Intestinal transplantation

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29th SATS conference, Stellenbsoch
November 2022

29th SATS & 6th SATiBA CONGRESS
11 – 13 November 2022
STIAS, STELLENBOSCH, CAPE TOWN

No disclosures for this talk

Topics

- Intestinal failure
- Intestinal transplant past and present
- Indications, types, who and when to transplant
- International data
- Immunosuppression strategies
- Long-term outcomes
- The future

Intestinal Failure

- Critical reduction of *functional* gut mass below the minimum required for adequate digestion and absorption to satisfy body fluid, nutrient and electrolyte requirements for maintenance in adults and growth in children

Gastroenterology. 2006 Feb;130(2 Suppl 1):S16-28. Causes and management of intestinal failure in children. Goulet O, Ruemmele F.

- Total, partial, temporary, permanent
- Limited options
- Parenteral Nutrition is mainstay of therapy


What could go wrong?

Problems of IF

- Growth failure
- High bowel fluid losses and malabsorption
- Dehydration
- Electrolyte deficiencies
- Nutrient deficiencies
- Bowel dilatation
- Dysmotility
- Complications of IF treatments


ADAMS, JOSEPHINE
CAUTION: SOLUTION CONTAINS HIGH CONCENTRATION OF POTASSIUM
12/13/06 5:12PM
Verified By
Do Not Use After: 12/15/06 22:00:00
Solution contains: 60 ml overfill
Final Solution Osmolarity 2464 mOsm/L
PARENTERAL NUTRITION Central
Bag Dung at _____ By _____
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BOLUS
STOP

Parenteral Nutrition

- Effective and safe therapy
  - Intrusive
  - Expensive
  - Significant morbidity
- Complications
  1. Catheter-related
  2. Metabolic
  3. Bone disease
  4. Organ dysfunction (liver, kidney)

Past

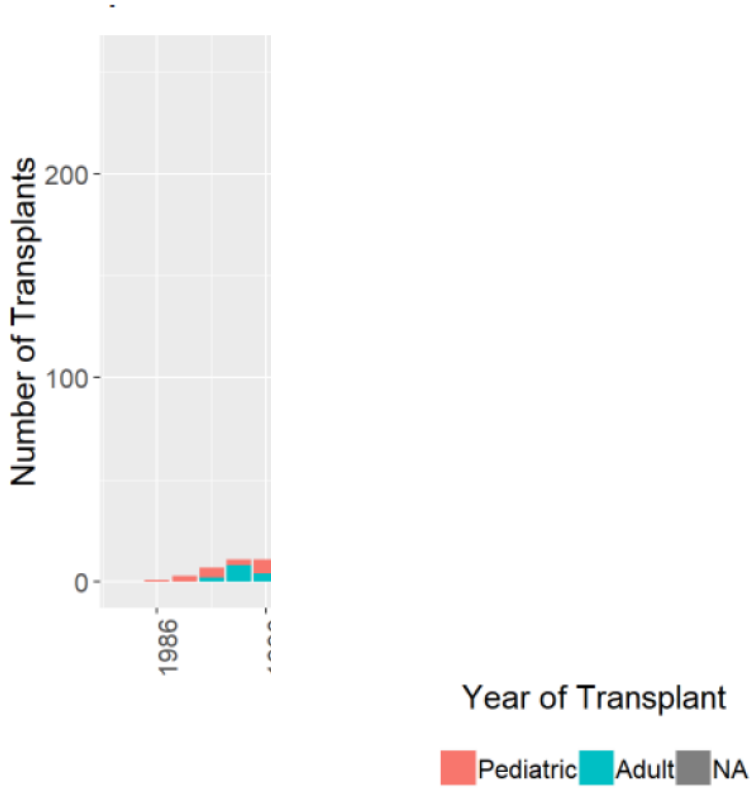
Poor outcomes

- Insufficient gut function was historically a non-survivable disorder
  - Pre-1970 – no TPN
  - Pre-1990's – few options if complications of TPN
  - Intestinal (± liver) transplantation

- For 25 years there were no survivors of intestinal transplantation
- Other organs such as liver and kidney were having successes
- Impetus to succeed was still present

Intestinal Transplants Performed

(All recipients transplanted between Jan 1985-Dec 2018)



Survival

Hess RA, Welch KB, Brown PI, Teitelbaum DH. Survival outcomes of pediatric intestinal failure patients: analysis of factors contributing to improved survival over the past two decades. J Surg Res. 2011 Sep;170(1):27-31.

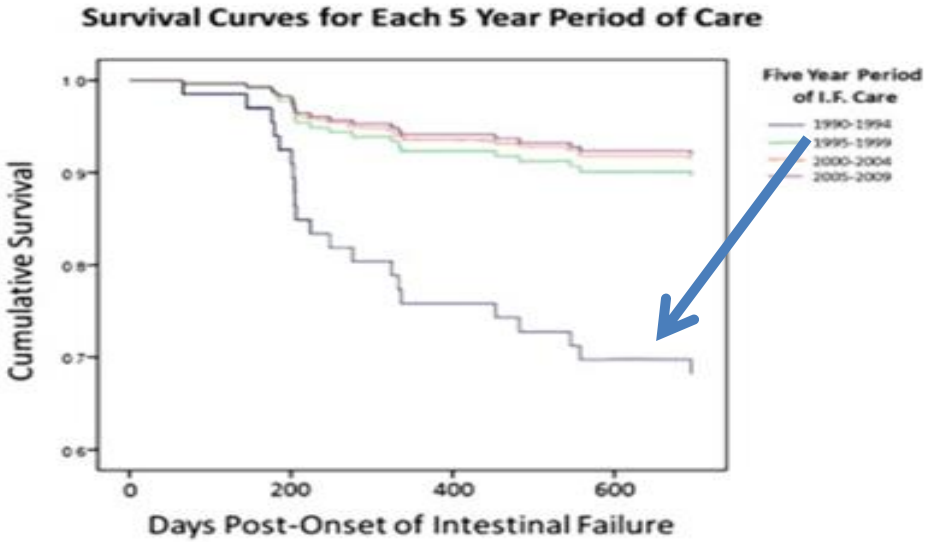
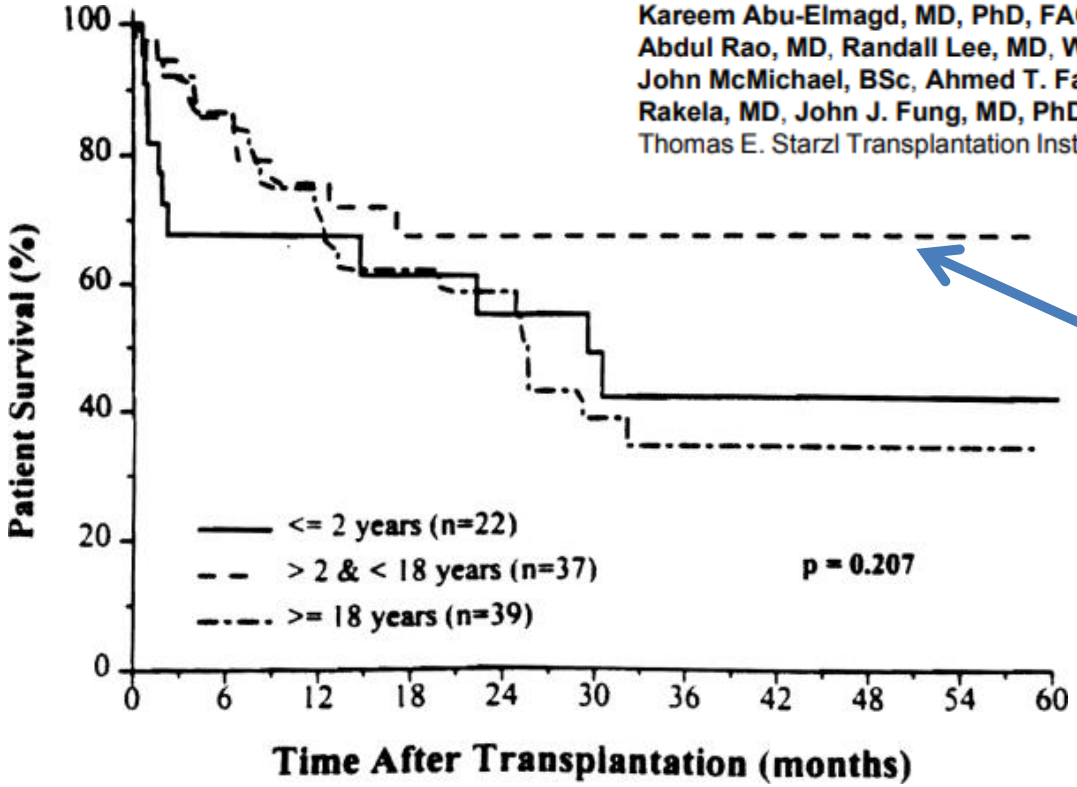


Fig. 2 Cox regression survival curves as broken down into 5-y periods.

Published in final edited form as:
J Am Coll Surg. 1998 May ; 186(5): 512–527.

