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A.S.P.E.N. Clinical Guidelines: Nutrition Support Therapy During Adult Anticancer Treatment and in Hematopoietic Cell Transplantation

David Allen August, MD[1]; Maureen B. Huhmann, DCN, RD, CSO[2]; and the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors

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Nutrition status has an important effect on quality of life and sense of well-being in cancer patients. Malnutrition and weight loss are often contributors to the cause of death in cancer patients.[1]

Cancer cachexia is a syndrome characterized by progressive, involuntary weight loss. Clinical features include host tissue wasting, anorexia, skeletal muscle atrophy, anergy, fatigue, anemia, and hypoalbuminemia. Causes of cancer cachexia include anorexia, mechanical factors affecting the gastrointestinal tract related to tumor, side effects of surgery, chemotherapy and/or radiation therapy, alterations in intermediary and energy metabolism, and changes in the host cytokine and hormonal milieu. The cancer cachexia syndrome (CCS), which is observed in approximately 50% of cancer patients, involves heterogeneous physiologic and metabolic derangements resulting in potentially life-threatening malnutrition.[2] Although often seen in patients with advanced malignancies, CCS may be present in the early stages of tumor growth.

Weight loss in cancer patients is of prognostic significance. For any given tumor type, survival is shorter in patients who experience pretreatment weight loss.[3-5] Furthermore, CCS is a problematic cause of symptom distress in cancer patients.[6,7] Early recognition and intervention to prevent worsening of CCS may afford the best opportunity to prevent its debilitating consequences.

Pharmacologic interventions play only a limited role in overcoming the anorexia and metabolic derangements seen in CCS. Research has focused on the use of nutrition support therapy (NST), bypassing oral intake to circumvent CCS related anorexia. Numerous studies, as summarized by Bozetti, have looked at the effect of nutrition support therapy on nutrition parameters in surgical cancer patients.[8] Other papers have also examined the use of NST in non-surgical cancer patients.[9,10] Parenteral nutrition (PN) consistently causes weight gain, increases body fat, and improves nitrogen balance. The effect of PN on lean body mass is minimal. The effects of enteral nutrition (EN) on body composition are less consistent; EN usually causes weight gain and improves nitrogen balance. Neither EN nor PN, when administered for 7-49 days, have demonstrably beneficial effects on serum proteins. NST has less of an effect on nutrition indices in cancer patients than in non-cancer patients, probably due to the changes that occur in the metabolism of macronutrient substrates in the presence of cancer.[8,11] Enthusiasm for the use of NST in cancer patients has historically been tempered by concern that provision of nutrients may stimulate tumor growth and metastasis, as observed in animal studies and cell culture.[12] There are few relevant clinical studies.[13-17] Most recently, a study of PN in malnourished gastric cancer patients indicated no significant difference in tumor cell proliferation with administration of PN preoperatively.[18] Absent any overt effects, it is reasonable to ignore this theoretical consideration when contemplating the use of NST in patients.

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The purpose of this paper is to examine the literature and develop guidelines only for NST in adult cancer patients (during anticancer treatment and in hematopoietic cell transplantation). Nutrition and cancer prevention or alternative medicine approaches using nutritional supplements in the treatment of cancer is beyond the scope of this paper.

Methodology

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) is an organization comprised of healthcare professionals representing the disciplines of medicine, nursing, pharmacy, dietetics, and nutrition science. The mission of A.S.P.E.N. is to improve patient care by advancing the science and practice of NST. A.S.P.E.N. vigorously works to support quality patient care, education, and research in the fields of nutrition and metabolic support in all healthcare settings. These clinical guidelines were developed under the guidance of the A.S.P.E.N. Board of Directors. Promotion of safe and effective patient care by nutrition support practitioners is a critical role of the A.S.P.E.N. organization. The A.S.P.E.N. Board of Directors has been publishing clinical guidelines since 1986.[19-21] Starting in 2007, A.S.P.E.N. has been revising these clinical guidelines on an ongoing basis, reviewing about 20% of the chapters each year in order to keep them as current as possible.

These A.S.P.E.N. Clinical Guidelines are based upon general conclusions of health professionals who, in developing such guidelines, have balanced potential benefits to be derived from a particular mode of medical therapy against certain risks inherent with such therapy. However, the professional judgment of the attending health professional is the primary component of quality medical care. Because guidelines cannot account for every variation in circumstances, the practitioners must always exercise professional judgment in their application. These Clinical Guidelines are intended to supplement, but not replace, professional training and judgment.

These clinical guidelines were created in accordance with Institute of Medicine recommendations as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."[22] These clinical guidelines are for use by healthcare professionals who provide nutrition support services and offer clinical advice for managing adult and pediatric (including adolescent) patients in inpatient and outpatient (ambulatory, home, and specialized care) settings. The utility of the clinical guidelines is attested to by the frequent citation of this document in peer-reviewed publications and their frequent use by A.S.P.E.N. members and other healthcare professionals in clinical practice, academia, research, and industry. They guide professional clinical activities, they are helpful as educational tools, and they influence institutional practices and resource allocation.[23]

These clinical guidelines are formatted to promote the ability of the end user of the document to understand the strength of the literature used to grade each recommendation. Each guideline recommendation is presented as a clinically applicable statement of care and should help the reader make the best patient care decision. The best available literature was obtained and carefully reviewed. Chapter author(s) completed a thorough literature review using MEDLINE®, the Cochrane Central Registry of Controlled Trials, the Cochrane Database of Systematic Reviews, and other appropriate reference sources. This paper includes older as well as current research related to the use of NST in individuals with cancer. Dates prior to 1990 were not excluded from the analyses, as there are no obvious trends over time to suggest that more modern practice has had an impact on outcome. These results of the literature search and review formed the basis of an evidence-based approach to the clinical guidelines. Chapter editors work with the authors to ensure compliance with the author's directives regarding content and format. Then the initial draft is reviewed internally to ensure consistency with the other A.S.P.E.N. Guidelines and Standards, and externally reviewed (by experts in the field within our organization and/or outside of our organization) for appropriateness of content. The final draft is reviewed and approved by the A.S.P.E.N. Board of Directors.

The system used to categorize the level of evidence for each study or article used in the rationale of the guideline statement and to grade the guideline recommendation is outlined in Table 1.[24]

The grade of a guideline is based on the levels of evidence of the studies used to support the guideline. A randomized controlled trial (RCT), especially one that is double blind in design, is considered to be the strongest level of evidence to support decisions regarding a therapeutic intervention in clinical medicine.[25] A systematic review (SR) is a specialized type of literature review that analyzes the results of several RCTs. A high-quality SR usually begins with a clinical question and a protocol that addresses the methodology to answer this question. These methods usually state how the literature is identified and assessed for quality, what data are extracted, how they are analyzed, and whether there were any deviations from the protocol during the course of the study. In most instances, meta-analysis (MA), a mathematical tool to combine data from several sources, is used to analyze the data. However, not all SRs use MA. SR is considered among the most important level of evidence in the field of Evidence-Based Medicine. A level of I, the highest level, will be given to large RCTs where results are clear and the risk of alpha and beta error is low (well-powered). A level of II will be given to RCTs that include a relatively low number of

Table 1. Grading of Guidelines and Levels of Evidence

Grading of Guidelines	
A	Supported by at least two level I investigations
B	Supported by one level I investigation
C	Supported by at least one level II investigations
D	Supported by at least one level III investigations
E	Supported by level IV or V evidence
Levels of Evidence	
I	Large randomized trials with clear-cut results; low risk of false-positive (alpha) and/or false-negative (beta) error
II	Small, randomized trials with uncertain results; moderate-to-high risk of false-positive (alpha) and/or false-negative (beta) error
III	Nonrandomized cohort with contemporaneous controls
IV	Nonrandomized cohort with historical controls
V	Case series, uncontrolled studies, and expert opinion

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patients or are at moderate-to-high risk for alpha and beta error (under-powered). A level of III is given to cohort studies with contemporaneous controls, while cohort studies with historic controls will receive a level of IV. Case series, uncontrolled studies, and articles based on expert opinion alone will receive a level of V.

Practice Guidelines and Rationales

Table 2 provides the entire set of guidelines recommendations for NST during adult anticancer treatment and in hematopoietic cell transplantation.

A. Nutrition Support Therapy During Anticancer Treatment

1. Patients with cancer are nutritionally-at-risk and should undergo nutrition screening to identify those who require formal nutrition assessment with development of a nutrition care plan. (Grade: D)

Rationale: There is clear evidence that nutrition screening with appropriate screening tools will identify cancer patients who are malnourished.[26-32] Among the developed screening tools are the patient generated subjective global assessment (PGSGA),[27,28] the subjective global assessment (SGA),[26,27,30,31] and the nutrition risk index (NRI).[30] They all have validated specificity and sensitivity in cancer patients, have been the subjects of prospective clinical trials, and share an emphasis on clinical data. Given the effectiveness of the instruments in detecting malnutrition in cancer patients, it makes sense to utilize these instruments to identify malnutrition and risk of malnutrition.

Although there is limited evidence available specifically examining the efficacy of nutrition screening in improving clinical outcomes in cancer patients, the detrimental effects of weight loss on outcomes has been demonstrated.[3,33,34] In addition, the benefits of nutrition counseling in cancer patients have been reported.[35-38] It seems logical that a formal nutrition screening should be performed in every cancer patient to identify individuals at-risk who require a formal nutrition assessment in an attempt to minimize weight changes and identify individuals who may benefit from further nutrition intervention. Clinical trials are needed to assess the impact of nutrition screening on outcomes in cancer patients.

See Table A1.

2. Nutrition support therapy should not be used *routinely* in patients undergoing major cancer operations. (Grade: A)

Rationale: Many studies have investigated the use of NST in patients undergoing major cancer operations, such as resections in the thoracic and abdominal cavities. The use of PN in surgical patients has been studied in prospective, randomized, controlled trials in comparison to standard oral diet (SOD) and EN. Likewise, EN has been examined in relation to SOD.

