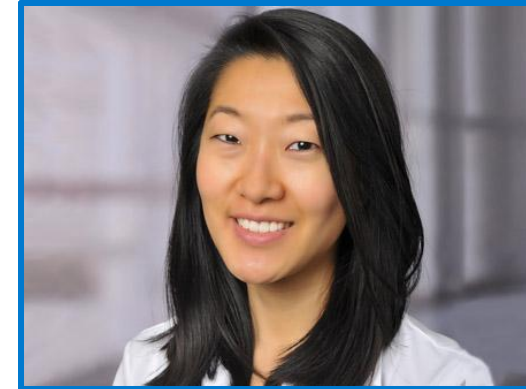


Graft-versus-Host Disease: Gastrointestinal Tract and Liver

**Celebrating a Second Chance at Life
Survivorship Symposium**

April 27 – May 3, 2024



Hannah Choe MD

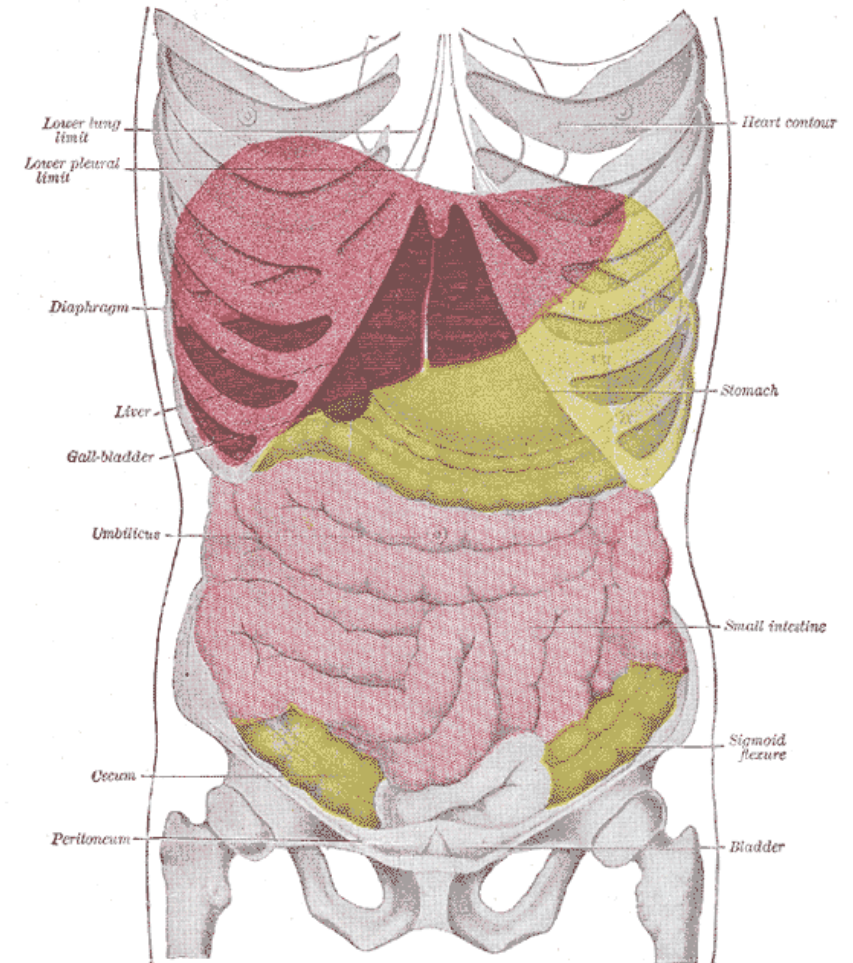
GVHD Program Director, Assistant
Professor, The Ohio State University
Comprehensive Cancer Center

Graft-versus-Host Disease (GVHD) of the GI Tract and Liver

Hannah K. Choe, MD

The Ohio State University

Director, OSU GVHD Program



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Learning Objectives:

GI tract:

1. Incidence of acute and chronic GVHD of GI tract following BMT
2. Risk factors for developing acute and chronic GVHD of GI tract
3. Therapies used to prevent and treat acute and chronic GVHD of GI tract

Liver:

