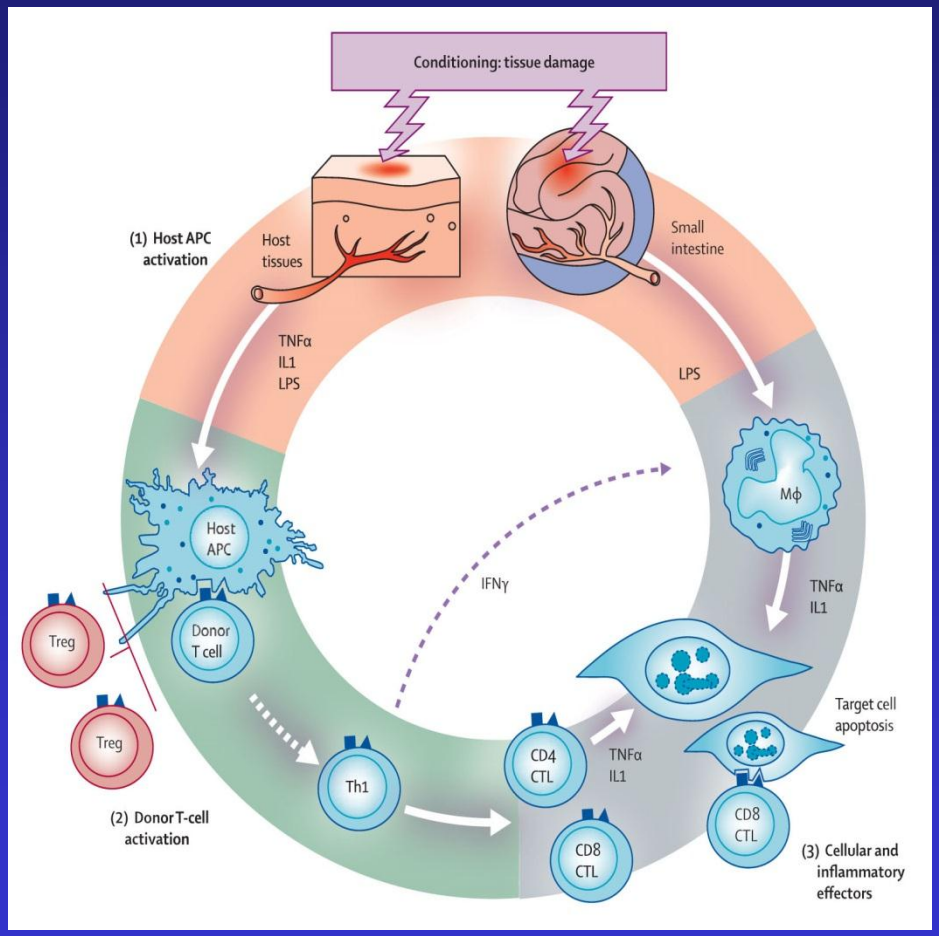
MEDIZINISCHE UNIVERSITÄT WIEN

Univ. Klinik für
Innere Medizin I

Graft-versus-host disease

Hildegard Greinix
Medical University of Vienna
Austria

Pathophysiology of Acute GVHD

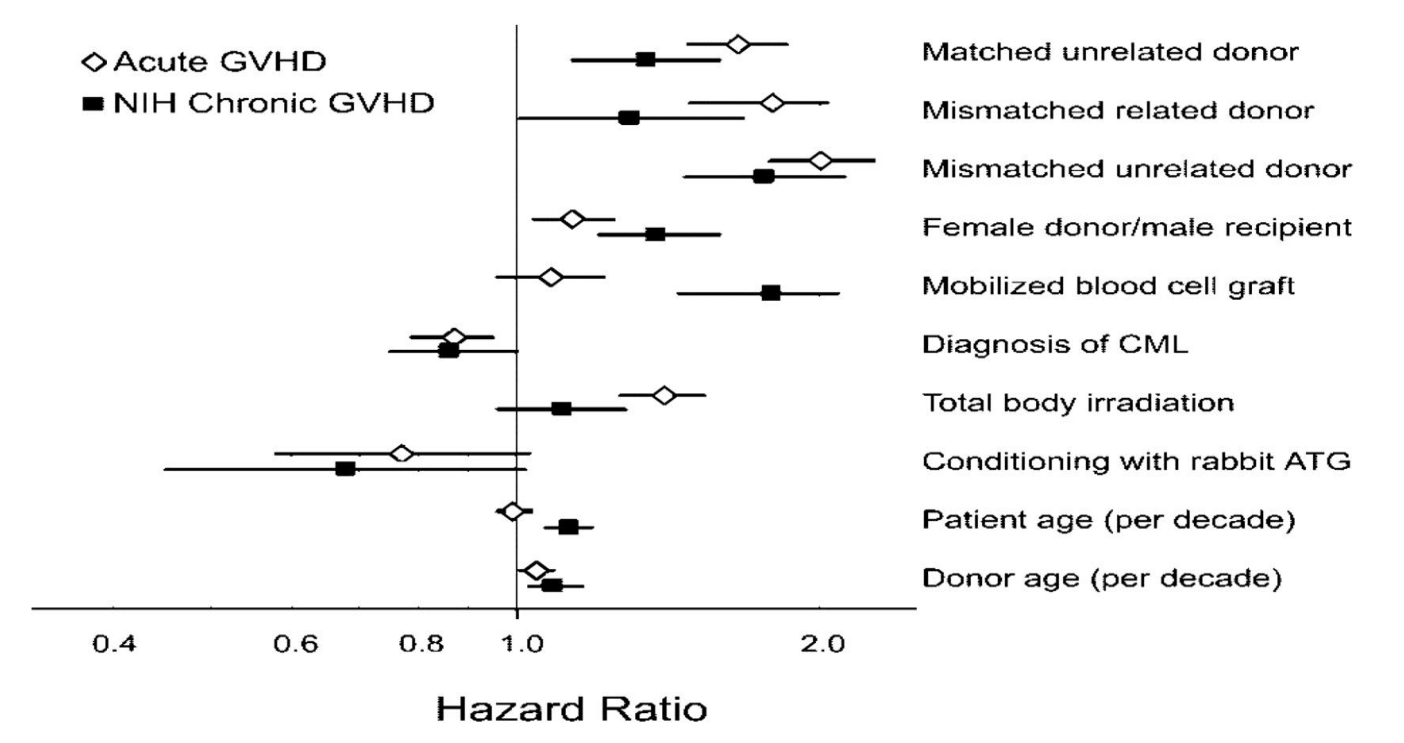


Requirements for GVHD: Billingham 1966

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

Ferrara J, Hill G, Holler E et al.

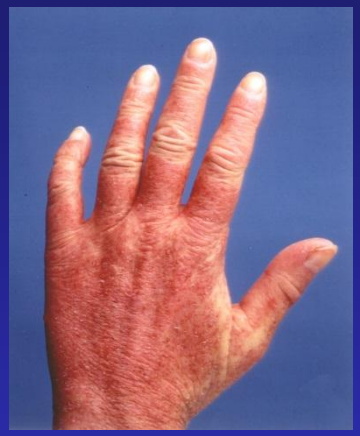
Risk Factors for Acute and Chronic GVHD According to NIH



