Introduction
Acute graft versus host disease is an immunologic process that involves 3 phases: 1) afferent phase where damage to the host tissue occurs by the preparative regimen; 2) induction and expansion phase where there is triggering and activation of donor-derived T-cells by recipient and donor antigen-presenting cells (APC) as well as inflammatory cytokines; 3) effector phase with target tissue damage induced directly by cytotoxic T cells and indirectly by inflammatory cytokines.1,2

Acute GVHD is a major post-transplant complication and is the leading cause of non-relapse mortality post hematopoietic stem cell transplantation (HSCT).7 The incidence is between 10-80% for adults and pediatric patients have a lower incidence than adults.3,4 Historically, acute GVHD was differentiated from chronic GVHD based on time of presentation with acute GVHD occurring before day 100 post-HSCT and chronic GVHD occurring after day 100.1 Classic acute GVHD usually occurs within the first 3 or 4 months after HSCT while both late-onset and overlap acute GVHD tend to occur after reduced-intensity conditioning, after initial taper of immunosuppression, or after donor lymphocyte infusion.3

This guideline has been developed to assist in the assessment and management of patients with acute Graft versus Host Disease. The recommendations include prophylaxis, staging and grading criteria to use, medication treatment recommendations, and supportive care recommendations such as nutritional guidance.

Scope
Disease/Condition(s): Acute Graft versus Host Disease (aGVHD)

Clinical Specialty: Hematology/Oncology/Blood and Marrow Transplant (BMT), Pharmacy, Nutrition, Social Work, Health Psychology

Intended Users: Physicians, Advanced Practice Providers, Registered Nurses, Pharmacists, Registered Dieticians, Social Workers, Health Psychologists

Objective(s): To outline evidence-based recommendations for the prophylaxis, screening, diagnosis, staging, treatment and monitoring of aGVHD.

Target Population: Adult and pediatric patients who have received allogeneic Bone Marrow Transplants (BMT) and are being seen in the BMT clinic or inpatient settings.

Interventions and Practices Considered:
- Prophylaxis
- Staging and Grading
- Risk Assessment for initial therapy response and transplant-related mortality
- Treatment
- Nutrition
- Patient Reported Quality of Life

Major Outcomes Considered:
- Overall survival
- Non-relapse mortality
- Quality of Life
Definitions

Acute Graft versus Host Disease (aGVHD): Acute GVHD is defined as the following:
1. classic acute GVHD (erythema, maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus, or cholestatic liver disease) occurring within 100 days after transplantation or donor lymphocyte infusion (DLI) in a patient not meeting criteria for the diagnosis of chronic GVHD and
2. persistent, recurrent, or late onset acute GVHD: features of classic acute GVHD occurring beyond 100 days after transplantation or DLI in a patient not meeting criteria for the diagnosis of chronic GVHD (often seen during the taper or after withdrawal of immune suppression.)

Chronic Graft versus Host Disease (cGVHD): Chronic GVHD is a syndrome of variable clinical features resembling autoimmune and other immunologic disorders, such as scleroderma, Sjögren’s syndrome, primary biliary cirrhosis, wasting syndrome, bronchiolitis obliterans, immune cytopenias, and chronic immunodeficiency. The pathophysiology of the cGVHD syndrome may involve inflammation, cell-mediated immunity, humoral immunity, and fibrosis. Clinical manifestations nearly always present during the first year after transplantation, but some cases develop many years after hematopoietic cell transplantation (HCT). Manifestations of cGVHD may be restricted to a single organ or site or may be widespread, with profound impact on quality of life. Other cases are self-limited and either smolder or resolve without immunosuppressive therapy. Chronic GVHD includes 2 subcategories: (1) classic cGVHD without features characteristic of acute GVHD, and (2) an overlap syndrome, in which features of chronic and acute GVHD appear together.

Overlap Syndrome: The term "overlap" refers to the presence of 1 or more acute GVHD manifestation in a patient with a diagnosis of cGVHD. Manifestations of acute GVHD can be present at initial diagnosis of cGVHD or can develop after the diagnosis of cGVHD and may recur with or without resolution of prior cGVHD manifestations. Findings indicating the overlap subcategory can be transient, often depend on the degree of immunosuppression, and are subject to changes during the disease course. Many patients who present with “overlap” cGVHD have resolution of the acute features, whereas cGVHD features persist. Similarly, patients with classic cGVHD may develop acute GVHD features when immunosuppression is tapered.

Recommendations

Prophylaxis for Acute GVHD

Recipients of allogeneic hematopoietic stem cells from matched, mismatched related, or unrelated donors will receive the acute GVHD prophylaxis regimen outlined below, unless the patient is enrolled on a treatment or research protocol which specifies an alternate form of aGVHD prophylaxis.

The disease-specific pathways and chemotherapy treatment plans should be followed unless there is a patient-specific reason for deviation. Patient-specific deviations will be discussed by the Blood and Marrow Transplant (BMT) clinical team and a note indicating the reason behind the deviation should be documented in the patient’s electronic medical record.

The schedules for tapering immunosuppressive regimens after hematopoietic stem cell transplant (HSCT) are determined by the disease-specific protocols. When there is not a current disease-specific protocol or SOP, the BMT physician should adjust the schedule for taper of immunosuppression in the individual patient according to best clinical judgment, taking
into consideration GVHD status of the patient, risk for disease relapse, end-organ toxicities from the transplant regimen and the presence of active infection.

### Table 1. Current Standard for Acute GVHD regimens includes:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Population</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-transplant cyclophosphamide</td>
<td>Adults</td>
<td>Given to all adult patients unless there is a specific treatment protocol that does not include it.¹⁹,¹⁰</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Adults</td>
<td>Patients receiving a mismatched transplant or a peripheral blood stem cell product or as specified by protocol</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Adults</td>
<td>May be used in lieu of tacrolimus in setting of tacrolimus intolerance or renal insufficiency</td>
</tr>
<tr>
<td>Mycophenolate Mofetil (MMF)</td>
<td>Adults</td>
<td>Patients receiving a mismatched transplant</td>
</tr>
<tr>
<td></td>
<td>Pediatrics</td>
<td>Patients receiving cord blood transplants</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Pediatrics</td>
<td>Standard of care; alternatives to cyclosporine would include tacrolimus or sirolimus and dependent on patient specific factors</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Pediatrics</td>
<td>Standard of care</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Pediatrics</td>
<td>Patients receiving cord blood transplants</td>
</tr>
</tbody>
</table>

**Medications for Adult Patients (Tables listed in Appendix B)**
- Table 10 – Chemotherapy and Immunosuppression Regimens – Adults
- Table 11 – Dose Adjustments - Adults and Pediatrics
- Table 12 – Immunosuppressant Monitoring of Drug Levels - Adults
- Table 15 – Drug Interactions and Side Effects of Immunosuppressive Drugs - Adult and Pediatrics

**Cyclophosphamide¹¹,¹²**

<table>
<thead>
<tr>
<th>Route</th>
<th>IV infusion over 2 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>based on IBW</td>
</tr>
</tbody>
</table>

**Notes**
- No corticosteroids will be given as an anti-emetic (from Day 0 to Day +5) with cyclophosphamide
- Mesna will be given IV in divided doses given 30 mins. pre- and at 3,6, and 8 hours post-cyclophosphamide
- Mesna dose: approx. 80% of total daily dose of cyclophosphamide (i.e., 40 mg/kg based on IBW)
- Hydration with NaCl IV at 2 mL/kg/hr will be started 2 hrs. prior to cyclophosphamide and continued at 2 mL/kg/hr for 8 hours post-cyclophosphamide

**Cyclosporine**

<table>
<thead>
<tr>
<th>Route</th>
<th>Oral route is preferred, using twice daily dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>If a patient cannot tolerate PO formulation due to gastrointestinal (GI) toxicity associated with the conditioning regimen or absorption concerns due to GI GVHD, the patient may be converted from PO to twice daily IV infusion cyclosporine</td>
<td></td>
</tr>
</tbody>
</table>

**Dose**
- Dose modifications should **NOT** be based exclusively on drug levels, but on the attending physician’s assessment of the patient’s toxicity from drug and GVHD status in combination with drugs levels
- Based on actual body weight
- Exhibits a linear pharmacokinetic profile and changes in dose will have predicted and proportional effects on cyclosporine levels once steady state is reached in 2-3 days (i.e., 25% dose increase will increase cyclosporine level by 25%)
- Renal insufficiency: no dose modification recommended as cyclosporine is not eliminated to any appreciable amount by kidneys
- Hepatic insufficiency: may require dose adjustment, monitor levels
### Methotrexate

<table>
<thead>
<tr>
<th>Route</th>
<th>IV</th>
</tr>
</thead>
</table>
| Dose  | • If ≤ 25% above IBW: calculate using actual body weight (ABW)  
• If patient >25% above IBW then use 25% adjusted actual body weight (AABW)  
• Dose may be omitted or reduced for significant renal dysfunction, severe mucositis with potential of airway obstruction, significant pleural effusion or ascites, or hepatic/renal dysfunction  
• Every attempt should be made to administer all methotrexate doses without reduction, especially in patients at increased risk for GVHD |
| Notes | |

### Mycophenolate

| Route | Oral route is preferred  
If need to transition to IV doses for GI toxicity due to conditioning regimen, the conversion is 1:1 for IV to PO |
|-------|----|
| Dose  | Based on actual body weight  
Maximum dose is 1000mg per dose or 3000mg per day  
Round up to nearest table size for oral doses |
| Notes | Discontinue at Day 35 unless otherwise specified by treatment plan  
No taper necessary  
Mycophenolate may be continued beyond Day 35 if there is active GVHD present |

### Sirolimus

**Considered for use when patients have experienced significant toxicity with tacrolimus or cyclosporine, or patients have otherwise failed with other prophylactic medications**

<table>
<thead>
<tr>
<th>Route</th>
<th>Oral only</th>
</tr>
</thead>
</table>
| Dose  | Loading dose 12 mg PO, followed by a daily oral dose of 4 mg PO daily  
Renal insufficiency: no recommendations as sirolimus is not eliminated to any appreciable amount by the kidneys  
Hepatic insufficiency: Use approximately one-third of normal maintenance dose  
Sirolimus has half-life of approximately 5 days  
Full effects of sirolimus dose changes may not be reflected in serum level for approximately 2-3 weeks. |
| Notes | Drug interactions:  
Sirolimus undergoes CYP 3A4 mediated metabolism thus high potential for drug interactions. Patient’s medication list should be carefully screened for interactions when initiating therapy or changing medications and already on sirolimus.  
Fluconazole: sirolimus AUC was increased by 1.7 in one study with AUC increases of 3.6-4.7 reported with fluconazole. If used together, a dose reduction of at least 50% is recommended.  
Posaconazole: AUC increase of 8.9 in sirolimus concentration was reported when used with posaconazole. When concomitant use is required, a 90% dose reduction in sirolimus is recommended  
Voriconazole: Due to extreme interactions with sirolimus, voriconazole is generally contraindicated during sirolimus therapy. When deemed clinically necessary to co-administer sirolimus and voriconazole, a 90% reduction of sirolimus dosing is an effective strategy |

Effective 02/05/2020. Contact CCKM@uwhealth.org for previous versions.
<table>
<thead>
<tr>
<th>Tacrolimus</th>
</tr>
</thead>
</table>
| **Route** | Oral route is preferred, using twice daily dosing  
If pt cannot tolerate oral tacrolimus due to GI toxicity associated with conditioning regimen or absorption concerns due to GI GVHD, patient may be converted from oral to twice daily IV infusion tacrolimus  
Conversion from IV to PO is an approximate 1:3 ratio (1 mg IV equal 3 mg PO) |
| **Dose** | If ≤ 25% above IBW: calculate using actual body weight (ABW)  
If patient >25% above IBW then use 25% adjusted actual body weight (AABW)  
PO doses will be rounded to the nearest 0.5 mg |
| **Notes** | Taper and eventual discontinuation only in the absence of GVHD  
If mismatched transplant (marrow or PBSC), taper at Day 180  
If matched peripheral blood stem product, taper at Day 100  
See disease specific plan for earlier taper recommendations for patients with high risk disease |

