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Invited Review

Nutrition Issues in Hematopoietic Stem Cell Transplantation: State of the Art

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ABSTRACT: There have been many changes in hematopoietic stem cell transplantation (HSCT) that affect the patient's nutrition support. In the early 1970s, allogeneic transplants were the most common types of HSCTs; today, autologous transplants are the most common. Bone marrow, peripheral blood, and umbilical cord blood all now serve as sources of stem cells. Conditioning therapies include myeloablative, reduced-intensity myeloablative, and nonmyeloablative regimens. New medications are being developed and used to minimize the toxicities of the conditioning therapy and to minimize infectious complications. Supportive therapies for renal and liver complications have changed. In the past, HSCT patients received parenteral nutrition (PN) throughout their hospitalization and sometimes as home therapy. Because of medical complications and cost issues associated with PN, many centers are now working to use less PN and increase use of enteral nutrition. The immunosuppressed diet has changed from a sterile diet prepared under laminar-flow hoods to a more liberal diet that avoids high-risk foods and emphasizes safety in food handling practices. This article will review these changes in HSCT and the impact of these changes on the nutrition support of the patient.

The number of hematopoietic stem cell transplants (HSCT) performed annually has increased dramatically in the last 15 years. Over 50,000 transplants were performed worldwide in 2004, somewhat fewer than in the peak years in the late 1990s. In the 1990s, several studies showed no benefit of stem cell transplantation for breast cancer, and most transplant centers no longer treat patients with breast cancer. Nonetheless, transplant remains a vigorous field in which new knowledge in cancer immunology and genetic tolerance find their way into clinical research, making this treatment available to an increasingly diverse population of patients. This review will highlight some of the trends in HSCT and provide an update on nutritionally relevant research. One of the daunting complications of HSCT remains graft-*vs*-host disease (GVHD), which is discussed in another article in this journal issue. We will focus on the expansion of treatment and indications for transplant, the progress in the management of non-GVHD complications, and the current evidence for best nutrition support practice.

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Diversity of Transplantation Practices and Impact on Nutrition Support

There have been many changes over the recent past in the methods of transplantation. Donor types have remained the same: autologous, allogeneic, and syngeneic. Changes have involved the sources of stem cells, the types and intensity of conditioning therapies, and the level of donor mismatch.

Donor Types

Autologous hematopoietic stem cell transplants have been the most common treatment in all age groups since 1990.[1] In autologous transplants, the patient's own marrow or stem cells are removed and frozen before high-dose conditioning therapy and reinfused later to the patient to rescue the patient's immune system after the myeloablative, marrow-toxic conditioning therapy. Autologous transplants are the predominant type of transplant performed in older adults. This is because older adults frequently have increased rates of comorbidities and reduced organ function. The autologous transplant regimens are better tolerated and associated with decreased morbidity and mortality compared with allogeneic transplants. It is estimated that during the years 2000–2002, approximately 30,000 autologous transplants were performed annually in a total of 458 centers worldwide.[1]

In autologous transplants, peripheral blood represents the stem cell source in >95% of patients >20

years of age and approximately 85% of patients <20 years of age. At this time, approximately 10% of autologous transplants involve bone marrow as the only source of stem cells, and 80% of autologous transplants use peripheral blood as the only source of stem cells. Approximately 10% of transplants are done using both peripheral blood and bone marrow as the source of stem cells.[1]

Syngeneic transplants are derived from a genetically identical twin and represent the perfect match of stem cells. (This type of transplant is ideal in some situations, although, unfortunately, most people are not lucky enough to have an identical twin.) Increasingly, allogeneic transplants have been used in younger healthy adults and children who have suitable donors. Allogeneic transplants use a different person than the patient themselves to serve as the stem cell donor. This could be a sibling, other relative, or an unrelated person. Use of allogeneic transplants involves a more toxic conditioning regimen than autologous transplants, with the hope that the patient will survive the toxicities and complications of this regimen in order to have a greater chance for disease-free survival. At this time, 6000–7000 allogeneic transplants are done per year in North America.[1] Approximately one-third of these transplants are with stem cell sources from unrelated donors. Unrelated donor use is more common in the patient population <20 years of age, and related donor use is much more common in patients >20 years of age. Allogeneic transplants can be either fully matched at each of the 6 human leukocyte antigens or may have some level of mismatch. Transplants are now being done with up to 2 antigen mismatches. Mismatched transplants can be risky because of the increased incidence of GVHD and its associated complications.

Indications for Transplant

Indications for transplant include aggressive hematologic malignancies, immunologic problems, genetic diseases, and some inborn errors. Almost 90% of the autologous transplants performed in North America are for multiple myeloma or non-Hodgkin's lymphoma. The other diseases that are frequently transplanted using autologous transplants in order of their frequency are acute myelocytic leukemia, Hodgkin's disease, acute lymphocytic leukemia (ALL), myelodysplastic syndrome/other leukemias, and chronic myelogenous leukemia. Diseases that are less commonly transplanted include neuroblastoma, chronic lymphocytic leukemia, breast cancer, other cancers, and nonmalignant diseases such as multiple sclerosis.[1]

Approximately two-thirds of the allogeneic transplants are for leukemias or myeloproliferative diseases, including acute myelogenous leukemia, ALL, chronic myelogenous leukemia, lymphoma, and myelodysplastic syndrome/myeloproliferative disease. A small percentage of the transplants performed worldwide are for nonmalignant diseases. Some examples of these nonmalignant diseases include aplastic anemia, hemoglobinopathies such as thalassemia and sickle cell disease, congenital disorders of hematopoiesis such as Fanconi's anemia and Blackfan Diamond syndrome, severe combined immunodeficiency syndromes and related disorders, osteopetrosis, and inborn errors of metabolism such as Gaucher's disease or Hurler's syndrome.[1]

Sources of Stem Cells

Pluripotent stem cells are capable of self-renewal and differentiation into erythrocytes, neutrophils, eosinophils, basophils, lymphocytes, monocytes, and platelets. Sources for stem cells traditionally have been bone marrow because this is where the largest concentration of stem cells is found. When bone marrow is used as the source of stem cells after a myeloablative conditioning regimen, the period of absolute neutropenia is about 21 days. The period of absolute neutropenia refers to the time after marrow ablation and before engraftment of the new immune system. The patient is said to have engrafted when their absolute neutrophil count is $>500/mm^3$ for >2 days. Nutrition support is often needed during most if not all of this neutropenic period in order for patients to meet their nutrient needs.

There has been steady decline in the use of bone marrow, such that in 1999–2002, peripheral blood stem cells (PBSC) from the blood became the predominant stem cell source for allogeneic HSCTs. The use of PBSCs represented 50%–60% of the transplants, whereas bone marrow was used in only 40%–50% of allogeneic transplants.[1] PBSC collection has the advantage of being less painful and does not require anesthesia, unlike a bone marrow harvest procedure. PBSC donors receive subcutaneous injections of growth colony stimulating factor (such as Filgrastim) before the collection of stem cells.

Recipients of PBSCs generally have a shorter period of absolute neutropenia than recipients of bone marrow, 14 days *vs* 21. Because of this shorter neutropenic period, the risk for infection may be lower than when other sources of stem cells are used. As engraftment of the new immune system begins, mucositis (the oral toxicity that occurs as a result of the conditioning therapy) heals. Therefore, the patient who received a PBSC transplant can generally begin to resume some oral intake at this time. Unless the patient develops severe GVHD, nutrition support weaning can begin.

Studies in adults with ALL[2,3] suggested equivalent survival when PBSCs are used as the stem cell source compared with bone marrow. This may not be true for children. A recent study by Eapen et al[4] suggests higher treatment-related mortality, treatment failure, and overall mortality in children with ALL who receive PBSC *vs* bone marrow transplants. The study is criticized[5] because the PBSC cohort

had a higher percent of patients who were in relapse or primary induction at the time of transplant. A second finding of the study by Eapen et al[4] was that the use of growth colony stimulating factor was associated with an increase in relapse and mortality. This finding has been reported previously.[6] Clearly, a prospective, randomized, controlled trial is needed in children to determine outcome differences between the use of bone marrow *vs* peripheral blood as the source of stem cells in children.

