Gastrointestinal complications of hematopoietic cell transplantation

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Disclosures

I am currently* or have been a consultant to:

- Soligenix*
- Calistoga*
- Genzyme
- Pfizer*
- Chimerix
- Gentium*
- Wyeth Oncology
- EMD Serono*
Man sieht nur das, was man weiss.
You only see what you know.

J.W. von Goethe, 1749 - 1832

Outline of this talk

1. Overview of acute gastrointestinal GVHD

2. Gastrointestinal problems to day 200

3. Hepatobiliary problems to day 200

4. Gastrointestinal and hepatobiliary problems in long-term transplant survivors
1. Overview of acute gastrointestinal GVHD

• the changing incidence of acute GVHD
• upper gut vs. mid-gut phenotypes
• GVH reaction and “secondary disease”
• algorithm for treatment based on mortality estimates at disease onset
Day-200 Non-Relapse Mortality reduced by 60%*

Overall survival improved by 41%*

Correlates of improved outcomes between 1993-7 and 2003-7

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR</th>
<th>% reduction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>0.26</td>
<td>74%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.48</td>
<td>52%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>0.64</td>
<td>36%</td>
<td>0.001</td>
</tr>
<tr>
<td>CMV disease</td>
<td>0.52</td>
<td>48%</td>
<td>0.009</td>
</tr>
<tr>
<td>GN bacteremia</td>
<td>0.61</td>
<td>39%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Invasive mold infection</td>
<td>0.49</td>
<td>51%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 3-4 GVHD</td>
<td>0.33</td>
<td>67%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Acute GVHD grade and stage in two eras*

Phenotypes of acute GVHD presentations

- Diarrhea ≥1 L
- Abdominal pain
- Bleeding
- Jaundice
- Skin necrosis

- Nausea
- Vomiting
- Anorexia
- Satiety
- Skin rash

(diarrhea)
Nausea
Vomiting
Anorexia
Satiety (diarrhea)

Gastric antrum

Mucosal edema
Crypt cell apoptosis
Distribution of the severity of Grade II-IV GVHD

- Grade II: 74.6%
- Grade III: 22.6%
- Grade IV: 2.8%

25% mortality at transplant Day 200\(^2,3\)

Diarrhea ≥1 L
Abdominal pain
Bleeding
Jaundice
Skin necrosis
Skin rash
Diarrhea $\geq 1$ L
Abdominal pain
Bleeding
Jaundice
Skin necrosis
Colon
Gastrointestinal Graft-vs.-Host Disease

GVH reaction in lymph nodes (primary event), followed by:

- Apoptosis of gut crypt cells
- Vascular permeability-mucosal edema
- Opening of zonula occludens

“Secondary disease”

- Gut mucosal necrosis
- Bacterial & endotoxin translocation
- Stimulation of innate immunity
Normal colonic mucosa

Location of epithelial stem cells
apoptotic body in acute GVHD
Crypt cell apoptosis and drop-out in acute GVHD

intact epithelial cells

apoptotic bodies and crypt cell loss
Barium Xray of acute GVHD involving the gastrointestinal tract

massive edema in small intestine

stomach
Gut protein loss in acute GVHD

Weisdorf S et al, Gastroenterology 1983; 85: 1076-1081
Gut protein loss in acute GVHD -- a biomarker for more severe GVHD*

A decrease in serum albumin from baseline of 0.5 g/dL discriminates between severity of GVHD: Sensitivity 69%, specificity 78%

*Rezvani A et al, Blood 2009; 114: Abstract 1146
Gut protein loss in acute GVHD

albumin

alpha-1 antitrypsin

vein

lymphatic
Translocation of bacteria and endotoxin from gut lumen to mesenteric lymph node
Gastrointestinal Graft-vs.-Host Disease

- Apoptosis of gut crypt cells
- Vascular permeability-mucosal edema
- Opening of zonula occludens

- Gut mucosal necrosis
- Bacterial & endotoxin translocation
- Stimulation of innate immunity

Delayed gastric emptying
Failure of ileal fluid resorption
Gut protein loss, low albumin
Lactase, sucrase down-regulation
Bile salt malabsorption
Etc.
What do they see in patients with GVHD?

