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Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient:

Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

Stephen A. McClave, MD; Robert G. Martindale, MD, PhD; Vincent W. Vanek, MD; Mary McCarthy, RN, PhD; Pamela Roberts, MD; Beth Taylor, RD; Juan B. Ochoa, MD; Lena Napolitano, MD; Gail Cresci, RD; the A.S.P.E.N. Board of Directors; and the American College of Critical Care Medicine

Preliminary Remarks

Guideline Limitation

Practice guidelines are not intended as absolute requirements. The use of these practice guidelines does not in any way project or guarantee any specific benefit in outcome or survival.

The judgment of the healthcare professional based on individual circumstances of the patient must always take precedence over the recommendations in these guidelines.

The guidelines offer basic recommendations that are supported by review and analysis of the pertinent available current literature, by other national and international guidelines, and by the blend of expert opinion and clinical practicality. The "intensive care unit" (ICU) or "critically ill" patient is not a homogeneous population. Many of the studies on which the guidelines are based are limited by sample size, patient heterogeneity, variability in definition of disease state and severity of illness, lack of baseline nutrition status, and lack of statistical power for analysis. Whenever possible, these factors are taken into account and the grade of statement will reflect the power of the data. One of the major methodological problems with any guideline is defining the exact population to be included.

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These guidelines are also being co-published by the Society of Critical Care Medicine (SCCM) in *Critical Care Medicine*, 2009; volume 37, number 5.

Periodic Guideline Review and Update

These guidelines may be subject to periodic review and revision based on new peer-reviewed critical care nutrition literature and practice.

Target Patient Population for Guideline

These guidelines are intended for the adult medical and surgical critically ill patient populations expected to require an ICU stay of > 2 or 3 days and are not intended for those patients in the ICU for temporary monitoring or those who have minimal metabolic or traumatic stress. These guidelines are based on populations, but like any other therapeutic treatment in an ICU patient, nutrition requirements and techniques of access should be tailored to the individual patient.

Target Audience

The intended use of these guidelines is for all individuals involved in the nutrition therapy of the critically ill, primarily physicians, nurses, dietitians, pharmacists, and respiratory and physical therapists where indicated.

Methodology

A list of guideline recommendations was compiled by the experts on the Guidelines Committee for the 2 societies, each of which represented clinically applicable definitive statements of care or specific action statements. Prospective randomized controlled trials were used as the primary source to support guideline statements, with each study being evaluated and given a level of evidence. The overall

Table 1. Grading System Used for These Guidelines

Grade of recommendation	
A	Supported by at least two level I investigations
B	Supported by one level I investigation
C	Supported by level II investigations only
D	Supported by at least two level III investigations
E	Supported by level IV or level V evidence
Level of evidence	
I	Large, randomized trials with clear-cut results; low risk of false-positive (alpha) error 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, contemporaneous controls
IV	Nonrandomized, historical controls
V	Case series, uncontrolled studies, and expert opinion

Note: Large studies warranting level I evidence were defined as those with ≥ 100 patients or those which fulfilled end point criteria predetermined by power analysis. Meta-analyses were used to organize information and to draw conclusions about overall treatment effect from multiple studies on a particular subject. The grade of recommendation, however, was based on the level of evidence of the individual studies.

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grade for the recommendation was based on the number and level of investigative studies referable to that guideline. Large studies warranting level I evidence were defined as those with ≥ 100 patients or those which fulfilled endpoint criteria predetermined by power analysis. The level of evidence for uncontrolled studies was determined by whether they included contemporaneous controls (level III), historical controls (level IV), or no controls (level V, equal to expert opinion). See Table 1.¹ Review papers and consensus statements were considered expert opinion and were designated the appropriate level of evidence. Meta-analyses were used to organize the information and to draw conclusions about an overall treatment effect from multiple studies on a particular subject. The grade of recommendation, however, was based on the level of evidence of the individual studies. An A or B grade recommendation required at least 1 or 2 large positive randomized trials supporting the claim, while a C grade recommendation required only 1 small supportive randomized investigation. The rationale for each guideline statement was used to clarify certain points from the studies, to identify controversies, and to provide clarity in the derivation of the final recommendation. Significant controversies in interpretation of the literature were resolved by consensus of opinion of the committee members, which in some cases led to a downgrade of the recommendation. Following an extensive review process by external reviewers, the final guideline manuscript was reviewed and approved by A.S.P.E.N. Board of Directors and SCCM's Board of Regents and Council.

Introduction

The significance of nutrition in the hospital setting cannot be overstated. This significance is particularly noted in the ICU. Critical illness is typically associated with a catabolic stress state in which patients commonly demonstrate a systemic inflammatory response. This response is coupled with complications of increased infectious morbidity, multi-organ dysfunction, prolonged hospitalization, and disproportionate mortality. Over the past 3 decades, the understanding of the molecular and biological effects of nutrients in maintaining homeostasis in the critically ill population has made exponential advances. Traditionally, nutrition *support* in the critically ill population was regarded as adjunctive care designed to provide exogenous fuels to support the patient during the stress response. This support had 3 main objectives: to preserve lean body mass, to maintain immune function, and to avert metabolic complications. Recently these goals have become more focused on nutrition *therapy*, specifically attempting to attenuate the metabolic response to stress, to prevent oxidative cellular injury, and to favorably modulate the immune response. Nutritional modulation of the stress response to critical illness includes early enteral nutrition, appropriate macro- and micronutrient delivery, and meticulous glycemic control. Delivering early nutrition support therapy, primarily using the enteral route, is seen as a proactive therapeutic strategy that may reduce disease severity, diminish complications, decrease length of stay in the ICU, and favorably impact patient outcome.

A. Initiate Enteral Feeding

A1. Traditional nutrition assessment tools (albumin, prealbumin, and anthropometry) are not validated in critical care. Before initiation of feedings, assessment should include evaluation of weight loss and previous nutrient intake prior to admission, level of disease severity, comorbid conditions, and function of the gastrointestinal (GI) tract. (Grade: E)

Rationale. In the critical care setting, the traditional protein markers (albumin, prealbumin, transferrin, retinol binding protein) are a reflection of the acute phase response (increases in vascular permeability and reprioritization of hepatic protein synthesis) and do not accurately represent nutrition status in the ICU setting. Anthropometrics are not reliable in assessment of nutrition status or adequacy of nutrition therapy.^{2,3}

A2. Nutrition support therapy in the form of enteral nutrition (EN) should be initiated in the critically ill patient who is unable to maintain volitional intake. (Grade: C)

Rationale. EN supports the functional integrity of the gut by maintaining tight junctions between the intraepithelial cells, stimulating blood flow, and inducing the release of trophic endogenous agents (such as cholecystokinin, gastrin, bombesin, and bile salts). EN maintains structural integrity by maintaining villous height and supporting the mass of secretory IgA-producing immunocytes which comprise the gut-associated lymphoid tissue (GALT) and in turn contribute to mucosal-associated lymphoid tissue (MALT) at distant sites such as the lungs, liver, and kidneys.⁴⁻⁷

Adverse change in gut permeability from loss of functional integrity is a dynamic phenomenon which is time-dependent (channels opening within hours of the major insult or injury). The consequences of the permeability changes include increased bacterial challenge (engagement of GALT with enteric organisms), risk for systemic infection, and greater likelihood of multi-organ dysfunction syndrome (MODS).^{4,5} As disease severity worsens, increases in gut permeability are amplified and the enteral route of feeding is more likely to favorably impact outcome parameters of infection, organ failure, and hospital length of stay (compared to the parenteral route).⁸

The specific reasons for providing early EN are to maintain gut integrity, modulate stress and the systemic immune response, and attenuate disease severity.^{6,8,9} Additional endpoints of EN therapy include use of the gut as a conduit for the delivery of immune-modulating agents and use of enteral formulations as an effective means for stress ulcer prophylaxis.

Nutrition support therapy (also called “specialized” or “artificial” nutrition therapy) refers to the provision of enteral tube feeding or parenteral nutrition. “Standard

therapy” refers to a patient’s own volitional intake without provision of specialized nutrition support therapy. The importance of promoting gut integrity with regard to patient outcome is being strengthened by clinical trials comparing critically ill patients fed by EN to those receiving standard (STD) therapy. In a recent meta-analysis¹⁰ in elective gastrointestinal surgery and surgical critical care, patients undergoing a major operation who were given early postoperative EN experienced significant reductions in infection (relative risk [RR] = 0.72; 95% confidence interval [CI] 0.54-0.98; $P = .03$), hospital length of stay (mean 0.84 days; range 0.36-1.33 days; $P = .001$), and a trend toward reduced anastomotic dehiscence (RR = 0.53; 95% CI 0.26-1.08; $P = .08$), when compared to similar patients receiving no nutrition support therapy.¹⁰⁻¹⁶ In a meta-analysis¹⁷ of patients undergoing surgery for complications of severe acute pancreatitis, those placed on EN 1 day postop showed a trend toward reduced mortality compared to controls randomized to STD therapy (RR = 0.26; 95% CI 0.06-1.09; $P = .06$).¹⁷⁻¹⁹ See Table 2.^{11-16,18,19}

A3. EN is the preferred route of feeding over parenteral nutrition (PN) for the critically ill patient who requires nutrition support therapy. (Grade: B)

Rationale. In the majority of critically ill patients, it is practical and safe to utilize EN instead of PN. The beneficial effects of EN when compared to PN are well documented in numerous prospective randomized controlled trials involving a variety of patient populations in critical illness, including trauma, burns, head injury, major surgery, and acute pancreatitis.^{8,20-22} While few studies have shown a differential effect on mortality, the most consistent outcome effect from EN is a reduction in infectious morbidity (generally pneumonia and central line infections in most patient populations, and specifically abdominal abscess in trauma patients).²⁰ In many studies, further benefits are seen from significant reductions in hospital length of stay,²¹ cost of nutrition therapy,²¹ and even return of cognitive function (in head injury patients).²³ All 6 meta-analyses that compared EN to PN showed significant reductions in infectious morbidity with use of EN.^{21,24-28} Noninfective complications (risk difference = 4.9; 95% CI 0.3-9.5; $P = .04$) and reduced hospital length of stay (weighted mean difference [WMD] = 1.20 days; 95% CI 0.38-2.03; $P = .004$) were seen with use of EN compared to PN in 1 meta-analysis by Peter et al.²⁸ Five of the meta-analyses showed no difference in mortality between the 2 routes of nutrition support therapy.^{21,24,26-28} One meta-analysis by Simpson and Doig²⁵ showed a significantly lower mortality (RR = 0.51; 95% CI 0.27-0.97; $P = .04$) despite a significantly higher incidence of infectious complications (RR = 1.66; 95% CI 1.09-2.51; $P = .02$) with use of PN compared to EN.²⁵ See Table 3.^{8,20,22,29-61}

Table 2. Randomized Studies Evaluating Enteral Nutrition (EN) vs No Nutrition Support Therapy (Standard [STD] Therapy) in Elective Surgery, Surgery Critical Care, and Acute Pancreatitis Patients

Study	Population	Study Groups	Infection ^a	Hospital LOS	Hospital Mortality	Other Outcomes
				Days, Mean ± SD (or Range)		
Sagar et al, 1979 ¹² Level II	GI surgery (n = 30)	EN STD	3/15 (20%) 5/15 (33%)	14 (10-26) 19 (10-46)	0/15 (0%) 0/15 (0%)	
Schroeder et al, 1991 ¹¹ Level II	GI surgery (n = 32)	EN STD	1/16 (6%) 0/16 (0%)	0 ± 4 15 ± 10	0/16 (0%) 0/16 (0%)	Anastomotic dehiscence 0/16 (0%) 0/16 (0%)
Carr et al, 1996 ¹³ Level II	GI surgery (n = 28)	EN STD	0/14 (0%) 3/14 (21%)	9.8 ± 6.6 9.3 ± 2.8	0/14 (0%) 1/14 (7%)	Lactulose:mannitol ratio 0.1 ± 0.03 ^b 0.5 ± 0.26
Beier-Holgersen et al, 1996 ¹⁴ Level II	GI surgery (n = 60)	EN STD	2/30 ^b (7%) 14/30 (47%)	8.0 ^c 11.5	2/30 (7%) 4/30 (13%)	Anastomotic leak 2/30 (7%) 4/30 (13%)
Heslin et al, 1997 ¹⁵ Level I	GI surgery (n = 195)	EN STD	20/97 (21%) 23/98 (23%)	11 (4-41) 10 (6-75)	2/97 (2%) 3/98 (3%)	Major complication 27/97 (28%) 25/98 (26%)
Watters et al, 1997 ¹⁶ Level II	GI surgery (n = 28)	EN STD	NR	17 ± 9 16 ± 7	0 (0%) 0 (0%)	Anastomotic leak 1/13 (8%) 3/15 (20%)
Pupelis et al, 2000 ¹⁸ Level II	Acute pancreatitis (n = 29)	EN STD	3/11 (27%) 1/18 (6%)	45 ± 96 29 ± 103	1/11 (9%) 5/18 (28%)	
Pupelis et al, 2001 ¹⁹ Level II	Acute pancreatitis, peritonitis (n = 60)	EN STD	10/30 (33%) ^d 8/30 (27%)	35.3 ± 22.9 35.8 ± 32.5	1/30 (3%) 7/30 (23%)	MOF 18/30 (60%) 20/30 (67%)

SD, standard deviation; NR, not reported; LOS, length of stay; GI, gastrointestinal; MOF, multiple organ failure.

^a All infections represent number of patients per group with infection unless otherwise stated.

^b $P \leq .05$.

^c $P = .08$.

^d Wound sepsis.

A4. Enteral feeding should be started early within the first 24-48 hours following admission. (Grade: C) The feedings should be advanced toward goal over the next 48-72 hours. (Grade: E)

Rationale. Attaining access and initiating EN should be considered as soon as fluid resuscitation is completed and the patient is hemodynamically stable. A "window of opportunity" exists in the first 24-72 hours following admission or the onset of a hypermetabolic insult. Feedings started within this time frame (compared to feedings started after 72 hours) are associated with less gut permeability, diminished activation, and release of inflammatory cytokines (ie, tumor necrosis factor [TNF] and reduced systemic endotoxemia).²¹ One meta-analysis by Heyland et al showed a trend toward reduced infectious morbidity (RR = 0.66; 95% CI 0.36-1.22; $P = .08$) and mortality (RR = 0.52; 95% CI 0.25-1.08; $P = .08$),²¹ while a second by Marik and Zaloga showed significant

reductions in infectious morbidity (RR = 0.45; 95% CI 0.30-0.66; $P = .00006$) and hospital length of stay (mean 2.2 days, 95% CI 0.81-3.63 days; $P = .001$) with early EN compared to delayed feedings.⁶² See Table 4.⁶³⁻⁷²

A5. In the setting of hemodynamic compromise (patients requiring significant hemodynamic support including high dose catecholamine agents, alone or in combination with large volume fluid or blood product resuscitation to maintain cellular perfusion), EN should be withheld until the patient is fully resuscitated and/or stable. (Grade: E)

Rationale. At the height of critical illness, EN is being provided to patients who are prone to GI dysmotility, sepsis, and hypotension and thus are at increased risk for subclinical ischemia/reperfusion injury involving the intestinal microcirculation. Ischemic bowel is a rare complication of EN, occurring in <1% of cases.^{73,74} EN-related

Table 3. Randomized Studies Evaluating Enteral Nutrition (EN) vs Parenteral Nutrition (PN) in Surgery, Trauma, Pancreatitis, and Critically Ill Patients

