

Nutrition in Clinical Practice

<http://ncp.sagepub.com/>

Specialized Enteral Formulas in Acute and Chronic Pulmonary Disease

Ainsley M. Malone

Nutr Clin Pract 2009 24: 666

DOI: 10.1177/0884533609351533

The online version of this article can be found at:

<http://ncp.sagepub.com/content/24/6/666>

Published by:



<http://www.sagepublications.com>

On behalf of:



The American Society for Parenteral & Enteral Nutrition

Additional services and information for *Nutrition in Clinical Practice* can be found at:

Email Alerts: <http://ncp.sagepub.com/cgi/alerts>

Subscriptions: <http://ncp.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

Specialized Enteral Formulas in Acute and Chronic Pulmonary Disease

Ainsley M. Malone, MS, RD, LD, CNSC

Financial disclosure: Ms Malone is a member of the Abbott Nutrition Speaker's Bureau.

The relationship between pulmonary disease and nutrition is significant. Nutrition support therapy is common in this patient population as a supportive and/or therapeutic measure. Historical reports of adverse respiratory function associated with high parenteral carbohydrate intakes have been the rationale for using high-fat enteral formulas in patients with chronic pulmonary dysfunction. Theoretically, providing a low-carbohydrate formula will reduce carbon dioxide production, result in a reduced respiratory quotient, and lead to associated improvement in pulmonary outcomes. In the patient with acute respiratory distress syndrome, an imbalance of mediators exists, with proinflammatory mediators being dominant,

ultimately affecting the disease course. An enteral formula with modified lipids designed to modulate eicosanoid production, and therefore influence the inflammatory cascade, is available. This article reviews the rationale for use of modified enteral formulas in both chronic and acute pulmonary disease, reviews the available studies evaluating the efficacy of these formulas, and provides overall recommendations for the use of specialized enteral formulas in individuals with pulmonary disease. (*Nutr Clin Pract.* 2009;24:666-674)

Keywords: enteral nutrition; fatty acids; lung diseases; pulmonary disease, chronic obstructive; respiratory distress syndrome, adult

A significant relationship exists between nutrition and pulmonary disease. Whether acute or chronic, pulmonary disease is associated with an increased risk and incidence of malnutrition. Malnutrition can result in further pulmonary system impairment, thereby leading to negative outcomes. Providing nutrition support to individuals with pulmonary disease is common, especially in hospitalized patients. Enteral nutrition (EN) is the modality of choice unless GI function is impaired, thus requiring the use of parenteral nutrition (PN). From the perspective of enteral tube feeding or oral supplement usage, an important clinical question is frequently asked: Do patients with pulmonary disease benefit from a specialized formula? The purpose of this article is to describe the use of specialized pulmonary formulas in individuals with acute or chronic pulmonary disease and to evaluate the evidence supporting efficacy with this practice.

Nutrition Support in Pulmonary Disease

Individuals with both acute and chronic pulmonary disease often require nutrition support during the course of

their illness. Hospitalized patients with acute respiratory failure related to exacerbation of their chronic disease are candidates for nutrition support because their ability to adequately consume an oral diet within 5 to 10 days is unlikely.¹ EN is the preferred nutrition support modality when adequate GI function is present.¹ Ambulatory patients with chronic obstructive pulmonary disease (COPD) often receive nutrition supplementation in the form of either oral supplements or enteral tube feedings. The recently published nutrition practice guidelines for individuals with COPD by the American Dietetic Association recommend that for both inpatients and outpatients with COPD and a body mass index <20 kg/m², clinicians should "recommend the consumption of medical food supplements" because their use is associated with increased energy intake and weight gain (rating = fair).²

Providing nutrition support to prevent or treat malnutrition without exacerbating existing lung disease can be a clinical challenge. Metabolism of macronutrients all yield carbon dioxide (CO₂) oxidative end products, with carbohydrate (CHO) producing the greatest amount. The respiratory quotient (RQ: amount of CO₂ produced, divided by amount of oxygen consumed) can reflect substrate utilization. When the value exceeds 1.0, oxygen consumption must increase, which in the individual with limited respiratory reserve can lead to an increased work of breathing.³ With significant pulmonary disease, the increased in workload can further impair respiratory function, resulting in respiratory failure or the inability to wean from mechanical ventilation. This was clearly demonstrated in

From Mt. Carmel West Hospital, Department of Pharmacy, Columbus, Ohio.

Address correspondence to: Ainsley M. Malone, MS, RD, LD, CNSC, Mt. Carmel West Hospital, Department of Pharmacy, 793 West State Street, Columbus, OH 43222; e-mail: AinsleyM@earthlink.net.

