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A.S.P.E.N. Clinical Guidelines: Nutrition Support of Neonates Supported with Extracorporeal Membrane Oxygenation

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Background

Extracorporeal membrane oxygenation (ECMO) utilizes a modified heart-lung machine with a membrane oxygenator in the setting of profound cardiorespiratory failure. ECMO has been used successfully in pediatric and adult applications, though the most frequent indication is neonatal respiratory failure in conditions such as persistent pulmonary hypertension, congenital diaphragmatic hernia, congenital heart disease, and meconium aspiration. ECMO use is associated with improved mortality,[1] however the nutritional and metabolic burden in these children is considerable.

ECMO does not provide a "metabolic rest." Rather, neonates on ECMO have demonstrated some of the highest rates of protein catabolism reported.[2] Appropriate provision of nutrition support in ECMO patients is predicated upon a clear understanding of the changes in their metabolism, metabolic reserves, and nutrition requirements. The purpose of this Clinical Guideline is to address the nutrition support of neonatal patients treated with ECMO.

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Methodology

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) is an organization comprised of healthcare professionals representing the disciplines of medicine, nursing, pharmacy, dietetics, and nutrition science. The mission of A.S.P.E.N. is to improve patient care by advancing the science and practice of nutrition support therapy. A.S.P.E.N. vigorously works to support quality patient care, education, and research in the fields of nutrition and metabolic support in all healthcare settings. These Clinical Guidelines were developed under the guidance of the A.S.P.E.N. Board of Directors. Promotion of safe and effective patient care by nutrition support practitioners is a critical role of the A.S.P.E.N. organization. The A.S.P.E.N. Board of Directors has been publishing Clinical Guidelines since 1986.[3-5] Starting in 2007, A.S.P.E.N. has been revising these Clinical Guidelines on an ongoing basis, reviewing about 20% of the chapters each year in order to keep them as current as practical.

These A.S.P.E.N. Clinical Guidelines are based upon general conclusions of health professionals who, in developing such guidelines, have balanced potential benefits to be derived from a particular mode of medical therapy against certain risks inherent with such therapy. However, the professional judgment of the attending health professional is the primary component of quality medical care. Because guidelines cannot account for every variation in circumstances, the practitioner must always exercise professional judgment in their application. These Clinical

Guidelines are intended to supplement, but not replace, professional training and judgment.

These Clinical Guidelines were created in accordance with Institute of Medicine recommendations as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."[6] These Clinical Guidelines are for use by healthcare professionals who provide nutrition support services and offer clinical advice for managing adult and pediatric (including adolescent) patients in inpatient and outpatient (ambulatory, home, and specialized care) settings. The utility of the Clinical Guidelines is attested to by the frequent citation of these documents in peer-reviewed publications and their frequent use by A.S.P.E.N. members and other healthcare professionals in clinical practice, academia, research, and industry. They guide professional clinical activities, they are helpful as educational tools, and they influence institutional practices and resource allocation.[7]

These Clinical Guidelines are formatted to promote the ability of the end user of the document to understand the strength of the literature used to grade each recommendation. Each Guideline recommendation is presented as a clinically applicable statement of care and should help the reader make the best patient care decision. The best available literature was obtained and carefully reviewed. Chapter author(s) completed a thorough literature review using Medline®, the Cochrane Central Registry of Controlled Trials, the Cochrane Database of Systematic Reviews, and other appropriate reference sources. These results of the literature search and review formed the basis of an evidence-based approach to the Clinical Guidelines. Chapter editors worked with the authors to ensure compliance with the author's directives regarding content and format. Then the initial draft is reviewed internally to promote consistency with the other A.S.P.E.N. Guidelines and Standards and externally reviewed (either by experts in the field within our organization and/or outside of our organization) for appropriateness of content. The final draft is reviewed and approved by the A.S.P.E.N. Board of Directors.

