National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hematopoietic Cell Transplantation (HCT):

Pre-Transplant Recipient Evaluation and Management of Graft-Versus-Host Disease

Version 1.2020 — October 30, 2019

NCCN.org

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NCCN Guidelines Version 1.2020
Hematopoietic Cell Transplantation

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Hematopoietic Cell Transplantation

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To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

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INTRODUCTION

The NCCN Guidelines for Hematopoietic Cell Transplantation (HCT) pertain to the management of adult patients undergoing HCT for malignant diseases.

The initial version of the Guidelines addresses pre-transplant recipient evaluation and management of acute/chronic graft-versus-host disease (GVHD). Additional topics will be addressed in subsequent versions.

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INDICATIONS FOR TRANSPLANTATION

Indications for hematopoietic cell transplantation (HCT) vary by disease.

Indications for HCT can be found in the following NCCN Guidelines:

- NCCN Guidelines for Acute Lymphoblastic Leukemia
- NCCN Guidelines for Acute Myeloid Leukemia
- NCCN Guidelines for B-Cell Lymphomas
- NCCN Guidelines for Central Nervous System Cancers
- NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- NCCN Guidelines for Chronic Myeloid Leukemia
- NCCN Guidelines for Gestational Trophoblastic Neoplasia
- NCCN Guidelines for Hodgkin Lymphoma
- NCCN Guidelines for Multiple Myeloma
- NCCN Guidelines for Myelodysplastic Syndromes
- NCCN Guidelines for Myeloproliferative Neoplasms (MPN)
- NCCN Guidelines for Primary Cutaneous Lymphoma
- NCCN Guidelines for Systemic Light Chain Amyloidosis
- NCCN Guidelines for Systemic Mastocytosis (SM)
- NCCN Guidelines for T-Cell Lymphomas
- NCCN Guidelines for Testicular Cancer
- NCCN Guidelines for Waldenström Macroglobulinemia

→ Pre-Transplant Recipient Evaluation (see HCT-2)

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PRE-TRANSPLANT RECIPIENT EVALUATION[a]

- **Clinical Assessment:**
  - Confirm histologic diagnosis
  - History & physical exam, including evaluation of performance status (ECOG or KPS) and body mass index (BMI)
  - Assess disease status[b] (including cytogenetic/molecular testing for risk stratification and assessment of minimal residual disease, if applicable)
  - Bone marrow aspiration & biopsy to confirm remission status (as indicated by underlying disease: pathology, flow cytometry, cytogenetics, molecular studies) and rule out other diseases
  - Pulmonary function tests (PFT) including spirometry, lung volumes, and diffusing capacity (DLCO)[c,d]
  - ECG (with QTc interval assessment)
  - Measure left ventricular ejection fraction (LVEF)[e] with echocardiogram (if valvular assessment required) or MUGA scan
  - Psychosocial evaluation[f]
  - HCT Comorbidity Index (HCT-CI)[g] score (in particular for allogeneic HCT)
- **Imaging:**
  - Disease-specific restaging studies (See NCCN Guidelines for Treatment of Cancer by Site)
  - Chest x-ray (if no other chest imaging done)
- **Laboratory Tests:**
  - CBC with differential
  - ABO/Rh typing
  - Chemistry profile (including blood glucose, creatinine/GFR,[h] electrolytes, and liver function tests [transaminases and bilirubin])[i,j]
  - Prothrombin time (PT)/partial thromboplastin time (PTT)
  - Urinalysis
  - Infectious disease testing: CMV, HSV, VZV, HBV, HCV, and HIV serology
  - HLA typing per FACT (Foundation for the Accreditation of Cellular Therapy) guidelines[k]

→ Additional evaluation as clinically indicated (HCT-3)

[a] The pre-transplant recipient evaluation generates data to estimate risks of post-transplant complications including non-relapse mortality (NRM). It also generates information that may inform the choice of the preparative regimen (drug choice, dose intensity, and immunosuppressive regimen).

[b] Disease risk index may be used to predict overall survival based on only disease-related risk factors: http://www.cibmtr.org/ReferenceCenter/Statistical/Tools/Pages/DRI.aspx.

[c] Diffusing capacity of the lungs for carbon monoxide (DLCO) should be corrected for hemoglobin concentration (Hb) using the Dinakara method. In patients with significantly reduced DLCO, caution should be exercised when using busulfan or carmustine-based regimens.

[d] Consider pulmonary consultation and/or arterial blood gas (ABG) analysis if DLCO <60%.

[e] Consider cardiac consultation in patients with compromised LVEF.

[f] Assess medication adherence, high-risk behavior, and caregiver availability to ensure patient compliance to treatment.

[g] The HCT-CI predicts the risk of NRM after transplant more accurately than age and performance status; however, it does not predict the risk of relapse. Detailed explanation of the HCT-CI has been published [Sorror ML. Blood 2013;121(15):2854-63]. Allogeneic HCT: Increased HCT-CI scores were predictive for increased risks of NRM and overall mortality. Autologous HCT: Scores ≥3 were predictive for increased risks of NRM and overall mortality. See HCT-CI score calculator: http://hctci.org.

[h] Calcineurin inhibitors (CNIs) are associated with increased risk of renal failure after HCT.

[i] Cirrhosis (in particular with portal hypertension) is generally considered a contraindication for allogeneic HCT.

