Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition*

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PRELIMINARY REMARKS

Guideline Limitations

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, 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 nutritional 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 methodologic problems with any guideline is defining the exact population to be included.

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 Guidelines

These guidelines are intended for the adult medical and surgical critically ill patient populations expected to require an ICU stay of greater than 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 experts on the Guidelines Committee for the two 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 grade for the recommendation was based on the number and level of

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The American College of Critical Care Medicine (ACCM), which honors individuals for their achievements and contributions to multidisciplinary critical care medicine, is the consultative body of the Society of Critical Care Medicine (SCCM) that possesses recognized expertise in the practice of critical care. The College has developed administrative guidelines and clinical practice parameters for the critical care practitioner. New guidelines and practice parameters are continually developed, and currents ones are systematically reviewed and revised.

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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 endpoint 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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investigative studies referable to that guideline. Large studies warranting level I evidence were defined as those with ≥100 patients or those which fulfilled end point 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) (Table 1) (1). Review articles 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 one or two large positive randomized trials supporting the claim, whereas a C grade recommendation required only one 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 the Boards for both the American Society for Parenteral and Enteral Nutrition and the Society of Critical Care Medicine.

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, multiorgan dysfunction, prolonged hospitalization, and disproportionate mortality. During the past three 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 three main objectives: to preserve lean body mass, maintain immune function, and avert metabolic complications. Recently, these goals have become more focused on nutrition therapy, specifically attempting to attenuate the metabolic response to stress, prevent oxidative cellular injury, and favorably modulate the immune response. Nutritional modulation of the stress response to critical illness includes early enteral nutrition (EN), appropriate macronutrient 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 (LOS) 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 before 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 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, and in turn contribute to mucosal-associated lymphoid tissue at distant sites such as the lungs, liver, and kidneys (4–6).

Adverse changes in gut permeability from loss of functional integrity is a dynamic phenomenon that 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 gut-associated lymphoid tissue with enteric organisms), risk for systemic infection, and greater likelihood of multiorgan dysfunction syndrome (4, 5, 7). As disease severity worsens, increases in gut permeability are amplified and the enteral route of feeding is more likely to favorably impact outcome pa-

Table 2. Randomized studies evaluating EN versus STD (or no nutrition support therapy) in elective surgery, surgery critical care, and acute pancreatitis patients

Study	Population	Study Groups	Infection[c]	Hospital Length of Stay Days, Mean ± SD (or range)	Hospital Mortality	Other Outcomes
Sagar et al (12)	GI surgery	EN	3/15 (20%)	14 (10–26)	0/15 (0%)	
Level II	(n = 30)	STD	5/15 (33%)	19 (10–46)	0/15 (0%)	
						Anastomotic dehiscence
Schroeder et al (11)	GI surgery	EN	1/16 (6%)	10 ± 4	0/16 (0%)	0/16 (0%)
Level II	(n = 32)	STD	0/16 (0%)	15 ± 10	0/16 (0%)	0/16 (0%)
						Lactulose:mannitol ratio
Carr et al (13)	GI surgery	EN	0/14 (0%)	9.8 ± 6.6	0/14 (0%)	0.1 ± 0.03[a]
Level II	(n = 28)	STD	3/14 (21%)	9.3 ± 2.8	1/14 (7%)	0.5 ± 0.26
						Anastomotic leak
Beier-Holgersen and Boesby (14)	GI surgery	EN	2/30[a] (7%)	8.0[b]	2/30 (7%)	2/30 (7%)
Level II	(n = 60)	STD	14/30 (47%)	11.5	4/30 (13%)	4/30 (13%)
						Major complication
Heslin et al (15)	GI surgery	EN	20/97 (21%)	11 (4–41)	2/97 (2%)	27/97 (28%)
Level I	(n = 195)	STD	23/98 (24%)	10 (6–75)	3/98 (3%)	25/98 (26%)
						Anastomotic leak
Watters et al (16)	GI surgery	EN	NR	17 ± 9	0 (0%)	1/13 (8%)
Level II	(n = 28)	STD		16 ± 7	0 (0%)	3/15 (20%)
Pupelis et al (18)	Acute pancreatitis	EN	3/11 (27%)	45 ± 96	1/11 (9%)	
Level II	(n = 29)	STD	1/18 (6%)	29 ± 103	5/18 (28%)	
						Multiple organ failure
Pupelis et al (19)	Acute pancreatitis, peritonitis	EN STD	10/30 (33%)[d]	35.3 ± 22.9	1/30 (3%)	18/30 (61%)
Level II	(n = 60)		8/30 (27%)	35.8 ± 32.5	7/30 (23%)	20/30 (67%)

EN, enteral nutrition; STD, standard therapy; NR, not reported; GI, gastrointestinal.
[a]$p \leq 0.05$; [b]$p = 0.08$; [c]all infections represent number of patients per group with infection unless otherwise stated; [d]wound sepsis.

rameters of infection, organ failure, and hospital LOS (compared with 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 end points 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 (PN). "Standard therapy" (STD) 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 STD. In a recent meta-analysis (10) in elective GI 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; $p = 0.03$), hospital LOS (mean 0.84 days; range 0.36–1.33 days; $p = 0.001$), and a trend toward reduced anastomotic dehiscence (RR = 0.53; 95% CI 0.26–1.08; $p = 0.08$), when compared with similar patients receiving no nutrition support therapy (10–16). In a meta-analysis (17) of patients undergoing surgery for complications of severe acute pancreatitis, those placed on EN 1 day after surgery showed a trend toward reduced mortality compared with controls randomized to STD (RR = 0.26; 95% CI 0.06–1.09; $p = 0.06$) (17–19) (Table 2) (11–16, 18, 19).

A3. EN is the preferred route of feeding over 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 use EN instead of PN. The beneficial effects of EN when compared with 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). Although 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 LOS (21), cost of nutrition therapy (21), and even return of cognitive function (in patients with head injuries) (23). All six meta-analyses that compared EN vs. PN showed significant reductions in infectious morbidity with use of EN (21, 24–28). Noninfective complications (RR = 4.9; 95% CI 0.3–9.5; $p = 0.04$) and reduced hospital LOS (weighted mean difference [WMD] = 1.20 days; 95% CI 0.38–2.03; $p = 0.004$) were seen with use of EN compared with PN in one meta-analysis by Peter et al (28). Five of the meta-analyses showed no difference in mortality between the two routes of nutrition support therapy (21, 24, 26–28). One meta-analysis by Simpson and Doig (25) showed a significantly lower mortality (RR = 0.51; 95% CI 0.27–0.97; $p = 0.04$) despite a significantly higher incidence of infectious complications (RR = 1.66; 95% CI 1.09–2.51; $p = 0.02$) with use of PN compared with EN (Table 3) (8, 20, 22, 29–61).

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).

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[c]	LOS Days, Mean ± SD (or range)	Other Clinical Outcomes	Cost
						Duration MV	
Rapp et al (29)	ICU head injury	EN	9/18 (50%)[a]	NR	49.4 Hosp	10.3 days	NR
Level II	(n = 38)	PN	3/20 (15%)		52.6 Hosp	10.4 days	
						Duration MV	
Adams et al (30)	Trauma	EN	1/23 (4%)	15/23 (65%)	30 ± 21 Hosp	12 ± 11 days	$1346/day[a]
Level II	(n = 46)	PN	3/23 (13%)	17/23 (74%)	31 ± 29 Hosp	10 ± 10 days	$3729/day
		EN			13 ± 11 ICU		
		PN			10 ± 10 ICU		
						Complications	
Bower et al (31)	GI surgery	EN	0/10 (0%)	0/10 (0%)		0/10 (0%)	
Level II	(n = 20)	PN	0/10 (0%)	0/10 (0%)		0/10 (0%)	
Szeluga et al (32)	Bone marrow		No difference			Complications	
Level II	transplant	EN	at 100 days, and	5/30 (17%)	33 ± 15 Hosp	11/30 (37%)	$1139/patient
	(n = 61)	PN	long term	8/31 (26%)	36 ± 18 Hosp	14/31 (45%)	$2575/patient
Young et al (33)	ICU head injury	EN	10/28 (36%)	5/28 (18%)	NR	NR	NR
Level II	(n = 58)	PN	10/23 (43%)	4/23 (17%)			
Peterson et al (34)	Trauma	EN		2/21 (10%)	13.2 ± 1.6 Hosp		
Level II	(n = 59)	PN	NR	8/25 (32%)	14.6 ± 1.9 Hosp	NR	NR
		EN			3.7 ± 0.8 ICU		
		PN			4.6 ± 1.0 ICU		
						Complications	
Cerra et al (35)	ICU	EN	7/33 (21%)	0/33 (0%)	NR	7/33 (21%)	$228 ± 59/day[a]
Level II	(n = 70)	PN	8/37 (22%)	0/37 (0%)		7/37 (19%)	$330 ± 61/day
Greenburg et al (36)	Inflamatory					Complications	
Level II	bowel	EN	0/19 (0%)	0/19 (0%)		0/19 (0%)	
	(n = 51)	PN	0/32 (0%)	0/32 (0%)		0/32 (0%)	
Moore et al (37)	Trauma	EN	0/29 (0%)	5/29 (17%)	NR	NR	
Level II	(n = 75)	PN	0/30 (0%)	11/30 (37%)			
Hamaoui et al (38)	GI surgery	EN	1/11 (9%)	1/11 (9%)		0/11 (0%)	$44.36/day[a]
Level II	(n = 19)	PN	0/8 (0%)	0/8 (0%)		0/8 (0%)	$102.10/day
						Duration MV	
Kudsk et al (20)	Trauma	EN	1/51 (2%)	9/51 (16%)[a]	20.5 ± 19.9 Hosp	2.8 ± 4.9 days	NR
Level II	(n = 98)	PN	1/45 (2%)	18/45 (40%)	19.6 ± 18.8 Hosp	3.2 ± 6.7 days	
Gonzales-Huit et al (39)	Inflamatory					Complications	
Level II	bowel	EN	0/23 (0%)	1/23 (4%)		11/23 (52%)	
	(n = 44)	PN	0/23 (0%)	8/21 (38%)		11/21 (52%)	
Iovinelli et al (40)	Head neck cancer	EN	0/24 (0%)	5/24 (24%)	26 ± 11 Hosp[a]	Complications 1/24 (4%)	
Level II	(n = 48)	PN	0/24 (0%)	4/24 (17%)	34 ± 11 Hosp	2/24 (8%)	
Kudsk-Minard et al (41)						Complications	
Level II	Trauma	EN	1/34 (3%)	5/34 (15%)		0/34 (0%)	
	(n = 68)	PN	0/34 (0%)	14/34 (41%)		0/34 (0%)	
						Complications	
Dunham et al (42)	Trauma	EN	1/12 (8%)	0/12 (0%)	NR	0/12 (0%)	NR
Level II	(n = 37)	PN	1/15 (7%)	0/15 (0%)		0/15 (0%)	
Borzotta et al (43)	Neurotrauma	EN	5/28 (18%)	51 per group	39 ± 23.1 Hosp	NR	$121,941[a]
Level II	(n = 59)	PN	1/21 (5%)	39 per group	36.9 ± 14 Hosp		$112,450
Hadfield et al (44)	ICU	EN	2/13 (15%)	NR	NR	NR	NR
Level II	(n = 24)	PN	6/11 (55%)				
						Complications	
Baigrie et al (45)	GI surgery	EN	4/50 (8%)	2/50 (4%)		15/50 (30%)	
Level II	(n = 97)	PN	6/47 (13%)	10/47 (21%)		23/47 (49%)	
McClave et al (46)	Acute pancreatitis						
Level II	(n = 32)	EN	0/16 (0%)	2/16 (13%)	9.7 ± 1.3 Hosp	NR	$761 ± 50.3[a]
		PN	0/16 (0%)	2/16 (13%)	11.9 ± 2.6 Hosp		$3294 ± 551.9
						Complications	
Reynolds et al (47)	Trauma	EN	2/33 (6%)	10/33 (30%)		11/33 (33%)	
Level II	(n = 67)	PN	1/34 (3%)	19/34 (56%)		6/34 (18%)	
						Complications	
Sand et al (48)	GI surgery	EN	0/13 (0%)	3/13 (23%)		3/13 (23%)	Cost of PN was 4 ×
Level II	(n = 29)	PN	1/16 (6%)	5/16 (31%)		3/16 (19%)	cost of EN
Kalfarentzos et al (22)	Acute pancreatitis	EN	1/18 (6%)	5/18 (28%)[a]	40 (25–83) Hosp		
Level II	(n = 38)	PN	2/20 (10%)	10/20 (50%)	39 (22–73) Hosp	Duration MV	Savings of
		EN			11 (5–21) ICU	15 (6–16) days	70 GBP/day
		PN			12 (5–24) ICU	11 (7–31) days	with EN[a]