2941 adult and pediatric pts with first allo HCT

Flowers MED et al, Blood 17:3214-3219, 2011

Acute GVHD as Major Complication of allo HCT



30-80% incidence

Old definition:

until d 100+ after HCT

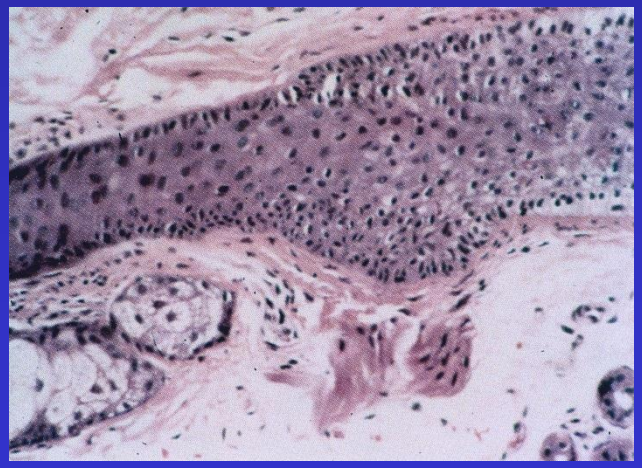
New definition:

classic acute

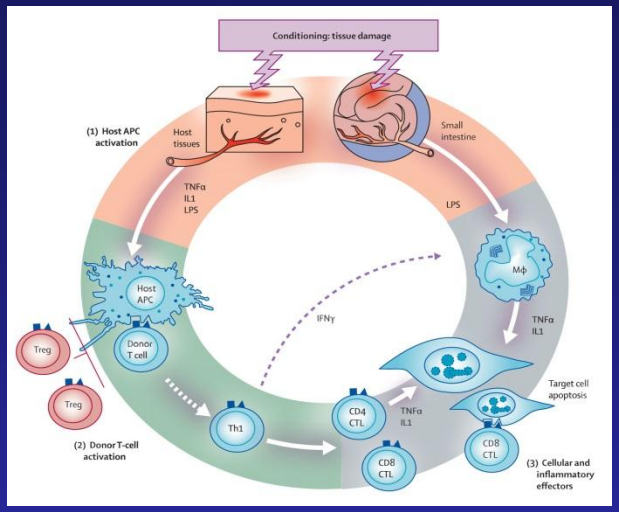
persistent, recurrent or late-onset acute

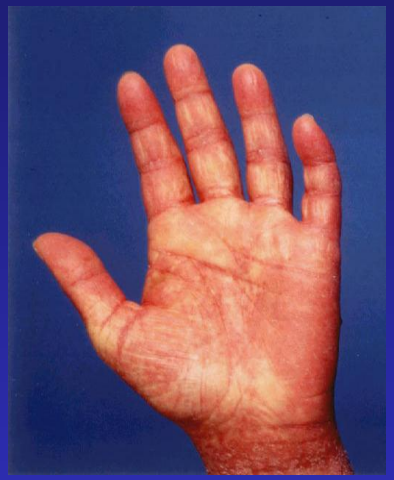
Consensus Conference on Acute GvHD Grading Przepiorka 1995

Stage	Skin	Liver (Bilirubin mg/dl)	Gut (diarrhea ml/day)
1 2 2 4	<25% 25-50% >50% Erythroderma	2-3 3-6 6-15 >15	>500 or nausea >1000 >1500 Pain/ileus
Functional	Skin	Liver	Gut
I II III IV	Stage 1-2 Stage 3 or - Stage 4 or	None Stage 1 or Stage 2-3 or Stage 4	None Stage 1 Stage 2-4 -



Filipovich et al. BBMT 2005;11:945-56.





Prophylaxis of GVHD

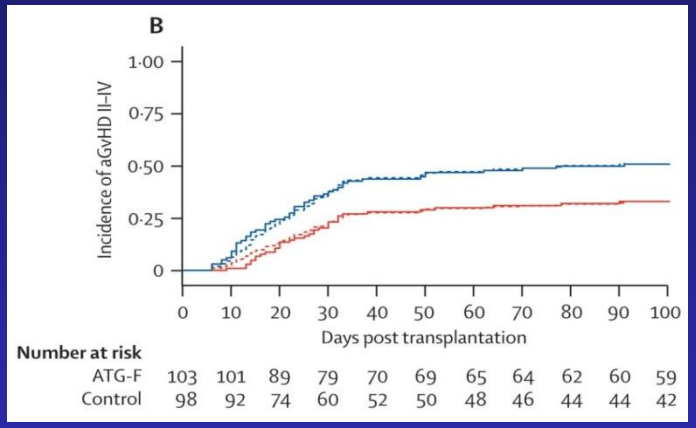
Standard Prophylaxis of GVHD: CNI (= Cyclosporine/Tacrolimus) + MTX

	regimen	Acute GvHD	Chronic GvHD	Overall survival
Storb (SAA)	MTX	53	36	58
1989	**MTX+CsA**	18	58	73
Storb (leuk)	CsA	54	24	54
1989	**MTX+CsA**	33	26	65
Chao (leuk)	MTX + CsA	20	54	51
2000	MTX+CsA+P	18	46	60
Ruutu (div)	MTX + CsA	56	48	72
2000	MTX+CsA+P	19	36	65
Ratanath.	MTX+CsA	44	49	57
1998	MTX+TACR	32	56	47
Nash (URD)	MTX+CsA	74	70	50
2000	MTX+TACR	56	76	54

Randomized Phase III Study in HCT with URD
Standard GVHD prophylaxis +/- ATG-F

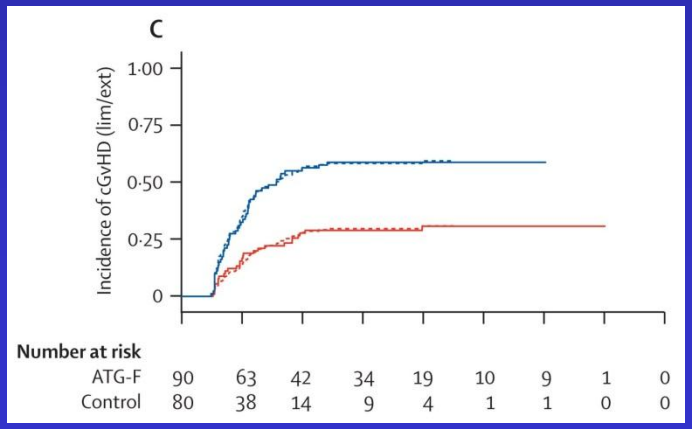
Acute GVHD II-IV

p=0.011



Chronic GVHD

p<0.0001



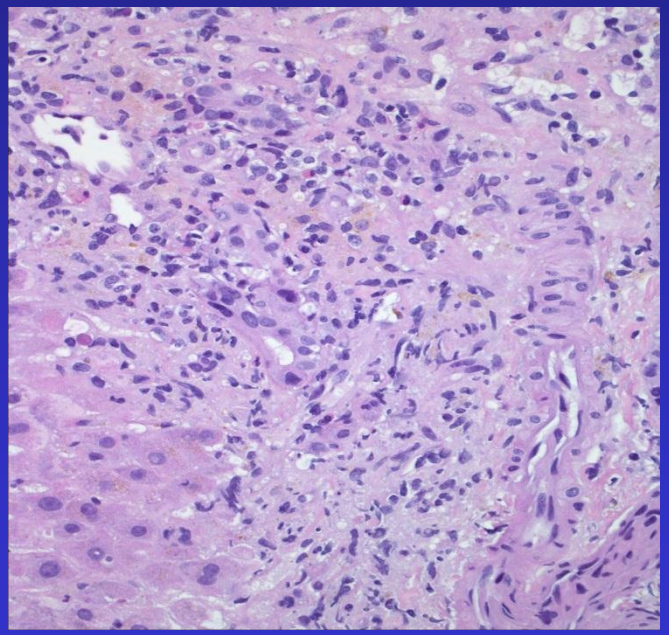
- 201 pts after MA-HCT
- **CSA/MTX+/- ATG-F** 20mg/kg days -3,-2,-1
- Significantly **lower acute GVHD II-IV** after ATG-F
- Significantly **lower chronic GVHD** after ATG-F
- No differences in relapse, NRM, OS, and mortality from infections