Study	Population	Study Groups	ICU Mortality	Infections ^a	LOS Days, Mean ± SD (or Range)	Other Clinical Outcomes	Cost
Rapp et al, 1983 ²⁹ Level II	ICU head injury (n = 38)	EN PN	9/18 (50%) ^b 3/20 (15%)	NR	49.4 Hosp 52.6 Hosp	Duration MV 10.3 d 10.4 d	NR
Adams et al, 1986 ³⁰ Level II	Trauma (n = 46)	EN PN EN PN	1/23 (4%) 3/23 (13%)	15/23 (65%) 17/23 (74%)	30 ± 21 Hosp 31 ± 29 Hosp 13 ± 11 ICU 10 ± 10 ICU	Duration MV 12 ± 11 d 10 ± 10 d	\$1346/d ^b \$3729/d
Bower et al, 1986 ³¹ Level II	GI surgery (n = 20)	EN PN	0/10 (0%) 0/10 (0%)	0/10 (0%) 0/10 (0%)		Complications 0/10 (0%) 0/10 (0%)	
Szeluga et al, 1987 ³² Level II	Bone marrow transplant (n = 61)	EN PN	No difference at 100 days and long-term	5/30 (17%) 8/31 (26%)	33 ± 15 Hosp 36 ± 18 Hosp	Complications 11/30 (37%) 14/31 (45%)	\$1139/patient \$2575/patient NR
Young et al, 1987 ³³ Level II	ICU head injury (n = 58)	EN PN	10/28 (36%) 10/23 (43%)	5/28 (18%) 4/23 (17%)	NR	NR	NR
Peterson et al, 1988 ³⁴ Level II	Trauma (n = 59)	EN PN EN PN	NR	2/21 (10%) 8/25 (32%)	13. 2 ± 1.6 Hosp 14.6 ± 1.9 Hosp 3.7 ± 0.8 ICU 4.6 ± 1.0 ICU	NR	NR
Cerra et al, 1988 ³⁵ Level II	ICU (n = 70)	EN PN	7/33 (21%) 8/37 (22%)	0/33 (0%) 0/37 (0%)	NR	Complications 7/33 (21%) 7/37 (19%)	\$228 ± 59/d ^b \$330 ± 61/d
Greenburg et al, 1988 ³⁶ Level II	Inflammatory bowel (n = 51)	EN PN	0/19 (0%) 0/32 (0%)	0/19 (0%) 0/32 (0%)		Complications 0/19 (0%) 0/32 (0%)	
Moore et al, 1989 ³⁷ Level II	Trauma (n = 75)	EN PN	0/29 (0%) 0/30 (0%)	5/29 (17%) 11/30 (37%)	NR	NR	
Hamaoui et al, 1990 ³⁸ Level II	GI surgery (n = 19)	EN PN	1/11 (9%) 0/8 (0%)	1/11 (9%) 0/8 (0%)		0/11 (0%) 0/8 (0%)	\$44.36/d ^b \$102.10/d
Kudsk et al, 1992 ²⁰ Level II	Trauma (n = 98)	EN PN	1/51 (2%) 1/45 (2%)	9/51 (18%) ^b 18/45 (40%)	20.5 ± 19.9 Hosp 19.6 ± 18.8 Hosp	Duration MV 2.8 ± 4.9 d 3.2 ± 6.7 d	NR
González-Huix et al, 1993 ³⁹ Level II	Inflammatory bowel (n = 44)	EN PN	0/23 (0%) 0/21 (0%)	1/23 (4%) 8/21 (38%)		Complications 11/23 (48%) 11/21 (52%)	

(continued)

Table 3. (continued)

Study	Population	Study Groups	ICU Mortality	Infections ^a	LOS Days, Mean ± SD (or Range)	Other Clinical Outcomes	Cost
Iovinelli et al, 1993 ⁴⁰ Level II	Head-neck cancer (n = 48)	EN PN	0/24 (0%) 0/24 (0%)	5/24 (21%) 4/24 (17%)	26 ± 11 ^b Hosp 34 ± 11 Hosp	Complications 1/24 (4%) 2/24 (8%)	
Kudsk et al, 1994 ⁴¹ Level II	Trauma (n = 68)	EN PN	1/34 (3%) 0/34 (0%)	5/34 (15%) 14/34 (41%)	NR	Complications 0/34 (0%) 0/34 (0%)	
Dunham et al, 1994 ⁴² Level II	Trauma (n = 37)	EN PN	1/12 (8%) 1/15 (7%)	0/12 (0%) 0/15 (0%)	NR	Complications 0/12 (0%) 0/15 (0%)	NR
Borzotta et al, 1994 ⁴³ Level II	Neurotrauma (n = 59)	EN PN	5/28 (18%) 1/21 (5%)	51 per group 39 per group	39 ± 23.1 Hosp 36.9 ± 14 Hosp	NR	\$121,941 ^b \$112,450
Hadfield et al, 1995 ⁴⁴ Level II	ICU (n = 24)	EN PN	2/13 (15%) 6/11 (55%)	NR	NR	NR	NR
Baigrie et al, 1996 ⁴⁵ Level II	GI surgery (n = 97)	EN PN	4/50 (8%) 6/47 (13%)	2/50 (4%) 10/47 (21%)		Complications 15/50 (30%) 23/47 (49%)	
McClave et al, 1997 ⁴⁶ Level II	Acute pancreatitis (n = 32)	EN PN	0/16 (0%) 0/16 (0%)	2/16 (13%) 2/16 (13%)	9.7 ± 1.3 Hosp 11.9 ± 2.6 Hosp	NR	\$761 ± 50.3 ^b \$3294 ± 551.9
Reynolds et al, 1997 ⁴⁷ Level II	Trauma (n = 67)	EN PN	2/33 (6%) 1/34 (3%)	10/33 (30%) 19/34 (56%)		Complications 11/33 (33%) 6/34 (18%)	
Sand et al, 1997 ⁴⁸ Level II	GI surgery (n = 29)	EN PN	0/13 (0%) 1/16 (6%)	3/13 (23%) 5/16 (31%)		Complications 3/13 (23%) 3/16 (19%)	Cost of PN was 4 × cost of EN Savings of 70 GBP/d with EN ^b
Kalfarentzos et al, 1997 ²² Level II	Acute pancreatitis (n = 38)	EN PN	1/18 (6%) 2/20 (10%)	5/18 (28%) ^b 10/20 (50%)	40 (25-83) Hosp 39 (22-73) Hosp	Duration MV 15 (6-16) d 11 (7-31) d	NR
Gianotti et al, 1997 ⁴⁹ Level I	Surgery GI cancer (n = 176)	EN PN	0/87 (0%) 0/86 (0%)	20/87 (23%) ^c 24/86 (28%)	11 (5-21) ICU 12 (5-24) ICU	MOF 0/16 (0%) 5/18 (28%)	NR
Windsor et al, 1998 ⁸ Level II	Acute pancreatitis (n = 34)	EN PN	0/16 (0%) 2/18 (11%)	0/16 (0%) 3/18 (17%)	12.5 (9.5-14) Hosp 15.0 (11-28) Hosp	NR	NR
Woodcock et al, 2001 ⁵⁰ Level II	ICU patients (n = 38)	EN PN	9/17 (53%) 5/21 (24%)	6/16 (38%) 11/21 (52%)	33.2 ± 43 Hosp 27.3 ± 18.7 Hosp	NR	NR

(continued)

Table 3. (continued)

Study	Population	Study Groups	ICU Mortality	Infections ^a	LOS Days, Mean ± SD (or Range)	Other Clinical Outcomes	Cost
Braga et al, 2001 ⁵¹ Level I	Surgery GI cancer (n = 257)	EN	3/126 (2%)	25/126 (20%)	19.9 ± 8.2 Hosp	Complications 45/126 (36%)	\$25/d
		PN	4/131 (3%)	30/131 (23%)	20.7 ± 8.8 Hosp	53/131 (40%)	\$90/d
Pacelli et al, 2001 ⁵² Level I	Major surgery (n = 241)	EN	7/119 (6%)	17/119 (14%)	15.2 ± 3.6 Hosp	Postop complications 45/119 (38%)	NR
		PN	3/122 (2%)	14/122 (11%)	16.1 ± 4.5 Hosp	48/122 (39%)	NR
Bozzetti et al, 2001 ⁵³ Level I	Surgery GI cancer (n = 317)	EN	2/159 (1.3%)	25/159 (16%) ^b	13.4 ± 4.1 Hosp ^b	Postop complications 54/159 (34%) ^b	NR
		PN	5/158 (3.2%)	42/158 (27%)	15.0 ± 5.6 Hosp	78/158 (49%)	NR
Oláh et al, 2002 ⁵⁴ Level II	Acute pancreatitis (n = 89)	EN	2/41 (5%)	5/41 (12%) ^c	16.8 ± 7.8 Hosp	MOF 2/41 (5%)	NR
		PN	4/48 (8%)	13/48 (27%)	23.6 ± 10.2 Hosp	5/48 (10%)	NR
Abou-Assi et al, 2002 ⁵⁵ Level II	Acute pancreatitis (n = 53)	EN	8/26 (31%)	5/26 (19%)	14.2 ± 1.9 Hosp	MOF 7/26 (27%)	\$394 ^b
		PN	6/27 (22%)	13/27 (48%)	18.4 ± 1.9 Hosp	8/27 (30%)	\$2756
Gupta et al, 2003 ⁵⁶ Level II	Acute pancreatitis (n = 17)	EN	0/8 (0%)	1/8 (13%)	7 (4-14) Hosp ^b	MOF 0/8 (0%)	55 GBP
		PN	0/9 (0%)	2/9 (22%)	10 (7-26) Hosp	6/9 (67%)	297 GBP
Louie et al, 2005 ⁵⁷ Level II	Acute pancreatitis (n = 28)	EN	0/10 (0%)	1/10 (10%)	26.2 ± 17.4 Hosp	MOF 4/10 (40%)	\$1375 ^c
		PN	3/18 (17%)	5/18 (28%)	40.3 ± 42.4 Hosp	8/18 (44%)	\$2608
Petrov et al, 2006 ⁵⁸ Level II	Acute pancreatitis (n = 70)	EN	2/35 (6%)	7/35 (20%) ^b	NR	MOF 7/35 (20%) ^b	NR
		PN	12/35 (34%)	16/35 (46%)		17/35 (49%)	NR
Eckerwall et al, 2006 ⁵⁹ Level II	Acute pancreatitis (n = 48)	EN	1/23 (4%)	3/23 (13%)	9 (7-14) Hosp	MOF 1/23 (4%)	NR
		PN	0/25 (0%)	0/25 (0%)	7 (6-14) Hosp	1/25 (4%)	NR
Casas et al, 2007 ⁶⁰ Level II	Acute pancreatitis (n = 22)	EN	0/11 (0%)	1/11 (9%)	30.2 Hosp	MOF 0/11 (0%)	NR
		PN	2/11 (18%)	5/11 (45%)	30.7 Hosp	2/11 (18%)	NR

SD, standard deviation; NR, not reported; ICU, intensive care unit; LOS, length of stay; Hosp, hospital; GBP, pounds sterling; MV, mechanical ventilation; neuro, neurologic; MOF, multiple organ failure; GI, gastrointestinal; Postop, postoperative; d, days.

^aAll infections represent number of patients per group with infection unless otherwise stated.

^bP ≤ .05.

^cP = .08.

Adapted from the Canadian Clinical Practice Guidelines,²¹ McClave et al,¹⁷ and adapted with permission from Braunschweig et al, *Am J Clin Nutr.* 2001;74:534-542, American Society for Nutrition.

Table 4. Randomized Studies Evaluating Early Enteral Nutrition (EN) vs Delayed EN in Critically Ill Patients

Study	Population	Study Groups	ICU Mortality	Infections ^a	LOS Days, Mean ± SD	Ventilator Days, Mean ± SD	Cost
Moore et al, 1986 ⁶³ Level II	Trauma (n = 43)	Early Delayed	1/32 (3%) 2/31 (6%)	3/32 (9%) 9/31 (29%)	NR	NR	\$16,280 ± 2146 \$19,636 ± 3396
Chiarelli et al, 1990 ⁶⁴ Level II	Burn (n = 20)	Early Delayed	0/10 (0%) 0/10 (0%)	3/10 (30%) ^b 7/10 (70%)	69.2 ± 10.4 ^c Hosp 89.0 ± 18.9 Hosp	NR	NR
Eyer et al, 1993 ⁶⁵ Level II	SICU trauma (n = 52)	Early Delayed	2/19 (11%) 2/19 (11%)	29 per group 14 per group	11.8 ± 7.9 ICU 9.9 ± 6.7 ICU	10.2 ± 8.1 8.1 ± 6.8	NR
Chuntrasakul et al, 1996 ⁶⁶ Level II	SICU trauma (n = 38)	Early Delayed	1/21 (5%) 3/17 (18%)	NR	8.1 ± 6.3 ICU 8.4 ± 4.8 ICU	5.29 ± 6.3 6.12 ± 5.3	NR
Singh et al, 1998 ⁶⁷ Level II	Peritonitis (n = 43)	Early Delayed	4/21 (19%) 4/22 (18%)	7/21 (33%) 12/22 (55%)	14 ± 6.9 Hosp 13 ± 7.0 Hosp	NR	NR
Minard et al, 2000 ⁶⁸ Level II	Closed head injury (n = 27)	Early Delayed	1/12 (8%) 4/15 (27%)	6/12 (50%) 7/15 (47%)	30 ± 14.7 Hosp 21.3 ± 13.7 Hosp 18.5 ± 8.8 ICU ^c 11.3 ± 6.1 ICU	15.1 ± 7.5 10.4 ± 6.1	NR
Kompan et al, 2004 ⁶⁹ Level II	SICU trauma (n = 52)	Early Delayed	0/27 (0%) 1/25 (4%)	9/27 (33%) 16/25 (64%)	15.9 ± 9.7 ICU 20.6 ± 18.5 ICU	12.9 ± 8.1 15.6 ± 16.1	NR
Malhotra et al, 2004 ⁷⁰ Level I	Postop peritonitis (n = 200)	Early Delayed	12/100 (12%) 16/100 (16%)	54/100 (54%) 67/100 (67%)	10.6 Hosp 10.7 Hosp 1.6 ICU 2.1 ICU	NR	NR
Peck et al, 2004 ⁷¹ Level II	Burn (n = 27)	Early Delayed	4/14 (29%) 5/13 (38%)	12/14 (86%) 11/13 (85%)	60 ± 44 Hosp 60 ± 38 Hosp 40 ± 32 ICU 37 ± 33 ICU	32 ± 27 23 ± 26	NR
Dvorak et al, 2004 ⁷² Level II	Spinal cord injury (n = 17)	Early Delayed	0/7 (0%) 0/10 (0%)	2.4 ± 1.5 per pt 1.7 ± 1.1 per pt	53 ± 34.4 Hosp 37.9 ± 14.6 Hosp	31.8 ± 35.0 20.9 ± 14.4	NR

SD, standard deviation; NR, not reported; ICU, intensive care unit; LOS, length of stay; Hosp, hospital; SICU, surgical ICU; pt, patient.

^a All infections represent number of patients per group with infection unless otherwise stated.

^b Bacteremia.

^c $P \leq .05$.

Adapted from the Canadian Clinical Practice Guidelines.²¹

ischemic bowel has been reported most often in the past with use of surgical jejunostomy tubes. However, more recently, this complication has been described with use of nasojejunal tubes.⁷⁵ EN intended to be infused into the small bowel should be withheld in patients who are hypotensive (mean arterial blood pressure <60 mm Hg), particularly if clinicians are initiating use of catecholamine agents (eg, norepinephrine, phenylephrine, epinephrine, dopamine) or escalating the dose of such agents to maintain hemodynamic stability. EN may be provided with caution to patients into either the stomach or small bowel

on stable low doses of pressor agents,⁷⁶ but any signs of intolerance (abdominal distention, increasing nasogastric tube output or gastric residual volumes, decreased passage of stool and flatus, hypoactive bowel sounds, increasing metabolic acidosis and/or base deficit) should be closely scrutinized as possible early signs of gut ischemia.

A6. In the ICU patient population, neither the presence nor absence of bowel sounds nor evidence of passage of flatus and stool is required for the initiation of enteral feeding. (Grade: B)

Rationale. The literature supports the concept that bowel sounds and evidence of bowel function (ie, passing flatus or stool) are not required for initiation of enteral feeding. GI dysfunction in the ICU setting occurs in 30%-70% of patients depending on the diagnosis, premorbid condition, ventilation mode, medications, and metabolic state.⁷⁷

Proposed mechanisms of ICU and postoperative GI dysfunction can be separated into 3 general categories: mucosal barrier disruption, altered motility and atrophy of the mucosa, and reduced mass of GALT.

Bowel sounds are only indicative of contractility and do not necessarily relate to mucosal integrity, barrier function, or absorptive capacity. Success at attaining nutrition goals within the first 72 hours ranges from 30% to 85%. When ICU enteral feeding protocols are followed, rates of GI tolerance in the range of 70%-85% can be achieved.⁷⁶ Ten randomized clinical trials,⁶³⁻⁷² the majority in surgical critically ill patients, have reported feasibility and safety of enteral feeding within the initial 36-48 hours of admission to the ICU. The grade of this recommendation is based on the strength of the literature supporting A3, where patients in the experimental arm of the above mentioned studies were successfully started on EN within the first 36 hours of admission (regardless of clinical signs of stooling, flatus, or borborygmi). See Table 4.⁶³⁻⁷²

A7. Either gastric or small bowel feeding is acceptable in the ICU setting. Critically ill patients should be fed via an enteral access tube placed in the small bowel if at high risk for aspiration or after showing intolerance to gastric feeding. (Grade: C) Withholding of enteral feeding for repeated high gastric residual volumes alone may be sufficient reason to switch to small bowel feeding (the definition for high gastric residual volume is likely to vary from one hospital to the next, as determined by individual institutional protocol). (Grade: E) (See guideline D4 for recommendations on gastric residual volumes, identifying high risk patients, and reducing chances for aspiration.)