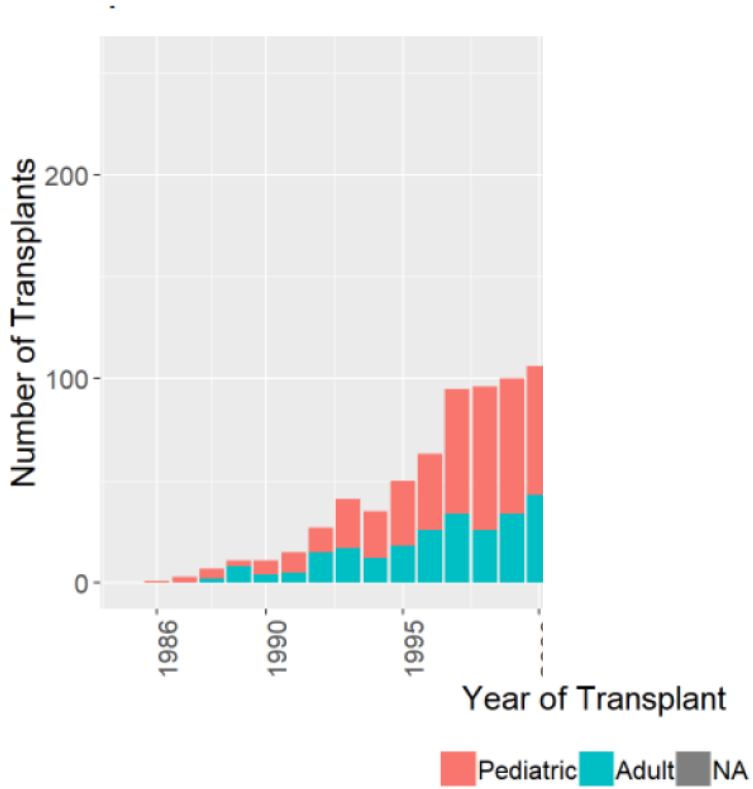
Clinical Intestinal Transplantation: New Perspectives and Immunologic Considerations

Kareem Abu-Elmagd, MD, PhD, FACS, Jorge Reyes, MD, FACS, Satoru Todo, MD, FACS, Abdul Rao, MD, Randall Lee, MD, William Irish, MSc, Hiro Furukawa, MD, Javier Bueno, MD, John McMichael, BSc, Ahmed T. Fawzy, MD, Noriko Murase, MD, Jake Demetris, MD, Jorge Rakela, MD, John J. Fung, MD, PhD, FACS, and **Thomas E. Starzl, MD, PhD, FACS**
Thomas E. Starzl Transplantation Institute, University of Pittsburgh Medical Center, Pittsburgh, PA.



Intestinal Transplants Performed

(All recipients transplanted between Jan 1985-Dec 2018)



Survival (circa 2005)

- The Pediatric Intestinal Failure Consortium

Squires RH, Duggan C, Teitelbaum DH, Wales PW, Balint J, Venick R, Rhee S, Sudan D, Mercer D, Martinez JA, Carter BA, Soden J, Horslen S, Rudolph JA, Kocoshis S, Superina R, Lawlor S, Haller T, Kurs-Lasky M, Belle SH; Pediatric Intestinal Failure Consortium. Natural history of pediatric intestinal failure: initial report from the Pediatric Intestinal Failure Consortium. J Pediatr. 2012 Oct;161(4):723-8.

- Between 2000 & 2005 - 272 subjects in 14 centers
- Median f/u 25.7 months (11-40)
- 58 (21%) deaths without intestinal transplantation
- 60 Intestinal transplants with 10 post-Tx deaths during follow-up period

Present

Case

- Mother – primary ovarian failure
- Baby antenatal mid-gut volvulus
- Surgery day 1 of life
  - 16cm small bowel surviving, 1cm distal ileum
  - Extra-hepatic biliary atresia, splenic malformation noted
  - Prognosis grim

- At KCH – liver management and intestinal rehabilitation
  - Surgery 11/7 – Modified Kasai (duodenoportoenterostomy), jejunostomy, colonic mucous fistula.
  - Maintained on PN (and HPN)
  - Surgery 8/12 – STEP, reconnection
  - Surgery 9/12 – Anastomotic imbrication and distal access point for refeeding
  - Parenteral nutrition management and HPN
  - Enteral feeding
- Course
  - Complicated by fistulating bowel, poor GI motility and intra-abdominal sepsis
  - Home on 16 hours per day PN, plus tube EN, plus dressings etc
  - Eventually deterioration of liver function
  - Assessed early for liver/bowel transplantation

- **Outcome**
  - Combined liver/bowel transplant at 17/12 age
  - PICU 6 days
  - Inpatient 30 days
  - Full EN

- **Current – age 12yrs (10.5yrs post-ITx)**
  - At home
  - Normal diet, no nutritional support, normal growth
  - Normal developmental progress, at school
  - Father back at work full time
  - 3 medications
  - Stoma reconnected

Indications

1. Irreversible intestinal failure
   a) Life-threatening complications of TPN
   b) Very poor quality of life thought to be correctable by transplantation

2. Extensive surgery requiring evisceration
3. Transplantation of other organs where excluding the intestine would adversely affect survival

20 years old

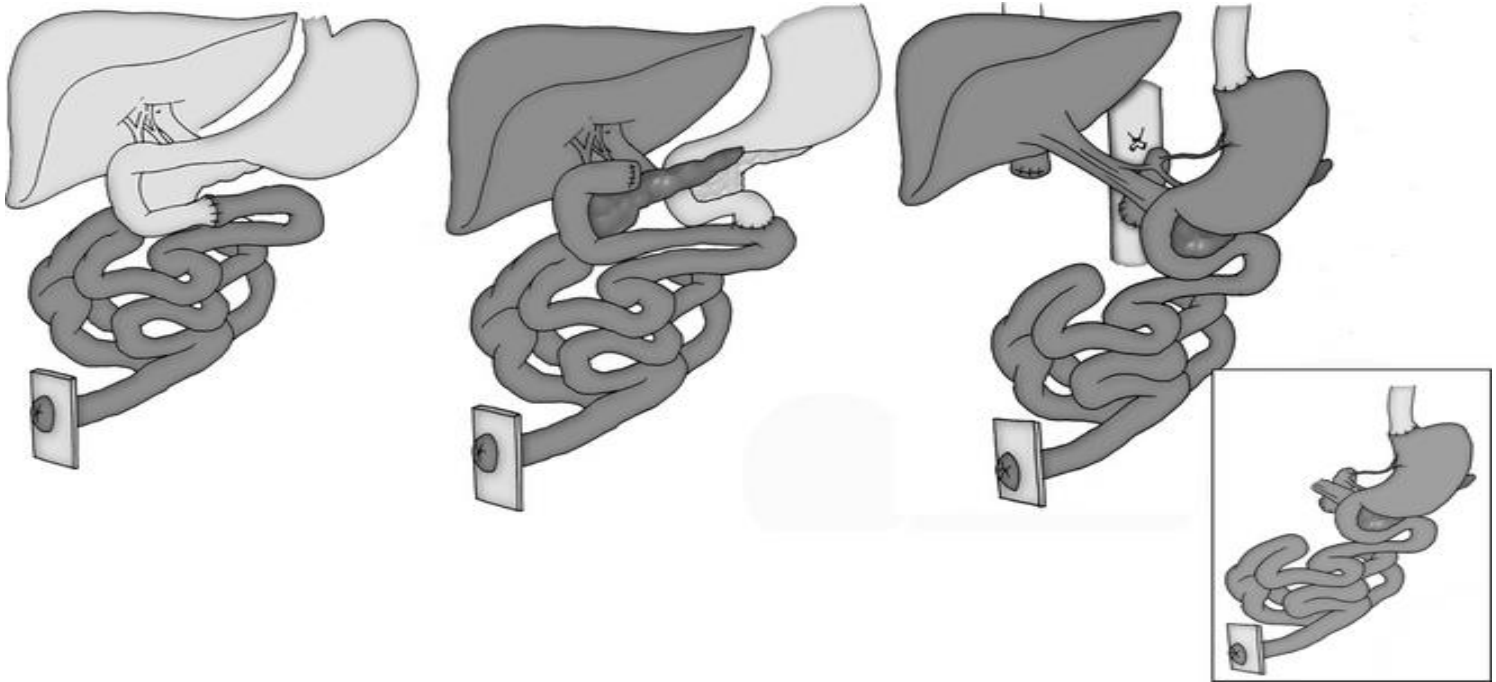
Pediatr Transplant. 2001 Apr;5(2):80-7.
Indications for pediatric intestinal transplantation: a position paper of the American Society of Transplantation. Kaufman SS, Atkinson JB, Bianchi A, Goulet OJ, Grant D, Langnas AN, McDiarmid SV, Mittal N, Reyes J, Tzakis AG; American Society of Transplantation.

Complications of PN

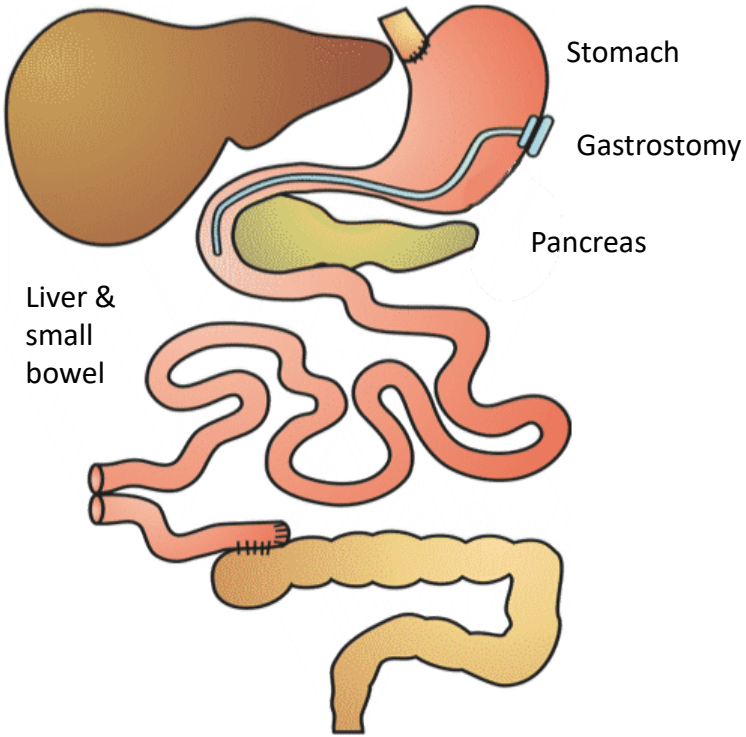
- Progressive liver disease despite remedial action
  - Objective
  - Judged on biochemistry and biopsy
    - Consider combined liver and bowel transplant rather than isolated small bowel
      - Liver/bowel candidates have higher priority than bowel alone on the UK waiting list
- Severe sepsis
  - More than one life-threatening episode of catheter-related sepsis
  - Endocarditis or other metastatic infection
- Limited central venous access
  - 3 major* venous access sites in adults (above and below the diaphragm)
  - 2 major* venous access sites in children (above the diaphragm)
    - * Internal jugular, subclavian, femoral

