MEDIZINISCHE UNIVERSITÄT WIEN

Univ. Klinik für
Innere Medizin I

NIH-Defined GvHD

Hildegard Greinix
Medical University of Vienna
Vienna, Austria

My Disclosure

Company	Speakers Bureau	Advisory Board
Therakos	√	√
Genzyme	√	√

Pathophysiological Requirements for Acute Graft-versus-Host Disease

Defined by Billingham 1966

- Graft contains immunocompetent cells.
- Host expresses minor or major transplantation antigens lacking in the donor.
- Host is incapable of rejecting the graft.

Risk factors for GvHD

Donor

- HLA disparity (related/unrelated)
- Sex mismatch (F – M)
- Age >35 yrs
- Alloimmunisation (pregnancy, transfusions)
- SC source (PBSC>BM>CB)
- NK-cell alloreactivity

Host

- Age >35 yrs
- Intensity of conditioning
- Prevention of GvHD
- CMV, infections
- Genetic predisposition
- Rapid establishment of donor T-cell chimerism

Acute GvHD

Clinical Presentations

NIH-Defined Features of Acute GvHD

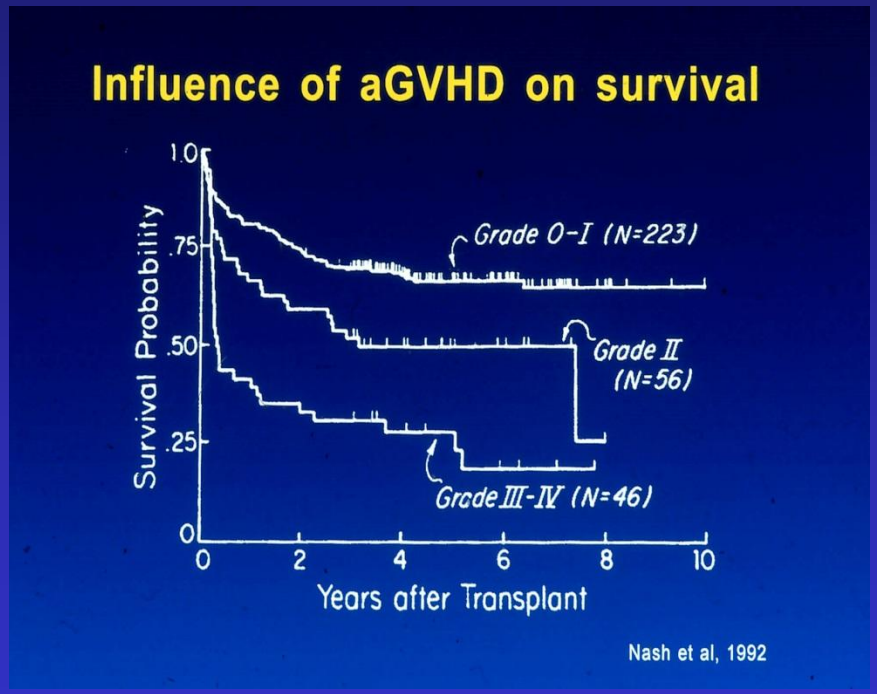
- Maculopapular rash
- Nausea, vomiting, anorexia
- Profuse diarrhea
- Ileus
- Cholestatic hepatitis

Filipovich et al, BBMT 11:945-955, 2005

Consensus Conference on Acute GvHD Grading Przepiorka 1995

Stage	Skin	Liver (Bilirubin mg/dl)	Gut (Diarrhea ml/day)
1 2 3 4	<25% 25-50% >50% Erythrodermia	2-3 3-6 6-15 >15	>500 or Nausea >1000 >1500 Pain/Ileus
Functional	**Skin**	**Liver**	**Gut**
I II III IV	Stage 1 or 2 Stage 3 or - Stage 4 or	None Stage 1 or Stage 2 or 3 or Stage 4	None Stage 1 Stage 2, 3 or 4 -

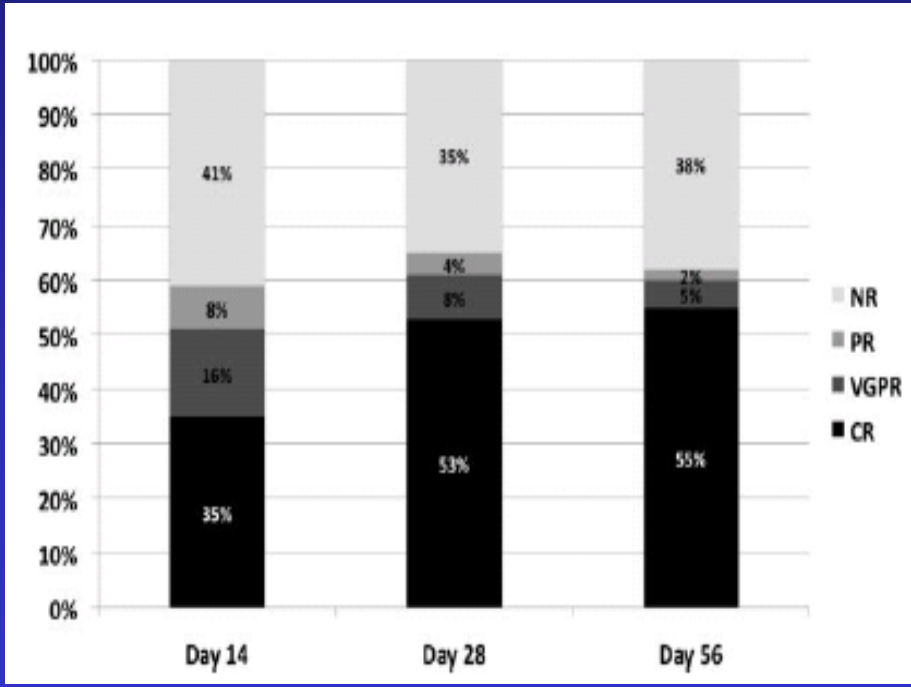
Acute GvHD is Serious Complication of Allo HCT



- **Challenge**: GvL effect vs. morbidity and mortality due to severe GvHD
- GvHD has significant negative impact on survival
- **Challenge**: Efficacy vs toxicity of IS

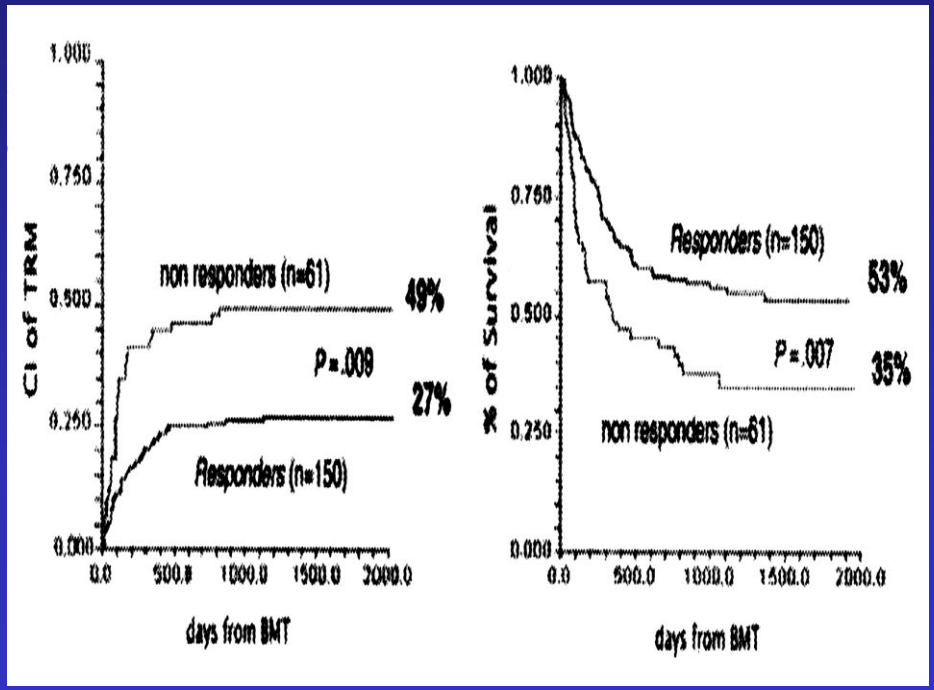
Response to First-Line Therapy with Steroids Impacts on Survival of Acute GvHD

