Brazilian workshop model to train investigators in chronic graft-versus-host disease clinical trials according to the 2005-2006 National Institutes of Health recommendations

**Background:** The lack of standardization of clinical diagnostic criteria, classification and severity scores of chronic graft-versus-host disease led the National Institutes of Health to propose consensus criteria for the purpose of clinical trials.

**Method:** Here we describe a one-day workshop model conducted by the Chronic Graft-versus-Host Disease Brazil-Seattle Consortium Study Group to train investigators interested in participating in multicenter clinical trials in Brazil. Workshop participants included eight transplant physicians, one dermatologist, two dentists, three physical therapists and one psychologist from five institutions. Workshop participants evaluated nine patients with varying degrees of severity of mucocutaneous lesions and other manifestations of the disease followed by a training session to review and discuss the issues encountered with the evaluation and scoring of patients and in the methods used to evaluate grip strength and the 2-minute walk test.

**Results:** Most participants had difficulties in rating the percentage of each type of mucocutaneous lesion and thought 20 minutes was insufficient to evaluate and record the scores of each patient using the National Institutes of Health criteria and other cutaneous assessments. Several specific areas of difficulties encountered by the evaluators were: 1) determining the percentage of erythema in movable and non-movable scleroses, 2) whether to score all cutaneous findings in a particular area or just the dominant lesion; 3) clarification of the definition of poikiloderma in chronic graft-versus-host disease; 4) discrepant interpretation of the mouth score and 5) clarification on the methodology used for the evaluation of grip strength and the 2-minute walk tests.

**Conclusions:** Results of this workshop support the need to train investigators participating in clinical trials on chronic graft-versus-host disease.

**Keywords:** Graft vs. host disease/diagnosis; Graft vs. host disease/classification; Hematopoietic stem cell transplantation; Training

**Introduction**

Chronic graft-versus-host disease (GvHD) remains the major cause of late mortality after allogeneic hematopoietic stem cell transplantation (HSCT) and accounts for major impairment in the quality of life of long-term survivors. Disease manifestations result from tissue insult from interactions between antigen-presenting cells of the recipient and T lymphocytes of the donor. Some manifestations of chronic GvHD resemble autoimmune disorders such as scleroderma, Sjögren’s syndrome, primary biliary cirrhosis, bronchiolitis obliterans, chronic immunodeficiency and immune cytopenias. Chronic GvHD is a syndrome with various manifestations and clinical courses, making the diagnosis, staging and when to start systemic immunosuppression difficult to standardize. Moreover, response criteria to determine treatment efficacy have remained a major area of research which were revived by the National Institutes of Health (NIH) consensus project in 2005-2006.

The NIH consensus criteria for the diagnosis of chronic GvHD for clinical trial purposes was proposed in 2005 and include defining minimum criteria for the initial clinical diagnosis, grading of severity of the sites involved and of the overall severity of chronic GvHD. According to the NIH criteria, the initial diagnosis requires the presence of clinical manifestations found exclusively in chronic GvHD. The NIH classification subdivides GvHD into two categories according to the type of manifestations: acute GvHD (‘classic’ - acute GvHD manifestations occurring before day 100 and ‘late acute’ - acute GvHD manifestations occurring after 100 days post transplant) and chronic GvHD (classic - signs and symptoms only found in chronic GvHD with no features of acute GvHD and overlap syndrome - concurrent manifestations of acute and chronic GvHD at any time). The NIH also proposed...
a categorical score from 0 to 3 according to the severity of each organ involved (skin, mouth, eyes, gastrointestinal tract, liver, joints and fascia, lungs and genital tract). The overall severity of chronic GvHD by the NIH criteria is stratified as mild, moderate or severe and is dependent of the number of organs involved and the categorical severity scores given to each organ.\(^5\)

The Brazilian Society of Bone Marrow Transplantation held a consensus meeting in June 2009 to establish general guidelines and recommendations for the diagnosis and classification of chronic GvHD for clinical trials according to the NIH consensus project.\(^6\)

