NIH-Defined GvHD

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Vienna, Austria
# My Disclosure

<table>
<thead>
<tr>
<th>Company</th>
<th>Speakers Bureau</th>
<th>Advisory Board</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therakos</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Genzyme</td>
<td>✓</td>
<td>✓</td>
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</tbody>
</table>
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
<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin</th>
<th>Liver (Bilirubin mg/dl)</th>
<th>Gut (Diarrhea ml/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;25%</td>
<td>2-3</td>
<td>&gt;500 or Nausea</td>
</tr>
<tr>
<td>2</td>
<td>25-50%</td>
<td>3-6</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>3</td>
<td>&gt;50%</td>
<td>6-15</td>
<td>&gt;1500</td>
</tr>
<tr>
<td>4</td>
<td>Erythrodermia</td>
<td>&gt;15</td>
<td>Pain/Ileus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Functional</th>
<th>Skin</th>
<th>Liver</th>
<th>Gut</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Stage 1 or 2</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>II</td>
<td>Stage 3 or Stage 4 or</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>III</td>
<td>-</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>IV</td>
<td>Stage 4 or</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
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

![Graph showing response rates to steroids over time]

- Day 14: 41% CR, 16% VGPR, 35% PR, 8% NR
- Day 28: 35% CR, 8% VGPR, 8% PR, 4% NR
- Day 56: 38% CR, 4% VGPR, 5% PR, 2% NR

NRM and OS

![Graph showing NRM and OS over time]

- Responders (n=150): 53% survival, P=0.007, 27% CI of TRM
- Non-responders (n=61): 35% survival, P=0.009, 49% CI of TRM

MacMillan et al, Blood 2010
Van Lint et al, Blood 2006
Using the NIH Consensus Criteria

Any features of GVHD → No

Yes

Fulfills definition of chronic GVHD
(1 diagnostic criteria OR 1 distinctive Criteria PLUS biopsy proof in an organ AND exclusion of other probable causes.

Presence of acute GVHD

No

Classic chronic GVHD

Yes

Overlap chronic GVHD

Acute GVHD

Classic acute GVHD
(first episode before day 100)

Recurrent acute GVHD
Delayed acute GVHD
(first episode after day 100)
Persistent acute GVHD

Filipovich et al, BBMT 11:945-955, 2005
## Acute GvHD: New NIH Definitions

<table>
<thead>
<tr>
<th>Category</th>
<th>Time of symptoms after HCT or DLI</th>
<th>Presence of acute GvHD features</th>
<th>Presence of chronic GvHD features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classic acute</strong></td>
<td>≤ 100 days</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Persistent acute</strong></td>
<td>&gt; 100 days</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Recurrent acute</strong></td>
<td>&gt; 100 days</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Late-onset acute</strong></td>
<td>&gt; 100 days</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

Filipovich et al, BBMT 11:945-955, 2005
Acute GvHD is reduced after nonmyeloablative vs myeloablative conditioning HCT

Mielcarek et al, Blood 2003

Acute GvHD: Delayed and reduced incidence

Chronic GvHD: No difference
Why Should we Distinguish Late Acute GvHD from Chronic GvHD?

• 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
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

Fulfills definition of chronic GVHD
(1 diagnostic criteria OR 1 distinctive
Criteria PLUS biopsy proof in an organ AND
exclusion of other probable causes.)

 Presence of acute GVHD

 Any features of GVHD → No

 Yes

 Acute GVHD

 Recurrent acute GVHD
(First episode after day 100)

Delayed acute GVHD
(First episode after day 100)

Persistent acute GVHD

Classic acute GVHD
(First episode before day 100)

No

Classic chronic GVHD

Yes

Overlap chronic GVHD

Filipovich et al, BBMT 11:945-955, 2005
# Categories of chronic GvHD

<table>
<thead>
<tr>
<th>Category</th>
<th>Time of symptoms after HCT or DLI</th>
<th>Presence of acute GvHD features</th>
<th>Presence of chronic GvHD features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic chronic GvHD</td>
<td>No time limit</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Overlap syndrome</td>
<td>No time limit</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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 biopsy 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

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Distinctive*</th>
<th>Other</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poikiloderma</td>
<td>Depigmentation</td>
<td>Sweat impairment</td>
<td>Erythema</td>
</tr>
<tr>
<td>Lichen planus-like features</td>
<td></td>
<td>Ichthyosis</td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td>Sclerotic features</td>
<td></td>
<td>Keratosis pilaris</td>
<td>Pruritus</td>
</tr>
<tr>
<td>Morphea-like features</td>
<td></td>
<td>Hypopigmentation</td>
<td></td>
</tr>
<tr>
<td>Lichen sclerosus-like features</td>
<td></td>
<td>Hyperpigmentation</td>
<td></td>
</tr>
</tbody>
</table>

Filipovich A et al, BBMT 2005; 11: 945-955
## Diagnostic/Distinctive Signs of Oral Chronic GvHD

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Distinctive</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichen-type features</td>
<td>Xerostomia</td>
<td>Gingivitis</td>
</tr>
<tr>
<td></td>
<td>Mucocele</td>
<td>Mucositis</td>
</tr>
<tr>
<td></td>
<td>Mucosal atrophy</td>
<td>Erythema</td>
</tr>
<tr>
<td></td>
<td>Pseudomembranes*</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td>Ulcers*</td>
<td></td>
</tr>
</tbody>
</table>

* Infection, drug effects, malignancy, or other causes must be excluded.
Signs of Chronic GvHD of the Eye

