



HEALTHCARE PROFESSIONAL TOOLKIT

FORTINI™ INFANT FORMULA

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EXECUTIVE SUMMARY

The current standard of care of concentrating and fortifying infant formulas for malnourished infants with failure to thrive (FTT) — whether disease-related or non-organic — can require a lengthy step-up, often trial-and-error approach^{1,2} designed to reduce tolerability issues.^{3,4} But this approach can lead to prolonged delays in reaching the feeding goals needed to address the urgency of growth failure and malnutrition, and result in inadequate or unbalanced nutrition.

Thus, the standard of care of concentrating infant formula can prolong the road to recovery from malnutrition. Malnutrition in infancy may:

- Delay surgery^{5,6} and/or result in suboptimal surgical outcomes⁷⁻⁹
- Create a significant cost burden for hospitals (e.g., increased length of stay⁹⁻¹¹)
- Result in negatively impacted cognitive^{12,13} and muscle development^{14,15} during a critical period of growth

Fortini™ Infant is a clinically supported alternative to concentrating standard infant formulas that addresses the significant shortcomings of the current standard of care. Created by Nutricia, the makers of Neocate® infant formulas, it's as well-tolerated as standard infant formula,¹⁶⁻¹⁸ provides complete nutrition, and has been found to help critically ill infants meet nutrient goals faster than standard infant formula.¹⁷⁻¹⁹ Fortini supports catch-up growth in infants with both disease- and non-disease-related growth failure.^{16,20-22}

Marketed in Europe as Infatrini, Fortini™ has been widely used for more than 20 years. It is available in more than 30 countries and is now available in the U.S.

CURRENT CHALLENGES WITH FAILURE-TO-THRIVE

Studies show that in the United States, the number of infants with FTT may be as high as about:

~10%
IN PRIMARY CARE SETTINGS²³

Because nutritional status of infants is an important predictor of surgical outcomes,²⁴⁻²⁶ low weight and malnutrition may delay surgery^{5,6} and/or negatively impact a range of perioperative and postoperative outcomes – including increased risk of infection,^{8,9} longer recovery times^{7,9} and increased risk of mortality.⁹

4%
OF HOSPITALIZED INFANTS²⁷

Additionally, when hospitalized infants with failure-to-thrive are critically ill, they're prone to increased length of stay,^{9,28} and may require extended time on mechanical ventilation.⁹

For infants who suffer from failure-to-thrive despite no underlying medical conditions (non-organic FTT), the potential for setbacks when hospitalized can be just as significant.

1,000 CRITICAL DAYS:

The time between conception and a child's second birthday is a critical time for brain development.^{12,13} Malnutrition at such a vulnerable age can impact cognitive^{12,13} and muscular^{14,15} development well into the future and can result in serious inpatient setbacks,⁹⁻¹¹ resulting in significant costs to the healthcare system.



SHORTCOMINGS WITH THE CURRENT STANDARD OF CARE

The current standard of care for failure-to-thrive, formula-fed infants has several drawbacks.

To increase calories and promote weight gain, dietitians and physicians (and eventually parents and other caregivers) must concentrate powdered formulas or add modular products — a complex and time-consuming process that can leave infants vulnerable to dehydration (due to insufficient free water) and osmotic diarrhea.²⁹⁻³¹

To address these and other tolerability issues, the transition to higher-calorie formulations is typically carried out gradually, with a “step-up,” trial-and-error approach¹² that can take up to 3-5 days. This delay can hinder progress and result in inadequate or unbalanced nutrition during a critical window of development.

The step-up approach also places a time-consuming burden on healthcare staff, who must carry out precise mixing and measuring instructions. These complex preparations add unnecessary risks, such as concentration errors³²⁻³⁴ and bacterial contamination.³⁵⁻³⁷ Eventually, post-discharge, the burden shifts to anxious parents and caregivers, who are asked to exercise the same level of precision, and trusted to maintain cleanliness in home settings.



