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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.

Contributions to these updated guidelines were made by Mary E. D. Flowers, M.D.; George McDonald, M.D.; Paul Carpenter, M.D.; Michael Boeckh, M.D.; Joachim Deeg, M.D.; Guang-Shing Cheng, MD; Jean Stern, M.S.R.D.; Leona Holmberg, M.D., P.H.D.; and Paul J. Martin, M.D.
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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) 606-7600 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/lfu 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.
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. PCR is the standard assay for CMV surveillance.

Initial CMV Monitoring

CMV seropositive recipients of non-cord blood 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/seropositive non-cord blood allogeneic or seronegative unmodified autologous transplant recipients should be monitored weekly until day 60 after transplant.

After day 100 to one year post transplant, CMV monitoring

CMV blood testing should be continued, initially weekly, until 1 year after transplant for allogeneic recipients at risk of late CMV disease which include:

- Patients treated for CMV viremia in the first 100 days after transplantation
- Cord blood transplant recipients who were CMV seropositive
- Patients who received Letemovir prophylaxis beyond day +60 after transplant
- For non-malignant patients except Sickle cell and Thalassemia that received either Anti-Human Thymocyte Globulin or Campath in transplant conditioning or for GVHD should have weekly CMV blood testing for at least 6 months after the last serotherapy dose or until absolute CD4 count is > 200 cells/microliters, whichever is later
- All other patients who received Anti-Human Thymocyte Globulin in conditioning or for GVHD should have weekly CMV blood testing for at least 6 months after the last dose of ATG or absolute lymphocyte count >300 cells/microliters, whichever is later (see Section I)
- Patients treated with ≥ 0.5 mg/kg/day prednisone or prednisone equivalent or other agents (e.g., MMF, ibrutinib, etc.) for either late acute or chronic GVHD.

Changes in initial surveillance frequency > 100 days after transplant and before one year post transplant for NON-CORD BLOOD transplant patients:

The weekly frequency of CMV blood surveillance after day 100 posttransplant may be changed for non-cord blood transplant ONLY as follows:

- Non-Cord Blood patients can be changed to every other week surveillance if on < 0.5 mg/kg/day prednisone or prednisone equivalent and on stable doses or tapering doses of other immunosuppressive agents AND have had three consecutive negative surveillance tests (PCR for CMV DNA)
• Surveillance may be stopped entirely after 2 additional negative tests if tapering of immunosuppression continues.
• Resume weekly CMV surveillance testing if treatment with immunosuppression is increased or re-initiated for GVHD.

**CMV monitoring after one year post transplant**
CMV monitoring as clinically indicated based on history of prolonged CMV prophylaxis, repeated episodes of CMV reactivation, or ongoing active GVHD requiring systemic immunosuppressive therapy.

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

• For non-malignant patients except sickle cell and Thalassemia that received either Anti-Human Thymocyte Globulin or Campath in transplant conditioning or for GVHD should have weekly blood monitoring by PCR for EBV, adenovirus, and CMV for at least 6 months after the last serotherapy dose or until absolute CD4 count is > 200 cells/microliters, whichever is later.

• All other patients who received Anti-Human Thymocyte Globulin in conditioning or for GVHD should have weekly blood monitoring by PCR for EBV, adenovirus, and CMV for at least 6 months after last dose of ATG or absolute lymphocyte count > 300 cells/microliter, whichever is later.

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 ≥ 20 kg: 1 single strength tablet p.o. b.i.d. on 2 consecutive days weekly
- Children < 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. For patients who cannot tolerate Bactrim or dapsone, atovaquone or pentamidine IV may be given.

Atovaquone:

Dosing

Adults and pediatric patients > 50 kg:
1500 mg oral suspension, once daily, to be taken with a meal.

Pediatric patients less than or equal to 50 kg:
30 mg/kg, once daily, to be taken with a meal.

Pentamidine

Dosing

Pediatric:

Children < 24 months:
4 mg/kg/dose (max 300 mg) IV over 90 minutes every two weeks.
Children ≥ 2 years:
4 mg/kg/dose (max 300 mg) IV over 90 minutes every four weeks.

Adult:
300 mg IV over 90 minutes, every four weeks.
B. Varicella-zoster virus

All VZV-seropositive patients (via vaccine or via disease) should receive prophylaxis with acyclovir or valacyclovir throughout the first year after the transplant or until 8 months after systemic immunosuppression ends, whichever is longer.

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

- Weight ≥ 40 kg, receiving < 0.5 mg/kg/day of corticosteroids: 800 mg P.O. B.I.D.*
- Weight < 40 kg, receiving < 0.5 mg/kg/day of corticosteroids: 600 mg/m² P.O. B.I.D.

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

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

*Note: In VZV seropositive/HSV seronegative, patients ≥ 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/m² (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 ≥ 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/m² 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 valacyclovir 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 as they are functionally asplenic*. 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
Encapsulated bacteria (continued)

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:

<table>
<thead>
<tr>
<th>Group</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and Children ($\geq 60$ kg)</td>
<td>500 mg PO BID</td>
</tr>
<tr>
<td>Adults ($&lt; 60$ kg) and Children ($&gt; 3$ years and $&lt; 60$ kg)</td>
<td>250 mg PO BID</td>
</tr>
<tr>
<td>Children ($&lt; 3$ years)</td>
<td>125 mg PO BID</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>HCT recipients with chronic GVHD</th>
<th>Until 6 months after immunosuppression d/c’d OR until age 6 OR 2 years after splenectomy (whichever occurs later)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All HCT recipients without chronic GVHD (allo, auto, syngenic)</td>
<td>1 year after BMT OR until age 6 OR 2 years after splenectomy (whichever occurs later)</td>
</tr>
</tbody>
</table>

**Table - Duration of prophylaxis for encapsualted organism in asplenic patients according to chronic GVHD**

**Note:**

Sickle Cell: All Sickle cell patients should receive prophylactic penicillin daily for two years post transplant or until their tenth birthday, whichever is longer. The dose is 125 mg PO BID for patients ≤ 3 years old and 250 mg PO BID for patients > 3 years.

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  
  OR 
  Levofoxacin 750 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

Patients with splenectomy post transplant

Also see Vaccination Section IX
D. Cytomegalovirus (CMV)
(See Section III, subsections H. and I for CMV monitoring frequency).

1. Table 1. Threshold CMV Viral Load for Preemptive Therapy

<table>
<thead>
<tr>
<th>PATIENT POPULATION</th>
<th>Post Transplant</th>
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<tbody>
<tr>
<td></td>
<td>DAY 0-60</td>
</tr>
<tr>
<td>Unmodified autologous, &lt; 1 mg/kg steroids</td>
<td>≥ 150 IU/mL (2.18 log10)</td>
</tr>
<tr>
<td>CMV seropositive CD34-selected autologous recipients</td>
<td>≥ 50 IU/mL (1.70 log10)</td>
</tr>
<tr>
<td>All transplants that do not meet above criteria</td>
<td>≥ 500 IU/mL (2.70 log10)</td>
</tr>
</tbody>
</table>

^a If protocol requires testing beyond day 100 ≥ 500 IU/mL (2.70 log 10)
^b Or rising DNA levels >5x baseline within 1 month
2. Preemptive Therapy

Table 2. Pre-emptive Induction Treatment Regimen for CMV Reactivation with Adequate Renal Function After Transplant

*Acyclovir/valACYclovir prophylaxis should be discontinued when pre-emptive treatment for CMV is started and resumed after anti-CMV therapy is completed.*

<table>
<thead>
<tr>
<th>INDUCTION</th>
<th>Preferred</th>
<th>Alternative</th>
</tr>
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<tbody>
<tr>
<td>ValGANCiclovir*** (ONLY for patients with good oral intake, no active gut GVHD, no significant liver disease and no severe diarrhea):</td>
<td>Foscarnet**&lt;br&gt;90 mg/kg&lt;br&gt;IV Q 12hrs</td>
<td></td>
</tr>
<tr>
<td>Adults and Peds ≥ 50 kg:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>900 mg PO Q 12 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peds ≥ 40 to &lt;50kg:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>675 mg PO Q 12 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peds ≥ 30 to &lt;40kg:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>450 mg PO Q 12 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peds ≥20 to &lt;30 kg:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>450 mg PO Q 12 hrs <strong>or</strong>&lt;br&gt;Liquid 14 mg/kg Q 12 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peds ≥ 15 to &lt;20 kg:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>225 mg PO Q12 hrs (= ½ pill) <strong>or</strong>&lt;br&gt;Liquid 14 mg/kg Q12 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peds ≥10 to &lt; 15 kg:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liquid 14 mg/kg Q12 hrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR

Ganciclovir**<br>5 mg/kg IV Q 12hrs

Duration of Induction:
- If CMV DNA levels are not declining at day 7 in non-cord blood patients treatment, continue twice daily induction dosing until levels start declining (minimum one additional week). If subsequent levels are declining or in case of moderate increases (i.e. < 2 times baseline), proceed to maintenance dose, EXCEPT in cord blood recipients.
- In cord blood recipients on induction therapy, if CMV PCR levels do not decline and are not negative by the 3rd subsequent test, continue induction dosing (twice daily) for at least one additional week.
- All patients failing induction should be considered to switch therapy and do UL97/UL54 resistance testing

* ValGANCiclovir absorption 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.

**Use actual weight unless actual weight is above 150% of ideal weight. For patients who are > 150% ideal body weight, the weight used should be capped at 150% of ideal body weight.
### Table 3: Preemptive Maintenance Treatment Regimen for CMV Reactivation with Adequate Renal Function After Transplant

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>ValGANCiclovir*,** (ONLY for patients with good oral intake, no active gut GVHD, no significant liver disease and no severe diarrhea):</td>
<td>Foscarnet**</td>
</tr>
<tr>
<td>Adults and peds ≥ 50 kg: 900 mg PO Q Day</td>
<td>90 mg/kg IV Q DAY</td>
</tr>
<tr>
<td>Peds ≥ 40 to &lt; 50 kg: 675 mg PO Q Day</td>
<td></td>
</tr>
<tr>
<td>Peds ≥ 30 to &lt; 40 kg: 450 mg PO Q Day</td>
<td></td>
</tr>
<tr>
<td>Peds ≥ 20 to &lt; 30 kg: 450 mg PO Q Day or Liquid 14 mg/kg QD</td>
<td></td>
</tr>
<tr>
<td>Peds ≥ 15 to &lt; 20 kg: 225 mg PO QD (= ½ pill) or Liquid 14 mg/kg QD</td>
<td></td>
</tr>
<tr>
<td>Peds ≥ 10 to &lt; 15 kg: Liquid 14 mg/kg QD</td>
<td></td>
</tr>
</tbody>
</table>

**OR**

Ganciclovir**

5 mg/kg IV Q DAY

**Duration of Maintenance therapy:**
- 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 (at least one week induction). Shorter courses may be appropriate for subsequent episodes of CMV reactivation. Please consult the LTFU office for questions (206-667-4415)

* ValGANCiclovir absorption 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.

**Use actual weight unless actual weight is above 150% of ideal weight. For patients who are > 150% ideal body weight, the weight used should be capped at 150% of ideal body weight.

**Note:** Any questions on maintenance therapy, including drug resistance, Contact the LTFU office (Appendix A).
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 ValGANCiclovir or ganciclovir.
- Daily CBC is mandatory if the absolute neutrophil count (ANC) is <1,500/mm$^3$.
- If ANC <1,000/mm$^3$ before ValGANCiclovir or ganciclovir is started, alternative therapy is foscarnet.
- Renal function tests must be measured at least weekly.

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

3. 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

<table>
<thead>
<tr>
<th>DOSING</th>
<th>PREFERRED</th>
<th>ALTERNATIVE</th>
<th>MONITORING BLOOD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Able to tolerate PO</td>
<td>Unable to tolerate PO</td>
<td>Weekly:</td>
</tr>
<tr>
<td></td>
<td>900 mg PO QD</td>
<td>Ganciclovir 5 mg/kg IV Q DAY</td>
<td>CMV PCR,</td>
</tr>
<tr>
<td>Adult or Pediatric ≥50 kg</td>
<td>ValGANCiclovir†</td>
<td>Valacyclovir* 2 grams PO TID</td>
<td>Creatinine,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CBC with</td>
</tr>
<tr>
<td></td>
<td>675 mg PO QD (=1½ pills)</td>
<td></td>
<td>Differential.</td>
</tr>
<tr>
<td>Pediatric ≥40 to &lt;50 kg</td>
<td>ValGANCiclovir†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>450 mg PO QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric ≥30 to &lt;40 kg</td>
<td>ValGANCiclovir†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>450 mg PO QD</td>
<td>Valacyclovir* 2 grams PO TID</td>
<td></td>
</tr>
<tr>
<td>Pediatric ≥20 to &lt;30 kg</td>
<td>ValGANCiclovir†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>225 mg PO QD (=½ pill)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric ≥15 to &lt;20 kg</td>
<td>ValGANCiclovir†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 mg/kg QD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric ≥10 to &lt;15 kg</td>
<td>ValGANCiclovir†</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liquid 14 mg/kg QD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† 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.

# Use actual weight unless actual weight is above 150% of ideal weight. For patients who are >150% ideal body weight, the weight used should be capped at 150% of ideal body weight.
### Table 4: CMV Prophylaxis and Monitoring after Day 100 for CMV-seropositive Cord Blood Recipients without Prior Posttransplant CMV Reactivation

<table>
<thead>
<tr>
<th>DOSING</th>
<th>PREFERRED</th>
<th>ALTERNATIVE</th>
<th>MONITORING BLOOD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Able to tolerate PO intake</td>
<td>Unable to tolerate PO intake</td>
<td>Weekly: CMV by PCR, Creatinine and CBC with Differential</td>
</tr>
<tr>
<td>Adult or Pediatric ≥50 kg</td>
<td>Valacyclovir* 2 grams PO TID</td>
<td>Acyclovir† 500 mg/m² IV Q 8 hr</td>
<td>Ganciclovir§ 5 mg/kg IV Q DAY</td>
</tr>
<tr>
<td>Pediatric ≥40 to &lt;50 kg</td>
<td>Valacyclovir* 2 grams PO TID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric ≥30 to &lt;40 kg</td>
<td>Valacyclovir* 1 gram PO TID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric ≥20 to &lt;30 kg</td>
<td>Valacyclovir* 1 gram PO TID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric ≥15 to &lt;20 kg</td>
<td>Acyclovir 600 mg/m² PO QID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric ≥10 to &lt;15 kg</td>
<td>Acyclovir 600 mg/m² PO QID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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.

§ Use actual weight unless actual weight is above 150% of ideal weight. For patients who are > 150% ideal body weight, the weight used should be capped at 150% of ideal body weight.

**Dose adjustment and other precautions during treatment:**
- STOP ganciclovir or ValGANCiclovir if the ANC is below 1,000/mm³ 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

A) Use of IVIG after hematopoietic cell transplantation (HCT) from day 100 through 1 year.

Reported IVIG studies are listed in the end of the LTFU general guidelines. For information regarding IVIG administration before 100 days after transplant see Standard Practice Committee guidelines.