The majority of PN vs SOD[41-51] studies find no differences in morbidity[41] or mortality,[41,48] or even increased morbidity[46,47,50] or mortality,[42] with the use of PN. Those studies that did indicate benefits from PN tended to include heterogeneous populations[43,45] that consisted of both malnourished and well nourished patients. Unfortunately, some studies reporting benefits also had faulty study designs.[44] These studies suggest that PN may be beneficial when used perioperatively in severely malnourished patients; however, PN is not beneficial when used routinely in all patients.

Comparisons of PN to EN[52-63] also indicate few differences in morbidity[53-56,58] or mortality[52-54,56] between the modalities. However, EN is favored to preserve gut integrity[56,60,64] and immune markers[55,57,61,63] and to simplify glycemic management.[56,59]

Similarly, the majority of studies comparing EN to SOD[65-69] indicate no benefit of EN over SOD with respect to morbidity[65,66,68,69] and mortality.[65,66,68,69]

The evidence does not indicate improved outcomes with *routine* use of NST in all patients undergoing major cancer operations.

See Table A2.

3. Perioperative nutrition support therapy may be beneficial in moderately or severely malnourished patients if administered for 7-14 days preoperatively, but the potential benefits of nutrition support must be weighed against the potential risks of the nutrition support therapy itself and of delaying the operation. (Grade: A)

Table 2. Nutrition Support Guideline Recommendations During Adult Anticancer Treatment and in Hematopoietic Cell Transplantation

Guideline Recommendations	Grade
A. Nutrition Support Therapy During Anticancer Treatment	
1. Patients with cancer are nutritionally-at-risk and should undergo nutrition screening to identify those who require formal nutrition assessment with development of a nutrition care plan.	D
2. Nutrition support therapy should not be used *routinely* in patients undergoing major cancer operations.	A
3. Perioperative nutrition support therapy may be beneficial in moderately or severely malnourished patients if administered for 7-14 days preoperatively, but the potential benefits of nutrition support must be weighed against the potential risks of the nutrition support therapy itself and of delaying the operation.	A
4. Nutrition support therapy should not be used *routinely* as an adjunct to chemotherapy.	B
5. Nutrition support therapy should not be used *routinely* in patients undergoing head and neck, abdominal, or pelvic irradiation.	B
6. Nutrition support therapy is appropriate in patients receiving active anticancer treatment who are malnourished and who are anticipated to be unable to ingest and/or absorb adequate nutrients for a prolonged period of time (see Guideline 6 Rationale for discussion of "prolonged period of time").	B
7. The palliative use of nutrition support therapy in terminally ill cancer patients is rarely indicated.	B
8. ω-3 Fatty acid supplementation may help stabilize weight in cancer patients on oral diets experiencing progressive, unintentional weight loss.	B
9. Patients should not use therapeutic diets to treat cancer.	E
10. Immune-enhancing enteral formulas containing mixtures of arginine, nucleic acids, and essential fatty acids may be beneficial in malnourished patients undergoing major cancer operations.	A
B. Nutrition Support Therapy in Hematopoietic Cell Transplantation	
1. All patients undergoing hematopoietic cell transplantation with myeloablative conditioning regimens are at nutrition risk and should undergo nutrition screening to identify those who require formal nutrition assessment with development of a nutrition care plan.	D
2. Nutrition support therapy is appropriate in patients undergoing hematopoietic cell transplantation who are malnourished and who are anticipated to be unable to ingest and/or absorb adequate nutrients for a prolonged period of time (see Guideline 6 Rationale for discussion of "prolonged period of time").When parenteral nutrition is used, it should be discontinued as soon as toxicities have resolved after stem cell engraftment.	B
3. Enteral nutrition should be used in patients with a functioning gastrointestinal tract in whom oral intake is inadequate to meet nutrition requirements.	C
4. Pharmacologic doses of parenteral glutamine *may benefit* patients undergoing hematopoietic cell transplantation.*	C
5. Patients should receive dietary counseling regarding foods which may pose infectious risks and safe food handling during the period of neutropenia.	C
6. Nutrition support therapy is appropriate for patients undergoing hematopoietic cell transplantation who develop moderate to severe graft-vs-host disease accompanied by poor oral intake and/or significant malabsorption.	C

*Note: parenteral glutamine is not available by the usual FDA-approved manufacturer process but rather as a prescription prepared by a compounding pharmacy in the U.S. Glutamine appears on the FDA List of Bulk Drug Substances That May Be Used in Pharmacy Compounding. (See *Federal Register* 1999;64:996-1003).

Rationale: Studies specifically assessing the use of perioperative NST in moderately or severely malnourished cancer patients, as assessed by the SGA, the PGSGA, or the NRI,[41,42,45,46,49,51,52,57] indicate a benefit in morbidity[8,45,46,51,52,57] and mortality.[8,51,57] These studies began administration of NST 7-14 days preoperatively.[46,49,51]

See Table A3.

4. Nutrition support therapy should not be used *routinely* as an adjunct to chemotherapy. (Grade: B)

Rationale: Malnutrition can occur in cancer patients starting or receiving chemotherapy as a result of the tumor-induced abnormalities or due to treatment-induced toxicity. Several studies have examined the use of NST during chemotherapy to prevent the development of malnutrition or to mitigate its consequences.[64,70-82] When used in this fashion, NST does not reduce chemotherapy-related toxicity[70-75,77,78,80,81] and does not improve tumor response[70-75,77,78,80,81] or patient survival.[70,71,75] All studies were limited by small sample size. Because of an associated increase in the risk of infection with the use of PN in this setting, *routine* adjunctive use in well-nourished patients receiving chemotherapy is actually deleterious.

See Table A4.

5. Nutrition support therapy should not be used *routinely* in patients undergoing head and neck, abdominal, or pelvic irradiation. (Grade: B)

Table A1. Nutrition Screening in Cancer

Citation Design Level	Assessment	Subjects	Results
Read et al[28] (2005) Time series Level: III	MNA vs PGSGA; cancer patients	157	Both tools reliably detected malnutrition; MNA lacks specificity
Sungurtekin et al[30] (2004) Cross-sectional Level: III	SGA vs NRI; abdominal surgery patients	100	Both tools reliably detected malnutrition and predicted postoperative complications (length of stay)
Bauer et al[26] (2003) Cross-sectional Level: V	MUST vs SGA; cancer patients	65	MUST had low sensitivity (59%) and specificity (75%)
Bauer et al[27] (2002) Cross-sectional Level: V	PGSGA vs SGA; cancer patients	71	PGSGA had 98% sensitivity and 82% specificity in predicting SGA categories
Ferguson et al[39](1999) Cross-sectional Level: V	MST vs SGA; cancer patients undergoing XRT	106	MST had 100% sensitivity and 81% specificity in predicting SGA category
Isenring et al[40] (2006) Cross-sectional Level: V	MST vs PGSGA; cancer patients receiving chemotherapy	50	MST had 100% sensitivity and 92% specificity in predicting PGSGA category
van Bokhorst-De Van Der Schueren et al[32] (1997) Cross-sectional Level: III	Standardized nutrition assessment; advanced head and neck cancer patients	64	Weight loss of >10% in the previous 6 months associated with increased risk of major post-operative complications
Unsal et al[31] (2006) Cross-sectional Level: V	SGA pre- and post-XRT; cancer patients	207	Incidence of malnutrition increased following XRT but generally resolved by 6 months post-XRT

MNA, Mini Nutritional Assessment® (Nestle Clinical Nutrition, Vevey, Switzerland); PGSGA, Patient Generated Subjective Global Assessment; NRI, nutritional risk index; MUST, Malnutrition Universal Screening Tool; SGA, Subjective Global Assessment; MST, Malnutrition Screening Tool; XRT, radiation therapy.

Rationale: Few clinical trials investigating the routine use of NST as an adjunct to radiation therapy in cancer patients have been reported.[83-86] One study of upper GI cancer patients indicated less weight loss and fewer treatment interruptions in patients who received EN prior to radiation therapy (XRT).[83] Two studies in head and neck cancer patients failed to demonstrate reduced weight loss[84]; furthermore, worse survival[85] was observed in patients who received PN and/or EN before XRT. The role for *routine* EN, PN, or oral supplement use during head and neck, abdominal, or pelvic irradiation is not clear. The use of NST should be reserved for those patients who are unable to eat as a result of tumor or treatment related side-effects who are becoming progressively malnourished.

See Table A5.

6. Nutrition support therapy is appropriate in patients receiving active anticancer treatment who are malnourished and who are anticipated to be unable to ingest and/or absorb adequate nutrients for a prolonged period of time. (Grade: B)

Rationale: NST is appropriate in patients receiving active anticancer treatment who are malnourished and who will be unable to absorb adequate nutrients for a prolonged period of time to minimize risk of poor outcomes associated with malnutrition. Seven to fourteen days seems an appropriate definition of "prolonged period of time"; this time period is referred to in many studies, although there are no well designed studies that specifically address this issue. Although no survival benefit with NST intervention has been reported, multiple studies have reported improvements in weight[81,83] and nitrogen balance.[81,82] The strength of this guideline is tempered by the fact that the best and largest RCT is limited to a head and neck population receiving radiation.[85]

See Table A6.

