

Lead Author (Year)	Patient Population Included	n of Groups	Average Age at Enrollment	Study Duration	Summary of Results
Clarke (2007)	Infants diagnosed with faltering growth due to cardiac lesions, CF, or other organic causes who are fed orally or enterally and weigh between 2 and 8 kg	26 in ENDF group, 23 in energy supplemented group	Median age = 5 weeks (range: 2-31 weeks)	6 weeks	<ul style="list-style-type: none"> • Growth: all infants gained weight and improved weight-for-age z-score • Tolerance: No difference in stool frequency or vomiting between the two groups • Nitrogen balance: Not evaluated • Safety: No formula-related safety events reported
Evans (2007)	Infants aged 0-12 months who weigh between 2.5 and 8 kg and have a diagnosis of faltering growth that required ENDF	18 in full strength ENDF group; 12 in stepwise ENDF group	Median age: Full strength ENDF group: 14.5 weeks (range: 2-43 weeks); stepwise ENDF group: 17.5 weeks (range: 6-43 weeks)	2 weeks	<ul style="list-style-type: none"> • Growth: 29 of 30 infants gained weight; all increased or stayed the same in length • Tolerance: Transient increase in bowel frequency was seen in the full strength group on days 1 and 2 (this was not significant on days 3 and 4); change in stool frequency was negatively correlated with age • Nitrogen balance: Not evaluated • Safety: No formula-related safety events reported
van Waardenburg (2009)	Hemodynamically stable infants age 4-12 weeks with viral bronchiolitis, but >40 weeks PMA, on mechanical ventilation and with indwelling arterial and venous catheters, hemodynamically stable, able to start EN <24 hours after PICU admission, expected LOS >96 hours	8 in ENDF group 10 in standard formula group (20 kcal/ounce)	Mean age, ENDF = 2.7 months (SEM: 0.5) Standard formula = 3.0 months (SEM: 0.6)	5 days	<ul style="list-style-type: none"> • Growth: Not evaluated • Tolerance: Both formulas were well tolerated; no gastric distention, vomiting, or diarrhea was seen; significantly greater gastric retention volumes seen in the ENDF group (which did not impact nutrient intake, gastric distention, or vomiting) • Nitrogen balance: Significantly greater nitrogen balance was seen in the ENDF group on days 2-5; positive nitrogen balance achieved on day 2 in ENDF group, whereas negative nitrogen balance seen until day 4 in the standard formula group • Safety: No formula-related safety events reported
deBeute (2011)	Same as vanWaardenburg (2009)				<ul style="list-style-type: none"> • Growth: Not evaluated • Tolerance: Not evaluated • Nitrogen balance: Whole body protein synthesis, whole body protein breakdown, and overall whole body protein balance was greater in the ENDF group than the standard formula group; 24-hour nitrogen balance was higher in the ENDF group on day 5

