A 700-g infant regained her birthweight 14 days after birth. She is receiving 120 kcal/kg per day (503 kJ/kg/day) of fortified infant formula. Three weeks later, she is noted to be growing at 10 g/kg per day, and her head circumference has increased 1 cm during the past 2 weeks. She requires 24% supplemental oxygen, has normal radiographic findings, and generally appears healthy. Blood cell count, electrolytes, and blood gases are normal.

Of the following, the BEST nutritional strategy for this infant would be to add:

- carbohydrate
- lipid
- nothing
- protein
- volume

You selected 4, the correct answer is 4.

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Although appearing well, this infant is growing suboptimally. Once having regained their birthweights, very-low-birthweight infants should demonstrate a weight gain of more than 18 g/kg per day, and their head growth should exceed 0.9 cm per week. As weight gain increases from 12 g/kg per day to 21 g/kg per day, the incidences of cerebral palsy, Bayley II Mental Developmental Index and Psychomotor Developmental Index scores less than 70, abnormal neurologic findings, neurodevelopmental impairment, and need for rehospitalization decrease. Gain in head circumference shows similar correlations, suggesting best outcomes with increases of more than 0.9 cm per week. When lower-than-desirable growth velocity is observed and not accounted for by comorbidities, nutritional adjustment by increasing the protein-energy ratio may be the best strategy.

Shortly after birth, preterm infants uniformly show weight loss. Part of this weight loss, approximately 50%, is the desirable loss of extracellular fluid required for extrauterine adaptation. The remainder reflects loss of lean body mass and intracellular fluid associated with inadequate nutrition. Early use of parenteral amino acid/glucose solutions and early enteral feeding may minimize this loss. The times for the infant to reach nadir weight and then to regain birthweight are inversely proportional to this loss of body mass and are directly proportional to the child's energy and protein deficits.

Had this infant remained in utero, she would have gained more than 15 g/kg of weight per day and accumulated approximately 3 g/kg of protein per day. Preterm infant formula or fortified breast milk provided at 120 kcal/kg per day (503 kJ/kg/day) can reasonably be predicted to meet her energy needs and to compensate for her energy deficit. Currently, energy intakes in excess of 120 kcal/kg per day are not considered desirable so as to avoid excess fat accretion. On the other hand, current feedings may not provide sufficient protein for adequate growth, especially when a significant protein deficit must be overcome, as in the infant in this vignette. Protein intakes up to 3.6 g/100 kcal per day (4.3 g/kg/day if fed 120 kcal/kg/day) result in an increase in the protein-energy ratio.
Supplementing her feedings with calories in the form of carbohydrate or lipid would decrease the protein-energy ratio and not facilitate better rates of restoring lean body mass. Increasing volume would increase both caloric intake and protein, but leave the nutritional composition unchanged. In the face of a low growth velocity, making no change in the nutritional strategy would not be the wisest approach.

References:


American Board of Pediatrics Content Specification(s):

Understand how to ascertain and calculate the caloric requirements to ensure optimal growth of preterm infants

Understand the protein requirements of preterm and full-term infants

Understand the consequences of feeding low-birthweight infants too little or too much protein

Know the interventions used to prevent mental retardation and their effects on cognitive outcome
A 5-hour-old newborn, who weighs 1,250 g at an estimated gestational age of 27 weeks, has respiratory distress. Maternal history was significant for spontaneous rupture of membranes about 3 days before delivery and subsequent onset of preterm labor. The mother is a carrier of group B *Streptococcus* and has had a history of *Chlamydia* infection. Administration of corticosteroids and antibiotics was completed before delivery. Apgar scores were 3 and 7 at 1 and 5 minutes after birth, respectively. The resuscitation included endotracheal intubation, positive pressure ventilation, and administration of surfactant. The infant is supported with a mechanical ventilator and has umbilical arterial and venous access. Narcotic analgesia is used for these procedures, but the infant remains irritable and has frequent oxygen desaturations when manipulated. You are considering adding midazolam for further sedation.

