CHAPTER 80

Enteral Nutrition

Andrew R. Davies and Anthony J. Hennessy

Objectives

This chapter will:

1. Describe the benefits that nutritional support can provide in the critically ill.
2. Explain the reasons why enteral nutrition should be preferred.
3. Discuss the risks associated with gastric feeding.
4. Outline three alternative strategies for patients with enteral feeding intolerance.
5. Discuss how to optimize the choice of substrates (particularly glutamine and omega-3 fatty acids) in the composition of enteral nutrition.

Nutritional support is considered to be the standard of care for critically ill patients based on the rationale that malnutrition is associated with increased morbidity and mortality[1] and that administration of nutritional support will improve wound healing,[2] reduce complication rates,[3] and reduce the duration of hospitalization.[4,5] In fact, optimal management of nutritional support may well be as important as the management of renal, cardiovascular, ventilatory, or other organ system support.

Three high-quality evidence-based clinical practice guidelines recently have been published,[6–8] and the use of one of these guidelines is advised strongly in clinical practice. Several of the specific recommendations are consistent across all three guidelines (Box 80.1) with a strong preference for enteral nutrition.

PREFERENCE FOR ENTERAL NUTRITION

Enteral nutrition is preferred to parenteral nutrition because delivering nutrition into the gut is more physiologic and less expensive.[9] In comparison to parenteral nutrition, enteral nutrition also has been associated with improved gut function in the critically ill,[10] reduced inflammatory cytokine levels,[11] and reduced rates of infectious complications.[3,6,12]

Parenteral nutrition appears to increase the risk of infectious complications when compared to no nutritional intake,[13] so it often has been maligned in critically ill patients as a harmful intervention.[14] Such views have been challenged,[15,16] and a recent meta-analysis found that parenteral nutrition may in fact be advantageous if given early when enteral nutrition would otherwise be delayed.[17] It also may be the case that parenteral nutrition is safer when used in a lower-energy formulation than it was previously,[18] particularly now that greater attention to glycemic control seems warranted.[19]

BOX 80.1

Recommendations Based on Consistent Statements From Recent Evidence-Based Guidelines for Feeding of the Critically Ill

Early gastric feeding (started within 24–48 hours) should be used in preference to parenteral nutrition in patients with no major gut dysfunction.
Promotility drugs should be used if gastric feeding is not tolerated.
Small bowel feeding should be used if gastric feeding is not tolerated.
Enteral nutrition should be supplemented with parenteral nutrition if nutritional goals are not met but only after attempts at a promotility drug and a small bowel feeding tube.
When enteral nutrition is used:
- It SHOULD NOT be supplemented with arginine or other select nutrients (immunonutrition) in patients with severe sepsis.
- It SHOULD be supplemented with omega-3 fatty acids and antioxidants in patients with acute lung injury.
- It SHOULD be supplemented with glutamine in burn and trauma patients.

When parenteral nutrition is used:
- It SHOULD be supplemented with glutamine.
- It SHOULD be limited in energy to avoid complications such as hyperglycemia.

Nevertheless, there is general consensus that when the gut is considered to be functioning adequately, enteral nutrition should be preferred to parenteral nutrition, and it should be started within 24 to 48 hours of admission.[6–8] Parenteral nutrition should be saved for those patients about whom there is a good clinical reason for not beginning enteral nutrition in this time frame. The most likely such reason is a condition in which the gut is expected to be dysfunctional for many days, although patients with esophageal surgery,[20] intestinal perforation and peritonitis,[21] colorectal surgery,[22,23] abdominal aortic aneurysm surgery,[24] and acute pancreatitis[25,26] can be readily enterally fed with few complications.

POTENTIAL RISKS ASSOCIATED WITH ENTERAL FEEDING

Enteral nutrition typically is delivered into the stomach with a nasogastric tube,[27–29] and in many cases this leads to satisfactory delivery of nutrition. However, gastric motility (particularly gastric emptying) and absorption are impaired in critical illness,[30–32] and this may lead to enteral feeding intolerance.[33]

Enteral feeding intolerance has been reported to occur in 31% to 46% of patients with gastric feeding[33,34] and usually is manifest by large gastric residual volumes and vomiting.[27,33,35] It leads to a large number of patients not achieving their expected energy delivery requirements[36] and appears to place patients at a higher risk of pneumonia and possibly mortality.[33] This often is exacerbated in critically ill patients when their enteral nutrition is withheld for diagnostic and therapeutic procedures.