Umbilical cord blood (UCB) is also being explored as a source of stem cells. Cord blood units are useful when there is no matched donor to provide stem cells from bone marrow or PBSC and the need to proceed to transplant is urgent due to disease process. Cord blood units also have the advantage of being able to be used in minorities because a greater degree of human leukocyte antigen disparity is tolerated if the stem cells are more immunologically naïve.

In children, UCB is used as a source of stem cells in 2%–5% of allogeneic transplants. Transplants in adults using cord blood are being performed[7–9] but not as often as bone marrow or PBSCs due to the limited cell dose in cord blood relative to body size. Single cord blood units generally have a 10-fold smaller dose of nucleated cells than bone marrow or PBSC sources. Engraftment with cord blood transplants is later, at approximately 28 days posttransplant.

The ideal cord blood unit would be well matched, with a sufficient volume of blood, total nucleated cells, and CD 34 cells but with a low number of maternal T cells and absence of transmissible agents. Research is now being done with "expansion" of the cord blood unit using megakaryocyte growth and development factors to make the cord blood source more available to adolescents and adults.[10,11] Researchers are also trying to combine cord blood units from 2 different donors in order to increase the cell dose because the most powerful predictor of engraftment is cell dose. Safety and efficacy of this approach is unknown.

Preparative/Conditioning Regimens

In malignancy, the goal of a conditioning regimen is disease reduction and eradication, with sufficient immunosuppression to prevent the host from rejecting the donor stem cells. The conditioning or preparative regimen will depend on the disease being treated and the type of donor. Aggressive malignant diseases will generally warrant a myeloablative approach. The conditioning therapy may be more intense if the donor is unrelated or less intense if the donor is related. Diseases such as aplastic anemia are generally treated with a less intensive regimen because there is no malignancy to be eradicated. Reduced-intensity regimens are also used in patients who are at high risk for regimen-related mortality.

Total body irradiation (TBI) has been the mainstay of conditioning regimens for >30 years. Doses are variable, depending upon whether the intent is myeloablation or nonmyeloablation. TBI can be delivered as a single dose or it may be delivered over several days in fractionated doses. The dose of TBI is limited by pulmonary and gastrointestinal toxicity. Long-term complications of high-dose TBI include impaired growth and development, thyroid dysfunction, reproductive failure, chronic pulmonary insufficiency, and secondary malignancies. High-dose chemotherapy is generally given either before or after the TBI therapy. Common agents in use include busulfan, carmustine, melphalan, and thiotepa. At maximum-tolerated dose levels, each has the potential for toxic effects on the gastrointestinal, pulmonary, and hepatic organs and significant other organ damage. Thiotepa can be toxic to the central nervous system. Other high-dose regimens may include mitoxantrone (cardiac toxicity), cisplatin (renal toxicity), carboplatin (hepatic and renal toxicity), and cytarabine (central nervous system toxicity).

Marrow ablation with the use of radiolabeled monoclonal antibodies is a less common technique than TBI. This method has the potential to focus higher doses of radiation on tumor sites than is possible with external beam TBI. The use of radiolabeled monoclonal antibodies also decreases the toxicity to the other organs because the radiation exposure to the normal organs is lower.

Sequential or tandem regimens of high-dose chemotherapy with HSCT and recovery, followed by a second round of chemotherapy and HSCT, can be an alternative to single, high-dose marrow ablative therapy.[12]

Nonmyeloablative allogeneic transplants (sometimes referred to as "minitransplants") have been used in approximately 1200 patients per year since 1998. This involves a reduced-intensity conditioning regimen and is especially useful in older patients, in patients with some level of organ insufficiency, and in patients at high risk for severe toxicities because of previous transplantation.[13–16] The nonmyeloablative approach has the benefit of decreased toxicity but carries the risk of increased graft failure and increased relapse of malignancy. Drugs used for nonmyeloablative conditioning include cyclophosphamide (cardiac toxicity), ifosfamide (renal, bladder, neurologic toxicities), etoposide (gastrointestinal toxicity), cisplatin, carboplatin, doxorubicin, mitoxantrone, and fludarabine. Most nonmyeloablative transplants use related donors from fully matched siblings and are generally done in patients with acute or chronic leukemias, non-Hodgkin's lymphoma, or multiple myeloma. PBSCs are used as the source of stem cells in approximately 80% of the nonmyeloablative transplants, with bone marrow serving as the source in the remainder of cases.

In nonmyeloablative transplants, the host hematopoietic stem cells survive, and the goal is a mixed

chimerism. Mixed chimerism is a state of mutual tolerance where the patient has 2 immune systems that coexist. The mixed chimerism is important in order to provide a boost to the host immune system. This boost to the host immune system is useful to produce the graft *vs* leukemia effect (GVL) in malignant disorders or to provide an immune system in situations such as immunologic, inborn errors, or metabolic disorders. Several options for conditioning therapy exist for the nonmyeloablative approach: high-dose cyclophosphamide with monoclonal anti–T-cell antibody, sublethal TBI given in fractionated doses, or fludarabine and single low-dose TBI. The TBI serves to create "space" in the marrow for engraftment. To ensure engraftment, both marrow "space" and immunosuppression of the host are needed.

Attempts to Reduce Toxicity of Conditioning Regimens

Antioxidants

Conditioning therapies, consisting of high-dose chemotherapy with or without TBI, have acute and chronic effects. These effects are thought to be related to release of reactive oxygen species (ROS) and exhaustion of antioxidants. Various agents are being investigated to attenuate the deleterious effects of oxidation leading to tissue damage.

One agent receiving attention is amifostine. Facorro et al[17] reported use of amifostine in patients receiving TBI. In this small study ($n = 21$), mucositis scores and free radical signals were reduced in the patients receiving amifostine.

Clemens et al[18] reported on pretransplant antioxidant supplementation. Patients receiving chemoradiation conditioning were given β-carotene (45 mg), α-tocopherol (825 mg), and ascorbic acid (450 mg) daily for 3 weeks before conditioning. A pretransplant control group did not receive the supplements, and a third group, healthy controls, also receive the supplements. Measurement outcomes included β-carotene and α-tocopherol plasma concentrations, and pre- and postconditioning plasma peroxide concentrations. Negative correlations were observed between antioxidant concentration levels and lipid peroxide concentrations levels; higher peroxide concentration levels were seen in patients who did not receive the antioxidant supplements. Although these are interesting observations, no conclusion can be made as to cause and effect or clinical outcome.

In an attempt to examine the possible relationship between antioxidant use and outcome, Bruemmer et al[19] reported on an observational cohort study in PBSCT patients. A questionnaire was utilized to gather information on supplement use before transplant. Nonrelapse mortality, recurrence/relapse, and mortality or relapse data were monitored for 2 years posttransplant. Results were varied, depending on disease. A suggestion was made that supplemental vitamin C pretransplant may be beneficial in persons with breast cancer, but vitamin C and vitamin E supplementation may increase risk of mortality or relapse in patients with acute leukemia.

An investigation into effects of parenteral nutrition (PN) on levels of antioxidants was undertaken by Jonas et al.[20] A comparison of conventional PN *vs* micronutrient support alone was done. Standard PN did not improve antioxidant status when compared with micronutrient support alone, raising further questions of the appropriate PN formulation to support antioxidant balance in PBSCT patients.

Glutamine

Interest in the use of glutamine, both oral and IV, to decrease morbidity and mortality of transplant has been abundant. Recent reviews and studies have confirmed the complexity of this issue and the varied results of supplementing glutamine in the transplant population. A recent meta-analysis performed in Europe suggested decreased hospital stays (103 subjects) and reduced number of positive blood cultures (73 subjects) for transplant patients who received glutamine-containing PN.[21] Zeigler[22] reviewed glutamine supplementation in HSCT and concluded that studies to date indicate glutamine is well tolerated and *potentially* efficacious in this population but further randomized, controlled, clinical trials are necessary. Buchman,[23] in a counterpoint discussion of glutamine, concluded that the available evidence does not support the supplementation of glutamine in the transplant population. Whether compounding glutamine is illegal is controversial, and furthermore, IV glutamine has not been designated "generally recognized as safe" (GRAS) by the US Food and Drug Administration, nor has it been approved for human use. Lenssen et al[24] have provided a nice summary of randomized glutamine trials in HSCT patients, noting no difference for several outcomes of concern.

