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The Development of the International Intestinal Failure Registry and an Overview of its Results

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Abstract

Pediatric intestinal failure (IF) is a rare disease that represents an evolving field in pediatric gastroenterology and surgery. With only a limited number of multicenter collaborations, much of the research in pediatric IF is often confined to single-center reports with small sample sizes. This has resulted in challenges in data interpretation and left many knowledge gaps unanswered. Over the past two decades, five large multicenter collaborations, primarily from North America and Europe, have published their findings. Apart from one ongoing European adult and pediatric registry, these relatively large-scale efforts have been concluded.

In 2018, the International Intestinal Failure Registry (IIFR) was initiated by the International Intestinal Rehabilitation and Transplant Association to continue these efforts and answer some of the knowledge gaps in pediatric IF. The IIFR goals are to prospectively assess the natural history of children diagnosed with IF and creating a worldwide platform to facilitate benchmarking and evidence-based interventions in pediatric IF. A pilot phase involving 204 enrolled patients was initiated in 2018 to assess the feasibility of an international IF registry and refine the study protocol and data collection forms. Following the successful completion of this phase, the current phase of the IIFR was launched in 2021. As of May 2023, the registry includes 362 prospectively followed children from 26 centers worldwide. This review provides an overview of the development, structure, and challenges of the IIFR, as well as the main findings from both the pilot and current phase.

Keywords

- intestinal failure
- registry
- children
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- structure

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Introduction

Pediatric intestinal failure (IF), as a distinct and independent field within pediatric gastroenterology, has evolved significantly over the past 20 years. The transition of home parenteral nutrition (HPN) programs into multidisciplinary intestinal rehabilitation programs (IRP) marked a fundamental shift in approach. These programs have adopted a protocolized and structured treatment strategy with the primary goal of achieving intestinal adaptation and weaning off PN.[1] Alongside this structural transformation, there have been clinical and therapeutic advancements, including improved central venous catheter (CVC) care, better infection control, reduced frequency and severity of IF-associated liver disease (IFALD), and the introduction of new autologous intestinal reconstruction surgeries. These developments have resulted in improved patient survival and reduced morbidity. In addition, research in IF has benefited from recent publications that have defined disease states and complications. These initiatives from international professional organizations are paving the way for the development of standardized trials and study definitions.[1–4]

However, further progress in clinical and translational research is limited by the rarity of pediatric IF. In Europe, estimates of disease prevalence reveal rates ranging from 3.2 to 66 individuals (children and adults) on HPN per million population,[5–7] whereas in the United States, the figure is approximately 79 individuals (children and adults) on HPN per million population.[8]

In 2018, the International Intestinal Failure Registry (IIFR) was established to overcome this challenge through multicenter collaboration aiming to promote clinical research in pediatric IF. This review describes previous multicenter research efforts in pediatric IF, the structure and development of the registry, and the results from the 2023 analysis of registry data.

Previous Multicenter Collaborations

A limited number of national or international multicenter collaborations aimed at studying pediatric IF have published their findings over the last two decades (►**Table 1**). Although most were short lived or established a priori with a limited research aim, the data obtained were valuable and provided important insights into the outcome, complications, disease course, and treatment of pediatric IF.

The Pediatric Intestinal Failure Consortium (PIFCon) was the first multicenter collaboration to study the natural history and disease progression in children with IF.[9] PIFCon enrolled 272 infants from 14 leading North American IRPs. Children were diagnosed with IF predominantly between 2000 and 2004. Patients were followed for at least 2 years after their diagnosis. Data were collected retrospectively, and the consortium ceased data collection after this period. The aggregate data showed a cumulative incidence for enteral autonomy, death, and intestine transplantation (IT) of 47, 27, and 26%, respectively, a novelty at the time. In addition, the group have reported on IF-related complications and predictors of enteral autonomy.[9–12]

A decade later, a multicenter collaboration of six large IRPs (five of which are also IT centers) from North America, United Kingdom, and New Zealand was created. The study cohort included 443 children diagnosed between 2010 and 2015 and follow-up was for a minimum of 1 year after IF diagnosis. Data were collected retrospectively and used for analysis of IF natural course and outcomes, risk analysis and prediction of enteral autonomy, and validation of the Toronto listing criteria for pediatric IT.[13–15] Overall, showing improved outcomes a decade after the PIFCon report (►**Table 1**) and a larger cohort of children requiring long-term PN (19% of patients).