Rationale. Multiple studies have evaluated gastric vs jejunal feeding in various medical and surgical ICU settings. One level II study comparing gastric vs jejunal feeding showed significantly less gastroesophageal reflux with small bowel feeding.⁷⁸ In a nonrandomized prospective study using a radioisotope in an enteral formulation, esophageal reflux was reduced significantly with a trend toward reduced aspiration as the level of infusion was moved from the stomach down through the third portion of the duodenum.⁷⁹ Three meta-analyses have been published comparing gastric with post-pyloric feeding in the ICU setting.⁸⁰⁻⁸² Only 1 of these meta-analyses showed a significant reduction in ventilator-associated pneumonia with post-pyloric feeding (RR = 0.76; 95% CI 0.59-0.99; $P = .04$),⁸² an effect heavily influenced by 1 study by Taylor

et al.²³ With removal of this study from the meta-analysis, the difference was no longer significant. The 2 other meta-analyses (which did not include the Taylor study) showed no difference in pneumonia between gastric and post-pyloric feeding.^{80,81} While 1 showed no difference in ICU length of stay,⁸⁰ all 3 meta-analyses showed no significant difference in mortality between gastric and post-pyloric feeding.⁸⁰⁻⁸² See Table 5.^{23,68,78,83-91}

B. When to Use Parenteral Nutrition

B1. If early EN is not feasible or available the first 7 days following admission to the ICU, no nutrition support therapy (ie, STD therapy) should be provided. (Grade: C) In the patient who was previously healthy prior to critical illness with no evidence of protein-calorie malnutrition, use of PN should be reserved and initiated only after the first 7 days of hospitalization (when EN is not available). (Grade: E)

Rationale. These 2 recommendations are the most controversial in these guidelines, are influenced primarily by 2 meta-analyses, and should be interpreted very carefully in application to patient care.^{24,92} Both meta-analyses compared use of PN with STD therapy (where no nutrition support therapy was provided). In critically ill patients in the absence of pre-existing malnutrition (when EN is not available), Braunschweig et al aggregated 7 studies⁹³⁻⁹⁹ and showed that use of STD therapy was associated with significantly reduced infectious morbidity (RR = 0.77; 95% CI 0.65-0.91; $P < .05$) and a trend toward reduced overall complications (RR = 0.87; 95% CI 0.74-1.03; P not provided) compared to use of PN.²⁴ In the same circumstances (critically ill, no EN available, and no evidence of malnutrition), Heyland et al⁹² aggregated 4 studies^{96,97,100,101} and showed a significant increase in mortality with use of PN (RR = 0.1.78; 95% CI 1.11-2.85; $P < .05$) and a trend toward greater rate of complications (RR = 2.40; 95% CI 0.88-6.58; P not provided), when compared to STD therapy. See Table 6.⁹³⁻¹²⁹

With increased duration of severe illness, priorities between STD therapy and PN become reversed. Sandstrom et al first showed that after the first 14 days of hospitalization had elapsed, continuing to provide no nutrition therapy was associated with significantly greater mortality (21% vs 2%, $P < .05$) and longer hospital length of stay (36.3 days vs 23.4 days, $P < .05$), when compared respectively to use of PN.⁹⁶ The authors of both meta-analyses speculated as to the appropriate length of time before initiating PN in a patient on STD therapy who has not begun to eat spontaneously (Braunschweig recommending 7-10 days, Heyland recommending 14 days).^{24,92} Conflicting data were reported in a Chinese study of patients with severe acute pancreatitis. In this study, a significant step-wise improvement was seen in

Table 5. Randomized Studies Evaluating Small Bowel (SB) vs Gastric Feeding in Critically Ill Patients

Study	Population	Study Groups	ICU Mortality	Pneumonia	LOS Days, Mean \pm SD (or Range)	Other Outcomes	Nutrition Outcomes
Montecalvo et al, 1992 ⁸³ Level II	MICU/SICU (n = 38)	SB Gastric	5/19 (26%) 5/19 (26%)	4/19 (21%) 6/19 (32%)	11.7 \pm 8.2 ICU 12.3 \pm 10.8 ICU	Duration MV, mean \pm SD 10.2 \pm 7.1 d 11.4 \pm 10.8 d	% Goal feeds delivered 61.0% \pm 17.0% 46.9% \pm 25.9%
Kortbeek et al, 1999 ⁸⁴ Level II	Trauma (n = 80)	SB Gastric SB Gastric	4/37 (11%) 3/43 (7%)	10/37 (27%) 18/43 (42%)	30 (6-47) Hosp 25 (9-88) Hosp 10 (3-24) ICU 7 (3-32) ICU NR	Duration MV, mean (range) 9 d (2-13 d) 5 d (3-15 d)	Time to goal feeds 34.0 \pm 7.1 h 43.8 \pm 22.6 h
Taylor et al, 1999 ²³ Level II	Trauma head injury (n = 82)	SB Gastric SB Gastric	5/41 (12%) at 6 mo 6/41 (15%) at 6 mo	18/41 (44%) 26/41 (63%) 25/41 (61%) ^{a,b} 35/41 (85%)		NR	% Goal feeds delivered 59.2% 36.8%
Kearns et al, 2000 ⁸⁵ Level II	MICU (n = 44)	SB Gastric SB Gastric	5/21 (24%) 6/23 (26%)	4/21 (19%) 3/23 (13%)	39 \pm 10 Hosp 43 \pm 11 Hosp 17 \pm 2 ICU 16 \pm 2 ICU	NR	% Goal feeds delivered 69% \pm 7% 47% \pm 7%
Minard et al, 2000 ⁶⁸ Level II	Trauma (n = 27)	SB Gastric SB Gastric	1/12 (8%) 4/15 (27%)	6/12 (50%) 7/15 (47%)	30 \pm 14.7 Hosp 21.3 \pm 14.7 Hosp 18.5 \pm 8.8 ICU ^a 11.3 \pm 6.1 ICU	Duration MV, mean \pm SD 15.1 \pm 7.5 d 10.4 \pm 6.1 d	# pts >50% goal \times 5 d 10/12 (83%) 7/15 (47%)
Lien et al, 2000 ⁷⁸ Level II	Neuro CVA (n = 8)	SB Gastric	NR	NR	NR	% Time esophageal pH <4 12.9 min (4.9-28.2) 24.0 min (19.0-40.6)	NR

(continued)

Table 5 (continued)

Study	Population	Study Groups	ICU Mortality	Pneumonia	LOS Days, Mean ± SD (or Range)	Other Outcomes	Nutrition Outcomes
Day et al, 2001 ⁸⁶ Level II	ICU (n = 25)	SB Gastric	NR	0/14 (0%) 2/11 (18%) NR	NR	NR	# tubes replaced 16 per group 9 per group % Goal feeds delivered 66.0% 64.0%
Esparza et al, 2001 ⁸⁷ Level II	MICU (n = 54)	SB Gastric	10/27 (37%) 11/27 (41%)	NR	NR	NR	Time to goal feeds 33 h 32 h
Boivin et al, 2001 ⁸⁸ Level II	MICU/SICU/neuro ICU (n = 80)	SB Gastric	18/39 (46%) 18/39 (46%)	NR	NR	NR	Time to goal feeds 43.0 ± 24.1 h 28.8 ± 15.9 h
Neumann et al, 2002 ⁸⁹ Level II	MICU (n = 60)	SB Gastric	NR	1/30 (3%) ^c 0/30 (0%)	NR	NR	Time to goal feeds 23.2 ± 3.9 h 23.0 ± 3.4 h
Davies et al, 2002 ⁹⁰ Level II	MICU/SICU (n = 73)	SB Gastric	4/34 (12%) 5/39 (13%)	2/31 (6%) 1/35 (3%)	13.9 ± 1.8 ICU ^a 10.4 ± 1.2 ICU	NR	% Goal feeds by day 7 80% ± 28% 75% ± 30%
Montejo et al, 2002 ⁹¹ Level I	ICU (n = 101)	SB Gastric	19/50 (38%) 22/51 (43%)	16/50 (32%) 20/51 (39%)	15 ± 10 ICU 18 ± 16 ICU	NR	

SD, standard deviation; NR, not reported; ICU, intensive care unit; MICU, medical ICU; SICU, surgical ICU; MV, mechanical ventilation; Pts, patients; CVA, cerebrovascular accident; Neuro, neurologic; d, day(s); h, hour(s); min, minute(s); mo, month(s).

^a $P \leq .05$.

^b Total infections.

^c Aspiration.

Adapted from the Canadian Clinical Practice Guidelines.²¹

Table 6. Randomized Studies Evaluating Parenteral Nutrition (PN) vs Standard Therapy (STD)

Study	Population	Protein Energy		Study Groups	Timing of PN	Complications	Hospital Mortality
		Malnutrition	Mortality				
Williams et al, 1976 ¹⁰² Level II	Esophagogastric Ca (n = 74)			PN STD	Preop 7-10 d	2/10 (20%) 3/9 (33%)	6/38 (16%) 8/36 (22%)
Moghissi et al, 1977 ¹⁰³ Level II	Esophageal Ca (n = 15)			PN STD	Preop 5-7 d	0/10 (0%) 1/5 (20%)	0/10 (0%) 0/5 (0%)
Holter et al, 1977 ⁹⁴ Level II	GI Ca (n = 56)	100%		PN STD	Preop 3 d	4/30 (13%) 5/26 (19%)	2/30 (7%) 2/26 (8%)
Preshaw et al, 1979 ¹⁰⁴ Level II	Colon Ca (n = 47)			PN STD	Preop 1 d	8/24 (33%) 4/23 (17%)	0/24 (0%) 0/23 (0%)
Heatley et al, 1979 ¹⁰⁵ Level II	Esophagogastric Ca (n = 74)			PN STD	Preop 7-10 d	3/38 (8%) ^{ab} 11/36 (31%)	6/38 (16%) 8/36 (22%)
Simms et al, 1980 ¹⁰⁶ Level II	Esophageal Ca (n = 20)			PN STD	NR	NR	1/10 (10%) 1/10 (10%)
Lim et al, 1981 ¹⁰⁷ Level II	Esophageal Ca (n = 20)	100%		PN STD	Preop 21 d	1/10 (10%) 4/10 (40%)	1/10 (10%) 2/10 (20%)
Thompson et al, 1981 ⁹⁸ Level II	GI Ca (n = 21)	100%		PN STD	Preop 5-14 d	2/12 (17%) 1/9 (11%)	0/12 (0%) 0/9 (0%)
Sako et al, 1981 ¹⁰⁸ Level II	Head-neck Ca (n = 66)			PN STD	NR	15/30 (50%) 18/32 (56%)	17/34 (50%) 8/32 (25%)
Jensen, 1982 ¹⁰⁹ Level II	Rectal Ca (n = 20)	100%		PN STD	Preop 2 d	NR	0/10 (0%) 4/10 (40%)
Moghissi et al, 1982 ¹¹⁰ Level II	Esophageal Ca (n = 52)			PN STD	Preop 6-8 d	1/25 (4%) 4/27 (15%)	1/25 (4%) 5/27 (19%)
Muller et al, 1982 ⁹⁵ /1986 ¹¹¹ Level I	GI Ca (n = 171)	60%		PN (gluc) PN (gluc/lipid) STD	Preop 10 d	11/66 (17%) ^b 17/46 (37%) 19/59 (32%)	3/66 (5%) ^b 10/46 (22%) 11/59 (19%)
Garden et al, 1983 ¹¹² Level II	Perioperative (n = 20)			PN STD	NR	1/10 (10%) 2/10 (20%)	0/10 (0%) 1/10 (10%)
Sax et al, 1987 ⁹⁷ Level II	Acute pancreatitis (n = 55)	0%		PN STD	NA	4/29 (14%) ^c 1/26 (4%)	1/29 (3%) 1/26 (4%)
Bellantone et al, 1988 ¹¹³ (JPEN) Level II	GI Ca (n = 91)	100%		PN STD	Preop ≥7 d	12/40 (30%) ^c 18/51 (35%)	1/40 (3%) 2/51 (4%)
Smith et al, 1988 ¹¹⁴ Level II	GI Ca (n = 34)	100%		PN STD	Preop 8-15 d	3/17 (18%) 6/17 (35%)	1/17 (6%) 3/17 (18%)
Meguid et al, 1988 ¹¹⁵ Level II	GI Ca (n = 66)	100%		PN STD	Preop 8 d	10/32 (31%) ^b 19/34 (56%)	1/32 (3%) 0/34 (0%)
Bellantone et al, 1988 ¹¹⁶ Level I	GI Ca (n = 100)			PN STD	Preop ≥7 d	8/54 (15%) ^{b,c} 22/46 (48%)	1/54 (2%) 1/46 (2%)
Fan et al, 1989 ¹¹⁷ Level II	Esophageal Ca (n = 40)	75%		PN STD	Preop 14 d	17/20 (85%) 15/20 (75%)	6/20 (30%) 6/20 (30%)
VA Co-OP 1991 ¹¹⁸ Level I	Perioperative (n = 459)	100%		PN STD	Preop 7-15 d	49/192 (26%) 50/203 (25%)	31/231 (13%) 24/228 (11%)

(continued)

Table 6. (continued)

Study	Population	Protein Energy Malnutrition	Study Groups	Timing of PN	Complications	Hospital Mortality
Von Meyenfeldt et al, 1992 ¹¹⁹ Level I	Perioperative (n = 101)	29%	PN STD	Preop 10-23 d	6/51 (12%) 7/50 (14%)	2/51 (4%) 2/50 (4%)
Fan et al, 1994 ¹²⁰ Level I	Hepatocellular Ca (n = 124)	26%	PN STD	Preop 7 d	22/64 (34%) ^b 33/60 (55%)	5/64 (8%) 9/60 (15%)
Xian-Li et al, 2004 ¹²¹ Level II	Acute pancreatitis (n = 44)		PN STD	NA	11/21 (52%) ^c 21/23 (91%)	3/21 (14%) 10/23 (44%)
Abel et al, 1976 ¹⁰⁰ Level II	Perioperative (n = 44)	100%	PN STD	Postop	2/20 (10%) 0/24 (0%)	4/20 (20%) 3/24 (13%)
Collins et al, 1978 ¹²² Level II	GI surgery (n = 20)	40%	PN STD	Postop	2/10 (20%) 0/10 (0%)	0/10 (0%) 0/10 (0%)
Freund et al, 1979 ¹²³ Level II	GI surgery (n = 35)	0%	PN STD	Postop	0/25 (0%) 0/10 (0%)	0/25 (0%) 0/10 (0%)
Yamada et al, 1983 ¹²⁴ Level II	GI surgery (n = 57)		PN STD	Postop	0/29 (0%) 5/28 (18%)	0/29 (0%) 1/28 (4%)
Jiménez et al, 1986 ¹²⁵ Level II	GI surgery (n = 75)	100%	PN STD	Postop	6/60 (10%) 3/15 (20%)	4/60 (7%) 1/15 (7%)
Askanazi et al, 1986 ¹²⁶ Level II	GU surgery (n = 35)		PN STD	Postop	1/22 (5%) 2/13 (15%)	0/22 (0%) 2/13 (15%)
Figueroa et al, 1988 ¹²⁷ Level II	GI surgery (n = 49)	0%	PN STD	Postop	4/25 (16%) 5/24 (21%)	0/25 (0%) 0/24 (0%)
Woolfson et al, 1989 ⁹⁹ Level I	Perioperative (n = 122)	0%	PN STD	Postop	6/62 (10%) 4/60 (7%)	8/62 (13%) 8/60 (13%)
Reilly et al, 1996 ¹⁰¹ Level II	Liver transplant (n = 28)	100%	PN PN/BCAA STD	Postop	NR	0/8 (0%) 1/10 (10%) 2/10 (20%)
Gys et al, 1990 ¹²⁸ Level II	GI surgery (n = 20)	0%	PN STD	Postop	1/10 (10%) 1/10 (10%)	0/10 (0%) 0/10 (0%)
Sandstrom et al, 1993 ⁹⁶ Level I	Surgery, trauma (n = 300)	23%	PN STD	Postop	NR	12/150 (8%) 10/150 (7%)
Hwang et al, 1993 ¹²⁹ Level II	GI surgery (n = 58)		PN STD	Postop	0/26 (0%) 0/32 (0%)	0/26 (0%) 0/32 (0%)
Brennan et al, 1994 ⁹³ Level I	Pancreatic Ca (n = 117)	100%	PN STD	Postop	27/60 (45%) 13/57 (23%)	4/60 (7%) 1/57 (2%)

Ca, cancer; GI, gastrointestinal; NA, not applicable; NR, not reported; BCAA, branch chain amino acids; Postop, postoperative; gluc, glucose; Preop, preoperative; d, day(s).

^a wound infection.

^b $P < .05$.

^c Infection.

Adapted from Heyland et al,²¹ Klein et al,¹³¹ and with permission from Braunschweig et al, *Am J Clin Nutr.* 2001;74:534-542, American Society for Nutrition and Detsky et al, *Ann Intern Med.* 1987;107:195-203,¹³⁰ American College of Physicians.

each clinical outcome parameter (hospital length of stay, pancreatic infection, overall complications, and mortality) when comparing patients randomized to STD therapy vs PN vs PN with parenteral glutamine, respectively.¹²¹ Because of the discrepancy, we attempted to contact the authors of this latter study to get validation of results but were unsuccessful. The final recommendation was based on the overall negative treatment effect of PN over the first week of hospitalization seen in the 2 meta-analyses.^{24,92} Although the literature cited recommends withholding PN for 10-14 days, the Guidelines Committee expressed concern that continuing to provide STD therapy (no nutrition support therapy) beyond 7 days would lead to deterioration of nutrition status and an adverse effect on clinical outcome.

