptoms.

B. Additional dietary recommendations:

1. Diet for patients receiving treatment with corticosteroids:

In addition to the Diet for Immunosuppressed Patients, nutritional recommendations to minimize the risk of osteoporosis are needed (see Section XI). These nutritional guidelines can also be found at www.seattlecca.org/ patientsandfamilies/nutrition/ nutritionDietsguidelines/osteoporosisNutritionguidelines.

2. Diet for patients with graft-versus-host disease of gastrointestinal tract*:*

In addition to the Immunosuppressed Patient Diet, specific diets are recommended for patients with GVHD of the GI tract to help alleviate the gastrointestinal symptoms. Two different gastrointestinal diets (GI1 and GI2) have been developed by the dietitians at the FHCRC and the SCCA. These GI1 and GI2 diets have limited amounts of fats, fiber, lactose, acidic items and GI irritants. The diets can be found at *www.seattlecca.org* under *patientsandfamilies/nutrition/nutritionDietsguidelines/.*

For patients with severe diarrhea (exceeds 8-10 ml/kg/day) or significant crampy abdominal pain, bowel rest (NPO) is recommended. TPN at 1.5 x basal energy needs or higher, 1.5-2.0 g protein/kg with supplemental zinc is also usually needed. Replacement of stool losses on a mL/mL basis with half-normal saline hydration is recommended. As diarrhea subsides, the response to oral feeding is highly variable.

When oral intake is appropriate, we recommend beginning with isotonic beverage in small amounts and gradually progressing to the GI1 diet and subsequently to the GI2 diet as tolerated (see Table next page).

GVHD of the upper intestine or stomach may present only as anorexia, nausea, and early satiety. High-fat foods are generally poorly tolerated. Empiric lactose restriction should be considered. Patients may find it easier to meet energy and protein needs with nutritional supplements sipped continuously throughout the day.

Gastrointestinal GVHD Diet Progression*

Phase	Symptoms	Diet	Diet Intolerance
1. Bowel rest	GI cramping Large volume watery diarrhea Depressed serum albumin Severely reduced transit time Small bowel obstruction or diminished bowel sounds Nausea and vomiting	Oral: NPO IV: stress energy and protein Requirements	
2. Introduction of oral feeding	Minimal GI cramping Diarrhea less than 500 ml/day Guaiac-negative stools Improved transit time (minimum 1.5 hours) Infrequent nausea and vomiting	Oral: isosmotic, low-residue, low-lactose beverages, initially 60 ml every 2-3 hours, for several days IV: as for Phase 1	Increased stool volume or diarrhea Increased emesis Increased abdominal Cramping
3. Introduction of solids	Minimal or no GI cramping Formed stool	Oral: allow introduction of solid food, once every 3-4 hours: minimal lactose[a], low fiber, low fat (20-40 gm/day)[b], low total acidity, no gastric irritants IV: as for Phase 1	As in Phase 2
4. Expansion of diet	Minimal or no GI cramping Formed stool	Oral: minimal lactose[a], low fiber, low total acidity, no gastric irritants; if stools indicate fat malabsorption: low fat[b] IV: as needed to meet nutritional requirements	As in Phase 2
5. Resumption of regular diet	No GI cramping Normal stool Normal transit time Normal albumin	Oral: progress to regular diet by introducing one restricted food per day: acid foods with meals, fiber-containing foods, lactose-containing foods. Order of addition will vary, depending on individual tolerances and preferences. Patients no longer exhibiting steatorrhea should have the fat restriction liberalized slowly IV: discontinue when oral nutritional intake meets estimated needs	As in Phase 2

[a]Lactose is one of the last disaccharidases to return following villous atrophy. A commercially-prepared lactose solution (Lactaid[R]) is used to reduce the lactose content of milk by >90%. Lactaid[R] milk (100% lactose-free) is also commercially available.

[b] Additional calories may be provided by commercially available medium chain triglycerides which do not exacerbate symptoms.

*Adapted from Darbinian J, Schubert MM. Special management problems. In: Lenssen P, Aker SN, eds. N*utritional Assessment and Management During Marrow Transplantation. A Resource Manual.* Seattle, WA: Fred Hutchinson Cancer Research Center; 1985;63-80.