A pharma-driven multicenter collaboration was initiated in 2013 to study the effect of Teduglutide in children with IF. This was an open-label study of 59 children with short bowel syndrome (SBS)–IF from North America and Europe.[16] Data were collected prospectively, and this collaboration was solely focused on the safety and efficacy of Teduglutide.[16–18]

Two registries supported by the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Parenteral and Enteral Nutrition (ESPEN) have enrolled adults and to a lower extend children, into their respective registries. The Sustain registry was established by ASPEN and enrolled patients prospectively between 2011 and the end of January 2015.[19,20] A total of 1,251 patients were enrolled, 187 of whom were children. Patients had either long-standing IF (> 90 days of home PN) or were newly diagnosed. Specifically to children, the registry reported patient demographics, nutrition therapy, medication use, and central line–associated blood stream infection (CLABSI) rates. The European counterpart to the Sustain registry was established by ESPEN in 2015. The HPN for chronic IF database enrolls adult and children with benign and malignant IF. Enrollment for adults was initiated on March 1, 2015, and for children in 2016. Once a patient is enrolled, data are prospectively updated on an annual basis. Enrollment is ongoing and new patients are entered into the registry. As per the last database publication in 2023, a total of 4,680 patients from 68 centers, mainly in Europe, were enrolled, 558 of them are children.[21,22] Active research areas for adults include HPN composition, classification of intravenous supplementation for chronic IF, coronavirus disease effect and overall patient outcome.[23,24] One pediatric focused analysis identified higher HPN needs in children with motility and mucosal disorders as well as in children with low-growth z-scores.[21]

The valuable data and observations derived from these multicenter collaborations have demonstrated the importance of international collaborations in the study of this rare condition. The reports also demonstrated the heterogeneity in inclusion criteria and definitions in times with no consensus definitions. The IIFR was established to bridge many remaining knowledge gaps and continue multicenter research efforts in a contemporary cohort of children with IF.

Knowledge Gaps and Challenges in Pediatric Intestinal Failure

Research progress and knowledge translation in pediatric IF face challenges that extend beyond the rarity of the disease and

Table 1 Multicenter collaborations in pediatric intestinal failure

Collaboration	Patients	Research area	Main findings
PIFCon—14 North American centers	272 children diagnosed 2000–2005	Disease course and outcome; race disparities; predictors of EA; IFALD	• Cumulative incidence for enteral autonomy 47%, death 27%, and IT 26% • Higher probability of death (0.4 vs. 0.16) and lower probability of IT (0.07 vs. 0.31) in non-White population • EA is associated with NEC, care at a non-IT center, longer residual SB and intact ICV • C.bil > 2 mg/dL at baseline is associated with higher mortality and with lower EA
6 North American, UK, and New Zealand centers	443 children diagnosed 2010–2015	Disease course and outcome; validation of IT listing criteria; predictors and probability of EA	• Cumulative incidence for enteral autonomy 53%, death 10%, and transplantation 17% • C.Bil ≥ 75 mmol/L, ≥ 2 ICU admissions, and loss of ≥ 3 CVC sites are validated pediatric listing criteria for IT • Rates of EA higher in residual SB and/or colon length > 50%; EA is associated with longer residual SB and colon, presence of ICV and treatment in low-volume IT center
Teduglutide clinical trial; 24 North American and European centers	59 children enrolled 2013–2017 (12 and 24-wk studies)	Safety and efficacy of Teduglutide	Teduglutide was well tolerated and associated with a reduction in PS at 12 and 24 wk of follow-up (69% of children experienced at 24 wk a ≥ 20% reduction of PS with Teduglutide dose 0.05 mg/kg)
Sustain (ASPEN)—29 adult and pediatric U.S. centers	187 children (15% of the whole cohort), enrolled 2011–2015	Demographics, baseline characteristics; CLABSI	• Most of the children were with SBS. Tunneled catheter in 72% of them, 58% received EN, 78% used GI medications, and 34% ethanol lock • Higher CLABSI rate in children vs. adults (1.17 vs. 0.35 episodes per 1,000 PN days)
HPN for chronic IF database (ESPEN)—68 adult and pediatric European centers	558 children (12% of the whole cohort), enrolled since 2016	Factors associated with nutritional status and IVS	IVS is associated with chronic IF mechanism and with nutritional status

Abbreviations: C.Bil, conjugated bilirubin, CLABSI, central line associated blood stream infection, CVC, central venous catheter, EA, enteral autonomy, EN, enteral nutrition, GI, gastrointestinal; HPN, home parenteral nutrition, ICU, intensive care unit, ICV, ileocecal valve, IF, intestinal failure, IT, intestine transplantation, IVS, intravenous supplementation, PS, parenteral support, PN, parenteral nutrition, pt, patients; SBS, short bowel syndrome.

issues related to sample size. In many cases, treatment approaches are not evidence based and often rely on low-grade evidence. Instead, these treatment approaches, whether they are nutritional, medical, or surgical, have frequently evolved based on the experiences of individual centers, which has led to large variations in care practices between centers, countries, and continents. Moreover, the rapid changes in the field in terms of patient outcomes and therapeutic approaches have rendered some previous reports obsolete and less relevant to the current reality of IF. The ability to generalize and compare findings from single-center studies was also limited by the inconsistent use of definitions for common states such as IF, SBS, IFALD, CLABSI, enteral autonomy, and others. The recent publications of formal definitions for some of these states are valuable contribution to shaping future research agendas and homogenous reporting of outcomes (►**Table 2**).[1–4] Lastly, only a small number of groups integrate basic or translational research in their work. This gap hinders the understanding of common pathological processes observed in IF and limits the development of therapies and interventions aimed at restoring and correcting abnormal pathophysiology.