Table 1. Nutrition Characteristics of Enteral Formulas Designed for Chronic Pulmonary Disease

Manufacturer	kcal/mL	Carbohydrate, g/L (% total kcal)	Protein, g/L (% total kcal)	Fat, g/L (% total kcal)
Abbott (Columbus, OH)	1.5	106 (28.2)	62.6 (16.7)	93.3 (55.1)
Nestlé (Minnetonka, MN)	1.5	100 (26.6)	68 (18)	94.8 (55.4)

the 1980s when case reports outlined hypercapnia and respiratory failure in patients receiving high-CHO parenteral formulations.⁴⁻⁷ Standard practice at that time was to provide 100% of nonprotein calories as dextrose and provide lipid intermittently as a source of essential fatty acids. Based on the detrimental effects observed with excessive dextrose intake, practice recommendations were made to alter PN formulas and provide increased lipid with reduced dextrose.^{7,8}

Enteral Nutrition in Chronic Pulmonary Disease

The practice of altering macronutrient distribution with PN to avoid detrimental respiratory effects was also applied to EN support in the mid-1980s.⁸⁻¹⁰ The rationale for using an altered macronutrient formulation suggests that the provision of a reduced amount of CHO will lead to a reduction in CO_2 production, thus minimizing the deleterious respiratory effects observed with high-CHO parenteral formulas. Current enteral formula manufacturers offer 2 types of such formulas (Table 1). Multiple studies exist evaluating the effects of a high-fat enteral formula on respiratory function and status in those with chronic pulmonary disease¹¹⁻¹⁵; these studies produced variable results depending on the population studied, the method of feeding used, and the nutrition status of the patients studied. These studies were limited by small sample sizes. Overall, in 6 studies with a total of 152 patients (ambulatory and hospitalized), the majority of the findings demonstrated a lack of clinical benefit with use of such enteral formulas.

In most of the early reports citing adverse effects with large dextrose intakes, patients received excessive calories (1.7–2.25 times the measured energy expenditure).^{5,6,16} In a well-known study by Talpers et al,¹⁷ 20 mechanically ventilated patients received either varying amounts of CHO (40%, 60%, or 75%) or total calories (1, 1.5, or 2 times the basal energy expenditure). Carbon dioxide production (VCO_2) was measured in both groups of patients 48 hours following a change in nutrient regimen. There was no significant difference in VCO_2 among the varying CHO regimens; however, VCO_2 significantly increased as the total caloric intake increased ($P < .01$). The authors concluded that avoidance of overfeeding is of greater significance than CHO intake in avoiding nutritionally related

hypercapnia. This along with early reports of excessive overfeeding lends support for the argument that total caloric intake is more important than intake of CHO in preventing adverse ventilatory effects.

Ambulatory Outpatients

High-fat, reduced-CHO enteral formulas have been studied frequently in ambulatory COPD patients with conflicting results. Angelillo et al¹¹ in 1985 were the first to report a benefit in respiratory function by decreasing the percentage of calories provided by CHO. The investigators studied 14 ambulatory, hypercapnic COPD patients, altering the CHO portion of an oral diet. CHO intake ranged from 28% to 78% of total calories. The lowest-CHO diet resulted in a significantly lower production of CO_2 ($P < .002$) and lower RQ ($P < .001$) compared with those moderate or high in CHO content. The authors concluded that a lower proportion of CHO calories favorably altered respiratory parameters and may be an important consideration in patients with COPD.

In an effort to compare the differences in gas exchange and ventilation between normal patients and those with COPD, Kuo et al¹⁸ evaluated a high-fat oral liquid diet (55.2% fat and 28.1% CHO) and a high-CHO oral liquid diet (31.5% fat and 54.5% CHO) in 12 stable ambulatory COPD patients and 12 healthy volunteers. Significantly greater increases in oxygen consumption (Vo_2) ($P < .05$), VCO_2 ($P < .001$), and expired minute ventilation (Ve) ($P < .001$) occurred in the COPD patient group receiving the high-CHO diet compared with those receiving the high-fat diet. The healthy volunteers experienced no change in ventilatory parameters with either diet.

A more recent evaluation of different nutrition supplements in ambulatory COPD patients demonstrated different results. In 2001, Vermeeren et al¹² conducted a 2-part evaluation of nutrition supplements on metabolism and exercise capacity in stable COPD patients. Part 1 compared a 250-kcal load with a 500-kcal load. Part 2 compared a high-CHO supplement (60% CHO and 20% fat) with a high-fat supplement (60% fat and 20% CHO). Significant increases in VCO_2 ($P < .05$), Vo_2 ($P < .05$), and RQ ($P < .01$) were observed when the higher caloric load was consumed. Conversely there were no significant differences in VCO_2 or Vo_2 between the high-CHO and high-fat supplements. The RQ, however, was significantly greater in those who received the high-CHO supplement ($P < .01$). In addition, the subjects

complained of dyspnea when consuming the high-fat supplement. Of particular note, the authors stated that the rise in RQ could not be due to an increased VCO_2 but rather was caused by a lower VO_2 , reflecting a more efficient metabolism. They concluded that a lower energy-containing supplement is preferred to one of higher energy content because of an improved ventilatory response with the reduced calorie intake. They also concluded that a high-CHO supplement is preferable to a high-fat version because the former may increase lung function and result in less dyspnea.

One important aspect to consider when evaluating nutrition modification studies in COPD patients is to identify the nutrition status of the patients studied. It is well-known that malnutrition leads to decreased respiratory function; are positive results with a high-fat formula more likely to be demonstrated with malnourished patients? Cai et al¹³ designed a study in 2003 to answer this question. Sixty COPD patients with documented weights of <90% ideal body weight were randomized to consume an oral diet with high-fat supplements or a diet with increased CHO content for 3 weeks. Total daily energy intake remained the same between groups, with the mean intake of 33.5 kcal/kg in the high-fat group and 32.5 kcal/kg in the high-CHO group. Significant decreases in RQ, VCO_2 , VO_2 , and VE ($P < .05$) were observed in the high-fat group compared with the high-CHO group. In addition, the forced expiratory volume decreased in both groups, although this was only significant in the high-fat group ($P < .05$). The authors proposed that this observation was most likely due to an improvement in nutrition status (not defined) rather than a change in actual airway obstruction. They concluded that in malnourished COPD patients, pulmonary function can be significantly improved with a high-fat, reduced-CHO oral supplement.