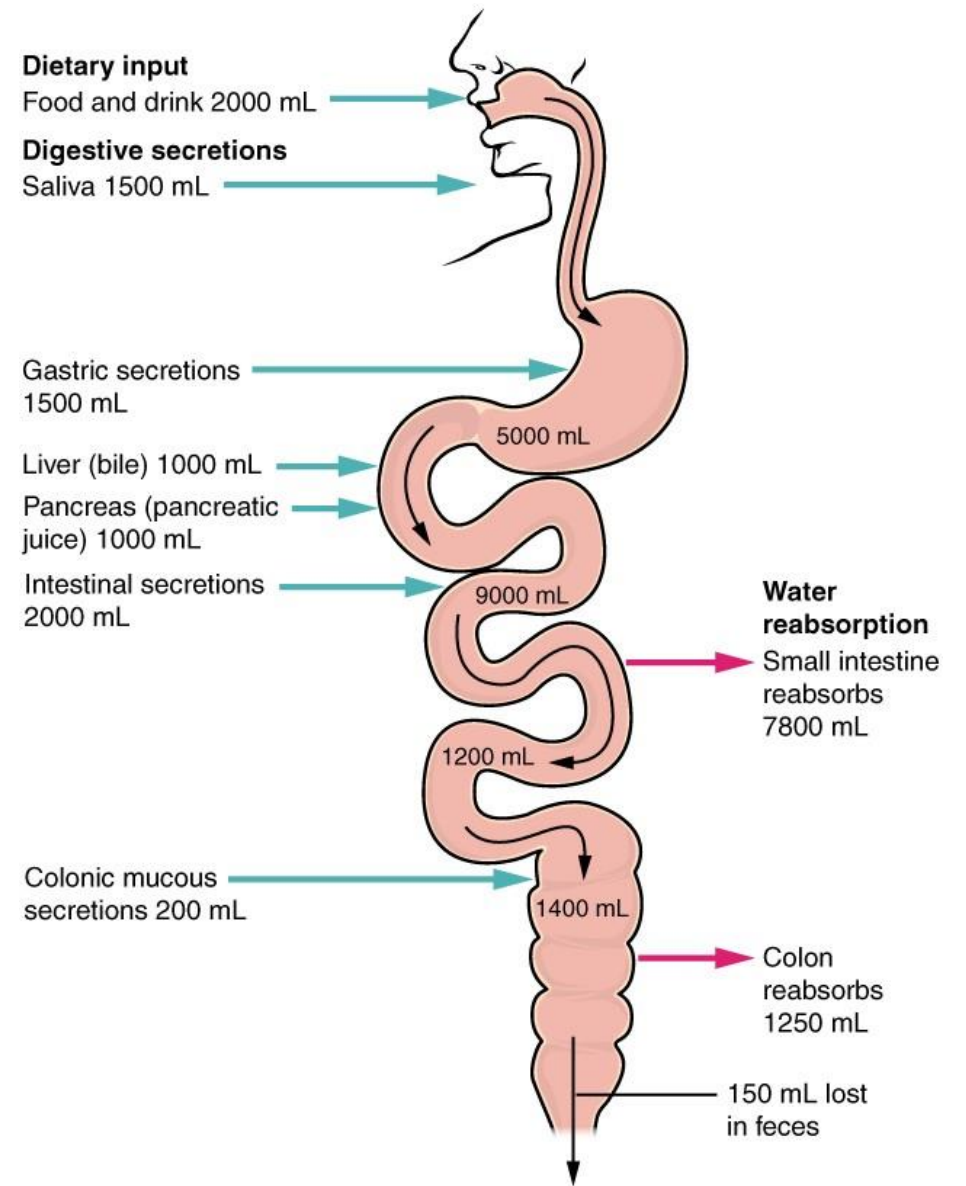
1. Incidence of liver GVHD after transplant
2. Therapies available to prevent and treat chronic GVHD of the liver

Table of Contents

- Acute and Chronic GI GVHD
 - Signs and symptoms
 - Work-up
- Acute and Chronic Liver GVHD
 - Signs and symptoms
 - Work-up
- Treatment Options for both acute and chronic GI and Liver GVHD

The GI Tract

- Responsible for nutrition (food nutrients and water reabsorption), digestion, and waste excretion
- Sensitive to chemotherapy and radiation, especially the conditioning regimens used for transplant
- Thus, risk of GI GVHD starts with chemotherapy and then further depends on the donor cell activity



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GI Tract is a Primary Site of GVHD Activation

- Roughly 70% of Grade 2-4 acute GVHD patients have GI involvement
- Lower GI acute GVHD is harder to treat than skin or upper GI acute GVHD and associated with non-relapse mortality
- 73% of patients with severe acute GI GVHD become steroid-refractory within 2 weeks

Ratanatharathorn et al. Blood. 1998; 92(7): 2303–14
(Harris et al. Bone Marrow Transplant. 2014; 49(7): 966–71
Castilla-Llorente et al. Bone Marrow Transplant. 2014; 49(7): 966–71

Acute GI GVHD Signs and Symptoms

- Upper GI (esophagus, stomach)
 - appetite loss
 - feeling full early
 - heartburn
 - nausea
 - weight loss
- Lower GI (small bowel, colon)
 - abdominal pain
 - diarrhea → malabsorption and malnutrition

Acute GI GVHD Staging

Stage	Upper GI	Lower GI (stool output per day)
0	No or intermittent nausea, vomiting or anorexia	Adult: <500 mL/day or <3 episodes per day Child: <10 mL/kg/day or <4 episodes/day
1	Persistent nausea, vomiting or anorexia	Adult: 500-999 mL/day or 3-4 episodes per day Child: 10-19.9 mL/kg/day or 4-6 episodes/day
2		Adult: 1000-1500 mL/day or 5-7 episodes per day Child: 20-30 mL/kg/day or 7-10 episodes/day
3		Adult: >1500 mL/day or >7 episodes per day Child: >30 mL/kg/day or >10 episodes/day
4		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of volume)

