Hematopoietic Cell Transplantation

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Objectives

- Identify nutrition assessment and monitoring parameters for adult and pediatric hematopoietic cell transplant (HCT) patients.
- Discuss nutrition management of HCT recipients experiencing transplant-related complications.
- Understand the pathophysiology of graft-versus-host disease (GVHD) and appropriate nutrition interventions.
- Describe long-term nutritional implications associated with HCT.

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Hematopoietic Cell Transplantation

- First successful transplant done in mid-1950s
- >50,000 HCT performed annually worldwide
  - SCCA performs 475-500 transplants per year
- Survival depends upon:
  - Type of malignancy and stage of disease
  - Donor type
  - Graft source
  - Patient age
  - Intensity of conditioning

Diseases and Conditions Treated by HCT

- **Hematologic malignancies** (ALL, AML, multiple myeloma)
- **Malignant solid tumors** (recurrent lymphoma, advanced-stage neuroblastoma, refractory Ewing's sarcoma)
- **Hematologic disorders** (severe aplastic anemia, sickle cell disease, myelodysplastic syndrome)
- **Immunodeficiency disorders** (Wiskott-Aldrich syndrome, severe combined immunodeficiency)
- **Pediatric non-neoplastic conditions** (infantile osteopetrosis, lysosomal storage diseases)

Hematopoietic Cell Transplantation

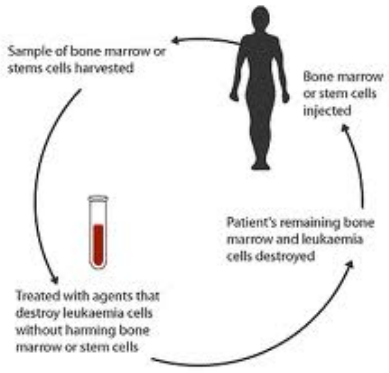
- **Objective**: to replace the malignant or defective bone marrow to restore hematopoietic and immunologic function
- **Myeloablative:** cytotoxic chemotherapy; may also include total body irradiation (TBI) and possibly local irradiation; some regimens utilize reduced intensity conditioning to decrease toxicity
- **Non-myeloablative:** lower dose chemotherapy and radiation; candidates include patients with non-malignant disorders or those with relapsed malignancy following myeloablative transplant

Hematopoietic Stem Cell Transplantation

- Stem cell source
  - Bone marrow
  - Peripheral blood
  - Umbilical cord blood
- An intravenous infusion of stem cells follows the conditioning regimen.

Autologous Transplantation

Patient's own stem cells are used as "rescue"



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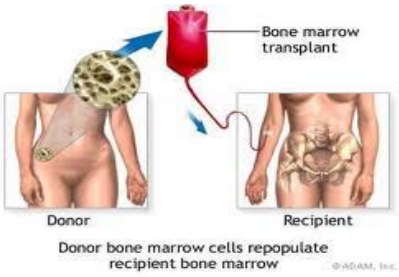
Allogeneic Transplantation

- Cells from a human-leukocyte antigen (HLA) compatible donor are harvested, stored and then transplanted into the patient
- Stem cells obtained from a related or unrelated donor



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Nutrition Assessment

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Nutrition Assessment

- Physical assessment
- Anthropometry (length/height; weight; occipital frontal circumference; arm anthropometry)
- Growth and weight history
- Biochemical indices
- Medications
- Other (medical history; prior therapy; activity level; pain control)

(Macris, 2012)

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Nutrition Anthropometry

- Baseline height, weight, occipital frontal circumference in children <2 years
  - Compromised growth and development
  - Growth hormone deficiency with decreased growth velocity
  - Delayed onset of puberty (Sanders, 2004)
- Arm anthropometry
  - Retrospective review of 733 pediatric HCT patients
  - Arm circumference and triceps skinfold
  - Association between low muscle reserves, pre-transplant, and poorer survival (Hoffmeister, 2013)