7. The palliative use of nutrition support therapy in terminally ill cancer patients is rarely indicated. (Grade: B)

Rationale: The palliative use of NST in cancer patients is rarely appropriate, although this issue remains controversial and is emotionally charged. The decision to initiate NST in patients with advanced cancer must include consideration of the patient's and family's wishes, potential risks and benefits, and the patient's estimated

Table A2. Routine Use of Nutrition Support Therapy (NST) in Major Cancer Operations

Citation Design Level	Intervention	Subjects	Results	Comments
PN vs SOD				
Holter et al[41] (1977) RCT Level: II	Pre- and post-op PN vs SOD: GI cancer; subjects with weight loss >10 lbs	56	No difference in morbidity or mortality	
Sako et al[42] (1981) RCT Level: II	Post- and/or pre-op PN vs SOD; poor prognosis in head and neck cancer patients	69	No difference in morbidity, 2 early deaths in PN group; 18-month survival better in SOD group	PN also not beneficial in patients stratified as malnourished
Muller et al[43] (1982) RCT Level: II	Pre-op PN vs SOD; GI cancer	125	Reduced major morbidity and mortality in PN group	Well-nourished patients included
Yamada et al[44] (1983) RCT Level: II	Post-op PN vs SOD; gastric cancer	34	Reduced morbidity and longer disease-free survival in PN group	Randomization scheme not clearly reported
Muller et al[45] (1986) RCT Level: II	Pre-op PN vs SOD; esophageal and gastric cancer	113	Reduced major morbidity in PN group	
VA[46] (1991) RCT Level: I	Pre- and post-op PN vs SOD: malnourished surgical patients (laparotomy or noncardiac thoracotomy)	395	More infectious complications in PN group; fewer non-infectious complications in severely malnourished PN group	Most but not all cancer patients; 99% male; overfeeding, poor glucose control
Brennan et al[47] (1994) RCT Level: II	Post-op PN vs SOD; major pancreatic resection for cancer	117	Fewer major complications in SOD group; trend to fewer minor complications and deaths in SOD group	Well-nourished patients included
Fan et al[48] (1994) RCT Level: II	Pre- and post-op PN vs SOD; hepatocellular carcinoma	124	Fewer septic complications in PN group; no differences in mortality	Differences seen in patients with and without cirrhosis
Bozzetti et al[49] (2000) RCT Level: II	Pre- and post-op PN vs SOD + post-op hypocaloric PN; GI cancer, >10% weight loss	90	Fewer complications and lower mortality in full PN group; longer LOS in full PN group	Malnourished patients only; hypocaloric PN included 960 kcal, 85 g protein
Hyltander et al[50] (2005) RCT Level: II	Post-op PN/EN vs SOD; upper GI malignancies	126	No difference in mortality, nutrition indices or hospital LOS; More complications in EN/PN group	10 non-cancer patients included
Wu et al[51] (2006) RCT Level: I	Pre- and post-op PN/EN vs SOD + post-op hypocaloric PN; GI cancer, moderately to severely malnourished by SGA	468	Fewer complications, lower mortality, shorter LOS in full PN group	Malnourished patients only; hypocaloric PN included 600 kcal, 60 g protein
EN vs PN				
Meijerink et al[52] (1992) RCT Level: II	Pre-op PN vs EN vs SOD; gastric or colorectal cancer	151	No differences in mortality; reduced intra-abdominal abscess with severe malnutrition in PN and EN groups; no differences between EN and PN groups	Malnourished patients only
Gianotti et al[53] (1997) RCT Level: I	Post-op PN vs EN vs isEN; gastric or pancreatic cancer	260	No differences in mortality or surgical morbidity; trend to fewer septic complications in isEN group; LOS shorter in isEN group	
Sand et al[54] (1997) RCT Level: II	Post-op PN vs EN; gastric cancer	29	No differences in morbidity or mortality	

(*continued*)

Table A2. (continued)

Citation Design Level	Intervention	Subjects	Results	Comments
Shirabe et al[55] (1997) RCT Level: II	Post-op PN vs EN; hepatic resection	26	No difference in nutrition parameters or morbidity; better maintenance of natural killer cell function in EN group	Primary or secondary liver tumors
Braga et al[56] (2001) RCT Level: I	Post-op PN vs EN; gastric, pancreatic, or esophageal cancer	257	No differences in complication rates, LOS, or mortality; higher incidence of hyperglycemia in PN group; improved intestinal oxygen tension in EN group	Fewer patients reached nutrition goals in EN group; adequate power in study
Bozzetti et al[57] (2001) RCT Level: I	Post-op PN vs EN; malnourished GI cancer	317	Decreased overall incidence of complications, incidence of minor complications, incidence of infectious complications, and LOS in EN group; increased incidence of GI side effects in EN group	Nine percent of patients in EN group switched to PN because of complications; adequate power in study
Aiko et al[58] (2001) RCT Level: II	Post-op PN vs EN; esophageal cancer	24	No difference in nutrition indices or morbidity	
Papapietro et al[59] (2002) RCT Level: II	Post-op PN + EN vs early EN alone; gastric cancer	28	Nutrition indices improved and less hyperglycemia in early EN group	EN initiated in PN group after resolution of post-op ileus
Jiang et al[60] (2003) RCT Level: II	Post-op PN vs EN; gastric or colon cancer	40	Decreased intestinal permeability in EN group	NST started post-op day 3
Aiko et al[61] (2003) RCT Level: II	Post-op PN vs EN; esophageal cancer (and/or thoracic duct ligation)	39	Increased lymphocyte count and decreased CRP in EN group with preserved thoracic duct; total bilirubin decreased in EN groups	Small numbers when stratified by thoracic duct status
Goonetilleke et al[63] (2006) Systematic review Level: II	PN vs EN; Whipple procedure	571	Higher incidence of complications in PN group; lower incidence of infectious complications in EN group	4 studies included in this systematic review
EN vs SOD				
Sagar et al[65] (1979) RCT Level: II	Post-op EN vs SOD; "major intestinal surgery"	30	No differences in morbidity or mortality; LOS shorter in EN group	Cancer status of patients not clearly reported
Smith et al[66] (1985) RCT Level: II	Post-op EN vs SOD; GI cancer	50	No differences in morbidity or mortality	Only 56% of EN patients successfully fed
Foschi et al[67] (1986) RCT Level: II	Pre-op EN vs SOD; patients with percutaneous biliary drains undergoing operation	60	Reduced morbidity and mortality in EN group	Cancer status of patients not clearly reported; 4 EN patients also received PN
Heslin et al[68] (1997) RCT Level: I	Post-op isEN vs SOD	195	No differences in morbidity or mortality	
Seven et al[69] (2003) RCT Level: I	EN vs SOD; laryngectomy	67	No differences in morbidity or mortality	

RCT, randomized controlled trial; PN, parenteral nutrition; GI, gastrointestinal; EN, enteral nutrition; isEN, immune-supplemented enteral nutrition; SOD, standard oral diet; LOS, length of hospital stay; CRP, C-reactive protein.

Table A3. Perioperative Nutrition Support Therapy (NST) in Severely Malnourished Cancer Patients

Citation Design Level	Intervention	Subjects	Results	Comments
Holter et al[41] (1977) RCT Level: II	Pre- and post-op PN vs SOD: GI cancer; weight loss > 10 lbs	56	No difference in morbidity or mortality	
Sako et al[42] (1981) RCT Level: II	Post- and/or pre-op PN vs SOD; poor prognosis head and neck cancer	69	No difference in morbidity, 2 early deaths in PN group; 18-month survival better in SOD group	PN not beneficial in patients stratified as malnourished
Muller et al[45] (1986) RCT Level: II	Pre-op PN vs SOD; esophageal and gastric cancer	113	Reduced major morbidity in PN group	
VA[46] (1991) RCT Level: I	Pre- and post-op PN vs SOD: malnourished surgical patients (laparotomy or noncardiac thoracotomy)	395	More infectious complications in PN group; fewer non-infectious complications in severely malnourished PN group	Most but not all cancer patients; 99% male; hypocaloric feeding; poor glucose control
Meijerink et al[52] (1992) RCT Level: I	Pre-op PN vs EN vs SOD; gastric or colorectal cancer	151	No differences in mortality; reduced intra-abdominal abscess with severe malnutrition in PN and EN groups; no differences between EN and PN groups	Malnourished patients only
Bozzetti et al[49] (2000) RCT Level: II	Pre- and post-op PN vs SOD + post-op hypocaloric PN; GI cancer, 10% weight loss	90	Fewer complications and lower mortality in full PN group; longer LOS in full PN group	Malnourished patients only; hypocaloric PN included 960 kcal, 85 g protein
Bozzetti et al[57] (2001) RCT Level: I	Post-op PN vs EN; malnourished GI cancer	317	Decreased overall incidence of complications, incidence of minor complications, incidence of infectious complications, and decreased LOS in EN group; increased incidence of GI side effects in EN group	Nine percent of patients in EN group switched to PN because of complications
Wu et al[51] (2006) RCT Level: I	Pre- and post-op PN/EN vs post-op hypocaloric PN; GI cancer, moderately to severely malnourished by SGA	468	Fewer complications, lower mortality, shorter LOS in full NST group	Malnourished patients only; hypocaloric PN included 600 kcal, 60 g protein

RCT, randomized controlled trial; PN, parenteral nutrition; EN, enteral nutrition; isEN, immune-supplemented enteral nutrition; SOD, standard oral diet; LOS, length of hospital stay; GI, gastrointestinal; SGA, Subjective Global Assessment.

survival. The primary objective for initiating NST in advanced cancer patients is to conserve or restore the best possible quality of life and to control any nutrition related symptoms that cause distress.[88] There are limited data on the use of PN in palliative care.[8,89-96] Although the adverse events caused by PN may actually worsen quality of life and overall palliative care of some patients, home PN may lengthen survival[89,92] and improve quality of life in carefully selected patients.[90,91,94] Examples of patients who have demonstrated a favorable response to PN include patients with a good performance status, such as Karnofsky score >50, those with inoperable bowel obstruction, those with minimal symptoms from disease involving major organs such as brain, liver, and lungs, and those with indolent disease progression.[88,97]

If patients are to benefit from this complex, intrusive, and expensive therapy they (1) must be physically and emotionally capable of participating in their own care; (2) should have an estimated life expectancy of >40-60 days; (3) require strong social and financial support at home, including a dedicated in-home lay care provider; and (4) must have failed trials of less invasive medical therapies