Table 3. —*Continued*

Study	Population	Study Groups	ICU Mortality	Infections[c]	LOS Days Mean ± SD (or range)	Other Clinical Outcomes	Cost
Gianotti et al (49)	Surgery GI						
Level I	cancer	EN	0/87 (0%)	20/87 (23%)[b]	19.2 ± 7.9 Hosp		NR
	(n = 176)	PN	0/86 (0%)	24/86 (28%)	21.6 ± 8.9 Hosp		
Windsor et al (8)	Acute pancreatitis					MOF	
Level II	(n = 34)	EN	0/16 (0%)	0/16 (0%)	12.5 (9.5–14) Hosp	0/16 (0%)	NR
		PN	2/18 (11%)	3/18 (19%)	15.0 (11–28) Hosp	5/18 (28%)	
Woodcock et al (50)	ICU patients	EN	9/17 (53%)	6/16 (38%)	33.2 ± 43 Hosp		
Level II	(n = 38)	PN	5/21 (24%)	11/21 (52%)	27.3 ± 18.7 Hosp	NR	NR
						Complications	
Braga et al (51)	Surgery GI cancer	EN	3/126 (2%)	25/126 (20%)	19.9 ± 8.2 Hosp	45/126 (36%)	$25/day
Level I	(n = 257)	PN	4/131 (3%)	30/131 (23%)	20.7 ± 8.8 Hosp	53/131 (40%)	$90/day
						Postop	
Pacelli et al (52)	Major					complications	NR
Level I	surgery	EN	7/119 (6%)	17/119 (14%)	15.2 ± 3.6 Hosp	45/119 (38%)	
	(n = 241)	PN	3/122 (3%)	14/122 (11%)	16.1 ± 4.5 Hosp	48/122 (39%)	
Bozetti et al (53)	Surgery GI			[a]		Postop complications	NR
Level I	cancer	EN	2/159 (1.3%)	25/159(16%)	13.4 ± 4.1 Hosp[a]	54/159 (34%)[a]	
	(n = 317)	PN	5/158 (3.2%)	42/158 (27%)	15.0 ± 5.6 Hosp	78/158 (49%)	
Olah et al (54)	Acute pancreatitis					MOF	
Level II	(n = 89)	EN	2/41 (5%)	5/41 (12%)[b]	16.8 ± 7.8 Hosp	2/41 (5%)	NR
		PN	4/48 (8%)	13/48 (27%)	23.6 ± 10.2 Hosp	5/48 (10%)	
Abou-Assi et al (55)	Acute pancreatitis					MOF	
Level II	(n = 53)	EN	8/26 (31%)	5/26 (19%)	14.2 ± 1.9 Hosp	7/26 (27%)	$394[a]
		PN	6/27 (22%)	13/27 (48%)	18.4 ± 1.9 Hosp	8/27 (30%)	$2756
Gupta et al (56)	Acute pancreatitis					MOF	
Level II	(n = 17)	EN	0/8 (0%)	1/8 (13%)	7 (4–14) Hosp[a]	0/8 (0%)	55 GBP
		PN	0/9 (0%)	2/9 (22%)	10 (7–26) Hosp	6/9 (67%)	297 GBP
Louie et al (57)	Acute pancreatitis					MOF	
Level II	(n = 28)	EN	0/10 (0%)	1/10 (10%)	26.2 ± 17.4 Hosp	4/10 (40%)	$1375[b]
		PN	3/18 (17%)	5/18 (27.8%)	40.3 ± 42.4 Hosp	8/18 (44%)	$2608
				Pancreas		MOF	
Petrov et al (58)	Acute pancreatitis	EN	2/35 (6%)	7/35 (20%)[a]	NR	7/35 (20%)[a]	NR
Level II	(n = 70)	PN	12/35 (35%)	16/35 (46%)		17/35 (49%)	
				Non-pancreas			
		EN		4/35 (11%)[a]			
		PN		11/35 (31%)			
Eckerwall et al (59)	Acute pancreatitis					MOF	
Level II	(n = 48)	EN	1/23 (4%)	3/23 (13%)	9 (7–14) Hosp	1/23 (4%)	NR
		PN	0/25 (0%)	0/25 (0%)	7 (6–14) Hosp	1/25 (4%)	
Casas et al (60)	Acute pancreatitis					MOF	
Level II	(n = 22)	EN	0/11 (0%)	1/11 (9%)	30.2 Hosp	0/11 (0%)	NR
		PN	2/11 (18%)	5/11 (45%)	30.7 Hosp	2/11 (18%)	

NR, not reported; ICU, intensive care unit; LOS, length of stay; Hosp, hospital; GBP, pounds sterling; MV, mechanical ventilation; MOF, multiple organ failure; GI, gastrointestinal.

[a]$p \leq 0.05$; [b]$p = 0.08$; [c]all infections represent number of patients per group with infection unless otherwise stated.

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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 with feedings started later (after 72 hours), are associated with less gut permeability, diminished activation and release of inflammatory cytokines, i.e., tumor necrosis factor and reduced systemic endotoxemia (21). One meta-analysis by Heyland et al (21) showed a trend toward reduced infectious morbidity (RR = 0.66; 95% CI 0.36–1.22; $p = 0.08$) and mortality (RR = 0.52; 95% CI 0.25–1.08; $p = 0.08$), whereas a second by Marik and Zaloga (62) showed significant reductions in infectious morbidity (RR = 0.45; 95% CI 0.30–0.66; $p = 0.00006$) and hospital LOS (mean 2.2 days, 95% CI 0.81–3.63 days; $p = 0.001$) with early EN compared with delayed feedings (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 less than 1% of cases (73, 74). EN-related 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

Table 4. Randomized studies evaluating early vs. delayed enteral nutrition in critically ill patients

Study	Population	Study Groups	ICU Mortality	Infections[b]	LOS Days, Mean ± SD	Ventilator Days Mean ± SD	Cost
Moore and Jones (63)	Trauma	Early	1/32 (3%)	3/32 (9%)	NR	NR	$16,280 ± 2,146
Level II	(n = 43)	Delayed	2/31 (6%)	9/31 (29%)			$19,636 ± 3,396
Chiarelli et al (64)	Burn	Early	0/10 (0%)	3/10 (30%)[c]	69.2 ± 10.4 Hosp[a]	NR	NR
Level II	(n = 20)	Delayed	0/10 (0%)	7/10 (70%)	89.0 ± 18.9 Hosp		
Eyer et al (65)	SICU trauma	Early	2/19 (11%)	29 per group	11.8 ± 7.9 ICU	10.2 ± 8.1	NR
Level II	(n = 38)	Delayed	2/19 (11%)	14 per group	9.9 ± 6.7 ICU	8.1 ± 6.8	
Chuntrasakul et al (66)	SICU trauma	Early	1/21 (5%)	NR	8.1 ± 6.3 ICU	5.29 ± 6.3	NR
Level II	(n = 38)	Delayed	3/17 (18%)		8.4 ± 4.8 ICU	6.12 ± 5.3	
Singh et al (67)	Peritonitis	Early	4/21 (19%)	7/21 (33%)	14 ± 6.9 Hosp	NR	NR
Level II	(n = 37)	Delayed	4/22 (18%)	12/22 (55%)	13 ± 7.0 Hosp		
Minard et al (68)	Closed head injury	Early	1/12 (8%)	6/12 (50%)	30 ± 14.7 Hosp	15.1 ± 7.5	
Level II	(n = 27)	Delayed	4/15(27%)	7/15 (47%)	21.3 ± 13.7 Hosp	10.4 ± 6.1	NR
		Early			18.5 ± 8.8 ICU[a]		
		Delayed			11.3 ± 6.1 ICU		
Kompan et al (69)	SICU trauma	Early	0/27 (0%)	9/27 (33%)	15.9 ± 9.7 ICU	12.9 ± 8.1	NR
Level II	(n =52)	Delayed	1/25 (4%)	16/25 (64%)	20.6 ± 18.5 ICU	15.6 ± 16.1	
Malhotra et al (70)	Postop peritonitis	Early	12/100 (12%)	54/100 (54%)	10.6 Hosp		
Level I	(n = 200)	Delayed	16/100 (16%)	67/100 (67%)	10.7 Hosp	NR	NR
		Early			1.6 ICU		
		Delayed			2.1 ICU		
Peck et al (71)	Burn	Early	4/14 (28%)	12/14 (86%)	60 ± 44 Hosp	32 ± 27	NR
Level II	(n = 27)	Delayed	5/13 (38%)	11/13 (85%)	60 ± 38 Hosp	23 ± 26	
		Early			40 ± 32 ICU		
		Delayed			37 ± 33 ICU		
Dvorak et al (72)	Spinal cord injury	Early	0/7 (0%)	2.4 ± 1.5 per pt	53 ± 34.4 Hosp	31.8 ± 35.0	NR
Level II	(n =17)	Delayed	0/10 (0%)	1.7 ± 1.1 per pt	37.9 ± 14.6 Hosp	20.9 ± 14.4	

