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THERAPEUTIC DILEMMA

Liver Disease and Parenteral Nutrition in an Adolescent with Cystic Fibrosis

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CASE

A 15-year-old female with cystic fibrosis (CF) was admitted to the hospital following a 7-day history of productive cough, shortness of breath, sore throat and malaise. Although the patient was diagnosed with CF at 2 years of age, her first hospitalization for a pulmonary exacerbation was not until age 13. Over the next 2 years, she developed rapidly progressive lung disease. The patient's history was also complicated by CF-associated biliary cirrhosis (hypersplenism, modest hepatomegaly, portal hypertension and varices) that began with modestly elevated liver function tests at approximately 7 years of age. Eighteen days prior to the admission described in this case, she completed a course of home antibiotics. Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 second (FEV_1) were 28% and 19% at admission. She was started on antibiotic therapy (ceftazidime 2 g IV q8h, tobramycin 130 mg IV q8h and colistimethate 75 mg q12h via nebulization). She was also receiving home medications which included ADEK vitamin 2 tablets qhs, omeprazole 20 mg bid, ursodiol 600 mg bid, pancreatic enzymes 5 tablets with meals and 2 tablets with snacks, beclomethasone 1 spray in each nostril bid, nadolol 10 mg (increased to 20 mg during this admission) bid; nebulization therapy with albuterol 0.5 ml tid, dornase alfa 2.5 mg qhs, and tobramycin 300 mg bid. Vest physical therapy was used in conjunction with nebulization treatments. During this admission, the patient was also initiated on 1 liter of oxygen via binasal cannula nightly.

Upon nutrition screening, she was noted to have decreased appetite with failure to gain optimal weight for 2 years. Her weight and height were 47 kg and 161.6 cm. Body mass index (BMI) was 17.3 kg/m^2, which was in the 10th–25th percentile of normal. She had been in the 75th percentile 2 years prior to this admission. During the first 3 weeks of her hospital stay, the Clinical Nutrition Service worked with the patient in an effort to promote weight gain by providing meal tickets and encouraging snacks and supplemental shakes. Gastrostomy tube placement was discussed but not done due to the risk of bleeding secondary to her degree of liver disease and portal hypertension (a relative contraindication to gastrostomy tube placement). On hospital day 23, the Parenteral Nutrition Service was consulted to begin total parenteral nutrition (TPN) for weight gain. At this time, the patient was awaiting liver, and potentially combined liver and lung, transplantation. Albumin concentrations prior to beginning TPN ranged from 2.3 to 2.8 g/dL (normal range 4.0–6.0 g/dL), and prealbumin concentration was 10.2 g/dL (normal range 12–40 g/dL).

ABBREVIATIONS: AAA, aromatic amino acids; BCAA, branched-chain amino acids; BiPAP, Bi-level positive airway pressure; BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; FEV_1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; GST, Glutathione S-Transferase; IPPV, intermittent positive pressure ventilation; MCT, medium-chain triglycerides; RDA, Recommended Dietary Allowance; TPN, total parenteral nutrition

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Although the patient was an adolescent, a pediatric amino acid product containing greater branched chain and essential amino acids and less phenylalanine and methionine (TrophAmine, B Braun Medical Inc., Bethlehem, PA) was initiated due to its theoretical protective benefit in patients with end stage liver disease. The solution also contained L-cysteine HCl at a dose of 40 mg/g of amino acid product. Trace element dosing was individualized with chromium (5 mcg/day), selenium (40 mcg/day), zinc (4 mg/day) and no manganese or copper (secondary to biliary cirrhosis). The patient received TPN for 12 days in the hospital followed by 10 days at home, and then another 17 days on a second admission before being transferred (still on TPN) to a liver transplant center. Intake via TPN, reported as mean ± SD (range), on the initial hospitalization provided 1210 ± 204 non-protein calories (884 – 1457), 1410 ± 222 total calories (1072–1683), 1.1 ± 0.1 g/kg/day protein (1–1.2) and 1.2 ± 0.3 g/kg/day lipids (1–1.5).