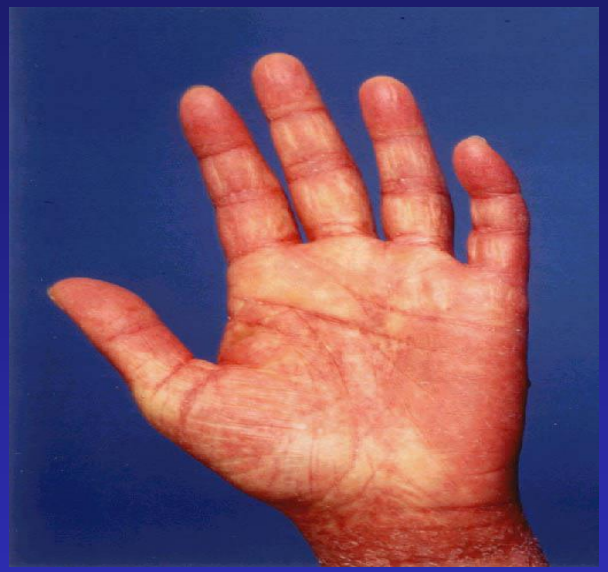
Finke et al, Lancet 2009
Socie et al, Blood 2011

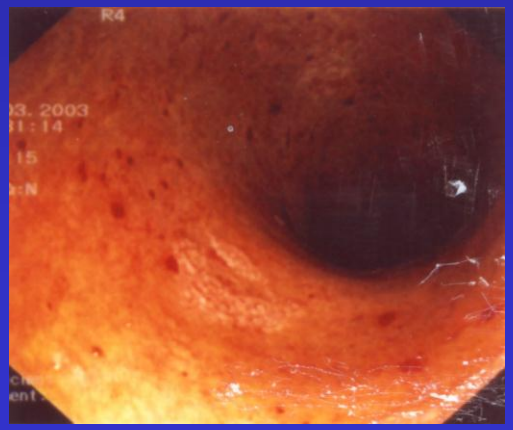
Prospective Randomised Studies with ATG for GVHD Prophylaxis in HCT with URD

Author	GvHD prophylaxis	aGVHD III/IV %	cGVHD %	NRM %	OS %	Med. FU mo
Bacigalupo 01	CSA/MTX+/-Thymo 7.5 mg CSA/MTX+/-Thymo 15 mg	36 vs 41 50 vs 11 (p=0.001)	65 vs 38 59 vs 41	43 vs 39 49 vs 62	56 vs 55 43 vs 32	33 vs 29 18 vs 18
Wagner 05	CSA/MTX vs CSA+TCD+ATGAM	37 vs 18 (p<0.0001)	34 vs 29	49 vs 49	34 vs 27	36 vs 36
Finke 09 Socie 11	CSA/MTX+/- ATG-F	24 vs 12 (p=0.054)	59 vs 31 (p<0.0001)	33 vs 19	43 vs 55	36 vs 36

Therapy of Acute GVHD





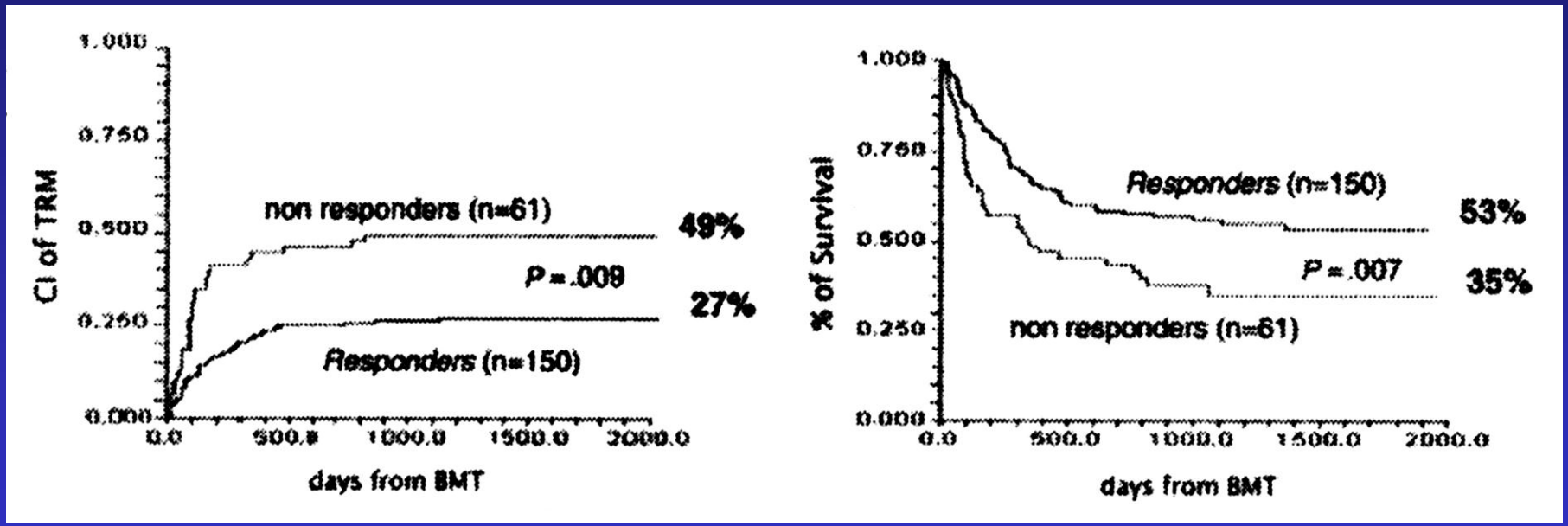


First-Line Therapy of Acute GVHD: Corticosteroids as Standard

Author	Number of patients	Design	Response	Comment
Martin 1990 [1]	197	MP	Up to 55% CR	Significantly higher CR rates in grade II and 1 organ involvement
Weisdorf 1990 [2]	160	MP	Up to 55%	Significantly higher CR rates in grade II and 1 organ involvement
Van Lint 1998 [5] *	47	MP 2 mg	68% RR	28% TRM, 63% 3-year OS
	48	MP 10 mg	71% RR	32% TRM, 62% 3-year OS
MacMillan 2002 [4]	443	MP	35% CR, 20% PR	
Cragg 2000 [6] *	46	MP	76% RR	2-year OS 50%
	50	ATG/MP	76% RR	2-year OS 40%, n.s.
Cahn 1995 [7]*	34	MP + P	54% CR	
	34	MP + anti-CD25	44% CR	OS n.s. different
Lee 2004 [8]*	49	MP + P	49% CR	1-year OS 60%
	53	MP + Daclizumab	43% CR	1-year OS 29%, p = 0.002

Transplant Outcome According to Response to First-line Steroid-Therapy

A

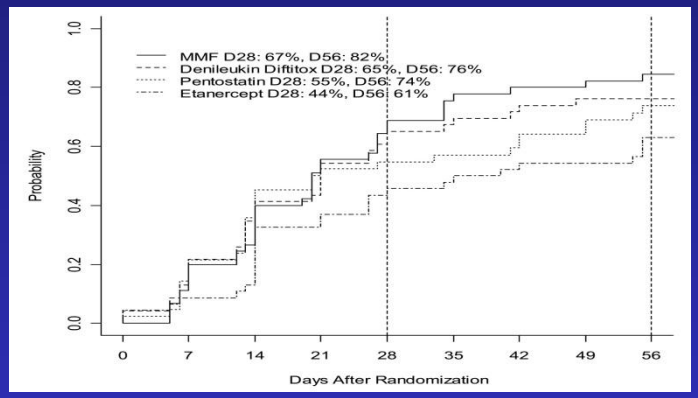


B

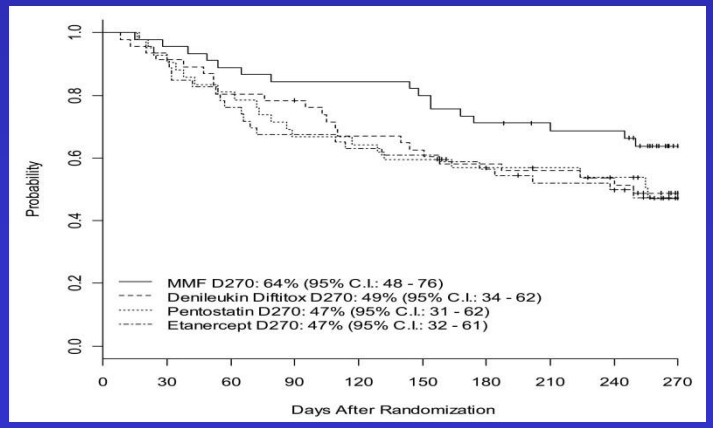
Van Lint et al, Blood 2006; 107:4177-81

Randomised Phase II Study on First-Line Therapy of Acute GVHD

CR by day 56



Survival at 9 months



- 180 pts grades I-IV
- Steroids at 2 mg/kg + etanercept, MMF, denileukin diftitox or pentostatin
- **Day 28 CR**: etanercept 26%, MMF 60%, denileukin 53%, pentostatin 38%
- **Severe infections**: etanercept 48%, MMF 44%, denileukin 62%, pentostatin 57%
- **MMF+steroids** most promising