In 2008, a consortium was established between five Brazilian institutions and specialists from the Fred Hutchinson Cancer Research Center (Seattle), with the purpose of developing collaborative research in HSCT such as the Brazil-Seattle Chronic GvHD Study Group (GeDECH). The Brazilian participating centers of the GeDECH are the Instituto Nacional de Câncer (INCA), Universidade de Campinas (Unicamp), Universidade Federal do Paraná (UFPR), Universidade Federal do Rio de Janeiro (UFRJ) and Hospital Amaral Carvalho. The GeDECH is a multidisciplinary team of HSCT physicians, a dermatologist, a psychiatrist, psychologists, dentists, physical therapists, nurses, an epidemiologist and a data manager. A multicenter pilot study on the feasibility of applying the criteria of the NIH consensus by the GeDECH was presented at the American Society for Blood and Marrow Transplantation in 2010\(^7\) and is now in press.\(^8\)

The GeDECH is also participating in a prospective international multicenter study to validate the proposed criteria for diagnosis, classification and staging according to the NIH, with Dr. Stephanie Lee and Mary Flowers coordinating the study in Seattle. This study was approved by the Research Ethics Committee of each institution and by the Brazilian National Council of Ethics in Research.

Here we describe a one-day chronic GvHD workshop model conducted by the GeDECH at the Instituto Nacional do Cancer (INCA) for the purpose of training investigators interested in prospective multicenter clinical trials to evaluate the NIH criteria for diagnosis, classification and staging of chronic GvHD in Brazil and to identify any difficulties in the use of the instruments to evaluate manifestations of chronic GvHD in the skin and other organs for future studies.

Materials and methods

The one-day chronic GvHD Workshop study was organized by a multidisciplinary team involving a dermatologist, bone marrow transplant physicians, a dentist and a physical therapist from the GeDECH at INCA. Workshop participants included eight transplant physicians, one dermatologist, two dentists, three physical therapists and one psychologist from five institutions.

This workshop was approved by the INCA’s Institutional Review Board. Informed consent was obtained from all nine patients with chronic GvHD to allow clinical evaluations by several workshop participants and from an additional three patients for the grip strength and 2-minute walk tests. Photographs of the patients’ skin and mouth were also obtained previously and were identified only by case numbers to be used in the training session after the clinical evaluation during the workshop. Also, a summary of the medical history of each case was available including: date of birth, diagnosis, transplantation date, cell source, donor type and gender, HLA compatibility, conditioning regimen, grade of acute GvHD, chronic GvHD diagnosis date, type of onset, sites involved, current treatment and description of recent manifestations concerning skin, mouth, eyes, gastrointestinal tract, liver, lungs and genital tract, results of relevant biopsies and functional assessment by Karnofsky performance status (KPS) or Lansky performance status (LPS) scales. Chronic GvHD forms were used to evaluate and score the skin, mouth, range of movements of joints and overall severity of chronic GvHD according to the NIH and other evaluation tools translated into Portuguese.

The tools used in the workshop to evaluate chronic GvHD are shown in Annexes 1 and 2 and included: 1) the NIH categorical skin and oral cavity scores (0-3) based on type of manifestation, extent of involvement, symptoms and degree of severity affecting activities of daily living; 2) skin response tool which scores 8 body regions according to percentage of body surface area (BSA) involved with erythema, moveable sclerosis and non-moveable sclerosis; 3) the Vienna Skin Scale tool which scores 10 body regions with percentage involvement of pigmented changes, lichen planus-like lesions and sclerosis (scores of each region are summed for a total Vienna Skin Score of 0-50; 4) the Hopkins Skin Sclerosis Score (0-4) and Fascia Score (0-3), the GeDECH additional Oral Score and 5) the Range of Motion of Joints Scores. All the scoring forms (Annex 1) and the overall chronic GvHD score (Annex 2) were attached to the summary of each patient to be completed by the evaluator of each patient during the workshop session.

Before the practical evaluation of each case, workshop participants (evaluators) received a quick explanation of the program and received a package with the summary of each case and the chronic GvHD scoring sheets. For the initial workshop session, patients were divided into two shifts and distributed between four consultation rooms. Groups of three evaluators per patient room were formed to evaluate and complete the chronic GvHD scoring sheets in twenty minutes per patient.

The dentist (MEC) accompanied each evaluator group after their initial practical evaluation to provide additional training on the oral exam, answered questions and pointed out oral lesions missed by the evaluators during the initial session.

