Pediatric Nutrition During Stem Cell Transplant:
Engraftment → Post-Transplant Complications and Follow Up

Susan Reese MS RDN CNSC CD
Inpatient Oncology/Hematology/HCT Dietitian
Intermountain Children’s Health
Primary Children’s Hospital

Disclosure

Susan Reese

- Nothing to disclose

Learning Objectives

- Understand common intermediate and late complications for pediatric hematopoietic cell transplant (HCT)
- Identify what complications require more frequent nutritional monitoring
- Evaluate patients and determine appropriate nutrition support interventions

Overview

- Intermediate Complications
- Discharge/Follow Up
- Late Complications and Survivorship

Complications Overview

- Complications related to HCT are due primarily to alloreactivity, risk of infections during hematopoietic and immune reconstitution, and toxicities from the conditioning regimen.

- Complications of HCT vary based on conditioning regimen used, donor type, degree of immunosuppression, and previous organ comorbidities.

- The timing of side effects and complications can be categorized according to when they occur during the transplantation process.

Early (Conditioning to Engraftment)	Intermediate (Engraftment to first 100 days)	Late (After 100 days)
Bone-marrow suppression	Infections	Immunosuppression
Engraftment syndrome	Acute GVHD	Chronic GVHD
Nausea, vomiting, diarrhea, anorexia, mucositis	Graft failure	Infections
Parotitis	Interstitial pneumonitis	Endocrine dysfunction
Infections	Bronchiolitis obliterans organizing pneumonia	Cataracts
Skin changes		Hemorrhage cystitis
Capillary leak syndrome, diffuse alveolar hemorrhage		Bronchiolitis obliterans syndrome
Acute renal insufficiency		Disease recurrence
Hemorrhagic cystitis		Secondary malignancies
Veno-occlusive disease		
Seizures		

Intermediate Complications

Engraftment to first 100 days

Engraftment Syndrome

- An inflammatory condition that occurs during neutrophil recovery after HCT
  - Thought that proinflammatory cytokines released during neutrophil recovery lead to local and systemic tissue injury.
- Signs/Symptoms: fever not related to infection, erythematous skin rash, and pulmonary edema (causing weight gain)
  - Can progress to encephalopathy, renal/liver dysfunction, or diffuse alveolar hemorrhage
- Usually resolved with engraftment, short course of IV steroids can help alleviate the symptoms
- **Nutrition Considerations**:
  - If patient is given a fluid restriction, may need to concentrate PN/lipids or switch to concentrated formula to ensure maximum calories are provided

Graft Failure

- Rejection of the stem cell graft due to host T cells
- Primary vs secondary
  - Primary: absence of donor cell engraftment (never engrafted)
  - Secondary: loss of a previously functioning graft
- Predisposing factors
  - T-cell depletion
  - Low cell count in graft
  - Previous blood transfusions
  - Less intensive conditioning regimens, immune system not completely ablated
- Goal to transplant again as soon as possible
  - Just coming out of high dose chemotherapy with potential of some organ toxicity

Cytomegalovirus (CMV)

- CMV enteritis
  - Nonspecific GI issues that can lead to ulcerations anywhere along the GI tract
- CMV gastritis
  - Often causes severe epigastric pain
- CMV esophagitis
  - Can present as odynophagia and dysphagia
- CMV colitis
  - May lead to diarrhea, abdominal pain, anorexia, and fever
- MNT depends on the location of CMV and associated symptoms

Treating with MNT

Oncology Nutrition Educational Handouts and Resources: Sore mouth and throat. Academy of Nutrition and Dietetics.
Oncology Nutrition Educational Handouts and Resources: Diarrhea. Academy of Nutrition and Dietetics.

Sore mouth and throat

- Drink through a straw to avoid sore areas in the mouth
- Choose soft, bland foods served cold or at room temperature
- Soothe mouth and throat with cold foods and drinks
- Puree or liquefy foods in a blender so they are easy to swallow
- Moisten foods with broth, soup, sauces, gravy or butter
- High calorie, high protein nutritional drinks

Diarrhea

- Eat several small meals throughout the day
- Lie down for 30 minutes after a meal to help slow digestion
- Eat foods with pectin (like applesauce or ripe bananas) to help firm stools
- Avoid greasy, fried, spicy, and sweet foods
- Limit high-fiber foods like raw fruits and vegetables, whole grains, beans, nuts and seeds as they are harder to digest.