Alousi et al, Blood 2009; 114:511-7

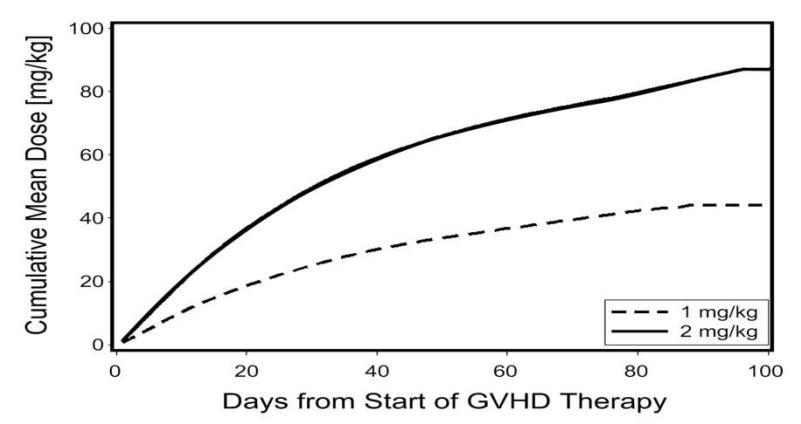
Randomised Phase III Study on First-Line Therapy of Acute GVHD

	MMF (n=117)	Placebo (n=119)	P value
GVHD free OS at day 56	61% (52-69.5%)	52% (43-61%)	0.78
cGVHD at 6 mo	24% (16-32%)	26.5% (18-35%)	0.69
NRM at 6 mo	16% (9-22%)	20% (13-28%)	0.83
OS at 6 mo	71% (62-79%)	74% (65-81%)	0.25

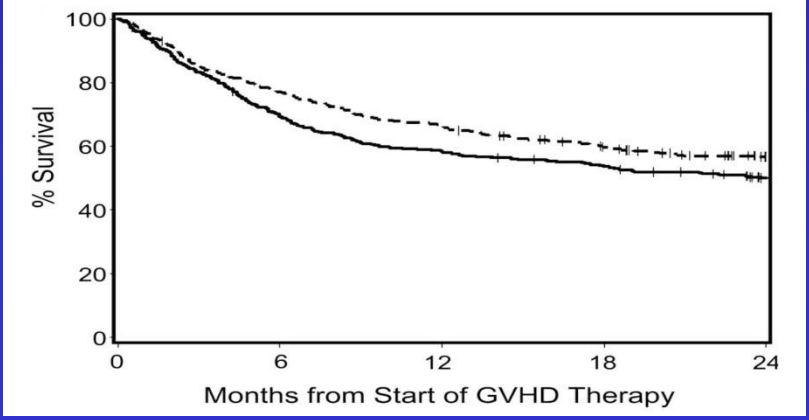
Bolanos-Meade J et al. BBMT 2013;19:S137 (abstract)

Low Dose Prednisone in Acute GVHD

Cum. steroid dose

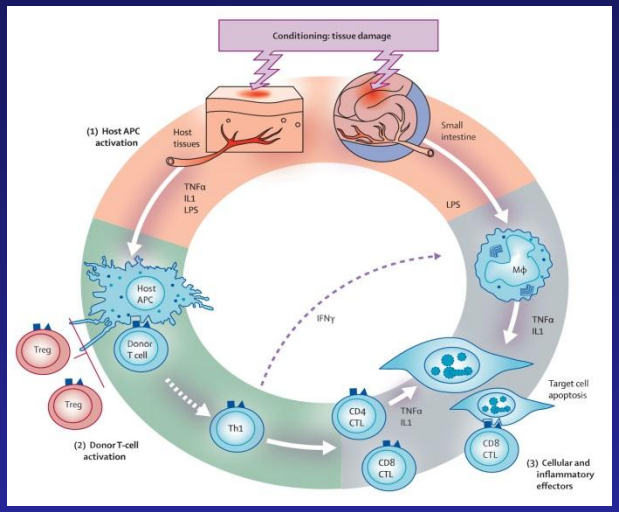


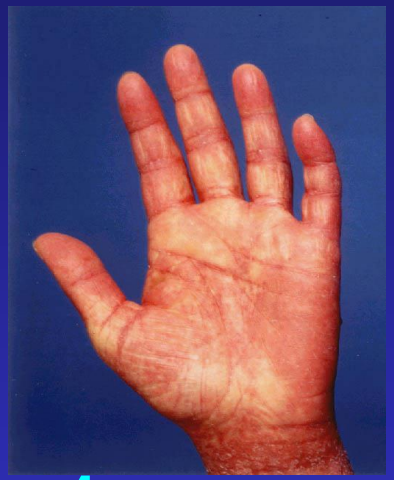
Survival



- 733 pts with mainly acute **GVHD I-II**
- Retrospective analysis
- **2 mg/kg vs 1 mg/kg** of steroids
- No difference in NRM, relapse and OS
- **Reduced fungal infections** in low-dose steroid group
- Reduced duration of hospitalization in low-dose steroid group.

Mielcarek et al, Blood 2009;113:2888-94





Salvage Therapy of Acute GVHD

ASBMT Recommendations
Second-line Therapy of Acute GVHD

- Second-line therapy indicated when:
  - After 3 days with **progression**
  - After 1 week with **persistent unimproving** grade III GVHD
  - After 2 weeks with **persistent unimproving** grade II GVHD

Martin PJ et al, BBMT 2012;18:1150-63.

ASBMT Recommendations: Second-line Therapy of Acute GVHD

- **Evaluation of CR rates** does not support the choice of any specific agent for secondary therapy of acute GVHD.
- No evidence that any specific agent should be avoided for secondary therapy of acute GVHD.

Martin PJ et al, BBMT 2012; 18:1150-63

ASBMT Recommendations: Second-line Therapy of Acute GVHD

- **Evaluation of 6-month survival** does not support the choice of any specific agent for secondary therapy of acute GVHD.
- No evidence that any specific agent should be avoided for secondary therapy of acute GVHD.

