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**H. Vilca Melendez**
**V. Vougas**
**P. Muiesan**
**P. Andreani**
**G. Mieli-Vergani**
**M. Rela**
**N. D. Heaton**

# Bowel perforation after paediatric orthotopic liver transplantation

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H. Vilca Melendez · V. Vougas
P. Muiesan · P. Andreani · M. Rela
N.D. Heaton (✉)
Liver Transplant Surgical Service,
King's College Hospital, Denmark Hill,
London SE5 9RS, UK
Fax: + 44 171 346 3575
e-mail:hector.vilca_melendez@kcl.ac.uk

G. Mieli-Vergani
Department of Child Health,
King's College Hospital, Denmark Hill,
London SE5 9RS, UK

**Abstract** Bowel perforation is a well-recognized complication following orthotopic liver transplantation. Of 194 paediatric liver transplantations performed in our hospital, 13 patients (6.7 %) developed bowel perforation post-transplantation. Contributory factors included previous operation, steroid therapy and viral infection. The incidence was higher in children who underwent transplantation for biliary atresia after a previous Kasai portoenterostomy. Seven patients (53 % of this group) reperforated. Diagnosis may be difficult and a high index of suspicion is needed.

**Key words** Liver transplantation, intestinal perforation · Intestinal perforation, liver transplantation

## Introduction

Bowel perforation following orthotopic liver transplantation (OLT) is a cause of surgical morbidity and, if the diagnosis is delayed, may become life-threatening [9]. Contributing factors include previous surgery [8, 9, 11], steroid therapy [7], cytomegalovirus (CMV) infection [5, 6, 10], prolonged portal venous crossclamp time [8, 9] and poor nutritional status [8]. Perforations may occur early or late. Early perforations are related either to anastomotic leak or to perforation of areas of denuded submucosa and diathermy injury. Late perforations are observed following regression of lymphoproliferative disease [LPD) [3]. Children who undergo transplantation for biliary atresia appear to be particularly at risk [8, 9]. We report our experience of bowel perforation following paediatric liver transplantation and review the literature.

## Materials and methods

From October 1989 to January 1996, 194 paediatric liver transplantations were performed at King's College Hospital. Thirteen patients (6.7 %) developed bowel perforation post-transplantation (Table 1). There were eight girls and five boys with a median age of 1.1 year (range 1 month to 12 years) and a median weight of 10.8 kg (range 3–58 kg). The underlying liver disease was biliary atresia in ten patients, acute hepatic failure due to Non-A Non-B hepatitis in two and Langerhans' cell histiocytosis in one. All received cadaveric grafts except for one (case 7) who underwent living related liver transplantation (LRLT). Venovenous bypass was not used. Biliary drainage was re-established with hepatico-jejunostomy. Immunosuppression was achieved with cyclosporin A (5–10 mg/kg), azathioprine (1 mg/kg) and steroids (1 mg/kg and gradually tapered), except for one patient (case 8) who was converted to tacrolimus for intractable acute rejection unresponsive to steroid therapy.

Data was collected from our surgical database and medical notes. Values are expressed as median, using the descriptive statistics of Microsoft Excel Analysis ToolPak (GreyMatter International, Cambridge, Mass., USA).

**Table 1** Paediatric patients with bowel perforation after OLT (*Pat. no.* patient number, *Prev. op. before OLT* previous operations before orthotopic liver transplantation, *No epis. perf.* number of episodes of perforation, *No. perf.* number of perforations, *T. ileum* terminal ileum, *T. colon* transverse colon, *FHFxNANB* fulminant hepatic failure caused by Non-A Non-B hepatitis, *LPD* lymphoproliferative disease, *LRLT* living related liver transplantation)