Acute GVHD Grading

Grade	Stage
0	No stage 1-4 of any organ
I	Stage 1-2 skin without liver, upper GI or lower GI involvement
II	Stage 3 rash, and/or stage 1 liver, and/or stage 1 upper GI, and/or stage 1 lower GI
III	Stage 2-3 liver, and/or stage 2-3 lower GI, with 0-3 skin, and/or stage 0-1 upper GI
IV	Stage 4 skin, liver or lower GI involvement with stage 0-1 upper GI

Chronic GI GVHD Signs and Symptoms

- Mouth:

- oral dryness
- mouth ulcers
- blistering

- Esophagus

- difficulty swallowing
- feeling food is “stuck”

GI tract

- nausea
- vomiting
- diarrhea
- weight loss

Chronic GI GVHD Grading

Organ Scoring of Chronic GVHD^a

	Score 0	Score 1	Score 2	Score 3
Mouth				
Lichen planus-like features present:	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
<input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Abnormality present but explained entirely by non-GVHD documented cause (specify):				

GI Tract

Check all that apply:	No symptoms	Symptoms without significant weight loss ^c (<5%)	Symptoms associated with mild to moderate weight loss ^c (5-15%) OR moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss ^c >15%, requires nutritional supplement for most calorie needs OR esophageal dilation OR severe diarrhea with significant interference with daily living
<input type="radio"/> Esophageal web/proximal stricture or ring <input type="radio"/> Dysphagia <input type="radio"/> Anorexia <input type="radio"/> Nausea <input type="radio"/> Vomiting <input type="radio"/> Diarrhea <input type="radio"/> Weight loss ≥5% ^c <input type="radio"/> Failure to thrive <input type="radio"/> Abnormality present but explained entirely by non-GVHD documented cause (specify):				

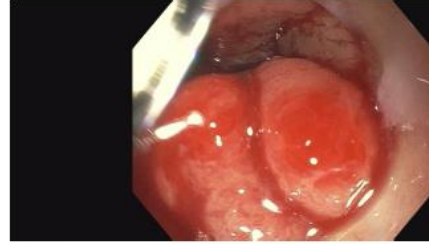
What Studies Will My Healthcare Providers Order?

- Stool studies to rule out infection
- Upper or lower endoscopy (also called “EGD” or colonoscopy)
- Blood work
 - Blood counts
 - Chemistry panel to check kidney and liver function (signs of other organ involvement)
 - GVHD biomarkers
 - Nutritional status (vitamin and mineral levels, albumin, prealbumin) to check for deficiencies related to malabsorption
- Sometimes CT or MRI of abdomen

