Post-Operative Nutritional Management of The Pediatric Liver Transplant Recipient

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Universitat Autònoma de Barcelona

2023

ACKNOWLEDGEMENTS

To my doctoral thesis supervisor, Professor Carlos Gonzalo Rodrigo de Liria, who has guided me along the way by contributing his valuable criteria and knowledge, for his advice and for his critical review of the work.

To Dr. Yaron Avitzur for his valued mentorship throughout all the stages of this work. I am grateful for the incredible training opportunities that he has provided me at The Hospital for Sick Children, Division of Pediatric Gastroenterology, Hepatology and Nutrition, and Transplant Regenerative Medicine Centre.

To all members of the "Chylous Ascites" research group without whom I would not have been able to complete this research: Dr. Eberhard Lurz, Aviva Levman Dr. Vicky Ng, Dr. David Grant, Dr. Anand Ghanekar and Dr. Mark Cattral.

To all the multi-disciplinary members of the "Standardized Feeding Protocol" quality improvement initiative for their enthusiasm and their contributions to the development, implementation, and success of this initiative: Penni Kean, Lori Tuira, Dr. Yasser Al Nasser, Maria De Angelis, Krista Van Roestel, Dr. Haifa Mtaweh, Dr. Anand Ghanekar, Dr. Mark Cattral and Dr. Vicky Ng. A special thanks to Dr. Marialena Mouzaki for her encouragement and supervision for this work.

A Gonzalo, mi mejor compañero de aventuras y a nuestros hijos Lucas y Olivia, gracias por vuestro amor y paciencia.

A tots els meus, gràcies pel vostre amor i suport incondicionals durant aquest treball de tesi.

Last but not least, my deepest gratitude goes to the children and their families who have enriched my days by courageously allowing me to participate in their liver transplantation journey.

CONTENTS

1 ABBREVIATIONS

AASLD, American Association for the Study of Liver Diseases

ACR, Acute cellular rejection

AST, American Society of Transplantation

BMI, Body mass index

CA, Chylous Ascites

CLABSI, Central line-associated bloodstream infection

EFA, Essential fatty acid

EN, Enteral nutrition

ESLD, End-stage liver disease

ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition

FEN, Full enteral nutrition

IQR, Interquartile range

LOS, Length of stay

LT, Liver Transplantation

MCT, Medium-chain triglyceride

NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

NG, Nasogastric

NJ, Nasojejunal

NPO, *Nil per os*

OR, odds ratio

PICU, Pediatric Intensive Care Unit

QI, Quality Improvement

PN, Parenteral nutrition

REE, Resting energy expenditure

SPC, Statistical process control

WHO, World Health Organization

2 THESIS SUMMARY

Background: End-stage liver disease (ESLD) represents the most common indication for liver transplantation (LT) in children and is commonly associated with malnutrition. In children with ESLD requiring LT, malnutrition has been associated with increased pre- and post-LT morbidity and mortality (1-10). Existing guidelines recommend and emphasize the need for aggressive nutrition support in children awaiting LT (6, 11). However, despite the undeniable importance of adequate post-operative nutritional support in children after LT, data on nutritional interventions immediately after LT remain scarce. In addition, there is limited data regarding the management of post-operative complications such as chylous ascites (CA) that may exacerbate pre-existing malnutrition or increase the post-operative risk of malnutrition.

Aims: The first study assesses the impact of a quality improvement (QI) project aimed at decreasing the time to initiate enteral nutrition (EN) and time to achieve full EN (FEN) in children after LT surgery by implementing a standardized post-operative feeding protocol. The aim of the second study is to determine the incidence, risk factors, treatment, and outcome of post-operative CA in a large cohort of children after LT.

Methods: In the first study, a QI project using the model for improvement framework was undertaken to design and implement a feeding protocol for children under the age of 18 years undergoing isolated LT surgery at the Hospital for Sick Children, Toronto, Canada. To assess the impact of this QI process, data was retrospectively collected for subjects in the pre-intervention group (January 2015 to December 2016) and prospectively collected for subjects in the intervention group (March 2017 to September 2018).

In the second study, a case-control observational method was used. All children under the age of 18 years old who underwent isolated LT surgery at the Hospital for Sick Children, Toronto, Canada, between January 2000 and December 2016 were included. Post-operative CA was defined as the presence of chylomicrons or a triglyceride value ≥187 mg/dL in the peritoneal fluid within 60 days from LT (12).

Results: Data from 49 children who received a LT prior to feeding protocol implementation were compared with data for 32 children undergoing LT after protocol implementation. The 2 groups did not differ with respect to baseline demographic data. After protocol implementation, EN was started earlier (2 versus 3 days after transplant; P = 0.005) and advanced faster when a feeding tube was used (4 versus 8 days; P = 0.03). Protocol

implementation was also associated with reduced parenteral nutrition (PN) use rates (47% versus 75%; P = 0.01). No adverse events occurred after protocol implementation.

In the second study, the cohort included 317 LTs (153 living donors and 164 deceased donors) in 310 recipients with a median age of 2.7 years. The incidence of CA was 5.4%, diagnosed after a median time of 10 days after LT. Compared with chylomicron detection in peritoneal fluid (gold standard), a triglyceride cut-off value of 187 mg/dL in peritoneal fluid showed insufficient sensitivity (31%) for CA diagnosis. In univariate logistic regression analyses, ascites before LT, younger age, and lower weight, height, and height-for-age z score at LT were associated with CA. Symptomatic management of CA included peritoneal drain (100%) and diuretics (76%). Therapeutic interventions included very low-fat or medium-chain triglyceride–rich diets (94%) and intravenous octreotide (6%), leading to CA resolution in all patients. CA was associated with prolonged hospital length of stay (LOS) but not with reduced patient or graft survival rates after a median follow-up time of 14 years.

Conclusions: Implementation of a post-operative feeding protocol for children undergoing LT surgery was associated with an earlier start of EN and faster advancement of EN. Protocol implementation was also associated with reductions in PN use without occurrence of adverse events associated with early EN delivery.

In the pediatric LT recipient, post-operative CA is a relatively uncommon complication associated with increased hospital LOS and morbidity. Measurement of chylomicrons is recommended in patients with ascites that is more severe or persistent than expected. Dietary interventions are effective in most patients.

3 INTRODUCTION

3.1 End-stage liver disease in children

ESLD in children is a life-threatening clinical syndrome, resulting of many chronic liver diseases leading to irreversible impairment of liver function, architecture (cirrhosis) and blood supply (portal hypertension). The etiology of ESLD in children varies with age of presentation. In infants, ESLD is most often caused by biliary atresia and genetic cholestatic disorders such as Alagille syndrome and progressive familial intrahepatic cholestasis, while in older children, ESLD is often the result of immune-mediated liver diseases such as autoimmune hepatitis and primary sclerosing cholangitis, Wilson disease, alpha-1-antirrypsin deficiency and cryptogenic cirrhosis (13).

Complications associated with ESLD include ascites, hepatic encephalopathy, hepatopulmonary syndrome, variceal hemorrhage, coagulopathy, cholestasis, pruritus, delayed growth and development, and malnutrition (11, 14). When complications of ESLD develop, LT should be considered, with the goal of extending life expectancy beyond what the natural history of underlying liver disease would predict or the improving quality of life.

ESLD represents the most common indication for LT in children, with biliary atresia representing the most common primary diagnoses leading to LT, followed by metabolic disease, tumors, paediatric acute liver failure, and re-transplantation.

3.2 Malnutrition in children with end-stage liver disease

The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) defines malnutrition as “an imbalance between nutrient requirement and intake, resulting in cumulative deficits of energy, protein or micronutrients that may negatively affect growth, development and other relevant outcomes” (15). By this definition, malnutrition in children with ESLD leads to adverse physical effects, which may manifest phenotypically as frailty (impaired muscle contractile function) and sarcopenia (loss of skeletal muscle mass)(16, 17).

The true impact and prevalence of malnutrition (undernutrition) in children with ESLD have historically been under-recognized due to a lack of consensus on definitions, heterogeneous nutritional screening practices, and variable accessibility to multidisciplinary nutrition support teams. Studies of children with cholestatic liver disease have reported a malnutrition prevalence of 39-64% (1, 2), with a higher prevalence of malnutrition of 50-76% among children with ESLD awaiting LT (3-5).

In the child with advanced liver disease, malnutrition results from complex interactions between inadequate oral intake, maldigestion/malabsorption and altered nutrient metabolism including increased energy requirements. Contributing factors to inadequate oral intake in children with chronic liver disease include anorexia, dysgeusia secondary to nutritional deficiencies (e.g., zinc or magnesium), decreased stomach volume and discomfort from organomegaly, and ascites that result in early satiety, nausea, and vomiting (18, 19). Inadequate oral intake is compounded by impaired digestion and absorption of nutrients, especially dietary fat and fat-soluble vitamins, due to decreased bile flow and altered bile salt pools, abnormal enterohepatic recirculation, pancreatic insufficiency, portal hypertension-related enteropathy with vascular congestion and mucosal inflammation, and increased losses (e.g., diarrhea). In children with chronic liver disease, altered nutrient metabolism also plays a role in malnutrition due to the effects of chronic catabolic illness, increased resting energy expenditure (REE), reduced hepatic glycogen stores and impaired gluconeogenesis, alteration in protein synthesis, insulin resistance and abnormal growth hormone signalling (19-21). Other factors may aggravate malnutrition in children with liver disease, such as the use of unpalatable nutrition products (e.g., hydrolyzed, or medium chain triglycerides-rich formulas) and diets (e.g., sodium-restricted diets for the management of ascites); iatrogenic dietary interventions such as avoidance of protein sources for those at risk for hepatic encephalopathy; interruptions to enteral feeding for conducting diagnostic procedures; and adverse effects of medications (e.g., lactulose for the management of hepatic encephalopathy causing diarrhea).

3.3 The impact of malnutrition on clinical outcomes before and after liver transplantation

Malnutrition in the pediatric LT candidate is associated with an increase in pre- and post-transplant morbidity and mortality (6-10). In a large multi-center cohort study of children with chronic liver disease awaiting LT, growth failure, defined as height or weight <2 standard deviations, was found to be an important factor associated with death or admission to the intensive care unit while on the waitlist list for LT. The results of this study allowed for the formulation of the pediatric end-stage liver disease score to assess the risk of poor outcomes in patients awaiting LT (5). In a cohort study of 755 children with biliary atresia, growth failure was also identified as an independent risk factor for pre- and post-transplant mortality and liver graft failure (7). Another study of 413 pediatric living donor LT recipients found that those with severe malnutrition (40%), defined as height or weight <2 standard deviations, had

worse patient and graft survival after LT (9). Pre-transplant growth retardation has also been associated with longer LOS and increased hospitalization costs (8, 10, 22, 23).

3.4 Nutrition assessment and support in the pediatric liver transplant candidate

It is now well established that optimized pre-transplant nutrition may hasten post-transplant recovery and improve survival and neurodevelopmental outcomes while simultaneously decreasing complications (6, 24). Therefore, the American Association for the Study of Liver Diseases (AASLD), the American Society of Transplantation (AST) and the North American and European Societies for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN and ESPGHAN) recommend a detailed assessment of the nutritional assessment in children with ESLD, and recommend an aggressive management of the nutritional issues that often arise in this population (11, 19).

Published recommendations suggest implementing a proactive, staged nutritional approach for children with ESLD, which is particularly important for those requiring LT. Recommended initial measures include increased feeding frequency, increased calorie density of foods consumed and use of modular nutritional supplements that should be used as needed. When oral intake becomes insufficient to meet caloric needs, initiation of nasogastric (NG) or nasojejunal (NJ) tube feeding should be considered, to complement oral feeds or provide the main source of nutrition. When EN -oral, gastric and jejunal- is either not tolerated or sufficient to achieve growth targets, PN is recommended, particularly in those requiring LT (19, 20).

3.5 Nutrition support in the pediatric liver transplant recipient

Despite the undeniable importance of adequate post-operative nutritional support in children after LT, there are few data on nutritional interventions immediately after LT in children. The traditional peri-operative care model in children undergoing LT surgery involves prolonged pre-operative fasting followed by delayed initiation or slow advancement of EN, with or without the concomitant use of PN. Such practices, paired with the catabolic response to surgical stress and loss of body protein, frequent interruptions to enteral feeding, and post-operative complications such as sepsis or CA, often pose barriers to the delivery of sufficient EN immediately after LT (25-27).

Post-operative CA occurs in about 6.3% to 24% of pediatric patients following LT and is associated with increased morbidity and mortality (28-31). Chyle is composed of predominantly fat, protein, lymphocytes, and electrolytes. The clinical consequences of

continued chylous drainage include electrolyte disturbances, risk of infection, and nutrient losses, all which can either exacerbate pre-existing malnutrition or add to the post-operative risk for malnutrition (28, 29). In the management of CA, the overarching nutritional goals are to decrease chylous drainage, maintain adequate volume and electrolyte status, and prevent further malnutrition. Age-specific recommendations regarding the management of post-operative CA in the pediatric LT recipient are lacking.

4 STUDY RATIONALE AND HYPOTHESES

4.1 Implementation of a standardized feeding protocol in children immediately after liver transplantation

Study rationale

Delivery of adequate nutrition immediately after LT surgery is an important goal of post-operative care. In 2017, evidence-informed expert guidelines were published providing recommendations for the provision of nutrition therapy in critically ill children, including those with a surgical diagnosis (32). In this population, EN is preferred over PN due to its benefits for gastrointestinal mucosal integrity and motility, lower complication rates and lower cost (32, 33). Additionally, early EN initiation (within 24–48 hours of admission) has been associated with lower mortality in critically ill children admitted to pediatric intensive care units (PICU) and with lower sepsis rates and hospital LOS in adult LT recipients (34-36). What remains unknown is the impact of early EN after LT surgery in pediatric LT recipients.

A limited number of controlled trials of adult LT recipients showed that enteral feeding can be safely introduced early in the post-operative period, suggesting the feasibility of introducing early EN post-LT (37, 38). Additional studies further described improved post-operative outcomes of adult LT recipients receiving early EN immediately after LT (34, 35, 39). In one study of 346 adult-to-adult living donor LT, early EN within 48 hours of LT was associated with significantly reduced risk of developing bacterial sepsis after LT (35). Others also reported lower rates of bacterial infection and reduced hospital LOS among LT recipients receiving early EN via jejunostomy within 12 hours after LT when compared to those receiving PN after LT (34). For the adult LT recipient, existing guidelines recommend early initiation of oral intake and/or EN within 12-24 hours after LT (40). However, no specific recommendations have been published on how best to initiate and advance EN in children immediately after LT.