### Medications/Regimens for Pediatric Patients (Tables listed in Appendix B)
- Table 13 - Immunosuppression Regimens - Pediatrics
- Table 11 - Dose Adjustments - Adults and Pediatrics
  **Dose adjustments should be reviewed and approved by pediatric BMT attending**
- Table 14 - Immunosuppressant Monitoring of Drug Levels - Pediatric
- Table 15 - Drug Interactions and Side Effects of Immunosuppressive Drugs - Adult and Pediatrics

<table>
<thead>
<tr>
<th>ATG (equine)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Notes</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cyclosporine</th>
</tr>
</thead>
</table>
| **Route** | Cyclosporine should NOT be infused through the same port concurrently with bone marrow  
Initiate in IV route (2-hour infusion)  
Change to PO when patient has recovered from GI toxicity post-transplant, can tolerate and absorb oral medication |
| **Dose** | Dose modifications should NOT be based exclusively on drug levels, but on the attending physician’s assessment of the patient’s toxicity from drug and GVHD status in combination with drug levels  
Conversion from IV to PO cyclosporine is an approximate 1:3 ratio (1 mg IV equal 3 mg PO)  
Exhibits a linear pharmacokinetic profile and changes in dose will have predicted and proportional effects on cyclosporine levels once steady state is reached in 2-3 days (i.e., 25% dose increase will increase cyclosporine level by 25%)  
PO daily doses should be divided into twice daily dosing with meals  
- Round each dose to the nearest 25 mg  
- Microemulsion formulations of cyclosporine (e.g., Neoral®) is preferred  
- Patients will be instructed to take cyclosporine with meals to ensure consistent absorption  
Renal insufficiency: no recommendations as cyclosporine is not eliminated to any appreciable amount by kidneys  
Hepatic insufficiency: may require dose adjustment, monitor levels |
| **Taper** | Taper - will begin only in the absence of GVHD. An earlier or rapid taper may be considered under certain conditions (e.g., JMML) at the discretion of treating physician  
Matched sibling donor: start taper on Day +100  
Decrease by 10% of original dose each week; complete taper over a 10-week period  
Matched unrelated donor: start taper on Day +180  
Decrease by 10% of the original dose each week, completing the taper over a 10-week period |

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Contact: CCKM@uwhealth.org

Last Revised: 03/2020
### Methotrexate

**Route**
- IV push at 10mg/minute

**Dose**
- Dosing is based on actual body weight
- Given Days +1, +3, +6, and +11
- 15mg/m² on Day+1 then 10 mg/m² IV on Days +3, +6, and +11

**Notes**
- Every attempt should be made to administer all methotrexate doses without reduction, especially in patients at increased risk for GVHD
- Dose may be omitted or reduced for significant renal dysfunction, severe mucositis with potential airway obstruction, significant pleural effusion, ascites, or hepatic/renal dysfunction

### Methylprednisolone

**Route**
- IV over 20 minutes

**Dose**
- **Taper** - *will begin only in the absence of GVHD*
  - 1 mg/kg Day 0 through Day +21
  - Start taper at Day +21
  - Decrease methylprednisolone/prednisone taper of 0.1 mg/kg/week

**Notes**
- Continue taper per MD discretion and presence/absence of GVHD

### Mycophenolate

**Route**
- IV over 2 hours
- May transition to PO; dosing conversion is 1:1 for IV to PO
- Round up to nearest tablet size for oral doses (if using tablets)

**Dose**
- 600 mg/m² IV every 12 hours Day -1 to Day +42

**Notes**
- Discontinue at Day 42 unless otherwise specified by treatment plan
- No taper is necessary
- Mycophenolate may be continued beyond Day 42 if there is active GVHD present

### Tacrolimus

*Tacrolimus may be considered in place of methotrexate in cases where the patient specific toxicities of cyclosporine necessitate a change in agents*

**Route**
- Initiate in IV route
- Convert to PO when patient has recovered from GI toxicity post-transplant, can tolerate and absorb oral medication
- Conversion from IV to PO tacrolimus is approximate 1:3 ratio (1 mg IV equals 3 mg PO)

**Dose**
- PO total daily dose is divided into every 12-hour dosing
- Round to the nearest 0.1 mg for patients who will receive liquid formulations or to nearest 0.5 mg for patients receiving capsules

**Notes**
- **Taper** - *will begin only in the absence of GVHD*
  - Matched sibling donor: start taper on Day +100
    - Decrease by 10% of the original dose each week, completing the taper over a 10-week period
  - Matched unrelated donor: start taper on Day +180
    - Decrease by 10% of the original dose each week, completing the taper over a 10-week period
Clinical presentation and differential diagnosis

Acute GVHD is usually suspected when a patient develops any or all symptoms in the skin, gastrointestinal tract, and/or liver. It is recommended that an acute GVHD diagnosis be based on clinical criteria versus post-transplant time only.\textsuperscript{16} (UW Health strong quality evidence, S recommendation)

The most commonly involved organ in acute GVHD is the skin, followed by the gastrointestinal (GI) tract and lastly the liver. A characteristic maculopapular rash that is pruritic and can spread on the body, sparing the scalp, is the most common skin presentation. GI involvement typically manifests as diarrhea but can include anorexia, vomiting, abdominal pain or a combination of these symptoms if severe. Liver involvement usually presents with cholestatic jaundice and elevated liver enzymes\textsuperscript{17,18} If overlap syndrome is present, treat according to the nature of the presentation (acute or chronic) of the most severely affected organ using the appropriate guidelines for acute or chronic GVHD. For example, if a patient presents with ocular and oral sicca with severe diarrhea that is consistent with Grade III acute lower GI GVHD, treat as Grade III acute GVHD.

High grade acute GVHD of the gastrointestinal (GI) tract is a medical emergency and associated with a high mortality rate.\textsuperscript{19} Patients who present with new watery diarrhea > 1000 mL per day should begin treatment as quickly as possible when clinical suspicion is high and while completing a diagnostic evaluation. In the setting of a high index of clinical suspicion, a negative GI biopsy does not rule out GVHD but does decrease the probability that GVHD is the cause of diarrhea.\textsuperscript{20} When biopsies are negative, ongoing treatment for GI GVHD should be considered carefully within the context of all available clinical and laboratory data.

Table 2. Acute GVHD symptoms and Differential Diagnosis\textsuperscript{3,4,17,18,21}

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td></td>
</tr>
<tr>
<td>Maculopapular skin rash</td>
<td>Drug hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>Allergic reaction</td>
</tr>
<tr>
<td></td>
<td>Infection (e.g. viral exanthem)</td>
</tr>
<tr>
<td></td>
<td>Regimen-related toxicity</td>
</tr>
<tr>
<td></td>
<td>Engraftment syndrome</td>
</tr>
<tr>
<td><strong>Upper gastrointestinal tract</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>Infection (viral, fungal, bacterial)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Regimen-related toxicity</td>
</tr>
<tr>
<td></td>
<td>Medication side-effect</td>
</tr>
<tr>
<td></td>
<td>Increased intracranial pressure</td>
</tr>
<tr>
<td></td>
<td>Phlegmonous gastritis</td>
</tr>
<tr>
<td><strong>Lower gastrointestinal tract</strong></td>
<td></td>
</tr>
<tr>
<td>Watery diarrhea (≥500 mL)</td>
<td>Infection (viral, fungal, bacterial, parasitic)</td>
</tr>
<tr>
<td>Severe abdominal pain</td>
<td>Opiate withdrawal</td>
</tr>
<tr>
<td>Bloody diarrhea or ileus</td>
<td>Regimen-related toxicity</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>Sinusoidal obstruction syndrome</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>Medication toxicities (e.g. azoles)</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>Viral infections (e.g. cytomegalovirus [CMV], Epstein-Barr virus, Hepatitis B)</td>
</tr>
<tr>
<td></td>
<td>Hemolysis</td>
</tr>
</tbody>
</table>
When to consider a biopsy
Given acute GVHD symptoms are quite non-specific, biopsies may be helpful in determining appropriate etiology if the diagnosis is unclear. However, histologic confirmation should not delay treatment or management when the probability of GVHD is high, which is always the case when a patient presents between day 28 and 100 with classic findings (rash, diarrhea, LFT abnormalities). The following are general recommendations on when to obtain a biopsy:

- A skin biopsy with review in dermatopathology should be considered in all patients where the skin is the only organ involved and lacking features of chronic GVHD, since it is minimally invasive and low-risk to the patient. A biopsy is especially recommended if the patient will receive systemic therapy for treatment. A skin biopsy cannot reliably distinguish between GVHD and drug eruption and results must be interpreted within the clinical context (UW Health Low quality of evidence, C recommendation.)
- Upper endoscopy is recommended for patients with persistent anorexia, nausea/vomiting, and/or unexplained gastrointestinal symptoms or weight loss. (UW Health Low quality of evidence, C recommendation.)
- Lower endoscopy with biopsies is strongly recommended for patients with new or worsening diarrhea (e.g., an adult patient with ≥ 3 watery stools per day or diarrhea ≥ 500 mL/day for more than 2 – 3 days, or with rapid progression of symptoms) given the broad differential that includes drug toxicity, and infectious causes such as CMV, C. Difficile, and other viral etiologies. (UW Health Low quality of evidence, C recommendation.)
- If the liver is the only organ involved, a biopsy and infectious evaluation is recommended because isolated hepatic GVHD is uncommon and other etiologies such as viral infectious should be considered. (UW Health Low quality of evidence, C recommendation.)

Staging and grading disease
Once a patient is diagnosed with acute GVHD, the severity of the disease is determined by assessing the degree of skin, gastrointestinal tract, and liver involvement. An overall grade is assigned based off the combination of specific organ stages. It is recommended to use the Consensus grading system (Table 3) to promote standardization across clinic workflows and support required registry reporting. (UW Health Low quality of evidence, S recommendation.)

Note: There is an Acute GVHD flowsheet in Health Link to facilitate easier grading.

Considerations when staging acute GVHD
There can be significant variance between transplant centers and between independent reviewers within an organization. Moreover, it may be difficult on occasion for a clinician to translate patient reported symptoms into staging criteria. For example, it can be difficult to extrapolate volume of diarrhea from patient reported episodes of diarrhea that are unmeasured. It is recommended to consider the following when staging patients to decrease practice variation and increase uniformity. Table 3 and Appendix B summarize these considerations with clinical staging and grading criteria for adult and pediatric patients.

Skin
- Document if desquamation or fluid-filled bullae are present because these are findings are key characteristics of stage 4 GVHD. Photographing a rash at the time of initial staging, and periodically during treatment course, is encouraged to help document response. (UW Health Low quality of evidence, C recommendation.)
Lower GI

- If a patient is found to have GI GVHD, note the presence of the following features, which indicate stage 4 disease, regardless of stool volume:
  - ileus and/or
  - stool with frank blood or melena and/or\(^{23,24}\)
  - severe abdominal pain (defined as pain attributed to GVHD that requires the initiation of high doses of narcotic pain medication or a significant increase in ongoing narcotic use and the abdominal pain significantly impacts a patient's performance status.\(^{24}\))
- When only number of diarrhea episodes is available, consider calculating average volume as 200 mL/episode or 3 mL/kg for children < 50 kg.\(^{25}\)
- When grading lower GI GVHD based on volume of diarrhea, use these indicators in the following order: (1) average of 3 consecutive days, (2) average of 2 consecutive days, or (3) the volume on day of assessment.\(^{24}\) (UW Health Low quality of evidence, C recommendation.)
  - Every attempt should be made to measure stool only volume while patient is inpatient/admitted
  - To estimate stool only volume for mixed urine/stool:
    - If only mixed output is documented: subtract 1440mL from 24-hour mixed total
    - If both measured urine and mixed output is documented: subtract 720mL from 24-hour mixed volume

Upper GI

- An upper GI biopsy is required for staging\(^{26}\) when utilizing Consensus criteria, however a biopsy may not always be done. This can result in under-reporting of the incidence of upper GI GVHD, thus it is recommended to stage upper GI if there is persistent nausea or vomiting with or without anorexia.\(^{24}\) (UW Health Low quality of evidence, S recommendation.)
- Consider staging upper GI GVHD only if:
  - Nausea persists > 3 day
  - 2 or more vomiting episodes per day for >/= 2 days
  - Anorexia WITH weight loss
Table 3. Staging and Grading Criteria for Acute GVHD
Clinical Staging for Acute GVHD in Adults and Children\textsuperscript{24-26}

