



Graft-versus-Host-Disease of the Gastrointestinal Tract and Liver

Celebrating a Second Chance at Life
Survivorship Symposium

April 30 - May 6, 2022



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Graft Versus Host Disease of the GI Tract and Liver

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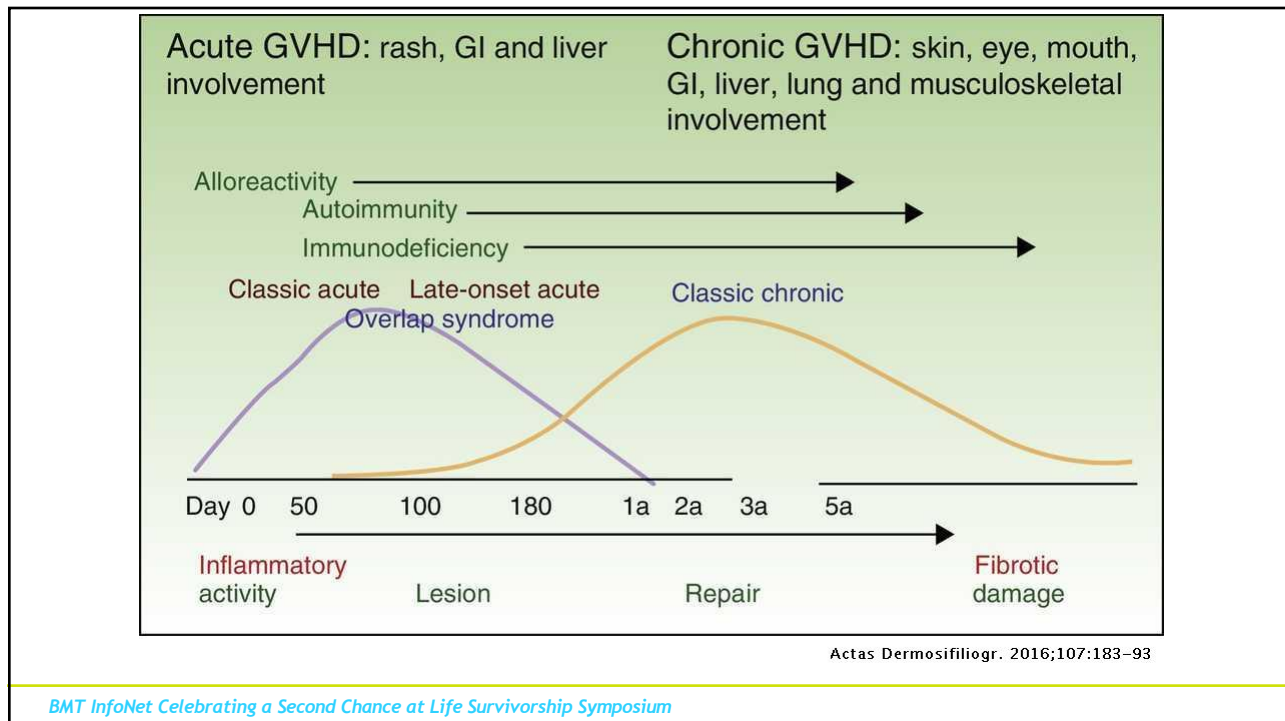
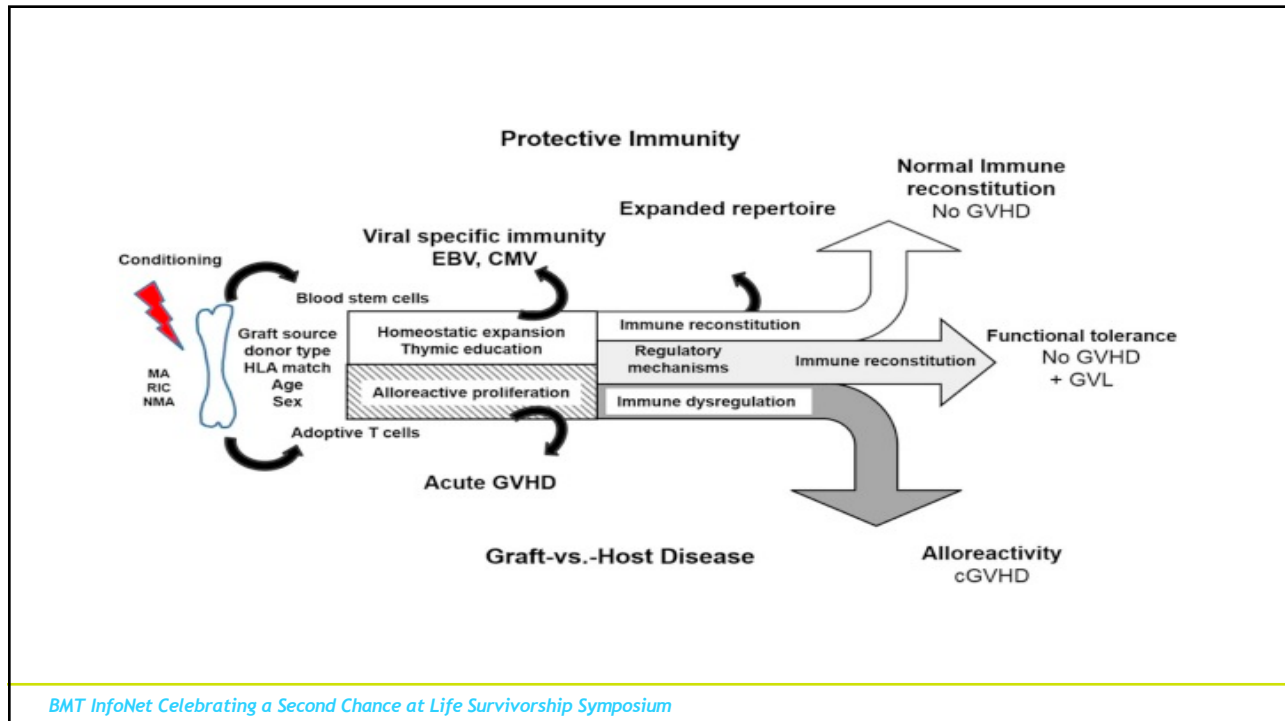
Today's Agenda