Types of intestinal transplant

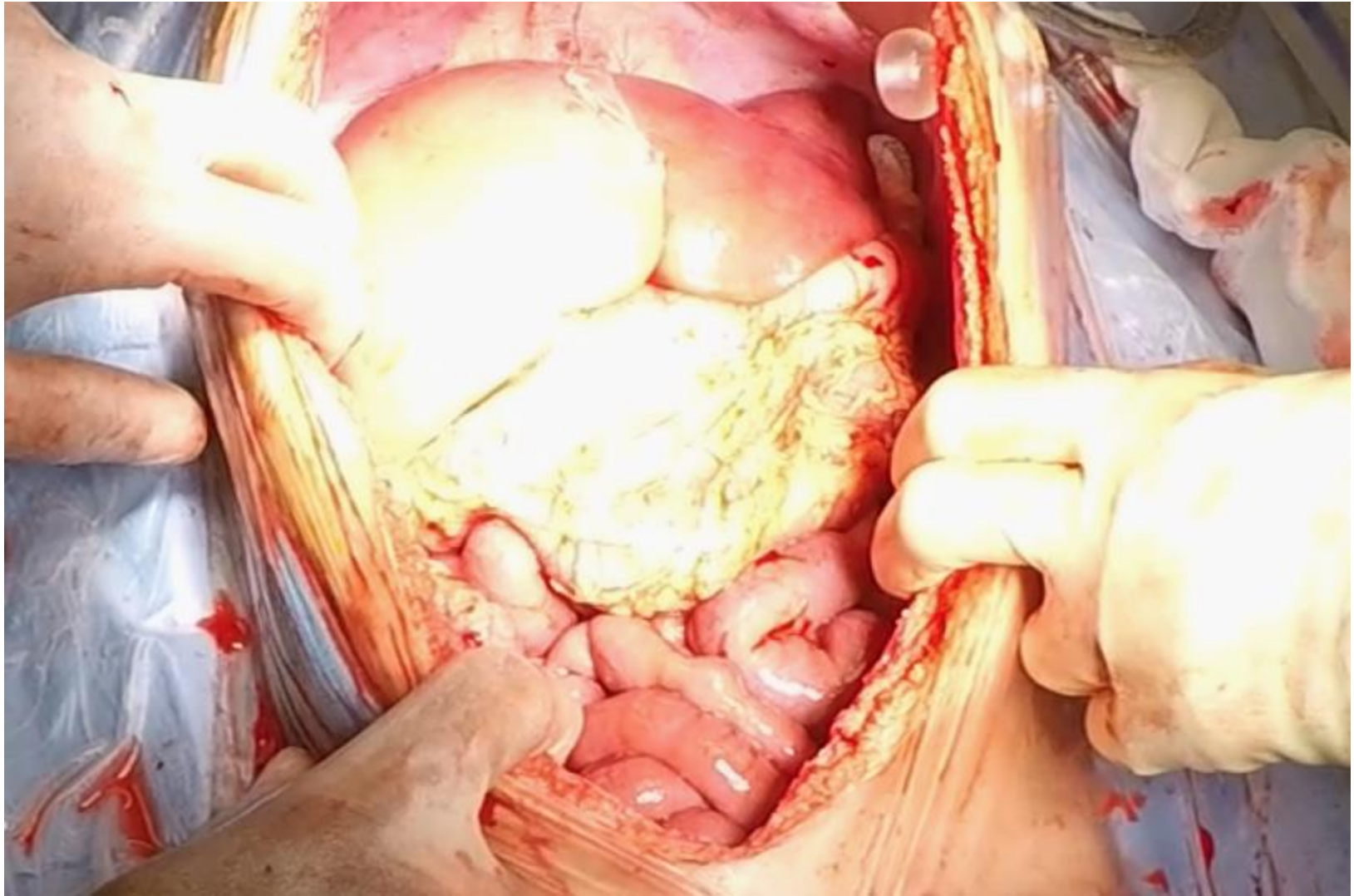
- Standardisation of surgical techniques
  - Isolated small bowel, Liver and small bowel, Multivisceral



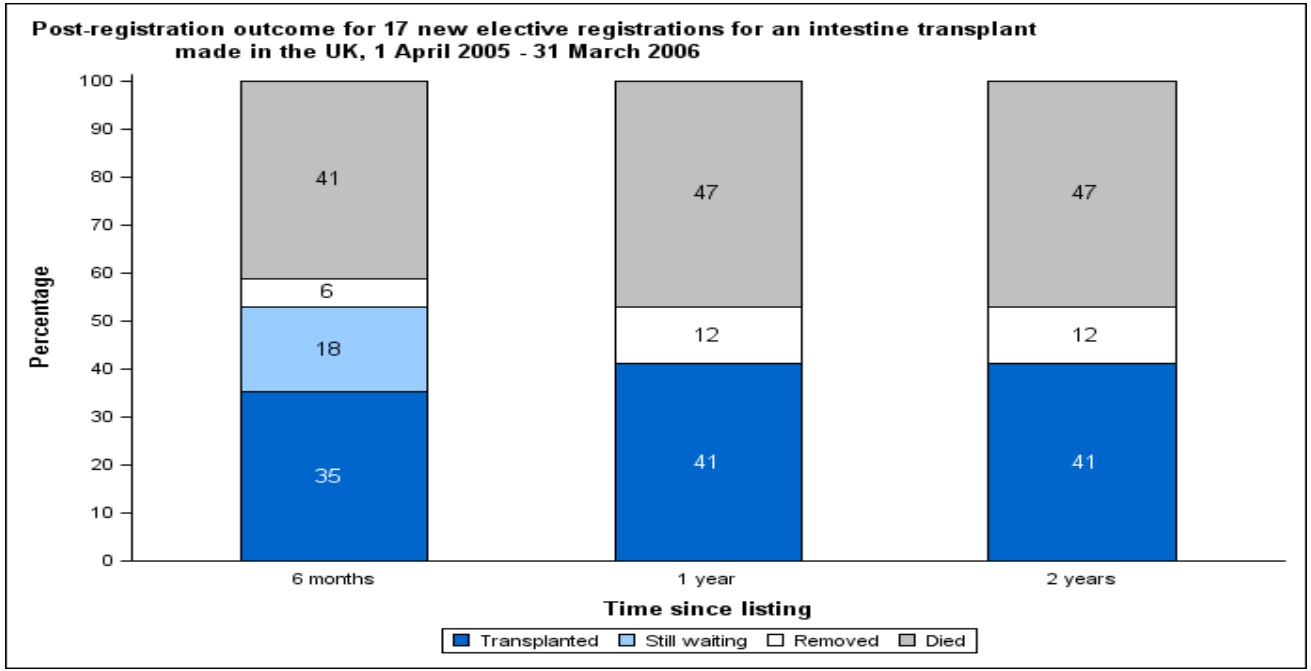
Types of Intestinal Transplantation



Multivisceral transplantation



When to transplant



NHS blood and transplant. Annual report on intestinal transplantation. Published August 2017

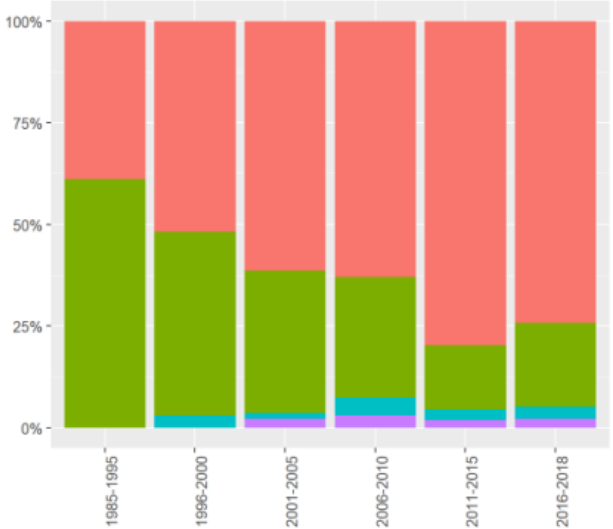
The right time

- High mortality on waiting list
  - Fryer J et al. *Liver Transpl* 2003;**9**:748-53
  - In 2015, this depends on the indication
- Pre-transplant morbidity affects post-transplant survival
  - Middleton SJ et al. *Transpl proc* 2010;**42**:19-21
- Patients should be discussed on a case by case basis with an intestinal transplant centre BEFORE life-threatening complications develop
  - Fecteau A et al. *J Pediatr Surg* 2001:**36**:681-84

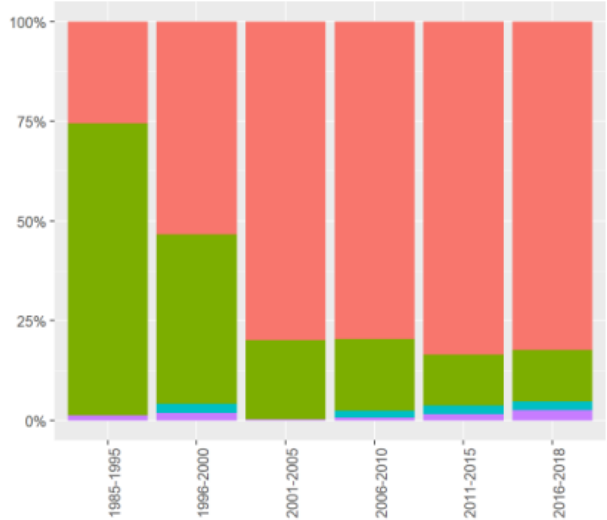
Pre-Tx Status Over Time

All recipients transplanted between Jan 1985-Dec 2018

Pediatric, n=2096



Adults, n=1951



Home
Hospitalized
ICU
Unknown

Selecting the right patients at the right time

International Intestinal Failure Registry

[International Intestinal Failure Registry (tts.org)]

