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Magnitude of Surgical Burden Associated with Pediatric Intestinal Failure: A Multicenter Cohort Analysis

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Abstract

Background—Pediatric intestinal failure (IF) patients require many surgical procedures over the course of their illness. The number and variety of surgical procedures, as well as patient characteristics associated with this burden of surgical procedures, remain largely unknown.

Methods—Data from a large, multicenter retrospective study of pediatric intestinal failure (PIFCON) were reviewed. Infants from 14 multidisciplinary IF programs were enrolled, with study entry defined as PN dependence for > 60 days.

Results—272 infants were followed for a median (IQR) of 33.5 (16.2, 51.5) months, during which time they underwent 4.0 (3.0,6.0) abdominal surgical procedures. Intestinal resections were performed in 88/97 (92%) necrotizing enterocolitis patients versus 138/175 (80%) in non-NEC patients ($p<0.05$). Patients who underwent ≥5 operations had more septic events, compared to those who underwent ≤2 operations (3(1,6) versus 1 (0,3), respectively, $p<0.01$). Patients treated at centers with transplantation capability had lower odds of undergoing > 2 abdominal operations [OR 0.37 (95% CI: 0.21, 0.65)] after multivariable adjustment.

Conclusions—Individual and center-specific characteristics may help determine surgical practices experienced by infants with IF. Further study may delineate additional details about the

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Appendix

List of participating programs in PIFCon.

nature of these characteristics, with the goal of optimizing patient care and minimizing individual and overall healthcare burden.

Keywords

Pediatric intestinal failure; short bowel syndrome; surgical burden; sepsis

Intestinal failure (IF) is characterized by inadequate functional bowel, resulting in the inability to maintain the nutrition, fluid and electrolyte homeostasis needed to sustain growth and development. [1] The primary cause of IF in children is a loss of intestine due to congenital or acquired conditions that results in short bowel syndrome (SBS). [2]

While the multidisciplinary care of patients with IF has improved mortality, the morbidity remains substantial. [3] In addition, care for patients with SBS is very complex and highly resource-intensive; 22.1 per 1000 neonatal intensive care unit (NICU) admissions are related to SBS and healthcare costs often total greater than $500,000 during the first year after diagnosis. [4] Potential contributions to this high resource utilization include prolonged hospital stays, multiple readmissions, and the need for multiple surgical procedures. [4]

However, data regarding resource requirements in this population are largely reported from small cohorts at single institutions. The Pediatric Intestinal Failure Consortium (PIFCon) represents a collaboration between 14 academic medical centers that have pooled data from a large and geographically diverse cohort of infants with IF to more accurately quantify the disease burden and track outcomes. [5] This study was performed as an ancillary analysis of previously collected, but as yet unreported data from the consortium. The study objectives were to: 1) define the number of abdominal surgical procedures (AP) performed in neonates with IF; 2) identify associations between the number of AP and outcomes, including death, intestinal transplantation, dependence on parenteral nutrition (PN), and septic events; and 3) identify patient, clinical, or hospital characteristics associated with increased surgical interventions.

1.Materials and Methods

This study was a multicenter retrospective cohort study performed through the Pediatric Intestinal Failure Consortium (PIFCon). PIFCon was initiated in June 2006 as a collaboration among 14 sites with established multidisciplinary programs for treatment of pediatric intestinal failure. These programs consisted of medical, surgical, nutritional and nursing services; nine of the 14 sites were also intestinal transplant centers. A list of participating programs is included as an appendix. After Institutional Review Board approval from each participating site, records of patients who met inclusion criteria were retrospectively reviewed. Infants with IF were included if they were less than 1 year of age and required prolonged support with PN, defined as ≥ 60 out of 74 consecutive days. This specific PN duration was chosen to allow for brief interruptions such as loss of intravenous access or perioperative cessation. Participants at 13 sites met the age and PN criteria and data were collected through December 2007

All surgical procedures performed between birth and the end of the study period were recorded. Surgical burden was defined according to total number of abdominal procedures (AP), and was stratified into three groups (1–2, 3–4, and ≥5). The outcomes recorded were death, intestinal transplantation, duration of parenteral nutrition (PN) dependence, and septic events. Clinical data were collected at 1, 3, 6, 9, and 12 months following study enrollment and annually thereafter.

