Chronic Graft-Versus-Host Disease (cGVHD): Diagnosis and Treatment - Adult/Pediatric - Inpatient/Ambulatory - Clinical Practice Guideline

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Introduction

Chronic GVHD is the primary cause of non-relapse morbidity and mortality in patients surviving longer than 100 days after allogeneic hematopoietic stem cell transplant (HSCT) and is the major determinant of long term quality-of-life for HSCT patients.[1] The greatest risk factor for the development of cGVHD is antecedent acute GVHD; therefore effective prophylaxis for acute GHVD is the best strategy for prevention of cGVHD. Approximately 30 to 70% of recipients of HSCT allografts will develop cGVHD. The known risk factors predicting poor outcome for cGVHD are: thrombocytopenia, progressive presentation of GVHD from acute to chronic, lichenoid skin histology, and elevation of serum bilirubin. The clinical syndrome resembles an overlap of various autoimmune diseases such as progressive systemic sclerosis, Sjogren's syndrome, systemic lupus erythematosus, lichen planus, and primary biliary cirrhosis. The pathophysiology of this disease process includes the formation of autoantibodies and the inability to produce protective antibodies against environmental pathogens. Patients with extensive, multi-organ cGVHD have a poor prognosis, but if they can be supported for the first few years post-transplant the usual course is for tolerance to occur and the disease process to eventually exhaust itself.

Scope

Intended Users: Blood and Bone Marrow Transplant (BMT) After-care Coordinator, BMT Physicians, BMT Advanced Practice Providers, Nurses, Pharmacists, Social Workers, Nutritionists

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

Target Population: Any patient (adult and pediatric) who has received an allogeneic HSCT and is being seen in the BMT clinic or inpatient setting with cGVHD.

Clinical Questions Considered:

- How is chronic GVHD diagnosed?
- What treatments are recommended to initially treat mild, moderate or severe cGVHD?
- When should a patient's chronic GVHD be re-assessed following the initiation of therapy?
- What are supportive care interventions for cGVHD patients?

Definitions

Acute Graft Versus Host Disease: Acute GVHD includes (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 cGVHD, 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 cGVHD (often seen during the taper or after withdrawal of immune suppression).[1]

Chronic Graft Versus Host Disease: 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.[2,3] 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 included 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.[1]

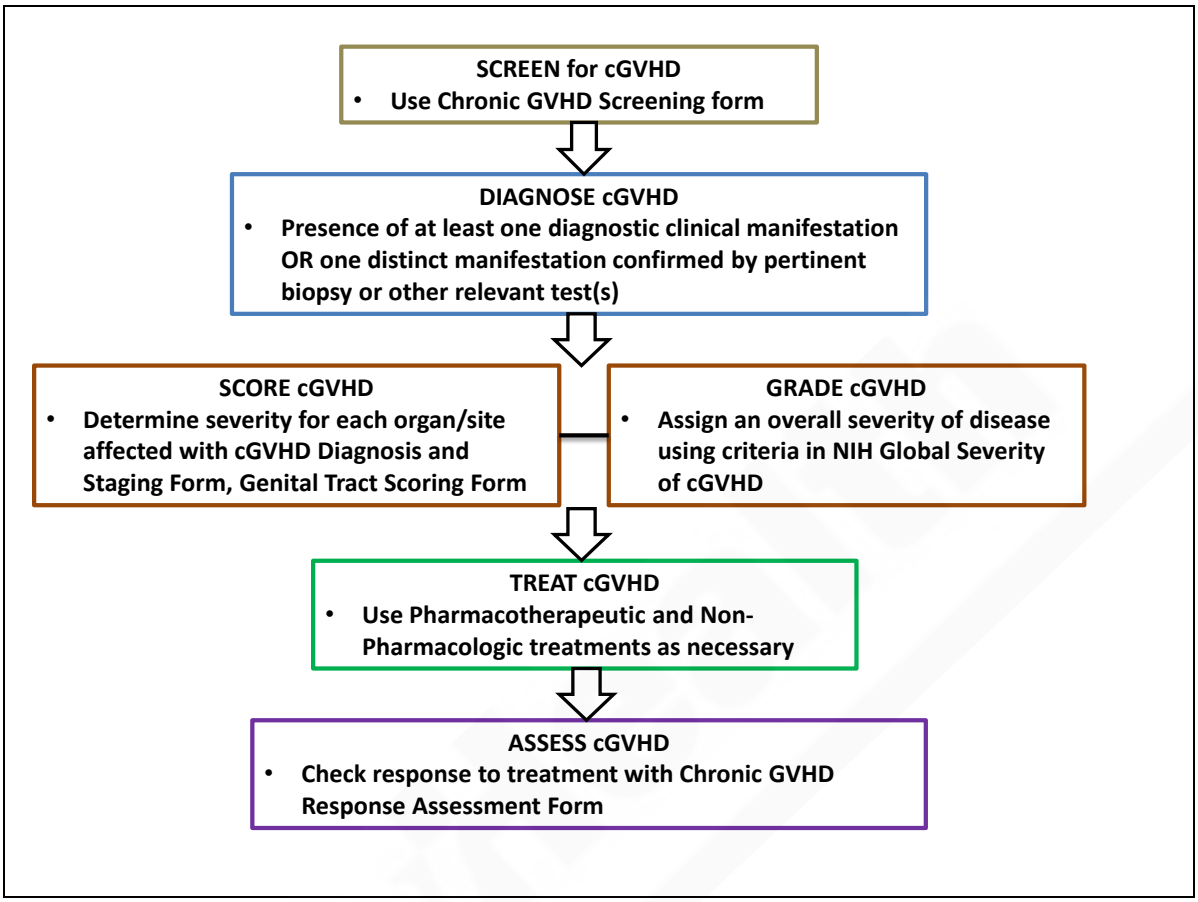
Diagnostic signs of cGVHD: Diagnostic signs and symptoms refer to those manifestations that establish the presence of cGVHD without need for further testing or evidence of other organ involvement.[1]

Distinctive signs of cGVHD: Distinctive signs and symptoms of cGVHD refer to those manifestations that are not ordinarily found in acute GVHD but are not considered sufficient in isolation to establish an unequivocal diagnosis of cGVHD.[1]

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.[1]

Recommendations

Overview of Chronic GVHD



Screening for GVHD

The strongest risk factor for chronic GVHD in adults and children is prior acute GVHD. The severity of chronic GVHD tends to increase with the severity of acute GVHD. Other risk factors for chronic GVHD in both children and adults are listed in **Table 1**.[4,5]

Table 1. Risk Factors for Chronic GVHD in Adults and Children[4,5]

• Prior acute GVHD • Female donor to male recipient • Peripheral blood stem cell transplant (PBSCT) versus bone marrow or umbilical cord source	• HLA mismatch • Non–T-cell-depleted grafts • Malignant diagnosis • History of total body irradiation • Increasing patient and donor age

The goal of screening patients is to prompt early diagnosis and staging of cGVHD. It is recommended to screen all allogeneic BMT patients for cGVHD. *(UW Health Very low quality evidence, C recommendation)* Screening should begin prior to transplant to establish a baseline. Screening should be repeated at each clinic visit after BMT. Screening should also be completed at any time when patients report symptoms or symptoms are suspected by clinical staff or a provider. *(UW Health Very low quality evidence, C recommendation)* It is recommended to assess patients for diagnosis and staging for those whose screening responses show a change in reported symptoms.[1,6] *(UW Health Low quality of evidence, S recommendation)*

How to screen for cGVHD (Chronic GVHD Screening Form)

A brief set of simplified questions have been developed to screen patients that may need further assessment for cGVHD. Common areas of concern are addressed (e.g. skin, lungs, joints, oral mucosa, eyes and genitalia).[7]

Screening for Lung GVHD
Many patients with bronchiolitis obliterans (BOS) are asymptomatic early in the disease process. Historically the preferred method of diagnosis was lung biopsy however that can be associated with high morbidity.[8] Pulmonary function test criteria is now sufficient for thus screening with spirometry is recommended at day 100 after transplant, 6 months after transplant, 1 year after transplant, and annually thereafter.[1,9,10] *(UW Health Very low quality evidence, S recommendation)*

Diagnosis of Chronic GVHD

Assessment for staging should occur at the time of initial diagnosis of cGVHD and at selected times thereafter (e.g., development of new symptoms, for recurrent disease, or major change in therapy). *(UW Health Very low quality evidence, C recommendation)*

Patients diagnosed with cGVHD other than bronchiolitis obliterans (BOS) are at increased risk of developing BOS. Because patients with BOS are asymptomatic early in the disease process, screening with spirometry is recommended at initial diagnosis of cGVHD and at 3 to 6-month intervals for the first 2 years after the initial diagnosis.[1,9-13] *(UW Health Very low quality evidence, S recommendation)*

How to diagnose cGVHD
For diagnostic purposes, the NIH recommends that each clinical manifestation be further classified into four categories: diagnostic features, which establish the presence of chronic GVHD even without biopsies or additional tests; distinctive manifestations, which, alone, are not sufficient for diagnosis; other features, referring to nonspecific, rare, or controversial eruptions, and common manifestations to both acute and chronic GVHD. (**Table 2**)[1] The diagnosis of cGVHD has no time limit and requires the presence of at least one diagnostic manifestation of cGVHD (e.g. poikiloderma or esophageal web) or one distinctive feature confirmed by biopsy or other relevant test (e.g. pulmonary function tests, Schirmer's test) in the same or another organ.

The criteria for the diagnosis of cGVHD include[1]:

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

When to consider biopsy

As cGVHD can be diagnosed by one distinctive manifestation as confirmed by biopsy, the following are general recommendations on when to obtain one:

- A skin biopsy should be considered in all patients where skin is the only organ involved with features of chronic GVHD, since it is minimally invasive. A biopsy is especially recommended if the patient will receive systemic therapy for treatment.[14] (*UW Health Low quality of evidence, C recommendation*.)
- Endoscope is recommended for patients with persistent anorexia, persistent nausea/vomiting, and/or unexplained gastrointestinal symptoms. (*UW Health Low quality of evidence, C recommendation.*)
- If the liver is the only organ involved, a biopsy is recommended. (*UW Health Low quality of evidence, C recommendation*.)

