Chronic Graft-versus-Host Disease:
Diagnosis & Treatment
Carina Moravec, ARNP

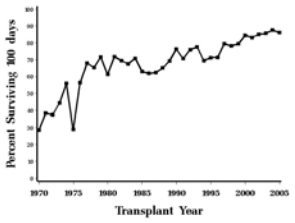
Chronic Graft-versus-Host Disease
Carina Moravec, ARNP &
Krista Rowe-Nichols, RN, MSN, AOCNS

Chronic GVHD (ARS)

- Among patients who are alive at 2 years post transplant, what percentage are still alive at 15 years?
  - A. 50%
  - B. 80%
  - C. 20%
  - D. 100%

Survival rates have increased in the past 30 years

% Patients Surviving ≥ 100 days after Allogeneic HCT in Seattle

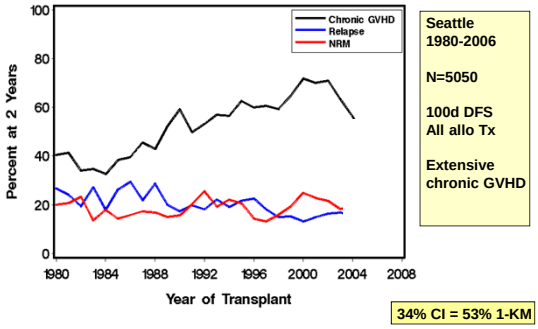


Flowers and Deeg, HJ in Thomas' s HCT, 4th Ed., 2009

- Among 2 year DFS, subsequent survival:
  - 90% at 5 years
  - 85% at 10 years
  - 80% at 15 years
- Among 5 year DFS, subsequent survival:
  - 80% at 20 years

Socie et al, NEJM 1999
Bhatia et al, Blood 2007
Martin et al, JCO 2010

Major events after allogeneic transplant



Seattle
1980-2006

N=5050

100d DFS
All allo Tx

Extensive chronic GVHD

34% CI = 53% 1-KM

Chronic GVHD (ARS)

- What is the median onset of chronic GVHD after allogeneic transplantation?
  - A. 2 months
  - B. 12 months
  - C. 6 months
  - D. 18 months

Chronic Graft-versus-Disease (GVHD)

- Most common late complication after allogeneic hematopoietic cell transplant
- Median onset 6 months after transplant (tapering off prophylactic immune suppression)
- 10% diagnosed beyond 1-year after transplant
- Affects multiple organs with inflammatory and fibrotic clinical phenotypes

Why is Chronic GVHD a Problem?

- Occurs in 20-70% of patients surviving more than 100 days (60% incidence in Seattle)
- Major cause of death despite lower relapse rate; 40% survival at 8 years
- Associated with decreased quality of life
- Secondary malignancies are more common in patients with chronic GVHD

NIH Concensus Criteria for Chronic GVHD

- In 2005, the National Institutes of Health (NIH) convened an experts conference to develop consensus on criteria for:
  - Diagnosis and Staging
  - Pathology
  - Biomarkers
  - Response Measurement
  - Supportive Care
  - Design of Clinical Trials

http://ccr.ncifcrf.gov/resources/gvhd/

Biomarker

http://www.ncbi.nlm.nih.gov/pubmed/16443511

•Identify an approach for the identification, validation, and application of biomarkers for chronic GVHD

Biology of Blood and Marrow Transplantation 12:126-137 (2006)

Design of Clinical Trials

http://www.ncbi.nlm.nih.gov/pubmed/16635784

Biology of Blood and Marrow Transplantation 12:491-505 (2006)

Response Criteria

http://www.ncbi.nlm.nih.gov/pubmed/16503494

Biology of Blood and Marrow Transplantation 12:252-266 (2006)

Response Criteria

- Summarizes and proposes measures and criteria for assessing outcomes in clinical trials involving patients with chronic GVHD
- Proposed chronic GVHD-specific Core measures:
  - Clinician or patient assigned signs and symptoms
  - The chronic GVHD symptom scale by Lee et.al.
  - The clinician or patient reported global rating scales

http://www.asbmt.org/GvHDForms

Biology of Blood and Marrow Transplantation 12:252-266 (2006)

Pathology

http://www.ncbi.nlm.nih.gov/pubmed/16399567

•Outlines optimal sampling and tissue preparation
•Minimal criteria for diagnosis of chronic GVHD
•Specific requirements for diagnosis of chronic GVHD
•Definition of diagnostic categories which reflect the integration of histopathology, clinical, laboratory and radiographic information:
  - No GVHD
  - Possible GVHD
  - Consistent with GVHD
  - Definite GVHD

http://www.asbmt.org/cGvHD_Guidelines

Biology of Blood and Marrow Transplantation 12:31-47 (2006)

Diagnosis and Staging

http://www.ncbi.nlm.nih.gov/pubmed/16338616

•Standardize the criteria for the diagnosis of chronic GVHD
•Proposes a new clinical scoring system (0-3) that describes the extent and severity of chronic GVHD for each organ or site at any given time taking functional impact into account
•Proposes new guidelines for global assessment of chronic GVHD severity that are based on the number of organs or sites involved and the degree of involvement of infected organs (mild, moderate, severe)

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

Diagnosis and Staging

- In the past, any manifestation of GVHD that was present or continued after day 100 was arbitrarily defined as chronic GVHD.

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

Diagnosis and Staging

- Diagnostic signs and symptoms
  - Refer to those manifestations that establish the presence of chronic GVHD without the need for further testing or evidence of other organ involvement
- Distinctive signs and symptoms
  - Refer to those manifestations that are not ordinarily found in acute GVHD, but not sufficient enough to establish an unequivocal diagnosis of chronic GVHD without further testing or additional organ involvement
- Other features
  - Rare, controversial or non-specific features of chronic GVHD that can not be used to establish a diagnosis
- Common features
  - Seen in both acute and chronic GVHD

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

Diagnosis and Staging

- Diagnosis of chronic GVHD requires the presence of at least 1 diagnostic clinical sign

OR

- The presence of at least 1 distinctive manifestation confirmed by pertinent biopsy or other relevant test in the same or other organ
- Distinction from acute GVHD
- Exclusion of other possible diagnoses

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

Diagnostic versus Distinctive Features

Organ or Site	Diagnostic (sufficient to establish the diagnosis of chronic GVHD)	Distinctive (seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)	Other Features * Can be acknowledged as part of the chronic GVHD symptomatology if the diagnosis is confirmed*	Common (seen in both Acute and Chronic GVHD)
SKIN	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
NAILS		Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric; affects most nails)❶		
SCALP & BODY HAIR		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Scaling, papulosquamous lesions	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes)	
MOUTH	Lichen-type features Hyperkeratotic plaques Restriction of mouth opening from sclerosis	Xerostomia Mucocele Mucosal atrophy Pseudomembranes❶ Ulcers❶		Gingivitis Mucositis Erythema Pain

Filipovich et al. Biol of Blood and Marrow Transplant 11:945-955 (2005)

Diagnostic versus Distinctive Features

Organ or Site	Diagnostic (sufficient to establish the diagnosis of chronic GVHD)	Distinctive (seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)	Other Features * Can be acknowledged as part of the chronic GVHD symptomatology if the diagnosis is confirmed*	Common (seen in both Acute and Chronic GVHD)
EYES		New onset dry, gritty, or painful eyes❷ Cicatricial conjunctivitis Keratoconjunctivitis sicca❷ Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
GENITALIA	Lichen planus-like features Vaginal scarring or stenosis	Erosions❶ Fissures❶ Ulcers❶		
GI TRACT	Esophageal web Stricture or stenosis in the upper to mid third of the esophagus ❶		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight Loss Failure to Thrive
LIVER				Total Bili, Alk Phos >2X ULN ❶ AST, ALT >2XULN ❶