NR, not reported; ICU, intensive care unit; LOS, length of stay; Hosp, hospital; pt, patient; SICU, surgical intensive care unit.
[a]$p \leq 0.05$; [b]all infections represent number of patients per group with infection unless otherwise stated; [c]bacteremia.
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(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 (e.g., norepinephrine, phenylephrine, epinephrine, dopamine) or escalating the dose of such agents to maintain hemodynamic stability. EN may be provided with caution to patients either into 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, i.e., passing flatus or stool, are not required for initiation of enteral feeding. GI dysfunction in the ICU setting occurs in 30% to 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 three general categories: mucosal barrier disruption, altered motility and atrophy of the mucosa, and reduced mass of gut-associated lymphoid tissue.

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% to 85% can be achieved (76). Ten randomized clinical trials (63–72), the majority in surgical critically ill, 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 abovementioned studies were successfully started on EN within the first 36 hours of admission (regardless of clinical signs of stooling, flatus, or borborygmi) (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 por-

Table 5. Randomized studies evaluating small bowel vs. gastric feeding in critically ill patients

Study	Population	Study Groups	ICU Mortality	Pneumonia	LOS Days, Mean ± SD (or range)	Other Outcomes	Nutritional Outcomes
						Duration MV	% Goal Feeds Delivered
Montecalvo et al (83)	MICU/SICU	SB	5/19 (26%)	4/19 (21%)	11.7 ± 8.2 ICU	10.2 ± 7.1	61.0 ± 17.0%
Level II	(n = 38)	Gastric	5/19 (26%)	6/19 (32%)	12.3 ± 10.8 ICU	11.4 ± 10.8 (Mean ± SD)	46.9 ± 25.9%
						Duration MV	Time to Goal Feeds
Kortbeek et al (84)	Trauma	SB	4/37 (11%)	10/37 (27%)	30 (6–47) Hosp	9 (2–13)	34.0 ± 7.1 hrs
Level II	(n = 80)	Gastric	3/43 (7%)	18/43 (42%)	25 (9–88) Hosp	5 (3–15)	43.8 ± 22.6 hrs
		SB			10 (3–24) ICU	(Mean + range)	
		Gastric			7 (3–32) ICU		
							% Goal Feeds Delivered
Taylor et al (23)	Trauma head injury	SB	5/41 (12%) at 6 mos	18/41 (44%) 26/41 (63%)	NR	NR	59.2% 36.8%
Level II	(n = 82)	Gastric	6/41 (15%) at 6 mos	25/41 (61%)[a,c]			
		SB		35/41 (85%)			
		Gastric					
							% Goal Feeds Delivered
Kearns et al (85)	MICU	SB	5/21 (24%)	4/21 (19%)	39 ± 10 Hosp	NR	69 ± 7%
Level II	(n = 44)	Gastric	6/23 (26%)	3/23 (13%)	43 ± 11 Hosp		47 ± 7%
		SB			17 ± 2 ICU		
		Gastric			16 ± 2 ICU		
						Duration MV	#Pts >50% Goal × 5 days
Minard et al (68)	Trauma	SB	1/12 (8%)	6/12 (50%)	30 ± 14.7 Hosp	15.1 ± 7.5	10/12 (83%)
Level II	(n = 27)	Gastric	4/15 (27%)	7/15 (47%)	21.3 ± 14.7 Hosp	10.4 ± 6.1	7/15 (47%)
		SB			18.5 ± 8.8 ICU[a]	(Mean ± SD)	
		Gastric			11.3 ± 6.1 ICU		
						% Time Esophag pH <4	
Lien et al (78)	Neuro CVA		NR	NR	NR	12.9 min	NR
Level II	(n = 8)	SB				(4.9–28.2)	
						24.0 min	
		Gastric				(19.0–40.6)	
							No. tubes replaced
Day et al (86)	ICU	SB	NR	0/14 (0%)	NR	NR	16 per group
Level II	(n = 25)	Gastric		2/11 (18%)			9 per group
							% Goal Feeds Delivered
Esparaza et al (87)	MICU	SB	10/27 (37%)	NR	NR	NR	66.0%
Level II	(n = 54)	Gastric	11/27 (41%)				64.0%
	MICU						Time to Goal Feeds
Boivin and Levy (88)	SICU	SB	18/39 (46%)	NR	NR	NR	33 hrs
Level II	Neuro ICU (n = 80)	Gastric	18/39 (46%)				32 hrs
							Time to Goal Feeds
Neumann and DeLegge (89)	MICU	SB	NR	1/30 (3%)[b]	NR	NR	43.0 + 24.1 hrs
Level II	(n = 60)	Gastric	0/30 (0%)				28.8 + 15.9 hrs
							Time to Goal Feeds
Davies et al (90)	MICU/SICU	SB	4/34 (12%)	2/31 (6%)	13.9 ± 1.8 ICU[a]	NR	23.2 ± 3.9 hrs
Level II	(n = 73)	Gastric	5/39 (13%)	1/35 (3%)	10.4 ± 1.2 ICU		23.0 ± 3.4 hrs
							% Goal Feeds by Day 7
Montejo et al (91)	ICU	SB	19/50 (38%)	16/50 (32%)	15 ± 10 ICU	NR	80 ± 28%
Level I	(n = 101)	Gastric	22/51 (43%)	20/51 (39%)	18 ± 16 ICU		75 ± 30%

NR, not reported; ICU, intensive care unit; MICU, medical ICU; SICU, surgical ICU; MV, mechanical ventilation; Pts, patients; SB, small bowel; LOS, length of stay; CVA, cerebrovascular accident.

[a]$p \leq 0.05$; [b]aspiration; [c]total infections.

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tion of the duodenum (79). Three meta-analyses have been published comparing gastric with postpyloric feeding in the ICU setting (80–82). Only one of these meta-analyses showed a significant reduction in ventilator-associated pneumonia with postpyloric feeding (RR = 0.76; 95% CI 0.59–0.99, p = 0.04) (82), an effect heavily influenced by one study by Taylor et al (23). With removal of this study from the meta-analysis, the difference was no longer significant. The two other meta-analyses (which did not include the Taylor study) showed no difference in pneumonia between gastric and postpyloric feeding (80, 81). Although one showed no difference in ICU LOS (80), all three meta-analyses showed no significant difference in mortality between gastric and postpyloric feeding (80–82) (Table 5) (23, 68, 78, 83–91).

B. When to Use PN

B1. If early EN is not feasible or available over the first 7 days following admission

to the ICU, no nutrition support therapy (ie, STD) should be provided (grade C). In the patient who was previously healthy before 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 two recommendations are the most controversial in the guidelines, are influenced primarily by two meta-analyses, and should be interpreted very carefully in application to patient care (24, 92). Both meta-analyses compared use of PN with STD (where no nutrition support therapy was provided). In critically ill patients in the absence of preexisting malnutrition (when EN is not available), Braunschweig et al aggregated seven studies (93–99) and showed that use of STD was associated with significantly reduced infectious morbidity (RR = 0.77; 95% CI 0.65–0.91; $p < 0.05$) and a trend toward reduced overall complications (RR = 0.87; 95% CI 0.74–1.03; *p* not provided) compared with use of PN (24). In the same circumstances (critically ill, no EN available, and no evidence of malnutrition), Heyland et al aggregated four 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; $p < 0.05$) and a trend toward greater rate of complications (RR = 2.40; 95% CI 0.88–6.58; *p* not provided), when compared with STD (92) (Table 6) (93–129).

With increased duration of severe illness, priorities between STD 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%, $p < 0.05$) and longer hospital LOS (36.3 days vs. 23.4 days, $p < 0.05$), when compared respectively with 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 who has not begun to eat spontaneously (Braunschweig et al recommending 7–10 days, Heyland et al 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 each clinical outcome parameter (hospital LOS, pancreatic infection, overall complications, and mortality) when comparing patients randomized to STD 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 two 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 (no nutrition support therapy) beyond 7 days would lead to deterioration of nutritional 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% to 15% or actual body weight less than 90% of ideal body weight), initial priorities are reversed and use of PN has a more favorable outcome than STD (Table 6) (93–129).