Intestinal Rehabilitation & Transplant
ASSOCIATION

a Section of The Transplantation Society

Participating Centers

Center	PI
Children's Hospital of Pittsburgh, USA	Dr. Jeffrey A Rudolph
Cincinnati Children's Hospital Medical Centre, USA	Dr. Conrad Cole
Duke University Medical Center, USA	Dr. Debra Sudan
Hospital Italiano de Buenos Aires, Argentina	Dr. Pablo Lobos
Hospital for Sick Children, Canada	Dr. Yaron Avitzur
King's College Hospital, UK	Dr. Jonathan Hind
Lucile Salter Packard Children's Hospital, USA	Dr. John Kerner
Nationwide Children's Hospital, USA	Dr. Molly Dienhart
Starship Child Health, New-Zealand	Dr. Amin Roberts
University of California, Los Angeles, USA	Dr. Robert Venick
University Hospital La Paz, Spain	Dr. Esther Ramos Boluda
University of Nebraska, USA	Dr. David Mercer

The JOURNAL of PEDIATRICS

ORIGINAL ARTICLE | VOLUME 237, P16-23.E4, OCTOBER 01, 2021

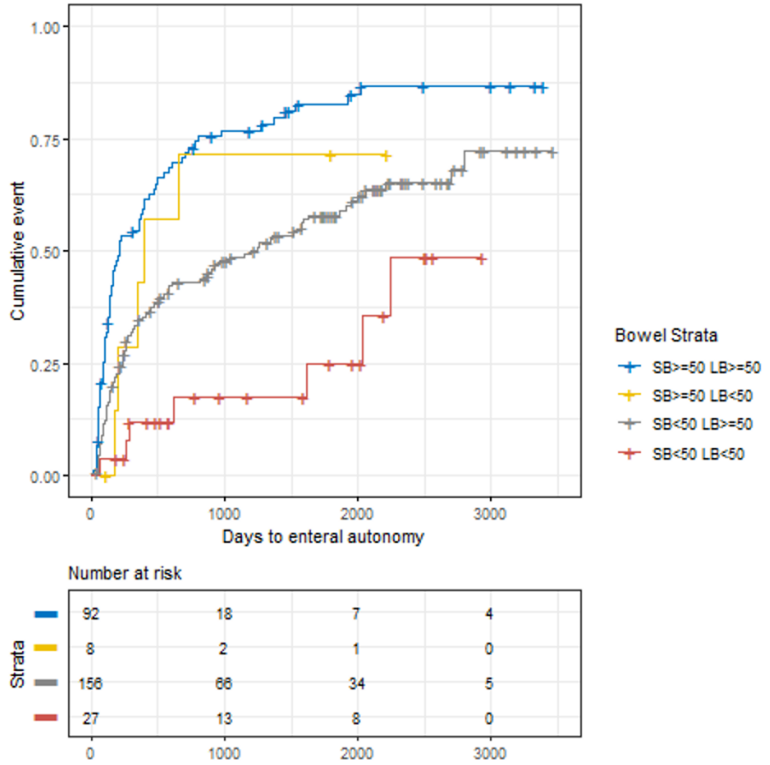
Trends in Pediatric Intestinal Failure: A Multicenter, Multinational Study

Daniela Gattini, MD * • Amin J. Roberts, MD * • Paul W. Wales, MD, MSc • Sue V. Beath, MD • Helen M. Evans, MD • Jonathan Hind, MD • David Mercer, MD, PhD • Theodoric Wong, MD • Jason Yap, MD • Christina Belza, MN • Koen Huysentruyt, MD, PhD • Yaron Avitzur, MD • Show less • Show footnotes

Published: June 17, 2021 • DOI: https://doi.org/10.1016/j.jpeds.2021.06.025 • Check for updates

- 443 children
- Rate of death and transplantation in children with IF has decreased
- Rate of children achieving enteral autonomy has changed little
- Large number of children remain on HPN long-term

Predicting Enteral Autonomy in Short Bowel Syndrome in the modern era of Intestinal Failure



Survival curve comparing time to achieve EA in the four anatomical strata

Log rank test: p<0.001.

- Ultrashort bowel (10cm children, 20cm adults)
- End duodenostomy
- Microvillus inclusion disease
- Multiple fistulae and frozen abdomen
- Radiation enteritis,
- IF after bariatric surgery,
- Loss of 2 out of 4 upper body central veins

Sanchez SE, Javid PJ, Healey PJ, et al.Ultrashort bowel syndrome in children. J Pediatr Gastroenterol Nutr. 2013;56:36–39.

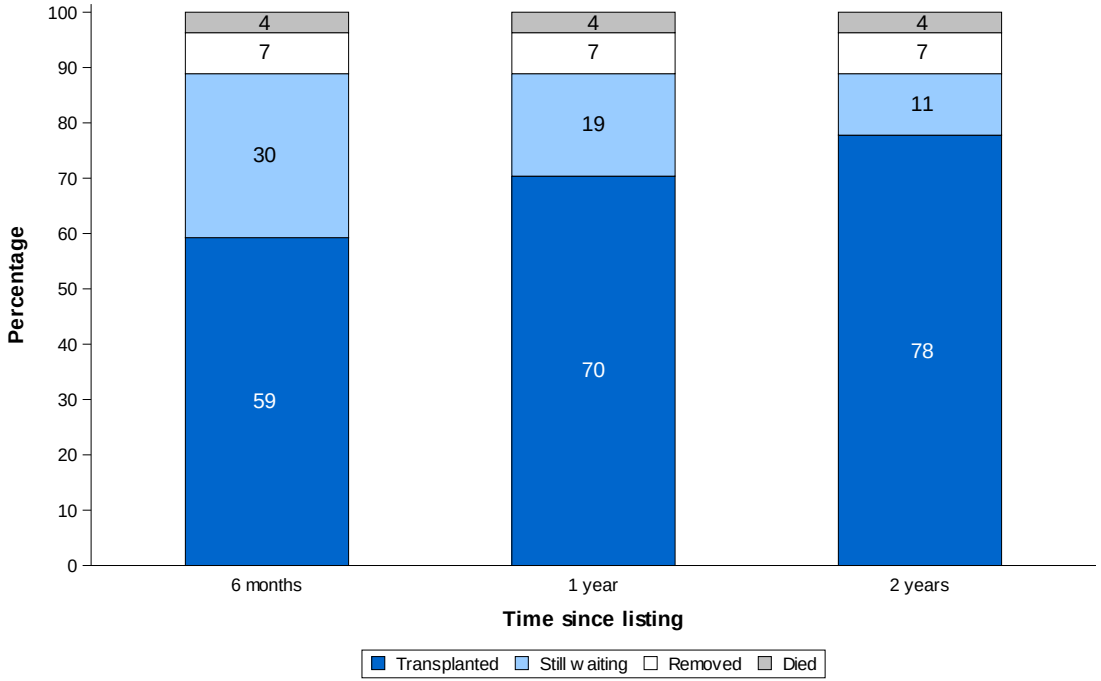
Pironi L, Arends J, Bozzetti F, et al.; Home Artificial Nutrition & Chronic Intestinal Failure Special Interest Group of ESPEN. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35:247–307.

Abu-Elmagd KM, Costa G, McMichael D, et al. Autologous reconstruction and visceral transplantation for management of patients with gut failure after bariatric surgery: 20 years of experience. Ann Surg. 2015;262:586–601.

When to transplant

Blood and Transplant

Figure 2.5 **Post-registration outcome for 54 elective registrations for an intestine transplant made in the UK, 1 April 2017 - 31 March 2019**



Source: Annual Report on Intestine Transplantation 2020/21, NHS Blood and Transplant

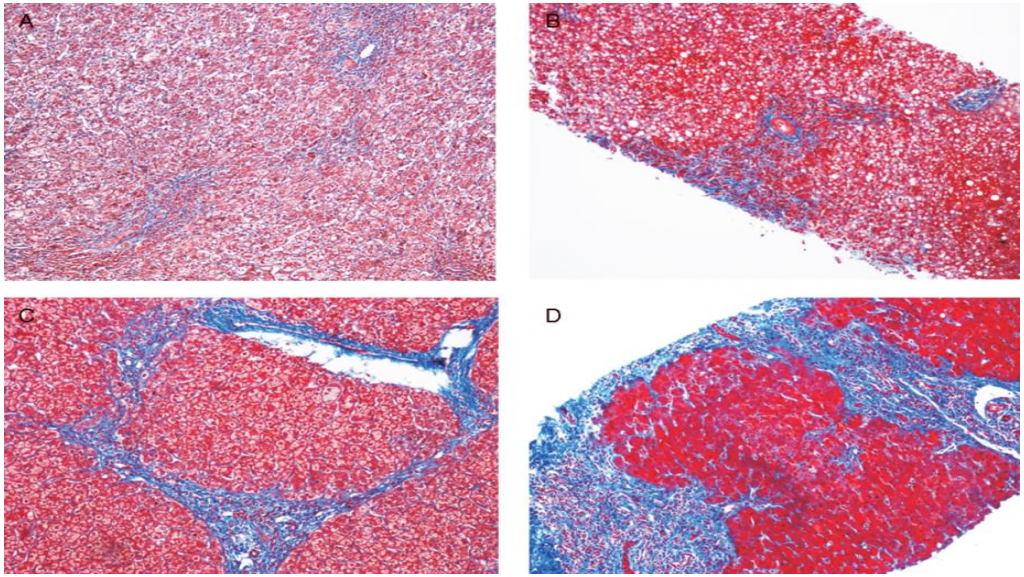
Changing indications

- Improvement in IF management and survival after transplant
- All patients should be managed by experienced MDT
- Referral for transplant assessment early when IF plus progressive liver disease / progressive loss of central venous access, or conditions likely to lead to such problems
- Avoid end-stage liver disease / loss of vascular access
- Avoid repeated complications which reduce chances of success eg sensitisation events or colonisation with resistant organisms