1. Dosing and administration of prophylactic IVIG:

a. For allogeneic patients transplanted for myeloma, low grade lymphoma or CLL,

Administer IVIG 400 mg/kg at monthly intervals to maintain serum IgG levels above 400 mg/dL for 10 months after transplant prior to start of vaccinations.

b. For primary immune deficiency disease (PID):

<table>
<thead>
<tr>
<th>Pre-infusion IgG serum level (mg/dL)</th>
<th>IVIG dosing regimen 1,2</th>
</tr>
</thead>
<tbody>
<tr>
<td>600 – 1000</td>
<td>Begin at 200 mg/kg/every 2 weeks and wean to 400 mg/kg/every 4 weeks if troughs remain satisfactory</td>
</tr>
<tr>
<td>&lt; 600</td>
<td>300 mg/kg/every 2 weeks up to 500 mg/kg every week2</td>
</tr>
<tr>
<td>≥1000</td>
<td>400 mg/kg/every 4 weeks until B cell function fully restored</td>
</tr>
</tbody>
</table>

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. Other than above diseases, for allogeneic patients with haploidentical donors or cord blood transplant, pediatric patients with unrelated donors or for patients with ongoing infections or chronic GVHD with severe hypogammaglobulinemia:

Continue to check IVIG levels monthly and administer IVIG 400 mg/kg at monthly intervals to maintain serum IgG levels above 400 mg/dL. Continue for 10 months after transplant prior to anticipated start of routine vaccinations.

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

e. Select immunoglobulin product according to precautions to decrease adverse effects as applicable (see cautionary note below).
B) Use of IVIG after hematopoietic cell transplantation (HCT) > 1 year

Dosing and administration of prophylactic IVIG beyond 1 year

For allogeneic patients with Chronic GVHD beyond 1 year with recurrent sinopulmonary infections and persistent hypogammaglobulinemia

Recommend to check IgG level monthly and administer IVIG 400mg/kg at monthly intervals to maintain serum IgG levels > 400mg/dl

C) 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.

D) 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.

E) Contraindication for IVIG:

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

F) 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)
**Cautionary note about IVIG, Renal insufficiency:**

### IVIG Preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Sugar Content</th>
<th>IgA Content</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CMV IVIG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogam</td>
<td>5% Sucrose</td>
<td>?</td>
</tr>
<tr>
<td><strong>IVIG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carimune</td>
<td>5% Sucrose</td>
<td>720mcg/ml</td>
</tr>
<tr>
<td>Panoglobulin</td>
<td>5% Sucrose</td>
<td>720mcg/ml</td>
</tr>
<tr>
<td>Gammar</td>
<td>5% Sucrose</td>
<td>?</td>
</tr>
<tr>
<td>Sandoglobulin</td>
<td>5% Sucrose</td>
<td>?</td>
</tr>
<tr>
<td>Octagam</td>
<td>10% Maltose</td>
<td>&lt;200 mcg/ml</td>
</tr>
<tr>
<td>Venoglobulin</td>
<td>5% Sorbitol</td>
<td>15-50mcg/ml</td>
</tr>
<tr>
<td>Flebogamma</td>
<td>5% Sorbitol</td>
<td>&lt;50mcg/ml</td>
</tr>
<tr>
<td>Gammar</td>
<td>5% Glucose</td>
<td>&lt;25 mcg/ml</td>
</tr>
<tr>
<td>Iveegam</td>
<td>5% Glucose</td>
<td>&lt;10mcg/ml</td>
</tr>
<tr>
<td><strong>Low IgA containing IVIG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polygam</td>
<td>2% Glucose</td>
<td>&lt;3.7mcg/ml</td>
</tr>
<tr>
<td>Gammagard SD (powder)</td>
<td>2% Glucose</td>
<td>&lt;1 mcg</td>
</tr>
<tr>
<td><strong>Sugar Free IVIG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamunex</td>
<td></td>
<td>45mcg/ml</td>
</tr>
<tr>
<td>Gammagard 10% (liquid)</td>
<td></td>
<td>37 mcg/ml</td>
</tr>
<tr>
<td>Privigen</td>
<td></td>
<td>&lt;25mcg/ml</td>
</tr>
<tr>
<td>Gammaplex</td>
<td></td>
<td>?</td>
</tr>
</tbody>
</table>
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 syndrome (BOS), cryptogenic organizing pneumonia (COP) 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.

3. If Infections Ruled Out, Then Consider BOS After Allogeneic Transplant
   See section X, I for work up and treatment
Tests Recommended for Bronchoalveolar Lavage Fluid or Lung Biopsy Specimens

ALWAYS:
- Bacteria & fungal cultures
- Gram Stains, KOH
- Histology / cytology (H & E, silver stain)

STRONGLY RECOMMENDED:
- Legionella (culture & DFA or PCR)
- AFB (culture & stain)
- Modified Gimenez stain
- Viral cultures
- Aspergillus by PCR
- Aspergillus Galactomannan Enzyme Immunoassay (GM EIA) (fluid only)

If patient or donor are CMV seropositive:
- Shell vial cultures for CMV

During respiratory season:
- RSV and others respiratory virus (for example influenzae A & B, parainfluenzae, adenovirus) by PCR

If VZV is suspected (skin lesions, hepatitis):
- DFA or PCR

If HSV is suspected:
- DFA or PCR

If EBV is suspected:
- EBV by PCR or immuno-histochemistry, IHC

- 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 or 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 recommended. 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*

Severity of illness

Asymptomatic or other symptoms limited to anorexia, nausea or vomiting

Chronic GVHD in other organs?

Yes

Test stool for C. difficile, giardia antigen, O&P

Pos

Treat

Neg

Consider need to document intestinal GVHD and to R/O CMV by biopsy

No

Other family members ill with similar symptoms?

Yes

Test stool for C. difficile, giardia antigen, O&P

Pos

Treat

Neg

Watchful waiting

No

Fever, rigors or bloody diarrhea

Test stool for
• enteric bacterial pathogens:
  Salmonella
  Shigella
  C. fetus jejuni
  H7:0157 E. coli
  Yersinia
  Aeromonas
• C. difficile
• viral culture-including adenovirus and norovirus
• E. histolytica
• Rotavirus EIA

Neg

Endoscopic biopsies and cultures

CMV

GVHD

Another Dx

Pos

Treat

Treat

Treat

*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 viremia. 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 or valacyclovir 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/m² 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 ≥ 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/m² 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.

Except for epidemics (e.g. seasonal influenza) or novel pandemics (e.g. COVID-19), the earliest time to start vaccinations is 6 months posttransplant 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: Early Vaccination option (if eligible)
- IX.A2 Adult Vaccination Schema- Inactivated Vaccines: Standard vaccination schedule
- IX.A3 - Adult Vaccination Schema- For Live and Non-Live Adjuvant Vaccines
- IX.P1 Pediatric Vaccination Schema: Vaccination before 12 months (if eligible)
- IX.P2 Pediatric Vaccination Schema: If patient not vaccinated before 12 months
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>&gt;3m</th>
<th>~4m</th>
<th>~5m</th>
<th>&gt;6m</th>
<th>&gt;8m</th>
<th>&gt;10m</th>
<th>&gt;12m</th>
<th>&gt;14m</th>
<th>&gt;16m</th>
<th>&gt;18m</th>
<th>&gt;24m</th>
<th>Minimal Time Interval Between Vaccinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenzae (inactivated) (Sept –March) Use age appropriate non-adjuvant formulation</td>
<td></td>
<td></td>
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<td>H. Influenzae type B</td>
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<td>1-2 months</td>
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<tr>
<td>Meningococcal ACWY (Menactra, Menveo, MCV4)</td>
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<tr>
<td>Meningococcal Group B (Bexsero®)</td>
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<tr>
<td>Pneumococcal-conjugate (Prevnar 13™)</td>
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<td>1-2 months</td>
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<tr>
<td>Pneumococcal-polysaccharide (Pneumovax®)</td>
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<tr>
<td>Polio (inactivated)</td>
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<tr>
<td>Hepatitis A</td>
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<td>6 months</td>
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<tr>
<td>Hepatitis B</td>
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<td>2 months</td>
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<tr>
<td>HPV (Gardasil), 9 to 45 years</td>
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<td></td>
<td></td>
<td>2 m after 1st; 4 m after 2nd dose</td>
</tr>
<tr>
<td>Acellular Pertussis-Tetanus-Diphtheria®</td>
<td></td>
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<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>See footnotes 10,11</td>
</tr>
</tbody>
</table>

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 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.
7 Recommended for patients with anatomic or functional asplenia condition (i.e. chronic GVHD) or increased environmental risk.
8 In certain clinical situations Tdap may also be appropriate.
9 Dose 1 of the SARS-CoV-2 vaccination series should begin at ≥ day + 90. For allogeneic transplant patients as part of the day+ 80 work up, the initial dose should be arranged to be given by the appropriate BMT Team. Communications with referring provider should be done to advise when subsequent doses are due.
10 Pfizer (Comirnaty®) primary series is 3 doses of 0.3 mL; 2nd dose is 21 days after 1st dose, 3rd dose is 28 days after 2nd dose; a booster (4th) dose of 0.3 mL may be given.
11 Moderna primary series is 3 doses of 0.5 mL; 2nd dose is 28 days after 1st dose, 3rd dose is 28 days after 2nd dose; a booster (4th) half-dose of 0.25 mL may be given.

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>
<thead>
<tr>
<th>Vaccine</th>
<th>&gt;3m</th>
<th>~4m</th>
<th>~5m</th>
<th>&gt;12m</th>
<th>&gt;14m</th>
<th>&gt;16m</th>
<th>&gt;18m</th>
<th>&gt;22m</th>
<th>&gt;24m</th>
<th>Minimal Time Interval Between Vaccinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenzae (inactivated) (Sept –March) Use age appropriate non-adjuvant formulation</td>
<td>Flu</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H. Influenzae type B</td>
<td>HiB</td>
<td>HiB</td>
<td>HiB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>Meningococcal ACWY (Menactra, Mencevo, MCV4)</td>
<td>MCV4</td>
<td>MCV4</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal Group B (Bexsero®)7</td>
<td>Bexsero®</td>
<td>Bexsero®</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pneumococcal-conjugate (Prevnar 13TM)</td>
<td>PCV13</td>
<td>PCV13</td>
<td>PCV13</td>
<td>titer2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>Pneumococcal-polysaccharide (Pneumovax) See note2</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>PCV13 or Pneumovax2</td>
</tr>
<tr>
<td>Polio (inactivated)</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hepatitis A4</td>
<td>HAV</td>
<td>HAV</td>
<td>HAV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 months</td>
</tr>
<tr>
<td>Hepatitis B5</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 months</td>
</tr>
<tr>
<td>HPV (Gardasil), 9 to 45 years</td>
<td>HPV</td>
<td>HPV</td>
<td>HPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 m after 1st; 4 m after 2nd dose</td>
</tr>
<tr>
<td>Acellular Pertussis-Tetanus-Diphtheria4,8</td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>SARS-CoV-2 (Comirnaty® by Pfizer10, Moderna11)</td>
<td>COVID</td>
<td>COVID</td>
<td>COVID</td>
<td>COVID</td>
<td>(booster)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>See footnotes10,11</td>
</tr>
</tbody>
</table>

1 For patients not markedly immunosuppressed (For adults transplanted for immunodeficiency disorders see following section, “Posttransplant Vaccination of Primary Immunodeficiency Disorders”) who did not begin early vaccination for conjugate vaccines (Hib, MCV4, PCV13) before 12 months.
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
7 Recommended for patients with anatomic or functional asplenia condition (i.e. chronic GVHD) or increased environmental risk.
8 In certain clinical situations Tdap may also be appropriate
9 Dose 1 of the SARS-CoV-2 vaccination series should begin at ≥ day + 90. For allogeneic transplant patients as part of the day+ 80 work up, the initial dose should be arranged to be given by the appropriate BMT Team. Communications with referring provider should be done to advise when subsequent doses are due
10 Pfizer (Comirnaty®) primary series is 3 doses of 0.3 mL: 2nd dose is 21 days after 1st dose, 3rd dose is 28 days after 2nd dose; a booster (4th) dose of 0.3 mL may be given.
11 Moderna primary series is 3 doses of 0.5 mL: 2nd dose is 28 days after 1st dose, 3rd dose is 28 days after 2nd dose; a booster (4th) half-dose of 0.25 mL may be given.

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: For Live and Non-Live Adjuvant Vaccines

#### A) Live Vaccines

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>&lt;24m</th>
<th>≥24m</th>
<th>Minimal Time Interval Between Vaccinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles/Mumps/Rubella (MMR)</td>
<td></td>
<td></td>
<td>MMR&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td><em>&quot;2-1-5 Rule&quot;</em>&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella-Zoster (Varivax) Seronegative ONLY</td>
<td></td>
<td></td>
<td>Second dose given 1 month later&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td><em>&quot;2-1-5 Rule&quot;</em>&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First dose may be given with MMR</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>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</strong></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> For live virus vaccine, vaccination should be at least 5 months post last dose of IVIG.

<sup>2</sup> *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.

<sup>3</sup> Check varicella serology at least 1-2 months after second dose of Varivax to ensure seroconversion of the VZV seronegative patient.

#### B) Non-Live Adjuvant Vaccines

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>&lt;24m</th>
<th>≥24m</th>
<th>Minimal Time Interval Between Vaccinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOR ALLOGENEIC PATIENTS, ONLY: VZV Seropositive ONLY and Adults ≥ 50 yr*</td>
<td></td>
<td>SHINGRIX (non-live, adjuvant vaccine)</td>
<td>Second dose given 2-6 months later</td>
</tr>
<tr>
<td><strong>No Adjuvant 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</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>*</sup>*Not until 2 years post HCT and ≥ 8 months off immunosuppressive therapy (IST) and no flare-up of GVHD. Recommend continue VZV prophylaxis (i.e. acyclovir or valacyclovir) until 1 month after first vaccination. Counsel patients regarding risks and benefits,

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>&lt;24m</th>
<th>≥24m</th>
<th>Minimal Time Interval Between Vaccinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOR AUTOLOGOUS PATIENTS ONLY: VZV Seropositive patients ONLY and ≥ 18 Years old&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>SHINGRIX (non-live, adjuvant vaccine)</td>
<td>Second dose 1-2 months later</td>
</tr>
<tr>
<td><strong>Do not give</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Continue VZV prophylaxis (i.e. acyclovir or valacyclovir) based on drug being used for maintenance therapy.

<sup>**</sup> For patients receiving immunotherapy (e.g. PD-1 inhibitors) for maintenance, consider use on case by case basis after immunotherapy is completed. Counsel patients regarding risks/benefits

<sup>#</sup> This indication is not yet FDA approved and insurance coverage might be variable for patients younger than 50 years of age.

