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National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. Diagnosis and Staging Working Group Report

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ABSTRACT

This consensus document is intended to serve 3 functions. First, it standardizes the criteria for diagnosis of chronic graft-versus-host disease (GVHD). Second, it proposes a new clinical scoring system (0-3) that describes the extent and severity of chronic GVHD for each organ or site at any given time, taking functional impact into account. Third, it proposes new guidelines for global assessment of chronic GVHD severity that are based on the number of organs or sites involved and the degree of involvement in affected organs (mild, moderate, or severe). Diagnosis of chronic GVHD requires the presence of at least 1 diagnostic clinical sign of chronic GVHD (e.g., poikiloderma or esophageal web) or the presence of at least 1 distinctive manifestation (e.g., keratoconjunctivitis sicca) confirmed by pertinent biopsy or other relevant tests (e.g., Schirmer test) in the same or another organ. Furthermore, other possible diagnoses for clinical symptoms must be excluded. No time limit is set for the diagnosis of chronic GVHD. The Working Group recognized 2 main categories of GVHD, each with 2 subcategories. The acute GVHD category is defined in the absence of diagnostic or distinctive features of chronic GVHD and includes (1) classic acute GVHD occurring within 100 days after transplantation and (2) persistent, recurrent, or late acute GVHD (features of acute GVHD occurring beyond 100 days, often during withdrawal of immune suppression). The broad category of chronic GVHD includes (1) classic chronic GVHD (without features or characteristics of acute GVHD) and (2) an overlap syndrome in which diagnostic or distinctive features of chronic GVHD and acute GVHD appear together. It is currently recommended that systemic therapy be considered for patients who meet criteria for chronic GVHD of moderate to severe global severity.

KEY WORDS
Chronic graft-versus-host disease • Allogeneic hematopoietic cell transplantation • Consensus • Diagnosis • Staging

BACKGROUND

Chronic graft-versus-host disease (GVHD) is a major complication of allogeneic hematopoietic cell transplantation (HCT). The syndrome has features resembling autoimmune and other immunologic disorders such as scleroderma, Sjögren syndrome, primary biliary cirrhosis, wasting syndrome, bronchiolitis obliterans (BO), immune cytopenias, and chronic immunodeficiency. The pathogenesis of chronic GVHD is poorly understood [1].

Symptoms usually present within 3 years after allogeneic HCT and are often preceded by a history of acute GVHD. Manifestations of chronic GVHD may be restricted to a single organ or tissue or may be widespread. Chronic GVHD can lead to debilitating consequences, e.g., joint contractures, loss of sight, end-stage lung disease, or mortality resulting from profound chronic immune suppression leading to recurrent or life-threatening infections. Historically, chronic GVHD was classified as limited or extensive on the basis of the results of a small retrospective study [2], although this classification has not been shown to be reproducible or predictive of late treatment-related mortality (TRM).

Reported incidence rates of chronic GVHD after allogeneic transplantation range from 6% to 80% according to recipient age, donor type, HCT source (peripheral blood, bone marrow, or umbilical cord blood stem cells), graft manipulation (T-cell depletion), and use of posttransplantation donor lymphocyte infusions (DLIs) [3-5]. Reliable incidence estimates in different cohorts of HCT recipients are compromised by (1) lack of standardized, widely used diagnostic guidelines; (2) variability in observer experience; (3) limited expert follow-up at a distance from transplant centers; (4) differences in the statistical methods applied (e.g., use of the Kaplan-Meier versus cumulative incidence estimates and variable requirement for some minimal survival [60-100 days] for patients to be considered at risk of chronic GVHD); and (5) the sometimes protean nature of early chronic GVHD symptoms, which mimic alternative diagnoses. Previous articles have identified risk factors for chronic GVHD after HCT, including prior acute GVHD, older patient age, the use of female donors for male recipients, use of DLI, use of unrelated or HLA-mismatched donors, and, more recently, the use of growth factor–mobilized peripheral blood leukocytes as opposed to marrow as a source of stem cells [6-18].