Martin PJ et al, BBMT 2012; 18:1150-63

ASBMT Recommendations
Second-line Therapy of Acute GVHD

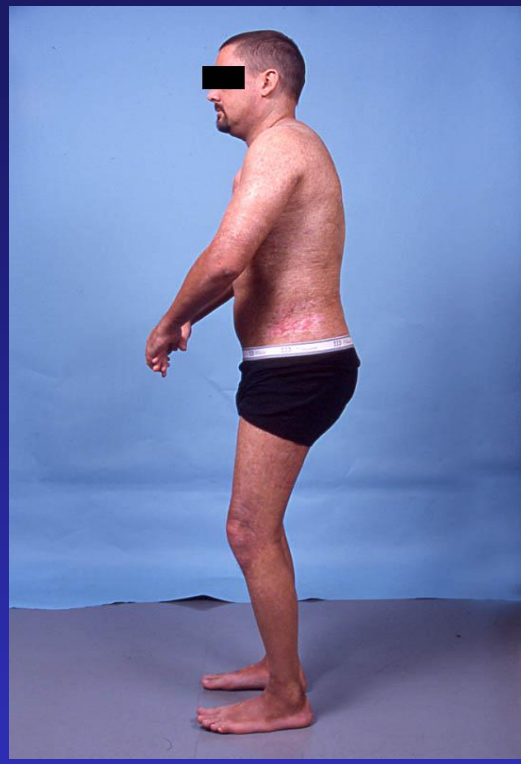
	Toxicity	Sig. interactions	Viral reactivation
ECP	**Limited**	**None**	**Not increased**
Steroids	High	None	High
MMF	Cytopenia, GI	Myelosuppress.	Moderately high
Denileukin Diftitox	↑ hepatic transam.	None	High
Sirolimus	Cytopenia, HUS/TAM	CYP3A or P-glyc.	Moderate
Infliximab	None	None	Very high
Etanercept	None	None	High
Pentostatin	Myelosuppress., liver, renal	None	Very high
Horse ATG	Anaphylaxis, cytopenia	None	Very high
Rabbit ATG	Cytopenia, infections	None	Very high
Alemtuzumab	Pancytopenia, infusion-AE	None	Very high

ASBMT Recommendations: Second-line Therapy of Acute GVHD

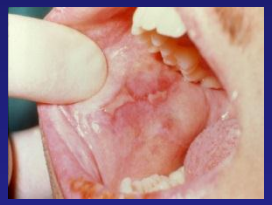
- **Choice of second-line regimen** should be guided by considerations of:
  - Effects of any previous treatment
  - Potential toxicity (infections)
  - Interactions with other agents
  - Familarity of physician with agent
  - Prior experience of physician with agent
  - Convenience
  - Expense
- **Steroids should be continued** after starting second-line agent for therapy of steroid-refractory acute GVHD.

Martin PJ et al, BBMT 2012; 18:1150-63

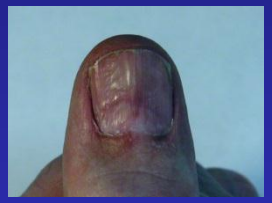
Chronic GVHD



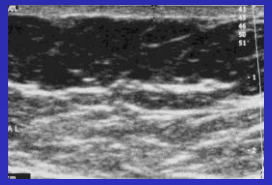
Dry eyes



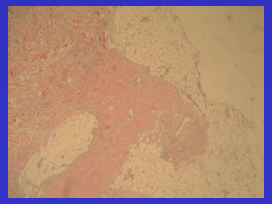
Oral lesions



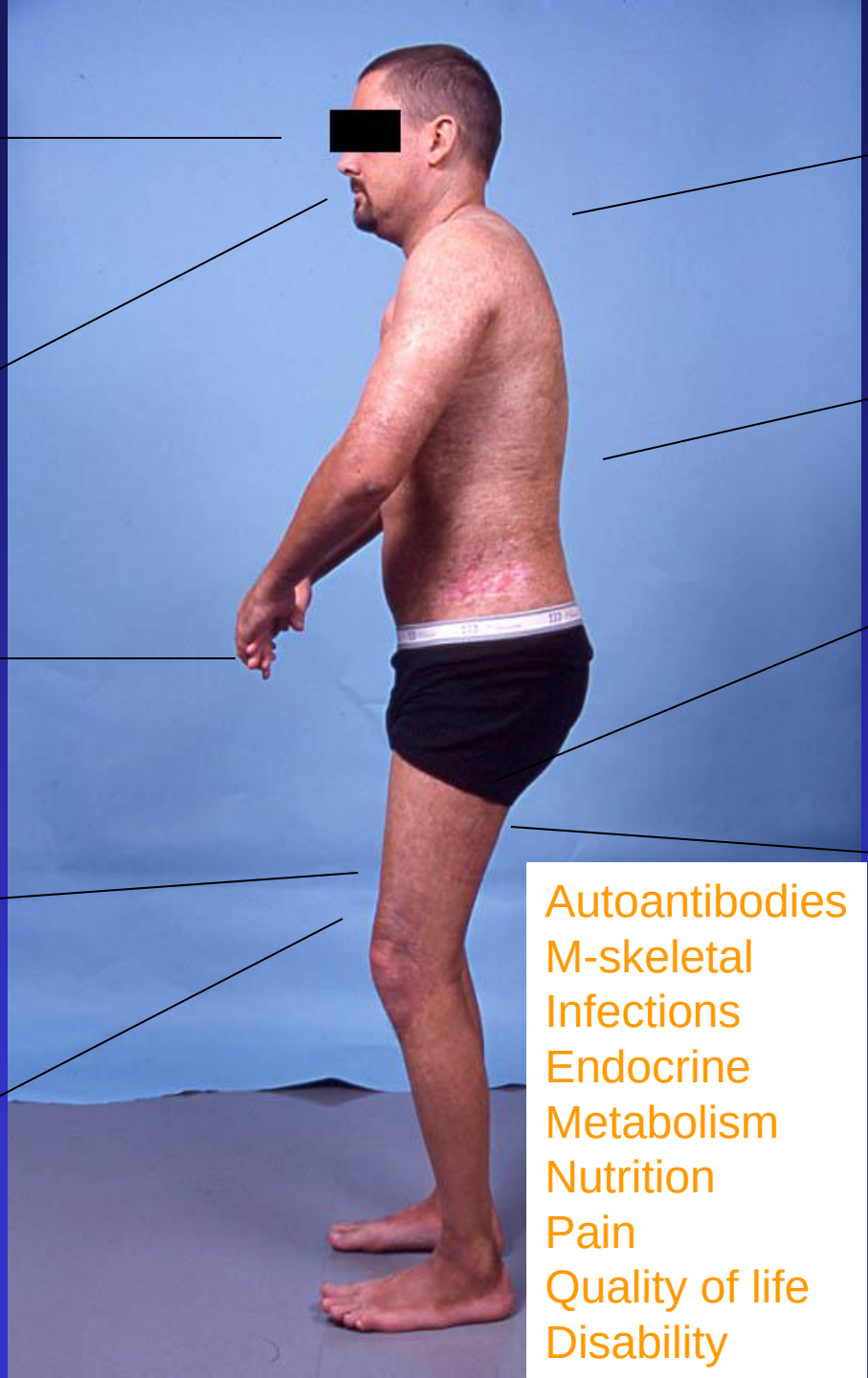
Nail dystrophy

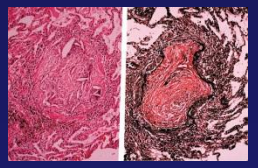


Skin sclerosis

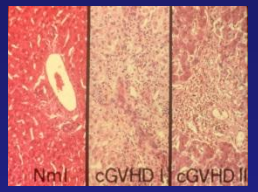


Deep sclerosis

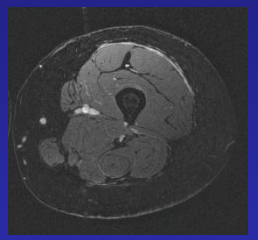




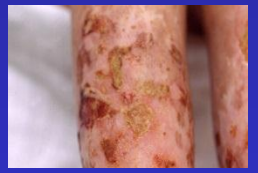
Bronchiolitis obliterans



Loss of bile ducts



Fasciitis



Skin ulcers

Autoantibodies
M-skeletal
Infections
Endocrine
Metabolism
Nutrition
Pain
Quality of life
Disability

Categories of Chronic GVHD according to the NIH Consensus

Category	Time of symptoms after HCT or DLI	Presence of acute GVHD features	Presence of chronic GVHD features
Acute GVHD			
Classic acute GVHD	≤ 100 days	yes	no
Persistent, recurrent or late onset acute GVHD	> 100 days	yes	no
Chronic GVHD			
Classic chronic GVHD	No time limit	no	yes
Overlap syndrome	No time limit	yes	yes