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: Vaccination before 12 months (if eligible) 1, 8

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>&gt;6m1</th>
<th>&gt;8m</th>
<th>&gt;10m</th>
<th>&gt;12m</th>
<th>&gt;14m</th>
<th>&gt;16m</th>
<th>&gt;18m</th>
<th>&gt;24m</th>
<th>&gt;25m</th>
<th>Minimal Time Interval Between Vaccinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenzae (inactivated) ≥0.5 years to &lt; 9 years</td>
<td></td>
<td></td>
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<td>1 month</td>
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<tr>
<td>[September –March] ≥ 9 years</td>
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<tr>
<td>H. Influenzae type B8</td>
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<tr>
<td>Meningococcal ACWY (Menactra, Menevo, MCV4)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>Meningococcal Group B (Bexsero®)10, 11</td>
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<tr>
<td>Pneumococcal-conjugate (Prevnar 13™)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>Pneumococcal-polysaccharide (Pneumovax)2b</td>
<td></td>
<td></td>
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<tr>
<td>Polio (inactivated)5</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Hepatitis A5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 months</td>
</tr>
<tr>
<td>Hepatitis B5, 6, 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 months</td>
</tr>
<tr>
<td>HPV (Gardasil), 9 to 45 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>2 m after 1st; 4 m after 2nd dose</td>
</tr>
<tr>
<td>Acellular Pertussis-Tetanus-Diphtheria (DTaP)5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>SARS-CoV-2 (Comirnaty® by Pfizer, Moderna)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Recommendations per pediatric attending

Measles/Mumps/Rubella (MMR) "2-1-5 Rule2

Varicella-Zoster (Varivax) Seronegative ONLY and "2-1-5 Rule"7

First dose may be given with MMR

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.

---

1 For patients not markedly immunosuppressed (For children transplanted for immunodeficiency disorders see following section, “Posttransplant Vaccination of Primary Immunodeficiency Disorders”.)
2 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), pedestalis = DTaP/HiB/IPV (age < 4 y), Pediarix = DTaP/HiB/IPV (age = 6-11 y), Pentacel = DTaP/HiB/IVP (age < 7 y), Prevnar = DTaP/HiB (age < 4 y), Adacel = Tdap (age ≥11 y), Twinrix = HBV/HAV (age ≥18 y)
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 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.
8 If using Hepatitis B vaccine Recombivax HBR, dosing schedule is 0, 1 and 6 months if patient is 0 to 19 years of age.
9 Recommended for patients ≥ 10 years old with anatomic or functional asplenia condition (i.e. GVHD) or increased environmental risk. For other patients 16-18 years of age, discuss with parents as optional recommendation.
10 If Bexsero® is not given, Trumenba® can be substituted in patients ≥ 10 years old as 3 doses (0, 2, 6 months apart)
11 In patients > 7 years old, Tdap may also be appropriate
### Table IX.P2: Pediatric Vaccination Schema: If patient not vaccinated before 12 months 1, 8

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>&gt;12m</th>
<th>&gt;14m</th>
<th>&gt;16m</th>
<th>&gt;18m</th>
<th>&gt;22m</th>
<th>&gt;25m</th>
<th>Minimal Time Interval Between Vaccinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenzae (inactivated) (September –March)</td>
<td>Flu</td>
<td>Flu</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 month</td>
</tr>
<tr>
<td>H. Influenzae type B6</td>
<td>HiB</td>
<td>HiB</td>
<td>HiB</td>
<td></td>
<td></td>
<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>Meningococcal ACWY (Menactra, Menveo, MCV4)</td>
<td>MCV4</td>
<td>MCV4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal Group B (Bexsero®)10, 11</td>
<td>Bexsero®</td>
<td>Bexsero®</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal-conjugate (Prevnar 13™)</td>
<td>PCV13</td>
<td>PCV13</td>
<td>PCV13</td>
<td>✓ titers2</td>
<td></td>
<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>Pneumococcal-polysaccharide (Pneumovax2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polio (inactivated)5</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A5</td>
<td>HAV</td>
<td>HAV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 months</td>
</tr>
<tr>
<td>Hepatitis B5, 6, 9</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>✓ titers6</td>
<td></td>
<td></td>
<td>2 months</td>
</tr>
<tr>
<td>HPV (Gardasil), 9 to 45 years</td>
<td>HPV</td>
<td>HPV</td>
<td>HPV</td>
<td></td>
<td></td>
<td></td>
<td>2 m after 1st; 4 m after 2nd dose</td>
</tr>
<tr>
<td>Acellular Pertussis-Tetanus-Diphtheria12 (DTaP5)</td>
<td>DTaP</td>
<td>DTaP</td>
<td>DTaP</td>
<td>✓ titers3</td>
<td></td>
<td></td>
<td>1-2 months</td>
</tr>
<tr>
<td>SARS-CoV-2 (Comimat® by Pfizer, Moderna)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles/Mumps/Rubella (MMR) &quot;2-1-5 Rule&quot;</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Varicella-Zoster (Varivax) Seronegative ONLY and &quot;2-1-5 Rule&quot; 7</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>First dose may be given with MMR</td>
<td></td>
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</tr>
</tbody>
</table>

**Recommendations per pediatric attending**

| 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 |
| MMRR | MMRR | 1-2 months |
| VZV7 | VZV7 | 1-2 months |

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), Twinrix = HBV/HAV (age ≥18 y)***

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 2nd 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

9 If using Hepatitis B vaccine Recombivax HBR, dosing schedule is 0, 1 and 6 months if patient is 0 to 19 years of age.

10 Recommended for patients ≥ 10 years old with anatomic or functional asplenia condition (i.e. GVHD) or increased environmental risk. For other patients 16-18 years of age, discuss with parents as optional recommendation.

11 If Bexsero® is not given, Trumenba® can be substituted in patients ≥ 10 years old as 3 doses (0, 2, 6 months apart)

12 In patients > 7 years old, Tdap may also be appropriate

---

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. Exceptions may be made for epidemics (e.g. seasonal influenza) or novel pandemics (e.g. COVID-19), per pediatric attending recommendations.
- 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 IgG 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 IgG therapy is low and
  C. All of the following laboratory criteria:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Trough IgG &gt; 600 mg/dL on standard IVIG dosing</td>
<td>Suggests numeric IgG reconstitution</td>
</tr>
<tr>
<td>2. Detectable serum IgA (&gt; 6 mg/dL)</td>
<td>A detectable IgA level indicates potential ability to “class switch”</td>
</tr>
<tr>
<td>3. Donor(^a) B cell count &gt; 200 per microliter</td>
<td>Arbitrarily set at 1-log higher than our standard practice for those transplanted for malignancy</td>
</tr>
<tr>
<td>4. Donor(^b) CD4 T cell count &gt; 200 per microliter</td>
<td>Same as our standard practice for those transplanted for malignancy</td>
</tr>
</tbody>
</table>

\(^a\) as determined by donor B cell chimerism divided by 100 x total absolute B cell count
\(^b\) as determined by donor CD4 cell chimerism divided by 100 x 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 donor chimerism and 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 IgG 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 remaining 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. SARS-CoV-2 and seasonal influenza vaccinations will be given per pediatric LTFU attending recommendations.

**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 8 months after last dose of gammaglobulin therapy

**Posttransplant 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 least 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/microliters | • CD19 or CD20 B cells < 20/microliters |
| • 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 |

*Note Lenalidomide alone maintenance therapy should not affect lymphocyte counts and patients can receive vaccination per standard schedule.

**General Recommendations:**

- All patients should receive seasonal flu and SARS-COV-2 vaccinations per tables 1XA1-A2 and Table 1XP1-P2
- If patient is on disease-associated maintenance therapy that can affect T or B cell numbers, then before beginning other vaccinations:
  ✓ Check CD 19 or CD 20 B cells to determine ≥ 20/microliters
  and
  ✓ Check CD4 T cells to determine ≥ 200/microliters.
  Note Lenalidomide alone maintenance therapy should not affect lymphocyte counts and patients can receive vaccination per standard schedule without checking B or T cell blood counts.

- 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.

- **Alternative Hepatitis B Vaccination Formulas:** In patients > 18 years old who did not respond to the initial Hepatitis B vaccination series, there is a new Hepatitis B vaccine formulation with (Toll-like receptor 9) adjuvant ((Heplisav)). However, its safety especially in allogeneic transplant patients and its impact on GVHD has not yet been studied.

- **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](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](http://www.bt.cdc.gov).

**Patients with splenectomy post transplant:**

Vaccination recommendations for the post-SCT, post-splenectomy patient are the same as for the BMT recipient who has an intact spleen (SEE LONG-TERM FOLLOW-UP AFTER HEMATOPOIETIC STEM CELL TRANSPLANT, GENERAL GUIDELINES FOR REFERRING PHYSICIANS, SECTION IX VACCINATIONS). Thus, vaccination against pneumococcus with 3 doses of PCV13 (Prevnar®) followed by a one dose of PPSV23 (Pneumovax®), and against *H. influenzae* with 3 doses is particularly important. Antibody titers should be checked at least 8 weeks later to ensure immunization responses.

Vaccination against *Neisseria meningitidis* groups A, C, W, Y with two doses of MCV4 (Menactra® or Menveo®) and against serogroup B with two doses of Bexsero® is recommended. If Bexsero is unavailable, vaccination against serogroup B with the Trumenba vaccine series could be considered if patient is ≥ 10 years old, and requires 3 immunizations on a 0, 2, 6 month schedule. Patients should receive a complete series with a single vaccine type (no mixing between Bexsero® and Trumenba®)³.

In addition to vaccinations recommended above, booster immunizations with PPSV23 (Pneumovax®) should be given 5 years after receipt of the initial PPSV23 vaccination. Re-Booster immunizations with MCV4 (Menactra® or Menveo®) and Bexsero® are recommended every 5 years².

Note: For non-elective splenectomy, vaccination should begin at or after post-operative Day 14. Post transplant with PCV13, H. influenzae B and *Neisseria meningitidis* groups A, C, W, Y, MCV4, and also group B.
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]

<table>
<thead>
<tr>
<th>Category</th>
<th>Time of symptoms after HCT or DLI †</th>
<th>Presence of Acute GVHD Features</th>
<th>Presence of Chronic GVHD Features*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute GVHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic acute GVHD</td>
<td>≤ 100 days</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Persistent, recurrent or late onset acute GVHD</td>
<td>&gt; 100 days</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Chronic GVHD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic chronic GVHD</td>
<td>No time limit</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Overlap syndrome</td>
<td>No time limit</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

† DLI (donor lymphocyte infusion)

* See Table 2 below
Table 2. Signs and Symptoms of chronic GVHD[^4]

<table>
<thead>
<tr>
<th>ORGAN OR SITE</th>
<th>DIAGNOSTIC (Sufficient to establish the diagnosis of chronic GVHD)</th>
<th>DISTINCTIVE (Seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)</th>
<th>OTHER FEATURES*</th>
<th>COMMON (Seen with both acute and chronic GVHD)</th>
</tr>
</thead>
</table>
| 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]

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

* 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 ≤ 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>
<thead>
<tr>
<th>Global severity</th>
<th>No. organs/sites affected</th>
<th>Maximum score in all affected organ/site*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>One or two (except lungs‡)</td>
<td>1‡</td>
</tr>
<tr>
<td>Moderate</td>
<td>Three or more or One or more</td>
<td>1‡‡</td>
</tr>
<tr>
<td>Severe</td>
<td>Any</td>
<td>3</td>
</tr>
</tbody>
</table>

* 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 obstructive lung defect may represent GVHD 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 prior history of chronic GVHD or concomitant GVHD in any other organ, the diagnosis of bronchiolitis obliterans (BO) requires specific spirometric criteria with negative workup for infection and evidence of signs of bronchiolitis by high resolution end-expiratory and end-inspiratory CT scan of the lungs, or confirmation by lung biopsy.

For information on monitoring of lung function post transplant and treatment of bronchiolitis obliterans syndrome (BOS), see section I.

**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 (≥ 500/microliter), hypogammaglobulinemia. Hypergammaglobulinemia and autoantibodies occur in some cases.

G. Monitoring and other chronic GVHD information

Karnofsky or Lansky Clinical Performance scores <60%, ≥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**

<table>
<thead>
<tr>
<th>Global severity*‡</th>
<th>High risk*</th>
<th>Prolonged systemic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Mild</td>
<td>Yes</td>
<td>Yes‡‡</td>
</tr>
<tr>
<td>Moderate</td>
<td>Yes or No</td>
<td>Yes‡‡</td>
</tr>
<tr>
<td>Severe</td>
<td>Yes or No</td>
<td>Yes‡‡</td>
</tr>
</tbody>
</table>

*‡ 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). For information on other medications used for glucocorticoid-resistant or dependent chronic GVHD or in combination, 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. Monitoring and Management of Bronchiolitis Obliterans Syndrome after HCT

Introduction

- Bronchiolitis obliterans syndrome (BOS) is a late non-infectious pulmonary complication that affects 5.5% of allogeneic HCT recipients and 14% of those with chronic GVHD (7).
- BOS is the clinical correlate of obliterative bronchiolitis which is considered a pulmonary manifestation of chronic GVHD.
- Lung function impairment is generally irreversible but may stabilize with treatment (8).
- The median time to BOS diagnosis is 1.5 years after HCT (8, 9) and 6 months after diagnosis of chronic GHVD (10).

Definition of BOS after allogeneic HCT

A. Definition of BOS by NIH Consensus Guidelines (adapted from Reference 11)
   1. Significant new obstructive change on spirometry:
      a. Decrease of the absolute FEV₁ (mL) by ≥ 10% in comparison in prior 2 years or pre-transplant baseline
      b. FEV₁ is <75% predicted
      c. FEV₁/VC¹ ratio < 0.7 or FEV₁/FVC <LLN
      d. Meet criteria for obstruction (a-c) after bronchodilator challenge even if there is a bronchodilator response
   2. BOS according to severity is clarified as:
      Mild or Asymptomatic = with mild FEV₁ decline (FEV₁ >70% predicted)
      Moderate/severe or symptomatic = FEV₁ decline (FEV₁ <70% predicted)
   3. Absence of other conditions that cause airflow obstruction including infection, asthma, chronic obstructive pulmonary disease (COPD)
   4. A history of chronic GHVD, or active chronic GVHD affecting other organs or presence of a distinctive manifestation of chronic GVHD by 2015 NIH consensus criteria is highly supportive of BOS if above criteria are met.
   5. Other supportive findings:
      a. Significant air-trapping: residual volume (RV) > 120%, or RV/TLC > 20% of predicted value
      b. Air-trapping or other features of bronchiolitis including centrilobular nodules, airway thickening, or bronchiectasis noted on high resolution computed tomography (HRCT).

B. Lung biopsy showing obliterative bronchiolitis may be required to make the diagnosis of lung GVHD in patients with no prior history of chronic GVHD or other organ manifestations of chronic GVHD for the purposes of enrollment into a clinical trial.