**Endoscopist**
- mucosal edema (antrum > small intestine > colon)
- erythema
- food, pills, bile in stomach
- ulceration
- mucosal slough

**Pathologist**
- apoptosis of crypt epithelial cells
- lymphocytic infiltrates ± PMNs ± eosinophils
- missing crypt epithelial cells in intact mucosa
- absence of epithelium
GVHD

Path

Attending

GI
Mimics of and co-existing conditions with gut GVHD

- MMF gut toxicity
- CMV > adenovirus infection
- Non-culturable virus infection
  - Astrovirus (Cox et al, Gastroenterology 1994)
  - Norovirus (Roddie et al, CID 2009)
  - Rotavirus
- Thrombotic microangiography from CNI
  (Inamoto et al, BMT 2009)
- Mycobacterial infection
- Cryptosporidial infection
  (Sebastián et al, BMT 2010)
Algorithm for initial treatment of acute GVHD of the gut

Stratify by risk of mortality

Lower risk
- Nausea
- Vomiting
- Anorexia
- Satiety
- Stable albumin (diarrhea)

High risk
- Younger
- N/V/A
- Diarrhea ~1L
- Pain
- Albumin drop >0.5 g/dL

Very high risk
- Adult
- Jaundice
- Diarrhea >>1L
- Albumin <1.6
- Ulceration
Algorithm for GVHD treatment failures

Assess severity of symptoms

- Flare of original symptoms
  - Increase immune suppression (prednisone-sparing if possible)

- Failure to respond

- Worsening symptoms
  - Re-stage for:
    - infection
    - MMF toxicity
    - apoptosis
    - ulceration / slough
2. Gastrointestinal problems to day 200

- dysphagia / odynophagia
- nausea / vomiting / anorexia / satiety
- diarrhea
- gastrointestinal bleeding
- abdominal pain
- peri-anal pain
Dysphagia (trouble swallowing) & Odynophagia (painful swallowing)

Still seen
- Mucositis
- Fungal infection
- CMV infection

Now rare
- Intramural hematoma
- HSV, VZV infection
- Bacterial esophagitis
- Acute GVHD
- Pill esophagitis
Grade 3 – 4 mucositis
Candida esophagitis

If patients are on fluconazole prophylaxis, suspect resistant Candida species or a mold infection.
CMV esophagitis
CMV-infection is in subepithelium, not squamous cells
<table>
<thead>
<tr>
<th>Nausea / vomiting / anorexia / satiety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Still seen</strong></td>
</tr>
<tr>
<td>Conditioning Rx</td>
</tr>
<tr>
<td>Acute GVHD</td>
</tr>
<tr>
<td>CMV infection</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Bacteremia</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Now rare</strong></td>
</tr>
<tr>
<td>HSV, VZV infection</td>
</tr>
<tr>
<td>Biliary sludge syndrome</td>
</tr>
<tr>
<td>CNS diseases</td>
</tr>
</tbody>
</table>
Normal colonic mucosa
Day +7 colon biopsy after high-dose myeloablative therapy
Day +16 colon biopsy after myeloablative therapy
Oral caloric intake after CY/TBI conditioning

IL2 30x
IL6 24x
TNFα 7x

Nausea, vomiting, and anorexia after day 20: 1980s\(^1\) vs. 1990s\(^2\) vs. now\(^3\)

<table>
<thead>
<tr>
<th>Causes</th>
<th>1980s</th>
<th>1990s</th>
<th>Now</th>
</tr>
</thead>
<tbody>
<tr>
<td>GVHD</td>
<td>26%</td>
<td>81%</td>
<td>~90%</td>
</tr>
<tr>
<td>HSV or CMV</td>
<td>30%</td>
<td>3%</td>
<td>~1%</td>
</tr>
<tr>
<td>GVHD + virus</td>
<td>16%</td>
<td>4%</td>
<td>~1%</td>
</tr>
<tr>
<td>Other</td>
<td>28%</td>
<td>12%</td>
<td>~8%</td>
</tr>
</tbody>
</table>


\(^3\)McDonald GB. Guesstimated data
Gastric antrum in acute GVHD with symptoms of anorexia, nausea, vomiting, satiety

