Biology of Blood and Marrow Transplantation 11:945-955 (2005)

1083-8791/05/1112-0002$30.00/0
doi:10.1016/j.bbmt.2005.09.004

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

Alexandra H. Filipovich,[1] Daniel Weisdorf,[2] Steven Pavletic,[3] Gerard Socie,[4] John R. Wingard,[5] Stephanie J. Lee,[6] Paul Martin,[7] Jason Chien,[7] Donna Przepiorka,[8] Daniel Couriel,[9] Edward W. Cowen,[3] Patricia Dinndorf,[10] Ann Farrell,[10] Robert Hartzman,[11] Jean Henslee-Downey,[12] David Jacobsohn,[13] George McDonald,[7] Barbara Mittleman,[14] J. Douglas Rizzo,[15] Michael Robinson,[16] Mark Schubert,[7] Kirk Schultz,[17] Howard Shulman,[7] Maria Turner,[3] Georgia Vogelsang,[18] Mary E.D. Flowers[7]

[1]Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio; [2]University of Minnesota, Minneapolis, Minnesota; [3]National Cancer Institute, National Institutes of Health, Bethesda, Maryland; [4]Hopital Saint Louis, Paris, France; [5]University of Florida Shands Cancer Center, Gainsville, Florida; [6]Dana-Farber Cancer Institute, Boston, Massachusetts; [7]Fred Hutchinson Cancer Research Center, University of Washington School of Medicine, Seattle, Washington; [8]University of Tennessee, Memphis, Tennessee; [9]University of Texas M.D. Anderson Cancer Center, Houston, Texas; [10]US Food and Drug Administration, Rockville, Maryland; [11]C.W. Bill Young/Department of Defense Marrow Donor Recruitment and Research Program, Naval Medical Research Center, Silver Spring, Maryland; [12]National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland; [13]Children's Memorial Hospital, Northwestern University School of Medicine, Chicago, Illinois; [14]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland; [15]Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin; [16]National Eye Institute, National Institutes of Health, Bethesda, Maryland; [17]University of British Columbia, British Columbia Children's Hospital, Vancouver, British Columbia, Canada; [18]Johns Hopkins University School of Medicine, Baltimore, Maryland

Correspondence and reprint requests: Alexandra H. Filipovich, MD, Division of Hematology/Oncology, Cincinnati Children's Hospital, 333 Burnet Ave., MLC 7015, Cincinnati, OH 45229 (e-mail: lisa.filipovich@cchmc.org).

Received September 9, 2005; accepted September 9, 2005

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

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.