# Acceptance type: Oral Presentation

### 1

## Impact of food intake on the efficacy of Teduglutide treatment in adult patients with short bowel syndrome

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#### Abstract

Introduction: Teduglutide (TED), a GLP-2 agonist, is effective to reduce Parenteral Nutrition (PN) dependence in patients with Short Bowel Syndrome (SBS), with some heterogeneity of response between patients. PN reduction at 6 months of TED treatment is significantly associated with patients’ oral intake at baseline (1). We aimed to study the impact of food intake on TED efficacy in the longer term and the evolution of food intake during treatment.

 Methods: This work was a monocentric retrospective study conducted in an expert center of PN. We enrolled 49 SBS patients treated with TED for at least one year. Information regarding oral food intake and PN prescription at the time of initiation and during treatment were collected in medical charts. Food intake is expressed using a ratio: FIR = Daily caloric intake (kcal) / Resting Energy Expenditure (REE) (kcal). REE is calculated using Harris and Benedict formula.

Results: Baseline food intake at treatment initiation was collected for 49 patients, and at least two values of food intake during treatment were available for 44 of these patients. The mean follow-up duration of the patients is 27 months (±2.8).

There is a positive correlation between food intake at treatment initiation and reduction of PN volume during treatment (r=0.38, p=0.007). Moreover, patients who reached PN weaning with TED (n=19) had a much higher food intake before TED than those who remained dependent to PN (n=30), p<0.001 (FIR=2.3 vs 1.6). These 19 weaned patients were all hyperphagic (FIR>1.5) before TED initiation.

In addition, patients who had the lowest food intake before TED initiation (non-hyperphagic, FIR<1.5, n=13) significantly increased their oral intake during treatment (p=0.001, FIR=1.0 vs 1.6).

Those who presented hyperphagia before TED maintained their oral intake.

Conclusion: This study confirms the positive impact of basal oral dietary intake on the efficacy of TED in the long term, which supports the idea of promoting food intake in SBS patients before TED initiation. Furthermore, treatment with TED seems to have a beneficial effect on patients’ food intake when it was low before TED initiation, which could be linked with the better physical and/or psychological condition of the patients.

(1) Joly F et al. Six-month outcomes of teduglutide treatment in adult patients with short bowel syndrome with chronic intestinal failure: A real-world French observational cohort study. Clin Nutr. 2020 Sep;39(9):2856-2862. doi: 10.1016/j.clnu.2019.12.019.

### 2

## Determinants of parenteral nutrition (PN) weaning in a pediatric cohort of short bowel syndrome (SBS) patients in the era of GLP-2 analogue treatment

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#### Abstract

Introduction: SBS is the main cause of chronic intestinal failure. New treatments such as GLP-2 analogues aim at improving intestinal mucosal trophicity and absorption while reducing PN dependence. The aim was to identify the factors determining PN weaning  in children with SBS.

Methods: A monocentric retrospective study involved all SBS children followed between 2015 and 2020. PN dependence was defined as non-protein PN calories (kcal/day)/ REE (kcal/day, from Schofield). Statistical analysis included non-parametric tests, Mann-Whitney and Chi-2 for quantitative and qualitative variables respectively, and a multivariate Cox model. Results were expressed as median and IQR.

Results: We included 137 patients with a median age at start of follow-up of 3.7 years (IQR 1.3-8.4). SBS types: 30% jejunostomy or ileo-rectal anastomosis (type 1), 41% jejuno-colic anastomosis (type 2) and 29 % jejuno-ileal anastomosis (type 3). The median length of the remaining SB was 50 cm (IQR 27-73). The main causes for SBS were: midgut volvulus (23.4%), necrotizing enterocolitis (22.6%), long-segment Hirschsprung disease (21.2%), gastroschisis (15.3%) and atresia (13.1%). The median PN dependence at inclusion was 104 % (IQR 80-122) and 83 % (IQR 50-111) at the end. Thirty patients received Teduglutide (TED) at 0.05mg/kg/day, from a median age of 8.5 yrs (IQR 7.2-11.0). The median treatment duration was 36 months (IQR 33-39); 27 patients were still treated at the end of follow-up. Fifty-five patients (40%) were weaned during the follow-up. Factors positively associated with PN weaning were: length of remaining SB (p<0.001) and TED treatment (p=0.05). Initial PN dependence was negatively associated with weaning (p<0.001), as well as SBS type 1 (p=0.04).

Conclusion: As expected, SB length and the presence of colon were predictive factors for PN-weaning. Teduglutide becomes one of the factors positively associated with weaning. It should be considered in SBS but timing remains debated.

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### 3

## Development of a Core Outcome Set for Pediatric Chronic Intestinal Failure

Drs. Aysenur Demirok1, Dr. Sjoerd Nagelkerke1, Prof. Dr. Marc Benninga1, Dr. Jutta Köglmeier2, Dr. Annika Mutanen3, Dr. Henrik Arnell4, Dr. Judith Felcht5, Dr. Dominique Guimber6, MoS RN Christina Wahlstedt4, Drs. Yaron Avitzur7, Dr. Cécile Lambe8, Dr. Merit Tabbers1

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#### Abstract

**Introduction**

In research on pediatric chronic intestinal failure, heterogeneity in reported definitions and outcomes exists. This results in reporting bias and impossibility of evidence synthesis. Also, reported outcomes should be clinical relevant to both healthcare providers, parents and patients in this field. Therefore, the aim of this study is to create a core outcome set for pediatric chronic intestinal failure. This is a set of standardized outcomes agreed upon by key stakeholders.

**Methods**

Based on data from a recent systematic review, reporting that almost hundred different outcome measures are used in research concerning pediatric chronic intestinal failure, a Delphi study was performed through quantitative questionnaires among key stakeholders. This was followed by  a consensus meeting with an expert panel including patient representatives and health care professionals from various disciplines throughout Europe to achieve consensus on the core outcome set.

**Results**

Seventy-two stakeholders (79%) completed all three rounds of the Delphi process. Ninety-eight outcomes were assessed and five new outcomes were added in the first round. During the consensus meeting two outcomes were modified to make it more specific and to prevent confusion. The following ten outcomes were included in the final COS: weaning from parenteral nutrition, growth, mortality, central line related infection, central line longevity, sepsis not related to central line infection, central line related thrombosis, IFALD, (serious) adverse events and health related quality of life.

**Conclusion**

This pediatric chronic intestinal failure COS consists of ten outcomes important for all key stakeholders. Usage of at least two outcomes from this set in future research will minimize outcome heterogeneity and enhance the value of evidence synthesis. This will eventually lead to better quality of research in this field, resulting to more evidence-based clinical practice.

Figure 1. Delphi Process

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### 5

## Development of a Transition Protocol for Pediatric Chronic Intestinal Failure

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#### Abstract

**Introduction**

Life expectancy of children with chronic intestinal failure has greatly improved. This is mainly due to improvement of home parenteral nutrition (HPN) and prevention and treatment of its complications. Children are now able to grow into adulthood which requires transfer from pediatric to adult health care. However, a protocol for a structured transition is lacking. Therefore, as first step in developing a protocol, we investigated the view of health care professionals from various disciplines in this field concerning transition.

**Methods**

A survey consisting of 20 items for transition was sent out to healthcare professionals throughout Europe, United Kingdom, United States and Canada. Next to 20 items, an open ended question to fill in other suggestions was also included. Interventions scoring higher than 80% by the participants, were included in the protocol. Interventions scoring between 50% and 80%  and other own suggestions were discussed during a consensus meeting and included when consensus was reached.

**Results**

A total of 80 healthcare professionals from seventeen various countries (Belgium, Canada, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, Portugal, Prague, Scotland, Spain, Sweden, United Kingdom and United States) participated in this survey study, see figure 1. A consensus meeting was held in Amsterdam, The Netherlands, with a panel of gastroenterologists, surgeons, dietitians, specialized nurses and patient representatives in the intestinal failure field. A list of most effective interventions was created. This is the final list outlined: transition starting 1-2 years prior to transfer, psychological screening and offering help if needed, assessment of knowledge, understanding and autonomy of the patient, providing patient with a medical summary, initiating discussion about transition, directing all questions to patients and instructing how to keep track on health care related practices, effective transmission of information from the pediatric to the adult team, combined consultation with the adult and pediatric team prior to transfer and if possible, nurse specialist working in both services.

**Conclusions**

A protocol for transition for pediatric chronic intestinal failure will contribute to a more structured transition process in this rather vulnerable patient group. Therefore, the next step is to assess the view of patients who soon will be transferred or are already have been transferred (aged between 16 and 24) and their parents through validated and reliable Transition Readiness Assessment Questionnaires (version 6.0). Finally, the combination of the most-effective-interventions list and the view and current experience of patients and their parents in various countries will help to create a more standardized protocol. This transition protocol will lead to better management of a complex process in a very vulnerable patient group.

Figure 1. Participation of health care professionals (n=80)

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### 6

## Anemia in pediatric intestinal failure: prevalence, etiology and predictors

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#### Abstract

**Introduction**: Anemia is an important health problem in children with intestinal failure (IF). It can contribute to neurodevelopmental delay and lower health related quality of life. Children with IF are at risk for iron deficiency anemia (IDA), anemia of inflammation (AI) and mixed IDA/AI. There is a paucity of data on the frequency of these types of anemias in children with IF and the contributions of the underlying etiologies is not well described. An improved understanding of the prevalence and causes of these anemias is needed to effectively treat and prevent anemia and its complications in children with IF.

**Methods**: All children ages 6 months-18 years-old with intestinal failure, defined as the need for PN > 60 days due to intestinal disease or dysfunction, followed by the Group for Improvement of Intestinal Function and Treatment (GIFT) Program at SickKids Hospital between January 1, 2012 and December 31, 2021 were included. Children required a minimum of 1 complete blood count (CBC) and were excluded if they had intestinal transplant or had discontinued PN or follow-up before December 31, 2019. Data was retrieved longitudinally from electronic medical records. Anemia was defined by age-specific norms for hemoglobin; iron status was determined using soluble transferrin receptor (sTfR) and sTfR-ferritin index (sTfR-F). Frequencies of IDA (defined by anemia with ferritin <30 ug/L and elevated sTfR or sTfR-F>1.5), AI (anemia with ferritin > 100 ug/L and normal sTfR or sTfR-F <1) and mixed IDA/AI (anemia with ferritin 30-100 ug/L and elevated sTfR or sTfR-F>2) were determined. Period prevalence was calculated using the number of patients with anemia at any time during the 10-year study as the numerator and total number of patients as the denominator. Persistent anemia was defined as having anemia on > 2 occasions in patients with anemia and >1 CBC measurement. Statistical analyses included χ2 and test of proportions.

**Results:** Fifty-four children met inclusion criteria. Median age at end of study was 4.8 ([IQR] 2.7-8.3) years, 52% male and median duration of follow up 3.4 (1.1-6.6) years. Short bowel syndrome (SBS) was present in 74%. The period prevalence of anemia was 76%; of 38 children with anemia and >1 annual CBC, 74% had persistent anemia. Of those with anemia, 11 (27%) had IDA, 27 (66%) AI and 7 (17%) mixed anemia; 7 children had >1 subtype of anemia. There was no difference in prevalence of anemia subtypes based on SBS status.

**Conclusions:** A high 10-year period prevalence of anemia (76%) was found in this study. Only 27% had IDA, compared to 66% with AI. The relatively lower rate of IDA may be a result of routine iron supplementation in TPN. Comparison of this single center data to other Canadian centers (study ongoing) will provide an additional insight into the connection between methods of iron supplementation and frequency of anemia.

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### 7

## Woman with intestinal and renal failure undergoing treatment with parenteral nutrition, GLP2, and hemodialysis. Accepting complexity

MD Martin Buncuga doctor, MD Dino Moretti doctor

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#### Abstract

Introduction: The mainstay for patients with II is home parenteral nutrition (HPN). Renal failure (RF) is a potential complication in this population, with a prevalence of 20 to 50% with II with HPN. GLP2 analogues and hemodialysis are therapeutic options. Intestinal and kidney transplantation (Tx) are options of last resort. Clinical case: A 67 woman, with type 3  II due to post-surgical short bowel syndrome with type 1 anatomy. She started cyclical daily HPN in 2007. In 2013 she was evaluated for Tx and did not qualify for it or for autologous reconstruction surgery. In 14 years of PN, he presented 3 catheter-related infections, one with septic symptoms and RF associated with good recovery. Start Teduglutide 0.05 mg/kg/ day in 2016 with good tolerance, achieving a 40% reduction in volume (ESPEN classification D3 to C2). She evolves with a depressive syndrome and poor adherence to oral diet and treatment. In 2018 she presented proteinuria. She complicates with confluent, jugular and right subclavian thrombosis in 2020, new evaluation for intestinal TX due to loss of vascular access. Semi-implantable right femoral vascular access for PN. Started oral acenocumarol with good absorption and range. She evolved with good Cl Cr, so she was maintained on the dose of Tedoglutide despite developing Nephrotic Syndrome in 2021 with a renal biopsy that reported focal and segmental glomerulosclerosis without IgA, IgG, C3, Fibrinogen, Kappa or Lamda deposits. Teduglutide was reduced to 50% and daily and NP intake is increased when ClCr<50. She entered hemodialysis in December 2021 due to a right femoral Permancath, with a three-week dialysis regimen. Renal transplantation is being discussed, but given the need for oral immunosuppressive medication, the decision was made to reassess the patient for combined SI and kidney transplantation. The patient died in 2022 during follow-up without reaching Tx due to septic shock at the starting point of the hemodialysis catheter.Discussion: HPN is a standard of care in II that has been carried out in our country with quality for more than 20 years. Tedoglutide was initiated as compassionate use and was monitored so all events were reported. No dose adjustment is required in adult patients with mild RF, in moderate or severe RF the daily dose should be reduced by 50%. An open-label study evaluated the pharmacokinetics of teduglutide in 36 RF patients. Compared with healthy individuals, in individuals with end-stage renal disease the area under the concentration versus time curve extrapolated to infinity (AUCinf) and maximum plasma concentration (Cmax) were approximately 2.59 and 2.08 times higher, respectively. There are no reports of associations of Tedoglutide use with focal segmental glomerulosclerosis. Conclusions: In Argentina, treatment can be offered for II in all its stages and with other installed organic insufficiencies, accepting its inherent complexity.

### 9

## Ex vivo Whipple procedure and intestinal auto-transplantation - 23 yo patient with gigantic solid pseudopapillary tumor involving the pancreas head and the root of the mesentery

Tomoaki Kato1, Joshua Weiner1, Masato Fujiki2

1Columbia University, New York, USA. 2Cleveland Clinic, Cleveland, USA

#### Abstract

23 yo female with a solid-pseudopapillary tumor of the pancreas.

The tumor is located at the body of the pancreas measuring 15.2 x 11.4 cm, encasing SMV, splenic vein, and portal vein, there are numerous collaterals around porta hepatis. The common hepatic artery and the splenic artery appeared to be encased as well.

The tumor was removed with the pancreas head, duodenum, entire small bowel, and the right hemi-colon. The tumor was removed at the back table. The vessels were separated from the tumor at the back table, and the entire small bowel and the right hemi-colon were re-implanted as an auto-graft without the stoma.

The patient did very well after the surgery. She restored 100% oral regular diet and had no recurrence of the tumor at her 11-month follow-up.

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### 10

## Ex vivo Whipple procedure and partial intestinal auto-transplantation - a 57yo with a retroperitoneal leiomyosatrcoma that involves root of mesentery

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#### Abstract

57 yo male with retroperitoneal leiomyosarcoma.

The patient underwent chemotherapy and radiation with slowly progressing disease.

The tumor is located at the retroperitoneum measuring 5 x 4.1cm involving pancreas head and mesenteric vessels.

The tumor was removed en block with the pancreas head, duodenum, and right hemi-colon. The organ block was moved to the back table and was flushed with cold preservation solution.

The secondary branches of the SMA and the SMV were disscted and the partial intestinal auto-graft was created. Approximately 250cm of the small bowel was re-implanted without the stoma.

The patient did well after the surgery. He required temporary fluid supplements. But subsequently achieved intestinal autonomy with oral intake. He is currently alive with no local recurrence at his 11-month follow up.

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### 11

## Incidence and management of mechanical and infectiologic complications of different central venous catheters in use for home parenteral nutrition

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#### Abstract

**Introduction**

Loss of access of central venous catheters (CVCs) increases the mortality of patients with short bowel syndrome (SBS) under long-term home parenteral nutrition (HPN). The aim of our investigation was to identify the incidence of mechanical and infectiologic complications comparing different CVC types in a typical SBS cohort and to analyze interventional CVC “shaving” procedures: CVC occlusions can be managed interventionally and surgical removal prevented, but long-term patency data after such procedures is scarce.

**Methods**

For this retrospective cohort study at a specialized intestinal failure and rehabilitation unit (University of Bonn), patient data from the clinical documentation system and a prospective database spanning 16 years was analyzed. CVC dwell times were distinguished by Kaplan Meier survival analysis between the CVC types (broviac “A”, broviac “B” and port catheters). Specific complications (occlusion, infection, displacement and material defect) were analyzed. Explantation rates and catheter dwell times (CDT) of “shaved” vs. “non-shaved” catheters as well as incidence of “complicated” vs. “uncomplicated” catheter related bloodstream infections (CRBSI, ESPEN classification) were identified and compared.

**Results**

Overall, 211 CVCs in 77 patients with SBS under HPN could be enrolled with a total of 70.451 “CVC-days”. Comparing the two different broviac catheter types, type “B” was found to be significantly superior to type “A” regarding complications of occlusion, infection and material defects (log rank test: p=0,05; p=0,026; p=0,005 respectively). Only catheter displacement occurred less frequently to type “A” (log rank test: p=0,023). Port catheters were found to be significantly inferior to both tunneled CVCs displaying the highest incidence of infection (2,13 events/1000 catheter days) and shortest CDT regarding the explantation due to CRBSI (log rank test: p=0,002) (**figure 1**).

Interventional catheter “shaving” was performed 91 times in 18 patients: It significantly increased the CDT from a median of 131 days (IQR: 62; 258) to 388,5 days (IQR: 262; 731) (Mann-Whitney-U-test: p= <0,001) (**figure 2**). Within the first 30 days after “shaving”, 9 CRBSI were diagnosed of which 6 catheters had to be removed.

Overall, 102 CRBSI occurred of which 20 % could be treated by specifically directed anti-infective therapy whereas 80 % had to be explanted; 22 % were “complicated” CRBSI and resulted in CVC explantation while 78 % were “uncomplicated”.

**Conclusions**

Different complication rates and CDT were seen depending on CVC type in our HPN cohort. For infectiologic complications, tunneled CVC systems (broviac) were significantly superior. Interventional catheter “shaving” is a viable alternative to the recommended approach with fibrinolytics to restore catheter patency. To ensure long term venous access for SBS patients, differentiated CVC management and monitoring for complications and device-related problems is mandatory.

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### 12

## The Czech Republic (EU) National Home Parenteral Nutrition Registry: Analysis of Current Data and Trends

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#### Abstract

Introduction: The Registry of Home Nutritional Support (REDNUP) was established in 1993 by the Society of Clinical Nutrition and Intensive Metabolic Care (SKVIMP) and collects data on adult and pediatric patients on home parenteral nutrition (HPN). It allows to evaluate trends in HPN by updated analysis and stratification.

Methods: Based on the data reported from 27 HPN centers providing HPN, prevalence, incidence, indications, diagnoses, weaning, and complications were analyzed for the time–to–event using the exploratory data analysis. Continuous data are presented as median or mean with 95% CI (p<0.05), categorical data as count and percentage.

Results: Short bowel syndrome (SBS) has the annual prevalence 5.92 and the incidence 1.5/100 000 in the Czech Republic. The registry contains data on 1661 patients. In 2021, there were 633 active patients, while the number of new patients for 2021 was 162. The prevalence has been increasing over the years, but the average number of catheter days per patient has been stable (268 days). Adult patients include 94.5% of the entire group, women slightly predominate (57.4%). The average age is 59.8 ± 19.4 years for the adult group. A lifelong HPN dependency is expected in 19.3% patients. Intestinal autonomy is achieved in 20% patients within the first year, and in 48% after 5 years. Patient survival is around 75% in the first year, 60% in five years, and 47% in 10 years. Higher early mortality is associated with inclusion of palliative care patients. Based on the analysis of data from 2007 to 2021, SBS was present in 35.3%, intestinal obstruction in 22.4%, and malabsorption in 13.3% patients. The rest was split among fistulas, anorexia, dysphagia, or remained unspecified. The majority of SBS were type I (51.8 %) and II (18.1 %). Dominant indications for HPN were non-malignant surgical indications (26.9%), malignancies (25.4%), Crohn disease (18.8%), mesenteric occlusions (17.4%), and pseudo-obstruction (5.7%). Mobility for a substantial part of the day was reported from 63.0% HPN patients, economic activity and independence from 24.3% out of 809 economically potent patients. A tunneled catheter was primarily used in 53.1%, IV port in 14.8%, and PICC in 31.6% patients with an increasing trend. Ready-to-use bags were used in 61.5% patients. A total of 58.6% patients were administered one bag per day / 7 days. The sepsis ratio per 1000 catheter days decreased from 0.79 in 2013 to 0.14 in 2021, catheter occlusions from 0.10 to 0.04, and thrombotic complications from 0.06 to 0.04. Prevalence of metabolic bone disease and PNALD was 15.2% and 26.4%.

Conclusion: Prevalence of HPN patients had the increasing trend until 2016, since then it has remains stable at 162 patients per year in average. Most patients are expected to terminate HPN within the first year. Incidence of catheter related complications has a decreasing trend, and remains in a low range. HPN has full reimbursement in the Czech Republic.