Erythema, edema

Crypt cell apoptoses
Medications that cause anorexia, nausea, and vomiting

- trimethoprim-sulfamethoxazole
- itraconazole/voriconazole
- mycophenolate mofetil
- cyclosporine/tacrolimus
- mu-agonist opioids
- nystatin
- intravenous amphotericin B
Diarrhea

Still seen
- Conditioning Rx
- Acute GVHD
- C. difficile colitis
- CMV, Adenovirus
- Medications (Mg++, MMF, macrolides)
- Non-culturable viruses (Norovirus, Astrovirus)

Now rare
- Rotavirus
- Cryptosporidium
- Giardia lamblia
- Other parasites
- Bacterial pathogens (except in endemic areas)
- Pancreatic insufficiency
Truisms about diarrhea in HCT patients

• The upper limit of normal stool volume is 200 mL per day.

• Fasting patients should have no stool output.

• In fed patients, ~8 liters of fluid flow through the gut per day:
  • most of this fluid is reabsorbed by the ileum
  • only 1.2 liters is presented to the colon per day

• Thus, daily stool volumes >1.2 liters means small intestinal mucosal disease and not solely colon mucosal disease.

• The standard staging of the severity of gut GVHD (by peak diarrheal volumes) correlates poorly with mortality.

• Gut infection can be found in ~10-20% of patients with diarrhea.
Incidence and etiology of diarrhea after day 20*

- Incidence: 126/290 patients (43%)

- Etiology of diarrhea:
  - Acute GVHD: 48%
  - Infection: 13%
  - Etiology unknown: 39%

*Cox et al, Gastroenterology 1994; 107: 1398 - 1407*
Early histologic findings in acute GVHD

- Intact differentiated epithelial cells
- Apoptosis of crypt epithelial cells
apoptotic body in acute GVHD (colonic mucosa)
Acute GVHD with crypt drop-out in small intestine
Stage 4 GVHD with sloughing of intestinal mucosa
Organisms causing diarrhea after day 20*

<table>
<thead>
<tr>
<th>Viruses (N=13)</th>
<th>Bacteria (N= 7)</th>
<th>Parasites (0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrovirus (6)</td>
<td>C. difficile (6)</td>
<td></td>
</tr>
<tr>
<td>Adenovirus (2)</td>
<td>Aeromonas (1)</td>
<td>Fungi (0)</td>
</tr>
<tr>
<td>Rotavirus (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple viruses (2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Cox et al, Gastroenterology 1994;107:1398-1407
(Note geographic variation: Kang et al, Transplantation 2002;73:1247-51)
Prevalence of enteric pathogens after HCT*

- Patient population: 169 patients during 2000 & 2001
- 1649 stool tests were ordered from the MSKCC clinical lab (10.6 tests per patient!) but no PCR or biopsy data

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Day -7 to 30</th>
<th>Day 31-90</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. difficile</td>
<td>19 (11.3%)</td>
<td>23 (13.7%)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>10 (5.9%)</td>
<td>6 (3.5%)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>3 (1.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Giardia</td>
<td>1 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Bacteria</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

What should you order on a stool specimen to find gut pathogens in patients with diarrhea?

<table>
<thead>
<tr>
<th>If the onset of Sx was in a protected hospital environment:</th>
<th>If Sx started after out-of-hospital exposure to the real world, add:</th>
<th>If Sx started after barn-yard type exposure, add:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• C. difficile</td>
<td>• Rotavirus EIA</td>
<td>• Salmonella</td>
</tr>
<tr>
<td>• Adenovirus DNA</td>
<td>• Norovirus RNA</td>
<td>• Shigella</td>
</tr>
<tr>
<td>• viral culture</td>
<td>• Astrovirus RNA</td>
<td>• Campylobacter</td>
</tr>
<tr>
<td>• (CMV DNA in blood)</td>
<td>• Giardia antigen</td>
<td>• Yersinia</td>
</tr>
<tr>
<td>• (gut biopsy-IHC, centrifugation culture)</td>
<td>• Cryptosporidia PCR</td>
<td>• Aeromonas</td>
</tr>
<tr>
<td></td>
<td>• Ova &amp; parasites</td>
<td>• E coli H7:O157</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fungi</td>
</tr>
</tbody>
</table>
Necrotizing colitis caused by some Adenovirus serotypes
Occam’s Razor is often disposable in patients with diarrhea after transplant

