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Review

# Total parenteral nutrition and hematopoietic stem cell transplantation: an expensive placebo?

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**Summary:**

**A majority of patients undergoing hematopoietic stem cell transplantation (HSCT) suffer from severe mucositis and enteritis due to cytotoxic therapy and immune dysregulation, resulting in prolonged decreased oral intake, nausea, vomiting and diarrhea. While total parenteral nutrition (TPN) is often given to patients in order to maintain their nutritional status during the peritransplant period, there is conflicting evidence to support its routine use. We evaluated the small number of prospective randomized and nonrandomized controlled trials that assessed important clinical outcomes such as time to engraftment, rates of infection, overall survival and length of hospitalization. We believe that the data do not support the routine use of parenteral nutrition as first-line therapy but should be reserved for those patients who are unable to tolerate enteral feedings. We also believe that glutamine supplementation cannot be recommended to all HSCT recipients as it has been shown to increase morbidity and mortality rates in autologous transplant patients. Further investigations that test accurate monitoring assessments and incorporate specific substrates such as lipids with parenteral and enteral nutrition are warranted. Novel therapies such as recombinant human keratinocyte growth factor and glucagon-like peptide show future promise in modulating the severity and duration of mucositis, minimizing further the need for TPN.**
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Since it was first introduced nearly 40 years ago hematopoietic stem cell transplantation (HSCT) has been used to cure a variety of malignant and nonmalignant diseases. While this modality may be a life-saving treatment for many patients, the cytotoxic regimens and the development of graft-versus-host disease (GVHD) often result in significant morbidity.[1] Toxicity to the rapidly dividing cells of the gastrointestinal tract manifests as severe mucositis and enteritis that causes painful oral ulcerations, decreased oral intake, nausea, vomiting and diarrhea. Regardless of nutritional status prior to transplant a majority of patients require nutritional supplementation during the peritransplant period. Total parenteral nutrition (TPN) can be an attractive alternative to enteral feedings in the setting of decreased gut function. Since Weisdorf *et al*[2] showed an increase in overall survival in adult and pediatric allogeneic and autologous stem cell transplant patients who received TPN, this adjunctive therapy has been considered a standard of care at many transplant centers.

## Limitations of TPN

TPN is a treatment potentially associated with significant limitations including a fluid overload state, hyperglycemia and hepatic dysfunction (Table 1). While some articles that were reviewed stated that there were no statistically significant increases in complications related to TPN, others reported trends towards more bacteremia, catheter-site infections, increased diuretic use and subclavian vein thromboses in those patients who received TPN support.[3]

HSCT is a rapidly changing field and the available data on the use of TPN appear to be outdated. The purpose of this review is to present the small number of prospective, randomized and nonrandomized controlled trials of TPN, review their limitations in the setting of current trends and provide insight into new preparations. This review also will present current data on glutamine, lipids and palifermin as well as monitoring techniques in the care of transplant patients.

## Methods

Pertinent English language publications were identified by searching PubMed using the keywords, alone or in combination, 'parenteral nutrition', 'glutamine', 'lipids', 'bone marrow transplantation', 'HSCT', 'anthropomorphic parameters', 'nutritional indices' and 'growth factor support.' Our research encompassed the years 1980 through 2004. Additional publications were identified using the reference lists of relevant papers.

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## Results

### *Nutritional assessment parameters (Table 2)*

Reviewed studies employed a variety of variables to assess nutritional states. Although the biochemical or serologic markers are easiest to measure, these tests are influenced significantly by many clinical events, in addition to nutritional states.[4–6] The most accurate methods such as nitrogen balance and bioelectric impedance measurements are tedious and impractical in the transplant setting, and may require special expertise.[7–9]