It is recommended that all biopsies obtained in patients for suspicion of chronic GVHD be reviewed by:

- Dermatopathology lab for skin biopsies
- Surgical pathology for GI, Liver and Non-derm biopsies *(UW Health Low quality of evidence, S recommendation.)*

Table 2. Signs and Symptoms of cGVHD in Adults and Children[1]

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of cGVHD)	Distinctive* (Seen in cGVHD, but Insufficient Alone	Other Features or Unclassified Entities†	Common‡ (Seen with Both Acute and cGVHD)
Skin	• Poikiloderma • Lichen planus-like features • Sclerotic features Morphea-like features • Lichen sclerosus-like features	• Depigmentation • Papulosquamous lesions	• Sweat impairment • Ichthyosis • Keratosis pilaris • Hypopigmentation • Hyperpigmentation	• Erythema • Maculopapular rash • Pruritus
Nails		• Dystrophy • Longitudinal ridging, splitting or brittle features • Onycholysis • Pterygium unguis • Nail loss (usually symmetric, affects most nails)		
Scalp and body hair		• New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) • Loss of body hair • Scaling	• Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes) • Premature gray hair	
Mouth	• Lichen planus-like changes	• Xerostomia • Mucoceles • Mucosal atrophy • Ulcers • Pseudomembranes		• Gingivitis • Mucositis • Erythema • Pain
Eyes		• New onset dry, gritty, or painful eyes • Cicatricial conjunctivitis • KCS • Confluent areas of punctate keratopathy	• Photophobia • Periorbital hyperpigmentation • Blepharitis (erythema of the eyelids with edema)	
Genitalia	• Lichen planus-like features • Lichen sclerosus-like features Females: Vaginal scarring or clitoral/labial agglutination Males: Phimosis or urethral/meatus scarring or stenosis	• Erosions • Fissures • Ulcers		

***** In all cases, infection, drug effect, malignancy, or other causes must be excluded.
† Can be acknowledged as part of the cGVHD manifestations if diagnosis is confirmed.
‡ Common refers to shared features by both acute and cGVHD.
¥ BOS can be diagnostic for lung cGVHD only if distinctive sign or symptom present in another organ (see text).
£ Pulmonary entities under investigation or unclassified.
± Diagnosis of cGVHD requires biopsy.

Table 2. Signs and Symptoms of cGVHD in Adults and Children[1] (continued)

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of cGVHD)	Distinctive* (Seen in cGVHD, but Insufficient Alone	Other Features or Unclassified Entities†	Common‡ (Seen with Both Acute and cGVHD)
GI Tract	• Esophageal web • Strictures or stenosis in the upper • to mid third of the esophagus		• Exocrine pancreatic insufficiency	• Anorexia • Nausea • Vomiting • Diarrhea • Weight loss • Failure to thrive (infants and children) • Liver Total bilirubin, alkaline phosphatase > 2 times upper limit of normal • ALT > 2 times upper limit of normal
Lung	• Bronchiolitis obliterans diagnosed with lung biopsy • BOS¥	• Air trapping and • bronchiectasis on chest CT	• Cryptogenic organizing pneumonia • Restrictive lung disease£	
Muscles, fascia, joints	• Fasciitis • Joint stiffness or contractures • secondary to fasciitis or sclerosis	• Myositis or polymyositis±	• Edema • Muscle cramps • Arthralgia or arthritis	
Hematopoietic and Immune			• Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulinemia • Autoantibodies (AIHA, ITP) • Raynaud's phenomenon	
Other			• Pericardial or pleural effusions • Ascites • Peripheral neuropathy • Nephrotic syndrome • Myasthenia gravis • Cardiac conduction abnormality or cardiomyopathy	

ALT indicates alanine aminotransferase; **AIHA**, autoimmune hemolytic anemia; **ITP**, idiopathic thrombocytopenic purpura.
***** In all cases, infection, drug effect, malignancy, or other causes must be excluded.
† Can be acknowledged as part of the cGVHD manifestations if diagnosis is confirmed.
‡ Common refers to shared features by both acute and cGVHD.
¥ BOS can be diagnostic for lung cGVHD only if distinctive sign or symptom present in another organ (see text).
£ Pulmonary entities under investigation or unclassified.
± Diagnosis of cGVHD requires biopsy.

Scoring each organ/site severity with cGVHD
Once cGVHD diagnosis is confirmed, severity of the affected organ(s) should be scored. A 4-point scoring system (0-3) is used and considers functional impact.

The Chronic GVHD Diagnosis and Staging Form contains a modified cGVHD Scoring and Assessment form to help physicians evaluate their patients with cGVHD. This form is also available as a flowsheet in HealthLink.

The Genital Tract Scoring Form contains a supplemental Genital Tract Scoring form. If a specialist is unavailable, external examination may be performed to determine "discomfort on exam" as described in this form.[1] Several studies have validated the scoring system as an indicator of disease severity.[15,16]

Global Assessment of cGVHD
Following the NIH Diagnosis and Staging method, an overall chronic GVHD grade (mild, moderate or severe) is assigned for prognostic and management purposes and is based on number of organs/sites involved and the degree of involvement in each site. (**Table 3**)[1]

Causes beyond GVHD should be investigated and ruled out (e.g., respiratory syncytial virus or drug rash). Organ dysfunction/abnormality that can be completely attributed to a non-GVHD source is not scored. If there is uncertainty or multi-factorial causes for symptoms (such as GVHD and infection), then the symptoms are still fully scored and graded.[1]

Table 3. NIH Global Severity of cGVHD[1]

Mild cGVHD
1 or 2 organs involved with no more than score 1
PLUS
Lung score 0
Moderate cGVHD
3 or more organs involved with no more than score 1
OR
At least 1 organ (not lung) with a score of 2
OR
Lung score 1
Severe cGVHD
At least 1 organ with a score of 3
OR
Lung score of 2 or 3
Key points: **In skin:** higher of the 2 scores to be used for calculating global severity. **In lung:** FEV1 is used instead of clinical score for calculating global severity. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Treatment for Chronic GVHD in Adults

Upon diagnosis of any stage of cGVHD, patients should be considered for ongoing clinical trials. *(UW Health Low quality of evidence, S recommendation)* If the patient does not quality of there are not any open trials, proceed with treatment as outlined below.

Mild cGVHD

- Upon diagnosis of mild cGVHD, therapy with organ-specific topical and adjunct therapies **(Table 4)** should be initiated.[17] *(UW Health Moderate quality evidence, S recommendation)*
- Assess response **two weeks** after initiation of topical treatment by conducting a formal cGVHD assessment. *(UW Health Moderate quality evidence, S recommendation)*
- If GVHD has not improved or progressed at **two** weeks, consider treating as moderate disease with the addition of prednisone 1mg/kg by mouth daily. *(UW Health Low quality evidence, C recommendation)*

Moderate cGVHD

Upon diagnosis of moderate cGVHD, concurrent therapy with prednisone 1 mg/kg by mouth daily (equivalent to methylprednisolone IV 0.8 mg/kg/day) with taper (see Table 9) and any applicable topical and/or adjunct therapies should be initiated.[17,18] *(UW Health Moderate quality evidence, S recommendation)* It is reasonable to add organ-specific topical therapy as an adjunct.

- Assess response **two weeks** after initiation of treatment (i.e., steroid) by conducting a formal cGVHD assessment. *(UW Health Moderate quality evidence, S recommendation)*
- If disease has not improved or progressed at **two** weeks, consider treating as severe disease with addition of sirolimus 2 mg by mouth daily and increasing prednisone to 2 mg/kg by mouth daily (equivalent to methylprednisolone IV 1.6 mg/kg/day). *(UW Health Low quality evidence, C recommendation)* If patient is taking posaconazole or voriconazole, a dose reduction of sirolimus (75% dose reduction) is recommended. [19-22] *(UW Health Moderate quality evidence, S recommendation)*

Severe cGVHD

- Initiate concurrent therapy with prednisone 2 mg/kg by mouth daily (equivalent to methylprednisolone IV 1.6mg/kg/day)[17,23] with taper (refer to Table 8.) For patients over the age of 65, diabetic patients or those with other significant comorbidities, may consider dosing 1 mg/kg prednisone. (See Table 9) sirolimus 2 mg by mouth daily, and any applicable topical and/or adjunct therapies. *[17,18,24-27] (UW Health Low quality evidence, S recommendation)*
    - If patient is on anti-infective prophylaxis (e.g., posaconazole or voriconazole), a dose reduction of sirolimus (75% dose reduction) is recommended.[19-22] *(UW Health Moderate quality evidence, S recommendation)*
- Assess response no sooner than **four weeks** after initiation of sirolimus treatment by conducting a formal cGVHD assessment. *(UW Health Moderate quality evidence, S recommendation)* Patients should be exposed to therapeutic drug levels for at least four weeks before concluding treatment failure
- If disease has progressed after four weeks, consider extracorporeal photopheresis and/or other refractory treatment (see Table 5).*[18] (UW Health Low quality evidence, C recommendation)*
- If disease is stable at four weeks and side effects of sirolimus are acceptable, continue for another 4-8 weeks. Most therapies did not reach therapeutic peak until 8-12 weeks in published literature.*[18]*

Exacerbation or recurrence of cGVHD during steroid taper
If a patient experiences an exacerbation or recurrence of cGVHD during the prednisone taper *(UW Health Very low quality evidence, C recommendation)*:

- Prednisone dose should be increased by **two dosing levels**
- If patient is on every other day dosing schedule, the patient should transition to daily dosing for **two weeks**
    - *Example: for a patient taking 0.5 mg/kg every other day, the dose would be increased to 0.35 mg/kg daily (equivalent to 0.7 mg/kg every other day)*