Managing potential enteral feeding intolerance by delaying the initiation of nasogastric feeding is illogical, because it will reduce the chance of the patient's meeting energy requirements, may worsen intestinal permeability,[37] and may lead to increased infectious complications and hospital length of stay.[4] There is therefore a much greater rationale for more proactive strategies such as the use of an evidence-based feeding guideline that includes the use of promotility drugs and small bowel feeding when patients develop features of intolerance.[5]

REDUCING THE RISKS OF ENTERAL NUTRITION

Promotility Drugs

Since it was discovered that critical illness leads to significant gastrointestinal dysmotility,[30] promotility drugs have been considered a sensible option. Metoclopramide and erythromycin improve gastric emptying.[38,39] Erythromycin seems the superior agent because of its ability to improve short-term tolerance in patients with enteral feeding intolerance[40,41] and also when administered routinely with gastric feeding.[42] Although the dose of oral erythromycin for this indication often is recommended as 200 to 250 mg four times daily, 70 mg seems equally effective.[43] Naloxone also reduces gastric residual volume,[44] but its effect on feeding tolerance has not been established. Cisapride accelerates gastric emptying and lowers gastric residual volume[45,46] but is unfortunately no longer commercially available because of the risk of cardiac dysrhythmia.[47] Several other novel promotility drugs are being investigated, but none is yet commercially available.[48]

Metoclopramide is the only promotility drug that has been subjected to a study large enough to determine its efficacy on clinically meaningful outcomes. Despite its useful gastric emptying effect, it had no effect on nosocomial pneumonia or mortality rate.[38] Given also that erythromycin may increase the risk of antibiotic resistance[49] and naloxone seems likely to be more effective only in the presence of large narcotic doses, it is difficult to make strong treatment recommendations about promotility drugs. Nevertheless, careful use of either erythromycin or metoclopramide seems warranted when the first signs of enteral feeding intolerance develop. Erythromycin is more likely to be effective, although if intolerance persists with the use of either drug, the combination of both seems reasonable practice.[50]

Small Bowel Feeding

Small bowel feeding has some inherent advantages over gastric feeding, because the small bowel has a greater absorptive capacity than the stomach,[51] has less impaired motility in critical illness,[52] and is further away from the pharynx and respiratory tree, thereby potentially reducing the risk of pneumonia caused by gastroesophageal reflux.[53] Clinical studies comparing small bowel and gastric feeding have shown that small bowel feeding lowers gastric residual volume,[34,54] and although this has sometimes led to improved nutritional intake,[55,56] this has not been a consistent finding.[34,54,57] One meta-analysis found that small bowel feeding was associated with a reduced risk of pneumonia,[6] although others have not been as conclusive.[58,59]

Gastric feeding therefore should be regarded as the initial method of enteral feeding for critically ill patients, but small bowel feeding is recommended when patients develop feeding intolerance. Whether a promotility drug should be tried before a small bowel feeding tube is placed is not well established at the present time, but recent clinical practice surveys have suggested that clinicians prefer promotility drugs to small bowel feeding,[60,61] seemingly because of the logistical and technical concerns that are associated with nasojejunal tube placement.

Numerous insertion techniques have been described,[62] and although "blind" placement at the bedside is certainly the least logistically challenging, this is time consuming and less successful than the placement of a nasogastric tube.[57] Erythromycin used specifically to assist insertion appears to improve success rates,[63] and specific mechanical maneuvers also have been described.[64] Fluoroscopy and endoscopy improve the success rates,[34,65] but logistical concerns remain a deterrent in many institutions. "Self-migrating" tubes such as the frictional nasojejunal (NJ) tube (Tiger Tube, Cook Critical Care, Bloomington, IN) may improve the insertion success and can be used safely and easily in clinical practice.[66,67]

Patients in the intensive care unit (ICU) who develop feeding intolerance during gastric feeding therefore should have a small bowel feeding tube placed. Institutional considerations should determine which insertion technique is chosen, and because gastric residual volumes often remain large (placing the patient at risk of pneumonia), a promotility drug, such as metoclopramide or erythromycin, is recommended, as is the use of a supplementary nasogastric tube to drain this gastric fluid.

