FRED HUTCHINSON CANCER CENTER

May 05, 2025

LONG-TERM FOLLOW-UP AFTER HEMATOPOIETIC STEM CELL TRANSPLANT

GENERAL GUIDELINES FOR REFERRING PHYSICIANS

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

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I. HOW TO CONTACT THE LONG-TERM FOLLOW-UP OFFICE AT THE FRED HUTCHINSON CANCER CENTER

We offer telephone consultation to all physicians caring for patients who have been transplanted at the Fred Hutchinson Cancer Center (Fred Hutch). 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/ltfu by clicking on "Information for Physicians" in the left hand navigation column. Then click on the right blue “GVHD Tips & Forms" button. Here you will find the Chronic GVHD Assessment and Scoring form (Appendix D), Range of Motion Assessment form (Appendix F), Skin Thickness Assessment form/ Rodnan Score for patients with sclerosis or fasciitis (Appendix E) and other helpful information. More detailed information about chronic GVHD is outlined in Section X.

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

III. LABORATORY TESTS

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

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

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

D. Drug levels:

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

Note: If patients is on immunosuppressive therapy like Cyclosporine, Tacrolimus, or Sirolimus with Maribavir because of drug-drug interaction, check two times per week immunosuppressive drug levels for the first two weeks at start of Maribavir and for two weeks after stopping of Maribavir. Otherwise, monitor immunosuppressive drug levels at least once a week or as clinically indicated. Adjust immunosuppressive drug dose as needed.

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

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

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

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

H **CMV monitoring** in blood should be instituted for all patients who are at risk of CMV disease after transplant. PCR is the standard assay for CMV surveillance.

Initial CMV Monitoring

CMV **seropositive recipients** of <u>non-cord blood</u> allogeneic transplants or CD34 selected autologous transplants should have CMV monitored in blood *weekly until day 100* after transplant. CMV **seropositive cord blood recipients** should have CMV monitored *twice weekly until day 100* after transplant. CMV **seronegative recipients of cord blood** should have CMV monitored *weekly until day 100 days* after transplant. CMV **seronegative/seronegative 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 Letermovir 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 <u>≥</u> 0.5 mg/kg/day prednisone or prednisone equivalent or other agents (e.g., MMF, ibrutinib, etc.) for either late acute or chronic GVHD.

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

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

Patients who are allergic to sulfa should be desensitized whenever possible. If desensitization is not feasible, Dapsone should be administered at a dose of 50 mg p.o. b.i.d. daily for adults and 1 mg/kg/day in two divided doses (up to 100 mg/day) for children. Before starting treatment with Dapsone, patients must be tested to rule out G-6-PD deficiency. 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 $\geq$ 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.

A. Acyclovir should be administered according to the following regimen (assuming adequate renal function) if receiving < 0.5 mg/kg/day of corticosteroids:
   - Weight ≥ 40 kg: acyclovir 800 mg P.O. B.I.D.*
   - Weight < 40-10 kg: acyclovir 600 mg/m^2 P.O. B.I.D. (max 800* mg/dose)
   - Infants < 10 kg: acyclovir 20 mg/kg P.O. B.I.D.

B. In patients receiving ≥ 0.5 mg/kg/day of corticosteroids with adequate renal function:
   - Weight ≥ 40 kg: valacyclovir 500 mg P.O. B.I.D.
   - Weight < 40-10 kg: valacyclovir 250 mg P.O. B.I.D. or in pediatric patient can consider acyclovir 600 mg/m^2 P.O. B.I.D. (max 800 mg/dose)
   - Infants < 10 kg without oral intake: acyclovir 8.3 mg/kg IV q 12 hours

*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 < 40-10 kg, the dose of acyclovir should be 300 mg/m^2 (maximum 400 mg) P.O. B.I.D.

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

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

C. Encapsulated bacteria

Patients with chronic GvHD are highly susceptible to recurrent bacterial infections, especially with encapsulated bacteria such as *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis 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≥ 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 ≤ 30 kg who do not tolerate daily trimethoprim-sulfamethoxazole (TMP/SMX) should receive Penicillin VK (See Table below).

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

Table - Penicillin VK dosing for encapsulated bacterial prophylaxis:

Adults and Children (≥ 60 kg)	500 mg PO BID
Adults (< 60 kg) and Children (> 3 years and < 60 kg)	250 mg PO BID
Children (≤ 3 years)	125 mg PO BID

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

Antimicrobial prophylaxis for asplenic patients

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

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

Antimicrobial regimens are the same as for prevention of encapsulated bacteria in patients with chronic GVHD, and include daily Trimethoprim/Sulfamethoxazole (TMP/SMX) or twice-daily Penicillin VK therapy. Penicillin VK provides no protection against PCP; thus dapsone or other PCP prophylaxis must be added.

The duration of antibiotic prophylaxis in the asplenic patient after transplant is dependent of the presence of chronic GVHD (See Table below).

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

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 <u>≤</u> 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
  Levofloxacin 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.

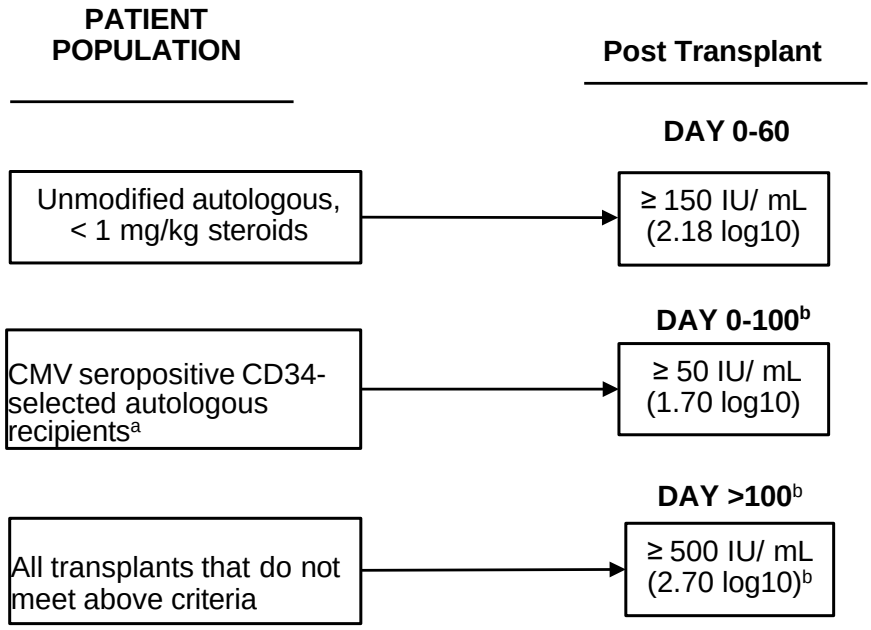
Empiric therapy for post-splenectomy sepsis (PSS) or other serious infections
Early recognition of infection followed by aggressive intervention is the cornerstone of PSS management. Initial empiric antimicrobial therapy for the splenectomized patient with unexplained fever, rigors, and other systemic 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



[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 used for CMV prophylaxis should be discontinued when pre-emptive therapy is started. Acyclovir/valAcyclovir should be continued, for HSV/VZV prophylaxis, if maribavir is initiated or restarted when ganciclovir or foscarnet is completed if indicated.

INDUCTION	
Preferred	**Alternative**
ValGANCiclovir*,** (ONLY for patients with good oral intake, no active gut GVHD, no significant liver disease and no severe diarrhea): Adults and Peds ≥ 40 kg: 900 mg PO Q 12 hrs Peds < 40kg: For SCH patients: consult SCH pharmacists For Non-SCH patients: Dose (mg) = 7 × BSA × CrCl^ administered every 12 hours; Use a maximum of 150 mL/minute/1.73 m^2 for CrCl in equation even if calculated value is higher. Maximum dose: 900 mg/dose. **OR** Ganciclovir** 5 mg/kg IV Q 12hrs	Foscarnet** Patients ≥ 24 months: 90 mg/kg IV Q 12hrs Peds < 24 months: 60 mg/kg/dose IV Q 8 hrs **OR** Maribavir*,***, **** 400mg PO BID (Age ≥ 12 years and weight ≥ 35kg)
Duration of Induction: • For Non-Cord blood transplant, if viral load at the end of week 1 of therapy is declining by at least one log from baseline go to maintenance dosing. However, if not declined, by at the end of one week at least one log from baseline, continue to monitor viral load weekly on induction dosing until viral load is declined by at least 1 log from baseline then move to maintenance dosing. • For Cord blood transplant, CMV DNA levels must be negative at one week in order to transition to maintenance dosing. Otherwise, continue induction dosing until CMV DNA levels are negative at which point a transition to maintenance is appropriate. • 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 ValGANCicovir or Maribavir 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.

***Maribavir to be considered in failure/intolerance of "Preferred" agents ; screen for drug-drug interactions.
****Because of drug-drug interaction, Maribavir should not be given simultaneously with CYP3 substrates like Cytoxan and a 48-hour washout period is recommended.
^CrCl calculation (based on the modified Schwartz formula): CrCl (mL/minute/1.73 m^2) = [k × height (cm)] ÷ SCr (mg/dL).
Calculated using a modified Schwartz formula where k =
• 0.33 in infants <1 year of age with low birthweight for GA
• 0.45 in infants <1 year of age with birthweight appropriate for GA
• 0.45 in children 1 to <2 years
• 0.55 in boys age 2 to <13 years
• 0.55 in girls age 2 to <16 years
• 0.7 in boys age 13 to 16 years

Table 3: Preemptive Maintenance Treatment Regimen for CMV Reactivation with Adequate Renal Function After Transplant

MAINTENANCE	
Preferred	**Alternative**
ValGANCiclovir*,** (ONLY for patients with good oral intake, no active gut GVHD, no significant liver disease and no severe diarrhea): Adults and peds ≥ 40 kg: 900 mg PO Q Day Peds < 40kg: For SCH patients: consult SCH pharmacists For Non-SCH patients: Dose (mg) = 7 × BSA × CrCl^ administered Q day; Use a maximum of 150 mL/minute/1.73 m^2 for CrCl in equation even if calculated value is higher. Maximum dose: 900 mg/dose. **OR** Ganciclovir** 5 mg/kg IV Q DAY	Foscarnet** 90 mg/kg IV Q DAY **OR** Maribavir*,***, **** 400mg PO BID (Age ≥ 12 years and weight ≥ 35kg)
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 or Maribavir 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.
***Maribavir to be considered in failure/intolerance of "Preferred" agents ; screen for drug-drug interactions.
****Because of drug-drug interaction, Maribavir should not be given simultaneously with CYP3 substrates like Cytoxan and a 48-hour washout period is recommended.
^CrCl calculation (based on the modified Schwartz formula): CrCl (mL/minute/1.73 m^2) = [k × height (cm)] ÷ SCr

(mg/dL).
Calculated using a modified Schwartz formula where k =
• 0.33 in infants <1 year of age with low birthweight for GA
• 0.45 in infants <1 year of age with birthweight appropriate for GA
• 0.45 in children 1 to <2 years
• 0.55 in boys age 2 to <13 years
• 0.55 in girls age 2 to <16 years
• 0.7 in boys age 13 to 16 years

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

	PREFERRED			ALTERNATIVE	
DOSING	***Able to tolerate PO***	***Unable to tolerate PO***	***Dosing***	***Able to tolerate PO***	**MONITORING BLOOD**
Adult or Pediatric ≥40 kg	**ValGANCiclovir**† 900mg PO QD	**Ganciclovir**# 5 mg/kg IV Q DAY	Adult or Pediatric ≥ 50 kg	**Valacyclovir*** 2 grams PO TID	Weekly: CMV PCR, Creatinine, CBC with Differential.
Peds < 40kg	**ValGANCiclovir**† For SCH patients: consult SCH pharmacists For Non-SCH patients: Dose (mg) = 7 × BSA × CrCl^ administered Q day; Use a maximum of 150 mL/minute/1.73 m^2 for CrCl in equation even if calculated value is higher. Maximum dose: 900 mg/dose.		Pediatric ≥40 to <50 kg	**Valacyclovir*** 2 grams PO TID	
			Pediatric ≥30 to <40 kg	**Valacyclovir*** 1 gram PO TID	
			Pediatric ≥20 to < 30 kg	**Valacyclovir*** 1 gram PO TID	
			Pediatric ≥15 to < 20 kg	**Acyclovir*** 600 mg/m^2 PO QID	
			Pediatric ≥10 to < 15 kg	**Acyclovir*** 600 mg/m^2 PO QID	

† 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.