					<ul style="list-style-type: none"> • Safety: Not evaluated
deBeute (2013)	Same as vanWaardenburg (2009)				<ul style="list-style-type: none"> • Growth: Not evaluated • Tolerance: Not evaluated • Nitrogen balance: Total arginine appearance greater in the ENDF group, indicating increased nitric oxide and improved circulation during critical illness • Safety: Not evaluated
Zhang (2019)	Infants <1 year of age with CHD undergoing cardiac surgery	30 in ENDF group, 29 in standard formula group (20 kcal/ounce)	Median age: 60 days (IQR: 35.2-127.5 days) in ENDF group; 63 days (IQR: 34.5-120 days) in standard formula group	7 days	<ul style="list-style-type: none"> • Growth: Both groups lost weight peri-operatively, however weight loss was lower in the ENDF group (-16g with ENDF vs. -181g with standard formula) • Tolerance: A small number of patients in the ENDF group experienced mild AEs (abdominal distention (n = 1), GRV <1/3 of previous feed (n = 2), and diarrhea (n = 1)) that improved by increasing formula density gradually over 3 days • Nitrogen balance: Not evaluated • Safety: No formula-related safety events reported
Cui (2018)	Age 4 weeks to 12 months old (born at term) who had biventricular repair due to congenital heart surgery and are in the PICU for at least 5 days	26 in ENDF group; 24 in standard formula group (20 kcal/ounce)	Mean age: 4.69 (SD: 3.54) months in ENDF group; 5.23 (SD 2.49) months in standard formula group	5 days	<ul style="list-style-type: none"> • Growth: The ENDF group demonstrated weight gain compared to the standard formula group, who lost weight (not statistically significant) • Tolerance: No significant differences between the ENDF and standard formula groups for stool volume (p=0.09) and frequency (p=0.07) for the overall study period. Transient increases in stool volumes were seen on day 3 and stool frequency were seen on days 3 and 4, which resolved by day 5 • Nitrogen balance: Nitrogen balance on days 2-5 was significantly higher in the ENDF group, positive nitrogen balance achieved on day 2 in ENDF group, but not achieved until day 5 in the standard formula group • Safety: No formula-related safety events reported
Scheeffler (2020)	Children <2 years old who underwent heart surgery	29 in ENDF group; 30 in eHF group	Median age = 4.8 months (IQR: 1.08 - 9.76 months)	30 days	<ul style="list-style-type: none"> • Growth: WAZ was significantly increased with ENDF; mean weight gain per day was higher in the ENDF group (not significant) • Tolerance: No significant differences in overall GI adverse effects (p=0.59). Six patients in the ENDF group experienced diarrhea (p=0.01, 4 resolved spontaneously after day one, 2 resolved with adjustment of feeding rate) • Nitrogen balance: not evaluated

					<ul style="list-style-type: none"> • Safety: No formula-related safety events reported. Serious adverse events, including death, were noted in each study group; no deaths were attributed to formula type
Yu (2020)	Orally feeding infants born <1500g and <37 weeks gestational age who were unable to receive breastmilk or preterm formula during hospitalization, and were at <10 th percentile of intrauterine growth expectation at discharge (participants were enrolled at discharge from hospital)	48 total infants enrolled: 24 in ENDF group and 24 in premature transitional (22 kcal/ounce) formula group (infants fed ad libitum)	At discharge, median weight (IQR): ENDF group: 2106g (1953 – 2305g), premature transitional (22 kcal/ounce) formula group: 2085g (1818 – 2375g)	6 months	<ul style="list-style-type: none"> • Growth: No difference between weight and head circumference z-scores between formula groups, significantly higher length-for-age z-score was seen in ENDF group at month 6 • Tolerance: Not evaluated • Nitrogen balance: Not evaluated • Safety: Not evaluated
Fernandez (2023)	Infants and toddlers aged 1-24 months who were admitted to the PICU and received enteral nutrition	37 in standard formula group, 38 in ENDF group, 38 in ENDF plus protein supplement group	Median age: 4 months (IQR: 4.5 months)	Up to 7 days	<ul style="list-style-type: none"> • Growth: Not evaluated • Tolerance: No difference in enteral feeding tolerance between groups • Nitrogen balance: Standard formula and ENDF groups saw significant increases in nitrogen balance; ENDF plus protein supplement group saw a non-significant increase • Safety: 15 patients withdrew from the study: <ul style="list-style-type: none"> • 8 due to hyperuremia (1 in the ENDF group and 7 in the ENDF plus protein supplement group) • 1 due to diarrhea (ENDF group) • 1 due to feeding tube obstruction (ENDF plus protein supplement group) • 4 due to development of chylothorax • 1 due to hemodynamic instability due to fluid overload requiring discontinuation of enteral nutrition

ENDF = energy and nutrient dense formula, eHF = extensively hydrolyzed formula, CF = cystic fibrosis, WAZ = weight-for-age z-score

PMA = post-menstrual age; SEM = standard error of the mean, PICU = pediatric intensive care unit, LOS = length of stay, IQR = interquartile range

AE = adverse event, GRV = gastric residual volume, CHD = congenital heart disease