
Change of Outcomes in Pediatric Intestinal Failure: Use of Time-Series Analysis to Assess the Evolution of an Intestinal Rehabilitation Program



Carol Oliveira, MD, PhD, Nicole T de Silva, MSc, Sanja Stanojevic, PhD, Yaron Avitzur, MD, Ahmed M Bayoumi, MD, MSc, Wendy J Ungar, PhD, Jeffrey S Hoch, PhD, Paul W Wales, MD, MSc, FACS

- BACKGROUND:** The clinical picture of pediatric intestinal failure has changed over the past 15 years, while effectiveness evolving treatment options remains unclear. This study explored evolution in care and quantified independent effects of new treatment options.
- STUDY DESIGN:** Consecutive patients ($n = 196$) with neonatal or infantile intestinal failure, born between July 1996 and December 2011, were derived from an intestinal rehabilitation program (IRP) patient registry. Change over time was analyzed using multivariable Box-Jenkins method-based autoregressive integrative moving average models (ARIMA), robust linear regression, and nonparametric trend analysis. Four systematically introduced treatment options (IRP, serial transverse enteroplasty, omega-3 lipid emulsions, and ethanol locks) were evaluated. Analyses were adjusted for patient characteristics and disease severity. The primary outcome was disease-specific mortality from liver failure and sepsis. Secondary outcomes included parenteral nutrition weaning, transplantations, catheter complications, and liver disease.
- RESULTS:** Patient characteristics remained unchanged over time, except for decreasing small bowel length ($-0.5\%/quarter$; 95% CI $-0.85, -0.16$) and ICU admission time (-0.6 days/quarter; 95% CI $-1.03, -0.18$). Disease-specific mortality diminished significantly over time (-0.02 deaths/quarter; 95% CI $-0.03, -0.01$) by IRP and omega-3 lipids introduction (-0.6 deaths/quarter each, 95% CI $-1.23, -0.02$ and $-0.77, -0.45$, respectively). Serial transverse enteroplasty and ethanol locks had no significant impact. Parenteral nutrition weaning and transplantations remained unchanged, while catheter sepsis and complication rates decreased by 0.3 episodes/1,000 catheter-days each (95% CI $-0.43, -0.2$ and $-0.45, -0.24$, respectively).
- CONCLUSIONS:** Introduction of IRP and omega-3 lipids independently decreased disease-specific mortality. For the first time, time series analysis was applied to evaluate effectiveness of treatment options in intestinal rehabilitation. (*J Am Coll Surg* 2016;222:1180–1188. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)
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Pediatric intestinal failure (IF) is a devastating condition caused by the inability to absorb sufficient nutrients to grow and survive, either due to anatomic or functional loss of intestine.^{1,2} The course and outcome have changed

in the last 15 years, however, with the introduction of multidisciplinary intestinal rehabilitation programs (IRP), and new medical and surgical treatment options.³⁻⁶ Multidisciplinary IRPs have been shown to

Disclosure Information: Nothing to disclose.

Support: The Swiss National Science Foundation, The Walter and Gertrud Siegenthaler Foundation and The University of Zurich, Switzerland; and The Hospital for Sick Children, Toronto, Canada, have financially supported Dr Oliveira with research scholarships during conduct of this research.

Abstract presented at the annual meeting of the Canadian Association of Paediatric Surgeons, Charlottetown, PEI, Canada, September 2013.

Received December 5, 2015; Revised March 2, 2016; Accepted March 2, 2016.

From the Group for Improvement of Intestinal Function and Treatment Program (GIFT) (Oliveira, de Silva, Avitzur, Wales), the Divisions of

General and Thoracic Surgery (Oliveira, de Silva, Wales), Respiratory Medicine (Stanojevic), and Gastroenterology, Hepatology and Nutrition (Avitzur), and the Child Health Evaluative Sciences (CHES) Program (Oliveira, Stanojevic, Ungar, Wales), The Hospital for Sick Children; The Institute of Health Policy, Management and Evaluation (IHPE), University of Toronto (Oliveira, Stanojevic, Bayoumi, Ungar, Hoch, Wales); the Centre for Research on Inner City Health, Li Ka Shing Knowledge Institute and Division of General Internal Medicine (Bayoumi) and the Centre for Excellence in Economic Analysis Research (CLEAR) (Hoch), St Michael's Hospital, Toronto, Canada.