| Pat. no. | Age (years) | Diagnosis | Prev. op. before OLT | No. epis. perf. | No. perf. | Localisation | Treatment | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | 4.5 | Biliary atresia | 2 | 2 | 4 | Stomach, small bowel, T. colon | Oversew, gastrostomy and colostomy | Alive |
| | | | | | 3 | Duodenum, T. ileum, colon | R. hemicolectomy and ileostomy | |
| 2 | 1 | Biliary atresia | 1 | 1 | 1 | Jejunum | Oversew | Alive |
| 3 | 6 | FHFxNANB hepatitis | 0 | 1 | 1 | Roux loop | Oversew | Alive |
| 4 | 4 | Biliary atresia | 2 | 2 | 1 | Roux loop | Oversew | Died (LPD) |
| | | | | | 2 | Roux loop, colon | New Roux loop and oversew colon | |
| 5 | 12 | Biliary atresia | 1 | 2 | 2 | Duodenum | Oversew | Alive |
| | | | | | 5 | Duodenum | Re-OLT and refashion old Roux loop | |
| 6 | 1.1 | Biliary atresia | 2 | 2 | 1 | T. ileum | Oversew | Alive |
| | | | | | 1 | T. ileum | Partial ileum resection and ileostomy | |
| 7 | 4 | Biliary atresia (LRLT) | 1 | 1 | 2 | Roux loop, T. ileum | Oversew and ileostomy | Alive |
| 8 | 2.9 | Langerhans' cell histiocytosis (LPD) | 0 | 2 | 2 | Jejunum, T. ileum | Oversew and resection | Alive |
| | | | | | 10 | small bowel | | |
| 9 | 0.9 | Biliary atresia | 1 | 1 | 1 | T. colon | Oversew | Alive |
| 10 | 0.8 | Biliary atresia | 1 | 3 | 1 | Proximal jejunum | Oversew | Alive |
| | | | | | 1 | Proximal jejunum | Oversew | |
| | | | | | 1 | Jejunum | Resection | |
| 11 | 0.6 | Biliary atresia | 2 | 1 | 1 | Duodenum | Oversew | Alive |
| 12 | 0.1 | FHFxNANB hepatitis | 0 | 2 | 1 | Colon | Oversew | Died (Sepsis) |
| | | | | | 1 | Roux Loop | Retransplant | |
| 13 | 1.1 | Biliary atresia | 1 | 1 | 1 | T. colon | Oversew | Alive |

## Results

Of the 13 patients with bowel perforation, 10 (77%) had undergone previous abdominal surgery (4 patients twice). Nine (70%) had difficult dissection due to dense adhesions at transplantation (two accidental bowel perforations occurred at transplant and loss of intestinal serosa was noted in a third patient). Seven patients (54%) required further mobilisation of the bowel to construct an arterial conduit to the infrarenal aorta. Nine patients (70%) underwent biliary reconstruction by refashioning of a previous Roux loop and four (30%) had a new Roux loop constructed. Median portal venous clamp time was 55 min (range 43–74 min), median cold ischaemia time was 13.5 h (range 5–17 h; 13 h median for all paediatric patients), median intraoperative blood loss was 114 ml/kg (range 34–193 ml/kg) and median operation time was 5 h (range 5–10 h).

Seven patients (53%) developed acute cellular rejection (median day 6 post-transplant) and were treated with high-dose steroids (methylprednisolone 10 mg/kg per day for 3 days). Three patients had early vascular complications post-transplant (hepatic artery thrombosis in two and portal vein thrombosis in one). One patient developed a biliary leak from the cut surface of the liver and required a laparotomy to correct it. One patient underwent a laparotomy for intra-abdominal bleeding on day 1 post-transplant. Eight patients (60%) developed infection early post-transplant, including chest infection in two, subphrenic collections in two and septicaemia in four. Two patients (cases 4 and 8) developed LPD after transplantation after increased immunosuppression for intractable acute cellular rejection. Bowel perforation was related to tumour regression after tacrolimus withdrawal and treatment with oral acyclovir and prednisolone, 20 mg/day, in one child (case 8).

The median onset of bowel perforation was 13 days (range 4–186 days) post-transplant. Features included fever (70%), high white cell count (60%; median $17 \times 10^9$/l), abdominal distension (54%) and abdominal tenderness and intestinal fluid in drain or through the wound (31%). Clinical signs were evident at a median of 3 days (range 1–7 days) before surgery and abdominal X-ray identified free gas in five patients (40%). The site of perforation was jejunum (31%), transverse colon (31%), ileum and Roux loop (23%), duodenum (15%) and stomach (7%). One child (case 1) had simultaneous small and large bowel perforations.

All but three patients had simple oversewing of the perforation. One (case 1) underwent gastrostomy and colostomy for multiple small and large bowel perforations. One child (case 7) had an ileostomy for terminal ileum perforation, and another (case 8) underwent a small bowel resection for multiple perforations.