An international registry can overcome and improve many of these knowledge gaps and enhance the understanding of pediatric IF through the availability of a large, high-quality, contemporary database extending beyond single-center experiences. Such dataset can provide the proper power for reliable statistical analysis, serve as a platform for the identification of evidence-based interventions, and compare the efficacy of various treatments across continents, countries, and specific centers of excellence. In addition, an international platform that brings many researchers together can support the networking and development of research collaborations in basic or translational research. These potential benefits of an international registry were at the core of the decision to establish the IIFR.

Table 2 Accepted definitions in pediatric intestinal failure

Term	Organization and year	Definition
Pediatric intestinal failure	NASPGHAN 2017	The need for PN for > 60 days due to intestinal disease, dysfunction, or resection
Pediatric intestinal failure	ASPEN 2021	The reduction of functional intestinal mass below that which can sustain life, resulting in dependence on supplemental parenteral support for a minimum of 60 d within a 74 consecutive day interval
Short bowel syndrome	NASPGHAN 2017	The need for PN for > 60 d after intestinal resection or a bowel length of < 25% of expected
Intestinal Rehabilitation Program	ASPEN 2021	An interdisciplinary, collaborative patient care paradigm that serves to coordinate care for children with intestinal failure through comprehensive management of their specialized nutrition and corollary needs, attention to and support for associated chronic comorbidities, and evaluation and treatment of acute complications
Intestinal Rehabilitation Program-Structure	NASPGHAN 2017	At minimum staffing for an intestinal rehabilitation program includes a gastroenterologist, surgeon, dietitian (or registered dietitian–nutritionist), and a nurse. Close collaboration with neonatologists is strongly recommended. The presence of other specialists may be helpful: social workers, child psychologists, occupational therapists/physical therapists, speech/feeding therapists, interventional radiologists, and child life specialists
Enteral Autonomy	ASPEN 2021	The maintenance of normal growth and hydration status by means of enteral support without the use of parenteral support for a period of > 3 consecutive months
Intestinal failure associated liver disease (IFALD)	ESPGHAN 2015	Hepatobiliary dysfunction as a consequence of medical and surgical management strategies for intestinal failure, which can variably progress to end-stage liver disease, or can be stabilized or reversed with promotion of intestinal adaptation
Intestinal failure associated liver disease (IFALD)	ASPEN 2021	IFALD describes liver injury, as manifested by cholestasis, steatosis, and fibrosis, in patients with intestinal failure that is independent of, or in addition to, other potential etiologies. The development of IFALD is multifactorial, typically as a consequence of metabolic abnormalities in intestinal failure and the medical and surgical management strategies of intestinal failure themselves. It can be stabilized or reversed with appropriate early modification of management strategies and promotion of intestinal adaptation, or it can progress to hepatic dysfunction and end-stage liver disease

Abbreviations: ASPEN, American Society for Parenteral and Enteral Nutrition; ESPGHAN, European Society of Pediatric Gastroenterology Hepatology and Nutrition; NASPGHAN, North American Society of Pediatric Gastroenterology Hepatology and Nutrition.

Development of the International Intestinal Failure Registry

The IIFR was established in 2018 by the International Intestinal Rehabilitation and Transplant Association (IIRTA), an organization with an experience of over three decades in managing the Intestinal Transplant Registry.[25,26] The registry was designed with the intention of achieving three goals:

- Creation of a large, international database of pediatric IF to provide information on the worldwide trends and outcomes beyond single center experiences.
- Creation of benchmarking and learning networks in pediatric IF.
- Identification of favorable interventions and treatments to inform on best practices and evidence-based treatment approaches.

To achieve these goals and create a robust, high-quality, sustainable database, it was decided to gradually develop the IIFR, first with a pilot phase and only after its completion and review of the findings to launch the IIFR in its current form.

Pilot Phase

The pilot phase was launched in July 2018 after the completion of the registry protocol and data collection forms. The goal of the pilot phase was to assess the feasibility of an international IF registry and refine the study protocol and data collection forms as a mean to streamline the launch of the IIFR worldwide.

The pilot phase was designed as a 2-year project. Children (< 18 years of age) diagnosed with IF (need for PN for more than 60 days) between 2017 and 2018 were eligible for enrollment. Data were collected retrospectively at the enrollment visit (2 months after IF onset, defined as date of total parenteral nutrition [TPN] initiation) and at the 6- and 12-month follow-up visits. All patients were followed at least until the 12-month visit, IT/isolated liver transplantation or death, whichever came first. Each participating center obtained ethics committee approval based on the local regulations in their country and institution. The IIFR follows Health Insurance Portability and Accountability Act guidelines, and an informed consent template was provided with the study protocol.