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Nutrient Requirements

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Nutrient Requirements

- **Energy**
  - Increased needs due to the preparative regimen, fever, infections, acute graft-versus-host disease (GVHD), and metabolic complications:
    - Adults: Basal needs x 1.3-1.5
    - Children: Basal needs x 1.4-1.6
  - Adjusted weight used for patients >120% ideal weight

Nutrient Requirements

- **Protein**
  - Birth-6 years 2.5-3 g/kg/day
  - 7-10 years 2.4 g/kg/day
  - 11-14 years 2 g/kg/day
  - 15-18 years 1.8 g/kg/day
  - Adults 1.5 g/kg/day
- **Fat**
  - Typical intake is 20-30% of total energy
  - Minimum needs: 4-8% of total energy to prevent essential fatty acid deficiency
  - Discontinue or reduce lipid support with hyperlipidemia

Nutrient Requirements

- Fluids
  - <10 kg: 100 mL/kg/day
  - 11-20 kg: 1,000 mL + 50 mL/kg for each kg >10 kg/day
  - 21-40 kg: 1,500 mL + 20 mL for each kg >20 kg
  - >40 kg: 1,500 mL/m^2/day

Nutrient Requirements

- **Vitamins and Minerals: Oral**
  - Iron-free oral multiple-vitamin mineral supplement with 100% DRI (for age) for one year post-transplant; longer for patients treated with long-term immunosuppressive medications
  - Calcium and vitamin D supplementation necessary with corticosteroid therapy:

Age (years)	Calcium (mg/day)	Vitamin D (IU/day)*
1-3	1,000	800
4-8	1,200	800
>9	1,500	1,000+

* dependent upon serum level

Nutrient Requirements

- **Vitamins and Minerals: Parenteral**
  - Standard pediatric/adult parenteral vitamin preparation
  - Additional vitamin C to promote tissue recovery via collagen biosynthesis following cytoreduction:
    - <31 kg: 250 mg/day
    - ≥31 kg: 500 mg/day
  - Vitamin C contraindicated if serum ferritin >1,000 ug/L to decrease oxidative damage from release of free iron

Nutrient Requirements

- **Vitamins and Minerals**
  - Hepatic dysfunction: may need to remove copper and manganese from PN solutions (serum bilirubin >10 mg/dL)
  - Diarrhea: supplement with zinc at a dose of 1 mg/100 mL stool when stool volume exceeds:
  - 250 mL for children <20 kg
  - 500 mL for children 20-40 kg
  - 1,000 mL for children/adults >40 kg
- **Electrolytes**
  - Monitor serum levels closely as medications and GI losses influence needs

Nutrition Support

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Goals of Nutrition Support

- Identify and prevent or correct protein-energy malnutrition and metabolic abnormalities.
- Preserve lean tissue.
- Promote growth and development in children.
- Maximize quality of life.

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Oral Feedings

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Oral Feedings/Neutropenic Diet

- Indicated for patients with a functional GI tract.
- Historically, “sterile,” “low microbial,” or “neutropenic” diets have been used with the HCT population.

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Efficacy of the Neutropenic Diet

- No difference in the rates of febrile admissions or positive blood cultures between compliant vs. non-compliant patients. (DeMille, 2006)
- Infection rates not significant between groups who followed vs. those who did not follow diet restrictions. (Moody, 2006)
- Retrospective review of 726 transplant patients: higher rate of infection in recipients who followed a neutropenic diet. (Trifilio, 2012)

Efficacy of the Neutropenic Diet

- The protective benefits of a neutropenic diet have not been established.
- Survey of 156 institutions affiliated with the Association of Community Cancer Centers: 78% restricted diets of neutropenic patients. (Smith, 2000)
- Most transplant centers utilize some type of neutropenic diet. (Smith, 2000; August, 2009)

Immunosuppressed Diet

- Purpose: minimize the introduction of pathogenic organisms into the GI tract, by food, while maximizing healthy food options for immunosuppressed patients.
- **Autologous** patients follow diet for the first three months post-transplant; **allogeneic** patients follow diet until all immunosuppressive therapy has been discontinued.
- Nutrition education regarding high risk foods and safe food handling is necessary during immunosuppression.

