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Nutrition Support of Blood or Marrow Transplant Recipients: *How Much Do We Really Know?*

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The number of adults undergoing blood or marrow transplantation has grown dramatically over the past two decades due to broader selection criteria for transplant and more sophisticated therapies. The nutritional management of these patients is difficult for clinicians due to the side-effects of chemotherapy provided and the subsequent decrease in the desire to eat related to many aspects of the transplant process. Most studies have focused on the consequences of administering short-term total parenteral nutrition and there is a paucity of evidence on oral or enteral support in the adult transplant population. This article describes the various types of transplants and the common side-effects encountered, and guides the reader through the strengths and flaws of the current literature as it relates to common practice.

INTRODUCTION

Intravenous bone marrow infusions have been reported as far back as 1939 (1) with curative attempts for hematologic disease dating to the 1950s (2–3). Since these early investigations, the field of bone marrow transplantation has experienced tremendous growth and advancement, especially in the last two decades. To date, there are over 200 transplant centers in the United States (4), 450 transplant centers worldwide and about 40,000 transplants conducted internationally each year (5).

Bone marrow transplantation (BMT) is a sophisticated therapeutic procedure consisting of the administration of chemotherapy and/or radiation therapy followed by intravenous infusion of hematopoietic stem cells to reestablish marrow function (6). It is most frequently used in the treatment of malignant solid tumors and hematologic diseases (Table 1), and generally offers better survival than traditional chemotherapy, despite potentially life-threatening transplant complications (7). As a reflection of technological advances, blood or marrow transplants are now often

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Table 1
Diseases Treated by Hematopoietic Stem Cell Transplant

Solid tumors	*Hematological malignancies*	*Other conditions*
Breast cancer	Acute lymphocytic leukemia	Amyloidosis
Brain tumors	Chronic lymphocytic leukemia	Aplastic anemia
Testicular cancer	Acute myelogenous leukemia	Autoimmune disorders
Ovarian cancer	Chronic myelogenous leukemia	Hereditary metabolic disorders
Melanoma	Hodgkin disease	Sickle cell disease
Neuroblastoma	Multiple myeloma	Thalassemia
Sarcoma	Myeloproliferative disorders	
Small-cell lung cancer	Non-Hodgkin lymphoma	
Non-small-cell lung cancer		

Adapted from references 9 and 53.

referred to as hematopoietic stem cell transplants (HSCT) due to the common use of stem cells harvested from the circulating blood, or peripheral blood stem cell transplants (PBSCT or PSCT).

Regardless of terminology, the transplant procedure continues to present unique challenges for clinicians in the nutritional management of these patients. This article will review the more common types of HSCTs, the nutritional complications relevant to transplant and the nutrition support of adult patients to aid clinicians in understanding the transplant process and to provide insight into the strengths and limitations reported in the current literature.

TYPE OF HEMATOPOIETIC STEM CELL TRANSPLANTION

Several factors are taken into consideration when determining the type of transplant that is optimal for a patient including the primary diagnosis, the stage of disease and the availability of a donor. Although all types of transplants "condition" the patient with chemotherapy, radiation or both prior to transplant, there are three basic types of HSCTs: autologous and allogeneic, the most common types, and syngeneic.

Autologous Stem Cell Transplant

With this type of transplant, the transplant recipient and the donor are the same person. Stem cells are harvested from the patient, frozen until transplant and then reinfused to restore marrow function following administration of high dose chemotherapy. Autologous transplantation has several advantages including stem cell accessibility and decreased risks for morbidity and mortality associated with graft rejection and graft versus host disease. The primary disadvantages are the potential reinfusion of diseased cells, disease relapse, secondary malignancies and the lack of graft versus tumor effect (8).

Allogeneic Stem Cell Transplant

Allogeneic transplantation involves the transfer of hematopoietic stem cells from a donor to a recipient. These types of transplants can be divided into two categories based on histocompatibility. Ideally, the recipient is a human leukocyte antigen (HLA)-genotypic match from a sibling donor, or alternatively, a phenotypically matched but unrelated donor usually identified through the National Marrow Donor Program (NMDP). Regardless of the donor, once a match has been identified, the patient typically receives high-dose chemotherapy or radiotherapy to induce immunosuppression and create room for the new donor marrow. Non-myeloablative, or "reduced intensity" regimens are relatively new and are used in patients who cannot withstand standard preparative regimens due to significant co-morbidities prior to transplant.