The design of the data collection forms aimed to strike a balance between the relevance and importance of the specific data points selected, the volume of data to be collected, and the associated workload and burden. This was done while considering the voluntary nature of participation in the registry. The selected data points focused on the following aspects of IF: patient demographics, surgical history and anatomy, nutritional data, mode of delivery and amount of PN and enteral nutrition, medications, IF-related complications (e.g., IFALD, CVC thrombosis, CLABSI, etc.), functional status, and overall outcome. The data collection forms were based on Research Electronic Data Capture (REDCap), a secure web-based online questionnaire and database and were completed online.

Participation in the IIFR was restricted to IRPs that met the North American Society of Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) definition for an IRP.[1] The IIFR aims to describe the outcomes of contemporary cohorts of patients in programs that follow current recommended standards in the field. Therefore, the NASPGHAN IRP criteria were chosen as the benchmark. Specifically for the pilot phase, only IRPs that consistently enrolled more than 10 new patients per year were invited to participate. This approach allowed us to rapidly gather data from at least 200 patients.

Eleven IRPs—from the United States, Canada, Argentina, United Kingdom, Spain, and New Zealand—recruited 204 patients, and data for analysis was available for 200 patients. Most patients (85%) had been diagnosed with IF before 1 year of age. SBS was the most common diagnosis (78%) with a predicted percentage remaining small bowel length for weight of 50.5% (interquartile range [IQR]: 29–78%). Over the study period, 5.4% of patients were listed for IT, 0.5% underwent IT, and 5.5% died mainly due to respiratory failure or sepsis. Of the children alive and not transplanted at 1 year after their IF diagnosis, 46.7% achieved enteral autonomy. A sub-analysis of risk factors for achieving enteral autonomy at 1 year after diagnosis showed that the presence of an ostomy was associated with an increased time required to attain enteral autonomy, whereas a greater percentage of remaining bowel was associated with shorter time to achieve enteral autonomy.[27] Health care utilization was substantial, with a median of 101.5 (IQR: 14–174) days of hospitalization and seven clinic visits (IQR: 3–12) within the first year. The most prevalent complication during the 1-year follow-up was CLABSI (43%), followed by CVC thrombosis (13.5%).

Upon the conclusion of the pilot phase, a group of IIFR representatives and the data management team conducted a quality assurance process in addition to data analysis. The group reviewed all data points and their completion rates. Fields with completion rate below 50% were either removed or, if deemed important, retained with revisions to the wording of the question on the data collection form. In addition, the study protocol included multiple definitions of IF-associated complications and disease states to ensure consistent completion of the study questionnaire by future centers. Any ambiguous or unclear definitions were revised and updated. The duration required for data entry per visit was assessed and estimated to be about 30 minutes for enrollment visits and around 15 to 20 minutes, for follow-up visits. Subsequent to the pilot phase, a new version of the study protocol and data collection forms was created to support the launch of the full and current phase of the IIFR.

Structure and Governance

The IIFR was initiated and is supported by the IIRTA council. An IIFR subcommittee, chaired by the IIFR director, reports to the IIRTA scientific committee. Members of the committee include the IIFR director, data manager, coordinator, and international experts in pediatric IF (►Fig. 1). The subcommittee developed and routinely updates the IIFR protocol and data collection forms, provides scientific oversight, reviews research proposals, advises on administrative and scientific management, and determines the research directions.

Data are collected through the REDCap research electronic data capture tool, allowing for a simple, secure, and reliable web-based data entry that can be done prospectively during or after a patient visit to the clinic. REDCap can also serve as a single-center electronic database for each participating center through a download of the center's reported data. This can be initiated by the participating center at any time and does not allow download of data from other centers. Over time, the captured data can serve as a valuable local tool for each center to enhance patient care via data-driven decisions. All PIs and participating centers are encouraged to initiate research queries using the IIFR database. Proposals are reviewed by the IIFR subcommittee, and if approved, the requested data are provided in kind. Research proposals are selected based on their novelty, research question and hypothesis, methodology, and feasibility.

The IIFR provides an annual report with relevant information to each participating center, which can serve to assess their outcomes against the registry average (►Fig. 2). The web-based report includes both center-specific and IIFR-aggregated data on the number of patients enrolled and their demographics, patient outcome, common complications, and functional data, as well as quality assurance data where fields with less than 80 and 50% completion rate are reported (the IIFR defines the satisfactory completion rate for a data point as $>80\%$ completion rate).

Funding is an integral part of any large-scale registry and is needed to support the daily operations such as administrative and legal support, research coordinator salary, and funding for data management and analysis. The pilot phase of the IIFR was supported in kind by the Terasaki Research Institute, whereas the first four years of the full phase are funded by a nonrestricted grant from Takeda Ltd and the Lucile Packard Children's Hospital, Stanford, California, United States. Other future funding opportunities can include grant support, collaboration with other organizations, and/or through nonrestricted grant support by pharmaceutical companies and medical institutions. Collaboration and endorsement by other organizations such as ASPEN and NASPGHAN that provided their endorsement of the IIFR further support the aim of the registry to reflect the current worldwide trends in IF and avoid duplication of research