Supplementary Parenteral Nutrition

Parenteral nutrition often has been considered an easy option for enteral feeding intolerance (especially when it is severe), as most critically ill patients already have central venous access. Although two recent clinical practice guidelines[7,8] recommend supplementary parenteral nutrition to assist meeting nutritional goals in the presence of enteral feeding intolerance, caution is advised, as supplementary parenteral nutrition has been shown to lead to excess mortality in burn patients[68] and has not been shown to improve clinical outcomes over enteral nutrition alone in meta-analyses.[6,7] It therefore seems prudent that parenteral nutrition should not be used to supplement enteral nutrition in critically ill patients until all other strategies to maximize enteral nutrition (including promotility drugs and small bowel feeding) have been attempted (Fig. 80.1).

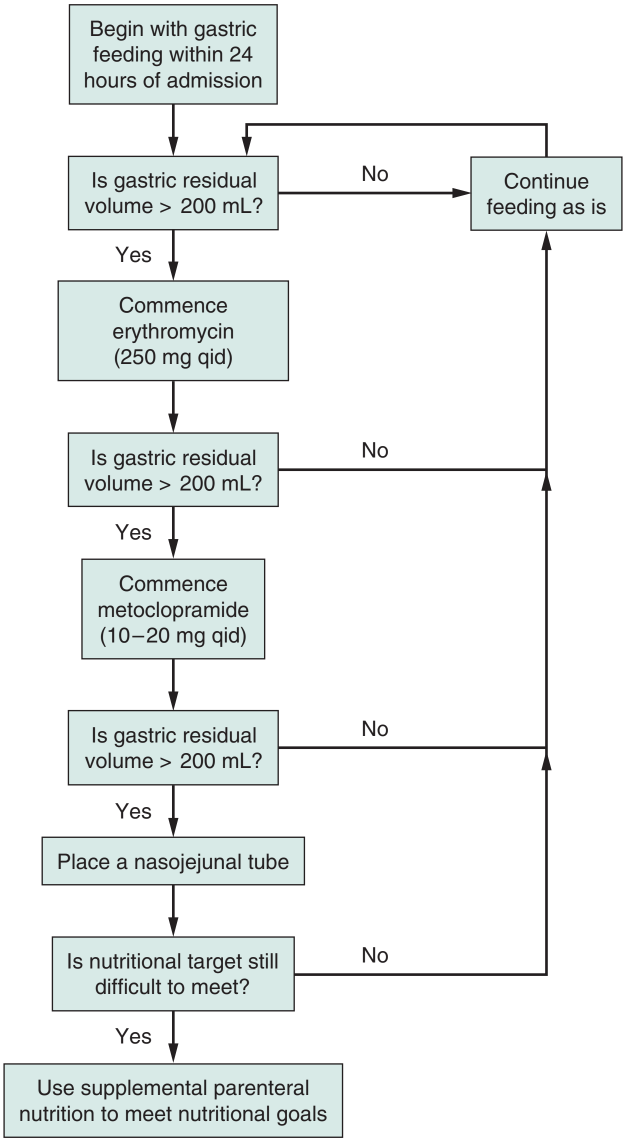

FIGURE 80.1 Simple algorithm for nutritional support in the critically ill patient.

CHOOSING THE OPTIMAL ENTERAL NUTRITION PRODUCT

The optimal macronutrient composition (i.e., carbohydrate, lipid, and protein content) of enteral nutrition for the heterogeneous critically ill patient remains largely unknown, and consequently there are dozens of commercially prepared enteral nutrition products with specific variations in the combination of carbohydrate, lipid, and protein.

All three recently published evidence-based guidelines have suggested that a standard polymeric enteral formula should be administered,[6–8] and this seems reasonable for most critically ill patients. Estimation of energy and protein requirements should be performed using standardized equations leading to an hourly goal rate being established. In some specific patient groups, evidence is accumulating that varying the nutrient composition with the aims of either replacing important deficiencies or modulating immune function may be useful, although controversy in this area continues.

Glutamine

There is recent consensus that glutamine-supplemented parenteral nutrition should be used in the ICU patient who requires parenteral nutrition[6–8]; this consensus is based on studies in ICU and abdominal surgical patients.[69–71] This is in contrast with enteral nutrition, in which glutamine has not been shown to improve clinical outcomes when administered enterally to heterogeneous groups of critically ill patients.[72,73]

However, glutamine-supplemented enteral nutrition may be efficacious in two homogeneous groups of patients: those with burns and those with trauma.[74,75] Glutamine therefore should be strongly considered in all ICU patients having parenteral nutrition and all burn and trauma patients having enteral nutrition, and although the exact dose remains controversial, a dose in the range of 0.4 to 0.5 g/kg body weight seems reasonable.

