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National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IIa. The 2020 Clinical Implementation and Early Diagnosis Working Group Report

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SUPPLEMENTARY MATERIALS

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Abstract

Recognition of the earliest signs and symptoms of chronic graft-versus-host disease (GVHD) that lead to severe manifestations remains a challenge. The standardization provided by the National Institutes of Health (NIH) 2005 and 2014 consensus projects has helped improve diagnostic accuracy and severity scoring for clinical trials, but utilization of these tools in routine clinical practice is variable. Additionally, when patients meet the NIH diagnostic criteria, many already have significant morbidity and possibly irreversible organ damage. The goals of this early diagnosis project are 2-fold. First, we provide consensus recommendations regarding implementation of the current NIH diagnostic guidelines into routine transplant care, outside of clinical trials, aiming to enhance early clinical recognition of chronic GVHD. Second, we

propose directions for future research efforts to enable discovery of new, early laboratory as well as clinical indicators of chronic GVHD, both globally and for highly morbid organ-specific manifestations. Identification of early features of chronic GVHD that have high positive predictive value for progression to more severe manifestations of the disease could potentially allow for future pre-emptive clinical trials.

Keywords

Chronic graft-versus-host; disease; Allogeneic hematopoietic cell; transplantation; Consensus; Early diagnosis

The field of allogeneic hematopoietic cell transplantation (HCT) has dramatically changed over the past decade due to practice changes, and the number of transplant procedures continues to increase. Despite prevention strategies such as T cell depletion and post-transplant cyclophosphamide, which are associated with reduced rates of chronic graft-versus-host disease (GVHD) as low as 10% to 15% in some studies [1–4], most allogeneic HCT recipients still receive peripheral blood stem cell grafts with other forms of GVHD prophylaxis and experience a 30% to 50% incidence of chronic GVHD [5–7]. This results in substantial long-term morbidity and mortality [8,9] and has been shown to significantly impact the health status, health-related quality of life, and return to social roles of affected HCT survivors [10–14].

The National Institutes of Health (NIH) Chronic GVHD Consensus projects in 2005 [15,16] and 2014 [17,18] provided the standardization of chronic GVHD diagnosis and severity for clinical trials. Multiple publications have supported the validity of the NIH diagnostic criteria and the prognostic importance of disease severity [19–21], and their use has allowed the development of better structured clinical trials, leading to US Food and Drug Administration approval of ibrutinib for chronic GVHD in 2017, the first agent approved for this indication [22]. However, many patients do not meet NIH diagnostic criteria until irreversible manifestations of the disease such as sicca symptoms and lung GVHD have already developed. Therefore, the field must develop tools to recognize or predict the imminent onset of chronic GVHD at an earlier stage before NIH diagnostic criteria are met to allow investigation of pre-emptive interventions that prevent progression to irreversible organ damage and avoid the need for systemic therapy.

PURPOSE OF THIS DOCUMENT

Chronic GVHD is a pleomorphic disease with an often insidious beginning and disease course. While the current diagnostic and severity criteria are well established, transplant providers struggle with their implementation [23–28], and providers with less experience with chronic GVHD, such as primary oncologists or other clinicians who sometimes resume the care of patients after HCT, may be even less adept at recognizing the earliest symptoms and signs. The first objective of this project was to improve recognition of chronic GVHD using the current NIH guidelines. Accordingly, we make several recommendations based on input from disease experts regarding the timing of routine clinical care and surveillance, which can be used at transplant centers as well as by referring oncologists and primary care

providers. Additionally, patient education regarding early signs and symptoms, increased education of primary health care providers, and utilization of better communication practices from patient and local clinicians to the transplant center could enhance timely diagnosis of chronic GVHD according to current NIH criteria. The second goal of this working group was to review approaches allowing earlier diagnosis of chronic GVHD before meeting NIH criteria when irreversible changes in organ function have occurred. As examples, we discuss 3 organs associated with a high incidence of irreversibility and morbidity: skin/fascia, eyes, and lungs. We outline future research efforts to identify new early diagnostic criteria or reproducible early markers of severe disease, to allow for the development of earlier interventions or even pre-emptive treatments. Future clinical trials could use these early diagnostic tools as eligibility criteria testing feasibility and efficacy of pre-emptive treatment strategies.

SUMMARY OF RECOMMENDATIONS

1. Earlier clinical recognition of chronic GVHD is needed and requires greater involvement of all HCT stakeholders, including nontransplant providers as well as patients and caregivers, and could be facilitated by eHealth technology such as telehealth (remote physician and patient assessment), teleconferences (remote multidisciplinary conferences), and electronic applications and reporting tools.
2. Early signs, symptoms, or other diagnostic determinants of chronic GVHD that are reliably associated with later progression to highly morbid forms of chronic GVHD need to be identified. Early detection of chronic GVHD requires careful and repetitive assessments, including physical examinations by providers with expertise in transplantation, starting before transplantation and continuing through post-transplant follow-up to allow formal diagnosis and assessment of disease trajectory.
3. Research into prognostic markers in blood, tissue, fluid, imaging, and functional testing is needed to identify actionable early indicators for potential pre-emptive therapy.

Methods

Four working groups were created to encourage global engagement in the topic [29]. Groups worked individually beginning in February 2020 to review the relevant literature and create the initial draft of the paper. The Steering Committee reviewed and discussed the initial draft and offered recommendations for revisions. Two iterative rounds of comments and revisions were collected before the November 18 to 20, 2020, Consensus Conference. The manuscript was further revised for submission after additional suggestions from external reviewers, the Steering Committee, and virtual conference participants, which included patient and caregiver representatives, and a 30-day public comment period.

