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Improved Outcome of Intestinal Failure in Preterm Infants

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ABSTRACT

Objective: The aim of the study was to evaluate the outcome and to identify predictors for survival and enteral autonomy in neonatal intestinal failure (IF).
Methods: A retrospective observational study in a Swedish tertiary centre of children born between 1995 and 2016 with neonatal IF, defined as dependency on parenteral nutrition (PN) ≥60 days, starting with PN before the age of 44 gestational weeks. Data were extracted from medical records and predictors for survival and enteral autonomy were identified by the Cox regression model. Time to death and weaning off PN analysis were performed with Kaplan-Meier curves including log rank test.
Results: In total, 105 children were included. Median gestational age was 28 weeks (22–42), 50% were born extremely preterm (<28 gestational weeks). PN started at a median age of 2 days (0–147) with a median duration of 196 days (60–3091). Necrotizing enterocolitis was the dominating cause of IF (61%). Overall survival was 88%, 5 children died of sepsis and 4 of intestinal failure-associated liver disease. Survival increased from 75% during 1995 to 2008 to 96% during 2009 to 2016 ($P = 0.0040$). Age-adjusted small bowel length of >50% and birth 2009 to 2016 were predictors for survival. Enteral autonomy was achieved in 87%, with positive prediction by small bowel length of >25% of expected for gestational age and remaining ileocecal valve.
Conclusions: Preterm neonates with IF, at high risk of IF-associated morbidity, showed a high overall survival rate. Small-bowel length and being born 2009 to 2016 were predictors for survival and remaining ICV and small-bowel length were predictors for enteral autonomy.

Key Words: intestinal failure-associated liver disease, neonatal surgery, parenteral nutrition, taurolidine+citrate lock

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What Is Known

- Pediatric intestinal failure is associated with significant morbidity and mortality.
- Intestinal failure-associated liver disease develops frequently in premature neonates in whom liver immaturity, frequent sepsis, and necrotizing enterocolitis facilitate liver inflammation and severe damage to bile ducts and liver cells.
- The role of intestinal rehabilitation multidisciplinary teams in improved outcome is well documented.

What Is New

- Preterm neonates with intestinal failure, at high risk of intestinal failure-associated morbidity, showed a high overall survival rate.
- Small-bowel length and being born 2009 to 2016 were predictors for survival and remaining ileocaecal valve and residual small-bowel length were predictors for enteral autonomy.

Pediatric intestinal failure (IF) is a condition of insufficient capacity of the intestines to absorb nutrients and fluids to sustain life and growth without supplemental parenteral nutrition (PN) (1). The aetiology of paediatric IF varies from short bowel syndrome (SBS) to motility disorders and enteropathies (2). SBS is the leading cause of IF in children with an estimated incidence of 24.5 cases per 100,000 live births, and the incidence is markedly greater in premature live births (3,4). The major causes of SBS in children are necrotizing enterocolitis (NEC), midgut volvulus, gastroschisis, intestinal atresia, and extensive Hirschsprung disease (2,5).

The prognosis of paediatric IF has improved during the last decade (6–8), which has been associated with treatment by intestinal rehabilitation multidisciplinary teams (MDT) (9–12). Yet, children with IF may suffer from serious complications, such as catheter-related bloodstream infections (CRBSI), loss of venous access, small intestinal bacterial overgrowth (SIBO), and intestinal failure-associated liver disease (IFALD) (2,13). IFALD develops predominantly in premature neonates in whom liver immaturity, frequent sepsis and NEC, facilitate inflammation and severe damage to bile ducts and liver cells (2,14). IFALD can progress to end-stage liver disease and has been identified as a negative predictor for survival (15,16). Gestational age, diagnosis, residual small- and colon bowel length and remaining ileocaecal valve have been identified as positive predictors for enteral autonomy in paediatric IF (17–19).

The aims of this study were to evaluate the outcome and to identify predictors for survival and enteral autonomy in neonatal IF.

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METHODS

Study Population

A retrospective observational study in children treated for neonatal IF at the Uppsala University Children's Hospital, Sweden. Patients were identified in the electronic patient chart system. Inclusion criteria were birth between January 1995 and December 2016 with neonatal IF defined as a PN dependency for ≥60 consecutive days (19) and PN start before the age of 44 gestational weeks. Patients with pseudoobstruction and primary enteropathy were excluded. On the basis of the introduction of an intestinal rehabilitation MDT in 2009, the study population was divided into 2 time periods 1995 to 2008 (n = 39) and 2009 to 2016 (n = 66) (Table 1).