Filipovich et al. Biol of Blood and Marrow Transplant 11:945-955 (2005)

Diagnostic versus Distinctive Features

Organ or Site	Diagnostic (sufficient to establish the diagnosis of chronic GVHD)	Distinctive (seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)	Other Features * Can be acknowledged as part of the chronic GVHD symptomatology if the diagnosis is confirmed*	Common (seen in both Acute and Chronic GVHD)
LUNG	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and Radiology❷		BOOP
MUSCLES, FASCIA, JOINTS	Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis❷	Edema Muscle cramps Arthralgia or arthritis	
HEMATOPOIETIC AND IMMUNE			Thrombocytopenia Eosinophilia Hypo or hypergammaglobulinemai Autoantibodies (AIHA and ITP)	
OTHER			Pericardial or pleural effusions Ascites Peripheral Neuropathy Nephrotic Syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

Filipovich et al. Biol of Blood and Marrow Transplant 11:945-955 (2005)

- Insert case study to highlight differences between distinctive and diagnostic features of chronic GVHD

Category	Time of Symptoms	Presence of acute GVHD features	Presence of chronic GVHD features
ACUTE GVHD			
Classic acute	<100 days	YES	NO
Persistent, Recurrent or Late Onset acute	>100 days	YES	NO
CHRONIC GVHD			
Classic chronic	No time limit	NO	YES
Overlap syndrome	No time limit	YES	YES

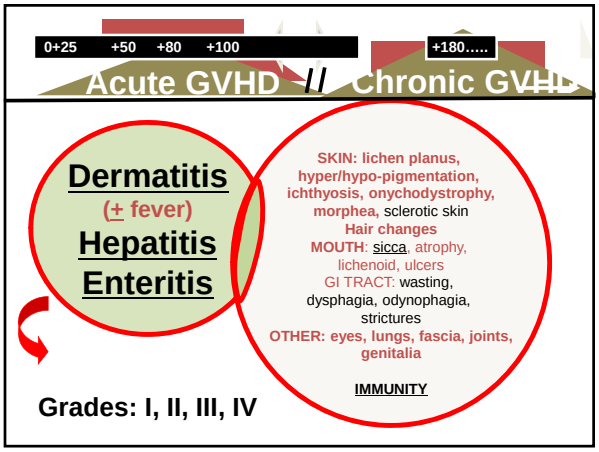
Filipovich et al. Biol of Blood and Marrow Transplant 11:945-955 (2005)

NIH Consensus Tool

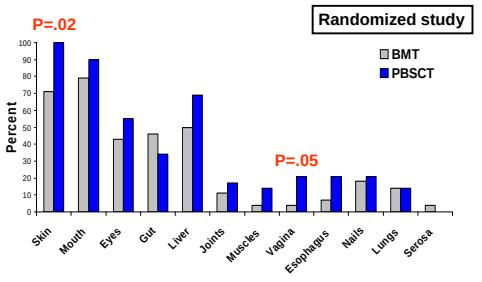
- Mild chronic GVHD
  - Involves only 1 or 2 organ sites (except lungs)with not clinically significant functional impairment (maximum score of 1 in all affected organs or sites)
- Moderate chronic GVHD
  - At least 1 organ or site with clinically significant but no major disability (max score of 2 in any affected organ or site) OR
  - 3 or more organs or sites with not clinically significant functional impairment (max score of 1)
  - A lung score of 1 will also be considered moderate
- Severe chronic GVHD
  - Major disability caused by chronic GVHD (score of 3 in any organ or site)
  - A lung score of >/=2 will also be considered

How do I approach an evaluation on a patient beyond day 100?

- GVHD
  - Late acute GVHD
  - Classic chronic GVHD, based on the NIH criteria
  - Overlap GVHD
  - Why is it important to distinguish between acute and chronic GVHD?
- Disease status
- Infections
- Other complications (AVN, osteoporotic fractures, psychological issues….)



Sites Affected by Chronic GVHD



Flowers et al, Blood 2002;100: 415-419

What to ask a patient at every visit

10 chronic GVHD-specific questions

1. Eyes: Feel dry, irritated, sensitive to wind or air conditioning? Painful? Sensitive to light? Vision changes?
2. Mouth: Dry? Sensitivities to spicy, acidic or rough foods? Taste alterations? Ulcers/sores?
3. Esophagus: Do foods or pills get stuck when you swallow? Size vs dryness.
4. GI: Loss of appetite, nausea, vomiting, diarrhea, voluminous stools, unintentional weight loss, inability to gain weight?

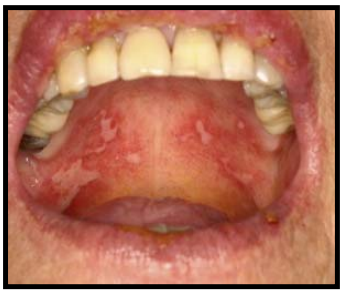
What to ask a patient at every visit

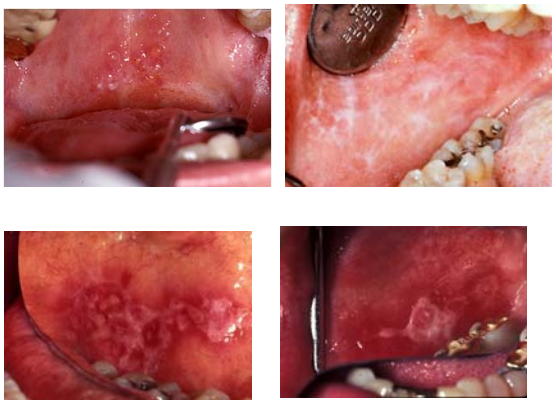
10 chronic GVHD-specific questions

5. Skin: Feel tight or hard, itchy, painful, burn, look different?
6. Do you sweat?
7. Loss of scalp or body hair? Premature graying. Ridged or brittle nails?
8. Lungs: Cough, dyspnea on exertion or rest
9. Joints: Stiffness or pain in any joint
10. GU: Vaginal dryness, dyspareunia; penile pain or dysuria

Physical exam elements at every visit

- Weight, vital signs, performance score (KPS/LKS)
- Oral exam: Buccal mucosa, tongue, gingiva, hard and soft palate: Lacy white or patchy white changes? Erythema? Ulcers? Mottled lips? Mucoceles?
- Eyes: Injected? Dry? Can't keep eyes open?
- Skin exam – Examine and touch the entire body
  - Color and texture changes
  - Touch and pinch for change in texture and mobility:
    - Thick but moveable
    - Thicker, moves poorly but pinchable
    - Not pinchable (hidebound)
- Range of motion: Fingers, wrists, elbows, shoulders, hips, knees, ankles





Physical exam elements at every visit

- Weight, vital signs, performance score (KPS/LKS)
- Oral exam: Buccal mucosa, tongue, gingiva, hard and soft palate: Lacy white or patchy white changes? Erythema? Ulcers? Mottled lips? Mucoceles?
- Eyes: Injected? Dry? Can't keep eyes open?
- Skin exam – Examine and touch the entire body
  - Color and texture changes
  - Touch and pinch for change in texture and mobility:
    - Thick but moveable
    - Thicker, moves poorly but pinchable
    - Not pinchable (hidebound)
- Range of motion: Fingers, wrists, elbows, shoulders, hips, knees, ankles