Additional recently published studies have not shown benefit to glutamine supplementation. Pytlik et al[25] conducted a controlled, double-blind study of parenteral glutamine supplementation to autologous transplant patients. Forty patients were randomized to receive isonitrogenous glutamine-containing (30 g alanyl-glutamine dipeptide) or glutamine-free PN. Glutamine patients had significantly fewer days of diarrhea ($p = .03$) but had more severe oral mucositis ($p = .04$), more days requiring opioids ($p = .03$), and increased cost of care ($p = .002$) and relapse rate compared with an unsupplemented group. A scientific correspondence by Canovas et al[26] reported a study of an unknown number of autologous transplant patients who received 20 g/day of either oral glutamine, whole protein, or dextrinomaltose. Primary endpoints were GI toxicity, and secondary endpoints included protein concentrations. No significant differences were noted in

the incidence, severity, or duration of GI toxicity or protein concentrations.

Piccirillo et al[27] studied lymphocyte reconstitution in 2 groups of autologous transplant patients receiving different levels of glutamine supplementation in PN *vs* controls who did not receive glutamine. Both glutamine-supplemented groups showed earlier rises in lymphocyte count than the placebo groups; day 16.5 *vs* day 29 ($p = .005$) in the group receiving 20 g of glutamine, and day 18 *vs* day 29 ($p = .009$) in the group receiving 13.46 g of glutamine per day.

Evidence available at this point does not seem to support the use of agents like glutamine. Future studies must look at appropriate timing (pretransplant *vs* peritransplant), route (oral *vs* IV where there is a choice), duration (with conditioning *vs* with transplant), and long-term effects on outcome, relapse, and GVHD.

Acute Complications and Therapies

Mucositis

Oral and gastrointestinal mucositis are frequent complications of PBSCT. These cause pain and affect quality of life, may be dose-limiting for cancer therapies, and may be risk factors for sepsis in the neutropenic patient. Some degree of oral mucositis in transplant has been reported to occur in 99% of patients, and grade 3 or 4 (severe) in approximately 70% of patients.[28] There is no "gold standard" tool to diagnose and assess the severity of oral mucositis. The variety of scales used includes aspects of anatomic site evaluation such as erythema, ulceration, atrophy, pseudomembranes, and edema as well as functional effects such as swallowing, communication, and ability to ingest nutrition and medication. Evaluation of pain may be included in mucositis assessment schemes or assessed separately. A common factor relating to the degree of mucositis is the intensity of the conditioning regimen. Wardley et al[29] reported that the most severe mucositis was seen in HSCT patients receiving high-dose melphalan and high-dose melphalan with TBI. Sonis et al[30] investigated the clinical and economic outcomes of oral mucositis in patients receiving PBSCT. Among 92 patients with mucositis, a 1-point increase in peak Oral Mucositis Assessment Scale revealed (a) 1 additional day with fever ($p < .01$), (b) 2.1-fold increase in risk of significant infection ($p < .01$), (c) 2.7 additional days of PN ($p < .0001$), (d) 2.6 additional days of injectable narcotic therapy ($p < .0001$), (e) 2.6 additional days in the hospital ($p < .01$), and (f) 3.9-fold increase in 100-day mortality risk ($p < .01$). Mean hospital charges were $42,749 higher among patients with evidence of ulceration compared to those without ($p = .06$). It appears that the presence of mucositis is associated with worse outcomes in transplant patients. Prevalence and severity of mucositis have been documented, and risk factors, which may predict the occurrence of severe mucositis, are now being investigated. Robien et al[31] studied a homogeneous group of 133 patients receiving allogeneic PBSCT for chronic myelogenous leukemia. Using multiple regression analyses, this retrospective study showed statistically significant predictors of oral mucositis, including conditioning regimens containing TBI, body mass index ≥ 25, and presence of MTHFR677TT genotype. The latter genotype has been associated with greater toxicity (including mucositis) among individuals who have received methotrexate. The use of pretransplant multivitamin supplementation showed a trend toward statistical significance as a protective factor for the development of severe mucositis.

Mucositis is a biologically complex process. The events leading to the development of mucositis, which continue to be clarified, have been summarized in a recent report.[32] Sonis et al[30] have outlined the development of mucositis in 5 phases as follows.

Initiation: Generation of ROS by chemotherapy or radiation, and endothelial and connective tissue damage seem to be primary steps in the process of mucositis. These changes seem to precede epithelial damage.

Up-regulation and generation of messenger signals: During the next phase, simultaneous changes occur. Activation of nuclear factor-κ B (NF-κB) appears to be pivotal and, once activated, leads to the up-regulation of many genes. The latter leads to the production of proinflammatory cytokines, including TNF-α , IL-1β , and IL-6. Consequences of the production of these cytokines include expression of adhesion molecules, activation of the cyclooxgenase-2 pathway (COX-2), angiogenesis, tissue injury, and apoptosis. Along with NF-κB, tissue damage also can be related to DNA breaks caused by ROS, chemotherapy- and radiotherapy-activated enzymes, fibronectin breakdown, and macrophage activation.

Signaling and amplification: Proinflammatory cytokines exert a direct damaging effect on mucosal cells and may also amplify the injury caused by radiation and chemotherapy. TNF-α may activate pathways that can lead to tissue injury, which leads to further production of the proinflammatory cytokines TNF-α , IL-1β , and IL-6. A consequence is that tissue is altered biologically even though the gross appearance may remain normal.

Ulceration: This phase is characterized by inflammatory infiltration composed of polymorphonuclear and round inflammatory cells. Bacterial colonization with gram-positive, gram-negative, and anaerobic organisms also occurs during this phase. The consequences of ulceration are further cytokine amplification, inflammation, and pain. The patient is at increased risk for bacteremia and sepsis.

Healing: The healing phase in PBSCT begins with leukocyte recovery. Epithelial proliferation and differentiation, and recovery of local microbial flora occur. It is of interest that after healing the oral

mucosa appears normal, but due to local milieu changes (including residual angiogenesis) the patient is at increased risk of future episodes of mucositis with subsequent cancer therapy.

Evidence-based guidelines have been developed by a group of expert panelists based upon an extensive literature review.[33] Those pertinent to PBSCT patients include use of oral care protocols that include patient education and patient-controlled analgesia with morphine as the treatment of choice for oral mucositis pain. Several other agents (including glutamine) lacked evidence to support a guideline.

As previously mentioned, mucositis is common in patients receiving PBSCT and has extensive clinical and economic impacts. Studies of various agents to attenuate mucositis are ongoing. A placebo-controlled, double-blind, phase III trial of one such agent was recently published.[34] Two hundred twelve patients with hematologic cancers received palifermin or placebo before and after receiving conditioning of chemotherapy and TBI in preparation for autologous PBSCT. Palifermin is a recombinant human keratinocyte growth factor (KGF) that has been shown in animal studies to decrease mucositis. Oral mucositis was evaluated daily for 28 days posttransplant. Mucositis was graded using standardized scales, with grades 3 and 4 mucositis being the most severe. Overall incidence of grade 3 or 4 mucositis was less in the palifermin group (63%) *vs* the placebo group (98%). Median duration of grade 3 or 4 mucositis was less in the palifermin group (3 days) *vs* placebo (9 days). Other significant findings in the palifermin group included reduction in patient-reported mouth and throat soreness, use of opioid analgesics, and use of PN. Long-term follow-up studies are ongoing. Presently the drug (trade name Kepivance, Amgen Inc, Thousand Oaks, CA) is approved for use in patients with leukemia and lymphoma receiving transplants.[35]

Strategies to Minimize Infectious Complications That Affect Nutrition Support

Infections are frequently the cause of mortality in HSCT patients. Because of the period of absolute neutropenia, it is standard for patients to be treated with prophylactic antibacterial, antiviral, and antifungal agents until engraftment. Viruses such as herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), human herpes virus 6 (HHV6), and human herpes virus 8 (HHV8) can be life threatening. Acyclovir is the usual standard prophylactic antiviral therapy for HSV, VZV, HHV6, and HHV8. During cold/flu season, respiratory syncytial virus (RSV) is also very dangerous. To minimize the spread of RSV, some facilities require that staff and family members stay at home if they have any respiratory symptoms. Each person entering the unit must sign a form daily stating that they have no respiratory symptoms. Patients who develop lower-tract RSV are treated with ribavirin. If the patient reactivates or develops a new primary viral infection, foscarnet or ganciclovir therapy will likely be required. Decisions about which drug to use may be based on the lesser of 2 toxicities because foscarnet is nephrotoxic and ganciclovir is myelosuppressive. Foscarnet is associated with severe wasting of potassium, magnesium, calcium, and phosphorus and requires daily electrolyte and mineral monitoring.