[j] Veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) risk calculator may be used to predict risk of VOD/SOS: http://www.cibmtr.org/ReferenceCenter/Statistical/Tools/Pages/VOD.aspx.

[k] Foundation for the Accreditation of Cellular Therapy and Joint Accreditation Committee-ISCT and EBMT. FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration (7th edition); 2018.

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PRE-TRANSPLANT RECIPIENT EVALUATION[a]
ADDITIONAL EVALUATION AS CLINICALLY INDICATED

As clinically indicated:

- **Additional Clinical Assessment**
  - **Lumbar puncture for cerebrospinal fluid (CSF) analysis**
  - **Discuss fertility preservation/sperm banking**
  - **Pregnancy test for women of child-bearing potential**
  - **Physical therapy evaluation (strength, flexibility, function)**
  - **Nutritional evaluation**
  - **Consider geriatric assessment for select patients (category 2B) (see NCCN Guidelines for Older Adult Oncology)**
  - **Dental evaluation (in particular for allogeneic HCT)**
- **Additional Imaging**
  - **CT (chest and/or sinuses)**
- **Additional Laboratory Tests**
  - **Epstein-Barr virus (EBV) testing or other infectious disease testing (if high risk) (eg, tuberculosis [TB], toxoplasma, strongyloides, human T-cell lymphotropic virus [HTLV] types I and II [for allogeneic HCT])**
  - **Human leukocyte antigen (HLA) antibody assessment if using HLA-mismatched donor (allogeneic HCT)**
  - **24-hour urine creatinine clearance (for borderline renal dysfunction or low muscle mass)**
  - **Urine toxicology screen if history of illicit drug use**
  - **Thyroid-stimulating hormone (TSH) level**
  - **Iron profile (including ferritin level)**
  - **Blood lipid panel**
  - **Vitamin D level**

[a] The pre-transplant recipient evaluation generates data to estimate risks of post-transplant complications including NRM. It also generates information that may inform the choice of the preparative regimen (drug choice, dose intensity, and immunosuppressive regimen).

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POST-TRANSPLANT FOLLOW-UP

Monitoring for post-transplant complications such as GVHD, infections[m] and disease relapse is recommended for all patients who have undergone HCT.

Additional recommendations for post-HCT follow-up will be addressed in subsequent versions of the NCCN Guidelines for Hematopoietic Cell Transplantation.

If GVHD is suspected, see Diagnosis/Workup of GVHD (GVHD-1).

[m] See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

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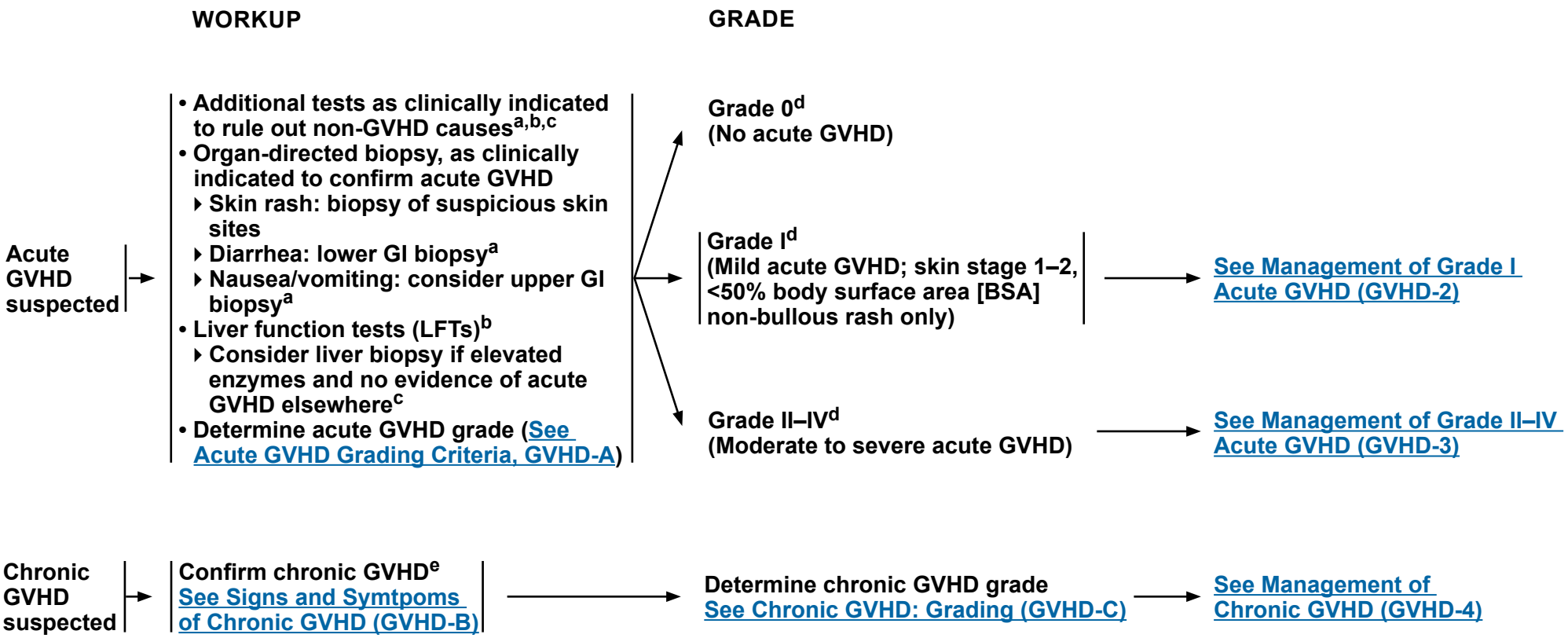
DIAGNOSIS/WORKUP OF GVHD



