



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

Celebrating a Second Chance at Life
Survivorship Symposium

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Karamjeet Singh Sandhu MD

City of Hope

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

Karamjeet Singh Sandhu, MD
Assistant Professor
City of Hope National Medical Center

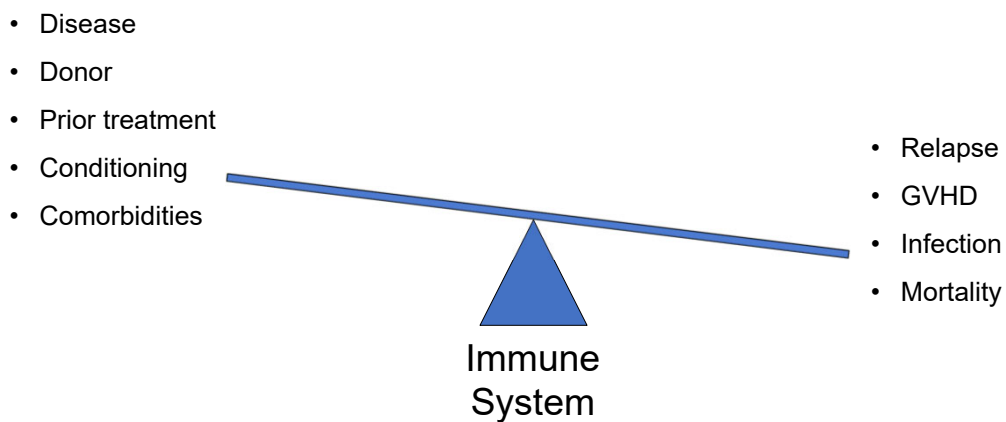
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Introduction

- What is GVHD?
- What are possible causes?
- How is it classified?
- How it may present?
- How to treat?

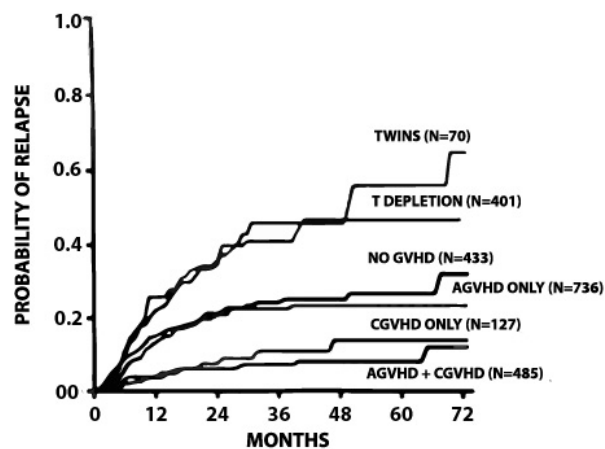
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Hematopoietic Stem Cell Transplant is an Immunotherapy Treatment



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GVHD and Graft-versus-Leukemia Effect (GVL)



Actuarial probability of relapse after bone marrow transplantation for early leukemia according to type of graft and development of GVHD.

Horowitz et al; Blood 1990

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Graft-versus-Host-Disease

- Immune reaction triggered when non-self cells (donor) react toward self-cell (recipient) recognizing them as foreign
- Immunosuppressive medications are used to prevent this reaction while donor cells develop tolerance toward foreign cells

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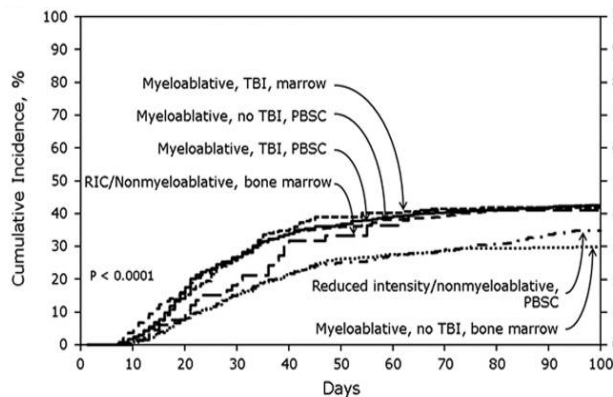
Factors Contributing to GVHD

- Non-identical graft (HLA or Gender)
- GVHD prevention regimen
- Conditioning regimen intensity
- Source of stem cells (peripheral blood vs bone marrow)
- Microbiome