Statistical analysis was conducted using SAS® version 9.3 (Cary, NC). Categorical data are summarized as frequency counts and percentages. Continuous data are shown as mean ± standard deviation (SD) when normally distributed and nonparametric data are presented as median and interquartile range (IQR) otherwise. Potential factors associated with surgical burden were evaluated using proportional odds ordinal logistic regression with a cumulative logit function. [6, 7] This method fits two parallel regression curves with equal slopes but different intercepts: $\text{logit}(\Pr(\geq 5 \text{ abdominal procedures}|X)) = \alpha 1 + \beta X$ and $\text{logit}(\Pr(\geq 3 \text{ abdominal procedures}|X)) = \alpha 2 + \beta X$. The proportional odds assumption, confirmed with the score test, results in the odds ratio (e^{β}) being the same for both regression curves. For surgical burden analysis, the common odds ratio (OR) is interpreted for ≥5 versus <5 abdominal procedures as well as for ≥3 versus <3 abdominal procedures. Stepwise regression was used to obtain a parsimonious model, where independent variables were iteratively entered into the model with threshold $P<0.10$ and retained only when $P<0.05$. Adjustment for multiple comparisons was not made since no more than three groups were compared. [8] Odds ratios (OR) are shown along with 95% confidence intervals (CI). *P* values <0.05 were considered statistically significant.

2. Results

The 272 infants who met study inclusion criteria were followed for 33.5 (16.2, 51.5) months. 156 (57%) were males and 210 (84%) of 250 with known race were Caucasian. Median estimated gestational age (EGA) was 34 (30, 36) months, median birth weight (BW) was 2.1 (1.2, 2.7) kilograms and 66 (30%) were classified as being very low birth weight (BW<1.5 kilograms). Approximately half of the cohort had been initiated on PN by 3 days of life and median age when study entry criteria were met was 63 (61, 74) days. Necrotizing enterocolitis (NEC, n=97, 36%) was the most frequently occurring single underlying diagnosis leading to IF, followed by gastroschisis (n=81, 30%). Select patient demographics and baseline characteristics at the time of inclusion into the study are summarized in Table 1. The main results of the original study population have been published. [5]

Of the 272 patients included, 268 underwent a total of 1,226 AP prior to and during the study (Table 2). Overall, patients underwent a median of 4.0 (3.0, 6.0) AP. Prior to meeting study entry criteria 248 (91%) patients had already undergone a median of 2.0 (1.5, 4.0) AP. During the follow-up period after study inclusion, 196 (72%) underwent AP with a median of 2.0 (1.0, 3.0) per patient. These procedures included 336 small bowel resections, 302 exploratory laparotomies, 209 stoma related procedures (creation, revisions and closures), 218 enteral access related procedures (insertions, removals and replacements) and 28 autologous intestinal reconstructive surgeries (Tables 3).

In order to evaluate outcomes associated with higher AP rates, patients were stratified into three groups based on the number of abdominal operations that they underwent (1–2, 3–4, and 5 or more AP). As depicted in Table 4, there were no differences between these groups in a combined outcome of transplantation or death (P=0.35), or duration of PN dependence (P=0.93). However, there were significantly more septic events in patients undergoing more AP, with a median of 3.0 (1.0, 6.0) septic events in the group who underwent ≥5 AP compared to 1.0 (0.0–3.0) in the group who underwent 1–2 AP (P=0.02).

Patient, clinical, and hospital factors associated with the number of AP on univariable analysis are shown in Table 5. Factors statistically associated with a higher number of operations included lack of transplant capability at the patient's IF center, Caucasian race, IV fluid supplementation, total number of septic events, bacterial overgrowth, baseline bowel length both as a continuous variable and as a dichotomous variables (<30 cm vs. ≥ 30 cm) and number of non-abdominal surgical procedures.