Distinct Feature

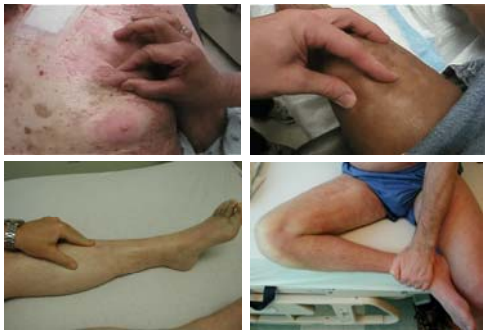
Keratoconjunctivitis Sicca

Physical exam elements at every visit

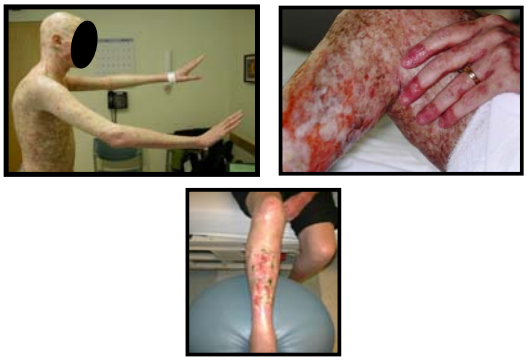
- Weight, vital signs, performance score (KPS/LKS)
- Oral exam: Buccal mucosa, tongue, gingiva, hard and soft palate: Lacy white or patchy white changes? Erythema? Ulcers? Mottled lips? Mucoceles?
- Eyes: Injected? Dry? Can't keep eyes open?
- Skin exam – Examine and touch the entire body
  - Color and lichenoid changes
  - Touch and pinch for change in texture and mobility:
    - Thick but moveable
    - Thicker, moves poorly but pinchable
    - Not pinchable (hidebound)
- Range of motion: Fingers, wrists, elbows, shoulders, hips, knees, ankles

Skin Exam

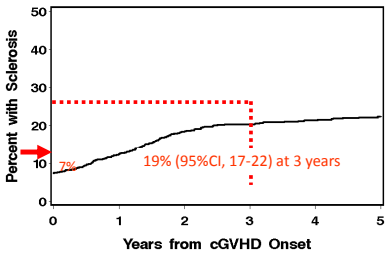
Look, touch and pinch



Chronic GVHD



Cumulative Incidence of Sclerotic GVHD



Inamoto Y et al. Blood 118: #322a, 2011

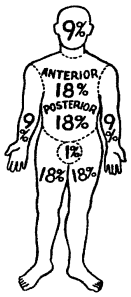
Sclerodermoid Manifestation of Chronic GVHD

Skin Assessment

- ****Photograph skin and range of motion****
- Modified Rodnan Skin Score[1]
  - Skin Thickness measured at 17 sites
  - Score 0-3
  - Total Score 0-51
- Vienna total skin score (Total Skin Score)[2]
- NIH skin scoring system[3] http://www.asbmt.org

[1] *Czirjak L et al on behalf of EUSTAR. Ann Rheum Dis 2007;66:966.*
[2] *Greinix HT et al. Biol Blood Marrow Transplant. 2007; 13: 715.*
[3] *Pavletic,S et al. Biol Blood Marrow Transplant 2006 12: 252.*

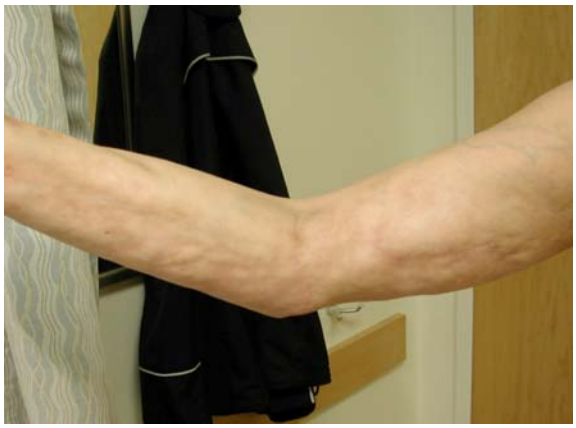
Record percentage of skin involved with GVHD

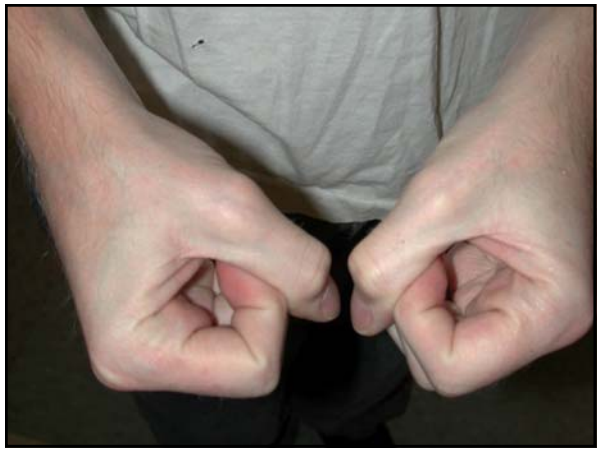


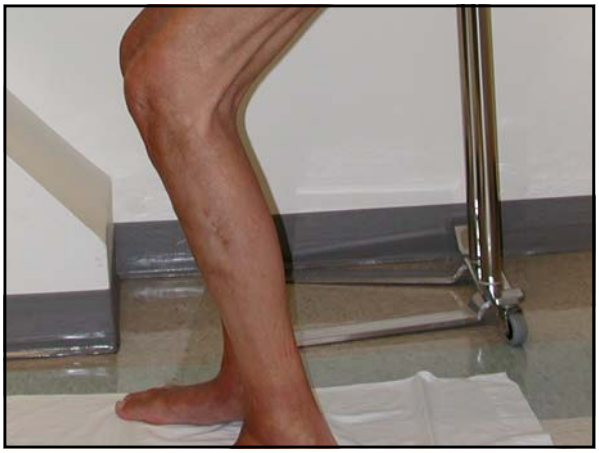
Physical exam elements at every visit

- Weight, vital signs, performance score (KPS/LKS)
- Oral exam: Buccal mucosa, tongue, gingiva, hard and soft palate: Lacy white or patchy white changes? Erythema? Ulcers? Mottled lips? Mucoceles?
- Eyes: Injected? Dry? Can't keep eyes open?
- Skin exam – Examine and touch the entire body
  - Color and texture changes
  - Touch and pinch for change in texture and mobility:
    - Thick but moveable
    - Thicker, moves poorly but pinchable
    - Not pinchable (hidebound)
- Range of motion: Fingers, wrists, elbows, shoulders, hips, knees, ankles

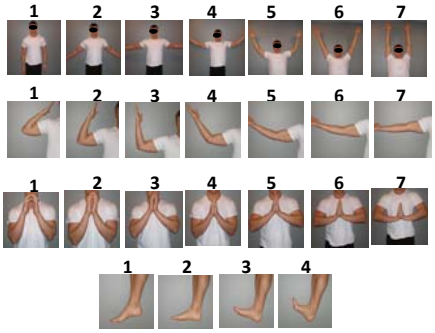
Range of Motion Assessment







Score the Range of Motion

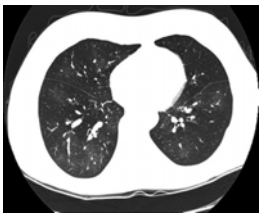


Pulmonary GVHD

- BOS (bronchiolitis obliterans syndrome)
  - 2-14% of allogeneic survivors
  - Dyspnea, dry cough, reduced exercise tolerance
  - Obstructive changes on PFTs + air trapping on HRCT
  - Responds poorly, high mortality
  - Treat with prednisone 1mg/kg + FAM (fluticasone inhaler, azithromycin M/W/F & montelukast) + CNI or other immunosuppressant
  - Monthly PFTs x 3 to monitor response, then every 3-6 months depending on response, monthly spirometry while tapering steroids (slowly)