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin</th>
<th>Liver (bilirubin)</th>
<th>Lower Gastrointestinal tract\textsuperscript{£}</th>
<th>Upper Gastrointestinal tract\textsuperscript{Ω}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No rash, no rash attributable to acute GVHD</td>
<td>No liver acute GVHD/bilirubin &lt; 2.0 mg/dL (34 µmol/L)</td>
<td>No diarrhea, no diarrhea attributable to aGVHD; Adult: Diarrhea &lt; 500mL/day, or &lt; 3 episodes/day Pediatric: Diarrhea &lt; 10 mL/kg/day, or &lt; 4 episodes/day</td>
<td>No persistent nausea or vomiting</td>
</tr>
<tr>
<td>1</td>
<td>Maculopapular rash, &lt; 25% of body surface</td>
<td>2.0-3.0 mg/dL (34-52 µmol/L)</td>
<td>Adult: Diarrhea 500-1000 mL/day, or 3-4 episodes/day Pediatric: Diarrhea 10-19.9 mL/kg/day or 4-6 episodes/day</td>
<td>Persistent nausea or vomiting, with or without anorexia\textsuperscript{Ω}</td>
</tr>
<tr>
<td>2</td>
<td>Maculopapular rash, 25-50% of body surface</td>
<td>3.1-6.0 mg/dL (53-103 µmol/L)</td>
<td>Adult: Diarrhea 1001-1500 mL/day (adult) or 5-7 episodes/day Pediatric: 20-30 mL/kg/day or 7-10 episodes/day</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Generalized erythroderma, &gt; 50% of body surface</td>
<td>6.1-15.0 mg/dL (104-256 µmol/L)</td>
<td>Adult: Diarrhea &gt; 1500 mL/day (adult) or &gt; 7 episodes/day Pediatric: Diarrhea &gt; 30 mL/kg/day or &gt; 10 episodes/day</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Generalized erythema with bullae formation and/or desquamation</td>
<td>&gt;15.0 mg/dL (256 µmol/L)</td>
<td>Adult/Pediatric: Severe abdominal pain with or without ileus, and/or grossly bloody stool (regardless of stool volume)</td>
<td></td>
</tr>
</tbody>
</table>

£ Diarrhea volumes of liquid stool should be based on the following order: (1) average of 3 consecutive days, (2) average of 2 consecutive days, or (3) the volume on day of assessment. If diarrhea reported only as episodes, consider average volume per diarrhea as 200 mL/episode or 3 mL/kg for children &lt; 50 kg. To estimate stool only volume for mixed urine/stool: Subtract 1440mL from 24-hour mixed total if only mixed output documented; subtract 720mL from 24-hour mixed volume if both measured urine and mixed output documented.
For Stage 4 Lower GI: Bloody diarrhea is staged as 4, independent of volume of diarrhea.
Ω Persistent nausea &gt; 3 days or 2+ vomiting episodes/day for 2 days or anorexia WITH weight loss only

<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin</th>
<th>Liver</th>
<th>Lower GI</th>
<th>Upper GI</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Stage 1-2</td>
<td>No liver involvement</td>
<td>No gut involvement</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Stage 3</td>
<td>Stage 1</td>
<td>Stage 1</td>
<td>Stage 1</td>
</tr>
<tr>
<td>III</td>
<td>Stage 0-3</td>
<td>Stage 2-3</td>
<td>Stage 2-3</td>
<td>Stage 0-1</td>
</tr>
<tr>
<td>IV</td>
<td>Stage 4</td>
<td>Stage 4</td>
<td>Stage 4</td>
<td>Stage 0-1</td>
</tr>
</tbody>
</table>
Risk Assessment

Given the therapeutic challenges faced in treating acute GVHD patients, various algorithms have been developed and identified to aid clinicians in determining a patient’s likelihood of achieving a complete or partial response to steroid therapy and risk of non-relapse mortality.27

Note: There is an Acute GVHD flowsheet in Health Link to facilitate easier risk assessment.

Refined Risk Score
The refined risk score is a validated risk assessment model, originally developed by the University of Minnesota that has since been refined. This tool stratifies a patient into a standard risk or high-risk group at the onset of aGVHD based on the severity of organ involvement. A patient deemed “high risk” is less likely to achieve a complete or partial response at day 28 and has a higher risk of non-relapse mortality.28-30

The criteria to stratify patients based on organ staging is summarized in Table 4 and listed in Appendix B. A web-based program is also available to determine a patient’s risk group and can be accessed at: http://z.umn.edu/MNAcuteGVHDRiskScore. It is recommended to calculate a risk score for a patient with aGVHD grade ≥ 2 and/or involvement of more than one organ for adult patients only; the refined risk score is not used in pediatric practice at UW Health at this time. (UW Health Low quality of evidence, S recommendation)

<table>
<thead>
<tr>
<th>aGVHD Risk Score</th>
<th>Organ Involvement</th>
<th>Three Organ</th>
</tr>
</thead>
</table>
| **Standard Risk** | • Stage 1-3 Skin  
• Stage 1-2 GI | • Stage 1-3 skin + stage 1 GI  
• Stage 1-3 skin + stage 1-4 liver | -- |
| **High Risk**    | • Stage 4 Skin  
• Stage 3-4 GI  
• Stage 1-4 Liver | • Stage 1-3 skin + stage 2 GI  
• Stage 1-2 lower GI + stage 1-3 liver  
• Stage 3-4 GI + stage 1-3 skin  
• Stage 3-4 GI + stage 1-4 liver | • Stage 1-3 skin + stage 1-2 GI + stage 1-3 liver  
• Stage 1-3 skin + stage 3-4 GI + stage 1-4 liver |

Note: Upper GI plus lower GI considered as single-organ disease

Acute GVHD Treatment

Grade 1 Skin aGVHD only
For patients with Grade 1 skin only acute GVHD, topical therapies should be initiated according to recommendations listed in Table 6 for adult and Table 8 for pediatric patients.

Initial Therapy for Adults
For adult patients, it is recommended to initiate treatment according to their refined risk score stratification. (UW Health Low quality of evidence, strong recommendation.) Specific therapy recommendations according to a patient’s risk score can be found in Table 6. For example, an adult aGVHD patient with Stage 1 skin and Stage 1 liver is considered “standard risk” and should be treated with prednisone and topical therapy recommendations. For patients who are already taking a calcineurin inhibitor who subsequently develop aGVHD, it is recommended to optimize calcineurin inhibitor therapy as part of aGVHD treatment. (UW Health Low quality of evidence, strong recommendation.) Any patient who received post-transplant
cyclophosphamide alone for GVHD prophylaxis AND has high-risk acute GVHD should be started on tacrolimus with prednisone as part of initial treatment. (UW Health Low quality of evidence, conditional recommendation.)

Additional initial therapy considerations when there is a concern of treating with systemic steroids for adults:
- When there is concern of using systemic corticosteroids dosed by weight due to existing co-morbidities:
  - It is reasonable to start at a lower dose (i.e., starting at 1 mg/kg instead of 2mg/kg).
  - Close monitoring is required. If there is progression by 3 days or no response by 7 days, full corticosteroid dosing is recommended. (UW Health Low quality of evidence, C recommendation)
- If there is considerable need to spare patient from steroids AND patient is considered standard risk, may consider treatment with sirolimus alone:
  - Sirolimus loading dose of 6 mg (if on voriconazole reduce by 50% - 90%, if on posaconazole, isavuconazole and fluconazole reduce by 50%). A trough sirolimus level should be performed 24-48 hours after loading dose.
  - Initial planned maintenance dose (revised as needed based on observed sirolimus levels): 2mg PO once daily (if on voriconazole, posaconazole or isavuconazole should receive 10% of recommended maintenance dose (as an initial dose adjustment)
  - When co-administered with sirolimus, recommend target levels are as follows:
    - Tacrolimus 3-7 ng/mL
    - Cyclosporine 120-200 ng/mL
    - Target sirolimus level from onset through resolution of acute GVHD is 10-14 ng/mL
    - After acute GVHD is completely resolved, the target therapeutic range can be decreased to 5-10 ng/mL

Initial Therapy for Pediatrics
For pediatric patients that do not have mild cutaneous skin aGVHD, it is recommended to initiate methylprednisolone IV 2 mg/kg/day in divided doses or prednisone/prednisolone by mouth 2.5 mg/kg/day in divided doses (Table 8.) (UW Health Low quality of evidence, S recommendation.)

Corticosteroid considerations for All Patients
- Initiate anti-infectious prophylaxis per the BMT anti-infective guideline
- Use adjusted bodyweight for patients who are greater than 100% of ideal weight
- When switching between methylprednisolone and prednisone, consider difference in potency (1 mg of methylprednisolone is equivalent to 1.25 mg of prednisone)

Steroid-refractory acute GVHD for Adult and Pediatric Patients
If a patient’s disease progresses after 3 days or has no response after 7 days of appropriately dosed systemic steroids, or a patient’s GVHD has progressed during taper before a 50% decrease in corticosteroids is achieved, the patient is considered to have “steroid refractory disease.” Patients with steroid-refractory GVHD should be tapered using a schedule similar to steroid-responsive GVHD and should not continue high-dose steroids indefinitely. (UW Health Moderate quality of evidence, S recommendation.) Recommendations for steroid-refractory acute
GVHD are listed in Table 7 and Table 9 for adults and pediatrics respectively. Figure 1 outlines the acute GVHD treatment pathway for adults.

Adults with lower GI involvement who are inpatient: It may be reasonable to add human chorionic gonadotropin (hCG) as supportive care for GI tissue repair.34

- **Dosing:** 2,000 units hCG/m²
- **Subcutaneous (SQ) injections** every other day for 7 days - 14 days
- **If response noted after 7-14 days,** it is reasonable to continue maintenance hCG/EGF SQ twice weekly for up to 5 weeks

**Tapering Medications**

**Glucocorticoids**
If aGVHD symptoms begin to resolve after 5-7 days of steroid therapy, it is reasonable to attempt a taper.2 (UW Health Strong quality of evidence, S recommendation.) Inappropriate rapid tapering poses a risk of GVHD exacerbation or recurrence while inappropriately slow tapering can increase the risk of steroid-related complications.35,36 Prednisone may be tapered by approximately 10% every 5 – 7 days over approximately 8 to 10 weeks depending on rapidity of response, GVHD risk, and other patient factors.24 If the patient has standard risk GVHD and achieved a full response at day 5, may consider a taper by 10% every 3 days. An example of a steroid taper schedule can be found in Appendix D.

**Non-steroidal immunosuppression**
There is little data for the best way to taper off medication; consider completing steroid taper prior to tapering non-steroid medications.

Consider tapering ruxolitinib after 6 months of therapy if response occurs and therapeutic corticosteroid doses have been discontinued; taper by one dose level approximately every 8 weeks (10 mg twice daily to 5 mg twice daily to 5 mg once daily). Consider retreatment if acute graft-versus-host disease (GVHD) signs/symptoms recur during or after tapering ruxolitinib.

**Flares while tapering immunosuppression for All Patients**

<table>
<thead>
<tr>
<th>Context</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>If steroid doses are &gt; 50% of original dose</td>
<td>Treat per steroid refractory recommendations</td>
</tr>
</tbody>
</table>
| If steroid doses are BELOW 1 mg/kg and ≤50% of original dose | • Restart non-steroid medications that may have been stopped and  
  • Increase steroids 50% of current dose for 1 week. After 1 week, continue steroid taper |
| In the setting of infection/acute illness | • See guidance for steroid doses below 1 mg/kg |
| If a GVHD flare occurs OFF prednisone AND in the setting of infection/acute illness | • Consider treating with 0.5 mg/kg prednisone until improved, the taper every 3 days. |
Figure 1. Acute Graft Versus Host Disease Treatment Pathway - Adults

**Prednisone dosing should be calculated using adjusted bodyweight for patients who are greater than 100% of ideal weight.**

**Anti-infectious prophylaxis should be initiated per the BMIT anti-infective guideline when starting high dose prednisone.**

Patient diagnosed with acute GVHD

Use Health Link flowsheet to determine grade and risk

**High Risk**
 Prednisone 2 mg/kg*^ AND start or optimize CNI AND add organ specific therapy/topicals

Progression at Day 3 assessment?