B2. If there is evidence of protein-calorie malnutrition on admission and EN is not feasible, it is appropriate to initiate PN as soon as possible following admission and adequate resuscitation. (Grade: C)

Rationale. In the situation where EN is not available and evidence of protein-calorie malnutrition is present (usually defined by recent weight loss of >10%-15% or actual body weight <90% of ideal body weight), initial priorities are reversed and use of PN has a more favorable outcome than STD therapy. See Table 6.⁹³⁻¹²⁹

In the Heyland meta-analysis, use of PN in malnourished ICU patients was associated with significantly fewer overall complications (RR = 0.52; 95% CI 0.30-0.91; $P < .05$) than STD therapy.⁹² In the Braunschweig meta-analysis, STD therapy in malnourished ICU patients was associated with significantly higher risk for mortality (RR = 3.0; 95% CI 1.09-8.56; $P < .05$) and a trend toward higher rate of infection (RR = 1.17; 95% CI 0.88-1.56; P not provided) compared to use of PN.²⁴ For these patients, when EN is not available, there should be little delay in initiating PN after admission to the ICU.

B3. If a patient is expected to undergo major upper GI surgery and EN is not feasible, PN should be provided under very specific conditions:

If the patient is malnourished, PN should be initiated 5-7 days preoperatively and continued into the postoperative period. (Grade: B)

PN should not be initiated in the immediate postoperative period but should be delayed for 5-7 days (should EN continue not to be feasible). (Grade: B)

PN therapy provided for a duration of <5-7 days would be expected to have no outcome effect and may result in increased risk to the patient. Thus, PN should be initiated

only if the duration of therapy is anticipated to be ≥ 7 days. (Grade: B)

Rationale. One population of patients that has shown more consistent benefit of PN over STD involve those patients undergoing major upper GI surgery (esophagectomy, gastrectomy, pancreatectomy, or other major reoperative abdominal procedures), especially if there is evidence of preexisting protein-calorie malnutrition and the PN is provided under specific conditions.^{24,92} Whereas critically ill patients in the Heyland meta-analysis experienced increased mortality with use of PN compared to STD therapy (see rationale for guideline B1 above), surgical patients saw no treatment effect with PN regarding mortality (RR = 0.91; 95% CI 0.68-1.21; $P = \text{NS}$).⁹² Critically ill patients experienced a trend toward increased complications, while surgical patients saw significant reductions in complications with use of PN regarding mortality (RR = 2.40; 95% CI 0.88-6.58; $P < .05$).⁹²

These benefits were noted when PN was provided preoperatively for a minimum of 7-10 days and then continued through the perioperative period. In an earlier meta-analysis by Detsky et al¹³⁰ comparing perioperative PN with STD therapy, only seven^{95,98,102,103,107,110,111} out of 14 studies^{94,100,104,106,108,109,112} provided PN for ≥ 7 days.¹³⁰ As a result, only 1 study showed a treatment effect⁹⁵ and the overall meta-analysis showed no statistically significant benefit from PN.¹³⁰ In contrast, a later meta-analysis by Klein et al¹³¹ aggregated the data from 13 studies,^{95,98,103,105,111,113-120} all of which provided PN for ≥ 7 days.¹³¹ Six of the studies showed significant beneficial treatment effects from use of PN,^{95,103,105,111,115,120} with the pooled data from the overall meta-analysis showing a significant 10% decrease in infectious morbidity compared to STD therapy.¹³¹ See Table 6.⁹³⁻¹²⁹

It is imperative to be aware that the beneficial effect of PN is lost if given only postoperatively. Aggregation of data from 9 studies that evaluated routine postoperative PN^{79,94,96,99-101,104,109,122} showed a significant 10% increase in complications compared to STD therapy.¹³¹ Because of the adverse outcome effect from PN initiated in the immediate postoperative period, Klein et al recommended delaying PN for 5-10 days following surgery if EN continues not to be feasible.¹³¹

C. Dosing of Enteral Feeding

C1. The target goal of EN (defined by energy requirements) should be determined and clearly identified at the time of initiation of nutrition support therapy. (Grade: C) Energy requirements may be calculated by predictive equations or measured by indirect calorimetry. Predictive equations should be used with caution, as they provide a less accurate measure of energy requirements than indirect calorimetry in the

individual patient. In the obese patient, the predictive equations are even more problematic without availability of indirect calorimetry. (Grade: E)

Rationale. Clinicians should clearly identify the goal of EN, as determined by energy requirements. Over 200 predictive equations (including Harris-Benedict, Scholfield, Ireton-Jones, etc) have been published in the literature.¹³² Energy requirements may be calculated either through simplistic formulas (25-30 kcal/kg/d), published predictive equations, or the use of indirect calorimetry. Calories provided via infusion of propofol should be considered when calculating the nutrition regimen. While it is often difficult to provide 100% of goal calories by the enteral route, studies in which a protocol was used to increase delivery of EN have shown that delivering a volume of EN where the level of calories and protein provided is closer to goal improves outcome.^{133,134} This recommendation is supported by two level II studies in which those patients who by protocol randomization received a greater volume of EN experienced significantly fewer complications and less infectious morbidity,²³ as well as shorter hospital lengths of stay, and a trend toward lower mortality¹³⁵ than those patients receiving lower volume.

C2. Efforts to provide >50%-65% of goal calories should be made in order to achieve the clinical benefit of EN over the first week of hospitalization. (Grade: C)

Rationale. The impact of early EN on patient outcome appears to be a dose-dependent effect. "Trickle" or trophic feeds (usually defined as 10-30 mL/h) may be sufficient to prevent mucosal atrophy but may be insufficient to achieve the usual endpoints desired from EN therapy. Studies suggest that >50%-65% of goal calories may be required to prevent increases in intestinal permeability in burn and bone-marrow transplant patients, to promote faster return of cognitive function in head injury patients, and to improve outcome from immune-modulating enteral formulations in critically ill patients.^{5,23,133,136} This recommendation is supported by one level II²³ and one level III study¹³⁶ where increases in the percent goal calories infused from a range of 37%-40% up to 59%-64% improved clinical outcome.

C3. If unable to meet energy requirements (100% of target goal calories) after 7-10 days by the enteral route alone, consider initiating supplemental PN. (Grade: E) Initiating supplemental PN prior to this 7-10 day period in the patient already receiving EN does not improve outcome and may be detrimental to the patient. (Grade: C)

Rationale. Early on, EN is directed toward maintaining gut integrity, reducing oxidative stress, and modulating systemic

immunity. In patients already receiving some volume of EN, use of supplemental PN over the first 7-10 days adds cost^{137,138} and appears to provide no additional benefit.^{42,137-140} In 1 small study in burn patients, EN supplemented with PN was associated with a significant increase in mortality (63% vs 26%, $P < .05$) when compared respectively to hypocaloric EN alone.¹³⁸ See Table 7.^{42,137-140}

As discussed in guideline B1, the optimal time to initiate PN in a patient who is already receiving some volume of enteral feeding is not clear. The reports by Braunschweig et al and Sandstrom et al infer that after the first 7-10 days, the need to provide adequate calories and protein is increased in order to prevent the consequences of deterioration of nutrition status.^{24,96} At this point, if the provision of EN is insufficient to meet requirements, then the addition of supplemental PN should be considered.

C4. Ongoing assessment of adequacy of protein provision should be performed. The use of additional modular protein supplements is a common practice, as standard enteral formulations tend to have a high non-protein calorie:nitrogen ratio. In patients with body mass index (BMI) <30, protein requirements should be in the range of 1.2-2.0 g/kg actual body weight per day, and may likely be even higher in burn or multi-trauma patients. (Grade: E)

Rationale. In the critical care setting, protein appears to be the most important macronutrient for healing wounds, supporting immune function, and maintaining lean body mass. For most critically ill patients, protein requirements are proportionately higher than energy requirements and therefore are not met by provision of routine enteral formulations. The decision to add protein modules should be based on an ongoing assessment of adequacy of protein provision. Unfortunately in the critical care setting, determination of protein requirements is difficult but may be derived with limitations from nitrogen balance, simplistic equations (1.2-2.0 g/kg/d) or non-protein calorie:nitrogen ratio (70:1-100:1). Serum protein markers (albumin, prealbumin, transferrin, C-reactive protein) are not validated for determining adequacy of protein provision and should not be used in the critical care setting in this manner.¹⁴¹

C5. In the critically ill obese patient, permissive underfeeding or hypocaloric feeding with EN is recommended. For all classes of obesity where BMI is >30, the goal of the EN regimen should not exceed 60%-70% of target energy requirements or 11-14 kcal/kg actual body weight per day (or 22-25 kcal/kg ideal body weight per day). Protein should be provided in a range ≥ 2.0 g/kg ideal body weight per day for Class I and II patients (BMI 30-40), ≥ 2.5 g/kg ideal body

Table 7. Randomized Studies Evaluating Enteral Nutrition (EN) vs EN Supplemented With Parenteral Nutrition (EN+PN) in Critically Ill Patients

Study	Population	Study Groups	Mortality	Infections	LOS Day(s), Mean \pm SD	Ventilator Days, Mean \pm SD	Cost
Herndon et al, 1987 ¹³⁹ Level II	Burn (n = 28)	EN+PN EN	8/13 (62%) ICU 8/15 (53%) ICU	NR	NR	NR	NR
Herndon et al, 1989 ¹⁴⁰ Level II	Burn (n = 39)	EN+PN EN	10/16 (63%) > 14 d ^a 6/23 (26%) > 14 d	NR	NR	NR	NR
Dunham et al, 1994 ⁴² Level II	Trauma (n = 37)	EN+PN EN	3/10 (30%) ICU 1/12 (8%) ICU	NR	NR	NR	NR
Chiarelli et al, 1996 ¹³⁷ Level II	ICU (n = 24)	EN+PN EN	3/12 (25%) ICU 4/12 (33%) ICU	6/12 (50%) 3/12 (25%)	37 \pm 13 Hosp 41 \pm 23 Hosp	19 \pm 6 19 \pm 2	EN+PN 50,000 ^a lira/yr more than EN
Bauer et al, 2000 ¹³⁸ Level I	ICU (n = 120)	EN+PN EN EN+PN EN	3/60 (5%) at 4 d 4/60 (7%) at 4 d 17/60 (28%) at 90 d 18/60 (30%) at 90 d	39/60 (65%) 39/60 (65%)	31.2 \pm 18.5 Hosp 33.7 \pm 27.7 Hosp 16.9 \pm 11.8 ICU 17.3 \pm 12.8 ICU	11 \pm 9 10 \pm 8	204 \pm 119 Euros/pt ^a 106 \pm 47 Euros/pt

SD, standard deviation; NR, not reported; ICU, intensive care unit; Hosp, hospital; LOS, length of stay; pt, patient; d, day(s); yr, year(s)
^a $P \leq .05$.

Adapted from the Canadian Clinical Practice Guidelines.²¹

weight per day for Class III (BMI \geq 40). Determining energy requirements is discussed in guideline C1. (Grade: D)

Rationale. Severe obesity adversely affects patient care in the ICU and increases risk of comorbidities (eg, insulin resistance, sepsis, infections, deep venous thrombosis, organ failure).^{142,143} Achieving some degree of weight loss may increase insulin sensitivity, improve nursing care, and reduce risk of comorbidities. Providing 60%-70% of caloric requirements promotes steady weight loss, while infusing protein at a dose of 2.0-2.5 g/kg ideal body weight per day should approximate protein requirements and neutral nitrogen balance, allowing for adequate wound healing.¹⁴² A retrospective study by Choban and Dickerson indicated that provision of protein at a dose of 2.0 g/kg ideal body weight per day is insufficient for achieving neutral nitrogen balance when the BMI is >40 .¹⁴² Use of BMI and ideal body weight is recommended over use of adjusted body weight.

D. Monitoring Tolerance and Adequacy of Enteral Nutrition

D1. In the ICU setting, evidence of bowel motility (resolution of clinical ileus) is not required in order to initiate EN in the ICU. (Grade: E)

Rationale. Feeding into the GI tract is safe prior to the emergence of overt evidence of enteric function, such as

bowel sounds or the passage of flatus and stool. EN promotes gut motility. As long as the patient remains hemodynamically stable, it is safe and appropriate to feed through mild to moderate ileus.²

D2. Patients should be monitored for tolerance of EN (determined by patient complaints of pain and/or distention, physical exam, passage of flatus and stool, abdominal radiographs). (Grade: E) Inappropriate cessation of EN should be avoided. (Grade: E) Holding EN for gastric residual volumes <500 mL in the absence of other signs of intolerance should be avoided. (Grade: B) The time period that a patient is made nil per os (NPO) prior to, during, and immediately following the time of diagnostic tests or procedures should be minimized to prevent inadequate delivery of nutrients and prolonged periods of ileus. Ileus may be propagated by NPO status. (Grade: C)

Rationale. A number of factors impede the delivery of EN in the critical care setting.¹⁴⁴ Healthcare providers who prescribe nutrition formulations tend to under-order calories, and thus patients only receive approximately 80% of what is ordered. This combination of under-ordering and inadequate delivery results in patients receiving only 50% of target goal calories from one day to the next. Cessation of feeding occurs in $>85\%$ of patients for an average of 20% of the infusion time (the reasons for which are avoidable in $>65\%$ of occasions).¹⁴⁴ Patient intolerance accounts

Table 8. Randomized Studies Evaluating Lower vs Higher “Cutoff Values” for Gastric Residual Volumes (GRVs)

Study	Population	Study Groups by GRVs ^a	% Goal kcal		Aspiration Mean ± SD	GI Intolerance Mean ± SD	Other
			Infused Mean ± SD	Pneumonia			
Taylor et al, 1999 ²³ Level II	Trauma, head injury (n = 82)	150/50 mL ^b	36%	26/41 (63%)	NR	NR	Infection 35/41 (85%) 25/41 (61%) ^c Complications 25/41 (61%) 15/41 (37%) ^c Hospital LOS 46 d 30 d ^c
		200 mL	59% ^c	18/41 (44%)			
		150/50 mL 200 mL					
		150/50 mL 200 mL					
Pinilla et al, 2001 ¹⁴⁶ Level II	ICU (n = 80)	150 mL	70% ± 25%	0/36 (0%)	NR		ICU LOS 13.2 ± 18.3 d 9.5 ± 9.4 d
		250 mL	76% ± 18%	1/44 (2%)			
McClave et al, 2005 ¹⁵¹ Level II	ICU (n = 40)	200 mL	77.0% ± 21.2%	NR	21.6% ± 25.6% ^d	35.0% ± 27.3% ^e	
		400 mL	77.8% ± 32.5%		22.6% ± 25.0%	27.8% ± 25.0%	
Montejo et al, 2008 ¹⁴⁷ Level I	ICU (n = 329)	200 mL	82.8% ± 1.7% ^f	46/169 (27%)	NR	107/169 (64%)	76/160 (48%) ^c
		500 mL	89.6% ± 1.8% ^c	45/160 (28%)			

SD, standard deviation; NR, not reported; ICU, intensive care unit; LOS, length of stay; GI, gastrointestinal; d, day(s).

^a Cutoff value of volume above which there is automatic cessation of EN.

^b EN advanced if GRVs <50 mL, automatic cessation if >150 mL.

^c $P \leq .05$.

^d Incidence of aspiration as a percentage of all bedside checks done every 4 hours.

^e Incidence of regurgitation as a percentage of all bedside checks done every 4 hours.

^f Percentage goal feeding on day 3 (similar to significant differences on day 7).

for one-third of cessation time, but only half of this represents true intolerance. Other reasons for cessation include remaining NPO after midnight for diagnostic tests and procedures in another third of patients, with the rest being accounted for by elevated gastric residual volumes and tube displacement.¹⁴⁴ In one level II study, patients randomized to continue EN during frequent surgical procedures (burn wound debridement under general anesthesia) had significantly fewer infections than those patients for whom EN was stopped for each procedure.¹⁴⁵

Gastric residual volumes do not correlate well to incidence of pneumonia,^{23,146,147} measures of gastric emptying,¹⁴⁸⁻¹⁵⁰ or to incidence of regurgitation and aspiration.¹⁵¹ Four level II studies indicate that raising the cutoff value for gastric residual volume (leading to automatic cessation of EN) from a lower number of 50-150 mL to a higher number of 250-500 mL does not increase risk for regurgitation, aspiration, or pneumonia.^{23,146,147,151} Decreasing the cutoff value for gastric residual volume does not protect the patient from these complications, often leads to inappropriate cessation, and may adversely affect outcome through reduced volume of EN infused.²³ Gastric residual volumes in the range of 200-500 mL should raise concern and lead to the implementation

of measures to reduce risk of aspiration, but automatic cessation of feeding should not occur for gastric residual volumes <500 mL in the absence of other signs of intolerance.¹⁵² See Table 8.^{23,146,147,151}

D3. Use of enteral feeding protocols increases the overall percentage of goal calories provided and should be implemented. (Grade: C)

Rationale. Use of ICU or nurse-driven protocols which define goal infusion rate, designate more rapid startups, and provide specific orders for handling gastric residual volumes, frequency of flushes, and conditions or problems under which feeding may be adjusted or stopped, have been shown to be successful in increasing the overall percentage of goal calories provided.^{23,76,133,135,153,154}

D4. Patients placed on EN should be assessed for risk of aspiration. (Grade: E) Steps to reduce risk of aspiration should be employed. (Grade: E)

The following measures have been shown to reduce risk of aspiration:

In all intubated ICU patients receiving EN, the head of the bed should be elevated 30°-45°. (Grade: C)

Table 9. Randomized Studies Evaluating Body Position During Tube Feeding in Critically Ill Patients, Supine vs Semirecumbent

Study	Population	Study Groups	Mortality	Pneumonia	Hospital LOS Days, Mean \pm SD (or Range)	Ventilator Days, Mean \pm SD (or Range)
Drakulovic et al, 1999 ¹⁵⁸ Level II	ICU (n = 90)	Semi-rec	7/39 (18%) ICU	2/39 (5%) ^a	9.7 \pm 7.8 ICU	7.1 \pm 6.9
		Supine	13/47 (28%) ICU	11/47 (23%)	9.3 \pm 7.2 ICU	6.0 \pm 6.2
van Nieuwenhoven et al, 2006 ¹⁵⁹ Level I	ICU (n = 221)	Semi-rec	33/112 (29%) ICU	13/112 (12%)	27 (2-301) Hosp	6 (0-64)
		Supine	33/109 (30%) ICU	8/109 (7%)	24 (0-186) Hosp	6 (0-281)
		Semi-rec	44/112 (39%) Hosp		9 (0-281) ICU	
		Supine	41/109 (38%) Hosp		10 (9-91) ICU	

SD, standard deviation; NR, not reported; ICU, intensive care unit; LOS, length of stay; Hosp, hospital; Semi-rec, semi-reclined.