### 13

## Renal function and complications in children with Intestinal Failiure on Long-Term Parenteral Nutrition

Dr. Eduardo Freitas Hatanaka MD1,2, Dr. Maria Fernanda Carvalho de Camargo MD1, Dr. Paulo Cesar Koch Nogueira MD, PhD1,2, Dr. Heitor Pons Leite MD, PhD1,2, Dr. Mariana Janiques Barcia Magalhães Fonseca MD1, Dr. Fernando Kazuaki Hamamoto MD, MSc1, Dr. Keilla Mayumi Castelo Branco Uchoa MD1, Giovana Sertori Galati Sabio RDN, MSc1, Amanda Michelly Braga da Mata RDN2, Dr. Camila Penteado Genzani MD1

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#### Abstract

**Introduction**:  Long-term parenteral nutrition (PN) has been associated with renal complications, including hypercalciuria, nephrocalcinosis/nephrolithiasis, proteinuria and reduced glomerular filtration rate (GFR). Pediatric data are scarce and mostly short-term or restricted to transversal studies. Our study aimed to evaluate renal complications in children with intestinal failure (IF) receiving long-term PN.

**Methods:** We performed an observational longitudinal study of patients with IF followed up in a pediatric intestinal rehabilitation center. Outcome variables were estimated glomerular filtration (eGFR) rate, hypercalciuria, nephrocalcinosis/nephrolithiasis, proteinuria, phosphaturia and oxaluria during the follow-up period. The exposure variables were age, duration of parenteral nutrition and type of short bowel syndrome (SBS). The study was approved by the hospital's ethics committee.

**Methods:** Twenty-four children (54% males), aged 74 months (16 ; 205) with a median time receiving parenteral nutrition of 47.5 months (IQ 26.5). Data related to renal function were evaluated in two moments, with a median interval of 8 months (IQ 4.5 months). Hypercalciuria was observed in 60.8% and 58.3%, increased phosphaturia in 25% and 18.7%, increased oxaluria in 36.8% and 25% and increased microalbuminuria/proteinuria was observed in 19% and 13.6% of patients, respectively, at moments 1 and 2. Despite de high incidence of hypercalciuria, nephrolithiasis was observed in one patient. In addition to the patient with nephrolithiasis, small and hyperechogenic kidneys were observed in another patient in the image evaluation. The median eGFR rate was 164.5 ml/min/1.73m2 (IQ 52.7) and 195 ml/min/1.73m2 (IQ 38.7) at moments 1 and 2, respectively. There was only one patient with reduced eGFR (77.7 and 78 ml/min/1.73m2) at both times. A significant association was observed between SBS (type 3) and eGFR, with β-coefficient = - 41.07 (95% confidence interval [CI], -66.5 ; -15.6, p=0,002).

**Conclusion:** The high frequency of hypercalciuria, microalbuminuria and proteinuria, in addition to the state of glomerular hyperfiltration represent risk factors for long-term renal dysfunction. Despite the high incidence of hypercalciuria, nephrocalcinosis/nephrolithiasis was observed in olnly one patient. Long-term monitoring of various aspects of renal function is essential to characterize the effects of prolonged PN on kidney functions in pediatric patients.

### 14

## Inflammation and micronutrient deficiency as major risk factors for anemia in children with intestinal failure

Dr. Eduardo Freitas Hatanaka MD1,2, Dr. Maria Fernanda Carvalho de Camargo MD1, Dr. Paulo Cesar Koch Nogueira MD, PhD1,2, Dr. Heitor Pons Leite MD, PhD1,2, Dr. Mariana Janiques Barcia Magalhães Fonseca MD1, Dr. Camila Penteado Genzani MD1, Dr. Fernando Kazuaki Hamamoto MD, MSc1, Dr. Keilla Mayumi Castelo Branco Uchoa MD1, Dr. André Ibrahim David MD, PhD1,2, Giovana Sertori Galati Sabio RDN, MSc1

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#### Abstract

**Introduction:** Most data on anemia in children with intestinal failure (IF) have been obtained from studies in which the data were collected at a single point in time. We aimed to identify the frequency of anemia and factors associated with hemoglobin levels in children with IF during their course of home parenteral nutrition.

**Methods:**We performed a longitudinal study of patients with IF followed up at a pediatric intestinal rehabilitation center, between May 2015 and June 2022. Outcome variables were hemoglobin levels and prevalence of anemia during the follow-up period. The exposure variables were age, duration of parenteral nutrition, chronic disease, and serum concentrations of C-reactive protein, iron, copper, selenium, vitamins A, D, B12, and folic acid.  The study was approved by the hospital's ethics committee.

**Results:**Twenty-five children with a median time of receiving parenteral nutrition of 40.7 months were included. A median (IQR) of 40.7 (25.2; 58) hemoglobin measurements were performed per patient. Mean (SD) hemoglobin was 10.7 (1.8) g/dL at baseline and 11.6 (0.9) g/dL in the last observation (paired t-test, p=0.07); 32% of patients had mean hemoglobin values below the lower limit for age. In a multivariable predictive model,   having C-reactive protein > 1 mg/dL was associated with a decrease of 0.57g/dL in hemoglobin (95% confidence interval [CI], -0.90; -0.24, p=0.01), and an increase of 1 mg/mL in serum vitamin A concentration represented an increase of 0.93 g/dL in hemoglobin level (95% CI, 0.24; 1.61, p=0.008).

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***(Figure 1 – Linear predictions of serum vitamin A concentrations on Hemoglobin levels during the follow-up period, adjusted for C-reactive protein concentrations)***

**Conclusion:** Anemia affects almost one-third of children with IF and its frequency decreases during the follow-up period. Hemoglobin levels are associated with inflammatory response and serum micronutrient concentrations.

### 16

## Understanding Wernicke’s Encephalopathy in Pediatric Intestinal Failure: a case series and risk analysis

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#### Abstract

**Introduction:** Vitamin and mineral deficiencies have been reported in numerous cohort studies and case series in children with intestinal failure (IF). Despite this emerging evidence there are no specific reports on thiamine (B1) deficiency or Wernicke's encephalopathy (WE). WE can present as oculomotor dysfunction, altered mental status and cerebellar dysfunction. The administration of dextrose in the setting of thiamine deficiency can be harmful because glucose oxidation is a thiamine-intensive process that may drive the insufficient circulating thiamine intracellularly, thereby precipitating neurologic injury. Since children with IF are highly dependent on constant glucose infusions, they may be at increased risk for developing complications of thiamine deficiency. Our objective was to review cases of WE and evaluate thiamine levels in children with significant parenteral nutrition (PN) dependence.

**Methods**: We completed a retrospective cohort study of children with IF. We included children ages 0-17 years old, with routine follow up thiamine levels (serum or whole blood), and significant dependency on PN, defined as a parenteral nutrition dependency index (PNDI) of > 80%. All patients received customized PN, and multivitamin product (Multi-12/K1 pediatric) added to PN at home with a set amount of thiamine (1.2 mg). Demographic data, PN composition, PN days and thiamine bloodwork levels were collected from patient charts. Statistical analysis included summary statistics and a logistic regression model to evaluate anatomical and PN variables that may influence thiamine levels. A p-value of <0.05 was considered significant.

**Results:** Thirty-five patients, median age 4.5 years old (IQR= 3 days-16 years old) were included in the analysis. Median length of PN therapy was 1450 days (IQR=78 - 6756 days). Logistic regression of whole blood thiamine levels demonstrated females (p<0.05) and older children (p<0.01) were more likely to have lower thiamine levels within the normal range. There were no asymptomatic patients identified with low thiamine levels. Four patients had thiamine deficiency and were diagnosed with WE. The four patients presented to hospital with altered levels of consciousness (LOC) and had common pre-clinical factors including recent increases in PN calories or glucose infusion rates and non-standard or missed vitamin administration.

**Conclusion:** Children with intestinal failure and high PN dependency are at risk for thiamine deficiency. Wernicke’s encephalopathy should be considered when these children present with altered LOC. Females and older children with high PNDI’s may be at highest risk. The development of age and sex specific pediatric multi-vitamins should be considered.

### 17

## Unexpected upper gastrointestinal polyps in patients with short bowel syndrome treated with teduglutide: need for a close monitoring

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#### Abstract

Introduction: Short bowel syndrome with intestinal failure (SBS-IF) requires use of parenteral support (PS) and highly impacts patients quality of life. Teduglutide (TED), a GLP-2-analog, has proven efficacy reducing the need for PS. After the publication of two case reports describing the development of duodenal and jejunal polyps in patients with SBS treated with TED (Ukleja 2018, Pevny 2020), we aimed to verify this risk in a cohort of SBS patients treated with TED in an expert center of chronic intestinal failure.

Methods: A retrospective study was conducted in 35 SBS patients treated with teduglutide for at least one year in a home parenteral nutrition expert center. All patients underwent at least one follow-up intestinal endoscopy during treatment. The lesions observed were described.

Results: In the 35 patients, the small bowel length was 74 cm [IQR 25-100], and 23 patients (66%) had a colon in continuity. Upper and lower gastrointestinal endoscopy was performed after a mean treatment duration of 23 months [IQR 13-27] and found a polypoid lesion in 10 patients (6 with a colon in continuity, 4 with an end-jejunostomy) and no lesion in 25 patients. In 8 out of these ten patients, the lesion was found in the small bowel. Five of these lesions presented an aspect of hyperplastic polyp without dysplasia, and three of a traditional adenoma with low-grade dysplasia. The clinical characteristics of these patients and their lesions are summarized in the table below.

Conclusion: Our study highlights the importance of performing follow-up upper and lower gastrointestinal endoscopy in SBS patients treated with teduglutide, and the potential need to make changes to the recommendations with respect to treatment initiation and follow-up.

References : Pevny S et al. De Novo Development of Distal Jejunal and Duodenal Adenomas After 41 Months of Teduglutide Treatment in a Patient With Short-Bowel Syndrome: A Case Report. JPEN J Parenter Enteral Nutr. 2021 Mar;45(3):652-656.

Ukleja A et al. De Novo Development of Hamartomatous Duodenal Polyps in a Patient With Short Bowel Syndrome During Teduglutide Therapy: A Case Report. JPEN J Parenter Enteral Nutr. 2018 Mar;42(3):658-660.

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SB: short bowel; CIPO: chronic intestinal pseudo-obstruction (Hirschsprung disease); AMI: arterial mesenteric ischemia; JCA: jejunocolic anastomosis; HP: hyperplastic polyp; FH: fundic heterotopia; TA: traditional adenoma; LGD: low-grade dysplasia; HGD: high-grade dysplasia

### 18

## GLEPAGLUTIDE INDUCES MEANINGFUL CLINICAL IMPROVEMENT IN PATIENTS WITH SHORT BOWEL SYNDROME CHRONIC INTESTINAL FAILURE: RESULTS OF A PHASE 3 TRIAL

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#### Abstract

**Introduction:**Management of patients with short bowel syndrome (SBS) and intestinal failure (IF) targets clinical and patient-centric outcomes including reducing need for parenteral support (PS) and improved quality of life (QoL). Glepaglutide is a novel long-acting GLP-2 analog. We conducted a phase 3 trial to evaluate the efficacy and safety (EASE) of glepaglutide in reducing the need for PS and improving QoL in patients with SBS chronic IF (SBS-CIF).

**Methods:**EASE SBS 1 is a multi-center, placebo-controlled, randomized, parallel-group, double-blind phase 3 trial (NCT:03690206). Key inclusion criteria were SBS-CIF adult patients with requirement for PS at least 3 days/week. Patients were randomized 1:1:1 to 24 weeks of treatment with subcutaneous injections of either 10 mg glepaglutide twice-weekly (TW), 10 mg once-weekly (OW), or placebo. PS volume requirements were evaluated and adjusted using regular fluid balance periods. Primary endpoint was change in weekly PS volume from baseline to 24 weeks. Key secondary efficacy endpoints included percentage of patients achieving clinical response (at least 20% reduction in PS), reduction in days on PS ≥1 day/week, and number of patients achieving oral/enteral autonomy (total PS weaning) at week 24. Patient Global Impression of Change (PGIC), a patient-reported outcome (PRO) tool, where patients rate their change in overall status since start of the trial on a 7-point Likert scale, was assessed at week 24.

**Results:**106 patients were randomized and 102 completed the trial. Treatment arms were well-balanced for patient demographics and baseline characteristics. Glepaglutide TW treatment significantly reduced PS requirements vs. placebo (mean change of -5.13 vs. -2.85 L/week; estimated difference of -2.28 L/week [-3.83; -0.73]95% CI; p=0.0039). Glepaglutide TW was also superior vs. placebo for proportion of patients achieving clinical response (65.7% vs. 38.9%; estimated difference of 26.6% [4.3; 48.9]95% CI; p=0.0243), and percentage of patients achieving a reduction in days on PS ≥1 day/week (51.4% vs. 19.4%; estimated difference of 31.7% [11.4; 51.9]95% CI; p=0.0043). No statistically significant difference was established for glepaglutide OW vs. placebo, however a dose-dependent trend was observed. Of special note, total PS weaning was achieved for 5 (14%), 4 (12%) and 0 patients receiving glepaglutide TW, OW and placebo, respectively. Improvement in PRO using PGIC was shown with significant differences relative to placebo for both glepaglutide TW (p=0.0020) and OW (p<0.0001). Glepaglutide was assessed to be safe and well-tolerated. More adverse events were reported in the glepaglutide treatment groups than for placebo, primarily attributable to mild injection site reactions.

**Conclusions:**Glepaglutide treatment of SBS-CIF patients was assessed to be safe and well-tolerated resulting in meaningful improvement in clinical and patient-centric outcomes (PS needs, oral/enteral autonomy, and PRO).

### 19

## Apraglutide, a novel long-acting GLP-2 analog, decreases the need for Parenteral Support in patients with Short Bowel Syndrome with Intestinal Failure and Colon-in-Continuity

Astrid Verbiest1,2, Mark Krogh Hvistendahl3, Federico Bolognani4, Carrie Li4, Omar Khwaja4, Palle Bekker Jeppesen3, Francisca Joly5, Tim Vanuytsel1,2

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#### Abstract

**Introduction:** Short bowel syndrome (SBS) is a rare gastrointestinal condition with a high risk of developing intestinal failure (SBS-IF) with a need for parenteral support (PS). Glucagon-like peptide-2 (GLP-2) analogs stimulate adaptation of the remaining gut resulting in increased intestinal absorption and reduced PS needs. Extensive literature is available on the effect of the short-acting GLP-2 analog teduglutide in patients without a remaining colon. However, the impact of GLP-2 analogs in SBS-IF with a colon-in-continuity (CiC) is unclear. Apraglutide (APRA) is a long-acting GLP-2 analog that is in development for SBS-IF.

**Aim:**We performed a pre-defined interim analysis in a phase 2 study in SBS-IF-CiC to investigate the safety and efficacy of APRA in reducing PS needs at 24 weeks.

**Methods:** STARS Nutrition is a 52-week multicenter, open-label, phase 2 study in adult patients with SBS-IF-CiC receiving once-weekly subcutaneous APRA injections. Metabolic balance studies were performed at baseline and 4 weeks with stable PS, followed by a 48-week PS adjustment period. Monthly 48h fluid balance periods were performed: oral fluid intake was kept constant by adhering to an individual predefined drinking menu while urine was collected. PS was reduced according to a pre-defined algorithm if an increase in mean daily urinary output of at least 10% was observed. Safety was the primary endpoint. Secondary endpoints include changes in weekly PS volume, energy content, and PS days, and proportion of clinical responders (PS reduction of at least 20%). Data are presented as mean (95% CI) unless specified otherwise. Nominal p-values are calculated using Wilcoxon matched-pairs signed rank tests with significance set at 0.05.

**Results:** Nine patients were included and comprise the full study population. Small bowel length was 19 (range 0-50) cm and 79 (range 43-100) % of the colon was in continuity. Patients had baseline weekly PS needs of 10 (range 4-21) L. APRA was well tolerated (no dose discontinuation or interruption). PS-related outcomes are presented in Table 1. Absolute weekly PS volume decreased significantly by 3510 (-4966 – -2054) mL/week (p=0.004). Accordingly, a significant decrease of 2764 (-4171 – -1357) kcal/week could be observed (p=0.004). Eight patients qualified as clinical responders. Five patients received at least 1 day off PS at week 24 and seven patients at week 28. The effect of APRA continues after 24 weeks with a significant additional PS reduction at week 28 (Figure 1). Body weight and daily urine output remained constant despite PS reductions.

**Conclusion:**APRA significantly reduces PS needs in patients with SBS-IF-CiC resulting in days without PS. STARS Nutrition is the first study prospectively showing evidence for clinical benefit of a long-acting GLP-2 analog in SBS-IF-CiC. One-year data should be awaited to assess the full effect on PS.

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### 20

## Long-term safety analysis of teduglutide treatment in adult patients with short bowel syndrome and intestinal failure (SBS-IF): analysis from a prospective, multinational SBS-IF registry

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Compensation received from Takeda as a member of the Scientific Advisory Committee for the SBS Registry study; study investigator for NPS Pharmaceuticals, Inc., Takeda; honoraria from Aposan, Takeda and Tauro-Implant as a speaker; advisory board member for Takeda.

#### Abstract

**Introduction**: Randomized clinical trials have found teduglutide (TED) to improve intestinal absorption in patients with short bowel syndrome and intestinal failure (SBS-IF). The ongoing, prospective, multinational, observational, SBS-IF registry (NCT01990040) records real-world data on the long-term safety of TED in adults with SBS-IF.

**Methods**: Safety data were compared between ‘ever-treated’ patients who received standard of care treatment (SOC) and TED, and ‘never-treated’ patients who received SOC and had never been exposed to TED. The never-treated patients had received parenteral nutrition and/or intravenous fluids for at least 6 months at study entry. Outcomes assessed include the occurrence and incidence rates (IRs) of colorectal cancer (CRC; primary safety outcome), new or worsening colorectal polyps, and adverse events (AEs). Cumulative data are reported for up to 5 years between enrollment and data cut-off (23/06/2014–30/06/2022). Baseline data were recorded at study enrollment.

**Results**: At data cut-off, 1403 patients (669 ever-treated; 734 never-treated) were included in the analysis. **Table 1** summarizes baseline data. The mean (standard deviation [SD]) cumulative TED exposure since baseline was 37.8 (29.0) months. No cases of CRC were reported in either group during the follow-up period. Colorectal polyps were reported more frequently in ever-treated patients than never-treated patients (IR, 30.4 vs 4.5/1000 patient-years [PY]). However, ever-treated patients underwent colonoscopies more frequently than never-treated patients (IR, 182.3 vs 64.6/1000 PY). Ever-treated patients had a lower rate of new or worsening diagnoses of any other type of malignancies than never-treated patients (IR, 16.7 vs 30.6/1000 PY). In addition, a lower proportion of ever-treated patients reported at least one AE or serious AE (SAE) than never-treated patients (**Table 2**). The most commonly reported AEs were abdominal pain, vascular device infection and device-related infection. Among ever-treated patients, 26.3% of AEs and 8.5% of SAEs were related to TED; 19.1% reported AEs led to treatment interruption or discontinuation. Overall, 59 SAEs associated with 49 (7.3%) deaths occurred in the ever-treated patients, while 112 SAEs associated with 98 (13.4%) deaths occurred in the never-treated patients; one fatal SAE (pancreatic carcinoma) was considered related to TED.

**Conclusions**: During the 5-year follow-up period, no new CRC cases were reported in patients ever-treated or never-treated with TED. Ever-treated patients had more new or worsening polyps than never-treated patients but also had a greater proportion of colonoscopies. A lower proportion of ever-treated patients had fatal SAEs than never-treated patients.

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### 21

## TEDUGLUTIDE REAL-LIFE COST IN CHILDREN WITH SHORT BOWEL SYNDROME

Doctor Ugo Cucinotta Resident1, Doctor Miriam Acunzo Resident1, Doctor Elise Payen MD1,2, Doctor Céline Chasport PhD1, Doctor Florence Lacaille MD1,2, Doctor Cecile Lambe MD1,2

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#### Abstract

Introduction: Home parenteral nutrition (HPN) is the mainstay therapy for short bowel syndrome with intestinal failure (SBS-IF). Teduglutide, a glucagon-like peptide 2 (GLP-2) analogue, may allow PN reduction or even PN weaning, but this new treatment is expensive. Our aim was to analyze the real-life health care costs of children with SBS-IF one year before and two years after treatment with Teduglutide, and to compare these costs in the children with SBS-IF who were not treated.

Methods: All consecutive children with SBS-IF on HPN treated with subcutaneous Teduglutide starting from 2018 in a third-level French referral center were included. They were matched to children with SBS-IF on HPN followed during the same 3-year period (2018-2020) who were eligible for the treatment but were not treated. HPN direct medical costs included: home-care charges, HPN bags, hospitalizations, and Teduglutide. A comparison of costs before/after treatment, and between patients treated/not treated was performed.

Results: Sixty children were included: 30 (50%) treated with Teduglutide and 30 (50%) not treated. Patients characteristics were similar. In the treated group, the median total costs for HPN significantly decreased after 1 year (p<0.001) and 2 years of treatment (p<0.001) from 59.454 Euros/year/patient to 43.885 Euros/year/patient and 34.973 euros/year/patient, respectively (table 1). Comparing patients treated and not treated, the total HPN costs/year/patient were similar at baseline (p=0.6) but were significantly lower in the Teduglutide-treated group after 1 year (p=0.006) and 2 years of treatment (p<0.001). When adding Teduglutide in the analysis, the total health-care cost increased significantly in the treated group compared to the not treated group, even assuming a reduction in the cost of the drug to 1/3 (p<0.001) and PN weaning.

Conclusions: Treatment with Teduglutide is associated with a significant reduction in the annual costs of HPN but still remains expensive. Finding cost-saving strategies is essential to widen its use.

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### 22

## Improvement in wet weight absorption after 4 weeks of apraglutide in patients with Short Bowel Syndrome with Intestinal Failure and Colon-in-Continuity

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#### Abstract

**Introduction:** Short bowel syndrome (SBS) is a rare gastrointestinal condition with a high risk of developing intestinal failure (SBS-IF) with a need for parenteral support (PS). Glucagon-like peptide-2 (GLP-2) analogs stimulate adaptation of the remaining gut resulting in increased intestinal absorption and reduced PS needs. Extensive literature is available on the effect of the short-acting GLP-2 analog teduglutide in patients without a remaining colon. However, the impact of GLP-2 analogs on fluid and energy absorption in SBS-IF with a colon-in-continuity (CiC) is unclear. Apraglutide (APRA) is a new, long-acting GLP-2 analog that is in development for SBS-IF.

**Aims:** We performed a pre-defined interim analysis of a phase 2 study in SBS-IF-CiC to investigate the safety and efficacy of 4-weeks APRA treatment based on metabolic balance studies (MBS).