The advantages of allogeneic transplant include: the capability of donor cells to induce an anticancer

effect of the graft following chemotherapy (i.e. graft versus tumor effect or graft versus leukemic effect) and the infusion of disease free cells into the host. The disadvantages include the susceptibility of the recipient to graft versus host disease (GVHD), the need for prolonged immunosuppression and its association with increased infection, disease relapse, graft failure and difficulties in identifying an HLA-matched donor (8).

Syngeneic Stem Cell Transplant

This is an unusual kind of transplant, potentially classified as a type of allogeneic transplant, but involves the donation of genetically identical hematopoietic stem cells from one identical twin to the other. These are rare, but they offer the primary advantage of availability, compatibility and lack of vulnerability of the host to GVHD. Consequently, syngeneic transplant recipients also lack the benefits of graft versus tumor effect (8).

Sources of Stem Cells

It is important to differentiate sources of hematopoietic stem cells from the type of transplantation. Hematopoietic stem cells are currently supplied from bone marrow, peripheral blood, or umbilical cord blood. Bone marrow cells are harvested during a surgical procedure. Peripheral stem cells are collected in an outpatient procedure via apheresis. Because the number of stem cells in peripheral circulation is low, the use of colony stimulating factors (CSFs) alone or in combination with chemotherapy, are used to mobilize stem cells from the bone marrow into the peripheral blood for collection. While this process offers no operative risks, it may require several apheresis sessions to obtain the minimum amount of stem cells necessary for engraftment. Since 1994, peripheral stem cells have been the most frequent source of cells used for transplant (9). They are associated with accelerated engraftment and result in reduced length of hospitalization. Stem cells collected from umbilical cord blood have the advantage of being immunological immature and can therefore be used with broader HLA disparity, but the quantity of stem cells from umbilical cord blood is often too low for adults and these transplants have been associated with delayed engraftment.

NUTRITIONALLY RELEVANT COMPLICATIONS

As part of the transplant process, patients receive chemotherapy and/or radiation therapy prior to transplant to eradicate the underlying disease and to provide immunosuppression of immunologically active cells. Myelosuppressive or myeloablative conditioning regimens are associated with the development of gastrointestinal (GI) toxicities within days of delivery, most prominently oroesophageal mucositis, nausea, vomiting and diarrhea (10). While the side effects of the conditioning regimen may vary with regard to degree of severity among individuals and between transplant types, the GI toxicities have an immense impact on the short-term nutritional status of the transplant patient. Additionally, patients who have undergone allogeneic transplant (related or unrelated) are uniquely susceptible to graft versus host disease, which has both short and long-term nutritional consequences.

Mucositis

Mucositis is a frequent but transient side effect of antineoplastic therapy. It coincides with profound changes in the integrity of the mucosal epithelia that line the oral cavity, esophagus, and gastrointestinal tract due to the effects of chemotherapy on cells with high turnover rates. Changes at the microscopic level result in a denuded mucosa, which can lead to bacterial, viral, or fungal invasion of the bowel wall, sepsis, ulceration, bleeding, malabsorption, diarrhea, and pain throughout the gastrointestinal tract (11). Oral mucositis affects up to 75% of patients undergoing HSCT (12) and results in reduced abilities to consume adequate nutrients orally, increased infection risk, and potentially, malnutrition. These factors are believed to increase morbidity and reduce survival times in the HSCT population (13). Because oral mucositis can be so debilitating, it is often treated with a variety of pharmaceutical agents (Table 2), including parenteral narcotics for pain relief, and frequently, total parenteral nutrition is initiated (14) with the notion that it will preserve the patient's nutritional status.