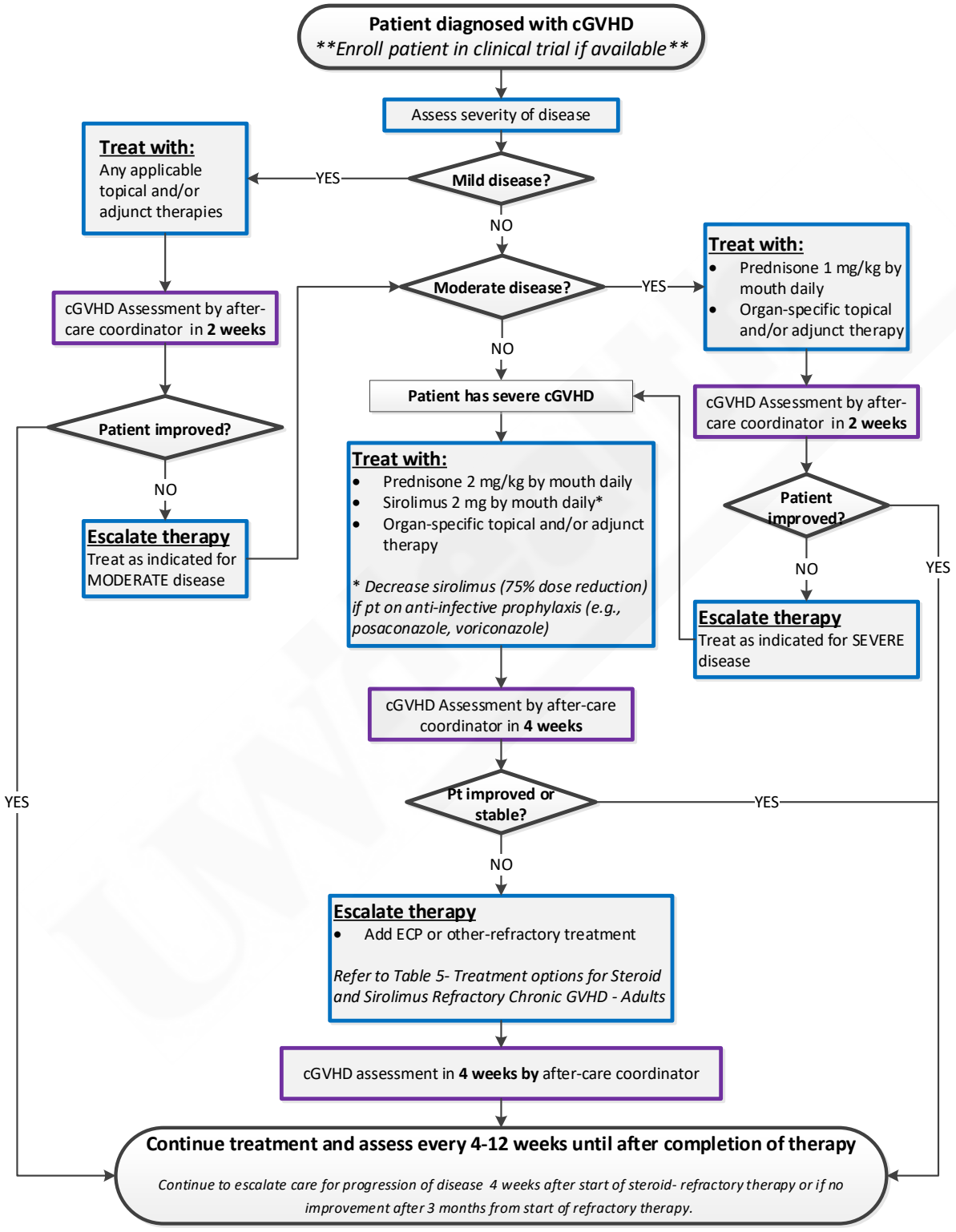
After two weeks of daily dosing, the patient can resume every other day dosing and should continue at that dosing level for **three months** before a taper is again attempted

Recurrence of cGVHD if patient is not on steroid therapy

- If cGVHD recurs following discontinuation of steroid therapy, assess and treat disease as if it was de novo cGVHD.[6] *(UW Health Low quality of evidence, S recommendation)*
- If the patient experiences more than 2 flares/recurrences of cGVHD, consider lifelong therapy.[6,28] *(UW Health Low quality of evidence, C recommendation)*

Figure 1 provides an overview of chronic GVHD treatment and response assessment in adults.

Figure 1. Treatment of Chronic GVHD in Adults



ECP = extracorporeal photopheresis (Extracorporeal Photopheresis Therapy)

Table 4. Topical and Adjunct Medications for Chronic GVHD - Adults

System		Medication	Evidence Strength	Recommendation
Ocular	General treatment	Artificial tears PRN[11,17,29 30] *Consider preservative-free formulations for usage frequency above 6 times per day. Ointment is more effective than solution for dry eyes but can lead to cloudy vision.*	*Very low*	*Strong*
		Prednisolone acetate 1% in affected eye(s) four times daily with ophthalmology consult[11,17,30]	*Low*	*Strong*
		Cyclosporine 0.05% in affected eye(s) twice daily[11,17,30]	*Low*	*Strong*
		Cyclosporine A0.09%in affected eye(s) twice daily [30,31]	*Low*	*Conditional*
		Lifitegrast 5% ophthalmic solution in affected eye(s) twice daily [30,32]	*Low*	*Conditional*
		Antibiotic drops or ointment may be considered if infectious concerns[11,17,29]	*Low*	*Strong*
		Scleral lens/bandage contact lenses/amniotic membrane *for corneal erosions, ulcers or perforation*	*Low*	*Conditional*
	Adjunctive therapy	Oral tetracyclines *for patients with corneal erosions, ulcers, perforation; or meibomian gland disfunction*	*Low*	*Conditional*
		Punctal occlusion	*Low*	*Conditional*
		Pilocarpine 5 mg by mouth three times daily[11,33,34]	*Low*	*Strong*
		Cevimeline 30 mg by mouth three times daily[11,33,34] *If inadequate response to pilocarpine after 8-12 weeks*	*Low*	*Conditional*
		Flax seed oil 2,000 mg/day *to increase tear film stability and decreased ocular inflammation*	*Low*	*Conditional*
		Warm compress 10 minutes 2X/day[30]	*Low*	*Conditional*
		Moisture goggles[30]	*Low*	*Conditional*
		Humidified environment[30]	*Low*	*Strong*
Oral	Generalized disease	Budesonide 3 mg/10 mL water mouthwash – swish 10 mL for 5 minutes and spit, 2-4 times daily[11,17,29,33-39] *Do not eat or drink for 15-20 minutes after*	*Moderate*	*Strong*
		Add tacrolimus to mouthwash (equal parts tacrolimus: budesonide) if inadequate response with budesonide after 2-4 weeks[11,17,29,33,34,40]	*Low*	*Conditional*
		Dexamethasone 0.1 mg/mL solution – swish 10 mL for 5 minutes and spit, 2-4 times daily[11,17,29,33,34,40] *Do not eat or drink for 15-20 minutes after* ***Use if patient is unable to obtain budesonide.***	*Low*	*Conditional*
	Focal disease	Clobetasol 0.05% gel to lesions 2-4 times daily[11,17,33,34] *Hold gel to area with gauze for 10-15 minutes*	*Low*	*Strong*
	Lip involvement	Tacrolimus 0.1% ointment 2-4 times daily[11,17,33,34]	*Low*	*Strong*
	Salivary gland (xerostomia)	Pilocarpine 5 mg by mouth three times daily[11,33,34]	*Low*	*Strong*
		Cevimeline 30 mg by mouth three times daily[11,33,34] *If inadequate response to pilocarpine after 8-12 weeks*	*Low*	*Conditional*
Cutaneous	Entire body	Tacrolimus 0.1% ointment to the affected area two times daily[11,17,29]	*Low*	*Strong*
	Neck and below	Betamethasone dipropionate 0.05% ointment to the affected area two times daily[11,17,29]	*Low*	*Strong*
		Triamcinolone 0.5% cream to the affected area two times daily[11,17,29] *Though slightly less potent than betamethasone ointment, this is a reasonable alternative for patients unable to obtain or tolerate ointment*	*Very low*	*Conditional*
	Face	Hydrocortisone 1% ointment twice daily[11,17,29]	*Very low*	*Strong*

Table 4. Topical and Adjunct Medications for Chronic GVHD – Adults (continued)

System		Medication	Evidence Strength	Recommendation
Pulmonary	**Adjunctive therapy (FAM)**	Fluticasone 440 mcg inhaled twice daily[41-43] Azithromycin 250 mg by mouth every Mon, Wed, Fri [41-43] Montelukast 10 mg by mouth daily[41-43]	*Moderate*	*Strong*
Gastrointestinal		Budesonide 9 mg by mouth one time daily[17]	*Moderate*	*Strong*
		Beclomethasone 2 mg PO four times daily[44,45]	*Moderate*	*Strong*
Esophageal/upper GI		Budesonide 3 mg/10 mL water mouthwash – swish 10 mL for 5 minutes and SWALLOW, 2-4 times daily[11,17,29,33-39] *Do not eat or drink for 15-20 minutes after*	*Low*	*Conditional*
		Dexamethasone 0.1 mg/mL solution – swish 10 mL for 5 minutes and SWALLOW, 2-4 times daily[11,17,29,33,34,40] ***Use if patient is unable to obtain budesonide. Do not eat or drink for 15-20 minutes after*	*Low*	*Conditional*
Genitourinary	**General treatment**	Tacrolimus 0.1% ointment twice daily[11,17,29] *for vulva involvement*	*Low*	*Strong*
		Tacrolimus cream/suppository 0.1% (2 mg tacrolimus per 2 g suppository) *for vaginal involvement – monitor for systemic absorption*	*Low*	*Conditional*
		Betamethasone dipropionate 0.05% to the affected area twice daily[11,17,29] *Gel preferred for vaginal involvement; ointment preferred for vulvar involvement;*	*Low*	*Strong*
		Hydrocortisone 25 mg suppository intravaginally twice daily[11,17]	*Very low*	*Strong*
		Dilator therapy per specialist's direction	*Very low*	*Conditional*
	Estrogen deficiency	Topical estrogen (*if no contraindications) for vulva involvement*	*Low*	*Conditional*
		Intravaginal estrogen *(if no contraindication) for vaginal involvement*	*Low*	*Conditional*
Liver		Ursodiol 13-15 mg/kg/day in 2-4 divided doses[17]	*High*	*Strong*
Musculoskeletal		*No topical therapies available*[17]	*High*	*Strong*

Table 5. Treatment options for Steroid and Sirolimus Refractory Chronic GVHD – Adults