Implementation of stepwise EN advancement algorithms in various surgical and critically ill pediatric populations has been associated with decreased time to initiation of EN and faster EN advancement (32, 41, 42). We hypothesized that pediatric LT recipients, considered both surgical and critically ill patients requiring PICU admission post-operatively, are likely to benefit from the implementation of a standardized nutrition protocol. A multidisciplinary QI team including pediatric hepatologists, surgeons, pediatric intensive care specialists, clinical dietitians and nurses at the Hospital for Sick Children in Toronto, Canada developed and implemented a standardized post-operative feeding protocol for children after LT. The aim of this QI initiative

was to shorten the time to initiation of EN and time to achieve FEN in children immediately after LT surgery.

Hypothesis

We hypothesized that in children immediately after LT, implementation of a post-operative feeding protocol will shorten the time to initiation of EN and time to achieve FEN.

4.2 Nutritional management of post-operative chylous ascites in children after liver transplantation

Study rationale

Strategies for optimizing nutritional support in the LT recipient include the prevention, prompt identification and early-directed management of post-operative complications that can negatively impact the nutritional status of the pediatric LT recipient, such as post-operative CA (28, 29).

The diagnosis of post-operative CA in the pediatric LT recipient can be challenging. First, its clinical presentation may mimic other post-transplant complications, such as hepatic arterial and portal venous abnormalities, hepatic venous outflow obstruction, small-for-size syndrome, and abdominal infection (31, 43). Second, diagnostic criteria for CA are not well established. Detection of chylomicrons by lipoprotein electrophoresis in peritoneal fluid is considered the gold standard diagnostic test (44). When not available, a triglyceride cut-off of 110 mg/dL (1.25 mmol/L) in peritoneal fluid was recommended in the pediatric LT literature (30). The latter recommendations were not supported by high-quality evidence, and it is recognized that triglyceride quantification in peritoneal fluid may not be a reliable diagnostic criterion for CA in fasting patients, particularly in the post-operative state (45). Recently, these gaps in the literature were addressed, and it is now accepted that a triglyceride cut-off value of 187 mg/dL (2.13 mmol/L) establishes the diagnosis of CA (12).

The optimal management of post-operative CA in children immediately after LT remains a controversial territory due to limited data regarding its incidence, the lack of well-established diagnostic criteria, and equivocal evidence regarding best treatment strategies, which range from nutritional interventions to pharmacologic therapy and surgical procedures (30, 46-48). We therefore aimed to determine the incidence, risk factors, treatment, and outcomes of post-operative CA in a large pediatric LT cohort.

Hypotheses

We hypothesized that CA is a rare complication in children immediately after LT surgery, and that for its diagnosis, the newly established triglyceride cut-off value of 187mg/dL (2.13 mmol/L) in peritoneal fluid will be inferior to chylomicron detection.

We also hypothesized that a large proportion of children with post-operative CA can be managed effectively with symptomatic management and nutritional interventions.

5 OBJECTIVES

5.1 Implementation of a standardized feeding protocol in children immediately after liver transplantation

- To assess for differences in time to initiation of EN in children immediately after LT before and after the implementation of a post-operative feeding protocol.

- To assess for differences in time to achieve FEN in children immediately after LT before and after the implementation of a post-operative feeding protocol.

5.2 Nutritional management of post-operative chylous ascites in children after liver transplantation

- To determine the incidence and risk factors of post-operative CA in a large pediatric LT cohort using detection of chylomicrons in peritoneal fluid.

- To compare a newly established triglyceride cut-off value of 187 mg/dL (2.13 mmol/L) in peritoneal fluid as a diagnostic tool for post-operative CA in pediatric LT recipients against chylomicron detection (gold standard).

- To describe the treatment and outcomes of post-operative CA in a large pediatric LT cohort.

6 METHODS

6.1 Implementation of a standardized feeding protocol in children immediately after liver transplantation

A QI project using the model for improvement framework was undertaken to design and implement a feeding protocol for children under the age of 18 years undergoing isolated LT surgery at the Hospital for Sick Children, Toronto, Canada (49). To assess the impact of this QI process, data was retrospectively collected for subjects in the pre-intervention group (January 2015 to December 2016) and prospectively collected for subjects in the intervention group (March 2017 to September 2018). Infants and children requiring PN at hospital discharge and those experiencing death within 30 days following LT were excluded from the analyses. Data collected in the intervention group was tracked monthly to assess compliance with the feeding protocol and occurrence of any potential adverse events. This allowed for rapid "plan-do-study-act" cycles, mostly centered around ensuring clarity in defining eligibility to initiate EN after surgery and addressing any identified barriers. This project received approval from the Quality Management department at The Hospital for Sick Children, Toronto, ON, Canada.

6.1.1 Pre-intervention group

Before the implementation of the feeding protocol, initiation, and advancement of enteral feedings after LT were encouraged, albeit without a standardized process and with practice variations among treating health-care professionals. The decision to initiate EN post-operatively was primarily made by physicians based on the patient's surgical characteristics and clinical condition. Dedicated dietitians, integral members of the multidisciplinary care teams in the PICU and the Liver Transplant team, reviewed all patients throughout their hospitalization.

6.1.2 Intervention group

The protocol was implemented in March 2017. Prior to this date, several steps were taken: presentation of the protocol at team rounds and, education and email distribution of the protocol to all members of the LT program and stakeholders in the PICU. A paper copy of the feeding protocol was added to the patient's chart on arrival to the PICU after LT surgery to ensure protocol access at bedside. The protocol guided EN order entry to the electronic medical record system.

Upon implementation of the post-operative feeding protocol, all pediatric LT recipients were

considered eligible for EN at 24 hours after their LT surgery. The determining criterion was presence of active bowel sounds by abdominal auscultation. Passage of a bowel movement pre-feeding was not required. Patients with post-operative ileus or known intraoperative surgical complications were not considered eligible for feeding. EN was initiated and advanced, either orally or by NG tube (continuous modality at start) based on neurodevelopmental and respiratory status. NG tube was routinely inserted in the operating room in all pediatric LT recipients and this practice remained unchanged between the pre-intervention and intervention groups. EN advancement strategy was standardized according to LT recipients' age, allowing for individualization based on gastrointestinal tolerance and energy goals. Total daily caloric goals were defined as calculated REE during the acute phase, REE x 1.3 during the stable phase and REE x 1.5 for activity and growth during the recovery phase. REE was calculated using the Schofield equation (50). For patients in whom EN was contraindicated or not feasible and, in those unable to advance past 50% of caloric goals enterally from 3 to 5 days after surgery, PN with SMOF lipid was recommended. A standardized bowel regimen to avoid and minimize post-operative constipation was added to the protocol in July 2017 following a "plan-do-study-act" cycle (**Table 1**).

Table 1. Post-operative Nutrition Protocol After Pediatric LT Surgery

<u>When to start enteral feeding</u>

- Time "0" is time when patient arrives to PICU after surgery
- After 24 post-operative hours, start feeds when bowel sounds present
- For patients with ileus (bilious gastric retentions and/or absence of bowel sounds) or any intraoperative complication, do not initiate feeds
- For patients requiring >1 inotrope drugs or any planned procedure within the next 6 hours, please discuss start of feeds with PICU Staff and/or Liver Transplant surgeon

<u>Initiating and advancing enteral feeding</u>

- *Oral route* (when patient safe and ready to feed orally):
  - Clears to regular diet (or formula) as tolerated
- *Enteral route:*
  - Select formula indicated below unless specified otherwise (i.e., food allergy or underlying metabolic disorder)
  - Identify goal volume (maintenance total fluid intake until dietitian reviews)
  - Start and advance continuous enteral feeds as follows:

Age	Formula	Initial rate	Advancement rate
0-3 months	Expressed breast milk and/or standard infant formula (0.68 Kcal/mL)	2mL/h	Increase by 3mL every 8h
4-12 months		5mL/h	Increase by 5mL every 8h
1-5 years	Polymeric formula (1 Kcal/mL)	5mL/h	Increase by 7mL every 8h
6-11 years		8mL/h	Increase by 8mL every 8h
>11 years	Concentrated formula (1.2 Kcal/mL)	10mL/h	Increase by 10mL every 8h

<u>Assessing gastrointestinal tolerance</u>

- If vomiting and/or according to clinical judgment, do not advance feeding rate and reassess 8 hours afterward. If needed, go back to previously tolerated rate and reassess 8 hours afterward.
- Consider increasing formula caloric concentration if volume advancement rate is not well tolerated.

<u>Additional recommendations</u>

- Consider initiating PN if reaching 50% of full feeds within 3 to 5 post-operative days is not anticipated.
- Consider starting docusate when initiating enteral feeding (5mg/kg/dose once daily or 1.7mg/kg/dose every 8 hours; dose limit [adult dose] is 100-200mg/day)

6.1.3 Data Acquisition

Data were retrieved from our institutional electronic medical record system and included age; sex; weight; height, primary diagnosis; surgical data; pre- and post-operative data including delivery and quantity of oral, enteral and PN nutrition; perioperative morbidity including graft related complications and outcome, and death. Height and weight z scores were calculated using the World Health Organization (WHO) Growth Standards (51). Additional data were collected for all cases in the intervention group and included time to return of bowel function, based on presence of bowel sounds and time to first bowel movement after surgery.

Compliance with the nutrition protocol in the intervention group was determined based on adequate assessment of eligibility to initiate EN and dietary order entry according to the

feeding protocol in our electronic medical record system (type of formula, initial rate and feeding advancement rate). Number and cause of interruptions to EN prior to reaching FEN were also recorded in the intervention group. All study patients received immunosuppression as per our institutional standard protocol and received either standard induction with corticosteroids and calcineurin inhibitor agents (tacrolimus) or renal/neurotoxic-sparing protocol with corticosteroids and either antithymocyte globulin or basiliximab (Simulect; Novartis, Basel, Switzerland) with a delayed introduction of calcineurin inhibitor agents (52).

6.1.4 Outcome measures

Time to initiation of EN before and after protocol implementation, was the primary outcome measure of interest. Time to initiation of EN was defined as the interval between arrival to the PICU after LT surgery and initiation of feeds either orally or through a feeding tube. Additional outcomes of interest included time to FEN that was defined as the interval between initiation of EN and time to reaching caloric goals, either exclusively by mouth or through a feeding tube, post-operative administration and duration of PN, weight at discharge, post-transplant hospital LOS, re-admission rates within 30 days from hospital discharge, occurrence of aspiration pneumonia and infection during hospitalization. Bacterial and fungal infections were diagnosed in the presence of symptoms and laboratory confirmation of causative microorganisms. Central line-associated bloodstream infection (CLABSIs) was defined as a laboratory-confirmed bloodstream infection not related to an infection at another site in a child with a central line.

6.1.5 Statistical analyses

Descriptive statistics were used to present the data, expressed as means and standard deviation or as median and interquartile range (IQR) when a non-normal distribution of data was identified. Categorial parameters were presented as proportions. The Students *t* test or Mann Whitney test were used based on data distribution characteristics for pairwise comparisons. A chi-squared test with Fisher's correction was employed for categorical variables. Linear regression analyses were performed to determine the association between the dependent variable: time to initiation of EN (days) and several predictor variables that included: feeding protocol (intervention), gender, age at LT, weight at LT, re-transplantation, graft type, biliary reconstruction type, delayed abdominal closure, surgical drain *in situ*, CA, time to extubation and duration of opioid infusion. Variables with p-value < 0.1 were included in a multivariate regression analysis and variables with p-value < 0.05 were considered

statistically significant. Statistical analyses were performed with SPSS 20.0 (SPSS, Inc., Chicago, IL).

The data were also monitored using statistical process control (SPC) charts for improvement over time, with control limits set at 3 sigma. Rules for special cause variation on the SPC charts were followed, including eight consecutive points, all above or below the center line and a point above or below the control limits being indicative of special cause variation and equivalent to $P < 0.01$.(53) SPC charts were created using QI Macros (V.2018.04, KnowWare International, Denver, Colorado, USA) for Microsoft Excel (Microsoft Corporation, V.14.5.9).

6.2 Nutritional management of post-operative chylous ascites in children after liver transplantation

6.2.1 *Study population*

The patient population in this case-control study included all children younger than 18 years old who underwent LT surgery at the Hospital for Sick Children, Toronto, Ontario, Canada, between January 2000 and December 2016. Infants and children receiving any organ in addition to liver, those transplanted at an outside institution, and those with CA diagnosed prior to LT were excluded. LT recipients experiencing graft loss or death within 30 days following LT were also excluded. Data were retrieved from a prospectively populated electronic database and retrospective chart review. Data captured for all patients for risk analysis and outcome reporting included demographics; primary diagnosis; pretransplant comorbidities; surgical data; perioperative morbidity, such as vascular thrombosis and biliary complications; long-term outcomes, such as re-transplantation; and death. Height and weight z scores were calculated using the WHO growth standards (51). Additional data were collected for all patients with CA and included information regarding diagnosis, management, and outcome of CA. All study patients followed institutional protocols for immunosuppression and received either standard induction with corticosteroids and a calcineurin inhibitor (tacrolimus) or a renal/neurotoxic-sparing protocol with corticosteroids and either antithymocyte globulin or 2 doses of basiliximab (Simulect; Novartis, Basel, Switzerland) with a delayed introduction of calcineurin inhibitor agents (52). The study received approval from the institutional research ethics board at the Hospital for Sick Children.

6.2.2 *Definitions and outcome measures*

Ascites prior to LT was defined as the presence of a moderate-to-large amount of peritoneal fluid on abdominal ultrasound or history of diuretic use for the treatment of ascites prior to LT. Post-operative CA was defined as the presence of chylomicrons or a triglyceride value ≥187 mg/dL (≥2.13 mmol/L) in the peritoneal fluid within 60 days from LT in the absence of a positive peritoneal fluid culture (12). Triglyceride values of ≥148 and and <187 mg/dL (≥1.69 and <2.13 mmol/L) in the peritoneal fluid were considered equivocal for the diagnosis of CA (12). Post-transplantation hospital LOS was defined as the interval between the day of transplantation and the day of first discharge from the hospital.