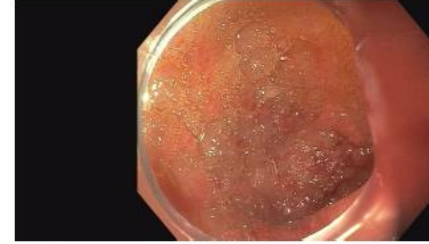
Upper Endoscopy



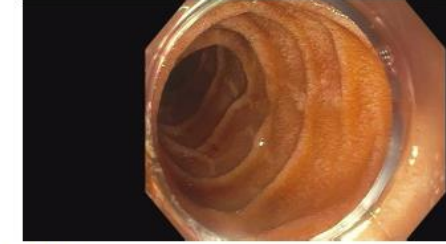
1 Gastroesophageal Junction



2 Oozing from GE junction



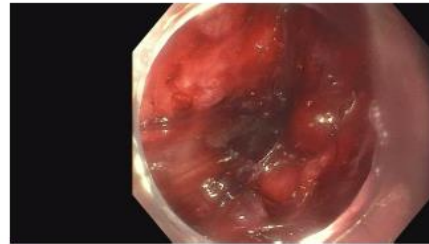
3 Duodenal Bulb



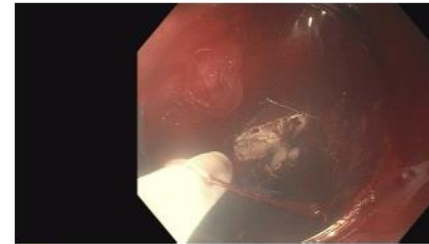
4 2nd Portion of the Duodenum



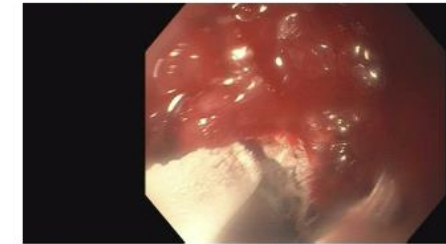
5 Major Papilla



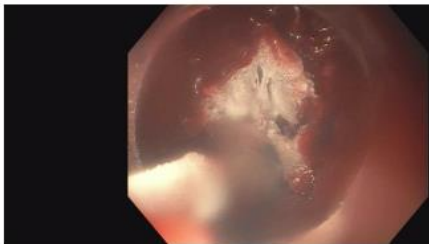
8 OG tube through pylorus



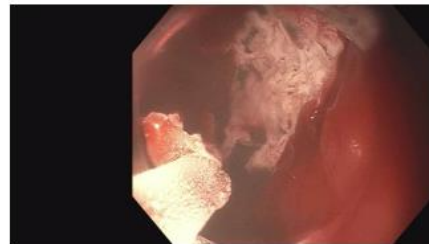
9 Cryotherapy



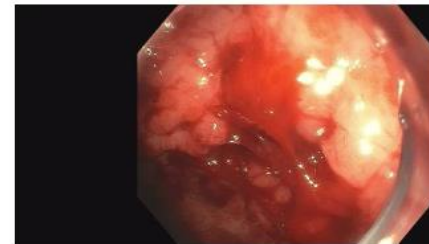
10 Cryotherapy



11 Cryotherapy



12 Cryotherapy



13 Cryotherapy



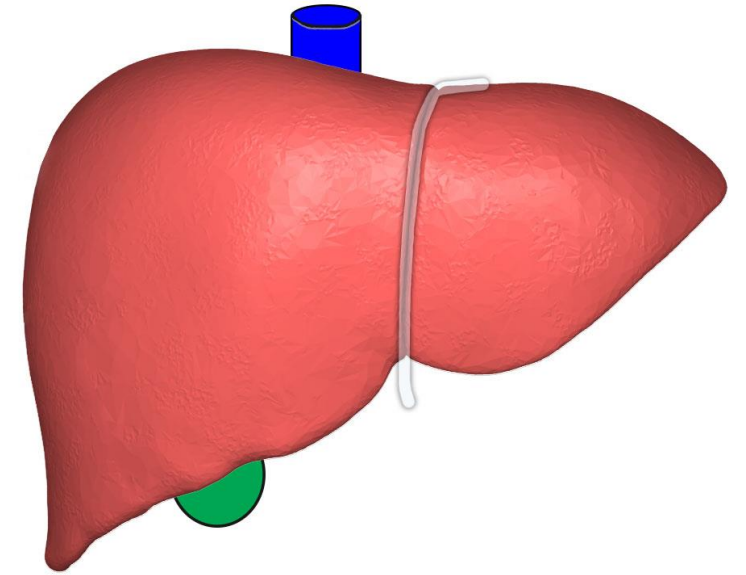
14 S/P cryotherapy

Biopsies (Tissue from the GI Tract)

- Not always required!
- But can be very helpful:
 - Assess severity of GVHD
 - Rule out infections (particularly viral)
- May be repeated because things can change
 - Particularly if symptoms change
 - to assess response

Liver

- Many different functions
 - Filters blood and removes toxins
 - Makes bile that helps us digest food
 - Makes important proteins that help us regulate our bodies, keep us from bleeding and balancing fluid
 - processes medications
- Damage over time (such as from GVHD) leads to scarring, aka cirrhosis, and decreased function



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Acute Liver GVHD Signs and Symptoms

- Upper GI (esophagus, stomach)
 - appetite loss
 - feeling full early
 - heartburn
 - nausea
 - weight loss
- Lower GI (small bowel, colon)
 - abdominal pain
 - diarrhea → malabsorption and malnutrition

Liver

- may be without symptoms or jaundiced

Chronic Liver GVHD Signs and Symptoms

- Mouth:

- oral dryness
- mouth ulcers
- blistering

- Esophagus

- difficulty swallowing
- feeling food is “stuck”

GI tract

- nausea
- Vomiting
- diarrhea
- weight loss

- Liver

- May be without symptoms, based on blood work

Signs and Symptoms of liver problems

- Jaundice (yellowing of the skin and eyes)
- Fluid overload (belly swelling and leg swelling)
- Bleeding or bruising
- Confusion
- Dark urine

Chronic Liver GVHD Grading

Liver Scoring of Chronic GVHD	
0	Normal total bilirubin and ALT or AP < 3 x ULN
1	Normal total bilirubin and ALT or AP \geq 3-5 x ULN
2	Elevated total bilirubin but \leq 3 mg/dL or ALT > 5 X ULN
3	Elevated total bilirubin >3 mg/dL

ALT: Alanine transaminase

AP: Alkaline phosphatase

ULN: Upper limit normal

How often does liver GVHD occur?

