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# Ileal exclusion for pruritus treatment in children with progressive familial intrahepatic cholestasis and other cholestatic diseases

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ABSTRACT

*Background:* Pruritus is a major health-related quality-of-life burden in progressive familial intrahepatic cholestasis (PFIC) and other childhood cholestatic liver diseases. Several nontransplant surgical techniques were developed in an attempt to ameliorate symptoms and slow disease progression. Very few case-series have been published on a particular intervention, ileal exclusion (IE), which has been considered to be inferior to the other approaches.
*Methods:* We conducted a single-center retrospective chart-review case-series of patients submitted to IE as the first-line surgical treatment at our institution from 1995 to 2018. The primary goal was pruritus relief, followed by survival with the native liver and improvement in biochemical parameters.
*Results:* Eleven patients were submitted to IE, with a mean follow-up of 60 months. Complete resolution or significant reduction of pruritus was obtained in 72.7% ($n = 8$) of patients. One patient (9.1%) had a major postoperative complication that required surgery. No other morbidities were reported. Two cases progressed to end-stage liver disease (ESLD) within the short-term and one year after surgery.
*Conclusions:* This case series study shows that IE provided excellent results in pruritus control and permitted survival with the native liver. We believe IE is a safe procedure, with few associated morbidities, and should be considered more often as primary surgical treatment for PFIC and other cholestasis.
*Level of evidence:* IV.



Progressive familial intrahepatic cholestasis (PFIC) is a set of rare autosomal recessive diseases in which hepatocyte bile export mechanisms are impaired, leading to intracellular cholestasis and abnormal bile flow [1]. It is a possible cause of intrahepatic cholestasis in children along with perinatal infections and other genetic syndromes, such as Alagille syndrome. There are three main PFIC subtypes (PFIC 1, 2 and 3), each associated with different mutations and clinical presentations, although new disease-associated mutations and subtypes have been reported recently [2,3].

Bile acid (BA) accumulation on the skin, mucous membranes and sclera is responsible for the hallmark symptoms of severe pruritus and jaundice in all subtypes. Other frequent cholestatic symptoms are choluria and fecal acholia. As there is sustained BA accumulation in the liver, hepatic damage may occur, leading from fibrosis to end-stage liver disease (ESLD) [4–7]. PFIC 1 may present extrahepatic symptoms, most commonly diarrhea, failure to thrive and hearing loss [8,9]; PFIC 2 patients are at higher risk of developing hepatocellular carcinoma and early fibrosis [10] and PFIC3 may present with milder disease forms and later onset [11].

Management of PFIC varies according to the liver disease stage, and comprises both clinical and surgical management [6]. First-line drugs are ursodeoxycholic acid and rifampicin [12,13], and the aim of treatment is to improve pruritus and nutritional status [14]. Surgical procedures may be indicated if no clinical response is achieved as an attempt to halt disease progression or in ESLD [15,16]. While the latter patients may benefit from orthotopic liver transplantation (OLT) [17], nontransplant surgical strategies can be used in noncirrhotic cases to ameliorate symptoms and promote longer transplant-free survival [15,18].

Whitington and Whitington first described the partial external biliary diversion (PEBD), which consists of a cholecystojejunal cutaneous stoma with the interposition of a free jejunal segment in the right lower abdominal quadrant between the gallbladder and the skin [19]. The first case series of ileal exclusion (IE) in patients was published in 1998 as a surgical alternative to PEBD by Hollands et al. in patients who had been previously cholecystectomized and therefore could not be submitted to PEBD. This new procedure was standardized as an ileocolonic anastomosis bypassing the last 15% of the ileum [20]. Other possible surgical strategies are partial internal biliary diversion (PBID) [21], in which a jejunal conduit connects the gallbladder to the colon for bile drainage and total biliary diversion (TBD), with full bile flow interruption to the gastrointestinal tract [22].

There is a general agreement that IE is less effective than PEBD [16], although few IE case series have been published [20,23,24] compared to

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0022-3468/

PEBD, and there are currently no clinical trials demonstrating superiority of one approach over the others [16,25]. Our institution is a quaternary pediatric hospital and is a national reference center for pediatric liver disease as well as a transplantation center. Here, we present our institutional experience in the surgical management of PFIC with IE, and the indication of IE for other intrahepatic cholestasis of childhood. This is the largest case-series to date of IE as the first-line surgical treatment for cholestatic pruritus, with promising results.