- Desmoids
- Acute splanchnic venous thrombosis

Hepatic Fibrosis Persists and Progresses Despite Biochemical Improvement in Children Treated With Intravenous Fish Oil Emulsion

David F. Mercer, Brandy D. Hobson, Ryan T. Fischer, Geoffrey A. Talmon, Deborah A. Perry, Brandi K. Gerhardt, Wendy J. Grant, Jean F. Botha, Alan N. Langnas, and Ruben E. Quiros-Tejeira JPGN Volume 56, Number 4, April 2013



Representative histology of subject 3. Increasing enteral feed, improving biochemistry.
Images A to D show Masson stain of liver biopsies from subject 3 at (A) 7 weeks, (B) 34 weeks, (C) 40 weeks, (D) 67 weeks of age

- 6 children on PN with fish oil lipid
- Synthetic liver function preserved
- Biochemical cholestasis improved

- **Fibrosis**
  - Regressed in only 1
  - Persisted in 2
  - Progressed in 3
    - Remained severe (ISHAK 2) in 5 of 6

Transplantation. 2020 May ; 104(5): 937–946. doi:10.1097/TP.0000000000003065.

New Insights Into the Indications for Intestinal Transplantation: Consensus in the Year 2019

Stuart S. Kaufman, MD[1], Yaron Avitzur, MD[2], Sue V. Beath, MD[3], Laurens J. Ceulemans, MD, PhD[4,5], Gabriel E. Gondolesi, MD[6], George V. Mazariegos, MD[7], Loris Pironi, MD[8]

Criteria for placement on a waitlist for intestinal transplantation[a]

Evidence of advanced or progressive intestinal failure–associated liver disease
Hyperbilirubinemia >75 μmol/L[b] (4.5 mg/dL) despite intravenous lipid modification strategies that persists for >2 mo
Any combination of elevated serum bilirubin, reduced synthetic function (subnormal albumin or elevated international normalized ratio), and laboratory indications of portal hypertension and hypersplenism, especially low platelet count, persisting for >1 mo in the absence of a confounding infectious event(s)
Thrombosis of 3 out of 4 discrete upper body central veins (left subclavian and internal jugular, right subclavian and internal jugular) or occlusion of a brachiocephalic vein in children (in adults, this criterion should be evaluated in a case-by-case basis)
Life-threatening morbidity in the setting of indefinite parenteral nutrition dependence of either anatomical or functional cause, as suggested by:
In children, 2 admissions to an intensive care unit (after initial recovery from the event resulting in intestinal failure) because of cardiorespiratory failure (mechanical ventilation or inotrope infusion) due to sepsis or other complications of intestinal failure
In adults, on a case-by-case basis.
Invasive intra-abdominal desmoids in adolescents and adults
Acute diffuse intestinal infarction with hepatic failure
Failure of first intestinal transplant

[a] Presuming that patients will have been assessed by a multidisciplinary team, rehabilitation options have been explored, and a state of permanent or life-limiting intestinal failure exists.

[b] A total serum bilirubin of 62 or 70 μmol/L is also associated with increased mortality. A bilirubin level of 75 μmol/L is simply a useful, consensus marker of progressive liver disease to be taken in context with other parameters.[66,67,69–71]

Waiting-list issues

- 2 years old
- TTC7A deficiency MIA-CID
- 2 HSCT – 2nd one partial engraftment
- Ultra-short gut, TPN
- End stage chronic liver disease
- Stomal bleeding daily
- Waiting on list but liver deteriorating

- Options?
  - Isolated liver transplantation
    - Survival 90% long-term, but immunosuppression and still on PN
  - Living-related liver bowel transplant
    - Has been done in the US, but not in children in Europe

Living-related liver bowel transplant

- Mum donor – LLS liver and 150cm ileum
  - Post-op diarrhoea and weight loss in the short term
- Child recovered slowly but surely
  - Organs were large so abdomen was left open
  - Rectus muscle fascia from another donor
  - Vac dressing until granulated over
- Outcome
  - Mum fully healthy
  - Child off PN and back in home country
  - Sadly died after 4 years from haematological malignancy

Pediatr Transplant. 2017 Jun;21(4). doi: 10.1111/petr.12910. Epub 2017 Mar 12.

Long-term outcomes of living-related small intestinal transplantation in children: A single-center experience

Sandra Garcia Aroz [1], Ivo Tzvetanov [1], Elizabeth Anne Hetterman [2], Hoonbae Jeon [1], Jose Oberholzer [1], Giuliano Testa [3], Eunice John [4], Enrico Benedetti [1]

- 2002-2013, 13 living-related ITx in 10 children
- Isolated small bowel in 6, liver+small bowel in 7
- Induction ATG, maintenance tacrolimus and prednisolone
- 7 children alive at publication, 6 with >10y follow-up
- Median time to oral diet 32 days

Intestinal Rehabilitation and Transplant Association

A section of the Transplantation Society

International Intestinal Transplant Registry

2019 Report

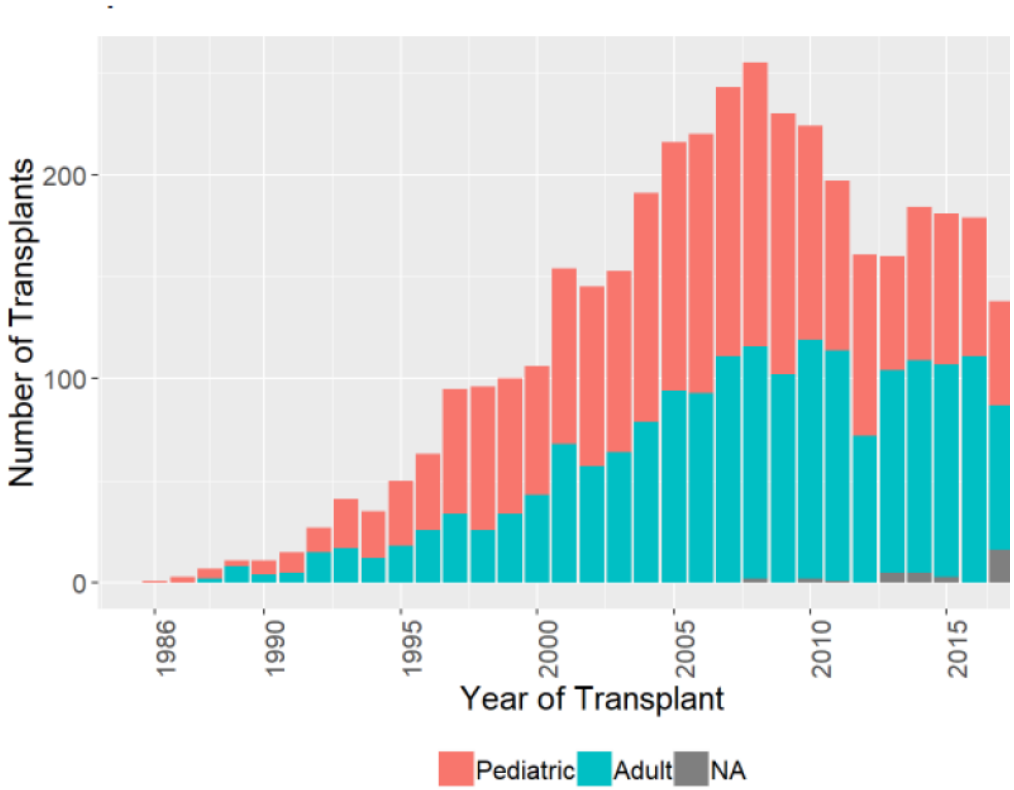
Global Clinical Experience: Intestinal Tx

(All recipients transplanted between Jan 1985-Dec 2018)

Number of Transplants:	4103
SB Alone	1842
SB+Liver	1251
MVT	810
Modified MVT	200
Current Survivors	2060/4130 (50%)

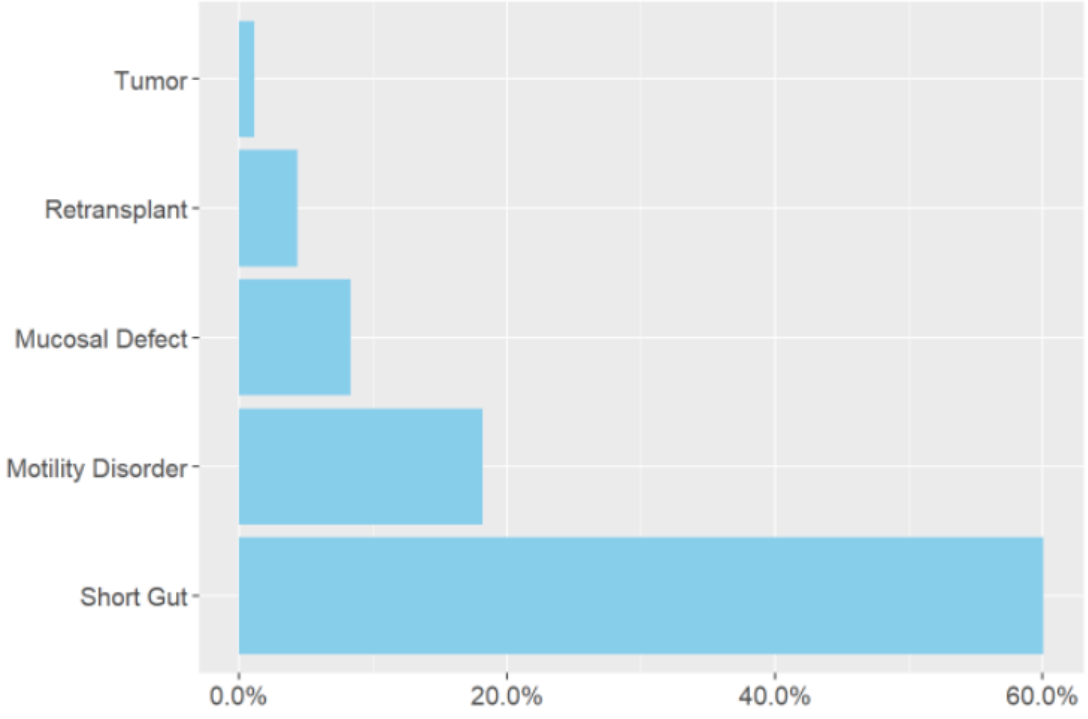
Intestinal Transplants Performed

(All recipients transplanted between Jan 1985-Dec 2018)