Hospitalized Patients

Two studies have been conducted evaluating the role of high-fat formulas in weaning patients from mechanical ventilation. In 1988, al-Saady et al¹⁴ studied the effects of a modified enteral formula on 20 ventilated patients in an intensive care unit (ICU). Patients were randomized to receive either a high-fat formula (55.2% fat and 28.1% CHO) or a standard formula (30% fat and 53.3% CHO) in amounts equal to their estimated energy requirements. Respiratory failure was due to a variety of underlying mechanisms, some of which included exacerbation of COPD. Significant decreases in $Paco_2$ ($P < .03$), tidal volume ($P < .009$), and peak inspiratory pressure ($P < .046$) were observed in the high-fat group, whereas these parameters all increased in the group receiving the standard formula. Time spent on artificial ventilation was 42% less in the high-fat group compared with time in the standard formula group ($P < .001$). The authors noted that sedative and muscle-relaxing agents may have affected the overall

results. They also suggested that because the underlying cause of the respiratory failure varied between the 2 groups, the duration of ventilation may have been affected. However, they concluded that a high-fat enteral formula appears to be beneficial in patients undergoing artificial ventilation.

Van den Berg et al¹⁵ conducted a similar study in 1994, with slightly different results. Their unblinded study compared a high-fat formula (55.2% fat and 28.1% CHO) with a standard formula (30% fat and 53.3% CHO) in 32 medical patients in the ICU. Patient diagnoses included COPD, pneumonia without COPD, and neurologic disease. The RQ during weaning was significantly lower in the high-fat formula group (0.72 ± 0.02 vs 0.86 ± 0.02 ; $P < .01$). There were, however, no significant differences in VCO_2 during weaning, and both groups had similar successful weaning episodes. The authors concluded that a high-fat formula can significantly decrease RQ values in ventilated patients. Nevertheless, it is important to consider whether the reported significant decreases were of actual clinical significance because the RQ was well below 1.0; values higher than 1.0 are associated with a significant increase in work of breathing.

Overall results demonstrating whether a high-fat enteral formula vs a standard formulation offers a clinical advantage to the patient with chronic pulmonary disease are inconclusive. One must look closely at the population studied and the clinical significance of the reported results. When considering use of such a formula in the hospitalized, mechanically ventilated patient, it is important to keep in mind potential disadvantages. Delayed gastric emptying and increased formula costs are reasons to avoid the routine use of a high-fat formula in mechanically ventilated patients.¹⁹⁻²¹ As with most nutrition support practices, patient monitoring is essential. If challenges in ventilatory management occur with the use of a standard enteral formula, offering an altered macronutrient formula is an option. Several organizations have stated that routine use of an altered macronutrient formula for those with chronic pulmonary disease is not recommended.²²⁻²⁴ (See Table 2 for specific recommendations and Table 3 for a description of the various organizations' grading systems.) However, in the ambulatory patient setting, where nutrition repletion and weight gain are desired goals, the use of a modified lipid/CHO formula may be advantageous to limit potential adverse ventilatory effects during a period of planned overfeeding. It is this setting for which a pulmonary formula may be best suited.²⁵

Nutrition Support in Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a clinical state characterized by severe hypoxemia, diffuse pulmonary infiltrates, and respiratory failure.²⁶ Despite advances in

Table 2. Guidelines and Recommendations for Use of an Altered Macronutrient Enteral Formula in Individuals With Chronic Obstructive Pulmonary Disease

Organization	Year Published	Recommendation	Grade
European Society for Parenteral and Enteral Nutrition	2006	In stable COPD, there is no additional advantage of disease-specific low-carbohydrate, high-fat oral nutrition supplements compared with standard high-protein or high-energy oral nutrition supplements.	B
American Dietetic Association Evidence Analysis Library	2008	Registered dietitians should advise that the selection of medical food supplements for individuals with COPD be influenced more by patient preference than by the percentage of fat or carbohydrate.	Fair
Canadian Clinical Practice Guidelines	2009	There are insufficient data to recommend high-fat/low-carbohydrate diets for critically ill patients. ^a	Not applicable
Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition	2009	Specialty high-lipid, low-carbohydrate formulations designed to manipulate the respiratory quotient and reduce carbon dioxide production are not recommended for routine use in intensive care unit patients with acute respiratory failure.	E

COPD, chronic obstructive pulmonary disease.