Seven patients (53%) reperforated at a median of 6 days and all but two at new sites. The site of reperforation was ileum (50%), Roux loop (30%), duodenum (30%), jejunum (16%) and colon (16%), including one child (case 1) with simultaneous small and large bowel reperforations. Symptoms of reperforation included fever (65%), intestinal fluid in drain or through the wound (65%), abdominal distension (30%) and high white cell count (30%; median $18 \times 10^9$/l). Abdominal X-ray demonstrated free gas in two children (30%). The perforation was oversewn in two cases and resected in one: Roux loop revision was performed in two patients and resection and ileostomy were performed in two.

Virological studies were negative in all but two children with Herpes simplex virus in case 1 and CMV, Epstein-Barr virus and parvovirus B19 in case 8. Histopathological studies of the bowel did not demonstrate viral inclusions, but one (case 8) showed extensive infiltration by B cells associated with LPD. All patients recovered with no long-term morbidity and no mortality.

## Discussion

The incidence of bowel perforation after liver transplantation ranges from 1% to 5.3% in adults [2, 4] and from 8.3% to 14% in children [1, 8, 11] (the latter series with 80% of the children being transplanted for biliary atresia). The overall incidence in our series was 6.7%, but it was 14% for children with biliary atresia who had undergone Kasai portoenterostomy. An increased incidence of 20%–83% [8, 9] has been reported following previous upper abdominal surgery [8]. Bowel perforation is an important cause of morbidity and predisposes to infection, particularly fungal, as observed in this group about 5 days after surgery for perforation [9]. Mortality due to sepsis secondary to bowel perforation has been reported to be as high as 30%–50% [8, 9] and 30%–78% [8, 9] following reperforation. In our series there were no deaths, possibly because of the low threshold for surgical re-exploration when there was any clinical suspicion of bowel perforation.

The aetiology of bowel perforation is multifactorial [8, 10]. Previous abdominal surgery and intraperitoneal adhesions may result in difficult or extensive dissection, and unrecognised diathermy injury is likely to be the underlying cause in the majority [1, 2, 3, 5]. Serosal injury or devascularisation of the bowel wall is another potential cause of perforation [2], and it has been suggested that postoperative immunosuppression makes it difficult to seal microperforations [11]. Accidental bowel perforations during transplantation do occur, but if repaired they are seldom a source of recurrent perforation [8]. Retransplantation has been associated with an increased incidence of bowel perforation [8]. Steroid therapy is another potential cause of bowel perforation, but this has not been convincingly demonstrated [8, 9, 11]. A recent study compared similar groups of patients with and without perforation with the same cumulative doses of steroids and this factor did not reach significance in a regression analysis [9]. Liver dysfunction or rejection was not associated with perforation [8]. Steroids and bowel ulceration and perforation have been reported in nontransplant patients, usually after long-standing treatment; however, 30% developed bowel perforation within 3 weeks of starting therapy [7]. CMV infection has also been associated with bowel perforation [5, 6, 10] but was not significant in our series, confirming reports from other centres [8, 9, 11].

A prolonged hepatectomy [9] and higher transfusion requirements have been considered as statistically significant predictors of bowel perforation in patients who have undergone one or more previous laparotomies, possibly because the haemostatic procedures caused bowel injury [9, 11]. Within our series these children had a higher intraoperative blood loss (median 114 ml/kg vs 97 ml/kg median for all paediatric patients); however, the operative time was not prolonged (median 5 h). It is possible that an ischaemic injury could be produced by compromised mesenteric venous flow during prolonged portal crossclamping [8, 9] or in the presence of severe portal hypertension. This could be exacerbated if a degree of mesenteric congestion persists after OLT, for example, in association with a hypoplastic portal vein [9]. Early postoperative portal vein thrombosis has been associated with bowel perforation [9] and suggests that this is a possible mechanism. Intra-abdominal bleeding post-transplant requiring re-operation has been reported as a risk factor for perforation [9]; however, this may reflect extensive dissection or difficult surgery. Poor nutrition is another reported risk factor [8].

Bowel perforation is usually identified between day 10 and day 13 post-OLT [8, 9], but the diagnosis remains

difficult because the immunosuppression tends to alter the clinical symptoms and signs. A high index of suspicion is required in those at risk [5, 8, 9, 11], as a delay in diagnosis is associated with significant morbidity and mortality [8].

Reported features suggesting bowel perforation include fever, the presence of bowel contents from a drain, a rise in white cell count and abdominal distension and tenderness [8, 9, 11]. It can also present as fever of unknown origin or generalised sepsis in the absence of abdominal signs. Free gas seen on a plain abdominal X-ray has been reported in 30%–70% of cases [8, 9, 11]. The presence of intestinal contents in drains and free gas on abdominal X-ray are considered late findings [8]. Abdominal ultrasound has been reported to be helpful in localising and aspirating intraperitoneal collections if perforation is suspected [11].

