Nutritional Management in Adult Hematopoietic Stem Cell Transplant

HEATHER KASBERG, RN, MSN, OCN®, and AUTUMN DILIGENTE, MS, RD, LD

From University Hospitals Case Medical Center, Cleveland, Ohio; Case Western Reserve University, Frances Payne Bolton School of Nursing, Cleveland, Ohio; and Seidman Cancer Center, Cleveland, Ohio

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Correspondence to: Heather L. Kasberg, RN, MSN, OCN®, Hematology/Oncology and Bone Marrow Transplant, University Hospitals Case Medical Center, 11100 Euclid Ave, Cleveland, OH 44106. E-mail: Heather.Kasberg@gmail.com

Abstract

Hematopoietic stem cell transplant (HSCT) patients are at risk for and vulnerable to malnutrition throughout all phases of the transplant process. Patients can develop symptoms that make it difficult to maintain a balanced fluid, electrolyte, and nutrition status. Symptoms such as poor appetite, severe mucositis, and the complication of acute graft-vs.-host disease may develop as a result of this intensive therapy. These symptoms frequently lead to malnutrition, which has an impact on the physical, psychological, social, and spiritual well-being of patients and caregivers. This article highlights the importance of pretransplant screening and ongoing nutritional assessment, as well as the management of common complications and symptoms affecting nutritional status. Emphasis is placed on nutritional issues related specifically to patients during the acute phase of HSCT. Advanced practitioners caring for patients undergoing HSCT should work closely with a registered dietitian to develop a nutritional management plan that will prevent malnutrition and enhance the quality of life of patients and their families.

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Malnutrition, which is seen in anywhere from 20% to 80% of oncology patients, has been associated with reduced response to treatment, survival, and quality of life (Kubrak & Jensen, 2007). Hematopoietic stem cell transplant (HSCT) patients are at risk for and vulnerable to malnutrition. Advanced practitioners (APs) must work closely with nutrition colleagues to assess nutritional needs, address deficiencies, and educate patients and families about the importance of nutritional support (Ezzone, 2009).

Hematopoietic stem cell transplant involves the administration of cytotoxic chemotherapy followed by the infusion of hematopoietic progenitor cells from one's self or donors. Following transplant and throughout the recovery phase, patients can develop symptoms that make it difficult to maintain a balanced fluid, electrolyte, and nutrition status. Symptoms such as poor appetite, severe mucositis, and acute graft-vs.-host disease (aGVHD) can develop as a result of the intensive therapy and may prolong the time to reintegration into pretransplant life, severely affecting quality of life (Jatoi, Loprinzi, & Kelly, 2009). These symp-

toms frequently lead to malnutrition, which may impact the physical, psychological, social, and spiritual well-being of patients (Jarden, Baadsgaard, Hovgaard, Boesen, & Adamsen, 2009).

The AP should assess the patient's nutritional status prior to transplantation. A dietician should be consulted for those who are identified as malnourished so that they can begin nutritional supplementation in the pretransplant period. Impaired nutritional status prior to transplant is a negative prognostic indicator of long-term survival for HSCT patients (Muscaritoli, Grieco, Capria, Iori, & Rossi Fanelli, 2002). Artificial nutritional support is considered the standard of care for HSCT patients, but there is a lack of current clinical practice guidelines for its implementation in this patient population (Muscaritoli et al., 2002). The purpose of this article is to highlight the importance of pretransplant screening, ongoing nutritional assessment, and the management of common complications and symptoms, while addressing nutritional issues related specifically to patients in the acute phase of HSCT.

Methods

We conducted a literature search to identify evidence-based practice for nutritional supplementation in the transplant population. The Cochrane Database of Systematic Reviews, PubMed, Cinahl, and UpToDate were all reviewed. Clinical guidelines for oncology and bone marrow transplant patients, published by the American Dietetic Association (ADA) and the American Society of Parenteral and Enteral Nutrition, were reviewed. However, data were found to be limited and often outdated, supporting the need for further research in this area.

The conceptual framework that guided the recommendations in this article is the Quality of Life Model for Bone Marrow Transplantation Pa-