^aIncluded 2 studies, one evaluating an altered enteral formula designed for those with pulmonary disease and 1 evaluating a formula designed for those with elevated glucose levels.

understanding the cause and pathogenesis of ARDS and its progression, therapy remains primarily supportive.²⁷⁻³⁰ Providing nutrition support as a therapeutic intervention to the patient with ARDS is essential, because most patients will require mechanical ventilation for some period of time. Current recommendations by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) and the Society of Critical Care Medicine (SCCM) outline that EN should be initiated in the critically ill patient who is unable to maintain volitional intake (grade B) and that it should be started early (within 24–48 hours; grade C).²⁴ The European Society for Parenteral and Enteral Nutrition (ESPEN) recommendations outline that “patients who are not expected to be on a full oral diet within 3 days should receive enteral nutrition (grade C).”²³ The American-European Consensus Conference on ARDS recommends that “nutrition supplementation should be attempted after a few days of critical illness because of its association with a more favorable outcome.”³¹ Moreover, the underlying clinical event leading to the development of ARDS, such as sepsis or trauma, often results in a hypermetabolic state that can significantly increase nutrition requirements. The use of EN is recommended for critically ill patients, such as those with ARDS, unless GI dysfunction is present.^{2,22,24,32}

Enteral Nutrition Modification in ARDS

The underlying mechanism for the development and proliferation of ARDS is not fully understood. The cascade of events is thought to involve uncontrolled inflammatory responses from alveolar macrophages and their release of proinflammatory eicosanoids derived from the metabolism

of arachidonic acid (AA). Several of these metabolites, thromboxane A₂, leukotrienes, and prostaglandin E₂, have been implicated in the development of acute lung injury.^{27,33,34} A specialized enteral formula is available to potentially modulate this inflammatory cascade. The enteral formula offers a modified lipid component containing borage and fish oils, sources of eicosapentaenoic acid (EPA) and γ -linolenic (GLA) acid.³⁵ (See Table 4 for nutrition information.) The presence of these fatty acids displaces the AA metabolized within the immune cellular membrane, leading to an increased production of prostaglandins of the 1 series and leukotrienes of the 5 series, metabolites associated with an anti-inflammatory and vasodilatory state (see Figure 1 for fatty acid metabolic pathway). Vasoconstriction, platelet aggregation, and neutrophil accumulation are reduced when the eicosanoid balance favors anti-inflammatory rather than proinflammatory mediators.^{33,36} The specialized enteral formula provides a greater amount of total lipid than do other formulas designed for metabolic stress. Approximately 55% of total calories are provided as lipid compared with a range of 30% to 39% for other metabolic enteral formulas.^{35,37} ARDS is also associated with a compromised antioxidative system, including reduced levels of α -tocopherol, β -carotene, and selenium.³⁸ Oxidative stress via lipid peroxidation products, high oxygen concentrations, and excessive free radicals may be a factor in the cause of acute lung injury.²⁷ Additionally, this specialty enteral formulation contains increased amounts of α -tocopherol, β -carotene, and ascorbic acid, antioxidants that may have a potentially beneficial role in the course of ARDS.³⁹

The evidence supporting the use of a specialized enteral formula for ARDS is increasing. Preclinical animal data have demonstrated positive effects of EPA and GLA

Table 3. Grading Systems Used by Various Organizations Offering Nutrition Support Guidelines

Organization	Grade or Rating	Definition
American Dietetic Association Evidence Analysis Library: Evidence-Based Guidelines	Strong	The benefits of the recommended approach clearly exceed the harms (or the harms clearly exceed the benefits in the case of a strong negative recommendation), and the quality of the supporting evidence is excellent/good (grade I or II). ^a In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.
	Fair	The benefits exceed the harms (or the harms clearly exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (grade II or III). ^a In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.
	Weak	The quality of evidence that exists is suspect, or well-done studies (grade I, II, or III) ^a show little clear advantage to one approach versus another.
	Consensus	Expert opinion (grade IV) supports the guideline recommendation even though the available scientific evidence did not present consistent results or controlled trials were lacking.
	Insufficient evidence	There is both a lack of pertinent evidence (grade V) ^a and an unclear balance between benefits and harms.
Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition	A	Supported by at least one level I investigation: large randomized trials with clear-cut results; low risk of false-positive (α) and/or false-negative (β) error.
	B	Supported by one level I investigation.
	C	Supported by level II investigations: small randomized trials with uncertain results; moderate to high risk of false-positive (α) or false-negative (β) error.
	D	Supported by level III investigations: nonrandomized cohort with contemporaneous controls.
	E	Supported by level IV or V evidence: nonrandomized cohort with historical controls, case series, uncontrolled studies, and expert opinion.
Canadian Clinical Practice Guidelines	Strongly recommended	If there were no reservations about endorsing an intervention.
	Recommended	If evidence was supportive but there were minor uncertainties about the safety, feasibility, or costs of the intervention.
	Should be considered	If the supportive evidence was weak or there were major uncertainties about the safety, feasibility, or costs of an intervention.
	No recommendation: ie, insufficient data	If there was either inadequate or conflicting evidence.
European Society for Parenteral and Enteral Nutrition	A	I-a Meta-analysis of randomized controlled trials; I-b At least 1 randomized controlled trial.
	B	II-a At least 1 well-designed controlled trial without randomization; II-b At least 1 other type of well-designed, quasi-experimental study; III Well-designed nonexperimental descriptive studies such as comparative studies, correlation studies, case-control studies.
	C	IV Expert opinions or clinical experience of respected authorities.

^aConclusion statements are assigned a grade based on the strength of the evidence. Grade I is good; grade II is fair; grade III is limited; grade IV signifies expert opinion only; and grade V indicates that a grade is not assignable because there is no evidence to support or refute the conclusion. The evidence and these grades are considered when assigning a rating (strong, fair, weak, consensus, insufficient evidence to make a recommendation).