### *Review of selected studies (Table 3)*

Nearly 20 years ago Weisdorf *et al*[2] performed a prospective, randomized controlled trial comparing TPN to an enriched dextrose solution in 137 adult and pediatric patients ages, 2–45 years, undergoing allogeneic or autologous HSCT for a variety of hematologic and metabolic derangements. Parenteral nutrition was started 7 days before stem cell infusion while the patients were receiving cytoreductive chemotherapy. A composite nutritional status score was calculated weekly for 5 weeks using serum albumin, prealbumin and transferrin concentrations, patient weight, triceps skin-fold thickness and arm muscle circumference. Clinical outcome parameters included overall survival, relapse rate, time to engraftment, disease-free survival, acute and chronic GVHD, bacteremia and duration of hospitalization. The 2-year overall survival and relapse-free survival were significantly longer in those patients receiving TPN (50 *vs* 35%, $P=0.011$ and 41 *vs* 22%, $P=0.026$, respectively). Autograft patients, however, did not show a difference in either category when analyzed separately. Allograft patients who received TPN had a significantly higher rate of bacteremia than the control group (72 *vs* 48%, $P=0.001$). Although caloric and protein intake and serum prealbumin concentrations were significantly higher in the group randomized to TPN, there were no differences in time to engraftment, duration of hospitalization or incidence of GVHD. In all, 61% of those patients randomized to the control arm required TPN due to malnutrition according to their nutritional status score. The authors concluded that the increased overall long-term survival in those patients who received TPN was either due to enhanced chemotherapeutic activity or to improved immune function and marrow recovery with the infusion of nutritional substrates.

That same year, Szeluga *et al*[3] conducted a smaller study ($N=61$) evaluating an individualized enteral feeding program (EFP) as compared to TPN starting the day prior to HSCT in allogeneic or autologous HSCT recipients with hematologic and solid tumors ranging from 10 to 58 years of age. Patients assigned to the EFP group were allowed oral intake *ad libitum*, supplemented with high-protein snacks or i.v. amino acids in cases of poor protein intake. If their oral intake remained below the minimum nutrient goals for at least 10 days, they were eligible for nasogastric tube feeding. Seven patients (23% of the EFP participants) were eventually deemed EFP failures; nasogastric tube feeding was attempted in a majority of those patients prior

**Table 1** Advantages and disadvantages of total parenteral nutrition

| *Disadvantages* | *Advantages* |
|---|---|
| High financial cost | Ease of administration |
| Catheter-associated infections | Easier correction of fluid and electrolyte disturbances |
| Fluid overload | |
| Hyperglycemia | Nutrition in setting of mucositis |
| Catheter-associated thrombosis | |
| Hepatic dysfunction | |
| Promotes enterocyte atrophy leading to loss of gut barrier function | |
| Blood electrolyte abnormalities | |
| Additional nursing time for nonclinical activities | |

**Table 2** Nutritional assessment parameters

| *Parameter* | *Advantages* | *Disadvantages* |
|---|---|---|
| Biochemical markers | Easy to measure | All influenced by hydration, inflammatory processes, chemotherapy, radiation therapy, sepsis, GVHD, liver function |
| Albumin | | |
| Pre-albumin | | |
| Transferrin | | |
| Retinol-binding protein | | |
| Nitrogen balance | Accurate | Difficult to quantify exact amount in urine, emesis, stool |
| Anthropometric measurements | Easy to measure | Influenced by fluid shifts, limited standards for comparison may not correlate with body mass composition |
| Body weight | | |
| Triceps skin-fold thickness | | |
| Midarm circumference | | |
| Serum immunoglobulins | Easy to measure | Inaccurate in the setting of bone marrow obliteration and hematologic malignancies |
| Underwater weighing | Accurate | Clinically impractical |
| Isotope dilution analysis | Accurate | Requires special laboratory equipment for measurements |
| Bioelectric impedance | Accurate | Not well studied in the hsct patient population |
| Respiratory quotient | Accurate | Requires specialized equipment and training to assure accuracy |