The second session was conducted by two physical therapists to demonstrate the grip strength and the 2-minute walk tests in three patients. The grip strength test was
performed with the hydraulic hand dynamometer with the patient using the dominant hand, seated with the elbow bent at 90°, shoulder and forearm in neutral position, wrist slightly extended, with three measurements of the maximum force reached in kilograms recorded by the pointer. The device was reset after each measurement. Finally, an average was calculated and compared to standard values for age and gender. The 2-minute walk distance test was performed on a 20 meter range track, marked at the beginning, every two feet and at the end. Patients had a rehearsal to understand the procedure and were placed at the start tag. One physical therapist encouraged them to walk as fast as possible and walked next to them all the way, while the other advised the time of departure, when the clock marked one minute and again 15 seconds from the end, and recorded the number of 'lips' in order to calculate the total distance in feet walked in 2 minutes.

The final session of the workshop consisted of a training session by the dermatologist (MM) and physical therapist (CS). The dermatologist presented photos of skin lesion types and percentage of affected area of each case and opened the discussion on a comparison of scoring between participants (evaluators) and the dermatologist's rating. The physical therapist clarified the methodology recommended by the NIH Consensus for functional assessment in particular about the grip strength and the 2-minute walk tests.

**Results**

The workshop was held on 30/7/2010 in Rio de Janeiro (CEMO/INCA) and included the evaluation of 9 patients by 14 multidisciplinary evaluators from 5 institutions. Patient demographic, transplant and chronic GvHD data of the nine cases evaluated during the workshop are shown in Tables 1 and 2.

The first session of the workshop included the evaluation of nine patients during 3.5 hours. Most of the evaluators thought that 20 minutes per patient was insufficient to read the medical summary, obtain the clinical evaluation and complete the chronic GvHD scoring forms.

Participants reported no problems with the scoring of joint movements and how to apply the "rule of 9" to record the percentage of affected cutaneous area of each body region. However, most evaluators had difficulties in scoring the fraction of erythema in movable and non-movable sclerosis according to the Vienna Score System (Grade 3 and 4) and assigning the percentage of BSA affected by certain types of skin lesions.

Participants observed the grip strength and 2-minute walk tests performed with three patients by the two physical therapists. Disagreement between the physical therapists from two different institutions on the methodology used to evaluate the 2-minute walk test was noted such as whether or not to encourage the patient to walk faster, the necessity or not to walk together with the patient during the entire test and setting standards in the methodology used in the grip strength test. Such discrepancies were later reconciled by standardizing the methodology for future multicenter studies.

After the conclusion of the clinical evaluation of the workshop, patients were invited to a lunch meeting with a psychologist from the transplant center to discuss about their workshop experience. Patients indicated that the workshop was what they had expected and that they were glad to have been able to contribute to this training session.

In addition to time limitations to evaluate and complete the scoring forms of each patient, specific difficulties in determining the percentage of BSA associated with certain types of skin and mouth lesions were discussed, reviewed and reconciled during the training sessions that followed the practical evaluation session.

Specific areas of difficulties and need for clarification identified during the training session included: a) determining the fraction of erythema in movable and non-movable sclerosis, (Figure 1); b) scoring all elements of cutaneous features (i.e., hypochromia, hyperpigmentation, erythema and not only the diagnostic manifestations of chronic GvHD of a particular area (i.e., lichen planus-like lesions, cutaneous

| Table 1 - Patient and transplant characteristics |
|-----------------------------------------------|
| Characteristics                              | n = 9 | %  |
| Patient age, median (range) - years           | 47 (13 - 53) | -   |
| Time since transplant, median (range) - years | 2 (1.1 - 8.4) | -   |
| Patient gender, male                         | 6     | 67  |
| Donor type, 6/6 HLA-identical related         | 9     | 100 |
| Diagnosis at transplant                      |       |     |
| Acute leukemia                                | 7     | 78  |
| Chronic myeloid leukemia                      | 1     | 11  |
| Myelodysplastic syndrome                      | 1     | 11  |
| Conditioning regimen types                   |       |     |
| Myeloablative                                 | 8     | 89  |
| Non-myeloablative                             | 1     | 11  |
| Source of stem cells                          |       |     |
| Bone marrow                                   | 5     | 55  |
| Mobilized blood                               | 4     | 45  |
| Donor gender                                  |       |     |
| Male                                          | 3     | 33  |
| Female                                        | 6     | 67  |
| GvHD prophylaxis                              |       |     |
| Cyclosporine + methotrexate                   | 8     | 89  |
| Cyclosporine                                  | 1     | 11  |
| Prior grade 2-4 acute graft-versus-host disease - yes | 9 | 100 |
| Chronic GvHD NIH subtype                      |       |     |
| Classic                                       | 6     | 67  |
| Overlap                                       | 3     | 33  |
| Onset type                                    |       |     |
| Progressive                                   | 7     | 78  |
| Quiescent (interrupted)                       | 2     | 22  |
| Overall severity                              |       |     |
| Mild                                          | 1     | 11  |
| Moderate                                      | 2     | 22  |
| Severe                                        | 6     | 67  |
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Table 2 - Chronic GVHD manifestations and therapies