Renal Impairment

- Renal impairment may be related to:
  - Chemotherapeutic agents, TBI, nephrotoxic medications (eg antibiotics and calcineurin inhibitors), VOD/SOS, intravascular volume depletion, and sepsis.
- **Nutrition Considerations**
  - Intervention can include maximizing nutrition support within the fluid allowance, correcting electrolyte imbalances, and maintaining sufficient intravascular volume.
  - During continuous renal replacement therapy (CRRT), protein and vitamin needs are altered.

Sinusoidal obstructive syndrome (SOS)

- Historically referred to as hepatic veno-occlusive disease (VOD)
  - Endothelial cell damage in the hepatic sinusoidal endothelial cells and hepatocytes that results in hepatocellular necrosis, fibrosis, and occlusion.
  - Creates clotting cascade which creates micro thrombi throughout the liver, blocks up the flow and causes back up
    - Ascites, fluid overload, liver congestion
- Occurring after a high-dose chemotherapy, HCT, ingestion of toxic alkaloids, after high doses of radiotherapy, or liver transplantation
- Clinical features:
  - Hepatomegaly, thrombocytopenia, RUQ pain, weight gain, ascites, hyperbilirubinemia

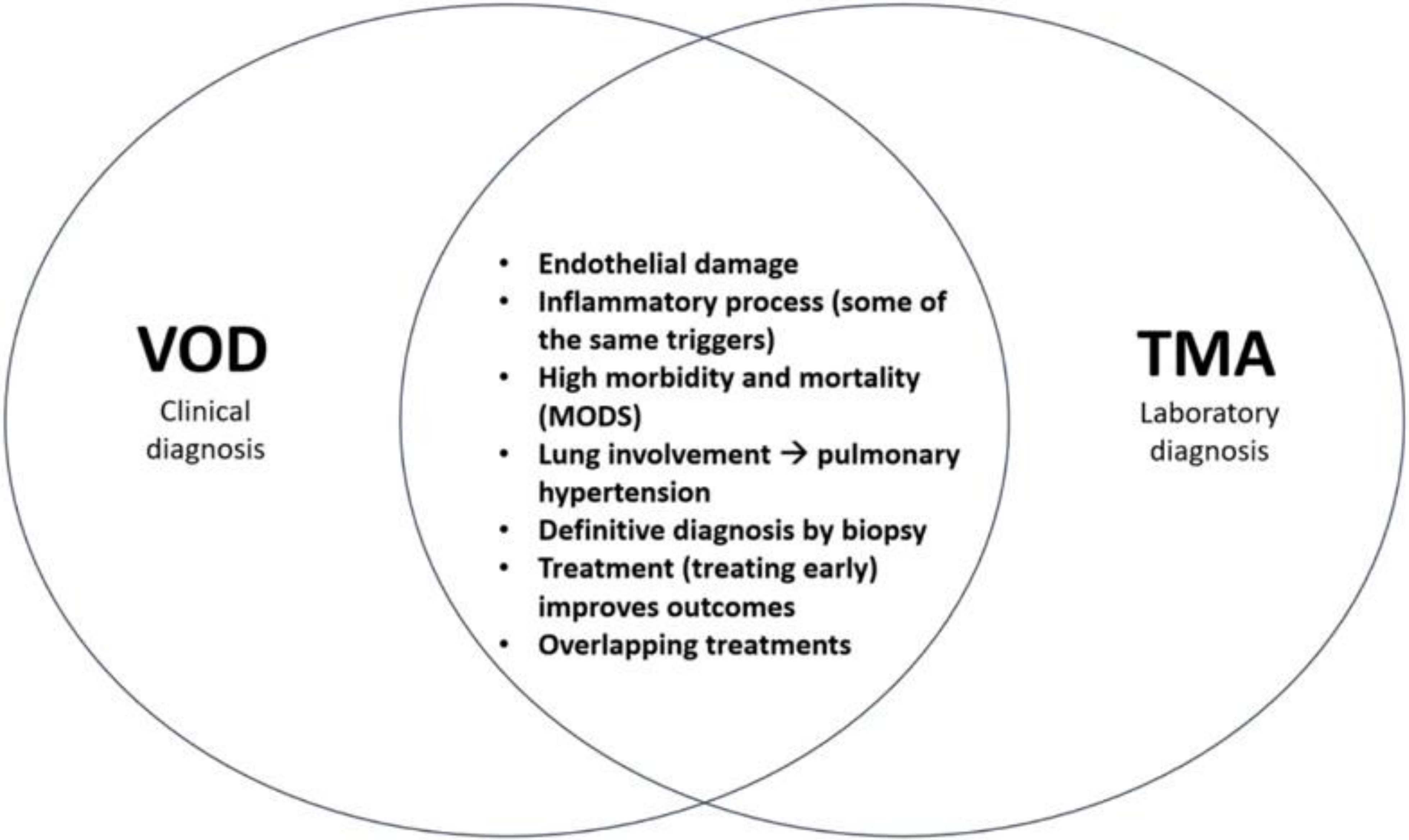
Risk Factors

- Prior and/or current liver dysfunction
- Prior intense chemotherapy and/or radiotherapy
- Younger age, lower body weight (smaller vasculature)
- Certain disorders/diagnoses:
  - HLH
  - Osteoporosis
  - JMML
  - Hemoglobinopathies (sickle cell anemia, thalassemia)

Nutrition Considerations

Treatment for VOD/SOS includes:

- Aggressive diuresis including diuretic drips
  - Often requires reduction in fluid of PN/lipids or EN
    - Use modulars or concentrated formula for tube feeds
- Defibrotide - requires its own dedicated line
  - If additional central line cannot be placed, PN/lipids may reduced significantly or stopped altogether
- Can progress to dialysis


VOD
Clinical diagnosis
TMA
Laboratory diagnosis
• Endothelial damage
• Inflammatory process (some of the same triggers)
• High morbidity and mortality (MODS)
• Lung involvement → pulmonary hypertension
• Definitive diagnosis by biopsy
• Treatment (treating early) improves outcomes
• Overlapping treatments