Graft Versus Host Disease (GVHD)

GVHD is an immunological entity characterized by skin, gastrointestinal and cellular changes caused by

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Table 2
Oral Mucositis Treatment Guidelines

General tips	*Methods used*
Good oral hygiene during treatment	• Brush teeth four times per day • Rinse regularly with a solution of 1 tsp. baking soda and 1 tsp. salt water in a large glass of lukewarm water before and after meals • Alternatively, rinse regularly with a non-alcohol containing antibacterial mouthwash, such as Stanimax Perio Rinse® or PerioMed®.
Select foods carefully	• Keep mouth and lips moist • Avoid hot, spicy or hard foods that can trigger pain • Encourage popsicles, ice chips or sips of water
Prevent infections with antifungals and/or antivirals	• The following agents may be used: Nystatin or amphotericin mouth rinses, Acyclovir, Clotrimazole or Fluconazole
Mild pain relief may be achieved with pharmacologic or natural agents	• Xylocaine® or Lidocaine® combined with Benedryl® and Mylanta or Maalox for oral rinses • Zyloprim® rinses with oral vitamin E supplementation • Vancocin® rinses Lilly Pharmaceuticals (www.lilly.com or 800-545-5979) • Hydroxypropyl cellulose gel with Xylocaine® applied to sores • Zylactin film is an over the counter dental anesthetic • Gelclair (www.gelclair.com/) • Carafate® rinses
Severe pain relief may require narcotics	• Oral or intravenous morphine, hydromorphone or fentanyl

For a nice review of Mucositis:
From: CancerConsultants.com
Exploring the Current Management of Mucositis by Buckner CD available at:
http://professional.cancerconsultants.com/cton.aspx?id=30366

Adapted from www.uspharmacist.com and Used with permission from the University of Virginia Health System Nutrition Support Traineeship Syllabus: (http://www.healthsystem.virginia.edu/internet/dietitian/dh/traineeship.cfm)

immunologically competent donor cells introduced into an immunoincompetent host (15). GVHD is classified as *acute* or *chronic* depending on the timing of symptoms and graded based on the clinical severity of the disease (Table 3); however, the pathophysiology, diagnosis and treatment vary for each. For additional information please refer to the following reviews (16–18).

Acute GVHD typically develops within the first 100 days after allogeneic transplant and is frequently characterized by one or more of the following: 1) dermatitis presenting as a maculopapular rash, 2) hepatitis as seen by the presence of jaundice, and/or 3) gastroenteritis, including crampy abdominal pain with or without secretory diarrhea (16). GVHD prophylaxis is now standard, usually involving the administration of methotrexate, cyclosporine or tacrolimus within days of transplant, however, the incidence of acute GVHD ranges from 40%–80% (19–20) and is inversely correlated with the number of HLA mismatches (21) between the donor and the recipient. The most common first-line therapy for acute GVHD involves the addition of methlyprednisolone until symptoms are controlled. Acute GVHD has been reported to be a dominant factor in persistent nausea and anorexia following transplant (22) and depending on the degree of GI involvement, symptomatic diarrhea often results in the cessation of oral intake and the initiation of TPN.

Table 3
Comparison of Acute and Chronic Graft-Versus-Host Disease (GVHD)

Characteristic	*Acute GVHD*	*Chronic GVHD*
Usual onset	Within 100 days of transplant	After 100 days post-transplant
Organs involved	Skin*, Liver, Gastrointestinal tract*	Skin*, Liver*, Gastrointestinal tract*, Eyes*, Musculoskelatal, Nervous, Hematopoietic, Pulmonary
Incidence	40%–80%	40%–70%
Basis of clinical grading	Severity of disease	Severity and extent of disease
Pharmacologic management	Cyclosporine, Methotrexate, Methylprednisolone, Tacrolimus, Mycophenolate mofetil, Anti-thymocyte globulin, Dicluzimab	Cyclosporine, Methotrexate, Prednisone, Tacrolimus, Thalidomide, Hydroxychloroquine, Mycophenolate mofetil, Azathioprine
Symptomatic management	Topical steroids, antiemetics, pain medications, fluid and electrolyte replacement, antidiarrheals	Topical steroids, antiemetics, pain medications, antidiarrheals, artificial tears, fluid and electrolyte replacement, blood product support, moisturizing lotion, total parenteral nutrition, physical or occupational therapy

Compiled and adapted from references 17, 57 and 58.
*= Most commonly affected

Chronic GVHD is the most common problem affecting allogeneic transplant patients (17) (other than disease relapse) and has similar clinical manifestations to acute GVHD. However, histological documentation of chronic GVHD by skin or other tissue biopsies is necessary for diagnosis. Predictive factors for chronic GVHD include HLA disparity, prior acute GVHD and older age, with a median diagnosis time of 4.5 and 4.0 months post-transplant for HLA-identical sibling and unrelated donor transplantation, respectively (23). Chronic GVHD is reported to occur in 40%–70% of all allogeneic transplant recipients (24) and its treatment primarily focuses on patient education and infection prophylaxis, specifically opportunistic infections as outlined by the Centers for Disease Control (25). Cyclosporine (CSA) and prednisone are the most frequently utilized first-line therapies in the pharmacologic management of chronic GVHD, while antiemetics, pain management, and antidiarrheals are used for symptomatic treatment.