Of the following, the most likely EXPECTATION if midazolam is given to this infant is that it will:

1. be safe without serious side effects
2. block γ-aminobutyric acid binding in the brain
3. have a half-life of less than 4 hours
4. have less bioavailability than in the adult if given orally
5. provide effective sedation

You selected 1, the correct answer is 5.

Midazolam is a short-acting benzodiazepine that provides sedation and muscle relaxation in adults and children. The structure of midazolam is shown in the Figure.
This drug can be administered intravenously, orally, sublingually, or nasally. Midazolam has come into wide use as a sedative for neonatal intensive care patients in recent years. Randomized controlled trials, using behavioral and physiologic outcome measures in premature infants of varying gestational ages and weights, have shown midazolam to be more effective than placebo. However, these trials were relatively small and did not specifically investigate whether the most immature infants responded as well as more mature infants.

Moreover, the safety of midazolam in premature infants has come under question, because adverse events including death, possible seizures, severe intracranial hemorrhage, and periventricular leukomalacia have occurred more frequently with midazolam use than with placebo. Such adverse outcomes, however, have not been consistently found. Further controlled trials are needed, especially in small and sick premature infants.

The mode of action of midazolam is to promote the binding of γ-aminobutyric acid (GABA) to the GABA\textsubscript{A} receptor by attaching itself to the benzodiazepine-binding site of that receptor. GABA acts as a central nervous system inhibitor (sedative) and the GABA\textsubscript{A} receptor functions as a ligand-gated transmembrane chloride channel.

The observed increases in adverse neurologic outcomes of premature infants treated with midazolam as compared with placebo are understandable when considering data from controlled studies of immature animals. These studies show that the effect of midazolam and its side effects are highly dependent on the maturity of the animal brain so exposed. Three-day-old rat pups (with brain development roughly comparable with that of premature infants of 24-28 weeks' gestation) receive no sedative effect from midazolam. Midazolam produces heightened sensitization to noxious stimuli in these immature animals. On the other hand, 10-day-old rats (comparable with term newborn infants) are sedated by midazolam. The introduction of midazolam to the early developing mammalian brain (before maturation of GABA\textsubscript{A} receptors) results in stimulation of neural activity (not inhibition) and an excess of neuronal apoptosis, similar to the effects of ethanol on the developing brain.

The half-life of midazolam in adults is 1.9 to 3.2 hours, justifying its reputation as a “short-acting” sedative. Metabolism and elimination kinetics depend on the following steps: demethylation and hydroxylation at the 1-position of midazolam; catalyzed by the mixed function oxidase, cytochrome P450 3A4 (CYP3A4); and subsequent glucuronidation of the same hydroxyl radical. CYP3A4 is found in adult liver and intestines but is absent from either tissue in the fetus. After parturition, CYP3A4 activity remains far below adult levels in premature and newborn infants. Consequently the half-life of midazolam in premature infants is considerably longer, with mean estimates of 6.3 hours (intravenous) to 7.6 hours (oral). Of interest, because of the similar developmental course of intestinal CYP3A4, almost half of a dose of midazolam administered orally to a premature infant is absorbed intact, while only one fourth survives to absorption in adults.

Midazolam clearance can be altered by interactions with other drugs. Reduced clearance of midazolam has been reported in the presence of CYP3A4 inhibitors such as cimetidine, fluconazole, and erythromycin. Infants treated with indomethacin, on the other hand, have been reported to clear midazolam more efficiently because of either the drug interaction or the patent ductus arteriosus itself.

References:


**American Board of Pediatrics Content Specification(s):**

Understand the mechanisms by which various drugs are metabolized

Identify the factors involved in the disposition of a drug and understand the differences between drug distribution in infants and adults
A growth-restricted female infant born at term gestation is being discharged from the newborn nursery 6 days after birth. Newborn screening shows that she has a high risk for cystic fibrosis and is scheduled to have a buccal smear. The infant's mother expresses her desire to have her infant drink a soy protein–based formula. She explains that the infant's sibling, a male born at term gestation, had severe colic and after several months of trying different formulas and potential remedies, a change to soy formula led to resolution of his colic. This child now has severe eczema and allergies to several foods. In addition to preventing colic and allergies, the mother would like to transition to soy formula because she has recently become a vegetarian and wishes that her children abide by this diet.

