A male neonate was delivered at 26 weeks gestational age by emergent cesarean section due to severe preeclampsia. Birth weight was 520 g, which was below the third percentile, indicating significant growth restriction. The immediate postnatal course included endotracheal intubation, administration of surfactant, and placement of umbilical catheters. Nutritional support started short-ly after birth with a pre-prepared solution containing dextrose and amino acids.

During the first weeks, parenteral nutrition (PN) provided the main source of calories and was delivered through a central venous catheter. In addition to the carbohydrate and protein infusions, intravenous fat was started soon after birth. The lipid was soybean oil-based, with a high ratio of omega-6:omega-3 fatty acids. Protein was advanced to a dose of 3.5 g/kg per day, carbohydrate to a glucose infusion rate of 12 mg/kg per minute and lipid dose to 3 g/kg per day. Micronutrient administration included electrolytes and minerals as well as a multivitamin, all included in the parenteral solution.

Minimal enteral nutrition was initiated on the second day of life with maternal breast milk, but was held due to the patient’s development of significant hypotension. By day of life 6, the hypotension resolved and feedings were restarted. After a few days of minimal enteral nutrition, feedings were advanced daily by 20 mL/kg per day. These were initially well tolerated as evidenced by minimal gastric residuals, passing of stool and a normal abdominal exam.

On day of life 17, bilious emesis occurred and feedings were stopped. Serial plain films of the abdomen showed a gasless abdomen but no evidence of pneumoperitoneum. Gastric decompression was started, blood cultures were obtained and antibiotics were administered. Within 48 hours, the abdomen became increasingly tense and distended with flank erythema.
The patient underwent an exploratory laparotomy on day of life 20 revealing full thickness necrosis of multiple segments of small bowel, as well as a healthy-appearing colon and as much as 5 cm of healthy distal ileum with an intact ileocecal valve; pathology specimens confirmed necrotizing enterocolitis. During the next 4 months, multiple surgical interventions addressed complications of abdominal wound dehiscence, enterocutaneous fistulae, and anastomosis of the remaining viable small bowel segments. Ultimately, at day of life 162, the small and large bowels were anastomosed, leaving 47 cm of small bowel and the entire colon intact. A multidisciplinary team of neonatologists, pediatric surgeons, and gastroenterologists managed this child’s nutritional support throughout.

During this 5-month interval, trophic amounts of breast milk, generally at 1 mL/hour, were given as tolerated to stimulate the intestinal mucosa. However, persistent bowel dysfunction only allowed trophic feeding to be delivered intermittently. Therefore, the bulk of nutrition provided continued to be parenteral.

Basic anthropometry measurements (weight, head circumference, length) showed continued growth failure and plateaus of all parameters throughout the ICU stay. Cholestasis, defined as a direct bilirubin of more than 2 mg/dL, developed and became significant with a peak value of 19.6 on day of life 140. The dose of intravenous lipid emulsion was limited to 1 g/kg per day and was only given three times per week to help cholestasis, as well as to meet essential fatty acid (EFA) requirements.

Due to the extreme elevation in direct bilirubin, a decision to temporarily stop lipid infusion was made. The patient’s triene:tetraene ratio became elevated, indicating EFA deficiency. The Food and Drug Administration has approved compassionate use of a fish oil-based lipid emulsion, containing a higher omega-3:omega-6 fatty acid ratio; use of this lipid lowered the triene:tetraene ratio, marking a reversal of EFA deficiency. After the final anastomosis of small and large bowel, the patient was also able to tolerate advancing feeds of breast milk via gastrostomy tube. By 7 months of age, the patient was able to tolerate significant enteral nutrition in the form of breast milk. The direct bilirubin started to decrease and lowered to 0.4 mg/dL during the seventh month.

Although calcium and phosphorous were provided in the PN, osteopenia developed and was detected by serum markers, including an elevated alkaline phosphatase with peak value of 1,316 IU/L, as well as multiple radiographic abnormalities. Plain films of the long bones revealed diffuse osteopenia and fractures in the left humerus and femur.

Other complications of extreme prematurity included severe bronchopulmonary dysplasia requiring long-term mechanical ventilation; grade 3 intraventricular hemorrhage; surgical ligation of a patent ductus arteriosus; and retinopathy of prematurity. He developed refractory pulmonary hypertension and worsening heart failure. The family chose to remove the patient from mechanical ventilation and provide comfort care until death.

### DISCUSSION

**Neonatal Cholestatic Liver Disease and Osteopenia**

**TREATMENT**

**Parenteral Nutrition vs. Enteral Nutrition**

**DIAGNOSIS**

**CME**

PN in the neonatal ICU can be considered life-saving in the context of extremes of prematurity and intestinal dysfunction. Before the availability of safe admixtures of protein and fat components, the smallest preterm neonates and babies with intestinal dysfunction died of malnutrition as they broke down body stores for energy while not receiving those macronutrients. Early administration of amino acid solutions now help maintain positive nitrogen balance and net gain of lean body mass. Intravenous lipid emulsions deliver a concentrated energy source as well as the EFA, linoleic and alpha-linolenic acids. Despite progress in formulations and prescribing practices, PN still does not yet match the quality of enteral nutrition, particularly breast milk, in supporting growth and long-term health in the premature population.