Filipovich et al, BBMT 2005

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 pertinent biopsy* or other relevant tests

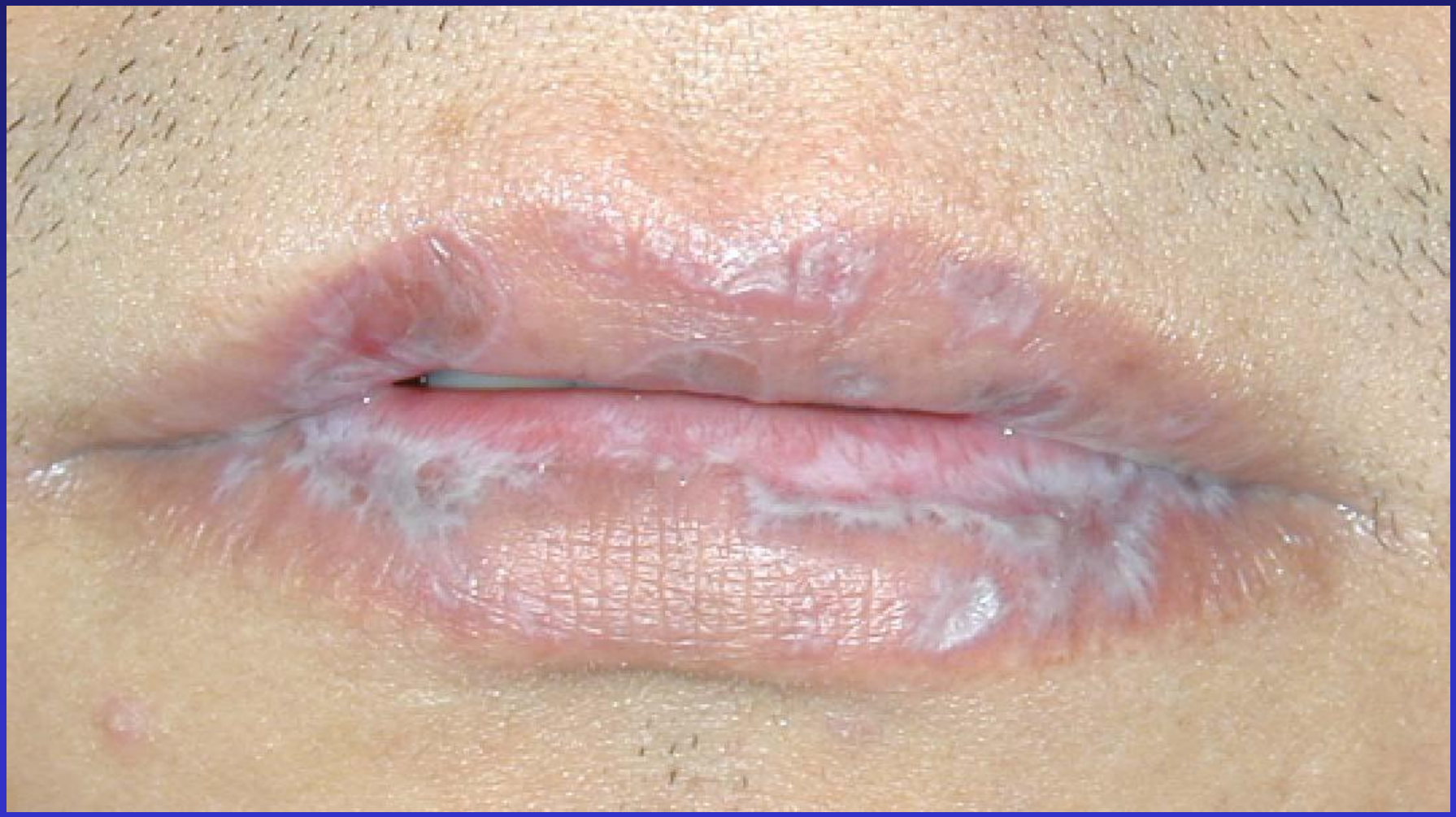
3. Exclusion of other possible diagnosis

Filipovich et al, BBMT 2005; 11:945-956

Diagnostic GVHD Manifestation

Deep sclerosis

Diagnostic GVHD Manifestation



Diagnosis of chronic GVHD according to NIH Consensus

NIH consensus severity grading permits severity grading according to the grade of impairment.

Differentiation of cGVHD in

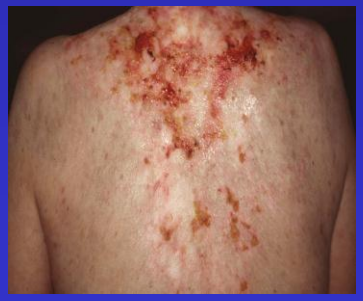
mild (≤ 2 organs, mild involvement only)

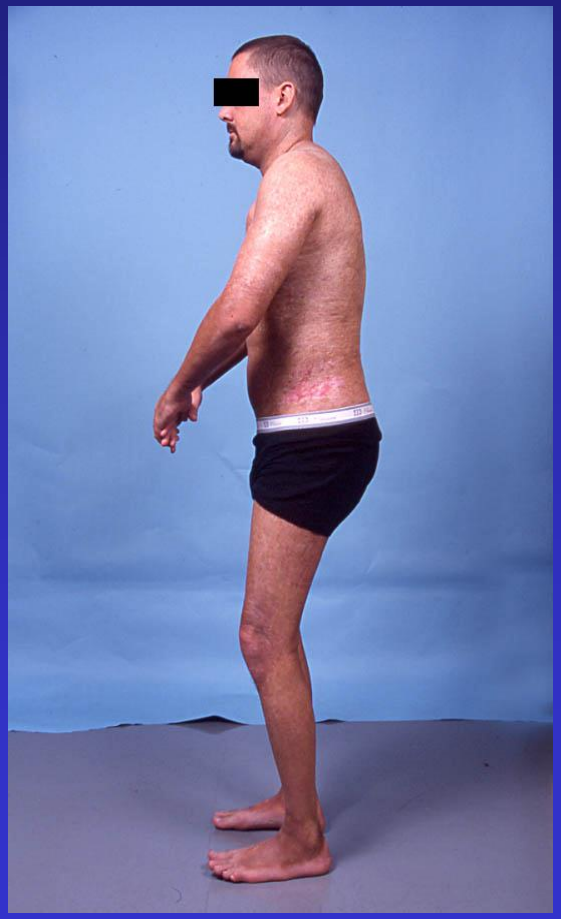
moderate (>2 organs mild or moderate involvement, mild lung involvement)

severe (severe organ involvement with significant impairment of function or moderate lung involvement)