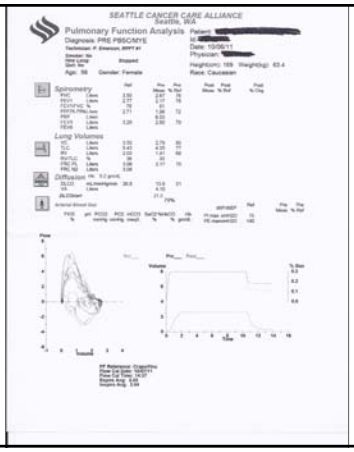
Bronchiolitis Obliterans Syndrome

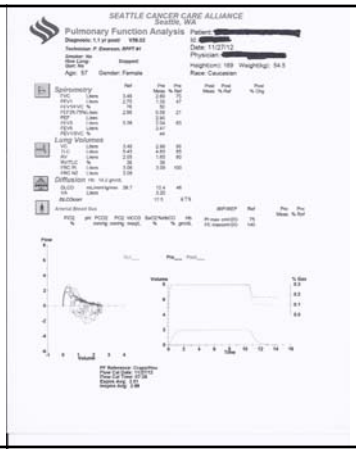
		Ref	Pre Meas	Pre % Ref
Spirometry				
FVC	Liters	5.05	5.06	100
FEV1	Liters	3.82	1.84	48
FEV1/FVC	%	75	36	
FEF25-75%	L/sec	3.25	0.49	15
PEF	L/sec		6.19	
FEV3	Liters	4.57	3.05	67
FEV6	Liters		3.86	
Lung Volumes				
VC	Liters	5.05	5.21	103
TLC	Liters	7.76	9.09	117
RV	Liters	2.67	3.87	145
RV/TLC	%	36	43	
FRC PL	Liters	4.18	5.28	126
FRC N2	Liters	4.18		
Diffusion	Hb: 17.4 gm/dL			
DLCO	mL/mmHg/min	35.9	26.2	73
VA	Liters		6.74	
DLCOcorr			21.6 60%	

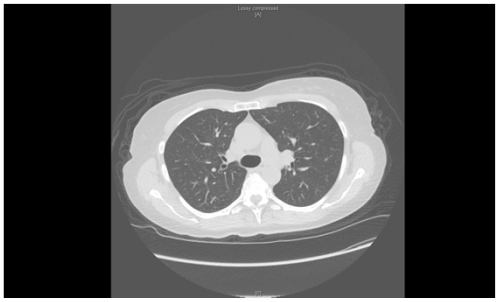


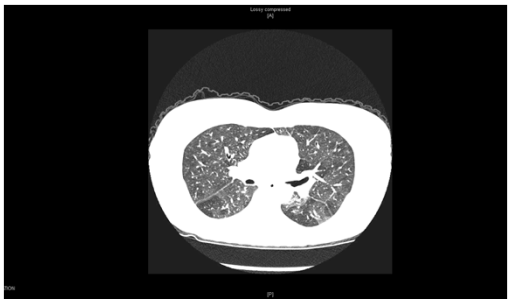
Case Study (BOS)

- DT is a 58 yo woman who had a non-myeloablative PBSC transplant from her sister in October 2011 for the treatment of myelofibrosis.
- Diagnosed with chronic extensive GVHD in November 2012 thirteen months after her transplant. Sites of involvement included her eyes, mouth, skin, joints, lungs (bronchiolitis obliterans) and vagina.
- Treated initially with prednisone 1 mg/kg, tacrolimus, and the FAM study (fluticasone inhaler, azithromycin, and montelukast) for the bronchiolitis obliterans.
- GVHD manifestations improved. PFTs remained abnormal but stable









Case Study (BOS)

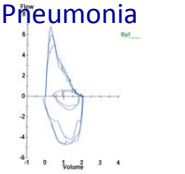
- Tapered off tacrolimus in January 2013 because of severe tremors and cognitive problems attributed to tacrolimus.
- The FAM study was completed in June 2013 after 6 months of treatment. She stopped using the fluticasone inhaler and taking montelukast at that time.
- GVHD manifestations have continued to improve. GVHD manifestations are mild to moderate with persistent eye dryness, mild oral sensitivities and lichenoid changes, mild to moderate vulvovaginal GVHD, and improvement in her pulmonary function tests. Prednisone was tapered and she reached 15 mg every other day in October 2013.

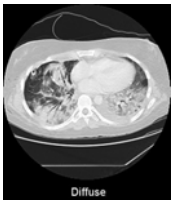
Case Study (COP)

- COP (cryptogenic organizing pneumonia = BOOP)
  - Presents like a pneumonia
  - Restrictive PFTs, low DLCO, patchy consolidation on CT
  - BAL to rule out infection and ideally lung bx
  - Most respond to steroids, better prognosis than with BOS
  - Treat with prednisone 1mg/kg (+ clarithromycin or azithromycin) x 1 month then attempt to taper off over ~ 6 months
  - Monthly PFTs to assess response, then every 1 to 3 months during the taper, depending on the tempo of the taper
  - Some patients will develop BOS

Cryptogenic Organizing Pneumonia

		Ref	Pre Meas	Pre % Ref
Spirometry				
FVC	Liters	4.93	2.09	42
FEV1	Liters	4.04	1.69	42
FEV1/FVC	%	82	81	
FEF25-75%	L/sec	4.16	1.60	38
PEF	L/sec		6.77	
FEV3	Liters	4.71	1.94	41
FEV6	Liters		2.05	
Lung Volumes				
VC	Liters	4.93	2.20	45
TLC	Liters	6.63	3.04	46
RV	Liters	1.75	0.84	48
RV/TLC	%	26	28	
FRC PL	Liters	3.28	1.19	36
FRC N2	Liters	3.28		
Diffusion	Hb: 11.2 gm/dL			
DLCO	mL/mmHg/min	37.3	11.4	30
VA	Liters		2.94	
DLCOcorr			14.6	
			39%	





Case Study (COP)

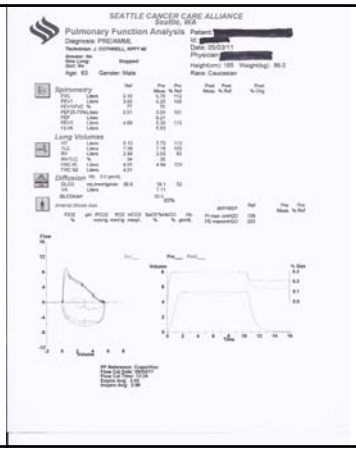
- RM is a 65 yo man, who is 2 ½ years after a non-myeloablative PBSC transplant from a matched unrelated male donor for the treatment of CMML.
- Has never been diagnosed with pathognomonic changes of chronic GVHD.
- Diagnosed with late acute GI tract GVHD in January 2012 at 8 months post transplant, treated with beclomethasone added to ongoing cyclosporine.

Case Study (COP)

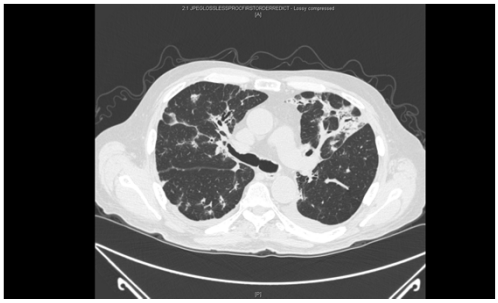
- Diagnosed with cryptogenic organizing pneumonia (COP/BOOP) in October 2012, based on dyspnea, new mild restrictive pattern on pulmonary function tests, chest CT that showed extensive bronchiectasis throughout all lobes, scattered nonspecific areas of consolidation and wall thickening, and a negative bronchoalveolar lavage.
- Prednisone 60 mg (0.75 mg/kg) was added. Dyspnea, cough, and exercise tolerance improved, appetite improved and he started to gain weight.