IMPROVING CLINICAL IMPLEMENTATION OF THE 2014 NIH CONSENSUS CRITERIA

Timely recognition of chronic GVHD could potentially be improved by (1) better education of health care providers about the diagnostic criteria or early indicators for chronic GVHD, potentially supported by the use of eHealth tools; (2) delineation of essential chronic GVHD documentation needed in clinical practice; and (3) empowering patients to participate actively in symptom monitoring.

Education of Health Care Providers: Potential Advancements With eHealth

Many health care providers, including transplant providers, have difficulty recognizing very early signs and symptoms of chronic GVHD. Application of the current NIH criteria to diagnose chronic GVHD can be challenging [24,27,30], and early signs may not be diagnostic. It is important to recognize that there is no global model of care post-HCT, and geographic and center-specific practices often dictate whether the patient continues to receive most clinical care in a transplant center versus transfer of care back to a local physician with limited transplant and GVHD-specific knowledge.

For transplant providers, knowledge and confidence can be improved by targeted training sessions [28]. Several online training platforms are available, although several encompass topics beyond chronic GVHD diagnosis (Supplementary Table S1). Development of shorter, more targeted training would be helpful. Similarly, eHealth tools can be used to educate and facilitate the implementation of the NIH criteria in clinical practice. Recently, the eGVHD app (www.uzleuven.be/egvhd) was shown to improve the accuracy of GVHD assessment among health care professionals [23,25,26]. The app has received CE Marking Type I approval, indicating compliance with European quality standards for medical devices, and has been used by providers worldwide, with the United States, China, France, and the United Kingdom being the top downloaders. The use of low-cost, ubiquitously available eHealth tools allows clinicians to access the GVHD criteria at the bedside, encourages systematic physical evaluation of patients, and decreases diagnosis and scoring errors. Ideally, such tools would be integrated in the electronic health record, although this requires a number of functionalities that could prove very costly (need for user identification mechanisms, data protection, interoperability and compatibility with other software, medical device regulation compliance, and availability of maintenance systems). Integration will therefore require partnership with funding agencies or the private sector. Epic, one of the largest electronic medical record systems in the United States, has collaborated with the Center for International Blood and Marrow Transplant Research (CIBMTR) and a group of transplant physicians to develop specialized flowsheets to document both acute and chronic GVHD data. Approximately 100 US-based transplant centers are using Epic, and approximately 40% of these centers routinely use the flowsheets. While important and useful to educate the community about the NIH diagnostic criteria, it is important to note that these criteria were meant for chronic GVHD clinical trials, and some patients who do not meet NIH criteria may still have chronic GVHD that requires treatment, particularly when the disease presents with rare manifestations such as serositis, nephrotic syndrome, or autoimmune cytopenias.

For patients followed locally by health care providers with less chronic GVHD expertise, teleconferences may also help support and educate community providers by facilitating consultation with experts at transplant centers. It is critical to establish this relationship before the patient is referred back to the community partner so that a proactive (rather than reactive) approach to chronic GVHD can be implemented. The COVID-19 pandemic has resulted in the development of more teleconferencing platforms, including many with appropriate security measures to allow Health Insurance Portability and Accountability Act compliance. The ability to show pictures of physical findings and ask experts questions about new signs and symptoms could facilitate accurate diagnosis of remote patients while also educating local providers about chronic GVHD.

Essential Chronic GVHD Evaluations Needed in Clinical Practice

Early recognition of chronic GVHD may offer an opportunity to prevent evolution to more severe disease with irreversible damage [31], although this hypothesis should be formally tested. The 2014 NIH recommendations for clinical trials advocate use of a form that captures diagnostic signs and organ severity scoring [17]. Such evaluations were developed for use in clinical trials and likely lack the granularity required to adjust treatments for individual patients. However, completion of the form does ensure that the main organs involved with chronic GVHD are assessed at each visit. The form is brief and available online at https://doi.org/10.1007/978-3-030-02278-5_44, appendix 1. [32]. One recommended modification to the 2014 form is the addition of a checkbox for “Abnormality thought to represent chronic GVHD plus other causes (specify),” since organ dysfunction can have multiple contributing causes, thereby allowing capture of both chronic GVHD and known non-GVHD causes.

Members of this working group unanimously agreed that it is crucial to properly document the pretransplant baseline status of multiple organ systems in patients in order to correctly identify new abnormalities developing after HCT. With the input of disease and organ experts, we propose the use of a checklist to be completed before HCT to document the presence of signs and symptoms (e.g., dry eyes, restrictions to joint range of motion, lung function tests) that could be subsequently confused with chronic GVHD if not documented before HCT (Table 1) [33]. Post-transplant evaluation for possible chronic GVHD is standard of care in many centers starting around 100 days after HCT, recognizing that chronic GVHD is diagnosed earlier in 5% to 10% of patients [34]. Thereafter, clinical evaluation is required every 1 to 3 months to screen for signs and symptoms of active chronic GVHD until the patient has discontinued immunosuppressive therapy for at least 6 months [35,36]. If abnormalities are detected, prompt referral to a specialized transplantation team for a detailed evaluation and therapy should be considered if the primary provider lacks expertise in diagnosing and managing chronic GVHD (Table 2).