6.2.3 *Statistical analysis*

Data were expressed as means and standard deviation or as median and IQR (IQR when a non-normal distribution of data was identified. Student *t* test was used for continuous variables. A nonparametric test (Mann-Whitney U test) was used for continuous variables when an abnormal distribution was identified. A chi-square test or Fisher's exact test was employed for categorical variables. The incidence of CA was calculated together with 95% confidence interval (CI) limits. Patient survival rates were estimated with the Kaplan-Meier method and compared with the log-rank test. Logistic regression univariate analyses were performed to explore the association between CA and variables with clinical significance. Statistical analyses were performed with SPSS, version 20.0 (SPSS Inc., Chicago, IL). A P value of <0.05 was considered statistically significant.

7 RESULTS

7.1 Implementation of a standardized feeding protocol in children immediately after liver transplantation

Standardized Feeding Protocol Improves Delivery and Acceptance of Enteral Nutrition in Children Immediately After Liver Transplantation.

Miserachs M, Kean P, Tuira L, Al Nasser Y, De Angelis M, Van Roestel K, Ghanekar A, Cattral M, Mouzaki M, Lee Ng V, Mtaweh H, and Avitzur Y.

Liver Transpl. 2021 Oct;27(10):1443-1453. PMID: 34018670.

Abstract:

Delivery of adequate nutrition after LT surgery is an important goal of post-operative care. Existing guidelines recommend early EN after abdominal surgery and in the child who is critically ill but data on nutritional interventions after LT in children are sparse. We evaluated the impact of a standardized post-operative feeding protocol on EN delivery in children after LT. Data from 49 children (ages 0-18 years) who received a LT prior to feeding protocol implementation were compared with data for 32 children undergoing LT after protocol implementation. The 2 groups did not differ with respect to baseline demographic data. After protocol implementation, EN was started earlier (2 versus 3 days after transplant; P = 0.005) and advanced faster when a feeding tube was used (4 versus 8 days; P = 0.03). Protocol implementation was also associated with reduced PN use rates (47% versus 75%; P = 0.01). No adverse events occurred after protocol implementation. Hospital length of stay and readmission rates were not different between the 2 groups. In conclusion, implementation of a post-operative nutrition protocol in children after LT led to optimized nutrient delivery and reduced variability of care.

Standardized Feeding Protocol Improves Delivery and Acceptance of Enteral Nutrition in Children Immediately After Liver Transplantation

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Delivery of adequate nutrition after liver transplantation (LT) surgery is an important goal of postoperative care. Existing guidelines recommend early enteral nutrition after abdominal surgery and in the child who is critically ill but data on nutritional interventions after LT in children are sparse. We evaluated the impact of a standardized postoperative feeding protocol on enteral nutrition delivery in children after LT. Data from 49 children (ages 0-18 years) who received a LT prior to feeding protocol implementation were compared with data for 32 children undergoing LT after protocol implementation. The 2 groups did not differ with respect to baseline demographic data. After protocol implementation, enteral nutrition was started earlier (2 versus 3 days after transplant; $P = 0.005$) and advanced faster when a feeding tube was used (4 versus 8 days; $P = 0.03$). Protocol implementation was also associated with reduced parenteral nutrition use rates (47% versus 75%; $P = 0.01$). No adverse events occurred after protocol implementation. Hospital length of stay and readmission rates were not different between the 2 groups. In conclusion, implementation of a postoperative nutrition protocol in children after LT led to optimized nutrient delivery and reduced variability of care.

Liver Transplantation 27 1443–1453 2021 AASLD.
Received November 5, 2020; accepted April 24, 2021.

Delivery of adequate nutrition immediately after liver transplantation (LT) surgery is an important goal of postoperative care. Existing guidelines recommend and emphasize the need to provide adequate nutrition support to pediatric LT candidates to reduce pre-LT complications and enhance post-LT recovery.[1-3] However, despite its unquestionable importance, data on nutritional interventions immediately after LT surgery in pediatric LT recipients are sparse. This gap in knowledge results in significant care variations in the pediatric LT recipient population.

In 2017, evidence-informed expert guidelines were published providing recommendations for the provision of nutrition therapy in children who were critically ill, including those with a surgical diagnosis.[4] In this population, enteral nutrition (EN) is preferred over parenteral nutrition (PN) because of its benefits for gastrointestinal mucosal integrity and motility,

Abbreviations: ACR, acute cellular rejection; BMI, body mass index; CL, center line; CLABSI, central line–associated bloodstream infection; EN, enteral nutrition; FEN, full enteral nutrition; LCL, lower control limit; LOS, length of stay; LT, liver transplantation; mR, moving range; PICU, pediatric intensive care unit; PN, parenteral nutrition; QI, quality improvement; REE, resting energy expenditure; SE, standard error; SPC, statistical process control; UCL, upper control limit.

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lower complication rates, and lower cost.[4,5] In addition, early EN initiation (within 24-48 hours of admission) has been associated with lower mortality rates in children who are critically ill and admitted to pediatric intensive care units (PICUs) and with lower sepsis rates and hospital length of stay (LOS) in adult LT recipients.[6-8] What remains unknown is the impact of early EN after LT surgery in pediatric LT recipients.

Implementation of stepwise EN advancement algorithms in various surgical and critically ill pediatric populations has been associated with decreased time to the initiation of EN and faster EN advancement.[4,9,10] We hypothesized that pediatric LT recipients, considered both surgical patients and patients who are critically ill requiring postoperative PICU admission, are likely to benefit from the implementation of a standardized nutrition protocol. With this in mind, a multidisciplinary quality improvement (QI) team including pediatric hepatologists, surgeons, pediatric intensive care specialists, clinical dietitians, and nurses at our institution (a quaternary academic transplant center) developed and implemented a standardized postoperative feeding protocol for children after LT. This collaborative group used audit data (preintervention group) and a combination of information from the available literature as well as already established institutional feeding guidelines for children after cardiac surgery.[4,11,12] The feeding protocol was implemented in March 2017 and continues to be in use. The QI initiative presented here aimed to shorten the time to the initiation of EN and time to achieve full EN (FEN) in children immediately after LT surgery.

Patients and Methods

A QI project using the model for improvement framework was undertaken to design and implement a feeding protocol for children younger than age 18 years undergoing isolated LT surgery at The Hospital for Sick Children, Toronto, Canada.[13] To assess the impact of this QI project, data were retrospectively collected for patients in the preintervention group (January 2015-December 2016) and prospectively collected for patients in the intervention group (March 2017-September 2018). Infants and children requiring PN at hospital discharge and those experiencing death within 30 days following LT were excluded from the analyses. Data collected in the intervention group were tracked on a monthly basis to assess the compliance with the feeding protocol and the occurrence of any potential adverse events. This allowed for rapid "plan-do-study-act" cycles, mostly centered around ensuring clarity in defining eligibility to initiate EN after surgery and addressing any identified barriers. This project received approval from the Quality Management Department at The Hospital for Sick Children, Toronto, Ontario, Canada.

PREINTERVENTION GROUP

Before the implementation of the feeding protocol, initiation and advancement of enteral feedings after LT were encouraged, albeit without a standardized process and with practice variations among treating health care professionals. The decision to initiate postoperative EN was primarily made by physicians based on the patient's surgical characteristics and clinical condition. Dedicated dietitians, integral members of the multidisciplinary care teams in the PICU, and the LT team reviewed all patients throughout their hospitalization.

INTERVENTION GROUP

The protocol was implemented in March 2017. Prior to this date, the following steps were taken: presentation of the protocol at team rounds and education and e-mail distribution of the protocol to all members of the LT program and stakeholders in the PICU. A paper copy of the feeding protocol was added to the patient's chart on arrival to the PICU after LT surgery to ensure protocol access at bedside. EN orders were entered into the patient's electronic medical record as per the feeding protocol.

On implementation of the postoperative feeding protocol, all pediatric LT recipients were considered eligible for EN at 24 hours after their LT surgery. The determining criterion was the presence of active bowel sounds by abdominal auscultation. Passage of a bowel movement before feeding was not required. Patients with postoperative ileus or known intraoperative surgical complications were not considered eligible for feeding. EN was initiated and advanced, either orally or by nasogastric tube (continuous modality at start),

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DOI 10.1002/lt.26102

based on neurodevelopmental and respiratory status. A nasogastric tube was routinely inserted in the operating room in all pediatric LT recipients, and this practice remained unchanged between the preintervention and intervention groups. EN advancement strategy was standardized according to the LT recipients' age, allowing for individualization based on gastrointestinal tolerance and energy goals. Total daily caloric goals were defined as calculated resting energy expenditure (REE) during the acute phase, REE × 1.3 during the stable phase and REE × 1.5 for activity and growth during the recovery phase. REE was calculated using the Schofield equation.[14] For patients in whom EN was contraindicated or not feasible and in those patients unable to advance past 50% of caloric goals enterally from 3 to 5 days after surgery, PN with SMOFlipid (Fresenius Kabi, Toronto, Ontario, Canada) was recommended. A standardized bowel regimen to avoid and minimize postoperative constipation was added to the protocol in July 2017 following a "plan-do-study-act" cycle (Table 1).

DATA ACQUISITION

Data were retrieved from our institutional electronic medical record system and included age; sex; weight; height, primary diagnosis; surgical data; preoperative and postoperative data including delivery and quantity of oral nutrition, EN, and PN; perioperative morbidity including graft-related complications and outcome, and death. Height and weight *z* scores were calculated using the World Health Organization Growth Standards.[15] Additional data were collected for all cases in the intervention group and included time to return of bowel function based on the presence of bowel sounds and time to first bowel movement after surgery.

Compliance with the nutrition protocol in the intervention group was determined based on adequate assessment of eligibility to initiate EN and dietary order entry according to the feeding protocol in our electronic medical record system (type of formula, initial rate, and feeding advancement rate). Number and cause of interruptions to EN prior to reaching FEN were also recorded in the intervention group. All study patients received immunosuppression as per our institutional standard protocol and received either standard induction with corticosteroids and calcineurin inhibitor agents (tacrolimus) or renal/neurotoxic-sparing protocol with corticosteroids and either antithymocyte globulin or basiliximab (Simulect; Novartis, Basel, Switzerland) with a delayed introduction of calcineurin inhibitor agents.[16]

TABLE 1. Postoperative Nutrition Protocol After Pediatric LT Surgery

When to start enteral feeding
- Time "0" is time when patient arrives to PICU after surgery
- After 24 postoperative hours, start feeds when bowel sounds present
- For patients with ileus (bilious gastric retentions and/or absence of bowel sounds) or any intraoperative complication, do not initiate feeds
- For patients requiring >1 inotrope drugs or any planned procedure within the next 6 hours, please discuss start of feeds with PICU staff and/or LT surgeon

Initiating and advancing enteral feeding
- *Oral route* (when patient is safe and ready to feed orally):
  - Clears to regular diet (or formula) as tolerated
- *Enteral route*:
  - Select formula indicated below unless specified otherwise (ie, food allergy or underlying metabolic disorder)
  - Identify goal volume (maintenance total fluid intake until dietitian reviews)
  - Start and advance continuous enteral feeds as follows:

Age	Formula	Initial rate	Advancement rate
0-3 months	Expressed breast milk and/or standard infant formula (0.68 Kcal/mL)	2 mL/hour	Increase by 3 mL every 8 hours
4-12 months		5 mL/hour	Increase by 5 mL every 8 hours
1-5 years	Polymeric formula (1 Kcal/mL)	5 mL/hour	Increase by 7 mL every 8 hours
6-11 years		8 mL/hour	Increase by 8 mL every 8 hours
>11 years	Concentrated formula (1.2 Kcal/mL)	10 mL/hour	Increase by 10 mL every 8 hours

Assessing gastrointestinal tolerance
- If vomiting and/or according to clinical judgment, do not advance feeding rate and reassess 8 hours afterward. If needed, go back to previously tolerated rate and reassess 8 hours afterward.
- Consider increasing formula caloric concentration if volume advancement rate is not well tolerated.

Additional recommendations
- Consider initiating PN if reaching 50% of full feeds within 3 to 5 postoperative days is not anticipated.
- Consider starting docusate when initiating enteral feeding (5 mg/kg/dose once daily or 1.7 mg/kg/dose every 8 hours; dose limit [adult dose] is 100-200 mg/day).

OUTCOME MEASURES

Time to the initiation of EN before and after protocol implementation was the primary outcome measure of interest. Time to the initiation of EN was defined as the interval between arrival to the PICU after LT surgery and the initiation of feeds either orally or through a feeding tube. Additional outcomes of interest included time to FEN that was defined as the interval between initiation of EN and time to reaching caloric goals, either exclusively by mouth or through a feeding tube, postoperative administration and duration of PN, weight at discharge, posttransplant hospital LOS, readmission rates within 30 days from hospital discharge, occurrence of aspiration pneumonia, and infection during hospitalization. Bacterial and fungal infections were diagnosed in the presence of symptoms and laboratory confirmation of causative microorganisms. Central line–associated bloodstream infection (CLABSI) was defined as a laboratory-confirmed bloodstream infection not related to an infection at another site in a child with a central line.

STATISTICAL ANALYSES

Descriptive statistics were used to present the data, expressed as mean ± standard deviation or as median and interquartile range (IQR) when a non-normal distribution of data was identified. Categorial parameters were presented as proportions. The Student *t* test or Mann Whitney U test was used based on data distribution characteristics for pairwise comparisons. A chi-square test with Fisher's correction was employed for categorical variables. Linear regression analyses were performed to determine the association between the dependent variable time to the initiation of EN (days) and several predictor variables, which included feeding protocol (intervention); sex, age, and weight at LT; retransplantation; graft type; biliary reconstruction type; delayed abdominal closure; surgical drain in situ; chylous ascites; time to extubation; and duration of opioid infusion. Variables with *P* values <0.1 were included in a multivariate regression analysis, and variables with *P* values <0.05 were considered statistically significant. Statistical analyses were performed with SPSS 20.0 (IBM Corp., Armonk, NY).

The data were also monitored using statistical process control (SPC) charts for improvement over time, with control limits set at 3 sigma. Rules for special cause variation on the SPC charts were followed, including 8 consecutive points, all above or below the center line (CL) and a point above or below the control limits being indicative of special cause variation and equivalent to $P < 0.01$.[17] SPC charts were created using QI Macros (version 2018.04; KnowWare International, Denver, CO) for Microsoft Excel (version 14.5.9; Microsoft Corp., Redmond, WA).