## 1. Methods

Patients diagnosed with PFIC and noninfectious chronic intrahepatic cholestasis of other etiology who were submitted to IE at our institution from January 1995 to July 2018 were included in this single-center retrospective case-series study. At this time, we sought primarily to determine retrospectively whether providing this patient population with IE could improve clinical intractable itching, and secondarily, enhance clinical status. Institutional Review Board approval was obtained for this study protocol.

Pruritus status after surgery was retrospectively classified into five different categories based on Whitington's pruritus score [19]: 0: none; 1: rubbing or scratching when undistracted; 2: active scratching without evident skin abrasions; 3: evident abrasions; 4: cutaneous mutilation, hemorrhage and evident scaring.

We also analyzed liver function improvement, other biochemical parameters and transplant-free survival. Charts were reviewed by a single reviewer for demographics, clinical presentation, age at which surgery was performed, surgical complications, symptom relief, biochemical parameters, rescue liver transplantation and mortality.

Results were described as the mean ± SEM for parametric data and as percentages for categorical data. Kaplan–Meier curves were generated for survival analysis. Biochemical parameters were tested for normality with D'Agostino's $K^2$ test of normality, and submitted to analysis of variance (ANOVA) followed by Tukey's test for multiple comparisons for parametric data or the Friedman test followed by Dunn's test for multiple comparisons for nonparametric data. All tests were performed with a 95% confidence interval. Statistical analysis and figure generation were performed with GraphPad Prism version 7.00 for Mac, GraphPad Software, La Jolla California, USA, www.graphdpad.com.

The underlying pathology of cholestasis presentation was diagnosed based on clinical features [5,26,27], and if needed, confirmed by liver biopsy [18] and/or genetic testing. All PFIC and non-PFIC patients were treated by a multidisciplinary team. First-line treatment was ursodeoxycholic acid. Add-on drugs were rifampicin, cholestyramine and ondansetron based on symptom control. Fat-soluble vitamins were supplemented and comorbidities were addressed. In case of failure of clinical treatment for pruritus, noncirrhotic patients were offered IE, while patients with severe pruritus and ESLD were referred to OLT at our institution. In the past, we had submitted non-ESLD patients to OLT for pruritus relief, but owing to complications associated with OLT, this has no longer been part of our treatment guidelines.

### 1.1. Surgical technique

Surgical technique was similar to that previously described by Hollands et al. [20]. Patients were submitted to a lateral laparotomy at the Mac Burney site, and small bowel total length was measured from the ligament of Treitz to the ileocecal valve with a surgical ruler. The ileum was divided distally at the 15% mark of the total length and the distal portion was excluded from the gastrointestinal tract. The proximal end of the ileum was anastomosed to the right colon 5 cm distal to the ileocecal valve, bypassing the excluded ileum. As the first operated patient presented with intussusception of the bypassed ileal segment, surgical technique was modified in the following patients for primary prevention of this complication. After making the ileal bypass, the loops of the excluded portion of the ileum were anchored with serosal sutures to prevent intussusception (Fig. 1). All operations were performed or overseen by the senior manuscript's authors (UT).

## 2. Results

Eleven children were submitted to IE in the period of study owing to intractable pruritus. Individual characteristics of the patients are described in Table 1. Genetic testing, histological findings and drug regimens of pre and postoperative periods are summarized in Table 2. Liver biopsies histological features are shown in Fig. 2. Liver biopsy was not performed in Cases 7 and 9, who have Alagille syndrome, and in Case 11, a PFIC V patient. In all these patients, the diagnosis was supported by strong evidence other than liver biopsy, such as clinical criteria and genetic testing available for siblings (Case 10 and 11 are sisters). Also, none of these patients displayed laboratory or imaging abnormalities that could suggest other biliary diseases. Therefore, outweighing risk and benefits, we choose not to perform a liver biopsy in these patients. Age at time of surgery was 4.98 ± 3.97 years, ranging from 2 to 14 years, with a postoperative follow-up ranging from 5 to 198 months (mean: 60 months). The most frequent cause of cholestasis was PFIC ($n = 8$; 72.72%), all of whom had a low GGT (median 60 U/L; range 7 U/L to 420 U/L). Moreover, diagnosis in these and other patients was based on additional clinical characteristics, liver biopsies (available for 7 PFIC cases and for Case 2) and genetic testing (available only for 2 patients). All patients, except for case 11, also presented with jaundice at the time of surgery.