Gut GVHD alone is more common than:

Gut GVHD + an enteric infection, which is more common than:

An enteric infection alone
Gastrointestinal bleeding

Still seen
Acute GVHD
CMV, adenovirus infection
Clostridial colitis (C. septicum, C. difficile)
Sites of mucosal Bx
Anal canal / hemorrhoidal vein

Now rare
Mucosal necrosis from conditioning therapy
Mucosal trauma from retching and vomiting
Acid-peptic esophagitis
Fungal infections (Rhizopus, e.g.)
Gastric antral vascular ectasia (GAVE)
Severe gastrointestinal bleeding, 1980s vs. 1990s*

<table>
<thead>
<tr>
<th>Causes of bleeding</th>
<th>1980s</th>
<th>1990s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral infection</td>
<td>15/467 (3.2%)</td>
<td>1/635 (0.2%)</td>
</tr>
<tr>
<td></td>
<td>(p&lt;.0001)</td>
<td></td>
</tr>
<tr>
<td>Fungal infection</td>
<td>4/467 (0.9%)</td>
<td>0/635</td>
</tr>
<tr>
<td></td>
<td>(p=.032)</td>
<td></td>
</tr>
<tr>
<td>GVHD</td>
<td>27/467 (5.8%)</td>
<td>7/635 (1.2%)</td>
</tr>
<tr>
<td></td>
<td>(p&lt;.0001)</td>
<td></td>
</tr>
</tbody>
</table>

CMV ulcer
Adenovirus colitis
Ulceration of small intestine caused by Rhizopus*

A thru E: active infection

F: after antifungal Rx

*Pinto Marques et al, BMT 2003; 32: 739-40
Intramural hematoma of the duodenum after endoscopic biopsy
Intramural duodenal hematoma
Gastric and duodenal erosions in acute GVHD
Acute GVHD involving small intestinal mucosa
Acute GVHD involving the cecum (autopsy)
Bleeding from denuded bowel in severe GVHD
Truisms about GI bleeding in HCT patients

• Trivial bleeding is common, serious bleeding is uncommon

• Bleeding when platelets are <50,000/mm$^3$ is usually from superficial mucosal vessels and rarely from a spurting artery.

• Superficial mucosal bleeding is responsive to platelets.

• Neither endoscopic nor radiologic methods of stopping bleeding are effective when platelet counts are very low, and endoscopic cautery / injection therapy leads to large ulcers.

• There are urgent diagnostic imperatives for patients who are bleeding despite decent platelet counts:
  Is the bleeding from one lesion or multiple lesions?
  Where is the site that is bleeding?
  What is causing the lesion that is bleeding?
Algorithm for managing GI bleeding after HCT

Is the bleeding clinically significant?
- Yes
- No

Is the medical situation hopeless?
- Yes

Is the platelet count >50,000?
- Yes
- No

Give platelets to >50,000

Is the rate of bleeding ≥2 units/24 hours?
- Yes
  - Blood pool scan Tc99
- No
  - Bleeding stops
  - Bleeding persists

Yes
Tc\textsuperscript{99} blood pool scan for detection of obscure sites of bleeding

ligament of Treitz
Blood pool scan $\text{Tc}^{99}$

- Single site bleeding
  - Is site within reach of an endoscope?
    - Yes: Endoscopic biopsy and hemostasis
    - No: Angiography and vessel occlusion vs. Surgery

- Multiple sites bleeding or cecal pooling of $\text{Tc}^{99}$
  - No site identified
    - Diagnostic endoscopy with biopsies ± endoscopic hemostasis
Gastric antral vascular ectasia (GAVE)

Diffuse oozing of blood from antral mucosa
Histology of GAVE*

Capillary dilation

Thrombosis

Fibromuscular hyperplasia


Abdominal pain

Still seen
- Pseudo-obstruction
- Acute GVHD
- Cystitis (BK, adeno)
- Narcotic bowel syndrome
- Biliary sludge syndrome
- Infection (C. difficile, viruses)

Now rare
- Perforation
- C. Septicum (typhilitis)
- Acute pancreatitis
- Visceral VZV infection
- EBV LPD
- Hematomas
- Liver abscess (fungal >> bacterial)
- Bowel infarct (Aspergillus, TMA)
Truisms about abdominal pain in HCT patients

• Most abdominal pain after HCT is not related to an impending catastrophic event and imminent death—but there are causes of pain that can be rapidly fatal.