Management of Patients

We established an intestinal rehabilitation MDT including paediatric gastroenterologists, paediatric surgeons, clinical pharmacist, registered dietitians, and nutrition specialist nurses in 2009. Before 2009, neonates with IF were managed by the neonatologists and paediatric surgeons. The intestinal rehabilitation MDT was involved in neonates with suspected IF from early neonatal care with weekly rounds at the NICU/neonatal ward and by using video consultations after the child had been discharged for home parenteral nutrition (HPN). All children with chronic IF visited our centre for an annual follow-up.

Parenteral Nutrition

During 1995 to 2005, a standard PN with a 20% soybean-based intravenous lipid emulsion (ILE) (Intralipid) was used. Between 2006 and 2009, the routine use of individually tailor-made PN (iPN) for children with IF was introduced to meet the patient's specific needs. Lipids were reduced to 2 to 3 $g \cdot kg^{-1} \cdot day^{-1}$ and the ILE was a 50-50 combination of a 100% fish oil-based ILE (Omegaven) and an 80% olive oil and 20% soybean oil-based ILE (Clinoleic), as previously reported (20). In the case of progressive IFALD, a further lipid reduction to 1 $g \cdot kg^{-1} \cdot day^{-1}$ and Omegaven monotherapy was used until conjugated serum bilirubin was stable below 100 μmol/L.

For iPN, a 2-bag system was used with lipids and vitamins in 1, and all water solubles in the other infusion bag. We routinely kept the lipid emulsion infusion time 2 hours shorter, thereby the CVC system was rinsed from lipids daily. Cycling of PN started when the child tolerated disconnection from PN without hypoglycaemia.

All care-givers were trained for HPN by our specialist nutrition nurses. Our policy is to discharge when the child reaches full-term and is in a general stable condition.

In premature neonates, PN was initially administered via a 1 Fr or 2 Fr piccline (Vygon GmbH &Co. KG). Eventually, it was changed to a tunnelled central venous catheter (CVC) (Cook Medical Europe). Since 2012, we have routinely used prophylactic antimicrobial CVC locks with heparin-free taurolidine+citrate (TauroLock) flushed before infusion of PN. Aspiration from the CVC was not allowed except for blood cultures when sepsis was suspected.

Enteral Feeding

Early enteral feeding was promoted with human breast milk that was later partly or fully replaced with hydrolysed MCT formula (Pregestimil). Introduction of solids followed the national guidelines for healthy children. PN was weaned off gradually and stopped when the child was able to maintain adequate hydration and growth with enteral feeding alone.

TABLE 1. Descriptive statistics of the study population in 2 different time periods

Variable	1995–2008	2009–2016	*P*-value
Number of patients	39	66	
Females, n (%)	17 (43.6)	28 (42.4)	
Gestational age, weeks (range)	32.0 (22.0–42.0)	27.0 (22.0–41.0)	0.1318
Birth weight, grams (range)	1515.0 (511.0–3990.0)	887.0 (457.0–4855.0)	0.0647
Diagnosis; n (%)			0.6530
Necrotizing enterocolitis	21 (53.8)	43 (65.2)	
Intestinal atresia	7 (17.9)	5 (7.6)	
Volvulus	3 (7.7)	6 (9.1)	
Gastroschisis	3 (7.7)	5 (7.6)	
Hirschsprung disease	3 (7.7)	5 (7.6)	
Other diagnosis	2 (5.1)	2 (3.0)	
Small bowel length of expected for gestational age	57.9 (2.5–100.0)	77.2 (10.5–100.0)	0.0679
Patients with an intact ileocecal valve, n (%)	25 (64.1)	50 (75.8)	0.2040
Number of laparotomies	3.0 (1.0–9.0)	3.0 (1.0–7.0)	0.0322
Age at start of parenteral nutrition, days	2.0 (0.0–134.0)	1.5 (0.0–147.0)	0.1208
Aetiology of death; n (%)			
Sepsis	4 (10.2)	1 (1.5)	
IFALD	3 (7.7)	1 (1.5)	
Pulmonary hypertension	1 (2.6)		
Asphyxia	1 (2.6)		
Pneumonia	1 (2.6)		
Renal failure		1 (1.5)	

Continuous variables are summarized by median (range) and categorical variables with frequency (%). Proportions are tested using Fisher Exact test, continuous variables are tested using Mann-Whitney *U*-test. IFALD = intestinal failure associated liver disease.