Few postoperative complications were observed in this case series. There were no intraoperative or postoperative deaths related to surgical procedure. Interestingly, despite the ileal diversion, no patient presented with postoperative diarrhea. Case 1 presented with intussusception of the bypassed ileal segment on the 17th postoperative day, and was submitted to laparotomy and resection of the bypassed segment, which was found to be ischemic. No other cases of bowel obstruction, either small or large bowel, were observed. Cases 3 and 9 presented with enterorrhagia on the sixth and fourth postoperative days, respectively. Bleeding was considered to be from suture lines in both cases, and patients were put on intravenous fluid therapy and received blood transfusions. Bleeding was self-limited, and no further therapy was performed.

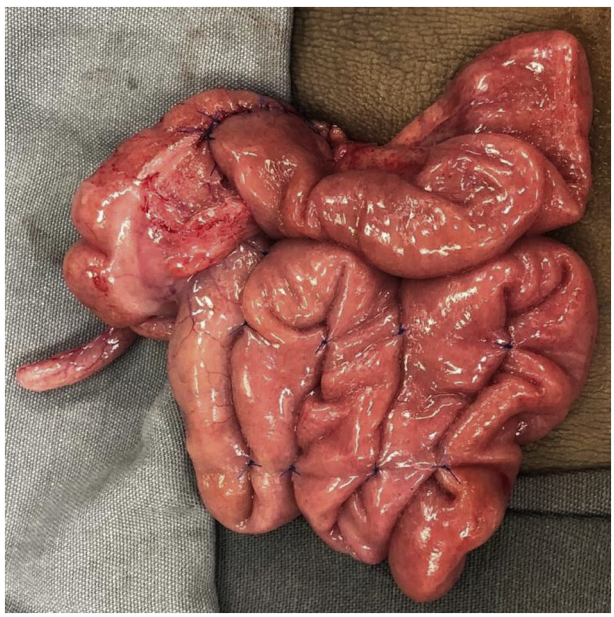

**Fig. 1.** Ileal exclusion: note the anastomosis of the proximal ileum to the ascending colon and the serosal sutures in the excluded loops of the ileum.

**Table 1**
Individual characteristic of patients submitted to ileal exclusion.

| Case | Gender | Diagnosis | Symptoms and additional clinical data | Age at surgery, y | Follow-up duration, mo | Pruritus score before surgery | Pruritus score after surgery (last follow-up) | Clinical status at last follow-up |
|---|---|---|---|---|---|---|---|---|
| **1** | M | PFIC I | pruritus, jaundice, choluria | 2 | 11 | 4 | 01/mar | ESLD and death |
| **2** | M | ARC syndrome | pruritus, jaundice, choluria, chronic diarrhea. delayed neuropsychomotor development, Fanconi syndrome, chronic kidney disease | 3 | 118 | 4 | 0 | chronic liver disease; alive |
| **3** | M | PFIC I | pruritus, jaundice, choluria, fecal acholia | 3 | 52 | 4 | 1 | liver transplantation; alive |
| **4** | M | PFIC I | pruritus, jaundice, | 14 | 55 | 4 | 0–1 | chronic liver disease; alive |
| **5** | M | PFIC II | pruritus, jaundice, delayed neuropsychomotor development | 4 | 68 | 4 | 1 | chronic liver disease; alive |
| **6** | F | PFIC I | pruritus, jaundice, choluria, fecal acholia | 11 | 198 | 4 | 2 | chronic liver disease; alive |
| **7** | F | Alagille syndrome | pruritus, jaundice. typical facies, "butterfly" vertebrae | 3 | 42 | 4 | 2 | chronic liver disease; alive |
| **8** | F | PFIC I | pruritus, jaundice, choluria, constipation | 2 | 22 | 4 | 1 | chronic liver disease; alive |
| **9** | M | Alagille syndrome | pruritus, jaundice, choluria. Typical facies, pulmonary artery stenosis, "butterfly" vertebrae, posterior embriotoxon, renal dysplasia, short stature. Father diagnosed with Alagille syndrome | 5 | 6 | 4 | 1 | chronic liver disease; alive |
| **10**[a] | F | PFIC V | pruritus, jaundice, choluria, fecal acholia. Delayed neuropsychomotor development, microcephaly, hypertricosis, dyslipidemia | 4 | 6 | 4 | 0 | chronic liver disease; alive |
| **11**[a] | F | PFIC V | pruritus, sister (case 10) diagnosed with PFICV | 4 | 6 | 4 | 0 | chronic liver disease; alive |

[a] siblings; M: male; F: female; ARC: arthogryposis–renal dysfunction–cholestasis; PFIC: progressive familial intrahepatic cholestasis; y: years; mo: months; ESLD: end-stage liver disease.