- Incidence of acute liver GVHD
 - 6.7-15.7%
- Incidence of chronic liver GVHD
 - 5.8-31%

Arai et al. BMT 2016. 10.1038/bmt.2015.205
Chen et al. PLoS One 2017. 10.1371/journal.pone.0185210
Modi et al. Am J Hematology 2019. 10.1002/ajh.25575
Arai et al. BBMT 2015. 10.1016/j.bbmt.2014.10.021

Reportedly 50% of chronic GVHD cases involve the liver

Characteristics	1995-1999 n (%)	2000-2003 n (%)	2004-2007 n (%)	P
cGVHD organ involved at maximum severity				
Skin±other	1650 (51)	1563 (65)	2192 (71)	
Eyes±other	1145 (36)	811 (34)	657 (21)	
Mouth±other	1384 (43)	1149 (48)	980 (32)	
Lung±other	456 (14)	398 (17)	522 (17)	
GI/weight loss±other	1261 (39)	995 (41)	1050 (34)	
Liver±other	1525 (48)	1178 (49)	1399 (45)	
Other organ involvement±other	1163 (36)	798 (33)	985 (32)	

Arai et al. *BMT* 2016. 10.1038/bmt.2015.205
 Chen et al. *PLoS One* 2017. 10.1371/journal.pone.0185210
 Modi et al. *Am J Hematology* 2019. 10.1002/ajh.25575
 Arai et al. *BBMT* 2015. 10.1016/j.bbmt.2014.10.021

Clinically...

- Liver GVHD in general
 - appears 2 months to 2 years after HSCT
- Affects up to 75% of all patients
- Typically, cholestatic picture
 - stagnation, or marked reduction, in bile secretion and flow
- But could be hepatitis
 - inflammation of the liver
- No diagnostic imaging findings

Snover et al. Hepatology 1984. 10.1002/hep.1840040122

Liver problems after BMT are not necessarily GVHD. It could be:

- Drug-induced liver injury (DILI)
- Veno-occlusive Disease/Sinusoidal Obstruction Syndrome
- Infection (viral, fungal)
- Iron overload
- Cholestasis of sepsis
- Malignancy
- Steatohepatitis
- Steatosis

What will my healthcare provider order?

- Blood work
- Ultrasound, CT, or MRI of abdomen
- Liver biopsy
- Referral to liver specialist (hepatologist)

Liver Biopsy: Needed for accurate diagnosis?

NIH Cross-Sectional study 2004-2014

- 315 patients assessed
- Diagnosis of clinical liver GVHD if ALT or total bilirubin >3x ULN and no other explanation
- 50% were diagnosed with liver GVHD
- 32 had a liver biopsy or autopsy (5 excluded) = 27 evaluated
- 59% actually had liver GVHD
- 41% diagnosed with liver GVHD actually had no liver GVHD

Yang et al. TCT 2022 10.1016/j.jtct.2022.07.017

Utility of Liver Biopsy

- 112 liver biopsies in 100 BMT patients
- 55/112 (49%) biopsy result led to change in treatment
 - Escalated in 14 patients
 - Discontinued in 4
- Across published studies, biopsies led to a change in treatment in 31-95% of cases

Modi et al. Am J Hematology 2019. 10.1002/ajh.25575

Ruggiu et al. BBMT 2018. 10.1016/j.bbmt.2018.07.037

Stueck et al. Human Pathology 2023. 10.1016/j.humpath.2023.07.007

What's Involved in a Liver Biopsy?

- Where is it done and by whom?
- How long does it take?
- Under anesthesia or not?
- Painful?
- Recovery time?

Safety of Transjugular and Percutaneous Liver Biopsy

- No adverse events in 92% of patients
- Adverse events:
 - Pain 7%
 - Small hematoma at needle entry site (0.4%)
 - Bleeding requiring transfusion (2/1300 = 0.0015%)
- In previous mentioned study of 112 liver biopsies
 - Total 3 patients with hematoma and/or pneumothorax

*Sasso et al. Journal of Vascular and Interventional Radiology 2023.
10.1016/j.jvir.2023.08.023*

Now that I have a diagnosis, what is the treatment?

- Clinical trial?
- First line: Steroids
- If steroids don't work or stop working, then what?
 - Ruxolitinib
 - Belumosudil
 - Clinical trial

Front-line Corticosteroid Day 28 Response

Minnesota **STANDARD** Risk Overall Response Rate 68%

Staging category	Number	Day 28 Complete/Partial Response
Upper GI only	115	78%
1-3 skin	901	68%
1-3 skin + Upper GI	90	69%
1-3 skin + 1-4 liver	51	71%
1-3 skin + 1 Lower GI	71	61%
1-3 skin + 1 Lower GI + Upper GI	62	61%
1 Lower GI + Upper GI	64	64%
1-2 Lower GI	100	73%