| Case | Skin/Fascia                      | Mouth                          | Other sites involved         | Therapy                                      |
|------|----------------------------------|--------------------------------|-------------------------------|----------------------------------------------|
| 1    | Erythema/Lichen planus-like     | Mucocoele/Lichen planus-like   | Liver/gastrointestinal tract/ Eyes | FK/PDN/PUVA/ Ursodiol/Topical steroids and tacrolimus |
| 2    | Movable and non-movable sclerosis/Fasciitis | Mucocoele/Lichen planus-like | Genitalia/ Liver/Lungs | CsA/PDN/MMF/ECP/ Ursodiol/Stereoids inhalators/Oral laser |
| 3    | Movable and non-movable sclerosis/Fasciitis | Lichen planus-like | Liver/Lungs | CsA/PDN/UVB-NB/Stereoids inhalators |
| 4    | Movable and non-movable sclerosis | Lichen planus-like             | Liver                         | CsA/PDN/MMF/PUVA/Ursodiol/Topical therapy*a |
| 5    | Movable and non-movable sclerosis | Lichen planus-like             | -                             | PUVA                                         |
| 6    | Movable and non-movable sclerosis/Fasciitis | Lichen planus-like | Liver                         | CsA/Ursodiol/Topical therapy *a               |
| 7    | Movable and non-movable sclerosis/Fasciitis | Lichen planus-like | Liver/Eyes/ Lungs             | MMF/PDN/PUVA/ECP/Ursodiol/ Topical therapy*a |
| 8    | Lichen planus-like              | Lichen planus-like             | Liver                         | MMF/PDN/PUVA/Ursodiol                        |
| 9    | Erythema                         | Lichen planus-like             | Liver                         | CsA/Ursodiol/Topical therapy *a               |

FK-tacrolimus, PDN-prednisone, PUVA-phototherapy UVA + psoralen, CsA-cyclosporine, MMF-mofetil mycophenolate; ECP-extracorporeal photopheresis; UVB-NB-phototherapy UVB - narrow band, a-topical steroids and tacrolimus

Figure 1 – Erythema over movable and non-movable sclerosis related to chronic GvHD. Example of a case to illustrate the potential difficulty on how to rate the fraction of erythema over the affected areas of sclerosis

Figure 2 – Cutaneous manifestations of chronic GvHD to illustrate the importance of complete skin examination (i.e., color changes, shape of lesion, surface, thickness and mobility). Example of a case difficult to rate with various skin manifestations in each affected area

Figure 3 – Illustration of poikiloderma which may be difficult to score in the absence of sclerosis