SCCA Immunosuppressed Patient Diet

- Let them eat their fruits and vegetables!

- See Table 1; www.seattlecca.org/nutrition

Enteral Nutrition

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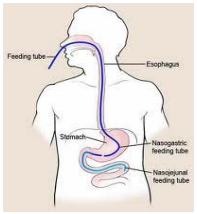
Enteral Nutrition

- Benefits:
  - Maintenance of mucosal integrity and gut barrier function
  - Stimulation of mucosal repair
  - ↓ incidence of hyperglycemia
  - ↓ incidence of infection
  - ↓ cost

  (Lipkin, 2005; Thompson, 2008)



- Specific to HCT population: EN may have a protective benefit against the development of acute GVHD and survival. (Seguy, 2012)

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Enteral Nutrition

- Indications for EN during HCT:
  - Intact GI tract
  - Non-myeloablative or reduced intensity conditioning regimens
  - Low risk transplant (autologous or matched sibling) with long-term eating problems
  - Chronic oral/esophageal GVHD with need for long-term nutrition support
  - Ongoing weight loss
  - Ventilation

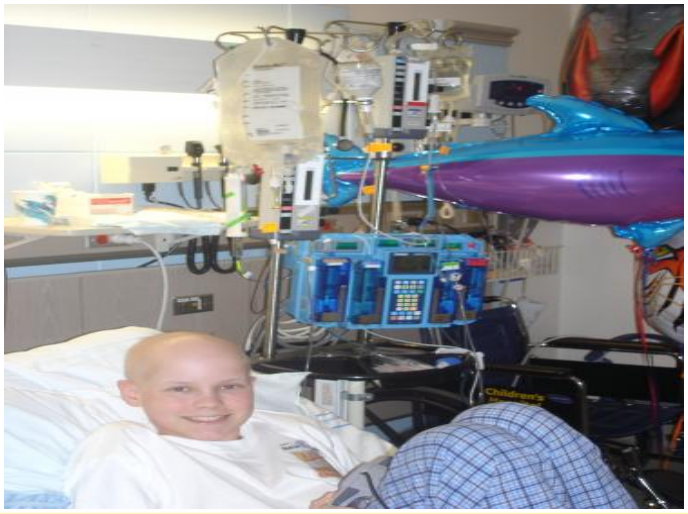
Enteral Nutrition

- Complications associated with EN support during HCT:
  - Dislodgment of nasoenteral tubes (Lenssen, 2001; Sefcick, 2001)
  - Delayed gastric emptying (Eagle, 2001)
  - Inadequate energy intake resulting in weight loss and decreased body cell mass (Szeluga,1987; Langdana, 2001; Sefcick, 2001)
  - Inadequate electrolyte and mineral intake (Papadopoulou, 1997)

Enteral Nutrition

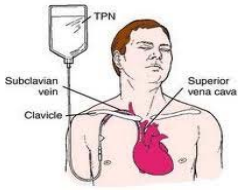
- For safe tube placement:
  - Absolute neutrophil count: >1,000 mm^2
  - Platelet count: >50,000 mm^2
- Nasoenteric and enterostomy feeding tubes
- Enteral formulas
  - Pediatric/adult specific
  - Semi-elemental
  - Renal
  - Concentrated
- Combined use of EN with PN support (Mulder, 1989)

Parenteral Nutrition



Parenteral Nutrition

- Indications for PN support during HCT:
  - Myeloablative conditioning regimen with severe GI toxicity
  - Severe intestinal GHVD or high-volume diarrhea
  - Suboptimal nutrition support from enteral route



Parenteral Nutrition

- Early studies on PN and the HCT population reported:
  - Improved visceral protein status
  - Maintenance of body weight
  - Increased disease-free survival in the allogeneic population (Weisdorf, 1987)
- More recent studies report conflicting evidence supporting the routine use of PN.