The opinions expressed here are those of the authors and do not represent the official position of the National Institutes of Health or the US Government.

PURPOSE OF THIS DOCUMENT

The goals of this consensus document are to establish standardized criteria for the diagnosis of chronic GVHD and to propose tools for scoring chronic GVHD organ involvement and assessing overall severity. Specifically, the Working Group sought to (1) develop minimal criteria for the clinical diagnosis of chronic GVHD; (2) propose a new scoring system that describes the extent and severity of chronic GVHD for each organ or site at any given time, taking functional impact into account; (3) propose new guidelines for global assessment of chronic GVHD severity; and (4) propose indications for topical or systemic therapies.

The recommendations of the Working Group represent a consensus opinion supplemented by evaluation of available peer-reviewed literature. The proposed methods and tools for diagnosis and scoring of chronic GVHD are provisional and will be updated according to the results of prospective validation studies.

SUMMARY OF RECOMMENDATIONS

The diagnosis of chronic GVHD requires the following:

1. Distinction from acute GVHD.
2. Presence of at least 1 diagnostic clinical sign of chronic GVHD or presence of at least 1 distinctive manifestation confirmed by pertinent biopsy or other relevant tests.
3. Exclusion of other possible diagnoses.

Scoring of organ manifestations requires careful assessment of signs, symptoms, laboratory values, and other study results.

A clinical scoring system (0-3) is provided for evaluation of the involvement of individual organs and sites.

The proposed global assessment of severity (mild, moderate, or severe) is derived by combining organ- and site-specific scores.

Systemic therapy should be considered for patients who meet criteria for moderate to severe global severity.

DIAGNOSIS OF CHRONIC GVHD

In the past, any manifestation of GVHD that was present (or continued) at 100 days after HCT or

thereafter was arbitrarily defined as chronic GVHD even if the clinical manifestation was indistinguishable from that of acute GVHD. Advances in HCT practice in the past 2 decades have profoundly altered the presentation and natural history of both acute and chronic GVHD and bring previous definitions into question. For instance, acute GVHD may present beyond 3 months in patients who have received reduced-intensity conditioning [19,20], whereas manifestations of acute and chronic GVHD can be present simultaneously, for example, in patients treated with DLI. Therefore, the current consensus is that clinical manifestations, and not the time to symptomatic onset after transplantation, determine whether the clinical syndrome of GVHD is considered acute or chronic.

Throughout this article, *diagnostic* signs and symptoms refer to those manifestations that establish the presence of chronic GVHD without the need for further testing or evidence of other organ involvement. *Distinctive* signs and symptoms of chronic GVHD refer to those manifestations that are not ordinarily found in acute GVHD but are not considered sufficient to establish an unequivocal diagnosis of chronic GVHD without further testing or additional organ involvement. *Other features* of chronic GVHD define the rare, controversial, or nonspecific features of chronic GVHD that cannot be used to establish the diagnosis of chronic GVHD. *Common* signs and symptoms of chronic GVHD refer to manifestations found in both chronic and acute GVHD (Table 1).

The Working Group recommends that the diagnosis of chronic GVHD require at least 1 diagnostic manifestation of chronic GVHD or at least 1 distinctive manifestation, with the diagnosis confirmed by pertinent biopsy, laboratory tests, or radiology in the same or another organ. As in acute GVHD, infection and other causes may confound or complicate the differential diagnosis of chronic GVHD (e.g., nail dystrophies associated with onychomycosis, herpes simplex, or *Candida albicans* infections of the oral cavity; drug toxicity) and must be excluded. Diagnostic and distinctive manifestations of chronic GVHD can be found in the skin and appendages, mouth, eyes, female genitalia, esophagus, lungs, and connective tissues. Biopsy or other testing is always encouraged and often valuable to confirm the presence of chronic GVHD, but it is not always feasible and is not mandatory if the patient has at least 1 of the diagnostic findings of chronic GVHD (Table 1). Please note that an in-depth discussion of recommended terminology for histopathologic interpretation may be found in a forthcoming histopathology working group report. A biopsy read as "consistent with" or "unequivocal" chronic GVHD will be considered sufficient to establish the diagnosis of chronic GVHD if accompanied by at least 1 distinctive clinical manifestation.