XXII. NATUROPATHIC REMEDIES: HERBAL AND NUTRIENT SUPPLEMENT PREPARATIONS

- **Allogeneic transplant patients:**
  Herbal/botanical preparations should not be given during immunosuppressive therapy or in patients with chronic GVHD. One month after discontinuation of all systemic immunosuppressive treatment and resolution of manifestations of chronic GVHD, herbal/botanical preparation may be given at the discretion of the primary physician.

- **Autologous transplant patients:**
  Herbal/botanical preparations should not be given until complete recovery of any gastrointestinal toxicity and until prednisone therapy has been discontinued for one month.

Further information regarding guidelines for the use of herbal and nutrient supplement preparations can be found at *www.seattlecca.org* under *patientsandfamilies/nuritionDietsguidelines, Guidelines for herbal & nutrient supplements during hematopoietic stem cell transplantation and high-dose chemotherapy*.

XXIII. RETURN TO SEATTLE FOR LONG-TERM FOLLOW-UP EVALUATION

All adults who have had an allogeneic transplant and all children who have had either an allogeneic or autologous transplant should return to the FHCRC/SCCA for a comprehensive evaluation at one year after the transplant. Depending on clinical indications, follow-up evaluations at subsequent intervals may be arranged. Children should return for subsequent evaluations at 2, 3, 5, 10, 15, and 20 years after the transplant. These evaluations focus on hematologic and immunologic function, assessment of the original disease, and thorough screening for any late transplant complications. The LTFU evaluation requires four to five working days to complete. A detailed summary of findings and recommendations will be forwarded to the referring physician. Appointments must be scheduled at least 4 months in advance by calling the LTFU office assistant at (206) 667-4415 or by sending a FAX to 1-800-376-8197 (toll-free, USA and Canada).

TYPE OF TRANSPLANT	TIME TO RETURN FOR COMPREHENSIVE EVALUATION	
Allogeneic (ADULT)	One year after the transplant	Follow-up evaluations at other times per protocol or as clinically indicated
Autologous (ADULT)	One year after the transplant based on protocol, patient or physician request	
Allogeneic & Autologous (PEDIATRIC)	One year, 2, 3, 5, 10, 15, and 20 years after the transplant	

XXIV. HOW TO SEND SPECIMENS FOR TESTING AT FHCRC / SCCA

Clinical laboratory testing for patients who received treatment at Fred Hutchinson Cancer Research Center / Seattle Cancer Care Alliance (FHCRC / SCCA) is available at the FHCRC/SCCA. The tests most often performed in our laboratories at the request of referring physicians include BCR/abl transcripts by polymerase chain reaction (PCR), CMV PCR, CMV antigenemia, and chimerism studies by assessment of variable number tandem repeat polymorphisms.

We ask that you notify the LTFU office by telephone at (206) 667-4415 or by FAX (Appendix A) to indicate the expected date and time of arrival for specimens that are sent for testing at the FHCRC / SCCA. The LTFU office will provide detailed instructions regarding sample collection and shipment information for the specific test(s) requested.

If surgery or biopsy is planned for evaluation of suspected secondary malignancy or recurrence of disease, please contact our LTFU office before the procedure, whenever possible.

<u>Guidelines for Sending Clinical Specimens</u>

1. Call the LTFU office at (206) 667-4415 before sending the specimen (Appendix A).
2. Do not send fresh / frozen samples to arrive on Fridays, weekends or government holidays.
3. Ship the specimen via an overnight courier service on the day the samples were obtained.
4. Label each tube with
    - Patient's name
    - Patient's social security number (if not available, date of birth)
    - Date that the sample was obtained
    - Type of specimen (i.e., peripheral blood, bone marrow, serum, left breast mass, etc.)
5. Please complete *Test Request Forms* that will be faxed to you by our office
6. SAMPLE(S) MUST BE ACCOMPANIED BY THE *SCCA TEST REQUEST FORM*S
7. Shipment charges are the responsibility of the patient or the facility sending the sample.

A study coordinator will forward shipment instructions to patients who are enrolled in specific protocols that require samples to be sent to the FHCRC / SCCA for research studies.