Transplant-Associated Thrombotic MicroAngiopathy (TA-TMA)

- A clinical syndrome of endothelial injury resulting in microangiopathic hemolytic anemia, consumptive thrombocytopenia, and microvascular thrombosis, which cause organ and tissue ischemia.
  - Can think of it as VOD of kidneys, very similar process. It is immune meditated, endothelial damaged.
- TMA can be generalized, most affected in kidneys because it has tiny vessels and high volume of blood goes through kidneys.
  - Can affect other organ systems: GI, lungs, neurologic
- Complications include:
  - Renal failure, pulmonary hypertension, pericardial effusions, GI bleeding, seizures, PRES, increased infection risk.

Nutrition Considerations

- If needing continuous renal replacement therapy (CRRT), protein and vitamin needs are altered.
  - Protein needs increase (1.5-2.5 gm pro/kg)
  - Carnitine, selenium, copper, vitamin C and B vitamins can be lost
  - PN/lipids: vitamins/minerals can be increased or added
  - EN: may need to add a renal vitamin
- Electrolytes will be adjusted through CRRT dialysate
- Fluid allowance may be reduced requiring concentrated formula or PN

Berger et al, 2024

Acute Graft-Versus-Host Disease (aGVHD)

- aGVHD is a proliferation of donor T cells that recognize the host as foreign
  - Result of the alloreactivity between the donor and recipient as the donor T lymphocytes recognize antigen disparities
  - When marrow/stem cells are transplanted, mature donor T cells get transplanted along with hematopoietic cells
- The onset of aGVHD occurs within the first 100 days after HCT; it usually coincides with engraftment
  - You can have classic (<100 days), late-onset (>100 days), or recurrent/persistent
  - New definitions rely more on the underlying process of aGVHD vs cGVHD, rather than just temporal definition
- The classic target organs of aGVHD include the skin, liver, and gut, although the lungs also can be affected

aGVHD Risk Factors

- Matched related donor at least risk → cord blood → marrow → peripheral blood is at highest risk
  - Higher dose of mature donor T cells
  - T cell depletion protects
- Greater HLA disparity, older age, sex difference and CMV reactivation
- aGVHD increases risk for chronic GVHD (cGVHD)