[a] GI biopsy and/or stool testing may be used to rule out other possible causes of GI symptoms (eg, bacterial/viral infection, drug-induced injury, other differential diagnoses).
[b] Consider imaging as clinically indicated for LFT abnormalities (eg, ultrasound and/or CT scan of the abdomen).
[c] Liver biopsy and/or viral reactivation testing may be used to rule out non-GVHD causes of liver dysfunction (ie, VOD/SOS, infection, effects of preparatory regimen, drug toxicity). Transjugular approach may be preferred, especially if thrombocytopenia or coagulopathy is present.
[d] See Acute GVHD Grading Criteria (GVHD-A).
[e] While a biopsy may be done to confirm chronic GVHD, a biopsy is not always feasible and is not mandatory if the patient has at least one of the diagnostic findings of chronic GVHD (Jagasia MH, et al. Biol Blood Marrow Transplant 2015;21:389-401).

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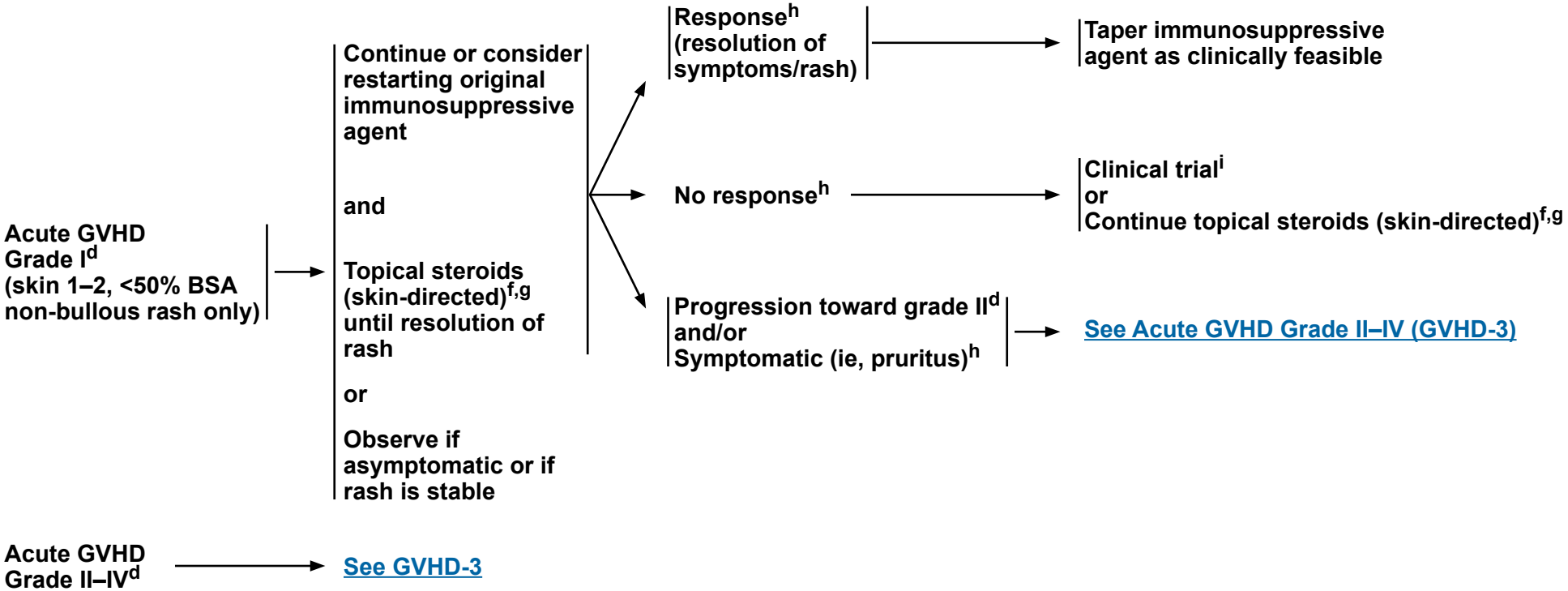
MANAGEMENT OF ACUTE GVHD

FIRST-LINE THERAPY



[d] See Acute GVHD Grading Criteria (GVHD-A).
[f] Topical steroids (eg, triamcinolone, clobetasol) and/or topical tacrolimus. Medium to high potency formulations are recommended except on the face or intertriginous areas where low potency hydrocortisone can be used.
[g] Antihistamines may be used for symptoms (eg, itching), as needed.
[h] See GVHD Steroid Response Definitons/Criteria (GVHD-D).
[i] Enrollment in well-designed clinical trials should be encouraged, since no standard, effective therapy for steroid-refractory GVHD has been identified. The selection of therapy for steroid-refractory GVHD should be based on physician experience, agent's toxicity profile, the effect of prior treatment, drug interactions, convenience/accessibility, and patient tolerability.