In the meta-analysis by Heyland et al, use of PN in malnourished ICU patients was associated with significantly fewer overall complications (RR = 0.52; 95% CI 0.30–0.91; $p < 0.05$) than STD (92). In the meta-analysis by Braunschweig et al, STD in malnourished ICU patients was associated with significantly higher risk for mortality (RR = 3.0; 95% CI 1.09–8.56; $p < 0.05$) and a trend toward higher rate of infection (RR = 1.17; 95% CI 0.88–1.56; *p* not provided) compared with 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 to 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 less than 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 who has shown more consistent benefit of PN over STD involves 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 with STD (see rationale for B1 earlier), surgical patients saw no treatment effect with PN regarding mortality (RR = 0.91; 95% CI 0.68–1.21; *p* = not significant) (92). Critically ill patients experienced a trend toward increased complications, whereas surgical patients saw significant reductions in complications with use of PN regarding mortality (RR = 2.40; 95% CI 0.88–6.58; $p < 0.05$) (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 al (130) comparing perioperative PN with STD, only seven (95, 98, 102, 103, 107, 110, 111) of 14 studies (94, 100, 104, 106, 108, 109, 112) provided PN for ≥7 days (130). As a result, only one study showed a treatment effect (95) and the overall meta-analysis showed no statistically significant benefit from PN (130). In contrast, a later meta-analysis by Klein et al (131) 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 with STD (131) (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 nine studies that evaluated routine postoperative PN (93, 94, 96, 99–101, 104, 109, 122) showed a significant 10% increase in complications compared with STD (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 deter-

Table 6. Randomized studies evaluating parenteral nutrition (PN) vs standard therapy (STD)

Study	Population	Protein Energy Malnutrition	Study Groups	Timing of PN	Complications	Hospital Mortality
Williams et al (102)	Esophagogastric Ca		PN	Preop	2/10 (20%)	6/38 (16%)
Level II	(n = 74)		STD	7–10 days	3/9 (33%)	8/36 (22%)
Moghissi et al (103)	Esophageal Ca		PN	Preop	0/10 (0%)	0/10 (0%)
Level II	(n = 15)		STD	5–7 days	1/5 (20%)	0/5 (0%)
Holter and Fischer (94)	GI Ca	100%	PN	Preop	4/30 (13%)	2/30 (7%)
Level II	(n = 56)		STD	3 days	5/26 (19%)	2/26 (8%)
Preshaw et al (104)	Colon Ca		PN	Preop	8/24 (33%)	0/24 (0%)
Level II	(n = 47)		STD	1 day	4/23 (17%)	0/23 (0%)
Heatley et al (105)	Esophagogastric Ca		PN	Preop	3/38 (8%)[a,d]	6/38 (16%)
Level II	(n = 74)		STD	7–10 days	11/36 (31%)	8/36 (22%)
Simms et al (106)	Esophageal Ca		PN	NR	NR	1/10 (10%)
Level II	(n = 20)		STD			1/10 (10%)
Lim et al (107)	Esophageal Ca	100%	PN	Preop	1/10 (10%)	1/10 (10%)
Level II	(n = 20)		STD	21 days	4/10 (40%)	2/10 (20%)
Thompson et al (98)	GI Ca	100%	PN	Preop	2/12 (17%)	0/12 (0%)
Level II	(n = 21)		STD	5–14 days	1/9 (11%)	0/9 (0%)
Sako et al (108)	Head Neck Ca		PN	NR	15/30 (50%)	17/34 (50%)
Level II	(n = 66)		STD		18/32 (56%)	8/32 (25%)
Jensen (109)	Rectal Ca	100%	PN	Preop	NR	0/10 (0%)
Level II	(n = 20)		STD	2 days		4/10 (40%)
Moghissi et al (110)	Esophageal Ca		PN	Preop	1/25 (4%)	1/25 (4%)
Level II	(n = 52)		STD	6–8 days	4/27 (15%)	5/27 (19%)
Muller et al (95, 111)	GI Ca	60%	PN (gluc)	Preop	11/66 (17%)[a]	3/66 (5%)[a]
Level I	(n = 171)		PN (gluc/lipid)	10 days	17/46 (37%)	10/46 (22%)
			STD		19/59 (32%)	11/59 (19%)
Garden et al (112)	Perioperative		PN	NR	1/10 (10%)	0/10 (0%)
Level II	(n = 20)		STD		2/10 (20%)	1/10 (10%)
Sax et al (97)	Acute pancreatitis	0%	PN	NA	4/29 (14%)[a]	1/29 (3%)
Level II	(n = 55)		STD		1/26 (4%)	1/26 (4%)
Bellantone et al (113)	GI Ca	100%	PN	Preop	12/40 (30%)[a]	1/40 (3%)
Level II JPEN	(n = 91)		STD	≥7 days	18/51 (35%)	2/51 (4%)
Smith Hartemink (114)	GI Ca	100%	PN	Preop	3/17 (18%)	1/17 (6%)
Level II	(n = 34)		STD	8–15 days	6/17 (35%)	3/17 (18%)
Meguid et al (115)	GI Ca	100%	PN	Preop	10/32 (31%)[a]	1/32 (3%)
Level II	(n = 66)		STD	8 days	19/34 (56%)	0/34 (0%)
Bellantone et al (116)	GI Ca		PN	Preop	8/54 (15%)[a,c]	1/54 (2%)
Level I	(n = 100)		STD	>7 days	22/46 (48%)	1/46 (2%)
Fan et al (117)	Esophageal Ca	75%	PN	Preop	17/20 (85%)	6/20 (30%)
Level II	(n = 40)		STD	14 days	15/20 (75%)	6/20 (30%)
VA Co-OP (118)	Perioperative	100%	PN	Preop	49/192 (26%)	31/231 (13%)
Level I	(n = 459)		STD	7–15 days	50/203 (25%)	24/228 (11%)
Von Meyenfeldt et al (119)	Perioperative	29%	PN	Preop	6/51 (12%)	2/51 (4%)
Level I	(n = 101)		STD	10–23 days	7/50 (14%)	2/50 (4%)
Fan et al (120)	Hepatocellular Ca	26%	PN	Preop	22/64 (34%)[a]	5/64 (8%)
Level I	(n = 124)		STD	7 days	33/60 (55%)	9/60 (15%)
Xian-Li et al (121)	Acute pancreatitis		PN	NA	11/21 (52%)[c]	3/21 (14%)
Level II	(n = 44)		STD		21/23 (91%)	10/23 (44%)
Abel et al (100)	Perioperative	100%	PN	Postop	2/20 (10%)	4/20 (20%)
Level II	(n = 44)		STD		0/24 (0%)	3/24 (12%)
Collins et al (122)	GI surgery	40%	PN	Postop	2/10 (20%)	0/10 (0%)
Level II	(n = 20)		STD		0/10 (0%)	0/10 (0%)
Freund et al (123)	GI surgery	0%	PN	Postop	0/25 (0%)	0/25 (0%)
Level II	(n = 35)		STD		0/10 (0%)	0/10 (0%)
Yamada et al (124)	GI surgery		PN	Postop	0/29 (0%)	0/29 (0%)
Level II	(n = 57)		STD		5/28 (18%)	1/28 (4%)
Jimenez et al (125)	GI surgery	100%	PN	Postop	6/60 (10%)	4/60 (7%)
Level II	(n = 75)		STD		3/15 (20%)	1/15 (7%)
Askanazi et al (126)	GU Surgery		PN	Postop	1/22 (5%)	0/22 (0%)
Level II	(n = 35)		STD		2/13 (15%)	2/13 (15%)
Figueras et al (127)	GI surgery	0%	PN	Postop	4/25 (16%)	0/25 (0%)
Level II	(n = 49)		STD		5/24 (21%)	0/24 (0%)
Woolfson and Smith (99)	Perioperative	0%	PN	Postop	6/62 (10%)	8/62 (13%)
Level I	(n = 122)		STD		4/60 (7%)	8/60 (13%)

mined 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

Table 6. —*Continued*

Study	Population	Protein Energy Malnutrition	Study Groups	Timing of PN	Complications	Hospital Mortality
Reilly et al (101)	Liver transplant	100%	PN	Postop	NR	0/8 (0%)
Level II	(n = 28)		PN/BCAA			1/10 (10%)
			STD			2/10 (20%)
Gys et al (128)	GI surgery	0%	PN	Postop	1/10 (10%)	0/10 (0%)
Level II	(n = 20)		STD		1/10 (10%)	0/10 (0%)
Sandstrom et al (96)	Surgery, trauma	23%	PN	Postop	NR	12/150 (8%)
Level I	(n = 300)		STD			10/150 (7%)
Huang et al (129)	GI surgery		PN	Postop	0/26 (0%)	0/26 (0%)
Level II	(n = 58)		STD		0/32 (0%)	0/32 (0%)
Brennan et al (93)	Pancreatic Ca	100%	PN	Postop	27/60 (45%)	4/60 (7%)
Level I	(n = 117)		STD		13/57 (23%)	1/57 (2%)

Ca, cancer; GI, gastrointestinal; NA, not applicable; NR, not reported; BCAA, branched chain amino acids; Postop, postoperative; GU, geniturinary. [a]$p < 0.05$; [b]$p = 0.05$; [c]infection; [d]wound infection.

Adapted and reprinted with permission from Braunschweig et al (24), Heyland et al (21), Detsky et al (130), and Klein et al (131).

energy requirements. More than 200 predictive equations (Harris-Benedict, Scholfield, Ireton-Jones, etc) have been published in the literature (132). Energy requirements may be calculated either through simplistic formulas (25–30 $kcal \cdot kg^{-1} \cdot day^{-1}$), published predictive equations, or use of indirect calorimetry. Calories provided via infusion of propofol should be considered when calculating the nutrition regimen. Although 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 mortality (135) than those patients receiving lower volume.

C2. Efforts to provide >50% to 65% of goal calories should be made 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/hr) may be sufficient to prevent mucosal atrophy, but may be insufficient to achieve the usual end points desired of EN therapy. Studies suggest that >50% to 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 II (23) and one level III study (136) where increases in the percent goal calories infused from a range of 37% to 40% up to 59% to 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 before this 7–10 day period in the patient already on 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 one small study in burn patients, EN supplemented with PN was associated with a significant increase in mortality (63% vs. 26%, $p < 0.05$) when compared, respectively, with hypocaloric EN alone (140) (Table 7) (42, 137–140).

As discussed under 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 and Sandstrom infer that after the first 7–10 days, the need to provide adequate calories and protein is increased to prevent the consequences of deterioration of nutritional 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 nonprotein 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 multitrauma 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 to 2.0 $g \cdot kg^{-1} \cdot day^{-1}$) or nonprotein calorie:nitrogen ratio (70:1 to 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

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

NR, not reported; ICU, intensive care unit; Hosp, hospital; LOS, length of stay; pt, patient.
[a] $p \leq 0.05$.
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goal of the EN regimen should not exceed 60% to 70% of target energy requirements or 11–14 kcal/kg actual body weight/day (or 22–25 kcal/kg ideal body weight/day). Protein should be provided in a range ≥2.0 g/kg ideal body weight/day for class I and II patients (BMI 30–40), ≥2.5 g/kg ideal body weight/day for class III (BMI ≥40). Determining energy requirements is discussed elsewhere (grade D).