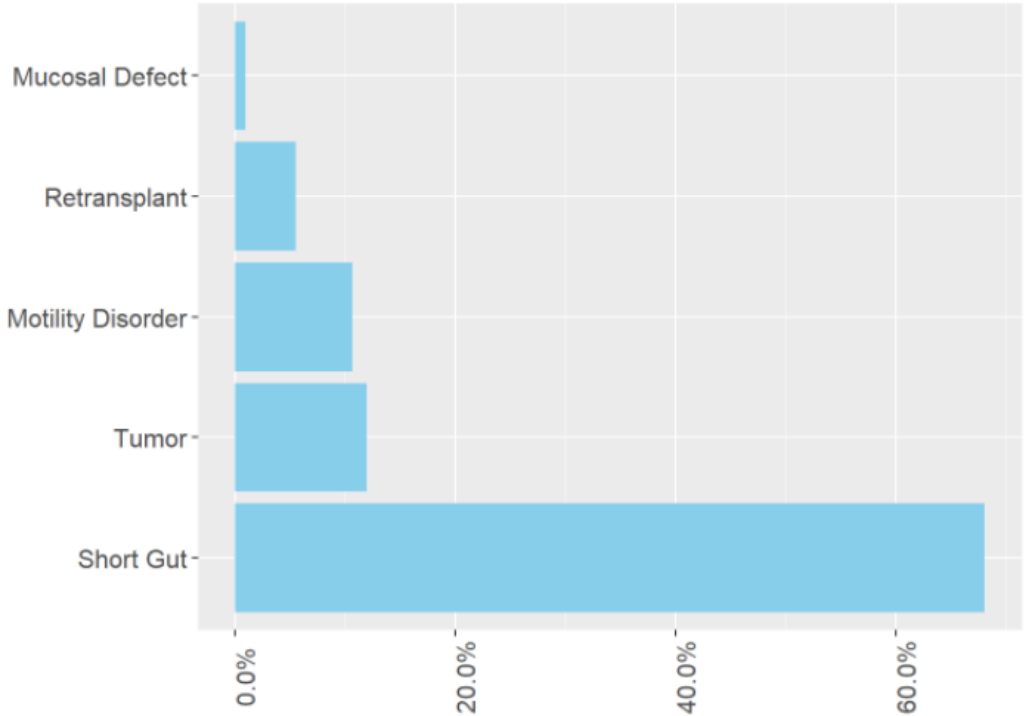
Indications for Transplant

All pediatric recipients transplanted between Jan 1985-Dec 2018, n=2096



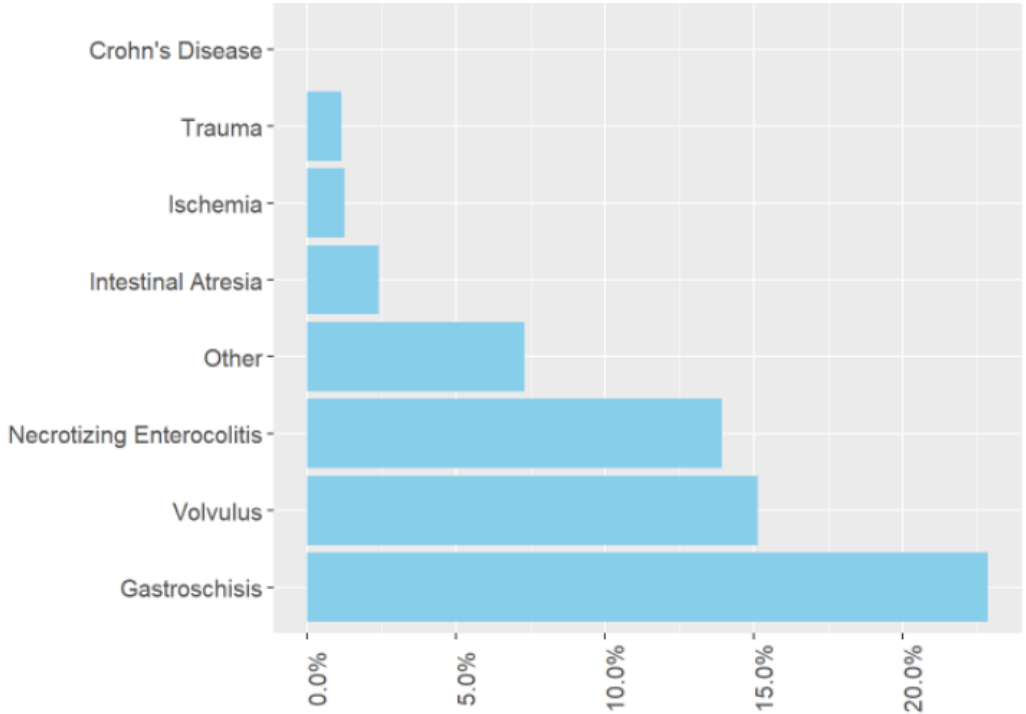
Indications for Transplant

All Adult recipients transplanted between Jan 1985-Dec 2018, n=1951



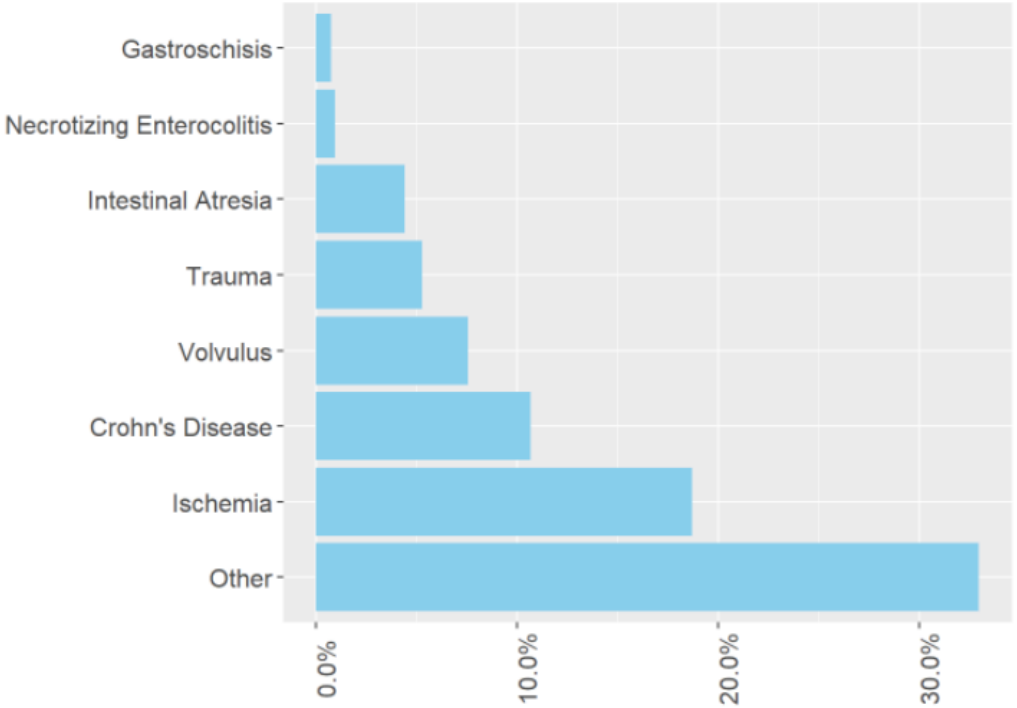
Types of Short Gut Diagnoses

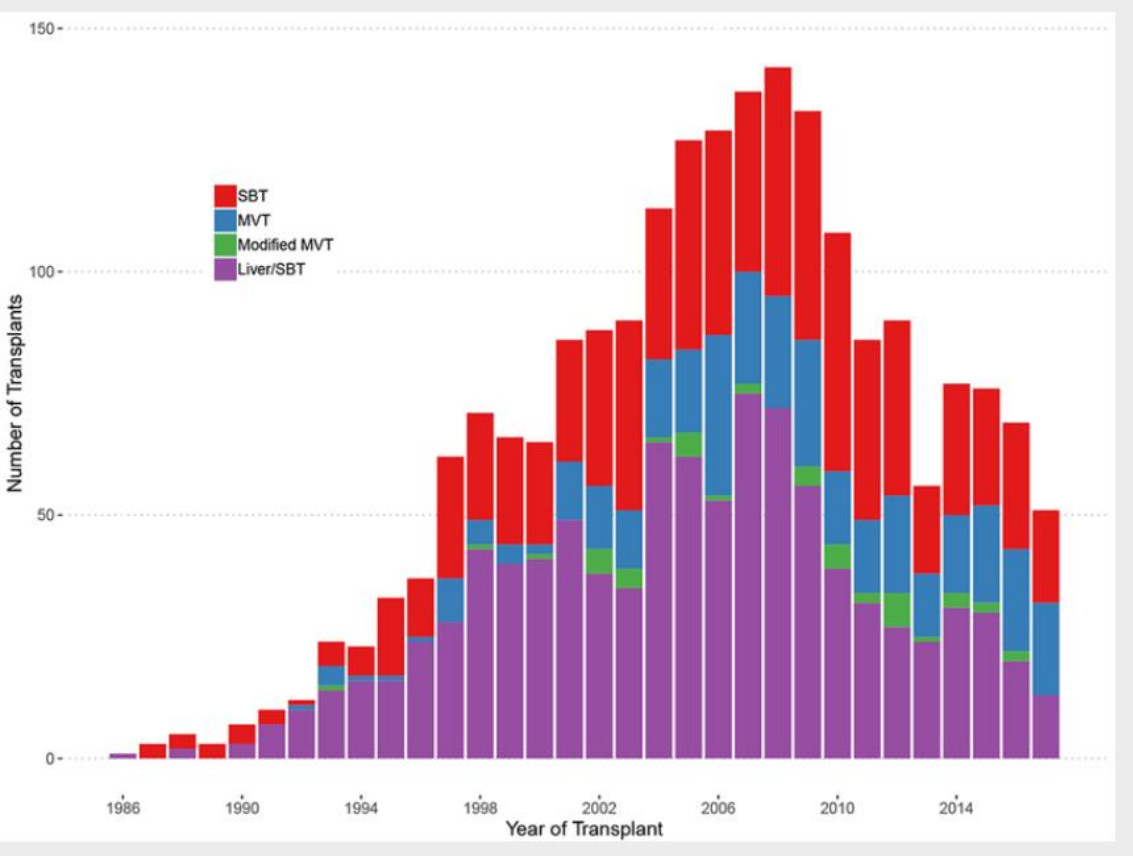
All pediatric recipients transplanted between Jan 1985-Dec 2018, n=2096



Types of Short Gut Diagnoses

All Adult recipients transplanted between Jan 1985-Dec 2018, n=1951





Raghu VK, Beaumont JL, Everly MJ, et al. Pediatric intestinal transplantation: Analysis of the intestinal transplant registry. Pediatric Transplantation. 2019 Dec;23(8):e13580.

Number and type of pediatric intestinal transplants performed each year
Decrease in liver+small bowel but less change in MVT and isolated SBT recently

Indication for transplant[†], n (%)	
Short gut	1245 (65)
Motility disorder	381 (20)
Mucosal defect	174 (9)
Re-transplant	91 (5)
Tumor	22 (1)
Cause of short gut[‡], n (%)	
