Chronic Graft versus Host Disease -cGVHD- and long-term consequences

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cGVHD

• remains the most common late complication after allogeneic SCT

• associated immunodeficiency and infections are the major cause of morbidity and mortality in the long-term follow-up

• still optimal treatment is required
cGVHD

incidence:
- 20-50% in children, 40-70% in adults
- Less in pediatric patients because
  » less acute GvHD
  » better thymic function

increasing incidence:
- Survival
- MM and MUD HSCT
- PBSC
- Adoptive cell therapies
Specific pediatric issues

- **Different indications for hSCT:**
  ▲ non malignant diseases: inborn errors, hematologic diseases, immunodeficiencies, metabolic diseases with different comorbidities

- **Different infectious complications**
  ▲ higher incidence, especially viral infections (ADV)

- **Different immunoreconstitution**
Specific pediatric issues

Different immune reconstitution:

▲ Engraftment kinetics and recovery of innate immunity

▲ More active thymic tissue and ▲ thymopoiesis →
  • rapid recovery of naive CD4/8
  • faster recovery of TREC levels + TCRBV spectratype repertoires

Klein AK, BBMT 2001

▲ Earlier B-cell reconstitution and improved T-cell help → sufficient clonal expansion and Ab-repertoire

>better outcome: resolved in 70% after median duration of 5 months (Zecca, Blood 2002)
Pathophysiology

- cGVHD = consequence of immunodysregulation
  - Persistence of alloreactive and autoreactive T cells
  - Direct versus indirect antigen presentation
  - Failure of peripheral tolerance
  - Thymic damage
  - Impaired T and B cell homeostasis
  - Th2 shift

- Clinical consequences
  - More immunosuppression is not necessarily better
  - Development of immunomodulating strategies
  - Development of targeted treatment strategies
Acute -> chronic GvHD

TLRs, NLRs

Host APC

Donor APC

donor T lymphocytes

Donor B lymphocytes

host reactive Th1

rapid AICD

Donor T reg´s

Thymic damage

dysfunctional T cell selection of newly formed T cells

host = allo - reactive Th2

Allo- and auto-reactive B cells

„Auto-reactive“ donor T cells

E.Holler, University Regensburg
Time of Onset of cGVHD

K. Schultz

- B cell: TLR9+ B cells, Anti-dsDNA ab, ANA, sBAFF
- T cell: IL-2R, sBAFF

Marker

Early  late

Quiescent  De novo  Acute GVHD  Chronic GVHD

Progressive

BMT
## GVHD Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Time of manifestation after HCT or DLI*</th>
<th>Presence of GVHD features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute GVHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic acute GVHD</td>
<td>≤ 100 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Persistent, recurrent or late onset acute GVHD</td>
<td>&gt; 100 days</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Chronic GVHD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classic chronic</td>
<td>No time limit</td>
<td>No</td>
</tr>
<tr>
<td>Overlap syndrome</td>
<td>No time limit</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Filipovich et al. Biol Blood Marrow Transplant 11: 945-955, 2005*
cGvHD: Risk factors

- UD, MM
- PBSC
- increased donor and recipient age
- female donor > male recipient
- malignant disease and disease status
- TBI
- prior acute GVHD III / IV
Prognosis of cGVHD at diagnosis according to risk factors (Akpek et al)

- Diagnosis requires histology or/and diagnostic values
- Before initiation of treatment staging is required
- Response has to be evaluated in standardized intervals
cGVHD: main clinical features

involvement of

- skin, sweat glands, nails, hair,
- mucosa of eyes, mouth and genitalia
- liver (hepatitis, bile duct vanishing, cirrhosis..)
- gut
- lung
- neuromuscular, musculoskeletal (myositis, fasciitis, myasthenia gravis)
- haematopoietic system
- immunodeficiency
- others
Infections  
Endocrine  
Metabolism  
Nutrition  
Pain  
Quality of life  
Disability

Dry eyes
Oral lesions
Nail dystrophy
Skin sclerosis
Deep sclerosis
Bronchiolitis obliterans
Loss of bile ducts
Fasciitis
Skin ulcers