**Materials and methods:** STARS Nutrition is a 52-week multicenter, open-label, phase 2 study in adult patients with SBS-IF-CiC receiving weekly subcutaneous APRA injections. 72-hour MBS were performed at baseline and after 4 weeks of treatment, and were followed by a 48-week PS adjustment period. During the MBS, oral fluid intake was kept constant by adhering to an individual predefined drinking menu. Duplicates of meals and fluids (wet weight intake) were collected as well as urine and feces (fecal wet weight output). PS was not adjusted in this period. Safety was the primary endpoint. Secondary endpoints included changes in fecal wet weight output, wet weight absorption, urinary output, and energy absorption by bomb calorimetry. Data are presented as mean (95% CI) unless specified otherwise. Nominal p-values are calculated using Wilcoxon matched-pairs signed rank tests with significance set at 0.05.

**Results:** Nine patients were included and comprise the full study population. Small bowel length was 19 (range 0-50) cm and 79 (range 43-100) % of the colon was in continuity. At baseline, patients received a weekly PS volume of 10 (range 4-21) L. Seven patients experienced a total of 23 adverse events (AEs) of which 4 patients experienced 6 treatment-emergent AEs. No AEs were considered notable based on their nature or severity. The individual changes in MBS results from baseline are shown in Table 1. Fecal wet weight output decreased significantly by 253 (-437 – -68) g/day (p=0.012). Relative wet weight absorption increased by 9 (1 – 18) % (p=0.039). There was a numeric increase in urinary output, which failed to reach statistical significance (p=0.129). For energy absorption, no statistically significant changes were observed.

**Conclusion:** These initial short-term results of APRA in SBS-IF-CiC support safety and efficacy in increasing fecal wet weight absorption. One-year treatment outcomes should be awaited to assess the full effect on wet weight, energy, and macronutrient absorption.

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### 23

## Inflammasome Activation Involved in the Early Inflammation following Intestinal Transplantation: Implications in Acute Rejection

Jiman Kang1, Digvijay Patil1, Kesha Oza1, Jedson Ligget1, Leonid Belyayev1, Oswaldo Aguirre1, Khalid Khan1, Yuriy Gusev2, Krithika Bhuvaneshwar2, Habtom Ressom2, Cal Matsumoto1, Thomas Fishbein1, Alexander Kroemer1

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#### Abstract

**Introduction**: Dysfunction of intestinal mucosal barrier plays an important role in alloreactive complications such as rejection, infection, and inflammation following intestinal transplantation (ITx). Inflammasome studies are of newly emerging interest due to their crucial regulatory capacity in intestinal homeostasis. We hypothesized that inflammasome-associated genes were differentially expressed between the rejecting and non-rejecting allografts prior to the onset of rejection.

 **Methods**: Serial ITx biopsy samples from 5 healthy and 9 rejecting patients were analyzed. Specifically, we studied the transcript abundance in rejecting allografts at baseline vs. healthy allografts at baseline (Test A) and rejecting allografts vs. healthy > 6 months’ allografts (Test B). The baseline time points are defined as samples obtained intraoperatively during transplantation ranging through five weeks postoperatively. We utilized RNA sequencing (RNA-seq) to evaluate the gene expression differences within allografts that subsequently experienced rejection. The false discovery rate (FDR) was employed to determine significance thresholds and quantify the overall error rate when the group comparison was analyzed.

 **Results**: We found 1,541 DEGs (FDR <0.01 and a fold change (FC) expression greater than 2.0) in Test A and 725 DEGs in Test B, respectively. Critically, we found a significantly higher transcript abundance of host inflammasome-related genes, including NLRP3 (NOD-like receptor (NLR) family pyrin domain containing 3), NLRC4 (NLR Family CARD Domain Containing 4), SOCS3 (Suppressor of Cytokine Signaling 3) and NOD2 both at baseline and during rejection. Interestingly, we identified NLRP12 was highly elevated in rejecting allografts but not at baseline. NLRP12 is known to play a negative regulator of inflammation by suppressing key components of the canonical and noncanonical NF-κB signaling. We also observed that the expression of AIM2 (Absent in Melanoma 2) was significantly altered in only rejecting allografts at baseline. Using a gene-list of significant differentially expressed gene (DEG), we observed enrichment of transcription factor NOD2-associated gene set during rejection.

**Conclusions**: We performed a transcriptomics analysis using RNA-seq and identified dynamic transcriptomic differences over time. Our results demonstrated a shared continuous upregulation of pro-inflammatory gene signatures related to NOD2-dependent NLRP3 inflammasome activation pathways. This finding warrants further investigations for novel therapeutic approaches for ITx patients.

### 24

## Heterogeneity and Plasticity of Alloreactive T Cells in Human Intestinal Allografts: New Insights Into Tissue Residency and Immune Tolerance after Transplantation

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Columbia University, New York, USA

#### Abstract

Introduction: The success of intestinal transplantation (ITx) is limited by high rejection rates, and the risk of infection and cancer due to overimmunosuppression. We have previously demonstrated that host-vs-graft (HvG)-reactive T-cell clones are enriched in intestinal allografts during early rejection and persist despite rejection resolution. Recipient T cells in the mucosa eventually took on resident memory T cell (TRM) features, likely posing a constant threat of late rejection.

Methods: We integrated clonotype, alloreactivity and gene expression profiles of graft-repopulating recipient T cells at the single cell level to assess the functional phenotype of alloreactive T cells in association with graft outcomes using the 10x Genomics single cell RNA sequencing and an upgraded version of our published method for identifying alloreactive TCR repertoires by integrating pre- and post-Tx mixed lymphocyte reactions (MLRs).

Results: Recipient T cells sorted from graft mucosa of six quiescent and five rejecting allograft samples and a deceased donor intestine shared at least five cluster groups: multifunctional (IL22+, IFNG+, GZMB+) TRM (CD69+, RGS1+, CXCR6+, RUNX3+, KLF2-), cytotoxic interchangeable effector T (Teff)/TRM (CD69low, RGS1+, RUNX3+, KLF2+, TBX21+, GZMB+), nonTRM (S1PR1+, SELL+, KLF2+, CCR7+), T follicular helper (Tfh: CXCR5+, PDCD1+, Bcl6+, CXCL13+) and regulatory T cells (Tregs: FOXP3+, CTLA4+). RNA velocity analysis indicates that the trajectory from TRM to Teff/TRM clusters associates with rejection and inflammation in the intestinal mucosa. We observed heterogeneous contributions of pre-existing HvG-reactive T cells mainly to TRM, Teff/TRM and Tfh compartments in allografts. In line with the hyporesponsiveness of circulating recipient T cells to donor vs third-party antigens in post-Tx MLRs, there was a significantly decreased likelihood of detecting HvG clones defined by post- compared to pre-Tx MLR in late quiescent (but not rejecting) allografts. This raises the possibility that pre-existing HvG-reactive cells in quiescent grafts might be tolerant and suggests reduced infiltration of newly developing recipient HvG-reactive T cells into quiescent grafts. By integrating both pre- and post-Tx MLR-determined alloreactivity, we defined six functional categories, including persistent HvG, tolerant HvG, missing HvG, acquired H’vG (H’: post-Tx host), de novo H’vG and persistent nonHvG. Dominant persistent tolerant HvG cells with TRM phenotypes were enriched in quiescent grafts, while rejection was associated with enrichment of cytotoxic de novo H’vG cells with interchangeable Teff/TRM phenotypes, “missing HvG” cells with active Teff features, and accumulation of acquired H’vG cells in clusters with Teff/Treg phenotypes.

Conclusion: Our data provide transcriptional and clonal insights into the biology of TRMs in human intestinal grafts and provide evidence for donor-specific tolerance locally and systemically after transplantation.

### 25

## INTESTINAL TRANSPLANT REJECTION IS DRIVEN BY A DISBALANCE BETWEEN REGULATORY AND INFLAMMATORY IMMUNE STATUS IN THE ALLOGRAFT

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#### Abstract

Introduction. Acute cellular rejection (ACR) remains as the major cause of graft loss and morbitidy in intestinal transplant (ITx) patients. Regulatory T cells (Tregs) have shown to play a pivotal role in the prevention of rejection in other solid organ transplants.

Aim. To evaluate the mucosal immunological status during the ACR focusing on the study of CD4 and CD8 Tregs.

Material and methods. Cells from the lamina propria of ileal biopsies and explants were isolated after ITx and categorized as follow: Non-rejection (NR)=16; Rejection (Rx)= 3; and non-transplant patients (NITx)=12. CD4+CD25+FoxP3+ and CD8+HLD-DR+ cells and the expression of CCR5 and PD-1 molecules among these populations were determined by flow cytometry. Total levels of functional markers of Tregs (Foxp3, TGF-β, IL-10), Th22/17 (RORγ, IL-22, IL-17A), and inflammatory response (IL-1, IL-6) in biopsies [NR=6; Rx=4; NITx=8] were measured by qPCR. CD4+, CD8+, FoxP3+, CD20+ and Ki-67+ cells were detected by immunohistochemical staining [NR=40; Rx= 16].

Results. Total percentage of Tregs CD4+CD25+Foxp3+ were decreased in ITx grafts during  ACR (Rx, p=0.039) in comparison with NITx patients. Although, non-statistical significant changes in Foxp3+ cells were observed (p=0.30), mucosal Foxp3+ mRNA expression was significantly diminished (p=0.04) accompanied by a tendency towards a reduction of the IL-10/IL-17 ratio (p=0.06). RORγ/Foxp3 ratio did not show a different expression between groups (p=0.9). As was expected, CD8+ cells were increased during the ACR (p=0.026), but a reduction of regulatory CD8+HLD-DR+ cells frequency was observed. Remarkably, CCR5+ PD-1+ CD8 T regs cells were reduced in the ITx patient in comparison to NITx. This reduction worsens during the rejection process.   Significant relative expression of IL-1 (p=0.04) and IL-6 (p=0.01) mRNA demonstrated a pro-inflammatory immune status during the rejection.

Conclusion. Our preliminary results indicate that ITx rejection is driven by a disbalance between regulatory and inflammatory immune status in the allograft. Therapies directed to expand Tregs population can potentially be used as an approach to prevent ACR.

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## The First Collective Examination of Immunosuppressive Practices Among American Intestine Transplant Centers

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#### Abstract

Purpose: No standardized treatment algorithms exist for intestine transplantation (ITx), unlike other solid organs. We established a consortium of American ITx centers to evaluate our widely varying practices, with the goal of establishing best practices.

Methods: All American centers performing ITx during the past 3 years were invited to participate. As a consortium, we generated questions to evaluate and collected data from each institution. The data were compiled and analyzed.

Results: Ultimately 10/15 centers participated, performing 211 intestine transplants over the past three years (range 3-46, mean 21.1). Induction regimens varied widely, even within individual centers. Thymoglobulin was the most common, used by 6 centers exclusively, as one of several options at the remaining 4 centers, and in the plurality of patients (85/211, 40.3%), but there was no consensus regimen (Figure 1).

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Similarly, first- and second-line regimens for treatment of acute cellular and antibody-mediated rejection varied widely between centers (data not shown). Thymoglobulin induction was associated with the highest rate of rejection events when used as monotherapy (47%) but also the lowest rate when rituximab was added (23%) (Figure 2A).

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On the other hand, rejection events associated with thymoglobulin monotherapy and alemtuzumab were mostly mild, while those associated with thymoglobulin/rituximab and basiliximab were mostly moderate or severe (Figure 2B). No regimen was associated with increased rates of GVHD or PTLD. Maintenance tacrolimus levels, presence of stoma, and frequency of scoping were not associated with differences in rejection events.

Conclusion: This collaboration reveals the extreme heterogeneity of practices among American ITx centers and the association of certain induction regimens with rejection. Future collaboration will explore survival data and outcomes related to treatment regimens for rejection, GVHD, and PTLD.

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## Significantly Reduced Acute Rejection with Steroid-free Alemtuzumab Induction in Intestinal Transplantation

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#### Abstract

**Introduction**: The rate of acute cellular rejection after intestinal transplantation (ITx) is the highest amongst all solid organ transplants, which remains a primary obstacle to increasing the activity of ITx. Proper immunosuppression protocol is essential to minimize immunological risk. We herein report our recent change in immunosuppression protocol and assess its impact on outcomes, focusing on the risk of rejection.

**Methods:** From 2012 to 2022, a total of 135 intestinal/multivisceral transplants were performed in our program. To assess the rejection risk without immunological benefit from liver graft, 98 recipients of liver-free intestinal graft were included in the study and divided into 2 groups based on immunosuppression protocol. In Regimen 1 (2012-12/2020, n=66), patients received alemtuzumab 30 mg x1 induction therapy followed by tacrolimus and steroid maintenance regimen. Rituximab was added for sensitized patients with the presence of donor-specific antibody (DSA). In Era 2, (12/2020 to present, n=22), induction was changed to alemtuzumab 30 mg/dose on day 0 and on day 1 (2 doses). Maintenance was tacrolimus monotherapy without steroids.

**Results:** Mean age of recipients was 38 ± 16 years. There were no differences in patient characteristics between the two groups, based on recipient age, cases of re-transplants, graft type, or presence of preformed DSA (17% vs. 19 %).

The one-year cumulative rejection rate was significantly improved from 41% to 11 % after introduction of the steroid-free, 2-dose Alemtuzumab regimen (Era-2) (P=0.03) [Figure 1A]. Rejection grades were comparable, but rejection-related graft loss was significantly higher in Era 1 (N=13/41,31%), compared to in Era 2 (N=0, 0%). Sepsis was the other common cause of graft/patient loss in Era 1. Overall one-year graft survival was 100 % in Era 2, significantly improved from 87% in Era 1 (P=0.045) [Figure 1B].

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There was no difference in length of hospital stay, readmission rate, or rate of regaining nutritional autonomy between the two groups. Multivariate Cox regression identified alemtuzumab 2 doses vs 1 dose (HR 3.8) and cold ischemic time (HR 1.3 per hour) as significant risk factors for rejection.

With a reduced rejection risk, the frequency of surveillance endoscopy was decreased in Era 2. Finally, after observation of successful outcomes in 15 patients with steroid-free 2-dose alemtuzumab protocol, we performed the first case of stoma-free intestinal transplant. First surveillance intestine biopsy was done with colonoscopy on postoperative day 10 without complications.

**Conclusions:** Induction therapy with a steroid-free 2-dose alemtuzumab regimen significantly reduced the risk of rejection and achieved excellent short-term graft survival in ITx. This regiment can reduce complexity of post-operative management and facilitate the transition to stoma-free ITx, that could further improve the activity of ITx.

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## Mesenchymal stem cell-derived exosomes for the treatment of acute rejection in pediatric and adult bowel transplant

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#### Abstract

Introduction: Mesenchymal stem cells (MSC) exert immunomodulatory effects mediated by cytokines, chemokines, growth factors and extracellular vesicles. MSC‐derived exosomes, a subtype of extracellular vesicle, recapitulate the broad therapeutic effects of MSC without inducing an allogenic immune response and are relatively easy to generate at large scale.  We describe the use of ExoFlo™, an MSC-derived exosome agent to treat refractory rejection in 2 patients following intestinal transplantation.

Methods: ExoFlo was administered to two patients, one adult (age 47) and one child (age 7) under an emergency investigational new drug (eIND) authorized by the FDA. Both patients met histologic criteria for ongoing acute cellular rejection persistent after standard treatment. The pediatric patient received one cycle of ExoFlo, consisting of 3 doses each separated by 72 hours. The adult patient received four cycles (12 total doses). Each dose contained 15 mL of ExoFlo combined with 85 mL of normal saline and was administered intravenously over 60 minutes. Pre- and post-treatment enteroscopy was performed within a week of the start and end of treatment. On the day of treatment, baseline lab parameters were obtained and vital signs were monitored during and after infusion.

Results: Both patients tolerated the infusions without any adverse effects. Post-treatment enteroscopy for the pediatric patient showed complete resolution of intestinal allograft ulcers and normal histopathology without evidence of inflammation or rejection (Figure 1). He underwent repeat enteroscopy on post-treatment day # 19 which showed superficial ulcers at the transplanted terminal ileum with histopathology showing focal increase in crypt apoptosis raising concerns for return of acute cellular rejection. The adult patient also showed complete resolution of intestinal allograft ulcers and normal histopathology without evidence of inflammation or rejection. She has not had return of graft dysfunction or rejection at 6 months post-treatment.

Figure 1a. Deep ulcers of intestinal allograft one day prior to starting ExoFlo therapy

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 Figure 1b. One day post-treatment with ExoFlo

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Conclusion: We demonstrate that MSC-derived exosome therapy can be administered safely in a pediatric and an adult intestinal transplant recipient. Histologic resolution was achieved within days of exosome therapy and the degree of resolution was profound. Because of the lack of standard dosing of MSC exosomes, we are unable to draw conclusions about therapeutic durability from such a small cohort. MSC exosomes do confer a significant advantage over traditional immunosuppressive agents because of their safety and toxicity profile. There may be a role for MSC-derived exosomes in the treatment of acute intestine allograft rejection, especially in cases where traditional anti-rejection therapy has failed or is contraindicated.

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## Predicting Enteral Autonomy in Short Bowel Syndrome in a Large Multicenter Multinational Cohort

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#### Abstract

**Introduction:** Previous studies that evaluated predictors of Enteral Autonomy (EA) in pediatric Short Bowel Syndrome (SBS) have conflicting results. Many were frequently limited by small sample size, single-center design, and the use of historical cohorts. The aim of this study was to assess predictors of EA in pediatric SBS in a large cohort of patients from six pediatric intestinal rehabilitation programs.

**Methods**: A multi-institutional retrospective cohort study of infants <12 months with SBS (N=367). The cohort was stratified according to the achievement of EA vs. parenteral nutrition (PN) dependency. Statistical testing included a two-sample t-test, Chi-Square, log-rank for univariate analysis, and Cox Proportional Hazards regression for multivariable analysis. To explore the impact of residual small bowel (SB) and large bowel (LB)  length on EA, a scatterplot of percent residual bowel (adjusted for age) divided patients into four anatomical quadrants – ≥ 50% vs. <50% of LB and SB. A Kaplan–Meier curve was created based on these anatomical strata. A time-to-event analysis was also performed comparing EA according to etiology (NEC vs. other etiologies).

**Results:**EA was achieved in 229 patients (62.3%). The mean time to achieve EA was 420 days, while the mean time of follow-up in the PN-dependent group was 1591 days.  In the univariate analysis, patients who remained PN dependent were more likely to have shorter percent residual small bowel (30.3 vs 54.4%; p<0.0001) and residual colon length (66.8 vs 87.9%; p<0.001), and less likely to have an ileocecal valve (ICV, 26 vs 68%; p<0.001). In the multivariable analysis, percentage of the residual colon (HR=1.02; 95% CI 1.01–1.02) and small bowel (HR= 1.01; 95% CI 1.01–1.02) length, and presence of ICV (HR= 2.02; 95% CI 1.41–2.88) were positively associated with EA, while the presence of a stoma at the time of shortest bowel length measurement was a negative predictor of EA (HR= 0.72; 95% CI 0.52–1.00).

The time-to-event analysis of the 4 anatomical strata revealed that: 80.4% of infants with ≥ 50% SB and LB weaned from PN, after a median time of 209 days; 62.5% with ≥ 50% SB and<50% LB weaned off PN, after a median time of 397 days; 58.3% of infants with < 50% SB and ≥ 50% LB weaned off PN after a longer median time of 1192 days, while only 25.9% of children with < 50% SB and LB weaned from PN (Log-rank p<0.001) (**Figure 1**). Diagnosis of NEC was not associated with a better achievement of EA (NEC vs. other SBS etiologies (Log-rank p = 0.33) (**Figure 2).**

**Conclusions:**Overall 62% of infants with IF secondary to SBS achieved EA. Residual small and large bowel length plays a major role in the achievement and duration of time to EA. A colon length of >50% can compensate for the loss of small bowel <50% and account for a similar EA rate as in children with residual SB>50%. Surgical preservation of maximal small and large bowel length early in life is critical for a favorable prognosis in pediatric SBS.

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## The Impact of Colonic Allograft on Intestinal Transplantation Outcomes: Results from UNOS/OPTN Database

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#### Abstract

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Introduction: The practice of donor colon inclusion in intestinal and multivisceral allografts has spread over the past two decades. Many transplant centers perform intestinal transplantation with colon allograft (ICTx) and achieve comparable graft survivals with those without donor colon (ITx). However, outcomes of intestinal transplantation with colon allograft remain controversial. We aimed to assess the outcomes of ICTx with comparison to ITx using UNOS/OPTN registry database.

Methods: We retrospectively reviewed the patients who received primary intestinal transplants from 1998 to 2017. The primary endpoint was comparing the rate of acute rejection within 6 months after transplant between ICTx and ITx. The factors associated with 6-month acute rejection were examined using multiple logistic regression model. The secondary endpoint was comparing short- and long-term graft and patient survival. Long-term survival was examined by conditional survival analysis, and the factors associated with long-term survival were determined using Cox proportional hazard model.

Results: A total of 2,372 recipients of primary transplants were enrolled. Of those, 372 (15.6 %) received ICTx and other 2,000 received ITx. Acute rejection within 6 months was more frequently seen in ICTx than ITx (39.3% vs. 28.2 %, p < 0.001), and logistic regression analysis revealed that the inclusion of colon was independently associated with increased risk of acute rejection within 6 months, which was incrementally affected by donor age. Although overall graft and patient survival in ICTx recipients were comparable to those in ITx recipients, ICTx recipients who developed acute rejection within 6 months showed poorer graft and patient survival than ICTx recipients who did not (P < 0.001 and p = 0.016, respectively). Among the patients without acute rejection within 6 months, Cox proportional hazard model revealed that the inclusion of colon was an independent factor associated with improved conditional graft survival.

Conclusions: Acute rejection within 6 months occurs more frequently in ICTx, which may affect the prognosis negatively. However, under the condition without acute rejection within 6 months, ICTx rather than ITx may provide favorable long-term outcomes. Further analysis might be warranted to determine the strategies for decreasing the risk of acute rejection after ICTx.