Malnourished Infants:

POSTSURGICAL COMPLICATIONS, INCREASED MORBIDITY, AND INCREASED LENGTH OF STAY (LOS)

Hospitalized infants with FTT or malnutrition face significantly greater challenges and can have significantly poorer outcomes than well-nourished infants:

- Higher rates of medical complications^{9,28} and poorer surgical outcomes⁷⁻⁹
- Higher rates of postoperative infection^{8,9}
- Poor wound healing linked to severe malnutrition^{39,40}
- More complex hospitalizations^{9,28}
- Increased time on mechanical ventilation^{12,13}

2.5x
LONGER LOS

for pediatric patients with a coded diagnosis of malnutrition (CDM) than children without a CDM³⁸

1.7x
LONGER
POST-OP LOS

for underweight infants, compared with those of normal weight⁷

LONGER
PICU LOS

for children with faltering growth²⁸

Additionally, underweight status has been significantly associated with⁹:

GREATER ODDS

of 60-day mortality

INCREASED RISK

of hospital-acquired infections

FEWER

ventilator-free days

LOWER

likelihood of discharge (increased LOS)

METABOLIC STRESS AND DECLINING NUTRITION STATUS

Children with severe acute illness or severe trauma often experience extreme metabolic stress, and **“nutrition status of children often declines after admission to the hospital, resulting in early and serious consequences, such as slowing of growth and increased susceptibility to various infections.”**³⁹

Malnutrition in young children requiring cardiac surgery was associated with an

8.7 FOLD INCREASED RISK

of postoperative infections, which was further linked to **increased length of stay**⁸

A pooled analysis of

1,622 CHILDREN

revealed that underweight status was significantly associated with **1.9-fold increased odds of hospital-acquired infections**⁹

51% OF PEDIATRIC PATIENTS

undergoing major surgery were malnourished and had significantly **higher rates of postsurgical infectious complications** than well-nourished children⁴¹

LONG-RANGE IMPACT

The longer-range effects of FTT and malnutrition are also well established, with broad implications for the healthcare system:

Nutrition during the 1,000 days between conception and a child’s second birthday is critical to brain development, with cognitive impacts throughout life^{12,13}

“ There is increasing evidence from preclinical and human studies that nutrition in the late fetal and early neonatal period has a significant impact on neurodevelopment across the lifespan.”¹²

“ Nutrition plays an important role in brain development from conception to 3 years of age. ... The ramifications are large because failure to optimize brain development early in life appears to have long-term consequences with respect to education, job potential, and adult mental health. ... These long-term consequences are the ‘ultimate cost to society’ of early life adversity.”¹³

Infancy represents a critical window for muscle development^{14,15}

“ Studies in the Helsinki Birth Cohort demonstrated that the combination of a small body size at birth, low weight gain during infancy, and rapid gain in BMI during childhood is associated with the metabolic syndrome, a body composition with low muscle mass in relation to fat mass, hypertension, and CHD in adult life.”



INCREASED COSTS AND BURDENS ON THE HEALTHCARE SYSTEM RELATED TO INFANT MALNUTRITION

Malnourished and FTT children account for a disproportionately high financial burden for hospitals.

3.2^x HIGHER HOSPITAL COSTS:

Children with a coded diagnosis of malnutrition vs. children without a CDM
(also less likely to have a routine discharge: 83% CDM vs. 94.2% non-CDM)³⁸

Note: Roughly half (475%) of the children with a CDM in this study were less than a year old.

3.5^x MORE LIKELY TO REQUIRE HOME CARE:

Children with a CDM vs. children without a CDM³⁸

55% LONGER STAY:

For malnourished children, compared with well-nourished children, based on
average 2.9-day increase in LOS following thoracic or abdominal surgery⁴¹



THE FORTINI INFANT DIFFERENCE

Fortini Infant is the only ready-to-feed infant formula designed to address the urgency of FTT and malnutrition. It not only provides 30 calories per ounce and complete nutrition, it's also clinically shown to be as well tolerated as standard infant formula. Fortini is made to power comebacks in infants in need of catch-up growth.