Results

A total of 83 pediatric LT recipients were included in this initiative: n = 49 in the preintervention group and n = 34 in the intervention group. A total of 2 patients, both in the intervention group, were excluded from analyses because of early postoperative death attributed to graft failure precluding the assessment of primary outcome (n = 1) and underlying intestinal failure requiring home PN before and after LT (n = 1). Among the 81 LT recipients included in the analyses, the median age at LT was 21.5 months (interquartile range [IQR], 9-72) and 41 of 81 patients (51%) were girls. Table 2 summarizes the demographic, surgical, and postoperative data of LT recipients in the preintervention and intervention groups.

BASELINE AND PERIOPERATIVE CHARACTERISTICS

The were no differences between the 2 groups with regard to underlying diagnosis, sex, age, or anthropometrics except for body mass index (BMI) *z* score, which was higher in the intervention group. The difference in BMI *z* score was not explained by the different use of PN prior to LT surgery between the preintervention and intervention groups (10/49 [20%] versus 6/32 [19%]; $P = 0.85$). More children in the preintervention group had a surgical drain in situ after surgery (32/49 [65%] versus 13/32 [41%]; $P = 0.03$) and received a living donor graft (39/49 [80%] versus 17/32 [53%]; $P = 0.01$) when compared with the intervention group, with no difference in the type of biliary reconstruction performed, which was predominantly a Roux-en-Y hepaticojejunostomy in both groups (Table 2). Median time to extubation, PICU LOS, surgical reintervention, and transplant-related complication rates, such as acute cellular rejection (ACR) during hospitalization, were similar between the 2 groups. A trend toward a shorter duration of continuous infusion of opioids in the intervention group was observed, but this was not statistically significant (Table 2).

TABLE 2. Baseline and Perioperative Characteristics in Pediatric LT Recipients

	Preintervention Group (n = 49)	Intervention Group (n = 32)	*P* Value
Baseline demographics			
Sex, female	27 (55)	14 (44)	0.32
Age at LT, months	26 (8-74)	19 (9-70)	0.55
BMI-for-age *z* score at LT	0.2 ± 1	0.8 ± 1.4	0.03*
Weight at LT, kg	10 (8-21)	11 (9-23)	0.44
Weight-for-age *z* score at LT	–0.8 ± 1.1	–0.3 ± 1.2	0.09
Height at LT, cm	78 (66-113)	76 (70-117)	0.97
Height-for-age *z* score at LT	–1.3 ± 1.5	–1.5 ± 1.5	0.59
Underlying diagnosis			0.16
Biliary atresia	19 (39)	12 (37)	
Alagille syndrome	9 (18)	1 (3)	
Acute liver failure	1 (2)	2 (6)	
Metabolic disease†	11 (22)	9 (28)	
Malignancy	0	2 (6)	
Other	9 (18)	6 (19)	
Retransplantation	2 (4)	2 (6)	0.66
Transplant surgery			
Graft type			0.01*
Living donor	39 (80)	17 (53)	
Deceased donor	10 (20)	15 (47)	
Biliary reconstruction type			0.18
Roux-en-Y hepaticojejunostomy, new	25 (41)	12 (37.5)	
Roux-en-Y hepaticojejunostomy, previous	20 (51)	13 (40.5)	
Duct-to-duct anastomosis	4 (8)	7 (22)	
Delayed abdominal closure	9 (18)	4 (12)	0.48
Surgical drain	32 (65)	13 (41)	0.03*
Postoperative course			
Time to extubation, days	1 (1-4)	1 (0-6)	0.69
Duration of opioid infusion, days	12 (7-18)	7 (4-14)	0.11
PICU stay, days	3 (2-9)	3 (2-10)	0.76
Biopsy-proven ACR	7 (14)	5 (16)	0.86
Surgical reintervention	11 (22)	4 (12.5)	0.26
Chylous ascites	7 (14)	2 (6)	0.26

NOTE: Data are provided as median (IQR), mean ± SD, or n (%).
*Significant *P* values.
†Metabolic disease includes alpha-1-antitrypsin deficiency, glycogen storage disease, primary hyperoxaluria, urea cycle defects, branched amino acid disorders, and citrullinemia.

POSTOPERATIVE NUTRITION

Use of a feeding tube for EN delivery was similar between the preintervention and intervention groups (30/49 [61%] versus 20/32 [62%]; $P = 0.91$), and this remained similar at time of hospital discharge (28/49 [57%] versus 15/32 [47%]; $P = 0.51$). Among children requiring tube feeding in both groups, the majority (48/50 [96%]) received gastric feeds, and only 2/50 (4%) received postpyloric feeds.

In the preintervention group, the median time to the initiation of EN was 3 days (IQR, 3-5), whereas the time to EN in the intervention group was 2 days (IQR, 2-3; $P = 0.005$; Fig. 1A,B). As a result, any EN delivery within the first 72 postoperative hours increased from 25/49 (51%) in the preintervention group to 27/32 (84%) in the intervention group ($P = 0.01$). All pediatric LT recipients in the intervention group (n = 5) who did not receive EN within the first 72 postoperative hours did not meet the EN initiation

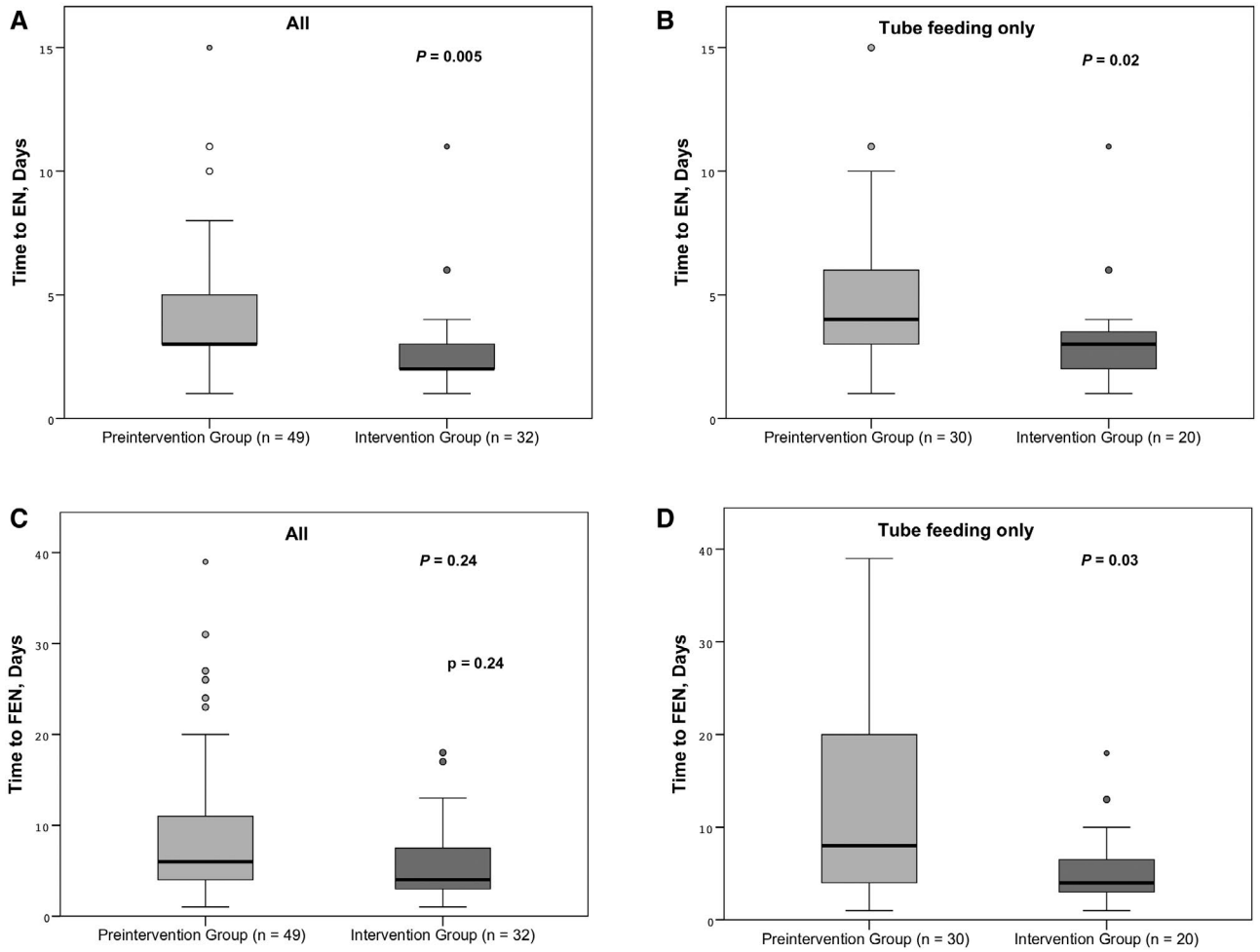

FIG. 1. Comparison between the preintervention and the intervention groups in time to the initiation of EN and time to FEN measured in (A and C) all LT recipients and (B and D) tube-fed LT recipients. Lighter horizontal lines framing the border of the box indicate 25th and 75th percentiles for each patient group. The open circles indicate the outliers in each patient group, and the whiskers depicted by the outer horizontal lines connected to the vertical lines indicate the minimum and maximum values, excluding the outliers.

criterion "presence of active bowel sounds." Among these, 1 was also considered to be noneligible to initiate EN because of an intraoperative surgical complication.

Time to the initiation of EN for each individual pediatric LT recipient is displayed on the XmR chart in Fig. 2. The mean time to the initiation of EN was reduced after feeding protocol implementation from 4.2 to 2.7 days ($P < 0.01$). Special cause variation with greater than 8 points below the CL was observed prior to protocol implementation, which may be attributed to improved performance by practitioners resulting from an awareness of data being collected and feeding protocol development. In addition, a reduction in moving range (mR; absolute difference between each adjacent pair of individual data values) was also observed following protocol implementation. Toward the end of the intervention period, data showed special cause variation with greater than 8 points below the CL, indicating a shift toward reduced process variability.

Median time to FEN was 6 days (IQR, 4-14) in the preintervention group and 4 days (IQR, 3-8) in the intervention group ($P = 0.24$). The reduction in time to FEN was only statistically significant among those fed through a feeding tube, in whom time to FEN decreased from a median of 8 days (IQR, 4-21) to 4 days (IQR, 3-7; $P = 0.03$; Fig. 1C,D).

Implementation of the feeding protocol led to a reduction in the rate of PN use after LT from 37/49 (75%) in the preintervention group to 15/32 (47%) in the intervention group ($P = 0.01$). Duration of PN also decreased from a median of 9 days (IQR, 7-16) in

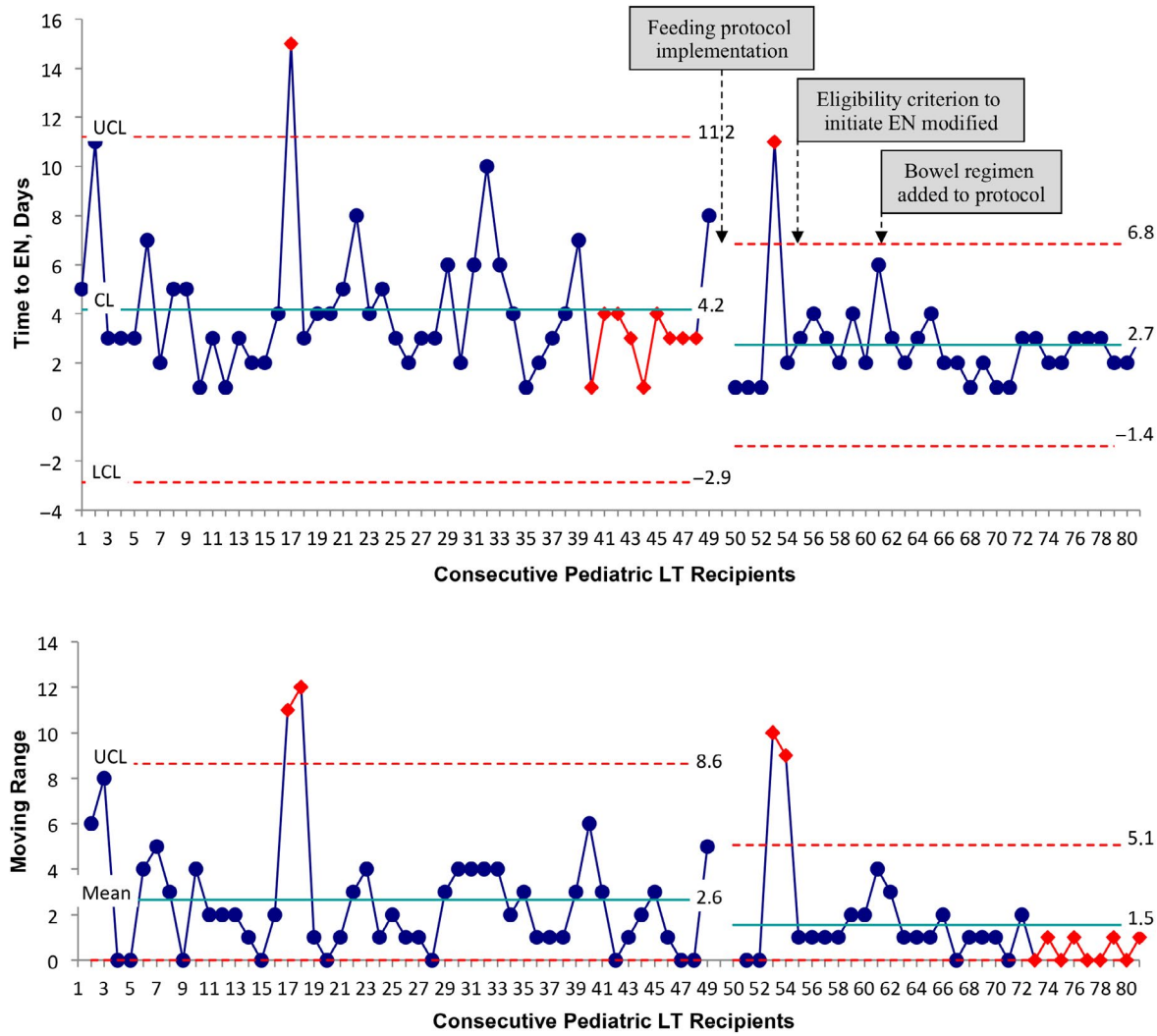

FIG. 2. SPC charts (individual and moving range, XmR charts) for time to the initiation of EN after LT surgery for each consecutive pediatric LT recipient.

the preintervention group to a median of 6 days (IQR, 6-8) in the intervention group ($P = 0.01$).