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## 30-year experience of children with Intestinal Failure Associated liver disease

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#### Abstract

30-year experience of children with Intestinal Failure Associated liver disease

Objectives and Study

Children developing intestinal-failure-associated liver disease (IFALD) presented with jaundice historically, but with recent advances in IF rehabilitation, children are no longer jaundiced, yet can have advanced IFALD as per literature reports. Hence, assessment of severity, management of IFALD with a timely referral for intestinal transplantation (ITx) can be challenging,

Aim was to describe 30-year experience on referral patterns, assessment & overall outcomes of IFALD.

Methods

Retrospective analysis of IFALD assessments at tertiary IF-center between 1989-2020 and grouped into 2 eras- Era-1 (1989-2005) & Era-2 (2006-2020). Demographics, severity of IFALD assessment with/without portal hypertension (PHT), outcomes after disease assessment (Transplantation (Tx)/Unsuitable for Tx/Intestinal rehabilitation) were recorded.

Results and Discussion

398 (194-Era-1, 204 Era-2) assessments were performed over 32years. In era-2, children were older (29mths vs. 9mths) had better nutritional status (weight z-score, -0.75 vs. -1.6), showed a significant decline in median bilirubin (18µmol/L vs 290µmol/L), had less thrombocytopenia (17% vs 43%) secondary to PHT but moderate-severe fibrosis was still present in 57 % of IFALD children. The presence of moderate-severe fibrosis in non-jaundiced children with no thrombocytopenia led us to introduce hepatic venous wedge pressure gradient (HVWPG) measurement to help in decision regarding presence/absence of PHT. Applying HVWPG measurement, 11 children were continued with intestinal rehabilitation who would otherwise have been recommended for ITx.  The outcomes of assessment are detailed in Fig-1. In era 2 children precluding ITx declined significantly (7.4% vs. 17.5%) suggesting early referral, children not needing transplantation increased (40.7% vs 33.5%) and similar proportion of children were recommended for Tx (52% vs 49% - p<0.05).

Conclusions

In the modern era, severe IFALD may exist in children without significant jaundice or conventional markers of PHT. Liver biopsy may not be best tool for assessment of severity of IFALD and HVWPG might be helpful select cases to decide about liver inclusion in intestinal grafts. Appropriate timing of referral /dialogue with a transplant center to assess severity of IFALD is crucial to ensure correct treatment option for improving long-term survival.

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## Does the Burden and Resource Utilization For Chronic Intestinal failure in the United States reflect decentralized care? Results of a third party payer claims-data analysis.

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#### Abstract

Introduction: Chronic intestinal failure (CIF) and home parenteral nutrition (PN) care in the United States (US) are decentralized. Disease burden and resource utilization are unknown.

Methods: We analyzed claims data from a single large third-party payer claims database to identify adult members who received at least 6 months of PN between June 2018 and June 2021. Eligible patients had a gastro-intestinal (GI) diagnosis and/or diagnosis of malabsorption and no cancer or HIV. We extracted data on demographics and clinical characteristics to understand patterns of care.

Results: Of 1,125 patients who received at least 3 months of PN, 419 patients received PN for at least 6 months, and met our criteria for Type III IF; 65% of patients were between the ages of 18 and 54, and 73% were female. Absent specific ICD Codes for IF and HPN, protein calorie malnutrition was the primary diagnosis in 92 (22%) and post-surgical malabsorption in 30 patients (7%).  Pharmacy data was available in 220 patients (52.5%). There was a high percentage of concomitant drug use – gastrointestinal drugs (90%), antibiotics (89%), analgesics (72%) and psycho-therapeutic drugs (72%) were the most frequent. Of 20 patients with Type III IF, treated with teduglutide, 7 patients achieved freedom from PN. 100 of the 419 patients with Type III IF had gastroenterology visits > 5 times, with 36 patients having > 10 visits in the 3-year period. A total of 91 commercial home care companies serviced the PN requirements of 419 patients. The top 8 commercial homecare companies by volume in this dataset accounted for 272 patients. The remaining 147 patients were serviced by 83 home care companies averaging less than 2 patients per company. 19 patients (5%) had no evidence of any biochemical monitoring, and 193 patients (46%) had no evidence of trace element monitoring at a median PN duration of 304 days. Frequency of laboratory testing is shown in Figure 1 as ratio of frequency of serum magnesium to trace element assays and frequency of ER visits and hospital admissions is shown in Figure 2. Median (range) costs of care significantly increased in patients with hospital admissions [$ 328,140 ($ 17,901 - $ 3,557,302)] versus those without [$ 100,477 ($ 7,931 - $ 1,860,068)]). Median (range) costs of care significantly increased for patients with any ER visits [$ 295,880 $ 177,520 - $ 3,557,302)]) versus those with no ER visits [$ 163,018 ($ 7,931 - $2,452,497)]. Bloodstream infections related to central venous catheter accounted for the majority of in-patient admissions and abdominal pain accounted for the majority of ER visits.

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Conclusions: This is the first detailed analysis of clinical characteristics, disease burden and resource utilization of CIF/HPN patients in the United States, based on a single third-party payer database. The results raise concerns with evidence of sub-optimal care in many CIF patients, likely related to decentralization of CIF care and home infusion services.

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## Outcomes of patients with paediatric intestinal failure and Serum Bilirubin >100umol/L referred for intestinal transplantation- Are current guidelines appropriate?

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#### Abstract

**Introduction:**

Intestinal failure associated liver disease (IFALD) is defined as hepatobiliary dysfunction resulting from medical/surgical management of intestinal failure (IF). It is the most prevalent complication of long term PN and can progress to end-stage liver disease, or be stabilized/reversed with promotion of intestinal adaptation.

ESPGHAN guidelines recommend referral for consideration of transplant if bilirubin persistently >100umol/L for >2-4 weeks, suspicion of portal hypertension, variceal/stoma bleeding or deranged synthetic hepatic function.

While incidence of IFALD has recently reduced dramatically with improved intestinal rehabilitation, we looked to evaluate outcomes of patients with high serum bilirubin referred for consideration of intestinal transplant.

**Methods:**

A retrospective case-note review of patients with IFALD referred to a tertiary IF/transplant centre

**Results:**

36 patients with IFALD were referred from 2009-2022.

At referral, median bilirubin was 72umol/L(5-580) and age was 8 months(2-132).

Summary of results and outcomes:

|  |  |  |
| --- | --- | --- |
| **Bilirubin** | **<100umol/L (n=19)** | **>100umol/L (n=17)** |
| Median referral age | 10 months (2-132)  | 7 months (3-75)  |
| Median INR  | 1.2 (1.1-1.4)  | 1.4 (1.1-2.2)  |
| % with INR >1.5  | 0  | 47  |
| Median Platelet Count  | 121(33-460)  | 139 (25-324)  |
| Median Fibrosis Grade  | 2 (0-4) | 4 (1-4) |
| Number with cirrhosis  | 5  | 10  |
| Number unsuitable for biopsy  | 1  | 7  |
| Number listed for transplant  | 14  | 16  |
| Number transplanted  | 8  | 10  |
| Median time to transplant (months)  | 13 (4-44)  | 7.5 (2-28)  |
| Appropriate organs transplanted  | 8  | 4  |
| Isolated liver transplant  | 0  | 6  |
| Delisted/died awaiting transplant | 1  | 6  |
| Median survival (years)  | 6 (1-11)  | 3 (0.3-12)  |

**Conclusion:**

Patients with a bilirubin >100umol/L, while having an earlier median referral age, appeared to have rapidly progressive liver disease. 47% had an INR >1.5, and of those suitable for biopsy, all apart from 1 had cirrhosis at referral.

Median time to transplant in this group was shorter, however 35% of patients initially referred for small bowel/liver graft, required rescue isolated liver transplant as a lifesaving measure due severe liver dysfunction, and a further 6 died before suitable organs became available.

Based on the poor outcomes of patients referred for consideration of intestinal transplantation with a bilirubin >100umol/L, we recommend a multicentre study to determine if current guidelines need revision.

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## Living Donor Intestinal Transplantation: a Single-Center Experience

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#### Abstract

Background: LDITx is not routinely performed because of surgical risks to the donor and the potential inferior physiologic performance of the segmental graft. However, data on the effectiveness of LDITx are scarce. This study aimed to examine outcomes of living-donor intestinal transplant (LDITx) recipients.

Methods: This retrospective cohort study included patients undergoing LDITx between May 1999 and December 2022 in intestinal transplant programs in two university-affiliated hospitals in China.

Results: Actuarial survival rates were 82%, 75.7%, 68.9% for patient and 76.3%, 66.6%, 63% for graft at 1, 3, and 5 years, respectively. Recipients with > 3/6 HLA-matched grafts had superior patient and graft survival rates than those with ≤ 3/6 HLA-matched grafts (P < 0.05). There were 12 deaths among the recipients, with infection being the leading cause (41.7%), followed by rejection (33.3%), surgical complications (16.7%), and others (8.3%). There were 16 graft losses among the recipients, with acute cellular rejection being the predominant cause (37.5%), followed by infection (25%), technical failure (12.5%), chronic rejection (12.5%), and others (12.5%). With an average follow-up of 3.8 (range, 0.7-24) years, the rates of acute and chronic rejection were 33% and 4%, and the rate of CMV disease and PTLD were 5% and 2.5%, respectively. Of the 46 patients, 34 (73.9%) are currently alive and have achieved enteral autonomy. None of the donors experienced life-threatening complications or mortality. Six (15%) of 46 donors experienced minor operative complications.

Conclusions: LDITx is a valuable treatment option for patients with end-stage intestinal failure. Living-donor ileal resection is associated with minimal short- and long-term morbidity and remains an attractive alternative for potential recipients when suitable deceased donors are unavailable.

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## Management of duodenal stump after total enterectomy. Is there any nutritional benefit of gastrointestinal reconstruction in patients with “no gut syndrome”?

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#### Abstract

Background: Total enterectomy (TE) is a rarely performed procedure. Re-establishment of bowel continuity, quality of life, and overall outcomes are important aspects to be considered in patients who might need a TE.  We describe our experience with the operative and medical management of patients with "no gut syndrome”, with special interest on the effects of GI reconstruction on the degree of parenteral nutritional dependency.  Methods: We retrospectively reviewed 1005 adult patients who were referred to our center between January 2013 and October 2022. Results: Twenty-seven patients (2.7%) with a mean age of 41.7 years (range 17 to 66 years) underwent total enterectomy. In two patients the duodenum was also resected as part of original operation. Main indications for small bowel resection were vascular event (n = 11), and trauma (n = 8). Ten patients (38%) had reestablishment of gastrointestinal tract continuity after total enterectomy with duodenocolostomy (n = 9) or gastrocolostomy (n=1). Tube decompression (n=11) or ostomy creation (n=6) was used for foregut decompression in the remaining patients. Duodeno- or gastrocolonic anastomosis were at mid transverse colon (n=7), cecum (n=2) and hepatic flexure (n=1). There were no intraoperative or perioperative (< 30 days) deaths. All patients were on home parenteral nutrition (PN) infused over a 10- to 16- hour period. Average PN volume and calories were 2,600 mL/day (range 1,600 to 4,000) and 1,624 Kcal/day (range 1,125 to 2,320), respectively. Patients who underwent duodeno- or gastrocolonic anastomosis received smaller PN volume (33.2 vs 44.4 mL/kg/day). PN dependency index (PN intake/ basal energy expenditure %, mean±STD) was 116±18% in patients with tube decompression and ostomy and 94±20% in patients with colon in continuity (P < 0.05). Patients who underwent autologous reconstruction of their GI tract presented better short- and long- term survival (p <0.05). Seven patients underwent uneventful isolated small bowel and multivisceral transplantation with one- and three- year patient and graft survival of 100% and 85%. Another six patients are being evaluated or are already listed for visceral transplantation. Conclusion: Long-term survival can be achieved after total enterectomy in intestinal failure specialized centers. In addition, reestablishment of gastrointestinal tract continuity after TE decreases the daily fluid and electrolyte requirements of approximately 25%.  The addition of the colon in patients with no gut also results in a reduction in the parenteral energy requirements. These data reinforce the idea of the colon as an energy-salvaging organ even in patients with no gut.

### 36

## LONG TERM RESULTS OF STEP PROCEDURE IN CHILDREN WITH IF

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#### Abstract

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INTRODUCTION

Bowel lengthening procedures have been widely used in pediatric patients with intestinal failure (IF) since the eighties. The Serial Transverse Enteroplasty  procedure (STEP) was first described in 2003, becoming more popular than the previously described Bianchi procedure. There is little published evidence about long term results of STEP. Our aim was to analyze our long term results of STEP with special focus on complications.

METHODS

Retrospective study. Intestinal failure database collected prospectively. Patients aged < 18 ys who received a STEP procedure and had more than 5 years of follow-up were included. Pts dead and lost of follow-up, and those who had less than 5 ys of follow-up were excluded. Data on survival, weaning off PN and late surgical complications were analyzed. Study period: 2008-2022.

RESULTS

156 pediatric pts with IF were evaluated during the study period; SBS in 125. 57/125 received a lengthening/ tapering procedure. 9/57 pts died (84.2% survival), causes not related to the surgical procedure. 3 pts were lost from follow-up. 32 pts met the inclusion criteria and were the subject population. Mean follow-up: 92.65 ms (SD 24.74). 23 (71%) were off TPN at last follow-up (2 on GLP2 analogs). Long term complications: 17/32 (53%) pts suffered at least 1 complication; 8/17 (47%) are off PN, compared with 100% of non-complicated pts. (p .001). Re-dilatation 15/32 (47%), stenosis 2 (6%) and anastomotic ulcer bleeding 5 (15%). 7/15 (46%) of re-dilated patients are off TPN, compared to 16/17 (94%) of non-dilated ones (p .0049). ⅗ pts with GI bleeding are off PN (60%) vs 20/27 (75%) without bleeding (p ns). 13 pts were reoperated (40.6%), with 6/13 (47%) off PN, compared with 16/19 (84%) non-reoperated pts. (p .049).

CONCLUSION

STEP procedure has gained universal acceptance by surgeons over the last 2 decades, but long term results have not been widely reported. A few comparative studies suggest better results with the Bianchi technique in terms of weaning off PN. Technique- associated complications are recently being described, as re-dilatation and  GI bleeding. Our long term results show that a high proportion of patients can be weaned off PN, although total surgical complications, reoperation and re-dilatation have a negative impact on outcomes.

### 37

## Impact of post-operative complications after AGIRS, report of a large single center series

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#### Abstract

Introduction: From the different approaches described to restore intestinal sufficiency (IS), when intestinal failure (IF) occurs, the combination of Autologous Gastro-intestinal Reconstruction Surgery (AGIRS) follow by medical rehabilitation has become the preferred practice in our program, and previously published. But there are no significant contributions describing the complications, morbidity and mortality after AGIRS, becoming the aim of this contribution.

Patients and Methods: Retrospective report of adult patients (pts) with type III-IF secondary to short bowel syndrome (SBS), requiring AGIRS ,  from  January 2007  to December 2022. The variables analyzed were: age, sex, weight, causes of IF, type of anatomy at the first visit and post-AGIRS, operating time (OT), blood transfusion, complications , need for using  enterohormones (sGLP-1 and sGLP -2), time to be weaned of parenteral nutrition (PN)  , impact of post-operative complications (POP, ≥Dindo-Clavien 3B) on patients freedom from PN and survival.

Results: From a total of 368 adult pts with type III- IF seen, 115 underwent AGIRS; in 8 cases (7%), 2 stage-surgeries were needed, therefore a total of 123 procedures were required. The average age was 49±15 years, 54% were male,  and the initial weight 64 ±12 kg. The most frequent causes of IF were: 56% postoperative complications  and 22% ischemia. At evaluation 105 pts  had type 1 anatomy (91%), 3 type 2 anatomy (3%), and 7 type 3 anatomy (6%),  after AGIRS, 8 patients were left with type 1 anatomy (7%), 37 with type 2 anatomy (32%), and 70 with type 3 anatomy (61%) (p=0.001). From the 123 surgeries, a single anastomosis was required in 85 cases, 2 anastomosis in 25 procedures, 3 anastomosis in 6 surgeries, 5 in 1 pts and in 6 cases there was no anastomosis. The mean OT were 314 ±155 minutes, 33% required blood transfusion. There were 34 major complications (28%): 13 intra-abdominal collections (11%), 8 bleeding (6.5%), 8 anastomotic dehiscence (5%), and 6 with controlled fistula (5%); 34 pts (28 %) underwent 1 reoperation. The mean total hospital stay was 23±21 days (4 ±6 in ICU); with 42 ± 13 days for complicated pts, and 16 ±11 for non-complicated pts (p=0.0001). 82/115 pts (71%) achieved IS; 9 required sGLP-2. The figure 1, show freedom for PN survival by complication, anastomotic dehiscence and fistula, impact on the possibility of achieving IS. Overall survival was 92% at one year, 87% at 5 years and 77% at 10 years.

Conclusion: AGIRS is a complex procedure, required in most cases by pts suffering from serious complications of abdominal surgeries, previous long hospitalizations and multiple morbidities; the  procedure is perceived by the pts as the last alternative to recover intestinal autonomy. Under a comprehensive MTD team,  AGIRS  becomes a safe procedure able to provide  high freedom from PN and   survival rate, which are only affected by the existence of anastomotic dehiscence or fistula among the  POP morbidities described.

### 38

## Intestinal Autotransplantation for Locally Advanced or Recurrent Right Colon Cancer Invading the Superior Mesenteric Artery

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#### Abstract

Introduction: Involvement of the superior mesenteric artery (SMA) by locally advanced or recurrent colon cancer is considered inoperable, associated with a dismal prognosis. Attempted resection may lead to uncontrolled massive bleeding, irreversible intestinal ischemic damage, or a noncurative resection (R1 or R2). This study aimed to examine outcomes of intestinal autotransplantation (IATx) alone or IATx plus pancreaticoduodenectomy in patients with right colon cancer invading SMA.

Methods: This retrospective cohort study included patients undergoing IATx between May 1999 and December 2021 in intestinal transplant programs in two university-affiliated hospitals in China.

Results: A total of ten patients underwent IATx combined with pancreaticoduodenectomy (n=8) or IATx alone (n=2).  Eight (80%) were male, and the median age were 55 years (range, 32-71 years). Kaplan-Meier estimates for recurrence-free and overall survival at 3 years after IATx were 80% and 100%, respectively. Postoperatively, 3 patients experienced no complications, whereas 7 experienced Clavien-Dindo complications of grade II (3), grade IIIA (2), and grade IIIB (2) including acute venous thrombosis, upper gastrointestinal bleeding, pleural effusions, and gastropareses.

Conclusions: This study’s findings of recurrence-free and overall survival rates suggest that select patients with unresectable, locally advanced or recurrent colon cancer may benefit from IATx.

### 39

## Spectrum of interventional procedures during hybrid central line placement in pediatric intestinal rehabilitation patients with end-stage vascular access

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#### Abstract

Introduction:

Loss of available central vein access sites for parenteral nutrition delivery represents one of the main indications for intestinal transplantation in children with intestinal failure. Placement of central venous catheters can be challenging in advanced loss of patent venous pathways. We recently described the hybrid technique (interventional plus surgical approach) of central line placement in children. The aim of this study was to describe and analyze the interventions used during the hybrid procedures regarding feasibility, safety and outcome.

Methods:

We retrospectively analyzed the course of all children in our intestinal rehabilitation program undergoing hybrid central line placement. We evaluated patients’ conditions, interventional techniques and surgical peculiarities as well as outcome.

Results:

Between 2010 and 2021, 203 children were treated in our intestinal rehabilitation program. Due to loss of venous access, hybrid technique was performed in 53 children during 76 interventions. In 40 cases the same vessel was reused via Seldinger technique. Among the 30 ultrasound-guided new vessel punctures, 12 were performed by puncture of collateral vessels. Extended interventions due to thoracic central venous obstruction and/or thrombosis requiring additional access via a femoral vein for rehabilitation of the vascular system was performed during 29 procedures including catheter extraction (1), angioplasties (18), stent placement (1), revascularization (5) and thrombectomy (4). Placement of a central line was not possible in 6 children which eventually underwent extended thoracic/vascular surgery: in three children the previously placed catheter could not be removed, in one child, placement of a thrombectomy-catheter was not possible because of inferior vena cava occlusion, and in two children, revascularization failed. Intestinal transplantation was considered in one patient because of impending loss of vascular access. Two self-limiting minor extravasations and one intervention-associated pericardial effusion occurred.

Conclusion:

Hybrid interventions for central venous catheter placement and vascular rehabilitation enable a high success rate in children with intestinal failure and end-stage vascular access, circumventing the need for intestinal transplantation or advanced surgery. The relevant procedures are complex and require a foresighted and individualized approach with a wide range of interventional techniques. If performed with expertise, this combined interventional/surgical approach is feasible and safe.

### 41

## The Stem Cell Niche in Short Bowel Syndrome

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#### Abstract

Introduction:

Small intestinal transplantation has emerged as an essential treatment for intestinal failure, but its relatively high graft rejection rate and mortality rate when compared to those of other transplanted organs has led to difficulties in post-transplantation treatment management.

Methods:

The recently-developed technique of creating organoids from somatic stem cells has created a challenging opportunity to develop a treatment that involves the creation of a substitute small intestine using autologous cells instead of transplanting another individual’s small intestines. The remaining partial large intestine is then used as the stem cell niche, and autologous small intestinal organoid transplantation is conducted on its epithelium in order to create a pedunculated hybrid graft.

Results:

This is a new surgical technique for interposing with the original ileocecal region. The hybrid large intestine acquires both the lymphatic vessels that are involved in nutrient absorption and the original peristaltic function of the large intestine.

Conclusions:

This lecture touches upon the history of the development of organoid medicine, after which an introduction is provided of the revolutionary surgical technique in which a functional small intestine is created by regenerating autologous cells.

### 42

## Distraction enterogenesis: a new frontier to treat Short Bowel Syndrome?

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#### Abstract

Background

Short Bowel Syndrome (SBS) is a malabsorption syndrome characterised by a severe reduction of the absorbent surface of the intestinal mucosa. Treatment of this condition needs multi-professional teams and different therapies, which are not always enough to ensure enteral autonomy. New techniques are being explored, particularly distraction enterogenesis, which can allow the lengthening of the residual intestines of these patients. This study aims to demonstrate the possibility of using biocompatible and biodegradable materials to design ingestible capsules which carry 3D-printed springs capable of reaching the patient's intestine. These devices can be used as a slightly invasive distraction enterogenesis technique, stimulating cell proliferation and intestinal elongation without surgery.