Parenteral Nutrition

- Standard criteria for malnutrition to determine appropriate use of PN during HCT. (Iestra, 1999)
- Indications differed significantly between treatment protocols:
  - 37% in autologous patients conditioned without TBI
  - Up to 92% of patients with mismatched allograft
- PN not uniformly indicated for all patients.

Complications Associated with PN

- Association between the degree of hyperglycemia during neutropenia and an increased risk of post-transplant complications and non-relapse mortality. (Fuji, 2007)
- Hyperglycemia
  - Maintain dextrose infusion rate at <4 g/kg/min
  - Ensure patient is not being overfed
  - Provide IV lipids with decrease in dextrose substrate to minimize degree of hyperglycemia
  - Goal: maintain serum glucose level as normal as possible
- Increased risk of bacteremia
- Thrombocytopenia (Cetin, 2002)

Parenteral Nutrition

- Provision of PN can be safely discontinued, without adverse effects during HCT, when:
  - Patients consume at least 30% energy needs
  - Patients are without evidence of malnutrition, malabsorption, or other significant GI toxicities

  (Stern, 2000)
- Discontinuation of PN results in earlier resumption of oral intake post-transplant. (Charuhas, 1997)

Glutamine Supplementation During HCT

- Oral glutamine has been shown to have no effect on:
  - Mortality
  - Infections
  - Time to neutrophil recovery
  - ↓ mucositis
- Parenteral glutamine has been reported to:
  - ↓ LOS
  - ↓ incidence of positive blood cultures

  (Crowther, 2009)

Glutamine Supplementation During HCT

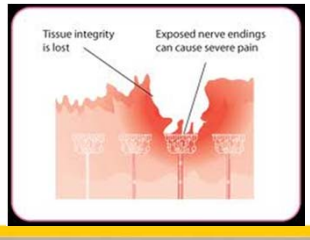
- Two studies found significantly higher relapse rates in patients randomized to receive parenteral glutamine supplementation.
  (Pytlik, 2002; Sykorova, 2005)

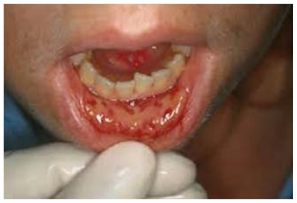
- Summary: additional studies are needed to determine appropriate dose and timing of glutamine supplementation in the HCT population. (Crowther, 2009)

Regimen Related Toxicities

Mucositis/Esophagitis

- Grade 3-4 mucositis occurs in ~70% of myeloablative patients, 46% of reduced intensity regimens, and only rarely with nonmyeloablative regimens. (Iestra, 1999; Diaconescu, 2004)
- Most severe cases: high dose melphalan ± TBI.
- Cryotherapy: ↓ severity with melphalan. (Lilleby, 2006)





Dysgeusia

- Chemo- and radiotherapy decrease and destroy taste receptor cells.
- Affects food selection and contributes to poor meal intake post-HCT.
- Dysgeusia continued to persist in 65% patients between day 90-100 post-transplant. (Epstein, 2002)
- Nutrition management requires a complete clinical and nutritional evaluation with appropriate diet counseling.

Nausea and Vomiting

- Most frequently associated with:
  - Preparative conditioning regimen
  - GVHD and/or
  - CMV enteritis
- Most common with alkylating agents ± TBI.
- Antiemetics routinely prescribed.

Diarrhea

- Common following:
  - High-dose cytoreductive therapy
  - Antibiotic therapy
  - Intestinal infections (CMV enteritis, clostridium difficile colitis)
  - Intestinal GVHD
  - Lactose intolerance

SCCA Gastrointestinal Diet Progression

Phase	Clinical Symptoms	Diet	Clinical Symptoms of Intolerance
1. Bowel rest	GI cramping, large volume watery diarrhea, severely reduced transit time, small bowel obstruction, N/V	Oral: NPO IV: Stress kcal and protein requirements	
2. Introduction of oral feeding	Minimal GI cramping, diarrhea <500 mL/day, improved transit time, infrequent N/V	Oral: Isotonic, low-residue, low-lactose fluids IV: same as phase 1	↑ stool volume or diarrhea, ↑ emesis, ↑ abdominal cramping
3. Introduction of solids	Minimal or no GI cramping, formed stool	Oral: Allow introduction of solid foods containing min lactose, low fiber/fat/acidity IV: same as phase 1	As in Phase 2