Case Study (COP)

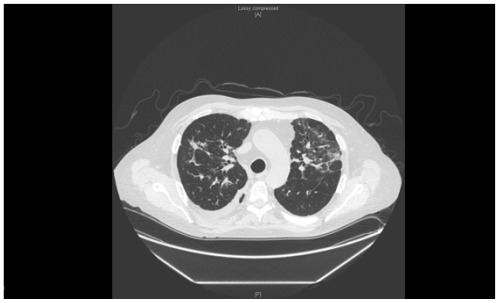
- Pulmonary function tests showed stable restrictive changes.
- Prednisone was tapered by 10 mg per month.
- Steroid induced myopathy improved with the taper and with physical therapy 3 times a week.
- Diagnosed with multiple pulmonary emboli in July 2013 when he presented with persistent hypoxemia despite improvement in the restrictive pattern on pulmonary function tests. Lovenox/ warfarin added.
- Now down to prednisone 5 mg daily. Uses oxygen to exercise on his treadmill.

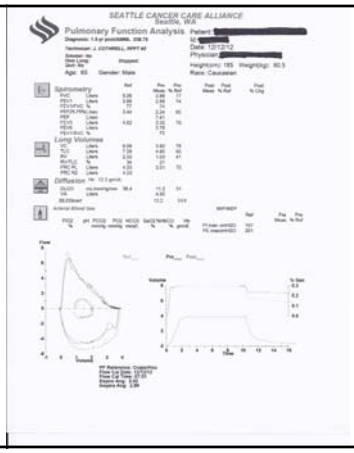


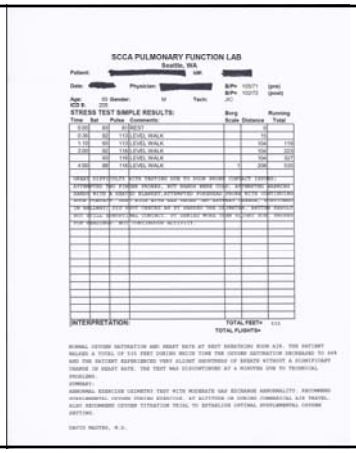
Case Study (COP)



Case Study (COP)







HOW DO I TREAT cGVHD?

- **Enroll patient in a study if available and if eligible**
- Standard of treatment if there are no available studies: Prednisone 1 mg/kg +/- CNI
- If limited site and severity, can consider:
  - PUVA for limited rash/ lichenoid skin changes
  - Resume the CNI or other IST if recently discontinued
  - Artificial tears, etc for dry eyes
  - Resume ursodiol if LFTs are elevated

Case study (severe late acute)

- TB is a 21 yo young lady who had a bone marrow transplant in May 2010 from her haploidentical mother for the treatment of T-cell lymphoma.
- Developed severe acute GVHD of the GI tract early after transplant.
- Responded to 2mg/kg of corticosteroids, & B&B, added to prophylactic tacrolimus, but had multiple severe exacerbations of GVHD during attempts to taper steroids, requiring secondary treatment with infliximab and photopheresis.

Case study

- Diagnosed with chronic GVHD of her mouth in January 2011.
- Developed avascular necrosis of her knees and hips, requiring high doses of narcotics for pain control, severely affecting the quality of her life. Eventually had 2 knee replacements and core decompression of both hips
- GVHD severity gradually improved and she is now on prednisone 7.5 mg daily, no other IS

STEROID TAPER

- If after 2 weeks on 1 mg/kg of steroids daily, GVHD is well controlled, taper to 1 mg/kg every other day over 4 to 5 weeks to reduce toxicity, protect adrenal function, reduce cushingoid effects, etc
- Typically treat at 1 mg/kg every other day for another 3 months, then if GVHD is well controlled, taper to 0.5 mg/kg every other day

CAVEATS

•No benefit to under-treating or over-treating chronic GVHD

•Chronic GVHD is a “chronic” disorder.

•Control of chronic GVHD manifestations is not the same as achieving tolerance.

CAVEATS

- Avoid the “yo-yo” effect of tapering IST off too soon
- Taper to the lowest steroid/ IST dose that controls GVHD (by trial and error).
- Patience. Taper slowly to avoid major exacerbation
- Do not taper off the last immunosuppressant if the patient has eosinophilia or oral GVHD

Case study (under treatment)

- NJ is a 49 yo man who had a PBSC transplant from a mismatched unrelated female donor in August 2011 for the treatment of CML with a history of myeloid blast crisis.
- Treated with nilotinib post transplant to prevent CML relapse.
- Mild late acute GVHD of the GI tract in February 2012 (5 mos post tx). Responded to beclomethasone and ongoing tacrolimus

Case study (under treatment)

- Rash in November 2012 shortly after tapering off tacrolimus (15 mos post tx).
- Treated with PUVA. No other systemic therapy.
- Developed molecular relapse when nilotinib was discontinued in December 2012 due to concern for lung toxicity. Responded to dasatanib; PCR negative ever since.
- Rash progressed while on PUVA.
- Diagnosed with chronic GVHD of his skin and mouth in May 2013.

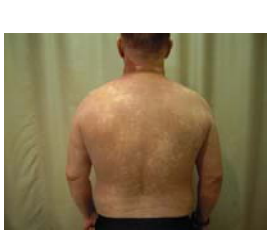
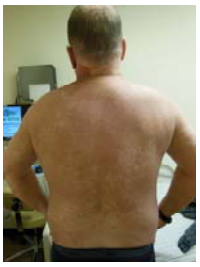
Case study (under treatment)

- Prednisone 110 mg added with improvement in the skin and mouth but developed CMV reactivation, requiring treatment with oral valganciclovir. Steroids were tapered to 60 mg every other day.
- Vitiligo was first noted in June 2013 while on prednisone 60 mg every other day. Sirolimus was added.
- Vitiligo progressed over 2 months to involve 25% BSA. UVB treatments were added.

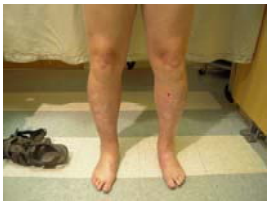
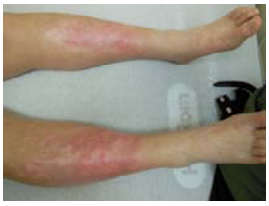
Case study (under treatment)

- Erythematous lichenoid/ morphea patches on his forearms and shins were first noted in October 2013 and he developed new ocular sicca.
- Prednisone was increased to 80 mg daily, but he declined additional treatment with tacrolimus, photopheresis, or rituximab due to concerns regarding CML recurrence and the impact of ECP and rituximab on his busy schedule.

June 2013 **October 2013**

June 2013 **October 2013**

Case study (under treatment)

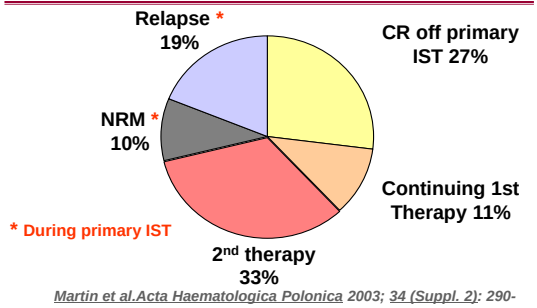
- Sclerosis progressed. In December he agreed to and received 4 weekly doses of Rituximab. Prednisone has been tapered to 60 mg every other day without progression in GVHD.

Chronic GVHD (ARS)

After 3 years of primary therapy for chronic GVHD, what percentage of patients achieved a complete response to treatment and are off immunesuppression?