^CrCl calculation (based on the modified Schwartz formula): CrCl (mL/minute/1.73 m^2) = [k × height (cm)] ÷ SCr (mg/dL).
Calculated using a modified Schwartz formula where k =
- 0.33 in infants <1 year of age with low birthweight for GA
- 0.45 in infants <1 year of age with birthweight appropriate for GA
- 0.45 in children 1 to <2 years
- 0.55 in boys age 2 to <13 years
- 0.55 in girls age 2 to <16 years
- 0.7 in boys age 13 to 16 years

Table 5: CMV Prophylaxis and Monitoring after Day 100 for CMV-seropositive Cord Blood Recipients without Prior Posttransplant CMV Reactivation

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

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

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

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

E. Fungal organisms

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

F. Intravenous immunoglobulin (IVIG) replacement and adjunctive therapy

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 [1-9]. For information regarding IVIG administration before100 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):

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

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

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

c. 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)*

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

IVIG Preparations

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

V. FEVER OF UNKNOWN ETIOLOGY

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

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

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

VI. EVALUATION OF RESPIRATORY PROBLEMS AND LUNG INFILTRATES

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

A. Diagnostic Evaluation

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

B. Tests Recommended for BAL and Transbronchial Biopsy Specimens

See algorithm on the end of this section for overview.

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

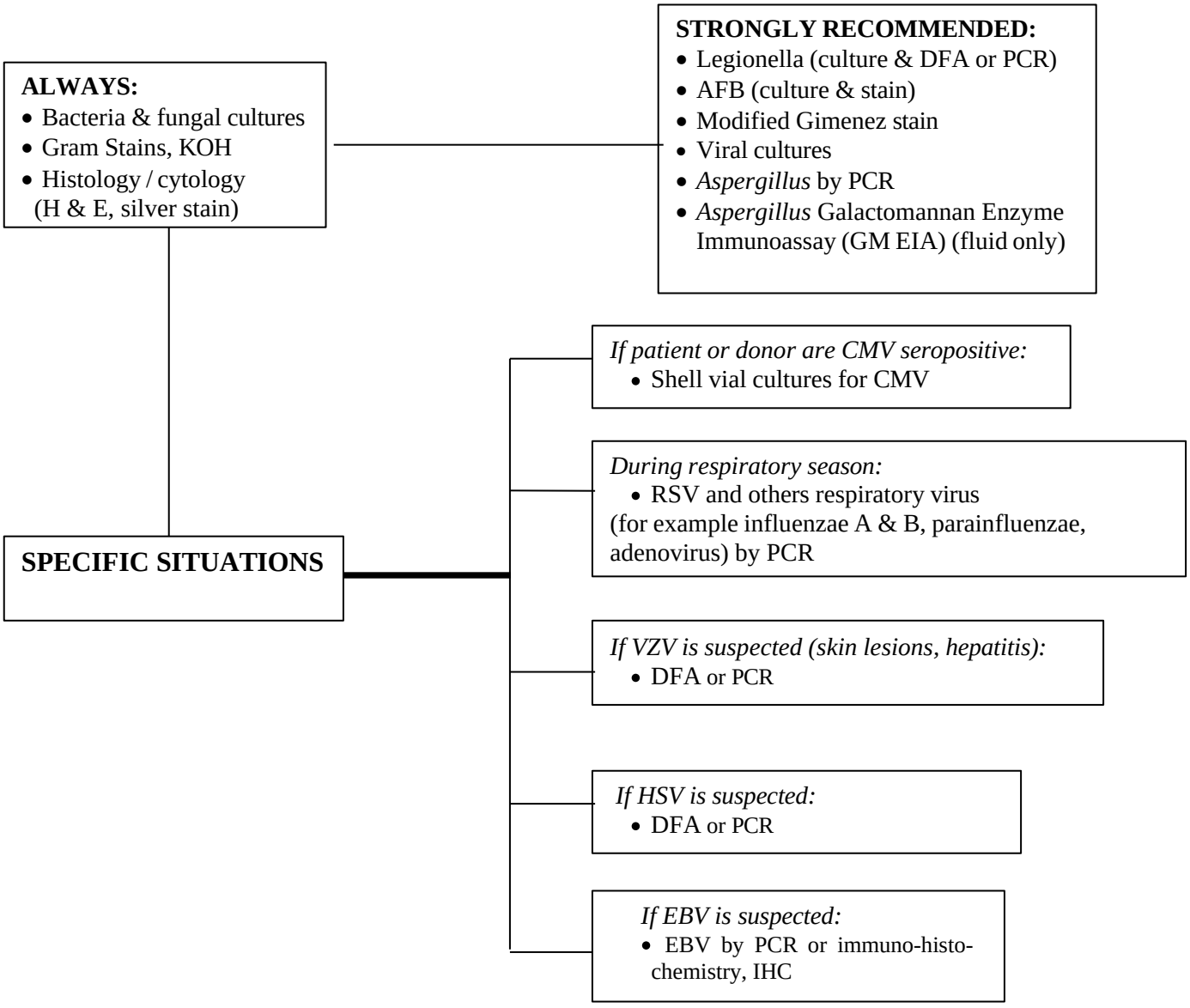
C. Evaluation of Pulmonary Nodules or Persistent Infiltrates with a Negative BAL

1. Thoracoscopic biopsy or open lung biopsy is recommended for patients with nodular infiltrates to rule out fungal, malignancy, bronchiolitis obliterans 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



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

VII. EVALUATION OF DIARRHEA AND OTHER GI COMPLICATIONS

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

A. Diagnostic Evaluation and Initial Management

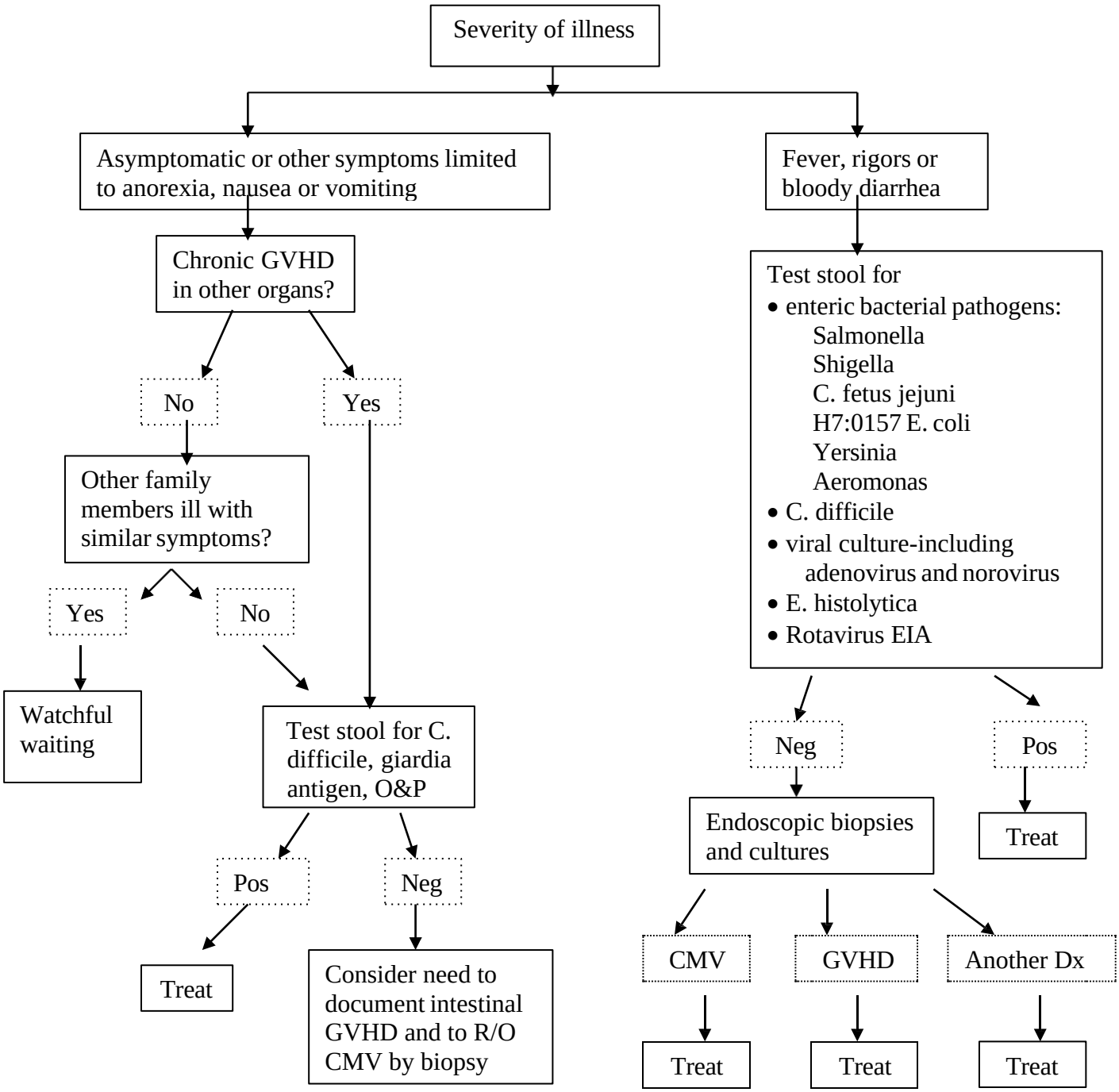
1. Diarrhea caused by oral magnesium supplementation should be ruled out. If necessary, patients should receive IV replacement of magnesium.
2. The clinical evaluation of diarrhea depends on its duration and volume, the presence of blood, and the occurrence of fever and other constitutional symptoms.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

B. Procedures for Gastrointestinal Endoscopic Biopsies

1. Maintain platelet counts >50,000 before and for 3 - 4 days after the procedure.
2. Esophagogastroduodenoscopy should be carried out with multiple biopsies. Biopsy of any erosion or ulcerations is indicated. If there are no macroscopic abnormalities found, we suggest 6-8 biopsies of the gastric antrum. To minimize the risk of bleeding, avoid biopsies of the duodenum unless this is the only site of abnormalities.
3. When diarrhea is the major GI symptom in a patient without other manifestations of GVHD, either upper endoscopy or colonoscopy may be indicated to rule out CMV infection or occult GVHD. All infections other than CMV can be identified from stool samples. Biopsies obtained from the gastric antrum are usually sufficient to diagnose GVHD, even in cases where the major symptom is diarrhea.
4. Biopsies samples (n = 4) should be placed in fresh buffered formalin.
5. Fresh biopsy samples (gastric, rectal or colon) should be placed in viral transport medium and sent to a virology lab to perform rapid testing (shell vial) for CMV and Varicella zoster as well as HSV if there are esophageal lesions. The last stomach sample should be placed in CLO media to test for H. Pylori.
6. Please send slides and biopsy blocks to the address below if you wish our pathologists to review the specimen. Because GVHD may be found in one but not all sites, it is important to send as many slides or blocks as possible.

7. Please label the material with the patient's name, the date obtained and sites.
8. Send the material to the following address:
   Fred Hutchinson Cancer Center
   825 Eastlake Ave. E. / Attn: LTFU G-1500
   PO Box 19023
   Seattle, WA 98109-1023
9. Please call (206) 667-4415 to notify our office when to expect the arrival of shipments.