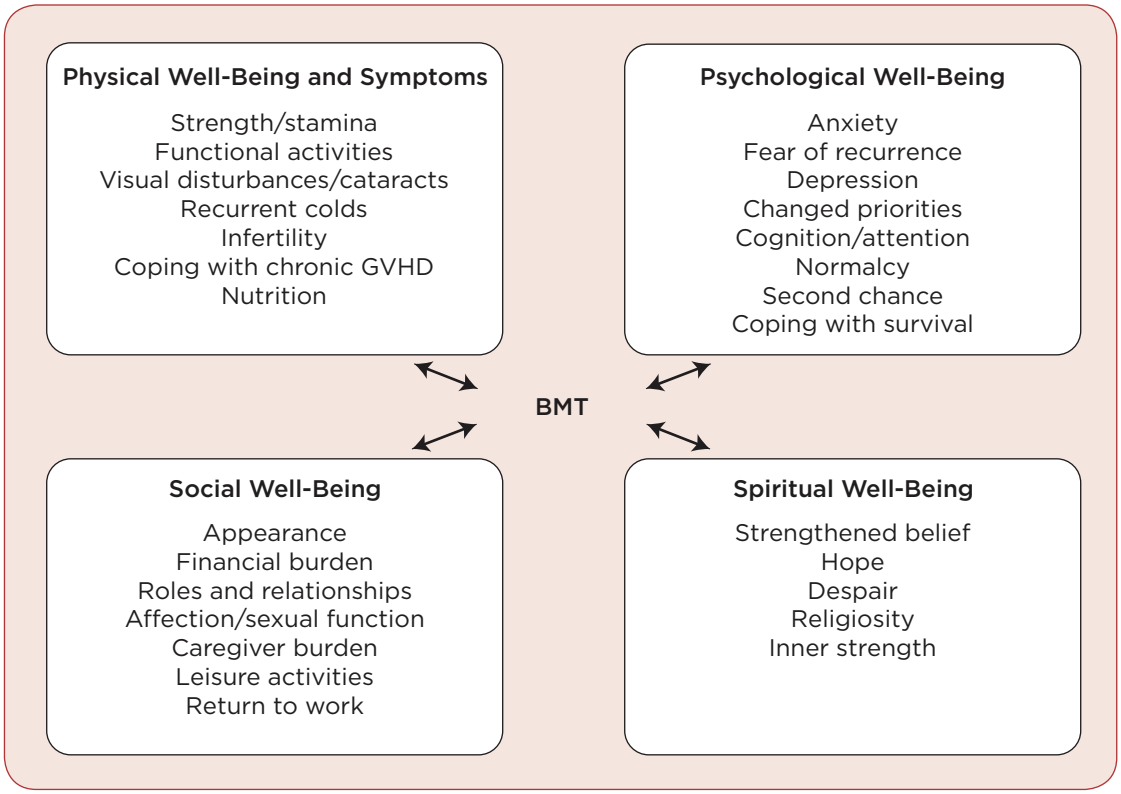

Figure 1. Conceptual framework utilized to support the need for quality nutritional care is the Impact of BMT on Quality of Life Model from City of Hope Pain and Palliative Resource Center. The model states nutrition is an integral part of attaining quality of life after bone marrow transplant, which affects physical well-being and symptoms. BMT = bone marrow transplant; GVHD = graft-vs.-host disease. Used with permission from Marcia Grant, DNSc, FAAN, and Betty Ferrell, PhD, FAAN, City of Hope Medical Center (2010).

tients from the City of Hope Pain and Palliative Resource Center; see Figure 1 (Grant & Ferrell, 2010). The model supports maintaining nutrition as an integral part in attaining quality of life (QOL) after bone marrow transplant. Although nutrition fits into the physical QOL domain of this model, physical QOL impacts social, psychological, and spiritual domains of QOL as well. This model is specific to the HSCT population.

Pretransplant Nutritional Assessment

An initial nutritional screening may be done by the AP, but it is recommended that a comprehensive pretransplant nutritional assessment be performed by a trained registered dietitian (Raynard et al., 2003). However, even for the dietitian, evaluating the degree of malnutrition in HSCT is difficult due to the lack of a "gold standard" for defining nutritional status (Jacobson, Parekh, & Kalaycio, 2006). An interdisciplinary approach to addressing nutritional deficiencies should include input from the nurses, physicians, pharmacists, and other team members.

The AP's screening should include questions pertaining to changes in appetite, oral pain or lesions, nausea, vomiting, early satiety, and alterations in bowel patterns (Raynard et al., 2003). When performing a nutritional assessment, it is important to note physical signs and symptoms that affect nutritional status. Signs such as temporal wasting, peripheral edema, ascites, and muscle wasting are often seen in the malnourished. Loss of muscle mass caused by malnutrition can lead to muscle atrophy, decreased stamina, and increased risk of skin breakdown, as well as altered GI or respiratory function (Raynard et al., 2003). There is no need to perform anthropometric measurements. These measurements have been shown to be inaccurate because they are often altered by fluid and electrolyte disturbances (Jacobson et al., 2006).

Weight is an important physical finding in the assessment of nutritional status. The AP should assess for weight change over time, as it is a reliable method for determining nutritional status in cancer patients. A weight reduction of 5% to 10% over 1 to 6 months is considered a significant nutritional risk for malnutrition (Jacobson et al., 2006). In addition, it has been shown that patients who have an ideal body weight (IBW) of 85% to 95%, or less than 85%, have an increased relative risk of mortality: 1.25 or 2.11, respectively (Horsley, Bauer, & Gallagher, 2005).