**Table 2**
Diagnosis and medical regimens for the patients submitted to ileal exclusion.

| Case | Genetic testing | Histopathology | Drug regimen before surgery | Drug regimen after surgery |
|---|---|---|---|---|
| **1** | none | cholestasis, lobular activity | hydroxyzine (0.3 mg/kg/day), ursodeoxycholic acid (10.0 mg/kg/day), cholestyramine (0.06 g/kg/day) | hydroxyzine (0.3 mg/kg/day) |
| **2** | ARC syndrome (homozygous c.734 + 2 T > C, gene VIPAS39); heterozygous for alpha 1 antitrypsin c.187C > T (p.R63C), gene SERPINA1 | bile ductular proliferation, hepatocellular ballooning | ursodeoxycholic acid (10.0 mg/kg/day) | ursodeoxycholic acid (10.0 mg/kg/day) |
| **3** | none | nodular transformation, bile ductular proliferation, cholestasis, giant cell transformation | rifampicin (10.0 mg/kg/day), ursodeoxycholic acid (15.0 mg/kg/day) | none |
| **4** | none | minimum fibrosis, bile ductular proliferation, cholestasis, hepatocellular ballooning | rifampicin (300.0 mg/day) | rifampicin (300 mg/day) |
| **5** | none | bile ductular proliferation, severe fibrosis, giant cell transformation, cholestasis, hepatocellular ballooning | rifampicin (15.0 mg/kg/day), loratadine (0.3 mg/kg/day) | ursodeoxycholic acid (10.0 mg/kg/day), cholestyramine (0.06 g/kg/day) |
| **6** | none | bile ductular proliferation, cholestasis, giant cell transformation | ursodeoxycholic acid (18.0 mg/kg/day), rifampicin (15.0 mg/kg/day), cholestyramine (0.06 g/kg/day) | ursodeoxycholic acid (10.0 mg/kg/day) |
| **7** | none | none | ursodeoxycholic acid (18.0 mg/kg/day), rifampicin (15.0 mg/kg/day), cholestyramine (0.12 g/kg/day) | rifampicin (20.0 mg/kg/day), cholestyramine (0.04 g/kg/day) |
| **8** | none | minimum fibrosis, bile ductular proliferation | ursodeoxycholic acid (45.0 mg/kg/day), cholestyramine (0.08 g/kg/day), rifampicin (17.0 mg/kg/day) | cholestyramine (0.02 g/kg/day) |
| **9** | none | none | ursodeoxycholic acid (28.0 mg/kg/d), cholestyramine (0.07 g/kg/day), rifampicin (30 mg/kg/day), loratadine (0.3 mg/kg/day) | ursodeoxycholic acid (10.0 mg/kg/day), |
| **10*** | heterozygous for PFIC 5; heterozygous disorder of 13A biogenesis peroxisome and kidney and liver polycystic disease without significant clinical variation | bile ductular proliferation, giant cell transformation, cholestasis, hepatocellular ballooning | ursodeoxycholic acid (25.0 mg/kg/day), cholestyramine (0.04 g/kg/day), rifampicin (20.0 mg/kg/day), loratadine (0.3 mg/kg/day) | cholestyramine (0.02 g/kg/day) |
| **11*** | none | none | ursodeoxycholic acid (13.0 mg/kg/day), cholestyramine (0.05 g/kg/day) | ursodeoxycholic acid (13.0 mg/kg/day) |