Active Patient Involvement in Monitoring Symptoms

Empowering patients to actively participate in monitoring and reporting their symptoms can facilitate early diagnosis and help monitor treatment response with the potential for improved outcomes. In several other settings, frequent patient symptom reporting was effective in improving survival [37] and lowering hospital readmission rates [38]. For

chronic GVHD and other post-HCT complications, research tools are being developed to determine whether patient education and recognition of sentinel symptoms could help guide appropriate patient reporting [39–45]. For now, patients should be encouraged to use available information platforms (Supplement 2) [46], with particular attention to educating patients about the signs and symptoms of chronic GVHD around day 100 (D100) or when patients are discharged back to their referring physicians. Targeted outreach to patients from the transplant center at regular intervals should be considered as well. Future studies should evaluate the timing and content of educational tools as well as the value of self-monitoring in the post-HCT setting. Care should also be taken to ensure that patients do not feel overly responsible for monitoring themselves. Additionally, it is important to recognize that as many as 17% to 26% of adult long-term HCT survivors have possible or probable limited health literacy [47], which could potentially impact compliance as well as the reliability of self-monitoring practices.

Telemedicine represents an attractive option for patients who have difficulty accessing chronic GVHD monitoring by their providers due to distance from the transplant center, limited resources, inconvenience, or restrictions on travel, such as in the COVID-19 pandemic [48–50]. The pandemic allowed very rapid advancement of telehealth capabilities, but issues that will need to be considered moving forward are the requirement for medical licensure where the patient resides, obtaining e-consent prior to the visit, variable coverage based on patient insurance and ability to collect copays for services rendered, and lack of access for some patients who do not have electronic devices or Internet. In addition, it will be important to ensure consistent provider-patient engagement, as inconsistent provider interactions may discourage patients from discussing new subtle signs or symptoms. Importantly, proper evaluation for chronic GVHD is incomplete without a thorough physical exam, which will be limited by the nature of the telemedicine platform that emphasizes the additional need for a qualified clinician to perform a clinical exam in collaboration with the transplant center as part of the telemedicine evaluation.

EARLIER RECOGNITION OF CHRONIC GVHD BEFORE MEETING NIH DIAGNOSTIC CRITERIA

Better integration of the 2014 NIH diagnostic criteria into routine clinical practice at transplant centers as described above may allow for earlier recognition of chronic GVHD and implementation of effective interventions. However, our current diagnostic strategies have limitations, and even with early diagnosis per the 2014 criteria, outcomes might not be improved. Patients meeting current NIH diagnostic criteria have low rates of responding to current best available initial therapies, as demonstrated in a prospective observational study that enrolled patients within 3 months of chronic GVHD diagnosis. In this study, 91% of patients had moderate to severe chronic GVHD, and less than 20% had a complete or partial response without additional systemic therapy at 1 year [51]. Therefore, identification of early systemic or organ-specific features that are highly correlated with later development of moderate to severe disease should be a goal for the next 5 years. Successful identification of these features may offer an opportunity to explore the efficacy of very early or even preemptive therapy. If new technology proves useful for early diagnosis, it will have

to be highly portable, not cost-prohibitive unless high value is demonstrated, and easily standardized across multiple centers; have high test-retest and intra- and interobserver reliability; require minimal training for operation; and provide easily interpretable data.

Research Goals for Non-Organ-Specific Early Chronic GVHD Identification

1. Development of prospective observational studies that monitor patients closely for the earliest changes associated with subsequent development of chronic GVHD is needed. Studies should enroll patients at the time of transplant or shortly after and follow them closely in order to detect early signs of disease before meeting current NIH diagnostic criteria. Patients will need to be followed for at least 1 to 2 years post-transplant in order to best correlate early findings with important late outcomes (Figure 1, Table 3). At least 2 current trials are attempting to identify diagnostic and prognostic signs of chronic GVHD, including both clinical characteristics and biomarkers, one in pediatric patients and one in adult patients ([NCT04372524](#) and [NCT04188912](#), respectively). More specifically, future research efforts should attempt to:
 - a. Validate that patient-reported symptoms can predate the development of current NIH diagnostic criteria and determine whether some of these symptoms are closely associated with later development of moderate or severe chronic GVHD. Assessment tools that capture common symptoms (pruritus, muscle cramps, etc.), such as the Lee Chronic GVHD Symptom Scale, already exist and would be easy to study [52,53]. Additional common symptoms not currently captured should be explored as well. Deploying these tools via telemedicine, diaries, or electronically (eg, wearable technology) should be studied to enable future dissemination to patients who are not actively followed at a transplant center on a regular basis.
 - b. Describe the clinical evolution of chronic GVHD, including the emergence of diagnostic, distinctive, other or unclassified, and common features as previously published in the 2014 NIH Consensus Criteria on Diagnosis and Staging to understand their true prevalence and prognostic value [17]. These studies could also better document and follow less common manifestations, such as serositis, nephrotic syndrome, immune-mediated cytopenias, polymyositis, and peripheral neuropathy, and provide a framework to study hypothesized chronic GVHD target tissues such as the central nervous system and the endothelium.
 - c. Collect clinically characterized blood and tissue samples for both discovery and validation of risk assignment, predictive, prognostic, and diagnostic biomarkers [54].
2. Application of machine learning (ML) could help identify risk factors or features or biomarker profiles that are highly associated with the development of chronic GVHD requiring systemic treatment. ML techniques have the advantage