Gastroschisis	473 (38)
Volvulus	315 (25)
Necrotizing enterocolitis	290 (23)
Intestinal atresia	49 (4)
Ischemia	24 (2)
Trauma	24 (2)
Other	150 (12)

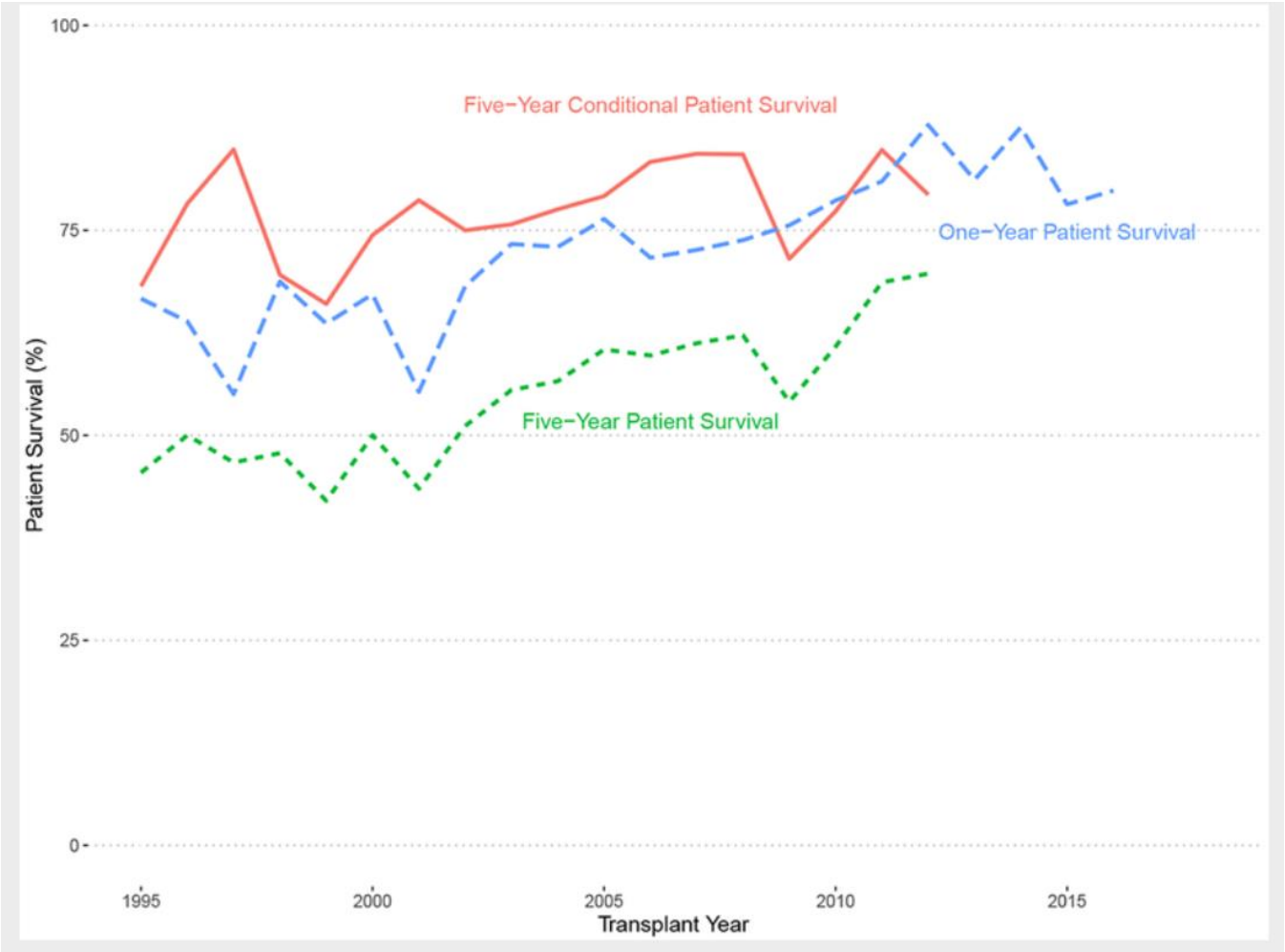
Raghu VK, Beaumont JL, Everly MJ, et al. Pediatric intestinal transplantation: Analysis of the intestinal transplant registry. Pediatric Transplantation. 2019 Dec;23(8):e13580.

Main indication for transplant remains short gut

Most common aetiology of short gut is gastroschisis (NEC is the most common reason for short gut in the paediatric population)

Motility not liver disease

Motility disorder as a reason for transplant has doubled in last decade

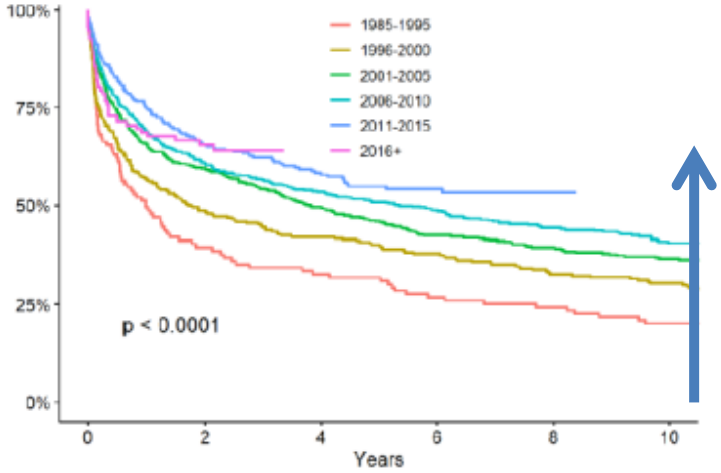


Raghu VK, Beaumont JL, Everly MJ, et al. Pediatric intestinal transplantation: Analysis of the intestinal transplant registry. Pediatric Transplantation. 2019 Dec;23(8):e13580.

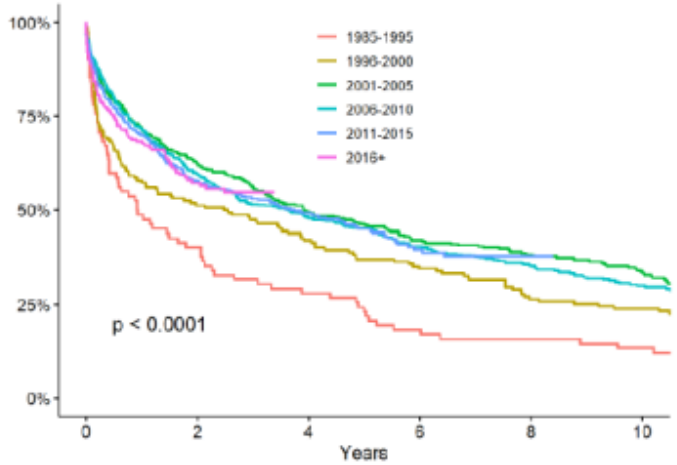
One-year patient survival, five-year patient survival, and five-year patient survival conditional on survival beyond the first post-transplant year