System	Drug	Evidence Strength	Recommendation
Treatment options are listed below to treat refractory disease in order from most recommended to least recommended. Refer to Tapering of cGVHD Systemic Therapies for Adults and Pediatrics for prednisone dosing.			
Any System	Extracorporeal photophoresis[1-7] *See Appendix G for schedule and treatment details*	*Moderate*	*Conditional*
	Ibrutinib 420 mg by mouth once daily* [46 46] Suggested dose adjustments for drug-drug interactions: • Moderate 3A4 inhibitor (Ex-isavuconazole, diltiazem): No modification • Voriconazole 200 mg twice daily: ibrutinib 280 mg daily • Posaconazole delayed release tabs, 300 mg daily: 140 mg daily • Other strong 3A4 inhibitors: avoid concomitant use	*Moderate*	*Conditional*
	Ruxolitinib 5-10 mg by mouth twice daily[47,48]	*Low*	*Conditional*
	Rituximab 375 mg/m2 IV weekly x 4 doses [18,24,49-54]	*Low*	*Conditional*
	Methotrexate 5-10mg/m2 by mouth weekly [18,24]	*Low*	*Conditional*
	Interleukin-2 (aldesleukin) 1x10^6 IU/m^2 subcutaneous daily *See* Interleukin-2 Therapy appendix for additional details	*Very low*	*Conditional*
	Calcineurin Inhibitors Tacrolimus 0.01-0.02 mg/kg by mouth twice daily (target 5-10 ng/mL) [17,18,24,55] Cyclosporine 1-2 mg/kg by mouth twice daily (target 120-200 ng/mL) [17,18,24,55]	*Very low*	*Conditional*
Treatments listed below are recommended for specific organ system and should be considered as 2nd/3rd line options for refractory cGVHD.			
Cutaneous	Imatinib 200 mg by mouth daily[18,24,51,56-59]	*Low*	*Conditional*
	Narrow band Ultraviolet-B therapy 3 times/week [14,60]	*Low*	*Conditional*
	Etanercept 25 mg subcutaneous 2 times weekly x 4 weeks, then 25 mg weekly x4 weeks[24,61,62]	*Low*	*Conditional*
	Hydroxychloroquine 200 mg by mouth twice daily[24,63]	*Low*	*Conditional*
	Infliximab 10 mg/kg IV weekly x4[18]	*Low*	*Conditional*
	PUVA [14,64] *While PUVA has been used to treat steroid-refractory cGVHD, an increased risk of squamous cell cancer is associated with its use [65]*	*Low*	*Conditional*
Gastrointestinal	Etanercept 25 mg subcutaneous 2 times weekly x 4 weeks, then 25 mg weekly x4 weeks[18,24,61,62]	*Low*	*Conditional*
	Imatinib 200 mg by mouth daily[18,24,51,56,57]	*Low*	*Conditional*
	Infliximab 10 mg/kg IV weekly x4[18]	*Low*	*Conditional*
Ocular	Imatinib 200 mg by mouth daily	*Low*	*Conditional*
Liver	(See above recommendations for systemic treatments for any system)		
Musculoskeletal	(see above recommendations for systemic treatments for any system)		
Oral	Hydroxychloroquine 200 mg by mouth twice daily[24,63]	*Low*	*Conditional*
Pulmonary	Etanercept 25 mg subcutaneous 2 times weekly x 4 weeks, then 25 mg weekly x4 weeks[24,61,62,66]	*Low*	*Conditional*
	Imatinib 200 mg by mouth daily[18,24,29,51,56,57,67]	*Low*	*Conditional*

Treatment for Chronic GVHD in Pediatrics

It is recommended that any patients with chronic GVHD be enrolled in a clinical trial for treatment, when possible. *(UW Health Low quality of evidence, C recommendation)* Clinical trials for GVHD may involve therapies that are steroid-sparing (e.g., mesenchymal stromal cells) or have a more favorable side effect profile than steroids [70]

Treatment of cGVHD in pediatrics is variable and most experience is extrapolated from adult data. Thus similar to adults, first-line treatment for chronic GVHD in children consists of topical agents (steroid, calcineurin inhibitors) for limited skin cGVHD.[5] **Table 6** suggests topical and adjunct medications that may be used while **Table 7** lists treatment options for steroid-refractory cGVHD.

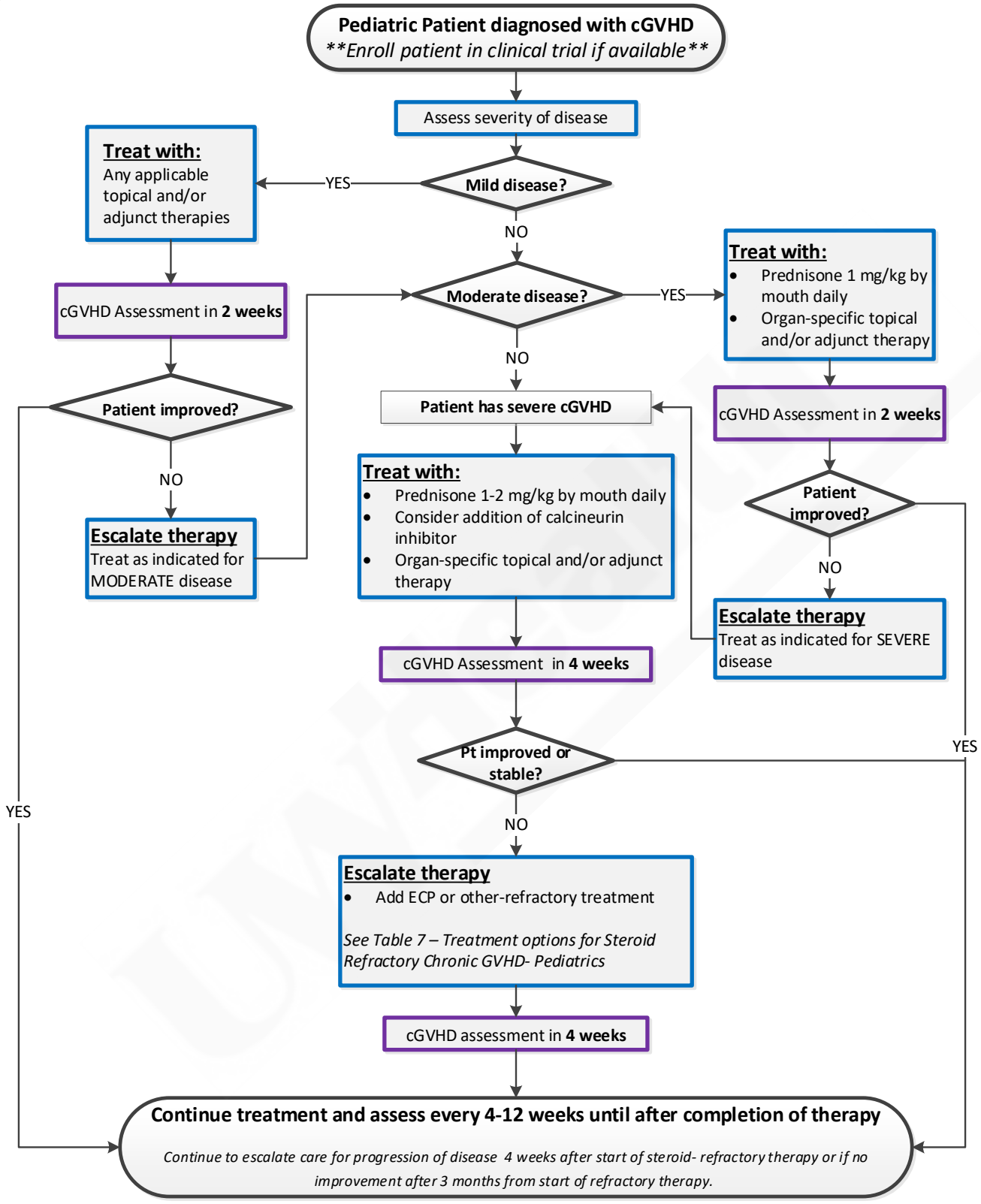
The systemic side effects of topical steroids and topical calcineurin inhibitors may occur more frequently in young children because of the larger skin surface area to body weight ratio.[11] The NIH 2014 Consensus Development Project on Criteria for Clinical Trials in CGVHD: Ancillary Therapy and Supportive Care Working Group Report recommends that the least potent topical steroids (1%-2.5% hydrocortisone) are safe, whereas middle to upper mid-strength topical steroids should generally be used sparingly, and on limited areas, for no more than 3-4 weeks.[11]

Topical steroids under occlusive dressings are not recommended.[11] In addition, the use of potent or super-potent steroids on the face, or at any site in infants < 1 year of age is not recommended.[11]

For more extensive skin cGVHD (>20% body surface area or sclerotic features) or cGVHD with visceral involvement, prednisone and cyclosporin A are most commonly used.[4,5] This combination therapy is based on an alternate day regimen that improved survival in high-risk patients with thrombocytopenia and extensive skin involvement. The general approach to treatment is immediate initiation of therapy, typically high-dose steroids (prednisone oral 1–2 mg/kg/day, equivalent to methylprednisolone IV 0.8-1.6 mg/kg/day) with calcineurin inhibitor, with steady weaning of steroid until the lowest allowable dose without cGVHD flare is achieved.[4] (Refer to Tapering of cGVHD Systemic Therapies for Adults and Pediatrics for steroid taper schedules.)

Figure 2 provides an overview of cGVHD treatment for pediatric patients.