NO

Progression or no change at Day 7 assessment?

NO

Start steroid taper and monitor/assess iteratively

YES

Progression or no change at Day 7 assessment?

YES

Prednisone 1 mg/kg*^ (refer to treatment table for exceptions) AND add organ specific therapy/topicals

Progression at Day 3 assessment?

NO

Progression or no change at Day 7 assessment?

NO

Start steroid taper and monitor/assess iteratively

YES

Prednisone 2 mg/kg*^ AND start or optimize CNI AND add organ specific therapy/topicals

Progression 3 days after prednisone increase?

NO

Progression or no change at Day 7 assessment?

NO

Start steroid taper and monitor/assess iteratively

YES

Progression or no change 5-7 days after first tocilizumab dose?

NO

Add etanercept or infliximab

YES

Add sirolimus 2 mg PO daily AND monitor/assess every 14-28 days

Progression or no change 5-7 days after start of etanercept or infliximab?

NO

Start steroid taper and monitor/assess iteratively

YES

Is lower GI the site that is progression or unchanged?

YES

Start tocilizumab AND start ruxolitinib AND start steroid taper

NO

Monitor/assess every 14-28 days
### Therapy Recommendations for Adults

<table>
<thead>
<tr>
<th>Risk/Topical Site</th>
<th>Medication Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard Risk</strong></td>
<td>Prednisone PO 1 mg/kg/day**^ AND site specific topicals</td>
</tr>
<tr>
<td>Site specific considerations:</td>
<td></td>
</tr>
<tr>
<td>Grade 1 Skin only</td>
<td>- It is reasonable to treat with topical treatment alone</td>
</tr>
<tr>
<td>- If rash progresses rapidly, patients should be initiated on systemic steroids.</td>
<td></td>
</tr>
<tr>
<td>Grade 1-2 GI +/- Grade 1 skin</td>
<td>It is reasonable to treat with topical treatment alone (skin topical + enteric coated budesonide + immediate release beclomethasone) and escalate to systemic prednisone only if initial treatment is ineffective.</td>
</tr>
<tr>
<td>If liver involved</td>
<td>Initiate tacrolimus in patients no already on a calcineurin inhibitor OR optimize existing calcineurin inhibitor (Tacrolimus goal serum level is 5-15 ng/mL) IN ADDITION to above (steroid therapy and topicals)</td>
</tr>
</tbody>
</table>

| **High Risk** | Prednisone PO 2 mg/kg/day in divided doses\[^{37}\] or methylprednisolone IV 1.8 mg/kg/day\[^{33,38}\] in divided doses PLUS topical therapy\[^{33,38}\]**^ AND |
| Initiate tacrolimus (per prophylaxis dosing) if not already on a calcineurin inhibitor or optimize existing calcineurin inhibitor for GVHD prophylaxis (Tacrolimus goal serum level is 5-15 ng/mL) AND Add Organ Specific Topical |

| Organ specific topical | Neck and below | Betamethasone dipropionate 0.05% ointment\[^{16}\] OR Clobetasol 0.05% to the affected area two times daily |
| Face | Triamcinolone 0.1% cream to the affected area two times daily This is a reasonable alternative for patients unable to tolerate or obtain betamethasone ointment |
| Entire body | Tacrolimus 0.1% ointment to the affected area two times daily Can increase serum levels if ointment is being applied to a large surface area. It is reasonable to use pimecrolimus cream instead of tacrolimus ointment if insurance dictates |

| Upper GI | Budesonide 3mg/10 mL water mouthwash- swish 10 mL for 5 minutes and SWALLOW 2-4 times daily\[^{42}\] Do not eat or drink for 15-20 minutes after |
| Lower GI | Budesonide EC 9 mg by mouth one time daily\[^{42}\] |
| Liver | Becloamethasone compounded liquid 2 mg by mouth four times daily (Grade I to II only)\[^{43}\] Usrsodiol 13-15 mg/kg/day in 2-4 divided doses\[^{49}\] |

** Prednisone dosing should be calculated using adjusted bodyweight for patients who are greater than 100% of ideal weight.  
^ Anti-infectious prophylaxis should be initiated per the BMT anti-infective guideline when starting high dose prednisone.
**Table 7. Treatment for Steroid-Refractory aGVHD for Adults** *(UW Health Low quality of evidence, C recommendation)*

**Steroid-refractory** defined as progression of aGVHD with 3 days of appropriately dosed systemic steroids OR no response with 7 days of appropriately dosed systemic steroids or patients with GVHD progression during tapering before a 50% decrease in corticosteroids is achieved. Steroid therapy should be tapered after 5-7 days, irrespective of disease response.

<table>
<thead>
<tr>
<th>aGVHD site</th>
<th>Medication Recommendation (Treatments are listed in preferential order of usage)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lower GI</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Clinical trial is always the first preferred treatment option for all sites</strong></td>
</tr>
</tbody>
</table>
| If lower GI is the main refractory site, follow this table due to high risk of mortality | Tocilizumab 8 mg/kg IV every 2 weeks until response, then every 4 weeks.  
AND  
Ruxolitinib 5 mg PO two times daily  
Consider increasing to 10 mg twice daily after 3 days of treatment (if ANC and platelets are not decreased by ≥ 50% compared to pre-ruxolitinib labs.)  
If progression or no change 5-7 days after first dose of tocilizumab:  
ADD etanercept 25 mg subQ twice weekly x 4 weeks (may be continued as clinically indicated)  
OR  
ADD infliximab 10 mg/kg IV once weekly  
If progression or no change 5-7 days after starting etanercept or infliximab:  
ADD sirolimus 2 mg PO daily (target trough 3-12 ng/mL)  
For patients already taking tacrolimus, it is recommended to transition off tacrolimus if starting sirolimus therapy. |
| Options for all other sites | Ruxolitinib 5mg PO two times daily  
Consider increasing to 10 mg twice daily after 3 days of treatment (if ANC and platelets are not decreased by ≥ 50% compared to pre-ruxolitinib labs.)  
Sirolimus 2 mg PO daily (target trough 3-12 ng/mL)  
For patients already taking tacrolimus, it is recommended to transition off tacrolimus if starting sirolimus therapy. |
| Skin specific options     | Non-pharmacologic treatment with psoralen and ultraviolet A irradiation (PUVA) starting three times weekly and tapering to twice weekly based on response, in conjunction with dermatology consult  
Etanercept 25 mg subQ twice weekly x 4 weeks initially (may be continued as clinically indicated)  
Tocilizumab 8 mg/kg IV every 3-4 weeks  
#

*There is little data for the best way to taper off medication; consider completing steroid taper prior to tapering non-steroid medications. Consider tapering ruxolitinib after 6 months of therapy if response occurs and therapeutic corticosteroid doses have been discontinued; taper by one dose level approximately every 8 weeks (10 mg twice daily to 5 mg twice daily to 5 mg once daily.) Consider re-treatment if aGVHD signs/symptoms recur during or after tapering ruxolitinib.*

*For clinically stable patients, consider a 28-day response rate before moving to another agent and/or addition of a third agent. *(UW Health Low quality of evidence, C recommendation.)*
Therapy Recommendations for Pediatrics

Table 8: Recommendations for Initial Therapy for aGVHD in Pediatric Patients

It is reasonable in mild GVHD that is confined to the skin and involves less than 50% of the total body surface area to treat with topical treatment alone. If rash progresses rapidly, patients should be initiated on systemic steroids.

<table>
<thead>
<tr>
<th>aGVHD</th>
<th>Medication Recommendation</th>
<th>Evidence Quality</th>
<th>Recommendation Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical therapy (Grade 1 cutaneous aGVHD)</td>
<td>Entire body: Tacrolimus 0.1% ointment to the affected area 2 to 3 times daily&lt;sup&gt;2&lt;/sup&gt; OR Triamcinolone 0.1% ointment or cream to the affected area 2 to 3 times daily&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Very low</td>
<td>Strong</td>
</tr>
<tr>
<td>Face</td>
<td>Hydrocortisone 1% cream to the affected area 2 to 3 times daily&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Very low</td>
<td>Strong</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Methylprednisolone IV 2 mg/kg/day&lt;sup&gt;2,33&lt;/sup&gt; in divided doses or Prednisone/prednisolone PO 2.5 mg/kg/day in divided doses</td>
<td>High</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Table 9: Treatment for Steroid Refractory aGVHD for Pediatrics

Steroid-refractory defined as progression of aGVHD with 3 days of appropriately dosed systemic steroids OR no response with 7 days of appropriately dosed systemic steroids or patients who progress during tapering before a 50% decrease in corticosteroids is achieved.

**Clinical trial is always the first preferred treatment option for all sites**

<table>
<thead>
<tr>
<th>aGVHD</th>
<th>Medication Recommendation</th>
<th>Evidence Quality</th>
<th>Recommendation Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td>Non-pharmacologic treatment with psoralen and ultraviolet A irradiation (PUVA) starting 3 times weekly and tapering to twice weekly based on response, in conjunction with dermatology consult&lt;sup&gt;59,60&lt;/sup&gt;</td>
<td>High</td>
<td>Conditional</td>
</tr>
<tr>
<td>Age ≥ 12 yrs: Ruxolitinib 5 mg PO twice daily, may be increased to 10 mg twice daily after 3 days in absence of toxicity&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Extracorporeal photopheresis (ECP) &lt;sup&gt;62,63&lt;/sup&gt;</td>
<td>Moderate</td>
<td>Conditional</td>
</tr>
<tr>
<td>Etanercept 0.4 mg/kg (max 25 mg) subQ twice weekly x 4 weeks&lt;sup&gt;51,64-66&lt;/sup&gt;</td>
<td>Moderate</td>
<td>Conditional</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab 8 mg/kg IV every 3-4 weeks&lt;sup&gt;67-69&lt;/sup&gt;</td>
<td>Moderate</td>
<td>Conditional</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Age ≥ 12 yrs: Ruxolitinib 5 mg PO twice daily, may be increased to 10 mg twice daily after 3 days in absence of toxicity&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Moderate</td>
<td>Conditional</td>
</tr>
<tr>
<td>Extracorporeal photopheresis (ECP) &lt;sup&gt;62,63&lt;/sup&gt;</td>
<td>Moderate</td>
<td>Conditional</td>
<td></td>
</tr>
<tr>
<td>Basiliximab 20 mg per week for 2–3 weeks&lt;sup&gt;70-73&lt;/sup&gt;</td>
<td>Low</td>
<td>Conditional</td>
<td></td>
</tr>
<tr>
<td>Pentostatin 1-1.5 mg/m2 on days 1–3 (defined as one course), repeated every 2 weeks as indicated&lt;sup&gt;74,75&lt;/sup&gt;</td>
<td>Low</td>
<td>Conditional</td>
<td></td>
</tr>
<tr>
<td>Infliximab 10 mg/kg IV once weekly for 4 doses&lt;sup&gt;76-78&lt;/sup&gt; OR Etanercept 0.4 mg/kg (max 25 mg) subQ twice weekly x 4 weeks&lt;sup&gt;51,64-66&lt;/sup&gt;</td>
<td>Low</td>
<td>Conditional</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab 8 mg/kg IV every 3-4 weeks&lt;sup&gt;67-69&lt;/sup&gt; (Consider measuring IL-6 activity if available)</td>
<td>Low</td>
<td>Conditional</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Age ≥ 12 yrs: Ruxolitinib 5 mg PO twice daily, may be increased to 10 mg twice daily after 3 days in absence of toxicity&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Low</td>
<td>Conditional</td>
</tr>
</tbody>
</table>
Supportive Care Recommendations

Nutrition

Patients with aGVHD are at risk for significant weight loss and malnutrition.\textsuperscript{79,80} Nutrition-related side effects of aGVHD that may contribute to poor nutrition include: protein-losing enteropathy, malabsorption, pancreatic atrophy, and exocrine pancreatic insufficiency.\textsuperscript{79} The common treatment for aGVHD, glucocorticoids, may lead to poor nutrition outcomes including hyperglycemia, steroid-induced diabetes, loss of lean body mass, and poor bone health.\textsuperscript{81} To prevent or resolve malnutrition, patients with aGVHD often require modified diets, oral nutrition supplements and/or nutrition support.\textsuperscript{82}

Stepwise oral diet progression based on the severity of aGVHD has been shown to improve symptoms.\textsuperscript{79,80,83} Nutrition by oral route should be maintained as appropriate to help preserve intestinal integrity.\textsuperscript{84}

The exact role of enteral nutrition (EN) and parenteral nutrition (PN) in aGVHD patients has not been well studied. In general, EN is associated with the preservation of the GI tract and maintenance of the gut-associated lymphoid tissue (GALT), which protects against infection.\textsuperscript{85-87} EN has been shown to be safe and feasible and is linked with decreased mortality from infection, less time to platelet recovery, and shorter length of stay.\textsuperscript{85,86-88,96} EN has shown distinct advantages for management and treatment of other inflammatory gastrointestinal conditions, such as Crohn’s disease and ulcerative colitis. Therefore, there is likely a role for EN in the GVHD population, even at a minimum as trophic feed.\textsuperscript{80,97-99}

PN is associated with less weight loss and loss of body fat.\textsuperscript{82,95,99} Disadvantages of PN include increased incidence of hyperglycemia, hypertriglyceridemia, volume overload, catheter-related complications (e.g., infections), and mucosal alterations.\textsuperscript{86,87,100,101} To decrease these incidences, clinicians should consider utilizing both PN and EN, as appropriate, in order to optimize nutrition status and prevent malnutrition and severe weight loss. Small amounts of EN may also help reduce infection rates and hepatic complications associated with PN.\textsuperscript{84}(UW Health Low quality of evidence, C recommendation.)