Materials and methods

Capsules were realised with gelatin from pigskin type A from Sigma-Aldrich mixed with regenerated silk fibroin (RS) obtained by reverse engineering method on Bombyx Mori cocoons. Springs are composed of a structure of regenerated silk (RS) modified with graphene nanoplatelets (GNP) externally covered with a biodegradable polyhydroxybutyrate-valerate (PHBV) shell. Springs were realised with 3D printing, through which, with an extruder, PHBV and RS compounds are deposited simultaneously in a 3D structure. The springs' capsules were then analysed with solvents simulating the gastric and intestinal environment to verify their resistance to degradation. PBS (Phosphate Buffered Saline), composed of calcium chloride and magnesium chloride (CaCl2 + MgCl2), with a pH value of 7.4, was used as a degradative agent; for the gastric tract, we chose the acetic acid, CH3COOH, at 12% with a pH value of 2.3.

Results

While the gelatin-only capsules showed poor resistance to degradation in PBS, the new compound based on gelatin and regenerated silk showed excellent resistance in gastric and intestinal environments, allowing the capsules to reach the intestine without dissolving. The results show variability in the release times of the springs as a function of the pH values and the elastic constants of the springs used: the latter determined that in acetic acid, the release time is increased at an increase of the elastic constant. In contrast, in PBS, an opposite trend was observed.

Conclusions

Our results confirm the possibility of using materials such as gelatin, silk fibroin and PHBV to design devices capable of transporting implantable endoluminal 3D structures, drugs or growth factors, laying the foundations for a new approach to distraction enterogenesis in SBS patients.

### 43

## DCD in intestinal transplantation: the path to prove its validity in both experimental and clinical models

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#### Abstract

Introduction

DCD has not been considered as a valid alternative for intestinal transplantation (IT). However, the use of normothermia has recently improved the results of the classic cold perfusion in other organs under this condition. Our aim was double: to test the viability and function of the intestinal grafts using normothermic regional perfusion (NRP) in an experimental model and to assess ischemic-reperfusion injury (IRI) of the small bowel in human DCD.

Methods

We used an experimental porcine model with 8 donor-recipient pairs (25.5 ± 2.5 kg). Donors were supported using a NRP for abdominal organs after the withdrawal of their life sustaining treatment. The small intestine was heterotopically transplanted into the recipients and they were followed-up for two weeks, using tacrolimus for daily immunosuppression. Blood and intestinal samples were obtained repeatedly throughout the procedure and 1, 2, 7 and 14 days after. IRI was evaluated using the Park-Chiu score (PCS) in samples taken during NRP and up to 48 hours after IT. Samples from 7 and 14 days were analyzed to assess graft rejection and GVHD.  The absorptive function of the grafts was tested at the endpoint. Glycemia from the draining veins of the graft was compared with that from the native small bowel and peripheral blood 15, 30 and 60 minutes after intra-graft glucose administration.

The small intestines from 26 human DCDs were also sampled for histological analysis while other organs were procured for transplantation with NRP after 30 and 60 minutes.

Results

All the intestines were successfully procured and presented an excellent appearance. One case was excluded due to venous stenosis. 6 animals (86%) reached the endpoint in good conditions. Grafts conserved architecture during NRP, with edema at the villus tip (PCS-1) only in two samples after 1h. The highest PCS was observed 1h after reperfusion, with denuded villi (PCS-4) in 3 samples (43%). All grafts recovered, with no or very subtle alterations after 48 hours. Five recipients (71%) did not show rejection signs at any time. 2 cases (29%) expressed mild rejection after 7 days. At the endpoint, one of them had recovered but the other had progressed to severe acute cellular rejection (14%). Grafts’ glycemia reached its maximum 30 minutes after glucose administration, demostrating their absorption capacity.

All intestines from human donors appeared macroscopically normal. Their samples did not show any significant IRI in 80% of the cases. PCS score was 1.23 [0-3] after 30 minutes and 1.65 [0-4] after 60 minutes.

Conclusion

This experimental model postulate DCD donation under NRP as an alternative source of organs to address the mismatch between the waiting list for IT and the scarcity of donors. Its clinical and functional results appear to be comparable to those of other organ procurement techniques. The analysis of the human samples suggests that this approach could be successfully translated to the clinical setting.

### 44

## Comparison of the Effects of Normothermic Machine Perfusion and Cold Storage Preservation on Porcine Intestinal Allograft Regenerative Potential and Viability

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#### Abstract

Historically, intestinal transplantation (IT) has been reserved as the last treatment option for patients with irreversible intestinal failure who are unable to tolerate total parenteral nutrition. Successful IT is reliant upon graft health at the time of donation, minimizing graft injury that may occur during procurement, storage, and IT, and the ability of the graft to heal following insult. Unfortunately, the intestine is easily damaged by ischemia-reperfusion injury (IRI). IRI induces intestinal epithelial cell apoptosis and damages the mucosal barrier, which can result in bacterial translocation and activation of the local and systemic immune and inflammatory response, ultimately contributing to graft failure, rejection, and decreased recipient survival. The current, preferred method of intestinal preservation prior to IT is static cold storage (CS), however the prolonged hypothermic ischemia of CS causes cell injury and intensifies the IRI that occurs during transplantation. Furthermore, IRI to the epithelial crypt region diminishes the intestine’s ability to heal by inducing loss of the highly proliferative intestinal stem cells (ISCs) that are responsible for maintenance, regeneration, and repair of the epithelium, critical to graft health. Thus, the investigation of alternative organ preservation techniques that reduce IRI, cellular damage, and graft injury are warranted to overall improve IT success. Normothermic machine perfusion (NMP) is a preservation method that reduces inflammation and promotes graft regeneration in other organs by preventing CS-associated IRI. However, NMP has not been described for intestine. We hypothesized that, compared to CS, intestinal NMP will induce less epithelial injury and better protect ISC regenerative potential and viability. 15 porcine intestines were flushed with UW solution, stored at 4°C (CS), or perfused with 34°C perfusate (NMP) for 6hr, and transplanted (n=9). Recipient pigs were recovered from anesthesia. Jejunal and ileal segments were collected immediately after flushing, serving as control tissue (CO), after 6hr of CS or NMP, and after 1hr of reperfusion post-IT. Histologic injury was assessed. Crypts isolated after flushing (CO), 6hr CS or NMP, and 1hr of reperfusion post-IT were cultured. Spheroid number, size, and EdU staining quantified ISC viability and proliferation. Expression of ISC and cellular proliferation genes and proteins were measured. Histologically, NMP tissue had mild epithelial erosion and increased columnar cell attenuation and expression of ISC and proliferation genes/proteins was observed. NMP spheroid areas and proliferating cell numbers were significantly larger than control and CS. Apoptotic cells were increased following CS. Post-graft reperfusion, CS had increased injury compared to uninjured control and NMP tissue. Compared to CS, NMP may improve graft regenerative potential, resulting in transplantation of healthier bowel and superior recipient survival.

### 45

## The fall of a myth: the first three cases of DCD in intestinal transplantation

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#### Abstract

Introduction

The universal shortage of organs has prompted the growing use of donations after circulatory

death (DCDs). Kidneys, liver, lungs, pancreas, and, more recently, the heart from DCDs have been successfully employed for transplantation in many centers worldwide. Nonetheless, the use of DCD as a source of intestinal grafts has been denied due to concerns regarding their ischemic susceptibility. This belief, in fact, has been widely accepted by the scientific community for years.

Now this myth is over: we present the first three DCD cases in intestinal transplantation in the world.

Methods

We reviewed the cases of intestinal transplantation after DCD performed at our center. Technical, demographic and clinical data relating both donors and recipients were collected. Recipients were also studied in detail during their clinical and histological follow-up.

Results

Three DCD multivisceral transplants (MVT) were performed at our institution in June and October 2022 and January 2023.

Donors (3M) had a mean age and weight of 3 months (1-6) and 5.3 kg (4-8). Their death was declared after their cardiac arrest and a 5-min “no-touch period”. Then, a rapid laparotomy was performed and a normothermic regional perfusion (NRP) was established by the cannulation of the aorta and the inferior vena cava. Mean warm-ischemia time was 25 minutes (23-29). During NRP, the grafts were prepared for procurement, when the same cannulas were used for cold perfusion with cold-preservation solution.

The recipients were 3 patients (2F/1M) with short bowel syndrome (jejunal atresia and meconium cyst, Hirschsprung's disease, multiple intestinal atresia with severe combined immunodeficiency). Their mean age and weight were 19 months (9-36) and 4.9 kg (3.88-6.8). They all received a MVT with preservation of the native spleen and a ileostomy for protection and study. Mean cold-ischemia time was 383 minutes (340-420).

After MVT, biopsies showed a complete recovery of the architecture of the intestinal epithelium in all cases. After a mean follow up of 3 months (0-7), two patients have done exceptionally well with only a mild self-limited cutaneous GVHD in one case and a humoral sensitization perfectly controlled in the other. Ileostomy could be taken-down in one 8 months after MVT. The third patient is being treated for enterocolitis and has needed a proximal jejunostomy.

Conclusion

The use of DCD donors in intestinal transplantation is feasible as demonstrated by our world-leading series. The ischemia-reperfusion injury in these grafts seems to be transient and reversible. Although experience is limited, their use could address the mismatch between the waiting list for intestinal transplantation and the scarcity of donors, especially in situations of need such as pediatric transplantation.

### 46

## 10 Years’ Experience of Transplant Oncology in the Management of Unresectable Desmoid Tumor: One-staged or Two-staged Approach

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#### Abstract

**Background:** There has been a growing interest in Transplant Oncology to achieve maximal debulking of neoplasms not amenable to conventional surgical resection. However, the surgical strategy and timing of desmoid tumor resection using visceral transplantation (VTx) remains controversial.

**Methods:** Retrospective chart review identified 25 patients who received radical resection of mesenteric and pelvic desmoid tumor in our intestinal transplant program for the last 10 years. Surgical strategy was classified into three groups: 1) no VTx group with aggressive tumor resection, 2) one-staged tumor removal at time of VTx, and 3) two-staged approach with an initial debulking surgery followed by VTx as a second stage. Surgical strategy was determined with the following factors: salvageability of intestine, growth rate of tumors, tumor proximity to pancreas and duodenum, Spigelman classification of duodenal polyposis, ureter involvement, and transplant candidacy. For one-staged VTx, to minimize cold ischemic time, recipient surgery was started before donor operation, anticipating a good quality of organ. Only perfect donors were accepted for this setting.

**Results:** The mean age of patients was 37.5 years (range 21-68) with 72 % male. The median time from diagnosis to referral was 12 years and number of previous surgeries was 3 (range 2-10). enterocutaneous fistulae and ureteric involvement were present in 9 (36%) and 12 patients (48%), respectively.

Without preparing VTx, 14 patients underwent radical tumor resection with ureteric reconstruction in 7 patients with lengthy operative time of 11 hours. Six of the 14 (43%) developed tumor recurrence and required further resections.

One-staged VTx was performed in 4 patients using isolated intestinal grafts. The tumors were in central mesentery without involvement of retroperitoneum/pelvic structures or upper abdominal organs. Cold ischemic time was managed in the range of 3-5.9 hours despite challenging tumor dissection. Two-staged VTx was done in 7 patients and associated with more organs’ involvement that required lengthy debulking in the initial surgery and required full- or modified multivisceral organ replacement at the second stage.  Waiting time for organ was significantly longer in two-staged group compared to one-staged group (240 days vs 17 days, p<0.01).

Tumor recurrence after transplant was limited to 2 patients and didn’t affect the patient’s survival. Four patients died after full-or modified MVTx due to infection, PTLD or GVHD. Intention-to-treat survival in the entire cohort was 77% at 5 years. No VTx group and one-staged group had an excellent 2-year survival of 90 % and 100 %, respectively.

**Conclusions:** Radical resection of unresectable mesenteric tumor can be done with organ replacement with favorable outcome for cases with lower tumor burden. Two-staged VTx remains a valid option for patients who have high tumor burden and no other alternatives.

### 47

## Luminal Preservation of the Human Intestine with a Polyethylene Glycol Solution Applicable for Transplantation.

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#### Abstract

BACKGROUND. Intestinal transplantation (ITx) has shown sub-optimal graft survival rates for the last ten years, mostly due to rejection and subsequent sepsis. This could be improved by reducing initial preservation injury. Experimental studies applying luminal preservation (LP) to animal and human intestines show promising results. Herewith presented is the first trial of luminal preservation LP of human intestines from suitable donors in a clinical setting.

METHODS. Twenty-five bowels (small intestine and ascending colon) from brain-dead donors meeting criteria for ITx (age extended to ≤ 70 years) were divided into four groups in two European centres that use different vascular perfusion solutions (University of Wisconsin, UW, or Institut Georges Lopez-1, IGL-1). Two groups served as controls (only vascular perfusion), two as LP treatment groups with additional ice-cold polyethylene glycol 3350 (PEG). LP occurred before and during vascular perfusion via the existing nasogastric tube, placed manually in the duodenum during procurement. Samples from procurement and after seven and fourteen hours of cold storage were scored histologically for intestinal preservation injury (IPI).

RESULTS. Implementation of LP did not prolong procurement times. PEG reached the terminal ileum but did not pass into the large intestine (colonic samples were thus not analysed). LP significantly reduced jejunal mucosal damage at procurement, independently of the vascular flush solution used, compared to control groups (median IPI scores 2 in control groups, 0 in treated groups 0, p < 0.001). LP protected the jejunum during cold storage when IGL-1 was the vascular preservation solution. LP had little effect on the ileum, though a marginally worsened mucosa was observed after seven hours in UW vascular flush group (IPI 3 in both groups, higher range values in treated group, p = 0.01).

CONCLUSION. Luminal preservation with ice-cold PEG is clinically applicable without generating changes in procurement times or techniques. LP reduced jejunal IPI at procurement and during cold storage in vascular IGL-1-preserved intestines, but not after vascular preservation with UW.

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## Avoiding encephalopathy after isolated small bowel transplantation through portal drainage

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#### Abstract

**Introduction:**

In isolated small bowel transplantation (SBTx), two methods of drainage have traditionally been described: systemic and portal. Although portal drainage (PD) is more physiological, allowing for the liver ‘first pass effect’, systemic drainage (SD) is often technically more feasible and has been shown in previous studies to have no significant side effects. In this single-centre study, we analyzed our experience over the years with both techniques.

**Methods:**

We performed a retrospective analysis of our prospectively maintained data collected between 2007 and 2022. The following data was included in the study: age, gender, cause of intestinal failure, indication for transplantation, type of portal anastomosis (SD vs PD), infection rate, rejection rate, rate of encephalopathy and patient/graft survival.

**Results:**

Between October 2007 and December 2022, 42 isolated SBTx were performed in 43 patients (n=23, 53%) males, median age 46 years (21-65)). The most common indication was short bowel (n=36, 84%) with either impending loss of vascular access (n= 12, 28%), IFALD (n=13, 31% or a combination (n = 5, 12%). Twenty-six patient (62%) had SD, while 16 had PD (38%). PD drainage was performed with a venous jump graft in 14 patients and directly in 2.

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Postoperatively, there were 12 patients (29%) with either transient or permanent encephalopathy (median ammonia level: 79 μmol/l (42-204)) and 8 patients (24%) with asymptomatic, raised ammonia levels (>30 μmol/l) but without clinical symptoms (38 μmol/l (34-64). All but one patient with clinical encephalopathy had SD. Median ammonia levels double in SD versus PD patients (62 vs 34 μmol/l; p=0.0039).

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One patient underwent a conversion from a systemic to portal drainage due to severe, intractable encephalopathy using a third-party venous graft. This resulted in a complete reversal of her symptoms and normalization of her ammonia levels from 136 to <10 μmol/l). In three additional patients, conversion from systemic to portal is being considered. Conversely, two patients underwent portal to systemic conversion due to insufficient portal inflow. There were no differences in rates of rejection or patient survival.

**Conclusion:**

Although, PD and SD yielded equal results in terms rejection and survival rates, encephalopathy was very frequent and occurred only after SD. Given this data, we advocate for PD whenever technically feasible, especially in patient with borderline liver function.

### 49

## INIGMA multicenter study report. Analysis of immune cells draining from the abdominal cavity as a novel tool to early predict abdominal clinical events.

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#### Abstract

“INIGMA- International Network for Intestinal Graft Monitoring and Analysis” project is a multicenter study started in 2015. Previously, we demonstrated that abdominal drainage fluid collected after intestinal transplant (ITx) contains immune cells trafficking from the implanted intestine, and kinetics of immune cell composition, (mainly neutrophilic shift), correlated with the appearance of future clinical events (rejection, infection, or other abdominal events).

Aim:  To present a follow-up of our multicenter study, focused on the analysis of draining cell composition and their correlation with clinical follow-up to validate a new non-invasive method predictive to predict the development of abdominal complications after the first post-operational days.

Material and Methods: this prospective observational study started in 2008 by Favaloro Foundation University Hospital, Argentina and turned into a multicenter study from 2015 to 2023 (involving Favaloro Foundation University Hospital, Argentina; University of Gothenburg, Sweden; University of Leuven, Belgium and La Paz University Hospital, Spain).  The complete leukocytes and differential count of cell composition of the abdominal draining fluid and blood collected during the first post-op days was analyzed by differential cell counter and was correlated with the clinical outcome.

Results: a total of 41 patients (pts) with complete biochemical and clinical information were enrolled by 3 of the 4 centers (Table 1). Blood samples showed a predominance of neutrophils and marked leukopenia, independently of the age, immunosuppressive protocol used, and clinical event reported. The draining cell composition showed neutrophilic predominance shifting then to a lymphocytic content. When a new shift to a neutrophil dominant content is observed in the drainage, it anticipates the development of a clinical event in the peritoneal cavity (27/41 pts; p<0,0001). Table 2 summarizes the association between neutrophils and clinical events. Sensitivity=90%; Specificity=90%; PPV=90%, NPV=82%.

Conclusion: this follow-up study, validates our preliminary results; suggesting that abdominal clinical events can be early predicted after ITx by a simple analysis of the changes in the drainage cell composition, particularly when a shift to a neutrophilic dominance is registered. Thus, cell counts from the drainage should be included as part of the daily evaluation of pts receiving an ITx. We encourage the international centers of apply to participle in this multicenter study at the IRTA.

Table 1. Characteristic of patients

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CR, chronic rejection; IR, immunosuppressive regimen; Ind, Induction; Man, maintenance; Simul, Simulect; Alemt., Alemtuzumab; SBS, short bowel syndrome; Tx, transplant; TAC, tacrolimus; Sir, sirolimus; St, steroids; MMF, mycophenolate mofetil; Ritux, rituximab. Spleen pres.: Spleen preservation. Re-Tx: re-transplantation.

Table 2. Association of neutrophils appearance and clinical events

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### 50

## Immunosuppression switching from tacrolimus to sirolimus improves renal function in adult intestinal transplant recipients

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#### Abstract

**Introduction:**  There is a 40% decline in renal function in the first 3 months post-intestinal transplant even with renal sparing strategies.  This retrospective, single centre study of the renal function of adult intestinal transplant recipients describes outcomes after switching from tacrolimus to sirolimus.

**Methods:**  Baseline characteristics, renal function and complications related to immunosuppression switch were collected.  Recipients were included if they had been switched to sirolimus based immunosuppression for at least six months.  Adverse outcomes were collected.

**Results:** There were 129 adult intestinal transplants from Dec 2007 to April 2022 with 45 recipients meeting the inclusion criteria.  35 of the 45 were colon containing grafts in 14 multivisceral transplant MVT, 9 liver and small bowel LSB, 6 modified multivisceral transplant MMVT and 16 small bowel SBT patients.   Follow up period ranged from 12.1 to 184.1 months (median 66.2 months).  The sirolimus switch occurred between 2.1 months and 146 months post-transplant (median 12.23).  At the time of switching, 16 recipients had an end colostomy, 12 had an end ileostomy,   3 had a Bishop-Koop stoma and 14 were in continuity.  Median eGFR at transplant was 100 ml/min/1.73m2.  The indication for switching was predominantly renal impairment (38 patients), the rest for other reasons such as intolerance to antimetabolites, anti-tumour properties and side effects of other immunosuppressants.   Before switching 5 patients had CKD stage 1 and 2, 26 patients had Stage 3, 10 patients had Stage 4 and 5.  At 12 months after switching, 9 patients had Stage 1 and 2, 17 patients had Stage 3 and only 2 patients had Stage 4.  This represented a change in median eGFR from 36 to 52ml/min/1.73m2 at 60 days post switch which remained stable thereafter.

Adverse events included acute cellular rejection resulting in graft loss in 3 recipients.  Four had   severe rejection and 2 moderate. Six recipients described symptomatic peripheral oedema and 2 had an albumin/creatinine ratio >100.

**Conclusion:**    In this small, single centre, adult cohort we have demonstrated a median increase in eGFR of 16ml/min/1.73m2, observed 60 days post switching.  Significant events included rejection and graft loss and intensive monitoring during this time is critical.

### 51

## Immunological Aspects of Experimental Isolated intestinal and Modified Multivisceral Transplantation. Comparative Study.

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#### Abstract

Introduction: Experimental models of isolated intestinal (IIT) and modified multivisceral (MMV) transplantation in rats constitute a valuable tool for research in the world of visceral transplantation. Knowing the immunobiology of these models is essential when proposing a research project that may be focused on acute cellular rejection (ACR) or  graft-versus-host disease (GVHD)  among others. Our aim is to study comparatively IIT vs MMV in rats, highlighting the immunilogical and clinical characteristics of each model.

Materials and methods: Allogeneic (Lewis donor, Brown Norway recipient) IIT (graft composed of jejunum-ileum) and MMV (graft composed of stomach, small intestine, pancreas, and spleen, with recipient splenectomy) were performed without any type of immunosuppression. Peripheral blood chimerism and plasma cytokines (IL-2, IFN, TNFa) were analyzed on days 3, 7 and 10  after transplantation. Clinical signs compatible with graft-versus-host disease (skin rash) or ACR (hardening of the graft) and transplanted intestine histological analysis (Wu Score) were evaluated.