XXV. REFERENCES

Chronic GVHD

1. Sullivan KM. Graft vs. Host Disease. In: Blume KG, Forman SJ, Appelbaum FR eds. *Thomas' Hematopoietic Cell Transplantation, 3rd Edition*. Blackwell Publishing; **2004**; 635-664.
2. Lee SJ, Vogelsang G, Flowers MED. Chronic graft-versus-host disease. *Biol Blood Marrow Transplant* **2003**; **9**: 215-233.
3. Flowers MED, Parker PM, Johnston LJ, et al. Comparison of chronic graft-versus-host disease after transplantation of peripheral blood stem cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomized trial. *Blood* **2002**; 100:415-419.
4. Filipovich AH, Weisdorf D, Pavletic S, et al: NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GraftVersus-Host Disease: I. Diagnosis and Staging Working Group Report: *Biol Blood Marrow Transplant* **2005**; 11: 945-955.
5. Shulman HM, Sullivan KM, Weiden PL, et al. Chronic Graft vs. Host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. *Am. J. Med.* **1980**; 69:204-217.
6. Stewart BL, Storer B, Storek J, et al. Duration of immunosuppressive treatment for chronic graft-versus-host disease. *Blood* **2004**; 104:3501-3506.

IV Immunoglobulin:

1. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. *N Engl J Med*. **1988**;319(14):902-7.
2. The National Institute of Child Health and Human Developments Intravenous Immunoglobulin Study Group. Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. *N Engl J Med*. **1991**;325(2):73-80.
3. Magny JF, Bremard-Oury C, Brault D, et al. Intravenous immunoglobulin therapy for prevention of infection in high-risk premature infants: report of a multicenter, double-blind study. *Pediatrics*. **1991**;88(3):437-43.
4. Winston DJ, Antin JH, Wolff SN, et al. A multicenter, randomized, double-blind comparison of different doses of intravenous immunoglobulin for prevention of graft-versus-host disease and infection after allogeneic bone marrow transplantation. *Bone Marrow Transplant*. **2001**;28(2):187-96.
5. Cordonnier C, Chevret S, Legrand M, et al. Should immunoglobulin therapy be used in allogeneic stem-cell transplantation? A randomized, double-blind, dose effect, placebo-controlled, multicenter trial. *Ann Intern Med.* **2003**;139(1):8-18.
6. Sokos DR, Berger M.and Lazarus HM. Intravenous immunoglobulin: appropriate indications and uses in hematopoietic stem cell transplantation [Review]. *Biol. Blood and Marrow Transplantation*. **2002**.8(3):117-30.
7 Sullivan, KM, Kopecky, KJ, Jocom, J, et al. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. *N.Engl.J.Med*. 323:705-712, **1990**.
8. Sullivan, KM, Storek, J, Kopecky, KJ, et al. A controlled trial of long-term administration of intravenous immunoglobulin to prevent late infection and chronic graft-vs.-host disease after marrow transplantation: clinical outcome and effect on subsequent immune recovery. *Biol. Blood and Marrow Transplantation* 2: 44-53, **1996**.

Hyperlipidemia:

References:

1. Chow et al, Ann Intern Med, 2011 in press
2. Majhail NS et al, High prevalence of metabolic syndrome after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 2009;43:49-54.
3. **http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm**
4. Wang B, Cao LX, Liu HL, et al. Myocardial infarction following allogeneic bone marrow transplantation. Bone Marrow Transplant. 1996; 18: 479-480.
5. O'Rourke B, Barbir M, Mitchell AG. Efficacy and safety of fluvastatin therapy for hypercholesterolemia after heart transplantation. Results of a randomized double blind placebo controlled study. Int. J. Cardiology. 2004; 94: 235-240.
6. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after cardiac transplantation. N Engl J Med. 1995; 333: 621-627.