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



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

VIII. TREATMENT OF SPECIFIC INFECTIONS

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

A. Cytomegalovirus (CMV)

Late onset CMV infections have become an increasingly difficult problem for patients who have had a hematopoietic stem cell transplant. Reconstitution of the T cells that respond to CMV is slow and may be delayed by prophylactic use of ganciclovir during the first 3 months after the transplant. Patients at risk of CMV infection should be monitored closely and should receive prophylactic antiviral treatment to prevent CMV disease. Note that some patients present with nausea and vomiting as initial manifestations of CMV infection, in the absence of CMV 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/m^2 administered as a one hour IV infusion q 8 hr until there is no evidence of new lesions for 72 hours. Treatment may then be continued with valacyclovir 1 gm t.i.d. p.o. for patients $\geq$ 40 kg and 500 mg t.i.d. p.o. for patients < 40 kg to complete the course of treatment (generally 10-14 days).

Localized zoster:

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

C. Pneumocystis Carinii Pneumonia (PCP)

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

IX. VACCINATIONS

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

Guidelines for vaccination after HCT have been published by relevant societies[1,2,3,] as well as the Advisory Committee on Immunization Practices (ACIP) within the Centers for Disease Control and Prevention (CDC)[4] and provides the foundation for our vaccination practices explained elsewhere in further detail.[5] Vaccination begins at 3 months for SARS-CoV-2, and 6 months for influenza (or 3-4 months when seasonal prevalence is high). Other non-live routine childhood vaccinations that must be repeated after HCT, may begin as early as 6 months in Non-Primary Immune Deficiency patients but should be considered in conjunction with factors that significantly delay immune reconstitution. Live vaccines (MMR or MMR-V) are generally not administered before 2 years after HCT.

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

- IX.A1 Adult Vaccination Schema-Non-Live Vaccines: Vaccination before 12months (if eligible)
- IX.A2 Adult Vaccination Schema- Non-Live Vaccines: Standard vaccinationschedule
- IX.A3 - Adult Vaccination Schema- For MMR(V) and Zoster Vaccines
- IX.P1 Pediatric Vaccination Schema: Vaccination before 12 months (if eligible)
- IX. P2 Pediatric Vaccination Schema: If patient not vaccinated before 12 months
- IX.P3: Pediatric Vaccination Schema: For MMR (V) and Zoster Vaccines

Table IX.A1: Adult Vaccination Schema for Non-Live Vaccines: starting before 12 months (if eligible)[1,2]

Vaccine	≥3m	~4m	~5m	≥6m	≥7m	≥8m	≥10m	≥12m	≥13m	≥14m	≥18m	≥24m
Influenzae (IIV4) (Sept – March), non-adjuvanted				IIV4 (Flu) High-Dose[3]	IIV4 (Flu) High-Dose[3]							
Pentacel® (DTaP-IPV/Hib)[4,5]				Pentacel®		Pentacel®	Pentacel®	✓ titers[6]				✓ titers[6]
Meningococcal ACWY (MenQuadfi, Menveo, MCV4)				MCV4		MCV4						
Meningococcal Group B (Bexsero®)[7]							Bexsero®	Bexsero®				
Pneumococcal-conjugate (Prevnar 20™)			✓ titers[8]	PCV20[9]		PCV20[9]	PCV20[9]					✓ titers[9]
Hepatitis A[11]								HAV			HAV	
Hepatitis B[10,11]								HBV	HBV	HBV	HBV	✓ titers[10]
HPV (Gardasil), 9 to 45 y								HPV		HPV	HPV	
SARS-CoV-2[12] (Moderna or Pfizer)	COVID	COVID		COVID[13]		COVID[13]						

Abbreviations: DTaP, Diphtheria-Tetanus-acellular Pertussis; Hib, H. Influenzae type B; HPV, human papilloma virus; IPV, inactivated polio vaccine; MCV4, meningococcal conjugate vaccine

Footnotes:

1 For adults transplanted for immunodeficiency disorders, refer to the following section, "Posttransplant Vaccination of Primary Immunodeficiency Disorders."

2 For non-live vaccine, vaccination may be deferred if receiving ongoing immunoglobulin replacement for delayed immune reconstitution or other factors in Table IX.1 are present.

3 Ideally start the 2-dose series at 6 months but during high prevalence influenza outbreaks may start as early as 3 months. If non-adjuvanted, high-dose quadrivalent inactivated influenza vaccine is unavailable, then give standard-dose formulation. The 2-dose series does not apply if no longer on immunosuppressive therapy and ≥2y post-HCT.

4 Separate component vaccines (shots) may be used instead for DTaP, IPV, and Hib if Pentacel® is unavailable.

5 If not using Pentacel® and DTaP is unavailable, then may use Adacel® = Tdap (age ≥ 10 y through 64 y) or Boostrix® = Tdap (age ≥ 10 y).

6 Check anti-tetanus toxoid and anti-Hib titers if not done at 12 months.

7 Recommended for patients with anatomic or functional asplenia condition (i.e., chronic GVHD) or increased environmental risk. ***Trumenba*®** can be substituted for Bexsero® (3 doses: 0, 2 and 6 months apart).

8 Check baseline titers for S. Pneumonia (IgG, 23 serotypes) before beginning PCV20 vaccination.

9 Check titers for S. Pneumonia (IgG, 23 serotypes) 1-2 months after each PCV20 is given. A positive response to PCV20 is defined: as achieving a seroprotective IgG level against S. pneumoniae in ≥15 out of 20 PCV20 serotypes at 1-2 months post-vaccination. A positive response requires no further PCV20 vaccination.

10 A complete series of Hepatitis B vaccination is accomplished preferably with a total of 4 x single 0.5 mL doses of Heplisav-B® based on data extrapolated from patients with chronic kidney disease or on hemodialysis for ESRF. Alternatively, a total of 4 x double (2 mL total) doses of Engerix-B® may be given. Post-vaccination testing for antibody to hepatitis B surface antigen is recommended 1-2 months after the 4th dose to ensure protection (Check titers at 24-month visit if not done at 20 months). Patients who do not respond to the primary vaccine series should receive an additional 1-3 doses of the same vaccine or, alternatively, repeat series with a different vaccine brand (e.g., double doses of Engerix-B® if did not respond to Heplisav-B® or single doses of Heplisav-B® if did not respond to Engerix-B®).

11 If NOT administering hepatitis B series using Heplisav-B®, Twinrix® can be administered on days when HAV and HBV are given together. (Twinrix® approved for age ≥ 18 y)

12 Dose 1 of the SARS-CoV-2 vaccination series should begin at ≥ day +90. For allogeneic transplant patients, the initial dose should be arranged to be given as part of the day +80 work up. Communications with referring provider should be done to advise when subsequent doses are due.

13 Dose 3 is preferably given 2 months after dose 2 but may be given as early as 1 month after dose 2 to avoid a missed vaccination opportunity; Dose 4 is 2 months after Dose 3.

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

Table IX.A2: Adult Vaccination Schema for Non-Live Vaccines: Standard vaccination schedule[1,2]

Vaccine	>3m	~4m	≥6m	≥7m	≥8m	≥12m	≥13m	≥14m	≥16m	≥18m	≥24m
Influenzae (IIV4) (Sept – March), non-adjuvanted			IIV4 (Flu) High-Dose[3]	IIV4 (Flu) High-Dose[3]							
Pentacel® (DTaP-IPV/Hib)[4,5]						Pentacel®		Pentacel®	Pentacel®		✓ titers[6]
Meningococcal ACWY (MenQuadfi, Menveo, MCV4)						MCV4		MCV4			
Meningococcal Group B (Bexsero®)[7]									Bexsero®	Bexsero®	
Pneumococcal-conjugate (Prevnar 20™)					✓ titers[8]	PCV20[9]		PCV20[9]	PCV20[9]		✓ titers[9]
Hepatitis A[11]						HAV				HAV	
Hepatitis B[10, 11]						HBV	HBV	HBV		HBV	✓ titers[10]
HPV (Gardasil), 9 to 45 y						HPV		HPV		HPV	
SARS-CoV-2[12] (Moderna or Pfizer)	COVID	COVID	COVID[13]		COVID[13]						

Abbreviations: DTaP, Diphtheria-Tetanus-acellular Pertussis; Hib, H. Influenzae type B; HPV, human papilloma virus; IPV, inactivated polio vaccine; MCV4, meningococcal conjugate vaccine.

Footnotes:

1 For adults transplanted for immunodeficiency disorders, refer to the following section, "Posttransplant Vaccination of Primary Immunodeficiency Disorders."

2 For non-live vaccine, vaccination may be deferred if receiving ongoing immunoglobulin replacement for delayed immune reconstitution or other factors in Table IX.1 are present.

3 Ideally start the 2-dose series at 6 months but during high prevalence influenza outbreaks may start as early as 3 months. If non-adjuvanted, high-dose quadrivalent inactivated influenza vaccine is unavailable then give standard-dose formulation. The 2-dose series does not apply if no longer on immunosuppressive therapy and ≥2y post-HCT.

4 Separate component vaccines (shots) may be used instead for DTaP, IPV, and Hib if Pentacel® is unavailable.

5 If not using Pentacel® and DTaP is unavailable, then may use Adacel® = Tdap (age ≥ 10 y through 64 y) or Boostrix® = Tdap (age ≥ 10 y).

6 Check anti-tetanus toxoid and anti-Hib titers.

7 Recommended for patients with anatomic or functional asplenia condition (i.e., chronic GVHD) or increased environmental risk). ***Trumenba®*** can be substituted for Bexsero® (3 doses: 0, 2 and 6 months apart).

8 Check baseline titers for S. Pneumonia (IgG, 23 serotypes) before beginning PCV20 vaccination.

9 Check titers for S. Pneumonia (IgG, 23 serotypes) 1-2 months after each PCV20. A positive response to PCV20 is defined: as achieving a seroprotective IgG level against S. pneumoniae in ≥ 15 out of 20 PCV20 serotypes at 1-2 months post-vaccination. A positive response requires no further PCV20 vaccinations.

10 A complete series of Hepatitis B vaccination is accomplished preferably with a total of 4 x single 0.5 mL doses of Heplisav-B® based on data extrapolated from patients with chronic kidney disease or on hemodialysis for ESRF. Alternatively, a total of 4 x double (2 mL total) doses of Engerix-B® may be given. Post-vaccination testing for antibody to hepatitis B surface antigen is recommended 1-2 months after the 4th dose to ensure protection (Check titers at 24-month visit if not done at 20 months). Patients who do not respond to the primary vaccine series should receive an additional 1-3 doses of the same vaccine or, alternatively, repeat series with a different vaccine brand (e.g., double doses of Engerix-B® if did not respond to Heplisav-B® or single doses of Heplisav-B® if did not respond to Engerix-B®).

11 If NOT administering hepatitis B series using Heplisav-B®, Twinrix® can be administered on days when HAV and HBV are given together. (Twinrix® approved for age ≥ 18 y).

12 Dose 1 of the SARS-CoV-2 vaccination series should begin at ≥ day +90. For allogeneic transplant patients, the initial dose should be arranged to be given as part of the day +80 work up. Communications with referring provider should be done to advise when subsequent doses are due.

13 Dose 3 is preferably given 2 months after dose 2 but may be given as early as 1 month after dose 2 to avoid a missed vaccination opportunity; Dose 4 is 2 months after Dose 3.

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 MMR(V) and Zoster (SHINGRIX)

A) Live MMR or Varicella Vaccines		**~24 m**	**24 m**	**≥25m**	**~27m**
Measles/Mumps/Rubella (MMR) ***2-1-8 Rule***[a]	***No Live Vaccines are given until at least 2 yr post-HCT and then only when certain other criteria are met***[a]		**MMR**	**MMR**	
Varicella-Zoster (Varivax) ***Seronegative ONLY*** and ***2-1-8 Rule***[a,d] First dose may be given with MMR		**✓ titers**[b]	**VZV**	**VZV**	**✓ titers**[c]

a. ***2-1-8 Rule*** **=** Not until 2 years post HCT plus > 1 year off all immunosuppressive therapy (IST) plus ≥8 months since last dose of IVIG/VZIG or most recent plasma transfusion.
b. Check baseline varicella serology at least 8 months off IVIG/VZIG when ready to vaccinate to determine if necessary.
c. Check at least 1-2 months after Varivax to ensure seroconversion of the VZV seronegative patient.
d. Stop acyclovir or valacyclovir a day prior to varivax vaccination.