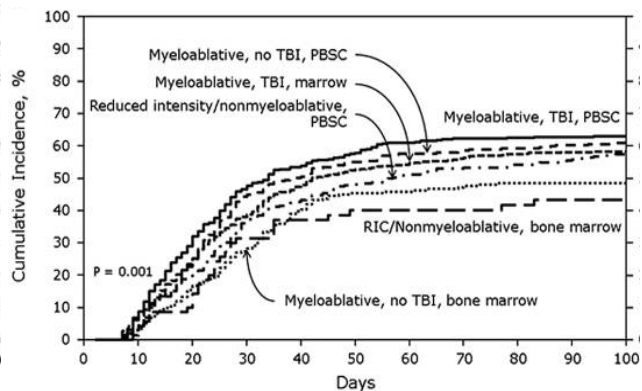
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Incidence of Acute GVHD

Acute GVHD Grade B-D (sibling donor)
Median 39%



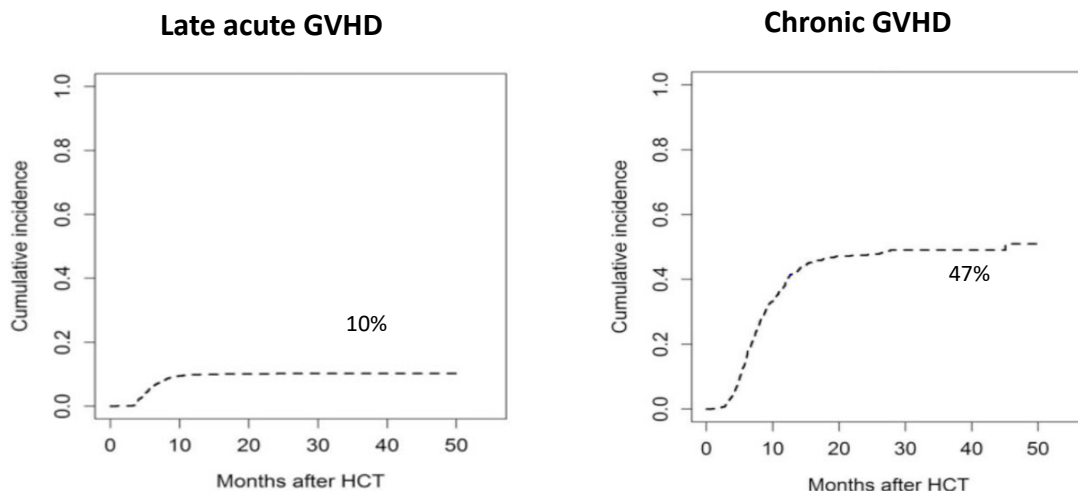
Acute GVHD Grade B-D (Unrelated donor)
Median 59%



Jagasia et al; BBMT 2015

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Incidence of Late Acute GVHD and Chronic GVHD



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GVHD Prevention

- Tacrolimus, Methotrexate
- Post-transplant Cyclophosphamide, Tacrolimus, Mycophenolate
- Tacrolimus, Sirolimus
- Post transplant Cyclophosphamide, Sirolimus, Mycophenolate
- Tacrolimus, mycophenolate
- T cell manipulation (e.g. Orca graft)
- Clinical trials (e.g Microbiota modification trials)

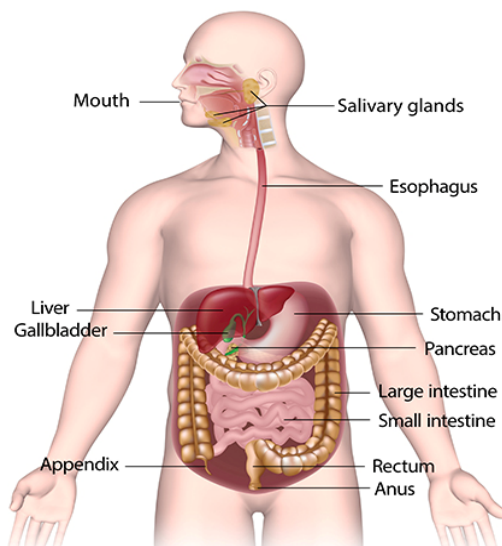
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Acute or Chronic GVHD?