**Table 3** Results of trials evaluating total parenteral nutrition in HSC transplantation

| *Ref* | *No. pt* | *Control arm* | *Overall survival* | | *Engraftment* | | *Relapse* | | *Infection* | | *Length of hospital stay* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | *TPN* | *Control* | *TPN (days)* | *Control (days)* | *TPN* | *Control* | *TPN* | *Control* | *TPN (days)* | *Control (days)* |
| 2 | 137 | IVF | **50%** | **35%**[a] | 26 | 31 | **35%** | **60%**[b] | **72%** | **48%**[c] | 48 | 40 |
| 3 | 61 | EFP | NS | NS[d] | 19 | 20 | NR | NR | 11 | 5 | 36 | 33 |
| 10 | 22 | PPN/EFP | NR | NR | 16.3 | 16.4 | NR | NR | 4 | 8 | 22.9 | 22.9 |
| 11 | 258 | IVF | 79% | 80%[e] | NR | NR | 17% | 18%[f] | NR | NR | NR | NR |
| 15 | 61 | PPN | NR | NR | 12.8/**15.5** | 11.9/**12.9**[g] | NR | NR | **64.5%** | **40%**[h] | NS | NS |
| 16 | 29/25[i] | IVF | NS | NS | 20 | 18 | NR | NR | **3 d/8** | **1 d/1**[j] | NS | NS |
| 17 | 55 | OD | 74% | 55% | 12.4 | 12.4 | NS | NS | 20.8d* | 17.7d* | 28.7 | 25.4 |

Data in bold print represent statistically significant values.
Control arm represents formula compared to TPN in trials. IVF = intravenous fluids (dextrose, electrolytes, minerals), EFP = enteral feeding program, PPN = partial parenteral nutrion (no consistent formula). OD: oral diet. NS = not stated–outcome reported but no numerical value reported. NR = no result – outcome not evaluated.
Infection (as percentage or absolute number of patients) can represent episodes of sepsis or bacteremia, line infections or positive blood cultures.
Length of hospital stay is represented as number of days post transplant.
*Days on antibiotics ($P = 0.045$).
[a]Two-year survival: when reviewed separately autograft transplant recipients ($n = 32$) did not show a difference in survival (16 *vs* 17%).
[b]Two-year relapse rate: when reviewed separately allograft transplant recipients ($n = 94$) who received TPN had a statistically significant difference in relapse rates (21 *vs* 67%) while autograft transplant recipients ($n = 32$) did not show a difference in relapse (86 *vs* 80%).
[c]Allograft transplant recipients who received TPN had a significantly higher incidence of bacteremia (72 *vs* 48%) while autograft recipients demonstrated no statistically significant difference.
[d]Includes short-term (100 days) and long-term (900 days) survival.
[e]Survival at 150 days.
[f]Relapse on or before 150 days.
[g]There was no significant time difference for leukocyte engraftment but time to platelet engraftment was significantly longer in the TPN group.
[h]While TPN patients had a significantly higher incidence of positive blood cultures, use of antibiotics and febrile days did not differ in the two groups.
[i]The data were analyzed after the exclusion of four patients who received TPN less than 1 week.
[j]Median number of days of fever and number of patients with positive blood cultures, respectively.

to initiation of TPN but was terminated because of nausea, vomiting or compliance. While patients receiving TPN had higher total energy and protein intake than those on an EFP, there were no differences in survival, hematologic recovery, duration of stay, GVHD or infection rates. There were no complications associated with the use of nasogastric tubes. The TPN group trended towards more catheter-related complications such as bacteremia, catheter-site infections and subclavian vein thromboses, but this was not a statistically significant increase. Those patients randomized to receive TPN also required more diuretics for fluid overload (11 *vs* 6 days of use, $P = 0.0001$). Subjects also had more days of hyperglycemia (9 *vs* 2 days, $P = 0.0002$) and fewer days of hypomagnesemia than their EFP counterparts (6 *vs* 15 days, $P < 0.0001$). The mean cost per patient for TPN support was more than two times the cost of enteral nutritional support, $2575/TPN patient *vs* $1139/EFP patient. While the authors cautioned that the EFP required intensive nutritional counseling, they stated that TPN should be reserved for those patients who fail *ad libitum* oral intake and nasogastric tube feedings.