The system used to categorize the level of evidence for each study or article used in the rationale of the Guideline statement and to grade the Guideline recommendation is outlined in Table 1.[8]

The grade of a Guideline is based on the levels of evidence of the studies used to support the Guideline. A randomized controlled trial (RCT), especially one that is double blind in design, is considered to be the strongest level of evidence to support decisions regarding a therapeutic intervention in clinical medicine.[9] A systematic review (SR) is a specialized type of literature review that analyzes the results of several RCTs. A high quality SR usually begins with a clinical question and a protocol that addresses the methodology to answer this question. These methods usually state how the literature is identified and assessed for quality, what data is extracted, how it is analyzed, and whether there were any deviations from the protocol during the course of the study. In most instances, meta-analysis (MA), a mathematical tool to combine data from several sources, is used to analyze the data. However, not all SRs use MA. SRs and MA are used in these Clinical Guidelines only to organize the evidence but not in the grading process.

A level of I, the highest level, was given to large RCTs where results were clear and the risk of alpha- and beta-error was low and the study well-powered (Table 1). A level of II was given to RCTs that include a relatively low number of patients or were at moderate-to-high risk for alpha- and beta-error (under-powered). A level of III was given to cohort studies with contemporaneous controls or

Table 1. Grading of Guidelines and Levels of Evidence

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

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Table 2. Nutrition Support Recommendations in Neonates Supported with Extracorporeal Membrane Oxygenation (ECMO)

Guideline Recommendations	Grade
1. Nutrition support should be initiated expeditiously in neonates treated with ECMO.	D
2. Neonates treated with ECMO have protein requirements of up to 3 g/kg/d.	D
3. Energy requirements in neonates treated with ECMO are equivalent to healthy subjects.	D
4. Enteral feedings should be initiated when the patient on ECMO has clinically stabilized.	D

Table 3. Clinical and Nutritional Outcomes in Neonates Supported with Extracorporeal Membrane Oxygenation (ECMO)

Study	Population	Study Groups	Results	Comments
Foglia[10] 1990 Level III	Neonates > 35 weeks gestational age (N=18)	PN 2% AA, 10% dextrose, fat emulsion 1-3 g/kg/d (increase to 2 g/kg/d on d2, then to 3 g/kg/d on d3)	Overall mortality 5.6%, ICH 11.1%, surgical PDA 5.6% At ECMO initiation, wt 111.1%± 4% birth wt; 6 d later wt 103% birth wt	Wt loss in spite of PN support
Van Meurs[11] 1993 Level III	Infants treated with ECMO (N=30), with or without CDH	ECMO not due to CDH (n=15) ECMO due to CDH (n=15)	ECMO time: CDH 193 hr, no CDH 134 hr; *P*<.05 Ventilator time: CDH 142 hr, no CDH 49 hr LOS: CDH 56 d, no CDH 18 d All with normal wt, length, & head circumference at birth; by 12 & 24 mo, infants with CDH had significantly shorter length, wt, wt:length percentiles than controls; 40% with CDH had wt:length ratios <5% at 12 mo At discharge: 44% with full EN, 89% with GERD symptoms which dissipated after age 18 mo	Growth failure persists long after ECMO completed
Bernbaum[12] 1995 Level III	Neonates (N=82)	Major diagnoses: MAS (n=21) CDH (n=28) PFC (n=13) sepsis (n=9)	Survival: MAS 100%, CDH 68%, total population 79% LOS: CDH 104.5 d, other diagnoses 62.5, (*P*<.05) GERD: CDH 79%, total population 40% EN: CDH 79%, total population 60% At 6 & 12 mo, 35% of CDH pts receive EN	Poor long-term nutrition status

AA, amino acids; PDA, patent ductus arteriosus; CDH, congenital diaphragmatic hernia; ICH,intracranial hemorrhage; PN, parenteral nutrition; EN, enteral nutrition; GERD, gastroesophageal reflux disease; PFC, persistent fetal circulation; LOS, length of stay; MAS, meconium aspiration syndrome; wt, weight.

validation studies, while cohort studies with historic controls received a level of IV. Case series, uncontrolled studies, and articles based on expert opinion alone received a level of V.