Rationale. Severe obesity adversely affects patient care in the ICU and increases risk of comorbidities (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% to 70% of caloric requirements promotes steady weight loss, while infusing protein at a dose of 2.0–2.5 g/kg ideal body weight/day should approximate protein requirements and neutral nitrogen balance, allowing for adequate wound healing (142). A retrospective study by Choban and Dickerson (142) indicated that provision of protein at a dose of 2.0 g/kg ideal body weight/day is insufficient for achieving neutral nitrogen balance when the BMI is greater than 40. Use of BMI and ideal body weight is recommended over use of adjusted body weight.

D. Monitoring Tolerance and Adequacy of EN

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

Rationale. Feeding into the GI tract is safe before 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). Making the patient nil per os *(NPO) surrounding 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 over 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 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 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) (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,

Table 8. Randomized studies evaluating lower versus higher "cutoff values" for gastric residual volumes (GRVs)

Study	Population	Study Groups by GRVs[a,b]	% Goal kcal Infused	Pneumonia	Aspiration	GI Intolerance	Other
							Infection
Taylor et al (23)	Trauma, head injury	150/50 mL[c]	36%	26/41 (63%)	NR	NR	35/41 (85%)
Level II	(n = 82)	200 mL	59%[a]	18/41 (44%)			25/41 (61%)[a]
							Complications
		150/50 mL					25/41 (61%)
		200 mL					15/41 (37%)[a]
		150/50 mL					46 d
		200 mL					30 d[a]
Pinilla et al (146)	ICU	150 mL	70 ± 25%	0/36 (0%)	NR	21/36 (58%)	13.2 ± 18.3d
Level II	(n = 80)	250 mL	76 ± 18%	1/44 (2%)		20/44 (45%)	9.5 ± 9.4 d
McClave et al (151)	ICU	200 mL	77.0 + 21.2%	NR	21.6 ± 25.6%[d]	35.0 ± 27.3%[e]	
Level II	(n = 40)	400 mL	77.8 + 32.5%		22.6 ± 25.0%	27.8 ± 25.0%	
Montejo et al (147)	ICU	200 mL	82.8 ± 1.7%[f]	46/169 (27%)	NR	107/169 (64%)	
Level I	(n = 329)	500 mL	89.6 ± 1.8%[a]	45/160 (28%)		76/160 (48%)[a]	

NR, not reported; ICU, intensive care unit; LOS, length of stay; GI, gastrointestinal.

[a] $p \leq 0.05$; [b] "Cut-off value" of volume above which there is automatic cessation of enteral nutrition; [c] enteral nutrition advanced if GRVs <50 mL, automatic cessation if >150 mL; [d] incidence of aspiration as a percentage of all q4-hour bedside checks; [e] incidence of regurgitation as a percentage of all q4-hour bedside checks; [f] %Goal feeding on day 3 (similar to significant differences on day 7).

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 used (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° to 45° (grade C).
- 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 postpyloric 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 more than 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 recommendation 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 three meta-analyses (as discussed under recommendation A6) suggest that any effect in reducing pneumonia is minimal (80–82) (Table 5) (23, 68, 78, 83–91).

Elevating the head of the bed 30° to 45° was shown in one study to reduce the incidence of pneumonia from 23% to 5%, comparing supine with semirecumbent position, respectively ($p = 0.018$) (158) (Table 9) (158, 159).

The potential harm from aggressive bolus infusion of EN leading to increased risk of aspiration pneumonia was shown in one 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 was seen between techniques with regard to patient outcome (161, 162) (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) (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 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 with placebo) (169).

Optimizing oral health with chlorhexidine mouthwashes twice daily was shown in two studies to reduce respiratory infection and nosocomial pneumonia in patients undergoing heart surgery (170, 171). Although studies evaluating use of chlorhexidine in general ICU populations have shown little outcome effect, two studies where 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).

D5. Blue food coloring and glucose oxidase strips, as surrogate markers for as-

Table 9. Randomized studies evaluating body position during tube feeding in critically ill patients, supine vs. semi-recumbent

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

ICU, intensive care unit; LOS, length of stay; Hosp, hospital.
[a] $p \leq 0.05$.
Adapted and reprinted with permission from the Canadian Clinical Practice Guidelines (21).

Table 10. Randomized studies evaluating continuous vs bolus delivery of enteral nutrition

Study	Population	Study Groups	Infection	Difference in Feeding	ICU Mortality	Other
			NR	Time to Goal Calories		Diarrhea (stool frequency)
Hiebert et al (163)	Burn	Continuous		3.1 ± 0.7 days[a]		1.8 ± 0.4[a]
Level II	(n = 76)	Bolus		5.2 ± 0.8 days		3.3 ± 0.7
			NR	%Goal Calories Infused	NR	Aspiration (blue food coloring)
Kocan and Hickisch (164)	Neuro ICU	Continuous		62.2%		1/17 (5.9%)
Level II	(n = 34)	Bolus		55.9%		3/17 (17.6%)
				Daily Caloric Deficit		Clogged tube
Ciocan et al (165)	Hospitalized	Continuous	5/30 (17%)[b]	783 ± 29 kcal/d	NR	15/30 (50%)[a]
	(n = 60)	Bolus	10/30 (34%)	795 + 25 kcal/d		5/30 (17%)
Level II	Dysphagia	Continuous				20/30 (67%)[a]
		Bolus				29/30 (97%)
				Interrupted EN		Mortality
Bonten et al (161)	ICU	Continuous	5/30 (17%)	2/30 (7%)	6/30 (20%)	6/30 (20%)
Level II	(n = 60)	Bolus[c]	5/30 (17%)	5/30 (17%)	9/30 (30%)	9/30 (30%)
				Interrupted EN		
Steevens et al (162)	Trauma ICU	Continuous	0/9 (0%)[b]	3/9 (33%)	NR	
Level II	(n = 18)	Bolus	1/9 (11%)	5/9 (56%)		

NR, not reported; ICU, intensive care unit; EN, enteral nutrition.
[a] $p \leq 0.05$; [b]aspiration; [c]intermittent feeding.

piration, 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, omega-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), being cautious 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 benefit and thus would be an appropriate candidate 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).

Table 11. Randomized studies with vs without motility agents in critically ill patients

Study	Population	Study Groups	ICU Mortality	Pneumonia	Nutritional Outcomes
Yavagal et al (167) Level I	ICU (n = 305)	Metoclopramide 10 mg NG Placebo	73/131 (56%) 92/174 (53%)	22/131 (17%) 24/174 (14%)	NR
Berne et al (168) Level II	Trauma (n = 48)	Erythromycin 250 mg IV q 6 hrs Placebo	2/32 (6%) 2/36 (6%)	13/32 (40%) 18/36 (50%)	EN tolerated at 48 hrs 58% 44%
		Erythromycin 250 mg IV q 6 hrs Placebo			EN tolerated during study 65% 59%
Meissner et al (169) Level II	ICU (n =84)	Naloxone 8 mg q 6 hrs NG Placebo	6/38 (16%) 7/43 (16%)	13/38 (34%)[a] 24/43 (56%)	Mean GRV 54 mL 129 mL Volume EN delivered higher after day 3 in naloxone group (trend)

NR, not reported; ICU, intensive care unit; GRV, gastric residual volume; IV, intravenous; NG, nasogastric; EN, enteral nutrition.
[a] $p \leq 0.05$.
Adapted and reprinted with permission from the Canadian Clinical Practice Guidelines (21).

A large body of data suggests that adding pharmaconutrients to enteral formulations provides even further benefits on patient outcome to use of standard formulations alone (181–183) (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 omega-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 omega-3 fatty acids eicosapentaenoic acid and docosohexaenoic acid displace omega-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. Eicosapentaenoic acid and docosahexaenoic acid (fish oils) have also been shown to down-regulate expression of nuclear factor-kappa B, intracellular adhesion molecule 1, and E-selectin, which in effect decreases neutrophil attachment and transepithelial migration to modulate systemic and local inflammation. In addition eicosapentaenoic acid and docosahexaenoic acid help to stabilize the myocardium and lower the incidence of cardiac arrhythmias, decrease incidence of acute respiratory distress syndrome, 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 LOS compared with use of standard enteral formulations. These same five meta-analyses showed no overall impact on mortality from use of immune-modulating formulations (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; $p \leq 0.05$) and hospital LOS (WMD = −0.76; 95% CI −1.14 to −0.37; $p < 0.05$) (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 = not significant), but a similar reduction in hospital LOS (WMD = −0.47; 95% CI −0.93 to −0.01; $p = 0.047$) (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 septic (213, 214). Based on one level I report (188), a 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 three 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 four 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 patients (196) with use of an arginine-containing formulation (compared with a standard enteral formulation). On review of this controversy, the Guidelines Committee felt that arginine-containing immune-modulating formulations were safe enough to use in mild to moderate sepsis, but that caution should be used if utilized in patients with severe sepsis.