DESIGNED FOR GROWTH

- **Clinically shown to be as well tolerated as standard formula¹⁶⁻¹⁸:** Fortini's osmolality is lower than standard infant formula concentrated to 30 kcal/fl oz⁴³ and below the American Academy of Pediatrics recommended maximum level.⁴⁴ It can be administered either orally or by tube, and most infants* can step up to its 30 kcal/fl oz formula immediately.
- **Calorically dense formula:** To reach target weights, FTT infants need as much as 150% of the recommended caloric intake of healthy infants.^{45,46} With its 30 kcal/fl oz formulation, Fortini provides the highest energy in the smallest volume, to help infants with higher energy requirements and/or volume restrictions.

*Infants <12 weeks of age may benefit from a graded introduction to Fortini over three days.

†Average level of DHA worldwide in breast milk of 0.32% ± 0.22% of total fatty acids⁴⁸



POWERED BY PROTEIN, NUTRITIONALLY COMPLETE

- **Provides a recommended percentage of energy from protein:** In accordance with WHO/FAO/UNU guidelines,⁴⁷ Fortini is within the recommended range for percentage of energy from protein, to support appropriate lean tissue gain specifically for catch-up growth.
- **Contains key nutrients inspired by breast milk:** Nutricia supports breast milk as the best option, when possible. Fortini can be used either to supplement breast milk when necessary, or as a sole source of nutrition when it isn't possible. Fortini provides DHA at a level comparable to that of breast milk.⁸¹ Fortini has an equal amount of ARA, in line with expert recommendations.⁴⁹ DHA and ARA promote brain and eye development. Fortini has:
 - A prebiotic blend that can help support infant digestive health^{50,51} and immune system development^{52,53}
 - Nucleotides, which have been shown to help support the immune system⁵⁴



CLINICALLY SUPPORTED

- Supported by 7 clinical studies^{16-18,20,21,55,56}
- Shown to help critically ill infants meet nutritional targets and achieve positive nitrogen balance in as little as 2 days¹⁷⁻¹⁹



A TRUSTED HERITAGE

- Made by Nutricia, the makers of Neocate[®] infant formulas
- Widely used for more than 20 years and available in over 30 countries (over 23 million bottles are consumed annually)

In short, Fortini helps FTT and malnourished infants who have high energy needs and/or volume restrictions get the highest number of calories in the smallest volume, and the complete nutrition they need, in a formulation that's as well tolerated as standard 20 kcal/fl oz formulas.

Fortini is specifically created to meet the unique nutritional needs of term infants and children up to 18 months of age or 19.8 lbs (9 kg) with or at risk of growth failure, increased energy requirements, and/or fluid restrictions due to conditions such as:

- CONGENITAL HEART DISEASE
- CHRONIC LUNG DISEASE
- RESPIRATORY SYNCYTIAL VIRUS
- NEUROLOGICAL SYNDROME OR NEURO-DISABILITIES
- CYSTIC FIBROSIS
- NON-DISEASE-RELATED FTT

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CLINICAL SUPPORT FOR FORTINI*

POSITIVE NITROGEN BALANCE IN AS LITTLE AS 2 DAYS POST-OP

- Cui et al found that Fortini helped achieve higher nutrition intakes and earlier nitrogen balance than standard infant formula during the early postoperative period after congenital heart disease repair surgery.¹⁷
 - Intakes of energy and protein were significantly higher in the Fortini group from day 1, and all infants in the Fortini group met the adequate intakes as early as day 2
 - Nitrogen balance in the Fortini group met positive balance from day 2, whereas the standard-formula group did not achieve this until day 5
 - The Fortini group had a significantly higher increase in plasma levels of the essential amino acids isoleucine and leucine

IMPROVED ENERGY AND NITROGEN BALANCE IN THE PICU

- Van Waardenburg et al found that in critically ill infants, Fortini promoted more adequate nutrient intake and improved energy and nitrogen balance, compared with standard infant formula.¹⁸
 - Nutrient intakes were higher in the Fortini group and met dietary reference intakes (DRIs) on days 3-5; standard-formula infants met DRI on day 5 only
 - Cumulative nitrogen balance and energy balance were significantly higher in the Fortini group than in the standard-formula group
 - Essential amino acid levels were higher in the Fortini group and within reference limits; levels were below reference limits in the standard-formula group