Characteristics that establish the diagnosis of chronic GVHD might not serve as the most appropriate parameters for assessing the severity of chronic GVHD. Valid and reliable diagnostic criteria might not be sufficiently sensitive to change to be useful as treatment-response criteria. Conversely, a sensitive measure of chronic GVHD response might not necessarily serve as an appropriate diagnostic and scoring tool.

ORGAN-SPECIFIC MANIFESTATIONS OF CHRONIC GVHD

In all cases, drug reaction, infection, recurrent or new malignancy, and other causes must be excluded. Diagnostic clinical or laboratory features sufficient for the diagnosis of chronic GVHD are italicized in the sections below.

Skin

Diagnostic manifestations include *poikiloderma* (e.g., atrophic and pigmentary changes), *lichen planus-like eruption* (e.g., erythematous/violaceous flat-topped papules or plaques with or without surface reticulations or a silvery or shiny appearance on direct light), *deep sclerotic features* (e.g., smooth, waxy, indurated skin—"thickened or tight skin," caused by deep and diffuse sclerosis over a wide area), *morphea-like* superficial sclerotic features (e.g., localized patchy areas of moveable smooth or shiny skin with a leathery-like consistency, often with dyspigmentation), or *lichen sclerosus-like lesions* (e.g., discrete to coalescent gray to white moveable papules or plaques, often with follicular plugs, with a shiny appearance and leathery consistency). Severe sclerotic features characterized by thickened, tight, and fragile skin are often associated with poor wound healing, inadequate lymphatic drainage, and skin ulcers from minor trauma.

A distinctive feature for chronic GVHD (not seen in acute GVHD, but not sufficiently unique to be considered diagnostic of chronic GVHD) is depigmentation. However, depigmentation would contribute to the diagnosis of chronic GVHD in combination with biopsy or laboratory confirmation of GVHD in skin or another organ. Sweat impairment and intolerance to temperature change from loss of sweat glands are seen in chronic GVHD. Other common, nondistinctive skin manifestations found with both acute and chronic GVHD include erythema, maculopapular rash, and pruritus.

Nails

Dystrophy consisting of longitudinal ridging, nail splitting or brittleness, onycholysis, pterygium unguis, and nail loss (usually symmetric and affecting most nails) are distinctive signs of chronic GVHD but are not sufficient for diagnosis.

Table 1. *Signs and Symptoms of Chronic GVHD*

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features*	Common (Seen with Both Acute and Chronic GVHD)
Skin	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric; affects most nails)†		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Scaling, papulosquamous lesions	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) Premature gray hair	
Mouth	Lichen-type features Hyperkeratotic plaques Restriction of mouth opening from sclerosis	Xerostomia Mucocele Mucosal atrophy Pseudomembranes† Ulcers†		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes‡ Cicatricial conjunctivitis Keratoconjunctivitis sicca‡ Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus-like features Vaginal scarring or stenosis	Erosions† Fissures† Ulcers†		
GI tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus†		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)
Liver				Total bilirubin, alkaline phosphatase >2 × upper limit of normal† ALT or AST >2 × upper limit of normal†
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology‡		BOOP
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis‡	Edema Muscle cramps Arthralgia or arthritis	

Table 1. *Continued*

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features*	Common (Seen with Both Acute and Chronic GVHD)
Hematopoietic and immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergammaglobulinemia Autoantibodies (AIHA and ITP)	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

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

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

†In all cases, infection, drug effects, malignancy, or other causes must be excluded.

‡Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer test for eyes).

Hair

Distinctive features of chronic GVHD include new scarring and nonscarring scalp alopecia (after recovery from chemotherapy or radiotherapy) and loss of body hair. Other characteristics seen with chronic GVHD include premature graying, thinning, or brittleness, but these findings are not diagnostic.