A 2008 study demonstrated a significant negative relationship between a patient's body mass index (BMI) and time to transplant engraftment ($p = .0001$). Engraftment of underweight patients was 3.0 days ($p = .002$) and 4.0 days ($p < .001$) later than normal for overweight and obese patients, respectively (Hadjibabaie et al., 2008). Since rapid engraftment is desirable, maintaining patients' baseline BMI can significantly reduce the window of time during which they are at risk for life-limiting postchemotherapy and transplant side effects.

Biochemical measurements used to monitor visceral protein status do not accurately reflect changes in nutrition status. These measurements, which include retinol binding protein, albumin, prealbumin, and transferrin, are influenced by fluid status and other non-nutrition variables such as infection and liver or renal insufficiency. Although the above biochemical parameters can be affected by a multitude of factors, the timing of the measurement of these parameters for specific patients may be helpful in making a decision about initiation of nutrition support (Rzepecki, Barzal, Sarosiek & Szczylik, 2007).

The Scored Patient-Generated Subjective Global Assessment (PG-SGA) is a tool used by the patient, the AP (or other clinician), and the dietitian to assess a patient's nutritional status and provide specific patient recommendations (Ottery, 2005). Sensitivity and specificity of its use in cancer patients is referenced by recent studies; it is also supported by the American Society of Clinical Oncology as a reliable screening tool in oncology patients (Vigano, Trutschnigg, Morais, Chaudhury, & Lucar, 2009). This tool enables nutrition status to be assessed quickly, and the appropriate nutrition support to be implemented, although it is not specific to the HSCT population (Vigano et al., 2009). It assesses percent weight

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Use your smartphone to view the scoresheet for the PG-SGA nutrition screening tool.

loss over a 6-month period, disease specifics, the presence of wounds and fistulas, and specific metabolic demands (i.e., fever, use of corticosteroids), and evaluates body composition, fat, muscle, and fluid status using the results of a physical exam (Vigano et al., 2009). In addition to the clinician's portion of the PG-SGA, there is a second section that is designed to be completed by the patient (Horsley et al., 2005). This patient-completed section assesses weight loss, food intake, nutrition symptoms, and functional capacity.

For each component of the PG-SGA, points (0–4) are awarded depending on the impact on nutritional status. Typical scores range from 0–35, with a higher score reflecting a greater risk of malnutrition and scores below 9 indicating a critical need for nutrition intervention (Horsley et al., 2005). Moreover, the total PG-SGA score is used to define the need for a dietitian consult and specific nutrition interventions, including patient and family education, symptom management, and appropriate nutrient intervention (food, nutritional supplements, or parenteral or enteral nutrition). Routine nutrition assessment of patients should be conducted by the dietitian at least once weekly throughout the patient's transplant stay (Horsley et al., 2005; Ottery, 2005).

Pretransplant Nutritional Intervention

Starting nutritional support earlier with supplements during the conditioning regime time period is desirable in order to achieve or maintain at least 95% of the patient's IBW. However, the best time to initiate supplemental nutrition support during the peritransplant period has not been studied in randomized controlled trials and warrants further research (Roberts & Mattox, 2007). For patients who are unable to intestinally absorb adequate nutrients for a prolonged period of time, parenteral nutrition intervention should be considered to minimize risk of poor outcomes associated with malnutrition. A "prolonged period" is defined as 7 to 14 days without baseline caloric intake, although better-designed studies are needed to support the evidence for this timeframe (Roberts & Mattox, 2007).

Hematopoietic Stem Cell Transplant

There are two main subdivisions of HSCT, depending on the origin of the cells: allogeneic (Allo, or from nonself) and autologous (Auto, from self). The type of transplant a patient has depends upon disease characteristics, patient characteristics, and prior therapy. Nutritional intervention may vary based on the type used, as the side effects may be different or may appear on a different timeline. Although the success of Allo transplantation has improved, in large part due to reduced intensity conditioning regimes, it is associated with higher morbidity and mortality than Auto transplantation (Jarden et al., 2009).

Because Allo transplants are more complex, patients tend to spend a much longer time in the hospital. The average length of stay is 35 days for Allo transplant patients, whereas Auto patients' average length of stay is 18 days (Mishra, Vaaler, & Brinch, 2001). Allo transplant patients receive high-dose cytotoxic drugs used for removal of all disease (or as much disease as possible) from the bone marrow, followed by the infusion of donor stem cells. Without reinfusion of the grafted stem cells, hematopoiesis is not possible, and the patient would not be able to survive in an aplastic state.

After achieving a complete remission through chemotherapy and/or radiation, in patients undergoing an Auto transplant, hematopoietic stem cells are collected, followed by the administration of high-dose chemotherapy to reduce the bone marrow in order to allow for the engraftment of their own stem cells (Muscaritoli et al., 2002). Engraftment is defined as an absolute neutrophil count (ANC) greater than 500 cells/μL for 2 consecutive days, or an ANC of 1,000 cells/μL for 1 day (Antin & Yolin-Raley, 2009).