All potential correlates of surgical burden were then entered into the multivariable stepwise regression model (Table 6). While patients with NEC were significantly more likely to undergo small bowel resections as compared to those with a non-NEC etiology of IF (92% vs. 80%; P=0.01), total AP were similar in the two groups (P=0.16; data not shown). Other patient characteristics such as gestational age, birth weight, underlying diagnosis (NEC vs. non-NEC, gastroschisis vs. non-gastroschisis), direct bilirubin, aspartate aminotransferase to platelet ratio (APRI) and achievement of enteral autonomy during the study period were not associated with number of AP. The only factors independently associated with abdominal procedures in this multivariable proportional odds ordinal logistic regression using a stepwise selection procedure were care at a facility with a transplant program, which was associated with fewer AP [OR (95% CI): 0.37 (0.21, 0.65)]; whereas IV fluid supplementation [OR 2.23 (1.23, 4.06)] and number of non-abdominal surgical procedures [1.08 (1.01, 1.15)] were both associated with more AP. No baseline patient characteristics (i.e., those known at study entry) were associated with the number of AP.

3. Discussion

While IF has recently seen significant improvements in mortality from 25–30% down to 10% following widespread implementation of multidisciplinary care, it remains an extremely resource intensive disease. [1, 3, 4, 9] These patients frequently require complicated medical care and are seemingly burdened with a plethora of surgical procedures. [4] Despite improved understanding of the natural history of IF, neither the frequency of abdominal surgical procedures, nor the interaction of these procedures with the characteristics or eventual outcome of these patients is well characterized.

From birth until the end of study followup (averaging a little less than three years) IF patients in this multicenter cohort underwent a median of 4 AP. While a higher number of surgical procedures did not impact survival or duration of PN dependence, an association with more frequent septic events was established. Additionally, need for IV fluid supplementation and higher number of non-abdominal procedures was associated with an

increase in the odds of AP whereas care at IF sites with transplant capability was associated with a reduced surgical burden.

Multidisciplinary teams frequently involved in the care of pediatric IF patients are cognizant of the high number of surgical procedures performed in this population. However, benchmark data describing the amount of procedures performed in the first several years after diagnosis is unavailable. Information pertaining to the frequency of surgical procedures obtained from this cohort can be utilized to guide discussions within multidisciplinary teams and with parents/care givers of patients with IF at the time of diagnosis. Additionally, knowledge of the substantial surgical burden complicating the care of these patients could be used for resource allocation planning by developing IF programs.

A large majority of patients with IF undergo multiple AP. Each additional surgical procedure, however, compounds the risk of complications associated with these procedures. Review of the patients enrolled in this study demonstrated that duration of PN therapy and achievement of enteral autonomy are not associated with the number of AP. There is, however, an associated increase in the number of septic events with an increasing surgical burden. Noting associations such as these could prove useful in anticipating events such as central line associated blood stream infections in patients requiring many abdominal procedures. In addition, knowledge that a subset of patients may have a higher level of IF-related morbidity could allow caretakers to coordinate preemptive transfer to centers with specific IF expertise.

As described, management of patients with IF is highly resource intensive. If specific patient or center characteristics associated with higher likelihood of multiple subsequent AP can be identified earlier in the course of illness, better triage practices could be developed. In this specific cohort of patients from established IF programs, no specific clinical variables known at the time of study entry were noted to be associated with a higher surgical burden. The only baseline characteristic associated with surgical burden was the receipt of care at an IF program with transplant capability. Having transplant capability resulted in a significantly lower number of AP per patient. Intestinal failure programs with an associated transplant center may have greater experience in treatment of more medically complex patients. Alternatively, this association may just imply a difference in approach among various centers. However, the nature of available data limits further characterization of this association. This finding, nonetheless, reinforces previously reported suggestions of improved outcomes for patients transferred to specialized centers at a relatively early phase of their clinical illness. [3,10]