Response to Steroids



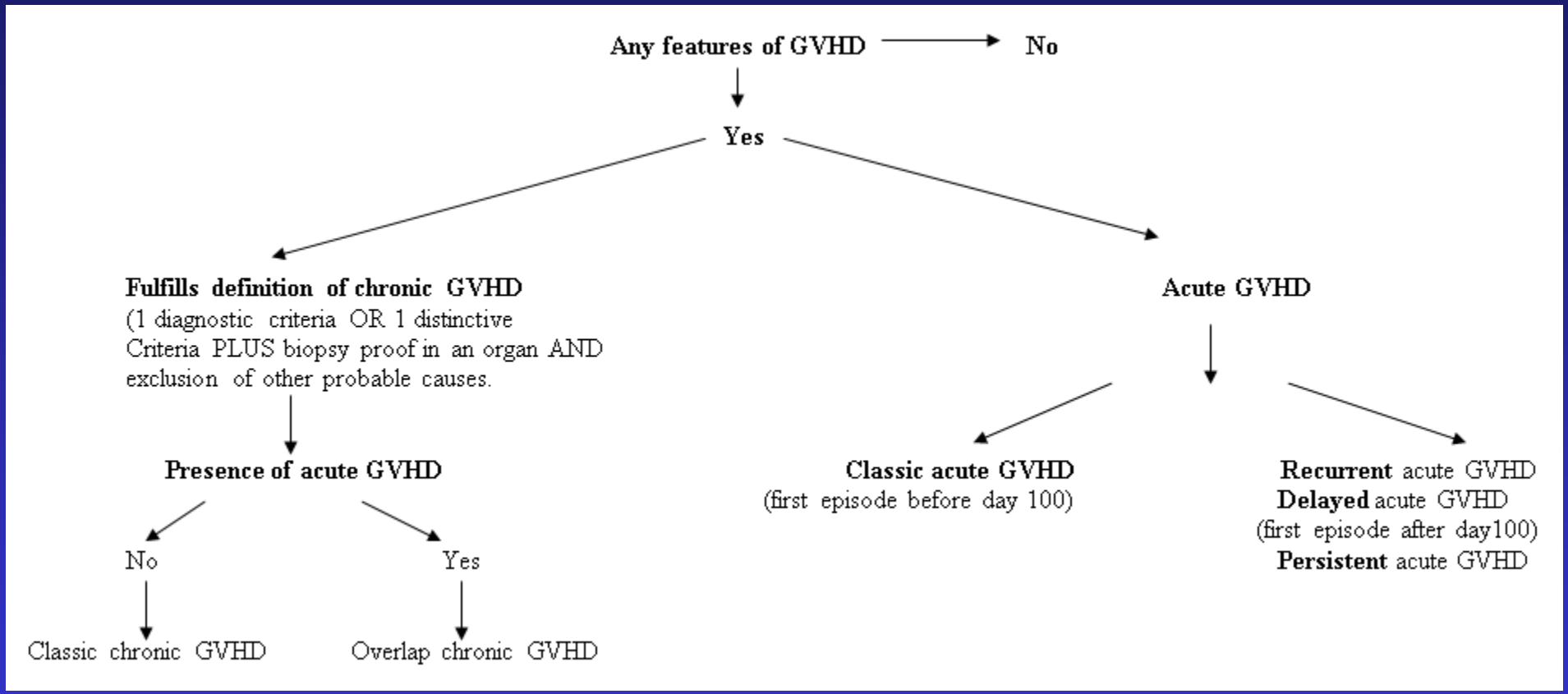
MacMillan et al, Blood 2010

NRM and OS



Van Lint et al, Blood 2006

Using the NIH Consensus Criteria



Filipovich et al, BBMT 11:945-955, 2005

Acute GvHD: New NIH Definitions

Category	Time of symptoms after HCT or DLI	Presence of acute GvHD features	Presence of chronic GvHD features
Classic acute	≤ 100 days	yes	no
Persistent acute	> 100 days	yes	no
Recurrent acute	> 100 days	yes	no
Late-onset acute	> 100 days	yes	no

Filipovich et al, BBMT 11:945-955, 2005

Acute GvHD is reduced after nonmyeloablative vs myeloablative conditioning HCT

Related

Unrelated

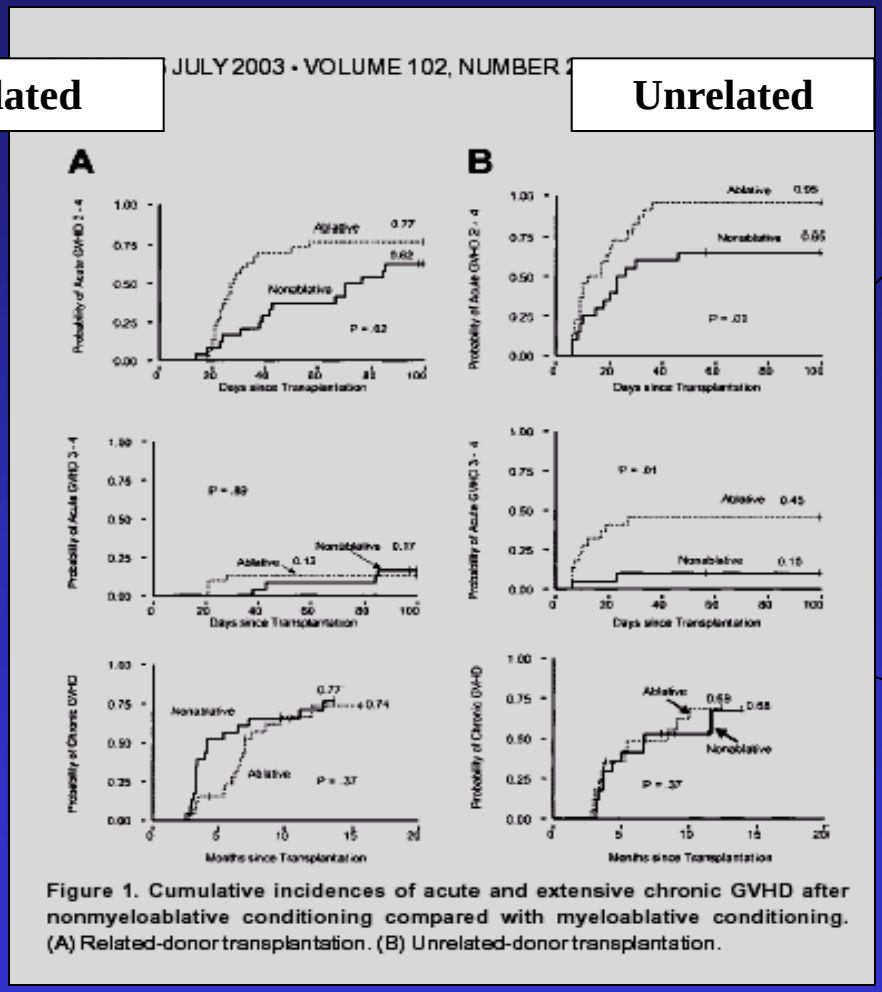


Figure 1. Cumulative incidences of acute and extensive chronic GVHD after nonmyeloablative conditioning compared with myeloablative conditioning. (A) Related-donor transplantation. (B) Unrelated-donor transplantation.