Immunonutrition

Enteral nutrition products with a mixture of arginine, nucleotides, and omega-3 fatty acids have been considered to modulate immune function and therefore considered "immunonutrition." Despite more than a decade of research, these products still remain controversial in critical care practice as they appear to elicit harmful effects in patients with sepsis and septic shock.[6] Of the various substrates, arginine appears to be the sole culprit of the substrates; a recent study in animals demonstrated the scientific rationale for the potential lethality of arginine in septic shock.[76]

Given immunonutrition had no effect in the largest of all the heterogeneous ICU patient studies,[77] the pragmatic view is that if immunonutrition causes harm in septic patients (presumably resulting from arginine), it therefore may have a beneficial effect in nonseptic patients (presumably resulting from omega-3 fatty acids). The way of the future must be to study the individual nutrients in specific disease states rather than the immunonutrition package in heterogeneous populations.[78] The present recommendation is not to administer immunonutrition products containing arginine to ICU patients.

Omega-3 Fatty Acids

There have now been two recent studies[79,80] in which enteral nutrition products containing fish oil (eicosapentaenoic acid), borage oil (gamma-linolenic acid), and antioxidants led to beneficial clinical outcomes in patients with acute lung injury and septic shock. Given a previous study demonstrated similar effects in patients with acute lung injury,[81] it appears that an enteral nutrition product containing these omega-3 fatty acids should be used when patients with acute lung injury and septic shock are treated in the ICU.

ISSUES SPECIFIC TO THE CRITICALLY ILL RENAL FAILURE PATIENT

The principles of nutritional support in critically ill patients with acute renal failure are similar to those in critically ill patients without renal failure. Although some clinicians feel that restriction of fluid and protein may be required when renal failure is present, there is little evidence to support this notion and there seems a greater rationale to use either earlier or more effective continuous renal replacement therapy to improve outcomes.

What is known is that amino acids (including glutamine), vitamins, and trace elements often are lost from the body through the filter in continuous renal replacement therapy, although the exact amount in individual patients varies.[82] Making sure that the nutritional prescription does not have inadequate amounts of energy, protein, vitamins, and trace elements is therefore extremely important, especially because gastric emptying also can be impaired more significantly in patients with renal failure. The threshold to use promotility drugs, small bowel feeding tubes, and supplemental parenteral nutrition therefore should be lowered to maximize nutritional intake.

CONCLUSION

Evidence-based guidelines for nutritional support in the ICU should be followed where possible, meaning that enteral nutrition is preferred to parenteral nutrition. When intolerance occurs, small bowel feeding and promotility drugs should be attempted before supplementary parenteral nutrition is used (see Fig. 80.1). Clinicians should consider carefully the composition of the enteral nutrition with regard to lipid content, antioxidants, and glutamine as clinical outcomes are improved in some specific groups of patients.

Key Points

1. Nutritional support leads to a reduction in complication rates and shorter hospitalization in critically ill patients, especially when evidence-based guidelines are followed.
2. Enteral nutrition should be preferred to parenteral because of improved gut function, reduced infectious complications, and less expense. It should be started within 24 to 48 hours of intensive care unit admission in any patient with a functioning gut.
3. Patients can be intolerant of gastric feeding as a result of impaired upper gut motility; this should be recognized and treated as it may lead to pneumonia. However, the balance appears to be in favor of early enteral nutrition rather than avoiding intolerance by delaying feeding.
4. Erythromycin and metoclopramide should be used when intolerance occurs; however, a nasojejunal tube should be inserted when the intolerance does not resolve quickly and in preference to supplementary parenteral nutrition.
5. Glutamine should be added to the enteral nutrition in burn and trauma patients. It always should be added to any supplemental parenteral nutrition used in patients in the intensive care unit.
6. Omega-3 fatty acids should be part of the enteral nutrition composition in patients with acute lung injury and sepsis because of their important antiinflammatory effects.
7. In patients with renal failure, there should be careful attention to the amount of energy, protein, vitamins, and trace elements administered depending on the patient and the type of continuous renal replacement therapy being used.