C. Diagnostic considerations for BOS:
   1. Alternative spirometric phenotype (12)
      a. Reduced FVC and FEV₁
      b. Normal FEV₁/FVC ratio
      c. Normal TLC
   2. Patients with baseline pretransplant supranormal FEV₁:
      a. FEV₁ decline >10 % (meets criteria 1a)
      b. FEV₁/VC <0.7 (meets criteria 1c)
      c. FEV₁ >75% predicted (does not meet criteria 1b)

Monitoring of lung function after day +100 after allogeneic transplant

¹ Slow VC, which is always greater than or equal to FVC, should be used for this calculation if available as per ATS/ERS guidelines (13). Otherwise FVC is used.
A. Pulmonary function test (PFT) monitoring including spirometry, lung volumes, and DLCO.

1. PFTs for asymptomatic allo-HCT recipients:
   a. At 6 months
   b. At 1 year
   c. Yearly thereafter until 5 years as clinically indicated

   d. At diagnosis of chronic GVHD (14)
      i. Full PFT testing including: spirometry, lung volumes, and DLCO
      ii. Q3 months after diagnosis of chronic GVHD for at least one year.
          (spirometry alone may be adequate)
      iii. Thereafter, at Q6 months for 1 year (spirometry alone may be adequate)
      iv. With at least yearly full PFT testing including: spirometry, lung volumes,
          and DLCO until year 5 post HCT

Evaluation and monitoring of new airflow decline detected by PFTs

A. Pulmonary consult should be initiated.
B. New lung function decline:
   Airflow obstruction is defined as decline in absolute FEV₁ ≥10%, with FEV₁/VC <0.7. Lung function decline may be due to obstructive, restrictive, or mixed processes.
   a. Evaluate for upper respiratory infection or other etiologies of airflow decline
      i. Nasal swab for respiratory virus PCR if indicated by symptoms
      ii. Perform high resolution chest CT (HRCT)
          o If there are infiltrates, consider bronchoscopy to evaluate for infection
   b. If diagnostic criteria for BOS are met → Start treatment promptly
   c. If alternative diagnosis is made, repeat spirometry monthly for at least 3 months
      i. If % FEV₁ stabilizes at 3 months, monitor PFTs every 3 months for one year
      ii. If stable at 1 year, q6 month intervals for one year
      iii. Thereafter, if stable, yearly.

C. High Resolution CT (HRCT):
   1. Indication: Unexplained lung function changes and/or suspicion for BOS
   2. Order with inspiratory and expiratory phases
   3. Radiographic findings consistent with BOS (15, 16):
      a. Mosaic attenuation (indicative of air-trapping)
      b. Peripheral ground glass opacities or centrilobular ground glass opacities/nodules
      c. Airway thickening or bronchiectasis (usually a late finding)
   4. Patient may still have diagnosis of BOS with normal chest CT

D. Bronchoscopy is indicated when there are signs and symptoms of potential infection.
   1. Clinical symptoms
      Productive cough, fever, runny nose, sore throat
   2. Imaging findings
      Pulmonary infiltrate including ground glass opacities and/or new pulmonary nodules

Treatment of suspected or confirmed BOS (Figure 1)

A. Prior to specific BOS treatment, all confounding etiologies of airflow obstruction should be investigated and treated. However, treatment for BOS should not be delayed if suspicion is strong.
   1. Infection: Diagnostic evaluation as directed by clinical symptoms include the following:
      a. Sinus CT, nasal washes for respiratory virus PCR panel, sinus aspiration, CXR, CT chest, sputum culture, bronchoalveolar lavage, and/or surgical lung biopsy.
   2. Gastroesophageal reflux
      a. Consider treating with proton pump inhibitor if not already on one
      b. Lifestyle modifications including elevation of the head of bed
3. Post-nasal drip/sinus symptoms
   a. Evaluate for URI
   b. Evaluate for environmental allergies/triggers
   c. Nasal saline, antihistamine, or steroid as needed
   d. Consider ENT evaluation if chronic sinusitis is suspected

B. Initial Treatment
1. Initiate Fluticasone, azithromycin and montelukast (Singulair) (FAM) + Long-Acting Beta-Agonist (LABA) (9,17,18)
   a. FAM = Fluticasone (Flovent) 440 mcg BID + azithromycin 250mg po MWF + montelukast (Singulair) 10mg po QD
   b. LABA = long-acting beta2-agonist (such as salmeterol)
   c. For FAM + LABA, inhaled corticosteroid (ICS)/LABA combination may be prescribed in lieu of separate inhaled medications.
   d. Inhaled corticosteroid combinations:
      i. First choice: Symbicort HFA 160/4.5 mcg 2 inh BID
      ii. Alternatives:
         o Advair HFA 230/21mcg 2 inh BID
         o Advair Diskus 500/50 mcg 1 inh BID
         o Dulera 200/5 mcg 2 inh BID
         o Breo Ellipta 200/25 mcg 1 inh QD
   e. Treatment should continue without exacerbation after resolution of active chronic GVHD, which is at least 6 months after discontinuation of all systemic immunosuppressive treatments for other organ manifestations of chronic GVHD.

2. Prednisone
   a. Asymptomatic with mild FEV₁ decline (FEV₁ >70% predicted): no new or increase in prednisone
   b. Symptomatic, or with moderate to severe FEV₁ decline (FEV₁ <70% predicted): Start or increase prednisone to 1mg/kg/day x 2 weeks then taper (see below)
   c. Other immunosuppressive treatments as indicated to control GVHD in other organs.
   d. After 2 weeks of therapy, begin taper over next 3 weeks to get down to a total dose of 0.25mg/kg/day or to pre BOS therapy dose by week 5, as tolerated by stability of FEV₁ and/or other organ manifestations of chronic GVHD.
   e. If prednisone is not required, taper prednisone off within 6-8 weeks as tolerated (including adrenal insufficiency issues).

C. PFT Monitoring during treatment of BOS
   1. After initial diagnosis: Q4-6 weeks x 6 months (Qmonthly) while on prednisone taper.
   2. If % FEV₁ stabilizes after 3 months, space out to q2-3 months for at least a year or longer per pulmonary recommendations.
   3. If % FEV₁ continues to decrease, see D below.
   4. If % FEV₁ normalizes, see E below

D. Persistent FEV₁ decline despite initiation of above treatment (FEV₁ decline of >/= 10%):
   1. Rule out infection or other confounding etiologies
   2. Consider enrollment in a clinical trial
   3. Consider extracorporeal photopheresis (ECP) or other immunosuppression therapies with LTFU attending
   4. If FEV₁ has stabilized, taper prednisone to 1mg/kg/day x 2 weeks and follow taper schedule in section B.#2.

---

 Dosages provided are for adult patients. For pediatric patients, please consult pharmacist for dosing.
E. After minimum 6 months of FAM and LABA therapy, a taper of BOS-specific medications can be considered if all the following conditions are met:
   a. Full PFTs with Lung volumes and DLCO remain stable or improved compared with BOS diagnosis
   b. There are no new extrapulmonary manifestations of cGVHD requiring an addition or increase in systemic immunosuppression
   c. Patient is on a stable prednisone taper of ≤10mg/day equivalent

F. Taper Schedule

1. Full PFTs with Lung Volume and DLCO before starting taper.
2. 
   a. Step 1: D/C Azithromycin first. Ensure that Spirometry without lung volumens are stable over 3 months.
   b. Step 2: D/C montelukast. Ensure that Spirometry without lung volumes is stable over 3 months.
   c. Step 3: D/C LABA. If Spirometry without lung volumes is stable after stopping azithromycin and montelukast, drop LABA component of ICS+LABA. This step may be skipped if the patient prefers to remains on a combination inhaler (such as Symbicort).
   d. Steps 4-6: If symptomatically stable after 1 month with stable Spirometry without lung volumes, drop ICS dose by 50%. If Spirometry without lung volumes is stable after 1 month, continue tapering ICS to off over 1-2 months.
   e. Step 7: Full PFTs with lung volumes and DLCO 1 month after completion of FAM and LABA therapy.
      i. Follow FEV1 closely with each step
      ii. If FEV1 is stable, then next step of taper can proceed.
      iii. After FAM+LABA are off, check Spirometry without lung volumes at 1 month 3 months and 6 months (assuming FEV1 is stable)
      iv. Full PFTs with lung volumes and DLCO is recommended at least once a year.
3. If FEV1 decline of >10% occurs during taper:
   a. Evaluate for respiratory infection, other exacerbating factors (GERD, post-nasal drip, new cGVHD manifestations, restrictive lung disease)
   b. If a reversible etiology is not identified, stop the taper and resume all components.

G. Supportive treatment
   1. Vaccinations
   2. Prophylactic antibiotics
   3. Treat infections
   4. Pulmonary rehabilitation
   5. Supplemental oxygen if resting or ambulatory O2 sat ≤88%

H. End-stage lung disease from BOS
   1. Consider lung transplantation (19)
   2. Discuss with UWMC Lung Transplantation service.
   3. Basic criteria for referral for lung transplant includes:
      a. >2 years after HCT without evidence of malignancy
      b. Life expectancy <2 years from respiratory failure
      c. No other end-organ damage
      d. No significant requirement for immunosuppression (prednisone < 20mg/qd
      e. BMI >/= 18
      f. Appropriate social support and compliance

For details on References, see Section XXV, References, Chronic GVHD

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3 There is no specific FEV1 criteria for lung transplant eligibility.
Figure 1. Schema for Treatment of Bronchiolitis Obliterans Syndrome (BOS) according to severity

A. Suspected or confirmed BOS

1. **Mild or asymptomatic**
   - Start FAM + LABA
   - No Prednisone
   - **Stable**
     - Continue FAM + LABA
   - **Progression**
     - Go to B

2. **Moderate/severe or symptomatic**
   - Start FAM + LABA + Prednisone 1mg/kg/d
   - **Stable**
     - Continue FAM + LABA
     - Taper prednisone
   - **Progression**
     - Go to B

---

\(^1\)Mild or Asymptomatic = with mild FEV\(_1\) decline (FEV\(_1\) >70\% predicted)
\(^2\)Moderate/severe or symptomatic = FEV\(_1\) decline (FEV\(_1\) <70\% predicted)

B. Progression of BOS on treatment

- Evaluate for infection

  + **Infection**
    - Treat Infection
      - **Improvement**
        - Continue FAM + LABA
        - Taper prednisone
      - **No Improvement**
        - Continue FAM + LABA
        - Taper prednisone

  - **No Infection**
    - Consider other chronic GVHD treatments
    - **Progression to chronic respiratory failure**
      - < 2 years from HCT Prednisone > 20 mg/qd
        - Supportive Care
        - Taper Prednisone
      - ≥ 2 years from HCT Prednisone < 20 mg/qd
        - Refer for Lung Transplantation
XI. GENERAL GUIDELINES FOR PREVENTION OF OSTEOPOROSIS AND GLUCOCORTICOSTEROID INDUCED OSTEOPOROSIS

Treatment with 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 (1).

Bone loss can be measured semi-quantitatively using a dual energy x-ray absorptiometry (DEXA) scan which can compare bone mineral density (BMD) of an individual to an appropriate normative population using a standard deviation score. BMD-standard deviation scores have been determined for healthy 30 year old male and female Caucasians (T-scores) or have been age adjusted (Z-score).

Osteopenia is defined as a bone mineral density T-score of –1 to –2.5 (standard deviations below the peak mean density of young healthy controls). Osteoporosis is defined by a T-score of <-2.5. It is also important to evaluate the individuals’ change in BMD over time when determining appropriate interventions to optimize BMD.

T-scores are used to report bone mineral density for post-menopausal women (regardless of age) and men ≥50 years. Z-scores are used to report bone marrow density in all pediatric patients, pre-menopausal women, and adult males < 50 years.

T-scores are less appropriate for the interpretation of pediatric DEXA scans, especially in the very young children where BMD is confounded by normal growth and development. Therefore, Z-scores are used with pediatric patients since they are too young to have achieved peak BMD. Z-scores obtained from the Hologic DEXA scanner (UWMC) for the spine are available for ages ≥4 years. Z-scores for the femoral neck are limited to age ≥12 years. Z-scores obtained from the General Electric Lunar DEXA scanner (SCCA) for the spine and total body are available for ages 5 through 19 years. Z-scores

Management of osteopenia and osteoporosis at a minimum includes: (a) minimizing daily and total cumulative glucocorticoid exposure, (b) optimizing calcium and vitamin D intake, and (c) participating in weight-bearing exercise. Bone strengthening drugs including bisphosphonate (5) may also be appropriate for some patients (2,3)

A. Patient Monitoring

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

Men: 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: with each clinic visit.
- DEXA SCANS:
  a) for all adult autologous lymphoma and myeloma transplant patients, Dexa scan at one year post transplant.
  b) for all adult allogeneic patients and for all autologous or allogeneic pediatric patients, DEXA scan at one year post transplant.
  c) for all allogeneic patients on steroid therapy beyond one year from transplant after completing initial Dexa scan at one year post transplant, continue yearly Dexa scan as clinically indicated.

Vitamin D blood level
- Vitamin D (25 Hydroxy) blood level should be checked at one year 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. Calcium Requirements

i. FOR PATIENTS ON STEROID THERAPY:

<table>
<thead>
<tr>
<th>Age</th>
<th>Daily Minimum Requirement after Transplant (milligrams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-12 months:</td>
<td>600</td>
</tr>
<tr>
<td>1-3 years:</td>
<td>1000</td>
</tr>
<tr>
<td>4-8 years:</td>
<td>1200</td>
</tr>
<tr>
<td>≥ 9 years:</td>
<td>1500</td>
</tr>
</tbody>
</table>

Calcium intake above these levels is not recommended, as it may interfere with the absorption of other nutrients.

ii. FOR PATIENTS NOT ON STEROIDS

<table>
<thead>
<tr>
<th>Age</th>
<th>Daily Minimum Requirement after Transplant (milligrams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 7-12 months</td>
<td>260</td>
</tr>
<tr>
<td>Children 1-3 years</td>
<td>700</td>
</tr>
<tr>
<td>Children 4-8 years</td>
<td>1000</td>
</tr>
<tr>
<td>Children 9-18 years</td>
<td>1300</td>
</tr>
<tr>
<td>Adult Males</td>
<td>1000-1200</td>
</tr>
<tr>
<td>Adult Females;</td>
<td></td>
</tr>
<tr>
<td>On hormone therapy</td>
<td>1000-1200</td>
</tr>
<tr>
<td>No hormone therapy</td>
<td>1500</td>
</tr>
</tbody>
</table>

Calcium intake above these levels is not recommended, as it may interfere with the absorption of other nutrients.
## C. Vitamin D Requirement

### Table 3: Vitamin D3 (or D2) Supplementation*****

<table>
<thead>
<tr>
<th></th>
<th>Adults (≥18 yrs)</th>
<th>Children (≤18 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment of Insufficiency</strong> [Vitamin D (25 Hydroxy) levels 20-30 ng/mL]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine</td>
<td>25 mcg/day</td>
<td></td>
</tr>
<tr>
<td>Malabsorption syndromes**</td>
<td>1,250 mcg per week</td>
<td>Age &lt; 1 yr:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— 10 mcg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(20 mcg in dark skinned)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age 1-8 yr:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— 15 mcg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age 9-18 yr:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— 20 mcg daily</td>
</tr>
<tr>
<td>Malabsorption syndromes**</td>
<td>1,250 mcg per week</td>
<td>Age &lt; 1 yr:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— Consult Endocrinology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age 1-18 yr:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>— 1,250 mcg per week or 125 mcg daily</td>
</tr>
<tr>
<td>Chronic Renal Disease</td>
<td>Consult Nephrology</td>
<td>Consult Nephrology</td>
</tr>
</tbody>
</table>

| **Treatment of Deficiency** [Vitamin D (25 Hydroxy) level <20 ng/mL]*** |                  |                    |
| Uncomplicated                  | 1,250 mcg per wk x 8 (Repeat if Vitamin D (25 Hydroxy) level < 30 ng/mL otherwise treat as for insufficiency above) | Age 1-12 months: |
|                                |                  | — 25-50 mcg daily x 8 wks |
|                                |                  | Age 1-18 yr:        |
|                                |                  | — 25-125 mcg daily x 8 wks or 1,250 mcg weekly x 8 (Repeat if Vitamin D (25 Hydroxy) level < 30 ng/mL otherwise treat as for insufficiency above) |
| Malabsorption syndromes**      | 250-1,250 mcg daily or every other day | Age < 1 yr: |
|                                | UVB irradiation in patients also with skin GVHD | — Consult Endocrinology |
|                                |                  | Age 1-18 yr:       |
|                                |                  | — 1,250 mcg per week |
| Chronic Renal Disease          | Consult Nephrology | Consult Nephrology |

*Currently there does not seem to be 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 50 mcg daily for 50 days is approximately equivalent to giving 1,250 mcg monthly for 2 months.