Hyperlipidemia References: (continued)

7. Wenke K, Meiser B, Thiery J, et al. Simvastatin initiated early after heart transplantation: 8-year prospective experience. Cirulation. 2003; 107: 93-97.
8. Holdaas H, Fellstrom B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicenter, randomized, placebo-controlled trial. Lancet. 2003; 361: 2024-2031.
9. Cosio F, Pesavento TE, Pelletier RP, et al. Patient survival after renal transplantation III: the effects of statins. AM J Kidney Dis. 2002; 40: 638-643.
10. Del Castillo D, Cruzado JM, Diaz MJ, et al. The effects of hyperlipidemia on graft and patient outcome in renal transplantation. Nephrol Dial Transplant. 2004; 19; Suppl 3: 67-71.
11. Chin C, Gamberg P, Miller J, et al. Efficacy and safety of atrovastatin after pediatric heart transplantation. J Heart Transplant. 2002; 21: 1213-1217.
12. Mahle WT, Vinvent N, Berg AM. Pravastatin therapy is associated with reduction in coronary allograft vasculopathy in pediatric heart transplantation. J. Heart Lung Transplant. 2005; 24: 63-66.
13. Argent E, Kainer G, Aitken M, et al. Atorvastatin treatment for hyperlipidemia in pediatric renal transplant recipients. Pediatr Transplantation. 2003; 7: 38-42.
14. Borghi C, Dormi A, Veronesi M, et al. Association between different lipid-lowering treatment strategies and blood pressure control in the Brisighella Heart Study. Am Heart J. 2004; 148: 285-292.
15. Tsira S, Elisaf M, Mikhailidis DP. Early vascular benefits of statin therapy. Curr Med Res Opin. 2003; 19: 540-556.
16. Mach F. Statins as immunomodulatory agents. Circulation. 2004; 109 (21 Suppl 1): II, 15-17.
17. Fehr T, Kahlert C, Fierz W, et al. Statin-induced immunomodulatory effects on human T cells in vivo. Atherosclerosis. 2004; 175: 83-90.
18. Prasad GV, Chiu R, Nash MM, et al. Statin use and bone mineral density in renal transplant recipients. Am J Transplant. 2003;3:1320-1321.
19. Pritchett JW. Statin use decreases the risk of osteonecrosis in patients receiving steroids. Clin Orthop. 2001; 386: 173-178.
20. Wang GJ, Cui Q, Balian G. The pathogenesis and prevention of steroid-induced osteonecrosis

Hypertension

1. Chow et al, Ann Intern Med, 2011 in press
2. Majhail NS et al, High prevalence of metabolic syndrome after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 2009;43:49-54.
3. http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf

Liver:

1. Strasser SI, McDonald GB. Hepatitis Viruses and Hematopoietic Cell Transplantation: A Guide to Patient and Donor Management. *Blood* **93**: 1127-1136, 1999.
2. Murakami CS, Louie W, Chan GS, et al. Biliary obstruction in hematopoietic cell transplant recipients: An uncommon diagnosis with specific causes. *Bone Marrow Transplantation* 23: 921-927, **1999**.
3. Strasser SI, Sullivan KM, Myerson D, et al. Cirrhosis of the liver in long-term marrow transplant survivors. *Blood* 93: 3259 – 3266, **1999**.
4. Strasser SI, Myerson D, Spurgeon CL, et al. Hepatitis C virus infection after bone marrow transplantation: A cohort study with 10 year follow-up. *Hepatology* 29: 1893 – 1899, **1999**.
5. Strasser SI, Shulman HM, McDonald GB. Cholestasis after hematopoietic cell transplantation. *Clinics in Liver Disease* 3: 651 – 668, **1999**.
6. Strasser SI, Shulman HM, Flowers MED, et al. Chronic graft-vs-host disease of the liver: Presentation as an acute hepatitis. *Hepatology* 32: 1265 – 1271, **2000**.
7. Strasser SI, McDonald GB. Chapter 56, Gastrointestinal and hepatic complications, in *Hematopoietic Cell Transplantation, Second Edition*, edited by Thomas ED, Blume KG, Forman SJ. Cambridge, MA., Blackwell Scientific Publications, **1999**, pp.627 – 658.
8. Strasser SI, McDonald GB. Chapter 67, Hepatobiliary complications of hematopoietic cell transplantation, in *Schiff's Diseases of the Liver, Ninth Edition*, edited by Schiff ER, Sorrell MF, Maddrey WC. Philadelphia, PA., J.B. Lippincott Company, **2002.**
9. McDonald GB. Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. Hepatology 51: 1450 – 1460, 2010.
10. Hockenbery DM, Strasser SI, McDonald GB. Chapter 96, Gastrointestinal and hepatic complications, in Thomas' Hematopoietic Cell Transplantation, Fifth Edition, edited by Appelbaum FR, Forman SJ, Negrin RS, Antin JH. Oxford, UK, Wiley-Blackwell Publishing, in press.
11. Kida A, McDonald GB. Gastrointestinal, hepatobiliary, pancreatic, and iron-related diseases in long term survivors of allogeneic hematopoietic cell transplantation. Seminars in Hematology 49:43-58, 2012).

12. AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES (AASLD) AND Infectious Diseases Society of America (IDSA) Recommendations for Testing, Managing, and Treating Hepatitis C. **http://hcvguidelines.org** Accessed on February 20, 2014.

Other Complications, Bone Complications:

1. McClune, Navneet S Majhail, and Mary E.D. Flowers Bone Loss and Avascular Necrosis of Bone After Hematopoietic Cell Transplantation. Semin Hematol 49:59-65, January 2012

APPENDIX A

FAX LTFU CONSULT

Date: _____

To: FRED HUTCHINSON CANCER RESEARCH CENTER From: _____
Long Term Follow Up
Fax: 1-800-376-8197 (toll-free, USA & Canada) Fax: _____

Phone: (206) 667-4415 Phone: _____

Patient name: _____ Date of birth: _____

Current GVHD Treatments (check all the apply):

- ❒ Corticosteroids: ❒daily ❒alternate day (dose: _____)
- ❒ Cyclosporine (Neoral, Sandimmune) (or equivalents)
- ❒ Tacrolimus (FK506)
- ❒ Mycophenolate Mofetil (MMF) (Cellcept)
- ❒ Thalidomide (Thalomid)
- ❒ Rapamycin (Sirolimus)
- ❒ Rituximab
- ❒ Extracorporeal photopheresis (ECP)
- ❒ Other:
- ❒ No immunosuppressive medications

- ❒ Trimethoprim-sulfamethoxazole
- ❒ Penicillin
- ❒ Dapsone
- ❒ Acyclovir or valacyclovir
- ❒ Ganciclovir, ValGANCiclovir
- ❒ Fluconazole or itraconazole

Current problems(s):

What questions would you like the consultant to address?

Laboratory and other reports are being sent with this FAX: ❒ YES ❒ NO

Reply to (if other than sender listed above): _____

Fax (____) _____ Phone (_____) _____

APPENDIX B

FAX **LTFU ALERT**

Date: _____

To: FRED HUTCHINSON CANCER RESEARCH CENTER From: _____
Long Term Follow Up
Fax: 1-800-376-8197 (toll-free, USA & Canada) Fax: _____

Phone: (206) 667-4415 Phone: _____

Patient name: _____ Date of birth: _____

❑ This **patient expired** on _____/_____/_____ due to _____.

❑ This patient was **newly diagnosed with clinical extensive chronic GVHD.**
(Please send copies of any records regarding this diagnosis.)
❑ Check here if you would like a consultation regarding the management of GVHD in this case.

❑ This patient has now **started immunosuppressive therapy.**

❑ This patient has now **stopped all immunosuppressive therapy.**

❑ The **immunosuppressive therapy for this patient has been changed.**

❑ The **original disease (see above) has recurred.**

❑ This patient was **diagnosed with a secondary malignancy** of (primary site)_____.

❑ **Surgery or biopsy has been planned** for evaluation of suspected secondary malignancy.
(We are interested in obtaining fresh tissue specimens.)