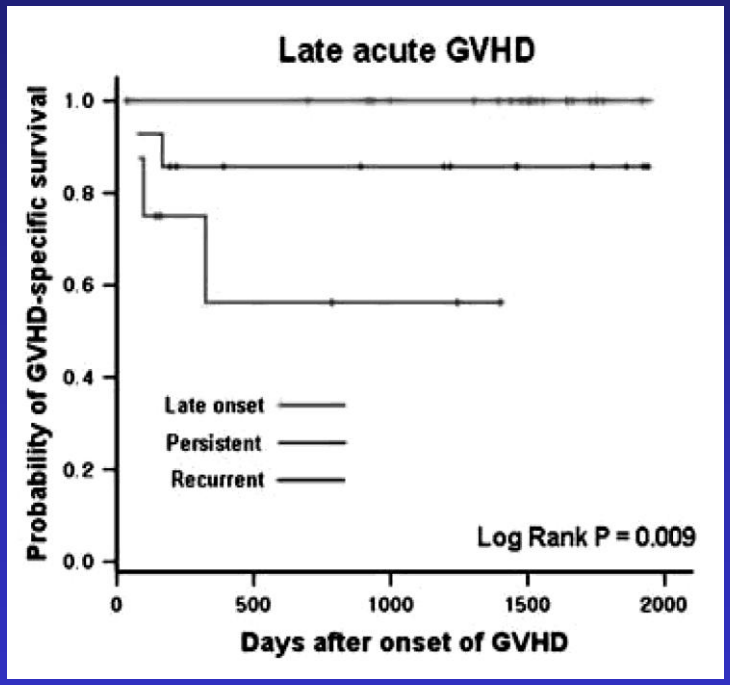
Acute GvHD: Delayed and reduced incidence

Chronic GvHD: No difference

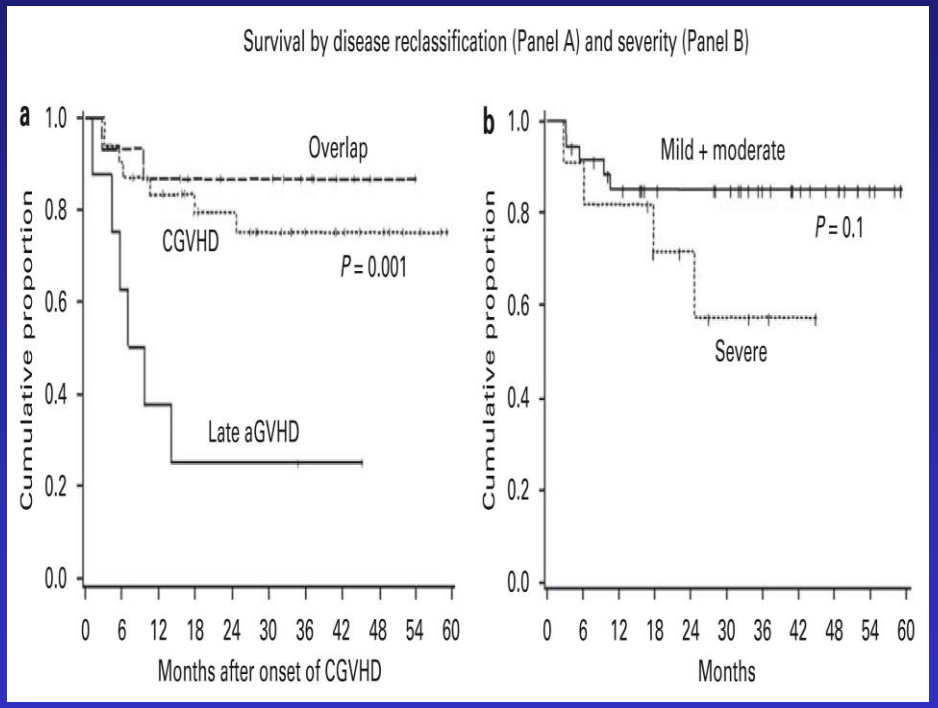
Mielcarek et al, Blood 2003

Why Should we Distinguish Late Acute GvHD from Chronic GvHD?

Cho et al, Leukemia 2009

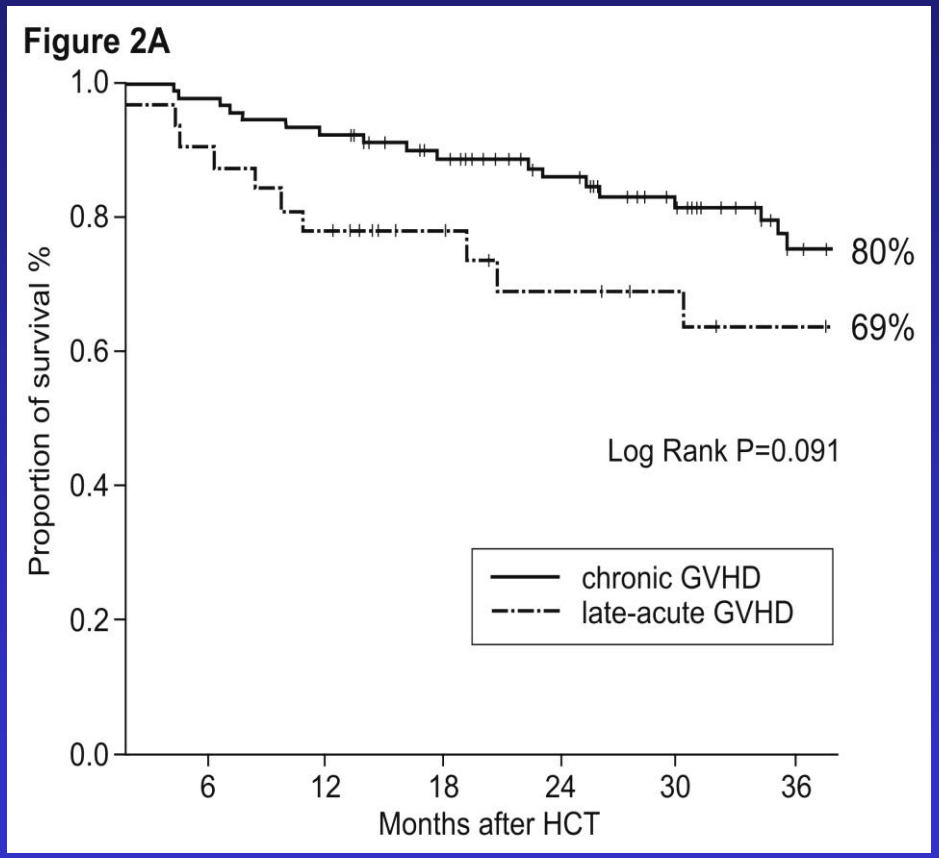


Arora et al, BMT 2009



- Cho et al. Leukemia 2009. 211 pts reclassified, late aGvHD 21%, overlap sy 30%, classic chronic 49%.
- Arora et al.BMT 2009. 54 patients reclassified.

Why Should we Distinguish Late Acute GvHD from Chronic GvHD?



- **Prospective study**: 115 pts with cGvHD, 11 pts with recurrent, 11 persistent, 10 late-onset acute GvHD
- Increased NRM only in recurrent aGvHD (HR 4.15)

Kuzmina Z et al, Leukemia 2012;26:746-56

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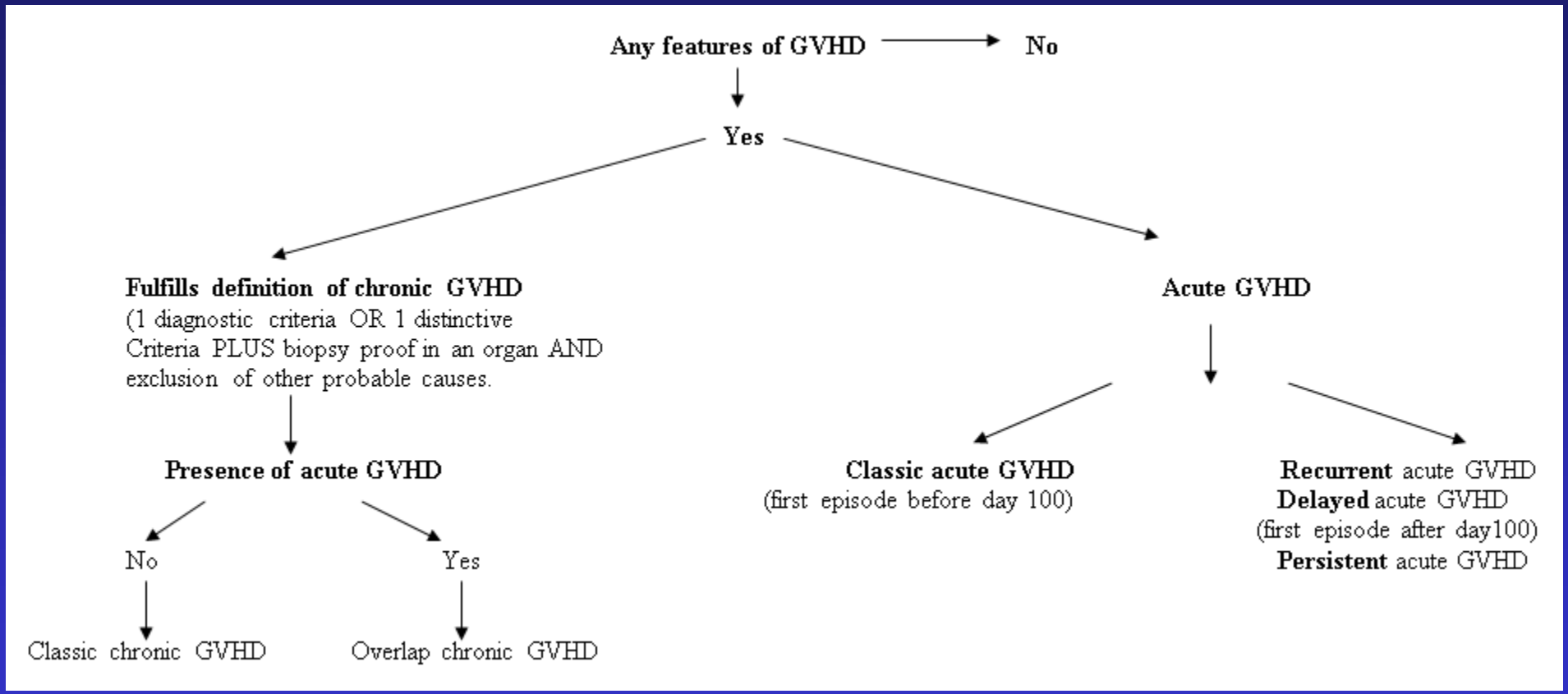
Distinction between Acute and Chronic GvHD

