Management of HSCT Complications

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Conditioning-induced mucositis

OM: reported by pts to be the single most debilitating complication of HCT

Occurs in 80% of patients undergoing HCT

Pathophysiology: DNA damage-production of reactive oxygen sp.-epithelial atrophy, bacterial translocation, and inflammation

Recent studies: genetic predisposition and gut microbiome

erythematous & ulcerative lesions: portal of entry for bacterial translocation

Moderate-to-severe mucositis: systemic infection and increased TRM

HSV infections of the oropharynx may mimic severe OM

MASCC/ISOO Clinical Practice Guidelines for the Management of Mucositis

Intensive oral hygiene: reduces the intensity and severity of mucositis

HCT pts with pain secondary to OM: patient-controlled analgesia with drugs such as morphine is recommended (level II evidence)

preventative strategies based on growing data supporting oral cryotherapy, recombinant human keratinocyte growth factor (KGF-1/palifermin), and photo biomodulation (previously low-level laser therapy or LLLT)

chewing gum: ineffective for prevention

Management of HSCT Complications

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Sinusoidal Obstructive Syndrome

TABLE 34.3 **Risk Factors for Sinusoidal Obstructive Syndrome**[23,24,56]

Patient/Disease Risk Factors	Treatment-Related Risk Factors	Transplant-Related Risk Factors
Age: < 1 year or older age Performance status (Karnofsky < 90) ECOG performance status 2–4	Prior radiation Total body irradiation Abdominal or hepatic irradiation	Unrelated donor HLA-mismatched donor Non–T-cell depleted transplant
Advanced disease—beyond CR2 or relapsed disease Prior myeloablative HCT	Use of hepatotoxic medications Cyclophosphamide Busulfan Melphalan Gemtuzumab Ozogamicin Inotuzumab Ozogamicin	Myeloablative conditioning regimen Oral or high-dose busulfan High-dose TBI
Preexisting hepatic dysfunction: Transaminases > 2.5 ULN Serum bilirubin > 1.5 ULN Cirrhosis Active hepatitis Iron overload Prior TPN use		Immunosuppression: Use of sirolimus with concurrent use of calcineurin inhibitors
Metabolic syndrome Female receiving norethisterone		
Genetic factors (GSTM1 polymorphism, C282Y allele, MTHFR 677CC/1298CC haplotype)		
Osteopetrosis Neuroblastoma Thalassemia Congenital MAS		

TABLE 34.4 Diagnostic Criteria for Sinusoidal Obstructive Syndrome in Adults and Pediatrics[24,56,58]

Adult EBMT Criteria[a]		Modified pEBMT Criteria[a]
Classical In the first 21 days after HCT	Late onset >21 days after HCT	No limitation for time of onset
Bilirubin ≥ 2 mg/dL and two of the following criteria must be present: - Painful hepatomegaly - Weight gain > 5% - Ascites	Classical SOS beyond Day 21 OR Histologically proven SOS OR Two or more of the following criteria must be present: – Bilirubin ≥ 2 mg/dL (or 34 µmol/L) – Painful hepatomegaly – Weight gain > 5% – Ascites AND Hemodynamical and/or ultrasound evidence of SOS	Two or more of the following: – Rising bilirubin above baseline on 3 consecutive days or bilirubin ≥ 2 mg/dL within 72 hours – Hepatomegaly above baseline[b,c] – Ascites above baseline[b,c] – Weight gain > 5% above baseline or otherwise unexplained weight gain on 3 consecutive days despite the use of diuretics – Unexplained consumptive and transfusion refractory thrombocytopenia[d]

EBMT Criteria for the Severity Grading of Suspected SOS in Adults[a]

	Mild[a]	Moderate[a]	Severe	Very Severe MOD/MOF[b]
Time since first clinical symptoms of SOS[c]	>7days	5–7 days	≤4 days	Any time
Bilirubin (mg/dL)	≥2 and <3	≥3 and <5	≥5 and < 8	≥8
Bilirubin (μmol/L)	≥34 and <51	≥51 and <85	≥85 and <136	≥136
Bilirubin kinetics			Doubling within 48h	
Transaminases	≤2 x normal	>2 and ≤5 x normal	>5 and ≤8 x normal	>8 x normal
Weight increase[d]	<5%	≥5% and <10%	≥5% and <10%	≥10%
Renal function	<1.2 x baseline at transplant	≥1.2 and <1.5 x baseline at transplant	≥1.5 and <2 x baseline at transplant	≥2 x baseline at transplant or other signs of MOD/MOF

Current management of SOS

definitive Rx: defibrotide in severe/very severe VOD
6.25 mg/kg every 6 hours given over 2 hours
duration: 21 days or until resolution of MOD and SOS

supportive care:
maintain euvolemia with fluid restriction, Controlled diuresis
drainage of ascites and/or pleural effusions if…
correction of coagulopathy & thrombocytopenia
pain control
DC hepatotoxic medications, such as antifungals

Current management of SOS

No universally accepted prophylaxis, though UDCA….