**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.

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

****1000 IU = 25mcg and 50,000 IU = 1,250 mcg
D. **Magnesium**
Magnesium depletion results in cessation of bone growth, decreased osteoblast and osteoclast activity. 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 low-impact walking, swimming, biking (on a stationary bike if the patient has poor balance), Nordic tracking, rowing, and other low impact aerobic activities. 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. But, the use of hormonal supplementation is not recommended as first line treatment or for prevention of osteoporosis or osteopenia.

*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** are effective for prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis (4, 5). Because the risks and benefits of bisphosphonates during the early posttransplant period are unclear, consideration of bisphosphonate therapy for osteoporosis is not recommended until at approximately 3 months posttransplant.

*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 osteopenia (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 (http://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 (6). 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 (7). One approach to consider for patients at mild risk for fracture is to stop bisphosphonate therapy after 3 to 5 years and remain off as long as bone mineral density is stable and no fractures occur. Higher risk patients may be treated longer than 3 to 5 years as clinically indicated and consider referral to endocrinology for alternative therapy (6).

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

**Note**
- For bisphosphonates, we recommend adequate calcium and Vitamin D supplementation.
- 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.
- Due to increased risk of AFF (Atypical Femoral Fractures) and MRO (Osteonecrosis of the jaw) with prolonged bisphosphonate therapy, after 3 to 5 years of treatment reassess the risks and benefits of continuing therapy, pursuing a drug holiday or getting and endocrinology consult for consideration of alternative treatment.

Commonly used bisphosphates include:

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. Pamidronate (Aredia®)
Pamidronate has been used primarily in patients who cannot receive oral bisphosphonates. In adults a regimen of 60 mg IV for the first dose followed by 30 mg every 3 months has been used successfully in the nontransplant setting.

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

a. **Rank Ligand Inhibitors:** Denosumab (Prolia®) 60 mg SQ every 6 months for adult osteoporosis. Denosumab has not been studied to treat osteoporosis in children. Strongly recommend an endocrinology consult prior to starting rank ligand inhibitors. Severe hypocalcemia can be seen in patients with renal dysfunction. Monitor for infection at injection site in patients on immunosuppressive therapy. Because there is an increased risk for vertebral fracture with discontinuation or missed doses of denosumab (8, 9), if you are considering discontinuing the drug, we highly recommend getting an endocrinology consult first.

Note: For rank ligand inhibitor therapy, we recommend adequate calcium and Vitamin D supplementation.

b. **Calcitonin** (secondary therapy for osteoporosis): Calcitonin (100-200 International Units nasal spray daily) may be given if bisphosphonates are inadequate or contraindicated. There are no data to support the use of calcitonin (salmon) nasal spray in children. Calcitonin may be given if bisphosphonate of Rank Ligand Inhibitors are inadequate or contraindicated. Recommend getting an endocrinology consult prior to starting Calcitonin therapy.

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

d. **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 omega-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.\textsuperscript{4-12} Additional roles for statins in mediating improved renal function, control of hypertension, osteopenia, avascular necrosis, and even GVHD have been suggested.\textsuperscript{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: \url{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:

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
<th>LDL level to begin TLC (mg/dL)</th>
<th>LDL level to consider drug therapy (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-yr risk &gt; 20%: CHD or CHD risk equivalents</td>
<td>&lt;100</td>
<td>≥100</td>
<td>≥130</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+ risk factors</td>
<td>&lt;130</td>
<td>≥130</td>
<td>≥130 if 10-yr risk 10-20% or ≥160 if 10-yr risk &lt;10%</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-yr risk ≤ 10% 0-1 risk factors</td>
<td>&lt;160</td>
<td>≥160</td>
<td>≥190</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose* mg</th>
<th>Class Effects</th>
<th>Precautions and Monitoring</th>
</tr>
</thead>
</table>
| **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 inhibitorsb 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 (80c)    |               |                             |
| Rosuavastatin (Crestor)           | 5-40          |               |                             |

* 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 rosuvastatin (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:

<table>
<thead>
<tr>
<th>Abdominal obesity:</th>
<th>Waist circumference:</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Men</td>
<td>&gt;102 cm (&gt;40 inches)</td>
</tr>
<tr>
<td>– Women</td>
<td>&gt;88 cm (&gt;35 inches)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypertriglyceridemia</th>
<th>≥ 150 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low HDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>– Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>– Women</td>
<td>&lt;50 mg/dL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Per JNC7 [<a href="http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf">http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf</a>]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting hyperglycemia</td>
<td>≥ 150 mg/dL</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Non-HDL Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong>: 10-yr risk &gt; 20%: CHD or CHD risk equivalents</td>
<td>&lt;130</td>
</tr>
<tr>
<td><strong>Moderate</strong>: 10-yr risk ≤ 20% 2+ risk factors</td>
<td>&lt;160</td>
</tr>
<tr>
<td><strong>Low</strong>: 10-yr risk ≤ 20% 0-1 risk factors</td>
<td>&lt;190</td>
</tr>
</tbody>
</table>
Therapies for Hyperlipidemia for Adult Patients

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

*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). 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. 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:

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

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>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Anti-Hypertensive Therapy</th>
<th>Monitoring</th>
</tr>
</thead>
</table>
| **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 plusisosorbide may be beneficial, particularly in African Americans |
### Table 1 - Antihypertensive Medications According to Clinical Setting (continued)

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

CCB; calcium channel blockers,

* Definition of chronic kidney disease (CKD) criteria

1. Kidney damage for ≥ 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 m² for ≥ 3 months, with or without kidney damage

**Due to rare, potential complication of angioedema, caution should be exercised with use of ACE-1 inhibitors in combination with sirolimus. Use of ARB is acceptable.

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

<table>
<thead>
<tr>
<th>Spot Urine Albumin/creatinine ratio \n(U\textsubscript{ACR})</th>
<th>Interpretation</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less 30 mg/g</td>
<td>Normal</td>
<td>– Repeat U\textsubscript{ACR} in 1 year</td>
</tr>
<tr>
<td>30-300 mg/g without hypertension and not on hypertensive medications</td>
<td>Abnormal</td>
<td>– Repeat U\textsubscript{ACR} in 3-6 months</td>
</tr>
</tbody>
</table>
| 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\textsubscript{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\textsubscript{ACR} in 3 months |

**Due to rare, potential complication of angioedema, caution should be exercised with use of ACE-I inhibitors in combination with sirolimus. Use of ARB is acceptable.
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 ≥ 35 years) & education to reinforce self breast exams
3. Prostate exam and PSA (men ≥ 45 years)
4. Occult blood in stool (≥ 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 (≥ 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 uterus) or combined with progesterone (women with uterus) 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 preferentially is treated with bone strengthening drugs in combination with adequate calcium and vitamin D intake (See LTFU Section of Osteoporosis, XI).
- 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
New oral pain or dryness beyond day + 100 after allogeneic transplant suggests development of chronic GVHD involving the salivary glands or mucosal surface. Cultures for candida and DFA or rapid cultures for herpes simplex virus should be obtained to rule out concomitant infections if clinically indicated. A dental/oral medicine consultation should be strongly considered in all patients with oral complications. If you have questions about dental care during treatment for GVHD that are unanswered below, please call the LTFU office who will provide instructions on how to take oral cavity photos that you can send to ltfu@seattlecca.org with your clinical impression and question. Our LTFU/Oral Medicine can then review these and provide further advice. General guidelines for dental care for autologous and allogeneic transplant recipients are provided in the Table below.

General guidelines for dental care in hematopoietic transplant recipients include (see Table 1):

- **Routine dental health examinations** (with radiographs as needed) are recommended to monitor for tooth decay and oral hygiene effectiveness, gingivitis and/or periodontitis. Dental exams can take place **any time** after transplant and should be done every 6-12 months for routine oral health assessment, to evaluate/treat chronic GVHD (allogeneic patients) and to screen for oral cancers. *(see Table 1)*
- **Routine dental exam/cleanings** should be delayed for first 6 months after transplant due to increased risk of bacteremia and pneumonia while patients are still immunocompromised. After the first 6 months, routine *(not deep)* cleaning either by ultrasonic or manual dental scaling are reasonable provided certain other criteria are met *(see Table 1)*.
- **Periodontal therapy** *(Deep cleaning)* can be done after the first 6 months if the additional criteria over and above those set for routine cleaning are met *(see Table 1)*.
- **Elective** *(non-urgent/non-emergency)* *restorative dental treatment* like fillings and crowns, or *elective surgical procedures* like dental extraction of non-infected teeth, implants and gum graft surgery should be delayed until immunity is recovered and patient has discontinued systemic immunosuppressive treatments. *(see Table 1)*
- “Cosmetic” *dental care* like dentures are considered safe so long as no extractions or surgeries are needed. Veneers and other elective restorative procedures should be delayed. Teeth whitening is reasonable beyond 6 months posttransplant. Invisalign therapy is not
recommended within the first 6 months. Traditional orthodontia is deferred until patient has no active GVHD and is off all systemic immunosuppression. *(see Table 1)*

- *Emergency or Urgent Care* should be carefully coordinated between managing dentist/oral surgeon and medical team so that appropriate supportive and medical care can be discussed. **Important considerations include:**

  1. Prophylactic and/or therapeutic antibiotics to minimize risk of bacteremia complications:
     - a. For patients with an indwelling central venous catheters, follow American Heart Association (AHA) recommendations for low-moderate endocarditis risk.
     - b. For short non-surgical/non-invasive surgical procedures, also follow AHA prophylactic antibiotic recommendations, and extend treatment if there is significant local dental infection and risk of subsequent spread of infection (local or disseminated).
  2. Other strategies to reduce spread of infection:
     - a. Chlorhexidine oral rinse for 3 minutes immediately prior to treatment.
     - b. Minimize aspiration of aerosolized bacteria by using a rubber dam, high volume suction, minimal air-water sprays during procedures.
  3. Platelet support depending on invasiveness of treatment and risk of bleeding.
     Other medical support (e.g. stress dose steroids, adjustments to anticoagulation therapy).

**Other key points / recommendations:**

- More frequent cleanings may be required based on oral health conditions. Ultrasonic cleaning carries slightly more risk of aspiration than manual scaling but is generally acceptable.

- Patients should carry out focused and effective oral hygiene (brushing, flossing, etc.) as good oral hygiene can be protective in preventing oral GVHD flares.

- Patients with dry mouth should be placed on dental decay prevention regimen that minimally includes daily brush-on prescription-strength fluoride gel or toothpaste or rinses to reduce the risk of dental decay. Other measures to promote salivation should be encouraged (oral moisturizing agents, sugar-free gums or candy, and prescription drugs to stimulate saliva flow).

- Patients who have received **bisphosphonate therapy** or on or just completed **denosumab therapy** are at a risk for **osteonecrosis of the jaw (ONJ)**. Risk depends on the type of bisphosphonate, dose, frequency, and total duration of treatment. Reclast (zoledronic acid) is considered to be at very low risk for ONJ. Zometa (another brand of zoledronic acid) and pamidronate (Aredia) are considered to be at highest risk for development of ONJ. The risk for MRONJ in patients treated with oral bisphosphonates increases steadily over time and is of higher concern in those with greater than 3 years of use. Bisphosphonates will persist in bone for as long as 10-15 years after discontinuation. Denosumab (Xgeva) has also been associated with ONJ but the risk for ONJ with denosumab will decrease over 6-7 months after discontinuation. Patients who previously received bisphosphonates and switched to denosumab may be at an even higher risk for ONJ compared to either agent used alone.
Recommendations for patients who have received **bisphosphonate therapy** or on or just completed **denosumab therapy** are at a risk for **osteonecrosis of the jaw (ONJ):**

a. Prevent trauma and irritation from dentures

b. Support excellent dental and periodontal health in order to avoid advancing dental infections or problems that would ultimately need dental surgery to manage.

c. When patients at risk for ONJ need dental procedures, the *least* invasive but effective procedure to solve the problem should be chosen. Stabilization/restoration of a tooth with a root canal or crown is preferable to extracting the tooth.

d. Any dental surgery – extractions, implants, periodontal, or endodontic, is considered high risk for development of ONJ if there has been prior or ongoing therapy with bisphosphonates or denosumab therapy.

e. If the risk/benefit ratio has been explored and a tooth must be removed, the procedure should be done by a skilled Oral Surgeon who will use extreme caution to avoid any excessive trauma to the bone and achieve primary closure of the site.

- Special attention should be paid to **potential head and neck cancers** in transplant survivors – especially lip and oral cavity cancer. Risk is related to cumulative total body or local irradiation exposure and chronic GVHD.