- **Old criteria**: All GvHD signs and symptoms on day 100 or at longer follow-up are chronic GvHD.

Seattle Classification of Chronic GvHD

- **Limited**
  - Localized skin and/or hepatic dysfunction due to cGvHD
- **Extensive**
  - Generalized skin involvement
  - Localized skin involvement and/or hepatic dysfunction plus liver histology or cirrhosis or involvement of eye or minor salivary glands or oral mucosa or any other target organ

Using the NIH Consensus Criteria



Filipovich et al, BBMT 11:945-955, 2005

Categories of chronic GvHD

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

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

ASBMT
American Society for Blood and Marrow Transplantation

National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. Diagnosis and Staging Working Group Report

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

Category	Time of symptoms after HCT or DLI	Presence of acute GvHD features	Presence of chronic GvHD features
Classic chronic GvHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

Filipovich et al, BBMT 11:945-955, 2005

Assessment of Chronic GvHD: Easily Done in Daily Practice

Establish diagnosis

1. Exclude acute GvHD
2. Diagnostic or distinctive signs
3. Rule out other disease

Organ score

8 organs
Based on symptoms, signs, function

Global score

Overall severity
Prognosis
Need for systemic/topical therapy

Diagnosis of Chronic GvHD according to NIH Consensus

1. **Distinction from acute GvHD**

2. Presence of at least 1 diagnostic clinical sign of chronic GvHD or presence of at least 1 distinctive manifestation confirmed by b*iopsy or other* relevant tests

3. Exclusion of other possible diagnoses

4. Severity scoring (0 to 3) for each organ and global

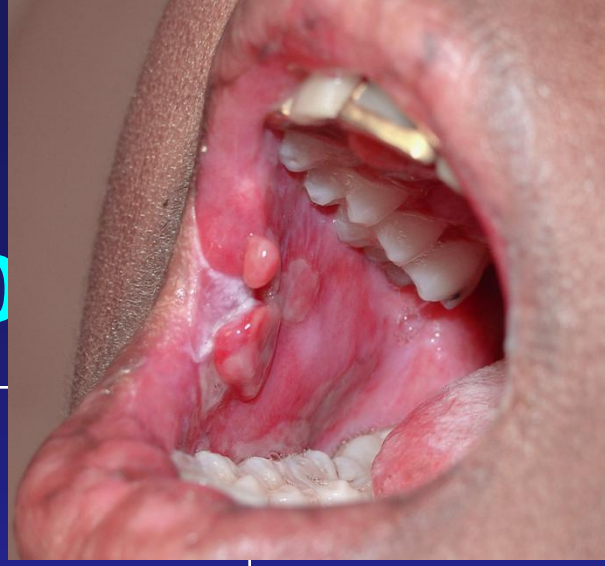
Filipovich et al, BBMT 11:945-955, 2005

Diagnosis: Skin chronic GvHD

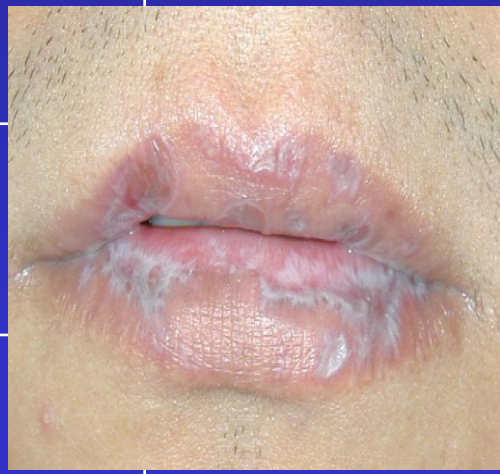
Diagnostic	Distinctive*	Other	Common
Poikiloderma	Depigmentation	Sweat impairment	Erythema
Lichen planus-like features		Ichthyosis	Maculopapular rash
Sclerotic features		Keratosis pilaris	Pruritus
Morphea-like features		Hypopigmentation	
Lichen sclerosus-like features		Hyperpigmentation	

Filipovich A et al, BBMT 2005; 11: 945-955

Diagnostic/Distinctive Signs of Oral Chronic GvHD

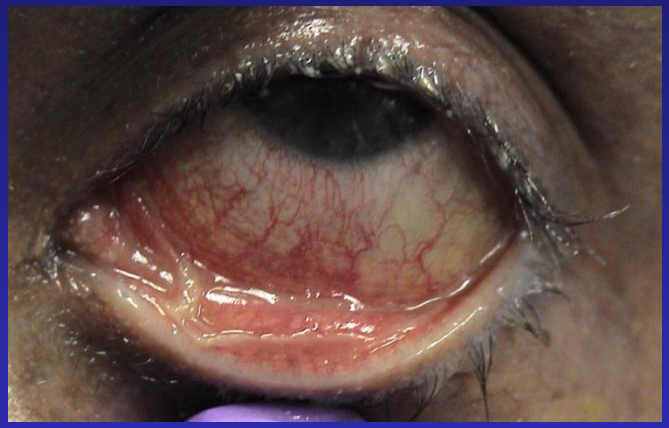


Diagnostic	Distinctive	Common
Lichen-type features	Xerostomia	Gingivitis
	Mucocele	Mucositis
	Mucosal atrophy	Erythema
	Pseudomembranes* Ulcers*	Pain



* Infection, drug effects, malignancy, or other causes must be excluded.

Signs of Chronic GvHD of the Eye



- **Score 1**: mild dry eye, eyedrops ≤ 3 x per day
- **Score 2**: Moderate dry eye, drops > 3x per day, no vision impairment
- **Score 3**: Severe dry eye, unable to work, severe pain, loss of vision caused by keratoconjunctivitis sicca

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Based on symptoms, signs, function

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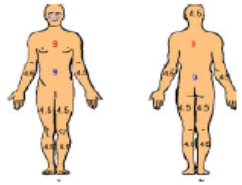
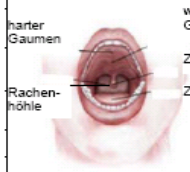
Need for systemic/topical therapy

Documentation of Chronic GvHD according to NIH Consensus

Name: _____ Vorname: _____ Gewicht: _____ kg Datum: _____

Körperteil	Untersuchungsbefund	Auswertung
Haut 	Erythem und/oder papuläres Hautexanthem	% Körperoberfläche
	oberflächliche Sklerose (verformbar)	% Körperoberfläche
	Tiefe Sklerose (starr)	% Körperoberfläche
	Ulcera (Wählen Sie eine Läsion aus, messen Sie und geben ihre größte Dimension in cm an. Markieren Sie die Läsion in nebenstehender Skizze)	Beschreibung der Lokalisation: Größte Dimension: _____ cm
Augen (beidseitiger Schirmer Tränen Test)	Rechtes Auge:_____ mm Durchnässung	Linkes Auge:_____ mm Durchnässung