Table A4. Nutrition Support Therapy (NST) as an Adjunct to Chemotherapy

Citation Design Level	Intervention	Subjects	Results	Comments
Parenteral Nutrition (PN)				
Jordan et al[70] (1981) RCT Level: II	PN vs SOD; advanced lung cancer	65	No differences in toxicity or response rate; reduced survival in PN group	Randomization scheme not strictly followed
Nixon et al[71] (1981) RCT Level: II	PN vs SOD; advanced colorectal cancer	50	No differences in toxicity or response rate; reduced survival in PN group	
Popp et al[72] (1981) RCT Level: II	PN vs SOD; advanced diffuse lymphoma	42	No differences in toxicity, response rate, or survival	High rate of catheter-related thrombosis
Samuels et al[73] (1981) RCT Level: II	PN vs SOD; stage III testicular cancer	30	No differences in toxicity, response rate, or survival; septicemia more frequent in PN group	Randomization scheme not strictly followed
Serrou et al[74] (1982) RCT Level: II	PN vs SOD; small cell lung cancer	39	No differences in toxicity, response rate, or survival	
Shamberger et al[75] (1984) RCT Level: II	PN vs SOD; adjuvant therapy in sarcoma patients	32	No differences in toxicity, response rate, or overall survival; disease-free survival reduced in PN group; treatment deaths more common in SOD group	
Clamon et al[77] (1985) RCT Level: II	PN vs SOD; small cell lung cancer	119	No differences in toxicity, response rate, or survival	No benefit to PN even in malnourished patients
Valdivieso et al[78] (1987) RCT Level: II	PN vs SOD; small cell lung cancer	65	No differences in toxicity or survival; trend toward improved complete response rate in SOD group	
Hyltander et al[64] (1991) RCT Level: II	PN + SOD vs SOD	33	More patients in positive energy balance, more weight gain in PN group; nitrogen loss similar between groups	PN group provided with 150% of caloric needs
De Cicco et al[80] (1993) RCT Level: II	PN vs SOD; bladder cancer, small cell lung cancer, and Hodgkin's disease	43	No differences in toxicity	Crossover study, 1 of 2 consecutive chemotherapy cycles with PN and 1 without
Jin et al[82] (1999) RCT Level: II	PN vs SOD; GI cancer patients with severe to moderate malnutrition	92	Improved prealbumin, transferrin, nitrogen balance in PN group; no difference in weight	10 day PN intervention; actual randomization scheme: PN vs PN + chemotherapy vs SOD + chemotherapy vs SOD
Enteral Nutrition (EN)				
Tandon et al[76] (1984) RCT Level: II	EN vs SOD; advanced GI cancer	70	Decreased toxicity, improved response rate in EN group	No formal statistical analysis
Evans et al[79] (1987) RCT Level: I	SOD vs SOD + nutrition counseling vs SOD + EN; metastatic lung and colorectal cancer	192	No differences in toxicity, response rate, or survival	Crossover of patients with poor intake to EN or PN
Bozzetti et al[81] (1998) RCT Level: II	EN vs SOD; esophageal cancer	50	Decreased body weight, total protein, and serum albumin in SOD group; no effect on chemotherapy tolerance, response, or survival	EN group more malnourished prior to treatment

RCT, randomized controlled trial; SOD, standard oral diet; Zn, zinc; Mg, magnesium; GI, gastrointestinal.

Table A5. Nutrition Support Therapy (NST) as an Adjunct to Radiotherapy

Citation Design Level	Intervention	Subjects	Results	Comments
Beer et al[83] (2005) Nonrandomized trial, historical controls Level: IV	EN within 2 wks vs 2-12 wks of start of XRT; upper GI malignancies	151	Less weight loss and fewer treatment interruptions in early EN group	All patients who received early EN had mucositis at time of PEG placement
Mangar et al[84] (2006) Nonrandomized trial, historical controls Level: IV	EN before XRT vs EN during XRT; head and neck cancer	160	No difference in weight loss between groups; increased age, poor PS, advanced stage of cancer, smoking, low BMI, and low serum albumin predicted need for EN	
Rabinovitch et al[85] (2006) RCT Level: I	PN/EN before XRT vs PN/EN during XRT vs PN/EN after XRT; head and neck cancer	1073	Less weight loss and grade III/IV mucositis in pre-XRT group; poorer 5-year survival and increased locoregional failure in pre-XRT group	Pre-XRT group had higher cancer stage, poorer nutrition and performance status

PN, parenteral nutrition; EN, enteral nutrition; XRT, radiation therapy; PEG, percutaneous endoscopic gastrostomy; PS, performance status; RCT, randomized controlled trial; BMI, body mass index.

Table A6. Nutrition Support Therapy (NST) in Malnourished Patients Receiving Anticancer Treatment

Citation Design Level	Intervention	Subjects	Results	Comments
Jordan et al[70] (1981) RCT Level: II	PN vs SOD; advanced lung cancer	65	No differences in toxicity or response rate; reduced survival in PN group	Randomization scheme not strictly followed
Nixon et al[71] (1981) RCT Level: II	PN vs SOD; advanced colorectal cancer	50	No differences in toxicity or response rate; reduced survival in PN group	
Tandon et al[76] (1984) RCT Level: II	EN vs SOD; advanced GI cancer	70	Decreased toxicity, improved response rate in EN group	No formal statistical analysis
Clamon et al[77] (1985) RCT Level: II	PN vs SOD; small cell lung cancer	119	No differences in toxicity, response rate, or survival	No benefit to PN seen even in malnourished patients
Evans et al[79] (1987) RCT Level: II	SOD vs SOD + nutrition counseling vs SOD + oral supplementation; metastatic lung and colorectal cancer	192	No differences in toxicity, response rate, or survival	Crossover of patients with poor intake to EN or PN
Bozzetti et al[81] (1998) RCT Level: II	EN vs SOD; esophageal cancer	50	Decreased body weight, total protein, and serum albumin in SOD group; no effect on chemotherapy tolerance, response, or survival	EN group more malnourished prior to treatment
Jin et al[82] (1999) RCT Level: II	PN vs SOD; GI cancer patients with severe to moderate malnutrition	92	Improved prealbumin, transferrin, nitrogen balance in PN group; no difference in weight	10 day PN intervention; actual randomization scheme: PN vs PN + chemotherapy vs SOD + chemotherapy vs SOD

(continued)

Table A6. (continued)

Citation Design Level	Intervention	Subjects	Results	Comments
Beer et al[83] (2005) Nonrandomized trial, historical controls Level: IV	EN within 2 wks vs 2-12 wks of start of XRT; upper GI malignancies	151	Less weight loss and fewer treatment interruptions in early EN group	All patients who received early EN had mucositis at time of PEG placement
Mangar et al[84] (2006) Nonrandomized trial, historical controls Level: IV	EN before XRT vs EN during XRT; head and neck cancer	160	No difference in weight loss between groups; increased age, poor PS, advanced stage of cancer, smoking, low BMI, and low albumin predicted need for EN	
Gavazzi et al[87] (2006) Nonrandomized concurrent controls Level: III	Home PN vs surgery + SOD; radiation enteritis	30	Nutrition autonomy reached in 100% of PN group and 59% of surgery group; 5 year survival higher in PN group	47% of PN group required surgery; 58% of the surgery group required PN
Rabinovitch et al[85] (2006) RCT Level: I	PN/EN pre-XRT vs PN/EN during XRT vs PN/EN post-XRT; head and neck cancer	1073	Less weight loss and grade III/IV mucositis in pre-XRT group; poorer 5 year survival and increased locoregional failure in group receiving PN/EN pre-XRT	Pre-XRT group had higher cancer stage, poorer nutrition and performance status

RCT, randomized controlled trial; PN, parenteral nutrition; SOD, standard oral diet; GI, gastrointestinal; EN, enteral nutrition; PEG, percutaneous endoscopic gastrostomy; XRT, radiation therapy; PS, performance status; BMI, body mass index.

Table A7. Nutrition Support Therapy (NST) in Palliative Care

Citation Design Level	Intervention	Subjects	Results	Comments
August et al[90] (1991) Historical cohort Level: V	Home PN; malignant bowel obstruction	17	Median survival 53 days; 82% perceived PN as highly beneficial/beneficial; low PN complication rate	No control group
King et al[91] (1993) Historical cohort Level: V	Home PN; gynecological cancer	61	Median survival 72 days; improvement in QOL post-PN initiation; 9% of hospital readmissions due to PN complications	No control group
McCann et al[93] (1994) Prospective cohort Level: V	SOD; terminal cancer	32	Most patients never experienced hunger or thirst; symptoms palliated with supportive management	No control group
Abu-Rustum et al[89] (1997) Nonrandomized trial Level: III	PN vs SOD; advanced ovarian cancer	21	Longer survival in PN group	All patients had gastrostomy tube for palliation of vomiting
Scolapio et al[95] (1999) Historical cohort Level: V	Home PN; advanced cancer	225	33.3% complications due to PN complications; 33% of patients experienced catheter infections	No control group; included non-cancer patients
Bozzetti[8] (2002) Prospective cohort Level: V	Home PN; advanced cancer	69	Median survival 4 months; QOL stable until 2-3 months prior to death; nutrition indices stable until death	No control group

(continued)

Table A7. (continued)

Citation Design Level	Intervention	Subjects	Results	Comments
Lundholm et al[92] (2004) RCT Level: I	PN + COX inhibitor/ EPO vs SOD + COX inhibitor/ EPO; advanced cancer with cachexia	309	*As Treated Analysis:* Improved survival, energy balance, body fat, and exercise capacity in PN group; *Intent to Treat Analysis:* Improvement in energy balance in PN group	23% (n = 26) of control group received unplanned nutrition support; As Treated Analysis excluded these patients
Brard et al[96] (2006) Nonrandomized trial Level: III	Home PN vs SOD; advanced ovarian cancer	55	Overall survival shorter in PN group; no difference in median survival; chemotherapy more prevalent in PN patients	
Orrevall et al[94] (2005) Prospective cohort Level: III	Home PN; advanced cancer	13	Sense of increased relief, security, QOL; increased restrictions on life	Structured interviews; patients felt positive outweighed negative aspects of PN

PN, parenteral nutrition; SOD, standard oral diet; QOL, quality of life; RCT, randomized controlled trial; COX inhibitor, indomethicin 50 mg twice a day; EPO, erythropoietin 15,000-40,000 units/week.