Time to engraftment for an Auto transplant is between 9 and 25 days, and time to engraftment for Allo transplants is between 10 and 40 days, depending on the source of the donor stem cells (Antin & Yolin-Raley, 2009). Protocols that utilize granulocyte colony-stimulating factor (G-CSF) account for significantly reduced time to engraftment and a reduction in the severity of neutropenia and mucositis (Antin & Yolin-Raley, 2009).

Posttransplant Nutritional Concerns for HSCT Patients

Negative nitrogen balance is a common problem for HSCT patients as a consequence of intestinal losses, such as diarrhea and emesis, with catabolic effects on muscle mass (Hadjibabaie et al., 2008). Nutritional deficits can result from trans-

plant, including chemotherapy-induced nausea, vomiting, diarrhea, anorexia, mucositis, early satiety, dysgeusia, xerostomia, neutropenic fevers, and septicemia. Complications and side effects specific to Allo HSCT include aGVHD and sinusoidal obstructive syndrome (SOS), which critically intensify the need for increased calories (Negrin, 2010). A reduction in the number of days patients are severely neutropenic allows for fewer days of severe mucositis, improving the ability to take in oral nutrition; however, patients may continue to have taste and sensation changes well after the engraftment phase (Muscaritoli et al., 2002).

Acute Graft-vs.-Host Disease

Acute GVHD, which can be one of the most devastating complications of Allo HSCT, is usually seen within the first 100 days of transplant. The gut, liver, and skin are the most affected organs in aGVHD. Common symptoms are nausea, vomiting, abdominal pain, anorexia, and diarrhea, which often severely impact nutritional status. Acute GVHD is scaled by organ, then graded on a scale of I through IV, with IV being the most severe. Clinicians often use the Glucksberg Scale for accurate grading of aGVHD (see Table 1). Relative risk of transplant-related mortality and risk of treatment failure appears to correlate with aGVHD staging (Antin & Yolin-Raley, 2009).

The National Cancer Institute (NCI) recommends bowel rest followed by a GVHD diet that includes food low in acid, fat, lactose, caffeine, and fiber to minimize GI irritation and promote wound healing. Examples of acceptable aGVHD foods are broth, Pedialyte, Jell-O, and Popsicles. Patients are able to slowly increase the complexity of food choices as long as GI symptoms are well controlled on clear liquids. New foods should be added one at a time to check for tolerance. Most patients require total parenteral nutrition (TPN) and lipids during this time period for nutritional support (National Cancer Institute, 2010).

MANAGEMENT STRATEGIES

The management of symptoms is crucial for improving nutritional deficits and may help increase the patient's ability to take in more food by mouth (Roberts & Mattox, 2007). Interventions to decrease the severity of these symptoms may allow patients to increase oral intake, which is the safest and most preferred means of nutritional intake (Roberts & Mattox, 2007). An overview of

Table 1. Acute GVHD—Modified Glucksberg Scale for Grading Acute GVHD

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Gut	< 50 mL diarrhea/day or persistent nausea	500–999 mL diarrhea/day or persistent N/V	1,000–1,500 mL diarrhea/day +/- N/V	1,500–2,000 mL/day	> 2 L diarrhea/day, abdominal pain
Liver	Bilirubin 2–3 mg/dL	Bilirubin 3–6 mg/dL	Bilirubin 6–15 mg/dL	Bilirubin 6–15 mg/dL	Bilirubin > 15 mg/dL
Skin	No GVHD rash	Maculopapular rash on < 25% of skin; no associated symptoms	Rash on 25%–50% of skin with pruritus or other associated symptom	Macular, papular, or vesicular eruption with bullous formation or desquamation of > 50% of skin	Generalized erythroderma with bullous formation

Acute GVHD Grading

	Skin		Liver		Gut
Grade I	Stage 1–2		None		None
Grade II	Stage 3	or	Stage 1	or	Stage 1
Grade III	–		Stage 2–3	or	Stage 2–4
Grade IV	Stage 4	or	Stage 4		–

Note. GVHD = graft-vs.-host disease; N/V = nausea and vomiting. Used with permission from Joseph Antin, MD, and Deborah Yolin-Raley, MS, PA-C, *Manual of Bone Marrow and Stem Cell Transplantation,* 2009.

Table 2. Symptom Management in Acute GVHD

Anorexia
Oral nutritional supplements
Eat small amounts to increase appetite
Trial appetite stimulant
Early satiety
Small frequent meals
Serve meals on smaller plates
Eat solids before drinking liquids
Dysgeusia
Attempt different flavors and spices
Supplement zinc
Avoid meats or add lemon to flavor
Dilute juice if too sweet
Mucositis and thrush
Oral care every 2–4 hours
Antifungal rinse
Avoid salty, spicy, and acidic foods
Avoid rough textured foods
Avoid alcohol and carbonated beverages
Avoid extreme temperatures
Xerostomia
Frequent oral care
Mouth moisturizer
Oral fluids
Sour flavors to stimulate saliva production
Avoid breads and meats unless in gravy
N/V and diarrhea
Antiemetics
Antidiarrheals
IV hydration
Introduce bland foods
Focus on cold foods, minimal smell

Note. N/V = nausea and vomiting. Interventions recommended by the American Society for Parenteral and Enteral Nutrition (ASPEN) for the management of post-BMT symptoms (Roberts & Mattox, 2007).

symptom management strategies is provided in this section (see Table 2).

