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

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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
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- 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
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

(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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Upper GI</th>
<th>Lower GI (stool output per day)</th>
</tr>
</thead>
</table>
| 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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No stage 1-4 of any organ</td>
</tr>
<tr>
<td>I</td>
<td>Stage 1-2 skin without liver, upper GI or lower GI involvement</td>
</tr>
<tr>
<td>II</td>
<td>Stage 3 rash, and/or stage 1 liver, and/or stage 1 upper GI, and/or stage 1 lower GI</td>
</tr>
<tr>
<td>III</td>
<td>Stage 2-3 liver, and/or stage 2-3 lower GI, with 0-3 skin, and/or stage 0-1 upper GI</td>
</tr>
<tr>
<td>IV</td>
<td>Stage 4 skin, liver or lower GI involvement with stage 0-1 upper GI</td>
</tr>
</tbody>
</table>
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**

<table>
<thead>
<tr>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mouth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>Mild symptoms with disease signs but not limiting oral intake significantly</td>
<td>Moderate symptoms with disease signs with partial limitation of oral intake</td>
<td>Severe symptoms with disease signs on examination with major limitation of oral intake</td>
</tr>
<tr>
<td>Lichen planus-like features present:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Abnormality present but explained entirely by non-GVHD documented cause (specify):</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GI Tract</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>Symptoms without significant weight loss (5-15%) OR moderate diarrhea without significant interference with daily living</td>
<td>Symptoms associated with mild to moderate weight loss (5-15%) OR moderate diarrhea with significant interference with daily living</td>
<td>Symptoms associated with significant weight loss (&gt;15%), requires nutritional supplement for most calorie needs OR esophageal dilation OR severe diarrhea with significant interference with daily living</td>
</tr>
<tr>
<td>Check all that apply:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Esophageal web/proximal stricture or ring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Dysphagia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Anorexia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Diarrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Weight loss ≥5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Failure to thrive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>○ Abnormality present but explained entirely by non-GVHD documented cause (specify):</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
6. OG tube through pylorus
7. Cryotherapy
8. Cryotherapy
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
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

<table>
<thead>
<tr>
<th>Liver Scoring of Chronic GVHD</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal total bilirubin and ALT or AP $&lt; 3 \times$ ULN</td>
</tr>
<tr>
<td>1</td>
<td>Normal total bilirubin and ALT or AP $\geq 3 - 5 \times$ ULN</td>
</tr>
<tr>
<td>2</td>
<td>Elevated total bilirubin but $\leq 3 \text{ mg/dL}$ or ALT $&gt; 5 \times$ ULN</td>
</tr>
<tr>
<td>3</td>
<td>Elevated total bilirubin $&gt; 3 \text{ mg/dL}$</td>
</tr>
</tbody>
</table>

**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
Arai et al. BBMT 2015. 10.1016/j.bbmt.2014.10.021
Reportedly 50% of chronic GVHD cases involve the liver

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>cGVHD organ involved at maximum severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin±other</td>
<td>1650 (51)</td>
<td>1563 (65)</td>
<td>2192 (71)</td>
<td></td>
</tr>
<tr>
<td>Eyes±other</td>
<td>1145 (36)</td>
<td>811 (34)</td>
<td>657 (21)</td>
<td></td>
</tr>
<tr>
<td>Mouth±other</td>
<td>1384 (43)</td>
<td>1149 (48)</td>
<td>980 (32)</td>
<td></td>
</tr>
<tr>
<td>Lung±other</td>
<td>456 (14)</td>
<td>398 (17)</td>
<td>522 (17)</td>
<td></td>
</tr>
<tr>
<td>GI/weight loss±other</td>
<td>1261 (39)</td>
<td>995 (41)</td>
<td>1050 (34)</td>
<td></td>
</tr>
<tr>
<td>Liver±other</td>
<td>1525 (48)</td>
<td>1178 (49)</td>
<td>1399 (45)</td>
<td></td>
</tr>
<tr>
<td>Other organ involvement±other</td>
<td>1163 (36)</td>
<td>798 (33)</td>
<td>985 (32)</td>
<td></td>
</tr>
</tbody>
</table>

Arai et al. BMT 2016. 10.1038/bmt.2015.205
Chen et al. PLoS One 2017. 10.1371/journal.pone.0185210
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

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
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

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%

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

## Front-line Corticosteroid Day 28 Response

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

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

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

[Table showing response rates for ruxolitinib and BAT]
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?

Hannah Choe MD
GVHD Program Director, Assistant Professor, The Ohio State University Comprehensive Cancer Center
Let Us Know How We Can Help You

Visit our website:  bmtinfonet.org

Email us: help@bmtinfonet.org

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X, twitter.com/BMTInfoNet