Standard antifungal prophylactic therapy is fluconazole. If the patient is suspected of having a fungal infection, therapy is intensified to include voriconazole (frequently not used in small children) or amphotericin, Ambisome (Fujisawa Healthcare Incorporated, Deerfield, IL), or Ablecet (Enzon Pharmaceutical Incorporated, Indianapolis, IN). Each of these amphotericin products is associated with potassium and magnesium wasting by the kidneys, and the patient will require daily electrolyte monitoring with potassium and magnesium replacement. Frequently, very large amounts of potassium are required until 2–3 days after the drug is discontinued.

The combination drug trimethoprim and sulfamethoxalone is the drug of choice for *Pneumocystis carinii* pneumonitis prophylaxis. Use of this drug can increase the patient's risk for folate deficiency, and daily multivitamins should be provided. Bacterial infections are common and are treated according to the antibiotic sensitivities.

Hyperglycemia is another common acute complication in the transplant setting. Patients may have preexisting diabetes, or they may develop hyperglycemia as a result of the extensive use of high-dose corticosteroids or as a result of an infection that occurs due to immunocompromised status. Transplant protocols may involve high-dose corticosteroids during part of the conditioning therapy or even throughout the entire conditioning and neutropenic period as a GVHD prophylaxis therapy. In hyperglycemia, the nutrition support regimen should be evaluated to ensure that the patient is not being overfed and that the patient is not receiving excess carbohydrate. Previous studies[36,37] suggest that aggressive insulin therapy to maintain euglycemia in critically ill patients will help decrease the number of bloodstream infections, renal failure requiring dialysis/filtration, red blood cell transfusions, and mortality. Corticosteroids for GVHD therapy necessitate vigilant blood-glucose monitoring and treatment in the patient with hyperglycemia. This can be challenging in patients who are tapering their corticosteroids, with doses that are different on alternating days.

Diarrhea occurs commonly in HSCT transplant patients. Myeloablative conditioning regimens may cause diarrhea during the first 2 weeks as a result of toxicity to the gastrointestinal mucosa. Mucosal regeneration is usually complete by days 15–20, and diarrhea that occurs after that time is usually attributed to GVHD or an infection. Infectious

sources include astrovirus, adenovirus, rotavirus, and *Clostridium difficile*. Handwashing is the most effective method of preventing iatrogenic spread of these infectious sources from patient to patient.

If large-volume diarrhea occurs, additional zinc should be added to the PN solution to compensate for zinc losses in the stool. Standard therapy is to provide 10–17 mg of zinc per liter of stool output.[38] Copper losses can also be significant with large-volume diarrhea. Serum copper levels should be monitored, and additional copper can be provided in the PN if needed. Many would also consider probiotic therapy as a treatment. The HSCT patient receiving long-term PN who is unable to eat and has diarrhea as a result of conditioning therapy or an infectious cause appears to be a suitable candidate for gut flora/probiotic replacement in the setting of multiple antibiotic coverage. However, probiotic therapy is not recommended in the immunocompromised patient. Published literature cites immunocompromised patients who developed sepsis of an identical strain to the probiotic therapy being used.[39–41]

Hepatic Complications

Sinusoidal obstructive syndrome (SOS), formerly called veno-occlusive disease, is a syndrome of jaundice, weight gain, ascites, and painful hepatomegaly developing within approximately 10–20 days after HSCT. The new name reflects toxic injury to the sinusoidal and venular epithelium and realization that involvement of the hepatic venules is not essential to the disease process. The process is thought to be related to drug metabolites and intracellular depletion of glutathione stores.[42] It is postulated that SOS occurs much more commonly than is appreciated because 20%–30% of autopsy cases found SOS that was not associated with clinical symptoms.[42] High-dose TBI of >13.2 Gy has been associated with the development of SOS in approximately 50% of patients. In patients who receive high-dose cyclophosphamide, the rate of SOS is variable and is thought to be affected by patient individuality in drug metabolism. SOS has not been found in patients after nonmyeloablative regimens. The overall risk for development of SOS is less than in the past for several reasons: the number of chronic hepatitis C patients who are receiving transplants is decreased, physicians are doing less dose escalation of the conditioning therapies, and many drugs that increased SOS risk are no longer being used. Positive predictors for developing SOS include the intensity of the conditioning regimen, the patient's metabolism of cyclophosphamide, the TBI dose, and whether underlying liver inflammation and fibrosis is present. Risk factors include chronic hepatitis C, hepatic fibrosis, cirrhosis, nonalcoholic steatohepatitis, systemic bacterial or viral infections, previous HSCT, and exposure to gemtuzumab ozogamicin (Mylotarg, Wyeth Laboratories, Philadelphia, PA).

Many patients with clinical symptoms of SOS will recover with management of sodium and water balance. Nutrition support volume, medication volumes, and sodium intake should be minimized. In patients receiving PN, all added sodium can be removed. If the patient is receiving sodium in IV medications, the pharmacist should evaluate whether those medications can be changed to a dextrose-based solution. For patients who are eating, their dietary sodium should be restricted as much as possible.

In patients with severe SOS and liver failure, copper and manganese levels should be monitored because these nutrients are frequently present as contaminants in the PN solution, and excessive blood levels can become toxic if biliary excretion is abnormal.[43] Symptoms of manganese toxicity include neuropsychiatric symptoms such as compulsive behavior, emotional lability, hallucinations, extrapyramidal symptoms, and signal changes in the globus pallidus striatum and midbrain on magnetic resonance imaging studies. Copper toxicity symptoms include severe nausea, vomiting, and diarrhea. More serious symptoms such as copper accumulation in the liver, brain, and cornea of the eye, followed by coma, hepatic necrosis, liver failure, and death, can occur with chronic toxicity. If manganese and copper accumulate, they can be removed from the PN, provided in smaller doses, or provided in decreased frequency. Management will depend on the flexibility and abilities of the pharmacy if these nutrients are being provided as part of a multiple trace-element package because attention still needs to be given to providing adequate zinc.