Practice Guidelines and Rationales

Table 2 provides the entire set of guideline recommendations for nutrition support of neonates supported with ECMO.

1. Nutrition support should be initiated expeditiously in neonates treated with ECMO. (Grade: D)

Rationale: Neonates are born with very limited nutrition reserves and require vigorous nutrition support to enhance their growth. When neonates are ill enough to require ECMO, optimal weight gain is difficult to achieve due to their baseline illness and fluid intolerance, which may limit nutrient infusion (Table 3). In addition, given the high protein catabolic rates, neonates can lose up to

Table 4. Protein Requirements in Neonates with Extracorporeal Membrane Oxygenation (ECMO)

Study	Population	Study Groups	Results	Comments
Keshen[2] 1997 Level III	Neonates (N=9)	During ECMO (n=9) & post-ECMO (n=5) tracer studies of protein metabolism	Net protein balance: during ECMO, -2.31±0.8 g/kg/d; post-ECMO, -0.33±1.1g/kg/d	Negative protein balance in the face of aggressive PN
		PN with 93.2±5.5 kcal/kg/d, protein 2.43±0.3 g/kg/d, fat emulsion 3.1±0.7 g/kg/d	Energy expenditure: during ECMO, 88.6±7.7 kcal/kg/d; post-ECMO, 84.3±9.2 kcal/kg/d	
Agus[14] 2004 Level III	Neonates (N=4)	Hyperinsulinemic euglycemic clamp vs saline control in random order cross-over PN with 62± 9 kcal/kg/d, protein 1.3± 0.3 g/kg/d, fat emulsion 1.7±0.3 g/kg/d, dextrose infusion 5.88±0.44 mg/kg/min increased to 15.41±1.40 mg/kg/min with clamp study	During insulin infusion, 32% reduction (3.1± 0.7 g/kg/d) in protein catabolism, $P<.05$	Anabolic effects of insulin possibly combined with greater energy intake
Weber[16] 1993 Level III	MAS (N=9), PFC (n=4), CDH (n=3), hyaline membrane disease (n=2)	5 groups based on caloric & nitrogen intake; nitrogen balance compared among groups	Positive nitrogen balance required > 250 mg/kg/d with >60 non-protein kcal/kg/d Maximal positive nitrogen balance with nitrogen intake >400 mg/kg/d	Newborns with ECMO can achieve positive nitrogen balance with modest caloric & nitrogen intake
Shew[19] 1999 Level III	Neonates (N=12) age 7.2 ± 0.8 d	PN with 88.1 ± 5.0 kcal/kg/d, protein 2.3 ± 0.2 g/kg/d	Protein balance -2.3 ± 0.6 g/kg/d related to protein turnover (R= -0.88, $P<.001$) CRP: ECMO 44.0 ± 7.6, control 1.9 ± 1.1 mg/L, $P<.001$	Excess PN energy does not improve protein catabolism, but increases carbon dioxide production;ECMO associated with inflammatory response, perhaps due to clinical condition

PN, parenteral nutrition; CRP, C reactive protein; CDH, congenital diaphragmatic hernia; MAS, meconium aspiration syndrome; PFC, persistent fetal circulation.

15% of their lean body mass during a 7-day course of ECMO.[2]

Neonatal and pediatric ECMO patients are highly susceptible to protracted catabolic stress. In addition to the risk of weight loss during ECMO support,[10] the nutritional and feeding problems of these neonates extend beyond discharge. Limited oral feeding success and resultant growth failure have been measured up to 24 months after ECMO was completed.[10-12] Thus, assessment of nutrition needs and initiation of appropriate nutrition support (100-120 kcal/kg/d and protein up to 3 g/kg/d) is imperative for neonates receiving ECMO. For clinically labile neonates, support should be initiated in the form of parenteral nutrition (PN).[13] Guidelines for energy and protein requirements are detailed in subsequent sections.