**General guidelines include:**

a. Patient counseling to avoid additional risks, specifically, to follow protection against sun exposure to lips, avoid tobacco products and avoid excess alcohol beverage intake.

b. Adjunctive examination techniques such as increased uptake of applied toluidine blue vital dye within dysplastic or neoplastic oral mucosal lesions may be diagnostically helpful for screening.

c. Serial lesion photographs can be an important component of patient management.

d. Suspicious lesions should be managed comprehensively and followed closely until resolved or definitive diagnosis is made.
<table>
<thead>
<tr>
<th>Dental Procedure</th>
<th>Until 6 months</th>
<th>After 6 months ****</th>
<th>HIGH-RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LOW-RISK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine Dental Care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exam every 6-12 months</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Routine Dental Cleanings</td>
<td>NO</td>
<td>YES, with antibiotics if central line still in place</td>
<td>YES, with antibiotics and/or IVIG** as clinically indicated</td>
</tr>
<tr>
<td>Peridontal Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scaling/root planning +/- curettage (dental deep cleaning)</td>
<td>NO</td>
<td>YES, for autologous (no contraindications)</td>
<td>NO</td>
</tr>
<tr>
<td>Restorative Dental Care***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crowns</td>
<td>Emergent ONLY with antibiotics</td>
<td>Emergent ONLY with antibiotics</td>
<td>Emergent ONLY with antibiotics and/or IVIG</td>
</tr>
<tr>
<td>Fillings</td>
<td>Emergent ONLY with antibiotics</td>
<td>Emergent ONLY with antibiotics</td>
<td>Emergent ONLY with antibiotics and/or IVIG</td>
</tr>
<tr>
<td>Surgical Treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental extractions</td>
<td>Emergent ONLY with antibiotics</td>
<td>Emergent ONLY with antibiotics</td>
<td>Emergent ONLY with antibiotics and/or IVIG</td>
</tr>
<tr>
<td>Implants</td>
<td>NO</td>
<td>Autologous – NO</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allogeneic – NO</td>
<td></td>
</tr>
<tr>
<td>Gingival grafts</td>
<td>NO</td>
<td>YES, for autologous (no contraindications)</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>YES, for allogeneic with considerations for additional medical support</td>
<td></td>
</tr>
<tr>
<td>Cosmetic Dental Care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teeth whitening</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Orthodontia</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Dentures</td>
<td>YES, if no surgery needed</td>
<td>YES, if no surgery needed</td>
<td>YES, if no extractions are needed</td>
</tr>
</tbody>
</table>

Abbreviation: IST = immunosuppression; ANC = absolute neutrophils count, Plts = platelets.

* Prophylactic IST or prednisone dose < 0.5mg/kg/day is OK if GVHD considered inactive

** IVIG should be considered if serum IgG level is below 400 mg/dL

*** If treatment is urgent/or emergency due to overall immune/GVHD status – that is, dental disease is at risk for seriously compromising patient status, planning should consider strategies to reduce local and systemic infection spread and bleeding.

**** Beyond 1 year posttransplant, all dental procedures without additional precaution are OK, if all conditions below are met:

- No indwelling central venous catheter
- At least 3 months recovery from the last Rituxan
- No active GVHD defined by discontinuation of all IST at least for 8 months
- IgG level ≥ 400 mg/dL
- ANC >1000 cells/ul
- Platelet count > 30K/ul
- Not receiving cytotoxic therapy as maintenance treatment
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, opioids, 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

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

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

* 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 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. Bone loss can be minimized by decreasing glucocorticoid dose, optimizing calcium and vitamin D intake, participating in weight-bearing exercise, using bone strengthening drugs, and if clinically indicated by hormonal replacement therapy. Section XI provides detailed guidelines for preventing and monitoring osteoporosis in patients. 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 FEV₁/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.

Monitoring of lung function after day +100 after allogeneic transplant. Pulmonary function test (PFT) monitoring including: spirometry, lung volumes, and DLCO. PFTs for asymptomatic allo-HCT recipients:

a. At 6 months
b. At 1 year
c. Yearly thereafter until 5 years as clinically indicated
d. At diagnosis of chronic GVHD
i. Full PFT testing including: spirometry, lung volumes, and DLCO
ii. Q3 months after diagnosis of chronic GVHD for at least one year.
   (spirometry alone may be adequate)
iii. Thereafter, at Q6 months for 1 year (spirometry alone may be
     adequate)
iv. With at least yearly full PFT testing including: spirometry, lung
     volumes, and DLCO until year 5 post HCT.

(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).

  Four 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 GVHD can present as an acute hepatitis, usually after tapering or discontinuation of immunosuppressive medications, particularly cyclosporine or tacrolimus, or after DLI.
  4) In Hepatitis C infected patients, a diagnosis of fulminant immune-rebound hepatitis should be considered, especially if patient is tapering immunosuppression, and, if clinically indicated, treatment with Direct Acting Antiviral (DAA) drugs.

*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/mm³ 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 blood products should be irradiated to prevent transfusion related Graft Versus Host Disease (GVHD), with the exception of pathogen reduced blood products that do not need to be irradiated. Red blood cells and platelets should 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.
XII. 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 entecavir is approximately 12%. In hematopoietic cell transplant recipients who are anti-HBe 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

- For allogeneic transplant patients who had a donor who was either HBsAg or antiHepB core positive:
  Serum ALT and HBV DNA monthly to six months post transplant or 6 months after stopping entecavir (whichever is longer).
- For allogeneic transplant patients where patient is HBsAg positive and on entecavir: Monitor HBV DNA and serum ALT monthly until 6 months after stopping entecavir. If increased Serum ALT consider testing for viral resistance and switching to TAF if checked HBV DNA increased >1.0 log above nadir.

- For allogeneic transplant patients where patient is antiHepB core positive: Serum ALT and HBV DNA monthly until 6 months after stopping entecavir.

- For autologous transplant patients who is either HBsAg or antiHepB core positive:
  - Monitor HBV DNA and Serum ALT monthly until 6 months after stopping entecavir. If HBV DNA increases > 1.0 log above nadir. Consider testing for viral resistance and switching if medically indicated to TAF.

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. For patients already on entecavir and not appropriately responding, consider alternative antiviral therapy. 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. 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.

**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.
- 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?
- All HCV-infected long-term HCT survivors should be evaluated for progression of liver disease every 6 to 12 months with a hepatic function panel, complete blood count, and evaluation of prothrombin time/international normalized ratio. If fibrosis is suspected in long-term HCT survivors, noninvasive tests such as serologic panels and transient elastography can be used to evaluate for the presence of advanced fibrosis (Scoring System for Histological Stage Metavir score ≥ F3) and cirrhosis (Metavir score F4).
- For HCV-infected HCT long-term survivors with advanced fibrosis (Metavir score ≥ F3), surveillance for hepatocellular carcinoma with ultrasonography every 6 months is recommended. For patients with cirrhosis, endoscopic surveillance for esophageal varices is recommended.
Therapy

Direct-acting 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. Be aware of possible drug-drug interactions (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 Direct Acting Antiviral (DAA) therapies. 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)

In all HCT survivors with active HCV infection, cofactors that can lead to fibrosis should be addressed. Patients should be counseled to avoid excessive weight gain, ethanol and medications or herbal supplements that are hepatotoxic, as well as on treatment of other causes of liver disease (nonalcoholic fatty liver disease, hepatitis B virus, HIV, and extrahepatic obstruction), and mobilization of excess iron.

HCT recipients who develop end-stage liver disease can be considered for liver transplant; in rare cases, a living donor liver transplant from the original hematopoietic cell donor may be feasible.

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)
A. Summary of evidence

1. Epidemiology
Iron overload occurs frequently in hematopoietic cell transplantation (HCT) patients, often caused by red cell transfusions prior and during HCT, in addition to ineffective erythropoiesis with associated intestinal hyperabsorption, and, in some patients, underlying genetic hemochromatosis. Elevated ferritin estimates 32-58% of HCT survivors may be overloaded with iron [1, 2, 3]. One autopsy study found 40% of patients with significantly high liver iron content (LIC) above 5.6mg/g [4]. A cross-sectional study showed 31/56 HCT recipients had elevated ferritin, and 50% of those with high ferritin had significant liver siderosis with LIC>6.5mg/g [1].

2. Natural history of iron overload in HCT and its consequences
Once transplant has restored normal hematopoiesis and red cell transfusions are no longer required, body iron stores decline over several years [5]. Elevated liver iron content (LIC) defined as >1.8mg/g by R2-magnetic resonance imaging (MRI) was not associated with survival or complications at 1 year post-HCT [6]. High LIC (above 7mg/g) as determined by magnetic resonance in patients post HCT for myelodysplastic syndromes or acute myeloid leukemia was a significant risk factor for non-relapse mortality (particularly in older patients undergoing reduced intensity conditioning), and ferritin above 1,000ng/mL has been associated with decreased survival. [7;8, 9]. Extreme tissue iron overload (> 15 mg/g dry weight) has been associated with extensive organ toxicity in the post-transplant survivors of thalassemia, in whom 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. Iron overload increases the susceptibility to mucormycosis, aspergillosis, and infections caused by Listeria monocytogenes, non-cholera Vibrio species, Yersinia enterocolitica and Yersinia pseudotuberculosis, among others [2, 4]. In patients with chronic hepatitis C, iron overload may accelerate the development of cirrhosis.

3. Assessment of iron overload post-HCT
Although ferritin measurement is recommended as part of long-term follow-up post-HCT, it also changes with inflammation and cell injury. Assessment of body iron by MRI is non-invasive and has been calibrated with liver biopsies and ex vivo heart tissue iron measurements, allowing accurate and more frequent assessment of iron overload than liver biopsy [10]. Liver or marrow iron content correlates poorly with number of transfused red blood cell units. Marrow and liver iron contents have been determined by spectrophotometry among 10 consecutive autopsied patients who were transplanted for hematological malignancy. The median liver iron content (LIC) at 50 to 100 days post-transplant was 4.307 mg/g dry weight (range 1.832-13.120; normal 0.530-0.900) and the median marrow iron content was 1.999 mg/g dry weight (range 0.932-3.942). 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 [11]. Earlier work also demonstrated a close relationship between biochemical concentration and histologic grading of marrow iron [12] although histological grading is subject to variation between and within observers [13]. Because the carrier frequency for homozygous High Fe (HFE) gene mutations is relatively high (0.3 to 0.5%) among individuals of Northern and Western European ancestry, the possibility of hereditary hemochromatosis (HH) contributing to post-transplant iron overload needs to be considered in relevant individuals. Two point mutations, C282Y (Cys282Tyr) and H63D (His63Asp), are the most frequently found within the HFE gene. Homozygosity for C282Y is associated with hemochromatosis with variable penetrance; the effect of compound heterozygosity (C282Y/H63D) on iron status in HCT recipients is variable.

4. Management of iron overload post-HCT
Mobilization of iron in heavily overloaded patients improves cardiac function, normalizes serum alanine aminotransferase (ALT) levels, and results in improved liver histology [14;15]. Phlebotomies were well-tolerated by 14/16 patients, and they reached the target ferritin below 500ng/mL after a median of 16.5 phlebotomies in a median of 287 days [3]. Ferritin levels decreased significantly in 49/55 (80%) of patients after a median of 9 phlebotomies in another study [16]. One study showed that recipients of marrows from donors with mutated HFE had lower reduction in ferritin levels per phlebotomy than those who received marrow from wild-type donors [16]. A retrospective study found that deferoxamine use post-HCT in 37 patients was associated with lower ferritin and lower relapse incidence [17]. Oral chelation with 20-30mg/kg/day of deferasirox has been evaluated retrospectively and showed a possible association with longer survival after HCT [18], and a prospective, phase IV, open-label trial showed 10mg/kg/day of deferasirox provided a significant reduction in serum ferritin and liver iron concentration over one year of treatment with mild to moderate adverse events [19].

B. Evaluation of Iron Overload after HCT for autologous and allogeneic patients

1. Timepoints of evaluation:
   a. at 80-100 days post HCT;
   b. 1 year post HCT;
   c. at least yearly if still receiving red blood cell transfusions.

2. Laboratory testing:
   a. Iron studies (ferritin, iron, total iron-binding capacity [TIBC], and transferrin saturation [TS])

   Biochemical lab tests are non-specific and can be significantly affected by inflammation, infection (which falsely elevate ferritin and decrease iron, TIBC and TS) and graft versus host disease (GVHD) (which increases iron absorption), so biochemical tests should NOT be used as sole criteria to consider the presence of iron overload and should be confirmed by MRI-T2*. 
**b. HFE genotype**

Consider for patients with:

i. family member with diagnosed hereditary hemochromatosis (HH)

ii. TS > 45% AND Northern or Western European ethnicity.

Genetic analysis for other rare mutations described in association with hemochromatotic phenotypes such as in *HAMP* (hepcidin), *SLC40A1* (ferroportin), *HJV* (hemojuvelin), *TFR2* (transferrin receptor 2) genes is recommended on a case-by-case basis.

### 3. Assessment of Tissue Iron

#### a. Magnetic resonance - MRI-T2*

T2*-weighted magnetic resonance imaging test (MRI-T2*) is highly accurate in measuring tissue iron and is mainly used to determine iron in the heart and liver, but can also evaluate the spleen and pancreas. MRI-T2* is the preferred method of evaluation and requires orders for both Cardiac and Abdominal MRI, specifying the exam is for iron evaluation.

All patients should undergo MRI-T2* when being evaluated for iron overload. Lack of more than modest correlations of LIC with laboratory tests, such as ferritin, or with history of transfusion supports this approach. Most (if not all) patients will fulfill one or more of the criteria classically used to indicate evaluation for iron overload, such as:

- Lifetime history of receiving 10 RBC units or more;
- Transferrin saturation >45%;
- Ferritin >1000ng/mL;
- Documented diagnosis of hereditary hemochromatosis (HH) before HCT and suboptimal ferritin >100ng/mL,
- Need for iron chelation therapy before HCT.

**Note:** DO NOT perform MRI-T2* in patients with documented iron deficiency (ferritin below 20ng/mL and/or absence of stainable iron in the bone marrow).

Patients who are particularly encouraged to undergo MRI-T2* to rule out cardiac iron overload are those with risk factors such as:

1. Lifetime history of receiving 75 RBC units or more;
2. Thalassemias;
3. Sickle cell disease (particularly if transfused to HbS <10%);
4. Other congenital anemias (Diamond-Blackfan; hereditary sideroblastic);
5. Myelodysplastic syndromes;
6. Associated hereditary hemochromatosis (HH);
7. Hepatitis C virus (HCV)-positive.

**Note:** DO NOT perform MRI-T2* in patients with documented iron deficiency (ferritin below 20ng/mL and/or absence of stainable iron in the bone marrow).
b. **Endocrine screen:** Patients that fulfill criteria for iron overload (LIC>2mg/g), particularly those with detectable cardiac iron (T2*<20ms), may benefit from earlier screening for endocrine gland abnormalities secondary to iron overload with fasting glucose, thyroid stimulating hormone (TSH), free thyroxine (T4), parathyroid hormone (PTH), follicle stimulating hormone (FSH), and luteinizing hormone (LH).

c. **Transient elastography:** This is the preferred method if assessment of liver fibrosis and cirrhosis is a concern, particularly in thrombocytopenic patients for whom a liver biopsy poses significant risk of bleeding.

d. **Liver biopsy:** Given the risks of the procedure, risk of sampling variability, and indolent course of hepatic siderosis, measurement of hepatic iron by spectrophotometry of liver biopsy should be an exception to be discussed case-by-case, e.g. in patients with absolute contraindications to MRI.