Table 4. Nutrition Characteristics of Enteral Formula Designed for Acute Respiratory Disease Syndrome

Manufacturer	kcal/mL	Carbohydrate, g/L (% total kcal)	Protein, g/L (% total kcal)	Fat, g/L (% total kcal)	Source of Fat	Elevated Levels of Antioxidants
Abbott (Columbus, OH)	1.5	105.3 (28.1)	62.7 (16.7)	93.8 (55.2)	Canola oil, medium-chain triglycerides, marine oil (anchovy, menhaden, salmon, sardine, tuna), borage oil	Vitamin C, 850 mg/L; vitamin E, 320 IU/L; β -carotene, 5 mg/L

Metabolism of PUFA by Macrophages

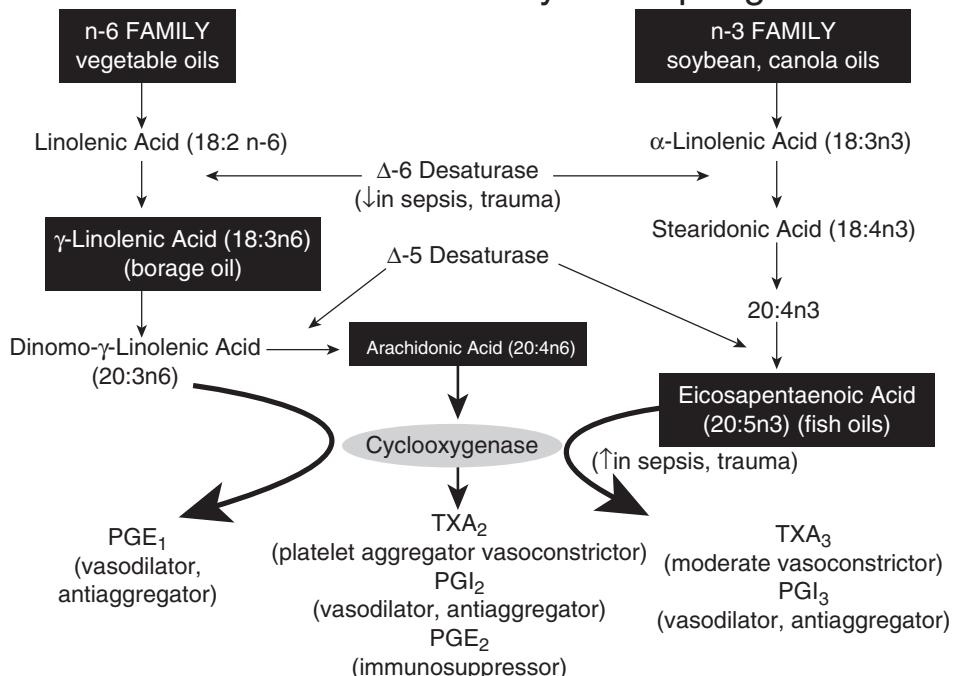


Figure 1. Metabolic pathway of fatty acids. PGE, prostaglandin E; PGI, prostaglandin I; PUFA, polyunsaturated fatty acids; TXA, thromboxane. Reprinted with permission from Mizock BA, DeMichele SJ. The acute respiratory distress syndrome: role of nutritional modulation of inflammation through dietary lipids. *Nutr Clin Pract*. 2004;19:563-574.³³

on proinflammatory mediator production, gas exchange, and oxygen delivery.^{34,40,41} Gadek et al⁴² published the first report of beneficial effects in using a specialized formula in patients with acute lung injury (ALI). Ninety-eight patients, defined by the American-European Consensus Guidelines as having ALI (oxygenation of $\text{PaO}_2/\text{FiO}_2 \geq 200$ or ≤ 300 mm Hg), were randomized to receive either a modified lipid formula for ARDS or control within 24 hours of study entry. Patients receiving the specialized formula showed a significant improvement in oxygenation ($P < .05$), required significantly fewer days of mechanical ventilatory support ($P = .011$), and demonstrated a decreased ICU length of stay ($P = .016$) compared with the control group. There was no difference in mortality between the 2 groups. The authors concluded that a specialized enteral formula would be useful in the management of those with, or at risk of

developing, ARDS. It is important to note that the control formula provided was a pulmonary formula with an equal macronutrient distribution as the study formula. The only difference between the 2 formulas was the type of lipid and the elevated levels of antioxidants.

Singer and colleagues⁴³ demonstrated similar results in their 2006 trial comparing a lipid-modulated enteral formula in ARDS patients. One hundred ventilated patients meeting the criteria for ALI³¹ were randomized to receive either a formula containing EPA, GLA, and antioxidant or a control pulmonary formula within 24 hours of ICU admission. Patients who received the EPA/GLA formula had a significantly shorter length of ventilator time ($P \leq .05$) as well as a reduced ICU length of stay ($P \leq .05$) compared with the control patients. There was no difference in either hospital length of stay or mortality between the 2 groups.