Spectrum of manifestations in cGVHD
Diagnosis of chronic GVHD

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. Flowers7
• Presence of at least one **diagnostic** sign
• or a constellation of **distinctive*** signs
  *supported by biopsy or other relevant diagnostic tests
• Distinction from acute GvHD
• Exclusion of other possible diagnoses
### Diagnostic/Distinctive Signs of Chronic GVHD: Skin

<table>
<thead>
<tr>
<th>Organ or Site</th>
<th>Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)</th>
<th>Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)</th>
<th>Other Features*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Poikiloderma</td>
<td>Depigmentation</td>
<td>Sweat impairment Erythema</td>
</tr>
<tr>
<td></td>
<td>Lichen planus-like features</td>
<td></td>
<td>Ichthyosis</td>
</tr>
<tr>
<td></td>
<td>Sclerotic features</td>
<td></td>
<td>Keratosis pilaris Maculopapular rash</td>
</tr>
<tr>
<td></td>
<td>Morphea-like features</td>
<td></td>
<td>Hypopigmentation Pruritus</td>
</tr>
<tr>
<td></td>
<td>Lichen sclerosus-like features</td>
<td></td>
<td>Hyperpigmentation</td>
</tr>
<tr>
<td>Nails</td>
<td></td>
<td>Dystrophy</td>
<td>Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Longitudinal ridging, splitting, or brittle features</td>
<td>Premature gray hair</td>
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<td></td>
<td></td>
<td>Onycholysis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Pterygium unguis</td>
<td></td>
</tr>
<tr>
<td>Scalp and body hair</td>
<td></td>
<td>Nail loss (usually symmetric; affects most nails)†</td>
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</tr>
<tr>
<td></td>
<td>New onset of scarring or nonscarring</td>
<td>New onset of scarring or nonscarring</td>
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</tr>
<tr>
<td></td>
<td>scalp alopecia (after recovery from chemoradiotherapy)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Scaling, papulosquamous lesions</td>
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<td></td>
</tr>
<tr>
<td>Mouth</td>
<td>Lichen-type features</td>
<td>Xerostomia</td>
<td>Gingivitis</td>
</tr>
<tr>
<td></td>
<td>Hyperkeratotic plaques</td>
<td>Mucocele</td>
<td>Mucositis</td>
</tr>
<tr>
<td></td>
<td>Restriction of mouth opening from sclerosis</td>
<td>Mucosal atrophy</td>
<td>Erythema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudomembranes†</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ulcers†</td>
<td></td>
</tr>
</tbody>
</table>
## Diagnostic Features*

<table>
<thead>
<tr>
<th>Skin</th>
<th>Mouth</th>
<th>GI Tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Poikiloderma</td>
<td>-Lichen-planus-like</td>
<td>-Esophageal web, strictures, or stenosis</td>
</tr>
<tr>
<td>-Lichen planus-like</td>
<td>-Hyperkeratotic plaques</td>
<td></td>
</tr>
<tr>
<td>-Sclerotic features</td>
<td>-Restriction of mouth opening from sclerosis</td>
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<td>-Morphea-like features</td>
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<td></td>
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<tr>
<td>-Lichen sclerosus-like</td>
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</tr>
</tbody>
</table>

* Sufficient to establish the diagnosis of C-GVHD
### New Clinical Scoring System

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No manifestation/symptoms</td>
</tr>
<tr>
<td>1</td>
<td>No significant impairment of function “activities of daily living” (ADL)</td>
</tr>
<tr>
<td>2</td>
<td>Significant impairment of ADL but no major disability</td>
</tr>
<tr>
<td>3</td>
<td>Significant impairment of ADL WITH major disability</td>
</tr>
</tbody>
</table>

Filipovich et al. Biol Blood Marrow Transplant 11: 945-955, 2005
**Global Severity of CGVHD***

* Global severity is replacing “limited-extensive” grading

**Mild** – no significant impairment of function
- Only 1-2 organs (except lungs)
- Maximum organ score 1

**Moderate** – significant impairment but no major disability
- Three or more organs with max score 1
- One organ with max score 2
- Lung score of 1

**Severe** – major disability
- Score of 3 in any organ or site
- Lung score of 2

Filipovich et al. Biol Blood Marrow Transplant 11: 945-955, 2005
Specific clinical manifestations

- **Skin and dermal appendages:** premature greying of hair, eyelashes and eyebrows
  - pruritus: sometimes first and only symptom
  - flares may be caused by superinfection

  for estimating body surface area the classic “rule of nines” has to be replaced by the child specific modification