A. 60%
B. 10%
C. 100%
D. 27%

Outcomes at 3 years after primary treatment of chronic GVHD (N = 330)



Martin et al.Acta Haematologica Polonica 2003; 34 (Suppl. 2): 290-301

Ancillary and Supportive Care for patients with Chronic GVHD

http://www.ncbi.nlm.nih.gov/pubmed/16545722

- Establish guidelines for ancillary therapy and supportive care in chronic graft versus host disease (GVHD), including treatment for symptoms and recommendations for patient education, preventative measures, and appropriate follow-up
- To provide guidelines for the prevention and management of infections and other common complications of treatment for chronic GVHD
- To highlight the areas with the greatest need for clinical research

Monitoring

- All organ systems potentially affected by chronic GVHD or its treatment should be monitored at least annually for 5 years after transplantation.
  - Individualized
  - Clinically indicated
  - Increased frequency for those with active chronic GVHD, those tapering or escalating treatment, and those participating in clinical trials

Monitoring

- Annual evaluation
  - Interval history, symptom assessment, medication review, physical exam
  - Weight, nutritional assessment
  - Laboratory Monitoring:
    - CBC with differential, Chemistry Panel (including renal and liver function), therapeutic drug monitoring, IgG, lipid profile, iron indicies, endocrine function evaluation
    - Pulmonary Function Tests

Subspecialty Evaluations

- Ophthamology
  - Consider Schirmer Test
  - Glaucoma assessment
- Dental
  - Comprehensive soft and hard palate examination
    - Culture, biopsy, or photographs of lesions
- Dermatology
  - Assessment of extent and type of skin involvement
    - Biopsy or photograph
- Gynecology
  - Assessment for vulvar or vaginal involvement
- Physiotherapy
  - ROM * if sclerotic features are present
- Neurophysical testing

Cutaneous

- Consider referral to dermatology (preferably with transplant experience)
- Those on prolonged immunosuppression should have annual skin assessment
- Growing/non healing lesions should be referred within 2 weeks to dermatology
- Emollients should be used for symptom control
- Topicals are recommended as first line therapy for mild disease
- Consider Physical therapy for those patients with sclerodermoid disease

Cutaneous

- Nursing Considerations/Patient Education
  - Maintain skin integrity/good skin hygeine
    - Encourage patients to "rub" not scratch skin
    - Wound management /compression
    - Skin function (Barrier/Temperature regulation)
  - Proper application (massage) of topical medications
  - Minimize exposure to UV light/sun protection during therapy
  - Sensitivity to alterations in body image/appearance
  - Response to phototherapy or ECP can take weeks

Gastrointestinal/Liver

- Consider referral to a gastroenterologist/hepatologist if GI or Liver GVHD is suspected
- Those patients experiencing diarrhea without jaundice or rash should undergo both upper and lower endoscopy over colonoscopy alone
- All patients should be assessed by a dietician experienced with the needs of transplant patients

Gastrointestinal/Liver

- Upper GI (dysphagia, nausea, vomiting, anorexia)
  - Malnutrition
- Lower GI (Loose Stool)
  - Often other diagnosis co-exists
  - Imperative to exclude infectious cause
    - *Clostridium difficile*
    - Cytomegalovirus (CMV)
  - In patients with established GVHD with whom other causes have been excluded:
    - anti-diarrheal agents
    - Maintain perirectal skin integrity

Genital

- All patients should be questioned regularly about genital tract symptoms (estimates 2-49%)
- Consider referral to specialist
- Consider high potency topical steriods (+/- Calineurin inhibitors) as first line therapy

Ocular

- Patients with symptoms should be evaluated by an ophthalmologist (preferably with ocular GVHD experience)
- First line treatment
  - Supportive care with artificial tears and topical anti-inflammatory/antibiotic
- Educate patients and family members
  - Prolonged steroid use for other manifestations of chronic GVHD may lead to reduction in vision and earlier development of cataracts

Ocular

- 25-45% of patients with chronic GVHD
  - Dry, gritty, painful
- Often associated with those with cutaneous +/- oral involvement
- Patients should be educated to seek the care of an ophthalmologist should they notice a reduction in vision

Oral

- Consider referral to oral medicine specialist for patients with significant symptoms
- Ancillary therapy may provide greater benefit than systemic therapy alone
- First Line therapy
  - Topical therapies
    - Steroid mouthwash

Oral

- Dental and oral health review every 6 months
  - Consider sodium bicarbonate mouthwash for taste disturbances/moisturizing rinse or gel for dry mouth
  - Use toothpaste for sensitive teeth
  - Analgesia rinses before meals when appropriate
- Awareness of the risk of oral malignancy
  - Patients with persistent or new oral lesions that occur >3 years after transplant should be evaluated for secondary malignancy (squamous cell carcinoma)
- Oral hygiene instruction
- Smoking/Tobacco product cessation
- Nutritional assessment as indicated

Case Study Oral chronic GVHD

Pulmonary

- Onset may be gradual
  - Slow progressive dyspnea and cough
  - May occur as other manifestations of chronic GVHD are improving
  - May occur as immunosuppression is being tapered
- Referral to pulmonologist if GVHD of the lungs is suspected
- All patients with any manifestation of chronic GVHD should be screened using Pulmonary Function Tests (PFTs)

Pulmonary

- Supportive Care
  - IVIG as indicated
  - Vaccinations
  - Prophylactic antibiotics as recommended by CDC
- Consider home monitoring with spirometry to allow for early detection
- Educate patients regarding the importance of treatment/medication use & compliance

Infection

- Higher rate of:
  - Viral: Zoster, CMV
  - Fungal: Aspergillus
  - Bacterial: encapsulated bacteria like Strep
  - Parasitic: PCP, Toxoplasmosis
- Regular monitoring for CMV infection should continue though treatment course

Infection

- Prophylaxis against viral, fungal, encapsulated bacteria should be considered for all patients receiving immunosuppressive therapy for chronic GVHD
  - Bacterial infections: PCN, Bactrim, Levaquin
  - Zoster: acyclovir, valacyclovir
  - PCP: Bactrim
  - Fungal (if on systemic steroids): Second generation Azole (posaconazole, voriconazole, itraconazole)
- Any prophylaxis generally continues until 6 months after GVHD therapy stops

Infection

- All patients with chronic GVH are highly immunocompromised
- Infection is the single most important non-relapse cause of mortality

Vaccinations

- Consider delaying vaccination IF:
  - Active GVHD and on >0.5mg/kg of corticosteriods
  - IVIG therapy <2 mos ago
  - Infusion of anti CD20 antibody < 6mos ago
  - Moderate to severe chonic GVHD
- Live vaccinations must NOT be administered in patients with chronic GVHD
- All patients with chronic GVHD should receive vaccination against pneumococcus, influenza, and *haemophilus influenzae*

Long Term Steroid Use

- All patients on any dose of steroids for long term use should have blood pressure and glucose monitored at clinic visits
- All patients on any dose of steroids for long term use should also be taking gastric protection

Chronic GVHD: Recommended Observation For:

- Skin cancer, Thyroid Cancer, Oral Cancer, and Lung Cancer if smoking
- Osteoporosis
- Hypertension
- Diabetes
- Hypothyroidism
- Lipid Abnormalities/Cardiac problems