• There are only three common causes of abdominal pain:
  1. Obstruction or distention of a hollow viscus
  2. Inflammation of a pain-sensitive structure
  3. Neuropathic pain

• A history, review of medications, and abdominal examination are usually much more useful and cheaper than CT in diagnosis of causes of abdominal pain.

• Using mu-agonist opioid medication to treat abdominal pain caused by mu-agonist opioids is plain stupid.
Intestinal pseudo-obstruction after transplant

Risk factors:

- prior vincristine Rx
- mu-opioid Rx
- anticholinergic Rx
- mucosal injury
- ventilator use
- visceral VZV
Fluid-filled loops of intestine in severe GVHD
Peri-anal pain

Still seen
- Anal fissure
- Cryptitis / cellulitis
- Peri-anal abscess
- Tenesmus & levator spasm from proctitis

Now rare
- Ischiorectal fossa abscess
- HSV infection
- Fungal infection
- Actinomyces infection
Truisms about peri-anal pain in HCT patients

• All patients with peri-anal pain should be considered to have bacterial soft tissue infections until proved otherwise.

• Peri-anal HSV and fungal infections are now extremely rare among patients on antiviral and antifungal prophylaxis.

• Include anaerobic coverage for all peri-anal bacterial infections.

• When in doubt about diagnosis or extent of infection, don’t dither in contacting a colorectal surgeon.
3. Hepatobiliary problems to day 200


Liver diseases after hematopoietic cell transplant

- Sinusoidal Obstruction Syndrome -- preventable

- Cholestatic liver diseases -- preventable
  - cholangitis lenta
  - calcineurin inhibitors
  - GVHD
  - drug toxicity
  - biliary obstruction from sludge, stones, CMV, etc.

- Hepatocellular necrosis and infections -- preventable
  - SOS
  - GVHD
  - shock (usually sepsis)
  - viral infection (Adeno, VZV, HSV, HCV, HBV, CMV)
  - fungal, bacterial infection
  - drug toxicity
Cubic spline curves of median bilirubin values, 1990s vs. now*

Prevention of cholestatic liver disease

Ursodiol for everyone!
4. Gastrointestinal and hepatobiliary problems in long-term transplant survivors


• McDonald GB. Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. Hepatology 2010; 51: 1450 – 1460.
## Gut and liver problems in survivors

<table>
<thead>
<tr>
<th>Gut</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protracted acute GVHD</td>
<td>Protracted acute GVHD</td>
</tr>
<tr>
<td>Viral infections (HSV, CMV)</td>
<td>Hepatitic GVHD</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>Iron overload</td>
</tr>
<tr>
<td>Chronic GVHD—esophagus</td>
<td>Chronic HBV, HCV</td>
</tr>
<tr>
<td>Visceral VZV syndrome</td>
<td>Cirrhosis, hepatoma (HCV)</td>
</tr>
<tr>
<td></td>
<td>Nodular regenerative hyperplasia</td>
</tr>
<tr>
<td><strong>Pancreas</strong></td>
<td>Ascites, varices</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td>Focal nodular hyperplasia</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>Gallstones, cholecystitis</td>
</tr>
<tr>
<td></td>
<td>Biliary obstruction</td>
</tr>
<tr>
<td></td>
<td>Fungal abscess</td>
</tr>
</tbody>
</table>
Phenotypes of GVHD presentations in long-term survivors of allogeneic HCT

- **Typical chronic GVHD**
  - Skin
  - Mucous membranes
  - Eyes
  - Esophagus
  - Tendons
  - Et cetera

- **Protracted acute GVHD**
  - Nausea
  - Vomiting
  - Anorexia
  - Satiety
  - Diarrhea

- **Liver GVHD**
Protracted acute GVHD

Day 200

1 year

5+ yrs

Severity of GVHD

Acute GVHD

Protracted acute GVHD
Protracted acute GVHD with fatal outcome

Severity of GVHD

Day 200
Those who do not remember the past are condemned to repeat it.

George Santayana, 1863 - 1952