of potentially identifying previously unknown associations that do not rely on a priori hypotheses based on currently known risk factors or patterns of disease. This approach has been applied to better identify survival patterns in patients with chronic GVHD based on multiple factors, including individual organ involvement and severity [55]. Future efforts using ML should focus on combining known risk factors, provisional early signs and symptoms of disease, biomarkers, patient-reported outcomes (PROs), and other data hypothesized to be associated with chronic GVHD or its outcome (eg, laboratory data, infectious history) to help identify patients at highest risk for morbidity and mortality (Table 3). It is important to note the limitations to ML such as lack of standard ML techniques for challenges such as data quality issues and methods for integration of high-dimensional data [56]. A planned CIBMTR study will investigate patient-, disease-, and transplant-specific factors available within the CIBMTR database with predictive ML models to develop a prototype clinical decision support tool to help identify patients at high risk for developing acute and chronic GVHD (GV20–01) [57].

Organ-Specific Early Chronic GVHD Identification

Another strategy to facilitate earlier diagnosis of chronic GVHD focuses on specific organs associated with high morbidity or mortality: skin and fascia, eyes, and lungs. Our working group included disease experts in each of these areas to help develop both screening recommendations and potential research approaches. These experts have provided a recommended schedule for screening that at times would involve examinations by a subspecialist or specialized testing, such as pulmonary function tests (PFTs). It is acknowledged that these recommendations might not always be feasible outside of a clinical trial due to need for insurance coverage or proximity to appropriate providers and facilities. Additionally, these experts have also provided alternative screening recommendations with triggers signaling the need to involve subspecialists (Table 2).

Skin and Fascial Disease

Skin fibrosis and fasciitis affect up to 20% of patients with chronic GVHD and are associated with high morbidity, disability, and prolonged immunosuppression [58,59]. New assessment techniques, including imaging and other biomarkers to diagnose prodromal or early sclerotic disease and reliably assess disease activity, are needed. Biomarkers based on skin biopsy materials could also be explored for their potential early diagnostic value for prodromal chronic GVHD in other organs.

Recommended Clinical Assessments

1. A comprehensive skin evaluation at every clinic visit is essential, with special attention to palpation of anatomic sites with propensity for the development of sclerotic features, particularly the lower legs and sites of repetitive skin friction and injury such as the waist [60,61]. The measurement of sclerotic skin and fascial disease is challenging, and no validated methods are available for precise quantification; thus, semiquantitative markers of severity, including skin

pliability, adherence to underlying tissue, and joint range of motion, are used to describe the extent of sclerosis.

2. Photographic range of motion (P-ROM) [62] has been refined [63] for response assessment of fasciitis and should be assessed at each clinic visit. Decreased range of motion in patients with chronic GVHD is usually related to deep sclerosis affecting the fasciae and may not be detectable by palpation. Arthralgias, arthritis, and prior injury can cause anatomic distortion, making the pre-HCT evaluation critical.

Research Goals

1. Biomarkers for patients at risk for or with early disease:
 - a. Systemic prognostic biomarkers: At present, no skin-specific chronic GVHD biomarkers have been identified, although elafin has previously been identified as a biomarker of cutaneous acute GVHD [64]. A proteomic analysis of patients with systemic sclerosis identified elevated levels of CXCL4 compared to other autoimmune diseases, and levels were associated with the presence of skin fibrosis and progression of disease [65,66]. Therefore, serial and unbiased -omic analyses of HCT patients prior to the onset of chronic GVHD skin fibrosis or fasciitis may be able to identify similar high-risk biomarkers in our patient population.
 - b. Tissue specific: Skin is one of the most accessible organs from which to develop tissue-based chronic GVHD biomarkers, but such biomarkers are lacking. Novel immunohistochemistry markers, especially those studied in connective tissue diseases or acute GVHD [67,68], and other means of adding specificity should be explored. Despite the skin being readily accessible, multiple biopsies may be too invasive to serve as a source of serial biomarkers. Improvements in tissue microsampling may enable serial biomarker assessment in a minimally invasive manner [69,70]. Studies should explore the use of multiplexed ion beam imaging based on time of flight that can detect in situ expression of up to 40 proteins in tissue samples [71] or other techniques that evaluate single-cell profiles together with noninvasive microscopic imaging technologies, such as bedside confocal microscopy [72,73] and photoacoustic microscopy [74].
2. Validation of early signs of disease:
 - a. Symptoms: Prodromal features suggestive of evolving chronic GVHD fibrosis include muscle cramping, edema [75], new subcutaneous pain, and eosinophilia [58,76]. These signs and symptoms should be assessed serially and prospectively to determine sensitivity and specificity for future development of sclerotic disease.

- b. Diagnostic assessment: Early detection of subclinical sclerotic chronic GVHD remains an urgent need, and technologies such as magnetic resonance imaging (MRI) [77], variants of ultrasound [78,79], and the Myoton device (Myoton AS, Tallinn, Estonia) [80,81] are being studied.
- c. Patient engagement: Self-assessment at regular intervals between clinic visits using the P-ROM scale could be performed and recorded in a logbook or app. The P-ROM scale has previously been reported as a sensitive marker of disease progression [62], but its utility in early diagnosis is unknown, especially since joint limitation is a late sign. Similarly, app-based patient-reported symptom assessment (eg, leg swelling, loss of flexibility, skin tightness) could provide information that triggers prompt evaluation of new-onset fibrosis.