Figure 2. Treatment of Chronic GVHD in Children



ECP = extracorporeal photopheresis (Extracorporeal Photopheresis Therapy)

Table 6. Topical and Adjunct Medications for Chronic GVHD - Pediatrics

System		Medication	Evidence Strength	Recommendation
Ocular	**General treatment**	Artificial tears PRN[11,17,29] *Ointment is more effective than solution for dry eyes but can lead to cloudy vision*	*Very low*	*Strong*
		Prednisolone acetate 1%, 1-2 drops in affected eye(s) four times daily with ophthalmology consult[11,17]	*Low*	*Strong*
		Cyclosporine 0.05% in affected eye(s) twice daily with ophthalmology consult [11,17 71]	*Low*	*Strong*
		Cyclosporine A0.09% in affected eye(s) twice daily with ophthalmology consult *(Adult dosing listed; may consider if inadequate response to other therapies)*	*Very Low*	*Conditional*
		Lifitegrast 5% ophthalmic solution in affected eye(s) twice daily with ophthalmology consult* *(Adult dosing listed; may consider if inadequate response to other therapies)*	*Very Low*	*Conditional*
		Antibiotic drops or ointment may be considered if infectious concerns[11,17,29]	*Low*	*Strong*
Oral	**Generalized disease**	Budesonide 3 mg/10 mL water mouthwash – swish 10 mL for 5 minutes and spit, 2-4 times daily[11,17,29,33-39] *Do not eat or drink for 15-20 minutes after*	*Moderate*	*Strong*
		Add tacrolimus to mouthwash (equal parts tacrolimus: budesonide) if inadequate response with budesonide after 2-4 weeks[11,17,29,33,34,40]	*Low*	*Conditional*
		Dexamethasone 0.1 mg/mL solution – swish 10 mL for 5 minutes and spit, 2-4 times daily[11,17,29,33,34,40] *Use of patient is unable to obtain budesonide*	*Low*	*Conditional*
	Focal disease	Clobetasol 0.05% gel to lesions 2-4 times daily[11,17,33,34] *Hold gel to area with gauze for 10-15 minutes*	*Low*	*Strong*
	Lip involvement	Tacrolimus 0.1% ointment 2-4 times daily[11,17,33,34 72] *Tacrolimus 0.03% may also be considered if 0.1% strength cannot be obtained or tolerated*	*Low*	*Strong*
	Salivary gland (xerostomia)	Pilocarpine 5 mg by mouth three times daily[11,33,34 73 74]	*Low*	*Conditional*
		Cevimeline 30 mg by mouth three times daily[11,33,34] * *(Adult dosing listed; may consider if inadequate response to pilocarpine)*	*Very Low*	*Conditional*
Cutaneous	**Entire body**	Tacrolimus 0.1% ointment to the affected area two times daily[11,17,29] *For duration greater than two weeks* *Tacrolimus 0.03% may also be considered if 0.1% strength cannot be obtained or tolerated*	*Low*	*Strong*
	Neck and below	Betamethasone dipropionate 0.05% ointment to the affected area two times daily[11,17,29] *Use is not recommended for longer than two weeks*	*Low*	*Strong*
		Triamcinolone 0.5% cream to the affected area two times daily[11,17,29] *Use is not recommended for longer than two weeks* *Though slightly less potent than betamethasone ointment, this is a reasonable alternative for patients unable to obtain or tolerate ointment*	*Very low*	*Conditional*
	Face	Hydrocortisone 1% ointment twice daily[11,17,29]	*Very low*	*Strong*
Pulmonary	**Adjunctive therapy (FAM)**	Fluticasone 220 mcg inhaled twice daily (age 6-11) Fluticasone 440 mcg inhaled twice daily (age 12-18) Azithromycin 5 mg/kg (max 250 mg/day) by mouth 3 times a week Montelukast 5 mg by mouth daily (age 6-13) Montelukast 10 mg by mouth daily[8,43] (age 14-18)	*Moderate*	*Strong*
Gastrointestinal		Budesonide 9 mg by mouth one time daily[1775,76]	*Moderate*	*Strong*
		Beclomethasone 2 mg PO four times daily[44,45]	*Low*	*Conditional*

Table 6. Topical and Adjunct Medications for Chronic GVHD - Pediatrics

System	Medication	Evidence Strength	Recommendation
Esophageal	Budesonide 3 mg/10 mL water mouthwash – swish 10 mL for 5 minutes and SWALLOW, 2-4 times daily[11,17,29,33-39] *Do not eat or drink for 15-20 minutes after*		
	Dexamethasone 0.1 mg/mL solution – swish 10 mL for 5 minutes and SWALLOW, 2-4 times daily[11,17,29,33,34,40] *Use of patient is unable to obtain budesonide. Do not eat or drink for 15-20 minutes after*		
Genitourinary	Tacrolimus 0.1% ointment twice daily[11,17,29] *For duration greater than two weeks*	*Low*	*Strong*
	Betamethasone dipropionate 0.05% to the affected area twice daily[11,17,29] *Gel preferred for vaginal involvement; ointment preferred for vulvar involvement;*	*Low*	*Strong*
	Hydrocortisone 25 mg suppository intravaginally twice daily[11,17]	*Very low*	*Strong*
Liver	Ursodiol 10-30 mg/kg/day in two divided doses[77-79]	*High*	*Strong*
Musculoskeletal	*No topical therapies available*[17]	*High*	*Strong*

Table 7. Treatment options for Steroid Refractory Chronic GVHD – Pediatrics

System	Drug	Evidence Strength	UW Recommendation
Treatment options are listed below to treat refractory disease. Treatment preferences are often based on individual patients' situation and fewer pediatric specific data for chronic GVHD exist. Refer to Tapering of cGVHD Systemic Therapies for Adults and Pediatrics for prednisone dosing.			
Any System	Extracorporeal photophoresis[80] *See Appendix G for schedule and treatment details*	*Low*	*Conditional*
	Calcineurin Inhibitors [77,80] • Tacrolimus 0.01-0.02 mg/kg by mouth twice daily (target 5-10 ng/mL • Cyclosporine 1-2 mg/kg by mouth twice daily (target 120-200 ng/mL)	*Low*	*Conditional*
	Interleukin-2 (aldesleukin) $1x10^6$ IU/m^2 subcutaneous daily x 8 weeks. May be continued if tolerated[55,56,81] *See* Interleukin-2 Therapy	*Low*	*Conditional*
	Weight ≥ 25 kg: Ruxolitinib 5 mg PO twice daily [82,83] Weight < 25 kg: Ruxolitinib 2.5 mg PO twice daily [82,83]	*Low*	*Conditional*
	Pentostatin 4 mg/m^2 every 2 weeks[84,85]	*Low*	*Conditional*
	Mycophenolate mofetil 15-40 mg/kg/day [18,24,80,86,87]	*Low*	*Conditional*
Treatments listed below are recommended for specific organ system and should be considered as 2nd/3rd line options for refractory cGVHD.			
Cutaneous	Imatinib 200-260 mg/m^2 daily[88]	*Low*	*Conditional*
	Phototherapy (e.g., narrow band UV-B, PUVA, etc.)	*Low*	*Conditional*
	Etanercept 0.4 mg/kg (max 25 mg) subQ twice weekly subcutaneous 2 times weekly x 4 weeks [89-91]	*Low*	*Conditional*
	Hydroxychloroquine 6 mg/kg/day by mouth twice daily[24,65] (max dose 200 mg twice daily)	*Low*	*Conditional*
	Infliximab 10 mg/kg IV weekly x4[18,92]	*Low*	*Conditional*
Gastrointestinal	Etanercept 0.4 mg/kg (max 25 mg) subQ twice weekly subcutaneous 2 times weekly x 4 weeks [90]	*Low*	*Conditional*
	Imatinib 200 mg by mouth daily[18,24,51,58,59]	*Low*	*Conditional*
	Infliximab 10 mg/kg IV weekly x4[18,92]	*Low*	*Conditional*
Ocular	Imatinib 200 mg by mouth daily[18,58,59]	*Very Low*	*Conditional*
Liver	(see above recommendations for systemic treatments for any system)		
Musculoskeletal	(see above recommendations for systemic treatments for any system)		
Oral	Hydroxychloroquine 6 mg/kg/day by mouth twice daily[24,65] (max dose of 200 mg twice daily)	*Low*	*Conditional*
	Methotrexate 5-10 mg/m2 by mouth weekly[18,24]	*Low*	*Conditional*
Pulmonary	Imatinib 200 mg by mouth daily[18,24,29,51,58,59,69]	*Low*	*Conditional*
	Etanercept 0.4 mg/kg (max 25 mg) subQ twice weekly subcutaneous 2 times weekly x 4 weeks	*Low*	*Conditional*

Alternate Pediatric Treatment Options for Chronic GVHD

Systemic treatment for chronic GVHD involves steroids and/or other immunosuppressive agents such as calcineurin inhibitors, which pose a significant risk for infectious morbidity and mortality. The long-term use of these drugs can be especially determinantal in pediatric patients and cause growth retardation, delayed puberty, and chronic organ dysfunction. Thus, it is important to consider when appropriate treatment modalities without such adverse consequences.

The skin is the most commonly affected organ in GVHD. When there is an extensive body surface area involved and ointments may not be feasible, risk of infection from systemic steroids is too high or the disease is already steroid-refractory, phototherapy (i.e., PUVA or extracorporeal photopheresis) may be considered.[14,66] *(UW Health Moderate quality of evidence, C recommendation)* Phototherapy may be used as monotherapy or as adjuvant treatment.

Tapering of cGVHD Systemic Therapies for Adults and Pediatrics

- **Non-Steroid Immunosuppresants**[93] *(UW Health Low quality evidence, C recommendation)*
  - Taper following initial treatment may begin after a period of stability (at least 1-3 months). For patients who have a first flare, consider taper after at least 6-12 months. For patients who have had more than one flare, consider long-term therapy.

- **Prednisone**[7] *(UW Health Low quality evidence, C recommendation)*

Table 8: Recommended Prednisone Taper – if starting at 2 mg/kg/day

If starting at prednisone 2 mg/kg/day		
Day (starting at initiation of prednisone)	AM prednisone dose	PM prednisone dose
1	1 mg/kg	1 mg/kg
6	1 mg/kg	0.8 mg/kg
8	1 mg/kg	0.6 mg/kg
10	1 mg/kg	0.4 mg/kg
12	1 mg/kg	0.2 mg/kg
Week 2 (day 14)	1 mg/kg	STOP PM doses
Week 3	(hold 1 week on 1 mg/kg)	
Week 4 (day 22)	0.9 mg/kg/daily	
Week 5 (day 29)	0.8 mg/kg/daily	
Week 6 (day 36)	0.7 mg/kg/daily	
Week 7 (day 43)	0.6 mg/kg/daily	
Week 8 (day 50)	1 mg/kg every other day	
Continue this dose for about 12 weeks until all reversible manifestations resolve before proceeding with taper. If cGVHD is not resolving, see **Table 5** (adults) or **Table 7** (pediatrics) for steroid refractory treatment options		
Week 20 (day 1)	0.9 mg/kg every other day	
Week 21 (day 8)	0.8 mg/kg every other day	
Week 22 (day 15)	0.7 mg/kg every other day	
Week 23 (day 22)	0.6 mg/kg every other day	
Week 24 (day 29)	0.5 mg/kg every other day	
Consider observing for 2 months prior to tapering completely off prednisone		
Week 32 (day 85)	0.4 mg/kg every other day	
Week 33 (day 93)	0.3 mg/kg every other day	
Week 34 (day 100)	0.2 mg/kg every other day	
Week 35 (day 107)	0.1 mg/kg every other day	
Week 36 (day 114)	**STOP**	