Prevention/Treatment

- Prevention strategies are aimed at preventing activation of T cells and eliminating mature alloreactive T cells from donor grafts.
  - The two prophylactic methods most commonly used
    - Administration of immunosuppressants to the recipient
    - T-cell depletion of CD34+ selection of the donor graft
- Decreased intensity conditioning regimens
  - Minimize tissue damage and antigen presentation
- First-line treatment of aGVHD is to decrease immunosuppression and initiate a short course of steroids.
  - Can use topical, luminal/enteral, or systemic depending on area affected and grading

aGVHD Staging

Staging and Grading Systems for Graft-Versus-Host Disease				
Staging of Individual Organ System(s)				
Organ	Stage	Description		
Skin	+1	Maculopapular eruption over <25% of body area		
	+2	Maculopapular eruption over 25-50% of body area		
	+3	Generalized erythroderma		
	+4	Generalized erythrodemia with bullous formation and often with desquamation		
Liver	+1	Bilirubin 2.0-3.0 mg/dl		
	+2	Bilirubin 3.1-6.0 mg/dl		
	+3	Bilirubin 6.1-15.0 mg/dl		
	+4	Bilirubin >15.0 mg/dl		
Gut	+1	Diarrhea >30 ml/kg or >500 ml/da		
	+2	Diarrhea >60 ml/kg or >1,000 ml/day		
	+3	Diarrhea >90 ml/kg or > 1,5000 ml/day		
	+4	Diarrhea >90 ml/kg or >2,000 ml/day, or severe abdominal pain and bleeding with or without ileus		
Overall Grading of Acute GVHD				
Grade	Skin staging	Liver staging		Gut staging
I	+1 to +2	0		0
II	+1 to +3	+1	And/or	+1
III	+2 to +3	+2 to +4	And/or	+2 to +3
IV	+2 to +4	+2 to +4	And/or	+2 to +4

Association of Pediatric Hematology/Oncology Nurses. *Essentials of Pediatric Hematology/Oncology Nursing: A Core Curriculum*. 4th ed.

Skin aGVHD

- Pruritis, erythema, maculopapular rash
- Location: initially palms, soles, shoulders, ears
  - Can progress to full body erythroderma
- Course: mild skin changes may wax and wane and resolve without treatment
- Differential Diagnosis: drug rash, viral infection
- Skin biopsy: classic finding is evidence of apoptosis

Liver aGVHD

- Hyperbilirubinemia
  - Also elevated Alk Phos, GGT, AST/ALT
  - Frank hepatic failure and encephalopathy rare
  - Can lead to weight gain, capsular pain, or ascites
- Differential Diagnosis:
  - VOD (can occur as late as 3 weeks or longer)
  - Medication (esp. Azoles)
  - TPN hepatitis
  - Viral infection (CMV, others)
- Liver Biopsy
  - May show segmental disruption of small bile ducts
  - Biliary cell apoptosis, bile duct damage, hepatocyte apoptosis
  - Rule out viral stain/PCR

Gut aGVHD

- Type
  - Lower: diarrhea, cramping pain, paralytic ileus
  - Upper: nausea/vomiting, epigastric pain
- Differential Diagnosis:
  - Slow healing of mucosal damage
  - Infection: HSV, CMV, candida, others
  - Medications
- Imaging: nonspecific bowel wall thickening, vascular engorgement
- Endoscopy
  - May show mucosal ulcerations and crypt apoptosis
  - Provides tissue for cultures
  - Should do upper and lower at same time

Gastrointestinal GVHD Diet Progression

Tables adapted from:

Academy of Nutrition and Dietetics. *Oncology Nutrition for Clinical Practice*. 2nd ed.

Samour & King's Pediatric Nutrition in Clinical Care. 5th ed.