Nutrition Assessment

It is recommended to order a nutrition consult (inpatient) or schedule a nutrition appointment for patients (outpatient) with aGVHD who are at nutrition risk. (UW Health Low quality of evidence, S recommendation.) A registered dietitian nutritionist (RDN) will complete a nutrition assessment. Characteristics that may place a patient with GVHD at nutrition risk include the following:

- History of malnutrition
- Significant or unintentional weight loss
- Inability to meet at least 50% of estimated calorie needs through oral diet alone
- Symptoms impacting oral intake: mucositis, nausea, vomiting, diarrhea, abdominal pain, early satiety, dry mouth, altered taste, altered smell
- Previous reliance on nutrition support
- \textit{For Pediatrics only}: Patient’s weight-for-age, BMI, or weight-for-length declining across ≥ 2 growth channels
- \textit{For Pediatrics only}: Patient with BMI or weight-for-length below the 5\textsuperscript{th} percentile for age
To schedule an outpatient nutrition appointment:

For Pediatrics: Nutrition appointments can be made at the American Family Children’s Hospital Nutrition Clinic by calling (608) 890-5500. Rather than calling to schedule a future appointment, you may send an In Basket message to the Pediatric Nutrition Schedulers Pool (37027101) to request a nutrition appointment. Please call the scheduler for same day appointments.

For Adults: Nutrition appointments can be made at the UW Carbone Cancer Center by calling (608) 265-1700. Future appointments may be made by sending an In-Basket message to the UWH CC Schedulers Pool (2212601) to request a nutrition appointment. Please call the scheduler for same day appointments.

Oral Diet
An oral diet is appropriate for patients who can tolerate foods by mouth. (UW Health Moderate quality evidence, S recommendation) The oral diet can be advanced depending on symptoms and tolerance. If the patient is in the hospital, the GVHD diet can be ordered. This diet is low in lactose, fiber, and fat. The RDN will provide education regarding nutrition supplements. (UW Health Low quality of evidence, C recommendation.)

Appetite Stimulants

For Adults:
For patients with persistent anorexia, consider addition of an appetite stimulant such as megestrol acetate (Megace®) or mirtazapine. (UW Health Low quality of evidence, C recommendation) Dexamethasone may be used short term for appetite stimulation as well.102-104 (UW Health Low quality evidence, C recommendation) Suggested dosing for megestrol and mirtazapine is:

- Megestrol acetate 400 mg by mouth twice daily.99,105-110
- Mirtazapine 15 mg by mouth daily at bedtime.99,111,112

For Pediatrics:
Appetite stimulants may be used to enhance oral intake in pediatric patients if other barriers to intake, such as nausea, abdominal pain, and mucositis, are not present. (UW Health Low quality evidence, C recommendation) Cyproheptadine is the most appropriate appetite stimulant to use in this population. Medications, such as dronabinol and mirtazapine can be considered, but these are typically reserved for instances where other conditions, such as nausea, insomnina, or depression, are present. Suggested dosing for cyproheptadine is as follows:

- For patients ≥ 2 years: cyproheptadine 0.25 mg/kg/day divided twice daily.113

These appetite stimulants are associated with adverse reactions such as drowsiness, depression, edema, insomnia, stomach cramps, cholestatic jaundice, and hepatotoxicity. It is recommended that their usage should be considered with reference to the complete clinical picture and only if all other methods of improving oral intake have been exhausted.80 (UW Health Low quality evidence, C recommendation.)

Enteral Nutrition (EN)
For patients with a functional GI tract but inability to ingest adequate nutrition orally to maintain weight/lean body mass, consider EN.82 (UW Health Low quality evidence, C recommendation) If a patient needs enteral nutrition, a nutrition consult is recommended for an individualized nutrition plan, including selection of the EN formula. (UW Health Low quality of evidence, C recommendation.) Additional guidance can be found in the UW Health Pediatric Enteral Nutrition Handbook, Nutrition.
Parenteral Nutrition (PN)

For Adults:
It is recommended to consider parenteral nutrition for patients with poor oral intake and significant malabsorption.82,84,96,100 (UW Health Moderate quality of evidence, C recommendation)
Examples of when to consider initiating PN include:

- Patients unable to take in and absorb adequate nutrition for 7-14 days.82
- Patients with diarrhea ≥ 500 mL/day96,100 (i.e., ≥ Stage 1 Lower GI GVHD)
- Patients who exhibit signs of nutritional depletion without indication of improvement within 7 days.96
- Severe malnutrition on admission84
- Patients unable to tolerate oral diet or fail to meet 60-70% of nutrition requirements over 3 days84

When beginning PN for a GVHD patient, the UW Health Surgical Nutrition Support Team (SNST) evaluates the patient’s gastrointestinal losses, acid-base status, and dose of corticosteroids. Given some patients with acute GI GVHD may have very large amounts of diarrhea (e.g., diarrhea >5 liters per day) these patients will often require sodium in the PN equivalent to sodium chloride 0.9%. However, instead of chloride, it is added as the acetate salt. It is important to remember that the PN will not meet the needed fluid requirements to replace losses, thus it is recommended that the SNST communicate with the primary team regarding rate and volume of the PN. (UW Health Very low quality of evidence, C recommendation)

Most GVHD patients will receive high dose corticosteroids and will require insulin in the PN. If a patient is hyperglycemic before PN is initiated, a dose of 0.15-0.2 units insulin/gram of dextrose should be added to the PN. (UW Health Very low quality of evidence, C recommendation)

Calorie requirements for aGVHD patients are generally higher, ranging from 30-40 kcal/kg. Protein requirements are usually higher as well, since patients with GI GVHD often have large protein losses in their stool. Patients will require 1.8 to 2 g protein/kg in the PN. Along with protein and electrolytes, patients also lose zinc in their stool, so it is customary to supplement zinc 5-15 mg/day in the PN. For additional guidance refer to the UWHC Clinical Nutrition Services Policy 3.6- Parenteral Nutrition Assessment, Ordering and Monitoring. For population specific guidance refer to the UW Health Parenteral Nutrition- Pediatric/Neonatal - Inpatient/Ambulatory Clinical Practice Guideline or the UW Health Parenteral Nutrition - Adult - Inpatient/Ambulatory Clinical Practice Guideline.

Parenteral nutrition may be discontinued when the patient’s GI symptoms resolve (i.e., no intractable vomiting, stool output <500 mL/day for at least 2 consecutive days) and the patient can tolerate an oral diet or EN is meeting at least 50% of daily estimated caloric needs.96 (UW Health Low quality of evidence, C recommendation)

For Pediatrics:
If a patient has severe GI dysfunction or is unable to meet nutrition requirements with EN alone, consider PN.82 (UW Health Low quality evidence, C recommendation) If a patient needs parenteral nutrition, it is recommended to order a nutrition consult and a Pediatric Nutrition Support Team or Adult Surgical Nutrition Support Team consult. (UW Health Very low quality of evidence, S recommendation)
Vitamin/Mineral Supplements

For Adults:
Common deficiencies among GVHD patients may include vitamin D, vitamin B12, zinc and magnesium. If a patient is not on nutrition support and does not have impaired kidney function, consider starting a multivitamin mineral tab daily. (UW Health Very low quality of evidence, C recommendation.) Also consider monitoring electrolytes and supplement if low (i.e., magnesium, potassium, and phosphate) and check calcium (total and ionized) and vitamin D levels yearly. (UW Health Very low quality of evidence, C recommendation.) For patients with normal serum calcium and vitamin D levels, consider daily supplementation of 1200 mg calcium and 1000 IU cholecalciferol (vitamin D3). For best absorption of calcium, take as single doses of less than or equal to 500 mg. For patients with low serum vitamin D levels, ergocalciferol (vitamin D2) 50,000 IU once weekly for at least 8 weeks to achieve a 25-hydroxyvitamin D level greater than 30 ng/mL is recommended. Once this level has been attained, a maintenance dose of cholecalciferol (vitamin D3) 1500-2000 IU daily should be started. (UW Health Very low quality of evidence, C recommendation.)

For Pediatrics:
Pediatric patients with aGVHD are at risk for vitamin and mineral deficiencies. If the patient is not on nutrition support, consider starting a daily multivitamin. (UW Health Low quality of evidence, C recommendation.) Patients with GVHD may require additional vitamin D supplementation thus it is recommended to check the vitamin D level. (UW Health Low quality of evidence, C recommendation.) For most children, dietary reference intakes (DRI) listed below are reasonable starting points for supplementation: (UW Health Low quality of evidence, C recommendation.)

- Infants (0-1 year): 400 IU
- Children (>1 year): 600 IU

Supplementation can be increased based on baseline level and response to supplementation. If a patient will be on corticosteroids for an extended period, consider having the patient supplement with at least 800 IU of vitamin D and ensure there is adequate calcium intake. (UW Health Low quality of evidence, C recommendation.) Calcium requirements while on steroids are listed below. Supplementation may be needed based on adequacy of intake.

- 0-6 months: 400 mg
- 6-12 months: 600 mg
- 1-3 years: 800 mg
- 4-8 years: 1200 mg
- 9-18 years: 1500 mg

If a patient is suspected to have vitamin or mineral deficiencies, it is recommended that patient have a nutrition consult/appointment for an assessment by an RDN including supplementation recommendations. (UW Health Very low quality of evidence, C recommendation.)

Nutrition Monitoring:
It is recommended that patients at nutrition risk with GVHD have ongoing nutrition monitoring by an RDN. (UW Health Low quality of evidence, C recommendation.)
**Distress/Psychosocial Concerns**

It is especially important for providers of HSCT patients to be aware of their patients’ psychosocial needs and distress level in the first six months following transplant. For pediatric patients, one review study noted the first six-month period post-transplant to be a risk factor for poor quality of life.\(^{120}\) In adults, patients with aGVHD six months after transplant had a measurable decline in quality of life compared to those without.\(^{121}\) An increased risk of aGVHD has also been associated with pre-transplant depression and post-transplant depression has been linked to increased mortality.\(^{122}\)

The National Comprehensive Cancer Network (NCCN) estimates that less than 10% of cancer patients receive adequate psycho-oncological support.\(^{123}\) Thus it is recommended providers be cognizant of their HSCT patients’ distress levels and to consider the following:

1. Patients with a new aGVHD diagnosis that will require systemic therapy or who are deemed “high risk” for not achieving a complete or partial response to therapy at 28 days should be assessed for distress using the NCCN Distress Thermometer (DT). (UW Health Moderate quality of evidence, S recommendation.)

2. If the patient has a level of ≥ 4 on the Distress Thermometer, consider further evaluating the patient.\(^{124,125}\) For example, if there is concern for depression or suicidal ideation, perform screening using a validated tool (e.g., PHQ-9.) (UW Health Moderate quality of evidence, C recommendation.)