The nutritional management of patients with chronic GVHD is often difficult because of the number of organ systems involved, the resultant multitude of symptoms and the concomitant side-effects of CSA and prednisone, which potentially lead to hyperkalemia, hypomagnesemia, hypertriglyeridemia, and hyperglycemia. Lennsen, et al (26) retrospectively evaluated pediatric and adult patients one year after allogeneic marrow transplant and found nutritionally related problems (oral sensitivity, stomatitis, anorexia diarrhea, steatorrhea), changes in anthropometric indices consistent with declines in nutritional status and inadequate energy intake to be more prevalent among patients with chronic GVHD when compared to those without GVHD. While TPN is often initiated in these patients after readmission to the hospital, there

is limited documentation on ideal TPN candidates, appropriate caloric and protein provision and the effect of TPN on outcomes in patients with chronic GVHD.

NUTRITIONAL REQUIREMENTS

Energy requirements of HSCT patients are believed to reach 130%–150% (27–28) of predicted basal energy expenditure with older studies targeting caloric delivery greater than 30 kcals/kg. (29–30). A more recent investigation using indirect calorimetry demonstrated similarities between predicted and measured energy requirements at baseline, but variations at different points following transplant, which were more pronounced in allogeneic than autologous recipients (31). Although clinical practice varies, there is general agreement that it is better to underfeed rather than overfeed, resulting in practical kilocalorie targets of 25 kcals/kg. Due to the catabolic nature of the transplant process and the inherent imprecision of nitrogen balance studies, true protein requirements are difficult to determine for these patients. Generally, recommendations for protein intake for adult transplant patients range from 1.2–1.5 g pro/kg (28).

NUTRITION SUPPORT IN HSCT

Most investigations regarding the nutritional outcomes of patients following HSCT have been conducted in the acute care setting and primarily target short term effects. Impaired nutritional status prior to transplant has been shown to be a negative prognostic indicator of outcome (33) and well nourished patients have experienced earlier engraftment (27). Because cytoreductive therapy can induce anorexia, nausea, vomiting and diarrhea, aggressive nutrition support is easily justified and is considered to be an essential component of successful transplant care. While studies have been conducted on oral and enteral support during transplant, the majority of nutritional investigations examine aspects of TPN administration, as TPN has been and continues to be widely used in this patient population.

Oral Nutrition

In the majority of transplant patients, the basic premise has been that patients cannot withstand nutritional deprivation without deleterious outcomes and therefore they must receive artificial nutrition support when there is little desire to eat. Despite the potential benefit of oral nutrition in this patient population, this type of nutrition support has received little research attention. Early studies focused on the food service practicalities of supplying low-bacteria diets (LBD) to transplant recipients (33–34), however, no study has directly addressed the need for this type of diet in the HSCT population. In theory a LBD, also called "neutropenic diet," "low microbial diet," or "reduced bacteria diet," is assumed to reduce infection risk by reducing potentially pathogenic organisms from the diet (Table 4). These diets are widely used in pediatric (35) and adult (36) immunocompromised cancer patients. Considering that HSCT patients struggle to consume adequate amounts orally from treatment side-effects and LBDs are frequently used for neutropenic patients (37), the use of an LBD poses unnecessary dietary restrictions compounding the problem of diminished oral intake.

