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

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

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

Preliminary Remarks

Guideline Limitation

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

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

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

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

Periodic Guideline Review and Update

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

Target Patient Population for Guideline

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

Target Audience

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

Methodology

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

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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 end point criteria predetermined by power analysis. Meta-analyses were used to organize information and to draw conclusions about overall treatment effect from multiple studies on a particular subject. The grade of recommendation, however, was based on the level of evidence of the individual studies.

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

Introduction

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

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A. Initiate Enteral Feeding

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

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

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

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

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

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

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

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

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

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

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

SD, standard deviation; NR, not reported; LOS, length of stay; GI, gastrointestinal; MOF, multiple organ failure.
[a] All infections represent number of patients per group with infection unless otherwise stated.
[b] $P \leq .05$.
[c] $P = .08$.
[d] Wound sepsis.

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

Rationale. Attaining access and initiating EN should be considered as soon as fluid resuscitation is completed and the patient is hemodynamically stable. A "window of opportunity" exists in the first 24-72 hours following admission or the onset of a hypermetabolic insult. Feedings started within this time frame (compared to feedings started after 72 hours) are associated with less gut permeability, diminished activation, and release of inflammatory cytokines (ie, tumor necrosis factor [TNF] and reduced systemic endotoxemia).[21] One meta-analysis by Heyland et al showed a trend toward reduced infectious morbidity (RR = 0.66; 95% CI 0.36-1.22; P =.08) and mortality (RR = 0.52; 95% CI 0.25-1.08; P = .08),[21] while a second by Marik and Zaloga showed significant reductions in infectious morbidity (RR = 0.45; 95% CI 0.30-0.66; P = .00006) and hospital length of stay (mean 2.2 days, 95% CI 0.81-3.63 days; P = .001) with early EN compared to delayed feedings.[62] **See Table 4.**[63-72]

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

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

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

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

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Table 3. (continued)

Study	Population	Study Groups	ICU Mortality	Infections[a]	LOS Days, Mean ± SD (or Range)	Other Clinical Outcomes	Cost
Iovinelli et al, 1993[40]	Head–neck					Complications	
Level II	cancer	EN	0/24 (0%)	5/24 (21%)	26 ± 11[b] Hosp	1/24 (4%)	
	(n = 48)	PN	0/24 (0%)	4/24 (17%)	34 ± 11 Hosp	2/24 (8%)	
Kudsk et al, 1994[41]	Trauma (n = 68)					Complications	
Level II		EN	1/34 (3%)	5/34 (15%)		0/34 (0%)	
		PN	0/34 (0%)	14/34 (41%)		0/34 (0%)	
Dunham et al, 1994[42]	Trauma (n = 37)				NR	Complications	NR
Level II		EN	1/12 (8%)	0/12 (0%)		0/12 (0%)	
		PN	1/15 (7%)	0/15 (0%)		0/15 (0%)	
Borzotta et al, 1994[43]	Neurotrauma	EN	5/28 (18%)	51 per group	39 ± 23.1 Hosp	NR	$121,941[b]
Level II	(n = 59)	PN	1/21 (5%)	39 per group	36.9 ± 14 Hosp		$112,450
Hadfield et al, 1995[44]	ICU (n = 24)	EN	2/13 (15%)	NR	NR	NR	NR
Level II		PN	6/11 (55%)				
Baigrie et al, 1996[45]	GI surgery					Complications	
Level II	(n = 97)	EN	4/50 (8%)	2/50 (4%)		15/50 (30%)	
		PN	6/47 (13%)	10/47 (21%)		23/47 (49%)	
McClave et al, 1997[46]	Acute	EN	0/16 (0%)	2/16 (13%)	9.7 ± 1.3 Hosp	NR	$761 ± 50.3[b]
Level II	pancreatitis	PN	0/16 (0%)	2/16 (13%)	11.9 ± 2.6 Hosp		$3294 ± 551.9
	(n = 32)						
Reynolds et al, 1997[47]	Trauma (n = 67)					Complications	
Level II		EN	2/33 (6%)	10/33 (30%)		11/33 (33%)	
		PN	1/34 (3%)	19/34 (56%)		6/34 (18%)	
Sand et al, 1997[48]	GI surgery					Complications	
Level II	(n = 29)	EN	0/13 (0%)	3/13 (23%)		3/13 (23%)	Cost of PN was
		PN	1/16 (6%)	5/16 (31%)		3/16 (19%)	4 × cost of EN
Kalfarentzos et al, 1997[22]	Acute	EN	1/18 (6%)	5/18 (28%)[b]	40 (25-83) Hosp		Savings of 70
Level II	pancreatitis	PN	2/20 (10%)	10/20 (50%)	39 (22-73) Hosp		GBP/d with EN[b]
	(n = 38)					Duration MV	
		EN			11 (5-21) ICU	15 (6-16) d	
		PN			12 (5-24) ICU	11 (7-31) d	
Gianotti et al, 1997[49]	Surgery GI	EN	0/87 (0%)	20/87 (23%)[c]	19.2 ± 7.9 Hosp		NR
Level I	cancer (n = 176)	PN	0/86 (0%)	24/86 (28%)	21.6 ± 8.9 Hosp		
Windsor et al, 1998[8]	Acute					MOF	NR
Level II	pancreatitis	EN	0/16 (0%)	0/16 (0%)	12.5 (9.5-14) Hosp	0/16 (0%)	
	(n = 34)	PN	2/18 (11%)	3/18 (17%)	15.0 (11-28) Hosp	5/18 (28%)	
Woodcock et al, 2001[50]	ICU patients	EN	9/17 (53%)	6/16 (38%)	33.2 ± 43 Hosp	NR	NR
Level II	(n = 38)	PN	5/21 (24%)	11/21 (52%)	27.3 ± 18.7 Hosp		

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Table 3. (continued)

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

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

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

[b] $P \leq .05$.

[c] $P = .08$.

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

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

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

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

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

[b] Bacteremia.

[c] $P \leq .05$.

Adapted from the Canadian Clinical Practice Guidelines.[21]

ischemic bowel has been reported most often in the past with use of surgical jejunostomy tubes. However, more recently, this complication has been described with use of nasojejunal tubes.[75] EN intended to be infused into the small bowel should be withheld in patients who are hypotensive (mean arterial blood pressure <60 mm Hg), particularly if clinicians are initiating use of catecholamine agents (eg, norepinephrine, phenylephrine, epinephrine, dopamine) or escalating the dose of such agents to maintain hemodynamic stability. EN may be provided with caution to patients into either the stomach or small bowel on stable low doses of pressor agents,[76] but any signs of intolerance (abdominal distention, increasing nasogastric tube output or gastric residual volumes, decreased passage of stool and flatus, hypoactive bowel sounds, increasing metabolic acidosis and/or base deficit) should be closely scrutinized as possible early signs of gut ischemia.

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

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

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

Bowel sounds are only indicative of contractility and do not necessarily relate to mucosal integrity, barrier function, or absorptive capacity. Success at attaining nutrition goals within the first 72 hours ranges from 30% to 85%. When ICU enteral feeding protocols are followed, rates of GI tolerance in the range of 70%-85% can be achieved.[76] Ten randomized clinical trials,[63-72] the majority in surgical critically ill patients, have reported feasibility and safety of enteral feeding within the initial 36-48 hours of admission to the ICU. The grade of this recommendation is based on the strength of the literature supporting A3, where patients in the experimental arm of the above mentioned studies were successfully started on EN within the first 36 hours of admission (regardless of clinical signs of stooling, flatus, or borborygmi). **See Table 4.**[63-72]

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

Rationale. Multiple studies have evaluated gastric vs jejunal feeding in various medical and surgical ICU settings. One level II study comparing gastric vs jejunal feeding showed significantly less gastroesophageal reflux with small bowel feeding.[78] In a nonrandomized prospective study using a radioisotope in an enteral formulation, esophageal reflux was reduced significantly with a trend toward reduced aspiration as the level of infusion was moved from the stomach down through the third portion of the duodenum.[79] Three meta-analyses have been published comparing gastric with post-pyloric feeding in the ICU setting.[80-82] Only 1 of these meta-analyses showed a significant reduction in ventilator-associated pneumonia with post-pyloric feeding (RR = 0.76; 95% CI 0.59-0.99; $P = .04$),[82] an effect heavily influenced by 1 study by Taylor et al.[23] With removal of this study from the meta-analysis, the difference was no longer significant. The 2 other meta-analyses (which did not include the Taylor study) showed no difference in pneumonia between gastric and post-pyloric feeding.[80,81] While 1 showed no difference in ICU length of stay,[80] all 3 meta-analyses showed no significant difference in mortality between gastric and post-pyloric feeding.[80-82] **See Table 5.**[23,68,78,83-91]

B. When to Use Parenteral Nutrition

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

Rationale. These 2 recommendations are the most controversial in these guidelines, are influenced primarily by 2 meta-analyses, and should be interpreted very carefully in application to patient care.[24,92] Both meta-analyses compared use of PN with STD therapy (where no nutrition support therapy was provided). In critically ill patients in the absence of pre-existing malnutrition (when EN is not available), Braunschweig et al aggregated 7 studies[93-99] and showed that use of STD therapy was associated with significantly reduced infectious morbidity (RR = 0.77; 95% CI 0.65-0.91; $P < .05$) and a trend toward reduced overall complications (RR = 0.87; 95% CI 0.74-1.03; P not provided) compared to use of PN.[24] In the same circumstances (critically ill, no EN available, and no evidence of malnutrition), Heyland et al[92] aggregated 4 studies[96,97,100,101] and showed a significant increase in mortality with use of PN (RR = 0.1.78; 95% CI 1.11-2.85; $P < .05$) and a trend toward greater rate of complications (RR = 2.40; 95% CI 0.88-6.58; P not provided), when compared to STD therapy. **See Table 6.**[93-129]

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

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

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

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Table 5 (continued)

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

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

[a] $P \leq .05$.

[b] Total infections.

[c] Aspiration.

Adapted from the Canadian Clinical Practice Guidelines.[21]

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

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Table 6. (continued)

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

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

[a] wound infection.

[b] $P < .05$.

[c] Infection.

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

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

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

Rationale. In the situation where EN is not available and evidence of protein-calorie malnutrition is present (usually defined by recent weight loss of >10%-15% or actual body weight <90% of ideal body weight), initial priorities are reversed and use of PN has a more favorable outcome than STD therapy. **See Table 6.**[93-129]

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

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

- **If the patient is malnourished, PN should be initiated 5-7 days preoperatively and continued into the postoperative period. (Grade: B)**
- **PN should not be initiated in the immediate postoperative period but should be delayed for 5-7 days (should EN continue not to be feasible). (Grade: B)**
- **PN therapy provided for a duration of <5-7 days would be expected to have no outcome effect and may result in increased risk to the patient. Thus, PN should be initiated only if the duration of therapy is anticipated to be ≥7 days. (Grade: B)**

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

These benefits were noted when PN was provided preoperatively for a minimum of 7-10 days and then continued through the perioperative period. In an earlier meta-analysis by Detsky et al[130] comparing perioperative PN with STD therapy, only seven[95,98,102,103,107,110,111] out of 14 studies[94,100,104,106,108,109,112] provided PN for ≥7 days.[130] As a result, only 1 study showed a treatment 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 to STD therapy.[131] **See Table 6.**[93-129]

It is imperative to be aware that the beneficial effect of PN is lost if given only postoperatively. Aggregation of data from 9 studies that evaluated routine postoperative PN[93,94,96,99-101,104,109,122] showed a significant 10% increase in complications compared to STD therapy.[131] Because of the adverse outcome effect from PN initiated in the immediate postoperative period, Klein et al recommended delaying PN for 5-10 days following surgery if EN continues not to be feasible.[131]

C. Dosing of Enteral Feeding

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

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

Rationale. Clinicians should clearly identify the goal of EN, as determined by energy requirements. Over 200 predictive equations (including Harris-Benedict, Scholfield, Ireton-Jones, etc) have been published in the literature.[132] Energy requirements may be calculated either through simplistic formulas (25-30 kcal/kg/d), published predictive equations, or the use of indirect calorimetry. Calories provided via infusion of propofol should be considered when calculating the nutrition regimen. While it is often difficult to provide 100% of goal calories by the enteral route, studies in which a protocol was used to increase delivery of EN have shown that delivering a volume of EN where the level of calories and protein provided is closer to goal improves outcome.[133,134] This recommendation is supported by two level II studies in which those patients who by protocol randomization received a greater volume of EN experienced significantly fewer complications and less infectious morbidity,[23] as well as shorter hospital lengths of stay, and a trend toward lower mortality[135] than those patients receiving lower volume.