DETERMINANTS OF TIME TO THE INITIATION OF EN

Linear regression analyses were performed to explore the relationship between time to the initiation of EN and other variables beyond feeding protocol implementation. In univariate analyses, implementation of a feeding protocol and increasing age (months) and weight (kg) were associated with decreased time to the initiation of EN, whereas increasing time to extubation and opioid infusion duration measured in days were associated with delayed initiation of EN. The multiple linear regression demonstrated an association between feeding protocol implementation and time to extubation and time to EN initiation. Pediatric LT recipient's time to initiate EN decreased 1.21 days with feeding protocol implementation and increased 0.16 days for each day until extubation (Table 3).

ADVERSE EVENTS, HOSPITAL LOS, AND READMISSION

No cases of aspiration pneumonia occurred before or after protocol implementation. Following implementation of the feeding protocol, a reduction in CLABSI

TABLE 3. Linear Regression Analyses of Determinants of Time to the Initiation of EN in Pediatric LT Recipients

	Univariate (n = 81)		Multivariate (n = 81)	
	β Coefficient (SE)	*P* Value	β Coefficient (SE)†	*P* Value
Intervention, feeding protocol	–1.44 (0.55)	0.01*	–1.21 (0.55)	0.03*
Baseline demographics				
Sex, female	0.38 (0.56)	0.50		
Age at LT, months	–0.01 (0.004)	0.02*	–0.001 (0.008)	0.85
Weight at LT, kg	–0.04 (0.02)	0.01*	–0.02 (0.03)	0.55
Retransplantation	–0. 36 (1.29)	0.78		
Transplant surgery				
Graft type, living donor	0.39 (0.61)	0.65		
Biliary reconstruction, Roux-en-Y hepaticojejunostomy	1.52 (0.80)	0.06	–0.02 (0.86)	0.98
Delayed abdominal closure	1.18 (0.75)	0.14		
Surgical drain	–0.08 (0.56)	0.88		
Postoperative course				
Time to extubation, days	0.20 (0.05)	<0.001*	0.16 (0.07)	0.02*
Duration of opioid infusion, days	0.08 (0.02)	<0.001*	0.01 (0.03)	0.67
Chylous ascites	0.46 (0.89)	0.61		

∗Significant *P* values.
†*F* test (numerator degree of freedom, denominator degree of freedom) 4.63 (6, 74), $P < 0.001$.

TABLE 4. Secondary Outcomes in LT Recipients

	Preintervention Group (n = 49)	Intervention Group (n = 32)	*P* Value
PN use	37 (75)	15 (47)	0.01*
PN duration, days	9 (7-16)	6 (6-8)	0.01*
Aspiration pneumonia	0	0	0.26
Infection, all types	25 (51)	13 (41)	0.36
CLABSI	10 (20)	2 (6)	0.08
Weight change at discharge, g	400 (–650 to 400)	–280 (–1280 to 210)	0.09
Weight-for-age *z* score at discharge	–0.8 ± 1.1	–0.7 ± 1.3	0.7
Hospital LOS, days	21 (14-34)	21 (13-29)	0.82
Hospital readmission	10 (20)	8 (25)	0.63

NOTE: Data are provided as median (IQR), mean ± SD, or n (%).
*Significant *P* values.

events (10/49 [20%] in the preintervention group versus 2/32 [6%] in the intervention group; $P = 0.08$) was observed, yet this was not statistically significant. Hospital LOS, readmission rates, and overall infection rates during hospitalization were not different between the 2 groups, as shown in Table 4.

GASTROINTESTINAL MOTILITY AND COMPLIANCE TO FEEDING PROTOCOL (INTERVENTION GROUP)

Among pediatric LT recipients in the intervention group (n = 32), the median time to bowel sounds was 20 hours (IQR, 11-46), and the median time to first bowel movement was 68 hours (IQR, 42-102). EN was initiated before the first bowel movement in 19/32 (59%) pediatric LT recipients.

Interruptions to enteral feeding prior to reaching FEN occurred 35 times (median of 1 interruption/patient [IQR, 0-1]) in 19/32 (59%) LT recipients. Nongastrointestinal factors accounted for 27/35 (77%) interruptions (intubation or extubation [n = 7], *nil per os* prior to anesthesia for peripherally inserted central catheters [n = 7] or liver biopsy [n = 6], clinical deterioration [n = 3], feeding tube insertion or replacement [n = 2], or other [n = 2]). Gastrointestinal factors accounted for only 8/35 (23%) interruptions (vomiting

[n = 4], ileus [n = 1], gastrointestinal bleeding [n = 2], or large gastric residual [n = 1]).

Among children in the intervention group, eligibility to initiate EN was adequately assessed (24 hours after PICU admission, upon the presence of active bowel sounds, and in the absence of ileus or known intraoperative surgical complications) in 31/32 (97%) of LT recipients. Only 1 patient was initiated on EN (clear fluid diet) prior to the 24-hour landmark without active bowel sounds and diet was held because of abdominal distention and vomiting. Adherence to protocol with regard to correct EN order entry—initial volume and advancement rates as per the protocol—in our electronic medical record system occurred in 30/32 (94%) children.

Discussion

Within a QI framework, implementation of a nutrition protocol in children immediately after LT surgery was associated with a shortened time to initiate EN and time to achieve FEN. Protocol implementation was also associated with reductions in PN use without the occurrence of adverse events associated with early EN delivery.

Our data show that early institution of EN in pediatric LT recipients with returned bowel function defined as the presence of bowel sounds after surgery was safe and feasible. In the absence of any validated outcome measure to determine bowel function return after surgery,[18] we relied on the presence of bowel sounds without waiting for a bowel movement as an indicator of bowel function prior to initiating EN. This strategy certainly allowed for earlier initiation of EN in the intervention group. This is consistent with a previous retrospective study in children after major intestinal surgery in whom early EN (<48 hours) was not associated with feeding intolerance-related outcomes.[12] Previous studies in adult LT recipients had reached similar conclusions with regard to the safety of early (within 12 hours) initiation of EN after surgery, with 1 study assessing nasogastric tube feeding and the other study assessing the delivery of EN via jejunostomy.[6,19] Although early EN (12 hours) after surgery is recommended in the adult LT recipient, as long as the patient is hemodynamically stable and has no nausea or vomiting,[11,20] a variety of challenges impedes the early initiation of EN in the pediatric population. A perceived barrier to early EN after LT in the pediatric population, likely associated with the delayed introduction of EN in our preintervention group, includes the perception that Roux-en-Y biliary reconstruction, which accounts for up to 86% of biliary reconstruction types in our study population, is less physiological and may delay the return of bowel function after surgery.[21] In our study, Roux-en-Y biliary reconstruction emerged from the univariate analyses as a potential predictor of delayed time to EN, but such an association was no longer observed after adjusting for other variables significant in the univariate analysis. Perhaps not surprisingly, time to extubation was positively associated with time to the initiation of EN. This may be explained by the fact that the initiation of EN might be held prior to extubation and the fact that other clinical factors associated with the need for mechanical ventilation might affect a patient's perceived readiness or eligibility criteria to start EN.

Implementation of a standardized nutrition protocol in our institution was also associated with faster FEN attainment, particularly in those receiving tube feeding. Our findings align with those described by others describing the benefits of implementing nutrition protocols to optimize EN delivery and reduce the variation of nutritional care.[22-24] Previous studies had pointed to frequent interruptions to EN as a barrier to optimal nutrient delivery in children admitted to the PICU.[25-27] Therefore, we were interested in prospectively collecting data on the frequency and causes of interruptions in the intervention group. We found that, prior to reaching FEN, feeds were withheld once per patient, mainly attributed to nongastrointestinal causes. This contrasts with other studies that point to higher interruption rates and feeding intolerance as the leading causes for withholding enteral feeding in hospitalized children.[27,28] It is likely that implementation of a nutrition protocol that not only included recommendations for the management of feeding intolerance but also a treatment strategy for the prevention of postoperative constipation led to the decreased feeding interruptions in the intervention group as previously shown in the PICU setting.[26] Unfortunately, we were unable to retrospectively collect data on feeding interruptions for the preintervention group as we could not determine this accurately.

Just as important, this study also identified that among children requiring tube feeding in both groups, only 4% were unable to tolerate gastric feeding and required postpyloric feeding. In the absence of perceived

or demonstrated risks of aspiration of gastric contents into the tracheobronchial tree, gastric feeding is the preferred route for tube feeding as it is more physiologic, requires less expertise, incurs lower costs, and has less adverse effects such as intussusception. Our findings suggest that the routine placement of the nasogastric tube in the operating room and the use of gastric feeding was well tolerated and not associated with any adverse outcomes. Equally important, this study identified that after protocol implementation, LT recipients received less PN when compared with the historical group. Reduced PN delivery in the intervention group was not associated with worsened nutritional outcomes at discharge. Although we did not identify differences in weight change and weight-for-age *z* score at discharge, in the context of fluid overload, ascites and/or organomegaly, additional descriptions of anthropometrics and body composition would have been more informative in assessing nutritional status.[29] Our findings only concern reduced PN use, but one could also except a decrease in PN-associated costs. Future research is needed to determine the cost-effectiveness of earlier EN delivery in children after LT. Other secondary outcomes such as LOS, readmission rates, and overall infection rates were not influenced by the implementation of our feeding protocol. Factors that may have contributed to this observation are the wide spectrum of medical and social determinants impacting these outcomes beyond achievement of FEN as well as our relatively small sample size.

There are several limitations and biases of this study. First, the retrospective nature of the data collection in the preintervention group can be incomplete. This is the result of the inherent interpretation of clinical judgment and the rationale for clinical care decisions. We addressed this limitation by specifically defining the terms and outcomes of interest at the beginning of our QI intervention, having only 1 researcher performing the data extraction to maintain consistency of interpretation of data. Second, the study compared 2 convenience samples cared for during 2 different time periods. As a result, there may have been additional differences in care that were not accounted for by the data, although this is unlikely as our protocols and team members have not changed significantly during these time periods.

In summary, our data show that implementation of a postoperative nutrition protocol in our institution reduced the variation in care and led to optimized nutrient delivery in children after LT surgery by promoting EN and decreasing reliance on PN. Our results may inform others on potential EN delivery problems and strategies for the improved delivery of EN after LT surgery.

Acknowledgments: The authors thank Lisha Lo, Research and Education Coordinator at the University of Toronto Centre for Quality Improvement and Patient Safety, for her contribution in the creation and interpretation of the SPC charts included in this article.

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7.2 Nutritional management of post-operative chylous ascites in children after Liver transplantation

Diagnosis, Outcome, and Management of Chylous Ascites Following Pediatric Liver Transplantation.

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Liver Transpl. 2019 Sep;25(9):1387-1396. PMID: 31301267.

Abstract:

Data on post-operative CA after pediatric LT are scarce. This retrospective study was conducted to identify the incidence, risk factors, management, and outcomes of post-operative CA in a large single-center pediatric LT cohort (2000-2016). The study cohort comprised 317 LTs (153 living donors and 164 deceased donors) in 310 recipients with a median age of 2.7 years. The incidence of CA was 5.4% (n = 17), diagnosed after a median time of 10 days after LT. Compared with chylomicron detection in peritoneal fluid (the gold standard), a triglyceride cut-off value of 187 mg/dL in peritoneal fluid showed insufficient sensitivity (31%) for CA diagnosis. In univariate logistic regression analyses, ascites before LT, younger age, and lower weight, height, and height-for-age z score at LT were associated with CA. Symptomatic management of CA included peritoneal drain (100%) and diuretics (76%). Therapeutic interventions included very low-fat or medium-chain triglyceride–rich diets (94%) and intravenous octreotide (6%), leading to CA resolution in all patients. CA was associated with prolonged hospital length of stay (LOS; 40 days in the CA group versus 24 days in the non-CA group; P = 0.001) but not with reduced patient or graft survival rates after a median follow-up time of 14 years. In conclusion, CA in the pediatric LT recipient is a relatively uncommon complication associated with increased hospital LOS and morbidity. Measurement of chylomicrons is recommended in patients with ascites that is more severe or persistent than expected. Dietary interventions are effective in most patients.

Diagnosis, Outcome, and Management of Chylous Ascites Following Pediatric Liver Transplantation

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Data on postoperative chylous ascites (CA) after pediatric liver transplantation (LT) are scarce. This retrospective study was conducted to identify the incidence, risk factors, management, and outcomes of postoperative CA in a large single-center pediatric LT cohort (2000-2016). The study cohort comprised 317 LTs (153 living donors and 164 deceased donors) in 310 recipients with a median age of 2.7 years. The incidence of CA was 5.4% (n = 17), diagnosed after a median time of 10 days after LT. Compared with chylomicron detection in peritoneal fluid (the gold standard), a triglyceride cutoff value of 187 mg/dL in peritoneal fluid showed insufficient sensitivity (31%) for CA diagnosis. In univariate logistic regression analyses, ascites before LT, younger age, and lower weight, height, and height-for-age *z* score at LT were associated with CA. Symptomatic management of CA included peritoneal drain (100%) and diuretics (76%). Therapeutic interventions included very low-fat or medium-chain triglyceride–rich diets (94%) and intravenous octreotide (6%), leading to CA resolution in all patients. CA was associated with prolonged hospital length of stay (LOS; 40 days in the CA group versus 24 days in the non-CA group; $P = 0.001$) but not with reduced patient or graft survival rates after a median follow-up time of 14 years. In conclusion, CA in the pediatric LT recipient is a relatively uncommon complication associated with increased hospital LOS and morbidity. Measurement of chylomicrons is recommended in patients with ascites that is more severe or persistent than expected. Dietary interventions are effective in most patients.

Liver Transplantation 25 1387–1396 2019 AASLD.
Received April 1, 2019; accepted June 25, 2019.