Table 9. Recommended Prednisone Taper – if starting at 1mg/kg/day

If starting at prednisone 1 mg/kg/day	
Day (starting at initiation of prednisone)	AM prednisone dose
Week 1-2	1 mg/kg daily
Week 3	0.9 mg/kg/daily
Week 4 (day 22)	0.8 mg/kg/daily
Week 5 (day 29)	0.7 mg/kg/daily
Week 6 (day 36)	0.6 mg/kg/daily
Week 7 (day 43)	1 mg/kg every other day
Continue this dose for about 12 weeks until all reversible manifestations resolve before proceeding with taper. If cGVHD is not resolving, see **Table 5** (adults) or **Table 7** (pediatrics) for steroid refractory treatment options	
Week 19	0.9 mg/kg every other day
Week 20	0.8 mg/kg every other day
Week 21	0.7 mg/kg every other day
Week 22	0.6 mg/kg every other day
Week 23	0.5 mg/kg every other day
Consider observing for 2 months prior to tapering completely off prednisone	
Week 31	0.4 mg/kg every other day
Week 32	0.3 mg/kg every other day
Week 33	0.2 mg/kg every other day
Week 34	0.1 mg/kg every other day
Week 35	**STOP**

Treatment Response Assessment for Adults and Pediatrics

It is recommended to assess response at approximately 4 weeks after systemic, non-steroidal treatment is initiated and then at 8 weeks after treatment is initiated. Further assessment frequency depends on response and complexity of medication regimen and should continue every 4 to 12 weeks until after end of therapy.[94] *(UW Health Very Low quality evidence, C recommendation)* (See Figure 1 for adults and Figure 2 for pediatrics)

Once chronic GVHD stability is achieved, monitoring may be extended to 3-6 months. *(UW Health Very Low quality evidence, C recommendation)*

How to assess response to cGVHD

The Chronic GVHD Response Assessment Form contains an Activity Assessment form to help physicians evaluate response assessment for their patients with cGVHD. This form is also available as a flowsheet in HealthLink.

How to score response assessment

To assess response, disease manifestations at 2 predefined time points must be compared, and a judgment must be made as to whether the magnitude of any change qualifies as improvement or deterioration. This magnitude of change should reflect genuine clinical change, and the criteria should be clarified and standardized as much as possible to avoid measurement error. The NIH Working Group proposes the following consensus definitions for assessment of overall response and for measurable organ response (Table 9).[94]

Table 10. Response Determination for Chronic GVHD[94]

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS Score 0 after previous involvement	Decrease in Modified OMRS of 2 more points	Increase in Modified OMRS of 2 more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except 0 to 1
Liver	Normal ALGT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 x ULN
Lungs	• Normal %FEV1 after previous involvement • If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	• Increase by 10% predicted absolute value of %FEV1 • If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	• Decrease by 10% predicted absolute value of %FEV1 • If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previously involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joints and Fascia Score by 1 or more or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinical overall severity score decreased by 2 or more points on a 0-10 scale	Clinical overall severity score increases by 2 or more points on a 0-10 scale

Quality of Life/Patient Reported Outcomes Measurement

Lee and colleagues developed a symptom scale designed for individuals with cGVHD.[95] The questionnaire asks patients to indicate the degree of "bother" that they experienced during the past 4 weeks due to symptoms in 7 domains potentially affected by cGVHD (skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, emotional distress). Published evidence supports its validity, reliability, and sensitivity to cGVHD severity.[16,96-100]

Consider utilizing the Lee Symptom Scale to further assess the patient's disease burden and distress when conducting formal cGVHD assessment.[94] *(UW Health Low quality evidence, C recommendation)*

How to monitor patient reported cGVHD symptoms

The Lee Symptom Scale can be completed in approximately 5 minutes. The reporting time frame may be decreased to 1 week to specifically capture more recent symptoms.[94]

How to score Lee Symptom Scale

See the Scoring Algorithm for Lee cGVHD Symptom Scale.

Drug-Related Supportive Care for Chronic GVHD

Acid Suppression

- Patients receiving long-term prednisone at doses greater than or equal to 20 mg daily should receive stress ulcer prophylaxis.[11] *(UW Health Very low quality evidence, C recommendation)*
- Initial therapy should begin with famotidine 2 times daily or equivalent histamine-2 receptor antagonist (H2RA).[101] *(UW Health Low quality evidence, C recommendation).*
- If H2RA therapy fails, pantoprazole 40 mg by mouth one time daily or equivalent proton pump inhibitor (PPI) should be used. *(UW Health Very low quality evidence, C recommendation).*

Bone Health/Prevention of Glucocorticoid-Induced Osteoporosis

Long-term and high dose steroid use can cause bone loss and increased risk of fractures. The highest rate of bone loss occurs within the first 3-6 months of glucocorticoid (GC) treatment.[102] Table 10 lists fracture risk categories for glucocorticoid-treated patients in adults. It is recommended that for all adults and children, an initial clinical fracture risk assessment should be performed as soon as possible, but at least within 6 months of initiation of long-term steroid treatment. [102]*(UW Health Moderate quality evidence, S recommendation)* Specific assessment recommendations include:

- Post-menopausal women and men greater than 50 years old should undergo a DEXA scan within the first month of treatment.[103,104] *(UW Health Moderate quality evidence, strong recommendation)*
- Pre-menopausal women and men less than 50 years old who are expected to be on prednisone for more than three months should be evaluated with a DEXA scan.[103] *(UW Health Low quality evidence, strong recommendation)*

Table 11. Fracture risk categories in GC-treated patients - Adult [102]

Risk Level	Adults ≥ 40 years of age	Adults < 40 years of age
High fracture risk	• Prior osteoporotic fracture(s) • Hip or spine bone mineral density • T score ≤ -2.5 in men age ≥ 50 years and postmenopausal women • FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ ≥ 0% • FRAX* (GC-adjusted†) 10-year risk of hip fracture≥ 3%	Prior osteoporotic fracture(s)
Moderate fracture risk	• FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ 10–19% • FRAX* (GC-adjusted†) 10-year risk of hip fracture >1% and <3%	• Hip or spine bone mineral density Z score <-3 • Rapid bone loss (≥ 10% at the hip or spine over 1 year) ***and*** *c*ontinuing GC treatment at ≥7.5 mg/day for ≥ 6 months
Low fracture risk	• FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ < 10% • FRAX* (GC-adjusted†) 10-year risk of hip fracture ≤ 1%	None of above risk factors other than GC treatment

*FRAX tool available online at https://www.shef.ac.uk/FRAX/tool.jsp
†Increase the risk generated with FRAX by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if glucocorticoid (GC(treatment is > 7.5 mg/day (e.g., if hip fracture risk is 2%, increase to 2.4%)
‡Major osteoporotic fracture includes fractures of the spine (clinical), hip, wrist or humerus

In patients with cGVHD, a baseline calcium (total and ionized) and vitamin D level should be obtained in patients on systemic steroid therapy.[11,29] *(UW Health Low quality evidence, S recommendation)*

Supplementation of calcium and vitamin D. Supplementation is recommended unless a patient has elevated serum calcium or vitamin D levels.[102] *(UW Health Very low quality evidence, S recommendation)* For calcium and vitamin supplementation recommendations, refer to Vitamin/Minerals section under Nutrition.

Treatment with bisphosphonates may be appropriate in adult patients with moderate or high-risk of major fracture due to steroid therapy and pediatric patients with history of osteoporotic fracture who are continuing steroid treatment to prevent GC-induced osteoporosis is recommended by the American College of Rhematology.[102]

For adults:
Consider referral to the Osteoporosis clinic if concern for GC-induced osteoporosis. *(UW Health Very low quality evidence, C recommendation)*

For Pediatrics:
Consider referral to Pediatric Endocrinology if concern for GC-induced osteoporosis. *(UW Health Very low quality evidence, C recommendation)*

Anti-infective Prophylaxis for Adult and Pediatrics
Patients on chronic immune suppression/being treated for cGVHD are at high risk for viral and fungal disease. Anti-infective prophylaxis is important for preventing morbidity. For anti-infective prophylaxis recommendations, refer to the UW Health Antimicrobial Prophylaxis in Hematopoietic Stem Cell Transplant Recipients – Adult/Pediatric - Inpatient/Ambulatory

Immunizations
See UW Health Bone Marrow Transplant Standard Operating Procedure (SOP) F2.200 Immunizations Post Hematopoietic Stem Cell Transplant for additional information

- Live vaccines [e.g., measles, mumps, rubella, intranasal influenza, herpes zoster (shingles), etc.] should be delayed until resolution of cGVHD and discontinuation of all immunosuppressive therapies.[11,105,106] *(UW Health Very low quality evidence, S recommendation)* Other vaccines may be administered without delay.[29,105-107] *(UW Health Very low quality evidence, S recommendation)*
- Patients should receive the inactivated influenza vaccine annually.[11,29,105,106] *(UW Health High quality evidence, S recommendation)*
- It may be beneficial to assess antibody levels before and after vaccination to determine if there is a need for booster immunizations.[105,106] *(UW Health Very low quality evidence, C recommendation)*
    - Pre-vaccination testing for: measles, mumps, rubella and varicella at the time patients are due for the vaccines. The recommended time is 2 years after transplant. If positive, then no vaccine is given.[108] *(UW Health Very low quality evidence, C recommendation)*
    - Post vaccination testing for: HBV, measles, tetanus, diphtheria, polio and pneumococcus. The recommended time varies from 2 to 4 years after transplant. It is also recommended that titers be checked every 4 years or so for those on chronic immune suppression.[108] *(UW Health Very low quality evidence, C recommendation)*
- It may be beneficial to assess antibody levels before and after vaccination to determine if there is a need for booster immunizations.[105,106] *(UW Health Very low quality evidence, conditional*
    - It may be beneficial to administer Pneumococcal Conjugate Vaccine, 13-Valent (PCV-13) rather than Pneumococcal Polysaccharide Vaccine, 23-Valent (PPSV-23) for the fourth dose in patients with cGVHD.[105,106] *(UW Health Very low quality evidence, C recommendation)*

Hypogammaglobulinemia
- Intravenous Immune Globulin (IVIG) may be considered for patients who have recurrent sinopulmonary infections and serum IgG levels less than 400 mg/dL more than 90 days after transplant[11,107] *(UW Health Moderate quality evidence, S recommendation)* Use of IVIG should be re-evaluated after 180 days of treatment. (*UW Health Very low quality evidence, C recommendation)* For additional information, refer to the UW Health Intravenous Immune Globulin- Adult/Pediatric clinical practice guideline.