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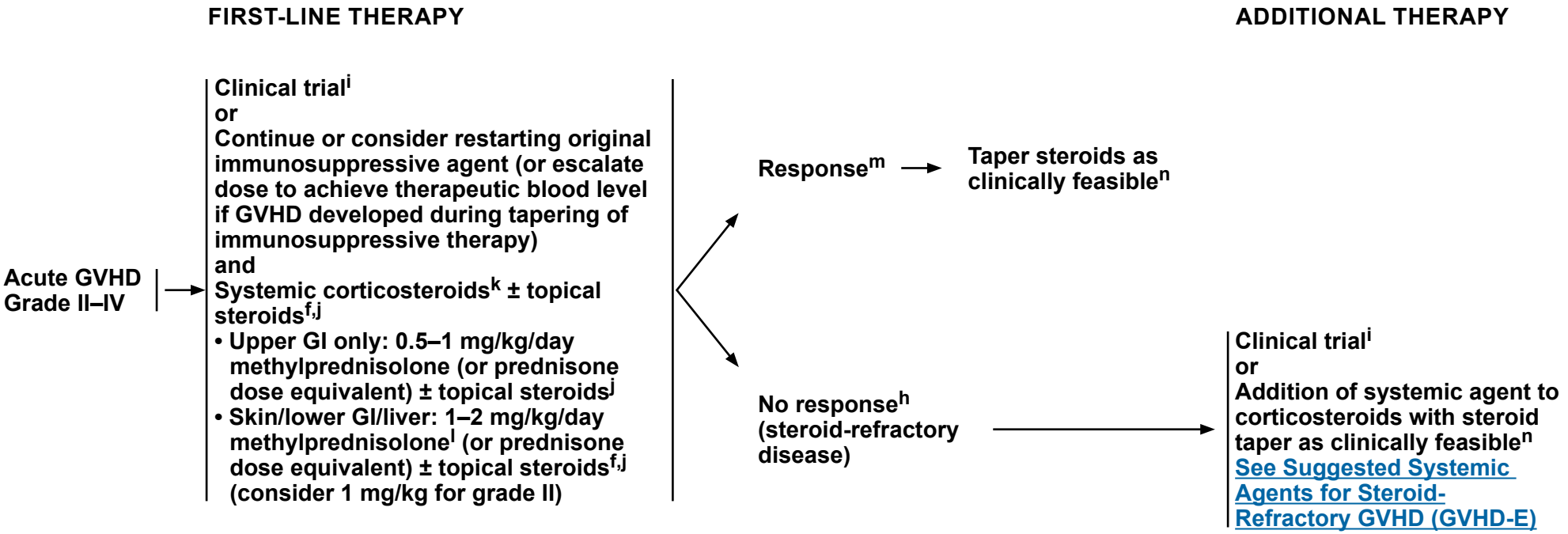
MANAGEMENT OF ACUTE GVHD



[f] Topical steroids (eg, triamcinolone, clobetasol) and/or topical tacrolimus. Medium to high potency formulations are recommended except on the face or intertriginous areas where low potency hydrocortisone can be used.

[h] See GVHD Steroid Response Definitions/Criteria (GVHD-D).

[i] Enrollment in well-designed clinical trials should be encouraged, since no standard, effective therapy for steroid-refractory GVHD has been identified. The selection of therapy for steroid-refractory GVHD should be based on physician experience, agent's toxicity profile, the effect of prior treatment, drug interactions, convenience/accessibility, and patient tolerability.

[j] In a phase III RCT, initial treatment with systemic prednisone at 0.5 mg/kg/day in conjunction with GI topical steroids (beclomethasone diproprionate ± budesonide) was safe and effective for upper GI symptoms (ie, nausea, vomiting, anorexia), with or without skin involvement (<50% BSA), in patients with diarrhea volumes of <1,000 mL/day. (Mielcarek M, et al. Haematologica. 2015:haematol.2014.118471.)

[k] Addition of other systemic agents in conjunction with systemic steroids as initial therapy for acute GVHD should not be done outside the context of a well-designed clinical trial.

[l] There is no role for escalation of methylprednisolone dose beyond 2 mg/kg/day.

[m] Complete resolution of GVHD or improvement in at least 1 organ without any progression in any other organs.

[n] If response, taper systemic steroids to mitigate long-term steroid side effects and risk of infection, as clinically feasible.