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

<table>
<thead>
<tr>
<th>Cardiac T2* (ms)</th>
<th>LIC (mg/g dry weight)</th>
<th>Marrow Iron Content</th>
<th>Mobilization of Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20ms (normal)</td>
<td>&gt;15</td>
<td>Very high ++++</td>
<td>Phlebotomy ± single iron chelator</td>
</tr>
</tbody>
</table>
| 7 – 15           | Moderately high ++ to +++ | 1st choice: Phlebotomy  
|                  |                       | 2nd choice: Single iron chelator (especially if HCV-positive) |
| 2-7              | Mildly increased +    | 1) HFE<sup>wildtype</sup>: observe  
|                  |                       | 2) HFE<sup>C282Y/C282Y or C282Y/H63D</sup>, Phlebotomy aiming at ferritin level <100 |
| <20ms            | Any                   | Any                 | Phlebotomy + combination iron chelation; consider admission if symptomatic or T2*<8ms; consider erythrocytapheresis for faster removal |

### C. Phlebotomy for iron overload after HCT
- If indicated, phlebotomy is likely to be the safest and most cost-effective approach for the mobilization of tissue iron.
- Regular phlebotomy requires adequate venous access, normal hematopoiesis or hematopoiesis that can respond satisfactorily to weekly or every-other-week erythropoietic stimulating agents (ESAs).
- **Phlebotomy Regimen:**
  - Phlebotomy volume: 5 mL/kg as tolerated
  - Frequency: every 3-4 weeks as tolerated
  - Monitoring monthly: CBC, ferritin, iron, TIBC, and TS
  - Discontinue Phlebotomy: Symptomatic anemia with hematocrit below 35%, or MRI-T2* LIC below 7mg/g (non-HH patients), or ferritin below 500ng/mL (non-HH patients), or ferritin below 100ng/mL (hereditary hemochromatosis (HH) patients)
Erythropoietic Stimulating Agents (ESAs) may be administered subcutaneously to facilitate regular phlebotomy. The smallest number of whole vials should be prescribed per dose:

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Erythropoietin1 (Units weekly)</th>
<th>Darbepoetin2 (micrograms every-other-week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14</td>
<td>6,000 to 8,000</td>
<td>25 to 60</td>
</tr>
<tr>
<td>15-20</td>
<td>10,000</td>
<td>60</td>
</tr>
<tr>
<td>21-24</td>
<td>10,000 to 14,000</td>
<td>60 to 100</td>
</tr>
<tr>
<td>25-29</td>
<td>14,000</td>
<td>100</td>
</tr>
<tr>
<td>30-39</td>
<td>20,000</td>
<td>100</td>
</tr>
<tr>
<td>40-60</td>
<td>40,000</td>
<td>200</td>
</tr>
<tr>
<td>&gt;60</td>
<td>Use darbepoetin</td>
<td>200</td>
</tr>
</tbody>
</table>

1 Erythropoietin (Epogen) vial sizes (2,000; 4,000; 10,000; 20,000; 40,000 units)
2 Darbepoetin (Aranesp) vial sizes (25; 60; 100; 150; 200; 300 micrograms)

Erythrocytapheresis is a grade 1B recommendation for iron overload in hereditary hemochromatosis (HH). It has been compared with phlebotomies in two randomized studies with hereditary hemochromatosis (HH) patients, with faster removal of iron, no differences in adverse events, and controversial differences in cost [20,21].

Note: Though patients with GVHD continue to hyperabsorb iron from dietary sources and may be an exception to the normal situation when patients mobilize their excessive iron stores when effective erythropoiesis returns after HCT.

D. Chelation therapy for iron overload after HCT

- If phlebotomy or erythrocytapheresis cannot be performed despite the use of ESAs within 3 - 6 months after transplantation, and if treatment to mobilize iron stores is indicated (see item 4 above), iron chelation therapy with single agents desferoxamine (DFO) - Desferal or deferasirox (DFX) - Exjade or Jadenu - should be initiated. Patients with evidence of cardiac iron overload should undergo combination therapy (DFO and deferiprone – DFP, Ferriprox).

1. Deferoxamine (DFO) - Desferal
   1.1. Administration:
   DFO can be administered by continuous subcutaneous or intravenous infusion with less toxicity if administered subcutaneously.

   1.2. Toxicity:
   Ocular and auditory abnormalities, sensorimotor neurotoxicity, renal insufficiency, pulmonary toxicity, and failure of linear growth. In rare cases, treatment with DFO has enhanced susceptibility to certain microorganisms, such as *Vibrio vulnificus*, *Yersinia enterocolitica* and *Yersinia pseudotubera*, among others, resulting in generalized infections by providing these agents with a siderophore otherwise missing.
   1.2.1. AVOID ascorbic acid (vitamin C) (>200mg/day) in patients receiving DFO due to possible impact on left ventricular function. DO NOT administer ascorbic acid with DFO in patients with heart failure.
1.2.2. Toxicity can be avoided by regular assessment of the body iron stores with annual MRI-T2*. In general, assessment of body iron stores should also follow when deferoxamine toxicity occurs.

1.3. Dosing:
20 to 40 mg/kg/day, administered 5-7 days per week by continuous overnight infusion, typically for 8-12 hours.
Dose should not exceed 50 mg/kg/day
Infusion rate should not exceed 15 mg/kg/hour to avoid hypotension.

1.4. Monitoring:
1.4.1. Prior to starting treatment: obtain baseline CBC, creatinine, ferritin, liver function tests, audiogram, and eye examinations.
1.4.2. Monthly complete blood count (CBC), ferritin, creatinine, and liver function tests.
1.4.3. Therapeutic index: Most of the toxicity caused by deferoxamine occurs when the dose exceeds 50 mg/kg/day or when the iron burden is not high. Dose reductions can be done by aiming at a therapeutic index below 0.025. Therapeutic index is calculated by: (number of days per week X daily dose in mg/kg) / (7 X serum ferritin in ng/mL) [22].
1.4.4. Discontinue for six months if LIC < 3 mg/g dry weight, or marrow iron content is not increased or only mildly increased. Thereafter, the dose of DFO should be adjusted to maintain liver iron content between 3 and 7 mg/g dry weight and therapeutic index below 0.025.

Suggested monitoring of DFO-related toxicity is shown below.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Tests</th>
<th>Frequency</th>
<th>Alteration In Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>High frequency sensorineural hearing loss</td>
<td>Audiogram</td>
<td>Annually; if symptomatic, check immediately</td>
<td>Stop DFO; repeat audiogram at 3 month intervals until normal or stable</td>
</tr>
<tr>
<td>Retinopathy (pigmentary degeneration); cataracts; corneal opacities; visual impairment</td>
<td>Eye exam including visual acuity, slit-lamp and fundoscopy</td>
<td>Annually; if symptomatic, check immediately</td>
<td>Stop desferoxamine if retinopathy or hearing impairment</td>
</tr>
<tr>
<td>Metaphyseal/Spinal</td>
<td>Plain x-ray of wrists, knees, spine; bone age in children</td>
<td>Annually</td>
<td>Reduce deferoxamine to 20-25 mg/kg/day</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>Sitting and standing height</td>
<td>Every 6 months</td>
<td>Reduce deferoxamine to 20-25 mg/kg/day; reassess every 6 months</td>
</tr>
</tbody>
</table>

2. Deferasirox (DFX) - Exjade, Jadenu, or Jadenu Sprinkles
2.1. Contraindications:
   a) Serum creatinine greater than two times the age-appropriate upper limit of normal or creatinine clearance less than 40 mL/min;
   b) Poor performance status;
c) High-risk myelodysplastic syndromes;
d) Advanced malignancies;
e) Platelet counts less than 50,000;
f) Known hypersensitivity to DFX or any component of the medication.

2.2. Toxicity:
Gastrointestinal (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 DFX. The relation to DFX in these cases is uncertain.

2.3. Dosing: see below, items 2.6 and 2.7.

2.4. Monitoring:
2.4.1. Prior to starting treatment: obtain baseline CBC, creatinine with clearance
estimation in duplicate, ferritin, liver function tests, audiogram, and eye
examinations.
2.4.2. Monthly CBC, ferritin, creatinine, urine protein levels, and liver function tests.
2.4.3. Discontinue temporarily if ferritin level falls below 500ng/mL.

Suggested monitoring of DFX-related toxicity is shown below.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Tests</th>
<th>Frequency</th>
<th>Alteration In Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>High frequency sensorineural hearing loss</td>
<td>Audiogram</td>
<td>Annually; if symptomatic, check immediately</td>
<td>Stop DFX; repeat audiogram at 3 month intervals until normal or stable</td>
</tr>
<tr>
<td>Retinopathy (pigmentary degeneration); cataracts; corneal opacities; visual impairment</td>
<td>Eye exam including visual acuity, slit-lamp and fundoscopy</td>
<td>Annually; if symptomatic, check immediately</td>
<td>Stop DFX if retinopathy or hearing impairment</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Creatinine and protein/creatinine ratio</td>
<td>Creatinine weekly for the first month, then monthly; Protein/creatinine ratio every 3 months</td>
<td>See dose modification below (items 2.5.4 and 2.6.4)</td>
</tr>
</tbody>
</table>

2.5. Specific information about Exjade
2.5.1. Exjade is available in 125mg, 250mg, and 500mg tablets;
2.5.2. Starting dose: 20mg/kg/day.
2.5.3. Dose modification: 5-10mg/kg/day increments every 3-6 months if necessary depending on serum ferritin trends. Doses should not exceed 40mg/kg/day.
2.5.4. Dose reduction: 50% for starting dose if creatinine clearance 40-60mL/min or moderate (Child-Pugh B) hepatic impairment. If the serum creatinine level increases more than 33% over the course of two consecutive visits, the dose 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.

2.5.5. **Administration**: Exjade 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 \(\geq 1\) 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.

2.6. **Specific information about Jadenu and Jadenu Sprinkles**

2.6.1. Jadenu is available in 90mg, 180mg, and 360mg tablets or granules (Jadenu Sprinkles).

2.6.2. **Starting dose**: 14mg/kg/day.

2.6.3. **Dose modification**: 3.5-7mg/kg/day increments every 3-6 months if necessary depending on serum ferritin trends. Doses should not exceed 28mg/kg/day.

2.6.4. **Dose reduction**: 50% for starting dose if creatinine clearance 40-60mL/min/1.73m² or moderate (Child-Pugh B) hepatic impairment. If the serum creatinine level increases more than 33% over the course of two consecutive visits, the dose should be reduced by 7mg/kg. For pediatric patients, the dose should be reduced by 7mg/kg if the serum creatinine is greater than the upper limit of normal on 2 consecutive visits.

2.6.5. **Administration**: Jadenu should be taken once daily preferably at the same time of the day, on an empty stomach or with a light meal (contains less than 7% fat content and approximately 250 calories). Examples of light meals include 1 whole wheat English muffin, 1 packet jelly (0.5 ounces), and skim milk (8 fluid ounces) or a turkey sandwich (2 oz. turkey on whole wheat bread w/ lettuce, tomato, and 1 packet mustard). Jadenu tablets may be crushed and mixed with soft foods (e.g., yogurt or apple sauce) immediately prior to use and administered orally. Commercial crushers with serrated surfaces should be avoided for crushing a single 90 mg tablet. The dose should be immediately and completely consumed and not stored for future use. Take Jadenu Sprinkles by sprinkling the full dose on soft food (e.g. yogurt or apple sauce) immediately prior to use and administered orally. Doses should be separated by 2 hours from aluminum containing antacids.

3. **Combination therapy: deferoxamine – Desferal, and deferiprone (DFP) - Ferriprox**

3.1. In combination therapy, deferoxamine should be prescribed as above, preferably 7 days a week; if patient is admitted, it may be placed as a 24-hour infusion.

3.2. Deferiprone is an oral medication for iron chelation, available in 500mg tablets and 100mg/mL oral solution.

3.3. **Contraindications**: severe hepatic impairment, creatinine clearance below 15mL/min/1.73m², known hypersensitivity to deferiprone or any component of the medication.

3.4. **Toxicity**: neutropenia (6.2%), agranulocytosis (1.7%), zinc deficiency, chromaturia (reddish brown discoloration of the urine), GI symptoms (nausea, vomiting, abdominal pain or discomfort), joint pain, headache.
3.4.1 Avoid concomitant use of drugs known to be associated with neutropenia or agranulocytosis if possible.

3.5. **Starting dose:** 25mg/kg tid (75mg/kg/day daily). Maximum dose is 33mg/kg tid (daily total 99mg/kg/day).

3.6. **Dose reduction:** not recommended for mild or moderate liver impairment, or creatinine clearance above 15ml/min/1.73m².

3.7. **Administration:** take first dose in the morning, second dose at midday, third dose in the evening, with meal. Allow at least 4-hour intervals between deferiprone and medications or supplements containing polyvalent cations, e.g. aluminum or zinc.

3.8. **Monitoring:**
   3.8.1. **Prior to starting treatment:** obtain complete blood count with neutrophil count, serum transaminases, and zinc levels.
   3.8.2. **Weekly neutrophil counts**
   3.8.3. **Monthly ferritin, transaminases, and zinc.**
   3.8.4. **Discontinue if ferritin level falls below 500ng/mL.**
   3.8.5. **Management of neutropenia:** discontinue DFP and all medications that can cause neutropenia and follow blood counts daily until recovery. DO NOT resume DFP in patients who develop agranulocytosis, DO NOT rechallenge patients with neutropenia above 500 unless benefit outweighs the risks.
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.

i. CALCIUM REQUIREMENTS FOR PATIENTS DURING STEROID THERAPY:

<table>
<thead>
<tr>
<th>Age</th>
<th>Daily Minimum Requirement after Transplant (milligrams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-12 months</td>
<td>600 mg/day</td>
</tr>
<tr>
<td>1-3 years</td>
<td>1000 mg/day</td>
</tr>
<tr>
<td>4-8 years</td>
<td>1200 mg/day</td>
</tr>
<tr>
<td>≥ 9 years</td>
<td>1500 mg/day</td>
</tr>
</tbody>
</table>

Calcium intake above these levels is not recommended, as it may interfere with the absorption of other nutrients.

ii. CALCIUM REQUIREMENTS FOR PATIENTS NOT ON STEROIDS

<table>
<thead>
<tr>
<th>Age</th>
<th>Daily Minimum Requirement after Transplant (milligrams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 7-12 months</td>
<td>260</td>
</tr>
<tr>
<td>Children 1-3 years</td>
<td>700</td>
</tr>
<tr>
<td>Children 4-8 years</td>
<td>1000</td>
</tr>
<tr>
<td>Children 9-18 years</td>
<td>1300</td>
</tr>
<tr>
<td>Adult Males</td>
<td>1000-1200</td>
</tr>
<tr>
<td>Adult Females; On hormone therapy</td>
<td>1000-1200</td>
</tr>
<tr>
<td>Adult Females; No hormone therapy</td>
<td>1500</td>
</tr>
</tbody>
</table>
### iii. Vitamin D requirement

#### Table 1: Vitamin D3 (or D2) Supplementation*,****

<table>
<thead>
<tr>
<th>Treatment of Insufficiency [Vitamin D (25 Hydroxy) levels 20-30 ng/mL]</th>
<th>Adults (&gt;18 yrs)</th>
<th>Children (&lt;18 yrs)</th>
</tr>
</thead>
</table>
| Routine | 25 mcg/day | Age < 1 yr:
- 10 mcg daily
(20 mcg in dark skinned)
Age 1-8 yr:
- 15 mcg daily
Age 9-18 yr:
- 20 mcg daily |
| Malabsorption syndromes** | 1,250 mcg per week | Age < 1 yr:
- Consult Endocrinology
Age 1-18 yr:
- 1,250 mcg per week or
- 125 mcg daily |
| Chronic Renal Disease | Consult Nephrology | Consult Nephrology |

<table>
<thead>
<tr>
<th>Treatment of Deficiency [Vitamin D (25 Hydroxy) level &lt;20 ng/mL]***</th>
<th>Adults (&gt;18 yrs)</th>
<th>Children (&lt;18 yrs)</th>
</tr>
</thead>
</table>
| Uncomplicated | 1,250 mcg per wk x 8 (Repeat if Vitamin D (25 Hydroxy) level < 30 ng/mL otherwise treat as for insufficiency above) | Age 1-12 months:
- 25-50 mcg daily x 8 wks
Age 1-18 yr:
- 25-125 mcg daily x 8 wks
or
- 1,250 mcg weekly x 8
(Repeat if Vitamin D (25 Hydroxy) level < 30 ng/mL otherwise treat as for insufficiency above) |
| Malabsorption syndromes** | 250-1,250 mcg daily or every other day
- UVB irradiation in patients also with skin GVHD | Age < 1 yr:
- Consult Endocrinology
Age 1-18 yr:
- 1,250 mcg per week |
| Chronic Renal Disease | Consult Nephrology | Consult Nephrology |

*Currently there does not seem to be 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 50 mcg daily for 50 days is approximately equivalent to giving 1,250 mcg monthly for 2 months.