Early initiation and advancement of enteral nutrition improves outcomes, including length of stay, and the use of breast milk over commercial formula clearly lowers rates of necrotizing enterocolitis and sepsis. This is attributed to the many immunologic as well as growth factors in human milk, which: 1) provide the neonate with passive immunity; 2) help establish intestinal integrity and function; and 3) normalize patterns of intestinal flora. Human milk also improves neurodevelopmental outcomes of preterm neonates. In fact, a dose effect has been described, suggesting that clinicians should view human milk not just as a nutritional source, but also as a medical treatment. Due to its anti-oxidative factors, human milk may also be protective against the need for surgery for retinopathy of prematurity.

In cases such as the neonate presented here, intestinal failure prevents the use of enteral nutrition and makes a child dependent on intravenous nutrition for long periods of time. It is often very possible to meet total caloric goals with PN infusions. However, the quality of the constituents may be a significant factor in some of the morbidities mentioned. Furthermore, the limitations of chemistry still prevent optimal delivery of some nutrients, such as calcium.

Many factors contribute to intestinal failure-associated liver disease, often called total PN cholestasis. Lack of enteral stimulation of bile flow, sepsis with its pro-inflammatory mediator release, multiple surgeries and prematurity itself are risk factors. The use of long-term PN requires infusion with a central catheter,
a risk factor for infection. Measures are often taken to minimize the progression of cholestasis once developed, but the main focus for researchers and clinicians has shifted to its prevention in chronically PN-dependent infants.

In infants, direct bilirubin levels directly correlate risk of death with short bowel syndrome. For this patient, two factors seemed to aid in the reversal of cholestasis: One key factor was the advancement of enteral nutrition after the final anastomosis. Achieving even only 50% of enteral nutrition goals can be helpful in preventing or reversing cholestasis.

Two factors make it plausible that the lipid emulsion involved in PN may lead to hepatocyte damage and impaired bile flow, causing and exacerbating cholestasis. Currently approved lipid emulsions in North America contain predominantly omega-6 FA, precursors of pro-inflammatory mediators. Plant-based sterols contained in the soy-based product likely impair bile flow based on in-vitro studies. Lowering the dose of soy-based emulsions to 1 g/kg per day may both prevent development of cholestasis and reverse established cholestasis.

Fish oil-based lipid emulsions contain a heavier balance of omega-3 FA, whose products are less pro-inflammatory, and do not contain plant-based sterols. After cholestasis has developed, initiation of fish oil-based emulsions, also at a dose of 1 g/kg per day may promote reversal of biochemical indicators of cholestasis. Prospective, randomized studies looking at prevention of cholestasis in the neonatal population through these interventions are under way. These studies will need to weigh the benefits of preventing cholestasis against risks of decreasing caloric provision with lower doses of fat on outcomes such as growth and development in this vulnerable population.

With an incidence inversely related to gestational age, osteopenia of prematurity is a disease of inadequate calcium provision and is not responsive to increasing doses of vitamin D. The bulk of calcium accretion by the fetus normally occurs during the third trimester. Preterm delivery thus prevents normal accumulation of calcium stores, 99% of which reside in bone. Enteral nutrition, with fortified preterm human milk to increase calcium and phosphorous delivery, will provide sufficient amounts of these minerals in most cases. However, multiple factors limit calcium provision via the parenteral route. In this case, bone disease developed due to both long-term PN use and the use of diuretics for chronic lung disease. Not only is long bone growth a concern, the decreased density of the thoracic cage may have consequences on pulmonary function.

Growth failure commonly occurs in the preterm neonatal ICU population. Early establishment of parenteral and enteral nutrition have allowed progress in many infants. However, morbidities such as necrotizing enterocolitis and frequent periods of surgery and recovery will divert calorie use from growth toward tissue repair and recovery, and will exacerbate growth failure. Although EFA deficiency can cause poor growth, the short time of EFA deficiency in this case probably did not play an important role in the growth failure of this patient.

CONCLUSION

Long-term PN use for preterm neonates with intestinal dysfunction can be life-sustaining. Limitations still exist in the quality of constituents. Cholestasis and osteopenia remain significant morbidities, and the liver disease becomes life-threatening if little to no significant enteral nutrition can be established. Emerging data reveal promising alternatives that may prevent cholestasis related to long-term PN use.

Breast milk feeding over commercial formula appears to support the healthiest early growth patterns for preterm infants and may have long-term health benefits. In addition to addressing suboptimal growth while in the NICU, nutritional interventions must also be tailored to prevent excessive growth during infancy and obesity in adulthood. The neonatal time period appears to be one of metabolic programming, during which excess nutrition may predispose the preterm population to metabolic syndrome and its associated morbidities.

This case report represents the extreme challenges to the nutritional support of the preterm neonate. As most achieve full enteral nutrition in a timely manner, neonatologists and pediatricians should hold focused conversations with all mothers who deliver preterm infants to discuss the significant health benefits that human milk affords the preterm neonate.

REFERENCES