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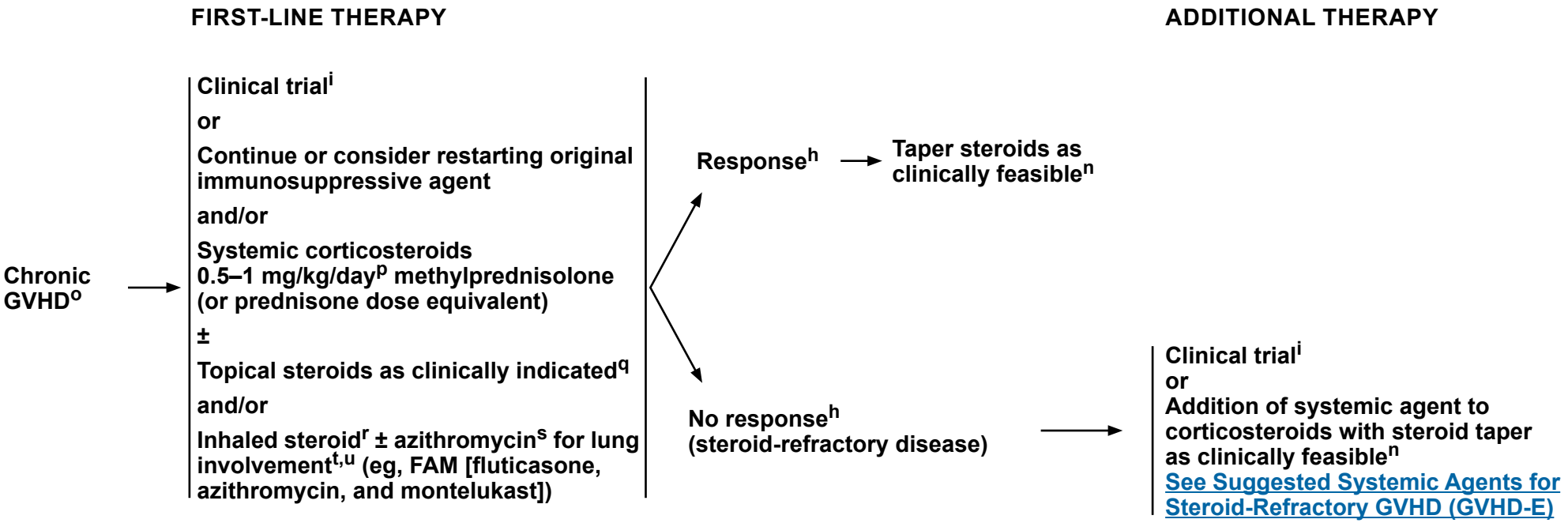
MANAGEMENT OF CHRONIC GVHD



[h] See GVHD Steroid Response Definitions/Criteria (GVHD-D).

[i] Enrollment in well-designed clinical trials should be encouraged, since no standard, effective therapy for steroid-refractory GVHD has been identified. The selection of therapy for steroid-refractory GVHD should be based on physician experience, agent's toxicity profile, the effect of prior treatment, drug interactions, convenience/accessibility, and patient tolerability.

[n] If response, taper systemic steroids to mitigate long-term steroid side effects and risk of infection, as clinically feasible.

[o] Multidisciplinary care aimed at avoiding organ damage and preserving function is recommended.

[p] Initial dose may vary depending on organs involved, GVHD severity, patient comorbidities, and overlapping syndromes.

[q] Topical steroids (eg, triamcinolone, clobetasol), topical estrogen (vulvovaginal GVHD), topical tacrolimus, or dexamethasone oral rinse (oral GVHD). Medium to high potency formulations are recommended except on the face or intertriginous areas where low potency hydrocortisone can be used.

[r] Examples of acceptable inhaled steroids include budesonide or fluticasone.

[s] Due to recent data suggesting an increased risk for cancer relapse, azithromycin should be used only for the treatment of bronchiolitis obliterans syndrome (BOS) and not for lung GVHD prophylaxis.

[t] Patients with progression/worsening of lung chronic GVHD following 2–3 lines of therapy may be evaluated for lung transplant.

[u] PFT at onset of chronic GVHD and subsequently as clinically indicated.

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ACUTE GVHD: STAGING AND GRADING

- **Keystone (modified Glucksberg) criteria are commonly used for the staging/grading of adults with acute GVHD.**
- **Other commonly used criteria include:**
  - **MAGIC criteria (Harris AC, et al. Biol Blood Marrow Transplant 2016;22:4-10).**
  - **Minnesota criteria (MacMillan ML, et al. Biol Blood Marrow Transplant 2015;21:761-767).**

Staging and Grading of Acute GVHD (Modified Glucksberg Criteria)*

	Extent of Organ Involvement		
	Skin	**Liver**	**Gut**
Stage			
1	Rash on <25% of skin[a]	Bilirubin 2–3 mg/dl[b]	Diarrhea >500 ml/day[c] or persistent nausea[d]
2	Rash on 25–50% of skin	Bilirubin 3–6 mg/dl	Diarrhea >1000 ml/day
3	Rash on >50% of skin	Bilirubin 6–15 mg/dl	Diarrhea >1500 ml/day
4	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dl	Severe abdominal pain with or without ileus
Grade[e]			
I	Stage 1–2	None	None
II	Stage 3	Stage 1	Stage 1
III	—	Stage 2–3	Stage 2–4
IV[f]	Stage 4	Stage 4	—

*Used with permission: Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 1995;15:825-828.

[a] Use 'Rule of Nines' or burn chart to determine extent of rash.
[b] Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.
[c] Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Gut staging criteria for pediatric patients was not discussed at the consensus conference. Downgrade one stage if an additional cause of diarrhea has been documented.
[d] Persistent nausea with histologic evidence of GVHD in the stomach or duodenum.
[e] Criteria for grading given as minimum degree of organ involvement required to confer that grade.
[f] Grade IV may also include lesser organ involvement but with extreme decrease in performance status.

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CHRONIC GVHD: DIAGNOSIS

Signs and Symptoms of Chronic GVHD[a]				
Organ Site	**Diagnostic** (sufficient to establish the diagnosis of chronic GVHD)	**Distinctive**[b] (Seen in chronic GVHD, but insufficient to establish a diagnosis)	**Other features for unclassified entities**[c]	**Common**[d] (seen with both acute and chronic GVHD)
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 non-scarring 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 • Keratoconjunctivitis sicca • Confluent areas of punctate keratopathy	• Photophobia • Periorbital hyperpigmentation • Blepharitis (erythema of the eye lids with edema)	

[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant; 2015,21:389-401.