HIGHER AND EARLY ANABOLIC STATE IN THE PICU

- In de Betue et al 2011, tube feeding with Fortini promoted better protein anabolism in critically ill infants in the first days after admission to the PICU, compared with a standard infant formula.¹⁹
 - Protein balance was significantly higher with Fortini than with standard infant formula, resulting from significantly increased protein synthesis, despite significantly increased protein breakdown
 - 87% of infants receiving Fortini had positive whole body protein balance (reflecting anabolism) on day 5; 40% of infants receiving standard formula had a negative nitrogen balance (reflecting catabolism) on day 5
 - The 24-hour nitrogen balance on day 5 was significantly higher in the Fortini group, compared with the standard infant formula group

INCREASED ARGININE AVAILABILITY IN SEVERE ACUTE ILLNESS

- De Betue et al 2013 found that Fortini increased availability of arginine, an essential amino acid, in critically ill infants, compared with standard infant formula. This led to increased nitric oxide synthesis, independent of plasma arginine concentrations.⁵⁷

See P. 20 for study details

*In countries outside the U.S., Fortini is known as Infatrini.



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Infant

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CLINICAL SUPPORT FOR FORTINI* (CONTINUED)

HIGHER NUTRIENT INTAKE, INCREASED WEIGHT, MORE STABLE LENGTH

- Clarke et al showed that increasing protein and micronutrients with Fortini provided significantly more favorable growth outcomes than energy-supplemented standard infant formula (ESF) in infants with faltering growth.²⁰
 - The Fortini group received 42% more protein and 15-40% more vitamins and minerals
 - Blood urea concentration in the ESF group fell by 50%, suggesting a suboptimal protein-energy ratio in the ESF feed
 - The Fortini group retained a normal mean blood urea concentration and higher urinary potassium concentration

SUPPORTED WEIGHT GAIN IN HOSPITALIZED INFANTS

- In their retrospective review, Eveleens et al found that a majority of infants with prolonged PICU stays showed weight improvement when given Fortini.²¹
 - Infants in PICU who were given Fortini daily for at least 21 days had a mean weight-for-age Z-score increase of 0.48 and a median weight gain of 5.80 g/kg/day

WEIGHT GAIN FOLLOWING SURGERY FOR CONGENITAL HEART DISEASE (CHD)

- Scheeffler et al found that Fortini was well tolerated following CHD surgery and supported higher weight gain than standard infant formula.¹⁶
- Exploratory findings included less use of antibiotics and a trend toward shorter LOS, which could be confirmed in further research.

AS WELL-TOLERATED AS STANDARD INFANT FORMULA

- Evans et al showed Fortini was generally well tolerated in infants under 12 months with faltering growth, when administered at full strength from day 1.⁵⁵
- Clarke et al found no significant differences in tolerance between the Fortini group and the ESF group.²⁰
- In van Waardenburg et al, early administration of Fortini in critically ill infants was well tolerated.¹⁸
- Cui et al found that Fortini was as well tolerated as standard formula¹⁷
- Eveleens et al found that Fortini was well tolerated²¹
- Scheeffler et al showed Fortini use after heart surgery for patients with CHD was well tolerated¹⁶

See P. 20 for study details

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APPENDIX

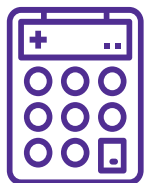
PRODUCT ACCESS & CLINICAL SUPPORT

Reimbursement: Fortini may be covered by WIC* in some states. Visit FortiniUS.com to learn more about reimbursement options.



Webinars: The Nutricia Learning Center provides access to live and recorded CE-eligible webinars for dietitians, RNs, and other clinical specialists, as well as a broad array of other resources, including case studies, flowcharts/guidelines, and reference libraries.

Nutricialearningcenter.com



Formula calculator: Our Fortini DRI calculator shows the nutrients Fortini feedings provide. By age and gender, it helps you assess how Fortini meets your patients' needs and your goals. It can also quickly calculate monthly supply needs based on a total amount of daily calories.