Small Intestinal Bacterial Overgrowth Prophylaxis

Routine administration of enteral cyclic antibiotic prophylaxis was abandoned in 2014 following a study where we found that severe intestinal dysbiosis in children with IF was associated with prolonged PN dependency (21).

Surgical Procedures

Autologous intestinal reconstructive (AIR) surgery was performed in children with adaptation-associated bowel dilatation with SIBO resistant to medical therapy with broad-spectrum antibiotics in combination with inability to increase enteral intake (22–24).

Data Collection

The following data was collected from the medical and surgical records: sex, gestational age, birth weight, diagnosis, presence of the ileocecal valve (ICV), length of colon, number of laparotomies, AIR surgery, transplantation, duration of PN, number of replacements of CVC per patient, number of CRBSI, presence of IFALD, ages and growth parameters at latest follow-up and deaths. We calculated remaining small bowel length at the latest laparotomy at which bowel was resected in relation to the expected for gestational age according to Struijs et al (25). The duration of PN was from initiation of PN until the last follow-up, weaning off PN or death. IFALD was defined as cholestasis occurring in the setting of PN for more than 2 weeks, with other specific causes of liver disease excluded. Cholestasis was defined as an elevated conjugated serum bilirubin level >34.2 μmol/L (26). CRBSI was defined as a positive blood culture (1 sample from the CVC and the other from a peripheral vein) in combination with clinical infectious symptoms (27). The incidence of CRBSI was calculated from PN start to latest follow-up or death.

Statistical Analysis

Descriptive statistics are presented as median and range for continuous variables and as absolute and relative frequencies for categorical variables. Proportions were tested using Fisher Exact test, and continuous variables were tested using Mann-Whitney *U*-test.

Time to death and weaning off PN analysis were performed with Kaplan-Meier curves including log rank test, the starting point was start of PN. Gestational age, diagnosis, small bowel length, and presence of ICV were variables tested in the time to wean off PN analysis. Subjects were censored by death, or end of follow-up period. *P*-values in Kaplan-Meier curves were from the log-rank test.

Cox univariate and multivariate regression were used to identify predictors for survival and enteral autonomy presented as hazard ratio (HR) with 95% confidence interval. Possible predictors included: gestational age, sex, diagnosis, remaining ICV, residual small bowel- and colon length, and time-period. To check if the assumptions for the proportional hazard regression were met, the correlation between the Schoenfeld residuals and the log of time was calculated.

Difference in the number of sepsis episodes/1000 PN days between with and without taurolidine-citrate was tested with the nonparametric Mann-Whitney *U*-test. Log rank test was used to analyse mortality in children with IFALD compared with those with no IFALD.

All significance tests are 2-sided using a significance level of 5% to determine statistical significance. All analyses were performed using R version 3.6.0 (28).

Ethics

This study was approved by the Regional Ethical Review Board in Uppsala (Dnr 2017/543, 2017/543/1). The STROBE checklist for observational cohort studies was used.

RESULTS

Study Population

In total, 105 children with IF were included (Table 2). The majority were boys (57%). The median gestational age was 28 weeks (22–42), 52 (50%) were born extremely preterm (<28 gestational weeks), 32 (30%) were preterm, and 21 (20%) were full term. Median birth weight was 1088 g (457–4855). The dominating cause of IF was NEC in 64 neonates (61%) followed by intestinal atresia in 12 (11%), volvulus in 9 (8%), gastroschisis in 8 (8%), extensive Hirschsprung disease in 8 (8%), and 4 neonates had other diagnoses (4%) (Fig. 1). The patients underwent in median of 3 laparotomies (1–9) and in 96 neonates (91%) an intestinal discontinuity stoma was formed, most commonly an ileostomy (n = 71, 68%). The stoma was closed after 2 to 3 months depending on the condition of the child. The median percentage of age-adjusted expected small bowel length was 75% (2.5–100) and the ICV remained in 75 children (71%) (Table 2). More than 50% of colon remained in 90 children (86%). The median length of the remaining small bowel was 70 cm (4–269) and median gestational age 33 weeks (23–92) at the latest laparotomy with significant bowel resection.