Results: While 100% of the animals receiving MMV presented transient skin rash (compatible with GVHD) between days 6-9 post-transplant, in the IIT group this percentage was 80%. From day 9, all recipients in both groups presented hardening of the graft (clinical sign of rejection) accompanied by weight loss and worsening of the general clinical state. In all recipients, the end point criterion was applied before day 14 post-transplant.

On day 3 post-transplant, peripheral blood chimerism was significantly higher in the MVM group (more than 30%) compared to the IIT group (less than 10%) (p<0.001). Analyzed plasmatic cytokines (IL-2, IFN, TNFa)  were significantly higher in MVM recipients at all analysis times. At the end-point, in all transplanted intestines of IIT and MMV recipients, histopathological signs of moderate and severe ACR were observed.

Conclusions: IIT and MMV models using  Lewis rats as a donor and Brown Norway as recipient, without immunosuppressive drugs, allow the reproduction of two of the main complications associated with visceral transplantation; transient GVHD (between days 6-9 after surgery) and graft rejection (10 post-transplantation day to the end point). MMV offers a more alloreactive and pro-inflammatory scenario, characterized by a high percentage of chimerism in peripheral blood and a considerable increase in pro-inflammatory cytokines. The characterization of these procedures is useful for the selection of an experimental model when planning and/or developing scientific research focused on intestinal or multivisceral transplantation.

### 52

## Extracorporeal Photopheresis for Refractory Rejection in Intestinal Transplantation

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#### Abstract

Introduction:

Extracorporeal photopheresis (ECP) is an immunomodulatory therapy, combining leukopheresis with phototherapy in the treatment of leukocytes with 8-methoxypsoralen and ultraviolet A radiation. ECP has been used in intestinal transplanted-associated GvHD and treatment of acute and chronic rejection in other solid organs (lung, heart, liver, kidney). To our knowledge, we present the first report of ECP as salvage therapy for steroid- and biologic-refractory rejection in pediatric and adult intestinal transplant patients.

Methods:

Intestinal transplant recipients who received ECP as rescue therapy for acute or chronic cellular rejection between 2016 and 2022 were included in this single-center retrospective analysis. Baseline demographics of the patients, as well as their pre- and post-ECP histopathological, endoscopic, and biochemical characteristics and long-term transplant outcomes, were analyzed.

Results:

Four patients (three pediatric and one adult) with histological diagnosis of acute and chronic steroid- and biologic-refractory rejection were treated with ECP between 2016 and 2022. Patients all received twice weekly ECP for 4 weeks and then once weekly thereafter. Three patients had acute cellular rejection, one had chronic rejection. Immunosuppression regimens at the time of ECP initiation were high-dose tacrolimus and sirolimus. All four patients failed treatment with high dose steroids and infliximab despite adequate infliximab trough levels. Histologic resolution of rejection was achieved in all patients over a 12 to 16 week course. Steroids were able to be weaned to low-dose or withdrawn in every patient within 4 weeks of ECP initiation. Pre- and post-ECP biochemical data reflected improvement in immune activation: C-reactive protein decreased from an average of 14.75 to 1.6 mg/dL and fecal calprotectin decreased from average 800 mg/kg to 31 mg/kg. CD154+ cytotoxic T cells, which have been implicated in intestinal allograft rejection, were quantified by the Pleximmune™ assay via flow cytometry and showed substantial decrease in peripheral blood. There were no complications associated with treatment. All patients are alive with graft function intact.

Conclusion:

ECP is a safe and effective salvage therapy for steroid- and biologic-refractory cellular rejection in pediatric and adult intestinal transplant recipients. Clinicians may consider early use in rejection to avoid toxicities associated with conventional anti-rejection regimens.

### 53

## Gene expression in intestinal transplant patients treated with vedolizumab. An exploratory analysis.

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#### Abstract

BACKGROUND. Two patients with different disease backgrounds underwent intestinal transplantation (ITx) and afterwards had either acute cellular rejection (ACR, patient 1) or chronic allograft enteropathy (CAE, patient 2). Both patients received vedolizumab, which successfully managed their rejection episodes and have been free of complaints ever since. Vedolizumab is a monoclonal antibody that targets the integrin α4β7, expressed in inflammatory cells of the intestine, and blocks the interaction with its endothelial cell receptor MAdCAM-1, preventing migration of these cells into the intestinal mucosa. This study aims to explore the effects of vedolizumab on the transcriptome of the gut mucosa in these patients.

METHODS. Small intestinal biopsies taken before and during treatment with vedolizumab were analysed by RNA sequencing. Nine sequential biopsies from patient 1 (five before treatment), seven from patient 2 (four before treatment), and three from another patient with ACR that received regular treatment (steroids, tacrolimus and anti-thymocyte globulin), where analysed for differential expression of their whole transcriptome associated to clinical, endoscopic, and histopathological data.

RESULTS. Twenty-one genes from the three patients were differentially expressed when treatment with vedolizumab was present. Pathway enrichment analyses showed decreased expression of genes involved in zinc homeostasis and no effect on vedolizumab targets was found. However, individual gene expression analyses showed that genes related to cell migration and adhesion were affected by treatment with vedolizumab. Patient-related effects were detected at this level on apoptosis-related genes in patient 1 and ischaemia-related genes in patient 2.

CONCLUSION. This is the first study presenting gene transcript profiling of small intestinal biopsies of patients with ACR and CAE after ITx  that were treated with vedolizumab. This drug may affect cell migration and adhesion other than, or in addition to, the α4β7-MAdCAM-1 axis. These broader effects than initially proposed may be at play to resolve rejection in these patients.

### 54

## Immune profiling of γδ T cells after human intestinal transplantation reveals their roles in lymphohematopoietic graft-vs-host responses and graft rejection

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#### Abstract

Introduction: Despite comprising a significant portion of lymphocytes residing in many organs, including gut, the role of γδ T cells in transplantation outcomes is unclear. Innate- and adaptive-like features of human γδ T cells are associated with different T cell receptor (TCR) repertoires, defined as Vγ9+δ2+ and non-Vγ9δ2, respectively.

Methods: We performed phenotypic and clonal tracking of donor- and recipient-derived γδ T cells after human intestinal transplantation (ITx) in blood, intestinal graft and bone marrow (BM). Integrated iRepertoire (γδ T cell primer sets) and 10x Genomics (5’cDNA library) platforms were applied to relate functional gene profiles within individual γδ T cell clonotypes.

Results: We previously demonstrated that donor T cell macrochimerism (peak level ≥4% in blood) is associated with less rejection. Here we found that increased γδ blood chimerism was present in patients with higher levels of total T cell chimerism. Remarkably, donor γδ T cells were detected in recipient BM 105–357 days post-Tx. Single-cell profiling of BM-infiltrating donor γδ T cells from 3 pediatric donors revealed both Vδ1- and Vδ2-dominant clonotypes with cytotoxic effector phenotypes that might contribute to lymphohematopoietic graft-vs-host responses (LGVHR). In one multivisceral Tx patient, the top dominant donor TCRγδ clone (Vγ8Vδ1) detectable during the period of peak T cell chimerism in blood (8–20 days post-Tx) was also predominantly present in the recipient BM 126 days post-Tx, with clear cytotoxic profiles (GZMB/PRF1/GNLY) but reduced proliferation (MKI67) and decreased BM-homing (CXCR4) features. BM-infiltrating donor δ2+ T cells were dominated by sequences with zero N-additions that likely originated during fetal life and are shared across pediatric, but not adult, donors, suggesting an age-related distribution and migration pattern. In contrast to αβ T cells, the turnover dynamics of γδ T cells in the graft showed a stronger association with donor age than with the status of macrochimerism. Graft-repopulating recipient γδ T cells showed effector phenotypes early post-Tx and gradually acquired cytotoxic resident-memory T cell phenotypes with “private” non-Vγ9δ2 clonotypes. In one patient, the top dominant Vδ2 sequence (mainly Vγ5δ2) in blood during quiescence was also the top dominant clone in later rejecting ileal graft samples, but with much lower frequencies in earlier quiescent grafts, suggesting active crosstalk of γδ T cells between blood and intestinal grafts during rejection. TCR distance analysis using tcrdist3 algorithm suggests that this top dominant Vδ2 sequence unlikely recognizes MICA or CD1d given higher distance scores (>150) from MICA- or CD1d-specific Vδ TCRs, but has more structural similarity with some TCRδ sequences presumably stimulated by cytokines produced by activated autologous αβ T cells, with TCR distance scores as low as 48.

Conclusions: γδ T cells may influence chimerism and rejection after ITx.

### 55

## GLP-2 modulated genes in adult patients with Short Bowel Syndrome (SBS) treated with Teduglutide (TED)

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#### Abstract

Introduction: TED, a GLP-2-analog, has proven efficacy reducing the need for Parenteral Nutrition (PN) in patients with SBS. However, there is some heterogeneity in the patients’ response to TED and the mechanisms of action of GLP-2 on intestinal cells are still poorly understood. The purpose of the study was to explore the mechanisms of response to treatment with TED.

Methods: For this purpose, intestinal biopsies of 41 SBS patients treated with TED, collected before and after the treatment initiation, were selected and analyzed. The mRNAs were extracted from the biopsies and analyzed with RNA sequencing. Statistical analyses for differential expression of genes and pathways were performed using R software (DESeq2 and GSEA). A modification of gene expression was considered significant with abs (log2 Fold-Change) >1.5 and padj (p-value adjusted with False Discovery Rate method) <0.05. Response to TED is defined as the PN reduction reached, as a percentage of baseline volume.

Results: Among the genes showing significant expression changes during treatment, this study focused on the two most significant upregulated genes in jejunum of treated patients, which are PAPPA2 (log2 Fold-change =2.4, padj=1.4e-13) and MMP1 (log2 Fold-change =3.4, padj=2.1e-05). These two genes encode for metallo-proteases (pappalysin-2 and matrix metalloproteinase-1) which are both responsible for the cleavage of Insulin-like Growth Factor Binding Proteins (IGFBPs), thus promoting Insulin-like Growth Factor (IGF) bioavailability, a known mediator of the trophic effect of GLP-2 on the intestinal mucosa. The signaling pathway of IGF transport and uptake is significantly enhanced after TED treatment (p-value=0.01), which confirms these observations.

Furthermore, there was an inverse correlation between PAPPA2 expression in the jejunum before TED initiation and the response to treatment (r=-0.65, p=0.006). Indeed, patients with the better response to TED are those who present an important upregulation of PAPPA2 during treatment (p<0.0001), whereas there is no significant increase in this gene expression in those who respond the least (p=0.39).

These results suggest that there could be an greater intestinal pre-adaptation in the poorer responders, potentially related to a higher level of endogenous GLP-2, leading to a lower sensitivity to TED treatment. This difference could be explained by the presence or the absence of colon, which is an important site of GLP-2 secretion.

Conclusion: This study highlights in SBS patients the involvement of IGF-1 as a mediator in the response to treatment by GLP-2 analogs such as TED and identifies two new factors - PAPPA2 and MMP1 - involved in this response by their implication in modulating the IGF transport and uptake pathway. Moreover, this study suggests a possible explanation for the heterogeneity of response to TED treatment which may be related to pre-adaptation by endogenous GLP-2 leading to a poorer response to GLP-2 analogues.

### 57

## Protective effect of the GLP-2 analogue on intestinal ischemia-reperfusion injury in mice

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#### Abstract

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**Introduction:**The intestinal ischemia-reperfusion injury (IRI) is inherent to the transplant procedure and responsible for direct (early mucosal damage) and indirect injury (lung disease). The loss of mucosal barrier function, the alteration in the permeability and structure of intestinal villi, would release pro-inflammatory cytokines, which cause tissue damage in remote organs. Glucagon-like peptide-2 (GLP-2) is a hormone secreted by enteroendocrine L cells of the intestinal epithelium that has a trophic effect on intestinal epithelium. Although therapeutic use of GLP-2 in intestinal rehabilitation is established, few experimental studies have shown a role in reducing intestinal damage upon IRI. Our aim was to evaluate a possible protective effect of GLP-2 in reducing local and remote organ damage by IRI in a mouse model, as preliminary analysis to be then applied in the transplant model.

**Methods:** An intestinal IRI model clamping the superior mesenteric artery for 40 minutes followed by 30 minutes of reperfusion was used. Five experimental groups were performed: 1) Sham Group without IRI model, 2) Sham Group without IRI model but with intraperitoneal GLP-2 pretreatment for 3 days before surgery and an intraoperative dose of 250µg/kg/day (Sham+GLP2), 3) IRI Control Group (Ct), 4) IRI Group with intraperitoneal GLP-2 pretreatment for 3 days before surgery and an intraoperative dose (GLP2-Pret) and 5) IRI Group with only one intraoperative dose of GLP-2 (GLP2-Intra). After the reperfusion period, mice were sacrificed and intestine and lung samples were obtained. H-E was performed on lung samples to assess tissue damage (degree of alveolar infiltration and hemorrhage among others), and in the intestine to quantify IRI through the Park index and morphological analysis using the Villus/Crypt index. Alcian Blue staining was performed to assess the presence of Goblet cells. One-way ANOVA and Kruskal-Wallis tests were used for statistical analysis.

**Results:** The Sham groups (1 and 2) and GLP2-treated groups (4 and 5), showed less histological intestinal and lung lesions compared to the Ct group (Fig. 1). Significant differences were observed in the number of Goblet cells per villus between the GLP2-Intra (5) (M 11.65 ±1.68) group and the Ct (3) (M 7.68 ±1.89) group (p=0.0156). There were differences between the villus/crypt indices of the Ct group (3) and the GLP2-Intra group (5), but only the differences between the Ct group (3) and the Sham groups (1 and 2) were statistically significant (p=0.0035).

**Conclusions:** A marked decrease in IRI was observed both directly in the intestine and remotely in the Lung using GLP-2 analogue as pretreatment or intraoperatively intraperitoneally. The scarce presence of Goblet cells and a marked morphological alteration of the villi seem to accompany more severe pictures of intestinal IRI damage. According to this study, the use of GLP 2 reduces the IRI opening a new line of research and a potential novel clinical use.

### 58

## Long-term outcome after non-vascularized rectus fascia transplantation in solid organ transplantation: A global multi-center IRTA survey.

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#### Abstract

Introduction

 Closure of the abdominal wall after solid organ transplantation (SOT) is of utmost importance since an open abdomen following SOT increases morbidity and mortality. Closure remains challenging and can, amongst other, be achieved by non-vascularized rectus fascia (NVRF) transplantation. Several reports have confirmed excellent short-term outcome. However, long-term outcome remains unknown. With this multicenter survey we aim to analyze the worldwide experience and long-term clinical outcome after NVRF transplantation.

 Methods

This study was approved by the International Rehabilitation and Transplantation Association (IRTA) scientific committee. All IRTA members were invited to participate to this anonymized survey via mail with 3 reminders and webpage announcement between September 22nd, 2021 and June 28th, 2022. The survey was excel based and included all NVRF after SOT, isolated intestinal (ITx), Liver (LTx), combined liver-intestine (cLITx), and multivisceral transplantation (MVTx). The survey was classified into a pre-, intra-, and postoperative questionnaire. Data analysis was performed after closure of the survey.

 Results

Twenty-nine centers responded of which 8 transplant centers included a total of 98 patients. From the 98 patients (25 children, 72 adults, 1 not mentioned), 28 underwent ITx (28.57%), 26 MVTx (26.53%), 20 cLITx (20.41%), and 24 other SOT (24.49%). The NVRF was sewed in as an inlay in 85 patients (86.73%). 30 NVRF (30.61%) were third party (NVRF different from the solid organ donor). In 30 patients (30.61%), surgical site infections (SSI) occurred. Seventy-one patients (72.44%) had reoperations, of them 18 patients (25.35%) had NVRF removal. At a median follow up of 31 months (10-63.5) 17 patients presented with bulging of the abdominal wall (17.35%), 5 with a clinical hernia (5.10%), and 2 with a radiographic diagnosis of a hernia (2.04%).

 Conclusion

With this survey, we collected 98 NVRF transplants from 8 transplant centers worldwide. Despite the major surgical interventions in high-risk patients under profound immunosuppression an excellent long-term outcome was observed.

### 60

## Evaluation of case-based learning to disseminate clinical knowledge in pediatric intestinal failure: Experience of The Pediatric LIFT-ECHO Program

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#### Abstract

**Introduction:** Pediatric intestinal failure (PIF) is a rare, complex disease that requires multidisciplinary care by providers with psycho-social, nutritional, medical and surgical expertise; however, this expertise is often lacking.  The Extension for Community Healthcare Outcomes (ECHO™) model is a tele-learning model created to disseminate expert knowledge to local communities.   Pediatric Learn Intestinal Failure Tele-ECHO (LIFT-ECHO), launched in July 2020, applies the ECHO™ model and connects medical professionals of all disciplines involved in the care of children with intestinal failure.  Monthly sessions include a case presentation with moderated discussion, followed by didactic continuing education lectures on PIF-related topics.  Case-based learning is a well-established pedagogical method utilized in medical education.  This study aims to evaluate the impact of Pediatric LIFT-ECHO case-based presentations and discussions in disseminating knowledge of key principles in PIF.

**Methods:** We developed a list of ‘best practice’ recommendations for the management of PIF based on current published evidence, systematic reviews and clinical guidelines.  A trained evaluator reviewed transcripts of the case discussion component of each Pediatric LIFT-ECHO session. Evaluations were audited to ensure review-accuracy.

**Results:** The 15 sessions evaluated from July 2021 to January 2023 were attended by a median of 120 participants (86 - 180 participants) attending each session.  Participants attended from 39 US states and 31 countries.  All 13 ‘best practices’ (BPs) were discussed during at least one of the 15 sessions evaluated (Figure 1). BP # 11, “Providing ongoing social psychosocial support for families and caregivers,” and BP # 13, “Monitoring of metabolic bone disease with Dexa and calcium balance,” were discussed with the lowest frequency.  Key principles such as BP # 1 “The Evaluation of children with short bowel syndrome should include the anatomy of residual gastrointestinal tract including bowel length and presence of ileocecal valve and ostomy,” and BP # 6, “Optimizing enteral nutrition strategies to enhance intestinal adaptation and promote enteral autonomy” were discussed in virtually all case presentations.

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**Conclusions:** Our preliminary evaluation of Pediatric LIFT-ECHO shows that case-based learning is an effective method in communicating best practices in the management of PIF. Pediatric LIFT-ECHO has been well attended, suggesting this initiative is meeting an unmet educational need. This evaluation allows program administrators to identify gaps in the educational content of case-based learning which may be better addressed by other methods such as didactic presentations.  Further evaluation will be undertaken to evaluate if Pediatric LIFT-ECHO improves participants’ knowledge, treatment practices and ultimately, patient outcomes.

### 61

## Noninvasive Biomarkers for Allograft Monitoring After Intestinal Transplantation: Promising Early Results from a Novel Peptide, REG3α

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#### Abstract

Background: The field of intestinal transplantation (ITx) lacks a specific biomarker for diagnosing acute allograft rejection. Currently, calprotectin and citrulline, biomarkers used classically in monitoring disease activity in inflammatory bowel disease (IBD) and short-bowel syndrome, are employed for detection of allograft rejection, but neither are specific in distinguishing rejection from other non-specific causes of intestinal inflammation. The regenerating islet-derived (REG) proteins, a family of anti-inflammatory/anti-bacterial proteins expressed in Paneth cells within the epithelium of the small intestine, are emerging as a potential biomarker for intestinal pathology. REG proteins are known to be highly expressed in several human intestinal pathologies related to epithelial injury and inflammation. REG3α specifically has been correlated with disease severity in IBD and intestinal graft vs host disease and has potential as a biomarker for intestinal allograft pathology but has not been extensively studied in ITx.

Methods: Our center has maintained a detailed prospective database on all ITx recipients since 1991. A protocol of weekly allograft monitoring with stool calprotectin, serum citrulline and endoscopy and biopsy is followed. In 2015, the novel peptide REG3α was added to this protocol. Biopsy-confirmed acute rejection (BCAR) is graded according to international standards. Markers are correlated to BCAR by post-operative week (POW). Analysis compared markers by severity of rejection (grade 0-2 vs 3-4) using standard statistical tests.

Results: Five adults underwent isolated ITx and one child underwent multivisceral transplantation. Median time to first BCAR was 3 weeks; all experienced at least 1 episode of BCAR. One-year patient and graft survival was 100%. Calprotectin, citrulline and REG3A were significantly associated with grade 3-4 BCAR (p=0.00). The median REG3α level was 5.5 times the upper limit of normal during grade 3-4 BCAR. Calprotectin had the highest positive predictive value (PPV) (76%); REG3A had the highest negative predictive value (NPV) (89%). Together, they demonstrate a high PPV and NPV (100% and 93%, respectively).

Conclusions: This is the first case series to describe a protocol of allograft monitoring after ITx using invasive and noninvasive testing including REG3A. Calprotectin, citrulline and REG3A are individually associated with moderate-severe BCAR and together demonstrate a high PPV and NPV. REG3A demonstrated a superior NPV for the presence of rejection. This preliminary experience indicates that REG3A may be useful for monitoring allograft function. Future work includes a prospective multicenter investigation to determine the association of REG3A with BCAR, and to determine the relationship of REG3A with calprotectin and citrulline in association with allograft pathology.

### 62

## RNA Sequencing (RNA-seq) Analysis Provides for Gene Signatures Specific to Intestinal Transplant Rejection

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#### Abstract

**Introduction**: Healthy intestinal barrier function and gut homeostasis are critical for the success of intestinal transplantation (ITx). In comparison, a disrupted mucosal barrier in intestinal grafts leads to alloreactive complications such as rejection, infection, inflammation, and subsequent graft loss. Our study hypothesizes that bulk-tissue transcriptomics analysis, such as RNA-seq, identifies novel genes and pathways associated with intestinal transplant rejection.

**Methods**:To test our hypothesis, RNA-seq experiments were performed on serial ITx biopsies from nine patients with rejecting allografts and five patients with healthy allografts. Specifically, we compared the transcript abundance in rejecting allografts vs. healthy allografts. The group comparison analysis was performed using the R-based Bioconductor software package, EdgeR, to identify differentially expressed genes.