[b] In all cases, infection, drug effect, malignancy, or other causes must be excluded.

[c] Can be acknowledged as part of the chronic GVHD manifestations if diagnosis is confirmed.

[d] Common refers to shared features by both acute and chronic GVHD.

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CHRONIC GVHD: DIAGNOSIS

Signs and Symptoms of Chronic GVHD[a]				
Organ Site	**Diagnostic** (sufficient to establish the diagnosis of chronic GVHD)	**Distinctive**[b] (Seen in chronic GVHD, but insufficient to establish a diagnosis)	**Other features for unclassified entities**[c]	**Common**[d] (seen with both acute and chronic GVHD)
Genitalia	• Lichen planus-like features • Lichen sclerosus-like features • Vaginal scarring or clitoral/labial agglutination (females) • Phimosis or urethral/meatus scarring or stenosis (males)	• Erosions • Fissures • Ulcers		
GI Tract	• Esophageal web • Strictures or stenosis in the upper to mid third of the esophagus		• Exocrine pancreatic insufficiency	• Anorexia • Nausea • Vomiting • Diarrhea • Weight loss • Failure to thrive (infants and children)
Liver				• Total bilirubin, alkaline phosphatase > 2 × upper limit of normal • ALT > 2× upper limit of normal
Lung	• Bronchiolitis obliterans diagnosed with lung biopsy • Bronchiolitis obliterans syndrome (BOS)[e]	• Air trapping and bronchiectasis on chest CT	• Cryptogenic organizing pneumonia (COP)[f] • Restrictive lung disease[f]	

[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant; 2015,21:389-401.

[b] In all cases, infection, drug effect, malignancy, or other causes must be excluded.

[c] Can be acknowledged as part of the chronic GVHD manifestations if diagnosis is confirmed.

[d] Common refers to shared features by both acute and chronic GVHD.

[e] BOS can be diagnostic for lung chronic GVHD only if distinctive signs or symptoms of chronic GVHD are present in another organ. BOS diagnosis requires the following criteria:

1. FEV1/VC ratio < 0.7 or the fifth percentile predicted.
2. FEV1 < 75% of predicted with ≥10% decline within 2 years. FEV1 should not be corrected to >75% of predicted after albuterol inhalation, and the absolute decline for the corrected values should still remain at ≥10% over 2 years.
3. Absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms, such as chest radiographs, computed tomographic (CT) scans, or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, bronchoalveolar lavage).
4. One of the 2 supporting features of BOS: Evidence of air trapping by expiratory CT or small airway thickening or bronchiectasis by high resolution chest CT; or evidence of air trapping by PFTs: residual volume > 120% of predicted or residual volume/total lung capacity elevated outside the 90% confidence interval.

If a patient already carries the diagnosis of chronic GVHD by virtue of organ involvement elsewhere, then only the first 3 criteria above are necessary to document chronic GVHD lung involvement.

[f] Pulmonary entities under investigation or unclassified.

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CHRONIC GVHD: DIAGNOSIS

Signs and Symptoms of Chronic GVHD[a]				
Organ Site	**Diagnostic** (sufficient to establish the diagnosis of chronic GVHD)	**Distinctive**[b] (Seen in chronic GVHD, but insufficient to establish a diagnosis)	**Other features for unclassified entities**[c]	**Common**[d] (seen with both acute and chronic GVHD)
Muscles, Fascia, Joints	• Fasciitis • Joint stiffness or contractures secondary to fasciitis or sclerosis	• Myositis or polymyositis[g]	• 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	

[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant; 2015,21:389-401.
[b] In all cases, infection, drug effect, malignancy, or other causes must be excluded.
[c] Can be acknowledged as part of the chronic GVHD manifestations if diagnosis is confirmed.
[d] Common refers to shared features by both acute and chronic GVHD.
[g] Diagnosis of chronic GVHD requires biopsy.

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CHRONIC GVHD: GRADING

Organ Scoring of Chronic GVHD[a]	Score 0	Score 1	Score 2	Score 3
Performance Score: _____ KPS ECOG LPS (circle one)	Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
Skin[b]				
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 pruritis
○ Hair involvement
○ Nail involvement
○ Abnormality present but explained entirely by non-GVHD documented cause (specify):

[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant; 2015,21:389-401.

[b] 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.

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CHRONIC GVHD: GRADING

Organ Scoring of Chronic GVHD[a]	Score 0	Score 1	Score 2	Score 3
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):				
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%[c] ○ Failure to thrive	No symptoms	Symptoms without significant weight loss[c] (<5%)	Symptoms associated with mild to moderate weight loss[c] (5-15%) OR moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss[c] >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):				

[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant; 2015,21:389-401.
[c] Weight loss within 3 months.