sclerosis) illustrated in Figure 2; c) how to score poikiloderma using the Vienna Score Scale when color changes are not associated with sclerosis (Grade 1?) versus when poikiloderma is secondary to moveable sclerosis (Grade 3?) - illustrated in Figure 3; d) where to record the percentage of BSA affected by keratosis pilaris like rashes in the NIH response criteria tool (erythema?); e) how to record erythema when attributed to phototherapy (PUVA) or other causes other than chronic GvHD - should it be described separately from the chronic GvHD scoring?; f) clarification for the definition of "back" in the study to include the entire back and buttocks; g) clinical interest in scoring lip atrophy and restrictions in mouth opening from sclerosis (Figure 4); h) lack of an objective evaluation of xerostomia by the NIH scoring criteria of the mouth (i.e., the absence of sublingual lake is not noted9); i) better definition to score the degree of limitations in oral intake (i.e., not significant, partially or
severity of each organ involved but also developed new
addition, the NIH proposed a 0-3 categorical score to assess
found in chronic GvHD (not present in acute GvHD).(10) In
standardized criteria in the diagnosis of chronic GvHD for
and soft palate.(9) All oral lesions should be scored according
tongue and soft palate, while mucocele only on labial mucosa
Hyperkeratotic plaques, ulcers and erythema manifestations
the four clinical signs of chronic GvHD including:
362                                                                                                                                             Rev Bras Hematol Hemoter. 2011;33(5):358-66
Discussion
GvHD and feasible tests to be conducted in clinical trials.
evaluate functional performance of patients with chronic
and the walk tests were thought to be important measures to
the patient to show the course as part of the explanation
or by walking together during the test or, to only walk with
the patient to show the course as part of the explanation
about the 2 minute test prior to testing). Both the grip strength
and the walk tests were thought to be important measures to
evaluate functional performance of patients with chronic
GvHD and feasible tests to be conducted in clinical trials.
Teaching points on Oral Medicine (MEC) during the
training session was the basic evaluation of the mouth to score
the four clinical signs of chronic GvHD including:
hyperkeratotic plaques, ulcers, erythema and mucocele.
Hyperkeratotic plaques, ulcers and erythema manifestations
should be evaluated on the lips, labial mucosa, buccal mucosa,
tongue and soft palate, while mucocele only on labial mucosa
and soft palate.(9) All oral lesions should be scored according
to the percentage of total area affected by each lesion. For the
subjective evaluation of oral symptoms, complaints of dry
mouth, altered taste, pain and tenderness with or without
limitations in oral ingestion are considered. It is important to
note that the definition of oral sensitivity is related to spicy
food ingestion or use of toothpaste, therefore distinct from
mouth pain, which is recorded separately in another scale.

Figure 4 – Lip atrophy and restriction of mouth opening from sclerosis
severe); j) clarification between the overall severity of chronic
GvHD by evaluators as a qualitative rating based on clinical
impression and thus independent from the NIH categorical
severity scores of each organ - for instance a patient with
only non-moveable score affecting less than 10% of total
BSA as the only manifestation of chronic GvHD would be
rated with mild overall severity by the physician and would
have a skin score of 3 by the NIH categorical organ scale
because of the non-moveable sclerosis; k) Clarification on
the methodology for the 2-minute walk due to discrepant
interpretation between the physical therapists of two different
centers (i.e., whether to encourage or not the patient verbally
or by walking together during the test or, to only walk with
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Discussion
The NIH consensus scoring system proposed
standardized criteria in the diagnosis of chronic GvHD for
clinical trials that require clinical manifestations exclusively
found in chronic GvHD (not present in acute GvHD).(10) In
addition, the NIH proposed a 0-3 categorical score to assess
severity of each organ involved but also developed new
criteria to evaluate treatment response.(4) A large prospective
multicenter clinical trial in chronic GvHD is underway in North
America(11) and in other countries including Brazil to validate
several NIH proposed tools to evaluate chronic GvHD and
determine their impact on major chronic GvHD-related
outcomes (i.e., overall survival, relapse, non-relapse mortality,
duration of immunosuppression, quality of life, etc.) compared
to other evaluation measurements including the Skin and
Fascia Scores by Johns Hopkins and the Vienna Skin Scale.(12)
Some of the results from this multicenter clinical trial have
been published or are in press.(13,14)

Our workshop was well received and viewed as an
appropriate model to evaluate chronic GvHD using the NIH
and other measurement tools and to train investigators
interested in participating in clinical trials in Brazil. In this
workshop, evaluators had difficulties in scoring the extent of
involvement of certain types of skin manifestations. As
reported by others,(12,13) variability in the chronic GvHD
scoring were also noted using the NIH and other scoring
measurement tools, but results of the inter and intra-evaluator
variability improved with subsequent training. The time
required for adequate evaluation and completion of various
tools used to score chronic GvHD in the current workshop
was greater than 20 minutes per patient. However, time to
evaluate and score patients with chronic GvHD may be
shorter for physicians who follow their own patients and
with increased experience in using the scoring tools.

One objective evaluation missing in the current NIH
and other available tools noticed by the dentist is the scoring
of xerostomia and oral mucosa atrophy, resulting in a gap in
the oral assessment of chronic GvHD that may underestimate
the oral score.

Difficulties in scoring certain types of skin manifestations
were noted. For instance, evaluation of erythema in patients
receiving PUVA could result in an overestimation of erythema
not related to chronic GvHD. The point was made that erythema
caused by photochemotherapy such as PUVA(16,17) is usually
diffuse, non-pruritic and limited to treatment-exposed areas
that often resolves within 48 to 72 hours.