Hyperglycemia became an issue on day 4 of TPN and was managed by adding regular human insulin to the TPN solution**.** Hyperglycemia remained a problem until insulin was titrated up to 1 unit per 4.7 g of dextrose. At that time, the patient was discharged home on nocturnal TPN infused over 12 hours per day. The patient weighed 50 kg at discharge.

While at home, the patient experienced frequent trips to the bathroom overnight which led to sleep deprivation; therefore, TPN administration was changed to daytime delivery. This change decreased appetite and oral intake, and the patient experienced essentially no weight gain while she was on home TPN. Her mother reported no glucose in the urine when randomly assessed, and blood glucose concentrations (measured by a home glucose monitor) fell between 130 and 140 mg/dL. Other changes made to the home TPN regimen included a slight decrease in protein and lipid provision (1 compared to 1.2 g/kg/day protein and 1.2 compared to 1.5 g/kg/day lipid) and a change in the protein source to an adult amino acid product (Travasol, Baxter Healthcare, Deerfield, IL). The home infusion company made all adjustments to the TPN once the patient was discharged from the hospital. Since the inpatient Parenteral Nutrition Service does not manage home TPN patients, it is unclear why the protein and lipid doses were decreased. The adult amino acid product was likely started in place of the pediatric product due to a failure to communicate the rationale for the pediatric product in this patient and also based on the patient's age and the increased cost of the pediatric product.

Ten days after home discharge, the patient presented to the pulmonology clinic and was noted to have an oxygen saturation of 74% and FEV_1 of 17%. The patient reported increasing her oxygen to 2 liters per day prior to the clinic appointment. The patient was referred to the emergency department and then transferred to the intensive care unit (on 60% oxygen by facemask) with a diagnosis of hypoxemia, respiratory distress and CF exacerbation. Admission weight was 50.1 kg.

Empiric antibiotic therapy was initiated with ceftazidime 2 g IV q8h and tobramycin 160 mg IV q8h. The following day her oxygen requirement decreased to 45%, and she was transferred to the respiratory floor of the hospital. Bi-level positive airway pressure (BiPAP) and nasal intermittent positive pressure ventilation (IPPV) were initiated on the respiratory floor. In addition, ciprofloxacin 400 mg IV q12h was added to the empiric antibiotic regimen. Once final culture and sensitivity results on sputum cultures returned (rare *Pseudomonas aeruginosa* sensitive to ciprofloxacin, tobramycin, and imipenem; intermediate resistance to ceftazidime), ceftazidime therapy was discontinued. Home medications were unchanged.

With respect to her nutritional status during this second hospital admission, the patient resumed nocturnal TPN administration with free water removed in an effort to reduce nighttime urination. The protein source was changed back to TrophAmine with supplemental L-cysteine HCl due to marginal liver function and in order to increase calcium and phosphorous solubility in the now concentrated formulation. Nocturnal TPN was given for the first 4 days of admission; however, due to continued decrease in appetite and oral intake, continuous TPN was given for 2 days while parenteral calories were increased and insulin dose adjusted. The TPN was then gradually weaned back over the next week to a 12-hour nocturnal infusion. Intake via TPN, reported as mean ± SD (range), during this hospital admission was 1580 ± 156 non-protein calories (1334–1780), 1823 ± 179 total calories (1534–2040), 1.2 ± 0.1 g/kg/day protein (1–1.3) and 1.5 ± 0.2 g/kg/day lipids (1.2–1.7). Insulin provision ranged from 1 unit per 4.7 g to 1 unit per 5.4 g of dex-

Table 1. Liver Function Tests Before and During TPN

Parameter, units, reference range	AST, Units/L (15–30)	ALT, Units/L (0–45)	Alkaline Phosphatase Units/L(35–117)	Total bilirubin mg/dL (0.2–1.0)	Albumin g/dL (4.0–6.0)	PT sec (9.7–12.3)	Platelets $1 \times 10^3/\mu L$ (140–450)
Before TPN	35 ± 7.1	12.7 ± 2.3*	154 ± 7.1	0.4 ± 0.1	2.5 ± 0.3	13.4	61 ± 17
During TPN	51.8 ± 13.5	30 ± 9.6*	216.7 ± 71.3	0.7 ± 0.2	2.5 ± 0.2	14.1 ± 1.0	47.5 ± 6.6

Data are mean ± SD.
**P < 0.05.*
AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; TPN, total parenteral nutrition.

trose (1 unit per 4.8 g of dextrose at discharge). Upon discharge to the liver transplant center, the patient weighed 52.8 kg.