Summary of Preventative Interventions

Organ System	Intervention
Skin	Photoprotection, surveillance for malignancy
Oral Cavity	Maintain good oral hygiene, routine dental cleaning, surveillance for infection and malignancy
Eyes	Photoprotection, surveillance for infection, cataract formation, increased intraocular pressure
Vulva and Vagina	Surveillance for estrogen deficiency, infection, malignancy
GI tract and Liver	Surveillance for infection (viral, fungal)
Lungs	Surveillance for infection (PCP, viral, fungal, bacterial)
Hematopoietic	Surveillance for infection (CMV, HHV6, parvovirus)
Neurologic	Drug level monitoring, Seizure prophylaxis,
Immunologic and Infectious Disease	Surveillance for infection Immunization, prophylaxis against PCP, VZV, encapsulated bacteria, consider immunoglobulin replacement
Musculoskeletal	Surveillance for decreased ROM, bone densitometry, calcium levels, 25-OH Vitamin D, PT, supplements (Ca, Vit D, bisphosphonates)

Caveats

Patient Education

- BMT infonet
  - http://bmtinfonet.org/after/chronicgvhd
- National Marrow Donor Program
  - https://bethematchclinical.org/post-transplant-care/chronic-gvhd/
  - Screening for chronic GVHD included in Post-Transplant Care Guidelines
  - Mobile App: HCT Guidelines for Referral Timing and Post-Transplant Care (Apple App Store and Android app on Google play)

Web Resources

How to proceed when a patient fails first line therapy

- Definition of failure:
  - Progression despite treatment with prednisone 1 mg/kg for 2 weeks.
  - No response or progression after 1 to 3 months of adequate treatment
  - Inability to to taper prednisone below 1 mg/kg/day after 2 months of adequate treatment

What if the patient fails first line therapy

- **No consensus regarding the optimal choice**
- **Preferable to enroll in a study for secondary treatment.**

Second line therapy for cGVHD

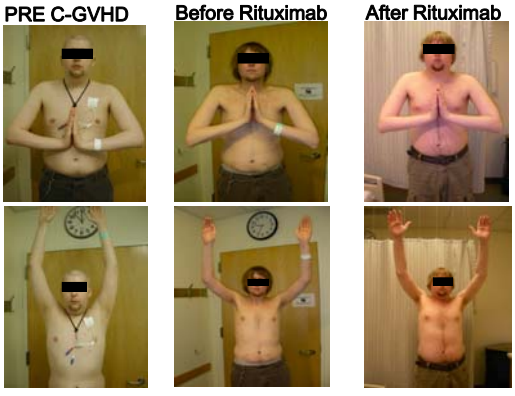
A LOT OF OYSTERS AND ONLY A FEW PEARLS……

If no study available or patient not eligible:

- **Decisions based on**
  - **Results of published studies**
  - **GVHD presentation**
  - **Experience**
  - **Cost/ insurance coverage (pred vs Rituxan)**
  - **Toxicity associated with each treatment choice (counts, hyperlipidemia, neuropathy etc)**
  - **Concurrent problems such as minimal residual disease, AVN, active fungal pneumonia, recurrent CMV reactivation, etc**

If no study available or patient not eligible:

- **Sclerosis**: Prednisone + ECP, rituximab, imatinib, pulsed lidocaine IV infusions
  - PUVA/ UVB NOT effective
- **Fasciitis/ joint contractures**: Prednisone + rituximab, ECP, low dose weekly methotrexate
- **Arthralgias +/- mild, limited contractures**: Low dose weekly methotrexate + low dose steroids



Severe chronicGVHD

- AG is a 36-year-old man who had tandem autologous and allogeneic PBSC transplants for the treatment of multiple myeloma. His donor was a mismatched unrelated male donor. The allogeneic transplant took place in June 2011.
- Diagnosed with de novo chronic GVHD in October 2011, 4 months after transplant.

Severe skin GVHD

- Sites of involvement include skin, liver, mouth, GI, esophagus, eyes, & GVHD-associated eosinophilia. Liver GVHD was confirmed by liver biopsy. Peak bilirubin was 22.
- Treated with prednisone, CSP, MMF, sirolimus, tacrolimus, ursodiol, 8 doses of rituximab in June & September 2012, UVB, and 4 months of photophoresis.

Severe skin GVHD

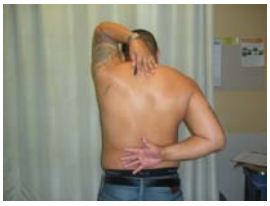
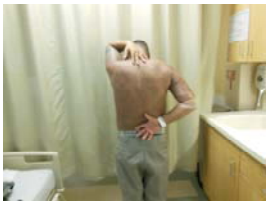
- Despite treatment with prednisone 60 mg every other day, sirolimus, photophoresis, GVHD progressed with new painful lichenoid changes and erythema in his antecubital areas, upper arms, and right lateral leg. He had only had 10 ECP treatments when we saw him in September. We did not consider this to be a treatment failure.

Severe skin GVHD

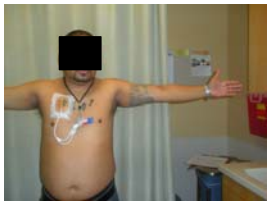
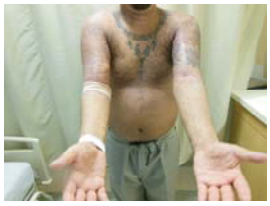
- Because of the progression, we increased his dose of prednisone to 60 mg daily for 2 weeks, and provided him with a taper to get to 60 mg every other day.
- No improvement in the discomfort and tightness in the upper arms with the higher dose of prednisone nor any progression when he tapered prednisone to 60 mg every other day.

Severe Skin GVHD

September 2011 **December 2013**

September 2011 **December 2013**

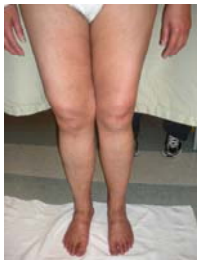
Severe skin GVHD

- We discontinued ECP and sirolimus and substituted low dose methotrexate (10 mg po once per week) and continued prednisone 60 mg every other day.
- No improvement at his last visit. Will consider alternate treatments

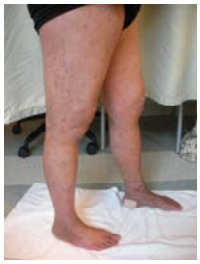
Severe skin GVHD

- RO was diagnosed with chronic GVHD at her day 80 departure evaluation June 2010. Sites of involvement include her skin, mouth, eyes and nails.
- Initially treated with prednisone 1 mg/kg and sirolimus, but skin GVHD progressed.
- Added PUVA, but developed blisters attributed to GVHD progression.

June 2010



June 2011



Severe skin GVHD

- Photopheresis added in November 2010 with some improvement in GVHD.
- GVHD progressed while tapering steroids
- Mycophenolate substituted for sirolimus in March 2011.
- ECP discontinued in June 2011 due to several episodes of bacteremia requiring line removal

Severe skin GVHD

- GVHD progressed after ECP was discontinued
- Mycophenolate increased to 2500 mg total dose per day.
- GVHD continued to progress
- Low-dose IL-2 daily injections January 2012 through March 2012; severe fatigue and nausea, some improvement in GVHD

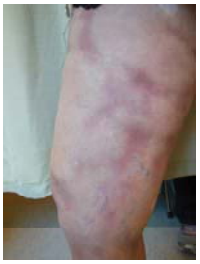
Severe skin GVHD

- GVHD manifestations stabilized for several months after IL-2
- Sclerosis progressed when we attempted to taper prednisone
- Four doses of rituximab in November and December 2012; no significant improvement in sclerosis.