Phase 1: Bowel Rest

Clinical symptoms	*Diet*	*Nutrition Support*
Gastrointestinal (GI) cramping Large-volume, watery diarrhea >500 mL/d Depressed serum albumin Severely reduced transit time Small bowel obstruction or diminished bowel sounds Nausea and vomiting	Oral: NPO	PN with supplemental zinc

Phase 2: Introduction of oral feeding

Clinical symptoms	*Diet*	*Nutrition Support*
Minimal GI cramping Diarrhea <500 mL/d Improved transit time Infrequent nausea and vomiting	Oral: isosmotic, low-residue, low-lactose beverages, initially 60 mL every 2-3 hours, for several days	PN Trophic enteral feeds of semi-elemental formula if patient unable to eat

Phase 3: Introduction of solids

Clinical symptoms	*Diet*	*Nutrition Support*
Minimal or no GI cramping Formed stool	Oral: Allow introduction of solid food, once every 3-4 hours: minimal lactose, low fiber, low fat (20-40 g/day), low total acidity, no gastric irritants -Progression I/Group 1 Diet	Begin to cycle and decrease PN Advance feeds slowly (small boluses or continuous infusion) if patient unable to eat

Phase 4: Expansion of diet

Clinical symptoms	*Diet*	*Nutrition Support*
Minimal or no GI cramping Formed stool	Oral: minimal lactose, low fiber, low total acidity, no gastric irritants; if stools indicate fat malabsorption → low fat -Progression 2/Group 2 Diet	Nighttime supplemental PN if oral intake less than needs or patient unable to maintain weigh owing to malabsorption Enteral feed schedule and formula dependent on any residual GI symptoms

Phase 5: Resumption of regular diet

Clinical symptoms	*Diet*	*Nutrition Support*
No GI cramping Normal stool Normal transit time Normal serum albumin	Oral: progress to regular diet by introducing one restricted food per day; acid foods with meals, fiber-containing foods, lactose-containing foods; order of addition will vary depending on individual tolerances and preferences; patients no longer exhibiting steatorrhea should have the fat restriction liberalized slowly	Discontinue PN Supplemental enteral feeds if patient unable to consume adequate nutrients

Food Group	Group 1 Recommended Foods	Group 2 Recommended Foods
Grains	Toast from white bread, bagels, or English muffins Saltine crackers Graham crackers White dinner rolls Steamed rice Plain noodles Cream of wheat or rice Corn flakes Rice Krispies Pretzels Vanilla wafers	All foods from Group 1
Milk and Milk Foods	None	Lactose-free reduced-fat milk Rice milk Soy milk
Meat and Other Protein Foods	None	Skinless baked chicken breast Turkey Tuna Low-fat ham Baked mild fish (catfish or cod) Hard-boiled egg

Nutrition Care Manual. Graft-vs-Host Disease Nutrition Therapy
https://www.nutritioncaremanual.org/client_ed.cfm?ncm_client_ed_id=255

Food Group	Group 1 Recommended Foods	Group 2 Recommended Foods
Fruit	Banana Applesauce Canned peaches or pears	All fruit from Group 1 Half-strength apple, cranberry, or grape juice (dilute with water)
Vegetables (well-cooked)	Green beans Carrots Plain mashed or baked potato Sweet potato	All vegetables from Group 1
Beverages (noncarbonated)	Gatorade Water	All beverages from Group 1 Boost Pediasure
Fats	None	Butter (1 tsp) Low-fat mayonnaise (1 tsp) Sour cream (1 tsp)
Soups	Chicken, vegetable, or beef broth	All broths from Group 1 Chicken rice soup Chicken noodle soup Ramen noodles made with half of the seasoning packet
Snacks	Popsicles Fruit-flavored gelatin	All from Group 1
Condiments	Salt Sugar Jelly	All from Group 1

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https://www.nutritioncaremanual.org/client_ed.cfm?ncm_client_ed_id=255

Delicate Balance: GVHD vs GVL

- Graft versus leukemia (GVL) is the process in which donor immune cells recognize and eliminate residual malignant cells within the recipient, thereby maintaining remission.
- One of the best examples of GVL is observed after donor lymphocyte infusions (DLI)
  - An established therapy for relapsed disease or incipient/anticipated relapse.
  - DLI involves infusion of peripheral blood lymphocytes from the original HSCT donor into the recipient.

Maurer et al, 2024

Discharge and Follow Up

General Discharge Criteria

- Patient has an absolute neutrophil count (ANC) of 500
- Patient is afebrile and preferably is off IV antibiotics
- Patient is able to take oral medications or receive through EN
- Family is able to care for the central venous line and any nutritional support that is needed
- Any transplant complication is resolved or controlled

Association of Pediatric Hematology/Oncology Nurses. *Essentials of Pediatric Hematology/Oncology Nursing: A Core Curriculum*. 4th ed.