Anorexia can be distressing to patients and caregivers. Recommendations for management include eating small frequent meals to increase appetite and including oral nutritional supplements. Patients with anorexia should be started on an appetite stimulant with careful titration when failure to thrive is suspected. Medications such as megestrol acetate or low-dose dexamethasone (off label) may be helpful appetite supplements, but are not without risk (Roberts & Mattox, 2007).

Patients with dysgeusia should avoid meat due to its leathery, metallic flavor; adding lemon to fish or chicken may help to mask this flavor. Diluting drinks may also be helpful in reducing the intensity of some flavors. Zinc supplementation has also been shown to be helpful (Roberts & Mattox, 2007).

Xerostomia can be combatted with oral care every 2 to 4 hours, mouth moisture, and an increase in oral fluids. It is also helpful to suggest sour flavors to stimulate saliva production. Patients should avoid spicy, salty, and acidic foods as well as foods with extreme temperatures and rough textures. Avoid foods that soak up moisture such as breads and meats unless they are in gravy. Attempting different flavors may be helpful to assist patients with food choices (Roberts & Mattox, 2007).

Mucositis and thrush, which are common during the immunosuppressive phase, can be treated with routine saline oral rinsing, soft tooth brushing, and nystatin rinsing as needed (Roberts & Mattox, 2007). The AP should teach patients about the importance of frequent oral care. The use of medicated oral rinses such as lidocaine or the administration of intravenous opioids has been shown to be helpful in pretreating oral pain in order to allow for patients to tolerate oral feeding (Roberts & Mattox, 2007).

Nausea, vomiting, and noninfectious diarrhea can be managed with antiemetics and antidiarrheals. Intravenous fluids are recommended to prevent dehydration and replace lost fluids. Patients should be reminded to eat for pleasure, so as not to develop negative associations with eating. When patients are ready to begin oral intake, they should begin with bland foods. If smell triggers nausea and vomiting, patients should start with cold foods, which generally carry a minimal smell.

Management With Nutritional Therapies and Side Effects

VITAMIN AND MINERAL NEEDS

For individuals not receiving supplemental nutrition support, iron-free oral multivitamin and mineral supplements that do not exceed 100% of the RDA are recommended. Iron is contraindicated in patients receiving red blood cell transfusions due to the risk of iron overload. In addition to a multivitamin, additional calcium supplementation is recommended for all people as regular health maintenance (Lenssen & Aker, 2002). In February 2011, the Institute of Medicine (IOM) released data stating that HSCT patients are at high risk

for osteoporosis, and that supplementation with calcium 1,200 mg/day and vitamin D 600 IU/day is necessary to prevent osteoporosis in patients who are < 70 years old (IOM, 2011). For individuals receiving corticosteroids, calcium 1,500 mg/day is recommended by the ADA (Lenssen & Aker, 2002). For optimal absorption, the dosage should be divided into two to three doses per day, only 500–600 mg per dose, and separate from the multivitamin. For individuals with diarrhea (stool output greater than 500 mL/day), additional zinc is needed to replenish losses (Lenssen & Aker, 2002). Serum copper values should be monitored when additional zinc is being provided, and replaced if low (Lenssen & Aker, 2002).

ORAL DIET AND SUPPLEMENTATION

During the conditioning and neutropenia phases, oral intake is relatively inadequate, as GI side effects limit tolerance to many food and beverages (Lenssen & Aker, 2002). Oral nutrition supplements can also be considered for those who find it difficult to tolerate solids. As a result of altered taste, many patients find it difficult to ingest oral supplementation drinks. For patients experiencing nausea and diarrhea, cold food items, small frequent meals, and lactose limitation may help to reduce the exacerbation of these symptoms. There are still no concrete data recommending one oral supplement over another.

LOW-MICROBIAL DIET (NEUTROPENIC DIET)

Early studies focused on the need to supply low-microbial diets to transplant patients (Gauvreau-Stern, Cheney, Aker, & Lenssen, 1989; Dezenhall, Curry-Bartley, Blackburn, De Lamerens, & Khan, 1987). However, there is limited and inconclusive evidence to support the need for this type of diet in the HSCT population. One study suggested a reduced incidence of infection in patients who received a sterile diet (Levine, Siegel, & Schreiber, 1973); however, a later study indicated no difference (Dietrich, Gaus, Vossen, van der Waajj & Wendt, 1977). A small randomized, controlled trial that compared a low-microbial neutropenic diet to the US Food and Drug Administration's general food safety guidelines indicated no additional benefit for the neutropenic diet in pediatric patients receiving myeloablative chemotherapy (Moody, Findlay, Mancuso, & Charleson, 2006).