Parenteral Nutrition

PN was started at a median age of 2 days (0–147). The median duration of PN was 196 days (60–3091) (Table 2). During

TABLE 2. Descriptive statistics of the study population

Number of patients	105
Females	45 (43)
Gestational age, weeks	28 (22–42)
Birth weight, grams	1088 (457–4855)
Prematurely born between 28 and 36 gestational weeks	32 (30)
Extreme prematurely born (<28 gestational weeks)	52 (50)
Small bowel length of expected, %	75 (2.5–100)
Patients with an intact ileocecal valve	75 (71)
Patients with >50% remaining colon	90 (86)
Number of laparotomies	3 (1–9)
Age at start with parenteral nutrition, days	2 (0–147)
Age at follow-up, years	8.2 (1.7–23.8)
Weight at follow-up, *z*-score	−2 (−4.5 to 3)
Height at follow-up, *z*-score	−1.5 (−4 to 2)
Duration of parenteral nutrition, days	196 (60–3091)
Maximum direct bilirubin, μmol/L	67.5 (1.7–650)
Patients with IFALD*	64 (65)
Numbers of CVC replacements/patient	1 (0–8)
Autologous intestinal reconstructive surgery	7 (7)
Intestinal transplantation	1 (1)
Patients weaned off parenteral nutrition	91 (87)
Patients alive	92 (88)

Continuous variables are summarized by median (range) and categorical variables with frequency (%). CVC= central venous catheter; IFALD = intestinal failure associated liver disease.

*n = 99, data missing in 6 patients.

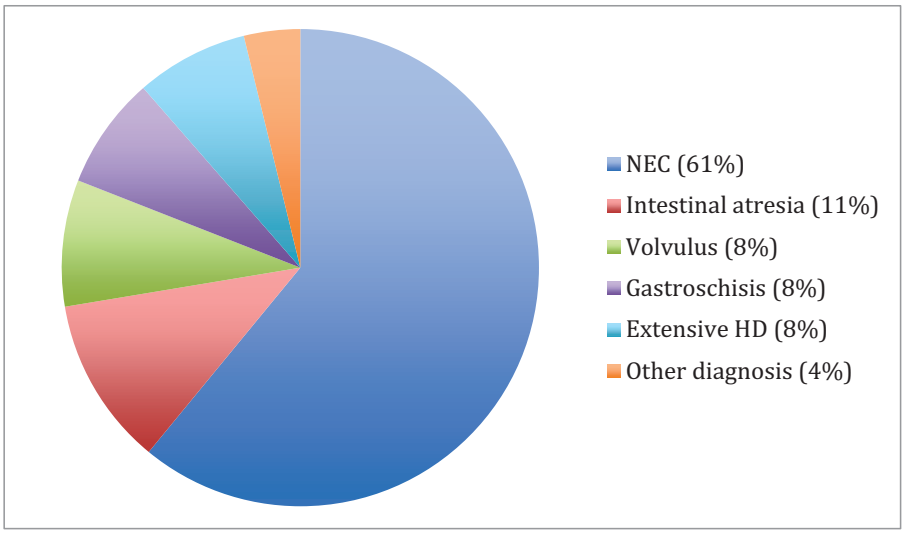

FIGURE 1. Proportions of the different diagnosis in the study group (n = 105). HD = Hirschsprung disease; NEC = necrotizing enterocolitis. Other diagnosis = diaphragmatic hernia, meconium ileus, mesenteric thrombosis and giant omphalocele.

2009 to 2016, median duration of PN was significantly increased to 244 days (60–3091) compared with 128 (61–1745) during 1995 to 2008 ($P = 0.0099$) (Supplemental Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B834*). The median follow-up time was 2.9 years (0.03–19.05). The median age at latest follow-up was 8.2 years (1.7–23.8), the median weight z-score was −2 SD and the median height *z*-score −1.5 SD according to the Swedish national growth charts (Table 2) (29).

Catheter-related Complications

The median numbers of CVC replacements per patient during the study period was 1 (0–8). The indications for CVC replacement were CRBSI with fungi, CRBSI refractory to antibiotic therapy, rupture of the CVC or insufficient length of the CVC after growth of the child.

The number of CRBSI/1000 PN days was significantly decreased in children treated with taurolidine+citrate locks compared with children without 0.77 and 5.37, respectively ($P = 0.002$).