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CHRONIC GVHD: GRADING

Organ Scoring of Chronic GVHD[a]	Score 0	Score 1	Score 2	Score 3
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 x ULN	Elevated total bilirubin >3 mg/dL
○ Abnormality present but explained entirely by non-GVHD documented cause (specify):				
Lungs[d]				
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 O_2)
Lung score: _____% FEV1 Pulmonary function tests: Not performed	FEV1 ≥80%	FEV1 60-79%	FEV1 40-59%	FEV1 ≤39%
○ Abnormality present but explained entirely by non-GVHD documented cause (specify):				
Joints and Fascia				
P-ROM score (see GVHD-C, 5 of 5) 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[e]				
○ Not examined Currently sexually active: ○ Yes ○ No	No signs	Mild signs[e] and females with or without discomfort on exam	Moderate signs[e] and may have symptoms with discomfort on exam	Severe signs[e] with or without symptoms
○ Abnormality present but explained entirely by non-GVHD documented cause (specify):				

[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant; 2015,21:389-401.

[d] 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 discrepency between symptoms and FEV1 scores.

[e] To be completed by specialist or trained medical providers.

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CHRONIC GVHD: GRADING

Organ Scoring of Chronic GVHD[a]

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

- ○ Ascites (serositis) _____
- ○ Pericardial effusion _____
- ○ Pleural effusion(s) _____
- ○ Nephrotic syndrome _____
- ○ Myasthenia gravis _____
- ○ Peripheral neuropathy _____
- ○ Polymyositis _____
- ○ Weight loss >5% without GI symptoms _____
- ○ Eosinophilia >500/µl _____
- ○ Platelets <100,000/µl _____
- ○ Others (specify): _____

Overall GVHD Severity

Opinion of the evaluator: ○ No GVHD ○ Mild ○ Moderate ○ Severe

NIH Global Severity of Chronic GVHD[a]

Mild chronic GVHD	Moderate chronic GVHD	Severe chronic GVHD
1 or 2 organs involved with no more than score 1 *plus* Lung score 0	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	At least 1 organ with a score of 3 OR Lung score of 2 or 3

Keypoints:

1. In skin: higher of the two scores to be used for calculating global severity.
2. In lung: FEV1 is used instead of clinical score for calculating global severity.
3. 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.
4. 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).

[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant; 2015,21:389-401.

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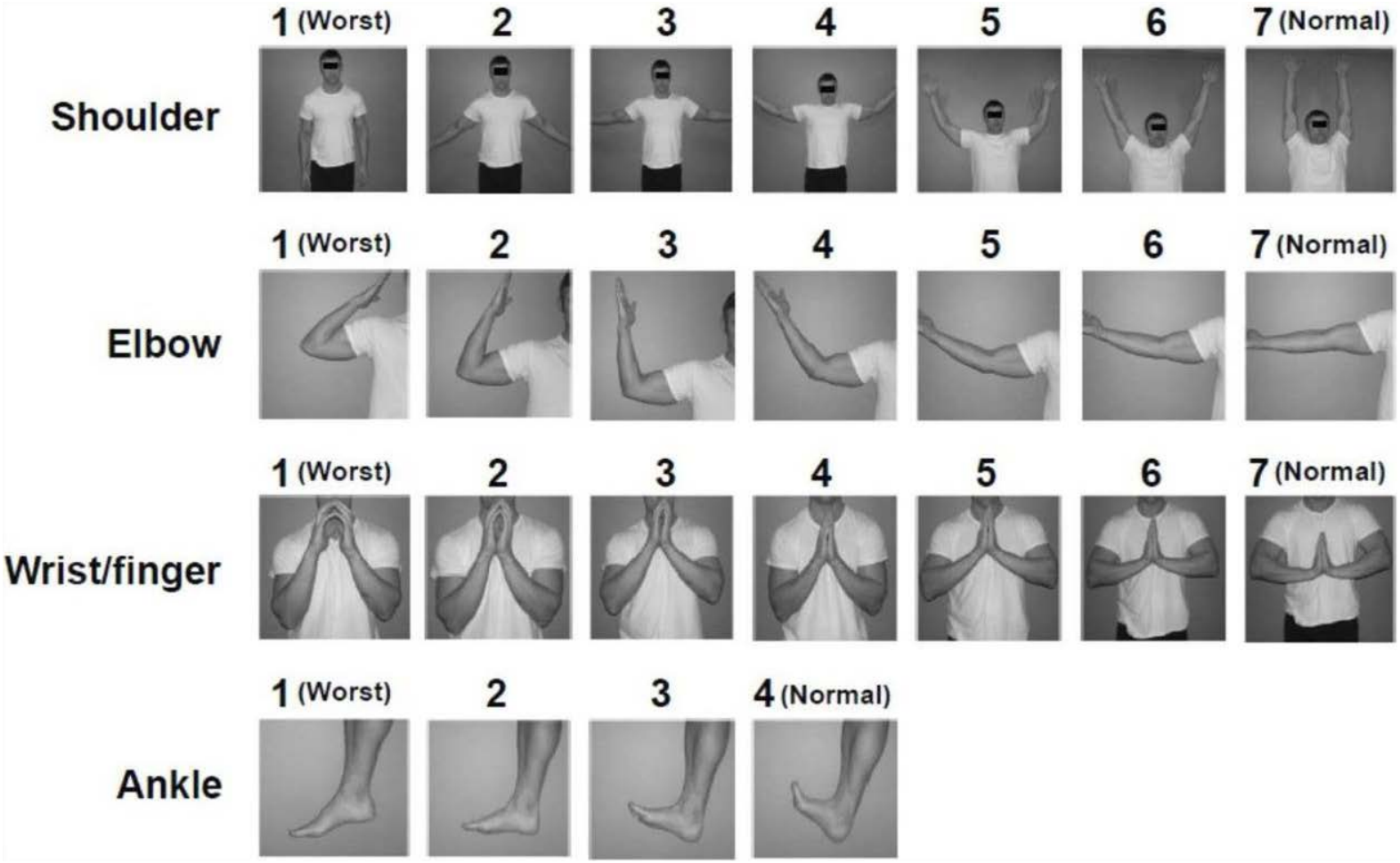
CHRONIC GVHD: GRADING

Photographic Range of Motion (P-ROM)[a]



[a] Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant; 2015,21:389-401.