Similar results were also found in a study of cooked vs. noncooked diets in patients undergoing remission induction therapy for acute myelogenous leukemia (Gardner et al., 2008). Participants placed on a noncooked diet did not have higher infection rates than those receiving a cooked diet (Gardner et al., 2008). The rates of infection and death were also similar between the two groups. Thus, the use of a low-microbial diet may pose unnecessary dietary restrictions, compounding the problem of diminished oral intake (Sheean, 2005).

Many transplant centers have liberalized the low-microbial diet, allowing thoroughly washed fresh fruits and vegetables, except for lettuce and sprouts (lettuce grows close to the ground where bacteria from irrigation systems thrive; bacteria growing on sprouts are difficult to remove). In addition to these recommendations, it is important to provide general guidelines regarding safe food-handling practices, as determined by the Centers for Disease Control, to help prevent food-borne illness.

ENTERAL FEEDING

Enteral nutrition (EN) supplementation may be used to support patients with an inability to take in oral nutrition, such as failure to thrive and anorexia-cachexia syndrome. Patients must have intact GI mucosa with normal function for absorption of the formula (Duro, Collier, & Duggan, 2010). Feedings can be infused through either a nasogastric (NG), gastrostomy, nasoduodenal, or nasojejunal (NJ) tube. However, this mechanism is rarely used in the immediate posttransplant time because of the difficulty of placing NG and percutaneous endoscopic gastrostomy tubes in the presence of mucositis, thrombocytopenia, nausea, and vomiting.

Most enteral nutrition trials have been conducted in the pediatric transplant population. In one randomized trial (Szeluga, Stuart, Brookmeyer, Utermohlen, & Santos, 1987), 57 children and adult allogeneic transplant patients received either TPN or nasoenteral feeds. No differences were found in hematologic recovery or survival. Greater oral intake was documented for the enteral vs. the TPN group posttransplant. The TPN group demonstrated a statistically significant weight gain at 28 days posttransplant vs. the enteral group (Sheean, 2005). The use of EN and oral feeding prevents mucosal atrophy by pro-

viding the gut with volume. Patients followed at home were found to have a larger volume of oral feeding with minimal use of TPN, whereas patients in the acute care setting were found to be unable to take in daily oral feeds (Mattsson, Westin, Edlung, & Remberg, 2006).

Aspiration pneumonia is an unfortunate and preventable complication of enteral feedings. Sefcick et al. (2001) found that safe insertion of tubes into the jejunum instead of the stomach or duodenum decreased the risk of aspiration pneumonia. The researchers noted that providing NJ feeding posttransplant was well tolerated, although the number of patients able to maintain weight was not increased. Seguy et al. (2006) recommended inserting the NJ tube during the first week after transplant, prior to the onset of mucositis, with a gradual increase in the rate of feeding to help overcome gastroparesis. The benefits of EN vs. PN include a reduced incidence of bacteremia and the provision of volume to the mucosa, therefore preventing atrophy of the gut (Sefcick et al., 2001). More research addressing feeding tube insertion in the adult patient prior to the neutropenic phase is needed (Jacobson et al., 2006).

TOTAL PARENTERAL NUTRITION

Parenteral nutrition consists of the infusion of calories, amino acids, electrolytes, vitamins, minerals, trace elements, and fluids through a parenteral route (Seres, 2009). Total parenteral nutrition is still widely used for the support of patients with transplant-related complications, mostly related to the gastric absorption–related side effects of transplant (Muscaritoli et al., 2002). Evaluating the effect of TPN in HSCT patients is difficult because of patient and treatment heterogeneity (August & Huhmann, 2009). Studies of TPN vs. solid oral diet have shown increased morbidity, hyperglycemia, and delayed time to engraftment with the use of TPN (Szeluga et al., 1987). In addition, there appear to be no differences in incidence or severity of aGVHD with the use of TPN (August & Huhmann, 2009).

A Cochrane review was done to establish the efficacy of EN or TPN support for patients undergoing bone marrow transplants. Data comparing TPN with EN is lacking (Murray & Pindoria, 2008). Clinical practice has taken advantage of administering TPN to transplant patients because of convenient central IV access, which is required due to the high osmotic load of the solution (Seres et al., 2009). In addition, TPN allows for better modulation of fluids, electrolytes, vitamins, and minerals in the presence of aGVHD and SOS for patients requiring frequent individualized nutritional adjustments (Muscaritoli et al., 2002). However, nutrition support is appropriate for patients who develop moderate to severe aGVHD with poor oral intake or those who are anticipated to be unable to ingest or absorb nutrients for a prolonged period of time (August & Huhmann, 2009).

Lipids may assist in achieving energy or caloric goals for patients who experience hyperglycemia secondary to steroid administration or infection (Muscaritoli et al., 2002). Exogenously administered essential fatty acids may play an important role in inflammation and synthesis of prostaglandins and leukotrienes, which play a role in aGVHD. Administration of IV lipids has been associated with a decrease in aGVHD rates in Allo transplant patients (Muscaritoli et al., 2002). Amino acids are added to solutions to address an increased need for protein metabolism. The timing of nutritional interventions may play a critical role in determining outcomes of HSCT patients (Muscaritoli et al., 2002).