Of the following, the MOST appropriate indication for initiating soy protein–based formula in this infant is to:

1. maintain a vegetarian diet
2. minimize malabsorption
3. maximize fat intake
4. obviate allergies
5. prevent colic

You selected 5, the correct answer is 1.

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Formulas with soy protein were developed to assist infants who were unable to tolerate milk protein. The popularity of soy protein–based infant formula doubled during the late 1980s to early 1990s. By the late 1990s, sales of soy formulas accounted for approximately 20% of the formula market in the United States. To clarify the indications for these formulas, the American Academy of Pediatrics (AAP) established specific recommendations in 1998, which were revised in 2008, for the use of soy formulas. The AAP recommends the use of soy formulas instead of cow milk–based formulas for the following infants:

- Term infants with galactosemia
- Term infants with hereditary lactase deficiency
- Term infants with a secondary lactose intolerance
- Term infants whose care providers are instituting a vegetarian diet

In this vignette, the mother's interest in maintaining a vegetarian diet for her infant is an indication for the use of a soy protein–based formula.

Protein hydrolysate formulas, rather than soy formulas, are the preferred diet for infants with significant malabsorption from gastrointestinal or hepatobiliary diseases such as cystic fibrosis, short gut syndrome, biliary atresia, or protracted diarrhea. Because the milk protein...
(either casein or whey) is heat-treated and enzymatically hydrolyzed, hydrolysate formulas contain free amino acids and peptides that are easily absorbed. In addition, these formulas contain medium-chain triglycerides to facilitate fat absorption. Polyunsaturated vegetable oil is added to supply essential fatty acids. Most of the protein hydrolysate formulas are lactose-free and the carbohydrate component contains various amounts of sucrose, tapioca starch, corn syrup solids, and/or cornstarch.

Because soy formulas contain the same amount and type of fats as found in cow milk–based formulas, soy formulas will not improve the growth of the growth-restricted term infant in this vignette. However, these two formulas have certain distinctive nutritional components. As expected, the source of protein in soy formulas is soy instead of cow milk protein. Methionine, taurine, and carnitine are added to soy formulas to compensate for the low concentration of these amino acids in soy protein. To avoid possible contamination with milk proteins, lactose is not used in soy formulas. Instead, the carbohydrate component of soy formulas consists of sucrose, cornstarch hydrolysates, or a mixture of these two. Similar to cow milk formulas, soy protein–based formulas meet the iron, vitamin, mineral, and electrolyte content specifications for feeding term infants that has been established by the US Food and Drug Administration. However, unlike cow milk–based formulas, soy formulas contain soy phytoestrogens; at present, there is no conclusive evidence that these compounds affect human development, reproduction, or endocrine function.

Some studies suggest that soy protein–based formulas can have a calming benefit for infants with colic but controlled trials of cow milk and soy formulas have not shown a significant benefit with soy exposure. Soy formulas have not been shown to prevent colic.

While studies have suggested that soy protein–based formulas can be useful to treat infants with a documented cow milk protein allergy, approximately 10% to 14% of these allergic infants will also have a soy protein allergy. Thus, the AAP recommends that clinicians should consider recommending hydrolyzed protein formulas instead of soy formulas to these infants. There is no evidence that a soy formula diet can obviate allergies.

The AAP guidelines also emphasize that soy protein–based formulas are not indicated for preterm infants. Studies have shown that preterm infants receiving a soy formula diet have lower serum phosphorus concentrations, higher alkaline phosphatase concentrations, and a greater degree of osteopenia than preterm infants receiving a cow milk protein–based formula.

Do you want to add anything to your Learning Plan?
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References:


Berseth CL, Johnston WH, Stolz SI, Harris CL, Mitmesser SH. Clinical response to 2 commonly used formulas occurs within 1 day [published online ahead of print October 2, 2008]. Clin Pediatr [Phila].


American Board of Pediatrics Content Specification(s):

Understand the benefits and risks of formulae that contain soy proteins
Understand the benefits and risks of formulae that contain hydrolyzed proteins