^a $P \leq .05$.

Adapted from the Canadian Clinical Practice Guidelines.²¹

For high-risk patients or those shown to be intolerant to gastric feeding, delivery of EN should be switched to continuous infusion. (Grade: D)

Agents to promote motility such as prokinetic drugs (metoclopramide and erythromycin) or narcotic antagonists (naloxone and alvimopan) should be initiated where clinically feasible. (Grade: C)

Diverting the level of feeding by post-pyloric tube placement should be considered. (Grade: C)

Use of chlorhexidine mouthwash twice a day should be considered to reduce risk of ventilator-associated pneumonia. (Grade: C)

Rationale. Aspiration is one of the most feared complications of EN. Patients at increased risk for aspiration may be identified by a number of factors, including use of a nasoenteric tube, an endotracheal tube and mechanical ventilation, age >70 years, reduced level of consciousness, poor nursing care, location in the hospital, patient position, transport out of the ICU, poor oral health, and use of bolus intermittent feedings.¹⁵² Pneumonia and bacterial colonization of the upper respiratory tree are more closely associated with aspiration of contaminated oropharyngeal secretions than regurgitation and aspiration of contaminated gastric contents.¹⁵⁵⁻¹⁵⁷

Several methods may be used to reduce the risk of aspiration. As mentioned in guideline A6, changing the level of infusion of EN from the stomach to the small bowel has been shown to reduce the incidence of regurgitation and aspiration,^{78,79} although the results from 3 meta-analyses (as discussed under guideline A6) suggest that any effect in reducing pneumonia is minimal.⁸⁰⁻⁸² See Table 5.^{23,68,78,83-91}

Elevating the head of the bed 30°-45° was shown in 1 study to reduce the incidence of pneumonia from 23% to 5%, comparing supine to semi-recumbent position, respectively ($P = .018$).¹⁵⁸ See Table 9.^{158,159}

The potential harm from aggressive bolus infusion of EN leading to increased risk of aspiration pneumonia was shown in 1 study.¹⁶⁰ Level II studies comparing bolus to continuous infusion have shown greater volume with fewer interruptions in delivery of EN with continuous feeding but no significant difference between techniques with regard to patient outcome.^{161,162} See Table 10.¹⁶¹⁻¹⁶⁵

Adding prokinetic agents such as erythromycin or metoclopramide has been shown to improve gastric emptying and tolerance of EN but has resulted in little change in clinical outcome for ICU patients.¹⁶⁶ See Table 11.¹⁶⁷⁻¹⁶⁹ Use of naloxone infused through the feeding tube (to reverse the effects of opioid narcotics at the level of the gut in order to improve intestinal motility) was shown in one level II study to significantly increase the volume of EN infused, reduce gastric residual volumes, and decrease the incidence of ventilator-associated pneumonia (compared to placebo).¹⁶⁹

Optimizing oral health with chlorhexidine mouthwashes twice daily was shown in 2 studies to reduce respiratory infection and nosocomial pneumonia in patients undergoing heart surgery.^{170,171} While studies evaluating use of chlorhexidine in general ICU populations have shown little outcome effect, 2 studies in which chlorhexidine oral care was included in bundled interventions showed significant reductions in nosocomial respiratory infections.^{172,173} Other steps to decrease aspiration risk would include reducing the level of sedation/analgesia when possible, minimizing transport out of the ICU for diagnostic tests and procedures, and moving the patient to a unit with a lower patient:nurse ratio.^{152,174}

Table 10. Randomized Studies Evaluating Continuous vs Bolus Delivery of Enteral Nutrition (EN)

Study	Population	Study Groups	Infection	Difference in Feeding	ICU Mortality	Other
Hiebert et al, 1981 ¹⁶³ Level II	Burn (n = 76)	Continuous	NR	Time to goal calories 3.1 ± 0.7 d ^a	NR	Diarrhea (stool frequency) 1.8 ± 0.4 ^a
		Bolus		5.2 ± 0.8 d		3.3 ± 0.7
Kocan et al, 1986 ¹⁶⁴ Level II	Neuro ICU (n = 34)	Continuous	NR	% Goal calories infused 62.2%	NR	Aspiration (blue food coloring) 1/17 (6%)
		Bolus		55.9%		3/17 (18%)
Ciocon et al, 1992 ¹⁶⁵ Level II	Hospitalized dysphagia (n = 60)	Continuous	5/30 (17%) ^b	Daily caloric deficit 783 ± 29 kcal/d	NR	Clogged tube 15/30 (50%) ^a
		Bolus	10/30 (33%)	795 ± 25 kcal/d		5/30 (17%)
Bonten et al, 1996 ¹⁶¹ Level II	ICU (n = 60)	Continuous	5/30 (17%)	Interrupted EN 2/30 (7%)	6/30 (20%)	Diarrhea 20/30 (67%) ^a
		Bolus ^c	5/30 (17%)	5/30 (17%)	9/30 (30%)	29/30 (97%) ^a Mortality 6/30 (20%) 9/30 (30%)
Steevens et al, 2002 ¹⁶² Level II	Trauma ICU (n = 18)	Continuous	0/9 (0%) ^b	Interrupted EN 3/9 (33%)	NR	
		Bolus	1/9 (11%)	5/9 (56%)		

SD, standard deviation; NR, not reported; ICU, intensive care unit; Neuro, neurologic; d, day(s).

^a $P \leq .05$.

^b Aspiration.

^c Intermittent feeding.

Table 11. Randomized Studies With vs Without Motility Agents in Critically Ill Patients

Study	Population	Study Groups	ICU Mortality	Pneumonia	Nutrition Outcomes
Yavagal et al, 2000 ¹⁶⁷ Level I	ICU (n = 305)	Metoclopramide 10 mg NG	73/131 (56%)	22/131 (17%)	NR
		Placebo	92/174 (53%)	24/174 (14%)	
Berne et al, 2002 ¹⁶⁸ Level II	Trauma (n = 48)	Erythromycin 250 mg IV q 6 h	2/32 (6%)	13/32 (40%)	EN tolerated at 48 h 58%
		Placebo	2/36 (6%)	18/36 (50%)	44%
Meissner et al, 2003 ¹⁶⁹ Level II	ICU (n = 84)	Erythromycin 250 mg IV q 6 h			EN tolerated during study 65%
		Placebo			59%
		Naloxone 8 mg q 6 h NG	6/38 (16%)	13/38 (34%) ^a	Mean GRV 54 mL
		Placebo	7/43 (16%)	24/43 (56%)	129 mL

Volume EN delivered was higher after day 3 in Naloxone group compared to controls (trend)

NR, not reported; ICU, intensive care unit; GRV, gastric residual volume; IV, intravenous; NG, nasogastric; EN, enteral nutrition; h, hour(s).

^a $P \leq .05$.

Adapted from the Canadian Clinical Practice Guidelines.²¹

D5. Blue food coloring and glucose oxidase strips, as surrogate markers for aspiration, should not be used in the critical care setting. (Grade: E)

Rationale. Traditional monitors for aspiration are ineffective. Blue food coloring, an insensitive marker for aspiration, was shown to be associated with mitochondrial

toxicity and patient death.¹⁷⁵ The United States Food and Drug Administration through a Health Advisory Bulletin (September 2003) issued a mandate against the use of blue food coloring as a monitor for aspiration in patients on EN.¹⁷⁶ The basic premise for use of glucose oxidase (that glucose content in tracheal secretions is solely related to aspiration of glucose-containing formulation)

has been shown to be invalid, and its use is thwarted by poor sensitivity/specificity characteristics.¹⁷⁷

D6. Development of diarrhea associated with enteral tube feedings warrants further evaluation for etiology. (Grade: E)

Rationale. Diarrhea in the ICU patient receiving EN should prompt an investigation for excessive intake of hyperosmolar medications, such as sorbitol, use of broad spectrum antibiotics, *Clostridium difficile* pseudomembranous colitis, or other infectious etiologies. Most episodes of nosocomial diarrhea are mild and self-limiting.¹⁷⁸

Assessment should include an abdominal exam, fecal leukocytes, quantification of stool, stool culture for *C. difficile* (and/or toxin assay), serum electrolyte panel (to evaluate for excessive electrolyte losses or dehydration), and review of medications. An attempt should be made to distinguish infectious diarrhea from osmotic diarrhea.¹⁷⁹

E. Selection of Appropriate Enteral Formulation

E1. Immune-modulating enteral formulations (supplemented with agents such as arginine, glutamine, nucleic acid, ω -3 fatty acids, and antioxidants) should be used for the appropriate patient population (major elective surgery, trauma, burns, head and neck cancer, and critically ill patients on mechanical ventilation), with caution in patients with severe sepsis.

(For surgical ICU patients, Grade: A)

(For medical ICU patients, Grade: B)

ICU patients not meeting criteria for immune-modulating formulations should receive standard enteral formulations. (Grade: B)

Rationale. In selecting the appropriate enteral formulation for the critically ill patient, the clinician must first decide if the patient is a candidate for a specialty immune-modulating formulation.¹⁸⁰ Patients most likely to show a favorable outcome, who thus would be appropriate candidates for use of immune-modulating formulations, include those undergoing major elective GI surgery, trauma (abdominal trauma index scores >20), burns (total body surface area >30%), head and neck cancer, and critically ill patients on mechanical ventilation (who are not severely septic).¹⁸⁰

A large body of data suggest that adding pharmaconutrients to enteral formulations provides even further benefits on patient outcome than use of standard formulations alone.¹⁸¹⁻¹⁸³ See Table 12.¹⁸⁴⁻²⁰⁴ Studies from basic science have provided a rationale for the mechanism of the beneficial effects seen clinically. Such findings include the discovery of specialized immune (myeloid suppressor) cells, whose role is to regulate the availability of arginine, necessary for normal T lymphocyte function.

These myeloid suppressor cells are capable of causing states of severe arginine deficiency which impact production of nitric oxide and negatively affect microcirculation. Immune-modulating diets containing arginine and ω -3 fatty acids appear to overcome the regulatory effect of myeloid suppressor cells.²⁰⁵ Agents such as RNA nucleotides increase total lymphocyte count, lymphocyte proliferation, and thymus function. In a dynamic fashion, the ω -3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) displace ω -6 fatty acids from the cell membranes of immune cells. This effect reduces systemic inflammation through the production of alternative biologically less active prostaglandins and leukotrienes. EPA and DHA (fish oils) have also been shown to down-regulate expression of nuclear factor-kappa B (NF κ B), intracellular adhesion molecule 1 (ICAM-1), and E-selectin, which in effect decreases neutrophil attachment and transepithelial migration to modulate systemic and local inflammation. In addition, EPA and DHA help to stabilize the myocardium and lower the incidence of cardiac arrhythmias, decrease incidence of acute respiratory distress syndrome (ARDS), and reduce the likelihood of sepsis.²⁰⁶⁻²⁰⁹ Glutamine, considered a conditionally essential amino acid, exerts a myriad of beneficial effects on antioxidant defenses, immune function, production of heat shock proteins, and nitrogen retention. Addition of agents such as selenium, ascorbic acid (vitamin C), and vitamin E provides further antioxidant protection.

Multiple meta-analyses^{181,182,210-212} have shown that use of immune-modulating formulations is associated with significant reductions in duration of mechanical ventilation, infectious morbidity, and hospital length of stay compared to use of standard enteral formulations. These same 5 meta-analyses showed no overall impact on mortality from use of immune-modulating formulations. See Table 13.^{181,182,210-212} The beneficial outcome effects of the immune-modulating formulations are more uniformly seen in patients undergoing major surgery than in critically ill patients on mechanical ventilation. This influence is even more pronounced when the formulation is given in the preoperative period. By differentiating studies done in surgical ICUs from those done in medical ICUs, Heyland et al showed that the greatest beneficial effect was seen in surgery patients with significant reductions in infectious morbidity (RR = 0.53; 95% CI 0.42-0.68; $P \leq .05$) and hospital length of stay (WMD = -0.76; 95% CI -1.14 to -0.37; $P < .05$).²¹⁰ In contrast, aggregating the data from studies in medical ICU patients showed no effect on infections (RR = 0.96; 95% CI 0.77-1.20; $P = \text{NS}$) but a similar reduction in hospital length of stay (WMD = -0.47; 95% CI -0.93 to -0.01; $P = .047$).²¹⁰

It has been hypothesized that there may be some increased risk with the use of arginine-containing formulations in medical ICU patients who are severely

Table 12. Immune-Modulating Enteral Nutrition (EN) vs Standard EN (Stand EN) in Critically Ill Patients

Study	Population	Study Groups	Mortality	Infections ^a	LOS Days, Mean ± SD (or Range)	Ventilator Days, Mean ± SD (or Range)
Cerra et al, 1990 ¹⁸⁴ Level II	Surgical ICU (n = 20)	Impact ^b Osmolite HN	1/11 (9%) ICU 1/9 (11%) ICU	NR	36.7 ± 8.5 Hosp ^c 54.7 ± 10.5 Hosp	NR
Gottschlich et al, 1990 ¹⁸⁵ Level II	Critically ill burns (n = 31)	Shriners burn formula ^d Osmolite HN + protein	2/17 (12%) ICU 1/14 (7%) ICU	NR	NR	9 ± 4.5 10 ± 2.5 NR
Brown et al, 1994 ¹⁸⁶ Level II	Trauma (n = 37)	Experimental formula ^d Osmolite HN + protein	0/19 (0%) ICU 0/18 (0%) ICU	3/19 (16%) ^c 10/18 (56%)	NR	NR
Moore et al, 1994 ¹⁸⁷ Level II	Trauma (n = 98)	Immun-Aid ^b Vivonex TEN	1/51 (2%) ICU 2/47 (4%) ICU	9/51 (18%) 10/47 (21%)	14.6 ± 1.3 Hosp ^c 17.2 ± 2.8 Hosp 5.3 ± 0.8 ICU ^c	1.9 ± 0.9 ^c 5.3 ± 3.1
Bower et al, 1995 ¹⁸⁸ Level I	ICU (n = 296)	Immun-Aid ^b Vivonex TEN	24/153 (16%) ICU 12/143 (8%) ICU	86/153 (56%) 90/143 (63%)	8.6 ± 3.1 ICU 27.6 ± 23 Hosp 30.9 ± 26 Hosp	NR
Kudsk et al, 1996 ¹⁸⁹ Level II	Trauma (n = 35)	Osmolite Immun-Aid ^b Stand EN	1/17 (6%) ICU 1/18 (6%) ICU	5/16 (31%) 11/17 (65%)	18.3 ± 2.8 Hosp ^c 32.6 ± 7.0 Hosp 5.8 ± 1.8 ICU ^c	2.4 ± 1.3 ^c 5.4 ± 2.0
Engel et al, 1997 ¹⁹⁰ Level II	Trauma (n = 36)	Immun-Aid ^b Stand EN	7/18 (39%) ICU 5/18 (28%) ICU	6/18 (33%) 5/18 (28%)	19.0 ± 7.4 ICU 20.5 ± 5.3 ICU	14.8 ± 5.6 16.0 ± 5.6
Mendez et al, 1997 ¹⁹¹ Level II	Trauma (n = 43)	Experimental formula ^d Osmolite HN + protein Experimental formula ^d	1/22 (5%) ICU 1/21 (5%) ICU	19/22 (86%) ^c 12/21 (57%)	34.0 ± 21.2 Hosp ^c 21.9 ± 11.0 Hosp 18.9 ± 20.7 ICU	16.5 ± 19.4 9.3 ± 6.0
Rodrigo et al, 1997 ¹⁹² Level II	Mixed ICU (n = 30)	Osmolite HN + protein Impact ^d Stand EN	2/16 (13%) ICU 1/14 (7%) ICU	5/16 (31%) 3/14 (21%)	11.1 ± 6.7 ICU 8.0 ± 7.3 ICU 10.0 ± 2.7 ICU	NR
Saffle et al, 1997 ¹⁹³ Level II	Burns (n = 50)	Impact ^d Replete	5/25 (20%) ICU 3/24 (13%) ICU	2.36 per patient 1.71 per patient	37 ± 4 Hosp 38 ± 4 Hosp	22 ± 3 21 ± 2
Weimann et al, 1998 ¹⁹⁴ Level II	Trauma (n = 29)	Impact ^d Stand EN	2/16 (13%) ICU 4/13 (31%) ICU	NR	70.2 ± 53 Hosp 58.1 ± 30 Hosp 31.4 ± 23.1 ICU	21.4 ± 10.8 27.8 ± 14.6
Atkinson et al, 1998 ¹⁹⁵ Level I	Mixed ICU (n = 390)	Stand EN Impact ^d Stand EN	95/197 (48%) ICU 85/193 (44%) ICU		47.4 ± 32.8 ICU 10.5 ± 13.1 ICU 12.2 ± 23.2 ICU	8.0 ± 11.1 9.4 ± 17.7
Galban et al, 2000 ¹⁹⁶ Level I	Critically ill septic (n = 176)	Impact ^d Stand EN	17/89 (19%) ICU ^c 28/87 (32%) ICU	39/89 (44%) 44/87 (51%)	18.2 ± 12.6 ICU 16.6 ± 12.9 ICU	12.4 ± 10.4 12.2 ± 10.3
Caparros et al, 2001 ¹⁹⁷ Level I	ICU patients (n = 235)	Experimental formula ^b Stand EN Experimental formula ^b Stand EN	27/130 (21%) ICU 30/105 (29%) ICU	64/130 (49%) ^c 37/105 (35%)	15 (10-25) ICU 13 (9-20) ICU 29 (17-51) Hosp 26 (18-42) Hosp	10 (5-18) 9 (5-14)