❑ This patient has been **diagnosed with myelodysplasia.**

❑ This **patient's name and/or address has changed** to:

❑ This **patient is now being seen by** (practitioner, address, phone number):

❑ This **office has moved/ changed it's phone number** to:

❑ This **patient requests discontinuation of further contact from the FHCRC** due to
(reason, if stated):

Reply to (if other than sender listed above): _____

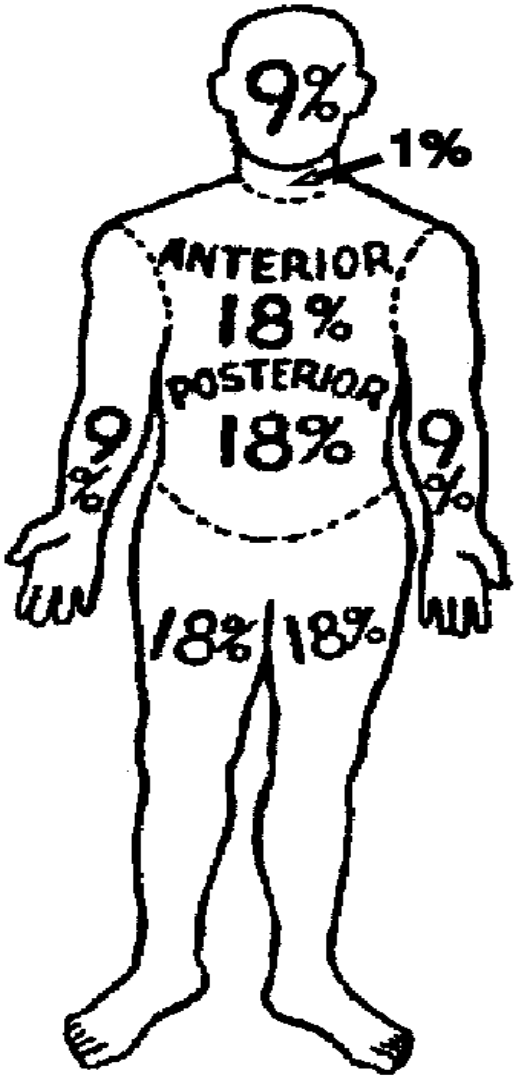
Fax (_____) _____ Phone (_____) _____

APPENDIX C

FORM FOR DESCRIPTION OF SKIN INVOLVEMENT

NAME:	Date of Birth:

DATE OF ASSESSMENT:_____



Region		% Area Involved		Region		% Area Involved
Head	(9%)			Right leg	(8%)	
Neck	(1%)			Right foot	(1%)	
Chest	(9%)			Left arm	(4%)	
Abdomen	(9%)			Left forearm	(4%)	
Back	(18%)			Left hand	(1%)	
Right arm	(4%)			Left thigh	(8%)	
Right forearm	(4%)			Left leg	(8%)	
Right hand	(1%)			Left foot	(1%)	
Right thigh	(8%)					

APPENDIX –D

Please Complete and FAX or Email this Form to the LTFU Office (800) 376-8197 or LTFU@seattlecca.org

CHRONIC GRAFT-VERSUS-HOST DISEASE (GVHD) ASSESSMENT AND SCORING FORM

Name:_____ **Date of birth:**_____ **Assessment date:**_____

	SCORE 0	**SCORE 1**	**SCORE 2**	**SCORE 3**
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐ Rodnan score: ☐	☐ No Symptoms/ Manifestation	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH *Diagnostic/Distinctive features* ☐ Present ☐ Absent	☐ No symptoms	☐ Mild symptoms with disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT **Lower GI Tract symptoms present**: ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Symptoms such as nausea, vomiting,anorexia,dysphagia, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation

☐ *Abnormality present but NOT thought to represent GVHD*

☐ *Abnormality thought to represent GVHD PLUS other causes* **List other causes:**_____

Please Complete and FAX or Email this Form to the LTFU Office (800) 376-8197 or LTFU@seattlecca.org

Name:

(continued) **CHRONIC GRAFT-VERSUS-HOST DISEASE (GVHD) ASSESSMENT AND SCORING FORM**

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN
LUNGS ‡ ☐ PFTs not done **FEV1** ☐ **DLCO** ☐	☐ No symptoms ☐ FEV1 > 80% **OR** LFS=2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) ☐ FEV1 60-79% **OR** LFS 3-5	☐ Moderate symptoms (shortness of breath after walking on flat ground) ☐ FEV1 40-59% **OR** LFS 6-9	☐ Severe symptoms (shortness of breath at rest; requiring 0_2) ☐ FEV1 ≤39% **OR** LFS 10-12
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT *Diagnostic/ Distinctive features* ☐ Present ☐ Absent ☐ Not examined	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