Mulder *et al*[10] compared TPN with partial parenteral nutrition (PPN) and enteral tube feedings commencing three days prior to transplantation in 22 autologous HSCT solid tumor patients ranging from 21 to 56 years of age. The lipid-free PPN formula contained two-thirds the amount of glucose and one-half the amount of protein as compared to the TPN regimen. There were no treatment-related differences in various parameters such as serum total protein, albumin, transferrin and prealbumin concentrations. Further, there were no differences in time to engraftment, days of fever or length of hospital stay. Patients who received TPN maintained their weight–height indices (WHI) unlike their PPN counterparts (nadir WHI 110.1 *vs* 90.7, $P < 0.001$). Patients randomized to the PPN and enteral feeding arm had fewer days of diarrhea (53.6 *vs* 26.8 days, $P < 0.005$) and had twice as many positive blood cultures although the latter was not statistically significant. The authors postulated that mucositis and nasogastric tube feeding could promote bacterial invasion across the gastrointestinal tract but concluded that in autologous HSCT patients, PPN and enteral feedings appear to be an alternative to TPN.

Charuhas *et al*[11] evaluated the effect of parenteral nutrition on resumption of oral intake after autologous, allogeneic or syngeneic HSCT for hematologic and solid tumors. In all, 258 patients from 2 to 64 years of age were randomized to receive a 5% dextrose solution or TPN until they were able to consume at least 85% of estimated energy requirements for three consecutive days. The primary endpoint was time to resumption of oral intake; other study endpoints were readmission to the hospital, weight change, relapse and survival. Patients randomized to TPN resumed complete oral intake six days later than the hydration group, regardless of fluid volumes received (median of 10 *vs* 16 days, $P = 0.049$). Although the hydration group lost more weight than their TPN counterparts (4.63% loss *vs* 1.27% loss, $P = 0.004$), there were no differences in readmission to the hospital, relapse or survival. The authors cited similar studies which demonstrate that amino-acid infusions delay oral intake in other patient populations.[12–14] The mechanisms of these interactions are not well understood. These investigators recommended that TPN not be given routinely upon discharge

but only used in patients who are unable to tolerate even minimal oral intake.

In a prospective, nonrandomized study Çetin *et al*[15] evaluated the effects of TPN *vs* PPN on time to engraftment, biochemical parameters (serum glucose, urea, creatinine, alanine aminotransferase, aspartate aminotransferase and electrolyte concentrations); nutritional indices including serum albumin and total protein concentrations, body mass index and body weight; antibiotic use, positive blood cultures and hospital stay. In all, 61 autologous HSCT patients, ages 14 to 56 years, received TPN or PPN starting the day after HSCT until they were able to tolerate total oral intake. All patients in the TPN group received granulocyte-macrophage colony-stimulating factor but only 57% of the PPN group received growth factor support (for reasons not explained by the authors). The TPN group resumed complete oral intake in 12.4 days while the PPN group resumed complete oral intake in 13.2 days (not a statistically significant difference). While mean times from HSCT to a leukocyte count of at least $1 \times 10^9$/l did not differ between the two groups, those patients randomized to received TPN had a significantly longer mean time to platelet engraftment (15.5 *vs* 12.9 days, $P = 0.014$). This difference was also seen when TPN patients were compared to only those PPN patients who received granulocyte-macrophage colony-stimulating factor (15.5 *vs* 12.6 days, $P = 0.017$). Accordingly, patients who received TPN required more platelet transfusions (1.93 *vs* 1.16 units, $P = 0.004$) without a difference in red blood cell transfusion requirements or duration of hospital stay. Patients in the TPN group had a greater number of positive blood cultures (64.5 *vs* 40%, $P = 0.05$) without more antibiotic use or febrile days. They also had higher concentrations of blood glucose and urea than the PPN group (159 *vs* 136 mg/dl, $P = 0.03$ and 34 *vs* 27 mg/dl, $P < 0.001$, respectively). Patients who received TPN maintained their albumin levels during the peritransplant period, but neither group maintained body mass index nor body weight. The authors could not explain the differences in platelet engraftment in this patient population, and this effect was not observed in any other studies that we reviewed.