Mouth

Diagnostic features of oral chronic GVHD include *lichen planus-like changes* (white lines and lacy-appearing lesions of the buccal mucosa, tongue, palate, or lips), *hyperkeratotic plaques* (leukoplakia), or *decreased oral range of motion in patients with sclerotic features of skin GVHD*. Distinctive features of chronic GVHD include xerostomia (dryness), mucoceles, mucosal atrophy, pseudomembranes, and ulcers (infectious pathogens such as yeast or herpesvirus; secondary malignancy must be excluded). Manifestations common to both acute and chronic GVHD include gingivitis, mucositis, erythema, and pain.

Eyes

Distinctive manifestations of chronic GVHD include new onset of dry, gritty, or painful eyes; cicatricial conjunctivitis; keratoconjunctivitis sicca; and confluent areas of punctate keratopathy. Other features include photophobia, periorbital hyperpigmentation, difficulty in opening the eyes in the morning because of mucoid secretions, and blepharitis (erythema of the eye lids with edema). New ocular sicca documented by low Schirmer test values with a mean value of both eyes $\leq$5 mm at 5 minutes or a new onset of keratoconjunctivitis sicca by slit-lamp examination with mean values of 6 to 10 mm on the Schirmer test is sufficient for the diagnosis of chronic GVHD if accompanied by distinctive manifestations in at least 1 other organ.

Genitalia

Diagnostic features for the genitalia include *lichen planus-like features* and *vaginal scarring or stenosis* (often associated with oral GVHD).

Gastrointestinal Tract

Diagnostic features for the gastrointestinal (GI) tract include *esophageal web*, *stricture*, or *concentric rings* documented by endoscopy or barium contrast radiograph. Chronic GVHD may be associated with pancreatic exocrine insufficiency, which often improves with enzyme supplementation. Manifestations common to both acute and chronic GVHD (as well as other causes, such as drug side effects, motility disorders, infections, or malabsorption) include anorexia, nausea, vomiting, diarrhea, weight loss, and failure to thrive. Wasting syndrome may be a manifestation of

chronic GVHD but is often multifactorial (e.g., decreased caloric intake, poor absorption, increased resting energy expenditures, and hypercatabolism). Endoscopic findings of mucosal edema and erythema or focal erosions with histologic changes of apoptotic epithelial cells and crypt cell dropout may be seen but are not considered diagnostic of chronic GVHD unless the patient also has distinctive features in a non-GI system. Patients with unresolved acute GVHD may have more severe intestinal mucosal lesions, including ulcers and mucosal sloughing.

Liver

Hepatic acute and chronic GVHD typically presents as cholestasis, with increased bilirubin or alkaline phosphatase, but it may also present as acute hepatitis [21,22]. Because of many possible alternative diagnoses, liver biopsy is required to confirm GVHD involvement of the liver. Note that because of the histologic similarity between acute and chronic liver GVHD, the diagnosis of chronic GVHD cannot be made on the basis of liver biopsy alone but requires a distinctive manifestation in at least 1 other organ system.

Lungs

The only diagnostic manifestation of chronic GVHD is biopsy-proven *BO*. BO diagnosed via pulmonary function and radiologic testing requires at least 1 other distinctive manifestation in a separate organ system to establish the diagnosis of chronic GVHD. BO is characterized by the new onset of an obstructive lung defect. Clinical manifestations may include dyspnea on exertion, cough, or wheezing. Some patients may be asymptomatic early in the disease process. Pneumothorax, pneumomediastinum, and subcutaneous emphysema are rare and often represent advanced disease. Restrictive pulmonary function abnormalities secondary to advanced sclerosis of the chest wall are attributable to skin GVHD. BO is clinically diagnosed when all of the following criteria are met:

1. Forced expiratory volume in 1 second/forced vital capacity ratio <0.7 and forced expiratory volume in 1 second $<75\%$ of predicted.
2. Evidence of air trapping or small airway thickening or bronchiectasis on high-resolution chest computed tomography (with inspiratory and expiratory cuts), residual volume $>120\%$, or pathologic confirmation of constrictive bronchiolitis.
3. Absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms, such as radiologic studies (radiographs or computed tomographic scans) or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, or bronchoalveolar lavage).
4. BO-organizing pneumonia not due to infections may represent a manifestation of either acute or chronic GVHD and is considered a common feature.