Table A8. ω-3 Fatty Acid in Weight Maintenance

Citation Design Level	Intervention	Subjects	Quantity ω-3 Consumed	Results	Comments
Gogos et al[107] (1995) Nonrandomized trial Level: V	SOD vs SOD + ω-3 FA liquid nutritional supplement; metastatic GI cancer and malnutrition	20	Dose not reported	Improved T-cell function; no difference in PS	
Wigmore et al[102] (1996) Timeseries Level: V	ω-3 FA capsules; unresectable pancreatic cancer patients	18	Median max dose: fish oil 12 g/d; EPA 2 g	Decrease in rate of weight loss; reduction in CRP; no increase in LBM over time	12 week treatment; no control group; initial dose: fish oil 2 g/d, increased by 2 g weekly to max dose 16 g/d
Gogos et al[103] (1998) RCT Level: II	ω-3 FA and vitamin E capsules vs placebo; solid tumors	60	Dose not reported	Improved T-cell and PBMC function in ω-3 FA group; increase in PS; increase in survival in fish oil group	6 week treatment; goal dose: EPA 3.06 g DHA 2.07 g, vitamin E 200 mg
Barber et al[109] (1999) Timeseries Level: V	SOD + ω-3 FA liquid nutritional supplement; pancreatic cancer and ongoing weight loss	20	EPA 2.1 g DHA 0.9 g	Weight gain compared to pre-intervention; increase in LBM; increase in PS; increase in appetite; no change in CRP	No comparison group; 7 week treatment
Barber et al[108] (1999) Nonrandomized trial Level: III	SOD + ω-3 FA liquid nutritional supplement vs SOD; pancreatic cancer; and ongoing weight loss	36	Dose not reported	Stable CRP and increase in APP in ω-3 FA group; reduction of albumin, prealbumin, and transferrin in control patients	4 week treatment; 6 healthy individual "comparison group"

(*continued*)

Table A8. (continued)

Citation Design Level	Intervention	Subjects	Quantity ω-3 Consumed	Results	Comments
Burns et al[104] (1999) Timeseries Level: V	SOD + ω-3 FA; unresectable cancer; advanced and ongoing weight loss	22	0.3 g/kg/d	Most common toxicity diarrhea; weight significantly associated with time on treatment	8 week treatment; open label, dose escalation study; no comparison group; max tolerated dose 0.30 g/kg/d
Wigmore et al[105] (2000) Timeseries Level: V	ω-3 FA capsules; unresectable pancreatic cancer patients	26	Actual dose not reported	Decrease in rate of weight loss; no increase in LBM over time	12 week treatment; no comparison group Week 1: 1 g/d Week 2: 2 g/d Week 3: 4 g/d Weeks 4-12: 6 g/d
Barber et al[110] (2001) Timeseries Level: V	SOD + ω-3 FA liquid nutritional supplement; pancreatic cancer; and ongoing weight loss	20	EPA 2.1 g DHA 0.9 g	Decrease in IL-6 production; weight gain	3 week treatment; no control group
Bauer et al[111] (2005) RCT Level: I	SOD + ω-3 FA liquid nutritional supplement vs SOD; pancreatic cancer; and ongoing weight loss	200	EPA 1.7 g	Supplement intake does not inhibit food intake; no difference in LBM	Post-hoc analysis
Bruera et al[106] (2003) RCT Level: II	ω-3 FA capsules vs placebo; advanced cancer and anorexia	60	EPA 1.8 g DHA 1.2 g	High doses not well tolerated; higher incidence of GI side effects in ω-3 FA group; no difference in LBM between groups	2 week treatment
Fearon et al[112] (2003) RCT Level: I	SOD + ω-3 FA liquid nutritional supplement vs SOD; pancreatic cancer; and ongoing weight loss	200	EPA 1.5 g DHA 1 g	Increase in caloric and protein intake and QOL in ω-3 FA group; no difference in LBM between groups	Both groups had high plasma EPA levels prior to treatment
Jatoi et al[113] (2004) RCT Level: I	ω-3 FA enriched oral supplement vs MA vs ω-3 FA enriched oral supplement + MA; incurable malignancies	421	EPA 1.09 DHA 0.46	Weight stabilization and improved appetite in all groups; no effect on mortality or QOL; MA achieved greater appetite stimulation	More of the MA group reached 10% weight gain goal; compliance not reported
Mantovani et al[114] (2004) Timeseries Level: V	Complex dietary and pharmacologic intervention; advanced cancer patients with weight loss	25	Dose not reported	Increase in body weight, LBM, appetite, global QOL; pro-inflammatory cytokines decreased	8 week treatment; no comparison group; nutrition components included polyphenols, ω-3 FA α-lipoic acid, carbocysteine lysine salt, vitamins A & E, ascorbic acid, medroxyprogesterone acetate, and celecoxib

(*continued*)

Table A8. (continued)

Citation Design Level	Intervention	Subjects	Quantity ω-3 Consumed	Results	Comments
Moses et al[116] (2004) RCT Level: II	SOD + standard oral supplement vs SOD + ω-3 FA enriched oral supplement; pancreatic cancer with weight loss	24	EPA 2.1 g DHA 0.9 g	No difference in LBM between groups; increased physical activity and total energy expenditure in ω-3 fatty acid group	Patients with BMI>30 excluded
de Luis et al[115] (2005) RCT Level: II	SOD + ω-3 FA liquid nutritional supplement vs SOD + ARG liquid nutritional supplement; post-surgical oral or laryngeal cancer	73	EPA 1.6 g	Improvement in weight and body composition in ω-3 FA group; improvement in albumin, prealbumin, transferrin, and lymphocytes in both groups	Weight stable patients only
Persson et al[117] (2005) RCT Level: II	SOD + ω-3 FA capsules vs SOD + melatonin; unresectable GI cancer patients with weight loss or hypoalbuminemia	24	EPA 4.9 g DHA 3.2 g	Elevated pro-inflammatory cytokines in both groups; poorer physical function and role functioning in the melatonin group	

FA, fatty acid; EPA, eicosapentanoic acid; DHA, docosahexanoic acid; PBMC, peripheral blood mononuclear cells; PS, performance status; LBM, lean body mass; RCT, randomized controlled trial; CRP, C-reactive protein; APP, acute phase protein; QOL, quality of life; MA, megestrol acetate; SOD, standard oral diet; GI, gastrointestinal; BMI, body mass index; ARG, arginine; IL, interleukin; max, maximum.

Table A10. Immune Enhancing Formulas in Cancer

Citation Design Level	Intervention	Subjects	Dosage Immunonutrient	Results	Comments
ARG, RNA, and ω-3 FA					
Daly et al[123] (1992) RCT Level: II	EN vs isEN	85	Not reported	Improved nutrition and immune parameters, clinical outcomes in isEN group	Study criticized because of post hoc grouping of endpoints
Daly et al[124] (1995) RCT Level: II	EN vs isEN; upper GI cancer	60	Not reported	Improved immune parameters, clinical outcomes in isEN group	
Heslin et al[68] (1997) RCT Level: I	IVF vs isEN; upper GI cancer surgery	195	Not reported	Trend toward increased morbidity, mortality in isEN group	Poorer isEN outcomes not attributable to jejunostomy-related complications
Braga et al[122] (1998) RCT Level: II	PN vs EN vs isEN; gastric and pancreatic cancer	166	Not reported	Increased incidence of cardiopulmonary complications in PN group; lower severity of post-op infections and shorter LOS in malnourished isEN group compared to PN	78% of subjects classified as malnourished pre-op

(*continued*)

Table A10. (continued)

Citation Design Level	Intervention	Subjects	Dosage Immunonutrient	Results	Comments
				group; earlier return of bowel function in EN groups; trend toward improved outcomes in isEN vs EN groups not statistically significant	
Di Carlo et al[125] (1999) RCT Level: II	PN vs EN vs isEN; pancreatic cancer	100	ω-3 FA: 5.3 g/d ARG: 18 g/d RNA: 1.8 g/d	Decreased morbidity, infections, LOS in the isEN group; earlier return of bowel function in EN groups; no significant differences between the EN groups	EN not tolerated in 16% of patients
Senkal et al[128] (1999) RCT Level: II	Pre- and post-op isEN vs pre- and post-op EN; upper GI cancer	154	ω-3 FA: 1.7 g/d ARG: 6.2 g/d RNA: 0.7 g/d	Decreased infectious complications and decreased cost of complications in isEN group	
Gianotti et al[127] (2002) RCT Level: I	Pre-op isEN + SOD vs pre- and post-op isEN + SOD vs SOD alone; GI cancer	305	Pre-op: ω-3 FA: 3.3 g/d ARG: 12 g/d RNA: 1.2 g/d Peri-op: ω-3 FA: 4.2 g/d ARG: 14.4 g/d RNA: 1.4 g/d	Decreased post-op infections and shorter LOS in isEN groups; no significant differences between the EN groups	Malnourished patients excluded
Braga et al[129] (2002) RCT Level: I	Pre- and post-op isEN vs pre-op isEN and post-op EN vs post-op EN; GI cancer, weight loss >10%	150	n-3FA: 3.3 g/d ARG: 12 g/d RNA: 1.2 g/d	Decreased morbidity and LOS in pre- and post-op isEN group	Malnourished patients only
Farreras et al[126] (2005) RCT Level: II	Post-op isEN vs EN; gastric cancer	66	ARG 15.6 g RNA 1.56 g EPA 4.6 g	Lower incidence of wound healing complications in isEN group	
ARG and ω-3 FA					
Braga et al[121] (2002) RCT Level: I	Pre-op enriched EN vs pre- and post-op enriched EN vs pre-op EN vs SOD alone; colorectal cancer	200	Not reported	Improved immune response, gut oxygenation, microperfusion in enriched EN groups; decreased infection rate in enriched EN groups	
ARG					
van Bokhorst-De Van Der Schueren[133] (2001) RCT Level: II	Post-op EN vs pre & post-op EN vs pre-op EN with ARG; malnourished head and neck cancer	49	Not reported	Trend toward better survival in ARG group; no effect on morbidity	

(*continued*)

Table A10. (continued)

Citation Design Level	Intervention	Subjects	Dosage Immunonutrient	Results	Comments
de Luis et al[131] (2004) RCT Level: II	Post-op EN vs EN with ARG; head and neck cancer	90	ARG 12.5 g/d	Decreased incidence of fistula and LOS in ARG group; increased GI intolerance in ARG group	Severely malnourished (weight loss > 10%) patients excluded
GLN					
Morlion et al[132] (1998) RCT Level: II	PN vs PN + GLN	28	GLN 0.3 g/d	Improved nitrogen balance and lymphocyte recovery in GLN group	Includes 4 non-cancer patients

RCT, randomized controlled trial; EN, enteral nutrition; isEN, enteral nutrition supplemented with arginine, RNA, and ω-3 fatty acids; GI, gastrointestinal; IVF, intravenous fluid; LOS, length of hospital stay; SOD, standard oral diet; ARG, arginine; GLN, glutamine; EPA, eicosapentaenoic acid.

such as appetite stimulants and enteral feedings.[98] Those patients with a life expectancy of <40 days may be palliated with home intravenous fluid therapy, although this is also controversial.[88,90,97,99]

See Table A7.