Perforation occurs in all parts of the gastrointestinal tract. Overall it has been reported in order of highest incidence in Roux loop (62%), ileum (50%), small bowel (43%), colon (20%), jejunum (10%), duodenum (9%) and stomach (2%) [8, 9, 11]. The initial surgical treatment is oversewing of the perforation [7, 11], particularly for the small bowel, but it has been suggested that resection should be performed for colonic lesions to prevent reperforation [9]. Segmental resection and primary anastomosis should be performed if multiple bowel perforations are present in a localised segment and an enterostomy/colostomy is helpful if there are multiple colonic perforations [5, 8]. Resection and proximal ileostomy have been recommended for terminal ileal and colonic perforations [8]. More radical suggestions have included planned re-exploration between 3 and 5 days post-OLT for high-risk cases, but we currently limit it to those children with ongoing, unexplained fever [8].

The overall incidence of reperforation reported in the literature ranges from 31% to 40% [8, 9, 11]. Our incidence of reperforation was also high (53%), occurring at different sites in 60% of cases [8]. The anatomical site of reperforation is variable, occurring in order of highest incidence in the small bowel (47%), Roux loop (25%), duodenum (14%), stomach, jejunum, ileum and colon (10%) [8, 9, 11]. Aggressive antifungal, and antibiotic therapy has been recommended in these cases [9].

The surgical approach to a reperforation should be excision of the affected segment or oversew if it occurs in a distant site or creation of a new Roux loop, despite loco-regional contamination. A diverting enterostomy is indicated if there is evidence of devascularisation or severe contamination, or if the distal ileum or colon is involved. Reperforation has not been found to be related to the method of primary repair [8]. Routine second look abdominal exploration [3] or surgical management with semiopen treatment of peritonitis has been recommended [1, 5], but we would prefer close monitoring with a low threshold for reoperation.

## References


1. Bilik R, Yellen M, Superina RA (1992) Surgical complications in children after liver transplantation. J Pediatr Surg 27: 1371–1375
2. Koep LJ, Starzl TE, Weil R III (1979) Gastrointestinal complications of hepatic transplantation. Transplant Proc 11: 257–261
3. Koneru B, Tzakis AG, Bowman J III, Casavilla A, Zajko AB, Starzl TE (1988) Postoperative surgical complications. Liver transplantation. Gastroenterol Clin North Am 17: 71–91
4. Lebeau G, Yanaga K, Marsh JW, Tzakis AG, Makowka L, Gordon RD, Todo S, Stieber AC, Iwatsuki S, Starzl TE (1990) Analysis of surgical complications after 397 hepatic transplantations. Surg Gynecol Obstet 170: 317–322
5. Marujo WC, Stratta RJ, Langnas AN, Wood RP, Markin RS, Shaw BW Jr (1991) Syndrome of multiple bowel perforations in liver transplant recipients. Am J Surg 162: 594–598
6. Mayoral JL, Loeffler CM, Fasola CG, Kramer MA, Orrom WJ, Matas AJ, Najarian JS, Dunn DL (1991) Diagnosis and treatment of cytomegalovirus disease in transplant patient based on gastrointestinal tract manifestations. Arch Surg 126: 202–206
7. Remine SG, McIlrath DC (1980) Bowel perforation in steroid-treated patients. Ann Surg 192: 581–586
8. Shaked A, Vargas J, Csete ME, Kiai K, Jurim O, Colquhoun S, McDiarmid SV, Ament ME, Busuttil RW (1993) Diagnosis and treatment of bowel perforation following pediatric orthotopic liver transplantation. Arch Surg 128: 994–999
9. Soubrane O, El Meteini M, Devictor D, Bernard O, Houssin D (1995) Risk and prognostic factors of gut perforation after orthotopic liver transplantation for biliary atresia. Liver Transplant Surg 1: 2–9
10. Wood RP, Rosenlof LK, Shaw BW Jr, Pillen TJ, Williams L (1988) Complications requiring operative intervention after orthotopic liver transplantation. Am J Surg 156: 513–518
11. Yamanaka J, Lynch SV, Ong TH, Balderson GA, Strong RW (1994) Post-transplant gastrointestinal perforation in pediatric liver transplantation. J Pediatr Surg 29: 635–638