2. Neonates treated with ECMO have protein requirementsof up to 3 g/kg/d. (Grade: D)

Rationale: The goal of protein provision in neonates and children on ECMO is to promote nitrogen balance and optimize growth and development. In patients on ECMO, the hallmark of their altered protein metabolism is a marked increase in whole-body protein degradation, causing these patients to manifest a negative net protein balance. This catabolic tendency persists in critically ill neonates even 3 weeks after they are successfully weaned from the ECMO circuit.[2] The provision of adequate dietary protein promotes positive protein balance and potentiates the anabolic effect of insulin.[14] In contrast to the 1.5 g/kg/d protein requirement for healthy neonates,[15] neonates who require ECMO have profound negative nitrogen balance (a

Table 5. Energy Requirements in Neonates Supported with Extracorporeal Membrane Oxygenation (ECMO)

Study	Population	Study Groups	Results	Comments
Jaksic[20] 2001 Level III	ECMO (N=10), Postoperative non-ECMO neonates (N=8)	CO_2 breath samples after $NaH^{13}CO_3$ infusion	REE:control 53±5.1 kcal/kg/d, ECMO 55±20 kcal/kg/d Mortality: controls 0%, ECMO 30% IL-6: controls 0.7±0.6 pg/mL, ECMO 29±11.5 pg/mL, *P*<.001; CRP: controls 0.6±1.3 mg/L, ECMO 31±22 mg/L, *P*<.001.	Energy needs not increased in neonates with ECMO, in spite of increased inflammation & mortality
Cilley[13] 1988 Level III	Neonates (N=10)	PN with 80-110 kcal/kg/d, protein 0.5-2 g/kg/d, fat emulsion 1-4 g/kg/d, 10-20% dextrose; repeated measures of respiratory gas exchange over 1-30 d of life during ECMO	REE 57±11 kcal/kg/d (range 38-80) PN with 75±25 kcal/kg/d (range 10-111)	Energy requirement for growth up to 45% > REE, with wide variation over time & among neonates

CRP, C reactive protein; IL-6, interleukin-6; PN, parenteral nutrition; REE, resting energy expenditure

surrogate for protein balance) even in the face of aggressive PN intake (Table 4). This negative protein balance is associated with inflammation and is reduced with insulin infusion, but is unresponsive to increased energy supply. Neonates on ECMO have been shown to achieve positive nitrogen balance when provided with nonprotein nitrogen calories >60 kcal/kg/d and nitrogen >240 mg/kg/d, with maximum positive nitrogen balance when nitrogen intake was >400 mg/kg/d.[16] Because nitrogen balance can be affected by renal failure and difficulties with collecting accurate balance data, measurements may be inaccurate in patients receiving ECMO support. Toxicity can occur with excessive protein administration, particularly in patients with marginal renal or hepatic function. Protein allotments of 6 g/kg/d in low birth weight infants have been associated with lethargy and pyrexia initially,[17] and strabismus and lower intelligence quotient at 3 years.[18]

3. Energy requirements in neonates treated with ECMO are equivalent to healthy subjects. (Grade: D)

Rationale: In contrast to the excess protein catabolism seen in neonates supported with ECMO, energy needs are equivalent to those of neonates who do not require ECMO support (Table 5). Excess calories do not serve to decrease the protein catabolism seen in these patients and can result in increased carbon dioxide (CO_2) production with exacerbation of respiratory failure.[19] Mean resting energy expenditure has been measured at 55[20] to 57[21] kcal/kg/d, though individual patients may have much higher requirements for growth.

The total energy expenditure for an individual patient is difficult to quantitate because both indirect calorimetry and nitrogen balance may be inaccurate in patients receiving ECMO support. Although stable isotopic techniques to measure energy expenditure exist, these are not widely available outside of the research setting. The best estimate of the energy requirement for an individual patient on ECMO is based on that of an age-matched healthy neonate[20] (generally 100-120 kcal/kg/d).