Ocular Disease

Ocular chronic GVHD can have a severe adverse impact on quality of life [82,83]. Therefore, early diagnosis and targeted therapy for ocular chronic GVHD could have significant clinical benefits. Ocular chronic GVHD should not be viewed as a severe form of dry-eye disease but rather as a rapidly progressive immune-mediated inflammatory and destructive process of the eye, but clinical distinction between the two remains a challenge. Current diagnostic criteria, which require an exam by an eye care provider, are not designed to detect preclinical ocular chronic GVHD. One clinical trial demonstrated that patients had detectable exam changes as early as 14 to 28 days post-HCT that were associated with an increased risk of later ocular chronic GVHD, but these changes were not associated with patient-reported ocular symptoms at the time of assessment [84]. These findings suggest that evaluation by an ophthalmologist may be required to detect early preclinical signs of ocular chronic GVHD, regardless of patient-reported symptoms.

Recommended Clinical Assessments

1. Comprehensive eye examination conducted by an eye care provider within a month prior to HCT or within 3 months afterward is necessary to identify baseline abnormal tissue function [85] (Table 4). During the same visit, patients should be educated about the incidence and potential serious sequelae of ocular GVHD and the warning signs such as dryness, light sensitivity, excessive tearing, foreign body sensation, pain, redness, swelling, mucoid aggregates, or change in vision.
2. Follow-up eye examination should be performed at the onset of any concerning eye symptoms post-HCT. Prompt referral to a specialist with experience in ocular GVHD is encouraged to confirm the diagnosis and begin treatment. Due to a high level of concern from ophthalmology experts that symptom onset may be too late in the disease course, an alternative strategy would include assessments by ophthalmology every 3 months during the first year post-transplant and at longer intervals afterward. This recommendation requires access to ophthalmology care that may impose a burden on patients due to travel

or cost. Future longitudinal chronic GVHD studies are strongly encouraged to investigate whether regularly scheduled ophthalmology care post-HCT is feasible, results in earlier diagnosis, and is associated with improved clinical outcomes.

Research Goals

1. Biomarkers for subclinical/early disease:
 - a. Tissue specific: Validated biomarkers for imminent ocular GVHD are needed using tears or impression cytology. Tear fluid osmolarity change does not differentiate ocular GVHD from other ocular surface diseases [86,87]. However, IL-6, IL-8, lactoferrin, and other neutrophil-related biomarkers may be useful [88–90]. EGFR, IL-1Ra, and fractalkine measured at time of HCT are associated with future development of ocular GVHD [91,92]. Noninvasive imaging such as optical coherence tomography [93] or confocal microscopy [94–97] are also being studied.
2. Validation of early clinical signs of disease:
 - a. Symptoms: An ocular GVHD-specific and validated questionnaire for early symptoms should be developed. Current instruments such as the modified Ocular Surface Disease Index [98] and Change in Dry Eye Symptoms-Questionnaire [99] emphasize late symptoms. In patients with established chronic GVHD, the patient-reported version of the NIH eye score and the 3 eye-specific questions of the Lee Chronic GVHD Symptom Scale were both strongly correlated with eye involvement [100]. Whether earlier utilization of the PROs would result in earlier referral to ophthalmology and diagnosis is not known but should be studied.
 - b. Serial exams: Early signs of ocular chronic GVHD may include changes in the eyelid margin, new conjunctival subepithelial fibrosis if present under the upper or lower palpebral conjunctiva, and hypervascularity and punctate staining of the superior bulbar conjunctiva and punctate staining of the superior cornea. The timing of these findings and their association with ocular chronic GVHD should be studied through frequent evaluations by an ophthalmologist to define the evolution of the disease.

Pulmonary Disease

Bronchiolitis obliterans syndrome (BOS) is the primary diagnostic manifestation of pulmonary chronic GVHD. The 2014 NIH chronic GVHD diagnostic criteria for BOS emphasize the presence of new-onset airflow obstruction on PFTs, plus supportive clinical and radiographic features [17]. When the NIH criteria are strictly applied, many patients already have severe obstructive lung disease, missing an opportunity for early recognition of the disorder. At present, the diagnostic workup for BOS is often initiated based on

symptoms, at which time, the forced expiratory volume in 1 second (FEV₁) may already be 30% to 50% of predicted normal values [101,102]. A randomized double-blind study of patients with newly diagnosed BOS (respiratory symptoms for <6 months) showed that patients receiving inhaled budesonide/formoterol had a statistically significant increase in FEV₁ after 1 month of therapy, and the improvement was maintained after 6 months of therapy [103], supporting the concept that earlier recognition of disease and intervention may improve outcomes.

Earlier recognition of BOS requires routine screening of asymptomatic patients to detect a decline in lung function. The threshold of FEV₁ <75% predicted as a criterion for significant airflow decline misleadingly implies that BOS is a binary condition present only when lung function is clearly below normal limits. The requirement for an FEV₁/forced vital capacity (FVC) (or slow vital capacity if it is greater) ratio less than 0.70 or the fifth percentile of predicted (the lower limit of the 90% confidence interval) in children could also result in missed diagnoses. In patients with BOS, it is not uncommon for the FVC to decline concurrently with a decline in FEV₁, resulting in an FEV₁/FVC ratio greater than 0.7. This would imply that a mixed restrictive/obstructive lung process may be present [104–106]. The criteria for BOS in the 2014 NIH guidelines provide other diagnostic challenges. The diagnostic requirement for “absence of infection in the respiratory tract” does not account for the clear association between respiratory viral infections and chronic GVHD of the lung [107–110] and can falsely reassure clinicians that declines in lung function are reversible and solely linked to an infectious event. Newer molecular methods of testing for viruses may detect nucleic acid remnants for months after initial infection, further complicating the application of current NIH-defined criteria. In addition, spirometric-based criteria cannot be used in children less than 6 to 8 years of age due to the inherent difficulties of performing PFTs in this age group.

