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Report

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

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A B S T R A C T

The 2005 National Institutes of Health (NIH) Consensus Conference proposed new criteria for diagnosing and scoring the severity of chronic graft-versus-host disease (GVHD). The 2014 NIH consensus maintains the framework of the prior consensus with further refinement based on new evidence. Revisions have been made to address areas of controversy or confusion, such as the overlap chronic GVHD subcategory and the distinction between active disease and past tissue damage. Diagnostic criteria for involvement of mouth, eyes, genitalia, and lungs have been revised. Categories of chronic GVHD should be defined in ways that indicate prognosis, guide treatment, and define eligibility for clinical trials. Revisions have been made to focus attention on the causes of organ-specific abnormalities. Attribution of organ-specific abnormalities to chronic GVHD has been addressed. This paradigm shift provides greater specificity and more accurately measures the global burden of disease attributed to GVHD, and it will facilitate biomarker association studies.

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BACKGROUND

Chronic graft-versus-host disease (GVHD) remains a serious and common complication of allogeneic hematopoietic cell transplantation (HCT), occurring in 30% to 70% of patients [1]. Chronic GVHD is a syndrome of variable clinical features resembling autoimmune and other immunologic disorders, such as scleroderma, Sjögren's syndrome, primary biliary cirrhosis, wasting syndrome, bronchiolitis obliterans, immune cytopenias, and chronic immunodeficiency [2,3]. The pathophysiology of the chronic GVHD syndrome may involve inflammation, cell-mediated immunity, humoral immunity, and fibrosis. Clinical manifestations nearly always present during the first year after transplantation, but some cases develop many years after HCT. Manifestations of chronic GVHD may be restricted to a single organ or site or may be widespread, with profound impact on quality of life. Other cases are self-limited and either smolder or resolve without immunosuppressive therapy.

Diagnosing and scoring the severity of chronic GVHD is challenging for several reasons: limited understanding of the pathophysiology, coexistence of acute GVHD manifestations, previously poorly validated measurement tools and scoring systems, and lack of biomarkers for the diagnosis and assessment of disease activity.

Overall risk profiles for acute GVHD and for chronic GVHD diagnosed according to 2005 National Institutes of Health (NIH) consensus criteria [4] were similar in a large comparative study [5]. Of interest, risk factors associated with chronic GVHD were not changed after adjustment for prior acute GVHD, suggesting that chronic GVHD is not simply an evolution of preceding acute GVHD [5].

Several retrospective and large prospective studies have validated many aspects of the 2005 NIH Chronic GVHD Diagnosis and Staging Consensus criteria [4] including organ scoring, global severity, and GVHD categories [6-21]. Although these criteria represent advancement in the field, many questions remain, including their role in clinical practice, biomarker discovery, and regulatory review of new drugs or devices seeking Food and Drug Administration approval. For certain organs and sites, the minimal criteria to diagnose chronic GVHD have not been clearly defined. Other unresolved issues of the 2005 consensus criteria include confusion about the chronic GVHD subcategories (especially overlap GVHD), the rules for scoring abnormalities (symptoms, signs, diagnostic testing) not due to GVHD, and lack of distinction between active disease and a fixed deficit resulting from prior tissue damage [6,22].

Members of the 2014 International NIH Chronic GVHD Diagnosis and Staging Consensus Working Group who contributed to this document were subdivided into organ-specific subgroups. Each subgroup reviewed all evidence new since 2005 and was asked to address controversies and unanswered questions about their assigned organ [22]. Their findings were reviewed by all members of the working group and the steering committee and then were agreed upon to establish the 2014 Consensus Criteria.

PURPOSE OF THIS DOCUMENT

The goals of this consensus document are to revise the 2005 NIH Chronic GVHD Consensus Criteria [4] based on available evidence, to (1) clarify controversies related to the minimal criteria needed to establish the diagnosis for clinical trials, and (2) refine the definition of GVHD subcategories and organ severity scoring. The changes proposed in this document will help to identify manifestations of the various clinical phenotypes of chronic GVHD at initial diagnosis and during the subsequent evolution of the disease for the purpose of clinical trials and biomarkers studies needed to advance the field. A summary of the 2014 NIH Chronic GVHD Diagnosis and Staging Consensus Recommendations is shown below.

Summary of recommendations that are new since the 2005 Consensus [4]

1. Definition of overlap chronic GVHD subcategory has been clarified, and specific manifestations of both acute and chronic GVHD have been added to the organ severity scoring form.
2. Diagnostic criteria for organ system involvement have been modified as follows:
   A. Mouth: Hyperkeratotic plaques have been removed as a diagnostic feature.
   B. Eyes: Evaluation by an ophthalmologist is recommended for eye-specific clinical trials. The Schirmer's test has been removed from the severity scoring form.
   C. Lungs: Bronchiolitis obliterans syndrome (BOS) diagnostic criteria have been modified to enhance diagnostic sensitivity in the presence of established chronic GVHD. BOS that meets the new clinical criteria, plus 1 other distinctive manifestation, is now sufficient for chronic GVHD diagnosis.
   D. Genitalia: Signs and symptoms for males have been added, and diagnostic criteria for females have been modified.
3. Organ-specific severity scoring has been modified as follows (Figure 1):
   A. Skin: The composite score has been split into 2 scores to separate the extent of skin involvement (body surface area [BSA]) from the specific skin features. Clinical features to be considered in the skin scores have been clarified, and rules for the final skin scoring have been added for calculation of global severity.
   B. Mouth: Asymptomatic lichen planus–like features (score 0) has been incorporated.
   C. Eye: Keratoconjunctivitis sicca (KCS) confirmed by an ophthalmologist in an asymptomatic patient (score 0) has been incorporated. Scoring for the eye drop usage criterion has been clarified to include only lubricant drops.
   D. Gastrointestinal (GI): Severity of diarrhea has been added to the GI tract severity score.
   E. Liver: Aspartate aminotransferase is no longer included in liver severity scoring. The cut-off values for bilirubin, alanine aminotransferase, (ALT) and alkaline phosphatase have been revised.
   F. Lungs: The lung function score, which included both forced expiratory volume in 1 second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO), has been simplified to include only the FEV1 (hereafter, FEV1 refers to percent predicted), thus increasing specificity for obstructive lung defects. Rules for final lung scoring have been modified to enhance specificity and for calculation of global severity.
   G. Joints: Photographic image-based range of motion [23] has been added to the joint assessment as an exploratory measure.