In addition to the paucity of evidence on the necessity of LBDs, there is conflicting evidence determining how much and what is the best source of nutrition for these patients. A logical question would be, *"What are transplant patients actually consuming during hospitalization?"* A single-centered trial examined intake patterns and found that of the 205 surveyed patients, most preferred clear liquids (i.e. soda, juice, and popsicles). The majority of patients were able to consume 60% of their estimated needs at the time of discharge (34), which is consistent with other indirect investigations of oral intake in autologous (31) and allogeneic (38) recipients. Charuhas, et al (39) prospectively examined the effects of outpatient TPN versus intravenous (IV) hydration in 258 transplant patients. The median time to resumption of oral intake (≥85% estimated needs) was better in the IV hydration group vs. the TPN group (10 vs. 16 days, respectively, $p = 0.05$). A study by Stern, et al (40) had conflicting results. Patients in this study either remained in the hospital receiving TPN and/or oral diets or were discharged home without TPN, but encouraged to eat. Both groups had to consume <33% of estimated needs to qualify for randomization and both met routinely with

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Table 4
Dietary guidelines for a low bacteria diet

- Avoid all fresh fruits and vegetables, including fresh garnishes
- Avoid raw or rare- cooked meats, fish, or eggs
- Avoid dried fruits and nuts
- Be sure all milk and dairy products are pasteurized. Avoid raw milk, naturally aged cheeses, cheeses with molds, and all yogurt and yogurt products with live cultures
- All fresh herbs must be cooked
- Avoid salad bars, buffets and deli counters. Be sure all luncheon meat is vacuum-packed
- Do not purchase perishable foods from street vendors, "coffee carts," or self-help bulk food containers
- Other things to avoid: shellfish, unpasteurized apple cider and raw honey
- Check "sell by" and "use by" dates on all foods

Practice safe food handling.

- Wash hands with soap and hot water when preparing food
- Wash all cutting boards, utensils and counter tops thoroughly during meal preparation
- Keep hot foods hot and cold foods cold
- Do not keep perishable foods such as milk, meat and/or sandwiches at room temperature for more than two hours

Adapted from:
www.jhbmc.jhu.edu/NUTRI/special/neutropenic.html,
www.leukemia.acor.org/neutro.html, and
www.bannerhealth.com.

a dietitian for dietary counseling. The hospitalized group resumed oral intake sooner (4.5 vs. 8.0 days, respectively; $p = 0.004$) than the discharged patients. Further investigations concerning direct examination of oral intake are needed to ultimately discern the feasibility, safety and impact of varying oral nutrition patterns during blood or marrow transplant.

Enteral Nutrition

Enteral nutrition is believed to be more beneficial than parenteral nutrition in non-transplant populations because it is associated with fewer infections, considered "more physiologic," and is considerably less expensive (41). Enteral nutrition trials have been predominantly conducted in the pediatric transplant population. Investigations in the adult transplant population are less prevalent and are theoretically difficult to conduct due to a general lack of acceptance by transplant patients and their physicians. In a widely cited prospective, randomized study by Szeluga, et al (30), 57 pediatric and adult autologous and allogeneic transplant patients received either TPN or an individualized enteral feeding program (EFP) (counseling, high protein snacks and/or nasoenteral tube feeding). Although it is difficult to discern the number of patients who ultimately received enteral tube feedings, no differences were found at baseline, or with regard to hematological recovery or survival. Greater *oral* intake was documented for the enteral vs. the TPN group post-transplant (15–20 kcal/kg/day and 0.5–0.7 g protein/kg/day vs. 5–10 kcal/kg/day and 0.1–0.4 g protein/kg/day, respectively), but the TPN group demonstrated significantly more weight gain 28 days after transplant than the EFP group ($108 \pm 9\%$ vs. $96 \pm 5\%$ from baseline, respectively; $p < 0.0001$).

In another study, Mulder, et al (42) prospectively examined 22 patients undergoing autologous transplant randomized to TPN or partial parenteral nutrition plus enteral nutrition (PPN/EN) via a nasogastric feeding tube. These authors concluded that both nutrition modalities were equivalent in maintaining body weight and nitrogen balance, despite the fact that only five patients actually received tube feedings. Moreover, Sefcick, et al (43) carried out a pilot study of 15 adult allogeneic patients with elective naso-jejunal (NJ) placements prior to conditioning chemotherapy. Although the authors deemed the study successful, patients lost 4.5% of body weight at the time of discharge and experienced profound difficulties with tube maintenance due to vomiting and reported epistaxis, and experienced difficulties with feeding tolerance owing to diarrhea and discomfort. Enteral studies in this population are fraught with difficulty as evidenced by the Sefcick pilot study, but also due to the confusion between enteral intolerance and the side effects of cytoreductive therapy, in the face of mucositis and thrombocytopenia. Additionally, enteral feeding is

often combined with parenteral nutrition and various enteral access methods are used, resulting in an unclear role of enteral nutrition or the superiority of percutaneous or nasoenteral feeding access in the adult patient population.