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GVHD STEROID RESPONSE DEFINITIONS/CRITERIA

NIH Response Criteria for Chronic GVHD Clinical Trials[a]

	Acute GVHD Steroid Response	Chronic GVHD Steroid Response
Steroid Refractoriness or Resistance	Progression of acute GVHD within 3–5 days of therapy onset with ≥2 mg/kg/day of prednisone OR Failure to improve within 5–7 days of treatment initiation OR Incomplete response after more than 28 days of immunosuppressive treatment including steroids	Chronic GVHD progression while on prednisone at ≥1 mg/kg/day for 1–2 weeks OR Stable GVHD disease while on ≥0.5 mg/kg/day (or 1 mg/kg every other day) of prednisone for 1–2 months
Steroid Dependence	Inability to taper prednisone below 2 mg/kg/day OR A recurrence of acute GVHD activity during steroid taper	Inability to taper prednisone below 0.25 mg/kg/day (or >0.5 mg/kg every other day) in at least two unsuccessful attempts separated by at least 8 weeks
Steroid Intolerance	Emergence of unacceptable toxicity due to the use of corticosteroids	

See Chronic GVHD Response Criteria, GVHD-D (2 of 2)

[a] Schoemans HM, Lee SJ, Ferrara JL, et al. EBMT−NIH−CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. Bone Marrow Transplant 2018;53:1401-1415.

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GVHD STEROID RESPONSE DEFINITIONS/CRITERIA

Chronic GVHD Response Criteria[b]

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 Oral Mucosa Rating Score 0 after previous involvement	Decrease in NIH Modified Oral Mucosa Rating Score of 2 or more points	Increase in NIH Modified Oral Mucosa Rating Score of 2 or 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 from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of one or more	Decrease by 50%	Increase by 2x 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 previous involvement by at least one 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 Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0–10 scale	Clinician overall severity score increases by 2 or more points on a 0–10 scale

[b] Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease: IV. The 2014 Response Criteria Working Group Report. Biol Blood Marrow Transplant 2015;21:984-999.

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SUGGESTED SYSTEMIC AGENTS FOR STEROID-REFRACTORY GVHD

- **Participation in clinical trials is encouraged.**
- **The following systemic agents are used in conjunction with corticosteroids for steroid-refractory GVHD. There is insufficient evidence to recommend one systemic agent as preferred over another. However, these are the most commonly used agents among the NCCN Member Institutions.**
- **The selection of systemic agent should be based on institutional preferences, physician experience, agent's toxicity profile, the effect of prior treatment, drug interactions, convenience/accessibility, and patient tolerability.**

Suggested Systemic Agents for Steroid-Refractory GVHD[a] (listed in alphabetical order)

Acute GVHD[1]	Chronic GVHD
The following agents are often used in conjuction with the original immunosuppressive agent.	*While the following systemic agents may be used in any site, some agents are used more commonly in certain sites based on available data (see Discussion).*
• Alemtuzumab[2,3] • Alpha-1 antitrypsin (AAT)[4] • Anti-thymocyte globulin (ATG)[5] • Basiliximab[6] • Calcineurin inhibitors (eg, tacrolimus, cyclosporine) • Etanercept[7] • Extracorporeal photopheresis (ECP)[b,8] • Infliximab[9] • mTOR inhibitors (eg, sirolimus)[10,11] • Mycophenolate mofetil[12,13] • Pentostatin[14,15] • Ruxolitinib[c,16,17] • Tocilizumab[18-21]	• Abatacept[22] • Alemtuzumab[23] • Calcineurin inhibitors (eg, tacrolimus, cyclosporine) • Etanercept[24] • ECP[b,8] • Hydroxychloroquine[25] • Ibrutinib[d,26] • Imatinib[27,28] • Interleukin-2 (IL-2)[29] • Low-dose methotrexate • mTOR inhibitors (eg, sirolimus)[30-32] • Mycophenolate mofetil[33] • Pentostatin[34-37] • Rituximab[38] • Ruxolitinib[39,40]

References

[a] For patients receiving immunosuppressive agents for GVHD, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[b] Psoralen and ultraviolet A irradiation (PUVA) may be used for sclerotic or cutaneous GVHD if ECP is not available or feasible.

[c] Ruxolitinib is FDA approved for the treatment of patients with steroid-refractory acute GVHD.

[d] Ibrutinib is FDA approved for the treatment of adult patients with chronic GVHD after failure of one or more lines of systemic therapy. Ibrutinib should be used with caution in patients with a history of heart arrhythmias or heightened risk of bleeding.

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SUGGESTED SYSTEMIC AGENTS FOR STEROID-REFRACTORY GVHD

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Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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SUGGESTED SYSTEMIC AGENTS FOR STEROID-REFRACTORY GVHD

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

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DISCUSSION
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