(continued)

Table 12. (continued)

Study	Population	Study Groups	Mortality	Infections ^a	LOS Days, Mean \pm SD (or Range)	Ventilator Days, Mean \pm SD (or Range)
Conejero et al, 2002 ¹⁹⁸ Level II	SIRS pts (n = 84)	Experimental formula ^b	14/47 (30%) at 28 d	11/47 (23%) ^c	14 (4-63) Hosp	14 (5-25)
		Stand EN	9/37 (24%) at 28 d	17/37 (46%)	15 (4-102) Hosp	14 (5-29)
Dent et al, 2003 ¹⁹⁹ Level I	ICU (n = 170)	Optimal ^b	20/87 (23%) ICU ^c	57/87 (66%)	14.8 \pm 19.6 ICU	14.3 \pm 22.4
		Osmolite HN Optimal ^b	8/83 (10%) ICU	52/83 (63%)	12 \pm 10.9 ICU 25.4 \pm 26 Hosp	10.8 \pm 12.8
Bertolini et al, 2003 ²⁰⁰ Level II	Severe sepsis (n = 39)	Osmolite HN	8/18 (44%) ICU	NR	20.9 \pm 17 Hosp	NR
		Parenteral nutrition Perative ^c	3/21 (14%) ICU 8/18 (44%) at 28 d 5/21 (24%) at 28 d	NR	13.5 (9-26) Hosp 15.0 (11-29) Hosp	NR
Chuntrasakul et al, 2003 ²⁰¹ Level II	Trauma burns (n = 36)	Parenteral nutrition Neimmune ^g	1/18 (6%) ICU 1/18 (6%) ICU	NR	3.4 \pm 5.8 ICU 7.8 \pm 13.6 ICU	2.7 \pm 5.2 7.4 \pm 1.3
		Traumacal (Stand EN) Neimmune ^g			44.9 \pm 30.2 Hosp 28.8 \pm 25.7 Hosp	
Tsuei et al, 2005 ²⁰² Level II	Trauma (n = 25)	Traumacal (Stand EN)	1/13 (8%) ICU	8/13 (62%)	13 \pm 6 ICU	10 \pm 5
		Stand EN + arginine ^d Stand EN + protein Stand EN + arginine ^d Stand EN + protein	0/12 (0%) ICU	6/11 (55%)	16 \pm 10 ICU 22 \pm 9 Hosp 27 \pm 17 Hosp	14 \pm 10
Kieft et al, 2005 ²⁰³ Level I	ICU (n = 597)	Stresson ^f	84/302 (28%) ICU	130/302 (43%)	7 (4-14) ICU	6 (3-12)
		Stand EN Stresson ^f	78/295 (26%) ICU 114/302 (38%) Hosp 106/295 (36%) Hosp	123/295 (42%)	8 (5-16) ICU 20 (10-35) Hosp	6 (3-12)
Wibbenmeyer et al, 2006 ²⁰⁴ Level II	Burn (n = 23)	Stand EN	2/12 (17%) ICU	9/12 (75%)	20 (10-34) Hosp	NR
		Crucial ^d Stand EN	0/11 (0%) ICU	7/11 (64%)	NR	NR

SD, standard deviation; NR, not reported; ICU, intensive care unit; LOS, length of stay; Hosp, hospital; SIRS, systemic inflammatory response syndrome.

^a All infections represent number of patients per group with infection unless otherwise stated.

^b Non-isonitrogenous.

^c $P \leq .05$.

^d Isonitrogenous.

^e Non-isocaloric.

^f Isocaloric but non-isonitrogenous.

^g Non-isocaloric and non-isonitrogenous.

Impact, Vivonex TEN, Replete, Traumacal (Stand EN), and Crucial are all products of Nestle Nutrition U.S., Minneapolis, MN; Osmolite HN, Optimal, and Perative are all products of Abbott Laboratories, Columbus, OH; Immun-Aid is a product of B. Braun/McGaw, Irvine, CA; and Stresson is a product of Nutricia Clinical Care, Trowbridge, Wiltshire, Great Britain.

Table 13. Meta-Analyses Reported Comparing Immune-Modulating Enteral Formulations to Standard Enteral Formulations

Author	Population	No. of Studies Included	General Conclusions (Effect of Immune-Modulating vs Standard Enteral Formulations)
Heys et al, 1999 ¹⁸¹	Medical, surgical critical illness, cancer (n = 1009)	11	Decreased infection (OR = 0.47, 95% CI 0.32-0.70, <i>P</i> < .05) Decreased length of stay (WMD = 2.5, 95% CI 4.0-1.0, <i>P</i> < .05) No change in mortality (OR = 1.77, 95% CI 1.00-3.12, <i>P</i> = NS)
Beale et al, 1999 ¹⁸²	Medical, surgical trauma, sepsis, major surgery (n = 1482)	12	Decreased infection (RR = 0.67, 95% CI 0.50-0.89, <i>P</i> = .006) Decreased ventilator days (WMD = 2.6, 95% CI 0.1-5.1, <i>P</i> = .04) Decreased length of stay (WMD = 2.9, 95% CI 1.4-4.4, <i>P</i> = .0002) No change in mortality (RR = 1.05, 95% CI 0.78-1.41, <i>P</i> = NS)
Heyland et al, 2001 ²¹⁰	Medical, surgical critical illness, major surgery (n = 2419)	22	Decreased infection (RR = 0.66, 95% CI 0.54-0.80, <i>P</i> < .05) Decreased length of stay (WMD = 3.33, 95% CI 5.63-1.02, <i>P</i> < .05) No change in mortality (RR = 1.10, 95% CI 0.93-1.31, <i>P</i> = NS)
Montejo et al, 2003 ²¹¹	Critical illness (n = 1270)	26	Decreased abdominal abscess (OR = 0.26, 95% CI 0.12-0.55, <i>P</i> = .005) Decreased bacteremia (OR = 0.45, 95% CI 0.35-0.84, <i>P</i> = .0002) Decreased pneumonia (OR = 0.54, 95% CI 0.35-0.84, <i>P</i> = .007) Decreased ventilator days (WMD = 2.25, 95% CI 0.5-3.9, <i>P</i> = .009) Decreased length of stay (WMD = 3.4, 95% CI 4.0-2.7, <i>P</i> < .0001) No change in mortality (OR = 1.10, 95% CI 0.85-1.42, <i>P</i> = NS)
Waitzberg et al, 2006 ²¹²	Elective surgery (n = 2305)	17	Decreased infection (RR = 0.49, 95% CI 0.42-0.58, <i>P</i> > .0001) Decreased length of stay (WMD = 3.1, 95% CI 3.9-2.3, <i>P</i> < .05) Decreased anastomotic leaks (RR = 0.56, 95% CI 0.37-0.83, <i>P</i> = .004) No change in mortality (RR = 0.72, 95% CI 0.39-1.31, <i>P</i> = NS)

WMD, weighted mean difference; RR, relative risk; CI, confidence intervals; OR, odds ratio; NS, not significant.

septic.^{213,214} Based on one level I report,¹⁸⁸ one prospective randomized unblinded study using a control group receiving PN,²⁰⁰ and a third study published in abstract form only,¹⁹⁹ use of arginine-containing formulations resulted in greater mortality than standard EN and PN formulations. Two of the 3 studies reporting a potential adverse effect had comparatively lower levels of arginine supplementation.^{199,200} The mechanism proposed for this adverse effect was that in severe sepsis, arginine may be converted to nitric oxide contributing to hemodynamic instability. This concept is contradicted by 4 other reports. One of these studies showed that infusion of arginine directly into the venous circulation of septic medical and surgical ICU patients caused no hemodynamic stability.²¹⁵ Three other studies showed that clinical outcome was better^{195,197} and mortality was *reduced* in moderately septic ICU patients¹⁹⁶ with use of an arginine-containing formulation (compared to a standard enteral formulation). Upon review of this controversy, the Guidelines Committee felt that immune-modulating formulations containing arginine were safe enough to use in mild to moderate sepsis, but that caution should be employed if utilized in patients with severe sepsis.

Unfortunately, few studies have addressed the individual pharmaconutrients, their specific effects, or their proper dosing. This body of literature has been criticized for the heterogeneity of studies, performed in a wide range of ICU patient populations, with a variety of experimental

and commercial formulations. Multiple enteral formulations are marketed as being immune-modulating, but vary considerably in their makeup and dosage of individual components. It is not clear whether the data from published studies and these subsequent recommendations can be extrapolated to use of formulations that have not been formally evaluated. Based on the strength and uniformity of the data in surgery patients, the Guidelines Committee felt that a grade A recommendation was warranted for use of these formulations in the surgical ICU. The reduced signal strength and heterogeneity of the data in nonoperative critically ill patients in a medical ICU was felt to warrant a grade B recommendation.

For any patient who does not meet the criteria mentioned above, there is a decreased likelihood that use of immune-modulating formulations will change outcome. In this situation, the added cost of these specialty formulations cannot be justified and therefore standard enteral formulations should be used.¹⁸⁰

E2. Patients with ARDS and severe acute lung injury (ALI) should be placed on an enteral formulation characterized by an anti-inflammatory lipid profile (ie, ω-3 fish oils, borage oil) and antioxidants. (Grade: A)

Rationale. In three level I studies involving patients with ARDS, ALI, and sepsis, use of an enteral formulation fortified with ω-3 fatty acids (in the form of EPA), borage

Table 14. Anti-inflammatory Immune-Modulating Enteral Nutrition (Oxepa) vs Standard Enteral Nutrition (Stand EN) in Patients With Acute Respiratory Distress Syndrome (ARDS), Acute Lung Injury (ALI), and Sepsis

Study	Population	Study Groups	Mortality	LOS Days, Mean \pm SD	Ventilator Days, Mean \pm SD	New Organ Dysfunction
Gadek et al, 1999 ²⁰⁷ Level I	ARDS ICU (n = 146)	Oxepa	11/70 (16%) ICU	11.0 \pm 0.9 ICU ^a	9.6 \pm 0.9 ^a	7/70 (10%) ^a
		Stand EN	19/76 (25%) ICU	14.8 \pm 1.3 ICU	13.2 \pm 1.4	19/76 (25%)
Singer et al, 2006 ²⁰⁸ Level I	ARDS and ALI (n = 100)	Oxepa	14/46 (30%) at 28 d ^a	13.5 \pm 11.8 ICU	12.1 \pm 11.3	NR
		Stand EN	26/49 (53%) at 28 d	15.6 \pm 11.8 ICU	14.7 \pm 12.0	
Pontes-Arruda et al, 2006 ²⁰⁹ Level I	Severe sepsis ICU (n = 165)	Oxepa	26/83 (31%) at 28 d ^a	17.2 \pm 4.9 ICU ^a	14.6 \pm 4.3 ^a	32/83 (39%) ^a
		Stand EN	38/82 (46%) at 28 d	23.4 \pm 3.5 ICU	22.2 \pm 5.1	66/82 (80%)

SD, standard deviation; NR, not reported; ICU, intensive care unit; LOS, length of stay; d, day(s).

^a $P \leq .05$.

Oxepa: Abbott Nutrition; Columbus, OH.

oil (γ -linolenic acid [GLA]), and antioxidants was shown to significantly reduce length of stay in the ICU, duration of mechanical ventilation, organ failure, and mortality compared to use of a standard enteral formulation.²⁰⁷⁻²⁰⁹ Controversy remains as to the optimal dosage, makeup of fatty acids, and ratio of individual immune-modulating nutrients which comprise these formulations. See Table 14.²⁰⁷⁻²⁰⁹

E3. To receive optimal therapeutic benefit from the immune-modulating formulations, at least 50%-65% of goal energy requirements should be delivered. (Grade: C)

Rationale. The benefit of EN in general,^{5,23,136} and specifically the added value of immune-modulating agents,^{182,188,195} appears to be a dose-dependent effect. Significant differences in outcome are more likely to be seen between groups randomized to either an immune-modulating or a standard enteral formulation in those patients who receive a "sufficient" volume of feeding.^{188,195} These differences may not be as apparent when all patients who receive *any* volume of feeding are included in the analysis.¹⁹⁵

E4. If there is evidence of diarrhea, soluble fiber-containing or small peptide formulations may be utilized. (Grade: E)

Rationale. Those patients with persistent diarrhea (in whom hyperosmolar agents and *C. difficile* have been excluded) may benefit from use of a soluble fiber-containing formulation or small peptide semi-elemental formulation. The laboratory data, theoretical concepts, and expert opinions would support the use of the small peptide enteral formulations but current large prospective trials are not available to make this a strong recommendation.²¹⁶

F. Adjunctive Therapy

F1. Administration of probiotic agents has been shown to improve outcome (most consistently by decreasing infection) in specific critically ill patient populations involving transplantation, major abdominal surgery, and severe trauma. (Grade: C) No recommendation can currently be made for use of probiotics in the general ICU population due to a lack of consistent outcome effect. It appears that each species may have different effects and variable impact on patient outcome, making it difficult to make broad categorical recommendations. Similarly, no recommendation can currently be made for use of probiotics in patients with severe acute necrotizing pancreatitis, based on the disparity of evidence in the literature and the heterogeneity of the bacterial strains utilized.

Rationale. Probiotics are defined as microorganisms of human origin, which are safe, stable in the presence of gastric acid and bile salts, and when administered in adequate amounts confer a health benefit to the host. Multiple factors in the ICU induce rapid and persistent changes in the commensal microbiota, including broad spectrum antibiotics, prophylaxis for stress gastropathy, vasoactive pressor agents, alterations in motility, and decreases in luminal nutrient delivery.^{217,218} These agents act by competitively inhibiting pathogenic bacterial growth, blocking epithelial attachment of invasive pathogens, eliminating pathogenic toxins, enhancing mucosal barrier, and favorably modulating the host inflammatory response.²¹⁹⁻²²¹ Unfortunately for the general ICU patient population, there has not been a consistent outcome benefit demonstrated. The most consistent beneficial effect from use of probiotics has been a reduction in infectious morbidity demonstrated in critically ill patients involving transplantation,^{222,223} major abdominal surgery,²²⁴ and trauma.^{225,226} While some of these

Table 15. Randomized Studies Evaluating Enteral Nutrition With Glutamine (EN/GLN) vs EN Alone

Study	Population	Study Groups	ICU Mortality	Infection	LOS Stay, Mean ± SD (or Range)
Houdijk et al, 1998 ²³⁸ Level II	Critically ill trauma (n = 80)	EN/GLN	4/41 (10%)	20/35 (57%) ^a	32.7 ± 17.1 Hosp
		EN	3/39 (8%)	26/37 (70%)	33.0 ± 23.8 Hosp
Jones et al, 1999 ²³⁵ Level II	Mixed ICU (n = 78)	EN/GLN	10/26 (38%)	NR	1(4-54) ICU
		EN	9/24 (38%)		16.5 (5-66) ICU
Brantley et al, 2000 ²³⁹ Level II	Critically ill trauma (n = 72)	EN/GLN	0/31 (0%)	NR	19.5 ± 8.8 Hosp
		EN	0/41 (0%)		20.8 ± 11.5 Hosp
Hall et al, 2003 ²³⁶ Level I	Mixed ICU (n = 363)	EN/GLN	27/179 (15%)	38/179 (21%)	25 (16-42) Hosp
		EN	30/184 (16%)	43/184 (23%)	30 (19-45) Hosp
Garrel et al, 2003 ²³⁷ Level II	Burns (n = 45)			Bloodstream	
		EN/GLN	2/21 (10%) ^a	7/19 (37%)	33 ± 17 Hosp
Zhou et al, 2003 ²⁴⁰ Level II	Burns (n = 41)	EN	12/24 (50%)	10/22 (45%)	29 ± 17 Hosp
		EN/GLN	0/20 (0%)	2/20 (10%) ^a	67 ± 4 Hosp
Peng et al, 2004 ²⁴¹ Level II	Burns (n = 48)	EN	0/20 (0%)	6/20 (30%)	73 ± 6 Hosp
		EN/GLN	NR	NR	46.6 ± 12.9 Hosp
		EN			55.7 ± 17.4 Hosp

SD, standard deviation; NR, not reported; ICU, intensive care unit; Hosp, hospital; LOS, length of stay.