**Results**: RNA-seq revealed genome-wide transcriptomic differences between rejecting allografts and healthy allografts. Among 725 differentially expressed genes (DEGs), 470 genes were up- or 255 -downregulated with statistical significance (False Discovery Rate (FDR) <0.01). Further to understand the biological importance of the DEGs, we performed Gene Set Enrichment Analysis (GSEA), EnrichR and Gene ontology (GO) pathway enrichment analysis. GSEA and GO pathway analysis showed that the DEGs for rejection vs. healthy allografts were particularly enriched in the inflammatory response, chemokine-mediated signaling pathway, and neutrophil degranulation. In addition, we found a markedly higher expression in genes related to the IL-17 signaling pathway, and TNF signaling pathways using Consensus Pathway Database Networks in the rejecting allografts. Using EnrichR transcription factor protein-protein interactions (PPIs) analysis, we observed enrichment of NOD2-associated gene-set in rejecting allografts

**Results**: RNA-seq of ITx biopsies identified dynamic transcriptomic differences in healthy and rejecting allografts. The expression of genes associated with IL-17 and TNF signaling pathways, chemokine-mediated signaling pathway, and neutrophil degranulation were markedly increased in intestinal allografts undergoing rejection. This finding emphasizes the potential for RNA-seq-based tissue immune surveillance to study acute rejection.

### 63

## The GUTSY Program: Gaining Understanding of Transition in Short Bowel Syndrome Among Youths

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**Dr. Sivan Kinberg**

**Who provided funding for your project? If it wasn't funded, mark "n/a"**

Takeda Pharmaceuticals

#### Abstract

**Introduction:** Short Bowel Syndrome (SBS) is a rare and chronic disease with complex life-sustaining therapies. Children with SBS grow up relying on teams of medical professionals and family caregivers for their everyday survival. As more children with SBS are now surviving into adulthood, patients often struggle with the transition to adult care. In general, transition to adulthood is a crucial and vulnerable time marked by changing roles and responsibilities, social flux, and new relationships. In adolescents and young adults (AYAs) with SBS, this difficult period is compounded by the burden of a serious and chronic disease. Studies on transition of care in AYAs with other chronic gastrointestinal conditions such as inflammatory bowel disease (IBD) suggest increased complications and psychosocial impairment, but there is a paucity of data in AYAs with SBS. The aim of this study was to assess transition readiness, resilience, mental health, health literacy and SBS-specific quality of life (SBS-QoL) in AYAs with SBS.

**Methods:** Patients with SBS over age 12 years were prospectively enrolled into our Center's SBS healthcare transition program, the “GUTSY Program.” Patients were administered the CD-RISC-25 to measure resilience, PHQ-9 to screen for depression, GAD-7 to screen for anxiety, The Newest Vital Sign (NVS) to assess health literacy, STARx and UNC TRxANSITION to assess transition readiness, and SBS-QoL tool to assess health-related quality of life. Parents were administered the NVS to assess parental health literacy, the Family Management Measure (FaMM) to assess parent’s perception of family management of SBS, and STARx to assess parent’s perception of patient’s transition readiness.

**Results:** Participants included 12 patients with SBS, of which 10 were patient-parent dyads (Mage=18; Range: 12-24 years; 50% Male; 50% Hispanic, 33% African American, 17% Asian). The STARx scores (MPatients=56.4, MParents=55) were lower than published scores in AYAs with IBD (M=59). The UNC TRxANSITION score (M=4.6) was lower than in AYAs with other chronic conditions (M=6.22). The CD-RISC-25 score (M=60.25) was lower than the general population (M=79.0). The PHQ-9 score (M=6.08) reflected mild depression (score range 5-9) and the GAD-7 score (M=5.3) reflected mild anxiety (score range 5-9). The NVS scores (MPatients=2.25, MParents=2.9) revealed lower health literacy compared to the general population (M=3.4). The SBS-QoL score (M=68.42) was lower than in the general SBS population (M=72.58). The FaMM score (MCondition Management Effort=13.89, MFamily Life Difficulty=36.11) indicated more time and work expended and slightly more difficulty in managing child’s SBS.

**Conclusion:** AYAs with SBS have lower transition readiness, resilience, health literacy and SBS-QoL and increased risk of mental health disorders. Targeted educational and psychological interventions to facilitate an easier transition to adulthood are needed in this population.

### 66

## Teduglutide treatment in adult patients with short bowel syndrome : real-life use and long term outcomes

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#### Abstract

Introduction: Short Bowel Syndrome (SBS) is a rare complex disease causing chronic intestinal failure (CIF) for which Parenteral Support (PS) is the reference treatment. Teduglutide (TED), a GLP-2 analogue, is available and reimbursed in France since 2015 for the treatment of SBS-CIF patients. The cost of this drug is very high and there is no data about the number of potential candidates in real life. The aim of the study was to analyze in a real-life setting the characteristics of SBS patients treated with TED over time, to evaluate the percentage of SBS-CIF patients treated with TED as well as the treatment outcomes since its market authorization.

Methods: This work was a monocentric retrospective study conducted in an expert center of Home PS. We enrolled all patients with SBS-CIF followed in the center between 2015 and 2020. Two sub-populations were defined for this study : the prevalent population, composed of the patients who were already followed in the center before 2015, and the incident population, composed of the new patients who initiated follow-up in the center between 2025 and 2020. Populations were compared using Wilcoxon-mann-withney or pearson chi2 tests. TED retention rate was calculated using Kaplan-Meier survival estimate.

Results : 331 patients were included in the study (156 prevalent and 175 incident patients). In total, 56 patients initiated a treatment with TED (16.9% of the cohort). 27.9% of prevalent patients initiated treatment, with an annual average rate of 4.3%, against 8.0% of incident patients, with an annual average rate of 2.5%. Treatment with TED allowed a median decrease of 60% (IQR 40-100) of PN volume in our cohort. The reduction of PN was significantly higher in the incident population than in the prevalent population (p=0.02). The long-term retention rate of treatment was 82% after 2 years, 67% after 3 years and 64% after 5 years. Among the non-treated patients, 50 patients (18.2%) were declared non suitable because of non-medical reasons (doubt about compliance, patient refusal, cognitive disorders…).

Conclusion : In the prevalent population of SBS patients, more than a quarter of patients were treated with TED, with a progressive reduction of the number of newly treated patients each year, against 8% of incident population. These figures can be important to evaluate the number of potentially treated patients for centers starting to use TED. Furthermore, this real-life study reports a better response to TED in the incident population, suggesting a benefit of early treatment compared to late treatment. The treatment retention rate higher than 80% after two years, which can be explained by the careful selection of patients that is important to examine.

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## Quality of life in children with chronic intestinal failure: parenteral nutrition- dependent versus rehabilitated

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#### Abstract

Introduction: Chronic intestinal failure (CIF) causes considerable morbidity and mortality and can impact on Health-Related Quality of Life (HRQoL) and survival of patients. Our aim is to explore the HRQoL in pediatric patients with CIF, analyzing patients dependent on parenteral nutrition (PN) in comparison with those who were weaned off PN.

Methods: HRQoL surveys for the pediatric population validated in Argentina (PedsQL) were conducted in patients aged 2-18 years with scores of physical, emotional, social and school functioning. A score of 0-100 was obtained, where 100 is considered excellent HRQoL. PN-dependent (PNd) patients were compared to rehabilitated patients (RP). The descriptive data were analyzed by chi2 test or Fisher's test for categorical variables and t-test or Mann Whitney for continuous variables, depending on the distribution.

Results: Between 3/2018 and 12/2019, 84 surveys were carried out on 67 patients and their families, 31/67 (2-4 years), 15/67 (5-7 years), 19/67 (8-12 years) and 2/67 (13-18 years). Median age: 5.53 years (IQR 3.8-8.7), males 69%. PNd 30/67 (44%), RP: 37/67 (56%). Global HRQoL score was higher in RP with a median of 86 (IQR 71-93) vs PNd, median 68 (IQR 51-76) (p 0.0001). This difference was significant in the physical, social, school and psychosocial functioning with better scores for RP. Perception of HRQoL of parents vs. children: PD had a trend to lower scores perceived by parents (median 67 (IQR 41-74)) vs children (median 72 (IQR 65-79)) (p ns). In RP trended to worse score perceived by children (median 66 (IQR 63-82)) with respect to parents (median 78 (IQR 73-96)) (p ns).

Conclusion: The evaluation of HRQoL in patients with CIF requires more attention from professionals, since it could be severely affected in some cases. Intestinal rehabilitation improves HRQoL but emotional aspects of patients once rehabilitated needs to be considered.

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## Early tissue modifications observed in a non immunosuppressed rat model of Abdominal Rectus Fascia Transplant

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#### Abstract

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**Introduction:** The impossibility of performing an adequate closure of the abdominal wall after an intestinal or multivisceral transplant increases the occurrence of complications and post-surgical death. The use of synthetic meshes can predispose to infections and fistulas, high costs and low availability on the market. Within the clinic, the use of different abdominal wall transplantation techniques has been proposed, however, many immunological phenomena are still unknown, the reason why further studies are necessary. Our aim was to characterize a new experimental model of rectus fascia transplantation.

**Methods:** The technique was developed by reproducing the technical aspects of "the Miami procedure” for avascular abdominal rectus fascia transplantation (TxARF) for humans in rats. Eighteen TxARF were performed, 9 were isogenic and 9 allogeneic transplants. Sprague Dawley and Wistar rats were used.  Recipients were sacrificed on day 30 post-surgery and graft samples were taken for elasticity measurement, histopathological evaluation by Weigert analysis for elastic fibers, Trichromic to stain collagenous connective tissue fibers, and immunohistochemistry for CD3+ cells. Six non-implanted fascias were taken as a control group (Ct). Relative amounts of CD4+ and CD8+ Tcells was determined by flow cytometry. Turnover of hematopoietic cells in the graft was analyzed by flow cytometry using GFP+Wistar rats as recipients.

**Results:** In the TxARF group, the 30 day survival was 100%; no adhesions between the intestines and the grafts were observed. The presence of neo-vascularization has been observed in all grafts. Isogenic and allogeneic grafts on day 30 presented less elasticity compared to the Ct (p=0.003), although no differences were observed in terms of the number of elastic fibers observed in TxARF grafts and Ct. The mean percentage of collagen fibers stained was more than 10 times higher in the TxARF allogeneic and isogenic groups than in the Ct (p<0.0001); significant increment in the percentage of CD3+ cells between isogenic or  allogeneic TxARF compared to the Ct and group was observed (p=0.0221). At 30 days post-transplant majority of the CD45+hematopoietic cells present in the graft were of recipient origin. No differences in CD4+ and CD8+ proportions were detected in the allogenic and isogenic TxARF compared with Ct.

**Conclusions:** Although there were no differences in the presence of elastic fibers, the observed reduction in physical elasticity of the TxARF, could be explained by the increasing development of collagen fibers in the grafts. The percentages of CD3+ cells between the isogenic and allogeneic TxARF groups in a non immunosuppressed model, favor a non immunological process as responsible for the evolving fibrosis. Those preliminary results allow us to better understand fascia transplantation in transplant patients, further knowledge in its immunogenicity are necessary to consider its future use in non immunosuppressed patients.

### 110

## Outcomes after Intestinal Re-Transplant: A detailed single-center analysis of clinical and technical factors

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#### Abstract

Introduction

Intestinal transplantation (ITx) is a treatment option for patients with intestinal failure. ITx can be performed as isolated ITx (iITx), liver and ITx (OLT+ITx), modified multivisceral (mMVTx), and multivisceral (MVTx). Long term success remains a challenge. Secondary-transplantation (2-ITx) is a viable option in this case. As the incidence of primary ITx (1-ITx) increases, the number of 2-ITx is likely to increase. 2-ITx is difficult due to the technical challenge of a re-do operation and the complexity of the immunosuppression. There are very few published reports on 2-ITx. The aim of our study was to identify characteristics of 1 vs. 2-ITx in order to understand predictors of success.

Methods

We retrospectively reviewed medical records of all 1-ITx or 2-ITx performed at UCLA between 1991-2021. Patients’ demographics were summarized using univariate statistics. Clinical characteristics were compared using chi-square and t-tests. A P value <.05 was considered statistically significant. Analyses were completed using Stata 14 (StataCorp LP, College Station, Tex).

Results

There were 157 total transplants in 132 patients. The incidence of 2-ITx was 18.9%. The five year survival of 1-ITx was 46.9% while the five year survival of 2-ITx was 44%. The number of pediatric 1-ITx was nearly twice that of adult (n = 84 vs 48). OLT+ITx was the most common surgical approach in 1-ITx (49%) and 2-ITx (60%). Children were more likely to have a successful 1-ITx than adults, but this was not significant (P=0.108). Female sex regardless of age was associated with successful 1-ITx (P=0.003). Having a pre-operative negative cross-match was associated with successful 1-ITx, but was not significant (P=0.086). A post-operative course free of antibody mediated rejection (ABR) was associated with successful 1-ITx (P=0.004). A post-operative course complicated by acute cellular rejection (ACR) was associated with having a 2-ITx (P=0.045), as were episodes of enteritis (P=0.004). Enterocolonic continuity of the 1-ITx was associated with successful 2-ITx (P=0.012). Induction with ATG prior to 2-ITx was associated with successful 2-ITx, but was not significant (P=0.091).

Discussion

Our center demonstrated a higher than national incidence of 2-ITx. We observed improved 1-ITx outcomes in children, females, and those with negative crossmatch. Enterocolonic continuity and induction with ATG were associated with improved 2-ITx outcomes. The most common type of 1- and 2-ITx was OLT-ITx, which demonstrated better chronic rejection-free survival compared with liver-free allografts. The most common reason for graft loss after 1-ITx and need for 2-ITx was ACR. Greater investigation is needed to understand how the field can optimize this particular treatment option.

### 111

## What is the Fate of Panel Reactive Antibodies in Intestinal Transplant and the Failed Graft?

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#### Abstract

Introduction: Despite remarkable advances in intestinal transplant (ITx) and immunosuppression, the immunogenicity of the bowel and regulating the immune system remains the biggest challenge. If the graft fails and the patient remains a viable retransplant candidate the difficult decision between graft explant and the ensuing battle against infection, chronic pain, fluid management, and prolonged hospitalization begins. We aim to explore the fate of the PRA in these cases and how it impacts the decision to explant the graft.
Methods: At our center we have performed 337 ITx in 324 patients from November 2003 to December 2022. Using a prospectively maintained database 21 were retransplants were identified, 8 of which the primary transplant occurred at another center. We retrospectively reviewed the PRA level of those who have been retransplanted, those who are listed for retransplant, and those who have been explanted but are not relisted
Results: 21 retransplants occurred over 180 months. There were 3 comparison groups: patients explanted prior to retransplant (n=12), patients explanted at the time of retransplant (n=9), and patients explanted but not retransplanted (n=8). Those explanted prior to retransplant, the PRA was 52 ranging from 0-99 and the median being 53.5. Those with graft enterectomy at the time retransplant the average PRA was 5 and the median was 0. The final group were those explanted and not retransplanted or still waiting for retransplant; the average PRA was 94 within 4.3 months of explant, ranging 44-100 with a median of 99.
Conclusions: Itx candidates tend to have higher PRA levels than other solid organ transplant candidates. Antibody-mediated rejection plays an important role in ITx and graft function. Highly sensitized patients (PRA>20) have worse outcomes and the higher the PRA is, the more difficult it is to obtain immunologically suitable grafts. If feasible, there may be a benefit to keeping the graft intact with immunosuppression until the patient is retransplanted. This invites us to explore further looking at different outcomes within these groups and how we can optimize those who are best candidates for retransplant.

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## Early infections after intestinal transplantation in adults. A comparison with liver transplantation.

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#### Abstract

Introduction: Infections are a leading cause of morbidity and mortality after intestinal (ITx). Although the infection risk is perceived as higher than with other types of transplants, any direct comparisons are lacking. Herein, we analysed the infectious complications during the first year after ITx and compared it with those occurring after liver transplantation (LTx).
Methods: We reviewed all adult ITx (n=28) performed at Sahlgrenska University Hospital between 2000-2022 and retrieved data on type, timing, etiology and management of infections. Similar data were collected on all adult LTx performed during 2017 at the same centre (n=73).
Results: Eighty-nine percent of ITx developed at least one infection during the first year post-transplant compared to 62% of LTx (p<0.01). About half of these infections occurred within three months and bacterial infections were the most common (64% and 70% for ITx and LTx, respectively). Bloodstream/sepsis (35% vs. 9.8%, p<0.001) and abscesses (10.3% vs 6.5%, p<0.01) were more frequent in ITx, whereas cholangitis (3.4 vs. 21.6%) and respiratory infections (9.4 vs. 14.1%) were numerically more prevalent in LTx. Infections were the leading cause of mortality in both groups. Overall, the risk of infections was higher in ITx compared with LTx (RR 1.44, 95% CI, 1.151 to 1.805, p=0.001). ITx receiving a similar immunosuppressive regimen (basiliximab induction, tacrolimus @ 10-12 ng/mL, mycophenolate mofetil, steroids) with LTx had a higher infection risk compared with the LTx (RR 1.622, 95% CI, 1.353 to 1.944, p<0.001).
Conclusions: Infections are almost universal after intestinal transplantation, with a majority occurring in the early post-transplant period. Recipients of intestinal transplants had a higher incidence and risk of infection than recipients of liver transplants. Further research and efforts to refine infection prophylaxis and management as well as understanding its relationship with immunosuppression are needed to improve outcomes after intestinal transplantation.

Figure: Timeline of infections according to etiology following intestinal transplantation (upper panel) and liver transplantation (lower panel).

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## Patient Variables Predictive of Post-Intestinal Transplantation Malignancy

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#### Abstract

Introduction

Immunosuppressed transplant recipients have a 3- to 4-fold increased risk of developing malignancy, with a 10-year prevalence as high as 30%. The rejection-prone intestinal allograft (ITx) requires a uniquely high level of immunosuppression, making it a more susceptible organ for malignancy. Post-transplant lymphoproliferative disorders (PTLD) are not uncommon in ITx recipients. PTLD has a highly variable presentation and disease course making it difficult to predict which patients will develop PTLD. The aim of our study was to describe factors related to development of PTLD and other malignancies following ITx.

Methods

We retrospectively reviewed medical records of all ITx performed at UCLA between 1991-2021. Patients’ demographics were summarized using univariate statistics. Clinical characteristics were compared using chi-square and t-tests. A P value <.05 was considered statistically significant. Analyses were completed using Stata 14 (StataCorp LP, College Station, Tex).

Results

There were 155 total transplants. The incidence of any malignancy after ITx was 21% over a median follow-up time of 9.0 (IQR 5.1,13.4) years. Of the 33 post-ITx cancers, 22 were PTLD, 4 were skin cancers, and 7 were a variety of adenocarcinoma, hepatocellular carcinoma (incidental in native liver), desmoid (recurrent in native rectum), and leukemias. One adenocarcinoma developed in the native rectum after ITx and was treated with surgery and chemotherapy; two adenocarcinomas were found in the native esophagus and jejunum and resulted in patient death; the last case of adenocarcinoma was incidentally discovered in a segment of transplanted small bowel with survival. All post-ITx skin cancers were found with screening and were successfully treated with surgical excision. The incidence of PTLD was higher in pediatric recipients (P=0.007) and combined liver and intestinal recipients (72.7%). Incidence of PTLD was higher in recipients with spleens present. No recipient who underwent splenectomy post-ITx developed PTLD, though this was not significant (P=0.112). Time on TPN greater than 12 months post-ITx was associated with PTLD (P<0.001). No patients with GVHD developed malignancy. Patients who remained EBV negative post-ITx did not develop cancer (81.82%, P=0.002).

Conclusion

The incidence of cancer following ITx was 21%. Late-onset PTLD was the most frequent malignancy observed and was more often seen among pediatric recipients. Recipients with EBV were more likely to develop cancer. Adenocarcinomas were the most with graft loss in 25% and patient death in 50%. Finally, skin cancers are observed and should be treated with screening and surgery for cure. A novel tolerogenic immunosuppressive strategy should be investigated and implemented to reduce the lifelong need for immunosuppression.

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## Indications and Success of Intestinal Transplantation in European Children

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#### Abstract

**Introduction.**

Intestinal transplantation (ITx) is a difficult procedure with high rates of rejection and treatment-related complications, so that many intestinal failure (IF) specialists in Europe hesitate to discuss it when complications of IF develop. We aimed to demonstrate that ITx can give children with total and definitive IF a life without parenteral nutrition, by collecting the results of ITx across Europe.

**Methods.**

A multicentre review of all patients <18y-old transplanted (and one re-transplanted at 20y-old) from 2010 to 2022 in the 8 European centres performing most ITx (Bergamo, Birmingham, Göteborg, London, Madrid, Paris, Rome, Tübingen). Data collected: age at ITx, original disease, indication for ITx, type of ITx, outcomes at 01/07/2022.

**Results.**

ITx was performed in 146 patients, 58 (40%) female. Median age at ITx was 9.3 years (range 7 m-20 y).

Underlying diagnosis: 58 (40%) short bowel syndrome, 37 (25%) motility disorder, 34 (23%) congenital enteropathy, 2 malignancy, 24 (16%) re-transplantation.

Indications for ITx were multiple in 80%:  76 (52%) intestinal failure-associated liver disease (IFALD), 28 (19%) hydroelectrolytic imbalance, 27 (18%) recurrent sepsis, 23 (16%) difficult vascular access, 24 (16%) re-transplantation, 33 (23%) other (poor quality of life, lack of availability of home parenteral nutrition).

Type of ITx: 68 (47%) multivisceral Tx, 39 (27%) isolated intestinal Tx, 34 (23%) combined liver-intestine Tx, 5 (3%) modified multivisceral Tx.

Outcomes: median follow up with a functional graft 7.5 years (1 m-12.5 y). There were 42 deaths (29%), of which 27 (64%) were in the first year after ITx. The graft was removed in 13 patients (9%),  9 (69%) in the first year. At the last follow up, 91 (62%) patients were alive and weaned from parenteral nutrition.

**Conclusion.**

The small number (146) of transplants in children across Europe in the last 12 years, and the patients’ age at ITx reflect the major improvements in intestinal rehabilitation seen in that period. Congenital enteropathies and motility disorders together were more frequent indications than short bowel syndrome, though half of the patients still had IFALD, and most had several IF complications. Two-thirds of transplants were liver-inclusive, because of IFALD or re-transplantation. The number of re-transplants was significant in the largest and more experienced centres.