Mund 

Mukosa Veränderungen	kein Anhalt für oGvHD		leicht		mäßig		schwer	
Erythem	kein	0	leichtes oder mäßiges Erythem (< 25%)	1	mäßiges (≥25%) oder schweres Erythem(<25%)	2	schweres Erythem (≥ 25%)	3
lichenoide Veränderungen	keine	0	Hyperkeratotische Veränderungen (<25%)	1	Hyperkeratotische Veränderungen (26-50%)	2	Hyperkeratotische Veränderungen (>50%)	3
Ulcerationen	keine	0	keine	0	Ulcerationen vorhanden (≤20%)	3	schwere Ulcerationen (>20%)	6
Mukozelen*	keine	0	1-5 Mukozelen	1	6-10 Mukozelen	2	mehr als 10 Mukozelen	3
			* nur Mukozelen der Unterlippe und des weichen Gaumens				**Gesamtzahl der Mukozelen Veränderungen:**	

- Documentation of percentage of affected BSA
- Distinction between superficial and deep sclerosis
- Documentation of erythema and ulcerations

Organ staging of chronic GVHD

NIH chronic GvHD Consensus Conference

Stagingbogen zur chronischen GvHD

Patient:_____Geburtsdatum:_____Untersuchungsdatum:__

Organbeteiligung				
Stadium	**0**	**I**	**II**	**III**
Allgemein-zustand	☐ Asymptomatisch und voll aktiv (ECOG 0, KPS/Lansky 100%)	☐ Symptomatisch; aber keine Einschränkung im Alltag, ambulante Betreuung; Körperliche Einschränkung bei Anstrengung (ECOG 1, KPS/Lansky 80-90%)	☐ Symptomatisch; ambulante Betreuung; Pat. kann sich selbst versorgen; > 50% der wachen Stunden außerhalb des Bettes (ECOG 2, KPS/Lansky 60-70%)	☐ Symptomatisch; Pat. kann sich nur eingeschränkt selbst versorgen; > 50% der wachen Stunden im Bett (ECOG 3-4, KPS/Lansky < 60%)
Haut ☐ maculopapilläres Exanthem ☐ ichenoides Exanthem ☐ papulär-squamös ☐ ichtiös (extreme Schuppung) ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythem ☐ Erythroderma ☐ Poikiloderma ☐ Scleroderma ☐ Pruritus ☐ Haarbefall ☐ Nägelveränderungen _____%KOF	☐ Keine Veränderungen	☐ < 18% KOF mit lichenoiden, oder Ichthyosis-artigen Veränderungen, keine sklerodermiformen Veränderungen	☐ 18-50% KOF mit lichenoiden oder sklerodermiformen oder Ichthyosis-artigen Veränderungen aber keine „gefesselte Haut“, (Falten können noch erzeugt werden)	☐ > 50% KOF mit lichenoiden oder sklerodermiformen oder Ichthyosis-artigen Veränderungen, sklerodermiforme Veränderungen, keine Faltenbildung möglich, „gefesselte Haut“ oder Einschränkung der Aktivitäten des täglichen Lebens durch eingeschränkte Beweglichkeit der Gelenke oder Ulzerationen oder extremen Pruritus
Mund	☐ keine Symptome Keine Veränderungen oder minimale unspezifische Veränderungen	☐ milde Symptome mit typischen Veränderungen, aber normale orale Ernährung möglich	☐ moderate Symptome und partielle Einschränkung der oralen Einfuhr	☐ schwere Symptome mit typischen Veränderungen erhebliche Einschränkung der oralen Einfuhr
Augen Schirmer-Test ☐ >10 ☐ 6-10 ☐ <5 ☐ nicht erfolgt	☐ Keine Veränderungen	☐ milde Augentrockenheit ohne Beeinträchtigung der allgemeinen Lebensqualität, <3x /Tag Augentropfen, asymptomatische Keratokonjungtivits sicca	☐ moderate symptomatische Keratokonjunktivitis, >3x/Tag Augentropfen oder Verschluß Tränenkanal ohne Beeinträchtigung des Sehvermögens	☐ schwere Beeinträchtigung des Sehvermögens durch ☐Pseudomembranen ☐ Cornealulcera ☐ Sehverlust ☐ Schmerzen, welche spezielle Brillengläser erfordert

Score 0: no symptoms

Score I: mild symptoms, no significant restriction of daily activities

Score II: moderate symptoms, mild restriction of daily activities

Score III: severe symptoms

Assessment of Chronic GvHD: Easily Done in Daily Practice

Establish diagnosis

1. Exclude acute GvHD
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3. Rule out other disease

Organ score

8 organs
Based on symptoms, signs, function

Global score

Overall severity
Prognosis
Need for systemic/topical therapy

Global Severity Grading of Chronic GvHD NIH Consensus Conference

Mild: ≤ 2 organs, mild involvement only

Moderate: >2 organs mild or moderate involvement, mild lung involvement

Severe: severe organ involvement with significant impairment of function or moderate lung involvement

Filipovich et al, BBMT 11:945-955, 2005

Who Should do the Grading of GvHD?

Who Should do the Grading of GvHD?

- Trained clinical transplant physician or GvHD nurse.
- Prospective grading and severity scoring is necessary.
- All 8 organs have to be documented as well as global severity.

Reclassification of NIH-Defined Chronic GvHD

Reclassification of Chronic GvHD according to NIH Consensus

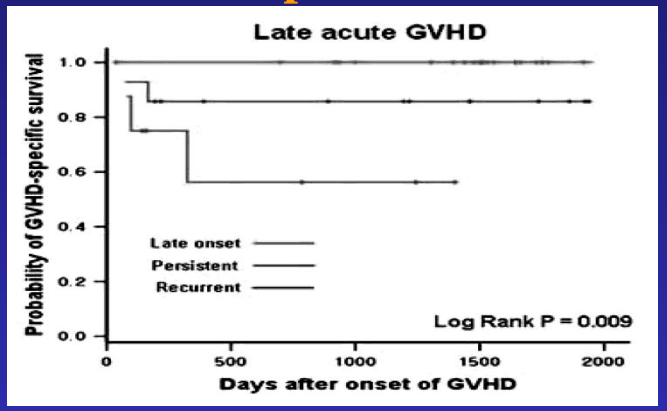
Author	No. pts	**Late acute %**	Overlap %	Classic chronic %
Jagasia 07	110	**37**	26	37
Arora 09	54	**15**	28	57
Cho 09	211	**21**	30	49
Vigorito 09	740	**48**		
Socie 09	116	**37**	10	53

Underestimation of acute GvHD incidence and overestimation of chronic GvHD incidence in literature.

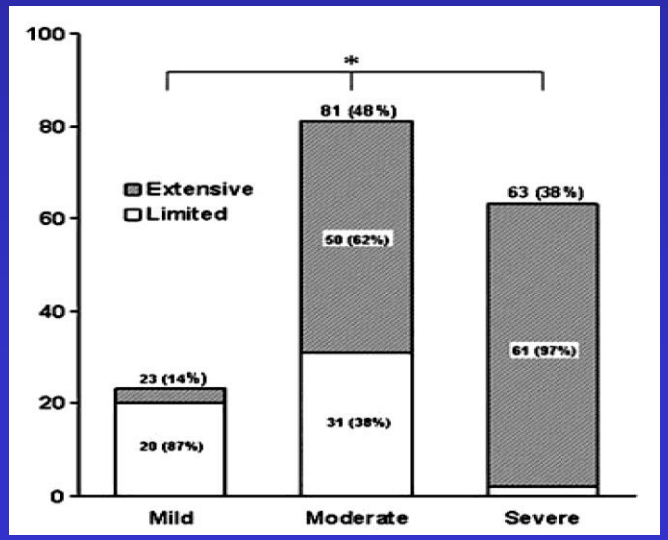
Reclassification of Chronic GvHD according to NIH Consensus