Key References

4. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: A systematic review. *Crit Care Med*. 2001;29:2264-2270.
5. Martin CM, Doig GS, Heyland DK, et al. Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). *CMAJ*. 2004;170:197-204.
6. Heyland DK, Dhaliwal R, Drover JW, et al. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN*. 2003;27:355-373.
10. Hadfield RJ, Sinclair DG, Houldsworth PE, et al. Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. *Am J Respir Crit Care Med*. 1995;152:1545-1548.
13. Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. *N Engl J Med*. 1991;325:525-532.

A complete reference list can be found online at ExpertConsult.com.

References

1. Giner M, Laviano A, Meguid MM, et al. In 1995 a correlation between malnutrition and poor outcome in critically ill patients still exists. *Nutrition*. 1996;12:23-29.
2. Schroeder D, Gillanders L, Mahr K, et al. Effects of immediate postoperative enteral nutrition on body composition, muscle function, and wound healing. *JPEN*. 1991;15:376-383.
3. 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;215:503-511.
4. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: A systematic review. *Crit Care Med*. 2001;29:2264-2270.
5. Martin CM, Doig GS, Heyland DK, et al. Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). *CMAJ*. 2004;170:197-204.
6. Heyland DK, Dhaliwal R, Drover JW, et al. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN*. 2003;27:355-373.
7. Doig GS, Simpson F, for the Australian and New Zealand Intensive Care Society Clinical Trials Group. Evidence-based guidelines for nutritional support of the critically ill: Results of a bi-national guideline development conference; 2005. Downloadable from. www.evidencebased.net.
8. Kreymann KG, Berger MM, Deutz NE, et al. ESPEN Guidelines on enteral nutrition: Intensive care. *Clin Nutr*. 2006;25:210-223.
9. Braga M, Gianotti L, Gentilini O, et al. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition. *Crit Care Med*. 2001;29:242-248.
10. Hadfield RJ, Sinclair DG, Houldsworth PE, et al. Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. *Am J Respir Crit Care Med*. 1995;152:1545-1548.
11. Takagi K, Yamamori H, Toyoda Y, et al. Modulating effects of the feeding route on stress response and endotoxin translocation in severely stressed patients receiving thoracic esophagectomy. *Nutrition*. 2000;16:355-360.
12. Braunschweig CL, Levy P, Sheean PM, et al. Enteral compared with parenteral nutrition: A meta-analysis. *Am J Clin Nutr*. 2001;74:534-542.
13. Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. *N Engl J Med*. 1991;325:525-532.
14. Marik PE, Pinsky M. Death by parenteral nutrition. *Intensive Care Med*. 2003;29:867-869.
15. Lipman TO. Grains or veins: is enteral nutrition really better than parenteral nutrition? A look at the evidence. *JPEN*. 1998;22:167-182.
16. Jeejeebhoy KN. Total parenteral nutrition: potion or poison? *Am J Clin Nutr*. 2001;74:160-163.
17. 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.
18. 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.
19. 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.
20. Han-Geurts IJ, Hop WC, Verhoef C, et al. Randomized clinical trial comparing feeding jejunostomy with nasoduodenal tube placement in patients undergoing oesophagectomy. *Br J Surg*. 2007;94:31-35.
21. Singh G, Ram RP, Khanna SK. Early postoperative enteral feeding in patients with nontraumatic intestinal perforation and peritonitis. *J Am Coll Surg*. 1998;187:142-146.
22. Andersen HK, Lewis SJ, Thomas S. Early enteral nutrition within 24 h of colorectal surgery versus later commencement of feeding for postoperative complications. *Cochrane Database Syst Rev*. 2006;4:CD004080.