Co-temporal factors during the follow up period associated with the magnitude of surgical burden included need for supplemental IV fluid administration and number of non-abdominal surgical procedures. The association of IV fluid supplementation with higher surgical burden could suggest that the need for IV hydration may be a marker for ongoing intestinal dysfunction that is being treated with operative intervention. While these data cannot fully elucidate this relationship, the use of autologous intestinal reconstruction (e.g., serial transverse enteroplasty) for this indication has been reported and may represent some of the surgical burden in this group of patients. [11, 12, 13]

The majority of non-abdominal procedures were either related to central venous access or were diagnostic in nature (e.g., endoscopies and liver biopsy). Presumably, association with the higher burden of AP is reflective of a more complicated patient subgroup.

This study is limited by its retrospective design. Definition of causative relationships are therefore not possible, and data collection not primarily designed for this study results in limited interpretation. Median follow up duration was greater than 2 years. While substantial, IF is a chronic disease and identification of some relationships may have been impaired by this relatively "mid-term" follow up.

This study defines a benchmark of surgical burden experienced by infants with intestinal failure. In addition, it begins to elucidate some associations between this surgical burden and patient and healthcare characteristics. Knowledge of these benchmark data and putative associations can help guide patient management and further inquiry into interventions aimed at limiting the surgical burden in this fragile patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Subject characteristics (n=272)

Subject characteristics with categorical data summarized as frequency counts and percentages. Continuous data are shown as mean ± standard deviation (SD) when normally distributed and nonparametric data are presented as median and interquartile range (IQR) otherwise.

Characteristic	N	N (%)	Median (IQR)
Age at study entry (days)	272		63 (61, 74)
GA (weeks)	265		34 (30, 36)
Months in study	271		33.5 (16.2, 51.5)
Malegender	272	156(57%)	
Race	257		
Caucasian		210 (84%)	
Black		30 (12%)	
Asian		13 (5%)	
Other		1(<1%)	
Birth weight (kg)	221		2.1 (1.2, 2.7)
Very low birth weight (≤1.5kg)	221	66 (30%)	
Diagnosis			
NEC		97 (36%)	
Gastroschisis		81 (30%)	
Small bowel atresia		62 (23%)	
Volvulus		58 (21%)	
Other		25 (10%)	
Status at end of study	272		
Enteral autonomy		118 (43%)	
Alive (still on PN/EN)		36 (13%)	
Transplant (alive)		50 (18%)	
Died		68 (25%)	

Table 2

Distribution of abdominal procedures. Based on 268 subjects with at least one abdominal surgery

Distribution of abdominal surgical procedures before and after study entry criteria met.

	N (%)	Range	Mean±SD	Median (IQR)
Subjects with APs	268 (99%)			
Abdominal procedures per subject		1 – 15	4.6±2.5	4.0 (3.0, 6.0)
Subjects with APs prior to study period	248 (91%)			
Abdominal procedures per subject		1 – 9	2.7±1.6	2.0 (1.5, 4.0)
Subjects with APs during study period	196 (72%)			
Abdominal procedures per subject		1 – 13	2.6±2.0	2.0 (1.0, 3.0)

Table 3

Abdominal surgical procedures from birth until the end of study period. Based on 268 subjects with at least one abdominal surgery

Surgical Procedure	N
Small bowel resection	336
Exploratory Laparotomy	220
Ostomy creation/revision/closure	209
Gastrostomy creation/revision/closure	218
Autologous intestinal reconstruction	28
Tapering procedure	14
Fundoplication	19
Others*	182
Total procedures	1226

*Abdominal wall closure; fistula closure; colon resection; placement of abdominal drain; cholecystectomy; cloacalexstrophy; feeding jejunostomy.