- 211 pts reclassified
- Late aGvHD 21%, overlap sy 30%, classic chronic 49%

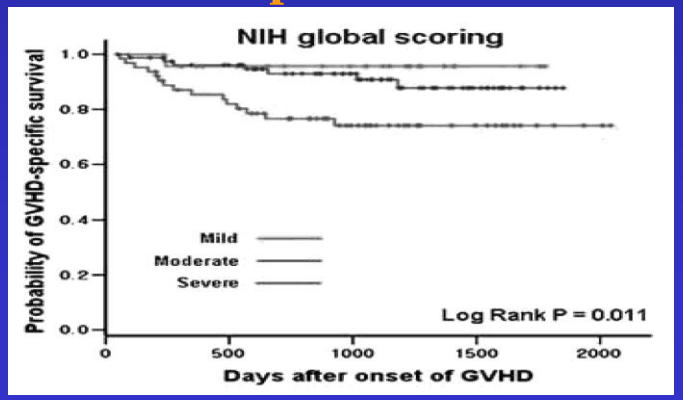
GvHD-Specific Survival



Reclassification of Severity



GvHD-Specific Survival



Cho et al, Leukemia 2009

Unsolved Issues of NIH Consensus

- Response evaluation
- Distinction between active (=reversible) and inactive (=irreversible, fixed deficits) chronic GvHD

New NIH Category of Chronic GvHD

Overlap Syndrome

Features of Acute and Chronic GvHD

	Acute GvHD	Chronic GvHD Common Features
Skin	Maculopapular rash	Maculopapular rash Erythema
GI tract	Nausea, vomiting, anorexia, diarrhea, **ileus**	Nausea, vomiting, anorexia, diarrhea, weight loss
Liver	Cholestatic hepatitis	Total bili, ALK>2 x normal, **ALT or AST>2 x normal**

Filipovich et al, BBMT 11:945-955, 2005

Incidence of Overlap Syndrome in Studies

Author	No pts	Late acute %	**Overlap %**	Classic chronic %
Jagasia 07	110	37	**20**	42
Vigorito 09	740	48	**47**	5
Arora 09	54	15	**28**	57
Cho 09	21	21	**30**	49
Kim 10	216	9.3	**13**	87
Thepot 10	177	3	**21**	79
Sato 11	211		**20**	80
Pidala 12	**394**		**82**	**18**

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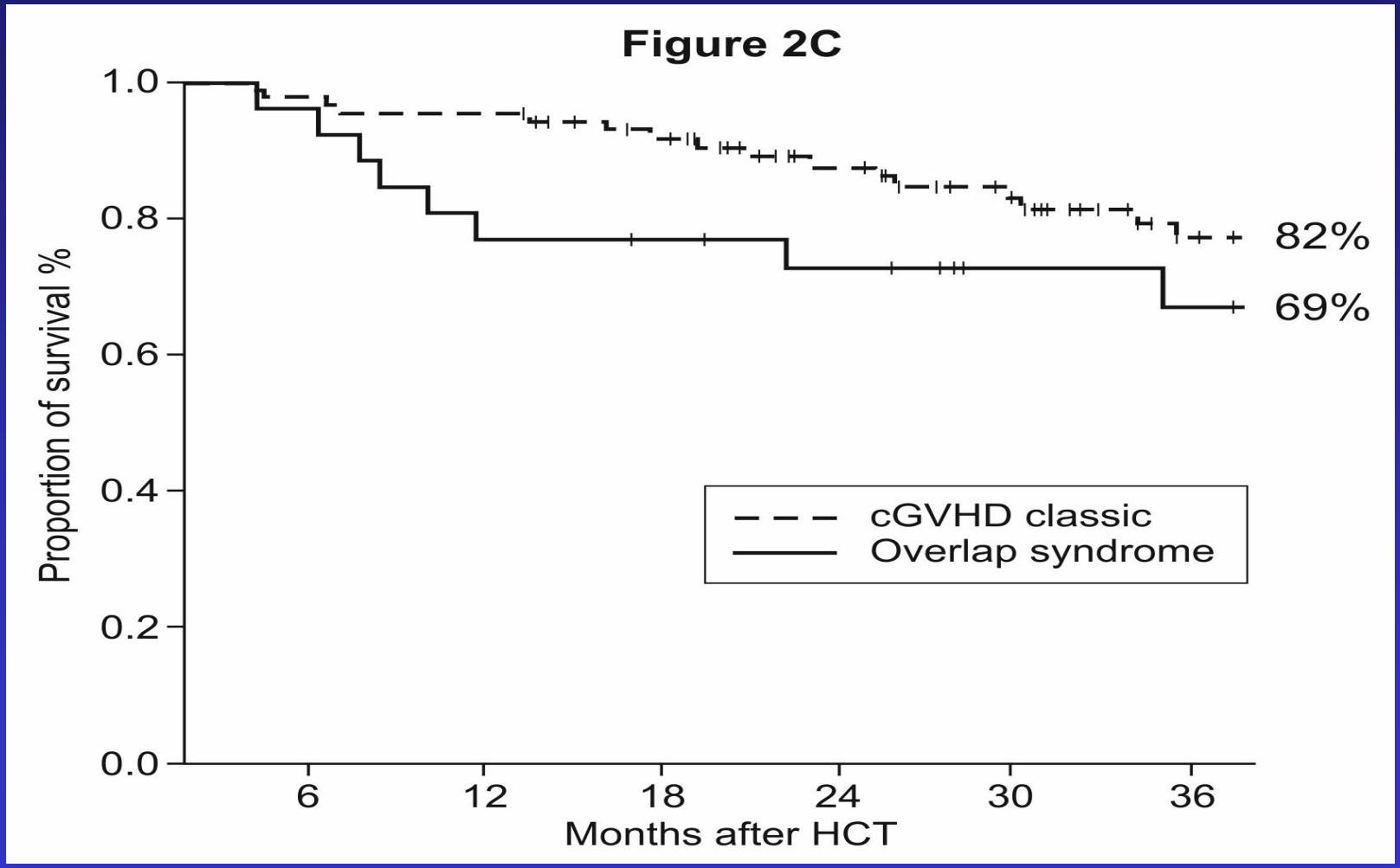
Survival According to Classic cGvHD and Overlap Sy

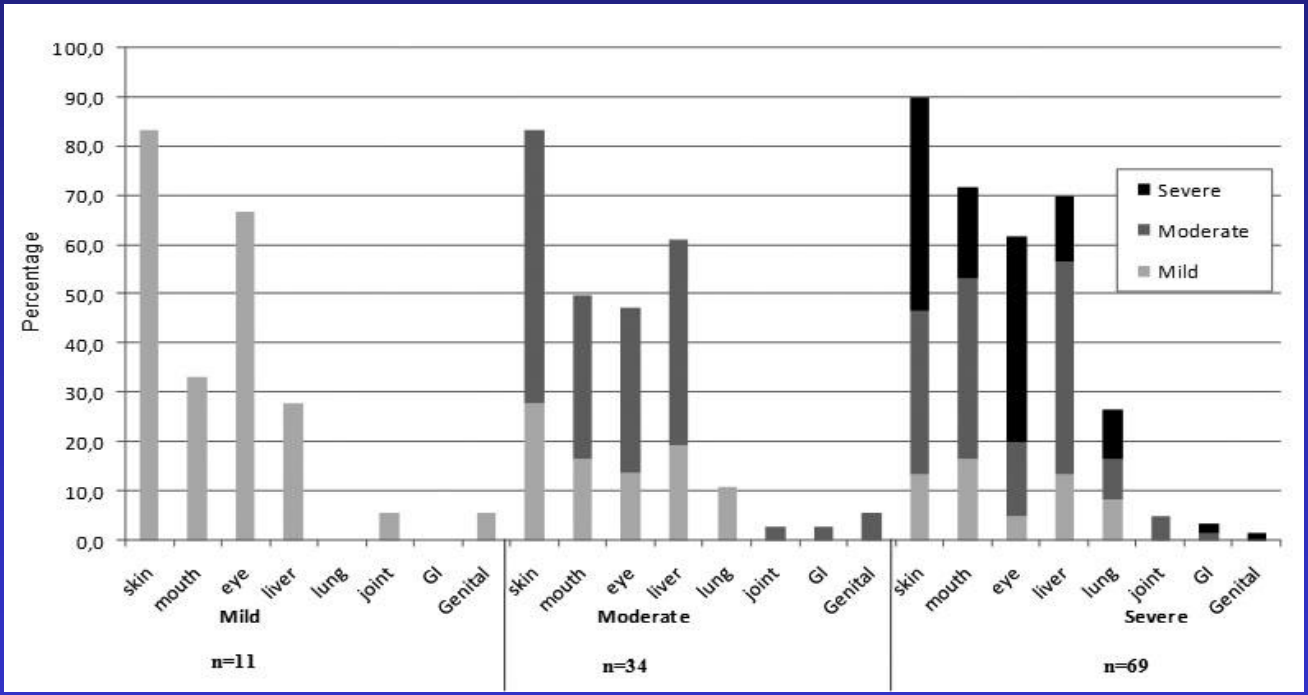


Kuzmina Z et al, Leukemia 26:746-756, 2012

Advantages of NIH Grading

- **Distinction between acute and chronic GvHD** according to defined signs and symptoms = **prognostic importance**.
- **Excellent documentation of all 8 organs**.
  - Definition of homogeneous subgroups for clinical studies
  - Studies on organ manifestations
  - Early interventions e.g. in BOS
- **Excellent documentation of global severity = prognostic importance**.