In a small, prospective, randomized controlled trial, Lough *et al*[16] compared TPN or a 5% dextrose solution using biochemical and anthropomorphic measurements on the outcomes of rates of infectious complications, days of fever, weight loss, time to engraftment and survival in 29 adult autologous and allogeneic HSCT patients with hematologic malignancies. TPN had to be discontinued in seven of 14 patients due to fluid overload. The group randomized to the TPN arm had significantly more days of fever (3 *vs* 1 day, $P < 0.05$) and a greater number of patients in the TPN group had positive blood cultures as compared to those patients who received only maintenance fluids (eight patients *vs* one patient, $P < 0.05$). Median serum bilirubin and gamma glutamyl transferase levels were higher in the TPN group (20.5 *vs* 16 $\mu$mol/l and 47.5 *vs* 33.0 units/l, respectively, with both $P < 0.05$). Median serum retinol binding protein, transferrin and albumin concentrations were not significantly different in the two groups, nor were loss of skin-fold thickness and mid-arm muscle circumference. The patients randomized to maintenance fluids lost more weight than those patients on TPN (4.7 *vs* 2.6 kg, $P < 0.001$). The two groups did not differ with respect to time to engraftment or survival at 200 days. The authors concluded that their group's less aggressive approach to nutritional therapy (patients received 80% of estimated basal energy expenditure as opposed to an average of 130% in the Weisdorf study) may have limited the benefits of TPN. The investigators recommended that TPN be used cautiously in HSCT patients given the greater incidence of fluid overload and sepsis in their study.

Roberts *et al*[17] randomized 55 breast cancer patients undergoing autograft to receive either prophylactic TPN ($N = 27$) beginning day $-1$ or an oral diet ($N = 28$). Half the group assigned to the oral diet were switched to TPN as a result of poor oral intake for at least 10 days. Use of prophylactic TPN did not improve engraftment (marrow recovery mean day 12.4 in both groups) nor the length of hospital stay (mean 28.7 days in the TPN group compared to mean 25.4 days in the oral diet subjects). Overall survival at 2 years was higher but not of statistical significance in the TPN patients (74 *vs* 57%) but no differences were detectable by 5 years after transplant. Further, the patients assigned to the oral diet required fewer days of antibiotic therapy (mean 17.7 *vs* 20.8 days, $P = 0.045$).

### *Conclusions derived from reviewed TPN studies*

When examining these studies as a group critically, it is a challenging task to construct clinically useful recommendations regarding the use of TPN in HSCT patients. All of the studies reviewed above possess flaws. Most included a small number of study patients and many studied a heterogeneous patient population, including pediatric and adult patients, solid tumors and hematologic malignancies and both allogeneic and autologous transplants. The different disease states required varied conditioning regimens and had very different prognoses with dissimilar risk factors for the development of nutritional depletion. The smaller, more homogenous studies may be too small to detect important clinical outcomes. Many of the older studies did not use hematopoietic growth factor support. Also, nutritional assessment parameters were used inconsistently; further, there are no uniformly accepted clinical outcomes to measure the need and efficacy of TPN. Some studies suggest that the use of TPN may be deleterious. For example, a retrospective study reported by Sheean *et al*[18] in 48 autologous and allogeneic stem cell recipients noted that use of TPN is strongly associated with hyperglycemia, which may be linked to an increased risk of infection. Because of these limitations, more effective approaches are required for patients receiving HSCT. Over the past 10 years, researchers have been studying the roles of glutamine and lipids in the care of HSCT patients, with mixed results. Newer agents such as palifermin and glucagon-like peptide show promise in minimizing mucositis and enteritis in these patients.

### *Glutamine (Table 4)*

The amino acid glutamine has been shown using animal models to be a constituent amino acid during physiological