4. Enteral feedings should be initiated when the patient on ECMO has clinically stabilized. (Grade: D)

Rationale: In patients on ECMO, initial nutrition support is generally provided via PN to allow for the rapid attainment of metabolic stabilization and adequate nutrition in the context of severe cardiopulmonary failure and, often, fluid restriction. In addition, there exists a theoretical concern regarding splanchnic hypoperfusion and the risk of increasing intestinal ischemia or bacterial translocation with enteral feeding in these patients. Although necrotizing enterocolitis has not been described in enterally fed patients on ECMO, it has been reported in an enterally-fed child with shock.[13] Large-scale studies have not been performed on the preferred route of nutrient provision in this specific patient population, however, enteral nutrition (EN) is preferable to PN in critically ill patients when gastrointestinal function is normal and the patient is clinically stable (Table 6). A large, retrospective study of neonatal and pediatric intensive care unit (ICU) patients revealed a lower rate of complications (hyperglycemia, hypertriglyceridemia, and cholestasis) in patients fed continuous post-pyloric enteral feedings as compared to PN-fed patients, and no difference in hospital-acquired infection or mortality.[22] A prospective cohort study of neonatal and pediatric

Table 6. Outcomes Associated with Enteral Feedings in Neonates Supported with Extracorporeal Membrane Oxygenation (ECMO)

Study	Population	Study Groups	Results	Comments
Piena[23] 1998 Level III	Neonates (N=16)	EN (BM or formula) 3-9 d after ECMO began (n=7)	Intestinal permeability increased (n=13), with sepsis (n=4); normal passive absorption, active carrier mediated transport reduced	Intestinal integrity compromised but EN does not worsen & should not be withheld
Pettignano[24] 1998 Level III	Neonates (N=29)	PN 2-122 hr after ECMO (n=14), EN within 48 h of ECMO (n=16)	Survival: PN 100%, EN 79% EN cost less than PN	Pts not randomized, pts with PN may have been more ill
Wertheim[25] 2001 Level III	Neonates (N=96)	EN (n=16), PN (n=35)	Septic complications not different ECMO duration: EN 161 hr PN 11 hr, *P*=.01 Mortality: EN 0%, PN 14%	Pts with PN may have been more ill
Hanekamp[26] 2005 Level III	Neonates (N=77)	PN & EN (n=67) No CDH PN 12 mL/kg/d on d1 (10% dextrose, 10% AA, 20% fat emulsion 6 mL/kg/d) PN doubled on d2, EN started 40 hr after ECMO with 40% energy intake by d3	EN tolerated without serious adverse effects	
Jadcherla[27] 2005 Level III	Neonates (N=10)	Full oral feedings by age 1 mo vs not full feeds	With feeding failure & EN, LOS increased 3.6 times over full oral feedings	Early intestinal dysmotility associated with feeding difficulty, prolonged hospitalization

AA, amino acids; BM, breast milk; CDH, congenital diaphragmatic hernia; EN, enteral nutrition; LOS, length of stay; PN, parenteral nutrition; SIRS, sepsis inflammatory response syn

patients in shock (defined as mean blood pressure < 2 SD below normal despite volume or vasopressors or both) showed that even the majority of these patients could tolerate enteral feeding, though they had a significantly higher risk of gastrointestinal complications (primarily gastric residuals, distention, and diarrhea) than patients not in shock.[13] Another series of pediatric ECMO patients retrospectively compared 13 patients receiving total EN to 14 matched patients receiving PN and again demonstrated that the EN was well tolerated and without complication.[24] These data suggest that ECMO patients may tolerate and perhaps even benefit from EN provided the physician is vigilant for signs of feeding intolerance. As these studies have not been replicated in neonates, caution is advised prior to starting EN in patients who have not yet stabilized clinically.

Most neonates treated with ECMO have PN initiated within 24 hours. Enteral feedings (either breast milk or standard formula given by feeding tube) are generally well-tolerated despite intestinal dysfunction. EN is usually provided in addition to PN support (rather than instead of it), and titrated up according to tolerance. While studies to date have been mostly cohort observations with limited statistical power due to small sample size, mortality was equivalent with PN alone when compared with both PN and EN. Neonates who have slow tolerance to EN have a 3.6-fold longer length of hospital stay than those who are feeding optimally by 4 weeks after ECMO.[27]

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