8. ω-3 Fatty acid supplementation may help stabilize weight in cancer patients on oral diets experiencing progressive, unintentional weight loss. (Grade: B)

Rationale: ω-3 Fatty acids favor production of prostaglandins in the 3-series (PGE3) and leukotrienes in the 5-series (which are associated with improved immunocompetence and reduced inflammatory responses) and reduce levels of the PGE2 and leukotrienes in the 4-series (immunosuppressive and proinflammatory) in comparison with ω-6 fatty acids.[100,101] ω-3 Fatty acids have been supplemented enterally in pill form[102-106] and in liquid nutritional supplements.[107-117] In addition to the effects of ω-3 fatty acids on prostaglandin synthesis and COX-2 inhibition (indomethicin 50 mg twice a day), they also seem to be effective in reducing proinflammatory cytokines in CCS.[102,103,108,110,114] Early studies of ω-3 fatty acids were performed in pancreatic cancer patients[102,105,108-112,116]; more recent studies have looked at other cancer types.[103,104,106,107,113,115,117] Enteral ω-3 fatty acids appear to stabilize weight[109,110,113-115] or decrease the rate of weight loss[102,105] in cancer patients, although this appears to occur with little or no increase in lean body mass.[102,105,106,111,112,116] A target dose of 2 g of eicosapentanoic acid daily appears appropriate. This may be administered as commercially available ω-3 enriched liquid nutritional supplements or as over-the-counter ω-3 fatty acid supplements (available in most pharmacies). Because these supplements are not commonly covered by health insurance, the cost of this intervention should be considered.

See Table A8.

9. Patients should not use therapeutic diets to treat cancer. (Grade: E)

Rationale: Peer-reviewed literature on the efficacy or safety of therapeutic diets for treatment of cancer is limited.[118-120] Studies of the "macrobiotic diet" (very low-fat, moderately high-fiber, and moderately reduced calories),[118] the Gonzalez regimen (large doses of orally ingested pancreatic enzymes, nutritional supplements, "detoxification" procedures, and an organic diet),[119] and the Gerson diet (lactovegetarian; low sodium, fat, and protein; high potassium, hourly raw vegetable/fruit juices; and coffee enemas)[120] are methodologically uninterpretable and poorly characterize both the patients studied and the regimens administered. There are no valid published data at this time to support the safety or efficacy of these regimens for the treatment of cancer. As such, they may in fact be harmful, given their dramatic deviations from recommended nutrition intakes. Therefore, these diets should be thought of as sham diets promoted to unsuspecting patients and clinicians until data from methodologically sound studies suggest otherwise.

10. Immune enhancing enteral formulas containing mixtures of arginine, nucleic acids, and essential fatty acids may be beneficial in malnourished patients undergoing major cancer operations. (Grade: A)

Rationale: Use of specific substances for effects beyond their nutrition role may be referred to as nutritional pharmacology. Four nutrients especially have been the subject of recent research: glutamine, arginine, nucleic acids, and essential fatty acids. Clinical trials

evaluating nutritional pharmacologic interventions in perioperative cancer patients using an enteral formula containing a mixture of "immune enhancing" substrates including arginine, RNA, and ω-3 fatty acids[68,121-129] have reported improved immune parameters[123-125] and clinical outcomes.[122-129] Unfortunately, the methodological diversity of these studies limits the ability to determine the best timing for initiation of immune enhancing EN. The U.S. Summit on Immune-Enhancing Enteral Therapy produced consensus recommendations regarding the use of these formulas in surgical patients.[130] It was recommended that individuals undergoing gastrointestinal or major head and neck surgery in whom there is preexisting malnutrition would benefit from 5-7 days preoperative supplementation.[130] Fewer studies have examined supplementation with single nutrients.[131-133] The data on the use of arginine- or glutamine-supplemented formulas are too limited at this time to make recommendations on the use of these formulations. However, based on the studies of combined use of arginine, RNA, and ω-3 fatty acids with clinical endpoints, EN supplemented with these nutrients may be beneficial in malnourished patients undergoing major cancer operations.

See Table A10.

B. Nutrition Support Therapy in Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) refers to an array of therapies whose short- and long-term outcomes are affected by diagnosis, disease stage, transplant type (autologous, family related allogeneic, unrelated allogeneic), degree of donor histocompatibility, preparative regimen (myeloablative vs non-myeloablative), stem cell source (bone marrow, peripheral blood, placental cord blood), age, prior therapy, and nutrition status.[134,135] Conventional HCT involves high-dose chemotherapy with or without irradiation to eradicate tumor in patients with malignancy, with subsequent autologous reconstitution of bone marrow with previously harvested cells. In allograft recipients, the patient's own immune system is completely ablated to prevent graft rejection. Such marrow ablative regimens are among the most intensive therapies used in oncology. Lower intensity cytoreduction (partial ablation) may alternatively be used to establish a mixed chimera, with preservation of host T-cell–mediated immunity.[136] Gastrointestinal tract or liver complications are almost always the dose-limiting toxicities for these therapies.[137] The disruption of the mucosal barrier contributes to the development of infections during the period of ablation-induced neutropenia that may last as long as 6 weeks. As a result of mucositis, intense diarrhea, and systemic effects of chemotherapy, patients experience a prolonged period of minimal oral intake. This may last well beyond the milestone of stem cell engraftment owing to the delayed effects of cytoreductive therapy on appetite, taste, salivary function, gastric emptying, and intestinal function.[138]

Especially problematic in recipients of allografts is donor T-lymphocyte–mediated graft-versus-host disease (GVHD). Acute GVHD occurs in the first few months posttransplant and targets the skin, liver, and gastrointestinal tract. A chronic form resembling collagen-like immune disorders may develop several months to years posttransplant and involve single or multiple organs (skin, liver, oral mucosa, eyes, musculoskeletal system, lung, esophagus, and vagina). Moderate to severe GVHD and the multi-drug regimens used in its prevention and treatment result in profound and prolonged immunosuppression. Despite advances in management, GVHD remains a significant problem because of the expanding use of unrelated and partially histocompatible related donors. Patients frequently have elevated nutrient requirements and altered carbohydrate, fat, and protein metabolism. They may also experience difficulty eating for a variety of reasons dependent on organ involvement and frequently require modified diets, oral supplements, or NST to prevent malnutrition.[137,139] Significantly higher mortality occurs in underweight patients undergoing HCT, even among those with only mild deficits.[135,140] Obesity also appears to have a negative influence on outcome.[140-142] The role, if any, for pretransplant intervention has not been investigated.

1. All patients undergoing hematopoietic cell transplantation with myeloablative conditioning regimens are at nutrition risk and should undergo nutrition screening to identify those who require formal nutrition assessment with development of a nutrition care plan. (Grade: D)

Rationale: HCT patients are predisposed to developing malnutrition because of their underlying disease, the conditioning regimen, and other treatment-related toxicities.[139,143-145] Increase in morbidity[139,143,145] and mortality[145] has been reported in malnourished patients receiving HCT. Alterations in nutrition status persist long after transplantation, with as many of 50% of patients not returning to pre-transplant weight at 1 year.[144]

Although evidence characterizing the clinical impact of nutrition in HCT patients is limited, appropriate screening of HCT patients should minimize risk of the detrimental effects of weight loss in patients with cancer including those undergoing HCT. Clinical trials are needed to assess the impact of nutrition screening on outcomes in cancer patients.

See Table B1.

2. Nutrition support therapy is appropriate in patients undergoing hematopoietic cell transplantation who are malnourished and who are anticipated to be unable to ingest and/or absorb

Table B1. Nutrition Screening in Hematopoietic Cell Transplantation (HCT)

Citation Design Level	Intervention	Subjects	Results	Comments
Layton et al[145] (1981) Time series Level: V	Standardized nutrition assessment protocol; allogeneic and autologous SCT in patients with hematologic and solid malignancies	8	Increased morbidity and mortality in malnourished group	Patients stratified by baseline nutrition status
Lessen et al[139] (1990) Historic cohort Level: V	Standardized nutrition assessment protocol; allogeneic and autologous SCT in patients with hematologic malignancies	192	63% of subjects had GVHD at time of nutrition evaluation: 28% of subjects had weight loss at 3-12 months; nutrition related problems more prevalent in GVHD group	Retrospective chart review; included 65 children
Iestra et al[144] (2002) Time series Level: V	Nutrition survey; allogeneic and autologous SCT in patients with hematologic and solid malignancies	135	Pre-transplant antineoplastic regimen predictive of weight at day 350; high prevalence of eating difficulties; body weight not restored at 1 year in 50% of TBI-treated patients	Questionnaire study
Horsley et al[143] (2005) Time series Level: III	PGSGA; allogeneic and autologous SCT in patients with hematologic and solid malignancies	66	Pre-transplant: 73% well nourished, 23% moderately malnourished, 4% severely malnourished; increased LOS in malnourished group	Nutrition status assessed 2 weeks pre-transplant

SCT, stem cell transplant; GVHD, graft-vs-host disease; TBI, total body irradiation; PGSGA, Patient Generated Subjective Global Assessment.

adequate nutrients for a prolonged period of time (see Guideline 6 Rationale for discussion of "prolonged period of time").When parenteral nutrition is used, it should be discontinued as soon as toxicities have resolved after stem cell engraftment. (Grade: B)

Rationale: NST is appropriate in patients undergoing HCT who are malnourished and who will be unable to absorb adequate nutrients for a prolonged period of time to minimize risk of poor outcomes associated with malnutrition. Seven to 14 days seems an appropriate definition of "prolonged period of time"; this time period is referred to in many studies, although there are no well designed studies that specifically address this issue.