Unfortunately, few studies have addressed the individual pharmaconutrients, their specific effect, or their proper

Table 12 Immune-modulating enteral nutrition (EN) vs. standard EN in critically ill patients

Study	Population	Study Groups	Mortality	Infections[b]	LOS Days, Mean ± SD (or range)	Ventilator Days, Mean ± SD (or range)
Cerra (184)	Surgical ICU (n = 20)	Impact (Novartis Nutrition, Minneapolis, MN)[c]	1/11 (9%) ICU	NR	36.7 ± 8.5 Hosp[a]	NR
Level II		Osmolite HN (Ross Nutrition, Columbus, OH)	1/9 (11%) ICU		54.7 ± 10.5 Hosp	
Gottschlich (185)	Critically ill burns (n = 31)	Shriners burn formula[d]	2/17 (12%) ICU	NR	NR	9 ± 4.5
Level II		Osmolite HN + protein	1/14 (7%) ICU			10 ± 2.5
Brown (186)	Trauma (n = 37)	Experimental formula[d]	0/19 (0%) ICU	3/19 (16%)[a]	NR	NR
Level II		Osmolite HN + protein	0/18 (0%) ICU	10/18 (56%)		
		Immun-Aid (B. Braun, Irvine, CA)[c]	1/51 (2%) ICU	9/51 (18%)	14.6 ± 1.3 Hosp[a]	1.9 ± 0.9[a]
Moore (187)	Trauma (n = 98)	Vivonex TEN (Novartis Nutrition, Minneapolis, MN)	2/47 (4%) ICU	10/47 (21%)	17.2 ± 2.8 Hosp	5.3 ± 3.1
Level II		Immun-Aid[c]			5.3 ± 0.8 ICU[a]	
		Vivonex TEN			8.6 ± 3.1 ICU	
Bower (188)	ICU (n = 296)	Impact[d]	24/153 (16%) ICU	86/153 (56%)	27.6 ± 23 Hosp	NR
Level I		Osmolite	12/143 (8%) ICU	90/143 (63%)	30.9 ± 26 Hosp	
		Immun-Aid[c]	1/17 (6%) ICU	5/16 (31%)	18.3 ± 2.8 Hosp[a]	2.4 ± 1.3[a]
Kudsk (189)	Trauma (n = 35)	STD EN	1/18 (6%) ICU	11/17 (65%)	32.6 ± 7.0 Hosp	5.4 ± 2.0
Level II		Immun-Aid[c]			5.8 ± 1.8 ICU[a]	
		STD EN				9.5 ± 2.3 ICU
Engel (190)	Trauma (n = 36)	Impact[c]	7/18 (39%) ICU	6/18 (33%)	19.0 ± 7.4 ICU	14.8 ± 5.6
Level II		STD EN	5/18 (28%) ICU	5/18 (28%)	20.5 ± 5.3 ICU	16.0 ± 5.6
		Experimental formula[d]	1/22 (5%) ICU	19/22 (86%)[a]	34.0 ± 21.2 Hosp[a]	16.5 ± 19.4
Mendez (191)	Trauma (n = 43)	Osmolite HN + protein	1/21 (5%) ICU	12/21 (57%)	21.9 ± 11.0 Hosp	9.3 ± 6.0
Level II		Experimental formula[d]			18.9 ± 20.7 ICU	
		Osmolite HN + protein			11.1 ± 6.7 ICU	
Rodrigo (192)	Mixed ICU (n = 30)	Impact[d]	2/16 (13%) ICU	5/16 (31%)	8.0 ± 7.3 ICU	NR
Level II		STD EN	1/14 (7%) ICU	3/14 (21%)	10.0 ± 2.7 ICU	
Saffle (193)	Burns (n = 50)	Impact[d]	5/25 (21%) ICU	2.36 per patient	37 ± 4 Hosp	22 ± 3
Level II		Replete (Nestle Nutrition, Minneapolis, MN)	3/24 (13%) ICU	1.71 per patient	38 ± 4 Hosp	21 ± 2
		Impact[d]	2/16 (13%) ICU		70.2 ± 53 Hosp	21.4 ± 10.8
Weimann (194)	Trauma (n = 29)	STD EN	4/13 (31%) ICU	NR	58.1 ± 30 Hosp	27.8 ± 14.6
Level II		Impact[d]			31.4 ± 23.1 ICU	
		STD EN			47.4 ± 32.8 ICU	
		Impact[d]	95/197 (48%) ICU		10.5 ± 13.1 ICU	8.0 ± 11.1
					12.2 ± 23.2 ICU	
					20.6 ± 26 Hosp	
Atkinson (195)	Mixed ICU (n = 390)	STD EN	85/193 (44%) ICU		23.2 ± 32 Hosp	9.4 ± 17.7
Level I		Impact[d]				
		STD EN				
Galban (196)	Critically ill septic	Impact[d]	17/89 (19%)[a] ICU	39/89 (44%)	18.2 ± 12.6 ICU	12.4 ± 10.4
Level I	(n = 176)	STD EN	28/87 (32%) ICU	44/87 (51%)	16.6 ± 12.9 ICU	12.2 ± 10.3
		Experimental formula[c]	27/130 (21%) ICU	64/130 (49%)[a]	15 (10–25) ICU	10 (5–18)
Capparos (197)	ICU patients (n = 235)	STD EN	30/105 (29%) ICU	37/105 (35%)	13 (9–20) ICU	9 (5–14)
Level I		Experimental formula[c]			29 (17–51) Hosp	
		STD EN			26 (18–42) Hosp	
Conejero (198)	SIRS patients (n = 84)	Experimental formula[c]	14/47 (33%) at 28 d	11/47 (26%)[a]	14 (4–63) Hosp	14 (5–25)
Level II		STD EN	9/37 (27%) at 28 d	17/37 (52%)	15 (4–102) Hosp	14 (5–29)
Dent (199)		Optimental (Abbott Nutrition, Abbott Park, IL)[c]	20/87 (23%)[a] ICU	57/87 (66%)	14.8 ± 19.6 ICU	14.3 ± 22.4
Level I	ICU (n = 170)	Osmolite HN	8/83 (10%) ICU	52/83 (63%)	12 ± 10.9 ICU	10.8 ± 12.8
		Optimental[c]			25.4 ± 26 Hosp	
		Osmolite HN			20.9 ± 17 Hosp	
		Perative (Abbott Nutrition, Abbott Park, IL)[e]	8/18 (44%) ICU		13.5 (9–26) Hosp	
Bertolini (200)	Severe sepsis (n = 39)	Parenteral nutrition	3/21 (14%) ICU	NR	15.0 (11–29) Hosp	NR
Level II		Perative[e]	8/18 (44%) at 28 d			
		Parenteral nutrition	5/21 (24%) at 28 d			
		Neoimmune[g]	1/18 (5%) ICU		3.4 ± 5.8 ICU	2.7 ± 5.2
					7.8 ± 13.6 ICU	

Table 12.—*Continued*

Study	Population	Study Groups	Mortality	Infections[b]	LOS Days Mean ± SD (or range)	Ventilator Days, Mean ± SD (or range)
Chuntrasakul (201)	Trauma burns (n = 36)	Traumacal (STD EN) (Nestle Nutrition, Minneapolis, MN)	1/18 (5%) ICU	NR	44.9 ± 30.2 Hosp	7.4 ± 1.3
Level II		Neoimmune[g]			28.8 ± 25.7 Hosp	
		Traumacal (STD EN)				
		STD EN + arginine[d]	1/13 (8%) ICU	8/13 (61%)	13 ± 6 ICU	10 ± 5
Tsuei (202)	Trauma (n =25)	STD EN + protein	0/12 (0%) ICU	6/11 (55%)	16 ± 10 ICU	14 ± 10
Level II		STD EN + arginine[d]			22 ± 9 Hosp	
		STD EN + protein			27 ± 17 Hosp	
		Stresson (NV Nutricia, Zoetermeer, The Netherlands)[f]	84/302 (28%) ICU	130/302 (43%)	7 (4–14) ICU	6 (3–12)
Kieft (203)	ICU (n = 597)	STD EN	78/295 (26%) ICU	123/295 (42%)	8 (5–16) ICU	6 (3–12)
Level I		Stresson[f]	114/302 (38%) Hosp		20 (10–35) Hosp	
		STD EN	106/295 (36%) Hosp		20 (10–34) Hosp	
Wibbenmeyer (204)	Burn (n =23)	Crucial (Nestle Nutrition, Minneapolis, MN)[d]	2/12 (17%) ICU	9/12 (75%)	NR	NR
Level II		STD EN	0/11 (0%) ICU	7/11 (64%)		

NR, not reported; ICU, intensive care unit; LOS, length of stay; Hosp, hospital; d, days; STD, standard.

[a]$p \leq 0.05$; [b]all infections represent number of patients per group with infection unless otherwise stated; [c]non-isonitrogenous; [d]isonitrogenous; [e]non-isocaloric; [f]isocaloric but non-isonitrogenous; [g]non-isocaloric and non-isonitrogenous.

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Table 13. Meta-analyses 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 (181)	Medical, surgical critical illness, cancer (n = 1009)	11	Decreased infection (OR = 0.47, 95% CI 0.32–0.70, $p < 0.05$) Decreased length of stay (WMD = 2.5, 95% CI 4.0–1.0, $p < 0.05$) No change in mortality (OR = 1.77, 95% CI 1.00–3.12, p = NS)
Beale et al (182)	Medical, surgical trauma, sepsis, major surgery (n = 1482)	12	Decreased infection (RR = 0.67, 95% CI 0.50–0.89, $p = 0.006$) Decreased ventilator days (WMD = 2.6, 95% CI 0.1–5.1, $p = 0.04$) Decreased length of stay (WMD = 2.9, 95% CI 1.4–4.4, $p = 0.0002$) No change in mortality (RR = 1.05, 95% CI 0.78–1.41, p = NS)
Heyland et al (210)	Medical, surgical critical illness, major surgery (n = 2419)	22	Decreased infection (RR = 0.66, 95% CI 0.54–0.80, $p < 0.05$) Decreased length of stay (WMD 3.33, 95% CI 5.63–1.02, $p < 0.05$) No change in mortality (RR = 1.10, 95% CI 0.93–1.31, p = NS)
Montejo et al (211)	Critical illness (n = 1270)	26	Decreased abdominal abscess (OR = 0.26, 95% CI 0.12–0.55, $p = 0.005$) Decreased bacteremia (OR = 0.45, 95% CI 0.35–0.84, $p = 0.0002$) Decreased pneumonia (OR = 0.54, 95% CI 0.35–0.84, $p = 0.007$) Decreased ventilator days (WMD = 2.25, 95% CI 0.5–3.9, $p = 0.009$) Decreased length of stay (WMD = 3.4, 95% CI 4.0–2.7, $p < 0.0001$) No change in mortality (OR = 1.10, 95% CI 0.85–1.42, p = NS)
Waitzberg et al (212)	Elective surgery (n = 2305)	17	Decreased infection (RR = 0.49, 95% CI 0.42–0.58, $p > 0.0001$) Decreased length of stay (WMD = 3.1, 95% CI 3.9–2.3, $p < 0.05$) Decreased anastomotic leaks (RR = 0.56, 95% CI 0.37–0.83, $p = 0.004$) No change in mortality (RR = 0.72, 95% CI 0.39–1.31, p = NS)

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

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 they 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 B grade recommendation.