Another area of difficulty was in scoring poikiloderma
(atrophic with pigmentedary skin changes) using the Vienna Skin
Scale. For example, a patient with hypo- and hyper-pigmentation
and erythema without sclerosis would be scored as Grade 1
but as Grades 3-4 if the poikiloderma is secondary to sclerosis
(movable or non-movable). Therefore, recognizing the
diagnosis of chronic GvHD lesions is critical for adequately
scoring the skin according to the Vienna Skin Scale.

Another teaching point by the dermatologist (MMS)
about the Vienna Skin Scale was on how to recognize skin
lichen planus-like lesions and cutaneous sclerosis in hyper-
or hypo-pigmentation areas. Considering that hyper- and
hypo-pigmentation are often associated with diagnostic
cutaneous manifestations of chronic GvHD, such lesions
should be scored in the Vienna Skin Scale as either Grade 2
(lichen-planus like presentation) or Grade 3 or Grade 4 if,
respectively, movable or non-movable sclerosis is present.

Variability in the scoring of chronic GvHD represents a limitation of available tools with potential impact on the interpretation of results in multicenter clinical trials. Appropriate training of investigators is therefore necessary in the utilization of the scoring tool chosen for consistency of the evaluator, especially in studies aimed to evaluate the extent and types of skin involvement of chronic GvHD.

This workshop was useful to clarify several questions related to the NIH and other evaluation tools that are used in studies of chronic GvHD. The feasibility of this study motivated the GeDECH to put together a similar education workshop session during the annual meeting of the Brazilian Society of Bone Marrow Transplantation in August 2011 to expand the training of new investigators interested in participating in future GeDECH studies. The second workshop had more than 30 participants from more than 8 institutions and was well received.

**Conclusion**

The 2005-2006 NIH chronic GvHD criteria for clinical diagnosis, staging and other proposed measures to evaluate treatment response in clinical trials represent an important first step towards the development of better treatment and to improve survival and quality of life of affected patients. We demonstrated the feasibility of conducting a workshop on the NIH chronic GvHD tools and other cutaneous measures as a model to evaluate and train Brazilian investigators participating in multicenter clinical trials.

Several areas of difficulties in the evaluation of patients with chronic GvHD according to the NIH and other tools were identified. Results of this workshop support the need of training investigators interested in participating in future chronic GvHD clinical trials and suggest the need for simplifying current tools to evaluate chronic GvHD especially regarding the cutaneous involvement measures.

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Glossary

Poikiloderma – combines reticulated pattern and epidermal atrophy. It is common to observe simultaneous erythema, and hyper- and hypo-pigmentation. It is a dermatological alteration of pigmentation.

Lichen planus-like lesions – erythematous-violaceous papules that may form annular plaques. Often, there are whitish lines on the surface (Wickham striae) similar to those of idiopathic lichen planus. Oral lesions may be presented in a reticular, plaque, atrophic, erosive and bullous pattern.

Movable lichen sclerosus-like lesions – change in skin texture, decreased skin turgor (skin looks like cigarette paper); lesions are grouped into gray to white movable plaques.

Morphea-like sclerotic features – localized patchy areas of fibrosis of the dermal tissue, often with dyspigmentation. Although the skin is movable, there is a decrease in the possibility of pinching.

Non-movable sclerosis – deep sclerosis features without the possibility of pinching or mobilization.

Fasciitis – skin surface may have varying degrees of fibrosis or be normal, depression marks are seen throughout the course of the tendons with reduced range of motion; inability to assume a "prayer posture".

Depigmentation (vitiligo-like) – the achronia appears isolated after lichen planus-like manifestations or on the top of an inflammatory healing process such as zoster. It can be segmental or generalized.

Follicular keratosis – erythematous papules with perifollicular corneal plugs inside the follicle opening.

Hyperpigmentation – pigmentary change without sclerosis. No active erythema.

Maculo-papular rash – erythematous papules (3-4 mm) that converge; often scaly, seen with both acute and chronic GvHD or after lymphocyte infusion.

PUVA – treatment using total body irradiation with ultraviolet A combined with prior oral photosensitizing (psoralen)

Mucocele – term used for leakage or retention of mucus.

Xerostomia – complaint of dry mouth due to lack of saliva.