Liver transplantation (LT) is an established curative treatment for children suffering from end-stage liver disease, liver malignancies, and selected metabolic disorders. Prevention of postoperative morbidity and early directed therapy of immediate posttransplant complications improves patient outcomes and survival. Postoperative chylous ascites (CA), defined as the accumulation of lipid-rich lymph (chyle) in the peritoneal cavity, has rarely been studied in pediatric LT recipients.[1-3] Continuous leakage of chyle into the peritoneal cavity can lead to the loss of lymphocytes, essential proteins, lipids, vitamins, electrolytes, and water.[4] The resultant clinical consequences beyond the physical accumulation of ascites include dehydration, electrolyte imbalance, malnutrition, lymphopenia, and increased susceptibility to infection.[4,5]

The diagnosis of postoperative CA in the pediatric LT recipient can be challenging. First, its clinical presentation may mimic other posttransplant complications, such as hepatic arterial and portal venous

Abbreviations: A1AT, alpha-1-antitrypsin deficiency; CA, chylous ascites; CI, confidence interval; CMV, cytomegalovirus; EFA, essential fatty acid; IQR, interquartile range; LOS, length of stay; LT, liver transplantation; MCT, medium-chain triglyceride; NPO, nil per os; OR, odds ratio; PFIC, progressive familial intrahepatic cholestasis; POD, postoperative day; TPN, total parenteral nutrition; VAC, vacuum-assisted closure.

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abnormalities, hepatic venous outflow obstruction, small-for-size syndrome, and abdominal infection.[3,6] Second, diagnostic criteria for CA are not well established. Detection of chylomicrons by lipoprotein electrophoresis in peritoneal fluid is considered the gold standard diagnostic test.[7] When not available, a triglyceride cutoff of 110 mg/dL (1.25 mmol/L) in peritoneal fluid was recommended in the pediatric LT literature.[8] The latter recommendations were not supported by high-quality evidence, and it is recognized that triglyceride quantification in peritoneal fluid may not be a reliable diagnostic criterion for CA in fasting patients, particularly in the postoperative state.[9] Recently, these gaps in the literature were addressed, and it is now accepted that a triglyceride cutoff value of 187 mg/dL (2.13 mmol/L) establishes the diagnosis of CA.[10]

The optimal management of postoperative CA is unclear. One study in pediatric LT recipients reported that dietary therapy is effective[11]; another advocated for the use of pharmacologic therapy as a first-line therapy in high-volume output chylous leakage (>20 mL/kg/day).[8] Our study aimed to determine the incidence, risk factors, treatment, and outcomes of postoperative CA in a large pediatric LT cohort using the detection of chylomicrons as the gold standard diagnostic test and the newly established triglyceride cutoff.[10]

Patients and Methods

STUDY POPULATION

The patient population in this case-control study included all children younger than 18 years old who underwent LT surgery at the Hospital for Sick Children, Toronto, Ontario, Canada, between January 2000 and December 2016. Infants and children receiving any organ in addition to liver, those transplanted at an outside institution, and those with CA diagnosed prior to LT were excluded. LT recipients experiencing graft loss or death within 30 days following LT were also excluded.

Data were retrieved from a prospectively populated electronic database and retrospective chart review. Data captured for all patients for risk analysis and outcome reporting included demographics; primary diagnosis; pretransplant comorbidities; surgical data; perioperative morbidity, such as vascular thrombosis and biliary complications; longterm outcomes, such as retransplantation; and death. Height and weight z scores were calculated using the World Health Organization growth standards.[12] Additional data were collected for all patients with CA and included information regarding diagnosis, management, and outcome of CA. All study patients followed institutional protocols for immunosuppression and received either standard induction with corticosteroids and a calcineurin inhibitor (tacrolimus) or a renal/neurotoxic-sparing protocol with corticosteroids and either antithymocyte globulin or 2 doses of basiliximab (Simulect; Novartis, Basel, Switzerland) with a delayed introduction of calcineurin inhibitor agents.[13] The study received approval from the institutional research ethics board at the Hospital for Sick Children.

DEFINITIONS AND OUTCOME MEASURES

Ascites prior to LT was defined as the presence of a moderate-to-large amount of peritoneal fluid on abdominal ultrasound or history of diuretic use for the treatment of ascites prior to LT. Posttransplant CA was defined as the presence of chylomicrons or a triglyceride value ≥187 mg/dL (≥2.13 mmol/L)[10] in the peritoneal fluid within 60 days from LT in the absence of a positive peritoneal fluid culture. Triglyceride values of ≥148 and <187 mg/dL (≥1.69 and <2.13 mmol/L) in the peritoneal fluid were considered equivocal for the diagnosis of CA.[10] Posttransplantation hospital length of stay (LOS) was defined as the interval between the day of transplantation and the day of first discharge from the hospital.

STATISTICAL ANALYSIS

Data were expressed as means and standard deviation or as median and interquartile range (IQR)

This study was supported by the Transplant and Regenerative Medicine Centre, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

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DOI 10.1002/lt.25604

Potential conflict of interest: Nothing to report.

when a nonnormal distribution of data was identified. Student *t* test was used for continuous variables. A nonparametric test (Mann-Whitney U test) was used for continuous variables when an abnormal distribution was identified. A chi-square test or Fisher's exact test was employed for categorical variables. The incidence of CA was calculated together with 95% confidence interval (CI) limits. Patient survival rates were estimated with the Kaplan-Meier method and compared with the log-rank test. Logistic regression univariate analyses were performed to explore the association between CA and variables with clinical significance. Statistical analyses were performed with SPSS, version 20.0 (SPSS Inc., Chicago, IL). A *P* value of <0.05 was considered statistically significant.

Results

PATIENT CHARACTERISTICS

The study cohort assembly is summarized in Fig. 1. The final study cohort comprised 317 isolated LTs performed in 310 pediatric patients with a median age at LT of 2.8 years (IQR, 0.8-10.3 years) and a median weight at LT of 13.8 kg (IQR, 8.0-29.8 kg). The median follow-up time of the whole cohort was 14.0 years (IQR, 11.0-15.0 years). There were 48.3% living donor and 51.7% deceased donor (24.6% whole liver, 14.2% reduced, and 12.9% split) grafts. Indications for LT included biliary atresia (38.2%), Alagille syndrome (4.7%), other cholestatic liver diseases (10.4%), metabolic diseases (17.4%), acute liver failure (14.5%), malignancy (7.3%), and other (7.6%).

INCIDENCE OF CA AND RISK ANALYSES

A total of 17 patients with postoperative CA were identified, giving an incidence of 5.4% (95% CI, 2.9%-7.9%). Table 1 summarizes the demographic and disease-specific data of the LT recipients with and without CA. Age, weight, and height at LT were significantly lower in LT recipients with CA compared with the non-CA group ($P < 0.005$). The groups were comparable with respect to sex, underlying diagnosis, and liver graft type. Pediatric LT recipients with CA had a significantly longer hospital LOS (CA group versus non-CA group; median [IQR], 40.0 [28.8-51.2] versus 24.0 [16.0-38.8] days; $P = 0.001$).

The incidence of postoperative hepatic artery thrombosis and portal vein thrombosis within the first 3 months after LT showed no statistical difference between the CA and the non-CA group. Two cases of bile leak were diagnosed and treated through laparotomy prior to CA diagnosis. Although a trend toward higher bile leaks was noted in the CA group, this did not reach statistical significance (CA group versus non-CA group; 11.8% versus 3.3%; $P = 0.20$). The incidence of CA per each of the 5 surgeons operating during the study period was similar ($P = 0.55$).

The 1-, 3-, and 5-year actuarial patient survival for patients without CA was 99%, 94%, and 93%, respectively, compared with 93%, 84%, and 84%, respectively, for patients with CA ($P = 0.26$; Fig. 2A). The 1-, 3-, and 5-year actuarial graft survival (Fig. 2B) for patients without CA was 98%, 93%, and 91%, respectively, compared with 93%, 84%, and 84%, respectively, for patients with CA ($P = 0.56$).

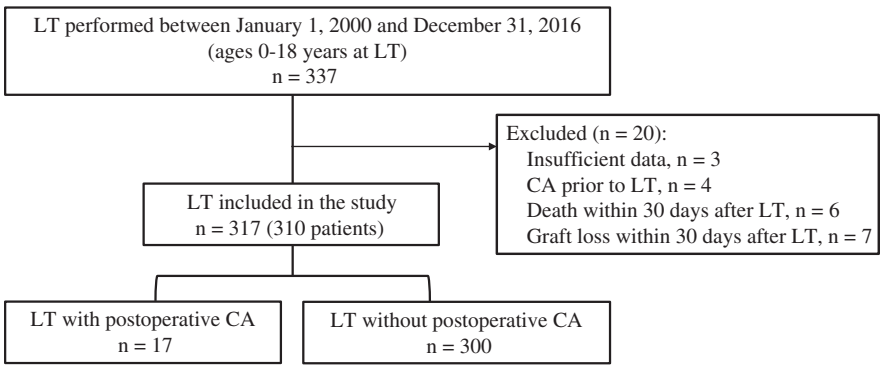

FIG. 1. A flowchart of the study cohort assembly.

TABLE 1. Patient Characteristics and Surgical Parameters of Patients With and Without Postoperative CA

	Postoperative CA (n = 17)	No Postoperative CA (n = 300)	*P* Value
Age at LT, years	0.8 (0.4-3.1)	2.9 (0.8-10.7)	0.002*
Sex, male	58.8	50.3	0.49
Underlying diagnosis			0.61
Biliary atresia	29.4	38.7	
Other cholestasis	23.5	14.7	
Acute liver failure	23.5	14.0	
Metabolic disease	17.6	17.3	
Other	6.0	15.3	
Weight at LT, kg	8.2 (6.0-10.4)	14.6 (8.2-31.9)	0.001*
Weight-for-age *z* score at LT	–1.4 ± 1.9	–0.6 ± 1.5	0.05
Height at LT, cm	66.6 (60.2-77.5)	91.0 (70.0-134.6)	0.001*
Height-for-age *z* score at LT	–1.7 ± 2.0	–0.7 ± 1.4	0.007*
Platelets, ×1000/mm^3	152.0 (59.5-190.5)	146.5 (81.2-242)	0.51
Ascites before LT	76.5	32.7	0.001*
Esophageal varices and/or variceal bleeding before LT	23.5	18.7	0.62
Abdominal surgery before LT	29.4	40.7	0.36
Re-LT	0	6.0	0.29
Graft type			0.21
Living donor	70.6	47.0	
Split	11.8	13.0	
Reduced	11.8	14.3	
Whole	5.8	25.7	
Aortic conduit reconstruction	0	7.0	0.26
Surgical drain in situ after LT	70.6	59.3	0.36
Abdominal wall closure			0.57
Closed	76.5	89.3	
Mesh placement	5.9	3.3	
VAC device	11.8	7.0	

NOTE: Data are shown as mean ± standard deviation, median (IQR), or %.
*Significant *P* values.

In univariate analyses, ascites before transplantation was identified as a significant risk factor for the development of CA after LT with an odds ratio (OR) of 6.69. Young age at transplantation (OR = 1.26 per year), lower weight at transplantation (OR = 1.10 per kg), lower height at transplantation (OR = 1.04 per cm), and lower height-for-age *z* score at LT (OR = 1.59; as a surrogate marker of nutritional status) were also associated with the development of CA (Table 2).

CHARACTERISTICS OF CA

Median time to diagnosis of CA was 10.0 days (IQR, 8.0-16.5 days) after LT surgery and 5.0 days (IQR, 3.0-12.0 days) after postoperative start of enteral feeding. There were 7/17 patients who did not have surgical drains in place at the time of diagnosis, and fluid testing results were obtained by paracentesis (n = 5) or a vacuum-assisted closure (VAC) device (n = 2). Also, 7 patients developed pleural effusion that required drainage, and 2 of the patients had chyle detected in pleural fluid. Table 3 provides details on the 17 patients who developed postoperative CA within 60 days after LT.

Diagnosis of CA was biochemically evident through chylomicron detection in 11 patients, triglycerides ≥187 mg/dL (≥2.13 mmol/L) in 1 patient not tested for chylomicrons, and both chylomicron detection and triglycerides ≥187 mg/dL (≥2.13 mmol/L) in the remaining 5 patients. Triglyceride levels in peritoneal fluid were measured in all 17 patients with CA. Triglyceride values were above the diagnostic cutoff value in 6/17 patients, within the equivocal range for CA diagnosis in 4/17 patients, and below the equivocal range in 7/17 patients. White cell count in peritoneal fluid was >500 cells/mm^3 in 10 of 14 cases analyzed. Median cell count was 740 cells/mm^3 (IQR, 396-1507 cells/mm^3), all with lymphocyte predominance (lymphocyte percentage >80%). All patients had negative peritoneal fluid cultures at the time of CA diagnosis.

MANAGEMENT AND OUTCOME OF CA

A peritoneal drain was used in all patients with CA for symptomatic management of ascites. Median duration of CA from diagnosis to the time of drain removal was 15.0 days (IQR, 11.5-22.5 days), with 2 patients draining for 30 days or more. Drain reinsertion after removal was not required in any of the patients. In total, 13/17 patients received diuretics.