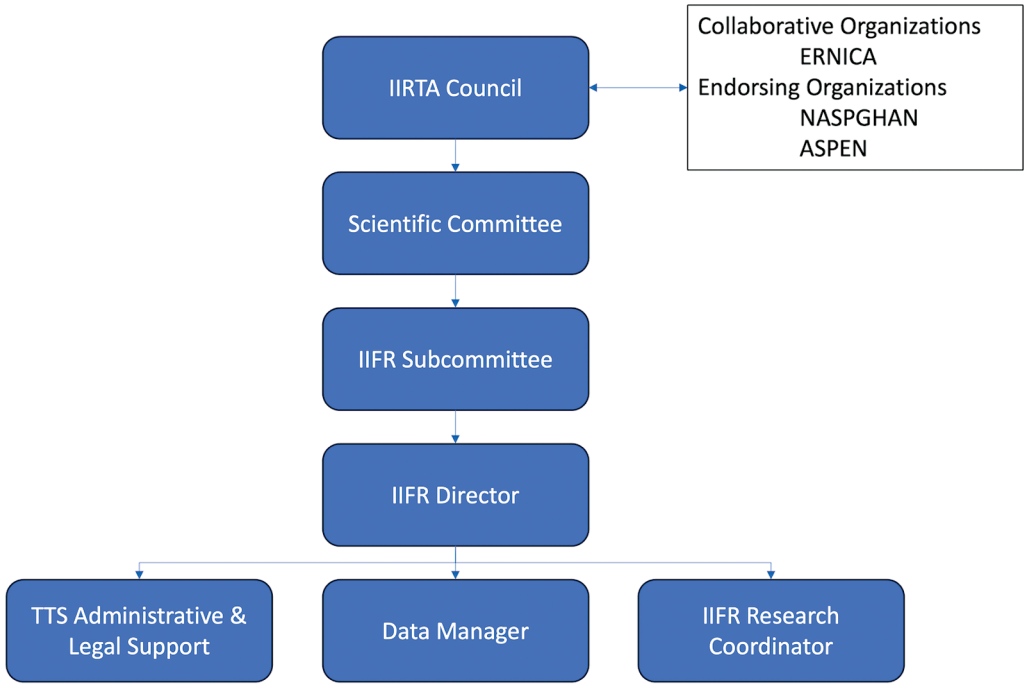

Fig. 1 The administrative and governance structure of the International Intestinal Failure Registry. ASPEN, American Society for Parenteral and Enteral Nutrition; ERNICA, European Reference Network for rare Inherited and Congenital Anomalies; IIRTA, International Intestinal Rehabilitation and Transplant Association; NASPGHAN, North American Society of Pediatric Gastroenterology Hepatology and Nutrition; TTS, The Transplantation Society.

efforts across the world. A unique collaborative model, where local regional efforts to enhance the study of pediatric IF can be achieved through the IIFR, was created with The European Reference Network for rare Inherited and Congenital Anomalies (ERNICA).[28] ERNICA seeks to concentrate knowledge and resources of rare and/or complex diseases across Europe, one of which is pediatric IF. The ERNICA centers enter data into the IIFR, and data analysis and research activity specific to ERNICA centers is supported by the registry. This model can serve as a collaborative model for other organizations within the IIFR or similar registries.

Registry sustainability and ongoing data entry by participating centers is a major challenge for any scientific registry. To support and encourage center involvement and the IIFR sustainability over time, a clear added value is needed for the site primary investigators and their teams. Few registry-initiated actions, some of which have been mentioned above, provide this added value. The annual center report and the opportunity to use REDCap as a center's own electronic database provide a unique opportunity for centers without these resources to review their own data and outcomes and revise their treatment approach based on their own collected data. Primary investigators and their teams can initiate research queries and projects through the IIFR or be part of IIFR publications based on their academic contribution to a specific project. Data are provided in kind by the IIFR, and the research team conducts analyses. This model provides ample opportunities for participants to enhance their academic career and their contribution to the IF literature. Lastly, a small monetary support is currently provided to large volume centers (> 10 patients) to support their time and efforts in data entry.

Current Phase and Initial Results

The full and current phase of the registry was launched in January 2021. In this phase, previous pilot phase centers as well as new centers enroll patients into the registry. Only prospective data collection is allowed, ensuring entry of high-quality and reliable data. IRPs from around the world are invited to join the IIFR with no limitation on the number of new patients that can be enrolled annually. As in the pilot phase, programs have to meet the NASPGHAN definition for IRP and its minimal staffing (gastroenterologist, surgeon, nurse, and a dietician).[1] Data are collected via REDCap at a patient's enrollment visit (2 months after diagnosis of IF), at the 6- and 12-month visits, and then annually. Follow-up continues until 1 year after the achievement of enteral autonomy, age 18, death, transplant (if IT is performed the patient is transferred to the IIRTA intestine transplantation registry) or loss of follow-up. A detailed IIFR study protocol was developed, including a detailed study design, the allowed time frame to add data for each visit, clear definitions for IF states and complications, as well as privacy and IIFR management aspects. Ethics Committee approval and Data Transfer Agreements are managed by each site as per local regulations and signed with the IIRTA.