After much research, the role of additives such as glutamate is unclear. In a study with the objective of evaluating the effect of glutamine in TPN solution for HSCT patients, researchers discovered there was no statistical difference in length of hospital stay, duration of antibiotic use, or hepatic enzyme levels for patients in this study, whether or not they received glutamine in their TPN (Perez et al., 2010).

Metabolic Side Effects of Nutrition Support

Nutrition therapy is a treatment associated with significant limitations, including refeeding syndrome, cholestasis, hyperglycemia, and fluid and electrolyte disturbances, requiring cautious prescription by a registered dietitian (Arfons & Lazarus, 2005). Clinicians caring for patients with nutritional deficits are required to choose between oral, enteral, and parenteral formulations for nutritional supplementation with the assistance and expertise of a registered dietitian (Duro et al., 2010). Clinical trials have been lacking in evidence to support any specific practice

because of either poor study design or high bias risk. Therefore, the providers must use their best clinical judgment in determining what route of nutrition support is best for each patient.

REFEEDING SYNDROME

After weeks of malnutrition, HSCT patients are often at risk for refeeding syndrome, which is characterized by the development of fluid and electrolyte disorders (especially hypophosphatemia) along with neurologic, pulmonary, cardiac, neuromuscular, and hematologic complications after the intake of large amounts of calories (Mehanna, Moledina, & Travis, 2008). Most effects result from a sudden shift from fat to carbohydrate metabolism and a sudden increase in insulin levels after refeeding, which leads to increased cellular uptake of phosphate. Formation of phosphorylated carbohydrate compounds in the liver and skeletal muscle depletes intracellular ATP and 2,3-diphosphoglycerate in red blood cells, leading to cellular dysfunction and inadequate oxygen delivery to the body's organs (Mehanna et al., 2008).

Refeeding increases the basal metabolic rate. Intracellular movement of electrolytes occurs, along with a fall in the serum electrolytes, including phosphate, potassium, magnesium, glucose, and thiamine. Significant risks arising from refeeding syndrome include confusion, coma, convulsions, and death. Refeeding syndrome is usually seen within the first 4 days of initiation of nutrition support; patients with high levels of weight loss are at the highest risk (Mehanna et al., 2008). When initiating feeds, slow advancement is often recommended to avoid metabolic abnormalities. To help avoid the development of refeeding syndrome, depleted electrolytes should be replaced prior to the start of nutrition support and electrolytes should be monitored twice daily as nutrition support is being advanced (McCray, Walker, & Parrish, 2005). For PN, initial dextrose infusion should not exceed 100 to 150 g or 2 mg/kg/mg (McCray et al., 2005). The rate should be advanced to goal over 3 to 7 days. A registered dietitian, with adequate nutrition support experience, should provide close monitoring and adjust feeding goals as needed.

HYPERGLYCEMIA

Hyperglycemia is a common complication with the administration of TPN, and to a smaller degree EN. Thus, TPN should be initiated at half of the estimated energy needs (150–200 g) for the first 24 hours or less than 100 g in the hyperglycemic patient (Kumpf & Gervasio, 2007). Hyperglycemia is associated with an increased risk for infection, as it creates an environment rich in dextrose, which harbors the growth of microbes. Tight glucose control reduces morbidity and mortality (Opilla, 2008). Uncontrolled hyperglycemia can result in increased risk for infection as well as increased risk for coma and death secondary to osmotic diuresis (Kumpf & Gervasio, 2007). Lipids may limit hyperglycemia, which may also reduce infection rates, diabetes mellitus, and GVHD (Arfons & Lazarus, 2005).

Daily carbohydrate administration should not exceed 20 to 25 kcal/kg/day. Blood glucose checks should be performed every 6 hours or every 4 hours in hyperglycemic patients (Kumpf & Gervasio, 2007). Regular insulin therapy is recommended, which may be given subcutaneously or added directly to the PN solution: 0.05 to 0.1 units of insulin per 1 g of dextrose in the PN solution is suggested, or 0.15 to 0.2 units of insulin per gram for those patients who already have hyperglycemia (Kumpf & Gervasio, 2007).