- Timing
 - Less than 100 days (acute) and more than 100 days (chronic)
 - Overlap
- Pathology
 - Acute: destruction as result of inflammatory T cells processes
 - Chronic: tissue injury with abnormal repair leading to fibrosis, scarring
- Organs affected
 - Acute: Skin, gastrointestinal, Liver
 - Chronic: Eyes, gastrointestinal, skin, joints, muscles, lungs, liver, kidneys, nervous system, serosal cavities, genitalia

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The Digestive System



<https://www.niddk.nih.gov/health-information/digestive-diseases/digestive-system-how-it-works>

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Symptoms of GVHD

- Mouth (chronic): Oral dryness, ulceration, pain, gum bleeding
- Esophagus (chronic): Difficulty swallowing, painful swallowing, choking
- Stomach (acute/chronic): abdominal pain, weight loss, loss of appetite
- Small and large bowel (acute/chronic) loss of appetite, abdominal pain, weight loss, diarrhea, bleeding, constipation
- Liver: no symptoms but elevated liver enzymes (Bilirubin, AST, ALT)

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GVHD in Mouth

- Oral dryness
- Ulcerations
- Pain/Irritation
- Gum bleeding
- Tooth decay



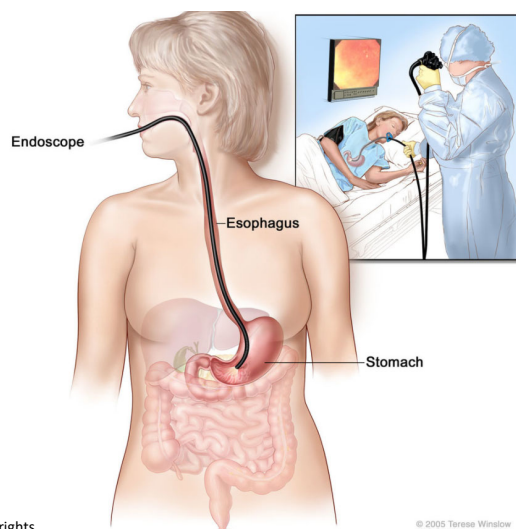
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GVHD in Esophagus

- Symptoms
 - Difficulty swallowing (Dysphagia)
 - Painful swallowing (Odynophagia)
 - Choking
- Diagnostic Terms
 - Schatzki ring
 - Esophageal stricture or stenosis
- Caused by chronic scarring of muscles
- Diagnosis
 - Clinical presentation
 - Endoscopic gastroduodenoscopy
 - Barium Swallow study

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Endoscopic gastroduodenoscopy



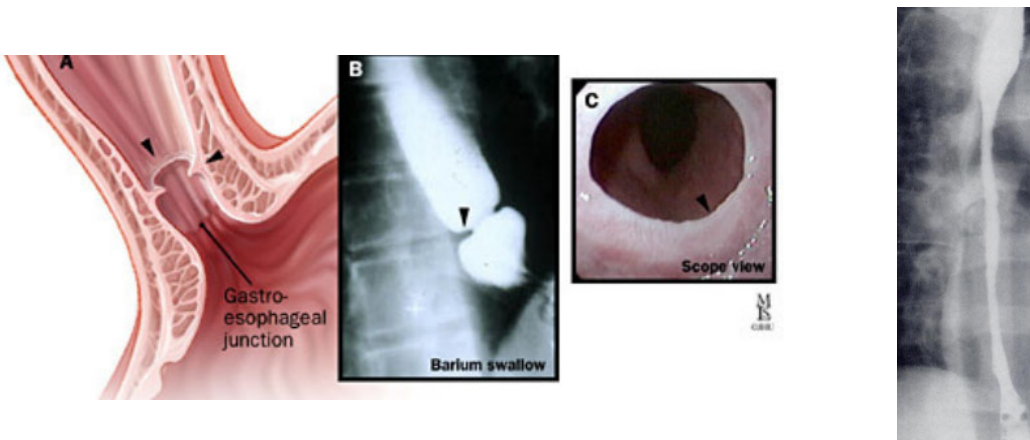
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Management