**Table 4** Results of trials evaluating glutamine supplementation in HSCT[a]

| *Author* | *# of patients* | *Mean age (years)* | *Allo* | *Auto* | *TBI* | *Daily dose & route* | *Length of stay* | *Infectious complications*[b] | *GVHD* | *Time to engraftment* | *Survival & relapse rates* | *Mucositis & diarrhea* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Studies in support of glutamine* | | | | | | | | | | | | |
| 26 | 45 | 33.8 | 45 | 0 | 40 | 0.57 g/kg I.V. | ↓ | ↓/ND[c] | ND | ND | ND | ND |
| 27 | 29 | 36.6 | 13 | 16 | Some[d] | 0.57 g/kg I.V. | ↓ | ↓/ND[e] | NR | ND | NR | ND |
| 28 | 193 | 28 | 106 | 87 | 144 | 4 g/m$^2$ oral | ND | ND | ND | NR | ↑/ND[f] | ↓/↑[g] |
| *Studies showing glutamine is potentially deleterious* | | | | | | | | | | | | |
| 29 | 40 | 45.5 | 0 | 40 | 1 | 20 g I.V. | ND | ND | NR | ND | ↓ | ↑ |
| *Studies showing no effect of glutamine* | | | | | | | | | | | | |
| 30 | Not stated | Not stated | | All auto | | 20 g oral[h] | NR | NR | NR | ND | NR | ND |
| 31 | 58 | 47 | 24 | 34 | 56 | 30 g oral | ND | NR | NR | ND | ND | ND |
| 32 | 66 | 42.2 | 18 | 48 | Some[d] | 30 g oral[i] | ND | ND | ND | ND | ND | ND |

[a]Outcome data is represented as glutamine group compared to control group, ND = no difference, NR = not reported.
[b]Infectious complications can represent days of fever, number of positive blood/stool/sputum cultures, antibiotic usage and incidence of clinical infections.
[c]Patients in the glutamine group had fewer clinical infections (defined as positive blood cultures or signs/symptoms consistent with localized infection), but there were no differences in incidence of fever or antibiotic requirements.
[d]All patients undergoing allogeneic transplants and patients with acute leukemia undergoing autologous transplants received TBI.
[e]Allogeneic transplant patients who received standard TPN had a higher rate of positive blood cultures than those allogeneic patients who received glutamine enriched TPN. There were otherwise no differences in infectious complications.
[f]Twenty-eight day survival was greater in the glutamine-treated group; survival at 100 days was similar between the two groups.
[g]The authors stated that opiate use was chosen as a measure of mucositis. There was less opiate use in autologous HSCT recipients, but there was more opiate use in matched sibling allogeneic HSCT recipients.
[h]Patients were divided into three groups – 20 g/day of glutamine, whole protein or placebo
[i]If TPN was necessary, those patients randomized to receive oral glutamine received glutamine-supplemented parenteral nutrition at a dose of 0.57 g/kg daily.

stress and is a required component of the plasma antioxidant glutathione.[19–21] Studies in noncancer patients have demonstrated improvements in gut mucosal integrity, nitrogen balance and immunologic function; further, hospitalizations, infectious complications and costs were reduced.[22–25] Since the early 1990s, researchers have been investigating the efficacy of various formulations of glutamine in HSCT patients.

In 1992, Zeigler *et al*[26] studied the effects of 0.57 g/kg/day of parenteral glutamine in 45 adult hematologic malignancy patients undergoing allogeneic HSCT. Nitrogen balance was improved in patients who received glutamine ($-1.4$ *vs* $-4.2$ g/day, $P=0.002$). Length of hospital stay (29 *vs* 36 days, $P=0.017$), positive blood, stool and throat cultures (variable, all with $P<0.05$) and clinical infections (three *vs* nine, $P=0.041$) were all reduced in the glutamine group. Conversely, days of antibiotic use, incidence of acute GVHD, time to engraftment, mucositis scores, maximum temperature and extent of blood product support did not differ between the two groups.

Schloerb and Amare[27] performed a double-blind, randomized controlled trial in 29 adult patients with hematologic and solid tumors administering parenteral glutamine supplementation. Allografts receiving standard TPN had a higher incidence of positive blood cultures than those subjects given glutamine supplemented TPN (33 *vs* 0% positive cultures, $P<0.05$). Patients who were randomized to the glutamine arm also had shorter lengths of hospital stays (26.9 *vs* 32.7 days, $P<0.05$). TPN use, clinical infections, antibiotic use, days of fever, mucositis scores and time to engraftment, however, did not differ between the two groups.