23. Hsu TC, Su CF, Huang PC, et al. Comparison of tolerance and change of intragastric pH between early nasogastric and nasojejunal feeding following resection of colorectal cancer. *Clin Nutr*. 2006;25:681-686.
24. Fraser RJ, Ritz M, Di Matteo AC, et al. Distal small bowel motility and lipid absorption in patients following abdominal aortic aneurysm repair surgery. *World J Gastroenterol*. 2006;12:582-587.
25. 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;23:336-345.
26. McClave SA, Chang WK, Dhaliwal R, et al. Nutrition support in acute pancreatitis: a systematic review of the literature. *JPEN*. 2006;30:143-156.
27. Heyland D, Cook DJ, Winder B, et al. Enteral nutrition in the critically ill patient: A prospective survey. *Crit Care Med*. 1995;23:1055-1060.
28. Hill SA, Nielsen MS, Lennard-Jones JE. Nutritional support in intensive care units in England and Wales: A survey. *Eur J Clin Nutr*. 1995;49:371-378.
29. Planas M, for the Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. Artificial nutrition support in intensive care units in Spain. *Intensive Care Med*. 1995;21:842-846.
30. Dive A, Moulart M, Jonard P, et al. Gastroduodenal motility in mechanically ventilated critically ill patients: a manometric study. *Crit Care Med*. 1994;22:441-447.
31. Heyland DK, Tougas G, King D, et al. Impaired gastric emptying in mechanically ventilated, critically ill patients. *Intensive Care Med*. 1996;22:1339-1344.
32. Ritz MA, Fraser R, Edwards N, et al. Delayed gastric emptying in ventilated critically ill patients: measurement by 13 C-octanoic acid breath test. *Crit Care Med*. 2001;29:1744-1749.
33. Mentec H, Dupont H, Bocchetti M, et al. Upper digestive intolerance during enteral nutrition in critically ill patients: Frequency, risk factors, and complications. *Crit Care Med*. 2001;29:1955-1961.
34. 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.
35. 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.
36. De Beaux I, Chapman M, Fraser R, et al. Enteral nutrition in the critically ill: a prospective survey in an Australian intensive care unit. *Anaesth Intensive Care*. 2001;29:619-622.
37. Kompan L, Kremzar B, Gadzijev E, et al. Effects of early enteral nutrition on intestinal permeability and the development of multiple organ failure after multiple injury. *Intensive Care Med*. 1999;25:157-161.
38. Jooste CA, Mustoe J, Collee G. Metoclopramide improves gastric motility in critically ill patients. *Intensive Care Med*. 1999;25:464-468.
39. Dive A, Miesse C, Galanti L, et al. Effect of erythromycin on gastric motility in mechanically ventilated critically ill patients: a double-blind, randomized, placebo-controlled study. *Crit Care Med*. 1995;23:1356-1362.
40. Chapman MJ, Fraser RJ, Kluger MT, et al. Erythromycin improves gastric emptying in critically ill patients intolerant of nasogastric feeding. *Crit Care Med*. 2000;28:2334-2337.
41. 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.
42. Reignier J, Bensaid S, Perrin-Gachadoat D, et al. Erythromycin and early enteral nutrition in mechanically ventilated patients. *Crit Care Med*. 2002;30:1237-1241.
43. Ritz MA, Chapman MJ, Fraser RJ, et al. Erythromycin dose of 70 mg accelerates gastric emptying as effectively as 200 mg in the critically ill. *Intensive Care Med*. 2005;31:949-954.
44. 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.
45. Spapen HD, Duinslaeger L, Diltoer M, et al. Gastric emptying in critically ill patients is accelerated by adding cisapride to a standard enteral feeding protocol: Results of a prospective, randomized, controlled trial. *Crit Care Med*. 1995;23:481-485.