Hyposalivation – decreased amount of saliva in the mouth.

Anexos

Annex 1- Forms with the tools used for the scoring of chronic GvHD and NIH skin response

| Indicate % of body part affected | Erythematous rash of any sort | Moveable sclerosis | Non-moveable subcutaneous sclerosis or fasciitis |
|----------------------------------|------------------------------|--------------------|-----------------------------------------------|
| Head/neck/scalp                  |                              |                    |                                               |
| Anterior torso                   |                              |                    |                                               |
| Posterior torso                  |                              |                    |                                               |
| L. upper extremity               |                              |                    |                                               |
| R. upper extremity               |                              |                    |                                               |
| L. lower extremity (including buttocks) |                      |                    |                                               |
| R. lower extremity (including buttocks) |                      |                    |                                               |
| Genitalia                       | Not examed                   |                    |                                               |

Hopkins' Sclerosis Assessment Tool

|                | 0 | 1 | 2 | 3 | 4 |
|----------------|---|---|---|---|---|
| Skin sclerotic changes | Normal | Thickened with pockets of normal skin | Thickened over majority of skin | Thicken, to move unable | Hidebound, unable to pinch |

NIH Categorical Skin Score and Fascia Score Tools

|                | 0 | 1 | 2 | 3 |
|----------------|---|---|---|---|
| Skin Score     | No signs or 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" (unlable to pinch) OR impaired mobility, ulceration or severe pruriitus |
| Fasciae        | Normal | hardened, tense with normal areas | hardened, tense | hardened, tense, unable to move |

Clinical Features

- Location: 
  - Ulcers
  - Maculopapular rash
  - Lichen planus-like lesions
  - Poikiloderma
  - Pruritus
  - Diffuse Erythema
  - Hypochromia (vitiligo)

- Largest dimension: cm
  - Keratosis follicular ("keratosis pilaris")
  - Papulosquamous lesions or icthyosis
  - Hair involvement
  - Nails involvement
  - Others, specify:
  - Others, specify:
### Vienna skin scale tool

| Region                  | Grade | % Area of Grade | Fraction of Grade 3 or 4 Areas with erythema (indicate up to what fraction is involved) | Region                  | Grade | % Area of Grade | Fraction of Grade 3 or 4 Areas with erythema (indicate up to what fraction is involved) |
|-------------------------|-------|-----------------|--------------------------------------------------------------------------------------|-------------------------|-------|-----------------|--------------------------------------------------------------------------------------|
| 1. Head, neck and scalp | 0     |                 |                                                                                      | 6. Right hand           | 0     |                 |                                                                                      |
|                         | 1     |                 |                                                                                      |                         | 1     |                 |                                                                                      |
|                         | 2     |                 |                                                                                      |                         | 2     |                 |                                                                                      |
|                         | 3     |                 |                                                                                      |                         | 3     |                 |                                                                                      |
|                         | 4     |                 |                                                                                      |                         | 4     |                 |                                                                                      |
|                         | Total | 100%            |                                                                                      |                         | Total | 100%           |                                                                                      |
| 2. Chest                | 0     |                 |                                                                                      | 7. Left arm             | 0     |                 |                                                                                      |
|                         | 1     |                 |                                                                                      |                         | 1     |                 |                                                                                      |
|                         | 2     |                 |                                                                                      |                         | 2     |                 |                                                                                      |
|                         | 3     |                 |                                                                                      |                         | 3     |                 |                                                                                      |
|                         | 4     |                 |                                                                                      |                         | 4     |                 |                                                                                      |
|                         | Total | 100%            |                                                                                      |                         | Total | 100%           |                                                                                      |
| 3. Abdomen and genitals | 0     |                 |                                                                                      | 8. Left hand            | 0     |                 |                                                                                      |
|                         | 1     |                 |                                                                                      |                         | 1     |                 |                                                                                      |
|                         | 2     |                 |                                                                                      |                         | 2     |                 |                                                                                      |
|                         | 3     |                 |                                                                                      |                         | 3     |                 |                                                                                      |
|                         | 4     |                 |                                                                                      |                         | 4     |                 |                                                                                      |
|                         | Total | 100%            |                                                                                      |                         | Total | 100%           |                                                                                      |
| 4. Back and buttocks    | 0     |                 |                                                                                      | 9. Right leg and foot   | 0     |                 |                                                                                      |
|                         | 1     |                 |                                                                                      |                         | 1     |                 |                                                                                      |
|                         | 2     |                 |                                                                                      |                         | 2     |                 |                                                                                      |
|                         | 3     |                 |                                                                                      |                         | 3     |                 |                                                                                      |
|                         | 4     |                 |                                                                                      |                         | 4     |                 |                                                                                      |
|                         | Total | 100%            |                                                                                      |                         | Total | 100%           |                                                                                      |
| 5. Right arm            | 0     |                 |                                                                                      | 10. Left leg and foot   | 0     |                 |                                                                                      |
|                         | 1     |                 |                                                                                      |                         | 1     |                 |                                                                                      |
|                         | 2     |                 |                                                                                      |                         | 2     |                 |                                                                                      |
|                         | 3     |                 |                                                                                      |                         | 3     |                 |                                                                                      |
|                         | 4     |                 |                                                                                      |                         | 4     |                 |                                                                                      |
|                         | Total | 100%            |                                                                                      |                         | Total | 100%           |                                                                                      |