Table 5. Guidelines and Recommendations for Use of an Altered Lipid Enteral Formula in Individuals With Acute Respiratory Distress Syndrome/Acute Lung Injury

Organization	Year Published	Recommendation	Grade
European Society for Parenteral and Enteral Nutrition	2006	Patients with acute respiratory distress syndrome should receive enteral nutrition enriched with ω -3 fatty acids and antioxidants.	B
Canadian Clinical Practice Guidelines	2009	Based on one level I study and four level II studies, this group recommends the use of an enteral formula with fish oils, borage oils, and antioxidants in patients with acute lung injury and acute respiratory distress syndrome.	Recommend
Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition	2009	Patients with acute respiratory distress syndrome and severe acute lung injury should be placed on an enteral formulation characterized by an anti-inflammatory lipid profile (ie, ω -3 fish oils, borage oil), and antioxidants.	A

A trial published in 2006 demonstrated positive outcomes in patients receiving a specialized lipid modulated formula.⁴⁴ Pontes-Arruda and colleagues⁴⁴ reported their results comparing an altered lipid formula with a control formula in 165 patients with sepsis. Study patients were enrolled if they required mechanical ventilation and demonstrated an oxygenation measurement of $\text{Pao}_2/\text{FiO}_2 < 200$ mm Hg. Patients were randomized to receive a control standard pulmonary formula or a formula with EPA, GLA, and antioxidants, which was initiated within 6 hours of study entry. Of the 103 patients who were deemed evaluable (intent-to-treat analysis was for mortality outcome only), those who received the EPA/GLA formula experienced improved oxygenation on study days 4 ($P = .033$) and 7 ($P < .02$) compared with the control group. In addition, a greater number of ventilator-free days ($P < .001$), a greater number of ICU-free days ($P < .001$), and a significant reduction in new organ failure ($P < .001$) were demonstrated in those who received the lipid-modulated formula. Unlike in the previously cited trials, the use of the EPA/GLA formula was associated with an increased survival rate ($P = .037$).

In an effort to determine the overall effectiveness of a specialized enteral formula on clinical outcomes in patients with ALI/ARDS, Pontes-Arruda and colleagues⁴⁵ conducted a meta-analysis on the cumulative evidence comparing EPA/GLA formula vs control. Three randomized controlled trials met inclusion and quality criteria, providing a total sample size of 411 patients, of whom 296 were evaluable. The use of an EPA/GLA formula was associated with a 60% reduction in the risk of 28-day mortality (odds ratio [OR], 0.040; 95% confidence interval [CI], 0.24–0.68; $P = .001$). With aggregation via intent to treat, a significant reduction in 28-day mortality was still evident with the use of an EPA/GLA formula (49% reduction) (OR, 0.51; 95% CI, 0.33–0.79; $P = .002$). Positive results were also demonstrated with use of an EPA/GLA formula with increased 28-day ventilator-free days ($P < .0001$), increased 28-day ICU-free days ($P < .0001$), improved oxygenation ($P < .0001$), and reduced risk of new

organ failure ($P < .0001$). The authors concluded that patients with ALI/ARDS given an EPA/GLA formula had a significant reduction in mortality risk as well as improvements in oxygenation and clinical outcomes compared with those who received a control formula.

Two abstracts have been published evaluating the use of an EPA/GLA formula. In 2005, Elamin and colleagues⁴⁶ reported results of their preliminary randomized controlled trial ($n = 16$) comparing an EPA/GLA formula with an isocaloric standard control formula in patients with ARDS.⁴⁶ In patients with higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores at enrollment, those who received the study formula experienced significant improvement in oxygenation ($P < .01$), a decrease in their APACHE II score ($P < .01$), and a reduced ICU length of stay ($P = .016$) compared with those who received the control formula. Moran and colleagues,⁴⁷ in 2006, reported their multicenter trial results comparing an EPA/GLA formula with an isocaloric control formula in septic patients ($n = 198$). Nosocomial pneumonia occurred less often in patients fed the EPA/GLA formula compared with controls ($P < .05$). There were no differences in other clinical outcomes including Sepsis-related Organ Failure Assessment score and mortality. In this evaluation, the formulas were administered at a minimum of 50% of estimated energy requirements from the fourth day onward. This is in contrast to the previously mentioned trials in which enteral formulas were administered from 6 to 24 hours of study entry or ICU admission. Perhaps earlier formula initiation with more optimal support (75% of estimated energy requirements) would produce different results.

A criticism often cited with the methods used in the above outlined trials is the use of a higher-fat control formula rich in ω -6 fats. Does the use of this type of control formula actually impede clinical recovery?⁴⁸ In the Gadek et al and Singer et al trials,^{42,43} the source of lipids in the control formula was 98% corn oil, a predominantly ω -6 fat (from linoleic acid). However, in the Pontes-Arruda 2006

trial,⁴⁴ the control formula contained 55.8% canola oil (an oil comprised of oleic, linoleic, and α -linolenic acids) and only 14% corn oil. Would the use of a formula with primarily ω -6 fats lead to, via the AA metabolic pathway, a greater production of proinflammatory mediators resulting in a reduced clinical benefit? A possible explanation offered by Pontes-Arruda and colleagues⁴⁵ is that in critical illness, the enzymes responsible for elongation of ω -6 fats to AA are rate-limiting with further activity limited by catabolic hormones. This rate-limiting step prevents a significant elevation in AA production, which, if it did occur, might be manifested by a substantial worsening of clinical parameters (eg, oxygenation) in the control patients. In the 3 studies described, oxygenation remained the same in the patients receiving the control formula compared with the significant improvements demonstrated with the study formula. In an animal model, Palombo et al⁴⁰ demonstrated that feedings with linoleic acid (ω -6 fat) in an endotoxic state did not increase the production of proinflammatory mediators seen with AA metabolism. From this illustration, it can be concluded that providing a diet containing linoleic acid (of which corn oil is a precursor) likely does not exacerbate a preexisting inflammatory state.