B) Non-Live Shingles Vaccine		**~12 m**	**≥12m**	**≥14m**
ALLOGENEIC *and* AUTOLOGOUS recipients AGE ≥18 y ONLY: ***VZV Seropositive ONLY***	***SHINGRIX is not given until at least 1-y post-HCT and then only when certain other criteria are met***[1]	**✓ titers**[2]	**SHINGRIX**[3]	**SHINGRIX**[3]

1. Allogeneic recipients must also be age >18 y and >1 y after HCT, >8 m off immunosuppressive therapy without GVHD flare-ups. Autologous recipients must have also completed maintenance immunotherapy (e.g. PD-1 inhibitors, proteosome inhibitors, daratumumab) which also prolongs duration of acyclovir/valacyclovir.
2. Patients should have VZV serology checked prior to vaccination (at least 8 months off IVIG/VZIG) to ensure still VZV-seropositive. If patient is VZV seronegative, do not give SHINGRIX but follow the table above and offer Varivax while still following the 2-1-8 Rule.
3. Continue acyclovir or valacyclovir until one month after second Shingrix vaccination.

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)[1,2]

Vaccine	≥3m	~4m	~5m	≥6m	≥7m	≥8m	≥10m	≥12m	≥14m	≥18m	≥24m
IIV4 – **Age 6 m to <5 y** (September –March)				**IIV4 (Flu) Std-Dose[3]**	**IIV4 (Flu) Std-Dose[3]**						
IIV4 – **Age ≥5 y** (September –March)				**IIV4 (Flu) High-Dose[3]**	**IIV4 (Flu) High-Dose[3]**						
Pentacel® (DTaP-IPV/Hib)[4,5]				**Pentacel ®**		**Pentacel®**	**Pentacel®**	**✓ titers[6]**			**✓ titers[6]**
Meningococcal ACWY (MenQuadfi, Menveo, MCV4)				**MCV4**		**MCV4**					
Meningococcal Group B (Bexsero®)[7]							**Bexsero®**	**Bexsero®**			
Pneumococcal-conjugate (Prevnar 20™)				**PCV20**		**PCV20**	**PCV20**	**✓ titers[8]**		**PCV20**	**✓ titers[8]**
Hepatitis A								**HAV**		**HAV**	
Hepatitis B[9]								**HBV**	**HBV**	**HBV**	**✓ titers [10]**
HPV9 (Gardasil), 9 to 45 years								**HPV**	**HPV**	**HPV**	
SARS-CoV-2 – Age ≥6 m[11] Pfizer or Moderna	**COVID**	**COVID**		**COVID[12]**		**COVID[12]**					

Abbreviations: DTaP, Diphtheria-Tetanus-acellular Pertussis; Hib, H. Influenzae type B; HPV, human papilloma virus; IIV4, inactivated quadrivalent influenza vaccine; IPV, inactivated polio vaccine; MCV4, meningococcal conjugate vaccine; PCV13, Prevnar 13; PPSV23, Pneumovax.

Footnotes:

1. For patients transplanted for immunodeficiency disorders see following section, "Posttransplant Vaccination of Primary Immunodeficiency Disorders".
2. For non-live vaccine, vaccination may be deferred if receiving *ongoing* immunoglobulin replacement for delayed immune reconstitution or other factors in Table IX.1 are present.
3. Ideally start the 2-dose series at 6 months but during high-prevalence influenza outbreaks may start as early as 3 months. If non-adjuvanted, high-dose quadrivalent inactivated influenza vaccine is unavailable for children ≥ 5 years then give standard-dose based on Pediatric HCT Flu Study. The 2-dose series does not apply if no longer on immunosuppressive therapy and ≥2y post-HCT.
4. Different combination vaccines may be used if ***Pentacel®*** is unavailable: ***Infanrix*** or ***Daptacel*** (= DTaP for age < 7 y), ***Pediarix*** = DTaP/HBV/IPV (age < 7 y).
5. If not using ***Pentacel®*** and DTaP is unavailable then may use ***Adacel*** = Tdap (age ≥ 10 y through 64 y) or ***Boostrix*** = Tdap (age ≥ 10 y).
6. Check Anti-tetanus toxoid and anti-Hib titers.
7. Recommended for anatomic or functional asplenia (i.e. chronic GVHD) or increased environmental risk. If patient is ≥10y, ***Trumenba®*** can be substituted for Bexero® (3 doses: 0, 2, and 6 months apart).
8. Check titers for S. Pneumonia (IgG, 23 serotypes) to determine if an additional dose of PCV20 should be given.
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. 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 an additional 1-3 double-doses of the same vaccine (or 4-single dose series of Heplisav-B if age ≥18y).
11. 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 OPD Team). Communications with referring provider should be done to advise when subsequent doses are due.
12. Dose 3 is preferably given 2 months after dose 2 but may be given as early as 1 month after dose 2 to avoid a missed vaccination opportunity; Dose 4 is 2 months after Dose 3.

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

Table IX.P2: Pediatric Vaccination Schema: If patient not routinely vaccinated before 12 months[1,2;]

Vaccine	≥3m	~4m	~5m	≥6m	≥7m	≥8m	≥12m	≥14m	≥16m	≥18m	≥24m
IIV4 – **Age 6 m to <5 y** (September –March)				**IIV4 (Flu) Std-Dose[3]**	**IIV4 (Flu) Std-Dose[3]**						
IIV4 – **Age ≥5 y** (September –March)				**IIV4 (Flu) High-Dose[3]**	**IIV4 (Flu) High-Dose[3]**						
Pentacel® (DTaP-IPV/Hib)[4,5]							**Pentacel®**	**Pentacel®**	**Pentacel®**		**✓ titers[6]**
Meningococcal ACWY (MenQuadfi, Menveo, MCV4)							**MCV4**	**MCV4**			
Meningococcal Group B (Bexsero®)[7]									**Bexsero®**	**Bexsero®**	
Pneumococcal-conjugate (Prevnar 20™)							**PCV20**	**PCV20**	**PCV20**	**✓ titers[8]**	**PCV20[8]**
Hepatitis A							**HAV**			**HAV**	
Hepatitis B[9]							**HBV**	**HBV**		**HBV**	**✓ titers [10]**
HPV9 (Gardasil), 9 to 45 y							**HPV**	**HPV**		**HPV**	
SARS-CoV-2 – Age ≥ 6 m[11] Pfizer or Moderna	**COVID**	**COVID**		**COVID[12]**		**COVID[12]**					

Abbreviations: DTaP, Diphtheria-Tetanus-acellular Pertussis; Hib, H. Influenzae type B; HPV, human papilloma virus; IIV4, inactivated quadrivalent influenza vaccine; IPV, inactivated polio vaccine; MCV4, meningococcal conjugate vaccine; PCV13, Prevnar 13; PPSV23, Pneumovax.

Footnotes:

1. For patients transplanted for immunodeficiency disorders see following section, "Posttransplant Vaccination of Primary Immunodeficiency Disorders".
2. For non-live vaccine, vaccination may be deferred if receiving ongoing immunoglobulin replacement for delayed immune reconstitution or other factors in Table IX.1 are present.
3. Ideally start the 2-dose series at 6 months but during high-prevalence influenza outbreaks may give as early as 3 months. If non-adjuvanted, high-dose quadrivalent inactivated influenza vaccine is unavailable for children ≥ 5 years, then give standard-dose based on Pediatric HCT Flu Study. The 2-dose series does not apply if no longer on immunosuppressive therapy and >2y post-HCT.
4. Different combination vaccines may be used if Pentacel® is unavailable: Infanrix or Daptacel (= DTaP for age < 7 y), Pediarix = DtaP/HBV/IPV (age < 7 y).
5. If not using Pentacel® and DtaP is unavailable, then may use Adacel = Tdap (age ≥ 10 y through 64 y) or Boostrix = Tdap (age > 10 y).
6. Check Anti-tetanus toxoid and anti-Hib titers.
7. Recommended for anatomic or functional asplenia (i.e. chronic GVHD) or increased environmental risk. If patient is ≤10y, Trumenba® can be substituted for Bexero® (3 doses: 0, 2 and 6 months apart).
8. Check titers for S. Pneumonia (IgG, 23 serotypes) about 2 months after vaccine to determine if an additional dose of PCV20 should be given.
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. 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 an additional 1-3 double-doses of the same vaccine (or 4-single dose series of Heplisav-B if age >18y).
11. 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 OPD Team). Communications with referring provider should be done to advise when subsequent doses are due.
12. Dose 3 is preferably given 2 months after dose 2 but may be given as early as 1 month after dose 2 to avoid a missed vaccination opportunity; Dose 4 is 2 months after Dose 3.

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.P3: Pediatric Vaccination Schema: For MMR(V) and Zoster (SHINGRIX)[1]

A) Live MMR or Varicella Vaccines		~24 m	24 m	≥25m	~27m
Measles/Mumps/Rubella (MMR) ***2-1-8 Rule***[1]	***No Live Vaccines are given until at least 2 yr post-HCT and then only when certain other criteria are met***[1]		**MMR**	**MMR**	
Varicella-Zoster (Varivax) ***Seronegative ONLY*** and 2-***1-8 Rule***[1,4] First dose may be given with MMR		✓ **titers**[2]	**VZV**	**VZV**	✓ **titers**[3]

1. 2-1-8 Rule = Not until 2 years post HCT plus > 1 year off all immunosuppressive therapy (IST) plus >8 months since last dose of IVIG/VZIG or most recent plasma transfusion.
2. Check baseline varicella serology at least 8 months off IVIG/VZIG when ready to vaccinate to determine if necessary.
3. Check at least 1-2 months after Varivax to ensure seroconversion of the VZV seronegative patient.
4. Stop acyclovir or valacyclovir a day prior to varivax vaccination.

B) Non-Live Shingles Vaccine	<12m	~12 m	≥12m	≥14m
ALLOGENEIC *and* AUTOLOGOUS recipients AGE ≥18 y ONLY: ***VZV Seropositive ONLY***	***SHINGRIX is not given until at least 1 yr post-HCT and then only when certain other criteria are met***[a]	✓ **titers**[b]	**SHINGRIX**[c]	**SHINGRIX**[c]

a. Allogeneic recipients must also be age >18 y and >1 y after HCT, >8 m off immunosuppressive therapy without GVHD flare-ups. Autologous recipients must have also completed maintenance immunotherapy (e.g. PD-1 inhibitors, proteasome inhibitors, daratumumab) which also prolongs duration of acyclovir/valacyclovir.
b. Patients should have VZV serology checked prior to vaccination (at least 8 months off IVIG/VZIG) to ensure still VZV-seropositive. If patient is VZV seronegative, do not give SHINGRIX but follow the table above and offer Varivax while still following the 2-1-8 Rule.
c. Continue acyclovir or valacyclovir until one month after second Shingrix vaccination

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:

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

[a] as determined by donor B cell chimerism 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 IVIG 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:

- The "Pink Book" recommends time intervals for pediatric vaccines.[10]
- All patients should receive seasonal flu[11] and SARS-COV-2 vaccinations per Tables IX.A1-A2 and Tables IX.P1-P2.
- If patient is on disease-associated maintenance therapy that can affect T or B cell numbers, then before beginning other vaccinations (Follow Table IX.1 above):
    ✓ Check CD 19 or CD 20 B cells to determine ≥ 20/microliters and
    ✓ Check CD4 T cells to determine ≥ 200/microliters.
- 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.
- **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 HCT patients and its impact on GVHD has not been studied. Our Hepatitis B vaccination policy parallels what is done for patients with chronic kidney disease or on hemodialysis who are considered immunocompromised.[6-8]

- **Smallpox vaccine** is comprised of live vaccinia virus. **Smallpox vaccination is contraindicated in HCT 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 membersor other persons who share living space with the patient during the first year after transplant and beyond one year if the patient continues treatment with immunosuppressive medications. If smallpox vaccination is administered to these close contacts, then these individuals should be prevented from having close contact with the immunocompromised HSCT recipient. See the CDC website for further detailed information http://www.bt.cdc.gov.
- **Other live vaccines (i.e., BCG, oral polio, yellow fever, typhoid)** should not be administered in patients with active manifestation of GVHD or receiving immunosuppressive therapy.
- **MMR or Varivax** should not be given within 8 months of IVIG and VZIG.[9]
- **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 thesame as for other at-risk individuals. Detailed information is available at the CDC website 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 HCT 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, a full series of vaccination against pneumococcus with PCV20 (Prevnar20®), 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 meningidtidis* groups A, C, W, Y with two doses of MCV4 Menactra® or Menveo®, (if under 2 years old, discuss with ID) and against serogroup B if ≥ 10y with two doses of Bexsero® is recommended. If Bexsero is unavailable, vaccination against serogroup B with the Trumenba vaccine series could be considered, 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].