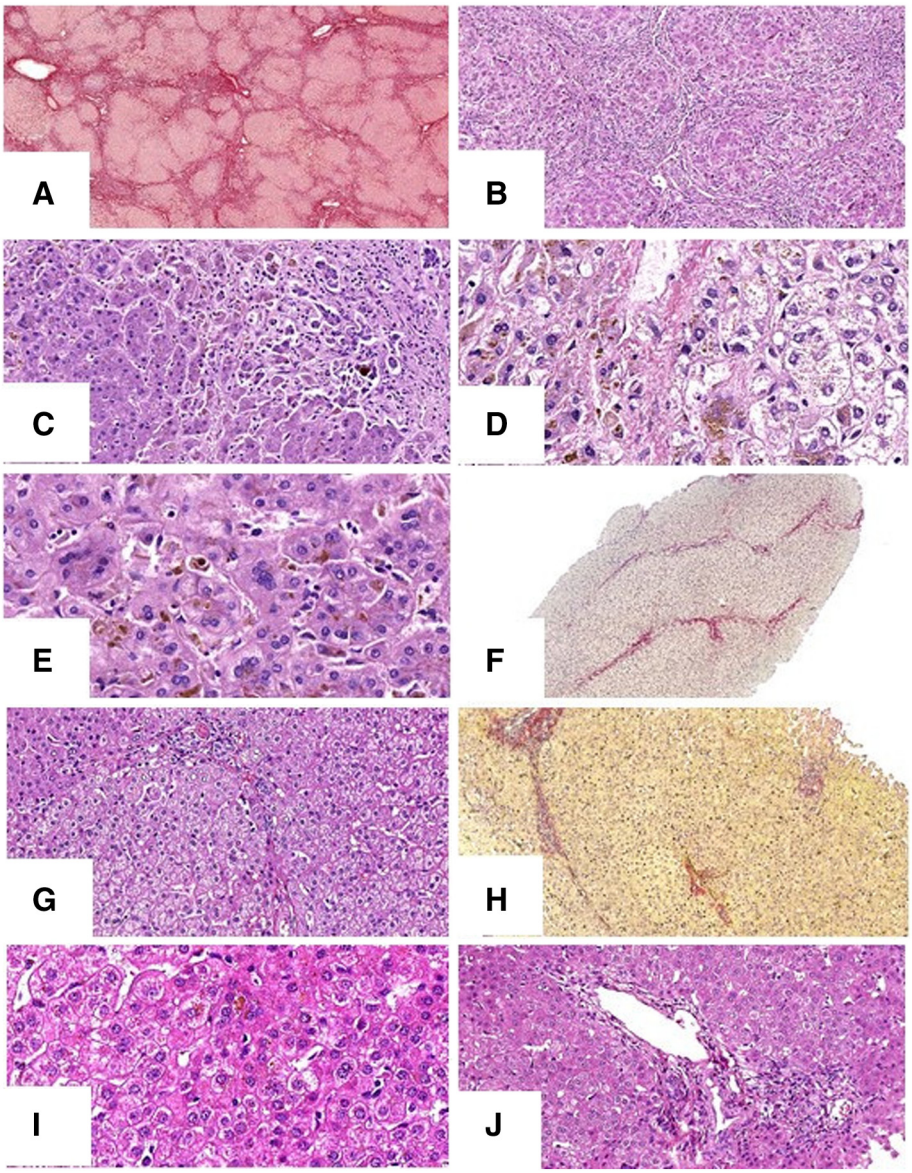


**Fig. 2.** Histological features of liver biopsies. A. Micronodular cirrhosis (Picrosirius red stain, 20×); B. Advanced biliary cirrhosis (H&E stain, 100×). C. Moderate bile ductular proliferation with focal bile infiltration (H&E stain, 200×). D. Marked hepatocellular and canalicular cholestasis along with ballooning degeneration (H&E stain, 400×). E. Bilirubinostasis, multinucleated giant hepatocytes and cholestatic liver cell rosettes (H&E stain, 400×). F. Bridging fibrosis with some thin fibrous septa (Picrosirius red stain, 40×). G. Portal tract with mild bile ductular proliferation and a thin fibrous septum (H&E stain, 200×). H. Portal fibrosis with rare fibrous septum (Picrosirius red stain, 200×). I. Cholestasis and pseudoglandular formation (H&E stain, 400×). J. Bile ductular proliferation and scarce inflammation in a portal tract (H&E stain, 200×).

The main outcome was after-surgery pruritus improvement. Most patients' pruritus remained clinically controlled postoperatively ($n = 8$; 72.7%). Case 1 progressed to ESLD in the very short-term and Case 3 progressed to ESLD within one year. Both cases experienced worsening of symptoms concurrent to hepatic failure. Case 7 sustained symptom relief for a period of 3 years postoperative, and eventually had a breakthrough of symptoms despite clinical treatment. This patient does not currently display any signs of ESLD and will be referenced for OLT if she develops hepatic failure.

Secondarily, we looked at survival with the native liver as another outcome (Fig. 3). One patient died 5 months after surgery owing to ESLD complications (*Case 1*), and another patient (Case 3) was submitted to OLT one year after IE. All other patients ($n = 9$; 81.8%) remained well, with no signs of ESLD during follow-up. Relevant biochemical parameters were evaluated at three different time-points, namely, preoperative, minimum/maximum and last follow-up, and are shown in Fig. 4. A statistically significant decrease was observed in alkaline phosphatase (ALP) levels when comparing the preoperative levels