Intestinal Failure-associated Liver Disease

Median maximum direct bilirubin was 67.5 μmol/L (1.7–650) during the study period and IFALD was present in 64 (65%) of the patients (Table 2). Mortality was higher in children with IFALD compared with those with no IFALD ($P = 0.0076$).

Surgical Management

AIR was performed in 7 children, 2 with longitudinal intestinal lengthening and tapering (22), and 5 with serial transverse enteroplasty as previously described (23,24). Four of them were weaned off from PN at the latest follow-up. One child with total intestinal Hirschsprung disease underwent a small bowel transplant at the age of 4 years and was 16 years old at the end of the study period. None of the patients had a liver transplant.

Survival

Overall survival was 88% in the study group and survival over time is demonstrated in Figure 2A. All deaths but 1 occurred during the child's first year of life. Nine deaths were related to IF. The causes of demise were sepsis in 5 children, IFALD in 4, pneumonia in 1, pulmonary hypertension in 1, asphyxia in 1 child and renal failure in 1. Five of the 13 deceased children were born extremely preterm. Children with a small bowel length of >50% of expected for age had a significantly higher survival probability than children with <25% small bowel ($P = 0.011$). Children born 2009 to 2016 with IF had an 84% lower risk to die than children born 1995 to 2008 ($P = 0.006$) (Supplemental Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/B834*). Survival was significantly increased for children born 2009 to 2016 compared with 1995 to 2008, 96% and 75%, respectively ($P = 0.0040$). (Supplemental Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/B834*). Gestational age, sex, diagnosis, presence of ICV, small bowel length of 25% to 50% of expected for age or remaining colon >50% were not found to be predictors of survival.

Enteral Autonomy

At the end of the study period, 91 patients had been weaned off from PN (87%) (Table 2).

Remaining ICV and an age-adjusted small bowel length of >25% were predictors for weaning off PN in the univariate Cox regression (Table 3) and in addition, remaining colon <50% in the multivariate analysis (Table 4). A child with IF with a small bowel length of >50% of expected had 5.23 times higher chance ($P < 0.001$) and children with a small bowel length of 25% to 50% of expected, had 3.49 times ($P = 0.004$) higher chance to wean off from PN compared with children with less than 25% of expected for gestational age. Gestational age, sex, or diagnosis were not predictors for weaning off PN.

Figure 2B displays the Kaplan-Meier curve for time to end of PN for the study population. Most events occurred during the first year. After 196 days, 50% of the patients had been weaned off from PN.

There was a significant difference in the probability to wean off PN for patients with a small bowel length of <25% and patients with >25% small bowel length of expected for gestational age ($P = 0.0002$) and for patients with present or absent ICV ($P = 0.0243$) (Fig. 2C and D). Patients with remaining ICV had