Re- Booster immunizations with MCV4 (Menactra® or Menveo®) and Bexsero® are recommended every 5 years[2] and strep pneumonia as clinically indicated.

Note: For non-elective splenectomy, vaccination should begin at or after post-operative Day 14. Post-transplant with PCV20, H. *influenzae B* and *Neisseria meningidtidis* groups A, C, W, Y, MCV4, and also group B

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

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

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

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

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

† DLI (donor lymphocyte infusion)

* See Table 2 below

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

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

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

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

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

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

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

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

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

C. How to diagnosis chronic GVHD

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

The criteria for the diagnosis of chronic GVHD include:

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

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

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

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

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

Table 3. Global assessment of chronic GVHD severity

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

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

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

Biopsy	(Skin, lip and other tissues). Histological confirmation is necessary in the absence of diagnostic clinical features or distinctive features confirmed by other pertinent test (Table 2). Nonetheless, diagnostic histological features of chronic GVHD are uncommon.
Lung	New 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 ($\geq$ 500/microliter), hypogammaglobulinemia. Hypergammaglobulinemia and autoantibodies occur in some cases.

G. Monitoring and other chronic GVHD information

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

H. Guidelines for treatment of chronic GVHD

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

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

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

Table 4. Indication for systemic treatment for chronic GVHD

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

‡ See Table 3

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

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

Standard treatment of chronic GVHD usually begins with administration of glucocorticoids (1mg/kg/day) followed by taper to eventually reach an alternate-day regimen, with or without daily cyclosporine or tacrolimus (FK506). 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 FEV_1 (mL) by ≥ 10% in comparison in prior 2 years or pre-transplant baseline
        b. FEV_1 is <75% predicted
        c. FEV_1/VC[1] ratio < 0.7 or FEV_1/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 FEV_1 decline (FEV_1 >70% predicted)
       Moderate/severe or symptomatic = FEV_1 decline (FEV_1 <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 FEV_1
        b. Normal FEV_1/FVC ratio
        c. Normal TLC
    2. Patients with baseline pretransplant supranormal FEV_1:
        a. FEV_1 decline >10 % (meets criteria 1a)
        b. FEV_1/VC <0.7 (meets criteria 1c)
        c. FEV_1 >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 FEV_1 >/=10%, with FEV_1/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)
            - 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 % FEV_1 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[2]
    1. Initiate **F**luticasone, **a**zithromycin and **m**ontelukast (Singulair) (FAM) + Long-Acting Beta-Agonist (LABA) (9,17,18)
        a. FAM = Fluticasone (Flovent) 440 mcg BID + **a**zithromycin 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:
                - Advair HFA 230/21mcg 2 inh BID
                - Advair Diskus 500/50 mcg 1 inh BID
                - Dulera 200/5 mcg 2 inh BID
                - 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 FEV_1 decline (FEV_1 >70% predicted): no new or increase in prednisone
        b. Symptomatic, or with moderate to severe FEV_1 decline (FEV_1 <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 FEV_1 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 % FEV_1 stabilizes after 3 months, space out to q2-3 months for at least a year or longer per pulmonary recommendations.
    3. If % FEV_1 continues to decrease, see D below.
    4. If % FEV_1 normalizes, see E below

D. Persistent FEV_1 decline despite initiation of above treatment (FEV_1 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 FEV_1 has stabilized, taper prednisone to 1mg/kg/day x 2 weeks and follow taper schedule in section B.#2.

[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 FEV_1 closely with each step
        ii. If FEV_1 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 FEV_1 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%

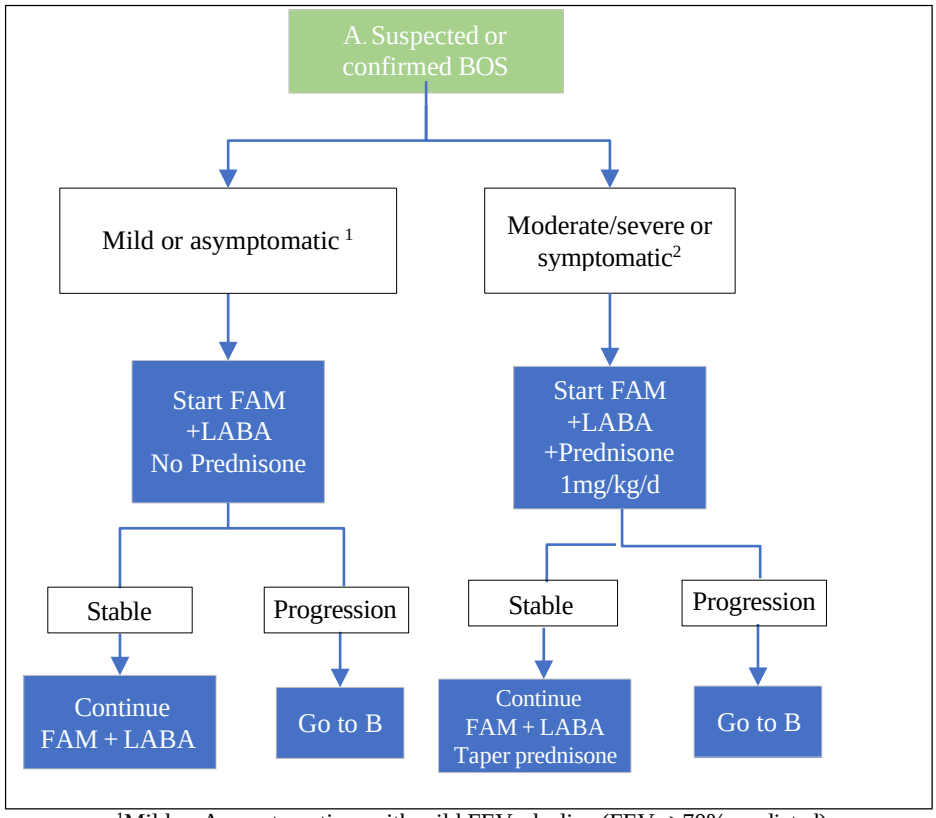
H. End-stage lung disease from BOS
    1. Consider lung transplantation (19)
    2. Discuss with UWMC Lung Transplantation service.
    3. Basic criteria for referral for lung transplant includes[3]:
        a. >2 years after HCT without evidence of malignancy
        b. Life expectancy <2 years from 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

[3] There is no specific FEV_1 criteria for lung transplant eligibility.

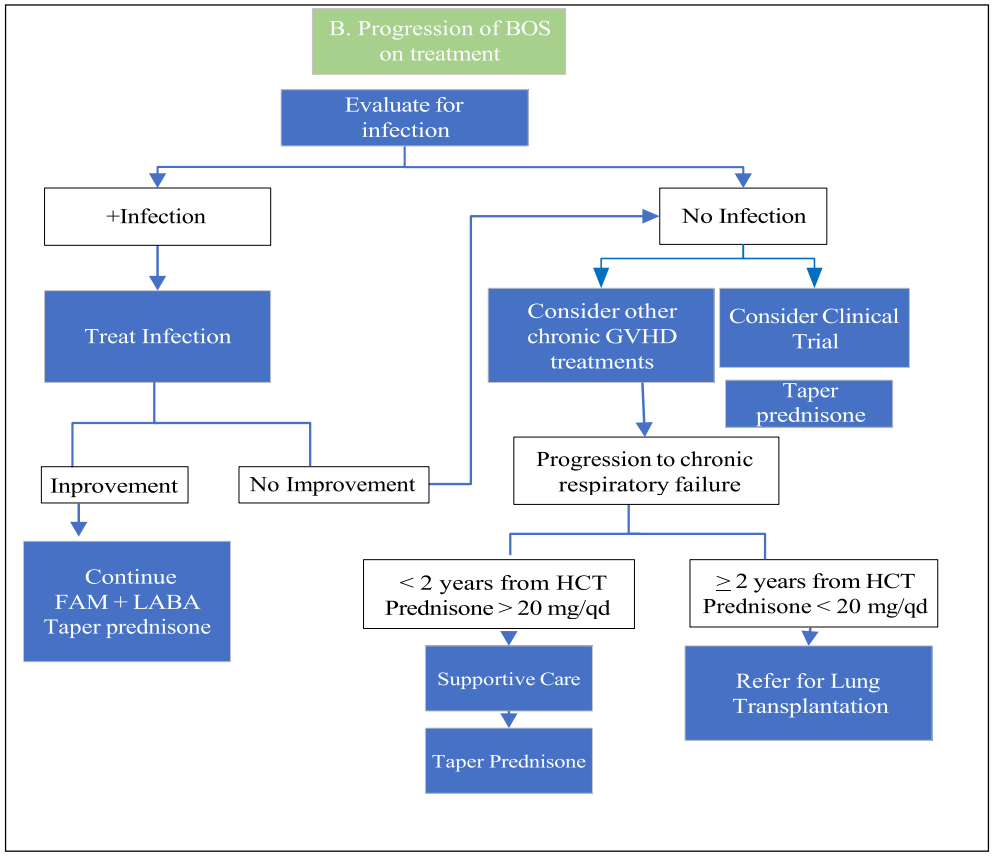
Figure 1. Schema for Treatment of Bronchiolitis Obliterans Syndrome (BOS) according to severity

A.



[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.



X. GENERAL GUIDELINES FOR PREVENTION OF OSTEOPOROSIS AND GLUCOCORTICOSTEROID INDUCED OSTEOPOROSIS AFTER HCT

Treatment with glucocorticoids has been recognized as the primary risk factor for development of osteoporosis after hematopoietic cell transplantation (HCT). 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 HCT 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 children, 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 children 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 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 ≥ 10 years and < 60 years,
Free testosterone 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:

i. Height: twice yearly

ii. Weight: with each clinic visit.

iii. DEXA SCANS:

a) 1-year after autologous HCT for lymphoma and myeloma in adults.

b) 1-year after allogeneic HCT in adults.

c) 1 year after allogeneic, or autologous-HCT in children

d) Continue annually after allogeneic HCT as clinically indicated for any patient on steroid therapy >1 year posttransplant after completing initial DEXA scan at 1 year

iv. **Vitamin D (25 Hydroxy) blood level**

a) Should be checked at 1-year post transplant for all patients.

b) Are generally rechecked 2-3 months after beginning therapy and target to be within normal range

v. **Patients treated with bisphosphonate or rank ligand inhibitors:** Recommend liver function tests, calcium, magnesium, creatinine and electrolytes be measured at baseline and as clinically indicated.