Demographics

A total of 362 children with IF (53% males) from 26 centers around the world were recruited to the IIFR until May 2023. The median follow-up duration for the whole cohort was 18 months (IQR: 9.1–32.1) and the median age at the last follow-up was 1.84 years (IQR: 1.0–3.9).

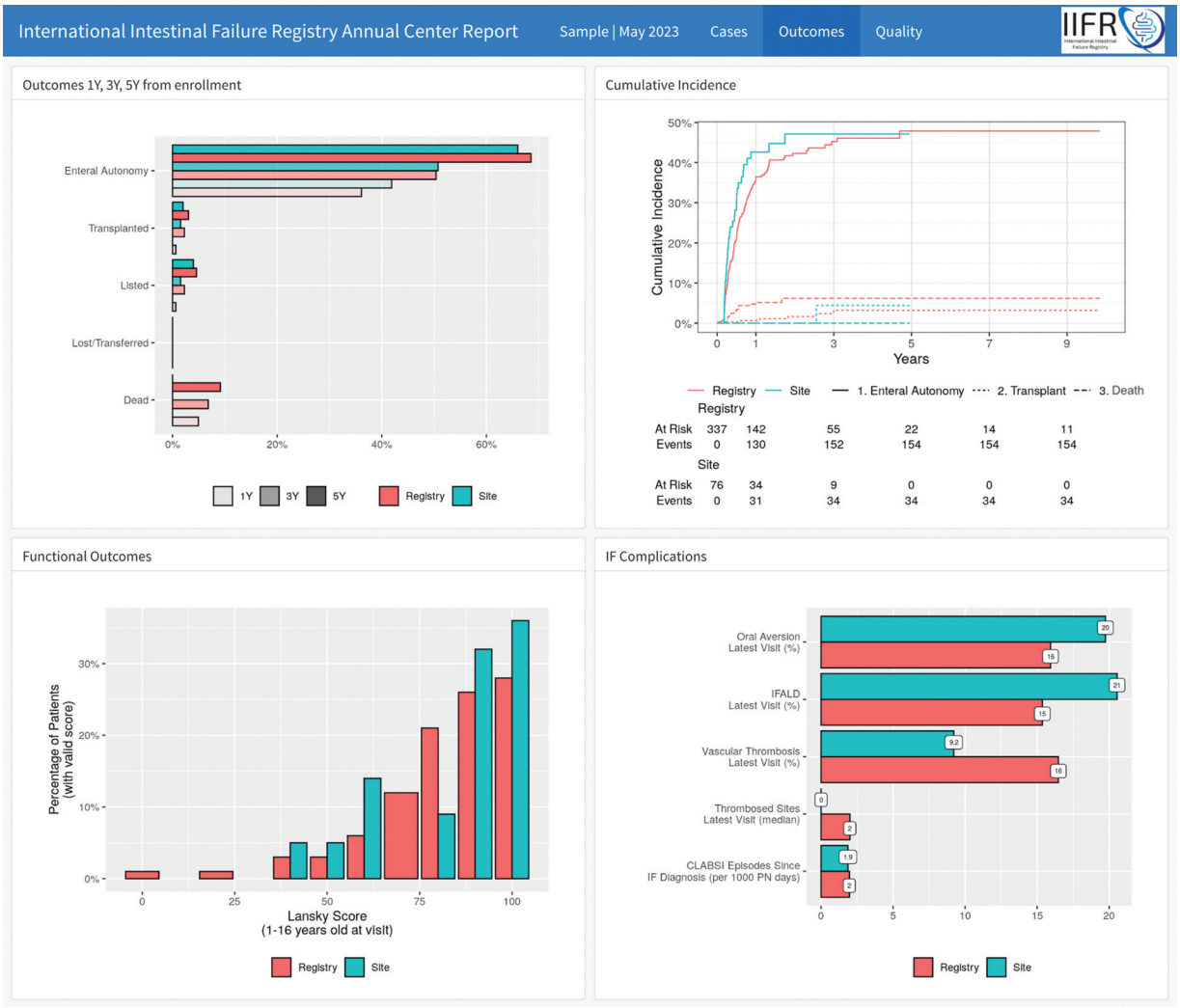

Fig. 2 IIFR annual center report—patient outcome. A template of an IIFR annual center report on patient outcome. Center data (*green*) are plotted against the IIFR data (*orange*). The full center report also includes patient demographics and quality assurance data. IIFR, International Intestinal Failure Registry.

The median age at IF diagnosis was 0.3 months (IQR: 0–2.3), with 85% of patients younger than 1 year and only 4% with an IF diagnosis above 10 years of age. The majority of children were premature (81%; < 38 weeks of gestational age) with a median birth weight of 2.1 kg (IQR: 1.1–3.0).