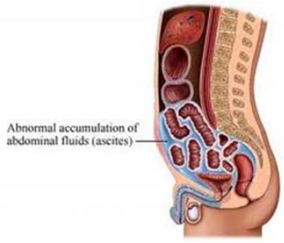
SCCA Gastrointestinal Diet Progression

Phase	Clinical Symptoms	Diet	Clinical Symptoms of Intolerance
4. Expansion of diet	Minimal or no GI cramping, formed stool	Oral: min lactose, low fiber and acidity, low fat diet if stools indicate malabsorption IV: prn to meet nutritional requirements	As in Phase 2
5. Resumption of regular diet	No GI cramping, normal stool, normal transit time, normal serum albumin	Oral: progress to regular diet IV: discontinue with oral intake meets nutrient needs	As in Phase 2

Sinusoidal Obstructive Syndrome (SOS)

- Characterized by toxic injury to the sinusoidal and venular liver epithelium.
- Clinical symptoms include:
  - Insidious weight gain
  - Ascites
  - RUQ tenderness and hepatomegaly
  - Hyperbilirubinemia and renal dysfunction

(McDonald, 2010)



Sinusoidal Obstructive Syndrome (SOS)

- Medical nutrition therapy:
  - Concentration of IV fluid volumes (PN, medication)
  - ↓ IV and oral sodium intake to <2 g daily
  - Removal of biliary trace elements (copper and manganese) if bilirubin >10 mg/dL or hyperbilirubinemia persists >1 week
  - ↓ IV lipids to 4-6% total calories to prevent essential fatty acid deficiency if hypertriglyceridemia develops
  - Frequent weight checks; abdominal girth measurements

Renal Complications

- Renal dysfunction prevalence as high as 70% of allogeneic recipients. (Parikh, 2002; Kogan, 2010)
- Ranges from pre-renal insufficiency to acute renal failure requiring dialysis.
- Etiologies include:
  - Sepsis
  - Nephrotoxic antibiotics
  - Chemo- and/or radiotherapy
  - Calcineurin inhibitors

Renal Complications

- Medical nutrition therapy:
  - Goals are to minimize uremic toxicity and metabolic derangements while preventing malnutrition
  - Maximize nutrition support within fluid allowance
  - Correct electrolyte imbalances
  - Maintain sufficient intravascular volume

Graft Versus Host Disease (GVHD)

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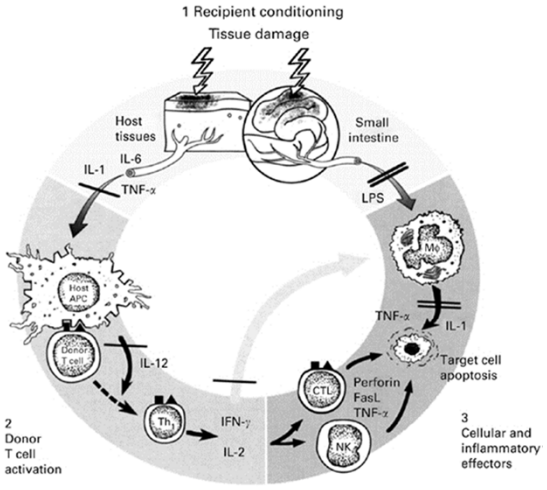
GVHD