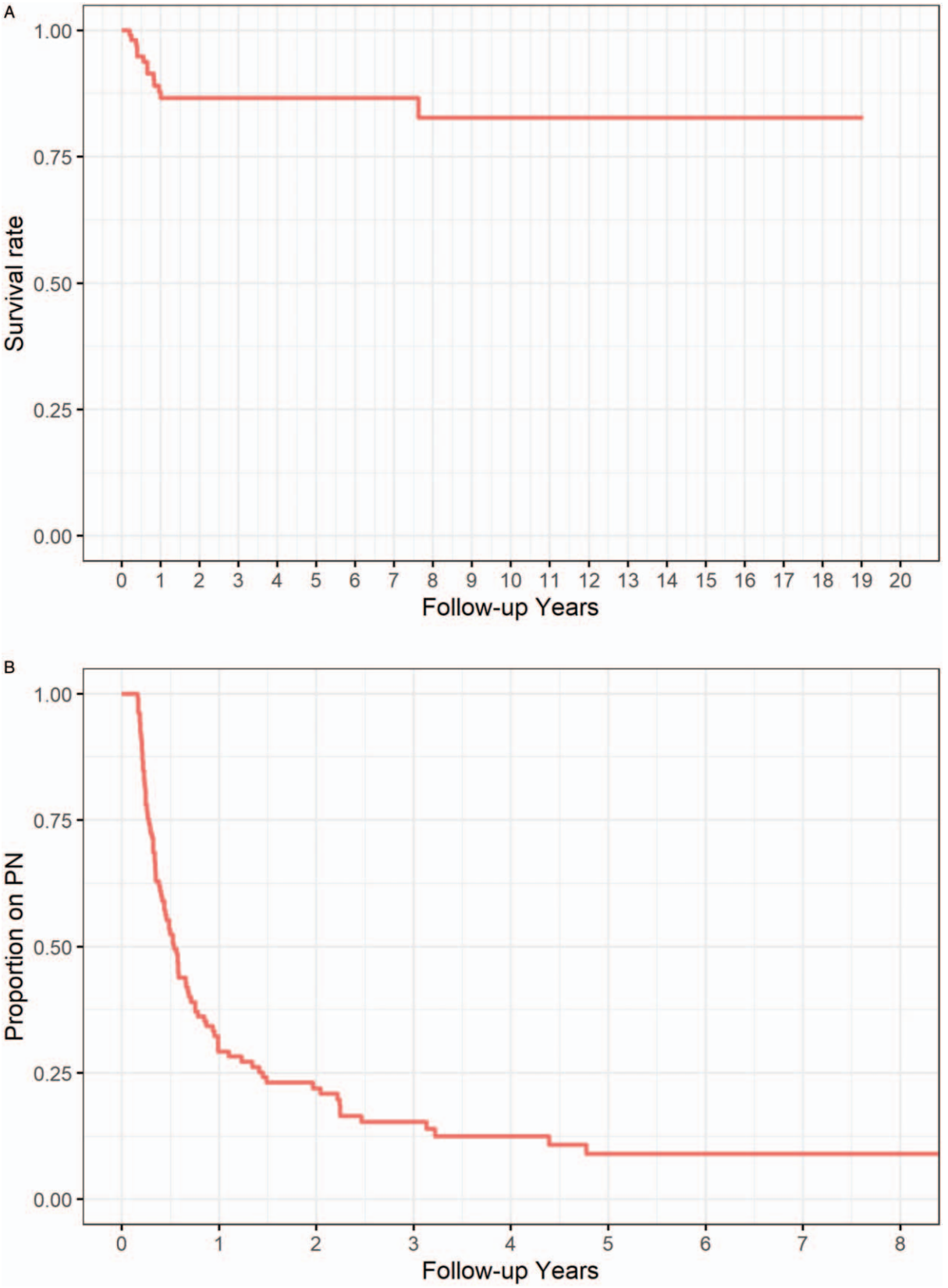

FIGURE 2. Kaplan-Meier curves for survival of the study population (A), for time to wean off from parenteral nutrition (PN) (B), for weaning off PN by small bowel length of expected for gestational age (C), and by remaining ICV (D). *P*-values for log rank test are shown. ICV = ileocoecal valve.