The most common diagnosis was SBS (78%), followed by motility disorders in 5% of patients and congenital diarrhea and enteropathy in 4%. Out of the patients with reported small bowel length ($N = 231$), the median shortest measured length was 40 cm (IQR: 21–60), which equaled to 21% (IQR: 10–39) of predicted small bowel length for age.[29] The ileocecal valve was resected in 41% of patients, and a stoma was created in 49%.

Surgical Procedures

Surgery and surgical procedures remain an essential component in intestinal rehabilitation. The most common surgeries at any time point after the initial bowel resection were stoma reversal ($N = 80$), additional bowl resection ($N = 53$), and creation of a new stoma ($N = 30$). The majority of these procedures (82%) were performed in the first 6 months after the IF diagnosis. An autologous bowel reconstruction was performed in 56 patients at a median age of 19 months (IQR: 7–72), with serial transverse enteroplasty as the most common procedure.[30]

Provision of enteral nutrition through feeding tubes was common and changed over time from use of temporary to permanent feeding tubes. Two hundred and forty-four patients (67%) had a feeding tube at their 2-month enrollment visit, in most cases a nasogastric tube ($N = 115$; 54%). At the 2-year annual visit, a feeding tube was still in situ in 57% of patients, in three-quarter of cases a G-tube.

Nutrition Management

Enteral nutrition was introduced early in the patient course, with 65% of patients receiving some amount of enteral nutrition at 2-month after their IF diagnosis. This proportion increases over time, with 79% of patients reaching a 2-year follow-up. Breast milk (24%), partially hydrolyzed (33%), or elemental formula (29%) were the most frequently used types of formula at 2 months after diagnosis, whereas elemental formula was the most frequently used formula at 1-year

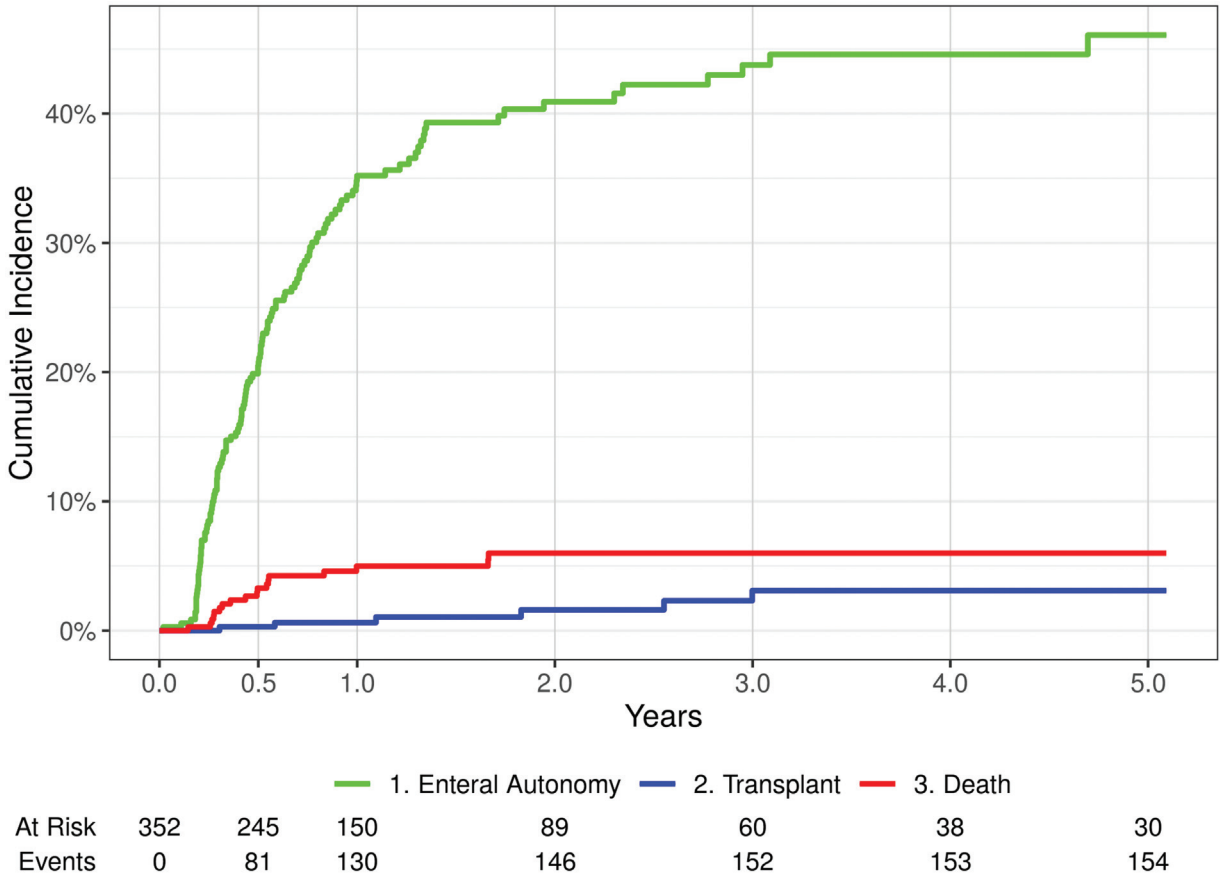

Fig. 3 Five-year cumulative incidence for the whole IIFR cohort. IIFR, International Intestinal Failure Registry.