Severe SOS is associated with renal and pulmonary failure for which renal replacement therapy and artificial ventilation will be required. Attention should also be given to vitamin K status in severe SOS. Vitamin K is generated by gut bacteria (nonviable if the patient is receiving broad-spectrum antibiotics), and it is not uncommon that vitamin K status is suboptimal in the HSCT patient with organ failure. Medical therapies for severe SOS include thrombolytic therapies such as tissue plasminogen activator and heparin. These therapies are efficacious in less than one-third of the patients with severe SOS, and efficacy is limited by the risk of intracerebral and pulmonary bleeds.[42] Defibrotide, a medication with antithrombotic, anti-ischemic, and antithrombolytic properties, has also been used.[42] Additional therapies that have been trialed include *N*-acetylcysteine, prostaglandin E1, prednisone, topical nitrate, and vitamin E with glutamine. Surgical therapies may include portosystemic shunts and liver transplants.[42]

A long-term problem affecting many HSCT patients is hemosiderosis. Many HSCT patients receive a large number of iron-containing blood products during their treatments. Patients with

Table 1
Seattle Children's Hospital and Regional Medical Center's multivitamin (MVI) recommendations for use in children receiving daily continuous renal replacement therapy (CRRT) with and without elevated vitamin A levels

Vitamins	CRRT: ≥11 years normal vitamin A	CRRT: ≥11 years elevated vitamin A	CRRT: <11 years normal vitamin A	CRRT: <11 years elevated vitamin A
Thiamine	Full MVI +50 mg	½ MVI +50 mg	Full MVI +25 mg	½ MVI +25 mg
Riboflavin	Full MVI +1 mg	½ MVI +1 mg	Full MVI +0.5 mg	½ MVI +0.5 mg
Niacin	Full MVI +50 mg	½ MVI +50 mg	Full MVI +25 mg	½ MVI +25 mg
Pantothenic acid	Full MVI +1 mg	½ MVI +1 mg	Full MVI +0.5 mg	½ MVI +0.5 mg
Pyridoxine	Full MVI +25 mg	½ MVI +25 mg	Full MVI +15 mg	½ MVI +15 mg
B_{12}	Full MVI +30 μg	½ MVI +30 μg	Full MVI +15 μg	½ MVI +15 μg
Folate	Full MVI +1 mg	½ MVI +1 mg	Full MVI +500 μg	½ MVI +500 μg
Biotin	Full MVI	½ MVI	Full MVI	½ MVI
Vitamin C	Full MVI +90 mg	½ MVI +90 mg	Full MVI +45 mg	Full MVI +45 mg
Vitamin K	200 μg	200 μg	200 μg	200 μg

Vitamin components include standard pediatric MVI (Infuvite Pediatric by Baxter, Deerfield, IL), B complex (100 injectable by Bioniche Pharma, Belleville, ON), and single vitamin doses (currently available for thiamine, pyridoxine, B_{12}, folate, vitamin C and vitamin K).

thalassemia, aplastic anemia, and hematologic malignancies who have received large numbers of iron-containing blood products before transplant are especially at risk. It is thought that as many as 90% of long-term survivors of HSCT for hematologic malignancy or aplastic anemia have hemosiderosis of the liver.[42] These patients most likely have iron deposits in other organs as well. It is recommended that these patients avoid iron supplements and iron-containing multivitamins after HSCT.

Renal Complications

Renal impairment occurs as part of the SOS syndrome but may also occur independently. The nephrotoxic nature of many of the medications is superimposed on the damage caused by the TBI and high-dose chemotherapy. Hemolytic uremic syndrome (HUS) and thrombotic thrombocytic purpura (TTP) are 2 examples of thrombotic microangiopathies. If renal replacement therapy is needed, the nutrition goals will be to meet nutrient needs within the allowed fluid volume, correct electrolyte and mineral imbalances, and maintain optimal vitamin and mineral status by preventing deficiencies and toxicities. Specific water-soluble vitamin complexes have been created for dialysis patients and are available to be given orally or *via* a feeding tube into the gut. If an HSCT patient requires extended renal replacement therapy, attention should be given to vitamin A, water-soluble vitamin, and micronutrient status. Vitamin A is known to accumulate in renal failure. The lowest reported intakes causing vitamin A toxicity have occurred in persons with liver function compromised by drugs, viral hepatitis, or protein-energy malnutrition.[44] Children and small adults receiving standard parenteral vitamin doses can accumulate vitamin A rapidly and have vitamin A levels 2–3 times normal within 2 weeks when receiving renal replacement therapy.[45] It is prudent to check vitamin A levels and adjust intake if needed in patients with renal failure and risk factors for early vitamin A toxicity. Chromium and molybdenum may also accumulate in renal failure and should be monitored for the need for dose reduction or discontinuation.[43] If the patient is undergoing continuous renal replacement therapy with large volumes of ultrafiltrate and or dialysate, there are water-soluble vitamin, glucose, amino acid, and some mineral losses.[46–50] It may be appropriate to provide extra amounts of these nutrients.

At Seattle Children's Hospital, we have decided to assume that standard renal vitamins are appropriate for 3-times-per-week dialysis therapy (and the associated losses). We extrapolated to 7-day-per-week therapy for patients requiring continuous renal replacement therapy and doubled the standard renal vitamin dose. Our policy is to provide 2 tablets daily to children 11 years of age or older, and half of a tablet twice a day to children <11 years old (excluding infants). For patients undergoing continuous renal replacement therapy who cannot receive an enteral vitamin, we adjust the vitamins in the PN as able per the availability of B complex and single vitamin products. The regimen is changed to enteral vitamins as soon as the patient is able to tolerate and absorb enteral medications. See Table 1 as an example of parenteral vitamin doses given for children receiving continuous renal replacement therapy in our institution.

Laboratory Monitoring

Baseline initial blood chemistries, glucose, blood urea nitrogen, creatinine, liver-function tests, and fasting cholesterol and triglyceride levels should be drawn before conditioning therapy. In the patient who has received extensive chemotherapy for resistant disease with resultant suppression of hematopoietic function requiring multiple transfusions, it is helpful to determine baseline ferritin levels. Patients who have been hospitalized for extensive

periods before HSCT and who have not been receiving therapy with adequate vitamin D may present to transplant with suboptimal vitamin D status and baseline low calcium levels. It is important to be aware of this potential problem, especially if the patient will be at high risk for GVHD and require corticosteroid therapy.

All of this initial information serves to guide decisions about changes in the patient's requirements over time if organ function changes. When a patient receives nutrition support, it is important that the patient's laboratories be monitored regularly. Blood chemistries such as blood urea nitrogen, creatinine, and glucose levels need to be checked daily. Although GVHD prophylaxis medications are being titrated, it is important that serum calcium, magnesium, and phosphorus levels be checked 3 times per week and after dose changes until the patient is stable. High-dose cyclosporine and tacrolimus can cause hyperkalemia; therefore, serum potassium levels need to be monitored regularly, especially when drug doses are increased.

Support for kidney failure will require monitoring of electrolytes and minerals to facilitate the appropriate adjustments in nutrition support. The patient with multiple-organ failure may well have metabolic problems that will result in hyperglycemia or hyperlipidemia. Special consideration needs to be given to laboratory monitoring when the patient is receiving drugs that can result in wasting of electrolytes or minerals. Furosemide is commonly used to manage volume retention and, if given in large or repeated doses, can result in large serum losses of potassium and sodium. Amphotericin products can also cause large losses of potassium and magnesium. Foscarnet can result in wasting of potassium, calcium, magnesium, and phosphorus. In all of these situations, the patient's serum electrolyte and mineral levels should be tested daily, with appropriate amounts of these electrolytes/minerals provided.

Nutrition Support Trends

Indications for PN

Extensive use of PN in HSCT evolved for 2 reasons: (1) the severity of the gastrointestinal toxicity induced by the high doses of conditioning therapy once considered necessary to destroy the patient's own immune system and, in patients with malignancy, tumor cells; and (2) the availability of central venous access established for other supportive therapies in all patients.[51,52] A Cochrane review (pooled data from all available published and unpublished studies) compared multiple clinical outcomes in patients randomized with PN or IV hydration or enteral nutrition after HSCT.[21] When compared with IV hydration, 2 studies met criteria for inclusion, and among these 166 patients, a significantly higher rate of infection occurred in those who received PN. Unfortunately, because of the way the data were presented, the review excluded the larger of the 2 studies from the analysis of the survival outcome. This excluded a randomized trial that had been the justification for several decades for the use of PN owing to the improved long-term survival among both pediatric and adult allogeneic graft recipients who were well nourished at the time of transplant and received PN.[53] Since the Cochrane review was reported, 1 randomized trial of 55 well-nourished patients with stages II-IV breast cancer undergoing autologous transplantation did not demonstrate a survival benefit with PN.[54] In all these clinical trials, patients receiving PN have shown improved nutrition status compared with IV hydration and oral diet.[21,53,54]