B. Calcium Requirements

i. FOR PATIENTS ON STEROID THERAPY:

Age	Daily Minimum Requirement after Transplant (milligrams)
7-12 months:	600
1-3 years:	1000
4-8 years:	1200
> 9 years:	1500

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

ii. FOR PATIENTS NOT ON STEROIDS

Age	**Daily Minimum Requirement after Transplant (milligrams)**
Children 7-12 months	**260**
Children 1-3 years	**700**
Children 4-8 years	**1000**
Children 9-18 years	**1300**
Adult Males	**1000-1200**
Adult Females; **On hormone therapy** **No hormone therapy**	 **1000-1200** **1500**

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*,****

	Adults (>18 yrs)	Children (<18 yrs)
Treatment of Insufficiency [Vitamin D (25 Hydroxy) **levels 20-30 ng/mL] *** **		
▪ 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
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 ▪ 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 should be within normal range.

****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

An exercise program that combines weight bearing (in which bones and muscles work against gravity as the feet and legs bear the body's weight) and muscle strengthening exercise is recommended. It is advised that daily duration of these activities be increased gradually. Thirty to 60 minutes daily has been recommended by the American Heart Association. Specific time guidelines have not been established for maintenance of bone density. However, exercise has been shown to minimize bone loss, strengthen skeletal muscle and prevent falls by improving balance.

Recommended forms of exercise include low-impact walking, low-impact aerobics, stair climbing, biking (on a stationary bike if the patient has poor balance), Nordic tracking, low impact dancing or rowing. Weight-lifting can help to improve muscle mass and bone strength. Speed and duration should be gradually increased. Although high impact exercise improves bone density more quickly (running, jumping, etc.), it should be avoided during steroid treatment due to potential harm caused by increased joint stress.

F. Lifestyle

Avoidance of smoking and excessive consumption of alcohol, caffeine, sucrose and animal protein is recommended as these activities increase urinary calcium excretion and risk of bone loss.

G. Gonadal hormone replacement

Females: FSH and estradiol levels should be tested annually for ages >10 and <61 years. (see section XVI about gonadal hormone insufficiency recommendations)

Males: Free testosterone, FSH and LH serum levels should be evaluated as follows:
Male patients ≥ 10 and < 60 years: LH, FSH, and free testosterone levels
Male patients ≥ 60 years: Free testosterone levels

(see section XVI about gonadal hormone insufficiency recommendations)

Females:

i. The use of hormonal therapy is not recommended as the first line of treatment or for prevention of osteoporosis/osteopenia in women except for children or young adults.

ii. If estrogen replacement therapy (ERT) is started in an individual, the duration of therapy should be individualized based on the clinical setting. A consultation is recommended with the gynecologist.

iii. 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, coronary artery disease or active liver disease.

iv. Transdermal ERT if given is preferred owing to lower risks of thromboembolism and stroke but like other forms of ERT, should not be used in patients with unprovoked DVT.

v. When ERT is prescribed for women with an intact uterus, low-dose progesterone is added to prevent endometrial hyperplasia, despite the only slightly increased risk of breast cancer.

Males:

vi. Male HCT survivors are at risk for developing hypogonadism which increases the risk for reduced BMD and fractures.

vii. If the free serum testosterone level is low, symptoms of hypogonadism are present, and there are no contraindications, including history or risk of prostate cancer, testosterone replacement can be considered.

Children:

Gonadal hormone replacement in children needs to be coordinated with age-appropriate linear growth and pubertal development. Pediatric Endocrinology consultation is advised for additional work-up as indicated including assessment of gonadal and growth hormones (See also Section G below).

H. Other treatments

An endocrinology consult may be appropriate for patients at high risk of osteoporosis and those for whom pharmaceutical therapy is being considered. Therapies to reduce osteoporosis may include:

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

1. **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 low bone mineral density (BMD) should be considered for referral to pediatric endocrinology if they:

a) develop a fracture in the setting of low bone mineral density,

b) have ongoing risk factors for low BMD and/or avascular necrosis (AVN) like steroid therapy or chronic GVHD , hypogonadism or growth hormone deficiency.

The Pediatric Oncologist and Pediatric Endocrinologist will jointly determine the need for bisphosphonate therapy. Pediatric Endocrinology will initiate additional work-up as indicated including assessment of gonadal and growth hormones. In children, initiation of hormonal therapy may precede bisphosphonate therapy in the appropriate clinical setting. Children should have an EKG and formal dental evaluation prior to initiation of bisphosphonate therapy.

For All Patients

- Intravenous bisphosphonates are not recommended for patients with creatinine clearance <35 ml/minute.
- Oral bisphosphonate therapy can cause esophageal ulceration (pill esophagitis) and 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 referring to Endocrinology for consideration of alternative treatment.

Commonly used bisphosphates include:

For Adults

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.

For Children

Drug selection and dosing of bisphosphonate therapy will be determined by Pediatric Endocrinologist

2. Rank Ligand Inhibitor

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.

3. Calcitonin

Calcitonin is 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.

4. Low Sodium Diet

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

5. Endocrinology

Refer for endocrinology consult if clinically indicated.

XII. HYPERLIPIDEMIA

The syndrome of abdominal obesity, dyslipidemia, hypertension, insulin resistance and prothrombotic or inflammatory states (metabolic syndrome) is a risk factor for premature cardiovascular disease. By itself, chronically elevated serum low-density lipoprotein cholesterol (LDL-C) is also strongly associated with premature cardiovascular disease (< age 55 years) in the general population. Hyperlipidemia is also associated with reduced survival in the recipients of solid organ transplants. Chronic immunosuppressive therapy (IST) in hematopoietic cell transplantation (HCT) or organ transplant recipients may aggravate pre- existing risk factors for premature cardiovascular disease, or promote development of new risk factors, notably hyperlipidemia and hypertension. Even after discontinuation of IST, the long-term survivors of allogeneic HCT appear to be at increased risk relative to their siblings for developing diabetes and hypertension. Adjustment was made in the analysis for age and gender, and the observation is independent of obesity.[1]

Based on a retrospective analysis at the Fred Hutch more than half of 349 HCT recipients had serum cholesterol >200 mg/dL at 75-100 days after HCT. Median cholesterol and triglyceride levels increased relative to before transplant by 34% and 65% respectively in adults, and 45% and 125% in children. Marked elevations of serum triglycerides (>750 mg/dL) were observed in 4.8% of adults and 8.1% of children. The prevalence of premature cardiovascular disease after HCT has not been determined but recent case reports have described premature and fatal coronary artery disease (CAD) in HCT recipients.[6-10] At least 30 patients who received HCT at the median age of 35 years (range 4-52 years) at Fred Hutch (08/73-05/98) died at a median of 7.5 years after the transplant due to CAD or heart failure of unspecified etiology. Hyperlipidemia was present in the majority of patients who had serum lipids levels documented beyond Day 90. Looking to the future, because the earliest successful HCT were performed in younger patients just over 40 years ago, it is possible that the prevalence of premature CAD might increase as earlier transplant survivors mature.

HMG-CoA reductase inhibitors (statins) effectively reduce serum total cholesterol, protect against premature cardiovascular disease, and improve survival in adults with a wide range of cholesterol levels whether or not they have a history of coronary artery disease.[2-5] Statin therapy has been safely administered to solid organ transplant recipients, it has been effective at lowering serum lipid levels, and appears to protect against premature cardiovascular disease and improve survival.[11-19] Similar benefits could be expected in HCT recipients with hyperlipidemia. Pleiotropic effects of statins suggest potential additional roles in mediating improved renal function, control of hypertension, osteopenia, avascular necrosis, and even control of GVHD.[20-28]

The following general guidelines begin with therapeutic lifestyle changes before drug therapies, in accordance with Adult Treatment Panel III/National Cholesterol Education Program (ATPIII/NCEP) guidelines for the management of hyperlipidemia in the general population.[30-31]

The risk benefit ratio of drug therapy always needs to be considered and should be individualized.

A. Working Definitions of Fasting Hyperlipidemia

1. Fasting serum LDL-C ≥ 130 mg/dL *or*
2. Fasting total cholesterol minus fasting HDL-C >160 and fasting serum triglycerides > 200 mg/dL *or*
3. Fasting serum triglycerides ≥ 500 mg/dL if >18 years old and > 400mg/dL if ≤18 years old[35] *or*
4. High-risk or very high-risk category patients with fasting serum LDL-C > 100 mg/dL

Table 1: ATP III Risk Categories and Definitions[29]**

**Electronic 10-year risk calculators are available at https://www.nhlbi.nih.gov/files/docs/guidelines/atglance.pdf

Risk category	Definitions
Very High Risk	1. Established cardiovascular disease and > 2 major risk factors 2. Severe and poorly controlled risk factors, 3. Multiple risk factors of the metabolic syndrome 4. An acute coronary syndrome
High-Risk (10 yr risk >20%)	CHD or CHD risk equivalents
Moderately High Risk (10 yr risk 10-20%)	2+ risk factors
Moderate Risk (10 yr risk < 10%)	2+ risk factors
Low-Risk**	0-1 risk factors
CHD	History of myocardial infarction, stable angina, coronary artery procedures (angioplasty or bypass surgery) or evidence of clinically significant myocardial ischemia.
CHD Risk Equivalents	Clinical manifestations of non-coronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm and carotid artery disease), diabetes, and 2+ risk factors.
Metabolic Syndrome	1. Abdominal obesity 2. Elevated triglycerides, small LDL particles and low HDL 3. Hypertension 4. Insulin resistance 5. Prothrombotic and proinflammatory states
Risk Factors	1. Cigarette smoking 2. Hypertension (BP ≥140/90 mmHg) or on antihypertensive medication 3. Low HDL cholesterol <40 ml/dL 4. Family History of premature CHD in male first-degree relative < 55 years of age 5. CHD in female first-degree relative < 65 years of age 6. Age (men ≥ 45 years; women > 55 years)

B. General Guidelines for Management of Hyperlipidemia in HCT Patients

1. Diet: If clinically appropriate, reduce daily fat: saturated fat <7% calories, cholesterol < 200 mg/day [NCEP] or <300 mg /day (American Heart Association).
2. 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 these fatty acids is currently 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).
3. Weight management
4. Regular exercise regimen.
5. Exclude untreated hypothyroidism.
6. Exclude nephrotic syndrome.
7. Exclude obstructive liver disease..

If patient has high CHD risk treat dyslipidemia also with appropriate drugs. If a patient has low to moderate CHD risk, consider drug therapy based on severity of dyslipidemia, estimated prognosis after transplant and risk of lipid lowering drug therapy. In patients with low CHD risk that develop secondary dyslipidemia this must likely can be managed conservatively if immunosuppressive therapy can be tapered off. Patients with low and moderate risk though with serum triglycerides >500 mg/dL should be treated to prevent pancreatitis.

C. Important Prescribing Precautions for Hyperlipidemia

Statins are the most widely used class of drugs, but proper selection of statin preparation and dose are important, as a number of drugs used specifically in the HCT setting can interact with them. Cyclosporine's metabolism is by the cytochrome CYP3A4 a key factor in drug-drug interactions, as it raises levels of statins (for example lovastatin, simvastatin and atorvastatin) also metabolized by this pathway and thus increases the risk for myopathy [32]. Tacrolimus and sirolimus also appear to be metabolized by his pathway [33]. Cyclosporine can also increase statin drug levels through inhibition of the member transport OATP1B1. Consequently, cyclosporine potentially increases the risk for toxicity of any statin [34]. Other inhibitors of CYP3A4 including azole antifungals, non-dihydropyridine calcium channel blockers and macrolide antibiotics also can interact with statins. For other drugs like Ruxolitinib that can impact CYP3A4 metabolism, contact pharmacy. **Since pravastatin, rosuvastatin and fluvastatin are metabolized by alternative pathways, these statins may be better choices for patients requiring coadministration of CYP3A4 inhibitory agents**.

NOTE: Toxicity may be increased in patients treated with calcineurin inhibitors, Ruxolitinib, sirolimus, antifungal azoles, or macrolide antibiotics. Patients on these medications should be started on the lowest dose of statin or fibrate therapy to limit toxicity. Patients coming to transplant on hyperlipidemia treatment should have their doses of statin or fibrate therapy reduced prior to start of calcineurin inhibitors, Ruxolitinib, sirolimus or antifungal azole therapy.