- Incidence of chronic GVHD of GI tract following HCT
- Risk factors for developing chronic GVHD of GI tract
- Therapies used to prevent and treat chronic GVHD of GI tract
- Incidence of liver GVHD after transplant
- Therapies available to prevent and treat chronic GVHD of the liver

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Incidence of Chronic GVHD of GI Tract

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Diagnosis of cGVHD requires at least one diagnostic clinical sign of GVHD, or one distinctive sign confirmed by biopsy

Organ 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)
Skin	<ul style="list-style-type: none"> Poikiloderma Lichen planus-like features Sclerotic-like features Lichen sclerosus-like features 	<ul style="list-style-type: none"> Depigmentation
Nails		<ul style="list-style-type: none"> Dystrophy Longitudinal ridging, splitting or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric; affects most nails)
Scalp and body hair	<ul style="list-style-type: none"> Lichen-type features Hyperkeratotic plaques Restriction of mouth opening from sclerosis 	<ul style="list-style-type: none"> New onset of scarring or non-scarring alopecia (after recovery from chemotherapy) Scaling, papulosquamous lesions
Mouth		<ul style="list-style-type: none"> Xerostomia Mucocele Pseudomembranes* Ulcers* New-onset dry, gritty or painful eyes**
Eyes		<ul style="list-style-type: none"> Cicatricial conjunctivitis Keratoconjunctivitis sicca** Confluent areas of punctate keratopathy
Genitalia	<ul style="list-style-type: none"> Lichen planus-like features Vaginal scarring or stenosis 	<ul style="list-style-type: none"> Erosions* Fissures* Ulcers*
GI tract	<ul style="list-style-type: none"> Esophageal web Strictures or stenosis in upper mid-third 	
Lung	<ul style="list-style-type: none"> Bronchiolitis obliterans diagnosed with lung biopsy 	<ul style="list-style-type: none"> Bronchiolitis obliterans diagnosed with pulmonary function tests and radiology**
Muscles, fascia, joints	<ul style="list-style-type: none"> Fasciitis Joint stiffness or contractures secondary to sclerosis 	<ul style="list-style-type: none"> Myositis or polymyositis

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Risk factors for developing chronic GVHD of GI tract