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

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

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

Rationale. Early on, EN is directed toward maintaining gut integrity, reducing oxidative stress, and modulating systemic immunity. In patients already receiving some volume of EN, use of supplemental PN over the first 7-10 days adds cost[137,138] and appears to provide no additional benefit.[42,137-140] In 1 small study in burn patients, EN supplemented with PN was associated with a significant increase in mortality (63% vs 26%, $P < .05$) when compared respectively to hypocaloric EN alone.[138] **See Table 7.**[42,137-140]

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

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

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

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

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

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

SD, standard deviation; NR, not reported; ICU, intensive care unit; Hosp, hospital; LOS, length of stay; pt, patient; d, day(s); yr, year(s)
[a] $P \leq .05$.
Adapted from the Canadian Clinical Practice Guidelines.[21]

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

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

D. Monitoring Tolerance and Adequacy of Enteral Nutrition

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

Rationale. Feeding into the GI tract is safe prior to the emergence of overt evidence of enteric function, such as bowel sounds or the passage of flatus and stool. EN promotes gut motility. As long as the patient remains hemodynamically stable, it is safe and appropriate to feed through mild to moderate ileus.[2]

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

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

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

Study	Population	Study Groups by GRVs[a]	% Goal kcal Infused Mean ± SD	Pneumonia	Aspiration Mean ± SD	GI Intolerance Mean ± SD	Other
Taylor et al, 1999[23] Level II	Trauma, head injury (n = 82)				NR	NR	Infection
		150/50 mL[b]	36%	26/41 (63%)			35/41 (85%)
		200 mL	59%[c]	18/41 (44%)			25/41 (61%)[c]
							Complications
		150/50 mL					25/41 (61%)
		200 mL					15/41 (37%)[c]
							Hospital LOS
		150/50 mL					46 d
		200 mL					30 d[c]
Pinilla et al, 2001[146] Level II	ICU (n = 80)				NR		ICU LOS
		150 mL	70% ± 25%	0/36 (0%)		21/36 (58%)	13.2 ± 18.3 d
		250 mL	76% ± 18%	1/44 (2%)		20/44 (45%)	9.5 ± 9.4 d
McClave et al, 2005[151] Level II	ICU (n = 40)	200 mL	77.0% ± 21.2%	NR	21.6% ± 25.6%[d]	35.0% ± 27.3%[e]	
		400 mL	77.8% ± 32.5%		22.6% ± 25.0%	27.8% ± 25.0%	
Montejo et al, 2008[147] Level I	ICU (n = 329)	200 mL	82.8% ± 1.7%[f]	46/169 (27%)	NR	107/169 (64%)	
		500 mL	89.6% ± 1.8%[c]	45/160 (28%)		76/160 (48%)[c]	

SD, standard deviation; NR, not reported; ICU, intensive care unit; LOS, length of stay; GI, gastrointestinal; d, day(s).
[a] Cutoff value of volume above which there is automatic cessation of EN.
[b] EN advanced if GRVs <50 mL, automatic cessation if >150 mL.
[c] $P \leq .05$.
[d] Incidence of aspiration as a percentage of all bedside checks done every 4 hours.
[e] Incidence of regurgitation as a percentage of all bedside checks done every 4 hours.
[f] Percentage goal feeding on day 3 (similar to significant differences on day 7).

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

Gastric residual volumes do not correlate well to incidence of pneumonia,[23,146,147] measures of gastric emptying,[148-150] or to incidence of regurgitation and aspiration.[151] Four level II studies indicate that raising the cutoff value for gastric residual volume (leading to automatic cessation of EN) from a lower number of 50-150 mL to a higher number of 250-500 mL does not increase risk for regurgitation, aspiration, or pneumonia.[23,146,147,151] Decreasing the cutoff value for gastric residual volume does not protect the patient from these complications, often leads to inappropriate cessation, and may adversely affect outcome through reduced volume of EN infused.[23] Gastric residual volumes in the range of 200-500 mL should raise concern and lead to the implementation of measures to reduce risk of aspiration, but automatic cessation of feeding should not occur for gastric residual volumes <500 mL in the absence of other signs of intolerance.[152] **See Table 8.**[23,146,147,151]

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

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

D4. Patients placed on EN should be assessed for risk of aspiration. (Grade: E) Steps to reduce risk of aspiration should be employed. (Grade: E)
The following measures have been shown to reduce risk of aspiration:

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

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

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

SD, standard deviation; NR, not reported; ICU, intensive care unit; LOS, length of stay; Hosp, hospital; Semi-rec, semi-reclined.
[a] $P \leq .05$.
Adapted from the Canadian Clinical Practice Guidelines.[21]

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

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

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

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

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

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

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

The potential harm from aggressive bolus infusion of EN leading to increased risk of aspiration pneumonia was shown in 1 study.[160] Level II studies comparing bolus to continuous infusion have shown greater volume with fewer interruptions in delivery of EN with continuous feeding but no significant difference between techniques with regard to patient outcome.[161,162] **See Table 10.**[161-165]

Adding prokinetic agents such as erythromycin or metoclopramide has been shown to improve gastric emptying and tolerance of EN but has resulted in little change in clinical outcome for ICU patients.[166] **See Table 11.**[167-169] Use of naloxone infused through the feeding tube (to reverse the effects of opioid narcotics at the level of the gut in order to improve intestinal motility) was shown in one level II study to significantly increase the volume of EN infused, reduce gastric residual volumes, and decrease the incidence of ventilator-associated pneumonia (compared to placebo).[169]

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

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

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

SD, standard deviation; NR, not reported; ICU, intensive care unit; Neuro, neurologic; d, day(s).
[a] $P \leq .05$.
[b] Aspiration.
[c] Intermittent feeding.

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

Study	Population	Study Groups	ICU Mortality	Pneumonia	Nutrition Outcomes
Yavagal et al, 2000[167] Level I	ICU (n = 305)	Metoclopramide 10 mg NG	73/ 131 (56%)	22/131 (17%)	NR
		Placebo	92/174 (53%)	24/174 (14%)	
Berne et al, 2002[168] Level II	Trauma (n = 48)				EN tolerated at 48 h
		Erythromycin 250 mg IV q 6 h	2/32 (6%)	13/32 (40%)	58%
		Placebo	2/36 (6%)	18/36 (50%)	44%
					EN tolerated during study
		Erythromycin 250 mg IV q 6 h			65%
		Placebo			59%
Meissner et al, 2003[169] Level II	ICU (n = 84)				Mean GRV
		Naloxone 8 mg q 6 h NG	6/38 (16%)	13/38 (34%)[a]	54 mL
		Placebo	7/43 (16%)	24/43 (56%)	129 mL
					Volume EN delivered was higher after day 3 in Naloxone group compared to controls (trend)

NR, not reported; ICU, intensive care unit; GRV, gastric residual volume; IV, intravenous; NG, nasogastric; EN, enteral nutrition; h, hour(s).
[a] $P \leq .05$.
Adapted from the Canadian Clinical Practice Guidelines.[21]

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

Rationale. Traditional monitors for aspiration are ineffective. Blue food coloring, an insensitive marker for aspiration, was shown to be associated with mitochondrial toxicity and patient death.[175] The United States Food and Drug Administration through a Health Advisory Bulletin (September 2003) issued a mandate against the use of blue food coloring as a monitor for aspiration in patients on EN.[176] The basic premise for use of glucose oxidase (that glucose content in tracheal secretions is solely related to aspiration of glucose-containing formulation)

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

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

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

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

E. Selection of Appropriate Enteral Formulation

E1. Immune-modulating enteral formulations (supplemented with agents such as arginine, glutamine, nucleic acid, ω-3 fatty acids, and antioxidants) should be used for the appropriate patient population (major elective surgery, trauma, burns, head and neck cancer, and critically ill patients on mechanical ventilation), with caution in patients with severe sepsis.
(For surgical ICU patients, Grade: A)
(For medical ICU patients, Grade: B)
ICU patients not meeting criteria for immune-modulating formulations should receive standard enteral formulations. (Grade: B)

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

A large body of data suggest that adding pharmaconutrients to enteral formulations provides even further benefits on patient outcome than use of standard formulations alone.[181-183] **See Table 12.**[184-204] Studies from basic science have provided a rationale for the mechanism of the beneficial effects seen clinically. Such findings include the discovery of specialized immune (myeloid suppressor) cells, whose role is to regulate the availability of arginine, necessary for normal T lymphocyte function. These myeloid suppressor cells are capable of causing states of severe arginine deficiency which impact production of nitric oxide and negatively affect microcirculation. Immune-modulating diets containing arginine and ω-3 fatty acids appear to overcome the regulatory effect of myeloid suppressor cells.[205] Agents such as RNA nucleotides increase total lymphocyte count, lymphocyte proliferation, and thymus function. In a dynamic fashion, the ω-3 fatty acids eicosapentaenoic acid (EPA) and docosohexaenoic acid (DHA) displace ω-6 fatty acids from the cell membranes of immune cells. This effect reduces systemic inflammation through the production of alternative biologically less active prostaglandins and leukotrienes. EPA and DHA (fish oils) have also been shown to down-regulate expression of nuclear factor-kappa B (NFκB), intracellular adhesion molecule 1 (ICAM-1), and E-selectin, which in effect decreases neutrophil attachment and transepithelial migration to modulate systemic and local inflammation. In addition, EPA and DHA help to stabilize the myocardium and lower the incidence of cardiac arrhythmias, decrease incidence of acute respiratory distress syndrome (ARDS), and reduce the likelihood of sepsis.[206-209] Glutamine, considered a conditionally essential amino acid, exerts a myriad of beneficial effects on antioxidant defenses, immune function, production of heat shock proteins, and nitrogen retention. Addition of agents such as selenium, ascorbic acid (vitamin C), and vitamin E provides further antioxidant protection.

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

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

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

Study	Population	Study Groups	Mortality	Infections[a]	LOS Days, Mean ± SD (or Range)	Ventilator Days, Mean ± SD (or Range)
Cerra et al, 1990[184]	Surgical ICU	Impact[b]	1/11 (9%) ICU	NR	36.7 ± 8.5 Hosp[c]	NR
Level II	(n = 20)	Osmolite HN	1/9 (11%) ICU		54.7 ± 10.5 Hosp	
Gottschlich et al, 1990[185]	Critically ill burns	Shriners burn formula[d]	2/17 (12%) ICU	NR	NR	9 ± 4.5
Level II	(n = 31)	Osmolite HN + protein	1/14 (7%) ICU			10 ± 2.5
Brown et al, 1994[186]	Trauma (n = 37)	Experimental formula[d]	0/19 (0%) ICU	3/19 (16%)[c]	NR	NR
Level II		Osmolite HN + protein	0/18 (0%) ICU	10/18 (56%)		
Moore et al, 1994[187]	Trauma (n = 98)	Immun-Aid[b]	1/51 (2%) ICU	9/51 (18%)	14.6 ± 1.3 Hosp[c]	1.9 ± 0.9[c]
Level II		Vivonex TEN	2/47 (4%) ICU	10/47 (21%)	17.2 ± 2.8 Hosp	5.3 ± 3.1
		Immun-Aid[b]			5.3 ± 0.8 ICU[c]	
		Vivonex TEN			8.6 ± 3.1 ICU	
Bower et al, 1995[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	
Kudsk et al, 1996[189]	Trauma (n = 35)	Immun-Aid[b]	1/17 (6%) ICU	5/16 (31%)	18.3 ± 2.8 Hosp[c]	2.4 ± 1.3[c]
Level II		Stand EN	1/18 (6%) ICU	11/17 (65%)	32.6 ± 7.0 Hosp	5.4 ± 2.0
		Immun-Aid[b]			5.8 ± 1.8 ICU[c]	
		Stand EN			9.5 ± 2.3 ICU	
Engel et al, 1997[190]	Trauma (n = 36)	Impact[b]	7/18 (39%) ICU	6/18 (33%)	19.0 ± 7.4 ICU	14.8 ± 5.6
Level II		Stand EN	5/18 (28%) ICU	5/18 (28%)	20.5 ± 5.3 ICU	16.0 ± 5.6
Mendez et al, 1997[191]	Trauma (n = 43)	Experimental formula[d]	1/22 (5%) ICU	19/22 (86%)[c]	34.0 ± 21.2 Hosp[c]	16.5 ± 19.4
Level II		Osmolite HN + protein	1/21 (5%) ICU	12/21 (57%)	21.9 ± 11.0 Hosp	9.3 ± 6.0
		Experimental formula[d]			18.9 ± 20.7 ICU	
		Osmolite HN + protein			11.1 ± 6.7 ICU	
Rodrigo et al, 1997[192]	Mixed ICU	Impact[d]	2/16 (13%) ICU	5/16 (31%)	8.0 ± 7.3 ICU	NR
Level II	(n = 30)	Stand EN	1/14 (7%) ICU	3/14 (21%)	10.0 ± 2.7 ICU	
Saffle et al, 1997[193]	Burns (n = 50)	Impact[d]	5/25 (20%) ICU	2.36 per patient	37 ± 4 Hosp	22 ± 3
Level II		Replete	3/24 (13%) ICU	1.71 per patient	38 ± 4 Hosp	21 ± 2
Weimann et al, 1998[194]	Trauma (n = 29)	Impact[d]	2/16 (13%) ICU	NR	70.2 ± 53 Hosp	21.4 ± 10.8
Level II		Stand EN	4/13 (31%) ICU		58.1 ± 30 Hosp	27.8 ± 14.6
		Impact[d]			31.4 ± 23.1 ICU	
		Stand EN			47.4 ± 32.8 ICU	
Atkinson et al, 1998[195]	Mixed ICU	Impact[d]	95/197 (48%) ICU		10.5 ± 13.1 ICU	8.0 ± 11.1
Level I	(n = 390)	Stand EN	85/193 (44%) ICU		12.2 ± 23.2 ICU	9.4 ± 17.7
		Impact[d]			20.6 ± 26 Hosp	
		Stand EN			23.2 ± 32 Hosp	
Galban et al, 2000[196]	Critically ill	Impact[d]	17/89 (19%) ICU[c]	39/89 (44%)	18.2 ± 12.6 ICU 16.6 ± 12.9	12.4 ± 10.4
Level I	septic (n = 176)	Stand EN	28/87 (32%) ICU	44/87 (51%)	ICU	12.2 ± 10.3
Caparros et al, 2001[197]	ICU patients	Experimental formula[b]	27/130 (21%) ICU	64/130 (49%)[c]	15 (10-25) ICU	10 (5-18)
Level I	(n = 235)	Stand EN	30/105 (29%) ICU	37/105 (35%)	13 (9-20) ICU	9 (5-14)
		Experimental formula[b]			29 (17-51) Hosp	
		Stand EN			26 (18-42) Hosp	