Correspondence address: Paul W Wales, MD, MSc, FACS, University of Toronto, Department of Surgery, Room 1526, 555 University Ave, Toronto, ON M5G 1X8, Canada. email: paul.wales@sickkids.ca

Abbreviations and Acronyms

ARIMA	= autoregressive integrative moving average models
CRBSI	= catheter-related bloodstream infections
CVC	= central venous catheter
IF	= intestinal failure
IQR	= interquartile range
IRP	= intestinal rehabilitation program
PN	= parenteral nutrition

improve clinical outcomes by integrating expert management, improving communication, and enhancing continuity and comprehensiveness of care.⁶

As previously reported, the early effects of IRP included significantly reduced mortality from liver failure, septic episodes, critical care unit admission length, and an increased rate of transplantation.³ A systematic literature review reported in 2012 that with increased experience and maturation of the IRP, novel medical and surgical treatment options were implemented that further improved the clinical outcomes of pediatric IF patients.⁶ Due to small sample sizes of IF studies, it was difficult to compare adjusted effectiveness of individual treatment options, and no conclusions on causal inference could be made.⁶ Time series analysis represents a valuable methodologic option that permits longitudinal analysis of change over time, overcoming previously encountered methodologic limitations related to small samples. It includes time as a factor in the analysis, accounts for delay of exposure and effect, and allows confounder adjustment in multivariate models. Although this statistical method has been derived from economics, it has been shown to be valid and useful in the medical setting.^{7,8}

The objective of the study was to evaluate changes in clinical outcomes of pediatric IF over time, and to identify and quantify the independent effect of newly introduced treatment options using novel methodology to overcome limitations experienced in the literature.

METHODS**Study design**

A retrospective analysis of prospectively collected, observational data from a single study site was performed. Ethics board approval was obtained from The Hospital for Sick Children and the University of Toronto, in agreement with which no consents were obtained.

Study sample

Study subjects were drawn from an institutional IRP database. The criteria for referral of new patients to the IRP are primarily functional, with dependence on parenteral

nutrition (PN) for greater than 42 days after bowel resection or injury.¹ For patients with less than 25% of expected age-specific small bowel length, referral is immediate. Patients suffering from primary dysmotility or mucosal enteropathy were excluded from this study. Patients with abdominal wall defects were permitted.

Data from patients diagnosed with IF between 0 and 365 days of age were derived from a prospective IRP patient registry and were included in the analysis. Data from patients managed at our institution before IRP inception were identified using an ICU patient database and added to the IRP registry retrospectively. The final database records extended from July 1996 to December 2011. Patients were categorized to quarterly time periods based on their date of birth. A fraction of these patients have been described in earlier studies.^{3,9}

Data collection

A single, experienced data coordinator performed data extraction and input. Any time interval was calculated using statistical software (Stata 11.2, Microsoft Access), and dates were extracted from patient records. Time 0 was defined as the date of primary surgery. Follow-up was continued until patients were discharged from IRP care, died, or until the study ended (February 10, 2013). Missing observations were missing at random and imputed based on time and whether treatment options were available using multivariate regression models (the first quarter of 1997, the third quarter of 1998, the first quarter of 2001, the third quarter of 2001 to the third quarter of 2002; representing 6.75% of the dataset, single and multiple imputation using 50 imputations, based on Poisson and linear regression).¹⁰⁻¹³ All variables were missing similarly frequently; no data were missing on treatment availability.

Data on patient characteristics, anatomy, etiology, surgical interventions, medical treatment, and outcomes related to nutrition, sepsis, IF-associated liver disease, transplantation and mortality were measured and analyzed. The primary outcome was disease-specific mortality from liver failure and sepsis. Secondary outcomes included parenteral nutrition weaning, transplantations, catheter complications, and liver disease. Age-adjusted expected small bowel length was calculated using normal values published by Struijs and colleagues.¹⁴ Intestinal failure secondary to necrotizing enterocolitis, perforation, or abdominal wall defect was regarded as inflammatory etiology. Clinical outcomes were defined as in previous studies by our group: cholestasis as conjugated bilirubin levels of $>50 \mu\text{mol/L}$ for at least 2 weeks without association with sepsis; advanced liver disease as conjugated bilirubin of $>100 \mu\text{mol/L}$ for at least 2 weeks and not associated with sepsis;

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