Musculoskeletal System

Diagnostic features include *fascial involvement* often affecting the forearms or legs and often associated with sclerosis of the overlying skin and subcutaneous tissue. Fascial involvement may develop without overlying sclerotic changes of the skin and can result in *joint stiffness or contractures* when present near joints. *Fasciitis* is detected on examination by stiffness, a restricted range of motion (e.g., often decreased dorsal wrist flexion or inability to assume a Buddha prayer posture), edema of the extremities with or without erythema (early sign), peau d'orange (edematous skin with prominent pores resembling the surface of an orange), or *joint contractures* (late complications). Clinical myositis with tender muscles and increased muscle enzymes is a distinctive but nondiagnostic manifestation of chronic GVHD. Myositis may present as proximal myopathy, but this complication is rare and does not explain the frequent complaints of severe cramps. Evaluation of myositis involves electromyography and measurement of creatine phosphokinase or aldolase. Arthralgia and arthritis are uncommon and are occasionally associated with the presence of autoantibodies.

Hematopoietic and Immune Systems

Abnormalities are common in chronic GVHD but cannot be used to establish the diagnosis of chronic GVHD. Cytopenias may result from stromal damage or autoimmune processes. Lymphopenia ($\leq 500/\mu L$), eosinophilia ($\geq 500/\mu L$), hypogammaglobulinemia, or hypergammaglobulinemia may be present. Autoantibodies may develop with autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura. Thrombocytopenia ($<100\,000/\mu L$) at the time of chronic GVHD diagnosis has been associated with a poor prognosis.

Other Findings

Serositis (pericardial or pleural effusions or ascites), peripheral neuropathy, myasthenia gravis, nephrotic syndrome, and cardiac involvement have been attributed to chronic GVHD, but these manifestations are rare. For these manifestations, chronic GVHD is often a diagnosis of exclusion.

DIFFERENTIAL DIAGNOSIS BETWEEN ACUTE AND CHRONIC GVHD

The Working Group recognized 2 main categories of GVHD, each with 2 subcategories (Table 2).

Table 2. *Categories of Acute and Chronic GVHD*

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

GVHD indicates graft-versus-host disease; HCT, hematopoietic cell transplantation; DLI, donor lymphocyte infusion.
*See Table 1 for features.

The broad category of acute GVHD includes (1) classic acute GVHD (maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus, or cholestatic hepatitis) occurring within 100 days after transplantation or DLI (without diagnostic or distinctive signs of chronic GVHD) and (2) persistent, recurrent, or late acute GVHD: features of classic acute GVHD without diagnostic or distinctive manifestations of chronic GVHD occurring beyond 100 days of transplantation or DLI (often seen after withdrawal of immune suppression). The broad category of chronic GVHD includes (1) classic chronic GVHD without features characteristic of acute GVHD and (2) an overlap syndrome in which features of chronic and acute GVHD appear together. In the absence of histologic or clinical signs or symptoms of chronic GVHD, the persistence, recurrence, or new onset of characteristic skin, GI tract, or liver abnormalities should be classified as acute GVHD regardless of the time after transplantation. With appropriate stratification, patients with persistent, recurrent, or late acute GVHD or overlap syndrome can be included in clinical trials with patients who have chronic GVHD.