Supportive Care for Chronic GVHD

Nutrition

Patients with GVHD are at risk for significant weight loss and malnutrition.[109,110] Nutrition-related side effects of GVHD that may contribute to poor nutrition include: protein-losing enteropathy, malabsorption, pancreatic atrophy, and exocrine pancreatic insufficiency.[109] The common treatment for GVHD, glucocorticoids, may lead to poor nutrition outcomes including hyperglycemia, steroid-induced diabetes, loss of lean body mass, and poor bone health.[111] To prevent or resolve malnutrition, patients with GVHD often require modified diets, oral nutrition supplements and/or nutrition support.[112]

Nutrition Assessment

It is recommended to order a nutrition consult (inpatient) or schedule a nutrition appointment for patients (outpatient) with GVHD 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
- *For Pediatrics:* Patient's weight-for-age, BMI, or weight-for-length declining across $\geq$ 2 growth channels
- *For Pediatrics:* Patient with BMI or weight-for-length below the 5th percentile for age

To schedule an outpatient nutrition appointment:

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.

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.

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.[113-115] *(UW Health Low quality evidence, C recommendation)* Suggested dosing for megestrol and mirtazapine is:

- Megestrol acetate 400 mg by mouth twice daily.[116-122]
- Mirtazapine 15 mg by mouth daily at bedtime.[117,123,124]

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)* Cyprohepatadine 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, insomnia, or depression, are present. Suggested dosing for cyproheptadine is as follows:

- For patients ≥ 2 years: cyproheptadine 0.25 mg/kg/day divided twice daily[125]

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.[110] *(UW Health Low quality of 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.[112] *(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 Standard of Practice for Pediatric Hematopoietic Stem Cell Transplant Policy Number E2.600 and the UW Health Adult Enteral Nutrition Support Handbook- Guidelines for Tube Feeding.

Parenteral Nutrition (PN)

For Adults:
It is recommended to consider parenteral nutrition for patients with poor oral intake and significant malabsorption.[112,126-128] *(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.[112]
- Patients with diarrhea ≥ 500 mL/day[126,128](i.e., ≥ Stage 1 Lower GI GVHD)
- Patients who exhibit signs of nutritional depletion without indication of improvement within 7 days.[126]
- Severe malnutrition on admission[127]
- Patients unable to tolerate oral diet or fail to meet 60-70% of nutrition requirements over 3 days[127]

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 GVHD 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.[126] *(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. [112] *(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.[109] 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 with 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.[103] 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.[129] *(UW Health Very low quality of evidence, C recommendation.)*

For Pediatrics:
Pediatric patients with GVHD 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[130] 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[131,132] 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.[133]

- 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 a 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 a 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.[134]

The National Comprehensive Cancer Network (NCCN) estimates that less than 10% of cancer patients receive adequate psycho-oncological support.[135] Thus it is recommended providers be cognizant of their HSCT patients' distress levels and to consider the following:

1. Patients with a new cGVHD diagnosis that will require systemic therapy 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.[136,137] 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 GVHD, 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 GVHD 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.[11,138,139] *(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.[140] *(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.[138,140,141] Patient should be careful in the setting of water and sand, which can reflect UV rays[140] and sun exposure cautions should also be followed during the cold weather season as well since snow can also reflect sunlight[138] and during long car rides and while sitting under an umbrella.[138]

Physical Fitness Rehabilitation for Chronic GVHD

Due to the impact of cGVHD on musculoskeletal and lung organ systems, physical therapy, occupational therapy and pulmonary rehabilitation are potential ancillary therapy options for patients.

The benefit of exercise for GVHD 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.[138,139,142] 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.[143]*(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 GVHD 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.

Patients with BOS may benefit from pulmonary rehabilitation.[11,144,145] *(UW Health Low quality evidence, C recommendation)* Pulmonary rehabilitation has been shown to improve 6-minute walk distance, subjective symptoms of dyspnea, and exercise tolerance in patients with BOS.[144]

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

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.

Methodology

Development Process

Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:

The following criteria were used by the guideline author(s) and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:

- Electronic database search (e.g., PubMed)

Time Period: October 2018 to January 2019

The following is a list of various search terms that were used individually or in combination with each other for literature searches on PubMed: chronic, graft versus host, FAM, ocular, cutaneous, phototherapy, ECP, PUVA.

Methods to Select the Evidence:

Literary sources were selected with the following criteria in thought: English language, subject ag, publication in a MEDLINE core clinical journal and strength of expert opinion (e.g., international or national guideline).

Methods Used to Formulate the Recommendations:

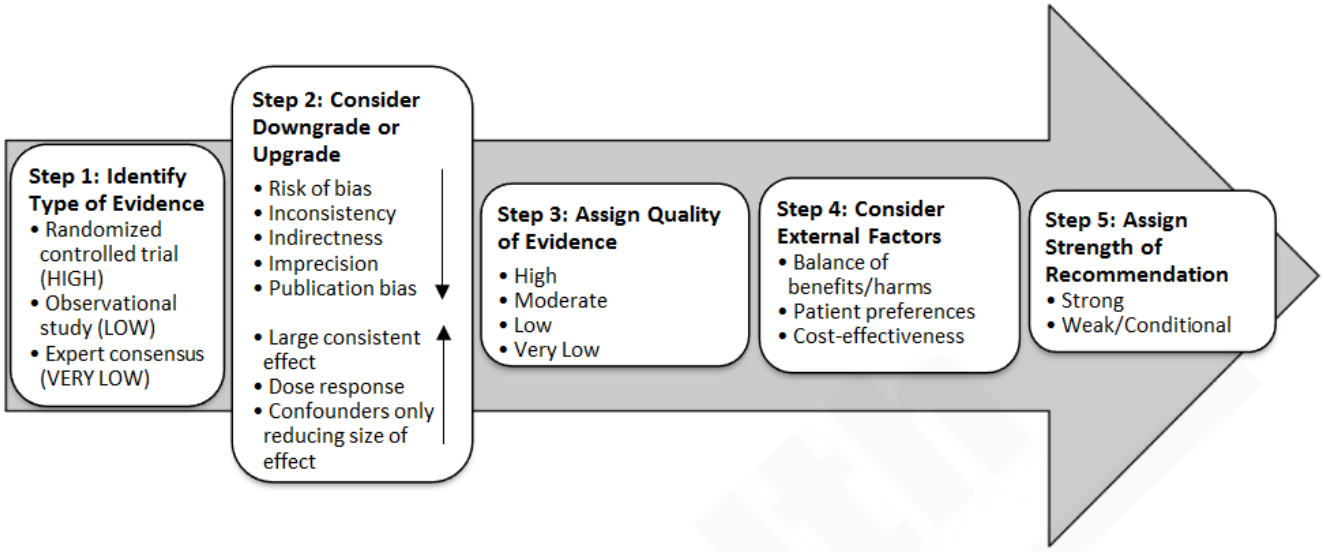
The workgroup members agreed to adopt recommendations developed by external organizations and/or created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:

Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1**).

Figure 1. GRADE Methodology adapted by UW Health



GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	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.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong (S)	Generally should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.)
Conditional (C)	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.)

Recognition of Potential Health Care Disparities:
Hispanics have been shown to be 53% less likely to report severe/life threatening/disabling conditions after *hematopoietic stem cell transplant (HCT)* than non-Hispanic whites. Chronic GVHD was significantly associated with severe/life threatening conditions.[146]

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

- % of patients with cGVHD who have a stage determined.
- % of patients with a given stage who have a response assessment.
- % of patients with patient reported outcome assessment (Lee symptom scale).
- % of patients screened for cGVHD
- % of patients with positive screen that were assessed for cGVHD diagnosis/staging

Beacon Protocols

CSC SC Immunizations Post Hematopoetic Stem Cell Transplant [1961]
CSC SC BMT Aldesleukin (Interleukin-2) [5271]
CSC SC Etanercept for GVHD [5772]

Order Sets & Smart Sets

OP – Day 100 Allogeneic Transplant Follow Up – Adult – Clinic Visit [5213]
OP – Day 180 Allogeneic Transplant Follow Up – Adult – Clinic Visit [5214]
OP – Day 270 Allogeneic Transplant Follow Up – Adult – Clinic Visit [5222]
OP – Year 1 Allogeneic Transplant Follow Up – Adult – Clinic Visit [5223]

Patient Resources

Health Facts For You: 415 – Graft Versus Host Disease Diet Recommendations
Healthwise: Graft Versus Host Disease
Lexicomp- Graft Versus Host Disease
BMT Patient Education Binder

Policies

UWHC Clinical, Department Specific: Nursing Patient Care 1.05A, Photopheresis (Adult)

Protocols

Post-Hematopoietic Stem Cell Transplant (HSCT) Immunosuppressive Therapy – Adult – Ambulatory - Oncology Clinic [125]

Appendix A. Chronic GVHD Screening Form

Check the symptoms you have had in the last week.

Does your skin:
- □ Feel tight or hard?
- □ Have increased dryness?
- □ Feel very itchy?
- □ Have new rashes or changes in the color of your skin?

□ Are you unable to sweat or unable to keep your body warm?
□ Do you have recent loss of hair (scalp or body)?
□ Do you have nail changes?

□ Do you have stiffness or pain in the wrists, fingers or other joints?

Are your eyes:
- □ Dry?
- □ Sensitive to wind or air conditioning?
- □ Painful or gritty?

Is your mouth:
- □ Dry?
- □ Sensitive to hot/cold or strong flavors?

□ Do you have mouth ulcers or sores?
□ Do you have taste changes?
□ Do foods or pills get stuck upon swallowing?

Are you short of breath:
- □ At rest?
- □ With activity?

□ Do you have a cough or wheeze?

□ Any unexplained weight loss or inability to gain weight?

Females:
- □ Do you have discomfort or pain with sexual intercourse?
- □ Do you have vaginal dryness or itching?

Males:
- □ Do you have burning or difficulty with urination?
- □ Do you have genital pain?

□ I have none of the above symptoms

Overall, since the last visit, are you feeling:
- □ Better?
- □ Worse?
- □ The same?