MacMillan ML et al. *Biol Blood Marrow Transplant.* 2015;21(4):761-767

Front-line Corticosteroid Day 28 Response

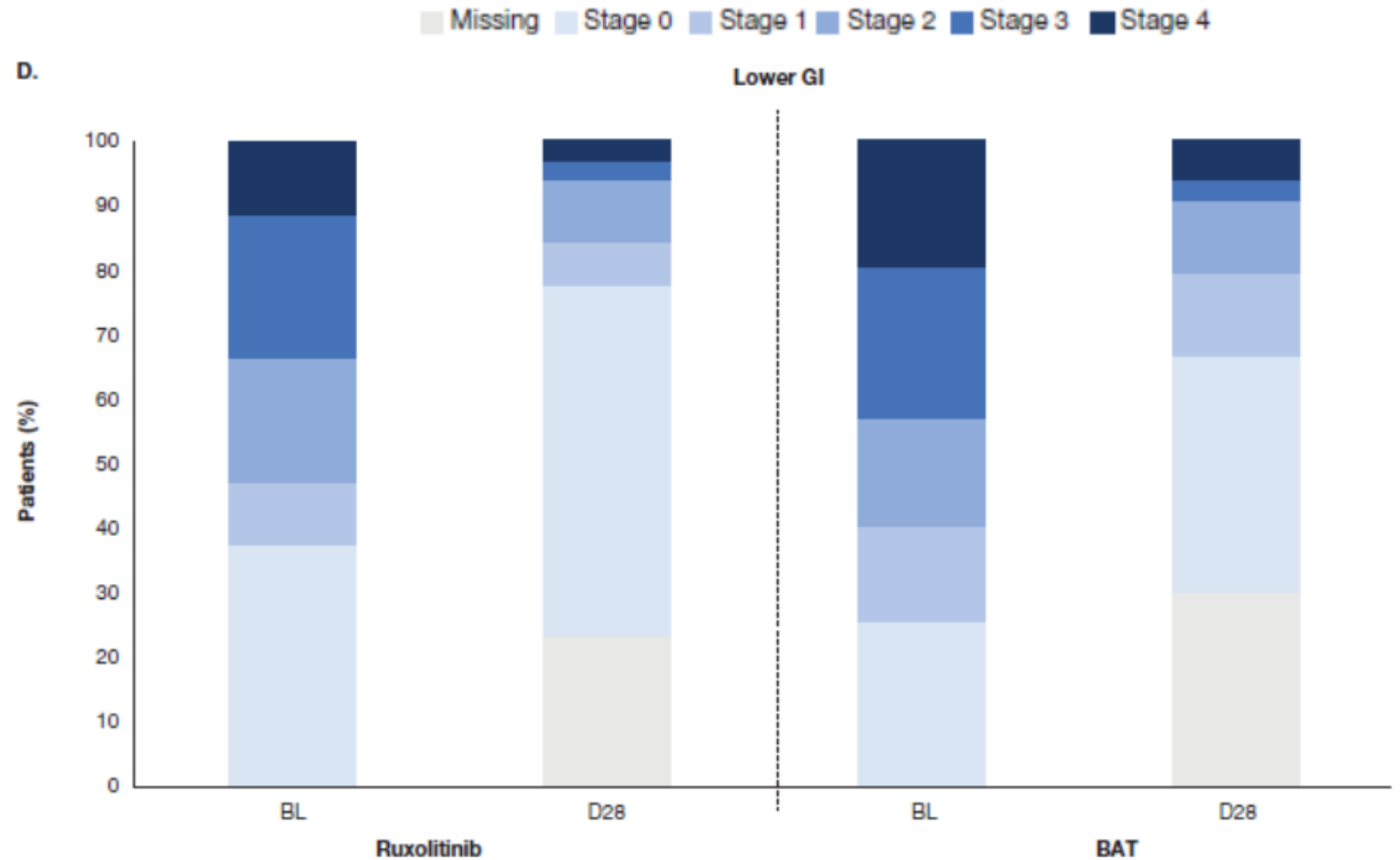
Minnesota **HIGH** Risk Overall Response Rate 44%

Staging category	Number	Day 28 Complete/Partial Response
1-2 Lower GI + 1-3 liver	12	50%
2 LGI + 1-3 skin	54	52%
3 LGI	65	55%
1-2 LGI/UGI + 1-3 skin + 1-3 liver	23	35%
3-4 LGI + 1-3 skin or 1-4 liver	55	36%
3-4 LGI + 1-3 skin + 1-4 liver	13	8%
1-4 liver	25	48%
4 skin	13	38%