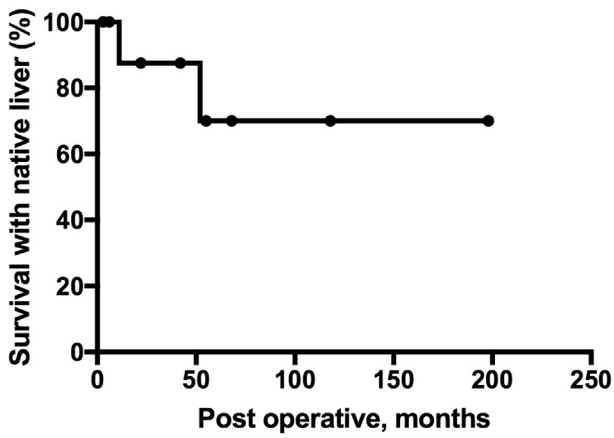


**Fig. 3.** Survival with the native liver in patients submitted to ileal exclusion.

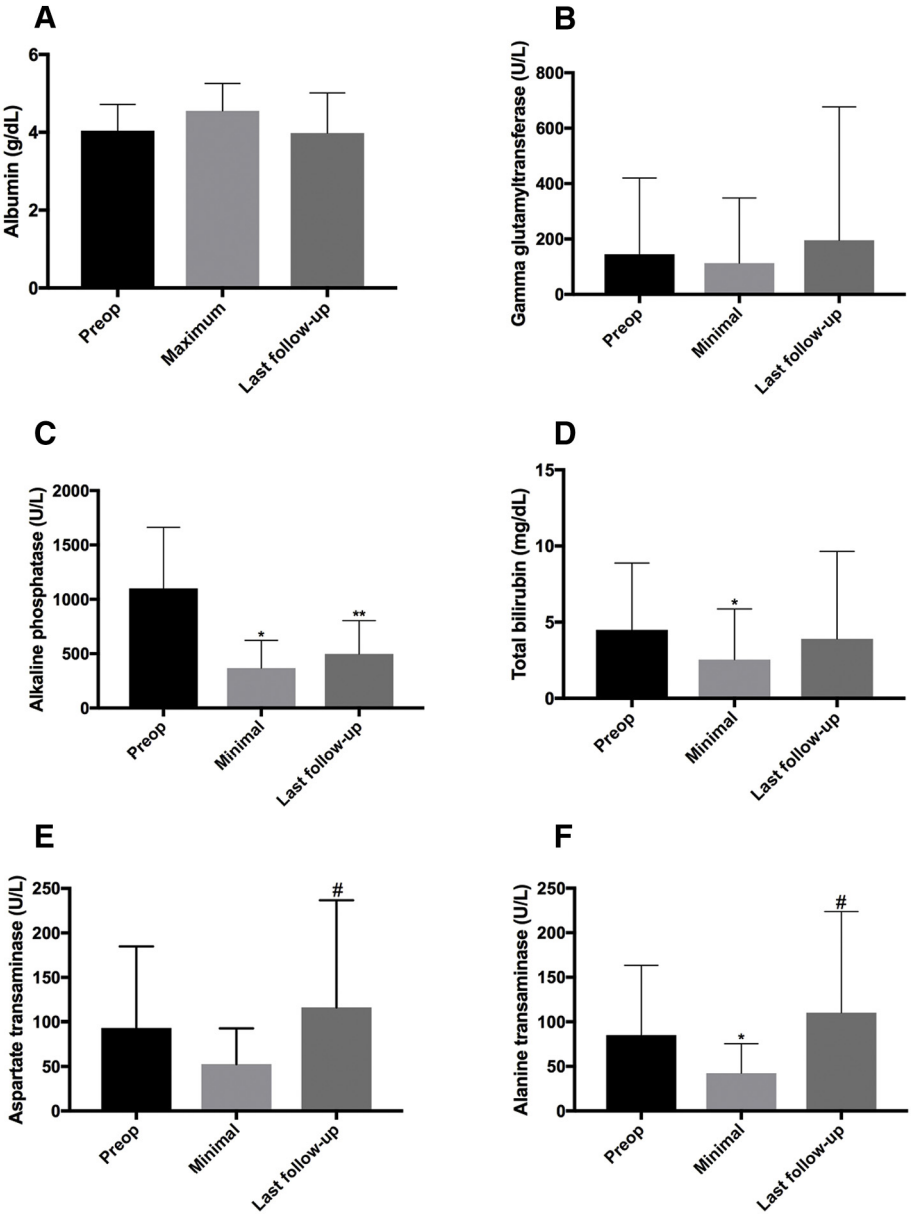


**Fig. 4.** Mean and SEM for biochemical parameters preoperatively, at minimum/maximum after surgery and at the last follow-up in patients submitted to ileal exclusion. A: Albumin and B: Gama glutamyltransferase: no significant differences; C: Alkaline Phosphatase *p = 0.0004 for Preoperative vs. Minimal levels; **p = 0.0036 for Preoperative vs. Last follow-up. D: Total bilirubin *p = 0.004 for Preoperative vs. Minimal levels. E: Aspartate transaminase #p = 0.0167 for Minimal levels vs. Last follow-up. F: Alanine transaminase *p = 0.0231 for Preoperative vs. Minimal levels; #p = 0.0167 for Minimal vs. Last follow-up.