3. A patient may be referred to Health Psychology if he/she has significant distress after assessment with distress thermometer (e.g., DT score >4 with any emotional concerns, treatment decisions, family problems, fatigue, pain and/or sleep disturbance.)

4. If there is clinician concern at any point while a patient is undergoing treatment for aGVHD, the patient should be assessed for distress.

In some cases, a direct referral to Health Psych may be warranted. Some considerations on when to refer aGVHD patients to Health Psych include (UW Health Moderate quality evidence, C recommendation):

- Provider has concerns about patient’s emotional or psychological function or feels patient would benefit from behavioral strategies to manage disease symptoms (e.g., fatigue, pain, sleep disturbance.)
- Patient seeks additional assistance in coping with disease, emotions or physical symptoms.

**Sun Exposure**

It is strongly recommended that HSCT patients, regardless of ethnicity and skin color, protect themselves from sun exposure because of the potential to cause or trigger GVHD.\(^{126,127}\) (UW Health Moderate quality evidence, S recommendation) Precautions must be taken indefinitely given the risk for acute or chronic GVHD post-transplant. Patients and parents should be advised to follow general sun safety recommendations such as limiting outdoor activities during the day when ultraviolet (UV) radiation peaks (i.e. from 10 a.m - 2 p.m. and during daylight saving time 11 a.m. – 3 p.m.) and limiting exposure to 30-60 minutes blocks. (UW Health Moderate quality of evidence, C recommendation.) Patients are also advised to wear sun-protective clothing such as long sleeve shirts, sunglasses, wide brim hats when outdoors.\(^{128}\) (UW Health Strong quality of evidence, C recommendation.)

Patients should be advised as well to follow sunscreen recommendations. For children and adults, a broad-spectrum sunscreen that is para-aminobenzoic acid free with SPF ≥ 30 should be applied to sun exposed skin 15 minutes before going outdoors and re-applying every 2
hours, especially after heavy perspiration or swimming.\textsuperscript{126,128,129} Patient should be careful in the setting of water and sand, which can reflect UV rays\textsuperscript{128} and sun exposure cautions should also be followed during the cold weather season as well since snow can also reflect sunlight\textsuperscript{126} and during long car rides and while sitting under an umbrella.\textsuperscript{126}

**Exercise and Referring to Physical/Occupational Therapy**

The benefit of exercise for aGVHD patients is not limited to maintaining bone health and building endurance, but can also help improve mood, health-related quality of life including cancer-related fatigue, and alleviate stress.\textsuperscript{126,127,130} One meta-analysis saw the best results for exercise at discharge, implying that starting intervention before or just after transplantation seems effective.\textsuperscript{131} Clinicians should encourage patients to exercise and to follow general physical activity guidelines if possible. For children and adolescents, 60 minutes or more of daily physical activity is recommended with bone-strengthening activity on at least 3 days of the week. For adults, the recommended exercise duration is 150 minutes a week of moderate-intensity.\textsuperscript{132}(UW Health Low quality of evidence, C recommendation.)

**For Pediatrics:**

It is recommended that pediatric patients be referred to physical therapy or occupational therapy upon hospital admission for acute GVHD. (UW Health Low quality of evidence, C recommendation.)

**For Adults:**

Patients may also be advised of special interest fitness classes such as “Living Falls Free,” an exercise class with a focus on balance enhancement and teaches falls reduction strategies. (UW Very Low quality evidence, C recommendation)

For aGVHD patients whose disease limits their exercise capacity and/or declining physical function, a referral to Physical Therapy or Occupational Therapy may be warranted. Some criteria for referral are (UW Health Low quality of evidence, C recommendation):

- Steroid induced myopathy and weakness
- Immobility/poor range of motion due to GVHD
- Neuropathy management
- Edema management due to graft versus host disease
- Balance rehabilitation- chemo induced neuropathy causing poor balance.

In patients with acute GVHD that require treatment for greater than 3 months, supportive care concerns are likely to closely mirror those for chronic GVHD. Additional guidance on supportive care recommendations for adults with chronic GVHD (i.e., acid suppression, bone health) may be found in the following documents:

- UW Health Chronic Graft versus Host Disease Diagnosis and Treatment Guideline.
- UW Health Antimicrobial Prophylaxis in Hematopoietic Stem Cell Transplant Recipients – Adult/Pediatric - Inpatient/Ambulatory Guideline
- UW Health Bone Marrow Transplant Standard Operating Procedure (SOP) F2.200
- Immunizations Post Hematopoietic Stem Cell Transplant
- UW Health Intravenous Immune Globulin- Adult/Pediatric – Inpatient/Ambulatory Guideline

**Disclaimer**

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.
Disclosure
A conflict of interest declaration must be signed/submitted by guideline workgroup and/or committee members to ensure balance, independence, objectivity, and scientific rigor in activities pertaining to the guideline development process. Guideline members must complete a conflict of interest statement annually or as new interest(s) arises. Potential, current and planned future, conflicts of interest will be identified and managed in accordance with institutional policies and procedures. This may include, but is not limited to, conflict disclosure, abstaining from voting, dismissal during comment and voting period, or recusal from requesting and/or participation in the decision-making process.

It is the policy of UW Health that all workgroup members and other persons who may influence content in this guideline disclose all relevant financial relationships with commercial interests. Any disclosure of a relationship listed is not intended to suggest bias in the information presented but rather to provide the reader with information that may be of importance in their evaluation of the information presented.

Contact for Content:
Name: Mark Juckett, MD – Medicine - Hematology/Oncology
Phone Number: (608) 265-4363
Email Address: mbj@medicine.wisc.edu

Name: Inga Hofmann, MD – Pediatric Hematology/Oncology
Phone Number: (608) 263-8558
Email Address: ihofmann@wisc.edu

Contact for Changes:
Center for Clinical Knowledge Management (CCKM)
Email Address: CCKM@uwhealth.org

Workgroup Members:
Amanda Świeciuchowski- RN, BSN, CHPN – Bone Marrow Transplant
Bethaney Campbell, MN, RN, AOCNS – Bone Marrow Transplant
Cameron Ninos, PharmD – Inpatient Pharmacy
Mary Mably, RPh – Inpatient Pharmacy
Katherine Le, PharmD - CCKM

Reviewer(s):
Sara Shull – Drug Policy

Committee Approvals/Dates:
Clinical Knowledge Management (CKM) Council (Last Periodic Review: 01/23/2020)
**Collateral Tools & Resources**

The following collateral tools and resources support staff execution and performance of the evidence-based guideline recommendations in everyday clinical practice.

**Metrics**
- Number of patients with acute GVHD with standard assessment at diagnosis
- Number of aGVHD patients with risk adjusted treatment
- Number of aGVHD patients enrolled in a clinical trial for aGVHD treatment

**Beacon Protocols**
- CSC SC Immunizations Post Hematopoietic Stem Cell Transplant [1961]
- CSC SC Etanercept for GVHD [5772]

**Best Practice Alerts (BPA)**
- Name [####]

**Order Sets & Smart Sets**
- OP-GVHD Lab and Procedure Delegation Protocol – Adult – Ambulatory [7584]
- OP- GVHD Consult Ordering Delegation Protocol – Adult- Ambulatory [7826]
- OP – Day 100 Allogeneic Transplant Follow Up – Adult – Clinic Visit [5213]
- Smart Set- IP- Hematopoietic Stem Cell Transplant – Pediatric – Admission [1710]
- Photopheresis- Adult Supplemental Order Set [301440-DT]

**Patient Resources**
- Health Facts For You #415 – Graft Versus Host Disease Diet Recommendations

**Policies**
- Name [####]

**Procedures**
- Name [####]

**Protocols**
- Graft versus Host Disease Lab, Procedure and Consult Ordering – Adult – Ambulatory [188]
- Post-Hematopoietic Stem Cell Transplant (HSCT) Immunosuppressive Therapy – Adult- Ambulatory – Oncology clinic [125]

**Pertinent UW Health Policies & Procedures**
1. UWHC 15.2 Medication Use in Outpatient Care Areas
2. UWHC 6.1.9 Restricted Primarily Ambulatory Administered Medications in Hospitalized Patients

**Clinical Practice Guidelines**
- Parenteral Nutrition – Adult – Inpatient/Ambulatory
- Parenteral Nutrition – Pediatric/Neonatal – Inpatient/Ambulatory
- Guideline for Pediatric Total Parenteral Nutrition
- Perioperative Medication Management – Adult/Pediatric – Inpatient/Ambulatory
- Renal Function-Based Dose Adjustment – Adult – Inpatient/Ambulatory
Appendix A. Evidence Grading Scheme(s)

Figure 1. GRADE Methodology adapted by UW Health

Rating Scheme for the Strength of the Evidence/Recommendations:

<table>
<thead>
<tr>
<th>GRADE Ranking of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are confident that the effect in the study reflects the actual effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>The true effect may differ significantly from the estimate.</td>
</tr>
<tr>
<td>Very Low</td>
<td>The true effect is likely to be substantially different from the estimated effect.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GRADE Ratings for Recommendations For or Against Practice</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong (S)</td>
<td>Generally, should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.)</td>
</tr>
<tr>
<td>Conditional (C)</td>
<td>May be reasonable to perform (i.e., may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.)</td>
</tr>
</tbody>
</table>

This guideline will be reviewed every 2 years.
### Appendix B. Clinical Staging, Grading and Refined Risk Score for Acute GVHD Patients

**Clinical Staging for Acute GVHD in Adults and Children**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin</th>
<th>Liver (bilirubin)</th>
<th>Lower Gastrointestinal tract</th>
<th>Upper Gastrointestinal tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No rash, no rash attributable to acute GVHD</td>
<td>No liver acute GVHD/bilirubin &lt; 2.0 mg/dL (&lt;34 µmol/L)</td>
<td>No diarrhea, no diarrhea attributable to aGVHD; Adult: Diarrhea &lt; 500 mL/day, or &lt; 3 episodes/day; Pediatric: Diarrhea &lt; 10 mL/kg/day, or &lt; 4 episodes/day</td>
<td>No persistent nausea or vomiting</td>
</tr>
<tr>
<td>1</td>
<td>Maculopapular rash, &lt; 25% of body surface</td>
<td>2.0-3.0 mg/dL (34-52 µmol/L)</td>
<td>Adult: Diarrhea 500-1000 mL/day, or 3-4 episodes/day; Pediatric: Diarrhea 10-19.9 mL/kg/day or 4-6 episodes/day</td>
<td>Persistent nausea or vomiting, with or without anorexia</td>
</tr>
<tr>
<td>2</td>
<td>Maculopapular rash, 25-50% of body surface</td>
<td>3.1-6.0 mg/dL (53-103 µmol/L)</td>
<td>Adult: Diarrhea 1001-1500 mL/day (adult) or 5-7 episodes/day; Pediatric: Diarrhea 20-30 mL/kg/day or 7-10 episodes/day</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Generalized erythroderma, &gt; 50% of body surface</td>
<td>6.1-15.0 mg/dL (104-256 µmol/L)</td>
<td>Adult: Diarrhea &gt; 1500 mL/day (adult) or &gt; 7 episodes/day; Pediatric: Diarrhea &gt; 30 mL/kg/day or &gt; 10 episodes/day</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Generalized erythema with bullae formation and/or desquamation</td>
<td>&gt;15.0 mg/dL (&gt;256 µmol/L)</td>
<td>Adult/Pediatric: Severe abdominal pain with or without ileus, and/or grossly bloody stool (regardless of stool volume)</td>
<td></td>
</tr>
</tbody>
</table>

Diarrhea volumes of liquid stool should be based in the following order: (1) average of 3 consecutive days, (2) average of 2 consecutive days, or (3) the volume on day of assessment. If diarrhea reported only as episodes, consider average volume per diarrhea as 200 mL/episode or 3 mL/kg for children <50 kg. To estimate stool only volume for mixed urine/stool: subtract 1550 mL from 24-hr mixed total if only mixed output documented; subtract 720 mL from 24-hr mixed volume if both measured urine and mixed output documented.

For Stage 4 Lower GI: Bloody diarrhea is staged as 4, independent of volume of diarrhea.