Check ONE area of the body as the sentinel lesion. Percentages must add up to 100

0 = normal skin; 1 = discoloration, hyperpigmentation, alopecia, erythema, maculopapular rash; 2 = lichenoid plaque, or skin thickened (able to move); 3 = skin thickened with limited motion but able to pinch [scleroderma or fascic involvement]; 4 = hidebound skin, unable to move, unable to pinch.

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### Evaluation of range of motions of joints scoring tool

#### (3 of 4)

**Shoulder**

1. **Elbow**

1. **Wrist and fingers**

1. **Foot Dorsiflexion**

1. **Foot Plantarflexion**

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Rev Bras Hematol Hemoter. 2011;33(5):358-66
### Evaluation of oral cavity using NIH and GeDECH Scoring Tools (4 of 4)

| Mouth scores                                      | 0 No symptoms | 1 Mild symptoms with disease signs but not limiting oral intake significantly | 2 Moderate symptoms with signs and partial limitation of oral intake | 3 Severe symptoms with disease signs on examination and major limitation of oral intake |
|---------------------------------------------------|----------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Erythema                                          | None           | Mild to moderate erythema over < 25% oral surface area (OSA)                    | Moderate erythema over > 25% OSA or severe erythema over < 25% OSA   | Severe erythema over > 25% OSA                                                     |
| LiEhena planus-like                               | None           | Hyperkeratotic changes (<25% OSA)                                              | Hyperkeratotic changes (25-50% OSA)                                   | Hyperkeratotic changes (>50% OSA)                                                  |
| Ulcers                                            | None           | No                                                                               | Ulcers (< 20%)                                                       | Sever ulcers (>20%)                                                                |
| Mucoceles (only lower lip and soft palatce)       | None           | 1-5 mucoceles                                                                    | 6-10 mucoceles                                                       | > 10 mucoceles                                                                     |
| Mouth pain                                        | None           | Sensitivity to foods                                                             | Oral pain that needs narcotics                                        | Unable to eat due to oral pain                                                      |
| Hyposalivation noticed in the oral examination?   | Yes            |                                                                                  |                                                                     |                                                                                     |

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**Diagram:**

- Labial mucosa
- Gingiva
- Hard palate
- Soft palate
- Tongue
- Cheek
- Right
- Left

**Ulcers:**

I Measurement of largest first ulcer noticed (Sentinel lesion) (S):

\[ X \_\_ \_ cm \]

Please mark the ulcer location in the Figure

II Other new ulcer (O) since last evaluation?

- Yes: Measure the largest ulcer (O) \[ X \_\_ \_ cm \]
- No

Estimation of the total surface of oral cavity

- 40% includes:
  - Lips (“vermillion lips”)
  - Labial mucosa
  - Buccal mucosa
- 20% includes:
  - Tongue
  - Palate (soft and hard)

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**Annex 2: Overall status of chronic GvHD by the evaluator (Physician)**

**Please rate the severity of this person’s chronic GvHD**

| Scale A: (mark one) | None (0) | Mild (1) | Moderate (2) | Severe (3) |
|---------------------|----------|----------|--------------|------------|
| cGvHD symptoms are not at all severe | | | | |
| Scale B: (circle one) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| cGvHD symptoms are the most severe possible | | | | | | | | | | | |