☐ *Abnormality present but NOT thought to represent GVHD*

☐ *Abnormality thought to represent GVHD PLUS other causes* **List other causes:**_____

Other indicators, clinical manifestations or complications related to chronic GVHD (check all that apply):

☐ Weight loss ☐ Bronchiolitis obliterans ☐ Bronchiolitis obliterans with organizing pneumonia

☐ Esophageal stricture or web ☐ Pericardial Effusion ☐ Pleural Effusion(s) ☐ Ascites (serositis)

☐ Nephrotic syndrome ☐ Peripheral Neuropathy ☐ Myasthenia Gravis ☐ Polymyositis

☐ Malabsorption ☐ Cardiac conduction defects ☐ Coronary artery involvement ☐ Cardiomyopathy

☐ Eosinophilia >500/microliter ☐ Other: _____ ☐ **None**

Biopsy obtained: ☐ **Yes** ☐ **No** **Organ system(s) biopsied:**_____ **GVHD confirmed by histology:** ☐ **Yes** ☐ **No**

OVERALL severity of GVHD: ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Change from previous evaluation: ☐ **No prior or current GVHD** ☐ **Improved** ☐ **Stable** ☐ **Worse** ☐ **N/A (baseline)**

Completed by:_____ **Date form completed:**_____

‡ **Pulmonary scoring** should be performed using both the symptom and pulmonary function testing (PFT) scale whenever possible. When discrepancy exists between pulmonary symptom or PFT scores the higher value should be used for final scoring. Scoring using the Lung Function Score (LFS) is preferred, but if DLCO (carbon monoxide diffusion capacity corrected for hemoglobin) is not available, grading using FEV1 (forced expiratory volume) should be used. The LFS is a global assessment of lung function after the diagnosis of bronchiolitis obliterans has already been established.[28] The percent predicted FEV1 and DLCO (adjusted for hematocrit but not alveolar volume) should be converted to a numeric score as follows: > 80% = 1; 70-79% = 2; 60-69% = 3; 50-59% = 4; 40-49% = 5; < 40% = 6. The LFS = FEV1 score + DLCO score, with a possible range of 2-12. Abbreviations: ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphatase); ALT (alanine aminotransferase); AST (aspartate aminotransferase); ULN (upper limit of normal); LFS (Lung Function Score); N/A (not applicable).

APPENDIX E

ASSESSMENT OF SKIN THICKNESS
Modified Rodnan Score*

Patient Name: _____Date of Birth: _____

Calculate skin score by summing the scores from all evaluated anatomic areas.

A. Evaluate skin thickness by clinical palpation:

0 = normal skin thickness
1 = mildly increased skin thickness
2 = moderately increased skin thickness
3 = severely increased skin thickness (inability to pinch skin into a fold)

B. Surface of anatomic areas evaluated (N = 17)

Area of Body		**Dates:**					
		Range	**Score**	**Score**	**Score**	**Score**	**Score**
Face		0-3					
Anterior chest		0-3					
Abdomen		0-3					
Fingers	R	0-3					
	L	0-3					
Dorsum of hands	R	0-3					
	L	0-3					
Forearms	R	0-3					
	L	0-3					
Upper arms	R	0-3					
	L	0-3					
Thighs	R	0-3					
	L	0-3					
Lower legs	R	0-3					
	L	0-3					
Dorsum of feet	R	0-3					
	L	0-3					
TOTAL		0-51					

"Skin Thickness Score in Systemic Sclerosis: An Assessment of Inter-observer Variability in 3 Independent Studies," Clements et al, The Journal of Rheumatology 1993, 20:11, 1892-1896

APPENDIX F

Name_____ **DOB**___/___/___ **Date**___/___/___

Circle the number that best matches how flexible you are in each of these positions

Flexibility

Mininum **Maximum**

Shoulder

1 2 3 4 5 6 7

Elbow

1 2 3 4 5 6 7

Wrist and fingers

1 2 3 4 5 6 7

Foot Dorsiflexion

1 2 3 4