Filipovich et al, BBMT 2005; 11:945-956

Therapy of Chronic GVHD





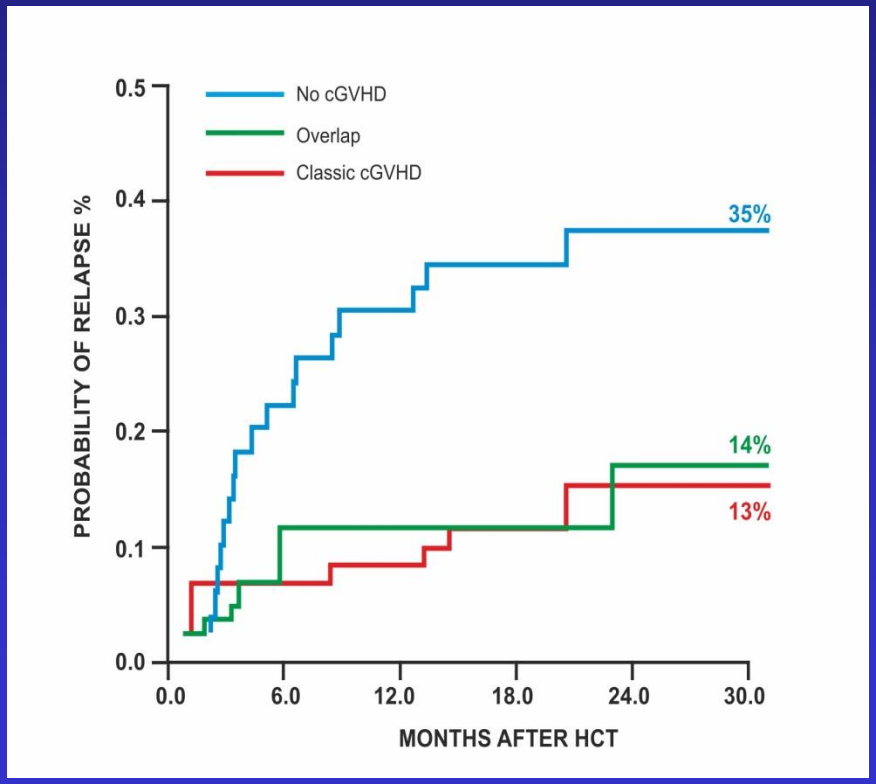
Treatment Challenges of Chronic GVHD

- **Control of GVHD activity**
  - TRM due to infections and organ toxicities
  - Impaired quality of life
- **Side effects of immunosuppression**
  - Steroid-sparing important for less toxicity, fewer infections
- **Relapse**

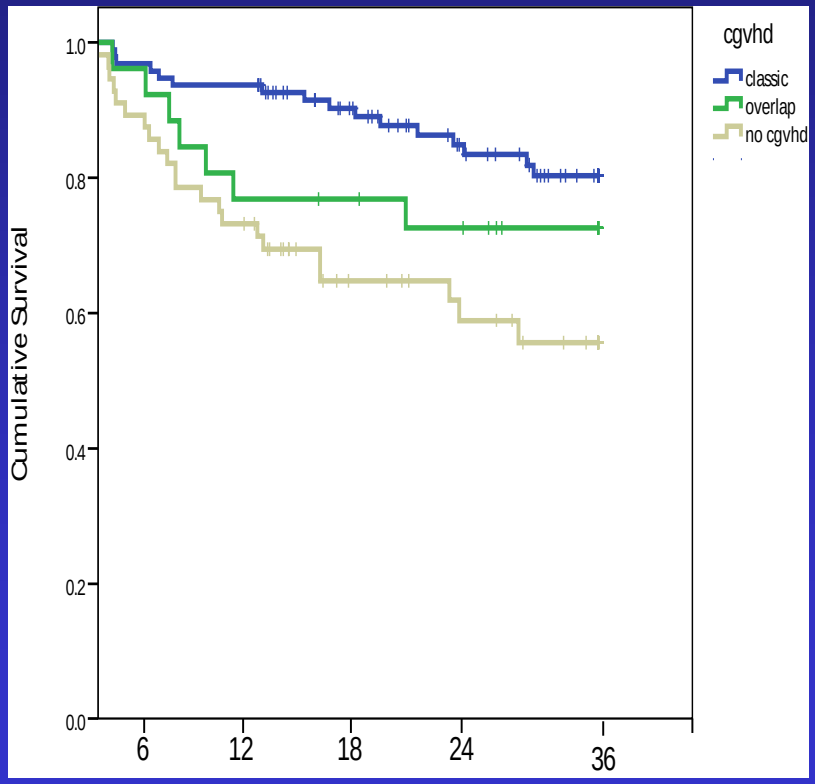
MEDIZINISCHE UNIVERSITÄT WIEN

Effect of Chronic GVHD on Relapse

Relapse



Survival



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

First-line Therapy of Chronic GVHD

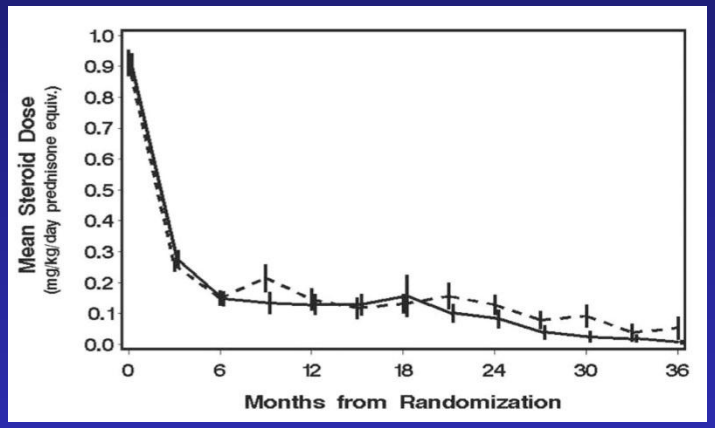
Author	Therapy	No. pts	Outcome
Sullivan 88	PDN+P	63	21% TRM, 61% 5-yr-OS
	PDN+AZA	63	40% TRM, 47% 5-yr-OS
	PDN high risk pts	38	58% TRM, 26% 5-yr-OS
Sullivan 88	Alt.day PDN+CSP	40	51% 4-yr-OS
Arora 01	CSP+PDN	27	73% RR, 54% 2-yr-OS
	CSP+PDN+Thal	27	85% RR, 66% OS,closed early
Flowers 02	CSP+PDN	126 SR	21% TRM, 62% 10-yr-OS
		111 HR	35% TRM, 39% 10-yr-OS
Koc 02	CSP+PDN	142	17% TRM, 67% 5-yr-OS
	PDN	145	13% TRM, 72% 5-yr-OS

Steroids are standard first-line therapy of chronic GVHD.

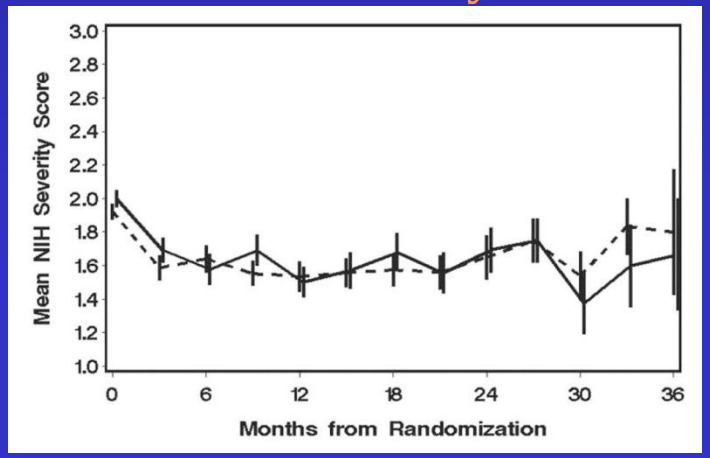
In pts with plts > $100x10^9$/L combination of steroids with CNIs doesn‘t improve results.