(continued)

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Table 12. (continued)

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

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

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

[b] Non-isonitrogenous.

[c] $P \leq .05$.

[d] Isonitrogenous.

[e] Non-isocaloric.

[f] Isocaloric but non-isonitrogenous.

[g] Non-isocaloric and non-isonitrogenous.

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

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

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

septic.[213,214] Based on one level I report,[188] one prospective randomized unblinded study using a control group receiving PN,[200] and a third study published in abstract form only,[199] use of arginine-containing formulations resulted in greater mortality than standard EN and PN formulations. Two of the 3 studies reporting a potential adverse effect had comparatively lower levels of arginine supplementation.[199,200] The mechanism proposed for this adverse effect was that in severe sepsis, arginine may be converted to nitric oxide contributing to hemodynamic instability. This concept is contradicted by 4 other reports. One of these studies showed that infusion of arginine directly into the venous circulation of septic medical and surgical ICU patients caused no hemodynamic stability.[215] Three other studies showed that clinical outcome was better[195,197] and mortality was *reduced* in moderately septic ICU patients[196] with use of an arginine-containing formulation (compared to a standard enteral formulation). Upon review of this controversy, the Guidelines Committee felt that immune-modulating formulations containing arginine were safe enough to use in mild to moderate sepsis, but that caution should be employed if utilized in patients with severe sepsis.

Unfortunately, few studies have addressed the individual pharmaconutrients, their specific effects, or their proper dosing. This body of literature has been criticized for the heterogeneity of studies, performed in a wide range of ICU patient populations, with a variety of experimental and commercial formulations. Multiple enteral formulations are marketed as being immune-modulating, but vary considerably in their makeup and dosage of individual components. It is not clear whether the data from published studies and these subsequent recommendations can be extrapolated to use of formulations that have not been formally evaluated. Based on the strength and uniformity of the data in surgery patients, the Guidelines Committee felt that a grade A recommendation was warranted for use of these formulations in the surgical ICU. The reduced signal strength and heterogeneity of the data in nonoperative critically ill patients in a medical ICU was felt to warrant a grade B recommendation.

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

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

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

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

Study	Population	Study Groups	Mortality	LOS Days, Mean ± SD	Ventilator Days, Mean ± SD	New Organ Dysfunction
Gadek et al, 1999[207] Level I	ARDS ICU (n = 146)	Oxepa	11/70 (16%) ICU	11.0 ± 0.9 ICU[a]	9.6 ± 0.9[a]	7/70 (10%)[a]
		Stand EN	19/76 (25%) ICU	14.8 ± 1.3 ICU	13.2 ± 1.4	19/76 (25%)
		Oxepa		27.9 ± 2.1 Hosp		
		Stand EN		31.1 ± 2.4 Hosp		
Singer et al, 2006[208] Level I	ARDS and ALI (n = 100)	Oxepa	14/46 (30%) at 28 d[a]	13.5 ± 11.8 ICU	12.1 ± 11.3	NR
		Stand EN	26/49 (53%) at 28 d	15.6 ± 11.8 ICU	14.7 ± 12.0	
Pontes-Arruda et al, 2006[209] Level I	Severe sepsis ICU (n = 165)	Oxepa	26/83 (31%) at 28 d[a]	17.2 ± 4.9 ICU[a]	14.6 ± 4.3[a]	32/83 (39%)[a]
		Stand EN	38/82 (46%) at 28 d	23.4 ± 3.5 ICU	22.2 ± 5.1	66/82 (80%)

SD, standard deviation; NR, not reported; ICU, intensive care unit; LOS, length of stay; d, day(s).
[a] $P \leq .05$.
Oxepa: Abbott Nutrition; Columbus, OH.

oil (γ-linolenic acid [GLA]), and antioxidants was shown to significantly reduce length of stay in the ICU, duration of mechanical ventilation, organ failure, and mortality compared to use of a standard enteral formulation.[207-209] Controversy remains as to the optimal dosage, makeup of fatty acids, and ratio of individual immune-modulating nutrients which comprise these formulations. **See Table 14.**[207-209]

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

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

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

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

F. Adjunctive Therapy

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

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

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

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

SD, standard deviation; NR, not reported; ICU, intensive care unit; Hosp, hospital; LOS, length of stay.
[a] $P \leq .05$.
Adapted from the Canadian Clinical Practice Guidelines.[21]

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

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

Rationale. Antioxidant vitamins (including vitamins E and ascorbic acid) and trace minerals (including selenium, zinc, and copper) may improve patient outcome, especially in burns, trauma, and critical illness requiring mechanical ventilation.[230,231] A meta-analysis aggregating data from studies evaluating various combinations of antioxidant vitamins and trace elements showed a significant reduction in mortality with their use (RR = 0.65; 95% CI 0.44-0.97; P =.03).[232] Parenteral selenium, the single antioxidant most likely to improve outcome,[233,234] has shown a trend toward reducing mortality in patients with sepsis or septic shock (RR = 0.59; 95% CI 0.32-1.08; P = .08).[232] Additional studies to delineate compatibility, optimal dosage, route, and optimal combination of antioxidants are needed. Renal function should be considered when supplementing vitamins and trace elements.

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

Rationale. **See Table 15.**[235-241] The addition of enteral glutamine to an EN regimen (non-glutamine supplemented) has been shown to reduce hospital and ICU length of stay in burn and mixed ICU patients,[235,237] and mortality in burn patients alone[237] compared to the same EN regimen without glutamine.

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

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

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

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

G. When Indicated, Maximize Efficacy of Parenteral Nutrition

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

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

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

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

G2. In all ICU patients receiving PN, mild permissive underfeeding should be considered at least initially. Once energy requirements are determined, 80% of these requirements should serve as the ultimate goal or dose of parenteral feeding. (Grade: C) Eventually, as the patient stabilizes, PN may be increased to meet energy requirements. (Grade: E) For obese patients (BMI ≥ 30), the dose of PN with regard to protein and caloric provision should follow the same recommendations given for EN in guideline C5. (Grade: D)

Rationale. "Permissive underfeeding" in which the total caloric provision is determined by 80% of energy requirements (calculated from simplistic equations such as 25 kcal/kg actual body weight per day, published predictive equations, or as measured by indirect calorimetry) will optimize efficacy of PN. This strategy avoids the potential for insulin resistance, greater infectious morbidity, or prolonged duration of mechanical ventilation and increased hospital length of stay associated with excessive energy intake. In 2 studies, lower dose hypocaloric PN was shown to reduce the incidence of hyperglycemia[247] and infections, ICU and hospital length of stay, and duration of mechanical ventilation compared to higher eucaloric doses of PN.[248] **See Table 16.**[247-250]

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

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

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

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

Study	Population	Study Groups	Mortality	Infections[a]	LOS Days, Mean ± SD (or Range)	Ventilator Days, Mean ± SD (or range)	Hyperglycemia
Battistella et al, 1997[248] Level II	Trauma (n = 57)			Pneumonia			NR
		Hypocal	2/27 (7%) ICU	13/27 (48%)[b]	18 ± 12 ICU[b]	15 ± 12[b]	
		Eucal	0/30 (0%) ICU	22/30 (73%)	29 ± 22 ICU	27 ± 21	
				Bloodstream			
		Hypocal		5/27 (19%)[b]	27 ± 16 Hosp[b]		
		Eucal		13/30 (43%)	39 ± 24 Hosp		
Choban et al, 1997[249] Level II	ICU (n = 13)	Hypocal	0/6 (0%) Hosp	NR	48 ± 30 Hosp	NR	NR
		Eucal	2/7 (29%) Hosp		45 ± 38 Hosp		
McCowen et al, 2000[250] Level II	ICU (n = 48)	Hypocal	2/21 (10%) ICU	6/21 (29%)	19 ± 14 Hosp	NR	4/21 (19%)
		Eucal	3/19 (16%) ICU	10/19 (53%)	17 ± 15 Hosp		5/19 (26%)
Ahrens et al, 2005[247] Level II	SICU (n = 40)	Hypocal	1/20 (5%) ICU	5/20 (25%)	14 (10-21) ICU	10 (4-15)	5/20 (25 %)[b]
		Eucal	3/20 (15%) ICU	2/20 (10%)	14 (10-37) ICU	19 (4-35)	14/20 (70%)
		Hypocal			15 (11-26) Hosp		
		Eucal			25 (15-39) Hosp		

SD, standard deviation; NR, not reported; ICU, intensive care unit; SICU, surgical ICU; Hosp, hospital; LOS, length of stay.
[a] All infections represent number of patients per group with infection unless otherwise stated.
[b] $P \leq .05$.
Adapted from the Canadian Clinical Practice Guidelines.[21]

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

Study	Population	Study Groups	ICU Mortality	Infections[a]	LOS Days, Mean ± SD	Ventilator Days, Mean ± SD
Battistella et al, 1997[248] Level II	Trauma (n = 57)			Pneumonia		
		Without	2/27 (7%)	13/27 (48%)[b]	27 ± 16 Hosp[b]	15 ± 12[b]
		With	0/30 (0%)	22/30 (73%)	39 ± 24 Hosp	27 ± 21
				Line sepsis		
				5/27 (19%)[b]	18 ± 12 ICU[b]	
				13/30 (43%)	29 ± 22 ICU	
McCowen et al, 2000[250] Level II	ICU (n = 48)	Without	2/21 (10%)	6/21 (29%)	19 ± 14 Hosp	NR
		With	3/19 (16%)	10/19 (53%)	17 ± 15 Hosp	

SD, standard deviation; NR, not reported; ICU, intensive care unit; LOS, length of stay.
[a] All infections represent number of patients per group with infection unless otherwise stated.
[b] $P \leq .05$.
Adapted from the Canadian Clinical Practice Guidelines.[21]

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

Rationale. Strict glucose control, keeping serum glucose levels between 80 and 110 mg/dL, has been shown in a large single center trial to be associated with reduced sepsis, reduced ICU length of stay, and lower hospital mortality when compared to conventional insulin therapy (keeping blood glucose levels <200 mg/dL).[253] The effect was more pronounced in surgical ICU than medical ICU patients.[254] **See Table 18.**[253-255]

However, an as yet unpublished large level I 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 to tighter control.[255] With a paucity of data, the Guidelines Committee felt that attempting to control

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

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

ICU, intensive care unit; NR, not reported; Hosp, hospital; d, day(s).
[a] Intensive control: 80-110 mg/dL.
[b] $P < .05$.
[c] Conventional control: 180-200 mg/dL.
[d] Moderate control: 140-180 mg/dL.