FortiniUS.com/HCP/resources-and-tools/formula-calculator/

You can find resources for managing your infants with failure to thrive on our website. **Visit: FortiniUS.com/HCP**

APPENDIX

FORTINI INGREDIENTS AND NUTRIENTS

Water, Nonfat Milk, Maltodextrin, Refined Vegetable Oils (Canola, Modified Coconut, High Oleic Sunflower, Sunflower, and Corn Oils), Lactose, and less than 2% of each of the following: Galacto-oligosaccharides (GOS), Whey Protein, Medium Chain Triglycerides (Palm Kernel and/ or Coconut Oil), Anhydrous Milk Fat, Citric Acid Esters of Mono- and Diglycerides (CITREM), Calcium Citrate, Fructooligosaccharides (FOS), Potassium Citrate, Calcium Phosphate, Sodium Chloride, Citric Acid, *C. cohnii* Oil, Inositol, *M. alpina* Oil, Sodium L-Ascorbate, Choline Chloride, Magnesium Carbonate, Calcium Hydroxide, Potassium Hydroxide, Ferrous Lactate, Taurine, Dipotassium Hydrogen Phosphate, Nucleotides (Cytidine 5'-Monophosphate, Adenosine 5'-Monophosphate, Disodium Uridine 5'-Monophosphate, Disodium Inosine 5'-Monophosphate, Disodium Guanosine 5'-Monophosphate), DL-Alpha Tocopheryl Acetate, L-Carnitine, Zinc Sulfate, Calcium D-Pantothenate, Niacin, Soy Lecithin, Copper Gluconate, Thiamine Hydrochloride, Potassium Iodide, Riboflavin, Pyridoxine Hydrochloride, Vitamin A Acetate, Manganese Sulfate, Folic Acid, Phylloquinone, D-Biotin, Sodium Selenite, Cholecalciferol, Cyanocobalamin.

NUTRIENTS	Per 100 Calories (100 mL)	Per Carton (4 fl oz / 118 mL)
Calories	100	118
Protein, g	2.6	3.0
Fat, g	5.4	6.3
Linoleic Acid, mg	790	934
α-Linolenic Acid, mg	141	167
DHA, mg	17.8	21.1
ARA, mg	17.8	21.1
Carbohydrate, g	10.1	12.0
Soluble Fiber, g	0.57	0.67
Water, g	85	100
VITAMINS		
Vitamin A, IU (mcg RE)	253 (76.0)	299 (89.7)
Vitamin D, IU (mcg)	76.0 (1.9)	89.9 (2.2)
Vitamin E, IU (mg α-TE)	3.1 (2.1)	3.7 (2.5)
Vitamin K, mcg	8.5	10.1
Thiamine, mcg	150	177
Riboflavin, mcg	200	237
Vitamin B ₆ , mcg	110	130
Vitamin B ₁₂ , mcg	0.30	0.35
Niacin, mcg	530	630
Folic acid, mcg	16.0	18.9
Pantothenic acid, mcg	800	946
Biotin, mcg	4.0	4.7
Vitamin C, mg	14.0	16.6
Choline, mg	23.0	27.2
Inositol, mg	25.0	29.6

MINERALS	Per 100 Calories (100 mL)	Per Carton (4 fl oz / 118 mL)
Calcium, mg (mmol) [mEq]	100 (2.5) [5.0]	118 (2.9) [5.9]
Phosphorus, mg (mmol)	50.0 (1.6)	59.1 (1.9)
Magnesium, mg (mmol) [mEq]	10.7 (0.44) [0.89]	12.7 (0.52) [1.0]
Iron, mg	1.6	1.9
Zinc, mg	0.70	0.83
Manganese, mcg	16.0	18.9
Copper, mcg	65.0	76.9
Iodine, mcg	20.1	23.8
Molybdenum, mcg	<8.0	<9.5
Chromium, mcg	<8.0	<9.5
Selenium, mcg	2.9	3.4
Sodium, mg (mmol, mEq)	37.0 (1.6)	43.8 (1.9)
Potassium, mg (mmol, mEq)	95.0 (2.4)	112 (2.9)
Chloride, mg (mmol, mEq)	62.0 (1.7)	73.3 (2.0)
Osmolality 360 mOsm/kg H₂O		



ABOUT NUTRICIA

Nutricia has been a pioneer in infant and medical nutrition for more than 100 years. In 1906, we developed the world's first medical nutrition products: a low-lactose milk for patients with diabetes and a nutritional product for patients suffering from goiter.