follow-up (46%; partially hydrolyzed formula 26%). Over time, the amount of enteral nutrition increased from a median of 31 kcal/kg/d at the 2-month visit to 50 kcal/kg/d at 1 year after diagnosis. In parallel to the increasing reliance on enteral calories, the amount of calories provided by PN reduced from 69 kcal/kg/d at the 2-month visit to 49 kcal/kg/d in patients who did not achieve enteral autonomy and remained PN-dependent at 1 year after diagnosis. Enteral autonomy was achieved in 52% of patients at 2 years after their diagnosis, with a median time to enteral autonomy of 5.3 months in those achieving enteral autonomy (IQR: 3.0–7.5).

SMOF lipid was the most frequently used lipid emulsion, with 77% of patients receiving SMOF lipids at their enrollment visit and 87% and 88% of those remaining on TPN at 1- and 5-year of follow-up, respectively. The median lipid dose was 1.9 g/kg/d (IQR: 1.2–2.4) at the enrollment visit, and 1.4 g/kg/d at the 1- and 5-year follow-up. Lipid minimization was employed in 13 patients at the enrollment visit and in 1 patient at the 1-year visit.

Health Care Utilization

The care of children with IF under IRP and the complex nature of pediatric IF require significant health care resources. Health care utilization is documented at the enrollment visit and the follow-up visits. This information can be valuable for IRPs in identifying resources necessary to establish a new IRP or sustain the operations of an existing one. Twenty-four percent of patients are still admitted at 6-month of follow-up, and 13% at 1 year after their diagnosis. The median length of stay for the first admission was 128 days (IQR: 84–223). In the first three years of follow-up, discharged patients had attended a median of three clinic visits per year, and about half of them had been re-admitted once.

Overall Outcome and Complications

At each follow-up visit, IF-related complications are assessed, and changes over time are documented. The incidence of IFALD, defined as conjugated or direct bilirubin above 34 mmol/l, has changed over the follow-up period. In the enrollment visit and the 6-month visit, 25% and 22% of patients, respectively, presented with IFALD, while only 10% of the patients at the 1-year visit ($N = 213$), and 16% at the 2-year visit ($N = 83$) had IFALD. Significantly fewer patients experienced major IFALD-related complications at 1-year follow-up, with either gastrointestinal bleeding ($N = 3$), ascites ($N = 1$), and portal hypertension ($N = 1$). However, IFALD with major complications remains a risk factor for poor prognosis. Out of 21 unique patients with a reported IFALD complication at any time point, six (28%) had died, two (10%) are listed for an IT, and one (5%) underwent multivisceral transplantation.

CVC-related complications remain a significant cause of morbidity. Vascular thrombosis in one of the main veins used for CVC insertion (bilateral internal jugular, subclavian, femoral, and superior vena cava) was identified through imaging modalities (ultrasound, computed tomography, or

magnetic resonance imaging) in 16% of the patients at their last visit. The occurrence of vascular thrombosis remains a concern for patients requiring TPN for years. The median number of thrombosed veins in this group was 2. The rate of CLABSI in the whole cohort was 1.9 infections per 1,000 PN days.

The children's general functional outcomes are assessed annually. Oral aversion—defined as reluctance, avoidance, or fear of eating, drinking, or accepting sensation in or around the mouth and an ability to tolerate partial or full tube feeding—was identified in 17% of the cohort. Twenty-four percent of the entire cohort attended kindergarten, school, or a higher education program at their last visit, and one-third of them required education support. This prevalence may change over time with an increasing age of the IIFR cohort and evolving patterns of oral aversion and school needs. The Lanski score was reported for children older than 1 year of age with the majority (57%) in the upper 20%.

Out of the 237 children who completed 2 years of follow-up, 52% had achieved enteral autonomy, 8% had died, and 2% had undergone IT. The cumulative incidence for the entire IIFR cohort is presented in ►Fig. 3.

Summary

An international and multicenter collaboration focused on studying pediatric IF through the creation of a comprehensive, reliable, and high-quality registry can significantly improve our understanding and clinical research in the field of IF. The successful completion of the pilot phase of the IIFR has demonstrated the feasibility and value of such an international effort. The prospective collection of data in the current long-term phase of the IIFR is anticipated to provide the data and tools to accomplish several key objectives, including: establishing international benchmarks for outcomes; supporting quality improvement projects; creating collaborative learning networks; leveraging artificial intelligence and other statistical methods to identify effective nutritional, medical, and surgical interventions; promoting the adoption of evidence-based medicine in IF; facilitating the development of patient-reported outcomes; employing IIFR data as a control group for interventional studies; and encouraging additional research collaborations within the IF community.

These objectives will remain central to the mission of the IIFR in the coming years, with an overarching goal of ensuring that this international collaboration continues to bring value to the participating centers and the broader IF community.

Conflict of Interest

None declared.

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