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

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

Rationale. The addition of parenteral glutamine (at a dose of 0.5 g/kg/d) to a PN regimen has been shown to reduce infectious complications,[121,256] ICU length of stay,[257] and mortality[258] in critically ill patients, compared to the same PN regimen without glutamine. A meta-analysis by Heyland et al combining results from 9 studies confirmed a trend toward reduced infection (RR = 0.75; 96% CI 0.54-1.04; $P = .08$) and a significant reduction in mortality (RR = 0.67; 95% CI 0.48-0.92; $P = .01$) in groups receiving PN with parenteral glutamine versus those groups getting PN alone.[21] **See Table 19.**[121,256-264]

The proposed mechanism of this benefit relates to generation of a systemic antioxidant effect, maintenance of gut integrity, induction of heat shock proteins, and use as a fuel source for rapidly replicating cells. Of note, the dipeptide form of parenteral glutamine upon which most of these data are based is widely used in Europe but not commercially available in North America (referring both to the United States and Canada). Use of L-glutamine, the only source of parenteral glutamine available in North America, is severely limited by problems with stability and solubility (100 mL water per 2 g glutamine).[256,264-267] All 3 reports which showed a positive clinical effect were level II studies,[121,256,258] warranting a grade C recommendation.

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

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

H. Pulmonary Failure

H1. Specialty high-lipid low-carbohydrate formulations designed to manipulate the respiratory quotient and reduce CO_2 production are not recommended for

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

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

SD, standard deviation; NR, not reported; ICU, intensive care unit; SICU, surgical ICU; Hosp, hospital; LOS, length of stay.
[a] All infections represent number of patients per group with infection unless otherwise stated.
[b] $P \leq .05$.
[c] Pneumonia.
Adapted from the Canadian Clinical Practice Guidelines.[21]

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

Rationale. There is a lack of consensus about the optimum source and composition of lipids (medium- vs long-chain triglyceride, soybean oil, olive oil, ω-3 fatty acids, 10% or 20% solution) in enteral and parenteral formulations for the patient with respiratory failure. One small level II study (20 patients) showed a clinical benefit (reduced duration of mechanical ventilation) from use of a high-fat low-carbohydrate enteral formulation compared to a standard formulation.[268] A second smaller level II study (10 patients) showed no clinical benefit.[269] Results from uncontrolled studies suggest that increasing the composite ratio of fat to carbohydrate becomes clinically significant in lowering CO_2 production only in the ICU patient being overfed and that composition is much less likely to affect CO_2 production when the design of the nutrition support regimen approximates caloric requirements.[270] Efforts should be made to avoid total caloric provision that exceeds energy requirements, as 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]

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

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

I. Renal Failure

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

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

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

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

J. Hepatic Failure

J1. Traditional assessment tools should be used with caution in patients with cirrhosis and hepatic failure, as these tools are less accurate and less reliable due to complications of ascites, intravascular volume depletion, edema, portal hypertension, and hypoalbuminemia. (Grade: E)

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

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

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

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

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

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

K. Acute Pancreatitis

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

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

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

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

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

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

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

Rationale. Two level II prospective randomized trials comparing gastric with jejunal feeding in patients with severe acute pancreatitis showed no significant differences between the 2 levels of EN infusion within the GI tract.[299,300] The success of gastric feeding in these 2 studies (where only 2 patients in the Eatock et al group[299] and 1 patient in the Kumar et al 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)**

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

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

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

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

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

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

Rationale. For patients with severe acute pancreatitis, when EN is not feasible, timing of initiation of PN (and the choice between PN and STD therapy) becomes an important issue. In an early level II randomized trial, Sax et al showed net harm from use of PN initiated within 24 hours of admission for patients with mild to moderate acute pancreatitis, with significantly longer hospital length of stay than those patients randomized to STD therapy (no nutrition support therapy).[97] In contrast, in a later level II study by Xian-Li et al in patients with severe pancreatitis whereby PN was initiated 24-48 hours after "full liquid resuscitation," significant reductions in overall complications, hospital length of stay, and mortality were seen when compared to STD therapy.[121] The design of this latter study may have led to a differential delay of several days in the initiation of PN, possibly after the peak of the inflammatory response.[17] The grade of the first recommendation (to consider use of PN) is based on the results of the level II study by Xian-Li et al,[121] whereas the grade for the second recommendation (regarding the timing of PN) is based on expert opinion and interpretation of the discrepancy between these 2 reports.[97,121]

L. Nutrition Therapy in End-of-Life Situations

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

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

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References

1. Dellinger RP, Carlet JM, Masur H, et al; Surviving Sepsis Campaign Management Guidelines Committee. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med.* 2004;32:858-873.
2. Martindale RG, Maerz LL. Management of perioperative nutrition support. *Curr Opin Crit Care.* 2006;12:290-294.
3. Raguso CA, Dupertuis YM, Pichard C. The role of visceral proteins in the nutritional assessment of intensive care unit patients. *Curr Opin Clin Nutr Metab Care*. 2003;6:211-216.
4. Kudsk KA. Current aspects of mucosal immunology and its influence by nutrition. *Am J Surg*. 2002;183:390-398.
5. Jabbar A, Chang WK, Dryden GW, McClave SA. Gut immunology and the differential response to feeding and starvation. *Nutr Clin Pract*. 2003;18:461-482.
6. Kang W, Kudsk KA. Is there evidence that the gut contributes to mucosal immunity in humans? *JPEN J Parenter Enteral Nutr*. 2007;31:246-258.
7. Kang W, Gomez FE, Lan J, Sano Y, Ueno C, Kudsk KA. Parenteral nutrition impairs gut-associated lymphoid tissue and mucosal immunity by reducing lymphotoxin beta receptor expression. *Ann Surg*. 2006;244:392-399.
8. Windsor AC, Kanwar S, Li AG, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut*. 1998;42:431-435.
9. Ammori BJ, Leeder PC, King RF, et al. Early increase in intestinal permeability in patients with severe acute pancreatitis: correlation with endotoxemia, organ failure, and mortality. *J Gastrointest Surg*. 1999;3:252-262.
10. Lewis SJ, Egger M, Sylvester PA, et al. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled studies. *Br Med J*. 2001;323:1-5.
11. Schroeder D, Gillanders L, Mahr K, Hill GL. Effects of immediate postoperative enteral nutrition on body composition, muscle function, and wound healing. *JPEN J Parenter Enteral Nutr*. 1991;15:376-383.
12. Sagar S, Harland P, Shields R. Early postoperative feeding with elemental diet. *Br Med J*. 1979;1:293-295.
13. Carr CS, Ling KD, Boulos P, Singer M. Randomised trial of safety and efficacy of immediate postoperative enteral feeding in patients undergoing gastrointestinal resection. *BMJ*. 1996;12:869-871.
14. Beier-Holgersen R, Boesby S. Influence of postoperative enteral nutrition on postsurgical infections. *Gut*. 1996;39:833-835.
15. Heslin MJ, Latkany L, Leung D, et al. A prospective, randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. *Ann Surg*. 1997;226:567-577.
16. Watters JM, Kirkpatrick SM, Norris SB, Shamji FM, Wells GA. Immediate postoperative enteral feeding results in impaired respiratory mechanics and decreased mobility. *Ann Surg*. 1997;226:369-377.
17. McClave SA, Chang WK, Dhaliwal R, Heyland DK. Nutrition support in acute pancreatitis: a systematic review of the literature. *JPEN J Parenter Enteral Nutr*. 2006;30:143-156.
18. Pupelis G, Austrums E, Jansone A, Sprucs R, Wehbi H. Randomised trial of safety and efficacy of postoperative enteral feeding in patients with severe pancreatitis: preliminary report. *Eur J Surg*. 2000;166:383-387.
19. Pupelis G, Selga G, Austrums E, Kaminski A. Jejunal feeding, even when instituted late, improves outcomes in patients with severe pancreatitis and peritonitis. *Nutrition*. 2001;17:91-94.
20. Kudsk KA, Croce MA, Fabian TC, et al. Enteral versus parenteral feeding: effects on septic morbidity after blunt and penetrating abdominal trauma. *Ann Surg*. 1992;215:503-513.
21. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P; Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr*. 2003;27:355-373.
22. Kalfarentzos F, Kehagias J, Mead N, Kokkinis K, Gogos CA. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. *Br J Surg*. 1997;84:1665-1669.
23. Taylor SJ, Fettes SB, Jewkes C, Nelson RJ. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. *Crit Care Med.* 1999;27:2525-2531.
24. Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: a meta-analysis. *Am J Clin Nutr*. 2001;74:534-542.
25. Simpson F, Doig GS. Parenteral vs. enteral nutrition in the critically ill patient: a meta-analysis of trials using the intention to treat principle. *Intensive Care Med*. 2005;31:12-23.
26. Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. *Nutrition*. 2004;20:843-848.

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27. Moore FA, Feliciano DV, Andrassy RJ, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. *Ann Surg.* 1992;216:172-183.
28. Peter JV, Moran JL, Phillips-Hughes J. A metaanalysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients. *Crit Care Med.* 2005;33:213-220.
29. Rapp RP, Young DB, Twyman D. The favorable effect of early parenteral feeding on survival in head-injured patients. *J Neurosurg.* 1983;58:906-912.
30. Adams S, Dellinger EP, Wertz MJ. Enteral versus parenteral nutritional support following laparotomy for trauma: a randomized prospective trial. *J Trauma*. 1986;26:882-891.
31. Bower RH, Talamini MA, Sax HC. Postoperative enteral vs parenteral nutrition: a randomized controlled trial. *Arch Surg.* 1986;121:1040-1045.
32. Szeluga DJ, Stuart RK, Brookmeyer R, Utermohlen V, Santos GW. Nutritional support of bone marrow transplant recipients: a prospective, randomized clinical trial comparing total parenteral nutrition to an enteral feeding program. *Cancer Res.* 1987;47: 3309-3316.
33. Young B, Ott L, Haack D. Effect of total parenteral nutrition upon intracranial pressure in severe head injury. *J Neurosurg.* 1987;67: 76-80.
34. Peterson VM, Moore EE, Jones TN, et al. Total enteral nutrition versus total parenteral nutrition after major torso injury: attenuation of hepatic protein reprioritization. *Surgery*. 1988;104:199-207.
35. Cerra FB, McPherson JP, Konstantinides FN, Konstantinides NN, Teasley KM. Enteral nutrition does not prevent multiple organ failure syndrome (MOFS) after sepsis. *Surgery.* 1988;104:727-733.
36. Greenberg GR, Fleming CR, Jeejeebhoy KN, Rosenberg IH, Sales D, Tremaine WJ. Controlled trial of bowel rest and nutritional support in the management of Crohn's disease. *Gut*. 1988;29:1309-1315.
37. Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN versus TPN following major abdominal trauma: reduced septic morbidity. *J Trauma*. 1989;29:916-923.
38. Hamaoui E, Lefkowitz R, Olender L, et al. Enteral nutrition in the early postoperative period: a new semi-elemental formula versus total parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 1990; 14:501-507.
39. González-Huix F, Fernández-Bañares F, Esteve-Comas M, et al. Enteral versus parenteral nutrition as adjunct therapy in acute ulcerative colitis. *Am J Gastroenterol.* 1993;88:227-232.
40. Iovinelli G, Marsili I, Varrassi G. Nutrition support after total laryngectomy. *JPEN J Parenter Enteral Nutr*. 1993;17:445-448.
41. Kudsk KA, Minard G, Wojtysiak SL, Croce M, Fabian T, Brown RO. Visceral protein response to enteral versus parenteral nutrition and sepsis in patients with trauma. *Surgery*. 1994;116:516-523.
42. Dunham CM, Frankenfield D, Belzberg H, Wiles C, Cushing B, Grant Z. Gut failure-predictor of or contributor to mortality in mechanically ventilated blunt trauma patients? *J Trauma* 1994;37: 30-34.
43. Borzotta AP, Pennings J, Papasadero B, et al. Enteral versus parenteral nutrition after severe closed head injury. *J Trauma* 1994;37: 459-468.
44. Hadfield RJ, Sinclair DG, Houldsworth PE, Evans TW. Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. *Am J Respir Crit Care Med*. 1995;152:1545-1548.
45. Baigrie RJ, Devitt PG, Watkin DS. Enteral versus parenteral nutrition after oesophagogastric surgery: a prospective randomized comparison. *Aust N Z J Surg.* 1996;66:668-670.
46. McClave SA, Greene LM, Snider HL, et al. Comparison of the safety of early enteral vs parenteral nutrition in mild acute pancreatitis. *JPEN J Parenter Enteral Nutr*. 1997;21:14-20.
47. Reynolds JV, Kanwar S, Welsh FK, et al. Does the route of feeding modify gut barrier function and clinical outcome in patients after major upper gastrointestinal surgery? *JPEN J Parenter Enteral Nutr*. 1997;21:196-201.
48. Sand J, Luostarinen M, Matikainen M. Enteral or parenteral feeding after total gastrectomy: prospective randomised pilot study. *Eur J Surg*. 1997;163:761-766.
49. Gianotti L, Braga M, Vignali A, et al. Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasms. *Arch Surg.* 1997;132:1222-1230.
50. Woodcock NP, Zeigler D, Palmer MD, Buckley P, Mitchell CJ, Macfie J. Enteral versus parenteral nutrition: a pragmatic study. *Nutrition.* 2001;17:1-12.
51. Braga M, Gianotti L, Gentilini O, Parisi V, Salis C, Di C. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition. *Crit Care Med.* 2001;29:242-248.
52. Pacelli F, Bossola M, Papa V, et al. Enteral vs parenteral nutrition after major abdominal surgery: an even match. *Arch Surg.* 2001; 136:933-936.
53. Bozzetti F, Braga M, Gianotti L, Gavazzi C, Mariani L. Postoperative enteral versus parenteral nutrition in malnourished patients with gastrointestinal cancer: a randomised multicentre trial. *Lancet.* 2001;358:1487-1492.
54. Oláh A, Pardavi G, Belágyi T, Nagy A, Issekutz A, Mohamed GE. Early nasojejunal feeding in acute pancreatitis is associated with a lower complication rate. *Nutrition*. 2002;18:259-262.
55. Abou-Assi S, Craig K, O'Keefe SJ. Hypocaloric jejunal feeding is better than total parenteral nutrition in acute pancreatitis: results of a randomized comparative study. *Am J Gastroenterol.* 2002;97: 2255-2262.
56. Gupta R, Patel K, Calder PC, Yaqoob P, Primrose JN, Johnson CD. A randomised clinical trial to assess the effect of total enteral and total parenteral nutritional support on metabolic, inflammatory and oxidative markers in patients with predicted severe acute pancreatitis (APACHE II ≥ 6). *Pancreatology.* 2003;3:406-413.
57. Louie BE, Noseworthy T, Hailey D, Gramlich LM, Jacobs P, Warnock GL. Enteral or parenteral nutrition for severe pancreatitis: a randomized controlled trial and health technology assessment. *Can J Surg.* 2005;48:298-306.
58. Petrov MS, Kukosh MV, Emelyanov NV. A randomized controlled trial of enteral versus parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. *Dig Surg.* 2006;23:336-344.
59. Eckerwall GE, Axelsson JB, Andersson RG. Early nasogastric feeding in predicted severe acute pancreatitis: a clinical, randomized study. *Ann Surg.* 2006;244:959-967.
60. Casas M, Mora J, Fort E, et al. Total enteral nutrition vs. total parenteral nutrition in patients with severe acute pancreatitis. *Rev Esp Enferm Dig*. 2007;99:264-269.
61. Shirabe K, Matsumata T, Shimada M, et al. A comparison of parenteral hyperalimentation and early enteral feeding regarding systemic immunity after major hepatic resection: the results of a randomized prospective study. *Hepatogastroenterology.* 1997;44:205-209.
62. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med.* 2001;29:2264-2270.
63. Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma: a prospective, randomized study. *J Trauma*. 1986;26:874-881.
64. Chiarelli A, Enzi G, Casadei A, Baggio B, Valerio A, Mazzoleni F. Very early nutrition supplementation in burned patients. *Am J Clin Nutr*. 1990;51:1035-1039.
65. Eyer SD, Micon LT, Konstantinides FN, et al. Early enteral feeding does not attenuate metabolic response after blunt trauma. *J Trauma*. 1993;34:639-643.
66. Chuntrasakul C, Siltharm S, Chinswangwatanakul V, Pongprasobchai T, Chockvivatanavanit S, Bunnak A. Early nutritional support in severe traumatic patients. *J Med Assoc Thai.* 1996;79:21-26.