^a $P \leq .05$.

Adapted from the Canadian Clinical Practice Guidelines.²¹

studies would warrant a grade B recommendation, the Guidelines Committee felt that the heterogeneity of the ICU populations studied, the difference in bacterial strains, and the variability in dosing necessitated a downgrade to a grade C recommendation. As the ease and reliability of taxonomic classification improve, stronger recommendations for use in specific populations of critically ill patients would be expected.^{222,224} Probiotics in severe acute pancreatitis are currently under scrutiny due to the results of two level II single center studies showing clinical benefit (significantly reduced infectious morbidity and hospital length of stay),^{227,228} followed by a larger level I multicenter study showing increased mortality in those patients receiving probiotics.²²⁹

F2. A combination of antioxidant vitamins and trace minerals (specifically including selenium) should be provided to all critically ill patients receiving specialized nutrition therapy. (Grade: B)

Rationale. Antioxidant vitamins (including vitamins E and ascorbic acid) and trace minerals (including selenium, zinc, and copper) may improve patient outcome, especially in burns, trauma, and critical illness requiring mechanical ventilation.^{230,231} A meta-analysis aggregating data from studies evaluating various combinations of antioxidant vitamins and trace elements showed a significant reduction in mortality with their use (RR = 0.65; 95% CI 0.44-0.97; $P = .03$).²³² Parenteral selenium, the single antioxidant most likely to improve outcome,^{233,234} has shown a trend toward reducing mortality in patients with sepsis or septic shock (RR = 0.59; 95% CI 0.32-1.08;

$P = .08$).²³² Additional studies to delineate compatibility, optimal dosage, route, and optimal combination of antioxidants are needed. Renal function should be considered when supplementing vitamins and trace elements.

F3. The addition of enteral glutamine to an EN regimen (not already containing supplemental glutamine) should be considered in burn, trauma, and mixed ICU patients. (Grade: B)

Rationale. See Table 15.²³⁵⁻²⁴¹ The addition of enteral glutamine to an EN regimen (non-glutamine supplemented) has been shown to reduce hospital and ICU length of stay in burn and mixed ICU patients,^{235,237} and mortality in burn patients alone²³⁷ compared to the same EN regimen without glutamine.

The glutamine powder, mixed with water to a consistency which allows infusion through the feeding tube, should be given in 2 or 3 divided doses to provide 0.3-0.5 g/kg/d. While glutamine given by the enteral route may not generate a sufficient systemic antioxidant effect, its favorable impact on outcome may be explained by its trophic influence on intestinal epithelium and maintenance of gut integrity. Enteral glutamine should not be added to an immune-modulating formulation already containing supplemental glutamine.^{237,238,240}

F4. Soluble fiber may be beneficial for the fully resuscitated, hemodynamically stable critically ill patient receiving EN who develops diarrhea. Insoluble fiber should be avoided in all critically ill patients. Both soluble and insoluble fiber should be avoided in

patients at high risk for bowel ischemia or severe dysmotility. (Grade: C)

Rationale. Three small level II studies using soluble partially hydrolyzed guar gum demonstrated a significant decrease in the incidence of diarrhea in patients receiving EN.²⁴²⁻²⁴⁴ However, no differences in days of mechanical ventilation, ICU, length of stay or multi-organ dysfunction syndrome (MODS) have been reported.²⁴²⁻²⁴⁴ Insoluble fiber has not been shown to decrease the incidence of diarrhea in the ICU patient. Cases of bowel obstruction in surgical and trauma patients who were provided enteral formulations containing insoluble fiber have been reported.^{245,246}

G. When Indicated, Maximize Efficacy of Parenteral Nutrition

G1. If EN is not available or feasible, the need for PN therapy should be evaluated (see guidelines B1, B2, B3, C3). (Grade: C) If the patient is deemed to be a candidate for PN, steps to maximize efficacy (regarding dose, content, monitoring, and choice of supplemental additives) should be used. (Grade: C)

Rationale. As per the discussion for guidelines B1-3 and C3, a critically ill ICU patient may be an appropriate candidate for PN under certain circumstances:

- (1) The patient is well nourished prior to admission, but after 7 days of hospitalization, EN has not been feasible or target goal calories have not been met consistently by EN alone.
- (2) On admission, the patient is malnourished and EN is not feasible.
- (3) A major surgical procedure is planned, the preoperative assessment indicates that EN is not feasible through the perioperative period, and the patient is malnourished.

For these patients, a number of steps may be used to maximize the benefit or efficacy of PN while reducing its inherent risk from hyperglycemia, immune suppression, increased oxidative stress, and potential infectious morbidity.^{24,92} The grade of the first recommendation is based on the strength of the literature for guidelines B1-3 and C3, while that of the second is based on the supportive data for guidelines G2-6.

G2. In all ICU patients receiving PN, mild permissive underfeeding should be considered at least initially. Once energy requirements are determined, 80% of these requirements should serve as the ultimate goal or dose of parenteral feeding. (Grade: C) Eventually, as the patient stabilizes, PN may be increased to meet energy requirements. (Grade: E) For obese patients (BMI \geq

30), the dose of PN with regard to protein and caloric provision should follow the same recommendations given for EN in guideline C5. (Grade: D)

Rationale. "Permissive underfeeding" in which the total caloric provision is determined by 80% of energy requirements (calculated from simplistic equations such as 25 kcal/kg actual body weight per day, published predictive equations, or as measured by indirect calorimetry) will optimize efficacy of PN. This strategy avoids the potential for insulin resistance, greater infectious morbidity, or prolonged duration of mechanical ventilation and increased hospital length of stay associated with excessive energy intake. In 2 studies, lower dose hypocaloric PN was shown to reduce the incidence of hyperglycemia²⁴⁷ and infections, ICU and hospital length of stay, and duration of mechanical ventilation compared to higher eucaloric doses of PN.²⁴⁸ See Table 16.²⁴⁷⁻²⁵⁰

G3. In the first week of hospitalization in the ICU, when PN is required and EN is not feasible, patients should be given a parenteral formulation without soy-based lipids. (Grade: D)

Rationale. This recommendation is controversial and is supported by a single level II study (which was also included in the hypocaloric vs eucaloric dosing in guideline G2 above).²⁴⁸ The recommendation is supported by animal data,²⁵¹ with further support from EN studies,²⁵² where long-chain fatty acids have been shown to be immunosuppressive. Currently in North America, the choice of parenteral lipid emulsion is severely limited to a soy-based 18-carbon ω -6 fatty acid preparation (which has proinflammatory characteristics in the ICU population). Over the first 7 days, soy-based lipid-free PN has been shown to be associated with a significant reduction in infectious morbidity (pneumonia and catheter-related sepsis), decreased hospital and ICU length of stay, and shorter duration of mechanical ventilation compared to use of lipid-containing PN.²⁴⁸ Combining the data from 2 studies,^{248,250} a meta-analysis by Heyland et al confirmed a significant reduction in infectious morbidity (RR = 0.63; 95% CI 0.42-0.93; $P = .02$) in the groups receiving no soy-based lipids.²¹ This recommendation should be applied with caution: these 2 studies were done prior to the Van den Berghe studies,^{253,254} and full dose PN without lipids might exacerbate stress-induced hyperglycemia. While 2 favorable level II studies would generate a grade C recommendation, the implications from a practical standpoint led to a downgrade of the recommendation to D. See Table 17.^{248,250}

G4. A protocol should be in place to promote moderately strict control of serum glucose when providing

Table 16. Randomized Studies Evaluating Lower Hypocaloric Doses (Hypocal) of Parenteral Nutrition (PN) vs Higher Eucaloric (Eucal) Doses of PN in Critically Ill Patients

Study	Population	Study Groups	Mortality	Infections ^a	LOS Days, Mean ± SD (or Range)	Ventilator Days, Mean ± SD (or range)	Hyperglycemia
Battistella et al, 1997 ²⁴⁸ Level II	Trauma (n = 57)	Hypocal	2/27 (7%) ICU	Pneumonia 13/27 (48%) ^b	18 ± 12 ICU ^b	15 ± 12 ^b	NR
		Eucal	0/30 (0%) ICU	22/30 (73%) Bloodstream 5/27 (19%) ^b	29 ± 22 ICU	27 ± 21	
Choban et al, 1997 ²⁴⁹ Level II	ICU (n = 13)	Hypocal	0/6 (0%) Hosp	NR	48 ± 30 Hosp	NR	NR
		Eucal	2/7 (29%) Hosp		45 ± 38 Hosp		
McCowen et al, 2000 ²⁵⁰ Level II	ICU (n = 48)	Hypocal	2/21 (10%) ICU	6/21 (29%)	19 ± 14 Hosp	NR	4/21 (19%)
		Eucal	3/19 (16%) ICU	10/19 (53%)	17 ± 15 Hosp		5/19 (26%)
Ahrens et al, 2005 ²⁴⁷ Level II	SICU (n = 40)	Hypocal	1/20 (5%) ICU	5/20 (25%)	14 (10-21) ICU	10 (4-15)	5/20 (25%) ^b
		Eucal	3/20 (15%) ICU	2/20 (10%)	14 (10-37) ICU	19 (4-35)	14/20 (70%)
		Hypocal			15 (11-26) Hosp		
		Eucal			25 (15-39) Hosp		

SD, standard deviation; NR, not reported; ICU, intensive care unit; SICU, surgical ICU; Hosp, hospital; LOS, length of stay.

^a All infections represent number of patients per group with infection unless otherwise stated.

^b $P \leq .05$.

Adapted from the Canadian Clinical Practice Guidelines.²¹

Table 17. Randomized Studies Evaluating Parenteral Nutrition (PN) With vs Without Lipids in Critically Ill Patients

Study	Population	Study Groups	ICU Mortality	Infections ^a	LOS Days, Mean ± SD	Ventilator Days, Mean ± SD
Battistella et al, 1997 ²⁴⁸ Level II	Trauma (n = 57)	Without	2/27 (7%)	Pneumonia 13/27 (48%) ^b	27 ± 16 Hosp ^b	15 ± 12 ^b
		With	0/30 (0%)	22/30 (73%) Line sepsis 5/27 (19%) ^b	39 ± 24 Hosp	27 ± 21
McCowen et al, 2000 ²⁵⁰ Level II	ICU (n = 48)	Without	2/21 (10%)	6/21 (29%)	19 ± 14 Hosp	NR
		With	3/19 (16%)	10/19 (53%)	17 ± 15 Hosp	

SD, standard deviation; NR, not reported; ICU, intensive care unit; LOS, length of stay.

^a All infections represent number of patients per group with infection unless otherwise stated.

^b $P \leq .05$.

Adapted from the Canadian Clinical Practice Guidelines.²¹

nutrition support therapy. (Grade: B) A range of 110-150 mg/dL may be most appropriate. (Grade: E)

Rationale. Strict glucose control, keeping serum glucose levels between 80 and 110 mg/dL, has been shown in a large single center trial to be associated with reduced sepsis, reduced ICU length of stay, and lower hospital mortality when compared to conventional insulin therapy (keeping blood glucose levels <200 mg/dL).²⁵³ The effect

was more pronounced in surgical ICU than medical ICU patients.²⁵⁴ See Table 18.²⁵³⁻²⁵⁵

However, an as yet unpublished large level I multi-center European study suggested that moderate control (keeping glucose levels between 140 and 180 mg/dL) might avoid problems of hypoglycemia and subsequently reduce the mortality associated with hypoglycemia compared to tighter control.²⁵⁵ With a paucity of data, the Guidelines Committee felt that attempting to control

Table 18. Randomized Studies Evaluating Intensive vs Moderate Control of Glucose in Critically Ill Patients

Study	Population	Study Groups	Episodes of Hypoglycemia	Clinical Outcomes	Mortality
Van den Berghe et al, 2001 ²⁵³ Level I	Surgical ICU (n = 1548)	Intensive control ^a	39/765 (51%) ^b	Septicemia 32/765 (4%)	35/765 (5%) ICU ^b
		Conventional control ^c	6/783 (1%)	61/783 (8%)	63/783 (8%) ICU
		Intensive control ^a			55/765 (7%) Hosp ^b
		Conventional control ^c			85/783 (11%) Hosp
Van den Berghe et al, 2006 ²⁵⁴ Level I	Medical ICU (n = 1200)	Intensive control ^a	111/595 (19%) ^b	New kidney injury 35/595 (6%) ^b	All patients at day 3 23/595 (3.9%) ICU
		Conventional control ^c	19/605 (3%)	54/605 (9%)	17/605 (2.8%) ICU
		Intensive control ^a			Patients in ICU >3 d 166/386 (43%) Hosp ^b
		Conventional control ^c			200/381 (52%) Hosp
Devos et al, 2007 ²⁵⁵ Level I	Mixed ICU (n = 1101)	Intensive control ^a	9.8% ^b	NR	17%
		Moderate control ^d	2.7%		15%

ICU, intensive care unit; NR, not reported; Hosp, hospital; d, day(s).

^a Intensive control: 80-110 mg/dL.

^b $P < .05$.

^c Conventional control: 180-200 mg/dL.

^d Moderate control: 140-180 mg/dL.

glucose in the range of 110-150 mg/dL was most appropriate at this time.

G5. When PN is used in the critical care setting, consideration should be given to supplementation with parenteral glutamine. (Grade: C)

Rationale. The addition of parenteral glutamine (at a dose of 0.5 g/kg/d) to a PN regimen has been shown to reduce infectious complications,^{121,256} ICU length of stay,²⁵⁷ and mortality²⁵⁸ in critically ill patients, compared to the same PN regimen without glutamine. A meta-analysis by Heyland et al combining results from 9 studies confirmed a trend toward reduced infection (RR = 0.75; 96% CI 0.54-1.04; $P = .08$) and a significant reduction in mortality (RR = 0.67; 95% CI 0.48-0.92; $P = .01$) in groups receiving PN with parenteral glutamine versus those groups getting PN alone.²¹ See Table 19.^{121,256-264}

The proposed mechanism of this benefit relates to generation of a systemic antioxidant effect, maintenance of gut integrity, induction of heat shock proteins, and use as a fuel source for rapidly replicating cells. Of note, the dipeptide form of parenteral glutamine upon which most of these data are based is widely used in Europe but not commercially available in North America (referring both to the United States and Canada). Use of L-glutamine, the only source of parenteral glutamine available in North America, is severely limited by problems

with stability and solubility (100 mL water per 2 g glutamine).^{256,264-267} All 3 reports which showed a positive clinical effect were level II studies,^{121,256,258} warranting a grade C recommendation.

G6. In patients stabilized on PN, periodically repeated efforts should be made to initiate EN. As tolerance improves and the volume of EN calories delivered increases, the amount of PN calories supplied should be reduced. PN should not be terminated until $\geq 60\%$ of target energy requirements are being delivered by the enteral route. (Grade: E)

Rationale. Because of the marked benefits of EN for the critically ill patient, repeated efforts to initiate enteral therapy should be made. To avoid the complications associated with overfeeding, the amount of calories delivered by the parenteral route should be reduced appropriately to compensate for the increase in the number of calories being delivered enterally. Once the provision of enteral feeding exceeds 60% of target energy requirements, PN may be terminated.