Total Parenteral Nutrition

Because most transplant patients are required to have central venous access, TPN has become convenient and allows for easy administration of fluid, electrolytes and macronutrients. In early studies, TPN was shown to promote earlier engraftment (27) and improve survival (44) compared to non-TPN BMT recipients. While these findings are of interest, they reflect transplant practices of the early 1980s and several design flaws limit their interpretation. Specifically, the investigators combined pediatric and adult patients whose treatment and response may be very different, and, further, in the later study (44), over 60% of the control group actually received TPN making the groups' treatments homogeneous, and the interpretation of the true effect of TPN on survival unlikely. Cetin, et al (45) conducted a prospective cohort study of autologous BMT patients (n = 61) who received either TPN (30 kcal/kg) or partial TPN (340 kcal/day). They found that patients receiving TPN had more hyperglycemic events, infections, and longer delays in platelet engraftment. Implications of their findings are limited due to the non-random design, failure to document similarities between groups for medical and nutritional status at the time of admission and exposure of all participants to parenteral nutrition.

The role of glutamine supplemented TPN drew a lot of attention in the last decade (44–48), however, these trials demonstrated very inconsistent outcomes. Other investigators examined lipid substrates as a component of TPN and found these could be safely administered without deleterious effects on cell function or risk of infection (49–50). Collectively, these investigations all suffer from a uniform exposure of TPN to all subjects. Considering the administration of growth factors and the use of peripheral blood are now common components of HSCT care, both significantly reducing the time until engraftment (9,51) (thereby reducing the length of time with inadequate nutrient intake), the need for routine TPN use in this population is questionable.

TPN is not without inherent risks. A meta-analysis evaluated the effectiveness of TPN in various populations, including 19 trials of cancer patients (four with BMT patients) receiving chemotherapy (54). When these cancer trials were aggregated, TPN was associated with significantly increased infectious complications (absolute risk difference: 16%; 95% CI: 8%–23%) and total complications (absolute risk difference: 40%; 95% CI: 14%–66%) and lower tumor-response rates to chemotherapy (absolute risk difference: –7%; 95% CI: –12 – –1%) were found in TPN recipients compared to the control group. The authors concluded that TPN did not improve survival, was associated with impaired tumor response to chemotherapy, and in general, was clearly associated with net harm in patients undergoing oncological treatment. However, no information was provided on how or why TPN exposure was related to outcomes.

Because of the potential impact of hyperglycemia on morbidity and mortality found in other patient populations (55–56), we conducted a retrospective cohort investigation to examine the incidence, temporality and dose-response relationship of TPN-induced hyperglycemia (blood glucose >110 mg/dL) in 357 patients undergoing either initial autologous or matched related allogeneic transplant at two university affiliated hospital transplant centers. Preliminarily, we found that hyperglycemia was a result of TPN administration and was associated with a greater risk of infection, greater blood product requirements and increased mortality in HSCT patients who received TPN when compared to non-TPN recipients, after controlling for necessary confounders (unpublished). This global analysis of autologous and allogeneic transplant, together with the meta-analysis, provides strong evidence to deduce that TPN is potentially harmful in this patient population.

CONCLUSIONS

TPN has been and continues to be the mainstay of nutrition support for HSCT patients because it is easy to administer, it is provided under the assumption that

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it is beneficial and it is preferred by transplant physicians. Because the majority of transplant patients are well-nourished and are required to be in relatively good physical condition in order to withstand the physical challenges posed by transplantation, and because the time of treatment-induced anorexia is now often less than 10 days, the assumption that these patients require aggressive nutrition support may no longer apply. Specifically, TPN seems unnecessary, imposes undue costs and most importantly, leads to significant increases in morbidity and mortality in a susceptible patient population. TPN should be reserved for patients with unintentional weight loss prior to transplant, who continue to lose weight and possess nonfunctioning GI tracts. Administration of TPN is not appropriate for patients with brief periods of treatment-induced anorexia, mucositis or diarrhea and the role of enteral and oral nutrition desperately warrants exploration with well-designed studies. For now, oral nutrition should be emphasized, enteral nutrition attempted and TPN use discouraged. ■

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