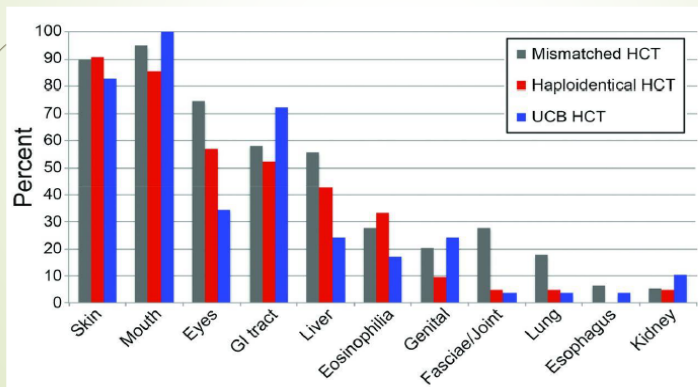
Table 1
cGVHD risk factors

	Patient	Donor/Graft	Transplant
Increased cGVHD risk	Older age Malignancy	Female donor to male patient Mismatched Unrelated Peripheral blood stem cells Donor lymphocyte infusions Older age	Acute GVHD Total irradiation in preparative regimen
Possible increased cGVHD risk	CMV positive CMV reactivation	CD 34+ cell dose	
Decreased cGVHD risk	Younger age	Cord blood	Anti-thyroglobulin in preparative regimen Campath-1H in preparative regimen
Possible decreased cGVHD risk			Methotrexate and cyclosporine prophylaxis

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Risk Factors and Organ Involved.

- MUD < Match sib < cord
- Peripheral blood > bone marrow
- Hx of acute GVHD
- Male recipient and donor female (multiple children)
- antibiotics



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Therapies used to prevent and treat chronic GVHD of GI tract

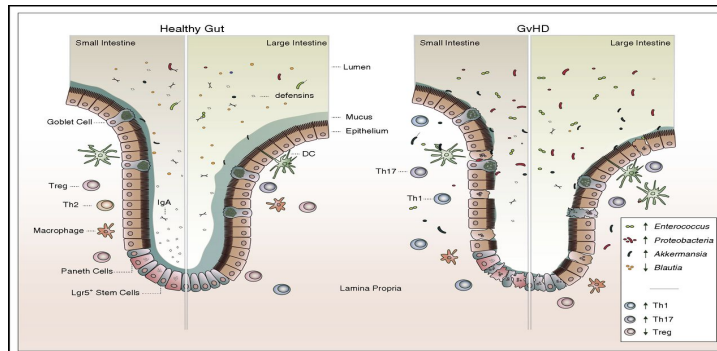
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Chronic GVHD - Prevention

- The best way to prevent chronic GVHD is to prevent acute GVHD
 - Optimal HLA match
 - Optimal GVHD prevention
 - Use of post transplant cyclophosphamide
 - Judicious use of broad-spectrum antibiotics that affect gut microbiota
 - Use of probiotics and fiber

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The intestinal microbiota in allogeneic hematopoietic cell transplant and graft-versus-host disease



Anna Staffas, Marina Burgos da Silva, Marcel R. M. van den Brink, The intestinal microbiota in allogeneic hematopoietic cell transplant and graft-versus-host disease, *Blood*, 2017, Figure 1.

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GVHD in the Mouth

- cGVHD in the mouth can be seen in approximately 60 percent of patients
- Changes are most often observed on the buccal mucosa and tongue, but all intraoral surfaces and the vermilion lip may be involved.
- Xerostomia (dry oral mucosa) is common.