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67. Singh G, Ram RP, Khanna SK. Early post-operative enteral feeding in patients with nontraumatic intestinal perforation and peritonitis. *J Am Coll Surg.* 1998;187:142-146.
68. Minard G, Kudsk KA, Melton S, Patton JH, Tolley EA. Early versus delayed feeding with an immune-enhancing diet in patients with severe head injuries. *JPEN J Parenter Enteral Nutr.* 2000; 24:145-149.
69. Kompan L, Vidmar G, Spindler-Vesel A, Pecar J. Is early enteral nutrition a risk factor for gastric intolerance and pneumonia? *Clin Nutr*. 2004;23:527-532.
70. Malhotra A, Mathur AK, Gupta S. Early enteral nutrition after surgical treatment of gut perforations: a prospective randomised study. *J Postgrad Med.* 2004;50:102-106.
71. Peck MD, Kessler M, Cairns BA, Chang YH, Ivanova A, Schooler W. Early enteral nutrition does not decrease hypermetabolism associated with burn injury. *J Trauma*. 2004;57:1143-1149.
72. Dvorak MF, Noonan VK, Belanger L, et al. Early versus late enteral feeding in patients with acute cervical spinal cord injury: a pilot study. *Spine*. 2004;29:E175-E180.
73. McClave SA, Chang WK. Feeding the hypotensive patient: does enteral feeding precipitate or protect against ischemic bowel? *Nutr Clin Pract*. 2003;18:279-284.
74. Melis M, Fichera A, Ferguson MK. Bowel necrosis associated with early jejunal tube feeding: a complication of postoperative enteral nutrition. *Arch Surg.* 2006;141:701-704.
75. Zaloga GP, Roberts PR, Marik P. Feeding the hemodynamically unstable patient: a critical evaluation of the evidence. *Nutr Clin Pract*. 2003;18:285-293.
76. Kozar RA, McQuiggan MM, Moore EE, Kudsk KA, Jurkovich GJ, Moore FA. Postinjury enteral tolerance is reliably achieved by a standardized protocol. *J Surg Res.* 2002;104:70-75.
77. Mutlu GM, Mutlu EA, Factor P. Prevention and treatment of gastrointestinal complications in patients on mechanical ventilation. *Am J Respir Med.* 2003;2:395-411.
78. Lien HC, Chang CS, Chen GH. Can percutaneous endoscopic jejunostomy prevent gastroesophageal reflux in patients with preexisting esophagitis? *Am J Gastroenterol.* 2000;95:3439-3443.
79. Heyland DK, Drover JW, MacDonald S, Novak F, Lam M. Effect of postpyloric feeding on gastroesophageal regurgitation and pulmonary microaspiration: results of a randomized controlled trial. *Crit Care Med.* 2001;29:1495-1501.
80. Ho KM, Dobb GJ, Webb SA. A comparison of early gastric and post-pyloric feeding in critically ill patients: a meta-analysis. *Intensive Care Med*. 2006;32:639-649.
81. Marik PE, Zaloga GP. Gastric versus post-pyloric feeding: a systematic review. *Crit Care*. 2003;7:R46-R51.
82. Heyland DK, Drover JW, Dhaliwal R, Greenwood J. Optimizing the benefits and minimizing the risks of enteral nutrition in the critically ill: role of small bowel feeding. *JPEN J Parenter Enteral Nutr*. 2002;26(6 suppl):S51-S55.
83. Montecalvo MA, Steger KA, Farber HW, et al. Nutritional outcome and pneumonia in critical care patients randomized to gastric versus jejunal tube feedings. The Critical Care Research Team. *Crit Care Med.* 1992;20:1377-1387.
84. Kortbeek JB, Haigh PI, Doig C. Duodenal versus gastric feeding in ventilated blunt trauma patients: a randomized controlled trial. *J Trauma*. 1999;46:992-996.
85. Kearns LJ, Chin D, Mueller L, Wallace K, Jensen WA, Kirsch CM. The incidence of ventilator-associated pneumonia and success in nutrient delivery with gastric versus small intestinal feeding: a randomized clinical trial. *Crit Care Med.* 2000;28: 1742-1746.
86. Day HE, Badiani A, Uslaner JM, et al. Environmental novelty differentially affects c-fos mRNA expression induced by amphetamine or cocaine in subregions of the bed nucleus of the stria terminalis and amygdala. *J Neurosci.* 2001;21:732-740.
87. Esparza J, Boivin MA, Hartshorne MF, Levy H. Equal aspiration rates in gastrically and transpylorically fed critically ill patients. *Intensive Care Med.* 2001;27:660-664.
88. Boivin MA, Levy H. Gastric feeding with erythromycin is equivalent to transpyloric feeding in the critically ill. *Crit Care Med.* 2001;29:1916-1919.
89. Neumann DA, DeLegge MH. Gastric versus small-bowel tube feeding in the intensive care unit: a prospective comparison of efficacy. *Crit Care Med.* 2002;30:1436-1438.
90. Davies AR, Froomes PR, French CJ, et al. Randomized comparison of nasojejunal and nasogastric feeding in critically ill patients. *Crit Care Med.* 2002;30:586-590.
91. Montejo JC, Grau T, Acosta J, et al. Multicenter, prospective, randomized, single-blind study comparing the efficacy and gastrointestinal complications of early jejunal feeding with early gastric feeding in critically ill patients. *Crit Care Med.* 2002; 30:796-800.
92. Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a meta-analysis. *JAMA.* 1998;280:2013-2019.
93. Brennan MF, Pisters PW, Posner M, Quesada O, Shike M. A prospective randomized trial of total parenteral nutrition after major pancreatic resection for malignancy. *Ann Surg.* 1994;220: 436-444.
94. Holter AR, Fischer JE. The effects of perioperative hyperalimentation on complications in patients with carcinoma and weight loss. *J Surg Res.* 1977;23:31-34.
95. Müller JM, Brenner U, Dienst C, Pichlmaier H. Preoperative parenteral feeding in patients with gastrointestinal carcinoma. *Lancet.* 1982;1:68-79.
96. Sandstrom R, Drott C, Hyltander A, et al. The effect of postoperative intravenous feeding (TPN) on outcome following major surgery evaluated in a randomized study. *Ann Surg.* 1993;217: 185-195.
97. Sax HC, Warner BW, Talamini MA, et al. Early total parenteral nutrition in acute pancreatitis: lack of beneficial effects. *Am J Surg*. 1987;153:117-124.
98. Thompson BR, Julian TB, Stremple JF. Perioperative total parenteral nutrition in patients with gastrointestinal cancer. *J Surg Res.* 1981;30:497-500.
99. Woolfson AM, Smith JA. Elective nutritional support after major surgery: a prospective randomised trial. *Clin Nutr.* 1989;8:15-21.
100. Abel RM, Fischer JE, Buckley MJ, Barnett GO, Austen WG. Malnutrition in cardiac surgical patients: results of a prospective, randomized evaluation of early postoperative parenteral nutrition. *Arch Surg.* 1976;111:45-50.
101. Reilly J, Mehta R, Teperman L, et al. Nutritional support after liver transplantation: a randomized prospective study. *JPEN J Parenter Enteral Nutr*. 1990;14:386-391.
102. Williams RH, Heatley RV, Lewis MH. Proceedings: a randomized controlled trial of preoperative intravenous nutrition in patients with stomach cancer. *Br J Surg*. 1976;63:667.
103. Moghissi K, Hornshaw J, Teasdale PR, Dawes EA. Parenteral nutrition in carcinoma of the oesophagus treated by surgery: nitrogen balance and clinical studies. *Br J Surg*. 1977;64:125-128.
104. Preshaw RM, Attisha RP, Hollingsworth WJ. Randomized sequential trial of parenteral nutrition in healing of colonic anastomoses in man. *Can J Surg.* 1979;22:437-439.
105. Heatley RV, Williams RH, Lewis MH. Pre-operative intravenous feeding: a controlled trial. *Postgrad Med J*. 1979;55:541-545.
106. Simms JM, Oliver E, Smith JAR. A study of total parenteral nutrition (TPN) in major gastric and esophageal resection for neoplasia. *JPEN J Parenter Enteral Nutr*. 1980;4:422.
107. Lim ST, Choa RG, Lam KH, Wong J, Ong GB. Total parenteral nutrition versus gastrostomy in the preoperative preparation of patients with carcinoma of the oesophagus. *Br J Surg*. 1981;68:69-72.