It is doubtful that the majority of these studies are applicable in the current diverse HSCT environment. In reduced-intensity regimens, PN appears to be less frequently required. Intestinal permeability (as a surrogate for gut damage) was not increased in 1 reduced-intensity regimen (fludarabine and antithymocyte globulin with either cyclophosphamide or busulfan), and average days of elevated C-reactive protein (0.3 *vs* 5.3) and days of PN (1.4 *vs* 18.3) were significantly less for the patients receiving reduced-intensity regimens compared with patients receiving myeloablative therapy (TBI and cyclophosphamide).[55] Only 2 patients receiving the reduced-intensity conditioning regimen experienced nausea, vomiting, oral pain, or diarrhea.[55] Other investigators have similarly documented a significant reduction in the need for PN as a reflection of the blunting of mucosal injury in lower intensity and nonmyeloablative regimens.[56,57] In patients with myelodysplastic syndrome treated with fludarabine (150 mg/m^2), busulfan (8 mg/kg), and alemtuzumab (20 mg IV, day −5 to day −1), only 4% required PN compared with 52% of patients receiving busulfan (16 mg/kg), cyclophosphamide (200 mg/kg), or busulfan (4 mg/kg) and cyclophosphamide (120 mg/kg) doses in combination with TBI 1440 cGy and alemtuzumab (10 mg IV, day −5 to day +5).[56]

Even for patients treated with high-dose preparative therapy, PN is not uniformly indicated. Iestra and colleagues[58] applied standard criteria for malnutrition in oncology patients to determine appropriate use of PN in HSCT: (1) severe malnutrition at admission (serum albumin <3 g/dL or body mass index <18.5 kg/m^2); (2) a prolonged period (7–10 days) of minimal oral intake; or (3) clinical weight loss >10%. Indications for PN differed significantly between treatment protocols, with PN indicated in only 37% of autologous patients conditioned without TBI and up to 92% of recipients of a mismatched allograft.[58] Etoposide and melphalan are associated with the highest degree of oral toxicity, whereas more moderate stomatitis occurs with busulfan, mitoxantrone, paclitaxel, TBI, and thiotepa. Moderate gastrointestinal toxicity (diarrhea) has been implicated with carmustine, cisplatin, etoposide, melphalan, and TBI, with more toxicity induced by

carboplatin, cyclophosphamide, and cytosine arabinoside.[59–61]

The need for PN may also be modified by "gut-protectant" therapy. A variety of pharmacologic agents, such as IL-11, sucaralfate, amifostine, transforming growth factor-β, and keratinocyte growth factor, are under investigation to protect the GI tract from the mucosal injury of conditioning and to reduce the severity of mucositis and need for narcotics and PN.[62] Palifermin, humanized keratinocyte growth factor, given immediately before TBI in autologous patients with hematologic malignancies was recently demonstrated to decrease significantly the percentage of days study patients ($n = 106$) required PN compared with controls ($n = 106$), 31% *vs* 55%, respectively.[34]

In lieu of a standard recommendation as to when PN is indicated, clinicians must use their expert judgment, reserving it for those patients in whom prolonged gastrointestinal failure is expected, that is, after myeloablative conditioning regimens with a high gastrointestinal toxicity profile, in refractory gut GVHD, and when malnutrition cannot be reversed by enteral nutrition alone.

Indications for Enteral Nutrition

Few transplant centers attempted tube feeding until the last 10 years owing to the formidable list of GI complications (Table 2). The Cochrane review, which evaluated PN *vs* enteral nutrition, included only 1 study from the 1980s and 2 abstracts for a total of 144 patients, but none of the data could be used on key outcomes: GVHD, survival, and infections.[21] Interest in tube feeding has been driven by a need to decrease cost and by the desire to mitigate the risks associated with PN, especially infection. There is additionally an attraction to the prospect that enteral feedings could enhance the gut-barrier function. Disruption of the mucosal barrier by intensive chemoradiotherapy is believed to the portal of infection for 25–75% of bacteremias.[63] Early intervention with enteral nutrition to maintain mucosal integrity may reduce infections and dampen the inflammatory response that amplifies mucosal toxicity and predisposes the patient to GVHD.[64]

Given the lack of sufficient data to show a benefit of enteral feedings over PN in HSCT, what is the evidence that enteral nutrition can be used? There have been 11 reports of enteral nutrition in HSCT that are case series or pilots involving 185 patients (Table 3). The collective experience of these investigators suggests some major challenges in using an exclusive enteral approach, primarily because of difficulties in maintaining access and in delivering adequate nutrition.

Vomiting and dislodgement of nasal tubes is a common complication of enteral nutrition in HSCT patients. Sefcick and colleagues[65] were able to successfully feed 8 of 15 adult patients undergoing allogeneic transplant with a self-propelling nasojejunal tube until day of engraftment. Their recommendation was to delay tube placement until the day after the conditioning therapy and stem cell infusion are completed, before onset of mucositis. However, this approach may miss a critical window during conditioning when enteral nutrition might exert its physiologic benefit on gut mucosal integrity and modulation of the inflammatory response. Research on timing of tube placement and start of feeding could help determine whether it is worth the effort for the patient and the team to endure repeated tube placements during conditioning.

The inability to infuse adequate nutrition has led to PN "rescue" rates ranging from 14%–100%.[66–72] In those studies that had lower PN rescue rates, an enteral approach resulted in significant weight

Table 2
GI symptoms presenting challenges to enteral feeding in hematopoietic stem cell transplantation

Symptom	Differential diagnosis
Nausea and vomiting	Chemotherapy, radiation
	Medications: antibiotics, cyclosporine
	GVHD
	Liver disease (GVHD, viral infection, cholestasis)
	Infections
	Pancreatitis
	Gastroparesis and delayed gastric emptying
Diarrhea	Chemotherapy, radiation
	GVHD
	Viral infections
	Antibiotics
	Pseudomembranous colitis (*Clostridium difficile*)
Bleeding	Ulcers (gastric, duodenal, small bowel or colon)
	GVHD
Dysphagia	Chemotherapy, radiation
	Viral or fungal infection
	Reflux esophagitis
	GVHD
Abdominal pain	GVHD
	Infections (*C difficile*, CMV)
	Liver disease (infection, SOS, abscess)
	Pancreatitis
	Duodenal or gastric ulcer
	Biliary sludge or gallbladder stones
	Typhlitis
Ileus	Opiate analgesics
	Sepsis
	GVHD
	Infections
	Pancreatitis
	Pneumonia

CMV, cytomegalovirus; GVHD, graft *vs* host disease; SOS, sinusoidal obstructive syndrome.
Adapted from Lenssen P. Hematopoietic stem cell transplantation. In: Rolandelli R, Bankhead R, Boullata J, Compher C, eds. *Clinical Nutrition: Enteral and Tube Feeding*. 4th ed. Philadelphia, PA: Elsevier Saunders; 2005:544–558, with permission from Elsevier.

