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Report

International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium

Andrew C. Harris [1,2], Rachel Young [1,3], Steven Devine [4], William J. Hogan [5], Francis Ayuk [6], Udomsak Bunworasate [7], Chantiya Chanswangphuwana [7], Yvonne A. Efebera [4], Ernst Holler [8], Mark Litzow [5], Rainer Ordemann [9], Muna Qayed [10], Anne S. Renteria [3], Ran Reshef [11], Matthias Wölfl [12], Yi-Bin Chen [13], Steven Goldstein [1], Madan Jagasia [14], Franco Locatelli [15], Stephan Mielke [16], David Porter [17], Tal Schechter [18], Zhanna Shekhovtsova [19], James L.M. Ferrara [3], John E. Levine [1,3,*]

[1] *Blood and Marrow Transplantation Program, University of Michigan, Ann Arbor, Michigan*
[2] *Blood and Marrow Transplantation Program, University of Utah, Salt Lake City, Utah*
[3] *Blood and Marrow Transplantation Program, The Icahn School of Medicine at Mount Sinai Hospital, New York, New York*
[4] *Blood and Marrow Transplantation Program, Ohio State University, Columbus, Ohio*
[5] *Blood and Marrow Transplantation Program, Mayo Clinic, Rochester, Minnesota*
[6] *Department of Stem Cell Transplantation, University Medical Center, Hamburg-Eppendorf, Germany*
[7] *Blood and Marrow Transplantation Program, Chulalongkorn University, Bangkok, Thailand*
[8] *Blood and Marrow Transplantation Program, University of Regensburg, Regensburg, Germany*
[9] *Blood and Marrow Transplantation Program, University Hospital TU Dresden, Dresden, Germany*
[10] *Pediatric Blood and Marrow Transplantation Program, Aflac Cancer and Blood Disorders Center, Emory University and Children's Healthcare of Atlanta, Atlanta, Georgia*
[11] *Blood and Marrow Transplantation Program, Columbia University Medical Center, New York, New York*
[12] *Pediatric Blood and Marrow Transplantation Program, Children's Hospital, University of Würzburg, Würzburg, Germany*
[13] *Bone Marrow Transplantation Program, Massachusetts General Hospital, Boston, Massachusetts*
[14] *Division of Hematology-Oncology, Vanderbilt University Medical Center, Nashville, Tennessee*
[15] *Pediatric Blood and Marrow Transplantation Program, Ospedale Pediatrico Bambino Gesu, Rome, Italy*
[16] *Blood and Marrow Transplantation Program, University of Würzburg, Würzburg, Germany*
[17] *Blood and Marrow Transplantation Program, University of Pennsylvania, Philadelphia, Pennsylvania*
[18] *Pediatric Blood and Marrow Transplantation Program, The Hospital for Sick Children, Toronto, Ontario, Canada*
[19] *Federal Clinical Research Center for Children's Hematology, Oncology and Immunology, Moscow, Russian Federation*

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A B S T R A C T

Acute graft-versus-host disease (GVHD) remains a leading cause of morbidity and nonrelapse mortality after allogeneic hematopoietic cell transplantation. The clinical staging of GVHD varies greatly between transplant centers and is frequently not agreed on by independent reviewers. The lack of standardized approaches to handle common sources of discrepancy in GVHD grading likely contributes to why promising GVHD treatments reported from single centers have failed to show benefit in randomized multicenter clinical trials. We developed guidelines through international expert consensus opinion to standardize the diagnosis and clinical staging of GVHD for use in a large international GVHD research consortium. During the first year of use, the guidance followed discussion of complex clinical phenotypes by experienced transplant physicians and data managers. These guidelines increase the uniformity of GVHD symptom capture, which may improve the reproducibility of GVHD clinical trials after further prospective validation.

INTRODUCTION

The practice of acute graft-versus-host disease (GVHD) clinical staging varies between transplant centers, and poor concordance has been recognized for over 25 years, with

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* Correspondence and reprint requests: John E. Levine, MD, MS, Blood and Marrow Transplantation Program, 1 Gustave L. Levy Place, Box 1410, New York, NY 10029.
E-mail address: john.levine@mssm.edu (J.E. Levine).

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agreement between independent reviewers ranging from 40% to 72% [1,2]. The threshold for diagnosis of GVHD and quantification of symptoms remain variable among centers, as evidenced by widely disparate cumulative incidences of grades II to IV GVHD ranging from 40% to 80% after T cell–replete blood and marrow transplantation (BMT) [3,4]. The difference in rates are likely due to multiple factors such as frequency of obtaining target organ biopsies when symptoms arise, appropriate consideration and application of measures to exclude alternative diagnoses, and absence of consensus guidelines to address inherent challenges in GVHD staging such as stool volume quantification. These variations in practice also result in differences in reporting of timing of GVHD onset and its severity, which poses a significant barrier to the successful conduct of multicenter trials. These barriers can only be overcome through the consistent application of guidelines to clinical GVHD data capture that can uniformly be applied by both clinicians and data managers.