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108. Sako K, Loré JM, Kaufman S, Razack MS, Bakamjian V, Reese P. Parenteral hyperalimentation in surgical patients with head and neck cancer: a randomized study. *J Surg Oncol.* 1981;16:391-402.
109. Jensen S. Parenteral nutrition and cancer surgery [abstract]. *JPEN J Parenter Enteral Nutr*. 1982;6:335. Abstract 112.
110. Moghissi M, Teasdale P, Dench M. Comparison between preoperative enteral (naso-gastric tube) and parenteral feeding in patients with cancer of the oesophagus undergoing surgery [abstract]. *JPEN J Parenter Enteral Nutr.* 1982;6:335. Abstract 111.
111. Müller JM, Keller HW, Brenner U, Walter M, Holzmüller W. Indications and effects of preoperative parenteral nutrition. *World J Surg*. 1986;10:53-63.
112. Garden OJ, Smith A, Harris NW, Shenkin A, Sim AJ, Carter DC. The effect of isotonic amino acid infusions on serum proteins and muscle breakdown following surgery. *Br J Surg*. 1983;70:79-82.
113. Bellantone R, Doglietto GB, Bossola M, et al. Preoperative parenteral nutrition in the high risk surgical patient. *JPEN J Parenter Enteral Nutr*. 1988;12:195-197.
114. Smith RC, Hartemink R. Improvement of nutritional measures during preoperative parenteral nutrition in patients selected by the prognostic nutritional index: a randomized controlled trial. *JPEN J Parenter Enteral Nutr*. 1988;12:587-591.
115. Meguid MM, Curtas MS, Meguid V, Campos AC. Effects of preoperative TPN on surgical risk: preliminary status report. *Br J Clin Pract Suppl.* 1988;63:53-58.
116. Bellantone R, Doglietto G, Bossola M, et al. Preoperative parenteral nutrition of malnourished surgical patients. *Acta Chir Scand*. 1988;154:249-251.
117. Fan ST, Lau WY, Wong KK. Preoperative parenteral nutrition in patients with oesophageal cancer: a prospective randomized clinical trial. *Clin Nutr.* 1989;8:23-27.
118. Veterans affairs total parenteral nutrition cooperative study group: perioperative total parenteral nutrition in surgical patients. *N Engl J Med*. 1991;325:525-532.
119. Von Meyenfeldt MF, Meijerink WJHJ, Rouflart MMJ, Buil-Maassen MTHJ, Soeters PB. Perioperative nutritional support: a randomised clinical trial. *Clin Nutr.* 1992;11:180-186.
120. Fan ST, Lo CM, Lai EC, Chu KM, Liu CL, Wong J. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. *N Engl J Med*. 1994;331:1547-1552.
121. Xian-Li H, Qing-Jui M, Kian-Guo L, Yan-Kui C, Xi-Lin D. Effect of total parenteral nutrition (TPN) with and without glutamine dipeptide supplementation on outcome in severe acute pancreatitis (SAP). *Clin Nutr Suppl.* 2004;1:43-47.
122. Collins JP, Oxby CB, Hill GL. Intravenous aminoacids and intravenous hyperalimentation as protein-sparing therapy after major surgery: a controlled clinical trial. *Lancet.* 1978;1:788-791.
123. Freund H, Hoover HC Jr, Atamian S, Fischer JE. Infusion of the branched chain amino acids in postoperative patients: anticatabolic properties. *Ann Surg*. 1979;190:18-23.
124. Yamada N, Koyama H, Hioki K, Yamada T, Yamamoto M. Effect of postoperative total parenteral nutrition (TPN) as an adjunct to gastrectomy for advanced gastric carcinoma. *Br J Surg*. 1983;70:267-274.
125. Jiménez FJ, Leyba CO, Jiménez LM, Valdecasas MS, Montero JG. Study of hypocaloric peripheral parenteral nutrition in postoperative patients. *Clin Nutr.* 1995;14:88-96.
126. Askanazi J, Hensle TW, Starker PM, et al. Effect of immediate postoperative nutritional support on length of hospitalization. *Ann Surg*. 1986;203:236-239.
127. Figueras J, Puig P, Rafecas A, et al. Postoperative hypocaloric parenteral nutrition: a study in patients without neoplasm. *Acta Chir Scand*. 1988;154:435-438.
128. Gys T, Peeters R, Hubens A. The value of short-term peripheral parenteral nutrition after colorectal surgery: a comparative study with conventional postoperative intravenous fluid. *Acta Chir Belg*. 1990;90:234-239.
129. Hwang TL, Mou SC, Chen MF. The importance of a source of sufficient protein in postoperative hypocaloric partial parenteral nutrition support. *JPEN J Parenter Enteral Nutr*. 1993;17:254-256.
130. Detsky AS, Baker JP, O'Rourke K, Goel V. Perioperative parenteral nutrition: a meta-analysis. *Ann Intern Med.* 1987;107:195-203.
131. Klein S, Kinney J, Jeejeebhoy K, et al. Nutrition support in clinical practice: review of published data and recommendations for future research directions. National Institutes of Health, American Society for Parenteral and Enteral Nutrition, and American Society for Clinical Nutrition. *JPEN J Parenter Enteral Nutr*. 1997;21:133-156.
132. Foster GD, Knox LS, Dempsey DT, Mullen JL. Caloric requirements in total parenteral nutrition. *J Am Coll Nutr.* 1987;6:231-253.
133. Barr J, Hecht M, Flavin KE, Khorana A, Gould MK. Outcomes in critically ill patients before and after the implementation of an evidence-based nutritional management protocol. *Chest*. 2004;125:1446-1457.
134. Artinian V, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. *Chest.* 2006;129:960-967.
135. Martin CM, Doig GS, Heyland DK, Morrison T, Sibbald WJ; Southwestern Ontario Critical Care Research Network. Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). *CMAJ*. 2004;170:197-204.
136. Ziegler TR, Smith RJ, O'Dwyer ST, Demling RH, Wilmore DW. Increased intestinal permeability associated with infection in burn patients. *Arch Surg.* 1988;123:1313-1319.
137. Chiarelli AG, Ferrarello S, Piccioli A, et al. Total enteral nutrition versus mixed enteral and parenteral nutrition in patients in an intensive care unit. *Minerva Anestesiol.* 1996;62:1-7.
138. Bauer P, Charpentier C, Bouchet C, Nace L, Raffy F, Gaconnet N. Parenteral with enteral nutrition in the critically ill. *Intensive Care Med.* 2000;26:893-900.
139. Herndon DN, Stein MD, Rutan TC, Abston S, Linares H. Failure of TPN supplementation to improve liver function, immunity, and mortality in thermally injured patients. *J Trauma*. 1987;27:195-204.
140. Herndon DN, Barrow RE, Stein M, et al. Increased mortality with intravenous supplemental feeding in severely burned patients. *J Burn Care Rehabil.* 1989;10:309-313.
141. Stroud M. Protein and the critically ill: do we know what to give? *Proc Nutr Soc.* 2007;66:378-383.
142. Choban PS, Dickerson RN. Morbid obesity and nutrition support: is bigger different? *Nutr Clin Pract*. 2005;20:480-487.
143. Elamin EM. Nutritional care of the obese intensive care unit patient. *Curr Opin Crit Care.* 2005;11:300-303.
144. McClave SA, Sexton LK, Spain DA, et al. Enteral tube feeding in the intensive care unit: factors impeding adequate delivery. *Crit Care Med.* 1999;27:1252-1256.
145. Jenkins ME, Gottschlich MM, Warden GD. Enteral feeding during operative procedures in thermal injuries. *J Burn Care Rehabil.* 1994;15:199-205.
146. Pinilla JC, Samphire J, Arnold C, Liu L, Thiessen B. Comparison of gastrointestinal tolerance to two enteral feeding protocols in critically ill patients: a prospective, randomized controlled trial. *JPEN J Parenter Enteral Nutr*. 2001;25:81-86.
147. Montejo JC, Minambres E, Bordeje L, et al. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. *Intensive Care Med.* 2009; in press.
148. Tarling MM, Toner CC, Withington PS, Baxter MK, Whelpton R, Goldhill DR. A model of gastric emptying using paracetamol absorption in intensive care patients. *Intensive Care Med*. 1997;23:256-260.

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149. Landzinski J, Kiser TH, Fish DN, Wischmeyer PE, MacLaren R. Gastric motility function in critically ill patients tolerant vs intolerant to gastric nutrition. *JPEN J Parenter Enteral Nutr*. 2008; 32:45-50.
150. Cohen J, Aharon A, Singer P. The paracetamol absorption test: a useful addition to the enteral nutrition algorithm? *Clin Nutr*. 2000;19:233-236.
151. McClave SA, Lukan JK, Stefater JA, et al. Poor validity of residual volumes as a marker for risk of aspiration in critically ill patients. *Crit Care Med*. 2005;33:324-330.
152. McClave SA, DeMeo MT, DeLegge MH, et al. North American summit on aspiration in the critically ill patient: consensus statement. *JPEN J Parenter Enteral Nutr*. 2002;26(6 Suppl): S80-S85.
153. Adam S, Batson S. A study of problems associated with the delivery of enteral feed in critically ill patients in five ICUs in the UK. *Intensive Care Med*. 1997;23:261-266.
154. Spain DA, McClave SA, Sexton LK, et al. Infusion protocol improves delivery of enteral tube feeding in the critical care unit. *JPEN J Parenter Enteral Nutr*. 1999;23:288-292.
155. Torres A, el-Ebiary M, Gonzalez J, et al. Gastric and pharyngeal flora in nosocomial pneumonia acquired during mechanical ventilation. *Am Rev Respir Dis*. 1993;148:352-357.
156. Bonten MJ, Gaillard CA, van Tiel FH, Smeets HG, van der Geest S, Stobberingh EE. The stomach is not a source for colonization of the upper respiratory tract and pneumonia in ICU patients. *Chest*. 1994;105:878-884.
157. Pingleton SK, Hinthorn DR, Liu C. Enteral nutrition in patients receiving mechanical ventilation: multiple sources of tracheal colonization include the stomach. *Am J Med*. 1986;80:827-832.
158. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet*. 1999;354:1851-1858.
159. van Nieuwenhoven CA, Vandenbroucke-Grauls C, van Tiel FH, et al. Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: a randomized study. *Crit Care Med*. 2006;34:396-402.
160. Ibrahim EH, Mehringer L, Prentice D, et al. Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. *JPEN J Parenter Enteral Nutr*. 2002;26:174-181.
161. Bonten MJ, Gaillard CA, van der Hulst R, et al. Intermittent enteral feeding: the influence on respiratory and digestive tract colonization in mechanically ventilated intensive-care-unit patients. *Am J Respir Crit Care Med*. 1996;154:394-399.
162. Steevens EC, Lipscomb AF, Poole GV, Sacks GS. Comparison of continuous vs intermittent nasogastric enteral feeding in trauma patients: perceptions and practice. *Nutr Clin Pract*. 2002; 17:118-122.
163. Hiebert JM, Brown A, Anderson RG, Halfacre S, Rodeheaver GT, Edlich RF. Comparison of continuous vs intermittent tube feedings in adult burn patients. *JPEN J Parenter Enteral Nutr*. 1981;5:73-75.
164. Kocan MJ, Hickisch SM. A comparison of continuous and intermittent enteral nutrition in NICU patients. *J Neurosci Nurs*. 1986;18:333-337.
165. Ciocon JO, Galindo-Ciocon DJ, Tiessen C, Galindo D. Continuous compared with intermittent tube feeding in the elderly. *JPEN J Parenter Enteral Nutr*. 1992;16:525-528.
166. Booth CM, Heyland DK, Paterson WG. Gastrointestinal promotility drugs in the critical care setting: a systematic review of the evidence. *Crit Care Med*. 2002;30:1429-1435.
167. Yavagal DR, Karnad DR, Oak JL. Metoclopramide for preventing pneumonia in critically ill patients receiving enteral tube feeding: a randomized controlled trial. *Crit Care Med*. 2000;28: 1408-1411.
168. Berne JD, Norwood SH, McAuley CE, et al. Erythromycin reduces delayed gastric emptying in critically ill trauma patients: a randomized, controlled trial. *J Trauma*. 2002;53:422-425.
169. Meissner W, Dohrn B, Reinhart K. Enteral naloxone reduces gastric tube reflux and frequency of pneumonia in critical care patients during opioid analgesia. *Crit Care Med*. 2003;31:776-780.
170. DeRiso AJ, Ladowski JS, Dillon TA, Justice JW, Peterson AC. Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. *Chest*. 1996;109:1556-1561.
171. Houston S, Hougland P, Anderson JJ, LaRocco M, Kennedy V, Gentry LO. Effectiveness of 0.12% chlorhexidine gluconate oral rinse in reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery. *Am J Crit Care*. 2002;11:567-570.
172. Zack JE, Garrison T, Trovillion E, et al. Effect of an education program aimed at reducing the occurrence of ventilator-associated pneumonia. *Crit Care Med*. 2002;30:2407-2412.
173. Simmons-Trau D, Cenek P, Counterman J, Hockenbury D, Litwiller L. Reducing VAP with 6 Sigma. *Nurs Manage*. 2004;35:41-45.
174. Kollef MH. Prevention of hospital-associated pneumonia and ventilator-associated pneumonia. *Crit Care Med*. 2004;32: 1396-1405.
175. Maloney JP, Ryan TA. Detection of aspiration in enterally fed patients: a requiem for bedside monitors of aspiration. *JPEN J Parenter Enteral Nutr*. 2002;26(6 Suppl):S34-S41.
176. Kohn-Keeth C, Frankel E. Taking blue dye out of tube feedings. *Nursing*. 2004;34:14.
177. Metheny NA, Clouse RE. Bedside methods for detecting aspiration in tube-fed patients. *Chest*. 1997;111:724-731.
178. Kenneally C, Rosini JM, Skrupky LP, et al. An analysis of thirty-day mortality for clostridium difficile-associated disease in the ICU setting. *Chest*. 2007;132:418-424.
179. Maroo S, Lamont JT. Recurrent clostridium difficile. *Gastroenterology*. 2006;130:1311-1316.
180. Consensus recommendations from the US summit on immune-enhancing enteral therapy. *JPEN J Parenter Enteral Nutr*. 2001;25:S61-S62.
181. Heys SD, Walker LG, Smith I, Eremin O. Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. *Ann Surg*. 1999;229:467-477.
182. Beale RJ, Bryg DJ, Bihari DJ. Immunonutrition in the critically ill: a systematic review of clinical outcome. *Crit Care Med*. 1999;27: 2799-2805.
183. Martindale RG, Cresci GA. The use of immune enhancing diet in head injury. *JPEN J Parenter Enteral Nutr*. 2001;25(2 Suppl): S27-S28.
184. Cerra FB, Lehman S, Konstantinides N, Konstantinides F, Shronts EP, Holman R. Effect of enteral nutrient on in vitro tests of immune function in ICU patients: a preliminary report. *Nutrition*. 1990;6:84-87.
185. Gottschlich MM, Jenkins M, Warden GD, et al. Differential effects of three enteral dietary regimens on selected outcome variables in burn patients. *JPEN J Parenter Enteral Nutr*. 1990;14: 225-236.
186. Brown RO, Hunt H, Mowatt-Larssen CA, Wojtysiak SL, Henningfield MF, Kudsk KA. Comparison of specialized and standard enteral formulas in trauma patients. *Pharmacotherapy*. 1994;14:314-320.
187. Moore FA, Moore EE, Kudsk KA, et al. Clinical benefits of an immune-enhancing diet for early postinjury enteral feeding. *J Trauma*. 1994;37:607-615.
188. Bower RH, Cerra FB, Bershadsky B, et al. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a