CLINICAL SCORING OF ORGAN SYSTEMS

Figure 1 shows the consensus scoring system for individual organs. Several considerations explain the selection of the features for the proposed scoring system versus the response criteria discussed in a separate article. (1) Scoring criteria are intended for baseline or cross-sectional use, whereas response criteria are intended for serial use in therapeutic trials over a relatively short period of time. (2) Scoring measures must be designed so that they can be easily performed in the office by general practitioners. By design, the only required laboratory testing needed to complete the scoring table is measurement of liver function. (3) The broad scoring categories help classify patients and provide immediate, clinically meaningful data about the disease extent and severity. (4) The scoring system does not attempt to distinguish between disease activity and fixed deficits.

Organ sites considered for scoring include skin, mouth, eyes, GI tract, liver, lungs, joints and fascia, and the female genital tract. Each organ or site is scored according to a 4-point scale (0-3), with 0 representing no involvement and 3 reflecting severe impairment. In addition, performance status is captured on a 0 to 3 scale, and check boxes note the presence or absence of other specific manifestations.

Note that Figure 1 should be completed on the basis of an assessment of current status without consideration of past manifestations or a requirement for attribution of abnormalities to chronic GVHD versus another preexisting condition.

GLOBAL SCORING OF CHRONIC GVHD

The time-honored description of limited versus extensive chronic GVHD was proposed from only 20 cases published in 1980 [2]. The Working Group proposes a new global assessment of chronic GVHD severity that is clinically suitable and is appropriate for use as an inclusion criterion in therapeutic clinical trials or as an indication for systemic immunosuppressive treatment. The global scoring system reflects the clinical effect of chronic GVHD on the patient's functional status.

Elements included in the proposed global scoring system include both the number of organs or sites involved and the severity within each affected organ (note that performance status scoring is not incorporated into the global scoring system). The global descriptions of mild, moderate, and severe were chosen to reflect the degree of organ impact and functional impairment due to chronic GVHD. Although scoring is often used at the time of initial diagnosis, evaluating the clinical score periodically during the course of chronic GVHD may revise prognostic expectations and better describe the current severity of chronic GVHD. Note that the global scoring system can be applied only after the diagnosis of chronic GVHD is confirmed by either (1) the presence of a diagnostic feature or, if a diagnostic feature is not present, (2) at least 1 distinctive manifestation of chronic GVHD with the diagnosis supported by histologic, radiologic, or laboratory evidence of GVHD from any site.

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
MOUTH	☐ 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
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca
GI TRACT	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN

Figure 1. Organ scoring of chronic GVHD. *AP may be elevated in growing children, and not reflective of liver dysfunction. †Pulmonary scoring should be performed using both the symptom and pulmonary function testing (PFT) scale whenever possible. When discrepancy exists between pulmonary symptom or PFT scores the higher value should be used for final scoring. Scoring using the Lung Function Score (LFS)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LUNGS[†] **FEV1** ☐ **DLCO** ☐	☐ No symptoms ☐ FEV1 > 80% **OR** LFS=2	☐ Mild symptoms (shortness of breath after climbing one flight of steps) ☐ FEV1 60-79% **OR** LFS 3-5	☐ Moderate symptoms (shortness of breath after walking on flat ground) ☐ FEV1 40-59% **OR** LFS 6-9	☐ Severe symptoms (shortness of breath at rest; requiring 0_2) ☐ FEV1 ≤39% **OR** LFS 10-12
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.)
GENITAL TRACT	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

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

Esophageal stricture or web___	Pericardial Effusion___	Pleural Effusion(s)___
Ascites (serositis)___	Nephrotic syndrome___	Peripheral Neuropathy___
M yasthenia Gravis___	Cardiomyopathy___	Eosinophilia > 500µl___
Polymyositis___	Cardiac conduction defects___	Coronary artery involvement___
Platelets <100,000/µl ___	Progressive onset___	

OTHERS: Specify:_____

Figure 1 (continued). is preferred, but if DLCO is not available, grading using FEV1 should be used. The LFS is a global assessment of lung function after the diagnosis of bronchiolitis obliterans has already been established [29]. The percent predicted FEV1 and DLCO (adjusted for hematocrit but not alveolar volume) should be converted to a numeric score as follows: >80% = 1; 70-79% = 2; 60-69% = 3; 50-59% = 4; 40-49% = 5; <40% = 6. The LFS = FEV1 score + DLCO score, with a possible range of 2-12. GVHD indicates graft versus host disease; ECOG, 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; AST, aspartate aminotransferase; ULN, upper limit of normal.