Anderson *et al*[28] studied enteral glutamine at a dose of 4.0 g/m$^2$/day *vs* placebo in 87 autologous and 106 allogeneic hematologic and solid tumor transplant patients. Autologous transplant patients who received glutamine had less mouth pain and less opioid use (5.0 *vs* 10.3 days, $P=0.005$). Matched sibling donor recipients given glutamine had more days of opiate use (23.2 *vs* 16.3 days, $P=0.002$) while unrelated donor recipients showed no difference in mouth pain or opiate use. These differences were thought to reflect glutamine interactions with methotrexate administration, resulting in higher concentrations and subsequent oral mucosal damage. Composite survival at 28 days was greater in patients randomized to glutamine but survival at 100 days did not differ statistically. Further, TPN use, antibiotic use, acute or chronic GVHD or days of hospitalization did not differ in any transplant type.

Pytlík *et al*[29] reported a comparison of parenteral glutamine 20 g/day or placebo in 40 patients undergoing autologous HSCT for hematologic and solid tumors or autoimmune disorders. Patients assigned to receive glutamine had fewer days of diarrhea (3.3 *vs* 4.3 days, $P=0.03$). Parenteral glutamine therapy, however, increased relapse rates (relapse-free survival $P=0.02$), was associated with higher mortality rates ($P=0.05$), more severe mucositis, more days of opioid use (3.5 *vs* 1.2 days, $P=0.04$) and higher costs of care ($P=0.002$). There were no differences in clinical infection rates, oral intake, and days of fever, antibiotic use, length of stay or times to engraftment.

Canovas *et al*[30] evaluated GI toxicity, serum glutamine levels, serum protein levels and recovery of neutrophil count in autograft patients randomized to placebo, oral

glutamine 20 g/day or an oral whole protein solution. There were no differences between the three groups in any outcomes measured.

Coughlin Dickson *et al*[31] performed a prospective, randomized, double-blinded study in 58 autologous and allogeneic HSCT recipients assigned to receive oral glutamine 30 g/day or placebo. Days of TPN use, length of hospital stay, mucositis severity, time to engraftment, survival, relapse, and severity and days of diarrhea did not differ, although patients received only 0.27 g/kg/day of glutamine, which is less than the accepted safe dose of 0.57 g/kg/day.

Schloerb and Skikne[32] studied 66 hematologic and solid tumor patients undergoing allogeneic and autologous HSCT. All patients randomized to the glutamine arm received oral glutamine 30 g/day; if those patients required TPN, parenteral glutamine was given in place of oral. There were no differences between the glutamine and control groups with respect to length of hospital stay, TPN use, and time to engraftment, positive blood cultures, sepsis, mucositis, GVHD and diarrhea.

### *Preliminary conclusions regarding glutamine supplementation*

The above data are difficult to interpret. Use of oral glutamine showed no benefit on reducing the incidence and severity of mucositis and diarrhea, nor was there improvement in patient survival. Administration of parenteral glutamine in allografts decreased length of hospital stay and rate of infectious complications in some studies but had no effect on mucositis or survival. Paradoxically, and for unclear reasons, parenteral glutamine appeared to be associated with worsened survival in autografts and in allografts receiving methotrexate prophylaxis, resulted in increased mucositis incidence, severity and duration. As a result, parenteral glutamine cannot be recommended as routine supportive care in HSCT patients.

### *Lipids*

The use of lipids in TPN is considered necessary to prevent essential fatty acid deficiency in patients undergoing HSCT. Lipids may also be used to minimize the hyperglycemia that can occur in HSCT patients who have sepsis, diabetes mellitus or GVHD with concomitant corticosteroid use.[33] While there is concern that lipids may cause immunosuppression and an increased incidence of infection as shown by some animal models, studies in HSCT, recipients have not demonstrated this finding.[34] Lipids may also play a role in decreasing the incidence of acute or chronic GVHD by altering the immunologic responses of prostaglandins and leukotrienes. Lenssen *et al*[35] compared the rates of bacteremia and fungemia in autologous and allogeneic HSCT receiving 6–8% (low dose) or 25–30% (standard dose) of total energy as a 20% lipid emulsion. There were no treatment related differences in incidence or time to first infection and acute or chronic GVHD rates. While the investigators did not comment on the incidence of hypertriglyceridemia, no patients developed essential fatty acid deficiency. Although there was no benefit in providing a higher dose of lipids to the population studied, it appeared to be safe if required to control hyperglycemia.