MacMillan ML et al. *Biol Blood Marrow Transplant.* 2015;21(4):761-767

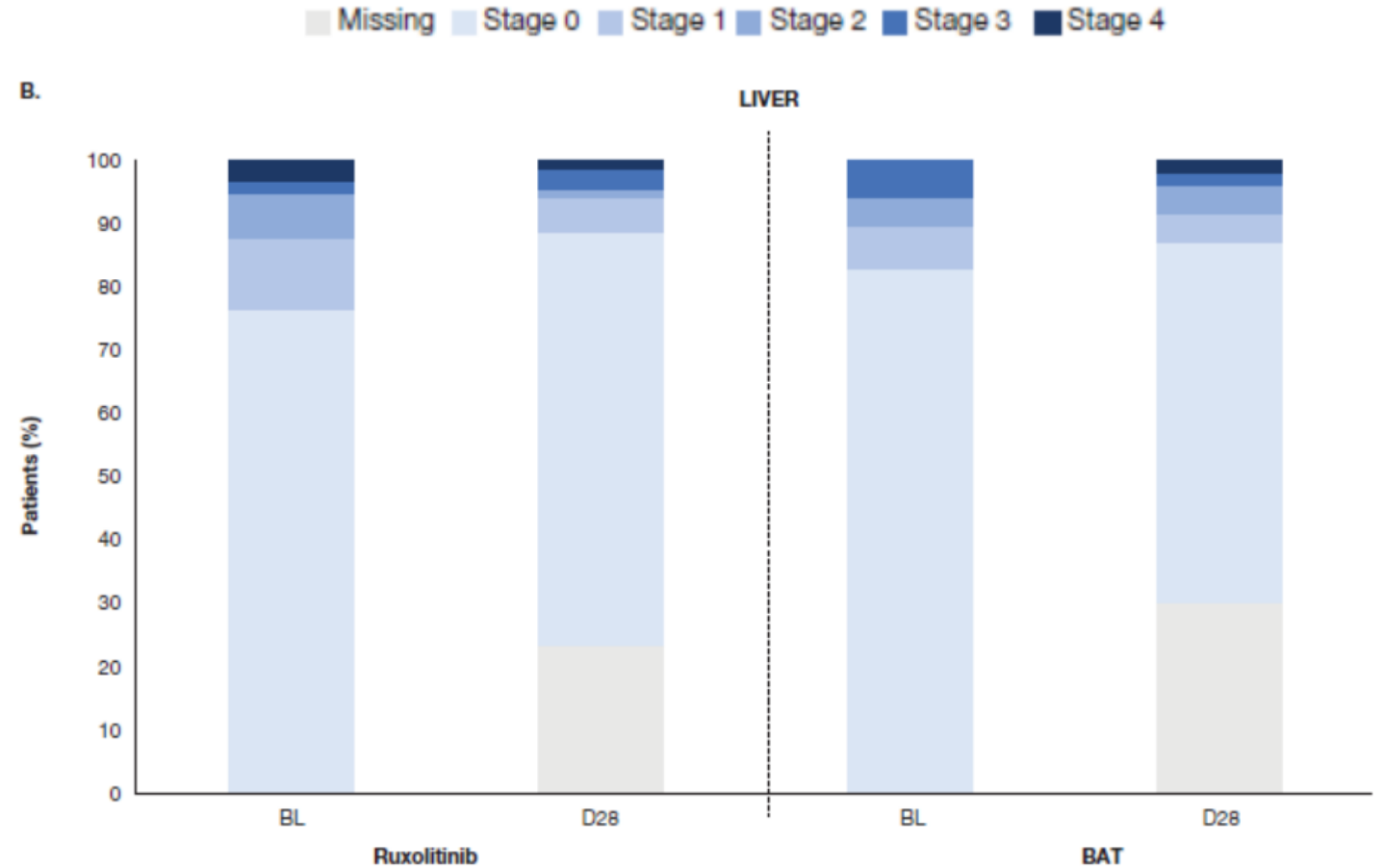
Acute GVHD ruxolitinib for lower GI – REACH2

- Stages of Lower GI acute GVHD with ruxolitinib (left) before and after versus with other therapies (right)
- Lighter colors reflect less severe GVHD
- Lower stages with ruxolitinib



Acute GVHD ruxolitinib for liver – REACH2

- Same for the liver with ruxolitinib (right) and other therapies (left)
- Roughly similar