First-Line Therapy of cGVHD with MMF

Mean steroid dose

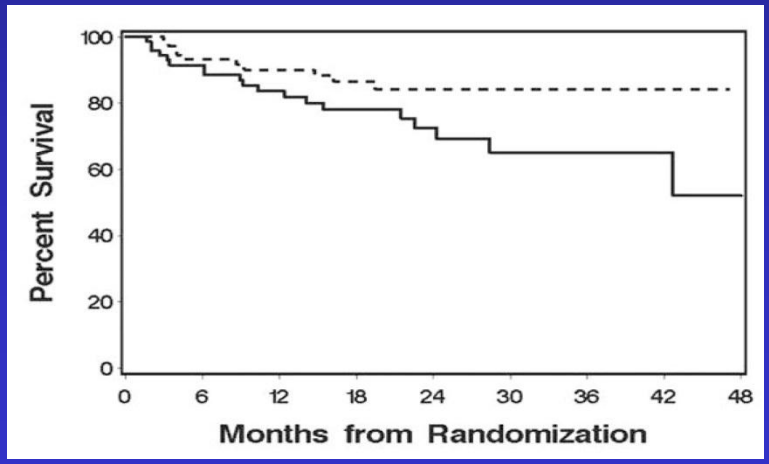


Mean NIH severity



- Double-blind, randomised study with 151 pts +/- MMF
- Closed after 4 years

Survival



Martin PJ et al, Blood 2009;113:5074-82

D/A/CH Consensus on First-Line Therapy of cGVHD

ASBMT
American Society for Blood and Marrow Transplantation

Agent	Recomm.	Evid.	Comment
Steroids	**A**	**I**	**Important but many side effects**
CNI	C-1	II	Steroid sparing, lowers risk for osteonecrosis
MMF + Steroids	C-1	III-1	↑ Risk for viral reactivation, steroid sparing
MMF + CNI + Steroids	D	II	No improved efficacy in rand. study
Azathioprine	D	II	Worse outcome in rand. study in combination with steroids
Thalidomide	D	II	Also used in myeloma patients in relapse

Wolff D et al, BBMT 2010;16:1611-1628.

Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease

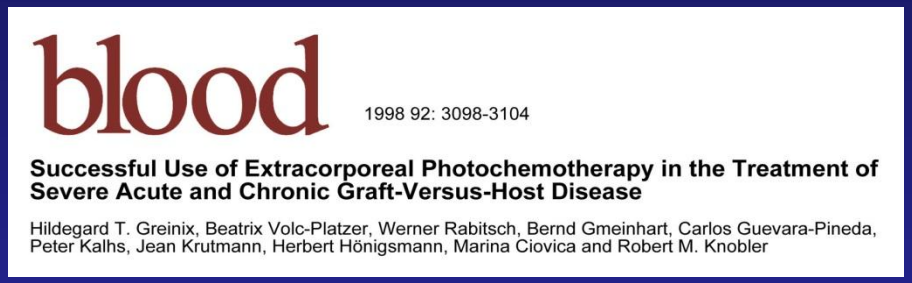
Daniel Wolff,[1] Michael Schleuning,[2] Stephanie von Harsdorf,[3] Ulrike Bacher,[4] Armin Gerbitz,[5] Michael Stadler,[6] Francis Ayuk,[4] Alexander Kiani,[7] Rainer Schwerdtfeger,[2] Georgia B. Vogelsang,[8] Guido Kobbe,[9] Martin Gramatzki,[10] Anita Lawitschka,[11] Mohamad Mohty,[12] Steven Z. Pavletic,[13] Hildegard Greinix,[14] Ernst Holler[1]

ASBMT American Society for Blood and Marrow Transplantation

Wolff et al BBMT 2011; 17:1-17

Therapy	Rec.	Evid.	Comment
Steroid	B	III-1	Serious side effects
Photopheresis	**C-1**	**II**	**Steroid-sparing, excellent safety profile**
mTOR – Inhib.	C-1	III-1	↑ TAM with CNI
Cyclosporin / FK506	C-1	III-1	Spare steroids
MMF	C-1	III-1	↑ viral infections, GI toxicity
Imatinib	C-2	III-1	Best in sclerodermoid GVHD and BO
Rituximab	C-2	II	Effective in autoAB mediated diseases
Total nodal Rx	C-2	III-2	Best in fasciitis and mucocutaneous cGVHD

ECP in Refractory Chronic GVHD



blood 1998 92: 3098-3104

Successful Use of Extracorporeal Photochemotherapy in the Treatment of Severe Acute and Chronic Graft-Versus-Host Disease

Hildegard T. Greinix, Beatrix Volc-Platzer, Werner Rabitsch, Bernd Gmeinhart, Carlos Guevara-Pineda, Peter Kalhs, Jean Krutmann, Herbert Hönigsmann, Marina Ciovica and Robert M. Knobler

Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD

Daniel R. Couriel, Chitra Hosing, Rima Saliba, Elizabeth J. Shpall, Paolo Anderlini, Beverly Rhodes, Veronica Smith, Issa Khouri, Sergio Giralt, Marcos de Lima, Yvonne Hsu, Shubhra Ghosh, Joyce Neumann, Borje Andersson, Muzzafar Qazilbash, Sharon Hymes, Stella Kim, Richard Champlin, and Michele Donato

BLOOD, 15 APRIL 2006 • VOLUME 107, NUMBER 8

Extracorporeal photochemotherapy for paediatric patients with graft-versus-host disease after haematopoietic stem cell transplantation

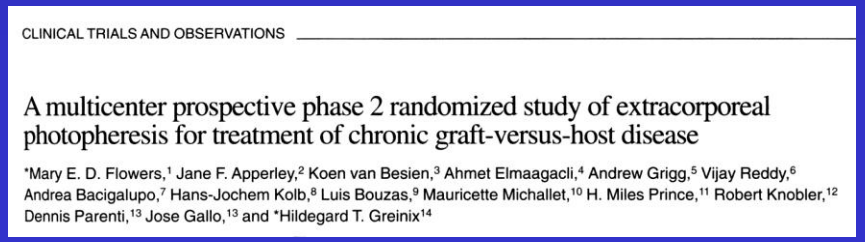
Chiara Messina,[1] Franco Locatelli,[2] Edoardo Lanino,[3] Cornelio Uderzo,[4] Graziella Zacchello,[5] Simone Cesaro,[1] Marta Pillon,[1] Cesare Perotti,[6] Claudia Del Fante,[6] Maura Faraci,[3] Lucia Rivabella,[7] Elisabetta Calore,[1] Pietro De Stefano,[2] Marco Zecca,[2] Giovanna Giorgiani,[2] Alessandra Brugiolo,[1] Adriana Balduzzi,[4] Giorgio Dini,[3] Luigi Zanesco[1] and Roberto Dall'Amico[5]* [1]*Paediatric Haematology and Oncology Unit, University of Padua,* [2]*Paediatric Haematology and Oncology Unit, IRCCS Policlinico San Matteo,* [3]*Paediatric Haematology and Oncology Unit, IRCCS G. Gaslini, Genova,* [4]*Department of Paediatrics, Nuovo Ospedale S. Gerardo, Monza,* [5]*Department of Paediatrics, Nephrology Unit, University of Padua, Thiene,* [6]*Immunohaematology and Transfusion Unit, IRCCS Policlinico San Matteo, Pavia, and* [7]*Immunohaematology and Transfusion Unit, IRCCS G. Gaslini, Genova, Italy*

British Journal of Haematology, 2003, **122**, 118–127

- **High response rates**
  - Skin 40-90%, liver 0-80%, mucosal 20-90%
- **Excellent safety profile**
- ECP as frequently applied **salvage therapy** in adults and children with steroid-refractory cGVHD

Randomized Study

Flowers MED et al, Blood 2008;112:2667-74



CLINICAL TRIALS AND OBSERVATIONS

A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease

*Mary E. D. Flowers,[1] Jane F. Apperley,[2] Koen van Besien,[3] Ahmet Elmaagacli,[4] Andrea Bacigalupo,[7] Hans-Jochem Kolb,[8] Luis Bouzas,[9] Mauricette Michallet,[10] H. Miles Prince,[11] Robert Knobler,[12] Dennis Parenti,[13] Jose Gallo,[13] and *Hildegard T. Greinix[14]

Current Challenges of GVHD

GVL vs GVHD

- Significantly lower relapse rate in patients with a+cGVHD
- No clear separation of beneficial vs harming cell populations in graft/post-transplant cell therapy available yet

Significant impact on **survival**

Prolonged immunosuppression required

Therapy: Efficacy vs toxicity

- Infections
- Quality of life
- Steroid-sparing
- Duration of IS

Lack of well-defined prospective studies

No progress in first-line therapy of cGVHD, ? aGVHD

Various strategies for **salvage therapy**

? Improved GVHD prophylaxis

? Biomarkers for GVHD