No universally accepted biomarkers for prediction or confirmatory tests for the diagnosis of SOS

Management of HSCT Complications

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Chronic GVHD

TABLE 33.3 Signs and Symptoms of Chronic Graft-Versus-Host Disease

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive* (Seen in Chronic GVHD but Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities†	Common‡ (Seen with Both Acute and Chronic GVHD)
Skin	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation Papulosquamous lesions	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)		
Scalp and body hair		New onset of scarring or nonscarring scalp Alopecia (after recovery from chemoradiotherapy) Loss of body hair Scaling	Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes) Premature grey hair	

Mouth	Lichen planus-like changes	Xerostomia Mucoceles Mucosal atrophy Ulcers Pseudomembranes		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes Cicatricial conjunctivitis KCS Confluent areas of punctuate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia **Females Males**	Lichen planus- like features Lichen sclerosus-like features Vaginal scarring or clitoral/labial Agglutination Phimosis or urethral/ meatus scarring or stenosis	Erosions Fissures Ulcers		
GI Tract	Esophageal web Strictures or stenosis in the upper to mid-third of the esophagus		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)

TABLE 33.3 Signs and Symptoms of Chronic Graft-Versus-Host Disease—Cont'd

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive* (Seen in Chronic GVHD but Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities†	Common‡ (Seen with Both Acute and Chronic GVHD)
Liver				Total bilirubin, alkaline phosphatase > 2× upper limit of normal ALT > 2× upper limit of normal
Lung	Bronchiolitis obliterans diagnosed with lung biopsy BOS§	Air trapping and bronchiectasis on chest CT	Cryptogenic organizing pneumonia Restrictive lung disease‖	
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to fasciitis or sclerosis	Myositis or Polymyositis¶	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and Immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergammaglobulinemia Autoantibodies (AIHA, ITP) Raynaud phenomenon	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

TABLE 33.4 **Organ Scoring of Chronic Graft-Versus-Host Disease**

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
GVHD features to be scored by BSA: **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD				
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration

Other skin GVHD features (NOT scored by BSA)
Check all that apply:
☐ Hyperpigmentation
☐ Hypopigmentation
☐ Poikiloderma
☐ Severe or generalized pruritus
☐ Hair involvement
☐ Nail involvement
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____

TABLE 33.4 **Organ Scoring of Chronic Graft-Versus-Host Disease**

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs). **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS** **Symptom score**:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **% FEV1** ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

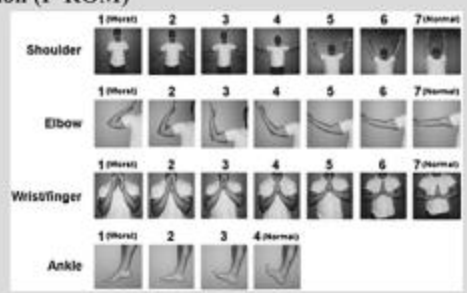
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Photographic Range of Motion (P-ROM)



Grading of Overall Severity of cGVHD

Overall severity	Mild	Moderate	Severe
Number of involved organs	1–2	≥3	≥3
Severity of involved organs	Mild (excluding lung)	Mild–moderate (lung only mild)	Severe (lung moderate or severe)

TABLE 33.5 National Institute of Health Global Severity of Chronic Graft-Versus-Host Disease

1. Mild chronic GVHD
   One or two organs involved with no more than score 1 plus
   Lung score 0
2. Moderate chronic GVHD
   Three or more organs involved with no more than score 1
   OR
   At least one organ (not lung) with a score of 2
   OR
   Lung score 1
3. Severe chronic GVHD
   At least one organ with a score of 3
   OR
   Lung score of 2 or 3

Key points:

- In skin: higher of the 2 scores to be used for calculating global severity.
- In lung: FEV1 is used instead of clinical score for calculating global severity.
- If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
- If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Mild cGVHD: treatment

As does not impair organ function, the use of topical IS (topical steroids, topical CNI, or phototherapy) should be considered.

If this is impossible, PRD treatment at an initial dose of 0.5–1 mg/kg body weight/day is recommended.

Topical IS can be used in addition to systemic IS, to improve efficacy, or to reduce systemic IS, but lack systemic efficacy.

Moderate or Severe cGVHD: treatment

Systemic treatment with PRD or methylPRD at an initial dose of 1 mg/kg body weight/day should be used.

Table 44.1 First-line treatment of cGVHD

Drug	Recommendation		Side effects in >25% patients	Response rate	Comment
	Grade	Evidence			
Steroids	A	I	Osteoporosis, osteonecrosis, diabetes mellitus	~30–50% CR	Main drug; strategies to reduce use due to SEs very important
CNI + steroids	C-1	II	Renal toxicity, hypertension	~30–50% RC	Reduces steroid use, reduced incidence of osteonecrosis
Rituximab + steroids/CNI	C-1	III-1[12]	Increased risk for late infectious complications	~75%	Randomized data are lacking
MMF + CNI/ steroids	D	II	GI complaints, infections		No increased efficacy compared to CNI and steroids, increased risk of relapse of malignancy
Azathioprine	D	II	Cytopenia, risk of infection		Increased mortality
Thalidomide	D	II	Neurotoxicity, drowsiness, constipation		Very little effect in first-line therapy

Adapted from Wolff et al. (2011), A: should always be used; C-1: use in first-line therapy justified, D: moderate evidence of lack of efficacy or unacceptably high risks, should generally not be offered, I: evidence from ≥1 properly randomized, controlled trials, II: evidence from more than one well-planned non-randomized clinical trial, from cohort or case-controlled, analytic studies (preferably at several sites), III-1: only one non-controlled study, III-2: only one retrospective, non-controlled study or retrospective evaluation. (Evidence and recommendations graded according to the 2005 NIH Consensus), *SE* side effect, *NIH* US National Institutes of Health, *MMF* mycophenolate mofetil

Definitions

Steroid-refractory cGVHD:

progression on prednisone 1 mg/kg/day for ≥7 days or

stable disease despite therapy with prednisone 0.5 mg/kg/day for ≥4 weeks.

Steroid-dependent cGVHD

inability to taper prednisone below 0.25 mg/kg/day after ≥2 unsuccessful attempts separated by ≥8 weeks

Treatment of steroid-refractory cGVHD FDA approved

Ibrutinib

Ruxolitinib (Category 1)

Belumosudil

Axatilimab-csfr

MANY THANKS FOR YOUR ATTENTION