During TPN administration, albumin ranged from 2.3 to 2.7 g/dL and BUN from 6 to 17 mg/dL. Blood ammonia, measured on TPN day 28, was 25 mmol/L (normal < 35 mmol/L). Liver function tests before and during administration of TPN are presented in Table 1. Sodium values were in the normal range with no signs of ascites or edema. The patient gained 5.8 kg with 39 days of supplemental TPN and conservative doses of a pediatric amino acid product without further compromise of respiratory or hepatic function.

RESPONSE

Cystic fibrosis (CF) is a common and potentially lethal genetic disease. Its incidence is higher in Caucasians, occurring in about 1:2000 live births.[1,2] The disease results from mutations in the gene for the CF transmembrane conductance regulator (CFTR), a cAMP-activated Cl^- channel in the secretory epithelia.[1] Pulmonary disease is usually the main cause of morbidity and mortality in CF patients. In the liver, CFTR is located in the cholangiocytes and gallbladder epithelia, where it appears to play a role in bile formation. However, how a defective CFTR protein leads to liver disease in a subset of CF patients is unknown.[1] Whereas the biliary tract disease is usually clinically evident, the liver involvement may progress silently, only manifesting as end-stage liver disease and portal hypertension.[3] Unlike the pancreatic involvement in CF, a genotype-phenotype correlation is not obvious in the expression of liver disease,[1] yet Glutathione S-Transferase (GST) P1-Ile encoding allele predisposes patients with CF to liver disease.[4]

Improvements in survival have led to an increasing recognition of CF-related liver disease.[3] The prevalence of CF-related liver disease could be as high as 41% by 12 years of life,[5] and cirrhosis could be present in around 5% of these patients.[6] All patients with CF should be screened for possible hepatobiliary disease by assessing liver enzymes, particularly if there is a history of neonatal meconium ileus.[5,6] Preventive therapy with ursodeoxycholic acid should be considered in these patients because of the potential benefits.[7]

The nutritional management of cystic fibrosis patients represents a great challenge. Unfortunately, the nutritional management is not as simple as placing patients on pancreatic enzyme supplementation and exceeding the recommended dietary allowance (RDA) for calories. Keeping up with malabsorption (because of pancreatic insufficiency and hepatobiliary disease) and increased metabolic rate (due to increased respiration and recurrent infection with or without febrile episodes) is the most difficult goal to accomplish in patients with CF. Nutritional deficiencies may occur at any time depending upon the severity of the disease and the organs affected. The emphasis of any nutritional therapy in children with CF should be "preserving normal nutritional status" rather than "achieving catch-up growth."

There is a clear association between malnutrition and deteriorating lung function. There is also an association between overall mortality and the inability to fulfill the nutritional requirement in these children with increased pulmonary complications such as susceptibility to infections.[2] Therefore, the quality of nutritional management will have a major impact on outcome. In addition to an increased caloric requirement due to compromised lung function, chronic lung infections are associated with anorexia and increased metabolic rate resulting in a further increase in caloric needs.[2] Nutritional deficiencies usually follow periods of rapid growth and pulmonary exacerbations. The main goal in the nutritional management of these children is to encourage caloric intake with adequate amounts of protein and fat, supplementing vitamins (especially fat-soluble) and minerals in adequate amounts to achieve a consistent growth pattern.

The degree of pancreatic insufficiency, chronic lung disease and liver disease in CF patients often will require additional nutrition management, along with the usual considerations of growth rate and quality and quantity of food intake. It is not uncommon for children with CF to require enteral tube feedings or parenteral nutrition to accomplish adequate nutrition and prevent further growth retardation. A potential challenge for children on continuous tube feedings is how to accomplish adequate pancreatic enzyme replacement therapy while receiving the continuous enteral infusion.