with the minimum levels and those at the last follow-up and in total bilirubin level (TBL) when comparing preoperative and minimum levels. Aspartate transaminase (AST) levels were higher at the last follow-up than preoperatively. Alanine transaminase (ALT) levels decreased between the minimum vs. preoperative levels, and eventually rose on the last follow-up. No significant differences were noted in the albumin and gamma glutamyltransferase levels.

## 3. Discussion

Cholestasis-associated pruritus relates to a significant health-related quality-of-life burden, being severely disabling, and causing sleep deprivation, loss of school days and suicidal intention [28]. The molecular pathogenesis of cholestasis pruritus is unclear and probably multifactorial, as it is linked to altered central neurotransmission and peripherally acting pruritogens, such as BA [29].

BA is synthesized de novo from cholesterol in hepatic cells [30], and excreted to the bile canaliculi against the concentration gradient by a superfamily of ATP-binding transporters [31,32]. Most PFIC-associated defects affect these transporters [33]. After reaching the gastrointestinal tract, 95% of BA in the terminal ileal lumen is absorbed via the apical sodium-dependent bile salt transporter to the portal circulation, to be later extracted by hepatic cells [34]. Impairment in the liver cell outflow systems in PFIC and other cholestatic diseases causes BA overload. Nontransplant surgical procedures aim to decrease the BA enterohepatic circulation [6,15,16], interfering in BA reabsorption to the portal circulation [20].

We evaluated clinical and laboratory postoperative outcomes in a case-series of 11 intrahepatic cholestasis, PFIC and non-PFIC patients who were submitted to IE as the first-line surgical treatment. Follow-up ranged from 6 to 198 months (mean: 60 months), and the primary outcome was pruritus relief in 72.72% of cases, followed by survival with the native liver and biochemical parameter improvement. We

may stress that the pruritus improvement was an important result evaluated by clinical evidence and based on the Whitington's pruritus score, before and after surgery. We observe in Table 1 that all patients had a decreased score in the postoperative period.

At our institution, failure of clinical treatment for pruritus is the major criterion for recommending IE to non-ESLD PFIC subjects. Few previous studies have addressed pruritus treatment as this surgery's primary goal. Nonetheless, many studies have approached this condition as a secondary goal. We believe our results are superior to these previous reports. Bull et al. recently published comprehensive outcomes of a large multicenter cohort of surgical management of PFIC. Complete and sustained pruritus resolution was obtained in 19% ($n = 4$) of PFIC 1 patients and in 32% ($n = 11$) of PFIC 2 subjects [35] who underwent PEBD. For IE, Bull et al. reported *2* patients with sustained response, 2 patients with partial/incomplete response and 2 patients with complications or liver function failure which ultimately led to OLT. Kalicinski et al. reported that in a case-series of patients primarily submitted to IE, 60% of them had pruritus relapse over time, and only 20% had sustained results. For Alagille syndrome, fewer reports on surgical strategies for its associated pruritus have been published. In these series, both PEBD and IE not only improved pruritus, but ameliorated xanthomas and total cholesterol levels [36–39]. Overall in our series, 72.72% of patients attained sustained tolerable pruritus after surgery.

Previous criticism of IE pointed to an eventual recurrence of symptoms, probably owing to an increase in BA reabsorption over time from adaptation mechanisms in the remaining ileus [24]. In our case-series, out of three patients who had time-limited pruritus control, worsening of symptoms occurred synchronously with progression to ESLD in two of them and only one experienced gradual pruritus recurrence that could suggest BA overload from intestinal adaptation. Based on our experience, pruritus recurrence after IE was more associated with liver dysfunction than with a potential temporary effect of surgery.