Table 3
Enteral feeding studies in hematopoietic cell transplantation

Study	Population	Age	Conditioning	Tube and formula	Clinical outcomes	Enteral complications
Szeluga, 1987[66] RCT PN *vs* enteral (oral and tube feeding) program	Allo (n = 46) Auto (n = 15) 45 With hematological malignancies; 10 other cancers; 6 aplastic anemia	Pediatric, >10 years, and adult	Busulfan/cyclophosphamide Cyclophosphamide/TBI Cyclophosphamide/ cyclosporine	NG placed when protein intake <0.5 g/kg (time not provided but before d 28 post-HSCT) Details of infusion and formula not provided	13% Failures PN group (unable to place catheter) 23% In "enteral" feeding program eligible for tube feeding (n = 7); all needed PN PN preserved body cell mass	100% Failures: 3 not placed due to severe GI symptoms; 1 refused; 3 placed but unsuccessful due to vomiting and diarrhea "Occasional" feeding-tube occlusion
Mulder, 1989[73] Phase I: Case series Phase II: RCT PN *vs* PPN + enteral	Auto with solid tumors Phase I: counseling and enteral feedings "as necessary" (n = 10; 5 had enteral) Phase II: PN (n = 11) PPN + enteral (n = 11)	Adult	Cyclophosphamide 7 g/m^2 Etoposide 0.9–2.5 g/m^2	NG (time of tube placement not provided); continuous Low lactose whole protein	Phase I: 10% weight loss Phase II: 2.5% wt loss; N balance same both groups Enteral group: twice rate of sepsis; less diarrhea	None noted for aspiration, parotitis, sinusitis, or inflammation of the nose
Papadapoulou, 1997[67] Pilot study	Hematological malignancies (57%), solid tumors (5%), other (38%) Tube at 5% wt loss Accepted (n = 21) Refused (n = 8)	Pediatric	Cyclophosphamide/TBI (n = 8) Cyclophosphamide/ busulfan (n = 8) Idarubicin/TBI (n = 5)	NG (time of tube placement not provided); continuous Low lactose whole protein <20 kg 1.0 kcal >20 kg 1.5 kcal	29% Needed PN Mean duration feedings 22 days Increase wt-for-ht z score 0.08	38% Failures due to vomiting (n = 7) and diarrhea (n = 1) Feedings <50% of needs
Roberts, 1998[68] Case series	Auto (n = 4); allo related (n = 5); unrelated (n = 7)	Adult	Auto: cyclophosphamide Allo: cyclophosphamide/ TBI	PEG placed median 104 days post-HSCT (32–1125 days); bolus Isotonic, intact protein (n = 13) Semi-elemental (n = 2) Elemental (n = 1)	25% Needed PN Mean wt gain 0.7 kg; 68% able to maintain or gain wt	25% Failures due to GVHD diarrhea (3); high residuals (1) 44% High residuals (most responded to prokinetic agent, 1 converted to PEG-J) 6% Local infection at PEG
Pietsch, 1999[79] Pilot study	N = 3 HSCT of 17 total cancer patients 2 Solid tumor, 1 Hodgkin's Transplant type not provided	Pediatric	ND	NG (time of tube placement not provided); continuous Pediatric free amino acid MCT-based	ND % HSCT needed PN	No sinusitis or epistaxis
Pederson, 1999[69] Case series	N = 5 HSCT of 32 total cancer patients Diagnosis/transplant type not provided	Pediatric	ND	PEG placed "during neutropenia" Details of infusion and formula not provided	All HSCT needed PN 1 Converted to PEG-J due to stomach GVHD	20% Local infection at PEG

(*Continued*)

Table 3 (*Continued*)

Study	Population	Age	Conditioning	Tube and formula	Clinical outcomes	Enteral complications
Barron, 2000[70] Case series	*N* = 27 HSCT of 44 total cancer patients	Pediatric	ND	G-tube placed by retrograde percutaneous technique mean 9 wk before (*n* = 9) or mean 34 wk post- (*n* = 18) HSCT Details of infusion and formula not provided	64% Needed PN (% HSCT patients not provided)	41% Local infection at G-tube 4.5% Peritonitis (% HSCT patients not provided)
Lenssen, 2001[24] Pilot study	Allo related (PEG-J) (*n* = 1); unrelated (NJ) (*n* = 5); preexisting gastrostomy (*n* = 2)	Adult and pediatric	ND	PEG or NJ placed before conditioning Isotonic, peptide-based	100% Needed PN	PEG infection: delay of HSCT 100% Failure NJ (3 vomit, 2 pulled at patient request) 100% Failure gastrostomy: typhlitis or severe diarrhea
Sefcick, 2001[65] Pilot study	Allo with hematological malignancies related (*n* = 8); unrelated (*n* = 7)	Adult	Cyclophosphamide 120 mg/m^2 TBI 12–14.4 Gy (+ ATG or T-cell depletion in unrelated donor)	NJ with Bengmark tube placed 1 wk before HSCT Peptide MCT-based; glutamine added day 7+	53% Retained tube until engraftment Mean duration feedings 16 days (range 0–34 days) Wt loss at discharge 4.5%, 3 mo 7%, 6 mo 5%	47% Vomited tubes during conditioning/early post-HSCT Epistaxis tube side (*n* = 1), opposite side (*n* = 1) Diarrhea requiring decreased infusion rate (*n* = 2)
Langdana, 2001[71] Case series	Allo matched related (*n* = 23); unrelated donor (*n* = 19) Auto (*n* = 11) Hematological malignancy (*n* = 31) Solid tumor (*n* = 9) Other (*n* = 13)	Pediatric	Cyclophosphamide TBI 7.5–14.4 Gy Busulfan/cyclophosphamide Cyclophosphamide/ATG (+ T-cell depletion in unrelated donor) High-dose melphalan BEAM	NG placed before or within 1 wk of HSCT Whole protein (*n* = 19) Semi-elemental (*n* = 28) Elemental (*n* = 2)	8% Excluded (early death) 14% Needed PN 8% Needed no nutrition support Median duration feedings 52 days (range 5–267 days) Mean change IBW 101%–97%; malnutrition (<85% IBW) increased 6%– 14%	No sinusitis Enteral feedings <50% of needs

(*Continued*)

Table 3 (*Continued*)

Study	Population	Age	Conditioning	Tube and formula	Clinical outcomes	Enteral complications
Hopman, 2003[72] 22 PN (9 Randomized, 13 Nonrandomized) 12 Enteral (6 Randomized, 6 nonrandomized)	Allo matched (n = 22); mismatched (n = 12) Family *vs* unrelated not specified Malignant (n = 24) Nonmalignant (n = 10)	Pediatric	Cyclophosphamide (n = 31) TBI (n = 18) ARA-C (n = 9) VP-16 (n = 12) Busulfan (n = 12) Melphlan (n = 9) Regimens not described; PN patients received more TBI (p = .04)	Details of tube not provided; continuous night; day also if necessary Intact protein age-appropriate 1.0 And 1.5 kcal	Median duration feedings enteral 43 days; PN 27 days (p = .0001) Higher total calorie/protein intake in enteral ($p < .05$); oral intake higher in PN ($p < .05$) No difference change in nutrition status, "hematological recovery," total days vomiting/diarrhea, sepsis episodes, mortality Less cholestasis (p = .057) and GVHD (p = .07) in enteral (p = .057); GVHD Mean cost lower in enteral ($1180) than PN ($1620)	50% Complete and 25% partial failure of enteral at median day 6 due to vomiting or diarrhea 25% Who tolerated enteral exclusively younger (3.3 years) than others (8 years)

Allo, allogeneic; ATG, antithymocyte globulin; auto, autologous; BEAM, brain electrical activity mapping; G tube, gastrostomy tube; GVHD, graft *vs* host disease; HSCT, hematopoietic stem cell transplant; IBW, ideal body weight; MCT, medium chain triglyceride; ND, not determined; NG, nasogastric tube; NJ, nasojejunal tube; PEG, percutaneous gastrostomy tube; PEG-J, percutaneous gastrojejunostomy tube; PN, parenteral nutrition; PPN, peripheral parenteral nutrition; RCT, randomized control trial; TBI, total body irradiation.
Adapted from Lenssen P. Hematopoietic stem cell transplantation. In: Rolandelli R, Bankhead R, Boullata J, Compher C, eds. *Clinical Nutrition: Enteral and Tube Feeding*. 4th ed. Philadelphia, PA: Elsevier Saunders; 2005:544–558, with permission from Elsevier.

Table 4
Characteristics of candidates to consider for enteral nutrition in HSCT

Conditioning regimen	Nonmyeloablative Reduced intensity Myeloablative with lower GI toxicity profile
Type of transplant	HLA-matched related donor (expected lower incidence of GVHD and earlier recovery)
Critically ill	Trophic feedings may be initiated without the intent to provide full nutrition support, OR full feedings may be used if no gut dysfunction is present.
Prolonged recovery	Has the patient failed to transition to oral intake after resolution of regimen-related toxicities (ie, is mucositis healed, is the patient off all IV analgesics, are diarrhea volumes minimal)? Is the patient malnourished or at high risk of becoming malnourished?
Access	Was enteral access established before HSCT (ie, gastrostomy tube)? Are central venous access options limited? Will the patient consent to an enteral feeding tube?