Table 4

Association of surgical burden with outcomes.Four subjects had no abdominal surgical procedures and have been omitted from the analysis (n=268)

	Total number of abdominal procedures (including before and during study interval)			
	1–2 (n=48)	**3–4 (n=100)**	**≥5 (n=120)**	***P***
Transplant or death (vs. alive at study end)	21 (44%)	48 (48%)	46 (38%)	0.35
Total number of days of PN: median (IQR)	240 (128 – 468)	280 (138 – 458)	246 (129 – 557)	0.93
Total number of sepsis events: median (IQR)	1.0 (0.0 – 3.0)[a]	2.0 (1.0 – 3.0)[ab]	3.0 (1.0 – 6.0)[b]	0.02

Groups with different superscripts are statistically different from one another at $P<0.05$.

Table 5

Unadjusted correlates of surgical burden. Four subjects had no abdominal surgical procedures and have been omitted from the analysis (n=268)

Variable	Abdominal Procedures 1–2 48 (18%)	3–4 100 (37%)	≥ 5 120 (45%)	*P*	OR (95% CI)
Transplant site	38 (79%)	73 (73%)	64 (53%)	0.0002	0.39 (0.24, 0.64)
Caucasian race	32 (67%)	77 (77%)	98 (82%)	0.05	1.72 (1.01, 2.93)
Supplemental IV fluids	9 (19%)	20 (20%)	47 (39%)	0.0007	2.48 (1.47, 4.20)
Total sepsis events during study	1 (0–3)	2 (1–3)	3 (1–6)	0.008	1.07 (1.02, 1.12)
Bacterial overgrowth during study	30 (63%)	76 (76%)	99 (83%)	0.008	2.04 (1.20, 3.47)
Baseline bowel length (cm)*	30 (16–65)	35 (25–60)	51 (30–75)	0.03	1.13 (1.01, 1.25)
Baseline bowel length <30 (cm)*	9 (43%)	23 (39%)	15 (23%)	0.04	0.50 (0.26, 0.97)
Number of non-abdominal procedures	3 (2–5)	3 (2–6)	4 (2.5–8)	0.005	1.10 (1.03, 1.17)

Shown are N (%) or median (Q1, Q3).Modeling reveals that the proportional odds assumption is met; therefore, the odds ratio (OR)corresponds to the comparison of ≥5 versus 1–4abdominal procedures as well as 3–4 versus 1–2 abdominal procedures

* Due to small bowel measurements not available, analysis based on n=144 subjects.

Investigated but not found to be significant:
Gestational age (P=0.47), birth weight (P=0.79), very low birth weight (P=0.43), gender (P=0.58), age at study entry (P=0.71), pre-term (P=0.63); NEC (P=0.19), gastroschisis (P=0.28), NEC vs. gastroschisis vs. other (P=0.42); baseline albumin (P=0.13), direct bilirubin <2 (P=0.22), APRI (P=0.74), baseline ventilator support (P=0.33), baseline vasopressors use (P=0.33); number of PN days (P=0.25), enteral autonomy during entire study (P=0.81).

Table 6

Multivariable correlates of surgical burden.Four subjects had no abdominal surgical procedures and have been omitted from the analysis. An additional 39 subjects with unknown number of non-abdominal procedures have also been excluded (n=229).

	Abdominal Procedures				
Variable	**1–2 48 (18%)**	**3–4 (37%)**	**≥ 5 120 (45%)**	***P***	**OR (95% CI)**
Transplant site	38 (79%)	73 (73%)	64 (53%)	0.0005	0.37 (0.21, 0.65)
Ever IV fluids	9 (19%)	20 (20%)	47 (39%)	0.008	2.23 (1.23, 4.06)
Number of non-abdominal procedures	3 (2–5)	3 (2–6)	4 (2.5–8)	0.03	1.08 (1.01, 1.15)

Shown are N (%) or median (Q1, Q3). Results are from a proportional odds ordinal logistic regression, using a stepwise selection procedure. Modeling reveals that the proportional odds assumption is met; therefore, the odds ratio (OR) corresponds to the comparison of ≥5 versus 1–4 abdominal procedures as well as 3–4 versus 1–2 abdominal procedures.