Recommended Clinical Assessments

1. Routine PFTs for all HCT recipients (even asymptomatic) should be performed pretransplant and then every 3 months for at least 1 year after HCT. Full PFTs, which include spirometry, lung volumes, and diffusing capacity of carbon monoxide, should be obtained when feasible at preHCT baseline, D100, and 1 year. Limited spirometry can be substituted for full PFTs at 6 and 9 months post-HCT. For patients with newly diagnosed chronic GVHD, it is recommended that spirometry be obtained every 3 months [33,111]. Alternative approaches to lung function are needed for evaluation of younger patients unable to perform PFTs to provide equivalent screening functionality.
2. Patients with documented respiratory viral infections and concomitant FEV₁ decline should be considered high risk for BOS and followed with serial PFTs (or spirometry) at short time intervals.
3. Asymptomatic decline in FEV₁ may be indicative of early BOS or other pulmonary disease. A decline in FEV₁ of 10% from preHCT baseline, or the immediate prior spirometry, in an asymptomatic patient should be followed up clinically with close interval spirometry or further workup. In lung allograft

recipients, changes in absolute values (in liters) for FEV₁ have been followed and are associated with the development of BOS and poor outcomes [112,113].

Research Directions

1. Identification and validation of biomarkers:
 - a. Systemic: Aberrant populations of circulating B cell pre-cursors and dysregulation of B cell homeostasis have been seen in BOS [114]. Potential cytokine and cellular injury markers such as endothelial markers, extracellular matrix proteins, and lung surfactant/lung proteins have all been reported [115–118]. Replication and validation studies should be performed.
 - b. Tissue specific: Novel radiographic techniques, including parametric response mapping and hyperpolarized Xenon-129 MRI, should be tested for their ability to distinguish BOS from other pulmonary conditions [119–121].
2. Validation of early clinical signs of disease:
 - a. Diagnostic assessments:
3. Define a “pre-BOS” stage that identifies airflow obstruction in patients prior to the development of clinical symptoms. BOS-0p is spirometric-based parameter that has been used in lung allograft recipients to identify patients at high risk of developing BOS [122,123]. In HCT recipients, application of similar spirometric criteria that includes a 10% decline in FEV₁ and/or a 25% decline in FEF_{25–75%} compared to pre-HCT baseline has been shown to be sensitive for the prediction of BOS (85%) with a high negative predictive value (98%) [124]. FEF_{25–75%} measures airflow in distal small airways and has known utility as an early marker of airflow obstruction following lung transplantation [125–127]. Early post-transplant declines in FEF_{25–75%} are strongly associated with the development of BOS after HCT and may be more important than FEV₁; therefore, both should be monitored and compared when developing an early diagnostic strategy [128,129].
4. The clinical evolution of BOS after HCT needs to be defined. The trajectory of decline of FEV₁ (ie, rate of change) in patients is heterogeneous, and the optimal testing interval for detection of subclinical changes, and in which high-risk patients, remains to be determined. It is clear that early diagnosis of BOS is more likely with a routine monitoring strategy than with a symptom-based testing approach [130]. Yet, frequent monitoring may be physically and economically challenging, particularly for children and patients living far from a PFT laboratory. Home spirometry with portable handheld devices is feasible in HCT recipients and can be coupled with Cloud-based telemonitoring solutions [131,132] to solve the practical concern of frequent spirometric monitoring of high-risk individuals [133].

5. Studies are needed to clarify the role of respiratory infections in the development of BOS and to update their consideration in BOS diagnostic criteria. Several studies have shown an increased risk of pulmonary impairment following respiratory viral infections and an associated increased risk of non-relapse mortality [107,108,110]. Currently, the diagnosis of BOS requires absence of infection in the respiratory tract documented with clinical investigations, including microbiologic testing, but patients with chronic GVHD often have persistent viral shedding and frequent recurrent infections. Therefore, some modification or clarification to the diagnostic criteria should be explored to allow for the diagnosis of BOS in patients who have a persistent decline in FEV₁ and a persistent respiratory pathogen.
6. Alternatives to PFTs in children are needed. Noninvasive pulmonary testing that is safe, feasible, and reproducible in children, such as the nitrogen multiple breath washout test that measures ventilation inhomogeneity as a measure of airway obstruction, has been successfully applied to infants with cystic fibrosis [134] and in children with early airway pathology following lung transplant [135]. This test is highly sensitive for detecting early lung chronic GVHD in adults after HCT [136]. Other approaches such as high-resolution computed tomography or Xenon MRI also need to be explored.