Outpatient Follow Up

- Outpatient follow-up appointments are tailored to meet the needs of the patient.
  - The frequency of clinic visits is based on the type of transplant, engraftment status, and unresolved complications
- Patients who receive an autologous transplant usually do not have to be followed as closely as patients who receive allogeneic transplants
  - Care can be transferred to the referring oncologist when engraftment has occurred and HCT complications have been resolved
- Patients who receive an allogeneic transplant are followed closely by the HCT team for the first 100 days, seen regularly for the first year after transplantation, and are seen annually thereafter

Readmission to the Hospital

- Fever
- Infection that requires intravenous antibiotics
- New onset or flare-up of GVHD
- Active bleeding
- Respiratory distress
- Uncontrolled hypertension
- Uncontrolled vomiting, diarrhea, or dehydration
- Alteration in mental status or seizures

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Late Complications and Survivorship

After 100 days

Chronic Graft-Versus-Host-Disease (cGVHD)

- cGVHD is a chronic immune disorder that occurs between 100 days and 2 years after HCT
- Risk factors include:
  - Prior aGVHD
  - Donor-recipient HLA disparity
  - Older patient age
- Can affect any body system, but typically tissues that form the physical immune barrier between the host and potential infectious pathogens
  - Skin, liver, eyes, pulmonary tract, mouth, GI tract, and genital tract.

Symptoms

- Difficulty eating and malnutrition
  - Malnutrition is a significant complication for patients with cGVHD
    - Xerostomia, dental abnormalities
    - Gastrointestinal strictures
- Additional symptoms include elevated liver enzymes and bilirubin, obstructive lung disease, contractures, immunosuppression, and thrombocytopenia

Treatment

- Treatment consist of immunosuppressant therapy that includes many of the same agents used to treat aGVHD
- Several new agents are available for the treatment of cGVHD of the skin, both psoralen and ultraviolet radiation (PUVA) and extracorporeal photophoresis (ECP) have been beneficial
- Use of PUVA and ECP can allow early tapering or discontinuation of steroids

Nutrition Impact Symptoms of Chronic GVHD

Oral	
Nutrition impact symptom	Increased sensitivity Xerostomia Dysphagia (due to esophageal webbing or stricture)
Manifestations	Affects ability to chew and to swallow food properly Reduced variety of foods in diet.
Medical nutrition therapy	For dysphagia, refer to a speech pathologist for swallowing evaluation Esophageal dilation for severe symptoms Gastrostomy tube for enteral nutrition if oral or esophageal symptoms preclude adequate calorie-protein intake for weight maintenance and support
Gastrointestinal	
Nutrition impact symptoms	Abnormal intestinal mucosa Intestinal bile salt deficiency Pancreatic enzyme insufficiency or atrophy Bacterial overgrowth
Manifestations	Diarrhea Nutrient malabsorption
Medical nutrition therapy	Screening tests (fecal elastase or serum trypsinogen) to confirm fat malabsorption Oral pancreatic enzyme replacement therapy Dietary fat restriction Supplementation with products containing medium-chain triglycerides
Pulmonary	
Nutrition impact symptoms	Pulmonary insufficiency
Manifestations	Increased metabolic demands leading to increased energy requirement to prevent weight loss and debilitation
Medical nutrition therapy	Monitor nutritional status closely

Academy of Nutrition and Dietetics. *Oncology Nutrition for Clinical Practice*. 2nd ed.

Growth and Development

- Growth and development in children undergoing HCT should be assessed regularly.
- Decreased growth velocity, growth hormone deficiency, and delayed onset of puberty occur frequently in children who have had HCT.
    - Occur in most children who receive total body irradiation or steroid therapy or who have GVHD
- When abnormal endocrine function is detected, initiation of appropriate hormone therapy may improve growth and development.