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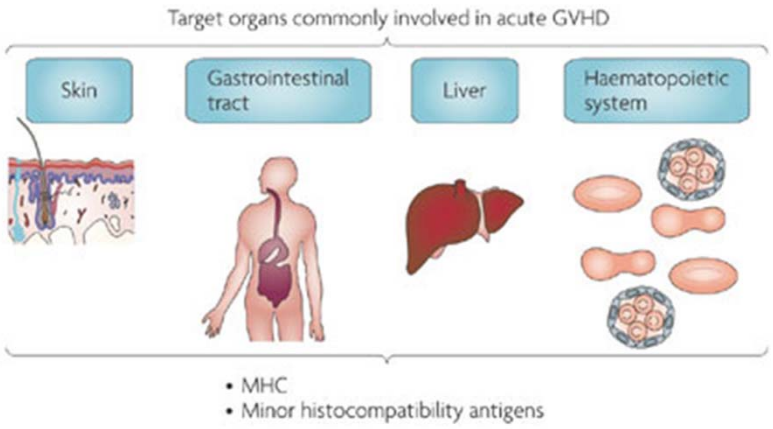
GVHD



Acute GVHD

- Predominantly targets the skin and GI tract.
- Generally occurs < day 100 post-transplant although features can occur beyond this time point.
- Clinical features of acute GI GVHD include:
  - Nausea
  - Vomiting
  - Early satiety
  - Anorexia
  - Diarrhea

Chronic GVHD

- Multisystem disease involving inflammation and fibrosis.
- Often occurs later in the transplant course.
- "Overlap" syndrome recently recognized where diagnostic or distinctive features of chronic and acute GVHD appear together.

Chronic GVHD

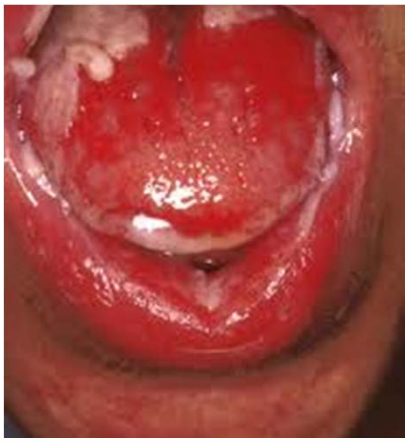
- Clinical features include:
  - Weight loss
  - Weight gain (due to corticosteroid tx)
  - Oral sensitivity
  - Xerostomia
  - Esophageal webbing, stricture
  - Anorexia
  - Reflux
  - Pancreatic insufficiency

Nutrient Requirements with GVHD

- Energy: 1.3-1.5 x BEE or 30-35 kcal/kg
- Protein: 1-1.5 g/kg up to 1.8-2.5 g/kg
- Fluid: 1,500 mL/m^2/day

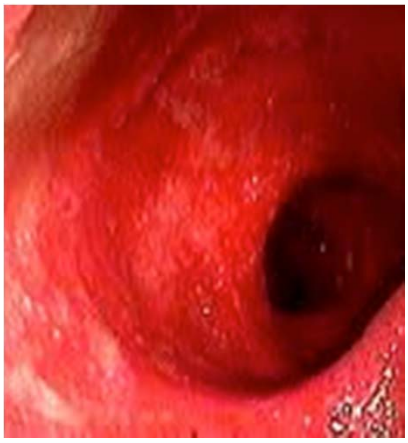
Oral GVHD

- 87% patients have oral GVHD symptoms at initial diagnosis of chronic GVHD. (Lee, 2008)
  - Sensitivities
  - Ulcerations
  - Dysgeusia (umami, zinc)
  - Xerostomia



Esophageal GVHD

- Strictures/web formation
- Dysphagia
- Swallow evaluation for texture modification
- Prevent aspiration



GVHD Grading for Diarrhea

Extent of Organ Involvement	
Stage	Gut (stool output per day)
0	< 500 mL/day or persistent nausea
1	500-999 mL/day, persistent nausea, vomiting, or anorexia with positive upper GI biopsy
2	1,000-1,400 mL/day
3	> 1,500 mL/day
4	severe abdominal pain with or without ileus or frank melena (regardless of stool volume)

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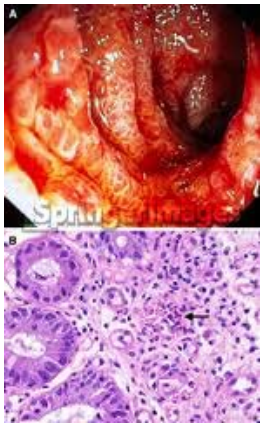
Diarrhea