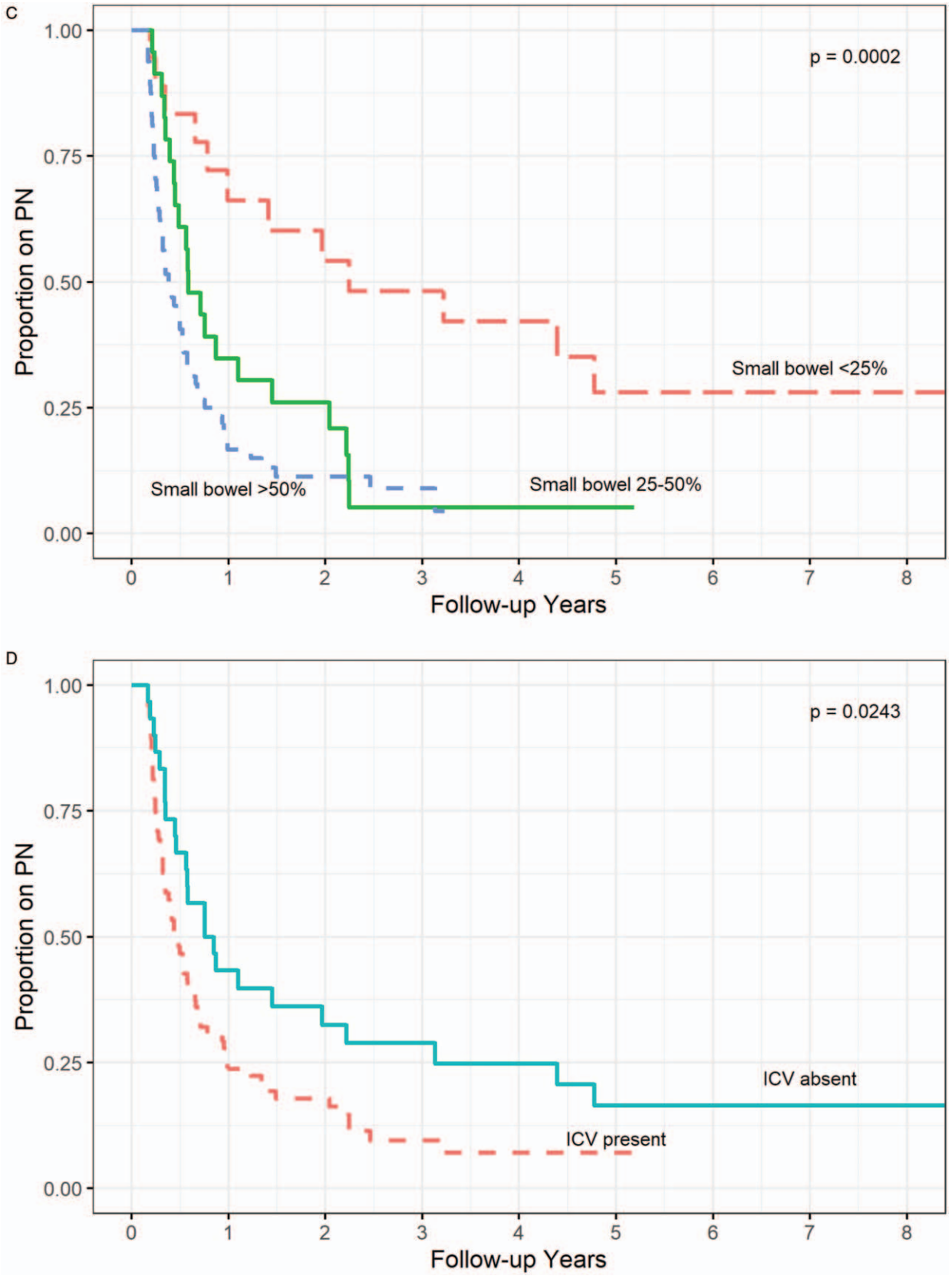

FIGURE 2. (*Continued*).

TABLE 3. Univariate Cox regression for weaning off parenteral nutrition

Variable	Hazard ratio	95% CI	*P*-value
Gestational age	0.99	(0.96–1.03)	0.772
Gender: male (ref: female)	1.42	(0.93–2.16)	0.101
Hirschsprung disease (ref: NEC)	0.84	(0.38–1.86)	0.671
Intestinal atresia (ref: NEC)	0.64	(0.34–1.23)	0.178
Other diagnosis (ref: NEC)	0.61	(0.35–1.06)	0.082
Remaining ileocecal valve: yes (ref: No)	1.72	(1.07–2.77)	0.026
Small bowel length of expected: 25% to 50% (ref: <25)	2.45	(1.18–5.11)	0.017
Small bowel length of expected: >50% (ref: <25)	3.71	(1.91–7.21)	<0.001
Remaining colon: >50% (ref: 50% or less)	1.02	(0.58–1.80)	0.944

CI = confidence interval; NEC = necrotizing enterocolitis.

a steeper curve during the first year. There was no significant difference in the probability of weaning off from PN between patients with gestational age more or less than 28 weeks or NEC compared with all other diagnoses combined.

DISCUSSION

In this study, we evaluated the outcome in a cohort of neonates with IF, all of whom started with PN before the age of 44 gestational weeks. Although these children were at high risk of developing IFALD, there was a high overall survival rate.

Our cohort differed from others as it included 80% preterm neonates whereof 50% were born extremely preterm. The median gestational age was lower (28 weeks) compared with 34 and 35 weeks in other studies (6,9,17,30). Moreover, there was a higher proportion of neonates with NEC (61%) compared with others ranging from 12% to 35% (7,10,30) probably explained by the lower gestational age in our cohort. The risk of NEC is inversely related to gestational age (31,32).

The median duration of PN was longer during 2009 to 2016, yet, there was no concomitant significant increase in the proportion of children who developed IFALD. On the other hand, the overall survival rate of children with IF increased significantly during this period. We speculate that a key to this was the major change in PN management with the routine use of individually tailor-made PN (iPN) containing a high proportion of fish oil ILE, that has proved effective in preventing reversing IFALD, and also allowing for a longer PN duration (20,33,34).