Combination of immunosuppressive therapy and endoscopic intervention

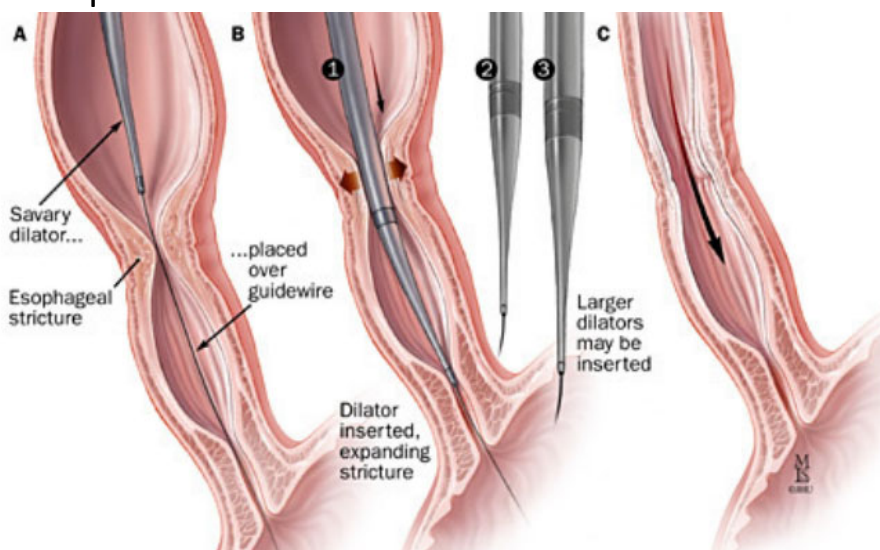


<https://www.ajronline.org/doi/pdf/10.2214/ajr.142.3.501>

https://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/esophagus_stomach/swallowing_disorders.pdf

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Endoscopic dilatation



https://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/esophagus_stomach/swallowing_disorders.pdf

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GVHD in Stomach

- Symptoms
 - abdominal pain
 - weight loss
 - loss of appetite
- Present in both acute and chronic GVHD
- Diagnosis
 - Endoscopic gastroduodenoscopy
- Management
 - Topical corticosteroids
 - Systemic immunosuppressive therapy

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Gastroparesis – Delayed Gastric Emptying

- Movement of food from stomach to small intestine is stopped or delayed
- Symptoms: inability to eat, feeling full after eating only a little food
- Gastric emptying scan can help with diagnosis
- Treatment
 - Immunosuppression
 - Gut motility agent
 - Proton pump inhibitor

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Symptoms of GVHD in Small and Large Bowel

- Abdominal pain
- Nausea
- Vomiting
- Diarrhea
- Blood in stool
- Weight loss

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Infectious Causes of Diarrhea

- Bacterial: (Clostridium difficile, campylobacter, Shigella)
- Viral: (CMV, Adenovirus, EBV, Rotavirus, norovirus)
- Cryptosporidium
- Mycobacterium

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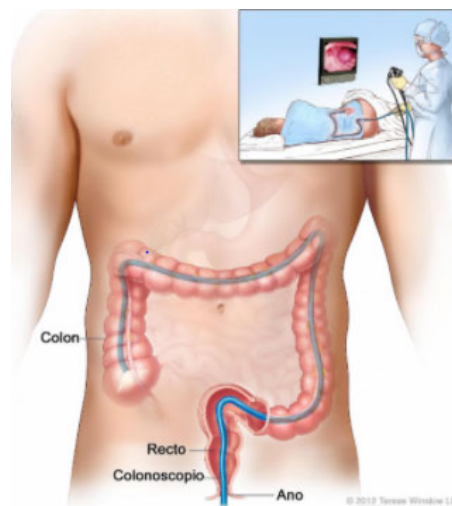
Other Causes of Diarrhea

- Inflammatory bowel disease
 - Crohn's disease, Ulcerative colitis
- Cord colitis syndrome
- Thrombotic microangiopathy syndrome
- Disease involvement of gastrointestinal system
- Pancreatic insufficiency
- Small bowel intestinal bacterial overgrowth
- Medications:
 - mycophenolate, antibiotics, conditioning chemotherapy

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Management of Diarrhea Caused by GVHD

- Diagnosis
 - Clinical work up
 - Flexible Sigmoidoscopy
 - Colonoscopy
- Treatment
 - Immunosuppressive therapy



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Liver GVHD

- Symptoms:
 - Jaundice
 - Sometimes no symptoms
- Can occur in both acute and chronic GVHD
- Usually, there are also other organs with GVHD

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Other Causes of Abnormal Liver Enzymes

- Medications
- Venooclusive disease
- Fatty Liver disease
- Iron overload
- Infections (Hepatitis, CMV, Adenovirus)
- Gall bladder disease