H. Pulmonary Failure

H1. Specialty high-lipid low-carbohydrate formulations designed to manipulate the respiratory quotient and reduce CO₂ production are not recommended for

Table 19. Randomized Studies Evaluating Parenteral Nutrition (PN) With vs Without Supplemental Parenteral Glutamine in Critically Ill Patients

Study	Population	Study Groups	Mortality	Infections ^a	LOS Days, Mean ± SD (or Range)
Griffiths et al, 1997 ²⁵⁹ & 2002 ²⁶⁰ Level II	ICU (n = 84)	With	18/42 (43%) Hosp	28/42 (67%)	10.5 (6-19) ICU
		Without	25/42 (60%) Hosp	26/42 (62%)	10.5 (6-24) ICU
Powell-Tuck et al, 1999 ²⁶¹ Level I	ICU (n = 168)	With	14/83 (17%) ICU	NR	43.4 ± 34.1 Hosp
		Without	20/85 (24%) ICU		48.9 ± 38.4 Hosp
Wischmeyer et al, 2001 ²⁶² Level II	Burn (n = 31)	With	2/15 (13%) ICU	7/12 (58%)	40 ± 10 Hosp
		Without	5/16 (31%) ICU	9/14 (64%)	40 ± 9 Hosp
Goeters et al, 2002 ²⁵⁸ Level II	SICU (n = 68)	With	7/33 (21%) ICU	NR	21.3 ± 13.5 ICU
		Without	10/35 (29%) ICU		20.8 ± 9.1 ICU
		With	11/33 (33%) at 6 mo ^b		46 ± 49.1 Hosp
Fuentes-Orozco et al, 2004 ²⁵⁶ Level II	Peritonitis (n = 33)	Without	21/35 (60%) at 6 mo		39.4 ± 31.1 Hosp
		With	2/17 (12%) ICU	4/17 (24%) ^b	7.2 ± 9.2 ICU
		Without	3/16 (19%) ICU	12/16 (75%)	7.3 ± 4.5 ICU
		With			16.5 ± 8.9 Hosp
Ziegler et al, 2004 ²⁵⁷ Level II	Postop surgery (n = 63)	Without			16.7 ± 7.0 Hosp
		With	1/32 (3%) Hosp	8/30 (27%)	12 ± 2 ICU Hosp ^b
Zhou et al, 2004 ²⁶³ Level II	Burn (n = 30)	Without	5/31 (16%) Hosp	13/29 (45%)	23 ± 6 ICU Hosp
		With	NR	3/15 (20%)	42 ± 7.0 Hosp
Xian-Li et al, 2004 ¹²¹ Level II	Acute pancreatitis (n = 69)	Without		4/15 (27%)	46 ± 6.6 Hosp
		With	0/20 (0%) ICU	0/20 (0%) ^b	25.3 ± 7.6 Hosp
Dechelotte et al, 2006 ²⁶⁴ Level I	ICU (n = 114)	Without	3/21 (14%) ICU	5/21 (24%)	28.6 ± 6.9 Hosp
		With	2/58 (3%) Hosp	23/58 (40%)	12.5 (1-430) ICU
		Without	2/56 (4%) Hosp	32/56 (57%)	11.5 (3-121) ICU
		With	16/58 (28%) at 6 mo	10/58 (17%) ^c	30 (1-560) Hosp
		Without	9/56 (16%) at 6 mo	19/56 (34%)	26 (4-407) Hosp

SD, standard deviation; NR, not reported; ICU, intensive care unit; SICU, surgical ICU; Hosp, hospital; LOS, length of stay.

^a All infections represent number of patients per group with infection unless otherwise stated.

^b $P \leq .05$.

^c Pneumonia.

Adapted from the Canadian Clinical Practice Guidelines.²¹

routine use in ICU patients with acute respiratory failure. (Grade: E) (This is not to be confused with guideline E2 for ARDS/ALI).

Rationale. There is a lack of consensus about the optimum source and composition of lipids (medium- vs long-chain triglyceride, soybean oil, olive oil, ω -3 fatty acids, 10% or 20% solution) in enteral and parenteral formulations for the patient with respiratory failure. One small level II study (20 patients) showed a clinical benefit (reduced duration of mechanical ventilation) from use of a high-fat low-carbohydrate enteral formulation compared to a standard formulation.²⁶⁸ A second smaller level II study (10 patients) showed no clinical benefit.²⁶⁹ Results from uncontrolled studies suggest that increasing the composite ratio of fat to carbohydrate becomes clinically significant in lowering CO₂ production only in the ICU patient being overfed and that composition is much less likely to affect CO₂ production when the design of the nutrition support regimen approximates

caloric requirements.²⁷⁰ Efforts should be made to avoid total caloric provision that exceeds energy requirements, as CO₂ production increases significantly with lipogenesis and may be tolerated poorly in the patient prone to CO₂ retention.²⁶⁸⁻²⁷⁰ **Rapid infusion** of fat emulsions (especially soybean-based), regardless of the total amount, should be avoided in patients suffering from severe pulmonary failure.

H2. Fluid-restricted calorically dense formulations should be considered for patients with acute respiratory failure. (Grade: E)

Rationale. Fluid accumulation and pulmonary edema are common in patients with acute respiratory failure and have been associated with poor clinical outcomes. It is therefore suggested that a fluid-restricted calorically dense nutrient formulation (1.5-2.0 kcal/mL) be considered for patients with acute respiratory failure that necessitates volume restriction.²⁶⁹

H3. Serum phosphate levels should be monitored closely and replaced appropriately when needed. (Grade: E)

Rationale. Phosphate is essential for the synthesis of adenosine triphosphate (ATP) and 2,3-disphosphoglycerate (2,3-DPG), both of which are critical for normal diaphragmatic contractility and optimal pulmonary function. Length of stay and duration of mechanical ventilation are increased in patients who become hypophosphatemic when compared to those who do not have this electrolyte imbalance. As suggested by several uncontrolled studies, it therefore seems prudent to monitor phosphate closely and replace appropriately when needed.^{271,272}

I. Renal Failure

I1. ICU patients with acute renal failure (ARF) or acute kidney injury (AKI) should be placed on standard enteral formulations, and standard ICU recommendations for protein and calorie provision should be followed. If significant electrolyte abnormalities exist or develop, a specialty formulation designed for renal failure (with appropriate electrolyte profile) may be considered. (Grade: E)

Rationale. ARF seldom exists as an isolated organ failure in critically ill patients. When prescribing EN to the ICU patient, the underlying disease process, preexisting comorbidities, and current complications should be taken into account. Specialty formulations lower in certain electrolytes (ie, phosphate and potassium) than standard products may be beneficial in the ICU patient with ARF.²⁷³⁻²⁷⁵

I2. Patients receiving hemodialysis or continuous renal replacement therapy (CRRT) should receive increased protein, up to a maximum of 2.5 g/kg/d. Protein should not be restricted in patients with renal insufficiency as a means to avoid or delay initiation of dialysis therapy. (Grade: C)

Rationale. There is an approximate amino acid loss of 10-15 g/d during CRRT. Providing <1 g/kg/d of protein may result in increased nitrogen deficits for patients on hemodialysis or CRRT. Patients undergoing CRRT should receive formulations with 1.5-2.0 g/kg/d of protein. At least 1 randomized prospective trial²⁷⁶ has suggested an intake of 2.5 g/kg/d is necessary to achieve positive nitrogen balance in this patient population.²⁷⁶⁻²⁷⁸

J. Hepatic Failure

J1. Traditional assessment tools should be used with caution in patients with cirrhosis and hepatic failure,

as these tools are less accurate and less reliable due to complications of ascites, intravascular volume depletion, edema, portal hypertension, and hypoalbuminemia. (Grade: E)

Rationale. While malnutrition is highly prevalent among patients with chronic liver disease and nearly universal among patients awaiting liver transplantation, the clinical consequences of liver failure render traditional nutrition assessment tools inaccurate and unreliable. The primary etiology of malnutrition is poor oral intake stemming from multiple factors. Malnutrition in patients with cirrhosis leads to increased morbidity and mortality rates. Furthermore, patients who are severely malnourished before transplant surgery have a higher rate of complications and a decreased overall survival rate after liver transplantation. Energy needs in critically ill patients with liver disease are highly variable, are difficult to predict by simple equations in liver disease, and consequently are best determined by indirect calorimetry in ICU patients with liver disease.²⁷⁹⁻²⁸⁷

J2. EN is the preferred route of nutrition therapy in ICU patients with acute and/or chronic liver disease. Nutrition regimens should avoid restricting protein in patients with liver failure. (Grade: E)

Rationale. Nutrition therapy is essential in patients with end-stage liver disease and during all phases of liver transplantation. EN has been associated with decreased infection rates and fewer metabolic complications in liver disease and after liver transplant when compared to PN. Long-term PN can be associated with hepatic complications, including worsening of existing cirrhosis and liver failure with the concomitant risks of sepsis, coagulopathy, and death. Nutrition-associated cholestasis usually present with prolonged PN is also a significant problem. EN improves nutrition status, reduces complications, and prolongs survival in liver disease patients and is therefore recommended as the optimal route of nutrient delivery. Protein should not be restricted as a management strategy to reduce risk of developing hepatic encephalopathy.^{279,282} Protein requirements for the patient with hepatic failure should be determined in the same manner as for the general ICU patient (in keeping with guidelines C4 and C5).

J3. Standard enteral formulations should be used in ICU patients with acute and chronic liver disease. Branched chain amino acid formulations (BCAA) should be reserved for the rare encephalopathic patient who is refractory to standard treatment with luminal acting antibiotics and lactulose. (Grade: C)

Rationale. There is no evidence to suggest that a formulation enriched in BCAA improves patient outcomes

compared to standard whole protein formulations in critically ill patients with liver disease. Findings from level II randomized outpatient trials suggest that long-term (12 and 24 months) nutritional supplementation with oral BCAA granules may be useful in slowing the progression of hepatic disease and/or failure and prolonging event-free survival. In patients with hepatic encephalopathy refractory to usual therapy, use of BCAA formulations may improve coma grade compared to standard formulations.^{279,288-292}

K. Acute Pancreatitis

K1. On admission, patients with acute pancreatitis should be evaluated for disease severity. (Grade: E) Patients with severe acute pancreatitis should have a nasoenteric tube placed and EN initiated as soon as fluid volume resuscitation is complete. (Grade: C)

Rationale. Based on the Atlanta Classification,²⁹³ patients with severe acute pancreatitis may be identified on admission by the presence of organ failure and/or the presence of local complications within the pancreas on computerized tomography (CT) scan, complemented by the presence of unfavorable prognostic signs.^{293,294} Organ failure is defined by shock (systolic blood pressure <90 mm Hg), pulmonary insufficiency (PaO₂ <60 mm Hg), renal failure (serum creatinine >2 mg/dL), or GI bleeding (>500 mL blood loss within 24 hours). Local complications on CT scan include pseudocyst, abscess, or necrosis. Unfavorable prognostic signs are defined by an Acute Physiology and Chronic Health Evaluation (APACHE) II score of ≥8 or by ≥3 Ranson Criteria.^{293,294} Patients with severe acute pancreatitis have an increased rate of complications (38%) and a higher mortality (19%) than patients with mild to moderate disease and have close to 0% chance of advancing to oral diet within 7 days.^{97,295,296} Loss of gut integrity with increased intestinal permeability is worse with greater disease severity.⁹

Patients with severe acute pancreatitis will experience improved outcome when provided early EN. Three meta-analyses of varying combinations of ten level II randomized trials^{8,22,46,54-60} showed that use of EN compared to PN reduces infectious morbidity (RR = 0.46; 95% CI 0.29-0.74; *P* = .001),¹⁷ hospital length of stay (WMD = -3.94; 95% CI -5.86 to -2.02; *P* < .0001),¹⁷ need for surgical intervention (RR = 0.48; 95% CI 0.23-0.99; *P* = .05),²⁹⁷ multiple organ failure (OR = 0.306; 95% CI 0.128-0.736; *P* = .008),²⁹⁸ and mortality (OR = 0.251; 95% CI 0.095-0.666; *P* = .005).²⁹⁸ See Table 3.^{8,22,46,54-60} In a meta-analysis of 2 studies^{18,19} in patients operated on for complications of severe acute pancreatitis, there was a trend toward reduced mortality with use of early EN started the day after surgery (RR = 0.26; 95% CI 0.06-1.09; *P* = .06) compared to STD therapy where no nutrition support therapy was provided.¹⁷

The need to initiate EN early within 24-48 hours of admission is supported by the fact that out of six level II studies done only in patients with severe acute pancreatitis, 5 studies which randomized and initiated EN within 48 hours of admission all showed significant outcome benefits^{22,56,58-60} compared to PN. Only 1 study in severe pancreatitis which randomized patients and started EN after 4 days showed no significant outcome benefit.⁵⁷

K2. Patients with mild to moderate acute pancreatitis do not require nutrition support therapy (unless an unexpected complication develops or there is failure to advance to oral diet within 7 days). (Grade: C)

Rationale. Patients with mild to moderate acute pancreatitis have a much lower rate of complications (6%) than patients with more severe disease, have close to a 0% mortality rate, and have an 81% chance of advancing to oral diet within 7 days.^{97,295,296} Providing nutrition support therapy to these patients does not appear to change outcome. Out of three level II randomized studies which included patients with less disease severity (62%-81% of patients had mild to moderate acute pancreatitis), none showed significant outcome benefits with use of EN compared to PN.^{8,46,55} Provision of nutrition support therapy in these patients should be considered if a subsequent unanticipated complication develops (eg, sepsis, shock, organ failure) or the patient fails to advance to oral diet after 7 days of hospitalization.

K3. Patients with severe acute pancreatitis may be fed enterally by the gastric or jejunal route. (Grade: C)

Rationale. Two level II prospective randomized trials comparing gastric with jejunal feeding in patients with severe acute pancreatitis showed no significant differences between the 2 levels of EN infusion within the GI tract.^{299,300} The success of gastric feeding in these 2 studies (where only 2 patients in the Eatock et al group²⁹⁹ and 1 patient in the Kumar et al group³⁰⁰ experienced increased pain only without a need to reduce the infusion rate) was attributed to early initiation of feeding within 36-48 hours of admission, thereby minimizing the degree of ileus.²⁹⁹

K4. Tolerance to EN in patients with severe acute pancreatitis may be enhanced by the following measures:

Minimizing the period of ileus after admission by early initiation of EN. (Grade: D)

Displacing the level of infusion of EN more distally in the GI tract. (Grade: C)

Changing the content of the EN delivered from intact protein to small peptides, and long-chain fatty acids to medium-chain triglycerides or a nearly fat-free elemental formulation. (Grade: E)

Switching from bolus to continuous infusion. (Grade: C)

Rationale. In a prospective level III study, Cravo et al showed that the longer the period of ileus and the greater the delay in initiating EN, the worse the tolerance (and the greater the need to switch to PN) in patients admitted with severe acute pancreatitis. Delays of ≥ 6 days resulted in 0% tolerance of EN, whereas initiating EN within 48 hours was associated with 92% tolerance.³⁰¹

Feeding higher in the GI tract is more likely to stimulate pancreatic exocrine secretion, which may invoke greater difficulties with tolerance. Conversely, feeding into the jejunum 40 cm or more below the ligament of Treitz is associated with little or no pancreatic exocrine stimulation.³⁰² In a level II prospective trial, McClave et al showed varying degrees of tolerance with different levels of infusion within the GI tract.⁴⁶ Three patients who tolerated deep jejunal feeding with an EN formulation developed an uncomplicated exacerbation of symptoms with advancement to oral clear liquids (an effect which was reversed by return to jejunal feeding). One patient who showed tolerance to jejunal feeds had an exacerbation of the systemic inflammatory response syndrome (SIRS) when the tube was displaced back into the stomach (an effect which again was reversed by return to jejunal feeding).⁴⁶

At the same level of infusion within the GI tract, content of EN formulation may be a factor in tolerance. In a prospective case series, patients hospitalized for acute pancreatitis who could not tolerate a regular diet showed resolution of symptoms and normalization of amylase levels after switching to an oral, nearly fat-free elemental EN formulation.³⁰³ In a patient operated on for complications of severe acute pancreatitis, feeding a nearly fat-free elemental EN formulation had significantly less pancreatic exocrine stimulation (measured by lipase output from the ampulla) than a standard EN formulation with intact long-chain fatty acids infused at the same level of the jejunum.³⁰⁴

The manner of infusion of EN also affects tolerance. A small level II randomized trial showed that continuous infusion of EN into the jejunum (100 mL over 60 minutes) was associated with significantly less volume, bicarbonate, and enzyme output from the pancreas than the same volume given as an immediate bolus.³⁰⁵ It is not clear whether the data from this study can be extrapolated to gastric feeding. (Note: The Guidelines Committee does not recommend bolus feeding into the jejunum.)

K5. For the patient with severe acute pancreatitis, when EN is not feasible, use of PN should be considered. (Grade: C) PN should not be initiated until after the first 5 days of hospitalization. (Grade: E)

Rationale. For patients with severe acute pancreatitis, when EN is not feasible, timing of initiation of PN (and

the choice between PN and STD therapy) becomes an important issue. In an early level II randomized trial, Sax et al showed net harm from use of PN initiated within 24 hours of admission for patients with mild to moderate acute pancreatitis, with significantly longer hospital length of stay than those patients randomized to STD therapy (no nutrition support therapy).⁹⁷ In contrast, in a later level II study by Xian-Li et al in patients with severe pancreatitis whereby PN was initiated 24-48 hours after "full liquid resuscitation," significant reductions in overall complications, hospital length of stay, and mortality were seen when compared to STD therapy.¹²¹ The design of this latter study may have led to a differential delay of several days in the initiation of PN, possibly after the peak of the inflammatory response.¹⁷ The grade of the first recommendation (to consider use of PN) is based on the results of the level II study by Xian-Li et al,¹²¹ whereas the grade for the second recommendation (regarding the timing of PN) is based on expert opinion and interpretation of the discrepancy between these 2 reports.^{97,121}

L. Nutrition Therapy in End-of-Life Situations

L1. Specialized nutrition therapy is not obligatory in cases of futile care or end-of-life situations. The decision to provide nutrition therapy should be based on effective patient/family communication, realistic goals, and respect for patient autonomy. (Grade: E)

Rationale. Healthcare providers are not obligated to initiate nutrition support therapy in end-of-life situations. Dehydration and starvation are well tolerated and generate little symptomatology in the vast majority of patients. In this unfortunate setting, provision of EN or PN therapy has not been shown to improve outcome. Nonetheless, cultural, ethnic, religious, or individual patient issues may in some circumstances necessitate delivery of nutrition support therapy.^{306,307}

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