Toxicity related to statins should be discussed before starting therapy:

1. Liver enzyme abnormalities.
2. Rhabdomyolysis with associated renal failure
3. Onset of toxicity may occur weeks to months after initiation of treatment
4. Combination fibrate-statin therapy can be medically appropriate but may increase the incidence of myopathy.
5. Patients should be advised to report immediately unexplained muscle pain, tenderness, or weakness, especially when accompanied by fever or malaise.

D. Intervention for Elevated LDL-C with Minimal Elevation of Triglycerides

Any patient who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

TABLE 2. ATP III LDL-C Goals and Cut points for TLC and Drug Therapy in Different Risk Categories and Proposed Modifications (adapted from reference 29) and **Based on Recent Clinical Trial Evidence**

Risk Category	**LDL-C Goal**	**Recommendations for Drug Therapy****
Very high risk	< 70 mg/dL	≥ 100 mg/dL††
High risk	< 100 mg/dL	> 100 mg/dL††
Moderately high risk	< 130 mg/dL	> 130 mg/dL
Moderate risk	< 130 mg/dL	≥ 130 mg/dL
Low risk	< 160 mg/dL	> 160 mg/dL

**When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

††If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

For persistent and clinically significant elevations of fasting serum LDL-C who have not responded sufficiently to therapeutic lifestyle changes, treatment with any of the following statins in Table 3 may be considered.

Table 3. Suggested Medication Options for High LDL-C in Adults* after BMT

Drug	Daily Dose mg	Class Effects	Precautions
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. • 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. • Toxicity may be increased in patients treated with calcineurin inhibitors, Ruxolitinib, sirolimus, antifungal azoles, or macrolide antibiotics. Patients on these medications should be started on the lowest dose of statin therapy to limit toxicity
• Atorvastatin (Lipitor)	10-80		
• Pravastatin (Pravachol)	10-40		
• Simvastatin (Zocor)	5-40		
• Rosuvastatin (Crestor)	5-40		

NOTE: Pediatric patients refer to hyperlipidemia specialty clinic.

E. Medical Intervention for Mixed Hyperlipidemia

1. For persistent and clinically significant elevations of fasting serum LDL-C and triglycerides who have not responded sufficiently to therapeutic lifestyle changes, it is reasonable to consider initial treatment with a statin.

2. If statin therapy alone does not result in a satisfactory lowering of both LDL-C and triglycerides then consideration of combination therapy with either a fibrate or ezetimibe is recommended through consultation with a subspecialty hyperlipidemia clinic, particularly for children.

F. Medical Intervention for Isolated Hypertriglyceridemia

Fasting serum triglycerides > 800 mg/dL may increase the risk for acute pancreatitis. Treatment with either of the following fibrates, omega-3-fatty acids, or icosapent ethyl may be considered at > 500 mg/dL of fasting serum triglycerides.

Fibrates reduce triglycerides by 20-50%. Potential side effects of fibrates include cholelithiasis, GI upset and myopathy. Risk for myopathy increases when fibrates are

Table 4: Triglycerides Lowering Agent for Adult Patients**

Drug	Daily Dose mg	Class Effects	Precautions and Monitoring
Omega-3-Acid Ethyl Esters[a] • Lovaza ®	4000 Daily OR 2000 BID	LDL may ↑ HDL ↑ 9% TG ↓45% VLDL↓40%	• Generally minimal side effects, eructation, dyspepsia • *May potentiate INR if on warfarin* • Avoid if fish/shellfish allergic • Monitor AST/ALT periodically • Has been combined with simvastatin for mixed hyperlipidemia
Fibric Acids • Fenofibrate (Tricor) • Gemfibrozil (Lopid)	*Start at lowest doses and rarely exceed middle of the dose range when taking concomitantly calcineurin inhibitors.* 48-145 600-1200	LDL ↓5-20% HDL ↑10-20% TG ↓20-50%	• Contraindicated in severe liver or renal disease • May cause myopathy especially when combined with statins, and in setting of impaired renal function in patients receiving cyclosporine or other drugs that interact with statins • May cause cholelithiasis and GI symptoms • May cause reversible increase in serum creatinine • Fenofibrate-statin combination may be better that gemofribrozil-statin therapy because gemfibrozil can increase statin levels by 2-6 fold • Counsel patient to report muscle pain, weakness, dark or cola-colored urine, especially when accompanied by fever and malaise. • 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.

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

**In patients with severe thrombocytopenia, recommend give lower doses.

NOTE: Pediatric patients refer to hyperlipidemia specialty clinic.

Table 5: Summary for Recommendations for Managing Hyperlipidemia

1.	Exclude untreated hypothyroidism, nephrotic syndrome or obstructive liver disease
2.	Adjust Diet to be high in fiber, (fruits, vegetables, whole grains), high in polyunsaturated and monounsaturated fats and low in saturated fat and devoid of trans fat Consider referral to dietitian Add omega 3 fatty acid supplements
3.	Determine Risk of CHD (see Table 1) a) If high or very high CHD risk, consider drug therapy b) If low to moderate CHD risk, consider drug therapy based on dyslipidemia, estimated prognosis of treatment, and risk of statins. c) If low risk CHD and immunosuppressive therapy can be tapered off, manage conservatively
4.	Assess LDL-C and TG levels to help determine drug therapy. a) If elevated LDL-C with minimal elevated TG, statin therapy **(Pravastatin, rosuvastatin, and fluvastatin) preferred because of drug-drug interactions with statins with calcineurin inhibitors, Ruxolitinib, sirolimus, or antifungal azole therapy.** If starting drug, begin dosing at lowest dose and monitor carefully. If already on drug, consider dose reducing statins. b) If mixed hyperlipidemia and on statin that fails to lower both LDC-C and TG Add fibrate or ezetimibe Consider Hyperlipidemia consult c) If isolated hypertriglyceridemia (>500 mg/dL), fibrate therapy for adults. For children, refer to hyperlipidemia specialty clinic.
5.	Begin long term plan for: Weight management Regular exercise program

G. Monitoring during treatment with statins or fibrates:

Table 6: Monitoring

CK measure if clinically indicated (i.e. symptoms of myalgia, muscle weakness, etc, develop).
LFT's at baseline, 2 and 4 weeks after start therapy and monthly while on therapy.
Stop therapy for significantly elevated serum transaminase or if symptoms of myositis or rhabdomyolysis occur.

1. Serum creatine kinase (CK) should be checked when clinically indicated (i.e. when symptoms such as myalgia, muscle weakness, etc. develop).
2. Doses of statins or fibrates may be adjusted at four-week intervals as needed.
3. Consultation with a subspecialty hyperlipidemia clinic is generally recommended in patients taking concomitant immunosuppressive therapy who do not respond adequately to the above measures.
4. Patients should be advised to report immediately any unexplained muscle pain, tenderness, or weakness, especially if accompanied by malaise or fever.
5. Statin or fibrate therapy should be withdrawn if serum transaminase concentrations are significantly elevated or if symptoms of myositis or rhabdomyolysis occur.
6. Liver function tests (LFT) levels should be checked at baseline and at 2 and 4 weeks after starting statin or fibrate therapy and at least monthly while on immunosuppressive therapy.

XIII. HYPERTENSION

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

A. Key Points about Hypertension and its treatment

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

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

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

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

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

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

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

Table 1 - Antihypertensive Medications According to Clinical Setting

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

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

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

CCB; calcium channel blockers,

* Definition of chronic kidney disease (CKD) criteria

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

**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

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

**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.

XIV. RECURRENT MALIGNANCY

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

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

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

XV. SECONDARY MALIGNANCIES

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

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

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

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

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

XVI. OTHER COMPLICATIONS

A. GONADAL HORMONE INSUFFICIENCY

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

MALES:

Post puberty: 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.

Prepubertal: For boys without signs of puberty at age 14 years or failure of pubertal progression or abnormal growth velocity with hypergonadotropic hypogonadism (high FSH and LH and low free testosterone) should be considered for androgen or gonadotropic therapy. Initially a lower dose should be considered to accelerate growth velocity without advancing bone age. Subsequently, the dose can be increased closer to end of growth spurt when fusion of growth plates is then acceptable. Hormonal replacement in prepubertal boys should be done in collaboration with a pediatric endocrinologist.

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. Survivors with hypergonadotrophic (high FSH, low estradiol) and hypogonadotropic (low FSH, low estradiol) should be considered for hormone replacement therapy. Initially low dose hormone therapy should be used . Cyclic dosing should be used at later stages to induce regular menstrual cycles. It is recommended to hold hormone replacement therapy for 2 months at regular intervals to check for resolution of gonadal insufficiency . 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, coronary artery disease, 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.

  Use of hormone of supplementation as first line of treatment is not recommended for osteoporosis/osteopenia except for children or young adults. Please see LTFU Section XI: General Guidelines For Prevention of Osteoporosis and Glucocorticosteroid Induced Osteoporosis After HCT
- 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.

  <u>General guidelines include</u>:
  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 1: Dental Care Guidelines for Autologous and Allogeneic Transplant Recipients

Dental Procedure	Time after Transplant		
	Until 6 months	After 6 months ****	
		LOW-RISK	HIGH-RISK
		Not receiving IST for active GVHD* or getting maintenance with anti-CD20 therapy or other cytotoxic therapy AND with ANC >1000, Plts >30K	Receiving IST or maintenance with anti-CD20 therapy or other cytotoxic therapy, CD34 selected transplant or ANC ≤1000, Plts <30K
Routine Dental Care			
Exam every 6-12 months	YES	YES	YES
Routine Dental Cleanings	NO	YES, with antibiotics if central line still in place	YES, with antibiotics and/or IVIG** as clinically indicated
Periodontal Therapy			
Scaling/root planning +/- curettage (dental deep cleaning)	NO	YES, for autologous (no contraindications) YES, for allogeneic with considerations for additional medical support	NO
Restorative Dental Care* **			
Crowns	Emergent ONLY with antibiotics	Emergent ONLY with antibiotics	Emergent ONLY with antibiotics and/or IVIG
Fillings	Emergent ONLY with antibiotics	Emergent ONLY with antibiotics	Emergent ONLY with antibiotics and/or IVIG
Surgical Treatments			
Dental extractions	Emergent ONLY with antibiotics	Emergent ONLY with antibiotics	Emergent ONLY with antibiotics and/or IVIG
Implants	NO	Autologous – NO Allogeneic – NO	NO
Gingival grafts	NO	YES, for autologous (no contraindications) YES, for allogeneic with considerations for additional medical support	NO
Cosmetic Dental Care			
Teeth whitening	NO	YES	YES
Orthodontia	NO	NO	NO
Dentures	YES, if no surgery needed	YES, if no surgery needed	YES, if no extractions are needed

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 <u>all</u> 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, opiods, benzodiazepines, high-dose steroids, voriconazole, etc) and check CSA/FK506 levels**
   - Metabolic abnormalities (hypo/hypernatremia, hypercalcemia, hypercapnia, hyperosmolarity, renal or hepatic failure, hypothyroidism, adrenal insufficiency, hypoglycemia, etc.)
   - Non-CNS infection such as UTI, pneumonia, etc.
   - Unremitting pain or insomnia
   - Intracranial hemorrhage
   - Hypovolemia – due to bleeding or other cause
   - Head trauma
   - CNS malignancy
   - CNS infection

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

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

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

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

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

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

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

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

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

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

G. Bone Complications (see Section XI)

Osteoporosis, fractures and avascular necrosis (AVN) are common complications after transplantation. Long-term treatment with corticosteroids is the primary risk factor for these complications, while gonadal failure, electrolyte imbalances, physical inactivity and treatment with cyclosporine play an additional contributory role. Approximately 50% of patients receiving long-term corticosteroid therapy will eventually develop bone fractures. Increased osteoclast-mediated bone resorption and decreased osteoblast-mediated bone formation cause trabecular bone loss. In 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 FEV_1/FVC is less than 70% in 15% of patients by one year after the transplant and in 30% of patients by three years after an allogeneic transplant. Among patients with chronic GVHD, 5-10% will develop severe obstructive airway disease that resembles obliterative bronchiolitis.