- Due to destruction of intestinal crypt cells:
  - Secretory diarrhea
  - Nitrogen losses
  - Mucosal ulcerations



Diarrhea

- Voluminous, secretory diarrhea and intestinal bleeding occur in advanced disease.
- Intestinal losses result in:
  - Dehydration
  - Loss of electrolytes, fat, and protein
  - Intolerance of oral and enteral feeding
  - Need for bowel rest and PN support

Nutrition Intervention for Diarrhea

- NPO status and PN support.
- Clear liquid diet advancement.
- Slow, systematic diet expansion per 5-step diet progression.

- Consider:
  - Lactose-free diet trial → disaccharide intolerance
  - Pancreatic enzymes → pancreatic insufficiency
  - Amylase-resistant starch

Long Term Complications and Management

Pancreatic Insufficiency

- Pancreatic atrophy causes diarrhea and steatorrhea. (Akpek, 2001)
- 5 of 30 long-term HCT survivors experienced pancreatic atrophy for which chronic intestinal GVHD was found to be an associated factor. (Nakasone, 2010)
- Clinical symptoms include:
  - Rapid weight loss
  - Urgent, frothy, greasy or foul smelling stools
- Tests and intervention
  - Sudan fecal fat
  - Fecal elastase
  - Pancreatic enzymes

Osteoporosis

- Osteopenia/osteoporosis → OR = 3.1 (Baker, 2010)
- Risk factors include:
  - Steroid exposure
  - TBI
  - Chemotherapy
  - Calcineurin inhibitors
- Prevention and management:
  - Adequate calcium intake (1,500 mg daily)
  - Adequate vitamin D supplementation to maintain normal serum level
  - Weight bearing and resistive exercise

Metabolic Syndrome

- Characterized by:
  - Obesity
  - Hyperlipidemia
  - Hypertension
  - Glucose intolerance
- 3:1 frequency of metabolic syndrome compared with NHANES data (n=86) in survivors >1 year post-transplant. (Majhail, 2009)
- Statistically significant difference in the incidence of cardiometabolic traits in childhood survivors compared to controls. (Chow, 2010)

Steroid-Induced Diabetes

- Frequent occurrence in patients treated with high dose prednisone.
- Aberrant glucose levels were associated with ↑ non-relapse mortality. (Pidala, 2011)
- Nutrition intervention:
  - Routine assessment and treatment of glycemic control
  - Diet education

Summary

- Optimal nutrition management for the HCT patient is vital.
- Routine nutrition monitoring and intervention recommended throughout the patient's transplant course.
- Appropriate education and counseling for nutrition-related problems.

Questions

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Table 1: Seattle Cancer Care Alliance

Diet Guidelines for Immunosuppressed Patients

Food Restrictions

- Raw and undercooked meat (including game), fish, shellfish, poultry, eggs, sausage and bacon
- Luncheon meats (including salami, bologna, hot dogs, ham) unless heated until steaming
- Refrigerated smoked seafood typically labeled as lox, kippered, nova-style, or smoke or fish jerky (unless contained in a cooked dish); pickled fish
- Raw tofu, unless pasteurized or aseptically packaged
- Raw milk products and unpasteurized milk, cheese, and yogurt
- Blue-veined cheeses including blue, Gorgonzola, Roquefort, and Stilton
- Uncooked soft cheeses including brie, camembert, feta, and farmer's
- Mexican-style soft cheese, including queso blanco and queso fresco
- Cheese containing chili peppers or other uncooked vegetables (e.g., pepper jack)
- Fresh salad dressings containing raw eggs or contraindicated cheeses (i.e., those from the refrigerated section)
- Unwashed raw and frozen fruits or vegetables, and those with visible mold; all raw vegetable sprouts
- Raw or unpasteurized honey
- Unpasteurized commercial fruit and vegetable juices
- Well water must be boiled for 15-20 minutes and consumed within 48 hours

Reference: www.seattlecca.org/nutrition