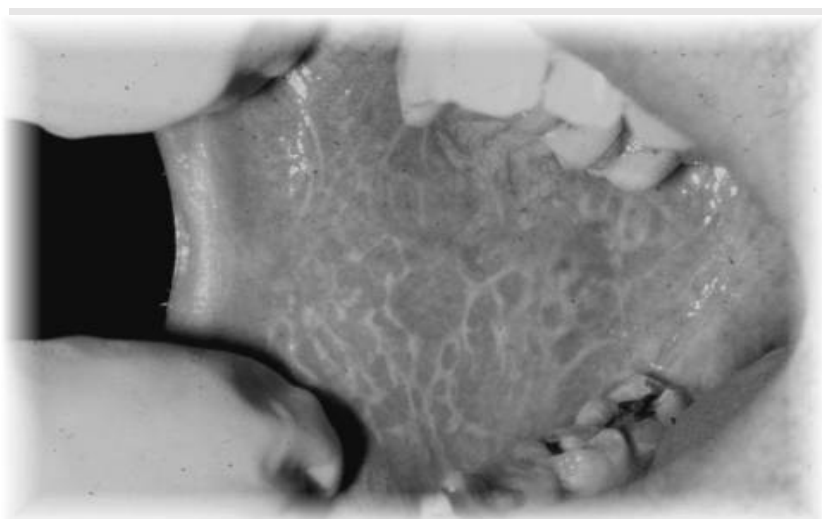
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GVHD in the Mouth – Other Manifestations

- Other manifestations may include:
 - erythema
 - mucositis
 - gingivitis
 - ulcers, pain (especially in association with ulceration)
 - mucosal atrophy
 - Mucocele
 - pseudomembranes.
- Oral manifestations may progress to lichen planus-type features, hyperkeratotic plaques, or restriction of the mouth opening from sclerosis.

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Oral cGVHD



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GVHD in the Mouth – Symptom Relief

- Carry a bottle of water and drink frequently
- Some find relief with artificial saliva.
- Steroid mouthwashes can help in areas of ulceration or leukoplakia.
 - Decadron rinse with or without tacrolimus rinse – made at compounding pharmacy
 - Topical tacrolimus (protopic ointment) to lips
 - Infection with *Herpes simplex*, human papilloma virus, and *Candida* and other fungal organisms should be ruled out before initiating topical steroids.

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GVHD in the Mouth – Prevention/Surveillance

- Hygiene
 - good oral/dental hygiene
 - topical fluorides to prevent caries are important
- Persistent or new oral lesions that occur >3 months after transplantation should be evaluated for a secondary cancer.

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Chronic GVHD and the Gastrointestinal (GI) Tract

- The GI tract is involved in one-third of patients with cGVHD.
- GI involvement can range from the esophagus to the lower GI tract.
- Patients may have nausea/vomiting without weight loss.
- Symptoms of cGVHD in the small bowel and colon may include:
 - anorexia
 - nausea
 - vomiting
 - chronic diarrhea
 - malabsorption
 - weight loss
 - failure to thrive (usually in infants and children)

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Chronic GVHD and the GI Tract – cont'd

- cGVHD can also result in exocrine pancreatic insufficiency. Symptoms include:
 - dysphagia
 - painful ulcer
 - weight loss caused by an esophageal stricture or ring
- Findings on endoscopy are variable and range from:
 - loss of vascular markings
 - focal mild erythema to severe erythema
 - edema, exudates, erosions, and ulceration

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Chronic GI GVHD: Diagnosis & Management

- Nausea, vomiting, and dysphagia can progress to diarrhea with weight loss and/or esophageal web or stricture, when severe.
- Referral to a gastroenterologist should be considered for patients with suspected gastrointestinal (GI) cGVHD.
- All patients with GI GVHD or malnutrition should be assessed by a dietician.
- Diarrhea
 - Evaluation should include cultures, testing for *Clostridioides difficile* toxin, and cytomegalovirus.
 - Diarrhea without associated jaundice or rash suggestive of GVHD should be investigated by upper endoscopy and flexible sigmoidoscopy or colonoscopy.

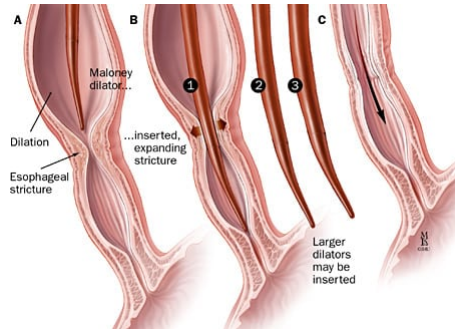
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Chronic GI GVHD: Diagnosis & Management cont'd

- Occasionally, patients may have persistent diarrhea/steatorrhea due to pancreatic insufficiency from cGVHD
- Mechanical dilation may be used to break apart the strictures
- Nutritional supplements can prevent weight loss
- Pancreatic enzyme replacement is beneficial in this setting