Evaluating the effect of PN and EN in HCT patients is difficult because of patient and treatment heterogeneity. The risks and benefits of using PN in HCT have been assessed comparing PN vs SOD[146-149] or EN[150-152] vs PN vs intravenous fluids (IVF) alone.[153-155]

Studies of PN vs SOD or EN demonstrate increased morbidity,[146] more diarrhea,[150] more hyperglycemia,[151,152] and delayed time to engraftment[149,152] but less weight loss[146,147] and less loss of body fat[148] with PN. There appear to be no differences in incidence or severity of GVHD.[146]

Comparison of PN to IVF[153-155] indicate earlier resumption of oral intake with IVF[153] but no difference in morbidity.[155] A study of children and adults reported a positive effect of PN on mortality compared to those who received IVF in patients who received allogeneic transplants, but not autologous transplants.[155] There was no difference in GVHD between groups; however, the allogeneic transplant patients had higher incidence of bacteremia which occurred sooner with PN. These results have not been repeated.

The effects of PN composition on outcome has been investigated.[156,157] Limited results indicate no benefit to use of "high nitrogen" PN.[156] There may be a decrease in the incidence of GVHD with the use of lipid-based PN (80% of non-protein calories from fat) compared to a glucose-based (100% of non-protein calories from dextrose) formula.[157]

If PN is used in HCT, it should be discontinued after stem cell engraftment when adequate EN or oral intake is feasible.

See Table B2.

3. Enteral nutrition should be used in patients with a functioning gastrointestinal tract in whom oral intake is inadequate to meet nutrition requirements. (Grade: C)

Table B2. Parenteral Nutrition (PN) and Condition Related Toxicities

Citation Design Level	Intervention	Subjects	Results	Comments
Weisdorf et al[155] (1987) RCT Level: II	PN vs IVF + vitamins and minerals; SCT in patients with hematologic and solid malignancies	137	Improved survival and time to relapse in PN group; no effect on GVHD or infection	
Mulder et al[150] (1989) RCT Level: II	PN vs PN + EN; autologous SCT in patients with solid tumors	22	No difference in weight or nitrogen balance; less diarrhea in EN + PN group	Few patients actually received EN
Lough et al[146] (1990) Historic cohort Level: IV	PN vs SOD; allogeneic and autologous SCT in patients with hematologic malignancies	29	Abnormal liver function tests, higher temperature and positive blood culture rates in PN group; greater weight loss in SOD group; no impact on GVHD	
Geibig et al[156] (1991) RCT Level: II	PN vs high nitrogen PN; allogeneic and autologous SCT in patients with hematologic and solid malignancies	28	No difference in weight gain, nitrogen balance, total iron binding capacity levels	
Charuhas et al[153] (1997) RCT Level: I	PN vs IVF; SCT in outpatients with hematologic and solid malignancies	258	Resumption of oral intake earlier in IVF group; less weight loss in PN group	PN received in hospital setting
Muscaritoli et al[157] (1998) RCT Level: II	Glucose-based PN vs lipid-based PN; allogeneic and autologous SCT in patients with hematologic malignancies	60	Increased incidence of acute GVHD and hyperglycemia in glucose group; trend toward better survival in lipid group	Glucose-based PN: 100% NPC from dextrose; IV-fat–based PN: 20% NPC from dextrose
Jonas et al[154] (2000) RCT Level: II	PN + SOD vs IVF (with MVI and lipids) + SOD; allogeneic SCT in patients with hematologic malignancies	24	No difference in weight loss	Calorie and nitrogen intake higher in PN group
Cetin et al[149] (2002) Nonrandomized trial Level: III	PN vs partial PN + SOD; autologous SCT in patients with solid tumors	61	No difference in weight loss; lower albumin in PN + SOD group; higher BUN and glucose, more positive blood cultures and infection, delay in platelet engraftment in PN group	
Roberts et al[147] (2003) RCT Level: II	PN vs SOD; autologous SCT in breast cancer patients	55	Improved nutrition status and preservation of LBM in PN group; trend toward improved QOL in PN group	PN started 1 day prior to HCT; 50% of SOD group subsequently received PN due to poor intake
Sheenan et al[151] (2004) Historical cohort Level: IV	PN vs SOD; allogeneic and autologous SCT in patients with hematologic and solid malignancies	48	More hyperglycemia, infections, positive blood cultures, increased LOS in PN group	Control received oral diet with or without liquid nutritional supplements and/or IVF

(continued)

Table B2. (continued)

Citation Design Level	Intervention	Subjects	Results	Comments
Skop et al[148] (2005) Nonrandomized trial Level: III	PN vs SOD; autologous SCT in hematologic malignancies	35	Similar weight loss in both groups; decrease in body fat in PN group	
Sheenan et al[152] (2006) Historic cohort Level: IV	PN vs SOD; allogeneic and autologous SCT in patients with hematologic and solid malignancies	357	More hyperglycemia, greater requirements for RBC and platelet transfusions; delays in engraftment time in PN group	Control received oral diet with or without liquid nutritional supplements and/or IVF

RCT, randomized controlled trial; IVF, intravenous fluids; MVI, multivitamin; SOD, standard oral diet; SCT, stem cell transplant; GVHD, graft-vs-host disease; NPC, non-protein calories; BUN, blood urea nitrogen; LBM, lean body mass; QOL, quality of life; LOS, length of stay; RBC, red blood cell; EN, enteral nutrition; HCT, hematopoietic cell transplantation.

Rationale: Use of peri-transplant EN after conditioning regimens has been investigated.[150-152,158-160] Studies have included small numbers of patients receiving enteral feeding or oral intake compared to PN alone or in combination of EN or PN, which makes evaluation of clinical outcomes difficult. In general, less diarrhea and less hyperglycemia (defined as blood glucose >110-150 mg/dL) have been reported in patients receiving EN.[151,152,158] The effect on time to engraftment is not clear.[149,152] EN may also be associated with a decreased risk of severe GVHD.[160]

The challenges of establishing safe enteral access after marrow-ablative preparative regimens are formidable owing to coagulopathy, the risk of aspiration pneumonia, sinusitis, diarrhea, ileus and/or abdominal pain, delayed gastric emptying, and vomiting.[161] However, safe enteral tube feeding has been reported in HCT patients during the peri-transplant period. Once neutrophil and platelet counts have returned and gastrointestinal tissues have healed, EN is safe as a transition step from PN to oral diet or when NST is indicated for late complications such as GVHD.

See Table B3.

4. Pharmacologic doses of parenteral glutamine *may benefit* patients undergoing hematopoietic cell transplantation.* (Grade: C)

*Note: parenteral glutamine is not available by the usual U.S. Food and Drug Administration (FDA)-approved manufacturer process but rather as a prescription prepared by a compounding pharmacy in the U.S. Glutamine appears on the FDA List of Bulk Drug Substances That May Be Used in Pharmacy Compounding. (See *Federal Register* 1999;64:996-1003).

Rationale: The roles of both enteral[162-165] and parenteral[165-172] glutamine (GLN) supplementation in HCT have been examined. Studies assessing the impact of enterally administered GLN indicate no reduction in morbidity[162-165] or mortality.[163-165] Parenterally administered GLN is associated with improved nitrogen balance,[172] shorter length of hospital stay,[171,172] and decreased morbidity.[167,171-173] One small, complex study of prophylactic PN vs PN initiated after a decrease in oral intake indicated that patients who received supplemental GLN had a shorter disease-free survival, with no impact on morbidity or overall survival.[170] The results indicated a decreased incidence of severe mucositis in patients receiving supplemental GLN parenterally. These results were not seen with orally supplemented GLN. A recent Cochrane review concluded that GLN in PN may not be associated with reduced length of hospital stay, but a benefit of fewer bloodstream infections remains.[173] Providing parenteral GLN remains complicated by a lack of commercially available intravenous formulation. More research is needed to determine appropriate dose and timing.

See Table B4.