Usually the caloric intake has to exceed 110% of the RDA,[8] however, it is not unusual to see requirements in CF patients as high as 150% of the RDA. Since patients with cholestasis and cirrhosis have increased oxygen consumption,[9] patients with CF-related liver disease will require more calories. Additionally, because of their cholestasis, enteral formulas or supplements containing high medium-chain triglyceride (MCT) content should be considered to promote better intestinal absorption of dietary lipids (fat malabsorption occurs due to diminished bile in the intestinal lumen; however, bile is not required for MCT absorption).

There have been attempts to objectively estimate the energy requirements for patients with CF, such as the following formula[2]:

Energy needed = [BMR × (Activity level + Disease Coefficient)] × Fat absorption
BMR = Basal metabolic rate obtained through indirect calorimetry or equations from body weight (kg)
Activity level: confined to bed (1.3), sedentary (1.5) or active (1.7)
Disease coefficient based on predicted FEV_1: = 80% (0), 40-79% (0.2) or < 40% (0.3-0.5)
Fat absorption: (0.93)/(% of fat absorbed)
% of fat absorbed = 100 – stool fat (g)/24 hours (while on a 100 g fat test diet)

However, in clinical practice, it is important and more practical to follow linear growth and establish the presence and/or degree of steatorrhea to adjust the caloric intake and pancreatic enzyme supplementation.

Even though the patient presented in the case had severe lung and liver disease, she portrayed some of the usual nutritional dilemmas in patients with CF-related liver disease. In this patient, the rapidly deteriorating lung and liver disease caused high caloric needs. In addition, children with CF-related liver disease have more significant failure to thrive, altered body composition and diminished FEV_1 when compared to CF children without liver disease.[10] Moreover, her severe liver disease further deteriorated her pulmonary function due to intrapulmonary shunting, portopulmonary hypertension and diaphragmatic splinting, thereby increasing her basal metabolic rate.

The decision to begin TPN was based upon her critical clinical condition. She was not only failing to thrive but also losing weight despite advanced enteral nutrition supplementation, which was impacting her overall clinical condition. Since a gastrostomy tube for enteral feeding was contraindicated because of the evidence of significant portal hypertension, a nasogastric tube may have been the only option to aggressively enterally feed this patient, and her intestinal absorptive capacity would likely have been affected by severe cholestasis, portal hypertension and cirrhosis in addition to her pancreatic insufficiency and severe lung disease. All of these factors decreased the likelihood of successful continuous enteral feeding to improve her nutritional status.

In the case presented, looking after not only the quantity but also the quality of the amino acid provided was appropriate. There are more potential benefits than risks by using a preparation, like TrophAmine, that contains higher branched-chain amino acids (BCAA) and lower aromatic amino acids (AAA). Generally speaking, it is not recommended to restrict the protein intake in patients with CF unless there is evidence of decompensated cirrhosis or acute liver failure. In those cases, impaired hepatic metabolism and portal-systemic shunting allows increased passage of AAA and biogenic amines to the brain.[11,12] In addition, there is an increased removal of BCAA by muscle resulting in a high AAA:BCAA ratio. During liver failure there is decreased competition by BCAA with AAA, specifically tryptophan and phenylalanine, for transport across the blood-brain barrier with a subsequent increase in the passage of neutral amino acids into the central nervous system. These neutral amino acids are precursors of inhibitory and false neurotransmitters responsible for chronic or acute encephalopathy.[11] For this reason, amino acid preparations with less AAA and greater BCAA are recom-

mended along with limited protein intake (1–1.5 g/kg/day) during chronic-decompensated or acute liver failure.