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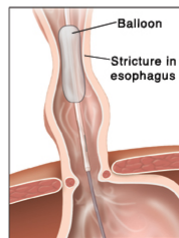
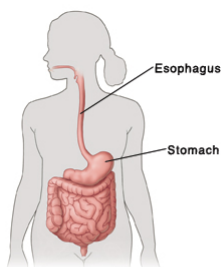
Esophageal Dilation



From:
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Esophageal Dilation



St Lukes Health System
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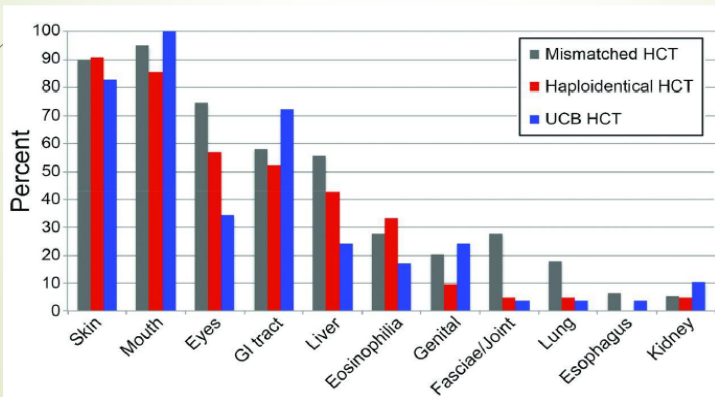
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Incidence of liver GVHD after transplant

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Risk Factors and Organ involved.

- MUD <Match sib < cord
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Therapies to prevent and treat chronic GVHD of the liver

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Chronic GVHD of the Liver – Incidence

- Liver abnormalities are present in half of patients with cGVHD and are commonly associated with
 - jaundice
 - anorexia
 - nausea
 - vomiting

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Chronic GVHD of the Liver - Symptoms

- Liver GVHD typically presents as either:
 - acute hepatitis with steeply rising serum alanine aminotransferase (ALT), with or without jaundice
 - usually arises after tapering immunosuppressive drugs or after donor lymphocyte infusion
 - requires a prompt diagnosis and treatment
 - liver biopsy may be needed in the absence of GVHD in another organ.
 - slowly progressive cholestatic disorder with elevated serum alkaline phosphatase and gamma-glutamyl transpeptidase, followed by jaundice.

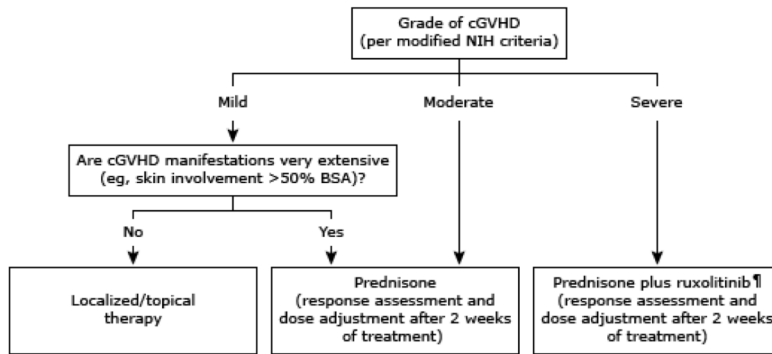
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Chronic GVHD of the Liver - Treatment Options

- Systemic steroids are mainstay of treatment for chronic GVHD
 - Multiple complications of steroids
- Can add back calcineurin inhibitor if not on one
- If disease is steroid refractory (does not respond to treatment with steroids):
 - roxolitinib Jack Kinase inhibitor
 - belumosudil Rock inhibitor
 - extra corporeal photopheresis ECP

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Initial management of chronic graft-versus-host-disease (cGVHD)