CONCLUSIONS

Redefining how we recognize chronic GVHD earlier in its clinical evolution will be a major undertaking but has the potential to improve outcomes for patients given the limitations of our current diagnostic criteria, particularly the concern of irreversible organ damage prior to meeting the current criteria. Validation of earlier prediagnostic signs and symptoms should enable the development of pre-emptive intervention strategies with the goal of preventing much of the morbidity and mortality that patients with moderate to severe chronic GVHD currently face. Discovery and validation of early features of chronic GVHD will involve patients and caregivers, transplant providers, and our subspecialty colleagues. Longitudinal studies should enroll patients before chronic GVHD has developed. These observational studies should include serial sample collections, including blood and tissue, for biomarker assessments, patient involvement to assess symptom burden, the use of handheld spirometry, and standardized documentation of physical exam findings, recognizing that screening tests may have variable performance in different populations. These studies should begin during the next 3 years because they will take years to yield definitive data. Diagnosis of ocular and genital involvement is a particular challenge because current diagnostic criteria require assessment by a subspecialist. Engagement with these subspecialists will be essential to help develop early assessment tools and patient symptom measures that could be used to prompt early referral for specialty evaluation. In the next 3 to 7 years, the ability to recognize subclinical chronic GVHD will allow studies of interventions targeted to underlying pathophysiology and delivered preemptively to test whether this approach leads to better transplant outcomes with less chronic GVHD morbidity and no increase in underlying risks of disease relapse or infectious complications. These approaches would be greatly facilitated by development of validated biomarker-based risk assignment strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

APPENDIX: 2020 NATIONAL INSTITUTES OF HEALTH CONSENSUS DEVELOPMENT PROJECT ON CRITERIA FOR CLINICAL TRIALS IN CHRONIC GVHD STEERING COMMITTEE

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Members: Hildegard Greinix, MD, University of Graz; Sophie Paczesny, MD, University of South Carolina; Bruce Blazar, MD, University of Minnesota; Stefanie Sarantopoulos, MD, PhD, Duke University; Joseph Pidala, MD, PhD, Moffitt Cancer Center; Corey Cutler, MD, MPH, FRCPC, Dana Farber Cancer Institute; Gerard Socie, MD, PhD, St-Louis Hospital, Paris; Paul Martin, MD, Fred Hutchinson Cancer Research Center; Meredith Cowden, MA, LPCC-S, Cowden Foundation.

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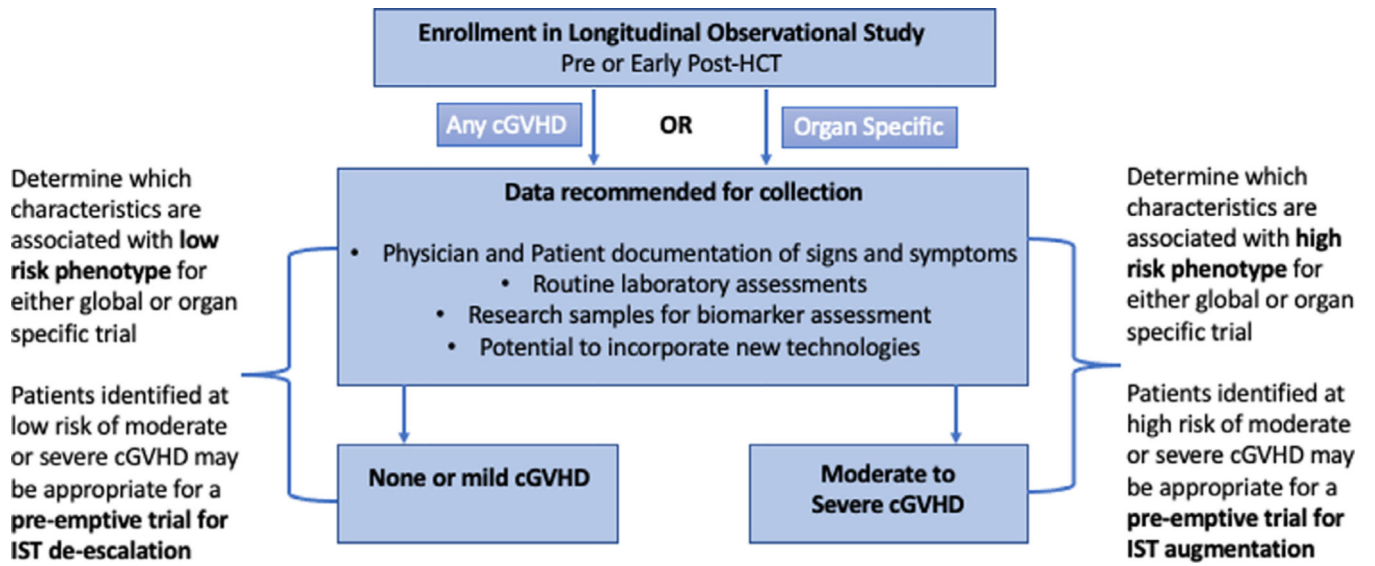


Figure 1. Design of studies to improve early chronic GVHD diagnosis. Studies may be designed to detect any manifestation of chronic GVHD or focus on specific organs that require subspecialty involvement, such as ocular or genital involvement. Patients should be enrolled prior to or shortly after HCT and followed serially every 2 to 3 months for clinical assessments and data collection.