For any patient who does not meet the mentioned criteria, there is a much lower 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 acute respiratory distress syndrome and severe acute lung injury should be placed on an enteral

Table 14. Anti-inflammatory immune-modulating enteral nutrition (Oxepa) vs standard enteral nutrition in patients with acute respiratory distress syndrome, acute lung injury, and sepsis

Study	Population	Study Groups	Mortality	LOS Days Mean ± SD	Ventilator Days Mean ± SD	New Organ Dysfunction
Gadek et al (207)	ARDS	Oxepa[b]	11/70 (16%) ICU	11.0 ± 0.9 ICU[a]	9.6 ± 0.9[a]	7/70 (10%)[a]
Level I	ICU	STD EN	19/76 (25%) ICU	14.8 ± 1.3 ICU	13.2 ± 1.4	19/76 (25)
	(n = 146)	Oxepa		27.9 ± 2.1 Hosp		
		STD EN		31.1 ± 2.4 Hosp		
Singer et al (208)	ARDS and ALI	Oxepa	14/46 (30%) at 28 d[a]	13.5 ± 11.8 ICU	12.1 ± 11.3	NR
Level I	(n = 100)	STD EN	26/49 (53%) at 28 d	15.6 ± 11.8 ICU	14.7 ± 12.0	
Pontes-Arruda et al (209)	Severe sepsis	Oxepa	26/83 (31%) at 28 d[a]	17.2 ± 4.9 ICU[a]	14.6 ± 4.3[a]	32/83 (38%)[a]
Level I	ICU (n = 165)	STD EN	38/82 (46%) at 28 d	23.4 ± 3.5 ICU	22.2 ± 5.1	66/82 (81%)

NR, not reported; ICU, intensive care unit; LOS, length of stay; d, days; STD EN, standard enteral nutrition; ARDS, acute respiratory distress syndrome; ALI, acute lung injury.

[a]$p \leq 0.05$; [b]Oxepa (Abbott Laboratories, Abbott Park, IL).

formulation characterized by an anti-inflammatory lipid profile (i.e., omega-3 fish oils, borage oil) and antioxidants (grade A).

Rationale. In three level I studies involving patients with acute respiratory distress syndrome, acute lung injury, and sepsis, use of an enteral formulation fortified with omega-3 fatty acids (in the form of eicosapentaenoic acid), borage oil (γ-linolenic acid), and antioxidants was shown to significantly reduce LOS in the ICU, duration of mechanical ventilation, organ failure, and mortality compared with 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 (Table 14) (207–209).

E3. To receive optimal therapeutic benefit from the immune-modulating formulations, at least 50% to 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 used (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 semielemental formula. The laboratory data, theoretical concepts, and expert opinion would support the use of the peptide-containing enteral formulas 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 because of 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 used.

Rationale. Probiotics are defined as microorganisms of human origin, which are safe, stable in the presence of gastric acid and bile salts, and confer a health benefit to the host when administered in adequate amounts. 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 competitive inhibition of pathogenic bacterial growth, blocking epithelial attachment of invasive pathogens, elimination of pathogenic toxins, enhancement of 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). Although some of these 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 because of the results of two level II single-center studies showing clinical benefit (significantly reduced infectious morbidity and hospital LOS) (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

Table 15. Randomized studies evaluating enteral nutrition with glutamine vs. enteral nutrition alone

Study	Population	Study Groups	ICU Mortality	Infection	Length of Stay Mean ± SD (or range)
Houdijk et al (238)	Critically ill trauma	EN/GLN	4/41 (10%)	20/35 (57%)[a]	32.7 ± 17.1 Hosp
Level II	(n = 80)	EN	3/39 (8%)	26/37 (70%)	33.0 ± 23.8 Hosp
Jones et al (235)	Mixed ICU	EN/GLN	10/26 (39%)	NR	11 (4–54) ICU
Level II	(n = 78)	EN	9/24 (38%)		16.5 (5–66) ICU
Brantley and Pierce (239)	Critically ill trauma	EN/GLN	0/31 (0%)	NR	19.5 ± 8.8 Hosp
Level II	(n = 72)	EN	0/41 (0%)		20.8 ± 11.5 Hosp
Hall et al (236)	Mixed ICU	EN/GLN	27/179 (15%)	38/179 (21%)	25 (16–42) Hosp
Level I	(n = 363)	EN	30/184 (16%)	43/184 (23%)	30 (19–45) Hosp
Garrel et al (237)	Burns	EN/GLN	2/21 (10%)[a]	7/19 (37%)	33 ± 17 Hosp
Level II	(n = 45)	EN	12/24 (50%)	10/22 (45%)	29 ± 17 Hosp
Zhou et al (240)	Burns	EN/GLN	0/20 (0%)	2/20 (10%)[a]	67 ± 4 Hosp
Level II	(n = 41)	EN	0/20 (0%)	6/20 (30%)	73 ± 6 Hosp
Peng et al (241)	Burns	EN/GLN	NR	NR	46.6 ± 12.9 Hosp
Level II	(n = 48)	EN			55.7 ± 17.4 Hosp

NR, not reported; ICU, intensive care unit; Hosp, hospital; EN, enteral nutrition; GLN, glutamine.
[a] $p \leq 0.05$.
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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; $p = 0.03$) (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; $p = 0.08$) (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. The addition of enteral glutamine (Table 15) (235–241) to an EN regimen (nonglutamine supplemented) has been shown to reduce hospital and ICU LOS in burn and mixed ICU patients (235, 237), and mortality in burn patients alone (237) compared with 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 two or three divided doses to provide 0.3–0.5 $g \cdot kg^{-1} \cdot day^{-1}$. Although 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, LOS, or multiorgan dysfunction syndrome 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 provided enteral formulations containing insoluble fiber have been reported (245, 246).

G. When Indicated, Maximize Efficacy of PN

G1. If EN is not available or feasible, the need for PN therapy should be evaluated (see guidelines recommendations 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 recommendations B1–B3 and C3, a critically ill ICU patient may be an appropriate candidate for PN under certain circumstances:

1. The patient is well nourished before 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 recommendations B1–B3 and C3, while that of the second is based on the supportive data for recommendations G2–G6.

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 ≥30), the dose of PN with regard to protein and caloric provision should follow the same recommendations given for EN in guideline recommendation 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/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 LOS associated with excessive energy intake. Lower dose hypocaloric PN in two studies was shown to reduce the incidence of hyperglycemia (247) and infections, ICU and hospital LOS, and duration of mechanical ventilation compared with higher eucaloric doses of PN (248) (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 recommendation 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. In North America at the present time, the choice of parenteral lipid emulsion is severely limited to a soy-based 18-carbon omega-6 fatty acid preparation (which has proinflammatory characteristics in the ICU population). During 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 LOS, and shorter duration of mechanical ventilation compared with use of lipid-containing PN (248). Combining the data from two 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; $p = 0.02$) in the groups receiving no soy-based lipids (21). Application of this recommendation should be done with caution. These two studies were done before the Van den Berghe et al (253, 254) studies, and full dose PN without lipids might exacerbate stress-induced hyperglycemia. Although two favorable level II studies would generate a grade C recommendation, the implications from a practical standpoint led to a downgrade of the recommendation to grade D (Table 17) (248, 250).

G4. A protocol should be in place to promote moderately strict control of serum glucose when providing nutrition supthat port 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 LOS, and lower hospital mortality, when compared with conventional insulin therapy (keeping blood glucose levels <200 mg/dL) (253). The effect was more pronounced in surgical ICU than medical ICU patients (254) (Table 18) (253–255).

A large level I multicenter 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 with tighter control (255). With a paucity of data, the Guidelines Committee felt attempting to control 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 $g \cdot kg^{-1} \cdot day^{-1}$) to a PN regimen has been shown to reduce infectious complications (121, 256), ICU LOS (257), and mortality (258) in critically ill patients, compared with the same PN regimen without glutamine. A meta-analysis by Heyland et al combining results from nine studies, confirmed a trend toward reduced infection (RR = 0.75; 96% CI 0.54–1.04; $p = 0.08$) and a significant reduction in mortality (RR = 0.67; 95% CI 0.48–0.92; $p = 0.01$) in groups receiving PN with parenteral glutamine vs. those groups getting PN alone (21) (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 (Dipeptiven and Glamin; Fresenius Kabi, Uppsala, Sweden) upon which most of these data are based is widely used in Europe but not commercially available in North America (referring both to 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 three reports that 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 ≥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. Speciality, high-lipid low carbohydrate formulations designed to manipulate the respiratory quotient and reduce CO_2 production are not recommended for routine use in ICU patients with acute respiratory failure (grade E). (This is not to be confused with guideline recommendation E2 for acute respiratory distress syndrome/acute lung injury.)

Rationale. There is a lack of consensus about the optimum source and composition of lipid (medium- vs. long-chain triglyceride, soybean oil, olive oil, omega-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 with a standard formulation (268). A second smaller level II study (10 patients) showed no clinical benefit (269).

Table 16. Randomized studies evaluating lower hypocaloric doses of parenteral nutrition (PN) vs. higher eucaloric doses of PN in critically ill patients

Study	Population	Study Groups	Mortality	Infections[b]	LOS Days Mean ± SD (or range)	Ventilator Days Mean ± SD (or range)	Hyperglycemia
				Pneumonia			
Battistella et al (248)	Trauma	Hypocaloric	2/27 (7%) ICU	13/27 (48%)[a]	18 ± 12 ICU[a]	15 ± 12[a]	NR
Level II	(n = 57)	Eucaloric	0/30 (0%) ICU	22/30 (73%)	29 ± 22 ICU	27 ± 21	
				Bloodstream			
		Hypocaloric		5/27 (19%)[a]	27 ± 16 Hosp[a]		
		Eucaloric		13/30 (43%)	39 ± 24 Hosp		
Choban et al (249)	ICU	Hypocaloric	0/6 (0%) Hosp	NR	48 ± 30 Hosp	NR	NR
Level II	(n = 13)	Eucaloric	2/7 (29%) Hosp		45 ± 38 Hosp		
McCowen et al (250)	ICU	Hypocaloric	2/21 (10%) ICU	6/21 (29%)	19 ± 14 Hosp	NR	4/21 (20%)
Level II	(n = 48)	Eucaloric	3/19 (16%) ICU	10/19 (53%)	17 ± 15 Hosp		5/19 (26%)
Ahrens et al (247)	SICU	Hypocaloric	1/20 (5%) ICU	5/20 (25%)	14 (10–21) ICU	10 (4–15)	5/20 (25%)[a]
Level II	(n = 40)	Eucaloric	3/20 (15%) ICU	2/20 (10%)	14 (10–37) ICU	19 (4–35)	14/20 (70%)
		Hypocaloric			15 (11–26) Hosp		
		Eucaloric			25 (15–39) Hosp		