Hyperglycemia in a patient on TPN is a common problem.[13] Moreover, the patient in this case had a higher risk for diabetes mellitus or impaired glucose tolerance. CF patients with impaired glucose tolerance exhibit diminished insulin secretion and increased peripheral insulin resistance.[14] In TPN-related hyperglycemia, other clinical conditions should be considered when hyperglycemia develops, including recent changes in TPN infusion rates, infusing TPN over shorter periods of the day (cycling), drug-induced hyperglycemia, or sepsis (infections may impair insulin-dependent hepatic glucose uptake during TPN).[15] Increased urinary frequency or polyuria in a patient on TPN is commonly associated with hyperglycemia and/or cyclic TPN as this involves 24-hour maintenance fluid volume that is infused over 8–14 hours/day. Polyuria usually resolves by controlling hyperglycemia and concentrating TPN (i.e., reducing free water). Using a sliding scale dosing regimen for subcutaneous regular insulin administration in TPN-induced hyperglycemia is recommended since the units of insulin required may vary greatly from patient to patient and with the amount of carbohydrate provided in the TPN regimen. Once hyperglycemia is controlled, the required insulin dosage can be calculated based upon daily needs and then may be added to the TPN. Another method of insulin dose calculation is to provide units of regular insulin per gram of dextrose, beginning with 1 unit of insulin per approximately 16 grams of dextrose and titrating insulin provision based on fingerstick blood glucose measurements.

Outside of neonatal and infant TPN, the administration of L-cysteine HCl is used to enhance calcium and phosphate solubility by lowering the pH of the solution. While not widely accepted, some advocate its addition to the TPN solution as a potential hepato-protector due to its antioxidant effects through a significant induction of glutathione synthesis.[16,17]

Although weight gain is usually a good sign of accomplished nutritional goals, this patient had potential for third-spacing fluid (development or worsening of ascites) which could have accounted for some of that weight gain (hyperaldosteronism mainly driven by hypoalbuminemia in end-stage liver disease). The degree of hypoalbuminemia, ascites and edema must be considered when assessing weight gain in these patients. Therefore, other anthropometric parameters have been used for assessment. Other issues include the potential need for fluid and sodium restriction. Daily fluid requirements may need to be decreased to 3/4 maintenance volume and daily sodium intake limited to 1–2 mEq/kg/day in patients with end-stage liver disease and ascites.

The patient in the case was awaiting liver or possibly combined liver/lung transplantation. Liver transplantation is becoming a reasonable approach to children with severe CF. In a cohort of 24 patients with CF and cirrhosis who were evaluated for liver or heart-lung-liver transplantation, the indications for isolated liver transplantation (n = 12) were portal hypertension, hepatic dysfunction, deterioration in nutritional status and increased frequency and severity of pulmonary infections.[18] The main indication for triple graft transplantation was advanced pulmonary failure in addition to liver disease. All 12 patients with isolated liver transplantation did well and their mean FVC increased from 61% to 82% six to nine months post-transplantation.[18] Liver transplantation in CF should be considered promptly after the diagnosis of end-stage liver disease has been made, primarily due to the potential for better outcome since growth failure and poor nutritional status are associated with high mortality.[18,19] This fact further supports the need for optimal nutritional management in this specific case.

Before transferring to the liver center, the patient became more clinically stable with steady weight gain. Complications associated with TPN, such as the development of cholestatic disease, impact morbidity and mortality particularly in patients receiving long-term TPN.[20] Liver disease, however, should not be considered a contraindication for TPN. While it is understandable to be concerned about TPN-related liver disease, the benefit of accomplishing adequate nutritional support in this patient whose clinical and nutritional states were rapidly deteriorating outweighed the risk of TPN-associated complications. Additionally, a deteriorated nutritional status would decrease the likelihood that she would be an acceptable candidate for liver or combined liver/lung transplantation. The presented case documents the successful provision of TPN with resultant positive nutritional outcomes in an adolescent with CF and end-stage liver disease.