- **Score 1:** mild dry eye, eyedrops $\leq 3$ x per day
- **Score 2:** Moderate dry eye, drops $> 3$ x per day, no vision impairment
- **Score 3:** Severe dry eye, unable to work, severe pain, loss of vision caused by keratoconjunctivitis sicca
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
Documentation of Chronic GvHD according to NIH Consensus

- 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

#### 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

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### Stagingbogen zur chronischen GvHD

| Patient: __________________________ | Geburtsdatum: ______ | Untersuchungsdatum: ______ |

<table>
<thead>
<tr>
<th>Stadium</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allgemeinzustand</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Asymptomatisch und voll aktiv (ECOG 0, KPS/Lansky 100%)</td>
<td>□ Symptomatisch, aber keine Einschränkung im Alltag, ambulante Betreuung, Körperliche Einschränkung bei Anstrengung (ECOG 1, KPS/Lansky 80-90%)</td>
<td>□ Symptomatisch, ambulante Betreuung, Patient kann sich selbst versorgen; &gt; 50% der wachen Stunden im Bett (ECOG 3-4, KPS/Lansky &lt; 60%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Haut | | | |
| □ Keine Veränderungen | □ < 18% KOF mit lichenoiden, oder Ichthyos-antigen Veränderungen, keine sklerodermiformen Veränderungen | □ 18-50% KOF mit lichenoiden oder sklerodermiformen oder Ichthyoses-antigen Veränderungen ohne „gefasste Haut“, (Falten können noch erzeugt werden) |
| □ Gastrointestinalen | □ > 50% KOF mit lichenoiden oder sklerodermiformen oder Ichthyoses-antigen Veränderungen, keine Fältelung möglich, „gefasste Haut“ oder Einschränkung der Aktivitäten des täglichen Lebens durch eingeschränkte Beweglichkeit der Gelenke oder Ulzerationen oder extremer 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 Ernährung möglich |

| Augen | | | |
| □ Keine Veränderungen | □ milde Augenbeteiligung ohne Beeinträchtigung des allgemeinen Lebensqualitäts, < 2x / Tag Augentropfen, asymptptomatische Keratoconjunctivitis vira - | □ moderate symptomatische Keratoconjunctivitis, > 2x / Tag Augentropfen oder Verschleifen, Tränenausfluss ohne Beeinträchtigung des Sehvermögens |
| □ schwere Symptome mit typischen Veränderungen und erhebliche Einschränkung der oralen Ernährung |

- Schmerztest: □ >10 □ 8-10 □ 5 □ nicht erfolgt

- □ schwere Beeinträchtigung des Sehvermögens durch Pseudomonassen, Entzündungen, Schmerzen, welche spezielle Brillengläser erfordern
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
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

<table>
<thead>
<tr>
<th>Author</th>
<th>No. pts</th>
<th>Late acute %</th>
<th>Overlap %</th>
<th>Classic chronic %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jagasia 07</td>
<td>110</td>
<td>37</td>
<td>26</td>
<td>37</td>
</tr>
<tr>
<td>Arora 09</td>
<td>54</td>
<td>15</td>
<td>28</td>
<td>57</td>
</tr>
<tr>
<td>Cho 09</td>
<td>211</td>
<td>21</td>
<td>30</td>
<td>49</td>
</tr>
<tr>
<td>Vigorito 09</td>
<td>740</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socie 09</td>
<td>116</td>
<td>37</td>
<td>10</td>
<td>53</td>
</tr>
</tbody>
</table>

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%

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

<table>
<thead>
<tr>
<th></th>
<th>Acute GvHD</th>
<th>Chronic GvHD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td>Maculopapular rash</td>
<td>Maculopapular rash Erythema</td>
</tr>
<tr>
<td><strong>GI tract</strong></td>
<td>Nausea, vomiting, anorexia, diarrhea, <strong>ileus</strong></td>
<td>Nausea, vomiting, anorexia, diarrhea, weight loss</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>Cholestatic hepatitis</td>
<td>Total bili, ALK&gt;2 x normal, ALT or AST&gt;2 x normal</td>
</tr>
</tbody>
</table>

Filipovich et al, BBMT 11:945-955, 2005
## Incidence of Overlap Syndrome in Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>No pts</th>
<th>Late acute %</th>
<th>Overlap %</th>
<th>Classic chronic %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jagasia 07</td>
<td>110</td>
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<td>42</td>
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<td>Vigorito 09</td>
<td>740</td>
<td>48</td>
<td>47</td>
<td>5</td>
</tr>
<tr>
<td>Arora 09</td>
<td>54</td>
<td>15</td>
<td>28</td>
<td>57</td>
</tr>
<tr>
<td>Cho 09</td>
<td>21</td>
<td>21</td>
<td>30</td>
<td>49</td>
</tr>
<tr>
<td>Kim 10</td>
<td>216</td>
<td>9.3</td>
<td>13</td>
<td>87</td>
</tr>
<tr>
<td>Thepot 10</td>
<td>177</td>
<td>3</td>
<td>21</td>
<td>79</td>
</tr>
<tr>
<td>Sato 11</td>
<td>211</td>
<td></td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>Pidala 12</td>
<td>394</td>
<td></td>
<td>82</td>
<td>18</td>
</tr>
</tbody>
</table>
Survival According to Classic cGvHD and Overlap Sy

Figure 2C

Proportion of survival %

Months after HCT

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
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.

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
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

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**
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- C. Zielinski

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- U. Körmöczy

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- A. Tanew
- G. Bauer

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- G. Leitner

**Dept. Gastroenterology**
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- H. Hofer

**Dept. Pulmonology**
- V. Petkov