Ω Persistent nausea > 3 days or 2+ vomiting episodes/day for 2 days or anorexia WITH weight loss only.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin</th>
<th>Liver</th>
<th>Lower GI</th>
<th>Upper GI</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Stage 1-2</td>
<td>No liver involvement</td>
<td>No gut involvement</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Stage 3</td>
<td>Stage 1</td>
<td>Stage 1</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Stage 0-3</td>
<td>Stage 2-3</td>
<td>Stage 2-3</td>
<td>Stage 0-1</td>
</tr>
<tr>
<td>IV</td>
<td>Stage 4</td>
<td>Stage 4</td>
<td>Stage 4</td>
<td>Stage 0-1</td>
</tr>
</tbody>
</table>

#### Refined Risk Score for Acute GVHD

**Risk Score**

<table>
<thead>
<tr>
<th>Standard Risk</th>
<th>One Organ</th>
<th>Two Organs</th>
<th>Three Organs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stage 1-3 Skin</td>
<td>• Stage 1-3 skin + stage 1 GI</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>• Stage 1-2 GI</td>
<td>• Stage 1-3 skin + stage 1-4 liver</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

**High Risk**

| • Stage 4 Skin | • Stage 1-3 skin + stage 2 GI |
| • Stage 3-4 GI | • Stage 1-2 lower GI + stage 1-3 liver |
| • Stage 1-4 Liver | • Stage 3-4 GI + stage 1-3 skin |
|                | • Stage 3-4 GI + stage 1-4 liver |
|                | • Stage 1-3 skin + stage 1-2 GI plus stage 1-3 liver |
|                | • Stage 1-3 skin + stage 3-4 GI plus stage 1-4 liver |

Note: Upper GI plus lower GI considered single organ.

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Contact: CCKM@uwhealth.org
Last Revised: 03/2020
## Appendix C. Acute GHVD Prophylaxis Tables

### Table 10 – Chemotherapy and Immunosuppression Regimens – Adult

<table>
<thead>
<tr>
<th>Cell Source</th>
<th>Donor Type</th>
<th>Regimen Intensity</th>
<th>Chemo Regimen</th>
<th>Immunosuppression Regimen</th>
<th>Time of Administration</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow / PBSC</td>
<td>Matched</td>
<td>Myeloablative</td>
<td>Fludarabine Busulfan</td>
<td>Tacrolimus: See disease specific plan for earlier taper recommendations for patients with high risk disease. Mycophenolate: May be continued beyond Day 35 if active GVHD present. Discontinue at Day 35 unless otherwise specified by treatment plan.</td>
<td>Day +3 (between 60-72 hrs after stem cell infusion; Day +4 (24 hr after last dose)</td>
<td>50 mg/kg IV daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tacrolimus (if PBSC)</td>
<td>+5 to Day +100</td>
<td>0.03 mg/kg orally BID</td>
</tr>
<tr>
<td>Marrow / PBSC</td>
<td>Mismatched</td>
<td>Myeloablative</td>
<td>Fludarabine Busulfan TBI 4Gy</td>
<td>Tacrolimus</td>
<td>Day +3 (between 60-72 hrs after stem cell infusion; Day +4 (24 hr after last dose)</td>
<td>50 mg/kg IV daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mycophenolate</td>
<td>+5 to Day +180</td>
<td>0.03 mg/kg orally BID</td>
</tr>
<tr>
<td>Marrow / PBSC</td>
<td>Matched</td>
<td>Reduced-Intensity</td>
<td>Fludarabine Melphalan</td>
<td>Tacrolimus</td>
<td>Day +3 (between 60-72 hrs after stem cell infusion; Day +4 (24 hr after last dose)</td>
<td>50 mg/kg IV daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mycophenolate</td>
<td>+5 to Day +180</td>
<td>15 mg/kg orally TID (max dose 3000mg/day)</td>
</tr>
<tr>
<td>Marrow / PBSC</td>
<td>Mismatched</td>
<td>Reduced-Intensity</td>
<td>Fludarabine Melphalan</td>
<td>Tacrolimus</td>
<td>Day +3 (between 60-72 hrs after stem cell infusion; Day +4 (24 hr after last dose)</td>
<td>50 mg/kg IV daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mycophenolate</td>
<td>+5 to Day +35</td>
<td>15 mg/kg orally BID</td>
</tr>
<tr>
<td>Marrow/ PBSC</td>
<td>Matched</td>
<td>Non-myeloablative</td>
<td>Fludarabine Cyclophosphamide TBI 2Gy</td>
<td>Tacrolimus (if mismatched or PBSC)</td>
<td>Day +3 (between 60-72 hrs after stem cell infusion; Day +4 (24 hr after last dose)</td>
<td>50 mg/kg IV daily</td>
</tr>
<tr>
<td></td>
<td>Mismatched</td>
<td></td>
<td></td>
<td>Mycophenolate (if mismatched)</td>
<td>+5 to Day +180 (mismatched) +5 to Day +100 (PBSC)</td>
<td>0.03 mg/kg orally BID</td>
</tr>
<tr>
<td>Cord Blood$^3$</td>
<td>Matched</td>
<td>Non-myeloablative</td>
<td>Fludarabine Cyclophosphamide TBI 2Gy</td>
<td>Cyclosporine</td>
<td>Day -3 until Day +100</td>
<td>3 mg/kg IV daily</td>
</tr>
<tr>
<td></td>
<td>Mismatched</td>
<td></td>
<td></td>
<td>Mycophenolate</td>
<td>Day -3 until Day+30 or 7 days after engraftment, whichever is later</td>
<td>1000mg IV q8h (or 15mg/kg IV q8h for patients &lt;50kg) (ABW). Maximum total daily dose not to exceed 3000mg (i.e., 1000mg PO tid)</td>
</tr>
<tr>
<td>Marrow</td>
<td>Matched</td>
<td>Myeloablative</td>
<td>Aplastic Anemia: Cyclophosphamide ATG (equine) TBI 2Gy (for unrelated donor)</td>
<td>Tacrolimus</td>
<td>+5 to Day +180</td>
<td>0.03 mg/kg orally BID</td>
</tr>
</tbody>
</table>
|                 |            |                   |                        | Methotrexate                | +1, +3, +6, +11                                                                    | Day +1: 15mg/m2 IV
<p>|                 |            |                   |                        |                                           | Day +3, +6, +11: 10mg/m2 IV |</p>
<table>
<thead>
<tr>
<th>Table 11 – Dose Adjustments – Adult and Pediatric</th>
<th>steadystate-trough-level-ngml</th>
<th>Suggested Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>&lt;2.5</td>
<td>Increase by 25-50%</td>
</tr>
<tr>
<td></td>
<td>2.5 – 4.9</td>
<td>Increase by 0-25%</td>
</tr>
<tr>
<td></td>
<td>5 – 10</td>
<td>No Change</td>
</tr>
<tr>
<td></td>
<td>10.01 – 15</td>
<td>Hold x1 dose and decrease dose by 0-25%</td>
</tr>
<tr>
<td></td>
<td>15.1 – 20</td>
<td>Hold until &lt;10 ng/mL and resume at 50% dose</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>Hold until &lt;10 ng/mL and resume at 50% dose</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>&lt;50</td>
<td>Increase by 25-50%</td>
</tr>
<tr>
<td></td>
<td>50 – 99.9</td>
<td>Increase by 0-25%</td>
</tr>
<tr>
<td></td>
<td>100 – 300</td>
<td>No Change</td>
</tr>
<tr>
<td></td>
<td>300.1 – 350</td>
<td>Hold x1 dose and decrease dose by 0-25%</td>
</tr>
<tr>
<td></td>
<td>&gt;350</td>
<td>Hold until &lt;300 ng/mL and resume at 25-50% of previous dose</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>&lt;1</td>
<td>Increase by 25-50%</td>
</tr>
<tr>
<td></td>
<td>1 – 2.9</td>
<td>Increase by 0-25%</td>
</tr>
<tr>
<td></td>
<td>3 – 12</td>
<td>No Change</td>
</tr>
<tr>
<td></td>
<td>12.1 – 15</td>
<td>Hold x1 dose and decrease dose by 0-25%</td>
</tr>
<tr>
<td></td>
<td>&gt;15</td>
<td>Hold until &lt;12 ng/mL and resume at 25-50% of previous dose</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Estimated Creatinine Clearance</td>
<td>Suggested Dose Adjustment</td>
</tr>
<tr>
<td>Adult</td>
<td>&gt;50 mL/min</td>
<td>100% of dose</td>
</tr>
<tr>
<td></td>
<td>10 – 50 mL/min</td>
<td>50% of dose</td>
</tr>
<tr>
<td></td>
<td>&lt;10 mL/min</td>
<td>Omit dose</td>
</tr>
<tr>
<td>Pediatric</td>
<td>Serum Creatinine &gt;2.0 mg/dL or 1.5 x ULN</td>
<td>Omit dose</td>
</tr>
<tr>
<td><strong>The following guideline may be used to dose reduce methotrexate for patients with impaired liver function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult and Pediatric</td>
<td>Direct Bilirubin (mg/dL)</td>
<td>Suggested Dose Adjustment</td>
</tr>
<tr>
<td></td>
<td>&lt;2.0</td>
<td>Administer full dose</td>
</tr>
<tr>
<td></td>
<td>2.1 – 3.0</td>
<td>Administer 50% of dose</td>
</tr>
<tr>
<td></td>
<td>3.1 – 5.0</td>
<td>Administer 25% of dose</td>
</tr>
<tr>
<td></td>
<td>&gt;5.0</td>
<td>Omit dose</td>
</tr>
</tbody>
</table>
Table 12 - Immunosuppressant Monitoring of Drug Levels – Adults

<table>
<thead>
<tr>
<th>Immunosuppressant</th>
<th>Monitoring Schedule</th>
<th>Therapeutic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inpatient</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>No recommended monitoring</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Twice weekly</td>
<td>Weekly or monthly unless: interactive medications, or suspected toxicity</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Days +7 and +12</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Methylprednisone</td>
<td>No recommended monitoring</td>
<td></td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>No recommended monitoring</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Twice weekly for one month, then once weekly until Day +100, then at least monthly until discontinued</td>
<td>Weekly or monthly, dependent on: interactive medications suspected toxicity, or questionable oral absorption</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Twice weekly for one month, then once weekly until Day +100, then at least monthly until discontinued</td>
<td>Weekly or monthly, dependent on: interactive medications suspected toxicity, or questionable oral absorption</td>
</tr>
</tbody>
</table>

*Drug levels should not be drawn from the catheter lumen used for the intravenous infusion of drug. A generous discard must be drawn before a drug level is drawn from an indwelling catheter to prevent contamination and falsely elevated levels.
<table>
<thead>
<tr>
<th>Cell Source</th>
<th>Donor Type</th>
<th></th>
<th>Immunosuppression Regimens - Pediatrics</th>
<th>Days</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow/PBSC</td>
<td>Matched</td>
<td></td>
<td>Cyclosporine</td>
<td>Day -1 until Day +100</td>
<td>1.5mg/kg IV bid (may be given q8h in small children when therapeutic levels are not achieved)</td>
</tr>
<tr>
<td></td>
<td>Related</td>
<td></td>
<td>Methotrexate</td>
<td>Days +1, +3, +6 and +11</td>
<td>15mg/m2 IV Day +1, then 10mg/m2 IV Days +3, +6, +11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tacrolimus (may be substituted for cyclosporine in cases of cyclosporine intolerance)</td>
<td>Day -2 until Day +100</td>
<td>0.03mg/kg IV continuous infusion every 24 hours</td>
</tr>
<tr>
<td>Marrow/PBSC</td>
<td>Unrelated</td>
<td></td>
<td>Cyclosporine</td>
<td>Day -2 until Day +180</td>
<td>1.5mg/kg IV bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Methotrexate</td>
<td>Days +1, +3, +6 and +11</td>
<td>15mg/m2 IV Day +1, then 10mg/m2 IV Days +3, +6, +11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Methylprednisolone</td>
<td>Begin Day 0 until Day +28</td>
<td>1mg/kg IV daily, taper begins at Day +22, at 10% q week until off (may substitute oral prednisone (dose ratio of 1:1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ATG (Equine)</td>
<td>Day -3, -2, -1 (May vary with protocol)</td>
<td>30mg/kg IV q 24 hours</td>
</tr>
<tr>
<td>Cord Blood$^b$</td>
<td>Matched</td>
<td></td>
<td>Cyclosporine</td>
<td>Day -1 until Day +180</td>
<td>1.5mg/kg IV bid (ABW).</td>
</tr>
<tr>
<td></td>
<td>Mismatched</td>
<td></td>
<td>Tacrolimus (may be substituted for cyclosporine in cases of cyclosporine intolerance)</td>
<td>Day -1 until Day +100</td>
<td>0.03mg/kg IV continuous infusion every 24 hours. When able, switch to oral medication at ratio of 1:3 (IV to oral). Daily dose should be divided twice daily.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mycophenolate</td>
<td>Day -1 to Day +42</td>
<td>600mg/m2 IV q 12 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ATG (equine)</td>
<td>Day -3, -2, -1</td>
<td>30mg/kg IV q 24 hours</td>
</tr>
</tbody>
</table>
Table 14 - Immunosuppressant Monitoring of Drug Levels – Pediatrics