We recently reported a new web-based remote data entry system we developed for GVHD data capture that is now being used in an international GVHD research consortium (the Mount Sinai Acute GVHD International Consortium, or MAGIC) [5]. The GVHD staging guidance outlined in this report was developed initially at a single institution (University of Michigan) and then tested in this multicenter group for clarity and ease of use. The guidance was then refined during its first year of use through discussion of complicated cases seen at these centers via international webinars to reach a consensus opinion. The guidelines outlined in this report are not intended to dictate clinical practice, but rather they are a tool to standardize the collection of complex clinical data for acute GVHD clinical and translational research. Although a few controversial topics remain to be resolved in this evolving guidance, the centers in our GVHD consortium have found this guidance for GVHD data collection clearer and easier to use than prior systems, and it could be used by other centers that conduct GVHD clinical research.

TARGET ORGAN SYMPTOM CAPTURE

Although the guidelines for GVHD staging by symptom severity have been well established [6], quantification of the severity of symptoms has not been standardized across centers. Many databases only record target organ staging, which limits retrospective review of severity without examining source documents from the medical record. To avoid this problem, we collect the absolute quantification of symptoms (extent of skin rash, total bilirubin level, volume of diarrhea), according to the guidance detailed below, regardless of suspected/proven etiology.

Skin

The skin is the most commonly involved GVHD target organ [7], but patients have multiple potential causes for rash after allogeneic transplantation (eg, GVHD, medications, viral exanthemata), and the clinical manifestations may not point to 1 specific etiology. Rash quantification can be clinically challenging, however, because inclusion of all areas of abnormal skin does not distinguish areas of active inflammatory erythema that are characteristic of GVHD [8] from areas of inactive hyperpigmentation or other non-GVHD changes that may lead to discrepancies in rash quantification from 1 clinician to the next. This distinction is important because the natural course of an erythematous rash while resolving is to appear hyperpigmented or "browned over." For example, a patient may have rash involving 60% body surface area (BSA) that if included in its entirety would be classified as stage 3 skin GVHD. Upon closer inspection, however, the skin changes may include petechiae, hyperpigmentation, and/or other changes not consistent with active GVHD. If the non-GVHD skin changes account for more than 10% of the skin changes in this example, the GVHD would be downgraded to stage 2 skin GVHD, which may impact the decision to initiate systemic GVHD therapy. Thus, only areas involved with active erythema should be used for determination of BSA staging of GVHD using the "rule of nines" [9].

A portion of a body area segment may be used for the quantification. For example, if erythema is observed only on the upper half of an arm, this would be quantified as 4.5%, or half of the arm's total 9% BSA. Additionally, one should report if desquamation or fluid-filled bullae are present, because these findings are the hallmark of stage 4 skin GVHD. Patients may have occasional blisters or small patches of dry skin with desquamation that do not reflect the massive inflammation implied by stage 4 skin GVHD. Therefore, this guidance requires both generalized erythema as well as $>5\%$ BSA involvement with blisters and/or desquamation to diagnose skin stage 4 GVHD.

Liver

The liver is the least frequently involved acute GVHD target organ [4,10,11]; however, it is important to document the presence of liver GVHD because of the poorer prognosis it portends [12]. Liver GVHD staging is based solely on total (not conjugated/direct) serum bilirubin levels. Liver GVHD manifesting as transaminitis without hyperbilirubinemia is not staged when applying modified Glucksberg GVHD staging [6,13,14], and transaminitis from non-GVHD causes is common after BMT. We therefore only diagnose liver GVHD manifesting as transaminitis without concomitant elevation in serum bilirubin when the presence of GVHD is confirmed by liver biopsy and score it as stage 0. Future revisions to staging acute liver GVHD presenting as isolated transaminitis will require correlation of transaminase levels, the diagnoses under consideration, and treatment decisions with clinical outcomes.

Because of the relatively infrequent involvement of the liver at GVHD onset and the fact that patients may have hyperbilirubinemia from other causes at the onset of GVHD (eg, chemotherapy toxicity, sinusoidal obstructive syndrome, parenteral nutrition–associated cholestasis), if bilirubin levels were elevated before the diagnosis of GVHD in another target organ and do not increase further, we do not diagnose liver GVHD in the absence of biopsy confirmation. If hyperbilirubinemia develops at the same time or after the onset of GVHD in another target organ, however, liver GVHD is presumed to be present in the absence of an identified alternative cause.

Upper Gastrointestinal Tract

The frequency of GVHD involving the upper gastrointestinal (GI) tract is highly variable between BMT centers, with incidences ranging from 24% to 60% [3,15]. Symptoms of concern for upper GI GVHD include anorexia, nausea, vomiting, and dyspepsia [16], but these can also be seen frequently as a result of infection, mucositis, conditioning regimen toxicity, and/or medication side effect. The timing, severity, and duration of symptoms sufficient for clinical