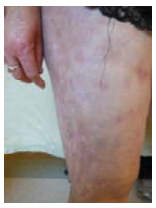
Severe skin GVHD

- Brief trial of imatinib; did not tolerate it well; not possible to evaluate response.
- Sclerosis and erythema progressed in September 2013. Prednisone doubled to 30 mg daily x 1 week, then tapered to 30 mg every other day; mycophenolate increaed from 1500 mg to 2500 mg total daily dose

January 2014



January 2014



Severe skin GVHD

- Higher doses of MMF did not result in improvement and MMF contributed to GI distress. In November 2013, MMF was reduced to 750 mg twice daily and prednisone was increased from 30 mg every other day to 40 mg daily x 2 weeks then tapered to 40 mg every other day.
- Azathioprine (Imuran) added in December 2013. Slight improvement at January visit.

Chronic GVHD

- CS is a 70 yo woman who had a PBSC transplant 5 years ago from a matched unrelated male donor for the treatment of NK/T-cell lymphoma.
- 6 month post tx marrow showed 0.3% abnormal T-cells by flow cytometry and PCR was positive for the T-cell gene rearrangement. In molecular remission since February 2010.

Chronic GVHD

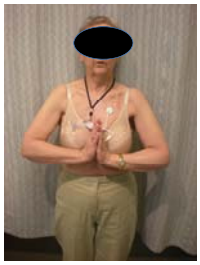
- Diagnosed with de novo onset chronic GVHD in September 2009, one month after stopping tacrolimus.
- Sites of GVHD involvement: skin, mouth, eyes, GI tract, and GVHD-associated eosinophilia.
- Initially treated with prednisone alone.
- New fasciitis, mild joint contractures, and vulvar GVHD noted in February 2010.

Chronic GVHD

- Tacrolimus added.
- New sclerotic skin changes noted in May 2010. Sirolimus substituted for tacrolimus.
- Sclerosis, fasciitis and joint contractures progressed. Prednisone was increased to 60 mg daily in August 2010.
- Sclerosis progressed. ECP added in February 2011.

Fasciitis

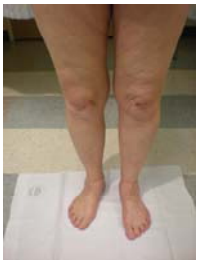
April 2009



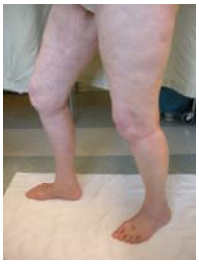
May 2011

Dimpling/ sclerosis

April 2009



May 2011



Chronic GVHD

- Sclerosis improved. Prednisone was tapered to 15 mg every other day. Improvement plateaued. ECP was discontinued in July 2012 after a year and a half of treatment.
- In December 2013, persistent sclerosis, fasciitis, mild joint contractures, none that affect quality of life. Prednisone 15 mg every other day. Sirolimus 0.5 mg daily; trough level 3 ng/ml. No change in IS.

If no study available or patient not eligible:

- **Eyes**: Artificial tears, lubricant ointment, plug tear ducts, Restasis, occlusive eye glasses, autologous serum eye drops, bandage contact lenses, Boston scleral lens
- **Oral**: Topical steroid rinses, clobetasol gel to ulcers, topical azathioprine rinses, sirolimus

If no study available or patient not eligible:

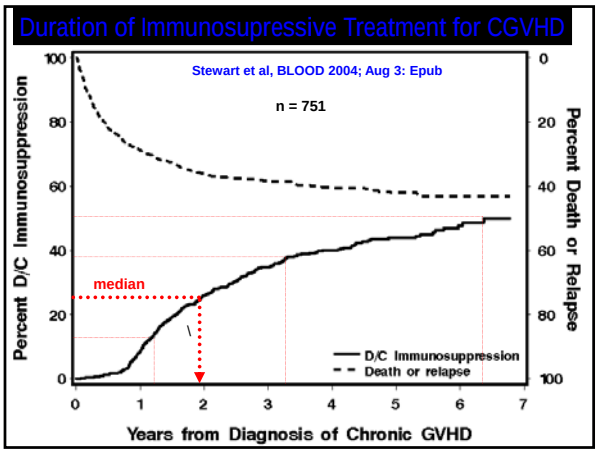
- **Diarrhea, weight loss:** Rule out CMV enteritis, medication effect (MMF), etc, then: Prednisone 1mg/kg +/- budesonide (Entocort)
- **Decreased appetite & weight loss:** Rule out CMV, medication effect, etc, then: Beclomethasone +/- prednisone (discontinue MMF/ Myfortic?)
- **Severe liver GVHD**: IV tacrolimus + steroids; evaluate for iron overload

If no study available or patient not eligible:

- **Sclerosis & other severe manifestations of GVHD, steroid refractory/ steroid dependent GVHD:** Low-dose daily subcutaneous IL-2
- **Severe, refractory GVHD:** Total lymphoid irradiation/ Low dose thoracoabdominal radiation
- **Lung**: Rule out infection; prednisone 1mg/kg, ECP, inhaled steroids, FAM for BOS,
- **Steroid refractory or steroid dependent GVHD:** Azathioprine 1.5 mg/kg po daily

What about……?

- **MMF?** Martin et al: No benefit from adding MMF to standard initial therapy in terms of achieving tolerance, lower steroid dose, etc, BUT trend toward increasing risk for recurrent malignancy
- **Thalidomide?** Use in a few select patients with skin or oral GVHD
- **ATG?** Increased mortality in chronic GVHD
- **Proteosome inhibitors?**: under investigation
- **Cyclophosphamide?** Increased risk for infection
- Pentostatin, mesenchymal stem cells, etanercept, clofazimine, chloroquine, alefacept



Patient Comments

- *The most important advice I could ever give to someone dealing with life after transplant is: waste no time wishing you could get back exactly to where you were before transplant. Your life will instantly become more fulfilling and enjoyable the moment you stop being, say 70%, of what you used to be and becoming 100% of what you are now!* Allogeneic transplant 2005 – now 52 years old

- *I do what I need to do. I take time to do what I want to do (every day). Even though I have serious concerns, I do NOT stress out over any of them. (At least try not to). Fatigue and the effects of premature aging will NOT stop me from thoroughly enjoying the good times that are also part of every day. Never thought I'd reach 60!! Given 2 mos. to live @ 35.* Autologous transplant 1991 – now 60 years old

Patient Comments

- *My "new 4th birthday" was 2 days ago, and honestly, I forgot about it. Now that says something about how my life has returned to normal! My new normal though isn't quite the same. I can't quite tell if my fatigue and poorer eyesight is due to my transplant or if I'm just getting older. My optometrist assures me it's my age! I do have to remind my family and my employer that my fatigue does occasionally impact my life, but, because I'm now fine in every other way, they forget. But I'll take my "new normal" a thousand times over for a trade-off with leukemia.* Allogeneic transplant 2008 – now 45 years old

Patient Comments

- *Today is my 24th anniversary (post-transplant). Every year this questionnaire reminds me that I actually had a bone marrow transplant. Otherwise, I am too busy working & enjoying life. This gives me an opportunity to take a deep breath & give thanks to those who took care of me. I plan to retire this fall at the age of 60. Life is great. 35 yrs. pre-transplant, 24 years post-transplant. I look forward to the day these numbers match. Then we'll see what happens beyond that. THANKS AGAIN!* Allogeneic transplant 1988 – now 59 years old

Patient Comments

- *I have been blessed with 26 years following 2 transplants, a miracle son ---, and wonderful doctors, nurses full of knowledge and care --- at the SCCA and Fred Hutch. Thank you all for this miracle of life!!* Allogeneic transplants 1986 &1996 – now 50 years old

Patient Comments

- *With Dr. E. Donnall Thomas' passing, I looked up his original 1957 NEJM publication on early marrow transplants at the "dawn" of this technology, and I realized what a leap in thinking this was at the time. So, to him as well, a very big posthumous "thank you."* Allogeneic transplant 2004 – now 70 years old