Spectrum of Clinical Manifestations of Chronic GvHD



Kuzmina et al, Leukemia 2012;26:746-56

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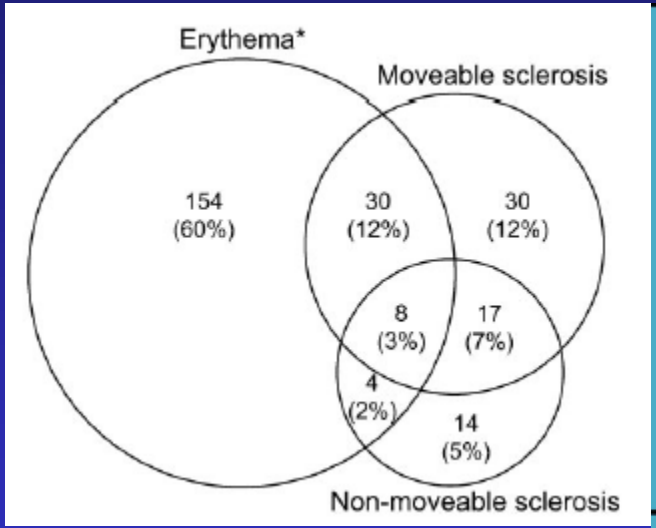
Correlation between NIH Skin Score, Lee Symptom Scale and Outcome

- 458 patients with chronic GvHD, followed prospectively. NIH skin score of 3 and Lee Sy Scale >15 at study entry correlated with OS.



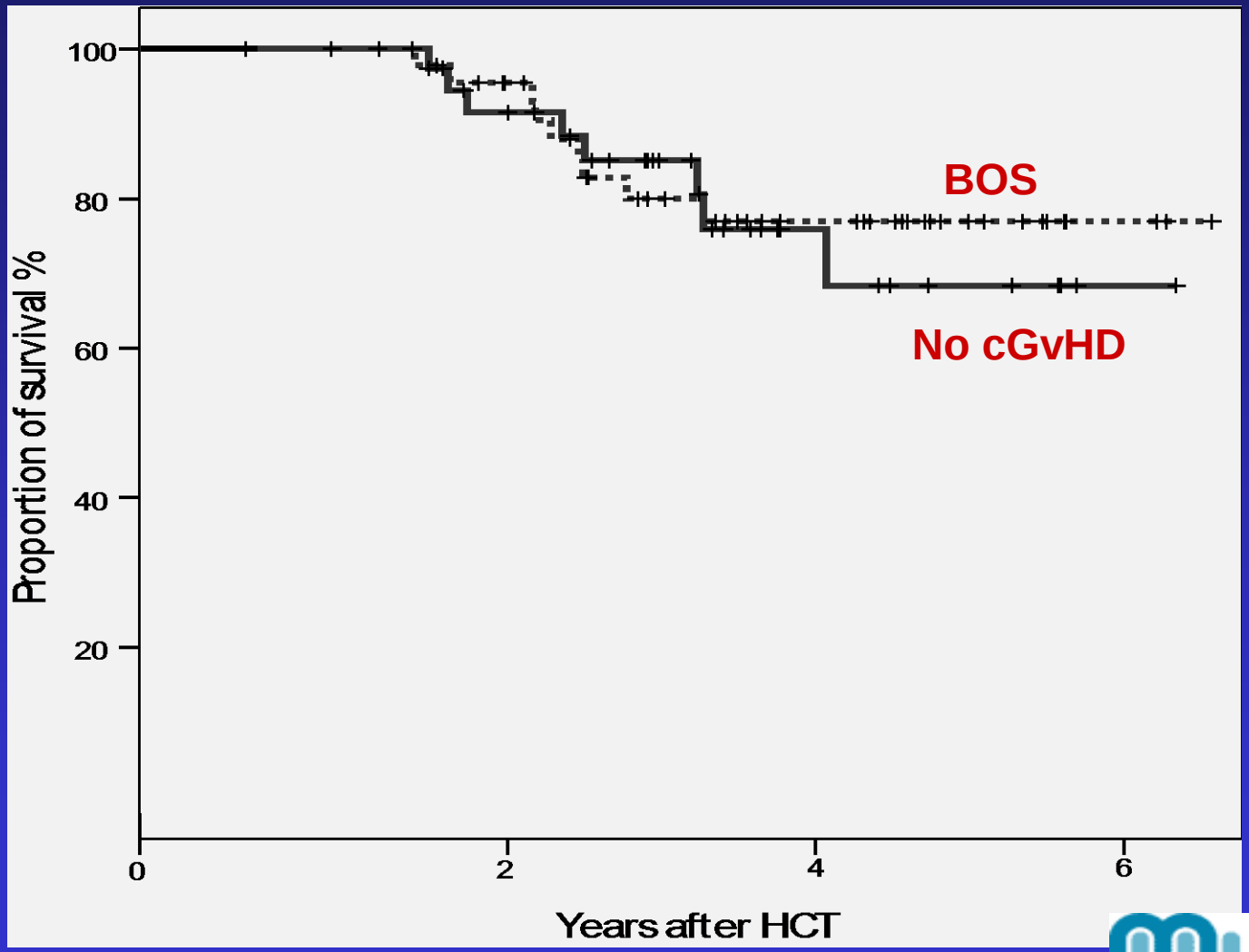
Score definition	0 No symptoms	1 < 18% BSA with disease signs but NO sclerotic feature	2 19%-50% BSA **OR** Involvement with superficial sclerotic feature "not hidebound" (able to pinch)	3 > 50% BSA **OR** Deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
Two-year overall survival	86%	83%	81%	69%
Two-year nonrelapse mortality	10%	13%	15%	30%

Figure 1b: Calculation of Lee skin symptom scale: If all items are completed, total score is the sum of the points multiplied by 5

	Not at all	Slightly	Moderately	Quite a bit	Extremely
Abnormal skin color	0	1	2	3	4
Rashes	0	1	2	3	4
Thickened skin	0	1	2	3	4
Sores on skin	0	1	2	3	4
Itchy skin	0	1	2	3	4

Jacobsohn D et al, Blood 2012; 120 (13): 2545-2552
Van Besien, Blood 2012; 120 (13): 2537-2538

Early Intervention in BOS Improves Survival



Kuzmina Z et al, Blood 2013;121:1886-95.