<table>
<thead>
<tr>
<th>Immunosuppressant</th>
<th>Monitoring Schedule</th>
<th>Collection Time</th>
<th>Therapeutic goal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inpatient</td>
<td>Outpatient</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Twice weekly</td>
<td>Weekly or monthly unless: interactive medications, or suspected toxicity or dose adjustments necessitated by reaching therapeutic target</td>
<td>IV: Trough level Oral: Trough level</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Morning rounds</td>
</tr>
<tr>
<td>Methylprednisone</td>
<td>No recommended monitoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>No recommended monitoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Daily until steady state (if continuous infusion), then twice weekly</td>
<td>Weekly, dependent on: interactive medications suspected toxicity, or questionable oral absorption</td>
<td>IV: Trough level Oral: Trough level</td>
</tr>
</tbody>
</table>

* Drug levels should not be drawn from the catheter lumen used for the intravenous infusion of drug. A generous discard must be drawn before a drug level is drawn from an indwelling catheter to prevent contamination and falsely elevated levels.
Table 15 - Drug Interactions and Side Effects for Immunosuppressive Drugs
(NOTE: Not an exhaustive list—consult Lexicomp or ask your pharmacist for more information)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient Type</th>
<th>Interactions</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>Adult</td>
<td>Tacrolimus is metabolized by the CYP 3A4 isoenzyme system and has many clinically significant drug-drug interactions.</td>
<td>• Hypertension – best treated with a dihydropyridine calcium channel blocker such as amlodipine</td>
</tr>
<tr>
<td></td>
<td>Peds</td>
<td>• Increased by azole antifungals, calcium channel blockers, and macrolide antibiotics.</td>
<td>• Electrolyte disturbances</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Decreased by phenobarbital, phenytoin and rifampin.</td>
<td>• Renal dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• When patients are on medications that interact with tacrolimus, consideration will be given to more frequent monitoring or tacrolimus levels to ensure adequate drug exposure.</td>
<td>• Abnormal hepatic function tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Absorption of tacrolimus is decreased by sucralfate and by antacids containing magnesium or aluminum. Patients will be instructed to take on empty stomach to avoid interactions regarding absorption.</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Adult and Pediatric</td>
<td>• Cyclosporine is metabolized by the CYP3A4 isoenzyme system and has many clinically significant drug-drug interactions.</td>
<td>• Hypertension – best treated with a dihydropyridine calcium channel blocker such as amlodipine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Levels are increased by azole antifungals, calcium channel blockers, and macrolide antibiotics.</td>
<td>• Renal dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Levels are decreased by phenobarbital, phenytoin, and rifampin.</td>
<td>• Increased triglycerides</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patients on medications that interact with cyclosporine, consideration will be given to more frequent monitoring of cyclosporine levels to ensure adequate drug exposure.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• It is advisable to check with the pharmacist for possible adverse drug interactions any time a patient receiving cyclosporine is started on a medication that is not routinely used in HSCT support care products.</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Adult</td>
<td>• Sirolimus is known to be a substrate for both cytochrome P450 CY3A4 and P-glycoprotein</td>
<td>• Hypertension – best treated with a dihydropyridine calcium channel blocker such as amlodipine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Drugs that increase levels include calcium channel blockers, cyclosporine, macrolide antibiotics, metoclopramide, azole antifungal agents, and iteomovir.</td>
<td>• Skin rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Due to extreme interactions with sirolimus, voriconazole and posaconazole are generally contraindicated during sirolimus therapy. When it is deemed clinically necessary to co-administer sirolimus and voriconazole, a 90% reduction of sirolimus dosing is an effective strategy.</td>
<td>• Peripheral edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sirolimus dose should be reduced approximately 50% when used with fluconazole</td>
<td>• Renal dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Arthralgia</td>
</tr>
</tbody>
</table>
Appendix D. Example Steroid Taper Schedule

Prednisone may be tapered by approximately 10% every 5 – 7 days over approximately 8 to 10 weeks depending on rapidity of response, GVHD risk, and other patient factors.

If the patient has standard risk GVHD and achieved a full response at day 5, may consider an every 3-day taper schedule (example below.)

<table>
<thead>
<tr>
<th>Taper starting at 2 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>Before taper</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>16</td>
</tr>
<tr>
<td>21</td>
</tr>
<tr>
<td>26</td>
</tr>
<tr>
<td>31</td>
</tr>
<tr>
<td>36</td>
</tr>
<tr>
<td>41</td>
</tr>
</tbody>
</table>

Start alternate day taper after at least 3 days of 0.2 mg/kg/day

<table>
<thead>
<tr>
<th>Standard Risk patients with full response by Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taper Every 3-days starting at 2 mg/kg/day prednisone</td>
</tr>
<tr>
<td>Day</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>Before taper</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>13</td>
</tr>
<tr>
<td>16</td>
</tr>
<tr>
<td>19</td>
</tr>
<tr>
<td>22</td>
</tr>
<tr>
<td>25</td>
</tr>
</tbody>
</table>

**Start alternate day taper after at least 3 days of 0.2mg/kg/day**

<table>
<thead>
<tr>
<th>Taper starting at 1 mg/kg/day prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of taper</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Before taper</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>16</td>
</tr>
<tr>
<td>21</td>
</tr>
<tr>
<td>26</td>
</tr>
<tr>
<td>31</td>
</tr>
<tr>
<td>41</td>
</tr>
</tbody>
</table>

**Start alternate day taper after at least 3 days of 0.2mg/kg/day**
**Standard Risk patients with full response by Day 5**  
**Taper every 3-days starting at 1 mg/kg/day prednisone**

<table>
<thead>
<tr>
<th>Day of taper</th>
<th>AM dose daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before taper</td>
<td>1 mg/kg</td>
</tr>
<tr>
<td>1</td>
<td>0.9 mg/kg</td>
</tr>
<tr>
<td>4</td>
<td>0.8 mg/kg</td>
</tr>
<tr>
<td>7</td>
<td>0.7 mg/kg</td>
</tr>
<tr>
<td>10</td>
<td>0.6 mg/kg</td>
</tr>
<tr>
<td>13</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>16</td>
<td>0.4 mg/kg</td>
</tr>
<tr>
<td>19</td>
<td>0.3 mg/kg</td>
</tr>
<tr>
<td>22</td>
<td>0.2 mg/kg</td>
</tr>
</tbody>
</table>

**Start alternate day taper after at least 3 days of 0.2mg/kg/day**

**Alternate day prednisone taper from above tables to cessation of prednisone**

<table>
<thead>
<tr>
<th>Day of taper</th>
<th>AM dose daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start alternate day taper only after prednisone dose has been at 0.2 mg/kg/day for at least 3 days</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.2 mg/kg (not to exceed 20 mg)</td>
</tr>
<tr>
<td>2</td>
<td>0.1 mg/kg (not to exceed 10 mg)</td>
</tr>
<tr>
<td>3</td>
<td>0.25 mg/kg (not to exceed 25 mg)</td>
</tr>
<tr>
<td>4</td>
<td>0.05 mg/kg (not to exceed 5 mg)</td>
</tr>
<tr>
<td>5</td>
<td>0.3 (not to exceed 30 mg)</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0.2 mg/kg (not to exceed 15 mg)</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0.15 mg/kg (not to exceed 10 mg)</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0.1 mg/kg (not to exceed 5 mg)</td>
</tr>
<tr>
<td>12</td>
<td>STOP</td>
</tr>
</tbody>
</table>
Appendix E. Extracorporeal Photopheresis Therapy

**Purpose:** To establish guidelines for the safe administration of ECP used to treat adult and pediatric allogeneic transplant patients with graft vs. host disease (GVHD).

**Principles:**
- There is no established standard of care to treat GVHD once patients become steroid refractory. ECP can be an effective treatment for some patients. \(^{39,133-139}\).
- Transplant provider or designee stages GVHD at diagnosis and other timepoints as outlined in the clinical practice guideline using NIH Consensus tools as built into the electronic medical record.
- Patient/caregiver education about ECP occurs throughout the process beginning with the transplant provider and team, including the BMT After Care Coordinator, and continues with the Transfusion Medicine provider and Infusion Center nursing staff.
- Extracorporeal photopheresis should be considered in patients with severe GVHD who have disease progression after four weeks of therapy with concurrent prednisone and sirolimus. \(^{1-7}\) *(UW Health Moderate quality evidence, S recommendation)*
- Patients are at increased risk of complications from ECP\(^1\) when they:
  - Take medications that cause photosensitivity
  - Have a history of heparin-induced thrombocytopenia (HIT)
  - Have difficulty handling fluid shifts
  - Need chronic blood product transfusions
  - Have an active and uncontrolled infection

**Procedure:**

**Before the Start of ECP**

1. Prior to placing a Transfusion Medicine consult, patient’s transplant provider/team determines that patient is a potential candidate for ECP, and completes the diagnosis and staging of GVHD.
2. Patient’s transplant provider/team enters a note including the following:
   a. Diagnosis and GVHD grade, including involved organs
   b. Intended timing for start of therapy
2. Patient’s transplant provider/team places a consult order to Transfusion Medicine via the electronic medical record.
3. Patient’s transplant clinical team contacts the Infusion Center nurse to coordinate a vein assessment and determine whether additional IV access may be required.
4. Upon receipt of consult order and prior to initiation of ECP, Transfusion Medicine physician conducts a thorough review of the patient’s medical record and writes a progress note outlining the patient’s therapy plan which is communicated with the ordering clinician. The written therapy plan includes:
   a. Diagnosis and GVHD grade, including involved organs (from transplant team notes)
   b. Intended timing for start of therapy and planned treatment course
   c. Other factors that may affect the safe administration of ECP
5. The Transfusion Medicine provider obtains written consent prior to the start of therapy.
**ECP Treatment Schedule**

- Treatment should be initiated with one cycle (two treatments on consecutive days) every week for four weeks (weeks 1 through 4), then every other week for four weeks (weeks 5, 7, 9, and 11), then every four weeks for four months. (*UW Health Low quality evidence, S recommendation*) Patients should complete their entire treatment schedule unless they meet stopping points as described below.
- If patient continues to respond to ECP therapy, it may be reasonable to continue beyond the above schedule. (*UW Health Very low quality evidence, C recommendation*)
- **Discontinue once patient has reached maximum, stable response if therapy has continued beyond initial treatment schedule.** (*UW Health Very low quality evidence, C recommendation*)

**Response Assessments**
The transplant provider or designee completes response assessments at the following time points:

- **Four weeks after initiation of therapy**
  - Discontinue if:
    - GVHD has rapidly progressed (*UW Health Moderate quality evidence, S recommendation*)
  - Continue if:
    - GVHD is stable or has improved (*UW Health Moderate quality evidence, S recommendation*)

- **Three months after initiation of therapy**
  - Discontinue if:
    - GVHD progression occurs at any time unrelated to an attempt to taper systemic immunosuppression (*UW Health High quality evidence, S recommendation*)
      - If flare correlates to a taper attempt, ECP therapy may be continued.¹ (*UW Health Moderate quality evidence, S recommendation*)
      - There is no improvement from initiation of ECP.¹ (*UW Health High quality evidence, S recommendation*)
  - Continue if:
    - There is any GVHD improvement and/or reduction in systemic immunosuppression (*UW Health Moderate quality evidence, S recommendation*)

- **Every three months for the duration of therapy and upon completion.** (*UW Health Very low quality evidence, S recommendation*)

**Upon ECP completion**
- A member of the patient’s clinical team will document an end of treatment summary in the medical record.
References