Dietary modifications were used in 15/17 children and included a very low-fat diet for 2 patients who were able to take solid food by mouth, low-fat formula (Tolerex) in 1 patient, and medium-chain triglyceride (MCT)–rich formula (Portagen; Mead Johnson Nutrition, Evansville, USA) in 13 patients. Diet modifications were maintained for a median of 49.0 days (IQR, 27.0-72.0 days). Total parenteral nutrition (TPN) and nil per os (NPO)

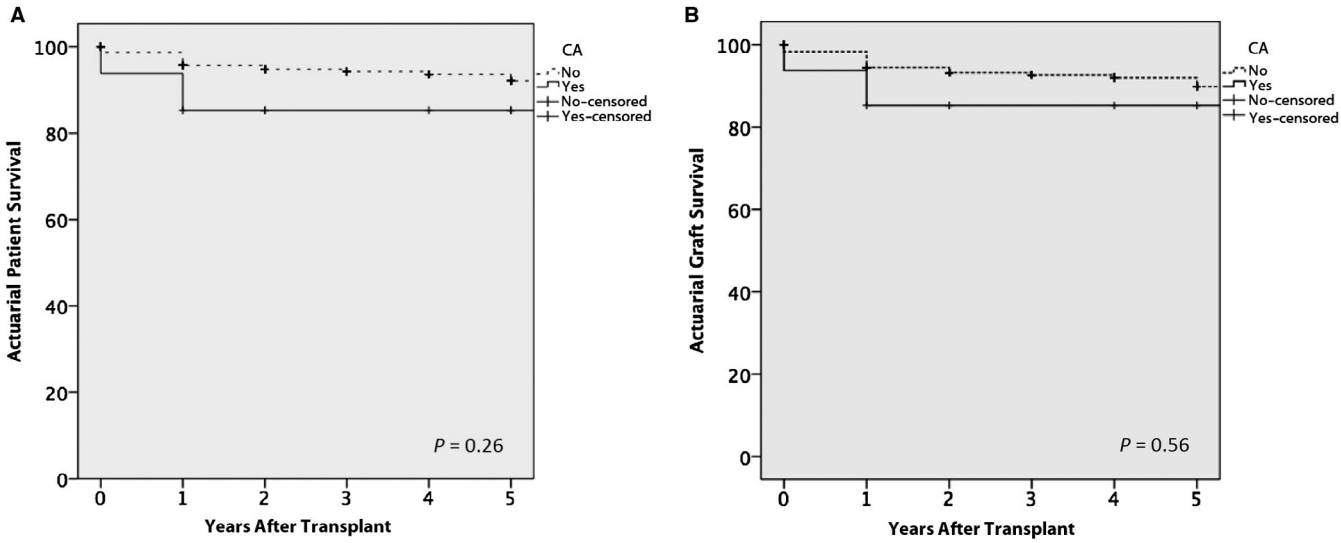

FIG. 2. The posttransplant survival outcomes. (A) Patient and (B) graft survival rates in patients with or without CA.

TABLE 2. Summary of Univariate Logistic Regression Models Evaluating the Effect of Independent Variables on the Development of CA

	OR	95% CI	*P* Value
Age (younger) at LT			
Overall (per year)	1.26	1.04-1.54	0.02*
≤1 year	2.90	1.07-7.84	0.04*
Weight (lower) at LT			
Overall (per kg)	1.10	1.01-1.19	0.02*
≤10 kg	6.04	1.92-18.97	0.002*
Weight-for-age *z* score (lower) at LT	1.38	0.99-1.91	0.05
Height (lower) at LT (per cm)	1.04	1.01-1.06	0.01*
Height-for-age *z* score (lower) at LT	1.59	1.13-2.24	0.01*
Platelet count (lower) at LT (per platelets x1000/mm^3)	1.00	1.00-1.01	0.37
Ascites before LT	6.69	2.12-21.07	0.001*
Surgical drain in situ after LT	1.63	0.56-4.74	0.37

*Significant *P* values.

was used in 4 patients for a median of 7.5 days (IQR, 4.5-9.8 days). Octreotide for 8 days at a maximum dose of 4 μg/kg/hour was added to the low-fat formula (Tolerex; Société des Produits Nestlé S.A., Vevey, Switzerland) in 1 patient for whom nutritional therapy failed to reduce chylous leakage volumes (Table 3).

Biopsy-proven liver allograft acute cellular rejection, defined as the rejection activity index according to the Banff schema ≥3 (range, 0-9), was diagnosed in 4/17 patients within the first 90 postoperative days (PODs). Severe lymphopenia (<0.5 × 10^9/L) was noted in 7/17 LT recipients with CA within 3 months after LT. Lymphopenia resolved in all patients except in 1 patient, for whom resolution could not be confirmed because of the transfer to another institution and death. There were 4/17 children with postoperative CA who received treatment for 5 documented infections following the diagnosis of CA and within 3 months after LT: cytomegalovirus (CMV) viremia (n = 1), urinary tract infection (*Enterococcus* spp.; n = 1), peritonitis while the peritoneal drain remained in situ (*Enterobacter* spp.; n = 1), upper respiratory tract infection (parainfluenza type 3; n = 1), and pneumonia (coronavirus; n = 1).

All children in the CA group except 1, who was transferred to another institution to receive palliative care, were discharged home after a median of 40.0 days (IQR, 28.8-51.2 days). Within 30 days of discharge, 2/16 patients were rehospitalized: 1 for pneumonia and 1 for biopsy-proven liver allograft acute cellular rejection. Also, 2 deaths occurred in the CA group due to posttransplant recurrence of hepatoblastoma and hemophagocytic lymphohistiocytosis at 4 and 6 months after LT, respectively.

Discussion

The findings of this large pediatric cohort reveal that postoperative CA is an uncommon complication in

TABLE 3. Clinical Course of Children With CA After LT

Demographics at LT				Diagnosis of CA			Management			Outcomes <3 Months After LT		
					Peritoneal Fluid Findings							
Patient Number	Sex	Age and Weight	Primary Diagnosis	Time of Diagnosis After LT, days	Chylomicron Detection	Triglyceride, mmol/L	Peritoneal Drain Duration, days	Treatment	Diuretics	Postoperative Complications	Infection	LOS, days
1	Male	0.2 years 6.4 kg	Neonatal liver failure	12	+	7.73	20	Portagen, 11 days	+	Bile leak and relaparotomy POD 4		33
2	Female	3 years 23.2 kg	Hepatoblastoma	8	Not tested	3.34	13	NPO/TPN, 4 days	+			*
3	Male	7 years 27.4 kg	Acute liver failure	15	+	1.79	16	NPO/TPN, 2 days Low-fat diet, 27 days	+	Bile leak and relaparotomy POD 4		46
4	Female	1 year 8.9 kg	Biliary atresia	19	+	2.77	13	Portagen, 12 days	–			31
5	Male	0.7 years 6.5 kg	Acute liver failure	10	+	2.14	5	Portagen, 90 days	–			123
6	Female	0.4 years 6.2 kg	Biliary atresia	7	+	0.86	15		+			28
7	Male	3 years 11.8 kg	Alagille syndrome	13	+	0.90	16	Portagen, 29 days	–			25
8	Male	0.2 years 4.5 kg	Neonatal liver failure	21	+	1.08	25	Portagen, 121 days	+		CMV viremia and urinary tract infection (*Enterococcus* spp.)	53
9	Male	1 year 8.2 kg	PFIC 1	18	+	1.10	35	Portagen, 61 days	+		Peritonitis (*Enterobacter* spp.)	87
10	Male	0.3 years 5.5 kg	Biliary atresia	8	+	1.40	15	Portagen, 86 days	+		Upper respiratory tract infection (parainfluenza type 3)	27
11	Female	0.4 years 5.8 kg	Biliary atresia	8	+	0.63	26	NPO/TPN, 9 days Portagen, 13 days	+			43
12	Male	0.8 years 8.4 kg	Biliary atresia	7	+	2.02	3	NPO/TPN, 6 days Portagen, 40 days	–			28

TABLE 3. *Continued*

Demographics at LT				Diagnosis of CA			Management			Outcomes <3 Months After LT		
					Peritoneal Fluid Findings							
Patient Number	Sex	Age and Weight	Primary Diagnosis	Time of Diagnosis After LT, days	Chylomicron Detection	Triglyceride, mmol/L	Peritoneal Drain Duration, days	Treatment	Diuretics	Postoperative Complications	Infection	LOS, days
13	Female	2 years 8.9 kg	PFIC 1	8	+	3.51	45	NPO/TPN, 10 days Portagen, 11 days Tolerex, 38 days Octreotide, 8 days (added to Tolerex)	+			63
14	Female	5 years 20.9 kg	A1AT	23	+	1.77	12	Low-fat diet, 56 days	+			37
15	Male	0.7 years 6.2 kg	A1AT	8	+	3.14	13	Portagen, 67 days	+			36
16	Female	0.2 years 4 kg	Neonatal liver failure	12	+	1.94	11	Portagen, 37 days	+		Viral pneumonia (coronavirus)	45
17	Male	0.9 years 8.5 kg	Alagille syndrome	8	+	1.42	7	Portagen, 72 days	+			46

*Patient 2 was transferred to another institution for palliative care after primary disease recurrence (death occurred 4 months after LT).

children after LT, leads to a prolonged hospital LOS and immediate postoperative morbidity, but does not impact longterm graft and patient survival. In all of our cases, early recognition of CA and symptomatic management of ascites using a peritoneal drain and dietary interventions (MCT-rich formula/very low-fat diet/NPO and TPN if there is no response to formula) led to the resolution of CA, with only 1 patient receiving pharmacologic therapy.

The incidence of CA in our study population (5.4%) is similar to values reported in other mixed pediatric and adult studies (6.3%) and adult studies (4.7%).[8,14] Yet, a recent study describing a series of 120 pediatric LTs reported a CA incidence of 24%.[3] The reason for the incidence discrepancy is unclear and probably relates to different practices around surgical drain insertion and peritoneal fluid testing. The rate of surgical drain insertion was lower in our study (60.1%) compared with that reported by Marseglia et al.[3] (87.5%). In addition, only 15% of our study patients were investigated for chylomicrons in the peritoneal fluid, raising the possibility that only symptomatic CA was diagnosed in our and other cohorts with similar incidence.

In our cohort, the development of ascites prior to transplantation, a sign of decompensated cirrhosis, was associated with a higher risk for the development of CA. Lymphangiogenesis has been described in the context of cirrhosis, and it has been speculated that it may help accommodate increased lymphatic flows and elevated portal pressures.[15,16] It is possible that the increased lymphatic circulation in patients with cirrhosis contributes to an increased risk of traumatic CA during LT; however, evidence supporting this hypothesis is lacking. Our findings are in keeping with those reported by Yilmaz et al.,[14] who also identified development of ascites prior to LT as an independent risk factor for CA. Nonetheless, a smaller study reported that children and young adult LT recipients with postoperative CA had similar rates of ascites on pretransplant radiological imaging as those without CA.[8] The main difference between this study and ours lies in the timing of the identification of ascites (anytime preoperatively in the latter), without being clear whether LT recipients in the first study had previously developed ascites.

Our analysis yielded additional risk factors for the development of postoperative CA, namely, age ≤1 year and weight ≤10 kg at time of transplantation. These findings may be related to the smaller caliber of vascular and lymphatic structures in younger children, putting small children at a greater risk for traumatic injury of the lymphatic vessels during surgery. Similarly, a lower height-for-age z score at LT, which generally implies failure to thrive and malnutrition, was also significantly associated with a higher risk of postoperative CA. These results support reports describing pretransplant malnutrition in children as a risk factor for posttransplant morbidity.[17] Given that the weight-for-age z score may underestimate the degree of undernutrition in children with chronic liver disease because of the effects of organomegaly and/or ascites, it is not surprising that no association was found between weight-for-age z score at LT and postoperative CA.

Concurrent with the initiation of enteral feeding, postoperative CA manifests primarily with persistent ascites or milky drainage through surgical drains in situ, often in the setting of otherwise adequate graft function. CA should be an integral part of the differential diagnosis of early ascites after transplant in addition to other common postoperative complications, such as hepatic arterial and portal venous abnormalities, hepatic venous outflow obstruction, small-for-size syndrome, and abdominal infection.[3,6] Suspicion of CA should prompt further investigation to confirm the diagnosis. Detection of chylomicrons in peritoneal fluid, obtained either through the peritoneal drain or through paracentesis, is considered the gold standard test for the diagnosis of CA.

Recently, a triglyceride cutoff of ≥187 mg/dL (≥2.13 mmol/L) in peritoneal fluid was suggested as an additional diagnostic tool for CA.[10] In our study, 16/17 and 30/300 LT recipients in the CA and non-CA groups, respectively, were investigated for both chylomicrons and triglycerides in the peritoneal fluid. We found the recently proposed triglyceride cutoff to be insufficiently sensitive (31.25%) as a diagnostic tool. These findings suggest that the triglyceride cutoff may not be a reliable criterion to exclude the diagnosis of CA in fasting or partially fed pediatric LT recipients. Maldonado et al. reported similar findings when determining the biochemical parameters of chylous pleural fluid in patients with chylothorax, particularly in those fasting in the postoperative state.[9] Peritoneal fluid should also be sent for cell count (lymphocyte predominance) and culture (negative).

There is a lack of consensus regarding the optimal management of postoperative CA, and treatment

options range from nutritional interventions to pharmacologic treatments and surgical procedures.[1,8,11,18-20] In contrast to what other groups have reported, in our series, we relied on symptomatic management of the ascites with diuretics and/or insertion of a peritoneal drain and nutritional interventions to manage CA.[1,8,18] Large peritoneal drain losses were generally replaced with 5% intravenous albumin (ratio of 1:1 or less), and drains were clamped when fluid output <5 mL/kg/day was reached. In our series, abdominal infection (bacterial peritonitis) occurred in only 1 patient and was easily managed.

Nutritional interventions were used in 16 patients and included dietary fat modifications in 11 children and dietary fat modifications plus a period of fasting and parenteral nutrition in 5 patients for whom dietary fat modification failed to diminish peritoneal drain losses. Patients following fat-free or MCT-rich diets as the only fat source for any length of time may need to supplement essential fatty acids (EFAs) and fat-soluble vitamins.[21] Therefore, given the potential for EFA deficiency in patients following dietary fat modifications, we implemented empiric supplementation with vegetable oil in 2015.[21] In contrast to recommendations from other groups, pharmacologic therapy with the somatostatin analogue octreotide was used in only 1 patient for whom nutritional strategies failed to reduce chylous leakage volumes. Considering that octreotide markedly reduces splanchnic blood flow and also has the potential to cause liver injury,[22] we believe nutritional interventions are a safer treatment option than octreotide.

The limitations and biases of this study relate to the retrospective nature of data collection, which can be incomplete in some respects, such as interpreting clinical judgment and the rationale for clinical care decisions. Given the low incidence of CA reported in our study, prospective controlled studies to determine efficacy of the therapeutic options for the management of CA would be difficult to conduct in children. Strengths of our study include the use of the gold standard diagnostic test (chylomicron detection) and a relatively large pediatric sample size, with a wide range of pediatric ages, underlying diagnoses, and surgical techniques.

In summary, we present a comprehensive analysis of the incidence, risk factors, outcomes, and management strategies of postoperative CA in the pediatric LT recipients. Although CA after LT is relatively uncommon, it was associated with prolonged hospital LOS and immediate postoperative morbidity. CA should be sought in children with increased peritoneal drain losses or ascites after LT, particularly in the younger population with a history of ascites and/or malnutrition before LT. Chylomicron detection in peritoneal fluid appears to be a more sensitive test that overran arbitrary triglyceride cutoff values in children undergoing LT. Symptomatic management of CA with peritoneal drains and dietary interventions are highly effective first-line treatment modalities in the majority of patients. Routine use of octreotide is not recommended or required. Early recognition and treatment of this unusual complication will shorten hospital LOS and reduce the degree of postoperative morbidity.