REFERENCES

1. Feranchak AP. Hepatobiliary Complications of Cystic Fibrosis. Curr Gastroenterol Rep 2004;6:231-9.
2. Ramsey BS, Farrell PM, Pincharz P. Nutritional assessment and management in cystic fibrosis: A consensus report. Am J Clin Nutr 1992;55:108-16.
3. Sokol RJ, Durie PR. Recommendations for Management of Liver and Biliary Tract Disease in Cystic Fibrosis. J Pediatr Gastroenterol Nutr 1999;28 Suppl 1:S1-13.
4. Henrion-Caude A, Flamant C, Roussey M, Housset C, Flahault A, Fryer AA, Chadelat K, Strange RC, Clement A. Liver Disease in Pediatric Patients with Cystic Fibrosis is associated with Glutathione S-Transferase P1 Polymorphism. Hepatology 2002;36:913-7.
5. Lamireau T, Monnereau S, Martin S, Marcotte JE, Winnock M, Alvarez F. Epidemiology of Liver Disease in Cystic Fibrosis: A longitudinal study. J Hepatol 2004;41:920-5.
6. Colombo C, Battezzati PM, Crosignani A, Morabito A, Costantini D, Padoan R, Giunta A. Liver Disease in Cystic Fibrosis: A Prospective Study on Incidence, Risk Factors and Outcome. Hepatology 2002;36:1374-82.
7. Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. Hepatology 2002;36:525-31.
8. George DE, Mangos JA. Nutritional Management and Pancreatic Enzyme Therapy in Cystic Fibrosis Patients: State of the Art in 1987 and Projections into the Future. J Pediatr Gastroenterol Nutr 1988;7 Suppl 1:S549-57.
9. Pierro A, Koletzko B, Carnielli V, Superina RA, Roberts EA, Filler RM, Smith J, Heim T. Resting Energy Expenditure is Increased in Infants and Children with Extrahepatic Biliary Atresia. J Pediatr Surg 1989;24:534-8.
10. Corbett K, Kelleher S, Rowland M, Daly L, Drumm B, Canny G, Greally P, Hayes R, Bourke B. Cystic Fibrosis-associated liver disease: A population-based study. J Pediatr 2004;145:327-32.
11. Munro HN. Metabolic integration of organs in health and disease. JPEN J Parenter Enteral Nutr 1982;6:271-9.
12. Schafer DF, Pappas SC, Brody LE, Jacobs R, Jones EA. Visual evoked potentials in a rabbit model of hepatic encephalopathy: I. Sequential changes and comparisons with drug-induced comas. Gastroenterology 1984;86:540-5.
13. Lienhardt A, Rakotoambinina B, Colomb V, Souissi S, Sadoun E, Goulet O, Robert JJ, Ricour C. Insulin secretion and sensitivity in children on cyclic total parenteral nutrition. JPEN J Parenter Enteral Nutr 1998;22:382-6.
14. Tofe S, Moreno JC, Maiz L, Alonso M, Escobar H, Barrio R. Insulin-secretion abnormalities and clinical deterioration related to impaired glucose tolerance in cystic fibrosis. Eur J Endocrinol 2005;152:241-7.
15. Donmoyer CM, Chen SS, Lacy DB, Pearson DA, Poole A, Zhang Y, McGuinness OP. Infection impairs insulin-dependent hepatic glucose uptake during total parenteral nutrition. Am J Physiol Endocrinol Metab 2003;284:E574-82.
16. Pollack PF, Rivera A Jr, Rassin DK, Nishioka K. Cysteine supplementation increases glutathione, but not polyamine, concentrations of the small intestine and colon of parenterally fed newborn rabbits. J Pediatr Gastroenterol Nutr 1996;22:364-72.
17. Malloy MH, Rassin DK. Cysteine supplementation of total parenteral nutrition: the effect in beagle pups. Pediatr Res 1984;18:747-51.
18. Milkiewicz P, Skiba G, Kelly D, Weller P, Bonser R, Gur U, Mirza D, Buckels J, Stableforth D, Elias E. Transplantation for Cystic Fibrosis: Outcome Following Early Liver Transplantation. J Gastroenterol Hepatol 2002;17:208-13.
19. Molmenti E, Nagata D, Roden J, Squires R, Molmenti H, Casey D, Prestidge C, McPhail W, Sanchez E, Goldstein R, Levy M, Fasola C, Andrews W, D'Amico L, Benser M, Emert L, Andersen J, Klintmalm G. Pediatric Liver Transplantation for Cystic Fibrosis. Transplant Proc 2001;33:1738.
20. Quiros-Tejeira RE, Ament ME, Reyen L, Herzog F, Merjanian M, Olivares-Serrano N, Vargas JH. Long-term parenteral nutritional support and intestinal adaptation in children with short bowel syndrome: a 25-year experience. J Pediatr 2004;145:157-63.