Academy of Nutrition and Dietetics. *Oncology Nutrition for Clinical Practice*. 2nd ed.
Chow et al, 2016
Sanders, 2008

Cardiometabolic Changes

- Cardiometabolic changes, including:
  - Central adiposity, hypertension, insulin resistance, and dyslipidemia
- Pediatric HCT survivors are more likely to develop diabetes and hypertension than the general population and should be monitored throughout adulthood.
- **Nutrition Consideration**:
  - Referral to a registered dietitian nutritionist for nutritional counseling

Academy of Nutrition and Dietetics. *Oncology Nutrition for Clinical Practice*. 2nd ed.
Chow et al, 2010
Chow et al, 2016
Hoffmeister et al, 2004
Kida et al, 2012

Vitamin D Deficiency and Insufficiency

- Vitamin D deficiency and insufficiency are common following HCT
- Emerging data suggest a potential benefit of vitamin D supplementation in reducing chronic GVHD, due to vitamin D's immunoregulatory properties in certain genotypes.
- **Nutrition Considerations**:
  - Draw vitamin D levels prior to transplant and supplement if needed
  - If unable to draw vitamin D during pre-transplant work up, draw at admission and begin supplementation
    - Vitamin D can be supplemented during transplant
  - Optimize levels and supplementation post transplant

Academy of Nutrition and Dietetics. *Oncology Nutrition for Clinical Practice*. 2nd ed.
Carrillo-Cruz E et al, 2019
Khan et al, 2021

Bone Disease

- Prevalence is as high as 50% as early as 1 year after transplantation.
- Chemotherapy, TBI exposure, calcineurin inhibitors, and glucocorticoids all contribute to bone loss.
- May require bisphosphonate therapy
- **Nutrition Considerations**:
  - Ensure adequate calcium and vitamin D intake to both prevent and manage bone disease
    - Draw vitamin D and ionized calcium levels
    - Provide supplementation of calcium and vitamin D if needed
  - Encourage patients to engage in regular weight-bearing and muscle-strengthening exercises

Chow et al, 2016
Tauchmanova et al, 2007

Endocrine Dysfunction

- Thyroid dysfunction
  - The result of increased thyroid-stimulating hormone and decreased thyroxin levels caused by TBI; treatment is thyroid replacement therapy
- Growth and developmental delays
- Ovarian dysfunction
  - Involves more permanent infertility and menopausal symptoms in females who receive chemotherapy after puberty than in those who receive chemotherapy before puberty; TBI can results in primary gonadal failure in females regardless of their age
- Testicular dysfunction
  - Includes sterility, azoospermia, and premature ejaculation in males who are treated with TBI; treatment can include hormone replacement therapy; TBI results in primary gonadal failure in males regardless of their age.

Association of Pediatric Hematology/Oncology Nurses. *Essentials of Pediatric Hematology/Oncology Nursing: A Core Curriculum*. 4th ed.
Chow et al, 2016

Secondary Malignancies

- Secondary malignancies can occur after autologous and allogeneic transplant.
- Transplant recipients have a two- to sevenfold increased risk of developing a secondary malignancy.
- Primary causes include high-dose chemotherapy, TBI, immune suppression, and Epstein-Barr virus (EBV).
- Common malignancies include leukemia, myelodysplastic syndrome (MDS), and EBV-lymphoproliferative disease.
- Leukemia and MDS are most common after autologous transplantation.
- The risk of secondary cancer persists for several years post transplantation and is reported to be as high as 11% at 15 years.

Bollard et al, 2011
Chow et al, 2016

Recurrence of Disease

- Despite intensive chemotherapy and radiation therapy, relapse does occur.
- The incidence of relapse varies with diseases treated with transplant and phase of disease at transplantation.
- The relapse rate for patients transplanted in remission is 15-40%.
- For patients with advanced disease who are transplanted, relapse rates can be as high as 80%.
- Most patients who relapse do so within the first year after transplantation.
- Although long-term prognosis is poor, some centers offer second transplants to the leukemia patient who can attain remission with induction chemotherapy.

Antier et al, 2024
Barrett et al, 2010
Dahllof et al, 2008

Clinician Resources

Books:
The A.S.P.E.N. Adult Nutrition Support Core Curriculum
The A.S.P.E.N. Pediatric Nutrition Support Core Curriculum
Essentials of Pediatric Hematology/Oncology Nursing: A Core Curriculum
Oncology Nutrition for Clinical Practice
Samour & King's Pediatric Nutrition in Clinical Care
Texas Children's Hospital Pediatric Nutrition Reference Guide

Website:
https://www.uptodate.com/contents/search

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Questions?