In the current group of patients, we observed a statistically significant decrease in TBL at the minimum level in comparison to preoperative levels (mean: 4.5 to 2.5 mg/dL, $p < 0.05$). We suppose that the BL most likely corresponds to an actual diminution in BA levels, although no direct measurement of BA levels was performed. Cholestasis-associated pruritus is known to have a multifactorial genesis, and BA overload leading to skin accumulation is only part of its pathophysiology. In addition, no study to date has correlated BA concentration to the degree of pruritus [44]. Recent studies pointed to BA deposition on the skin stimulating cutaneous nerve terminals and causing pruritus [45]. Strategies to diminish BA overload, such as IE, might decrease not only BA concentration but also the interaction of BA with other pruritogenic agents at the central or inflammatory level.

Another promising benefit of nontransplant surgical interventions in PFIC and non-PFIC intrahepatic cholestasis is mitigation of the progression of liver disease [25], similar to Kasai portoenterostomy in biliary atresia. Preclinical studies have demonstrated hepatic fibrosis amelioration in cholestasis animal models after distal ileum resection [40] or drug-induced BA reabsorption blockage in the gut [41]. In humans, a possible outcome is survival with the native liver, as we verified that only two patients progressed to failure of liver function. Transaminase behavior in our case-series also corroborates that IE decreases liver damage at first, although it might eventually progress. ALT levels were lower at the minimum in comparison with preoperatively, but higher at the last follow-up (mean: 85.2; 42.5 and 110.4, $p < 0.05$). AST levels were also higher at the last follow-up than preoperatively (mean: 52.6 and 116.4, $p < 0.05$). Cumulative damage over time might lead to synthetic failure, but it was not observed in other cases in this series despite a mean follow-up of 60 months, suggesting that either liver damage following IE is nonsignificant or a longer follow-up would be needed to observe it. Therefore, we believe IE could be used as a bridge for OLT to be performed later in life, when subjects are less prone to surgical complications and more organs are available. Maybe, in some cases, OLT could be avoided entirely.

In addition, IE was a safe procedure, with only one major postoperative complication requiring exploratory laparotomy and revision of the surgical site. Similarly, another case report has described intussusception of the bypassed ileal segment as a possible complication of IE [42]. However, no other case of intussusception was reported in the present case-series after the technique modification to prevent this complication as described. No long-term complications or postoperative-associated morbidities were reported. Nonetheless, several stoma-related complications and morbidities were reported after PEBD, such as dehydration, electrolyte imbalance, increased risk for cholangitis, stoma prolapse, parastomal hernia and adjustment to life with a stoma and social stigma [24,25,39,43].

We observed a significant decrease in ALP levels pre- and postoperatively at the minimum and at the last follow-up (mean: 1100.4; 367.6 and 497.9 U/L, $p < 0.05$), which may correlate to improvement in cholestasis-associated bone disease. Hepatic osteodystrophy patients usually present with osteopenia or osteoporosis, probably for multifactorial reasons that relate to low bone formation, transient increase in bone resorption, malnutrition and bone matrix alterations owing to low levels of vitamin D, vitamin K, calcium, trophic factors and accumulation of bilirubin among others [29,46]. Lower ALP levels were associated with higher body mineral density in subjects with biliary atresia [47], and an increase in vitamin D levels was observed post-Kasai portoenterostomy and associated with decreased ALP [47]. IE might ameliorate metabolic bone disease by increasing vitamin D absorption in PFIC similarly to Kasai portoenterostomy in biliary atresia and promote bone formation with TBL and BA decrease. However, data relating to osteodystrophy status were not available for patients in our investigation and further study must be done on the effect of IE on bone metabolism, with conduction of a full metabolic panel, confirmation of ALP bone origin with electrophoresis or heat stability testing and body mineral density evaluation.

In the current series, a family history of PFIC was known in only 2 cases, which were pointed as siblings in Table 1. Other family history of liver disease disclosed in Table 1 was self-reported by patients' families, and no accurate diagnosis was known. In addition, we did not make confirmatory genetic testing for 9 patients, since it was not available at the time they were followed at our institution. Recent PFIC studies have assessed surgical outcomes based on different associated mutations [35] , and this information could have added to the understanding of which PFIC patients could benefit more from IE. This information could also have explained the outcome discrepancies in different study populations as pointed out above. Notably, this is the first case-series of PFIC and non-PFIC cholestasis in Latin American patients submitted to a nontransplant surgical intervention, and different mutations could be involved in comparison to North-American and European populations.

Finally, based on the results of this single-center case-series of PFIC and non-PFIC patients submitted to IE as the first surgical treatment option for pruritus, we may conclude that the procedure is safe, with excellent pruritus response after surgery and it permitted survival of the patients with the native liver during medium to long-term follow-up with good quality-of-life. We believe IE should be offered more often as the first-line surgical treatment for non-ESLD cholestasis patients.

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