GI, gastrointestinal; GVHD, graft *vs* host disease; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplant.

loss,[65] decrease in body cell mass,[66] and an increase in the frequency of malnutrition in children.[71] The study with the lowest percentage of patients requiring rescue with PN (14%) excluded the patients who died during their initial hospitalization,[71] and thus the data asserting an 86% success rate with exclusive enteral feedings are not representative of the spectrum of experience with HSCT. In this study, Langdana and coworkers[71] provided <50% of the estimated average energy requirement *via* tube feeding for a median length of 52 days (range 5–267 days) in patients between the ages of 6 months and 17 years old undergoing allogeneic ($n = 42$) or autologous ($n = 11$) HSCT. Six percent of the children were considered malnourished pretransplant (defined as <85% ideal body weight). Using the same criteria at hospital discharge, >14% of the children were considered malnourished. Diarrhea and vomiting were common, and during the period of maximal gut toxicity, elemental feedings were used.

Other complications of enteral feedings include deficiencies of magnesium, phosphorus, zinc, and selenium[67,71]; delayed gastric emptying[73]; infections at gastrostomy tube sites; and the inability to feed in the presence of large-volume diarrhea either postconditioning or with GVHD.[24,66,68,71] No sinusitis was observed.[71,73,74]

The placement of surgical or percutaneous gastrostomy tubes is concerning for safety issues in patients with neutropenia or thrombocytopenia. The most common practice is to ensure that the patient has an absolute neutrophil count of at least 500-1000/mm^3 and a platelet count boosted by transfusions of >50,000/mm^3. For nasal tubes, platelets in the 10,000–20,000/mm^3 range are probably adequate, but the risk for bleeding needs to be determined by the attending oncologist. Adequate flushing of the enteral tube is essential in order to maintain tube patency. Patients undergoing allogeneic HSCT typically have dozens of pills to take over the course of the day, and occlusion of nasoenteric tubes is a risk if medication administration *via* the tube occurs. At our center, we do not have a protocol for replacing functional nasoenteric tubes that have been in place for an extended period but recommend the team consider changing it after 8 weeks.

The ideal administration of enteral formulas is *via* a closed feeding system. This presents a dilemma when a pediatric elemental formula is desired. If open administration systems must be used, nursing should never put more than a 4-hour infusion volume in the bag at a time. Nursing must also be very conscientious about the length of time the formula is allowed to hang if the feeding is disrupted. Strict adherences to 4-hour maximum time periods should be emphasized. The enteral feeding should always be considered a potential infectious source in the patient with unexplained fever or diarrhea, and a stool culture should be obtained. For patients receiving feedings in the home setting, food and formula safety guidelines need to be presented, reviewed, and monitored by a nutrition professional. When beginning enteral feedings, some authors report beginning with whole protein-based formulas and resorting to peptide-based or elemental formulas when intact protein is not tolerated.[71] Others use semielemental formulas.[24,65] In this authors' experience, a range of pediatric and adult formulas has been necessary, dependent on organ dysfunction, and has included renal formulas in patients requiring dialysis or with elevated serum phosphorus or potassium, 2 kcal/mL formulas in patients with fluid overload, low-calcium formulas in infants with osteopetrosis, fat-free formulas in patients with chylous leakage, etc. The tube-feeding schedule is affected by the enteral goals of feeding and whether the feedings are intended to provide complete or partial support, the overall gut function, and whether there is any contraindication to bolus feedings (such as delayed gastric emptying or suspected gastroparesis). If enteral feedings are begun in order to transition the patient off of PN after major gut toxicity, continuous-drip feedings started at a very low rate and advanced slowly seem to be most successful. Table 4 summarizes potential applications of enteral feedings in HSCT.

Immunosuppressed Diet

The provision of a diet low in microbial content has been common for a number of years in patients receiving HSCT. Factors leading to concern related to the diet for immunocompromised patients include emergence of new pathogens, increased variety of foods available for consumption in the developed world, and increased number of susceptible persons.[75] The interpretation of "immunosuppressed diet" varies widely between facilities, but the use of labor- and resource intense "sterile diets" appears to be less common. A recent survey of dietary restrictions was conducted in 156 facilities with inpatient centers, who were members of the Association of Community Cancer Centers.[76] Seventy-eight percent of patients with neutropenia were receiving restricted diets, 92% when neutropenia was documented and 9% from the initiation of cancer treatment. The most commonly restricted foods were fresh fruit and juices (92%), fresh vegetables (95%), and raw eggs (74%). Similar lack of consistency in timing of initiation of the restricted diet and types of foods restricted was found in a survey of 7 pediatric bone marrow transplant programs.[77] Ladas[78] recommends the following be considered in determining the diet for the neutropenic patient: severity and duration of neutropenia, overall nutrition status of the patient, and impact of the recommendation on the quality of life. Paramount in any specific diet is the observation of safe food handling practices. Guidelines can be found at the following websites: www.foodsafety.gov, www.fda.gov, www.fsis.usda.gov, and www.cdc.gov.

There continues to be a lack of research regarding "best practice" for diet in neutropenic patients, but present practice suggests advising patients to follow a low-risk immunosuppressed diet.[79] See Table 5 for immunosuppressed diet precautions recommended during the transplant process and while patients continue to be immunocompromised.

Autologous transplant and chemotherapy patients may discontinue diet guidelines 3 months postchemotherapy or posttransplant if all immunosuppressive therapy has been stopped. Allogeneic patients may discontinue immunosuppressed diet guidelines when off all immunosuppressive therapy (cyclosporine, prednisone, methylprednisolone, tacrolimus, etc).

Conclusion

The field of HSCT has undergone many changes over the past few years. Among these changes are a shift from marrow collection to peripheral blood collection and cord blood, inclusion of nonmyeloablative and reduced-intensity conditioning regimens, and increased use of enteral nutrition support. As well, various agents are being investigated to mitigate complications such as mucositis. With the rapid pace of change in support care for infection prevention, infection treatment, and organ toxicities, we

Table 5
Immunosuppressed diet guidelines indicating foods to be avoided during immunosuppressive therapy

Meats/protein	Raw and undercooked meat (including game), fish, shellfish, poultry, eggs, hotdogs, sausage, bacon
	Raw and uncooked eggs, unpasteurized egg products
	Raw tofu, unless pasteurized or aseptically packaged
	Luncheon meats (including salami, bologna, hot dogs, ham, others), unless heated until steaming
	Refrigerated smoked seafood typically labeled as lox; kippered, nova-style, smoked or fish jerky (unless contained in a cooked dish)
	Pickled fish
Dairy products	Unpasteurized milk and raw milk products, unpasteurized cheese, and unpasteurized yogurt
	Aged cheeses (including brie, camembert, blue, Gorgonzola, Roquefort, Stilton, etc)
	Mexican-style soft cheese, including queso blanco and queso fresco; farmer's cheese; feta cheese
	Cheese containing chili peppers or other uncooked vegetables
	Refrigerated cheese-based salad dressings (eg, blue cheese), not shelf stable; salad dressings containing raw unpasteurized eggs
Fruits/vegetables	Unpasteurized commercial fruit and vegetable juices
	Unwashed raw vegetables and fruits and those with visible mold
	All raw vegetable sprouts (alfalfa, mung bean, all others)
	Unroasted nuts and any nuts in the shell
	Refrigerated salsa products
Breads/cereals	Uncooked raw grains
	Unrefrigerated cream or custard-filled baked goods (ie, donuts)
Miscellaneous	Raw or non–heat-treated honey
	All miso products (eg, miso soup); tempe (tempeh); maté tea
	All moldy and outdated food products
	Unpasteurized beer (not cold filtered)
	Raw, uncooked brewer's yeast
	Well water, unless boiled for 1 minute
	Sun tea
	Herbal preparations and nutrient supplements (contraindicated due to food safety, potential for known and unknown interactions with medications, potentially excessive quantities, potential for contamination with unintentional additives, etc)

Adapted with permission from Tables: special diets. In: Charuhas PM, ed. *Hematopoietic Stem Cell Transplantation: Nutrition Care Criteria*. 2nd ed. Seattle, WA: Seattle Cancer Care Alliance; 2002: 195–197.

have seen the need to be vigilant in our nutrition support monitoring. Due to the diversity of conditioning regimens, the provision of the most appropriate level of nutrition support continues to be a question best left to expert clinical judgment.

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