After ITx, 2/3 of patients survived with a functional graft in the mid- and long-term. Graft removal and/or death occurred mainly in the first post-transplant year. Early discussions between IF and ITx specialists, when significant complications of IF are incipient, should decrease pre-transplant complications, and therefore improve ITx results further.

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## Hepatic Venous Wedge Pressure Gradient Measurements in Intestinal Failure Associated Liver Disease in management of children referred for Intestinal Transplantation

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#### Abstract

Background: Children with Intestinal Failure Associated Liver Disease (IFALD) irrespective of jaundice, may develop fibrosis without typical features of portal hypertension, with absence of varices in conventional locations. The presence or absence of portal hypertension determines the decision about safe continuation of parenteral nutrition, nutritional rehabilitation or recommendation for intestinal transplantation. Hepatic venous wedge pressure gradient (HVWPG) is an objective measurement used in chronic liver diseases for assessing the severity of portal hypertension. We postulated that HVWPG may be useful to assess the severity of portal hypertension in children with IFALD.

Methods: Retrospective analysis of children with IFALD who had HVWPG measured between 2005- 2020. Demographic details, liver biopsy, HVWPG and clinical outcomes were reviewed. Significant portal hypertension was defined as HVWPG ≥10mmHg. Children were grouped into two categories based on HVWPG gradient: HVWPG ≥10 mmHg and HVWPG ≤10mmHg) and outcomes analysed.

Results: Between 2005-2020, 96 children underwent 123 assessments for intestinal transplantation. 43 HVWPG measurements were performed in 33 patients (median age- 42 months, IQR- 16- 93). 39 liver biopsies were done simultaneously. Bilirubin level, platelet count, splenomegaly and presence of oesophageal varices did not correlate with the severity of hepatic fibrosis or HVWPG. 6/33 children had HVWPG ≥10 mmHg at initial measurement. Out of the six children, 4 had a liver inclusive ITx and 1 died as family declined ITx while 1 child had isolated ITx. 27/33 children had HVWPG <10mmHg. 5 (out of 27) children underwent transplantation with 3 of the children receiving isolated ITx while 2 children received liver inclusive ITx. 9 patients had repeat HVWPG measurements at median interval of 14 months (IQR, 7- 64) due to change in clinical status requiring re-assessment. 5 children with HVWPG <10mmHg on initial assessment had gradient >10mmHg on repeat assessment of which 3 children then received a liver inclusive ITx while 2 children died on the waiting list for liver inclusive grafts. Out of the 4 children with HVWPG <10mmHg on repeat measurements, 2 received isolated ITx, the other 2 children continued parenteral nutrition. Simultaneous liver biopsies were available in 39 patients. Four children had histological moderate-severe hepatic fibrosis but HVWPG ≤10mmHg, which enabled us to offer isolated intestinal transplantation, otherwise these children would have received liver inclusive intestinal graft. All four are alive with native liver with a median follow-up of 104 months (IQR, 40-156).

Conclusion: HVWPG measurements can guide in the decision-making process in children with IFALD for intestinal transplantation. Sequential measurements may help to assess the progression of IFALD

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## INTESTINAL TRANSPLANTATION IN PEDIATRIC RECIPIENTS YOUNGER THAN  1 YEAR OF AGE. INDICATIONS AND OUTCOMES

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#### Abstract

Intestinal transplantation (ITx) is a proven treatment for pediatric patients with irreversible intestinal failure. Intestinal transplants in recipients younger than 1 year of age (<1yo) are infrequent and somewhat controversial. In the United States, only a few cases are performed each year in this age group.

We retrospectively reviewed our experience with ITx in this particular population. Immunosuppression consisted of IL-2 receptors for induction and steroids, tacrolimus and sirolimus for maintenance. Thymoglobulin was administered per protocol to sensitized recipients or in the setting of a positive crossmatch

During this period 337 ITx have been performed in 324 recipients at our institution. 161 transplants were performed in pediatric recipients (49.7% of the entire cohort). Of those, 34 cases (21.1%) were performed in <1yo recipients. The most common indication was Gastroschisis (10 cases) followed by Necrotizing Entercolitis and Atresia (8 and 7 cases respectively). The median age was 9 months old (range 5 to 11 mo). The median recipient weight was 7,4 kg (range 4 to 10Kg). Types of grafts were Liver-small bowel (and pancreas) transplant in 27 cases (79.4%), multivisceral tx in 6 cases  and isolated intestinal transplant only 1 case.

In this particular group of patients, 1-year and 3 year patient survival was 82.3%, compared to 84.4% and 71.4% for the entire cohort; and 88.1% and 79% respectively when considering only pediatric recipients. Technical (reoperation rates), and immunological complications(rejection, PTLD, GVHD) were not different among reciopients younger than 1 year of age and older pediatric recipients

This study demonstrates that Intestinal Transplantion can be safely performed in pediatric recipients younger than 1 year of age. This data should favor the option of transplanting these patients in experienced centers versus waiting until they are older with other potential complications

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## Regulatory T-Cell Mediated Split Immunological Tolerance After Intestinal Transplantation in a Porcine Model

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#### Abstract

Background. Intestinal transplantation (ITx) is the only remaining treatment for patients with intestinal failure who have failed parenteral nutrition. Unfortunately, high rates of rejection, graft-vs-host disease, and complications of immunosuppression make this therapy a last resort. Induction of tolerance would overcome these limitations. Furthermore, we have developed an MHC-defined miniature swine ITx model that provides a unique opportunity to assess chimerism and tolerance induction in the setting of defined histoincompatibilities. In this study, we utilized our model to evaluate chimerism, tolerance, and cellular immune responses after a full MHC-mismatch ITx.

Methods. The recipient was T-cell depleted using CD3-immunotoxin and anti-CD8 antibody since thymoglobulin is ineffective in swine. The entire recipient small intestine was removed and replaced by a full MHC-mismatched donor small intestine. A stoma was created to assess the graft visually and collect biopsies. Immunosuppression, mimicking our clinical protocol, consisted of tacrolimus (goal level 16-18ng/ml) and 1mg/kg prednisone for 90 days and was subsequently weaned over 30 days to assess tolerance. Peripheral, mucosal, and bone marrow chimerism were tracked weekly, biweekly, and monthly, respectively. Endoscopic biopsies were collected biweekly and evaluated for rejection. Donor-specific antibody (DSA) assays were done before and 45 days after the transplant. Mixed lymphocyte assays (MLR) with and without CD25-depletion were done monthly using peripheral and mucosal lymphoid cells.

Findings. The recipient was successfully weaned from immunosuppression on day 132 without clinical or pathological signs of rejection of the full MHC-mismatched allograft. Peripheral blood donor lymphoid chimerism was 15.6% on day 1, peaked at 20.3% on day 8, and was lost by day 10 after transplantation. T-cell replacement by the recipient in the graft intraepithelial lymphocytes was 69.2% 27 days after transplantation and 88.83% at the time of euthanasia. T-cell replacement by the recipient in the graft lamina propria was 86.3% 27 days after transplant and 93.87% at the time of euthanasia. Bone marrow showed 3.6% donor lymphoid and 0.36% myeloid chimerism on day 56 and 0.5-1% for both lineages at the time of euthanasia. DSA was negative for IgM and IgG before and 45 days after transplantation. Peripheral blood lymphocytes in MLRs maintained a robust response against the donor, while the mucosal lymphocytes showed donor-specific unresponsiveness that was abrogated when CD25+ cells were depleted, indicating that tolerance was locally mediated by regulatory T-cells.

Conclusion. We achieved tolerance to a full MHC-mismatched intestinal graft in our pig model which appears to have been locally mediated by regulatory T-cells within the graft.  We intend to repeat this experiment to see if the findings are reproducible and if the mechanisms favoring tolerance are applicable to our clinical regimen.

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## Iron-deficiency Anaemia in Paediatric Intestinal Transplant Recipients, a single-centre review

Dr Sunitha Vimalesvaran MBBS, MRCPCH, Miss Carly Bambridge RN, Mr Hector Vilca-Melendez MD, Dr Jonathan Hind MD

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#### Abstract

Introduction:

Outcomes for paediatric intestinal transplantation continue to improve. However, studies have shown that attaining catch-up growth after successful transition to enteral nutrition may not occur. This may be due to micronutrient deficiencies, although limited data exists. Iron deficiency anaemia (IDA) is often under-recognised and under-treated in children post-intestinal transplantation. IDA may be secondary to inflammation, medications, and increased need for iron after transplantation. The aim of this study was to assess the prevalence of, and risk factors for, IDA in paediatric intestinal transplant recipients.

Methods:

A retrospective case-notes review of all patients who underwent intestinal, liver-intestinal, or multivisceral transplant between January 2009 and December 2022 at our centre. Diagnosis of IDA was based on a composite measure of microcytic, hypochromic anaemia (haemoglobin <110g/L), low ferritin (<30ng/ml) and low iron (<10micromol/L), at least 1-year post-transplant. Data including demographics, aetiology of intestinal failure, type of transplant and mortality were retrieved.

Results:

28 patients  (16 male), median age of 5.0 years (4.0-8.8), underwent an intestine-containing transplant. Aetiologies included:  Paediatric intestinal pseudo-obstruction in 6 (21%), gastroschisis in 5 (18%), and microvillous inclusion disease in 2 (7%). All patients received Basiliximab and methylprednisolone at induction, followed by tacrolimus and low-dose prednisolone as maintenance immunosuppression, with the addition of sirolimus in 12 patients (43%). 19 patients (76%) achieved enteral autonomy (Table 1).

Of the 25 children who survived to 1-year, 17 children (68%) had haemoglobin <110g/L with a microcytic, hypochromic appearance on blood film. Of these, 14 children (82%) had low ferritin (mean 16.9ng/ml, SD 8.2) and 12 (71%) had low iron levels (mean 7.65micromol/L, SD 6.5). 3 patients had high levels of ferritin (mean 1151ng/ml, SD 424.1), despite low haemoglobin and iron stores.

Age at transplant (p=0.23), enteral autonomy (p=0.61), type of transplant (p=0.43) and addition of sirolimus (p=0.21) were not significant variables in predicting IDA. Longer time on the waiting list, with longer duration on parenteral nutrition pre-transplant had a higher risk of iron deficiency (p<0.001) (Table 2). IDA was not associated with higher mortality (p=0.82).

Conclusion:

The composite measure of haemoglobin, iron and ferritin levels was a useful screening tool for IDA, although ferritin levels alone may be falsely elevated due to inflammation. We showed that post-transplant IDA may be due to poorer pre-transplant state, reflected by longer transplant waiting time. Second-line immunosuppressive agents and achievement of enteral autonomy were not risk factors for IDA in this cohort.  Monitoring and appropriate supplementation is essential to prevent and treat IDA.

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## THE FIRST SERIES OF ANORECTAL TRANSPLANTATION IN SWINE WITH EXTENDED SURVIVAL

Dr. Juliana B. Salen MD1, Dr. Daniel R. Waisberg MD1, PROFESSOR Jun Araki M.D., Ph.D.2, Biol. Cinthia Lanchotte M.Sc.1, DVM Julia B. Guarana M.Sc.3, DVM Eduardo Pompeu Ph.D.4, PROFESSOR Flavio V. Meirelles Ph.D.3, PROFESSOR Silvio H. Freitas Ph.D.3, DR. Andre D. Lee M.D., Ph.D.1, PROFESSOR Luiz A. Carneiro-D'Albuquerque M.D., Ph.D.1, PROFESSOR Flavio H. Galvao M.D., Ph.D.1

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#### Abstract

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Introduction: Anorectal transplantation is a potential treatment for complex fecal incontinence and permanent colostomy. Murine model for translational research of this transplantation showed good graft recovery after few days (1-4). Autotransplantation is a good model to study graft function without rejection. In this survey we describe long evolution in a swine model of anorectal autotransplantation.

Method: Four male swine (Landrace) weighting 35 to 55 kg were used. Technique - After general anesthesia, abdominal and perianal incision was performed. The graft containing perianal skin, anus and the rectum were removed in block with a vascular pedicle containing the inferior mesenteric artery (IMA) in continuity with aorta patch and inferior mesenteric vein (IMV). The graft was washed with cold Lactate Ringer and immediately implanted by anastomoses between aorta patch and aorta and IMV and vena cava. After reperfusion, we performed pudendal nerves synthesis and colorectal anastomosis to reestablish the digestive tract. Perianal and abdominal reconstitution concluded the surgery. The animals were kept in appropriated facilities for clinical, manometric and colonoscopic evaluation.

Results: All recipients presented good postoperative evolution and clinical signs of functional graft recovery within two postoperative weeks. One animal presented an auto limited perianal fistula that cure spontaneously. Three animals were euthanized after one month and one after six months for autopsy and graft histological study. Anal manometry performed in all animals at 30th POD observed sphincter function recovery in three animal (figure 1 A and B) and partial recovery in one animal when compared to manometry performed in normal animals (p≤0,50). Colonoscopy performed after transplantation observed normal graft mucosa and motility. Graft histology observed normal anorectal tissues in three animals and mild inflammatory infiltration in one case.

Conclusion: Here we describe the first pre-clinical remark of anorectal transplantation in swine with extended survival and observed good morphological and functional graft recovery within 30 post-operative days.

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3. Seid VE, et al. Functional outcome of autologous anorectal transplantation in an experimental model. Br J Surg. 2015;102:558–562.

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Figura 1

Figure 1A - Aspect of the anus at 30th POD showing continent appearance and good muscle tone.

Figure 1B - Manometry performed at 30th POD of showing anal sphincter curves pressure levels compatible with normality.

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## Multivisceral transplantation: variations on technical approaches according to different etiologies

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#### Abstract

Introduction: Grade IV or diffuse porto-mesenteric venous thrombosis (DPMT) and tumors compromising the mesenteric root have become the leading indications for multivisceral transplantation (MTVTx). Both diseases pose different challenges that need to be overcome, some of which are related to the timing of transplantation, implying changes in the regulations for organ allocation. Others are related to the surgical approach for visceral exenteration and engraftment. In this video, we aim to compare the current approach to both disorders in our program.

Materials and methods: The aim was to compare two patients who underwent MTVTx, one with an unresectable cystic lymphangioma compromising the root of the mesentery (MRCL) without portal hypertension (PH) (case 1), and the other case, a DPMT with severe portal hypertension and collateral veins (case 2).

Results: The video begins by showing the standard approach of an MTV donor. Then, we show the pitfalls encountered during the abdominal exenteration of our 7-year-old recipient with the MRCL, in comparison to the challenges of the second patient, a 46-year-old recipient with DPMT secondary to complicated polycythemia vera and JAK-2 associated thrombophilia. He also had a short bowel syndrome secondary to mesenteric ischemia, leaving him with a type 3 anatomy. In the first case, the challenge was not the initial approach but the mobilization and retroperitoneal dissection around the intestines containing the tumor, which caused significant retraction of the mesentery and adhesions. The DPMT patient developed significant venous collaterals along the course of the disease, causing an immediate challenge from the beginning of the procedure in order to be able to visualize the remaining organs. New coagulation devices helped along the process. The resection of all abdominal organs was carried out without significant loss but under a controlled approach (ligating or cauterizing each visible vessel), only possible by starting the procedure simultaneously with the donor surgery to optimize ischemic times. Then the MTV grafts (liver, stomach, duodenum-pancreas, and small bowel) were engrafted using the standard technique in both cases. Table 1 compares blood loss and time frames for both procedures.

Conclusion: Understanding each MTV case allows planning the procedure ahead of time. The use of current hemostatic devices, together with a controlled approach, reduces the need for the proposed “rapid exenteration” or the need for presurgical arterial embolization. Although it prolongs surgical times, a bloodless operation will benefit patients by having less shock, shorter ICU and hospital stays, and improving long-term outcomes.

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## Recurrence After Enterocutaneous Fistula Surgery: Results from a Multidisciplinary approach an Intestinal Rehabilitation Team (MAIRT)

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#### Abstract

Introduction: Enteric fistulas (EF) or proximal stomas are usually consequence of abdominal surgery resulting in intestinal failure (IF) mainly type II and requires parenteral nutrition (PN) for long time.  Despite recent advances, the recurrence rate after intestinal reconstruction surgery is still high, 19% approximately. Multidisciplinary approach an intestinal rehabilitation team (MAIRT) is crucial to improve the results. This study aimed to evaluate factors associated with recurrence in patients submitted to fistula surgery.

Methods: Analytic observational study, records were reviewed of patients who had EF surgery (2020-2022). Management strategy involved early MAIRT, the team consist of a nursing staff, clinical dietitian, pharmacist, social worker, physical therapist and surgeon. All patients were in PN and oral intake; also, they performed physical therapy every day.  The surgical procedure was indicated after 10 to 12 weeks after the last abdominal procedure and when the patient got a good physical and lab nutritional parameters. To determine independent risk factors, significant variables found through univariate analyses were then submitted to multivariate analyses (logistic regression). Odds ratios were calculated for these factors.

Results: There were 40 male and 46 female patients. Mean age was 55 years (Standard deviation 13); EF recurred in 14 patients (16%).   Univariate analysis showed albumin (p=0.04) and prealbumin (p=0.01) as a risk factors for recurrence.  After multivariate analysis, both albumin and prealbumin were found to be independent factors related to recurrence with a risk over seven and two times higher respectively.  Although not statistically significant, age (p=0.1) and a history of smoking (p=0.16) were factors that clearly showed a tendency to increase the risk of recurrence. For the adjustment of the model, the Hosmer Lemeshow test was obtained, p= 0.78, indicating a good fit and that it was adequately explained by the data.

Conclusion: Our findings indicate that patients with poor nutrition and performance status have the highest chances of recurrence after surgery. Our study demonstrated that low levels of albumin and prealbumin before surgery are independent factors to recurrence. A Multidisciplinary approach an intestinal rehabilitation team is essential in order to achieve successful results.

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## Rejection Profile in a Swine Model of Anorectal Transplantation

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#### Abstract

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Introduction. Anorectal transplantation is a logical treatment for complex fecal incontinence and permanent colostomy. We performed murine anorectal transplantation observing technical feasibility, good graft recovery (1-2) and the profile of rejection (3). Here we describe the rejection in a swine model of anorectal transplantation

Method: Twelve male swine (Landrace) weighting 35 to 50 kg were used for four anorectal transplantation and Surgical technique – We used a similar technique previous described for autotransplantation in swine (4). After general anesthesia, abdominal and perianal incision was performed. The graft containing perianal skin, anus and the rectum were removed in block with a vascular pedicle containing the inferior mesenteric artery with an aorta patch and inferior mesenteric vein (IMV). The graft was washed with cold Lactate Ringer and implanted by anastomosis between aorta patch and recipient aorta and IMV and recipient vena cava. After reperfusion, we performed pudendal synthesis, colorectal anastomosis to reestablished the digestive tract and perianal and abdominal reconstitution. The animals were kept in appropriated facilities for clinical and histological evaluation.

Results: We observed progressive signs of clinical rejection (abdominal distention, obstipation, intense hyperemia, edema and mucorrhea in the anal region) in all animals since the fourth POD (1A). All animals were sacrificed at 6th and 7th POD because clinical status deterioration. During autopsy, we observed intense inflammatory process inside and around the enlarged and inflamed graft (1B). Rejection was confirmed by histological examination (1C, 1D).

Conclusion: Here we describe the first observation of rejection in a swine model of anorectal transplantation.

Figure captions

1A- Anal rejection showing intense hyperemia, edema and desquamation of the mucosae and perianal skin.

1B- Features of rectal anastomosis (green arrow) showing normal rectum above and graft rejection with enlargement and hyperemia of the intestine and anal channel due to inflammation and edema ( blue arrow),

1C- Anastomosis site (green arrow) showing the normal rectum donor segment above and diffuse trans-mural lymphomononuclear inflammatory infiltrate and edema (blue arrow) in the graf.

1D- Rejection in anal channel (200 Xs) with lymphomononuclear inflammatory infiltrate and edema (green arrow) in the anal mucosae, internal and external anal sphincter (yellow arrow) and the perianal skin (green arrow).

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## Title - The role of the social worker in the intestinal rehabilitation and transplantation contest in at São Paulo University Hospital

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#### Abstract

Introduction: Social work is fundamental for patients with intestinal failure (IF), especially regarding the decision to include them in home parenteral nutrition (HPN) program or indication for intestinal transplantation (ITX). This activity inspires as multidisciplinary norms for the indication of these procedures that involve high complexity, high monetary cost and the need for bioethical regulations for the allocation of resources for this type of patient. In this study, we evaluated the socioeconomic profile of IF patients in HPN program and/or with indication for intestinal or multivisceral transplantation.  São Paulo University Hospital ( HC-FMUSP) is the public health reference program for HPN and ITX in Brazil.  The Aim-  The social worker evaluate the socialeconomic profile, life style, quality of life correlation with the adherence to support this complex treatment.  Methods- Adult patients from HC-FMUSP with FI, under HPN program and/or with indication for intestinal or multivisceral transplantation were included in this survey. To assess the socioeconomic profile, a single social worker specialized in abdominal organ transplantation applied a social report system form from to evaluate patient’s age, gender, civil status, worksituation, local of origin, monetary income and schooling.   Results: From January 2017 to December of 2019, twenty patients from HC-FMUSP with IF were evaluated, 13 were male and 7 female. The period of patient’s HPN dependence ranged from one  to 16  years. The age ranged from 16 to 56 years old and   65% lives were out from the HC-FMUSP (São Paulo City). Only one patient were actively working when the report were performed. 40% of the patients obtained fundamental education, 50% median education and 10% college education. 45% earned 250-500 USD/month, 40% earned 500-900 USD/month and 15% earned more than 1000 USD/month. Four patients died during this survey period, six patients were submitted to ITX,  four obtained HPN weaning and six keep HPN yet .Social worker evaluation is fundamental to assess the level of patient’s treatment adherence for  HPN and  ITX to support the treatment team and families to correlate the changes of life-style and quality of life. Patients from HC-FMUSP under HPN and/or with indication for intestinal or multivisceral transplantation obtained 80% of survival during this study period and encloses low superior education and monetary income.