The evidence supporting use of a lipid-modified formula with added EPA and GLA and elevated antioxidants in patients with ARDS/ALI is highly supportive, which has translated to usage recommendations by several organizations.²²⁻²⁴ Table 5 outlines the available recommendations. Providing an inflammation-modulating combination of nutrients as a treatment option for this patient population is an exciting development, one that is currently being studied in septic patients requiring mechanical ventilation.⁴⁹

Conclusion

The potential for altered nutrition status in individuals with either acute or chronic pulmonary disease is significant, and nutrition support is often indicated as a therapeutic and/or treatment modality. The use of specialized enteral formulas in individuals with both chronic and acute pulmonary disease is controversial. Data supporting the routine use of a high-fat enteral formula in hospitalized patients with pulmonary dysfunction are limited and inconsistent. It is suggested that this type of formula should not be routinely used, however, and should be reserved for patients with marginal respiratory reserve (severely malnourished and/or severe COPD) who fail to wean from mechanical ventilation despite prevention of overfeeding or for malnourished patients who require nutrition repletion. In the patient with ALI/ARDS, a modified formula with added EPA, GLA, and increased antioxidants may offer a mortality benefit as well as

improvements in other important clinical outcomes. Based on recommendations by several nutrition organizations, this specialized formula should be used in patients with ALI and ARDS.

References

1. A.S.P.E.N. Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr.* 2002;26:1SA-138SA.
2. American Dietetic Association Evidence Analysis Library. Chronic Obstructive pulmonary disease evidence based nutrition practice guideline. <https://www.adaevidencelibrary.com/topic.cfm?cat=3707>. Accessed May, 1, 2009.
3. Wooley JA. Indirect calorimetry in critical illness. In: Merritt R, ed. *The A.S.P.E.N. Nutrition Support Practice Manual*. 2nd ed. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2005:277-280.
4. Askanazi J, Elwyn DH, Silverberg PA, Rosenbaum SH, Kinney JM. Respiratory distress secondary to a high carbohydrate load: a case report. *Surgery.* 1980;87:596-598.
5. Covelli HD, Black JW, Olsen MS, Beekman JF. Respiratory failure precipitated by high carbohydrate loads. *Ann Intern Med.* 1981;95:579-581.
6. Askanazi J, Rosenbaum SH, Hyman AI, et al. Respiratory changes induced by the large glucose loads of total parenteral nutrition. *JAMA.* 1980;243:1444-1447.
7. Askanazi J, Nordenstrom J, Rosenbaum SH, et al. Nutrition for the patient with respiratory failure: glucose vs. fat. *Anesthesiology.* 1981;54:373-377.
8. Garfinkel F, Robinson R, Price C. Replacing carbohydrate calories with fat calories in enteral feedings for patients with impaired respiratory function [abstract]. *JPEN J Parenter Enteral Nutr.* 1985;9:106.
9. Baker JP, Detsky AS, Stewart S, Whitwell J, Marliss EB, Jeejeebhoy KN. Randomized trial of total parenteral nutrition in critically ill patients: metabolic effects of varying glucose-lipid ratios as the energy source. *Gastroenterology.* 1984;87:53-59.
10. 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.
11. Angelillo VA, Bedi S, Durfee D, Dahl J, Patterson AJ, O' Donohue WJ Jr. Effects of low and high carbohydrate feedings in ambulatory patients with chronic obstructive pulmonary disease and chronic hypercapnia. *Ann Intern Med.* 1985;103:883-885.
12. Vermeeren MA, Wouters EF, Nelissen LH, van Lier A, Hofman Z, Schols AM. Acute effects of different nutritional supplements on symptoms and functional capacity in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr.* 2001;73:295-301.
13. Cai B, Zhu Y, Ma Y, et al. Effect of supplementing a high-fat, low-carbohydrate enteral formula in COPD patients. *Nutrition.* 2003;19:229-232.
14. 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.
15. van den Berg B, Bogaard JM, Hop WC. High fat, low carbohydrate, enteral feeding in patients weaning from the ventilator. *Intensive Care Med.* 1994;20:470-475.
16. Dark DS, Pingleton SK, Kerby GR. Hypercapnia during weaning: a complication of nutritional support. *Chest.* 1985;88:141-143.