**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.

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

****1000 IU = 25mcg
50,000 IU = 1,250 mcg
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.
<table>
<thead>
<tr>
<th>Phase</th>
<th>Symptoms</th>
<th>Diet</th>
<th>Diet Intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Bowel rest</td>
<td>GI cramping</td>
<td>Oral: NPO</td>
<td>Increased stool volume or diarrhea</td>
</tr>
<tr>
<td></td>
<td>Large volume watery diarrhea</td>
<td>IV: stress energy and protein Requirements</td>
<td>Increased emesis</td>
</tr>
<tr>
<td></td>
<td>Depressed serum albumin</td>
<td></td>
<td>Increased abdominal Cramping</td>
</tr>
<tr>
<td></td>
<td>Severely reduced transit time</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Small bowel obstruction or diminished bowel sounds</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea and vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Introduction of</td>
<td>Minimal GI cramping</td>
<td>Oral: isosmotic, low-residue, low-lactose beverages, initially 60 ml every 2-3 hours, for several days</td>
<td></td>
</tr>
<tr>
<td>oral feeding</td>
<td>Diarrhea less than 500 ml/day</td>
<td>IV: as for Phase 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Guaiac-negative stools</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Improved transit time (minimum 1.5 hours)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infrequent nausea and vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Introduction of solids</td>
<td>Minimal or no GI cramping</td>
<td>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</td>
<td>As in Phase 2</td>
</tr>
<tr>
<td></td>
<td>Formed stool</td>
<td>IV: as for Phase 1</td>
<td></td>
</tr>
<tr>
<td>4. Expansion of diet</td>
<td>Minimal or no GI cramping</td>
<td>Oral: minimal lactose(^a), low fiber, low total acidity, no gastric irritants; if stools indicate fat malabsorption: low fat(^b)</td>
<td>As in Phase 2</td>
</tr>
<tr>
<td></td>
<td>Formed stool</td>
<td>IV: as needed to meet nutritional requirements</td>
<td></td>
</tr>
<tr>
<td>5. Resumption of regular</td>
<td>No GI cramping</td>
<td>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.</td>
<td>As in Phase 2</td>
</tr>
<tr>
<td>diet</td>
<td>Normal stool</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal transit time</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal albumin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Lactose is one of the last disaccharidases to return following villous atrophy. A commercially-prepared lactose solution (Lactaid\(^b\)) is used to reduce the lactose content of milk by >90%. Lactaid\(^b\) 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.

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](http://www.seattlecca.org) under *patientsandfamilies/nutritionDietsguidelines, 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).

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

Guidelines for Sending Clinical Specimens
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 FORMS
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


**Iron Overload:**


14. Emanuele Angelucci, Pietro Muretto, Guido Lucarelli, Marta Ripalti, Donatella Baroncianl, Buket Erer, Maria Galimberti, Claudio Giardini, Djavid Gaziev, Paola Polchi and the Italian Cooperative Group for Phlebotomy


### IV Immunoglobulin:


References:
20. Wang GJ, Cui Q, Balian G. The pathogenesis and prevention of steroid-induced osteonecrosis

Hypertension


Liver:

Prevention of Osteoporosis and Glucocorticosteroid Induced Osteoporosis:
APPENDIX A

FAX LTFU CONSULT

Date: __________

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

From: ______________________________
Fax: ________________________________

Phone: (206) 667-4415

Phone: ______________________________

Patient name: _______________________________ Date of birth: ______________________

Current GVHD Treatments (check all the apply):

☐ Corticosteroids: ☐ daily ☐ alternate day (dose: _________) ☐ Trimethoprim-sulfamethoxazole
☐ Cyclosporine (Neoral, Sandimmune) (or equivalents) ☐ Penicillin
☐ Tacrolimus (FK506) ☐ Dapsone
☐ Mycophenolate Mofetil (MMF) (Cellcept) ☐ Acyclovir or valacyclovir
☐ Thalidomide (Thalomid) ☐ Ganciclovir, ValGANCiclovir
☐ Rituximab ☐ Fluconazole or itraconazole
☐ Extracorporeal photopheresis (ECP)
☐ Other:
☐ No immunosuppressive medications

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 (______) _________________

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## APPENDIX C

### FORM FOR DESCRIPTION OF SKIN INVOLVEMENT

<table>
<thead>
<tr>
<th>Region</th>
<th>% Area Involved</th>
<th>Region</th>
<th>% Area Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>(9%)</td>
<td>Right leg</td>
<td>(8%)</td>
</tr>
<tr>
<td>Neck</td>
<td>(1%)</td>
<td>Right foot</td>
<td>(1%)</td>
</tr>
<tr>
<td>Chest</td>
<td>(9%)</td>
<td>Left arm</td>
<td>(4%)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>(9%)</td>
<td>Left forearm</td>
<td>(4%)</td>
</tr>
<tr>
<td>Back</td>
<td>(18%)</td>
<td>Left hand</td>
<td>(1%)</td>
</tr>
<tr>
<td>Right arm</td>
<td>(4%)</td>
<td>Left hand</td>
<td>(1%)</td>
</tr>
<tr>
<td>Right forearm</td>
<td>(4%)</td>
<td>Left thigh</td>
<td>(8%)</td>
</tr>
<tr>
<td>Right hand</td>
<td>(1%)</td>
<td>Left leg</td>
<td>(8%)</td>
</tr>
<tr>
<td>Right thigh</td>
<td>(8%)</td>
<td>Left foot</td>
<td>(1%)</td>
</tr>
</tbody>
</table>

**DATE OF ASSESSMENT:** _______________

**NAME:**

**Date of Birth:**
### APPENDIX –D (Pages 1-3 of the CHRONIC GVHD ASSESSMENT AND SCORING FORM)

<table>
<thead>
<tr>
<th>Patient:</th>
<th>/ UW#</th>
<th>Date Evaluation:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>PERFORMANCE SCORE:</th>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS ECOG LPS</td>
<td>□ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)</td>
<td>□ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)</td>
<td>□ Symptomatic, ambulatory, capable of self-care, &gt;50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)</td>
<td>□ Symptomatic, limited self-care, &gt;50% of waking hours in bed (ECOG 3-4, KPS or LPS &lt;60%)</td>
</tr>
</tbody>
</table>

| SKIN† | | |
|-------| | |
| SKIN % BSA | | |
| **GVHD features to be scored by BSA:** | No BSA involved | 1-18% BSA | 19-50% BSA | >50% BSA |
| **Check all that apply:** | | | | |
| □ Maculopapular rash/erythema | | | | |
| □ Lichen planus-like features | | | | |
| □ Sclerotic features | | | | |
| □ Papulosquamous lesions or ichthyosis | | | | |
| □ Keratosis pilaris-like GVHD | | | | |

| SKIN FEATURES SCORE: | | |
|----------------------|-----------------------|
| □ No sclerotic features | □ Superficial sclerotic features “not hidebound” (able to pinch) | □ Deep sclerotic features | □ “Hidebound” (unable to pinch) |
| | | □ Impaired mobility | □ Ulceration |

**Other skin GVHD features (NOT scored by BSA):**
<table>
<thead>
<tr>
<th>Check all that apply:</th>
<th>Abnormality present but explained entirely by non-GVHD documented cause (specify):</th>
<th>Abnormality thought to represent GVHD PLUS other causes (specify):</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Hyperpigmentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Hypopigmentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Poikiloderma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Severe or generalized pruritus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Hair involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Nail involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Abnormality present but explained entirely by non-GVHD documented cause (specify):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Abnormality thought to represent GVHD PLUS other causes (specify):</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MOUTH**
<table>
<thead>
<tr>
<th>Lichen planus-like features present:</th>
<th>No symptoms</th>
<th>Mild symptoms with disease signs but not limiting oral intake significantly</th>
<th>Moderate symptoms with disease signs with partial limitation of oral intake</th>
<th>Severe symptoms with disease signs on examination with major limitation of oral intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Yes</td>
<td></td>
<td>□ No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormality present but explained entirely by non-GVHD documented cause (specify):</th>
<th>Abnormality thought to represent GVHD PLUS other causes (specify):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.
## Appendix D

**Pages 1-3 of the Chronic GVHD Assessment and Scoring Form**

### Patient:

<table>
<thead>
<tr>
<th><strong>Score</strong></th>
<th><strong>Score 0</strong></th>
<th><strong>Score 1</strong></th>
<th><strong>Score 2</strong></th>
<th><strong>Score 3</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eyes</strong></td>
<td>No symptoms</td>
<td>Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)</td>
<td>Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops &gt; 3 x per day or punctal plugs), <strong>WITHOUT</strong> new vision impairment due to KCS</td>
<td>Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) <strong>OR</strong> unable to work because of ocular symptoms <strong>OR</strong> loss of vision due to KCS</td>
</tr>
</tbody>
</table>

- Abnormality present but explained entirely by non-GVHD documented cause (specify): __________________________________________________________________________________________
- Abnormality thought to represent GVHD **PLUS** other causes (specify): __________________________________________________________________________________________

### GI Tract

**Check all that apply:**

- Esophageal web/proximal stricture or ring
- Dysphagia
- Anorexia
- Nausea
- Vomiting
- Diarrhea
- Weight loss ≥ 5%*
- Failure to thrive

- Abnormality present but explained entirely by non-GVHD documented cause (specify): __________________________________________________________________________________________
- Abnormality thought to represent GVHD **PLUS** other causes (specify): __________________________________________________________________________________________

### Liver

- Normal total bilirubin and ALT or AP < 3 x ULN
- Normal total bilirubin with ALT ≥ 3 to 5 x ULN or AP ≥ 3 x ULN
- Elevated total bilirubin but ≤ 3 mg/dL or ALT > 5 ULN
- Elevated total bilirubin > 3 mg/dL

- Abnormality present but explained entirely by non-GVHD documented cause (specify): __________________________________________________________________________________________
- Abnormality thought to represent GVHD **PLUS** other causes (specify): __________________________________________________________________________________________

### Lungs**

**Symptom score:**

- No symptoms
- Mild symptoms (shortness of breath after climbing one flight of steps)
- Moderate symptoms (shortness of breath after walking on flat ground)
- Severe symptoms (shortness of breath at rest; requiring O2)

**Lung score:**

- % FEV1
- FEV1 ≥ 80%
- FEV1 60-79%
- FEV1 40-59%
- FEV1 ≤ 39%

- Pulmonary function tests: Not performed

- Abnormality present but explained entirely by non-GVHD documented cause (specify): __________________________________________________________________________________________
- Abnormality thought to represent GVHD **PLUS** other causes (specify): __________________________________________________________________________________________

*Weight loss within 3 months. **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. ***FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.*
<table>
<thead>
<tr>
<th>Patient:</th>
<th>SCORE 0</th>
<th>SCORE 1</th>
<th>SCORE 2</th>
<th>SCORE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>JOINTS AND FASCIA</td>
<td>□ No symptoms</td>
<td>□ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL</td>
<td>□ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL</td>
<td>□ Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)</td>
</tr>
<tr>
<td>P-ROM score</td>
<td>(see below)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoulder (1-7)</td>
<td>□</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbow (1-7)</td>
<td>□</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wrist/finger (1-7)</td>
<td>□</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle (1-4)</td>
<td>□</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Abnormality present but explained entirely by non-GVHD documented cause (specify):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Abnormality thought to represent GVHD PLUS other causes (specify):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GENITAL TRACT</td>
<td>□ No signs</td>
<td>□ Mild signs† and females with or without discomfort on exam</td>
<td>□ Moderate signs† and may have symptoms with discomfort on exam</td>
<td>□ Severe signs† with or without symptoms</td>
</tr>
<tr>
<td>(See Supplemental figure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently sexually active</td>
<td>□ Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Abnormality present but explained entirely by non-GVHD documented cause (specify):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Abnormality thought to represent GVHD PLUS other causes (specify):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0, mild -1, moderate -2, severe – 3)</td>
<td>□ Ascites (serositis)</td>
<td>□ Myasthenia Gravis</td>
<td>□ Eosinophilia &gt; 500/μl</td>
<td></td>
</tr>
<tr>
<td>□ Pericardial Effusion</td>
<td>□ Peripheral Neuropathy</td>
<td>□ Platelets &lt; 100,000/μl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Pleural Effusion(s)</td>
<td>□ Polyosomatosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Nephrotic syndrome</td>
<td>□ Weight loss &gt; 5%* without GI symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Others (specify):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy obtained: □ Yes □ No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ biopsied:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ GVHD confirmed by histology: □ Yes □ No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall GVHD Severity (Opinion of the evaluator)</td>
<td>□ No GVHD</td>
<td>□ Mild</td>
<td>□ Moderate</td>
<td>□ Severe</td>
</tr>
<tr>
<td>Change from prior evaluations: □ No prior or current GVHD</td>
<td>□ Improved</td>
<td>□ Stable</td>
<td>□ Worse</td>
<td>□ N/A (baseline)</td>
</tr>
<tr>
<td>Photographic Range of Motion (P-ROM):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed by:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date form completed:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>Area of Body</th>
<th>Dates:</th>
<th>Range</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior chest</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingers R</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsum of hands R</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearms R</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper arms R</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thighs R</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower legs R</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsum of feet R</td>
<td></td>
<td>0-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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APPENDIX F

Name________________________ DOB____/____/____ Date____/____/____

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

<table>
<thead>
<tr>
<th>Minimum</th>
<th>Flexibility</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
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</table>

Shoulder

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<th>Flexibility</th>
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</tr>
</thead>
<tbody>
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<td>6</td>
</tr>
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Elbow

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<th>Flexibility</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
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Wrist and fingers

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Foot Dorsiflexion

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<tbody>
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