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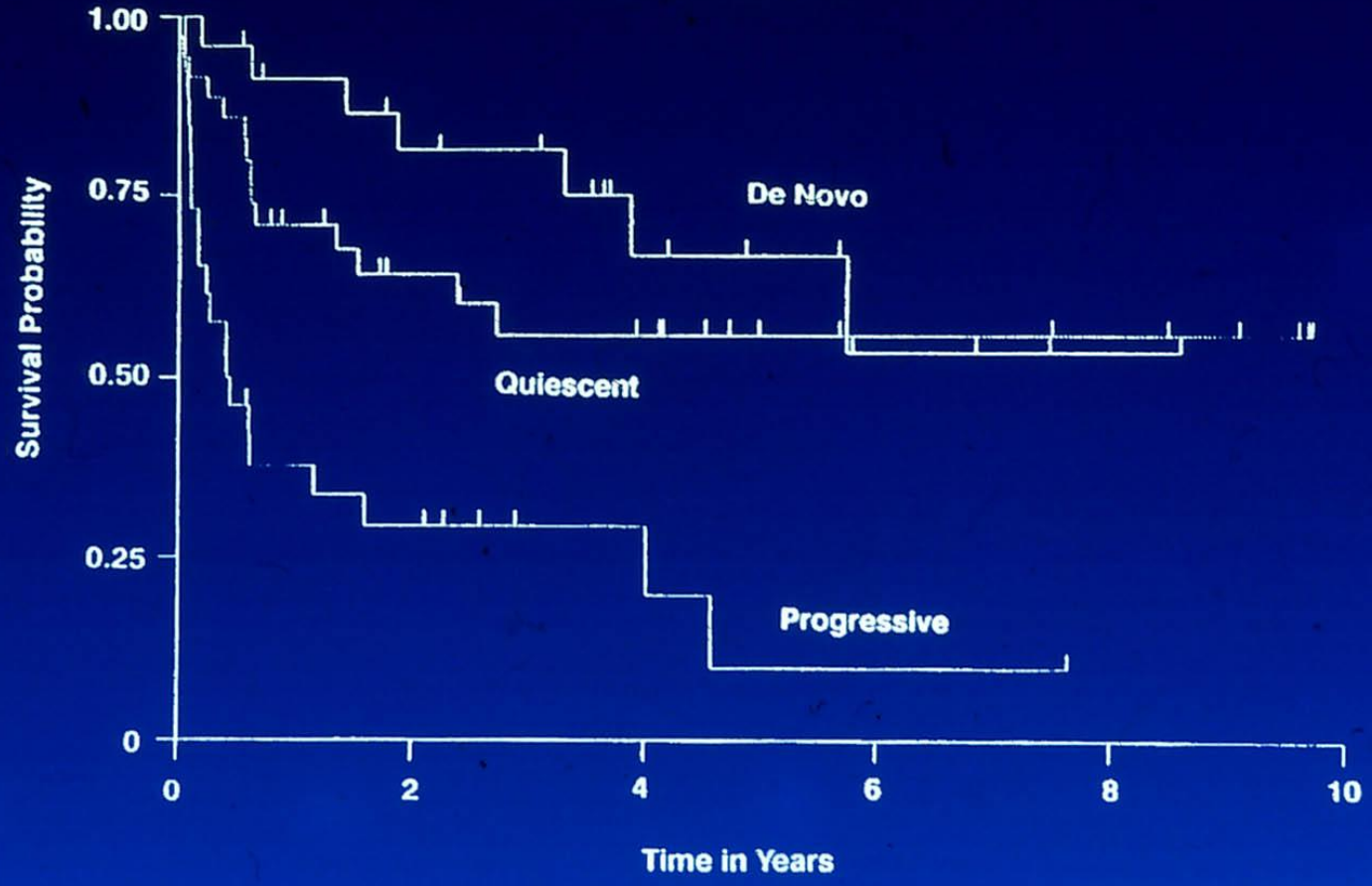
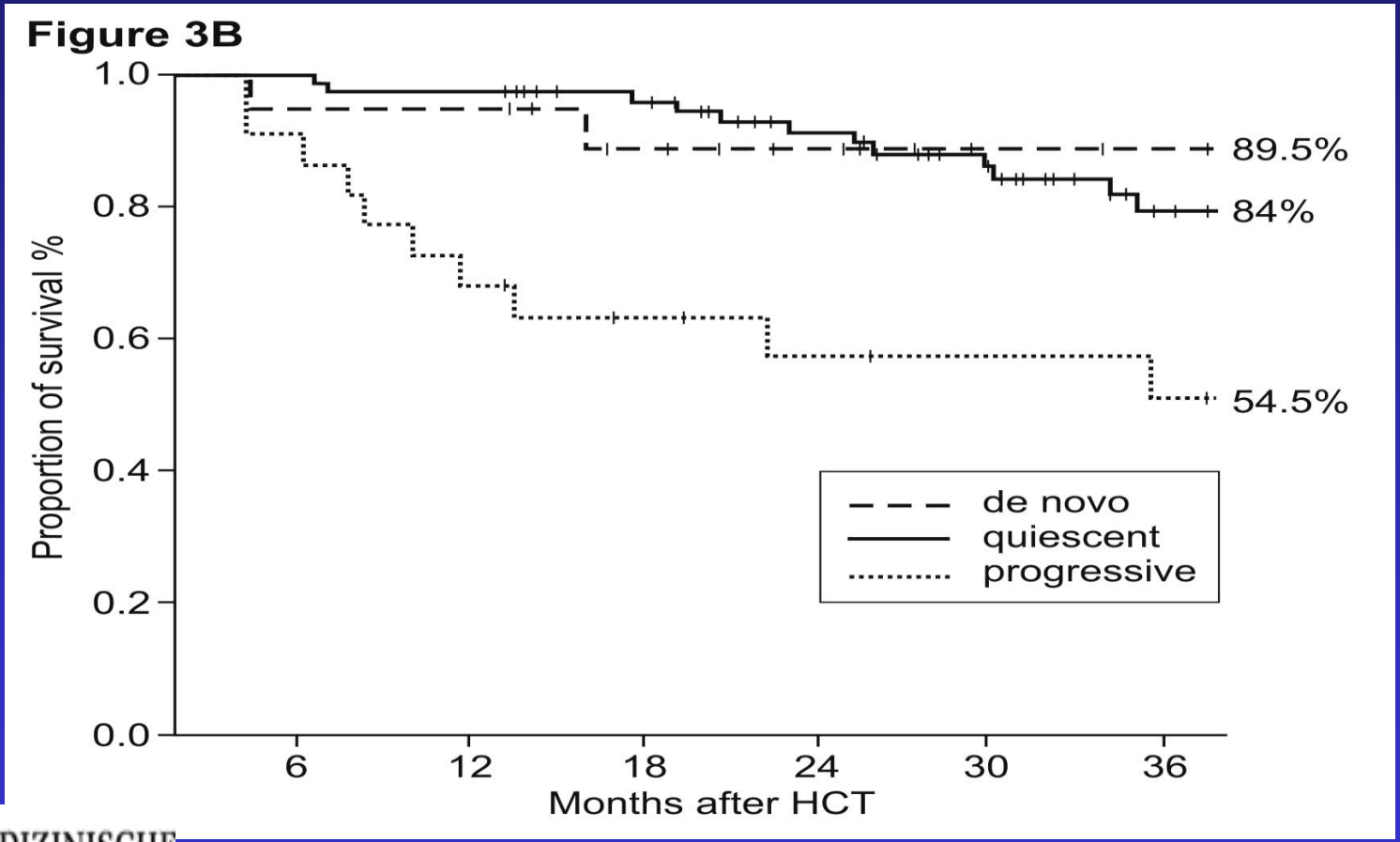
Does it Make a Difference to the Outcome Statistics if we use Seattle or NIH Criteria?

Survival of patients with chronic GVHD



Wingard et al, 1989

Survival of Patients with Chronic GvHD according to Onset Type



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Kuzmina Z et al, Leukemia 26:746-756, 2012

Is Treatment Outcome Different?

- **No comparisons between old Seattle criteria and new NIH criteria** possible since all publications during the last years used NIH criteria.
- **Changes in HCT cohorts over time**
  - Less BM, more PBSC as stem cell source
  - More unrelated donors
  - High-resolution HLA typing and improved donor selection
  - Dose-reduced conditioning regimens
  - New immunosuppressive agents for GvHD prophylaxis
  - Post-transplant cell therapies

Is there a Cost Implication for Using one or the other Criteria?

- State of the art diagnosis and treatment of GvHD requires
  - Specialist care in **multidisciplinary team**
  - Access to novel diagnostic and therapeutic procedures
  - **Extensive supportive care** measures incl. rehabilitation and psychosocial care
  - Dedicated **Outpatient Clinics** with life-long follow-up

Conclusions

- The NIH consensus criteria have improved diagnosis and severity scoring of chronic GvHD.
- The NIH consensus criteria on diagnosis are of prognostic significance.
- Validation of criteria for response evaluation are pending.
- A follow-up meeting at the NIH in June 2014 discussed remaining challenges and pending issues.

GvHD Study Group Vienna

BMT Unit

–R. Weigl
–P. Kalhs
–W.Rabitsch
–A. Schulenburg
–C. Zielinski

Dept. Immunology

–W.F. Pickl
–U. Körmöczy

Dept. Dermatology

–R. Knobler
–U. Just
–A. Tanew
–G. Bauer

Dept. Transfusion Medicine

–N.Worel
–G. Leitner

Dept. Gastroenterology

- G. Vogelsang
- H. Hofer

Dept. Pulmonology

- V. Petkov