Muscaritoli *et al*[36] compared an 80% lipid-based TPN to a 100% glucose-based formula in 60 allogeneic HSCT recipients and showed a similar incidence of acute GVHD. Five patients in the control group, however, died of acute GVHD compared to none in the lipid-based group, possibly due to improved activity of immunosuppressive therapy with a higher lipid dose. Santos and co-workers,[37] however, showed no effect on cyclosporine pharmacokinetics between lipid-enriched (30%) and lipid-free TPN when given to 10 allogeneic HSCT patients.

Lipids appear safe in the HSCT patient population without an increased risk of bacteremia or fungemia, and their effects on GVHD will require further studies.

### *Palifermin and glucagon-like peptide*

In recent years, research has focused less on simply maintaining an adequate nutritional state during transplantation and more on specific substrates that could minimize gastrointestinal toxicity such as palifermin and glucagon-like peptide. In a recent multicenter, placebo-controlled, double-blind, randomized phase three clinical trial, Spielberger *et al*[38] demonstrated the efficacy of palifermin, a recombinant human keratinocyte growth factor, in reducing the incidence, duration and severity of oral mucositis in autologous HSCT patients. The patients randomized to the palifermin arm had a lower incidence of febrile neutropenia, used less opioid analgesics, had less subjective complaints of mouth pain and required fewer days of TPN. Further multi-center, randomized, placebo-controlled trials are necessary to corroborate this study, and expanding the patient population to include allogeneic HSCT recipients is desirable.

A glucagon-like peptide 2 (GLP-2) analog known as ALX-0600 shows promise in preventing gut mucosal atrophy in patients undergoing chemotherapy. Thought to decrease mucosal apoptosis and increase crypt cell production, GLP-2 has been shown, in several animal models, to increase gut mucosal growth, decrease breakdown of gut mucosa and decrease mucosal permeability in a variety of pathologic intestinal processes.[39]

## Future directions

For patients undergoing HSCT, the best nutritional support remains a mystery, and based on data currently available, we cannot recommend that TPN be used uniformly as prophylaxis against nutritional depletion in HSCT recipients. Iestra *et al*[40] concluded that TPN is not universally required for all transplant patients and cited their data in which 37% of lymphoma autografts met their criteria for needing TPN (severe malnutrition at admission, prolonged period of minimal oral intake and clinical weight loss $>10\%$) compared to 92% of mismatched allografts. Future studies incorporating many aspects of TPN support are necessary (Table 5). This approach should be conducted through a large, multicenter, randomized, controlled trial comparing patients with similar diagnostic and prognostic

**Table 5** Questions regarding TPN and HSCT

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| What nutritional and clinical criteria should be used to denote the need to initiate TPN? |
| How best to determine and accurate assessment of the patient's nutritional needs? |
| Accepted/desirable/proven need for specific patient caloric requirements |
| Influence of the patient's diagnosis and planned treatment on the above factor |
| When to initiate? |
| Induction |
| Infusion of stem cells |
| Signs of nutritional inadequacy |
| What formula is best? |
| Lipids |
| Glutamine |
| Energy level |
| PPN (partial parenteral nutrition) and enteral feedings versus TPN |
| What outcomes should we measure? |
| Biomarkers |
| Anthropomorphic measurements |
| Bioimpedance |
| Do we need TPN in conjunction with the use of: |
| Anti-emetic therapy and appetite stimulants? |
| Hematopoietic growth factor support? |
| Palifermin and glucagons-like peptide? |

profiles. Glutamine deserves further cautious study to elucidate its interactions with methotrexate and to study its effects on autologous HSCT patients. TPN also needs to be studied along with the use of growth factor support, appetite stimulants and newer agents such as palifermin and glucagon-like peptide.

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