Our pioneering spirit lives on with an ongoing commitment to provide life-transforming nutrition at key moments throughout life. Together with our partners around the world, we've built on more than a century of nutritional research and innovation, with science-based products and services that support healthy growth and development during the first 1000 days. We're also addressing some of the world's biggest health challenges, including faltering growth, food allergy, epilepsy and rare metabolic diseases, as well as age-related conditions and chronic disease, such as frailty.

Our driving purpose is to help people live longer, more joyful, and healthier lives. Fortini is a reflection of that purpose. We know that the right nutrition at the right time can change a health journey for life, and for FTT babies, the right time is immediately.



OTHER NUTRICIA MEDICAL FOODS AND PRODUCTS

Specialized pediatric nutrition

Neocate® — For the dietary management of cow milk allergy, multiple food allergies and related GI and allergic conditions, including short bowel syndrome, eosinophilic esophagitis, food protein-induced enterocolitis syndrome, malabsorption and gastroesophageal reflux

Duocal® — For the dietary management of conditions in which a high-energy, low-fluid, low-electrolytes diet is indicated

Ketogenic:

KetoCal® — For the dietary management of intractable epilepsy

Liquigen® — For the management of the medium chain triglyceride (MCT) ketogenic diet for intractable epilepsy and other conditions in which MCT is a part of the dietary management

Metabolics:

Anamix® range — For patients diagnosed with an inherited metabolic disorder

Monogen® — For the dietary management of individuals over the age of one with long chain fatty acid oxidation disorders or chylothorax

Periflex®, PhenylAde®, Lophlex® — For patients who are medically diagnosed with an inherited metabolic disorder

REFERENCED CLINICAL STUDIES:

Clarke et al., 2007:²⁰ Open, parallel, randomized trial to compare the effectiveness of a nutrient-dense formula with an energy-supplemented formula in infants with faltering growth. Infants (n=49) with faltering growth received either Fortini or an energy-supplemented standard infant formula for 6 weeks.

Cui et al., 2018:¹⁷ Double-blind, randomized, controlled trial to evaluate nutrition effects and tolerance of Fortini compared with a standard formula in infants (n=50) in the first 5 days after congenital heart surgery. Plasma amino acid concentrations were measured. Cumulative energy balance and nitrogen balance were calculated.

de Betue et al., 2011:¹⁹ Extension of van Waardenburg et al., 2009. Primary outcome: whole body protein balance. Secondary outcome: first pass splanchnic phenylalanine extraction.

de Betue et al., 2013:⁵⁷ Extension of van Waardenburg et al., 2009, and de Betue et al., 2011. Investigated arginine kinetics in critically ill infants (n=18).

Evans et al., 2006:⁵⁵ Random allocation. To evaluate feeding tolerance, 30 infants (aged 2–43 weeks) requiring a high-energy formula for faltering growth were given either Fortini at full strength from day 1 or the same formula in diluted form, graded to full strength over 3 days.

Eveleens et al., 2019:²¹ Records from infants (n=70) admitted to a multidisciplinary PICU and given Fortini for at least 21 days were analyzed retrospectively. Predominant admission diagnoses were post-cardiac surgery, respiratory and cardiac diagnosis. Weight achievement was determined as the difference between weight-for-age (WFA) Z-scores at the start and end of Fortini use. Gastrointestinal symptoms, including gastric residual volume, constipation and vomiting, were evaluated as tolerance parameters.

Scheeffter et al., 2020:¹⁶ Randomized controlled trial with 59 patients undergoing heart surgery. The intervention group received Fortini; the control group received standard (normocaloric) infant formula. The researcher in charge of anthropometric evaluation was blinded to the randomization.

van Waardenburg et al., 2009:¹⁸ Double-blind, randomized, controlled trial. Infants (n=18) admitted to the pediatric intensive care unit with respiratory failure due to viral bronchiolitis were randomized to continuous enteral feeding with Fortini or standard infant formula during 5 days after admission. Primary outcomes: nutrient delivery, energy and nitrogen balance, and plasma amino acid concentrations. Secondary outcomes: tolerance and safety.

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