17. Talpers SS, Romberger DJ, Bunce SB, Pingleton SK. Nutritionally associated increased carbon dioxide production. Excess total calories vs high proportion of carbohydrate calories. *Chest*. 1992;102:551-555.
18. Kuo CD, Shiao GM, Lee JD. The effects of high-fat and high-carbohydrate diet loads on gas exchange and ventilation in COPD patients and normal subjects. *Chest*. 1993;104:189-196.
19. Akrabawi SS, Mobarhan S, Stoltz RR, Ferguson PW. Gastric emptying, pulmonary function, gas exchange, and respiratory quotient after feeding a moderate versus high fat enteral formula meal in chronic obstructive pulmonary disease patients. *Nutrition*. 1996; 12:260-265.
20. Malone AM. Is a pulmonary enteral formula warranted for patients with pulmonary dysfunction? *Nutr Clin Pract*. 1997;12:168-171.
21. Malone AM. The use of specialized enteral formulas in pulmonary disease. *Nutr Clin Pract*. 2004;19:557-562.
22. Critical Care Nutrition. Canadian Clinical practice guidelines for nutrition support in adult critically ill patients. http://www.criticalcarenutrition.com/docs/cpg/10.4_insulin_07.pdf. Accessed May 1, 2009.
23. Kreymann KG, Berger MM, Deutz NE, et al. ESPEN guidelines on enteral nutrition: Intensive care. *Clin Nutr*. 2006;25:210-223.
24. Martindale RG, McClave SA, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: executive summary. *Crit Care Med*. 2009;37:1757-1761.
25. Shapses S. Letter to the editor. *Nutr Clin Pract*. 1998;13:47.
26. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet*. 1967;2:319-323.
27. Suratt BT, Parsons PE. Mechanisms of acute lung injury/acute respiratory distress syndrome. *Clin Chest Med*. 2006;27:579-589.
28. Bream-Rouwenhorst HR, Beltz EA, Ross MB, Moores KG. Recent developments in the management of acute respiratory distress syndrome in adults. *Am J Health Syst Pharm*. 2008;65:29-36.
29. Raghavendran K, Pryhuber GS, Chess PR, Davidson BA, Knight PR, Notter RH. Pharmacotherapy of acute lung injury and acute respiratory distress syndrome. *Curr Med Chem*. 2008;15: 1911-1924.
30. Schuster KM, Alouidor R, Barquist ES. Nonventilatory interventions in the acute respiratory distress syndrome. *J Intensive Care Med*. 2008;23:19-32.
31. Artigas A, Bernard GR, Carlet J, et al. The American-European Consensus Conference on ARDS, part 2: ventilatory, pharmacologic, supportive therapy, study design strategies, and issues related to recovery and remodeling. acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1998;157:1332-1347.
32. The American Dietetic Association. Critical illness recommendations. http://www.adaevidencelibrary.com/template.cfm?key=1048&cms_preview=1. Accessed May 1, 2009.
33. Mizock BA, DeMichele SJ. The acute respiratory distress syndrome: role of nutritional modulation of inflammation through dietary lipids. *Nutr Clin Pract*. 2004;19:563-574.
34. Mancuso P, Whelan J, DeMichele SJ, Snider CC, Guszcz JA, Karlstad MD. Dietary fish oil and fish and borage oil suppress intrapulmonary proinflammatory eicosanoid biosynthesis and attenuate pulmonary neutrophil accumulation in endotoxic rats. *Crit Care Med*. 1997;25:1198-1206.
35. Abbott Nutrition. Oxepa product information. <http://abbottnutrition.com/products/products.aspx?pid=5>. Accessed May 2009.
36. DeMichele SJ, Wood SM, Wennberg AK. A nutritional strategy to improve oxygenation and decrease morbidity in patients who have acute respiratory distress syndrome. *Respir Care Clin N Am*. 2006;12:547-566.
37. Nestle Nutrition. Product information. <http://www.nestle-nutrition.com/Products/Default.aspx>. Accessed May 2, 2009.
38. Metnitz PG, Bartens C, Fischer M, Fridrich P, Steltzer H, Druml W. Antioxidant status in patients with acute respiratory distress syndrome. *Intensive Care Med*. 1999;25:180-185.
39. Nelson JL, DeMichele SJ, Pacht ER, Wennberg AK; Enteral Nutrition in ARDS Study Group. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants on antioxidant status in patients with acute respiratory distress syndrome. *JPEN J Parenter Enteral Nutr*. 2003;27:98-104.
40. Palombo JD, Bistrian BR, Fechner KD, Blackburn GL, Forse RA. Rapid incorporation of fish or olive oil fatty acids into rat hepatic sinusoidal cell phospholipids after continuous enteral feeding during endotoxemia. *Am J Clin Nutr*. 1993;57:643-649.
41. Mancuso P, Whelan J, DeMichele SJ, et al. Effects of eicosapentaenoic and gamma-linolenic acid on lung permeability and alveolar macrophage eicosanoid synthesis in endotoxic rats. *Crit Care Med*. 1997;25:523-532.
42. 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. Enteral Nutrition in ARDS Study Group. *Crit Care Med*. 1999;27:1409-1420.
43. 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.
44. 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.
45. Pontes-Arruda A, Demichele S, Seth A, Singer P. The use of an inflammation-modulating diet in patients with acute lung injury or acute respiratory distress syndrome: a meta-analysis of outcome data. *JPEN J Parenter Enteral Nutr*. 2008;32:596-605.
46. Elamin E, Hughes L, Drew D. Effect of enteral nutrition with eicosapentanoic acid (EPA), gamma-linolenic acid (GLA) and antioxidants reduces alveolar inflammatory mediators and protein influx in patients with acute respiratory distress syndrome (ARDS) [abstract]. *Chest*. 2005;128:225S.
47. Moran V, Teodoro G, de Lorenzo A, et al. Effect of an enteral feeding with eicosapentanoic and gamma-linolenic acids on the outcome of mechanically ventilated critically ill septic patients [abstract]. *Crit Care Med*. 2006;34:A70.
48. Preiser JC. Nutrition therapy for acute respiratory distress syndrome. *JPEN J Parenter Enteral Nutr*. 2008;32:669-670.
49. The effects of eicosapentaenoic acid (EPA), gamma-linolenic acid (GLA) and antioxidants in the treatment of sepsis. <http://clinicaltrials.gov/ct2/show/NCT00329680>. Accessed April 10, 2009.