German-Austrian-Swiss Consensus Conference on clinical practice in chronic graft-versus-host disease (GVHD): guidance for supportive therapy of chronic cutaneous and musculoskeletal GVHD.
Musculoskeletal:
diagnosis of joint contractures, myositis or fasciitis is often delayed in sclero cGVHD

→ range of motion measurements (ROM)

→ cooperation with a physiotherapist
Specific clinical manifestations

Ocular:

children rarely communicate dry eye symptoms,
Photophobia may be only symptom

>> children and parents have to be asked specific questions regarding symptoms such as pain, eye-rubbing or secretion

>> close cooperation with a pediatric ophthalmologist, who is experienced in GVHD

Dietrich T. Et al, *Cornea* 2011; *(In Press)*

Diagnosis and treatment of ocular chronic graft-versus-host disease (GVHD): report from the German-Austrian-Swiss Consensus Conference on clinical practice in chronic GVHD.
Specific clinical manifestations

Oral:
• children often don‘t communicate dry mouth symptoms, taste alteration, foodsensitivity and difficulties of swallowing
• ↓ reduced oral intake and ↑ increased drinking during eating may be only symptoms
• beware of coexisting viral infections: Coxsackie, HHV6/7, ADV, Echo- and Enterovirus, HS,

Meier JK et al, Clin Oral Investig 2011
Oral chronic graft-versus-host disease: report from the International Consensus Conference on clinical practice in cGVHD
GI:

- Malnutrition is very common and multifactorial
- May be predictive for ↑ risk for NRM
  - gastroesophagial reflux  
  - esophagial involvement with dysphagia and stenosis

>> Attention to fluid status, electrolyte management and protein losing enteropathy

>> Feeding / nutrition is a common field of interaction between caretakers and children

>> Early cooperation with pediatric nutritionist!
Specific clinical manifestations

Lung:

chronic sinusitis and sinubronchial syndrome even in young children,

↔ mucociliary dysfunction ( ? TBI, cranial irradiation) and coexisting IgA and IgG deficiency

 souvent underdiagnosed

BOS: adult and ped. pats, incidence 5-20%, poor 5-year survival 10%

(Dudek AZ, BMT 2003)

Hildebrandt GC et al, BMT 2011

Diagnosis and treatment of pulmonary chronic GVHD: report from the consensus conference on clinical practice in chronic GVHD.
Specific clinical manifestations

• **Organ function and development:**
  may be inhibited by cGVHD and its treatment

• **Hormone balance, Growth and bone density:**
  cgvhd and long term steroids in a growing child
  
  – bone density: use age adjusted Z-score
  – peak bone mass hits the maximum in the late teens

Hautmann AH et al, *Transpl Int 2011*

Metabolic bone diseases in patients after allogeneic hematopoietic stem cell transplantation: report from the Consensus Conference on Clinical Practice in chronic graft-versus-host disease.
Specific clinical manifestations

Vulvovaginal GVHD:

• Rare in children, vag. irritation is often multifactorial
• Phimosis even in adolescent patients
• our experience: vaginal synechia could lead to hematocolpos long after GVHD has resolved
• → Examination by pediatric gynecologist is recommended
Potential LE

- Endocrinopathies
- Musculoskeletal disorders
- Pulmonary function disorders
- Cardiovascular complications
- GI and hepatic sequelae
- Renal dysfunctions
- Ocular abnormalities
- Oral and dental complications
- Hearing problems
- Skin problems/ alopecia
- Immunological dysfunctions
- Neurological and cognitive consequences
- Psychosocial sequelae
- Secondary malignancies
LE - specific pediatric issues

- Age at SCT
- Growing and developing organ system
- Extended period to deal with long term complications
- Difficult transition from pediatric to adult medicine
Multidisciplinary Follow-up

- physiotherapists
- social worker
- dieticians
- rehabilitation
- teachers
- SCT-outpatient clinic
- pediatrician
- endocrinologists
- cardiologists
- neurologists
- gynecologists
- ophthalmologists
- hematooncologists
Further efforts

>> Improvement of networking and clinical research:

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German-Austrian Pediatric HSCT- WG (PAS&T)
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