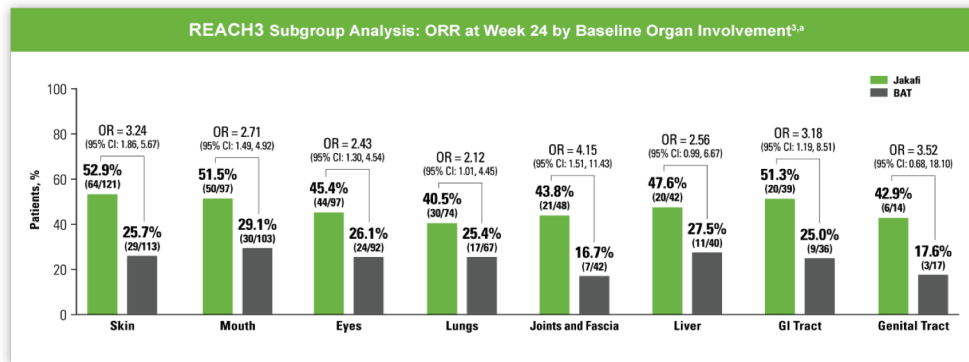


Summary of cGVHD grading[†]:

- Mild: Involves ≤2 organs/sites with no clinically significant functional impairment
- Moderate: ≥3 organs/sites with no clinically significant functional impairment or ≥1 organ/site with clinically significant functional impairment, but no major disability
- Severe: Major disability caused by cGVHD

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Jakafi for steroid refractory chronic GVHD

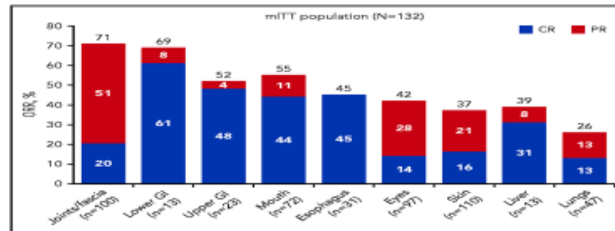


Zeiser R, Polverelli N, Ram R, et al; REACH3 Investigators. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med.* 2021;385(3):228-238

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Belumosudil for Chronic GVHD

Belumosudil prior lines of therapy: the ROCKstar Study

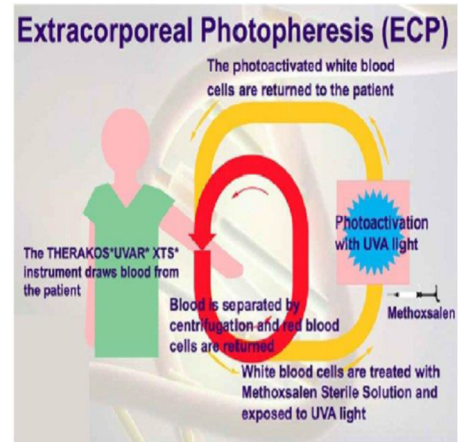
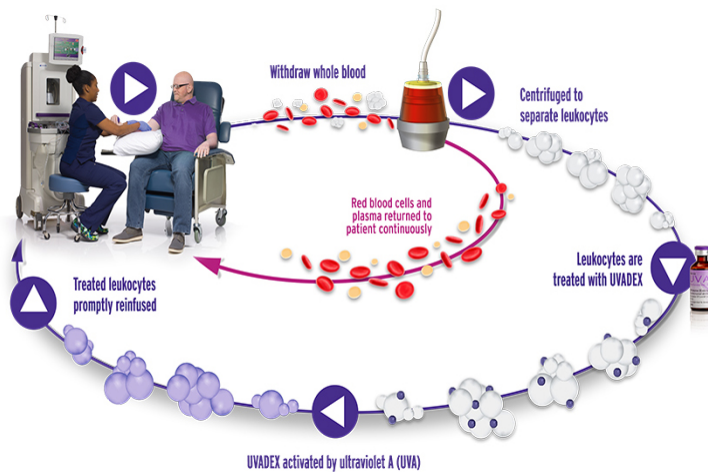


Corey Cutler, Stephanie J. Lee, Sally Arai, Marcello Rotta, Behyar Zoghi, Aleksandr Lazaryan, Aravind Ramakrishna, Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study, Blood, 2021, Figure 3.

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THERAKOS® CELLEX® Photopheresis System Operator's Manual. 1470493_Rev06_EN-US. Mallinckrodt; 2019

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Conclusion

- About half of all allogeneic transplant patients are affected by chronic GVHD.
- Life-long immunosuppression is needed in some patients.
- Prevention and treatment are improving.
- Oral, GI and liver GVHD can be mild to severe and can be treated and managed in most patients.
- Regular care by primary care physicians, gastroenterologists, and dentists can be helpful.

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Questions?



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