Table 1

Baseline Evaluation to Be Done before Transplantation and Day +100 Post-Transplantation

Organ System	Required Clinical Documentation
Skin (including nails and hair)	Baseline skin abnormalities (scars, vitiligo, etc.) with photo-documentation, if possible
Mouth	Presence of linea alba, lichen-planus-like changes, and mucosal abnormalities
Eye	Presence of dry eyes and other eye symptoms, use of prescribed or over-the-counter eye drops
Lung	Pulmonary function tests including spirometry (FEV ₁ , FVC, FEV ₁ /FVC ratio, FEF _{25-75%}), lung volumes (VC, TLC, RV), and DLCO *
Liver	Bilirubin, AST, ALT, alkaline phosphatase
Gastrointestinal tract	Presence of anorexia, nausea, vomiting, diarrhea, dysphagia, food allergies/intolerance, etc.
Fascia/joints	Baseline limb mobility issues and P-ROM [63] For the pediatric adaptation of P-ROM, see EBMT handbook/chronic GVHD [32]
Genital	Evidence of lichen-planus-like lesions, erythema, ulcers, fibrosis, or phimosis in males (ideally women will be evaluated by a gynecologist)

Adapted from Jagasia et al. [17] and Carpenter et al. [33].

FEF_{25-75%} indicates forced expiratory flow between 25% and 75% of FVC; VC, Vital capacity; TLC, Total lung capacity; RV, Residual volume; DLCO, diffusing capacity of carbon monoxide; AST, aspartate transaminase; ALT, alanine aminotransferase; EBMT, European Society for Blood and Marrow Transplantation.

* PFTs may not be feasible in patients <7 years of age.

Table 2

Follow-up Evaluation Starting from D100 Post-HCT

Organ System	Required Items	Threshold for Referral to Specialized Transplant Team
Skin (including nails and hair)	Conduct a complete skin, nails, and hair evaluation. The patient should be asked whether any change in appearance has been noticed.	New onset of lesions suggestive of chronic GVHD per 2014 NIH consensus conference guidelines
Mouth	Evaluate for any lichen-planus-like changes, ulcers, erythema, and restriction of mouth opening. The patient should be asked about any pain, difficulty swallowing, or dryness.	New onset of lesions suggestive of chronic GVHD per 2014 NIH consensus conference guidelines
Eye	Ask about any ocular symptoms (dryness, excessive tearing, foreign body sensation, redness, difficulties opening eyelids, photophobia, etc.). Serial assessments by ophthalmology every 3 months during the first year post-HCT as feasible	Symptoms suspicious of onset of ocular GVHD and change from pre-HCT or previous post-HCT examination
Lung	Obtain pulmonary function tests, including spirometry, lung volumes, and DLCO at D100, 1 year, and yearly. Spirometry is recommended at 6 and 9 months post-HCT, and every 3 months in patients with chronic GVHD. Lung volumes and DLCO can be performed more frequently if clinically indicated.	Decline in the FEV ₁ of 10% or greater from the patient's baseline or D100 assessment; recommend short interval repeat testing (within 2–4 weeks)
Liver	Obtain bilirubin, AST, ALT, alkaline phosphatase	Rise of bilirubin or liver enzymes above 2014 NIH consensus conference thresholds
Gastrointestinal tract	Assess for nausea, anorexia, dysphagia, diarrhea, or weight loss	New onset of signs/symptoms suggestive for chronic GVHD per 2014 NIH consensus conference guidelines
Fascia/joint	Conduct functional and P-ROM assessment; for the pediatric adaption of P-ROM, see EBMT handbook/ chronic GVHD [32].	In clinical trials, a 2-point difference in total P-ROM is considered clinically relevant [63], but as a screening measure, any change from baseline, even by 1 point, may be significant.
Genital	Evaluate for any evidence of lichen-planus-like lesions, erythema, ulcers, fibrosis, or phimosis in males (ideally women would be evaluated by a gynecologist). Ask about any change in appearance, pain, or dryness.	New onset of signs/symptoms suggestive for chronic GVHD per 2014 NIH consensus conference guidelines

Adapted from Jagasia et al. [17] and Carpenter et al. [33].

Potential Factors to Be Assessed in Clinical Studies for Discovery and Validation of Early Chronic GVHD Markers

Table 3

Factor	Considerations
Clinical characteristics	Known risk factors (eg, peripheral blood stem cells, acute GVHD) Other demographic/clinical information
Signs/symptoms	Provider-assessed signs/symptoms; all signs/symptoms of chronic GVHD per the 2014 Diagnosis and Staging NIH consensus conference; subspecialty engagement for certain organ-specific assessments (eg, ophthalmology, dermatology, gynecology, urology, pulmonology); patient engagement/PRO; PRO (eg, Lee Chronic GVHD Symptom Scale, Ocular Surface Disease Index); home monitoring of P-ROM; handheld spirometry
Biologic	Routine lab monitoring (eg, eosinophils); cellular and protein biomarkers; additional -omics (eg, epigenetics, transcriptomics)
Technology	Lungs—parametric response mapping, hyperpolarized Xenon-129 MRI, multiple breath washout evaluations Skin—optical coherence tomography (noninvasive “biopsy”), myoton (stiffness and elasticity measurement)

PRO indicates patient-reported outcome.

Table 4

Recommended Best Practice and Optional Components of Ophthalmology Assessments

Component	Examination Pre- and Post-HCT
Best practice components	Best-corrected visual acuity
	Intraocular pressure
	Schirmer's test without anesthesia
	Tear-film breakup time
	Slit-lamp examination including lid/blepharitis assessment, ocular surface staining, conjunctival redness and fibrosis, lens
	Assessment of Meibomian gland function: quality and quantity of meibum
	Symptom questionnaire
Optional components	Meibography; corneal esthesiometry; confocal microscopy; photographic documentation of lids, tarsal and bulbar conjunctiva, cornea, fundus, InflammDry (Quidel Corporation, San Diego, CA); impression cytology; specular microscopy