Chronic GVHD ruxolitinib – REACH 3

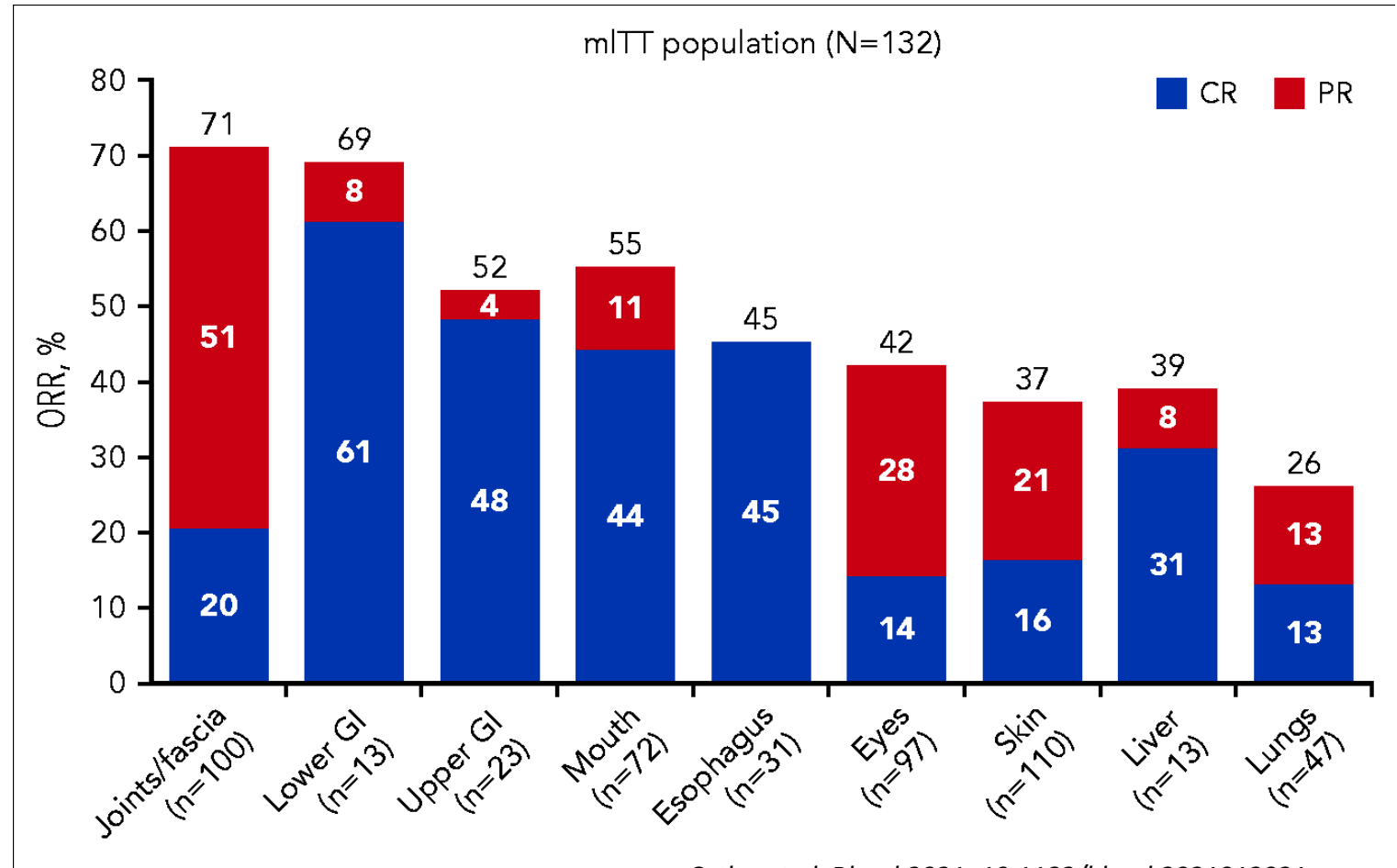
- Response rates for **chronic** GVHD in GI tract and liver
- Higher response with ruxolitinib except with mouth and liver

Organ	Ruxolitinib n=165		BAT n=164	
	Baseline involvement ^a	Organ response ^b	Baseline involvement ^a	Organ response ^b
	n (%)	m/n (%)	n (%)	m/n (%)
Mouth	96 (58.2)	48/96 (50.0)	99 (60.4)	25/99 (25.3)
Esophagus	18 (10.9)	9/18 (50.0)	17 (10.4)	5/17 (29.4)
Upper GI tract	20 (12.1)	8/20 (40.0)	21 (12.8)	8/21 (38.1)
Lower GI tract	15 (9.1)	8/15 (53.3)	10 (6.1)	3/10 (30.0)
Liver	86 (52.1)	21/86 (24.4)	83 (50.6)	18/83 (21.7)

Zeiser et al. NEJM 2021. 10.1056/NEJMoa2033122

Chronic GVHD belumosudil - ROCKstar

- Response rates for belumosudil for chronic GVHD by organ
- High response rates in lower GI and upper GI and esophagus
- Lower response rates in the liver



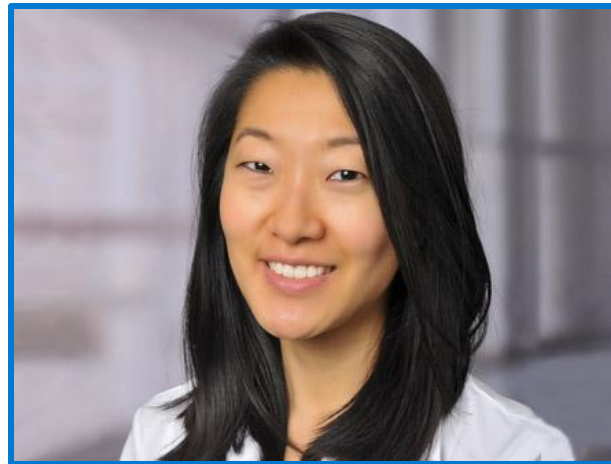
Cutler et al. Blood 2021. 10.1182/blood.2021012021

Summary

- GI tract involvement in acute GVHD is common, 70% of patients with Grade 2 or higher GVHD
- Liver involvement in acute GVHD is less common but common in chronic GVHD
- GI tract or liver involvement increases the risk of mortality in acute GVHD, not in chronic GVHD
- Biopsy is helpful in liver GVHD to confirm the diagnosis
- Treatments include steroids, ruxolitinib, and belumosudil
- Consider clinical trials



Questions?



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