Mild chronic GVHD involves only 1 or 2 organs or sites (except the lung: see below), with no clinically significant functional impairment (maximum of score 1 in all affected organs or sites). Moderate chronic GVHD involves (1) at least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site) or (2) 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites). A lung score of 1 will also be considered moderate chronic GVHD. Severe chronic GVHD indicates major disability caused by chronic GVHD (score of 3 in any organ or site). A lung score of 2 or greater will also be considered severe chronic GVHD.

INDICATIONS FOR SYSTEMIC THERAPY

Symptomatic mild chronic GVHD may often be treated with local therapies alone (e.g., topical steroids to the skin). However, in patients with chronic GVHD that involves 3 or more organs or with a score of 2 or greater in any single organ, systemic immunosuppressive therapy may be considered. Good medical practice and judgment dictate flexibility in this recommendation. Some experts incorporate the presence or absence of published high-risk features (e.g., thrombocytopenia) and the underlying reason for transplantation (e.g., malignant versus nonmalignant underlying disease) into the decision of whether or not to treat with systemic immunosuppression. Early intervention with effective systemic therapy may prevent progression to severe chronic GVHD, whereas comorbid infections may also modify decisions regarding the timing and intensity of therapy. Effective immune modulating therapy given to patients with clinically significant chronic GVHD involvement has the potential to ameliorate the clinical manifestations, reduce TRM, or both. In patients who are already receiving immune-suppressive medications, the dosage may be increased, or other agents can be added. Patients with chronic GVHD, especially those receiving systemic immunosuppressive therapy, are immunocompromised and should receive infection-prevention measures as outlined in the forthcoming Ancillary Therapy and Supportive Care Working Group document.

ASSESSMENT OF RISK OF TRM

Chronic GVHD is the major cause of late TRM after allogeneic HCT. Previous studies have identified several factors associated with an increased risk of TRM among patients with chronic GVHD, including the involvement of multiple organs or sites, a decreased clinical performance score, thrombocytopenia (platelet count $<100\,000/\mu L$) at the time of diagnosis, progressive onset of chronic GVHD from prior acute GVHD, hyperbilirubinemia, a higher percentage of skin involvement at the time of diagnosis, and others [18,23-28]. Across studies, the characteristics consistently associated with an increased risk of late TRM among patients with chronic GVHD are thrombocytopenia and progressive onset of chronic GVHD from acute GVHD.

Validation of risk factors for late TRM in patients with chronic GVHD should be a major goal of future research, so that patients with the poorest prognoses will be included in clinical trials of systemic therapies aimed at changing the natural history of chronic GVHD. Conversely, patients judged at low risk for TRM might be preferentially enrolled in studies of new topical or organ-specific therapies. The standardized approach for scoring chronic GVHD proposed here is suitable for use in future clinical studies to evaluate the extent to which the severity of specific and combined organ/site involvement correlates with late TRM in patients with chronic GVHD.

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APPENDIX: NATIONAL INSTITUTES OF HEALTH CONSENSUS-DEVELOPMENT PROJECT ON CRITERIA FOR CLINICAL TRIALS IN CHRONIC GVHD STEERING COMMITTEE

Members of this committee included Steven Pavletic and Georgia Vogelsang (project chairs), LeeAnn Jensen (planning committee chair), Lisa Filipovich (Diagnosis and Staging), Howard Shulman (Histopathology), Kirk Schultz (Biomarkers), Dan Couriel (Ancillary and Supportive Care), Stephanie Lee (Design of Clinical Trials), James Ferrara, Mary Flowers, Jean Henslee-Downey, Paul Martin, Barbara Mittleman, Shiv Prasad, Donna Przepiorka, Douglas Rizzo, Daniel Weisdorf, and Roy Wu (members).

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