Downloaded from http://pen.sagepub.com by on May 26, 2009

multicenter, prospective, randomized, clinical trial. *Crit Care Med*. 1995;23:436-449.
189. Kudsk KA, Minard G, Croce MA, et al. A randomized trial of isonitrogenous enteral diets after severe trauma: an immune-enhancing diet reduces septic complications. *Ann Surg*. 1996;224:531-540.
190. Engel JM, Menges T, Neuhauser C, Schaefer B, Hempelmann G. Effects of various feeding regimens in multiple trauma patients on septic complications and immune parameters. *Anasthesiol Intensivmed Notfallmed Schmerzther*. 1997;32:234-239.
191. Mendez C, Jurkovich GJ, Garcia I, Davis D, Parker A, Maier RV. Effects of an immune-enhancing diet in critically injured patients. *J Trauma*. 1997;42:933-940.
192. Rodrigo Casanova MP, Garcia Pena JM. The effect of the composition of the enteral nutrition on infection in the critical patient. *Nutr Hosp*. 1997;12:80-84.
193. Saffle JR, Wiebke G, Jennings K, et al. Randomized trial of immune-enhancing enteral nutrition in burn patients. *J Trauma*. 1997;42:793-802.
194. Weimann A, Bastian L, Bischoff WE, et al. Influence of arginine, omega-3 fatty acids and nucleotide-supplemented enteral support on systemic inflammatory response syndrome and multiple organ failure in patients after severe trauma. *Nutrition*. 1998;14: 165-172.
195. Atkinson S, Sieffert E, Bihari D. A prospective, randomized, double-blind, controlled clinical trial of enteral immunonutrition in the critically ill. Guy's Hospital Intensive Care Group. *Crit Care Med*. 1998;26:1164-1172.
196. Galban C, Montejo JC, Mesejo A, et al. An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. *Crit Care Med*. 2000;28:643-648.
197. Caparros T, Lopez J, Grau T. Early enteral nutrition in critically ill patients with a high-protein diet enriched with arginine, fiber, and antioxidants compared with a standard high-protein diet: the effect on nosocomial infections and outcome. *JPEN J Parenter Enteral Nutr*. 2001;25:299-308.
198. Conejero R, Bonet A, Grau T, et al. Effect of a glutamine-enriched enteral diet on intestinal permeability and infectious morbidity at 28 days in critically ill patients with systemic inflammatory response syndrome: a randomized, single-blind, prospective, multicenter study. *Nutrition*. 2002;18:716-721.
199. Dent DL, Heyland DK, Levy H, et al. Immunonutrition may increase mortality in critically ill patients with pneumonia: results of a randomized trial. *Crit Care Med*. 2003;30:A17.
200. Bertolini G, Iapichino G, Radrizzani D, et al. Early enteral immunonutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial. *Intensive Care Med*. 2003;29:834-840.
201. Chuntrasakul C, Siltham S, Sarasombath S, et al. Comparison of a immunonutrition formula enriched arginine, glutamine and omega-3 fatty acid, with a currently high-enriched enteral nutrition for trauma patients. *J Med Assoc Thai*. 2003;86:552-561.
202. Tsuei BJ, Bernard AC, Barksdale AR, Rockich AK, Meier CF, Kearney PA. Supplemental enteral arginine is metabolized to ornithine in injured patients. *J Surg Res*. 2005;123:17-24.
203. Kieft H, Roos A, Bindels A, et al. Clinical outcome of an immune enhancing diet in a heterogenous intensive care population. *Intensive Care Med*. 2005;31:524-532.
204. Wibbenmeyer LA, Mitchell MA, Newel IM, et al. Effect of a fish oil and arginine-fortified diet in thermally injured patients. *J Burn Care Res*. 2006;27:694-702.
205. Popovic PJ, Zeh HJ III, Ochoa JB. Arginine and immunity. *J Nutr*. 2007;137(6 Suppl 2):1681S-1686S.
206. Calo L, Bianconi L, Colivicchi F, et al. N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *J Am Coll Cardiol*. 2005;45: 1723-1728.
207. Gadek JE, DeMichele SJ, Karlstad MD, et al. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. *Crit Care Med*. 1999;27:1409-1420.
208. Singer P, Theilla M, Fisher H, Gibstein L, Grozovski E, Cohen J. Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. *Crit Care Med*. 2006;34:1033-1038.
209. Pontes-Arruda A, Aragao AM, Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. *Crit Care Med*. 2006;34:2325-2333.
210. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA*. 2001;286:944-953.
211. Montejo JC, Zarazaga A, Lopez-Martinez J, et al. Immunonutrition in the intensive care unit: a systematic review and consensus statement. *Clin Nutr*. 2003;22:221-233.
212. Waitzberg DL, Saito H, Plank LD, et al. Postsurgical infections are reduced with specialized nutrition support. *World J Surg*. 2006;30:1592-1604.
213. Heyland DK, Novak F. Immunonutrition in the critically ill patient: more harm than good? *JPEN J Parenter Enteral Nutr*. 2001;25:S51-S55.
214. Zhou M, Martindale RG. Arginine in the critical care setting. *J Nutr*. 2007;137(6 Suppl 2):1687S-1692S.
215. Luiking YC, Poeze M, Preiser J, Deutz N, et al. L-arginine infusion in severely septic patients does not enhance protein nitrosylation or haemodynamic instability. *e-SPEN*. 2006;1:14-15.
216. Edes TE, Walk BE, Austin JL. Diarrhea in tube-fed patients: feeding formula not necessarily the cause. *Am J Med*. 1990;88:91-93.
217. Alverdy J, Zaborina O, Wu L. The impact of stress and nutrition on bacterial-host interactions at the intestinal epithelial surface. *Curr Opin Clin Nutr Metab Care*. 2005;8:205-209.
218. Arvans DL, Vavricka SR, Ren H, et al. Luminal bacterial flora determines physiological expression of intestinal epithelial cytoprotective heat shock proteins 25 and 72. *Am J Physiol Gastrointest Liver Physiol*. 2005;288:G696-G704.
219. Sartor RB. Microbial and dietary factors in the pathogenesis of chronic, immune-mediated intestinal inflammation. *Adv Exp Med Biol*. 2006;579:35-54.
220. Yan F, Cao H, Cover TL, Whitehead R, Washington MK, Polk DB. Soluble proteins produced by probiotic bacteria regulate intestinal epithelial cell survival and growth. *Gastroenterology*. 2007; 132:562-575.
221. Bengmark S. Bioecologic control of inflammation and infection in critical illness. *Anesthesiol Clin*. 2006;24:299-323.
222. Rayes N, Seehofer D, Theruvath T, et al. Supply of pre- and probiotics reduces bacterial infection rates after liver transplantation: a randomized, double-blind trial. *Am J Transplant*. 2005;5:125-130.
223. Rayes N, Seehofer D, Hansen S, et al. Early enteral supply of lactobacillus and fiber versus selective bowel decontamination: a controlled trial in liver transplant recipients. *Transplantation*. 2002;74:123-127.
224. Rayes N, Seehofer D, Theruvath T, et al. Effect of enteral nutrition and synbiotics on bacterial infection rates after pylorus-preserving pancreatoduodenectomy: a randomized, double-blind trial. *Ann Surg*. 2007;246:36-41.
225. Kotzampassi K, Giamarellos-Bourboulis EJ, Voudouris A, Kazamias P, Eleftheriadis E. Benefits of a synbiotic formula (Synbiotic 2000Forte) in critically Ill trauma patients: early results of a randomized controlled trial. *World J Surg*. 2006;30:1848-1855.
226. Spindler-Vesel A, Bengmark S, Vovk I, Cerovic O, Kompan L. Synbiotics, prebiotics, glutamine, or peptide in early enteral nutrition: a randomized study in trauma patients. *JPEN J Parenter Enteral Nutr*. 2007;31:119-126.