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Management of Liver GVHD

- Investigation
 - Ultrasound or CT Abdomen
 - HiDA Scan
 - Transjugular liver biopsy
 - Infectious work up
 - Medication review
- Treatment
 - Immunosuppression

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Acute GVHD Grading

Stage	Skin	Liver (Bilirubin)	Upper GI	Lower GI
0	No rash	< 2.0 mg/dl	No protracted nausea	<500 ml diarrhea
1	<25% Body surface area	2.0-2.9 mg/dl	Persistent nausea, vomiting or anorexia with histologic changes	>500 diarrhea
2	25-50% Body surface area	3.1-6.0 mg/dl		>1000 diarrhea
3	>50% generalized redness and scaling on skin	6.1-15 mg/dl		>1500 diarrhea
4	Large blisters and/or peeling skin	>15 mg/dl		Severe abdominal pain, poor movement of stool, frank blood in stool

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Chronic GVHD Grading

Mild	<ul style="list-style-type: none">• 1 or 2 organs or sites (except lung) with score of 1<ul style="list-style-type: none">• Mild oral symptoms, no decrease in oral intake• Mild dry eyes , lubricant eyedrops \leq 3X/day
Moderate	<ul style="list-style-type: none">• 3 or more organs with score 1• At least 1 organ site with score 2<ul style="list-style-type: none">• 19-50% body surface area involved or superficial sclerosis• Moderate dry eyes, eyedrops > 3X/day or punctal plugs• Lung score 1 (FEV1 60-79% or dyspnea (shortness of breath) with stairs)
Severe	<ul style="list-style-type: none">• At least 1 organ or site with score 3<ul style="list-style-type: none">• >50% body surface involved• Deep sclerosis, impaired mobility or ulceration• Severe oral symptoms with major limitation in oral intake• Severe dry eyes affecting activities of daily living• Lung score 2 (FEV1 40-59% or dyspnea (shortness of breath) walking on flat ground)

Lee et al; Blood 2017

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Intestinal Microbiota

- Microorganisms in gut
- Play valuable role in promoting patient immune system
- Decrease in diversity and presence of certain microbial species has been shown to be associated with:
 - risk of graft versus host disease
 - failure to respond to treatment
 - non-relapse mortality
- Several clinical trials are undergoing to modulate gut microbiome to prevent and improve treatment responses

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Microbiome Clinical Trials – Fecal Transplant

- Fecal microbiota transplant for steroid refractory GVHD¹
 - Received fresh donor stool suspension through nasoduodenal tube
 - 10 of 15 patients achieved remission
- Third-party fecal microbiota transplantation following allogeneic-HCT reconstitutes microbiome diversity²

1. Van der Lier et al Science Translational Medicine 2020; 2. DeFlipp et al; Blood Adv 2018

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Other Microbiome Clinical Trials

- **Gluten free diet** in preventing GVHD in patients undergoing HCT
- **Lactobacillus rhamnosus GG** doesn't reduce incidence of GVHD in patients who have undergone HCT¹
- **CBM588** in Improving Clinical Outcomes in Patients Who Have Undergone Donor Hematopoietic Stem Cell Transplant
- **Human Lysozyme Goat Milk** for the Prevention of Graft Versus Host Disease in Patients With Blood Cancer Undergoing a Donor Stem Cell Transplant

1. Gorshein et al; Clin transplant 2017

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Treatment Options for GVHD

- Corticosteroids
 - Systemic (Oral vs Intravenous)
 - Topical (Budesonide, Beclomethasone)
- Tacrolimus, Sirolimus, Mycophenolate Mofetil (Cellcept®)
- Ruxolitinib (Jakafi®)
- Belumosudil (FDA Breakthrough designation)
- Ibrutinib
- Infliximab, Etanercept
- Extracorporeal photopheresis (ECP)
- Clinical trials

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Extracorporeal photopheresis

- Blood is drawn from patient
- Blood is separated.
- Plasma and red blood cells are returned to patient
- White blood cells are photoactivated with UVA radiation
- Photoactivated white blood cells are returned to the patient



Illustration, Norm Bendell

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Managing GVHD is a Team Effort

- Complex disease and treatment requires:
 - close communication with transplant team
 - patient compliance with treatment plan
- Outcomes improving:
 - better understanding of mechanisms and available treatments
 - better supportive care
- Emotional and social support
- Work with dietitian to overcome nutritional challenges
- Physical rehabilitation
- Multiple drugs
- Multispecialty support

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Questions?



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