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 GHVD 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/mm^3 and the risk of bleeding is small (including normal PT/PTT) but transvenous biopsy through either the femoral or jugular route is satisfactory for diagnosis of any diffuse hepatitis or GVHD. Tissue should be cultured for viruses and fungi and should be fixed in freshly-prepared neutral buffered formalin.

J. Gastrointestinal Complications:

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.

XVIII. VIRAL HEPATITIS in long term transplant survivors

(see References, section XXV, Liver)

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

A. Hepatitis B

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

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

Posttransplant HBV infection may result from

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

1) Monitoring of Patients at Risk for HBV Infection

- 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 $\geq$ F3) and cirrhosis (Metavir score F4).
- For HCV-infected HCT long-term survivors with advanced fibrosis (Metavir score $\geq$ 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)

XIX IRON OVERLOAD

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 T2- magnetic resonance imaging (MRI) was not associated with survival or complications in adult patients 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 pseudotubera*, 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*

All patients should undergo T2*-weighted magnetic resonance imaging test (MRI-T2*) if there are concerns about iron overload. MRI-T2* is highly accurate in measuring tissue iron in heart, liver, spleen, and pancreas. Recommend first getting MRI of abdomen for assessing liver, spleen, and pancreas. If abnormal uptake in pancreas or other high-risk factors see below, get cardiac MRI.

Cardiac MRI are indicated for patients with the following high-risk factors:

1. Lifetime history of receiving 75 RBC units or more;
2. Thalassemia;
3. Sickle cell disease ;
4. Other congenital anemias (Diamond-Blackfan; hereditary sideroblastic);
5. Associated hereditary hemochromatosis (HH)

b. Endocrine screen: Patients that fulfill criteria for iron overload (LIC>2mg/g), particularly those with detectable cardiac iron (T2*<20ms) in adult patients, or below 1 standard deviation or age based references in pediatric patients, 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

Cardiac T2* (ms)	**LIC** (mg/g dry weight)	**Marrow Iron Content**	**Mobilization of Iron**
>20ms* (normal)	>15	Very high ++++	Phlebotomy ± single iron chelator
	7 – 15	Moderately high ++ to +++	1st choice: Phlebotomy 2nd choice: Single iron chelator (especially if HCV-positive)
	2-7	Mildly increased +	1) $HFE^{wildtype}$: observe 2) $HFE^{C282Y/C282Y\ or\ C282Y/H63D}$: Phlebotomy aiming at ferritin level <100 3) Hemoglobinopathies and other congenital anemia disorders Phlebotomy aiming at ferritin level <500
<20ms*	Any	Any	Phlebotomy + combination iron chelation; consider admission if symptomatic or T2*<8ms; consider erythrocytapheresis for faster removal

For pediatric patients: Use age-based reference ranges for cardiac T2 values. Abnormal cardiac iron content is defined as below 1 standard deviation for age-based reference values

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 and patients with hemoglobinopathies/other congenital anemias), 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:

Body Weight (kg)	Erythropoietin[1] (Units weekly)	Darbepoetin[2] (micrograms every-other-week)
10-14	6,000 to 8,000	25 to 60
15-20	10,000	60
21-24	10,000 to 14,000	60 to 100
25-29	14,000	100
30-39	20,000	100
40-60	40,000	200
≥60	Use darbepoetin	200

[1] Erythropoetin (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 $\leq$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.

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

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.

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

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 ≥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/1.73m^2 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/1.73m^2, 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/1.73m^2.
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**:

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

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

Age	**Daily Minimum Requirement after Transplant (milligrams)**
Children 7-12 months	**260**
Children 1-3 years	**700**
Children 4-8 years	**1000**
Children 9-18 years	**1300**
Adult Males	**1000-1200**
Adult Females; **On hormone therapy** **No hormone therapy**	 **1000-1200** **1500**

iii. Vitamin D requirement

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

	Adults (>18 yrs)	Children (<18 yrs)
Treatment of Insufficiency [Vitamin D (25 Hydroxy) **levels 20-30 ng/mL]*** **		
▪ 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
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 ▪ 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 within normal range.

****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 Fred Hutch. These GI1 and GI2 diets have limited amounts of fats, fiber, lactose, acidic items and GI irritants. The diets can be found at *www.seattlecca.org* under *patientsandfamilies/nutrition/nutritionDietsguidelines/.*

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

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

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

Gastrointestinal GVHD Diet Progression*

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

[a]Lactose is one of the last disaccharidases to return following villous atrophy. A commercially-prepared lactose solution (Lactaid[R]) is used to reduce the lactose content of milk by >90%. Lactaid[R] milk (100% lactose-free) is also commercially available.
[b] Additional calories may be provided by commercially available medium chain triglycerides which do not exacerbate symptoms.

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

XXII. NATUROPATHIC REMEDIES: HERBAL AND NUTRIENT SUPPLEMENT PREPARATIONS

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

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

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

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

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

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

XXIV. HOW TO SEND SPECIMENS FOR TESTING AT FRED HUTCH

Clinical laboratory testing for patients who received treatment at Fred Hutchinson Cancer Center (Fred Hutch) is available at the Fred Hutch. 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 Fred Hutch. The LTFU office will provide detailed instructions regarding sample collection and shipment information for the specific test(s) requested.

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

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

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

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

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APPENDIX A

FAX LTFU CONSULT

Date: _____

To: FRED HUTCHINSON CANCER 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: _____)
- ❒ Cyclosporine (Neoral, Sandimmune) (or equivalents)
- ❒ Tacrolimus (FK506)
- ❒ Mycophenolate Mofetil (MMF) (Cellcept)
- ❒ Thalidomide (Thalomid)
- ❒ Rapamycin (Sirolimus)
- ❒ Rituximab
- ❒ Extracorporeal photopheresis (ECP)
- ❒ Other:
- ❒ No immunosuppressive medications
- ❒ Trimethoprim-sulfamethoxazole
- ❒ Penicillin
- ❒ Dapsone
- ❒ Acyclovir or valacyclovir
- ❒ Ganciclovir, ValGANCiclovir
- ❒ Fluconazole or itraconazole

Current problems(s):

What questions would you like the consultant to address?

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

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

Fax (____) _____ **Phone (____)** _____

APPENDIX B

FAX **LTFU ALERT**

Date: _____

To: FRED HUTCHINSON CANCER 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: _____

❑ 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 Fred Hutch** due to
(reason, if stated):

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

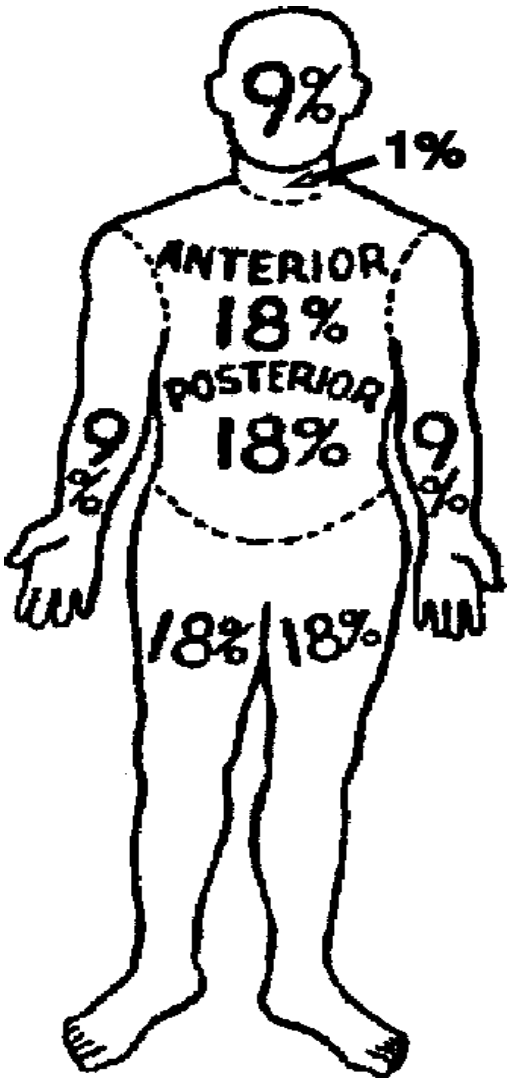
Fax (_____) _____ **Phone (_____) _____**

APPENDIX C

FORM FOR DESCRIPTION OF SKIN INVOLVEMENT

NAME:	Date of Birth:

DATE OF ASSESSMENT:_____



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

Patient:_____ **/ UW#** _____ **Date Evaluation:**_____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† ☐ **SCORE % BSA** *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration

Other skin GVHD features (NOT scored by BSA)
Check all that apply:
☐ Hyperpigmentation
☐ Hypopigmentation
☐ Poikiloderma
☐ Severe or generalized pruritus
☐ Hair involvement
☐ Nail involvement
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____
☐ *Abnormality thought to represent GVHD PLUS other causes (specify):* _____

MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms **with** disease signs with partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake

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

† 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.

TEAM
NAME
PT NO
DOB

PLACE EPIC LABEL HERE

[M]
[F]

Seattle Cancer Care Alliance

SLTF003

LTF003 (10/15)

CHRONIC GVHD ASSESSMENT AND SCORING FORM

Patient: _____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day))	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *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	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *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 0_2)
Lung score: **%** FEV1 ☐ *Pulmonary function tests* ☐ Not performed	☐ FEV1 ≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
☐ *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.

TEAM

NAME PLACE EPIC LABEL HERE [M]

PT NO [F]

DOB

Seattle Cancer Care Alliance

SLTF003

LTF003 (10/15)

CHRONIC GVHD ASSESSMENT AND SCORING FORM

Patient: _____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7) _____ Elbow (1-7) _____ Wrist/finger (1-7) _____ Ankle (1-4) _____	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM *AND* significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
GENITAL TRACT *(See Supplemental figure‡)* ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms

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

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)

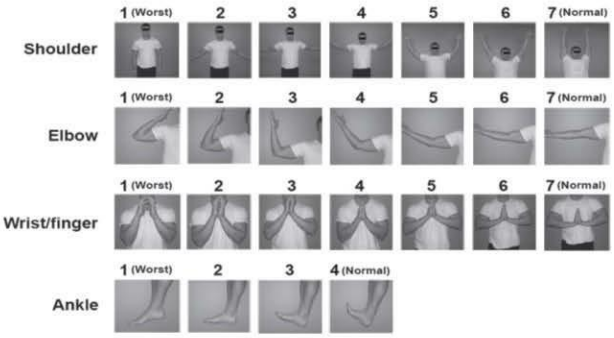
☐ Ascites (serositis) _____
☐ Pericardial Effusion _____
☐ Pleural Effusion(s) _____
☐ Nephrotic syndrome _____
☐ Myasthenia Gravis _____
☐ Peripheral Neuropathy _____
☐ Polymyositis _____
☐ Weight loss >5%* without GI symptoms
☐ Eosinophilia > 500/µl _____
☐ Platelets < 100,000/µl _____
☐ Others (specify): _____

Biopsy obtained: ☐ **Yes** ☐ **No** **Organ biopsied:** _____ **GVHD confirmed by histology:** ☐ **Yes** ☐ **No**

Overall GVHD Severity *(Opinion of the evaluator)* ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

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

Photographic Range of Motion (P-ROM):



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

TEAM
NAME
PT NO
DOB

PLACE EPIC LABEL HERE

[M]
[F]

Seattle Cancer Care Alliance

SLTF003

LTF003 (10/15)

CHRONIC GVHD ASSESSMENT AND SCORING FORM

APPENDIX E

ASSESSMENT OF SKIN THICKNESS
Modified Rodnan Score*

Patient Name: _____ **Date of Birth:** _____

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

A. Evaluate skin thickness by clinical palpation:

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

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

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

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

APPENDIX F

Name_____ **DOB**___}____*j*__ **Date**___}____*j*__

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

Flexibility

Mininum Maximum

Shoulder

Elbow

Wrist and fingers

Foot Dorsiflexion