CHOLESTASIS

Hematopoietic stem cell transplant patients may develop SOS, aGVHD of the liver, drug-induced cholestasis, or other posttransplant liver complications (Negrin, 2010). Thus, for those patients requiring TPN, it is necessary to review the nutrient composition of the solution to avoid excessive infusion of fat, carbohydrates, and total calories to help avoid exacerbation of existing liver abnormalities (Jeejeebhoy, 2005). If a patient is cholestatic and/or serum bilirubin is persistently elevated, copper and manganese should not be given in TPN due to reduced excretion and increased retention (Jeejeebhoy, 2005). Zinc, selenium, and chromium should still be provided. Cyclic (running over 12–14 hours) vs. continuous TPN is also recommended, as continuous administration maintains a high insulin level, which can promote a fatty liver. Lastly, lipid infusion should be infused to ≤ 0.5 g/kg/day with carbohydrate intake at 15 kcal/kg/day (Jeejeebhoy, 2005). A hepatic panel should be performed weekly along with serum triglycerides to monitor for the development of cholestasis. If serum triglycerides exceed 500 mg/dL, lipids should be provided at

a dose to prevent essential fatty acid deficiency, as determined by the registered dietitian. If the level exceeds 1,000 mg/dL, lipids should be discontinued and a gastroenterology consult may be needed (Lenssen & Aker, 2002).

PARENTERAL NUTRITION–INDUCED ANOREXIA

Patients receiving TPN often complain of anorexia interfering with their ability to resume normal intake. Although the mechanisms underlying parenteral nutrition–induced anorexia remain controversial, several theories exist. It has been suggested that the feeling of satiety may be related to an elevated serum insulin level that is similar to that of a postprandial state (VanderWeele, 1994). In addition, Meguid, Yang, & Koseki (1995) suggest that spontaneous food intake during parenteral nutrition is reduced due to lack of oral-nasal stimuli and a blunted dopamine response. Although this is controversial, many clinicians believe it may be beneficial to cycle TPN overnight to allow for appetite stimulation. Cycling at night also allows for time away from the pump for increased mobility and a greater opportunity to eat oral foods.

Bloodstream Infections and Catheter-Related Complications

Total parenteral nutrition has been associated with an increased risk of catheter-related bloodstream infections (Opilla, 2008). It provides a milieu for bacteria and fungus growth due to its dextrose components, rich fatty acids, and fat emulsions. Proper refrigerated storage and administration for only 24 hours greatly reduces the chance of microbial growth or contaminations within the formula. Patients receiving TPN are at higher risk for developing candidemia, the most common fungal bloodstream infection in the United States. Other risk factors for developing candidemia include broad spectrum antibiotics, corticosteroids, immune suppression, dialysis, prolonged mechanical ventilation, and diabetes (Dimopoulos, Karabinis, Samonis & Falagas, 2007).

During the neutropenic phase of transplant, patients should receive antimicrobial prophylaxis (Stratman, Martib, Rapp, Berger, & Magnuson, 2010). Neutropenic patients or patients with mucositis or GVHD of the gut may have increased risk of central venous catheter infections with intestinal organisms. Biofilm on central venous catheters and/or fibrin clots to the catheter create an environment fostering the growth of microbes as well. In hospitalized patients, the most common organisms for bloodstream infections are coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, *Enterococcus, Candida* species, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* (Stratman et al., 2010). Most infected catheters should be removed based on infectious disease recommendations, and some patients may require a 24- to 48-hour line holiday from any central line to clear a bacteremia (Opilla, 2008). There are limited data stating antimicrobial locks may be helpful in preventing catheter-related bloodstream infections. More studies are needed to confirm the efficacy of this therapy (Opilla, 2008). Newly placed peripheral access is allowed and preferred. Treatment with appropriate antibiotic and/or antifungal therapy is initiated and a new central line may be placed when negative blood cultures are obtained (Stratman et al., 2010).

Conclusions

Patients undergoing HSCT are prone to varying degrees of malnutrition, long hospital stays, and intensive conditioning therapy. The acute posttransplant period is a time of significant morbidity and mortality in which nutrition plays a large role. Patients experience poor appetite and symptoms preventing appropriate oral intake. Furthermore, the development of inflammatory syndromes, such as aGVHD and septicemia, creates a large catabolic demand on the body. Severe malnutrition can happen quickly in this population in the absence of appropriate nutritional support (Seguy et al., 2006).

Current recommendations suggest that oral intake is preferred over other forms of nutrition support with the addition of vitamins and minerals, which requires a healthy GI tract. For those who are unable to eat or drink, enteral nutrition may be promising but evidence for this practice requires more data. If TPN is used it should be discontinued after stem cell engraftment when adequate EN or oral intake is feasible and/or as soon as toxicities have resolved (August & Huhmann, 2009).

Advanced practitioners should monitor for side effects of transplant, manage symptoms related to the treatments, and teach patients and caregivers ways to increase oral intake. Care pro-

vided by APs is instrumental in identifying malnutrition, providing treatments, and teaching interventions to patients and families to reduce the severity of transplant-related complications associated with prolonged malnutrition. Teaching appropriate eating habits may increase tolerance of oral feeding, which may decrease the need for further supplementation during the acute transplant period.

Routine nutrition assessment of patients by a dietitian should be ongoing at least once weekly throughout the patient's transplant stay (Horsley et al., 2005; Ottery, 2005). There is a need for further study of BMT patients throughout this phase in order to identify the patterns of events and characteristics that would allow APs to assist with the development of clinical guidelines for the nutritional management of these patients.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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