NR, not reported; ICU, intensive care unit; SICU, surgical ICU; Hosp, hospital; LOS, length of stay.
[a]$p \leq 0.05$; [b]all infections represent number of patients per group with infection unless otherwise stated.
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Table 17. Randomized studies evaluating parenteral nutrition with vs without lipids in critically ill patients

Study	Population	Study Groups	ICU Mortality	Infections[b]	LOS Days Mean ± SD	Ventilator Days Mean ± SD
				Pneumonia		
Battistella et al (248)	Trauma	Without	2/27 (7%)	13/27 (48%)[a]	27 ± 16 Hosp[a]	15 ± 12[a]
Level II	(n = 57)	With	0/30 (0%)	22/30 (73%)	39 ± 24 Hosp	27 ± 21
				Line sepsis		
				5/27 (19%)[a]	18 ± 12 ICU[a]	
				13/30 (43%)	29 ± 22 ICU	
McCowen et al (250)	ICU	Without	2/21 (10%)	6/21 (29%)	19 ± 14 Hosp	NR
Level II	(n = 48)	With	3/19 (16%)	10/19 (53%)	17 ± 15 Hosp	

NR, not reported; ICU, intensive care unit; LOS, length of stay.
[a]$p \leq 0.05$; [b]all infections represent number of patients per group with infection unless otherwise stated.
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Results from uncontrolled studies would suggest that increasing the composite ratio of fat to carbohydrate becomes clinically significant in lowering CO_2 production only in the ICU patient being overfed, that composition is much less likely to affect CO_2 production when the design of the nutrition support regimen approximates caloric requirements (270). Effort should be made to avoid total caloric provision that exceeds energy requirements, as CO_2 production increases significantly with lipogenesis and may be tolerated poorly in the patient prone to CO_2 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 and 2,3-diphosphoglycerate, both of which are critical for normal diaphragmatic contractility and optimal pulmonary function. LOS and duration of mechanical ventilation are increased in patients who become hypophosphatemic when compared with those who do not have this electrolyte imbalance. As suggested by several uncontrolled studies, it seems prudent to monitor phosphate closely and replace appropriately when needed (271, 272).

I. Renal Failure

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

Rationale. Acute renal failure 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 (i.e., phosphate and potassium) than standard products may be beneficial in the ICU patient with acute renal failure (273–275).

I2. Patients receiving hemodialysis or continuous renal replacement therapy should receive increased protein, up to a maximum of 2.5 g·kg^{-1}·day^{-1}. 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/day during continuous renal replacement therapy. Providing less than 1 g protein·kg^{-1}·day^{-1} of protein may result in increased nitrogen

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
				Septicemia	
Van den Berghe et al (253) Level I	Surgical ICU (n = 1548)	Intensive control (80–110 mg/dL)	39/765 (51%)[a]	32/765 (4%)	35/765 (5%) ICU[a]
		Conventional control (180–200 mg/dL)	6/783 (1%)	61/783 (8%)	63/783 (8%) ICU
		Intensive control			55/765 (7%) Hosp[a]
		Conventional control			85/783 (11%) Hosp
				New kidney injury	All Patients at day 3
Van den Berghe et al (254) Level I	Medical ICU (n = 1200)	Intensive control (80–110 mg/dL)	111/595 (18.7%)[a]	35/595 (5.9%)[a]	23/595 (3.9%) ICU
		Conventional control (180–200 mg/dL)	19/605 (3.1%)	54/605 (8.9%)	17/605 (2.8%) ICU
		Intensive control			Patients in ICU >3 days 166/386 (43%) Hosp[a]
		Conventional control			200/381 (52%) Hosp
Devos and Preiser (255) Level I	Mixed ICU (n = 1101)	Intensive control (80–110 mg/dL)	9.8%[a]	NR	17%
		Moderate control (140–180 mg/dL)	2.7%		15% (Mortality rate significantly higher in those patients with hypoglycemia)

ICU, intensive care unit; NR, not reported; Hosp, hospital.
[a] $p \leq 0.05$.

Table 19. Randomized studies evaluating parenteral nutrition with vs without supplemental parenteral glutamine in critically ill patients

Study	Population	Study Groups	Mortality	Infections[b]	LOS Days Mean ± SD (or range)
Griffiths et al (259) and (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 (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 (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 (258) Level II	SICU (n = 68)	With	7/33 (21%) ICU	NR	21.3 ± 13.5 ICU
					20.8 ± 9.1 ICU
		Without	10/35 (29%) ICU		46 ± 49.1 Hosp
		With	11/33 (33%) at 6 mos[a]		39.4 ± 31.1 Hosp
		Without	21/35 (60%) at 6 mos		
Fuentes-Orozco et al (256) Level II	Peritonitis (n = 33)	With	2/17 (12%) ICU	4/17 (23%)[a]	7.2 ± 9.2 ICU
					7.3 ± 4.5 ICU
		Without	3/16 (19%) ICU	12/16 (75%)	16.5 ± 8.9 Hosp
					16.7 ± 7.0 Hosp
		With			
		Without			
Ziegler et al (257) Level II	Postop surgery (n = 63)	With	1/32 (3%) Hosp	8/30 (27%)	12 ± 2 ICU[a] Hosp
		Without	5/31 (16%) Hosp	13/29 (45%)	23 ± 6 ICU Hosp
Zhou et al (263) Level II	Burn (n = 30)	With	NR	3/15 (20%)	42 ± 7.0 Hosp
		Without		4/15 (26%)	46 ± 6.6 Hosp
Xian-Li et al (121) Level II	Acute pancreatitis (n = 69)	With	0/20 (0%) ICU	0/20 (0%)[a]	25.3 ± 7.6 Hosp
		Without	3/21 (14%) ICU	5/21 (24%)	28.6 ± 6.9 Hosp
Dechelotte et al (264) Level I	ICU (n = 114)	With	2/58 (3%) Hosp	23/58 (40%)	12.5 (1–430) ICU
		Without	2/56 (3%) Hosp	32/56 (58%)	11.5 (3–121) ICU
		With	16/58 (28%) at 6 mos	10/58 (17%)[c]	30 (1–560) Hosp
		Without	9/56 (16%) at 6 mos	19/56 (34%)	26 (4–407) Hosp

NR, not reported; ICU, intensive care unit; SICU, surgical ICU; Hosp, hospital; LOS, length of stay.
[a] $p \leq 0.05$; [b] all infections represent number of patients per group with infection unless otherwise stated; [c] pneumonia.
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deficits for patients on hemodialysis or continuous renal replacement therapy. Patients undergoing continuous renal replacement therapy should receive formulations with 1.5–2.0 g protein·kg^{-1}·day^{-1}. At least one randomized prospective trial (276) has suggested an intake of 2.5 g·kg^{-1}·day^{-1} 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 because of complications of ascites, intravascular volume depletion, edema, portal hypertension, and hypoalbuminemia (grade E).

Rationale. Although 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 nutritional assessment tools to be 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, 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. Enteral feeding has been associated with decreased infection rates and fewer metabolic complications in liver disease and after liver transplant when compared with 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 (per recommendations C4 and C5).

J3. Standard enteral formulations should be used in ICU patients with acute and chronic liver disease. The branched-chain amino acid formulations should be reserved for the rare encephalopathic patient who is refractory to STD with luminal acting antibiotics and lactulose (grade C).

Rationale. There is no evidence to suggest that a formulation enriched in branched-chain amino acid 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 branched-chain amino acid 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 STD, use of branched-chain amino acid formulations may improve coma grade compared with 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, 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 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 (Pao_2 $<$60 mm Hg), renal failure (serum creatinine $>$2 mg/dL), or GI bleeding ($>$500 mL blood loss within 24 hours). Local complications on computerized tomography scan include pseudocyst, abscess, or necrosis. Unfavorable prognostic signs are defined by an Acute Physiology and Chronic Health Evaluation II score of $\geq$8, or by $\geq$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 with PN reduces infectious morbidity (RR = 0.46; 95% CI 0.29–0.74; p = 0.001) (17), hospital LOS (WMD = −3.94; 95% CI −5.86 to −2.02; $p < 0.0001$) (17), reduced need for surgical intervention (RR = 0.48; 95% CI 0.23–0.99; p = 0.05) (297), multiple organ failure (odds ratio = 0.306; 95% CI 0.128–0.736; p = 0.008) (298), and mortality (odds ratio = 0.251; 95% CI 0.095–0.666; p = 0.005) (298) (Table 3) (8, 22, 46, 54–60). In a meta-analysis of two 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 = 0.06) compared with STD where no nutrition support therapy was provided (17).

The need to initiate EN early within 24 to 48 hours of admission is supported by the fact that of six level II studies done only in patients with severe acute pancreatitis, five studies that randomized and initiated EN within 48 hours of admission all showed significant outcome benefits (22, 56, 58–60) compared with PN. Only one study in severe pancreatitis that 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. Of three level II randomized studies that included patients with less disease severity (62% to 81% of patients had mild to moderate acute pancreatitis), none showed significant outcome benefits with use of EN compared with PN (8, 46, 55). Provision of nutrition support therapy in these patients should be considered if a subsequent unanticipated complication develops (e.g., 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 severe acute pancreatitis showed no significant differences between the two levels of EN infusion within the GI tract (299, 300). The success of gastric feeding in these two studies (where only two patients in the Eatock group [299] and one patient in the Kumar group [300] 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 (46) showed varying degrees of tolerance with different levels of infusion within the GI tract. 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 reversed by return to jejunal feeding). One patient who showed tolerance to jejunal feeds had an exacerbation of the systemic inflammatory response syndrome when the tube was displaced back into the stomach (an effect again 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) becomes an important issue. In an early level II randomized trial, Sax et al (97) 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 LOS than those patients randomized to STD (no nutrition support therapy). In contrast, a later level II study by Xian-Li et al (121) in patients with severe pancreatitis where PN was initiated 24–48 hours after "full liquid resuscitation," significant reductions in overall complications, hospital LOS, and mortality were seen when compared with STD. 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 two 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 under obligation 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 enteral 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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