In the present study, the median number of replacements of CVC was low; we attribute this to successful HPN training. Loss of CVC access sites is a serious complication and an indication for intestinal transplantation. Careful handling of CVC was found to be of major importance for long-term transplant-free survival in patients with HPN (1).

CRBSI is associated with the development of IFALD, along with prematurity and NEC. The incidence of CRBSI decreased significantly after we introduced taurolidine+citrate locks with an incidence comparable with other recent studies (6,30,35).

The combination of prematurity and IF is a known risk factor for IFALD. It affects up to 85% of neonates who require long-term PN and signs of liver dysfunction may occur as early as 14 days after initiating PN in neonates (36). In our study, 65% of the patients were affected by IFALD and it was the cause of death in 4 children. In all the other children, IFALD was reversed.

The first national AIR surgery was performed in our unit. The indications for AIR was to improve motility by reducing the diameter of dilated intestinal loops, in order to increase enteral tolerance.

The overall survival rate of 88% in our study was higher than in a multicentre study reporting a survival rate of 75% (17), but in line with results from large centres reporting a survival rate between 89% and 92% (6,9,30). Furthermore, in the present study, survival was significantly improved in children born between 2009 and 2016 compared with 1995 and 2008. The high survival rate of 96% was achieved despite a very high proportion of extremely preterm children. Small bowel length <25% was a negative predictor of survival, probably related to limited tolerance for oral feeding, extended duration of PN, and a higher risk of sepsis and IFALD.

In this study, enteral autonomy was achieved in a higher proportion of patients (87%) than in previous studies that reported weaning from PN ranging between 43% and 67% of children with

TABLE 4. Multivariate Cox regression for weaning off parenteral nutrition

Variable	Hazard ratio	95% CI	*P*-value
Gestational age	1.03	(0.98–1.08)	0.324
Gender: male (ref: female)	1.22	(0.78–1.90)	0.382
Hirschsprungs disease (ref: NEC)	0.58	(0.22–1.54)	0.272
Intestinal atresia (ref: NEC)	1.20	(0.52–2.81)	0.668
Other diagnosis (ref: NEC)	0.67	(0.35–1.28)	0.227
Remaining ileocecal valve: yes (ref: No)	1.98	(0.98–3.99)	0.056
Small bowel length of expected: 25% to 50% (ref: <25)	3.49	(1.50–8.12)	0.004
Small bowel length of expected: >50% (ref: <25)	5.23	(2.29–11.91)	<0.001
Remaining colon: >50% (ref: 50% or less)	0.32	(0.14–0.76)	0.010

CI = confidence interval; NEC = necrotizing enterocolitis.

IF (6,9,17,18). This may be explained by the high proportion of premature neonates (80%) in our study. Premature neonates are known to have a great capacity to compensate for lost bowel length because of intestinal adaptation (37,38). Although most children were weaned off within their first year of age, weaning continued up to 5 years, as earlier reported (5,34).

Residual small bowel length and remaining ICV were positive predictors for weaning off PN, which was in agreement with previous studies (17,18). A recent meta-analysis, however, presented evidence that small bowel length but not the presence of ICV was related to enteral autonomy (39).

The favourable outcome in the present study was probably a combined effect of our intestinal rehabilitation MDT, the successful HPN training, fish-oil containing ILE, taurolidine+citrate locks, and improved neonatal care.

The strength of the present study is that, to our knowledge, this is the first report of early onset IF with half of the study population constituting extremely preterm neonates. Another strength is that a relatively high number of patients was included.

The limitations of the study are the retrospective design with the risk of missing some patients from the early days of the study period. Another limitation of the retrospective design is that the effects of several interventions cannot be fully attributed to the researched intervention, as during the study period more protocols changed than only the researched intervention.

CONCLUSIONS

Preterm neonates with IF at high risk of developing IF-associated morbidity showed a high overall survival rate. Small-bowel length and being born in 2009 to 2016 were predictors for survival and presence of ICV and small-bowel length were predictors for enteral autonomy. Most children with IF achieved enteral autonomy within their first year of life. We wish to share our findings to motivate further developments for the successful management of neonatal IF and to inform professionals who counsel care-givers of premature neonates with IF.

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