5. Patients should receive dietary counseling regarding foods which may pose infectious risks and safe food handling during the period of neutropenia. (Grade: C)

Rationale: Although the effect of low-microbial or sterile diets on risk of infection is unknown, neutropenic HCT patients should avoid foods associated with an increased infectious risk. Several studies have examined the role of diet and infectious risk in combination with other interventions such as isolator units and laminar airflow rooms.[174-180] It is hard to make comparisons between these groups because the dietary restrictions were not adequately described. One study suggested a reduced incidence of infection in patients who received a sterile diet[177]; however, a subsequent study indicated no difference.[176] A descriptive survey by Smith et al found

Table B3. Enteral Nutrition (EN) in Hematopoietic Cell Transplantation (HCT)

Citation Design Level	Intervention	Subjects	Results	Comments
Szeluga et al[158] (1987) RCT Level: II	PN vs EN/SOD; allogeneic SCT in patients with hematologic malignancies	57	More diuretic use, hyperglycemia, catheter complications and higher cost in PN group; more hypomagnesemia in EN group; no differences in mortality or LOS	50% of patients in EN group received IV AA support
Mulder et al[150] (1989) RCT Level: II	PN vs PN + EN; autologous SCT in patients with solid tumors	22	No difference in weight or nitrogen balance; less diarrhea in EN + PN group	
Sheenan et al[151] (2004) Historical Cohort Level: IV	PN vs SOD; allogeneic and autologous SCT in patients with hematologic and solid malignancies	48	More hyperglycemia, infections, positive blood cultures, LOS in PN group	Control received oral diet with or without liquid nutritional supplements and/or IVF
Sheenan et al[152] (2006) Historic cohort Level: IV	PN vs EN/SOD; allogeneic and autologous SCT in patients with hematologic and solid malignancies	357	More hyperglycemia, greater requirements for RBC and platelet transfusions; delays in engraftment time in PN group	
Seguy et al[160] (2006) RCT Level: II	PN/SOD vs EN; allogeneic SCT in patients with hematologic malignancies	45	Reduced acute grade III/IV GVHD and infection-related mortality in EN group	EN via NGT

RCT, randomized controlled trial; PN, parenteral nutrition; SOD, standard oral diet; SCT, stem cell transplant; LOS, length of stay; IV AA, intravenous amino acid; RBC, red blood cell; NGT, nasogastric tube; GVHD, graft-vs-host disease.

that 78% (n = 120) of Association of Community Cancer Centers (ACCC) member institutions utilized low microbial diets. There were wide variations in the white blood cell and neutrophil counts used to trigger ordering of low microbial diets.[181] A more recent small RCT that compared neutropenic diet to the FDA's food safety guidelines indicated no additional benefit of the neutropenic diet in pediatric patients receiving myeloablative chemotherapy.[182] This was also seen in a study of cooked and noncooked diets in patients undergoing remission induction therapy for acute myeloid leukemia.[183] Overall, there is a need for more systematic research on this topic. Until this is available, it seems prudent to continue to provide dietary restrictions on high-risk foods during the period of neutropenia, while paying attention to the palatability of food choices in these anorectic patients.

See Table B5.

6. Nutrition support therapy is appropriate for patients undergoing hematopoietic cell transplantation who develop moderate to severe graft-vs-host disease accompanied by poor oral intake and/or significant malabsorption. (Grade: C)

Rationale: Limited data are available on the impact of NST on the incidence of GVHD.[146,155,157,160,162,184] PN does not seem to decrease the incidence of GVHD in individuals undergoing HCT.[146,155] In fact, high dextrose (100% nonprotein calories) PN has been associated with an increased incidence of GVHD.[157] Incidence of GVHD appears to decrease with increased protein intake in patients consuming SOD[184] or EN.[160] Once GVHD occurs, oral nutrition can become increasingly challenging. Although there are no data on the impact of NST on the resolution of GVHD, it seems logical that NST should be used to maintain/improve nutrition status during prolonged nutrition compromise resulting from GVHD.

See Table B6.

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Table B4. Glutamine (GLN) and Hematopoietic Cell Transplantation (HCT)

Citation Design Level	Intervention	Subjects	Dose GLN	Results	Comments
Ziegler et al[172] (1992) RCT Level: II	PN vs PN + GLN (in PN); allogeneic bone marrow transplants for hematologic malignancies	45	GLN 0.57 g/kg	Improved nitrogen balance, shorter LOS, and reduced incidence of infection in GLN group	
Young et al[171] (1993) RCT Level: II	PN vs PN + GLN (in PN); allogeneic SCT in hematologic malignancies	23	GLN 40 g/d	Maintenance of mood and reduced feelings of anger, shorter LOS and fewer infections in GLN group	Included subjects in the Ziegler study[172] (1992)
Schloerb et al[169] (1993) RCT Level: II	PN vs PN + GLN (in PN); allogeneic and autologous SCT in hematologic and solid malignancies	29	GLN 2.8 g/100 mL	Decrease in TBW and shorter LOS in GLN group; no difference in morbidity	
Jebb et al[164] (1995) RCT Level: II	SOD vs SOD + GLN (oral); autologous SCT in hematologic malignancies	24	GLN 16 g/d	No differences in morbidity, mucositis, or diarrhea	Mean dose consumed GLN 11 g/d
Anderson et al[162] (1998) RCT Level: II	SOD vs SOD + GLN (oral); autologous and allogeneic SCT in hematologic malignancies	193	GLN 1 g/kg	Autologous SCT: less mouth pain and opiate use in GLN group Allogeneic SCT: increased use of opiates and improved 28-day survival in GLN group; no effect on GVHD	
Schloerb et al[165] (1999) RCT Level: II	SOD/PN vs SOD/PN + GLN (oral or in PN); autologous and allogeneic SCT in hematologic and solid malignancies	66	GLN 30 g/d	No differences in morbidity or mortality	PN provided if oral intake was inadequate; GLN provided in PN if oral intake inadequate
Coghlin Dickson et al[163] (2000) RCT Level: II	SOD vs SOD + GLN (oral); autologous and allogeneic SCT in hematologic malignancies	58	GLN 30 g/d	No differences in morbidity or mortality	
Pytlik et al[167] (2002) RCT Level: II	PN vs PN + GLN (in PN); autologous SCT in hematologic and solid malignancies	40	30g/d GLN	Decreased diarrhea, grades III and IV mucositis in GLN group; increased use of opioids, relapse, and mortality in GLN group	
Piccirillo et al[166] (2003) RCT Level: II	PN vs PN + GLN (in PN); autologous SCT in hematologic malignancies	27	Study 1: GLN 20 g/d Study 2: GLN 13.5 g/d	Earlier return of lymphocyte count, decreased mucositis score in GLN group	GLN dose decreased due to formulary change
Scheid et al[168] (2004) RCT Level: II	PN vs PN + GLN (in PN); high dose chemotherapy in leukemia	54	GLN 20 g/d	Faster neutrophil recovery in GLN group; no impact on incidence of neutropenic fevers	
Sykorova et al[170] (2005) RCT Level: II	PN + GLN (in PN) vs PN ad hoc + GLN (in PN); autologous SCT in hematologic malignancies	44	GLN 0.5 g/kg	No difference in overall survival; decreased disease-free survival in GLN group	

RCT, randomized controlled trial; PN, parenteral nutrition; SOD, standard oral diet; SCT, stem cell transplant; LOS, length of stay; TBW, total body weight.

Table B5. Diet During Neutropenia

Citation Design Level	Intervention	Subjects	Results	Comments
Levitan et al[178] (1967) Prospective cohort Level: IV	LI + sterile diet + Abx; hematologic malignancies	11	Clinical infection in 45% patients; 52%-74% stool cultures positive	Combination intervention
Bodey et al[175] (1968) Prospective cohort Level: IV	LI + sterile diet + Abx; hematologic malignancies	11	Clinical infection in 38% patients; Abx controlled most pathogens	Combination intervention
Bodey et al[174] (1968) Prospective cohort Level: IV	LI + sterile diet + Abx; hematologic and solid malignancies	13	Clinical infection in 38% patients	Combination intervention; 2 Abx regimens used
Levine et al[177] (1973) RCT Level: II	LI/LAF + sterile diet + Abx vs Abx vs conventional care; hematologic malignancies	88	Fewer infections in the diet group; no difference in remission rate or duration	Combination intervention
Yates[180] (1973) RCT Level: II	Reverse isolation + low microbial diet + Abx vs LI/LAF + low microbial diet + Abx vs LI/LAF + low microbial vs conventional care; AML	116	More infections in conventional care and reverse isolation groups	Combination intervention; 9 patients received sterile diet
Dietrich et al[176] (1977) RCT Level: II	LI/LAF + sterile diet + Abx vs LI/LAF + sterile diet vs ward; hematologic malignancies	97	No difference in infection rate	Combination intervention
Moody et al[182] (2006) RCT Level: II	Neutropenic diet vs FDA food safety guidelines; pediatric patients receiving myeloablative chemotherapy	19	No difference in neutropenic fever; poor adherence in neutropenic diet group	
Gardner et al[183] (2008) RCT Level: II	LAF + antibacterial/antiviral/antifungal + sterile diet vs LAF + antibacterial/antiviral/antifungal + diet including raw fruits and vegetables; AML or high-risk MDS receiving remission induction therapy	153	No difference in infection or fever; no difference in survival	Combination intervention; more patients in the sterile diet group received voriconazole prophylaxis

RCT, randomized controlled trial; LI, life island (isolator unit with tented HEPA filter); Abx, antibiotics; LAF laminar airflow room; AML, acute myeloid leukemia, FDA, U.S. Food and Drug Administration; MDS, myelodysplastic syndrome.

Table B6. Nutrition Support Therapy (NST) and Graft-vs-Host Disease (GVHD)

Citation Design Level	Intervention	Subjects	Results	Comments
Weisdorf et al[155] (1987) RCT Level: II	PN vs IVF + vitamins and minerals; SCT in patients with hematologic and solid malignancies	137	Improved survival and time to relapse in PN group; no effect on GVHD or infection rate	
Lough et al[146] (1990) Historic cohort Level: IV	PN vs SOD; allogeneic and autologous SCT in patients with hematologic malignancies	29	Elevated liver function tests, higher temperature and positive blood culture rates in PN group; greater weight loss in SOD group; no impact on GVHD	

(*continued*)

Table B6. (continued)

Citation Design Level	Intervention	Subjects	Results	Comments
Cheney et al[184] (1991) Timeseries Level: III	Evaluation of food records; allogeneic SCT in hematologic malignancies	575	Lower incidence of GVHD in those consuming any amount of protein	aGVHD developed in 54% (n = 308) of patients
Seguy et al[160] (2006) RCT Level: II	PN/SOD vs EN; allogeneic SCT in patients with hematologic malignancies	45	Lower incidence acute grade III/IV GVHD and lower mortality from infection in EN group	EN via NGT

RCT, randomized controlled trial; SCT, stem cell transplant; aGVHD, acute GVHD; SOD, standard oral diet; PN, parenteral nutrition; NGT, nasogastric tube; IVF, intravenous fluids; EN, enteral feeding

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