Downloaded from http://pen.sagepub.com by on May 26, 2009

227. Oláh A, Belágyi T, Issekutz A, Gamal ME, Bengmark S. Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis. *Br J Surg*. 2002;89:1103-1107.
228. Oláh A, Belagyi T, Poto L, Romics L Jr, Bengmark S. Synbiotic control of inflammation and infection in severe acute pancreatitis: a prospective, randomized, double blind study. *Hepatogastroenterology*. 2007;54:590-594.
229. Besselink MG, van Santvoort HC, Buskens E, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;371:651-659.
230. Berger MM, Spertini F, Shenkin A, et al. Trace element supplementation modulates pulmonary infection rates after major burns: a double-blind, placebo-controlled trial. *Am J Clin Nutr*. 1998; 68:365-371.
231. Nathens AB, Neff MJ, Jurkovich GJ, et al. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. *Ann Surg*. 2002;236:814-822.
232. Heyland DK, Dhaliwal R, Suchner U, Berger MM. Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient. *Intensive Care Med*. 2005;31:327-337.
233. Crimi E, Liguori A, Condorelli M, et al. The beneficial effects of antioxidant supplementation in enteral feeding in critically ill patients: a prospective, randomized, double-blind, placebo-controlled trial. *Anesth Analg*. 2004;99:857-863.
234. Angstwurm MW, Engelmann L, Zimmermann T, et al. Selenium in intensive care (SIC): results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. *Crit Care Med*. 2007;35:118-126.
235. Jones C, Palmer TE, Griffiths RD. Randomized clinical outcome study of critically ill patients given glutamine-supplemented enteral nutrition. *Nutrition*. 1999;15:108-115.
236. Hall JC, Dobb G, Hall J, de Sousa R, Brennan L, McCauley R. A prospective randomized trial of enteral glutamine in critical illness. *Intensive Care Med*. 2003;29:1710-1716.
237. Garrel DR, Patenaude J, Nedelec B, et al. Decreased mortality and infectious morbidity in adult burn patients given enteral glutamine supplements: a prospective, controlled, randomized clinical trial. *Crit Care Med*. 2003;31:2444-2449.
238. Houdijk AP, Rijnsburger ER, Jansen J, et al. Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet*. 1998;352:772-776.
239. Brantley S, Pierce J. Effects of enteral glutamine on trauma patients [abstract]. *Nutr Clin Pract*. 2000;15:S13. Abstract P0095.
240. Zhou YP, Jiang ZM, Sun YH, Wang XR, Ma EL, Wilmore D. The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns: a randomized, double-blind, controlled clinical trial. *JPEN J Parenter Enteral Nutr*. 2003;27:241-245.
241. Peng X, Yan H, You Z, Wang P, Wang S. Effects of enteral supplementation with glutamine granules on intestinal mucosal barrier function in severe burned patients. *Burns*. 2004;30:135-139.
242. Spapen H, Diltoer M, Van Malderen C, Opdenacker G, Suys E, Huyghens L. Soluble fiber reduces the incidence of diarrhea in septic patients receiving total enteral nutrition: a prospective, double-blind, randomized, and controlled trial. *Clin Nutr*. 2001; 20:301-305.
243. Rushdi TA, Pichard C, Khater YH. Control of diarrhea by fiber-enriched diet in ICU patients on enteral nutrition: a prospective randomized controlled trial. *Clin Nutr*. 2004;23:1344-1352.
244. Dobb GJ, Towler SC. Diarrhoea during enteral feeding in the critically ill: a comparison of feeds with and without fibre. *Intensive Care Med*. 1990;16:252-255.
245. Scaife CL, Saffle JR, Morris SE. Intestinal obstruction secondary to enteral feedings in burn trauma patients. *J Trauma*. 1999;47: 859-863.
246. McIvor AC, Meguid MM, Curtas S, Warren J, Kaplan DS. Intestinal obstruction from cecal bezoar: a complication of fiber-containing tube feedings. *Nutrition*. 1990;6:115-117.
247. Ahrens CL, Barletta JF, Kanji S, et al. Effect of low-calorie parenteral nutrition on the incidence and severity of hyperglycemia in surgical patients: a randomized, controlled trial. *Crit Care Med*. 2005;33:2507-2512.
248. Battistella FD, Widergren JT, Anderson JT, et al. A prospective, randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. *J Trauma*. 1997;43:52-58.
249. Choban PS, Burge JC, Scales D, et al. Hypoenergetic nutrition support in hospitalized obese patients: a simplified method for clinical application. *Am J Clin Nutr*. 1997;66:546-550.
250. McCowen KC, Friel C, Sternberg J, et al. Hypocaloric total parenteral nutrition: effectiveness in prevention of hyperglycemia and infectious complications: a randomized clinical trial. *Crit Care Med*. 2000;28:3606-3611.
251. Joban N, Garrel DR, Champoux J, Bernier J. Improved immune functions with administration of a low-fat diet in a burn animal model. *Cell Immunol*. 2000;206:71-84.
252. Garrel DR, Razi M, Lariviere F, et al. Improved clinical status and length of care with low-fat nutrition support in burn patients. *JPEN J Parenter Enteral Nutr*. 1995;19:482-491.
253. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345: 1359-1367.
254. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354:449-461.
255. Devos P, Preiser JC. Current controversies around tight glucose control in critically ill patients. *Curr Opin Clin Nutr Metab Care*. 2007;10:206-209.
256. Fuentes-Orozco C, Anaya-Prado R, Gonzalez-Ojeda A, et al. L-alanyl-L-glutamine-supplemented parenteral nutrition improves infectious morbidity in secondary peritonitis. *Clin Nutr*. 2004; 23:13-21.
257. Zeigler TR, Fernandez-Estivariz C, Griffth P, et al. Parenteral nutrition supplemented with alanyl-glutamine dipeptide decreases infectious morbidity and improves organ function in critically ill post-operative patients: results of a double-blind, randomized, controlled pilot study. *Nutrition Week Abstracts*. 2004;023:52.
258. Goeters C, Wenn A, Mertes N, et al. Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. *Crit Care Med*. 2002;30:2032-2037.
259. Griffiths RD, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. *Nutrition*. 1997;13:295-302.
260. Griffiths RD, Allen KD, Andrews FJ, Jones C. Infection, multiple organ failure, and survival in the intensive care unit: influence of glutamine-supplemented parenteral nutrition on acquired infection. *Nutrition*. 2002;18:546-552.
261. Powell-Tuck J, Jamieson CP, Bettany GE, et al. A double blind, randomised, controlled trial of glutamine supplementation in parenteral nutrition. *Gut*. 1999;45:82-88.
262. Wischmeyer PE, Lynch J, Liedel J, et al. Glutamine administration reduces gram-negative bacteremia in severely burned patients: a prospective, randomized, double-blind trial versus isonitrogenous control. *Crit Care Med*. 2001;29:2075-2080.
263. Zhou Y-D, Jiang Z-M, Sun Y-H, He G-Z, Shu H. The effects of supplemental glutamine dipeptide on gut integrity and clinical outcomes after major escharectomy in severe burns: a randomized, double blind, controlled clinical trial. *Clin Nutr Suppl*. 2004;1:55-60.
264. Dechelotte P, Hasselmann M, Cynober L, et al. L-alanyl-L-glutamine dipeptide-supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in

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critically ill patients: the French controlled, randomized, double-blind, multicenter study. *Crit Care Med.* 2006;34:598-604.
265. Heyland D, Drover J, Dhaliwal R; Canadian Clinical Practice Guidelines Committee. Does the addition of glutamine to enteral feeds affect patient mortality? *Crit Care Med.* 2006;34: 2031-2032.
266. Schloerb PR. Immune-enhancing diets: products, components, and their rationales. *JPEN J Parenter Enteral Nutr*. 2001;25(2 Suppl): S3-S7.
267. Washizawa N, Gu LH, Gu L, Openo KP, Jones DP, Ziegler TR. Comparative effects of glucagon-like peptide-2 (GLP-2), growth hormone (GH), and keratinocyte growth factor (KGF) on markers of gut adaptation after massive small bowel resection in rats. *JPEN J Parenter Enteral Nutr*. 2004;28:399-409.
268. al-Saady NM, Blackmore CM, Bennett ED. High fat, low carbohydrate, enteral feeding lowers PaCO2 and reduces the period of ventilation in artificially ventilated patients. *Intensive Care Med.* 1989;15:290-295.
269 Barale F, Verdy S, Boillot A, et al. Calorimetric study of enteral low-carbohydrate diet in patients with respiratory insufficiency and decompensation. *Agressologie*. 1990;31:77-79.
270. Radrizzani D, Iapichino G. Nutrition and lung function in the critically ill patient. *Clin Nutr.* 1998;17:7-10.
271. Chassard D, Guiraud M, Gauthier J, Gelas P, Berrada KR, Bouletreau P. Effects of intravenous medium-chain triglycerides on pulmonary gas exchanges in mechanically ventilated patients. *Crit Care Med.* 1994;22:248-251.
272. Mizock BA. Metabolic derangements in sepsis and septic shock. *Crit Care Clin*. 2000;16:319-336.
273. Marin A, Hardy G. Practical implications of nutritional support during continuous renal replacement therapy. *Curr Opin Clin Nutr Metab Care*. 2001;4:219-225.
274. Cano N, Fiaccadori E, Tesinsky P, et al. ESPEN guidelines on enteral nutrition: adult renal failure. *Clin Nutr.* 2006;25:295-310.
275. Bozfakioglu S. Nutrition in patients with acute renal failure. *Nephrol Dial Transplant*. 2001;16(suppl 6):21-22.
276. Scheinkestel CD, Kar L, Marshall K, et al. Prospective randomized trial to assess caloric and protein needs of critically ill, anuric, ventilated patients requiring continuous renal replacement therapy. *Nutrition*. 2003;19:909-916.
277. Wooley JA, Btaiche IF, Good KL. Metabolic and nutritional aspects of acute renal failure in critically ill patients requiring continuous renal replacement therapy. *Nutr Clin Pract*. 2005;20:176-191.
278. Bellomo R, Tan HK, Bhonagiri S, et al. High protein intake during continuous hemodiafiltration: impact on amino acids and nitrogen balance. *Int J Artif Organs*. 2002;25:261-268.
279. Plauth M, Cabre E, Riggio O, et al. ESPEN guidelines on enteral nutrition: liver disease. *Clin Nutr.* 2006;25:285-294.
280. Henkel AS, Buchman AL. Nutritional support in patients with chronic liver disease. *Nat Clin Pract Gastroenterol Hepatol*. 2006;3:202-209.
281. Campillo B, Richardet JP, Bories PN. Validation of body mass index for the diagnosis of malnutrition in patients with liver cirrhosis. *Gastroenterol Clin Biol*. 2006;30:1137-1143.
282. Florez DA, Aranda-Michel J. Nutritional management of acute and chronic liver disease. *Semin Gastrointest Dis*. 2002;13:169-178.
283. Aranda-Michel J. Nutrition in hepatic failure and liver transplantation. *Curr Gastroenterol Rep*. 2001;3:362-370.
284. Sanchez AJ, Aranda-Michel J. Nutrition for the liver transplant patient. *Liver Transpl*. 2006;12:1310-1316.
285. Plevak DJ, DiCecco SR, Wiesner RH, et al. Nutritional support for liver transplantation: identifying caloric and protein requirements. *Mayo Clin Proc*. 1994;69:225-230.
286. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M; Educational and Clinical Practice Committee, European Society of Parenteral and Enteral Nutrition (ESPEN). ESPEN guidelines for nutrition screening 2002. *Clin Nutr.* 2003;22:415-421.
287. Schutz T, Bechstein WO, Neuhaus P, Lochs H, Plauth M. Clinical practice of nutrition in acute liver failure: a European survey. *Clin Nutr.* 2004;23:975-982.
288. Horst D, Grace ND, Conn HO, et al. Comparison of dietary protein with an oral, branched chain-enriched amino acid supplement in chronic portal-systemic encephalopathy: a randomized controlled trial. *Hepatology*. 1984;4:279-287.
289. Yoshida T, Muto Y, Moriwaki H, Yamato M. Effect of long-term oral supplementation with branched-chain amino acid granules on the prognosis of liver cirrhosis. *Gastroenterol Jpn*. 1989;24:692-698.
290. Marchesini G, Bianchi G, Merli M, et al. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. *Gastroenterology.* 2003;124:1792-1801.
291. Muto Y, Sato S, Watanabe A, et al. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. *Clin Gastroenterol Hepatol*. 2005;3:705-713.
292. Sato S, Watanabe A, Muto Y, et al. Clinical comparison of branched-chain amino acid (l-leucine, l-isoleucine, l-valine) granules and oral nutrition for hepatic insufficiency in patients with decompensated liver cirrhosis (LIV-EN study). *Hepatol Res*. 2005;31:232-240.
293. Bradley EL. A clinically based classification system for acute pancreatitis: summary of the international symposium on acute pancreatitis. *Arch Surg.* 1993;128:586-590.
294. Forsmark CE, Baillie J. AGA Institute medical position statement on acute pancreatitis. *Gastroenterology.* 2007;132:2019-2021.
295. Wilson C, Heath DI, Imrie CW. Prediction of outcome in acute pancreatitis: a comparative study of APACHE II, clinical assessment and multiple factor scoring systems. *Br J Surg*. 1990;77:1260-1264.
296. Agarwal N, Liebson C. Acute pancreatitis: systemic complications and prognostic assessment. *Pract Gastroenterol*. 1991;15:22-32.
297. Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. *BMJ*. 2004; 328:1407.
298. Cao Y, Xu Y, Lu T, Gao F, Mo Z. Meta-analysis of enteral nutrition versus parenteral nutrition in patients with severe acute pancreatitis. *Ann Nutr Metab*. 2008;53:268-275.
299. Eatock FC, Chong P, Menezes N, et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. *Am J Gastroenterol.* 2005;100:432-439.
300. Kumar A, Singh N, Prakash S, Saraya A, Joshi YK. Early enteral nutrition in severe acute pancreatitis: a prospective randomized controlled trial comparing nasojejunal and nasogastric routes. *J Clin Gastroenterol*. 2006;40:431-434.
301. Cravo M, Camilo ME, Marques A, Pinto Correia J. Early tube feeding in acute pancreatitis: a prospective study. *Clin Nutr.* 1989;8(suppl):14.
302. O'Keefe SJ, Broderick T, Turner M, Stevens S, O'Keefe JS. Nutrition in the management of necrotizing pancreatitis. *Clin Gastroenterol Hepatol*. 2003;1:315-321.
303. Parekh D, Lawson HH, Segal I. The role of total enteral nutrition in pancreatic disease. *S Afr J Surg*. 1993;31:57-61.
304. Grant JP, Davey-McCrae J, Snyder PJ. Effect of enteral nutrition on human pancreatic secretions. *JPEN J Parenter Enteral Nutr*. 1987;11:302-304.
305. Harsanyi L, Bodoky G, Pap A. The effect of jejunal nutrition on pancreatic exocrine function. *Acta Chir Hung*. 1992-93;33:13-21.
306. DeLegge MH, McClave SA, DiSario JA, et al. Ethical and medicolegal aspects of PEG-tube placement and provision of artificial nutritional therapy. *Gastrointest Endosc*. 2005;62:952-959.
307. Van der Riet P, Brooks D, Ashby M. Nutrition and hydration at the end of life: pilot study of a palliative care experience. *J Law Med*. 2006;14:182-198.

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