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8 DISCUSSION

8.1 Implementation of a standardized feeding protocol in children immediately after liver transplantation

Within a QI framework, implementation of a nutrition protocol in children immediately after LT surgery was associated with shortened time to initiate EN and time to achieve FEN. Protocol implementation was also associated with reductions in PN use without occurrence of adverse events associated with early EN delivery.

Our data shows that early institution of EN in pediatric LT recipients with returned bowel function defined as presence of bowel sounds after surgery was safe and feasible. In the absence of any validated outcome measure to determine bowel function return after surgery (54), we relied on the presence of bowel sounds without waiting for a bowel movement as an indicator of bowel function prior to initiating EN. This strategy certainly allowed for earlier initiation of EN in the intervention group. This is consistent with a previous retrospective study in children after major intestinal surgery, in whom early EN (<48 hours) was not associated with feeding intolerance-related outcomes (55). Previous studies in adult LT recipients had reached similar conclusions with regards to safety of early (within 12 hours) initiation of EN after surgery, one assessing NG tube feeding and the other assessing delivery of EN via jejunostomy (34, 38). While early EN (12h) after surgery is recommended in the adult LT recipient, as long as the patient is hemodynamically stable and has no nausea or vomiting (56, 57), a variety of challenges impedes early initiation of EN in the pediatric population. A perceived barrier to early EN after LT in the pediatric population, likely associated with the delayed introduction of EN in our pre-intervention group, includes the perception that Roux-en-Y biliary reconstruction, which accounts for up to 86% of biliary reconstruction types in our study population, is less physiological and may delay return of bowel function after surgery (58). In our study, Roux-en-Y biliary reconstruction emerged from the univariate analyses as a potential predictor of delayed time to EN but such association was no longer observed after adjusting for other variables significant in the univariate analysis. Perhaps not surprisingly, time to extubation was positively associated with time to initiation of EN. This may be explained by the fact that initiation of EN might be held prior to extubation and the fact that other clinical factors associated with need for mechanical ventilation might affect patient's perceived readiness or eligibility criteria to start EN.

Implementation of a standardized nutrition protocol in our institution was also associated with faster FEN attainment, particularly in those receiving tube feeding. Our findings align with those described by others, describing the benefits of implementing nutrition protocols to optimize EN delivery and reduce variation of nutritional care (59-61). Previous studies had pointed at frequent interruptions to EN as a barrier to optimal nutrient delivery in children admitted to the PICU (25, 62, 63). Therefore, we were interested in prospectively collecting data on frequency and causes of interruptions in the intervention group. We found that, prior to reaching FEN, feeds were withheld once per patient, mainly due to non-gastrointestinal causes. This contrasts with other studies that point at higher interruption rates and at feeding intolerance as the leading cause for withholding enteral feeding in hospitalized children (63, 64). It is likely that implementation of a nutrition protocol that not only included recommendations for the management of feeding intolerance but also treatment strategy for the prevention of post-operative constipation, led to decreased feeding interruptions in the intervention group as previously shown in the PICU setting (25). Unfortunately, we were unable to retrospectively collect data on feeding interruptions for the pre-intervention group, as we could not determine this accurately.

Just as important, this study also identified that among children requiring tube feeding in both groups, only 4% were unable to tolerate gastric feeding and required post-pyloric feeding. In the absence of perceived or demonstrated risks of aspiration of gastric contents into the tracheobronchial tree, gastric feeding is the preferred route for tube feeding as it is more physiologic, requires less expertise, incurs lower costs, and has less side effects such as intussusception. Our findings suggest that routine placement of NG tube in the operating room and use of gastric feeding was well tolerated and not associated with any adverse outcomes. Equally important, this study identified that after protocol implementation, LT recipients received less PN when compared to the historical group. Reduced PN delivery in the intervention group was not associated with worsened nutritional outcomes at discharge, with the limitations of weight and weight-for-age z-scores as indicators of nutritional status in children with liver disease and in the absence of body composition assessments which would be more informative (4). Our findings only concern reduced PN use, but one could also except a decrease in PN-associated costs. Future research is needed to determine cost-effectiveness of earlier EN delivery in after LT in children. Other secondary outcomes such as LOS, re-admission rates and overall infection rates were not influenced by the implementation of our feeding protocol. Factors that may have contributed to this observation are the wide spectrum

of medical and social determinants impacting these outcomes beyond achievement of FEN as well as our relatively small sample size.

The limitations and biases of this study are several. First, the retrospective nature of data collection in the pre-intervention group can be incomplete. This is due to inherent interpretation of clinical judgment and the rational for clinical care decisions. We addressed this limitation by specifically defining the terms and outcomes of interest at the beginning of our QI intervention, having only one researcher performing the data extraction to maintain consistency of interpretation of data. Second, the study compared two convenience samples cared for over two different time periods. As a result, there may have been additional differences in care that were not accounted for by the data although this is unlikely as our protocols and team members have not changed significantly over these time periods.

In summary, our data show that implementation of a post-operative nutrition protocol in our institution reduced variation in care and led to optimized nutrient delivery in children after LT surgery by promoting EN and decreasing reliance on PN. Our results may inform others on potential EN delivery problems and strategies for improved delivery of EN after LT surgery.

8.2 Nutritional management of post-operative chylous ascites in children after Liver transplantation

The findings of this large pediatric cohort reveal that post-operative CA is an uncommon complication in children after LT, leads to a prolonged hospital LOS and immediate post-operative morbidity, but does not impact long-term graft and patient survival. In all of our cases, early recognition of CA and symptomatic management of ascites using a peritoneal drain and dietary interventions (MCT-rich formula/very low-fat diet/NPO and PN if there is no response to formula) led to the resolution of CA, with only 1 patient receiving pharmacologic therapy.

The incidence of CA in our study population (5.4%) is similar to values reported in other mixed pediatric and adult studies (6.3%) and adult studies (4.7%) (30, 65). Yet, a recent study describing a series of 120 pediatric LTs reported a CA incidence of 24% (31). The reason for the incidence discrepancy is unclear and probably relates to different practices around surgical drain insertion and peritoneal fluid testing. The rate of surgical drain insertion was lower in our study (60.1%) compared with that reported by Marseglia et al. (87.5%) (31). In addition, only 15% of our study patients were investigated for chylomicrons in the peritoneal fluid, raising

the possibility that only symptomatic CA was diagnosed in our and other cohorts with similar incidence.

In our cohort, the development of ascites prior to transplantation, a sign of decompensated cirrhosis, was associated with a higher risk for the development of CA. Lymphangiogenesis has been described in the context of cirrhosis, and it has been speculated that it may help accommodate increased lymphatic flows and elevated portal pressures (66, 67). It is possible that the increased lymphatic circulation in patients with cirrhosis contributes to an increased risk of traumatic CA during LT; however, evidence supporting this hypothesis is lacking. Our findings are in keeping with those reported by Yilmaz et al. (65), who also identified development of ascites prior to LT as an independent risk factor for CA. Nonetheless, a smaller study reported that children and young adult LT recipients with post-operative CA had similar rates of ascites on pre-transplant radiological imaging as those without CA (30). The main difference between this study and ours lies in the timing of the identification of ascites (anytime pre-operatively in the latter), without being clear whether LT recipients in the first study had previously developed ascites.

Our analysis yielded additional risk factors for the development of post-operative CA, namely, age ≤1 year and weight ≤10 kg at time of transplantation. These findings may be related to the smaller caliber of vascular and lymphatic structures in younger children, putting small children at a greater risk for traumatic injury of the lymphatic vessels during surgery. Similarly, a lower height-for-age z score at LT, which generally implies failure to thrive and malnutrition, was also significantly associated with a higher risk of post-operative CA. These results support reports describing pre-transplant malnutrition in children as a risk factor for post-transplant morbidity (7). Given that the weight-for-age z score may underestimate the degree of malnutrition in children with chronic liver disease because of the effects of organomegaly and/or ascites, it is not surprising that no association was found between weight-for-age z score at LT and post-operative CA.

Concurrent with the initiation of enteral feeding, post-operative CA manifests primarily with persistent ascites or milky drainage through surgical drains in situ, often in the setting of otherwise adequate graft function. CA should be an integral part of the differential diagnosis of early ascites after transplant in addition to other common post-operative complications, such as hepatic arterial and portal venous abnormalities, hepatic venous outflow obstruction, small-for-size syndrome, and abdominal infection (31, 43). Suspicion of CA should prompt further investigation to confirm the diagnosis. Detection of chylomicrons in peritoneal fluid,

obtained either through the peritoneal drain or through paracentesis, is considered the gold standard test for the diagnosis of CA.

Recently, a triglyceride cut-off of ≥187 mg/dL (≥2.13 mmol/L) in peritoneal fluid was suggested as an additional diagnostic tool for CA (12). In our study, 16/17 and 30/300 LT recipients in the CA and non-CA groups, respectively, were investigated for both chylomicrons and triglycerides in the peritoneal fluid. We found the recently proposed triglyceride cut-off to be insufficiently sensitive (31.25%) as a diagnostic tool. These findings suggest that the triglyceride cut-off may not be a reliable criterion to exclude the diagnosis of CA in fasting or partially fed pediatric LT recipients. Maldonado et al. reported similar findings when determining the biochemical parameters of chylous pleural fluid in patients with chylothorax, particularly in those fasting in the post-operative state (45). Peritoneal fluid should also be sent for cell count (lymphocyte predominance) and culture (negative).

There is a lack of consensus regarding the optimal management of post-operative CA, and treatment options range from nutritional interventions to pharmacologic treatments and surgical procedures (30, 46-48, 68, 69). In contrast to what other groups have reported, in our series, we relied on symptomatic management of the ascites with diuretics and/or insertion of a peritoneal drain and nutritional interventions to manage CA (30, 46, 68). Large peritoneal drain losses were generally replaced with 5% intravenous albumin (ratio of 1:1 or less), and drains were clamped when fluid output <5 mL/kg/day was reached. In our series, abdominal infection (bacterial peritonitis) occurred in only 1 patient and was easily managed.

Nutritional interventions were used in 16 patients and included dietary fat modifications in 11 children and dietary fat modifications plus a period of fasting and PN in 5 patients for whom dietary fat modification failed to diminish peritoneal drain losses. Patients following fat-free or MCT-rich diets as the only fat source for any length of time may need to supplement essential fatty acids (EFAs) and fat-soluble vitamins (70). Therefore, given the potential for EFA deficiency in patients following dietary fat modifications, we implemented empiric supplementation with vegetable oil in 2015 (70). In contrast to recommendations from other groups, pharmacologic therapy with the somatostatin analogue octreotide was used in only 1 patient for whom nutritional strategies failed to reduce chylous leakage volumes. Considering that octreotide markedly reduces splanchnic blood flow and also has the potential to cause liver injury (71), we believe nutritional interventions are a safer treatment option than octreotide.

The limitations and biases of this study relate to the retrospective nature of data collection, which can be incomplete in some respects, such as interpreting clinical judgment and the rationale for clinical care decisions. Given the low incidence of CA reported in our study, prospective controlled studies to determine efficacy of the therapeutic options for the management of CA would be difficult to conduct in children. Strengths of our study include the use of the gold standard diagnostic test (chylomicron detection) and a relatively large pediatric sample size, with a wide range of pediatric ages, underlying diagnoses, and surgical techniques.

In summary, we present a comprehensive analysis of the incidence, risk factors, outcomes, and management strategies of post-operative CA in the pediatric LT recipients. Although CA after LT is relatively uncommon, it was associated with prolonged hospital LOS and immediate post-operative morbidity. CA should be sought in children with increased peritoneal drain losses or ascites after LT, particularly in the younger population with a history of ascites and/ or malnutrition before LT. Chylomicron detection in peritoneal fluid appears to be a more sensitive test that overran arbitrary triglyceride cut-off values in children undergoing LT. Symptomatic management of CA with peritoneal drains and dietary interventions are highly effective first-line treatment modalities in the majority of patients. Routine use of octreotide is not recommended or required. Early recognition and treatment of this unusual complication will shorten hospital LOS and reduce the degree of post-operative morbidity.

9 CONCLUSIONS

9.1 Implementation of a standardized feeding protocol in children immediately after liver transplantation

- After standardized post-operative feeding protocol implementation, EN was started earlier (2 versus 3 days after transplant; P = 0.005). The percentage of children receiving any EN within the first 72 post-operative hours increased from 51 to 84% (*P* = 0.01).

- After standardized post-operative feeding protocol implementation, EN was advanced faster towards FEN (4 versus 6 days; P = 0.24), although this was only statistically significant when a feeding tube was used (4 versus 8 days; P = 0.03).

- Protocol implementation was also associated with reduced PN use rates (47% versus 75%; P = 0.01), and no adverse events were associated with early EN delivery.

9.2 Nutritional management of post-operative chylous ascites in children after Liver transplantation

- In a large cohort of 317 pediatric LT recipients, the incidence of post-operative CA was 5.4% (95% CI, 2.9%-7.9%).

- Compared with chylomicron detection in peritoneal fluid, a triglyceride cut-off value of 187 mg/dL (2.13 mmol/L) in peritoneal fluid showed insufficient sensitivity (31%) for CA.

- Ascites prior transplantation was identified as a significant risk factor for the development of CA after LT with an odds ratio (OR) of 6.69. Additional risk factors associated with the development of CA included young age at transplantation (OR = 1.26 per year), lower weight at transplantation (OR = 1.10 per kg), lower height at transplantation (OR = 1.04 per cm), and lower height-for-age z score at LT (OR = 1.59; as a surrogate marker of nutritional status).

- In our series, early recognition of CA and symptomatic management of ascites using a peritoneal drain and dietary interventions (MCT-rich formula/very low-fat diet/NPO and TPN if there is no response to formula) led to the resolution of CA, with only 1 patient receiving pharmacologic therapy.

- Pediatric LT recipients with CA had a significantly longer hospital LOS (40 days; IQR, 29-51) when compared to those without CA (24 days; IQR, 16-39; P = 0.001).

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