Appendix B. Chronic GVHD Diagnosis and Staging Form

Organ Specific Severity Scoring

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				

Organ Scoring of Chronic GVHD: *ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit.* ***Weight loss within 3 months.** *†Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. ‡To be completed by specialist or trained medical providers (see Supplement Figure – Genital Tract Scoring Form).* ***Lung scoring should be performed using both the symptoms

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS** **Symptom score**:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **%** FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Organ Scoring of Chronic GVHD: *ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit.*Weight loss within 3 months. †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. ‡To be completed by specialist or trained medical providers (see Supplement Figure – Genital Tract Scoring Form). **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.*

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)

☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____

GENITAL TRACT (*See Supplemental figure*†) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms

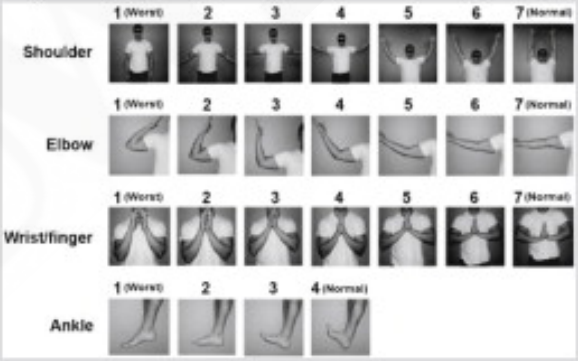
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

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

Photographic Range of Motion (P-ROM)



Organ Scoring of Chronic GVHD: *ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit.*Weight loss within 3 months. †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. ‡To be completed by specialist or trained medical providers (see Supplement Figure – Genital Tract Scoring Form). **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.*

Appendix C. Chronic GVHD Genital Tract Scoring Form

Supplement Figure – Genital Tract Chronic Graft-versus-Host Assessment and Scoring Form				
Name:_____ Date of birth: _____Assessment date: _____				
	SCORE 0	**SCORE 1**	**SCORE 2**	**SCORE 3**
GENITAL TRACT ***Check:*** Male Female	No signs	Mild signs and females may have symptoms* WITH discomfort on exam	Moderate signs and may have symptoms* with discomfort on exam	Severe signs with or without symptoms *
Currently sexually active: Yes No ***Check all signs that apply:*** Lichen planus-like features Lichen sclerosis-like features Vaginal scarring (female) Clitoral/labial agglutination (female) Labial resorption (female)			Erosions Fissures Ulcers Phimosis (male) Urethral meatus scarring/ stenosis (male)	
Abnormality present but NOT thought to represent GVHD (specify cause):_____ *Abnormality thought to represent GVHD PLUS other causes (specify cause):_____*				
****Genital symptoms are not specific to cGVHD and can represent premature gonadal failure or genital tract infection*.				

Appendix D. Chronic GVHD Response Assessment Form

FORM A

Current Patient Weight: _____ Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Health Care Provider Global Ratings: 0=none 1= mild 2=moderate 3=severe	**Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:** 0 1 2 3 4 5 6 7 8 9 10 **cGvHD symptoms not at all severe** — **Most severe cGvHD symptoms possible**	**Over the <<time>> would you say that this patient's cGvHD is** +3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse

Mouth	**Erythema**	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
	Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
	Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
								Total score for all mucosal changes	

Gastrointestinal-Esophageal • Dysphagia OR Odynophagia	*0= no esophageal symptoms* *1=Occasional dysphagia or odynophagia with solid food or pills during the past week* *2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week* *3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week*
Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR • Nausea & Vomiting	*0= no symptoms* *1=mild, occasional symptoms, with little reduction in oral intake during the past week* *2=moderate, intermittent symptoms, with some reduction in oral intake during the past week* *3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week*
Gastrointestinal-Lower GI • Diarrhea	*0= no loose or liquid stools during the past week* *1= occasional loose or liquid stools, on some days during the past week* *2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion* *3=voluminous diarrhea on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion*

Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)		TLC	RV
Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: ❑ 2 min ❑ 6 min		Karnofsky or Lansky	Platelet Count K/uL	Total WBC K/uL	Eosinophils %

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash / erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____ How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe … Most severe symptoms possible				
EYES	☐ No symptoms symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
LUNGS	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	☐ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	☐ Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

Shoulder

❑ Not done

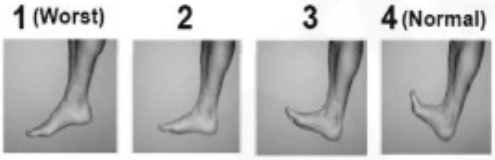
Elbow

❑ Not done

Wrist/finger

❑ Not done

Ankle



❑ Not done

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

Appendix E.

Lee cGVHD Symptom Scale

Please let us know if you have been bothered by any of the following problems in the past month.

	Not at all	Slightly	Moderately	Quite a bit	Extremely
SKIN:					
a. Abnormal skin color	0	1	2	3	4
b. Rashes	0	1	2	3	4
c. Thickened skin	0	1	2	3	4
d. Sores on skin	0	1	2	3	4
e. Itchy skin	0	1	2	3	4
EYES AND MOUTH:					
f. Dry eyes	0	1	2	3	4
g. Need to use eyedrops frequently	0	1	2	3	4
h. Difficulty seeing clearly	0	1	2	3	4
i. Need to avoid certain foods due to mouth pain	0	1	2	3	4
j. Ulcers in mouth	0	1	2	3	4
k. Receiving nutrition from an intravenous line or feeding tube	0	1	2	3	4
BREATHING:					
l. Frequent cough	0	1	2	3	4
m. Colored sputum	0	1	2	3	4
n. Shortness of breath with exercise	0	1	2	3	4
o. Shortness of breath at rest	0	1	2	3	4
p. Need to use oxygen	0	1	2	3	4
EATING AND DIGESTION:					
q. Difficulty swallowing solid foods	0	1	2	3	4
r. Difficulty swallowing liquids	0	1	2	3	4
s. Vomiting	0	1	2	3	4
t. Weight loss	0	1	2	3	4
MUSCLES AND JOINTS:					
u. Joint and muscle aches	0	1	2	3	4
v. Limited joint movement	0	1	2	3	4
w. Muscle cramps	0	1	2	3	4
x. Weak muscles	0	1	2	3	4
ENERGY:					
y. Loss of energy	0	1	2	3	4
z. Need to sleep more/take naps	0	1	2	3	4
aa. Fevers	0	1	2	3	4
MENTAL AND EMOTIONAL:					
bb. Depression	0	1	2	3	4
cc. Anxiety	0	1	2	3	4
dd. Difficulty sleeping	0	1	2	3	4

Appendix F. Scoring Algorithm for Lee cGVHD Symptom Scale

The Lee Chronic GVHD Symptom Scale is a 30 item instrument with 7 subscales (skin, eyes, mouth, lung, nutrition, energy and psych) containing 2-7 items. Response options for "let us know if you have been bothered by any of the following in the past month" range from 0-4 (Not at all, Slightly, Moderately, Quite a bit, Extremely). Some investigators have used the scale in reference to the past 7 days. (Lee SJ, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2002; 8:444-452)

Subscale name	Number of items	Items
Skin	5	a. Abnormal skin color b. Rashes c. Thickened skin d. Sores on skin e. Itchy skin
Eye	3	f. Dry eyes g. Need to use eyedrops frequently h. Difficulty seeing clearly
Mouth	2	i. Need to avoid certain foods due to mouth pain j. Ulcers in mouth
Lung	5	l. Frequent cough m. Colored sputum o. Shortness of breath at rest p. Need to use oxygen **aa. Fevers**
Nutrition	5	**k. Receiving nutrition from an intravenous line or feeding tube** q. Difficulty swallowing solid foods r. Difficulty swallowing liquids s. Vomiting t. Weight loss
Energy	7	**n. Shortness of breath with exercise** **u. Joint and muscle aches** **v. Limited joint movement** **w. Muscle cramps** **x. Weak muscles** y. Loss of energy z. Need to sleep more/take naps
Psych	3	bb. Depression cc. Anxiety dd. Difficulty sleeping

Bold indicates items that are scored under a different subscale than where they are located

Scoring rules:

1. Note that the subscales do not conform exactly to the categories in the patient survey.
2. Subscales may be scored if 50% of more of the items in the subscale are completed.
3. Scores are linearly transformed to a 0-100 scale where 0 means all answered items were a "0" and "100" means that all answered items were a "4"
4. Missing items are not included in the scoring.
5. The summary score is the average of the subscale scores, as long as 4 or more subscales are available.
6. Higher scores indicate more severe symptoms.
7. A clinically meaningful difference for each subscale or the summary score is considered to be half a standard deviation of the baseline score for the population, based on the distribution method of determining clinically meaningful change

Appendix G. Extracorporeal Photopheresis Therapy

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

Principles:

There is no established standard of care to treat cGVHD once patients become steroid refractory. ECP can be an effective treatment for some patients. [17,18,147-152].

- 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 cGVHD 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:
    - cGVHD has rapidly progressed *(UW Health Moderate quality evidence, S recommendation)*
  - Continue if:
    - cGVHD is stable or has improved *(UW Health Moderate quality evidence, S recommendation)*
- Three months after initiation of therapy
  - Discontinue if:
    - cGVHD 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 cGVHD 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.

Appendix H. Interleukin-2 Therapy

1. There is no established standard of care to treat cGVHD once patients become steroid refractory. IL-2 can be an effective treatment for some patients with active cGVHD. *(UW Health Very low quality evidence, C recommendation)*
   1.1. Patients receiving both sirolimus and tacrolimus concurrently should not receive IL-2 due to the risk of renal failure.[79,80] *(UW Health Moderate quality evidence, S recommendation)*
2. Treatment may be initiated at a dose of aldesleukin 1 x 10^6 international units/m^2 subcutaneous daily.[80] *(UW Health Very low quality evidence, C recommendation)*
   2.1. If patient begins to experience toxicities, the daily dose may be reduced to aldesleukin 0.3 x 10^6 international units/m^2 subcutaneous.
   2.2. Aldesleukin should not be administered by intravenous bolus or infusion.
3. Aldesleukin may be administered in the home or outpatient setting. *(UW Health Very low quality evidence, S recommendation)*
   3.1. Patients should receive education about appropriate storage, preparation, and administration of this product upon initiation of therapy and reinforcement of proper technique throughout therapy. *(UW Health Very low quality evidence, S recommendation)*
4. Patients receiving IL-2 should be monitored according to the supportive care plan. (CSC SC BMT Aldesleukin (Interleukin-2) [5271])[79,80] *(UW Health Very low quality evidence, S recommendation)*
   4.1. If patient develops common terminology criteria for adverse events (CTCAE) grade 3 toxicity, therapy should be discontinued. *(UW Health Very low quality evidence, S recommendation)*

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