46. Heyland DK, Tougas G, Cook DJ, et al. Cisapride improves gastric emptying in mechanically ventilated, critically ill patients. A randomized, double-blind trial. *Am J Respir Crit Care Med*. 1996;154:1678-1683.
47. Layton D, Key C, Shakir SA. Prolongation of the QT interval and cardiac arrhythmias associated with cisapride: Limitations of the pharmacoepidemiological studies conducted and proposals for the future. *Pharmacoepidemiol Drug Saf*. 2003;12:31-40.
48. Roberts DJ, Banh HL, Hall RI. Use of novel prokinetic agents to facilitate return of gastrointestinal motility in adult critically ill patients. *Curr Opin Crit Care*. 2006;12:295-302.
49. Lonks JR. What is the clinical impact of macrolide resistance? *Curr Infect Dis Rep*. 2004;6:7-12.
50. Nguyen NQ, Chapman MJ, Fraser RJ, et al. Erythromycin is more effective than metoclopramide in the treatment of feed intolerance in critical illness. *Crit Care Med*. 2007;35:483-489.
51. Berger MM, Berger-Gryllaki M, Wiesel PH, et al. Intestinal absorption in patients after cardiac surgery. *Crit Care Med*. 2000;28:2217-2223.
52. Moore FA, Cocanour CS, McKinley BA, et al. Migrating motility complexes persist after severe traumatic shock in patients who tolerate enteral nutrition. *J Trauma*. 2001;51:1075-1082.
53. Heyland DK, Drover JW, MacDonald S, et al. Effect of postpyloric feeding on gastroesophageal regurgitation and pulmonary microaspiration: Results of a randomized controlled trial. *Crit Care Med*. 2001;29:1495-1501.
54. 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.
55. Montecalvo MA, Steger KA, Farber HW, et al. Nutritional outcome and pneumonia in critical care patients randomized to gastric versus jejunal tube feedings. *Crit Care Med*. 1992;20:1377-1387.
56. Kearns PJ, Chin D, Mueller L, et al. 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.
57. 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.
58. Marik PE, Zaloga GP. Gastric versus post-pyloric feeding: a systematic review. *Crit Care*. 2003;7:R46-R51.
59. 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.
60. Gillanders L, Davies A, Marshall K, et al. The AuSPEN Nutritional Support Study: An observational study of nutritional support practice in Australasian hospitals: Do ICU and non-ICU practice patterns differ? *Clin Nutr*. 2004;23:924-925.
61. Heyland DK, Schroter-Noppe D, Drover JW, et al. Nutrition support in the critical care setting: current practice in Canadian ICUs: Opportunities for improvement? *JPEN*. 2003;27:74-83.
62. Haslam D, Fang J. Enteral access for nutrition in the intensive care unit. *Curr Opin Clin Nutr Metab Care*. 2006;9:155-159.
63. 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.
64. Zaloga GP. Bedside method for placing small bowel feeding tubes in critically ill patients: a prospective study. *Chest*. 1991;100:1643-1646.
65. Foote JA, Kemmeter PR, Prichard PA, et al. A randomized trial of endoscopic and fluoroscopic placement of postpyloric feeding tubes in critically ill patients. *JPEN*. 2004;28:154-157.
66. Orford N, Davies AR, Marshall K, et al. The new frictional nasojejunal tube: A high success rate in achieving small bowel placement in critically ill patients; 2004. Proceedings of the 29th Australian and New Zealand Scientific Meeting on Intensive Care, p 53.
67. Samis AJ, Drover JW, Heyland DK. Evaluation of three different strategies for post-pyloric placement of enteral feeding tubes. *Intensive Care Med*. 2004;30:S149.
68. 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.
69. Novak F, Heyland DK, Avenell A, et al. Glutamine supplementation in serious illness: a systematic review of the evidence. *Crit Care Med*. 2002;30:2022-2029.
70. Zheng YM, Li F, Zhang MM, et al. Glutamine dipeptide for parenteral nutrition in abdominal surgery: a meta-analysis of randomized controlled trials. *World J Gastroenterol*. 2006;12:7537-7541.
71. Dechelotte P, Hasselmann M, Cynober L, et al. L-alanyl-L-glutamine dipeptide-supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in critically ill patients: the French controlled, randomized, double-blind, multicenter study. *Crit Care Med*. 2006;34:598-604.
72. Hall JC, Dobb G, Hall J, et al. A prospective randomized trial of enteral glutamine in critical illness. *Intensive Care Med*. 2003;29:1710-1716.
73. Schulman AS, Willcutts KF, Claridge JA, et al. Does the addition of glutamine to enteral feeds affect patient mortality? *Crit Care Med*. 2005;33:2501-2506.
74. Garrel D, 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.
75. Houdijk AP, Rijnsburger ER, Jansen J, et al. Randomized trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet*. 1998;352:772-776.
76. Kalil AC, Sevransky JE, Myers DE, et al. Preclinical trial of L-arginine monotherapy alone or with N-acetylcysteine in septic shock. *Crit Care Med*. 2006;34:2719-2728.
77. Kieft H, Roos AN, van Drunen JD, et al. Clinical outcome of immunonutrition in a heterogeneous intensive care population. *Intensive Care Med*. 2005;31:524-532.
78. Heyland D, Dhaliwal R. Immunonutrition in the critically ill: From old approaches to new paradigms. *Intensive Care Med*. 2005;31:501-503.
79. Singer P, Theilla M, Fisher H, et al. 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.
80. 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.
81. 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.
82. Marin A, Hardy G. Practical implications of nutritional support during continuous renal replacement therapy. *Curr Opin Clin Nutr Metab Care*. 2001;4:219-225.