Graft Survival by Era

Pediatric, n=2096



Adults, n=1951

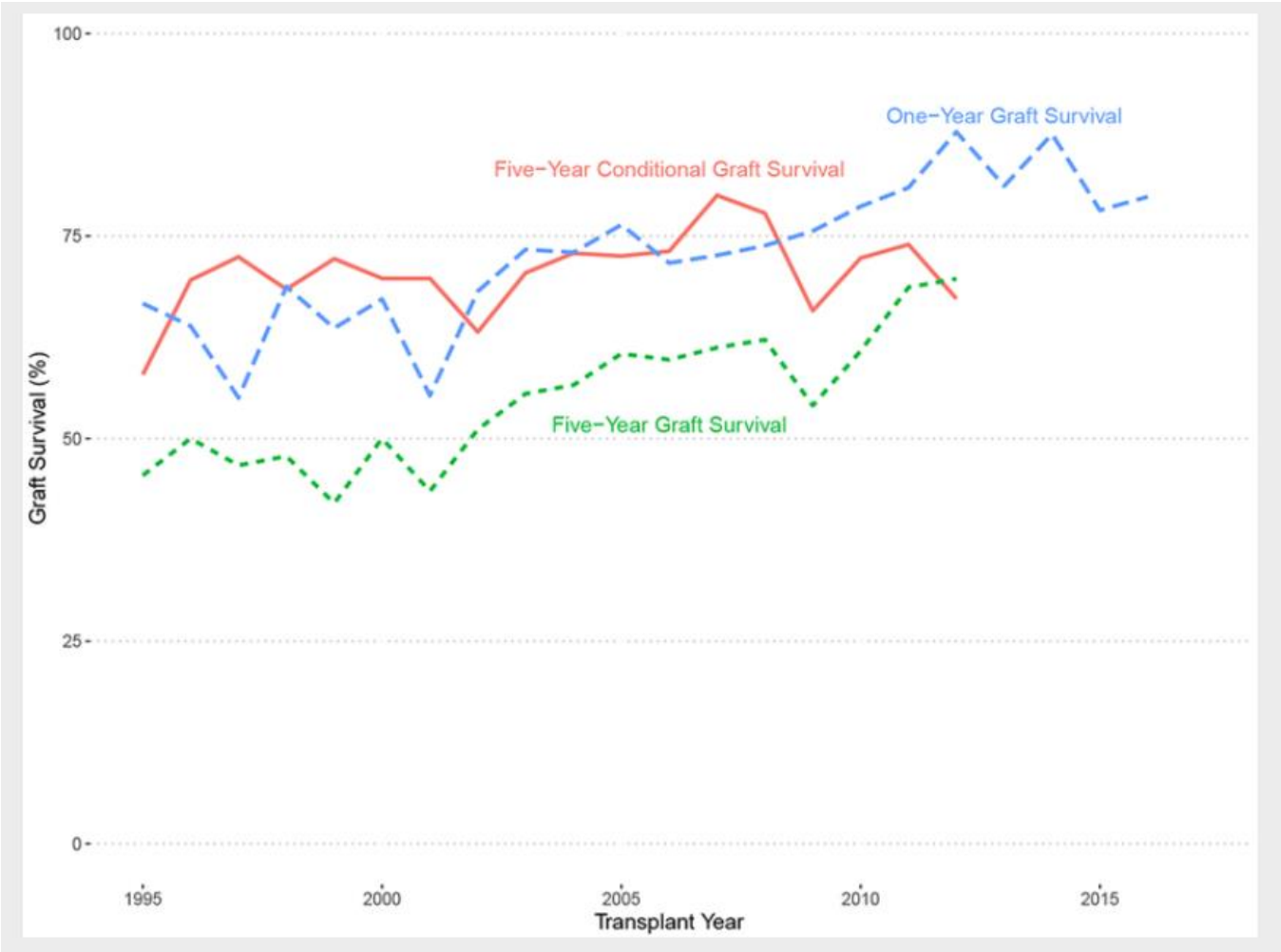


TERASAKI

Causes of death in each transplant era†

Year of transplant	1986-1995	1996-2005	2006-2016	Total
Total number of deaths	97	482	388	967
Death following sepsis	57 (59%)	240 (50%)	177 (46%)	474 (49%)
PTLD/Lymphoma	13 (13%)	20 (4%)	24 (6%)	57 (6%)
Graft failure	9 (9%)	77 (16%)	52 (13%)	138 (14%)
Kidney failure	1 (1%)	9 (2%)	13 (3%)	23 (2%)
Liver failure	2 (2%)	10 (2%)	7 (2%)	19 (2%)
Cardiovascular death	4 (4%)	26 (5%)	25 (6%)	55 (6%)
Technical complication	12 (12%)	15 (3%)	13 (3%)	40 (4%)
Other causes of death	36 (37%)	270 (56%)	196 (51%)	502 (52%)

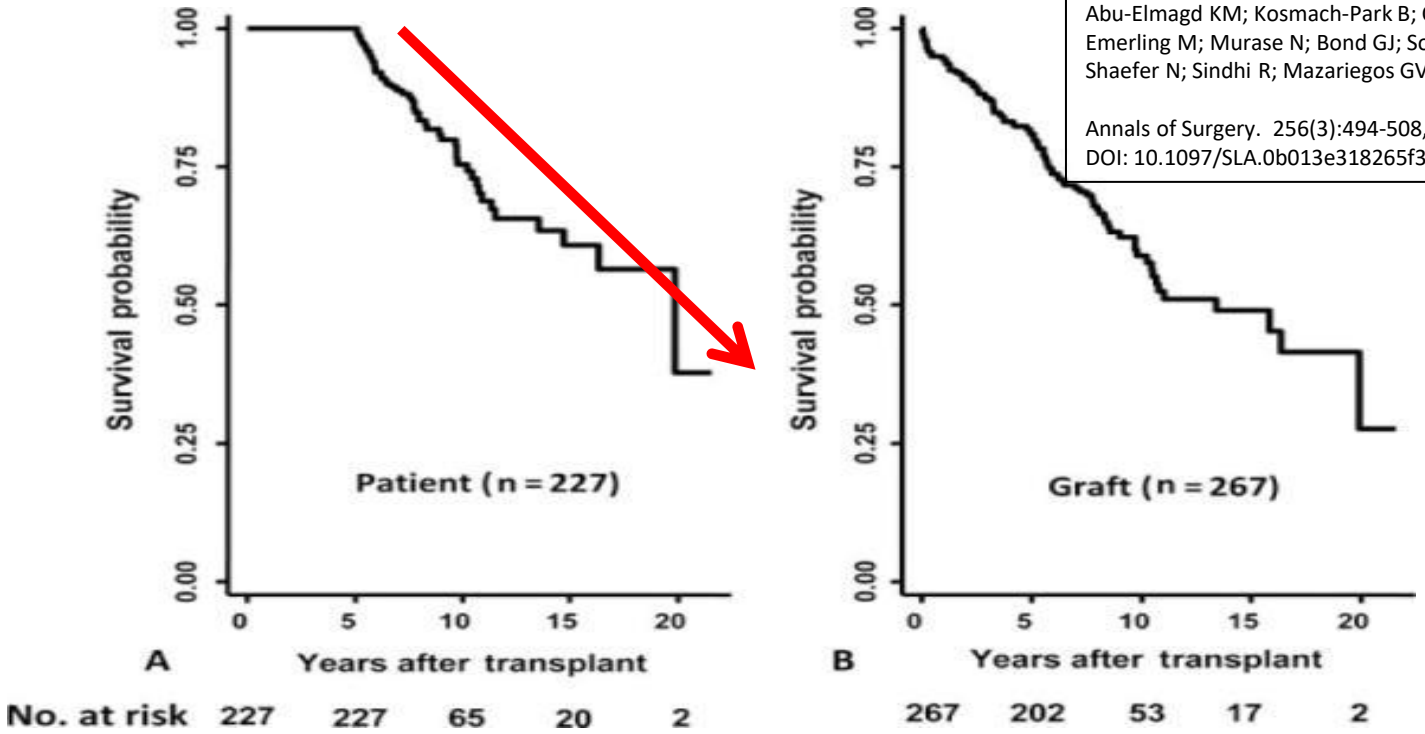
†More than one cause of death may have been listed for each patient



Raghu VK, Beaumont JL, Everly MJ, et al. Pediatric intestinal transplantation: Analysis of the intestinal transplant registry. Pediatric Transplantation. 2019 Dec;23(8):e13580.

Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation.
Abu-Elmagd KM; Kosmach-Park B; Costa G; Zenati M; Martin L; Koritsky DA; Emerling M; Murase N; Bond GJ; Soltys K; Sogawa H; Lunz J; Al Samman M; Shaefer N; Sindhi R; Mazariegos GV

Annals of Surgery. 256(3):494-508, 2012 Sep.
DOI: 10.1097/SLA.0b013e318265f310



Largest single-centre series, ***excluding those who died before 5 years***
Patient survival 75% at 10 years and 61% at 15
Graft survival 59% at 10 years and 50% at 15

Leading Causes of Death

Cause	<5 yr (n = 149)	5–10 yr (n = 39)	>10 yr (n = 11)	P
Graft failure (n = 74)	56 (38)	15 (38)	3 (27)	0.084
Rejection (chronic/acute)	45 (80)	8 (53)	2 (67)	
Graft dysfunction	9 (16)	7 (47)	1 (33)	
Primary nonfunction	2 (4)	0 (0)	0 (0)	
Complications of therapy (n = 95)	75 (50)	15 (38)	5 (45)	0.081
Technical	12 (16)	0 (0)	0 (0)	
Infection	36 (48)	6 (40)	3 (60)	
Posttransplant lymphoproliferative disorder	14 (19)	1 (7)	0 (0)	
Graft versus host disease	6 (8)	1 (7)	0 (0)	
Renal failure	3 (4)	4 (27)	1 (20)	
De novo malignancy	3 (4)	0 (0)	0 (0)	
Others	1 (1)	3 (20)	1 (20)	
Progression of primary disease (n = 17)	11 (7)	4 (10)	2 (18)	0.462
Atherosclerosis	6 (55)	2 (50)	2 (100)	
Vascular thrombosis	1 (9)	2 (50)	0 (0)	
Others	4 (36)	0 (0)	0 (0)	
Substance abuse/suicide/lack of support (n = 7)	4 (3)	3 (8)	0 (0)	—
Others (n = 6)	3 (2)	2 (5)	1 (9)	—

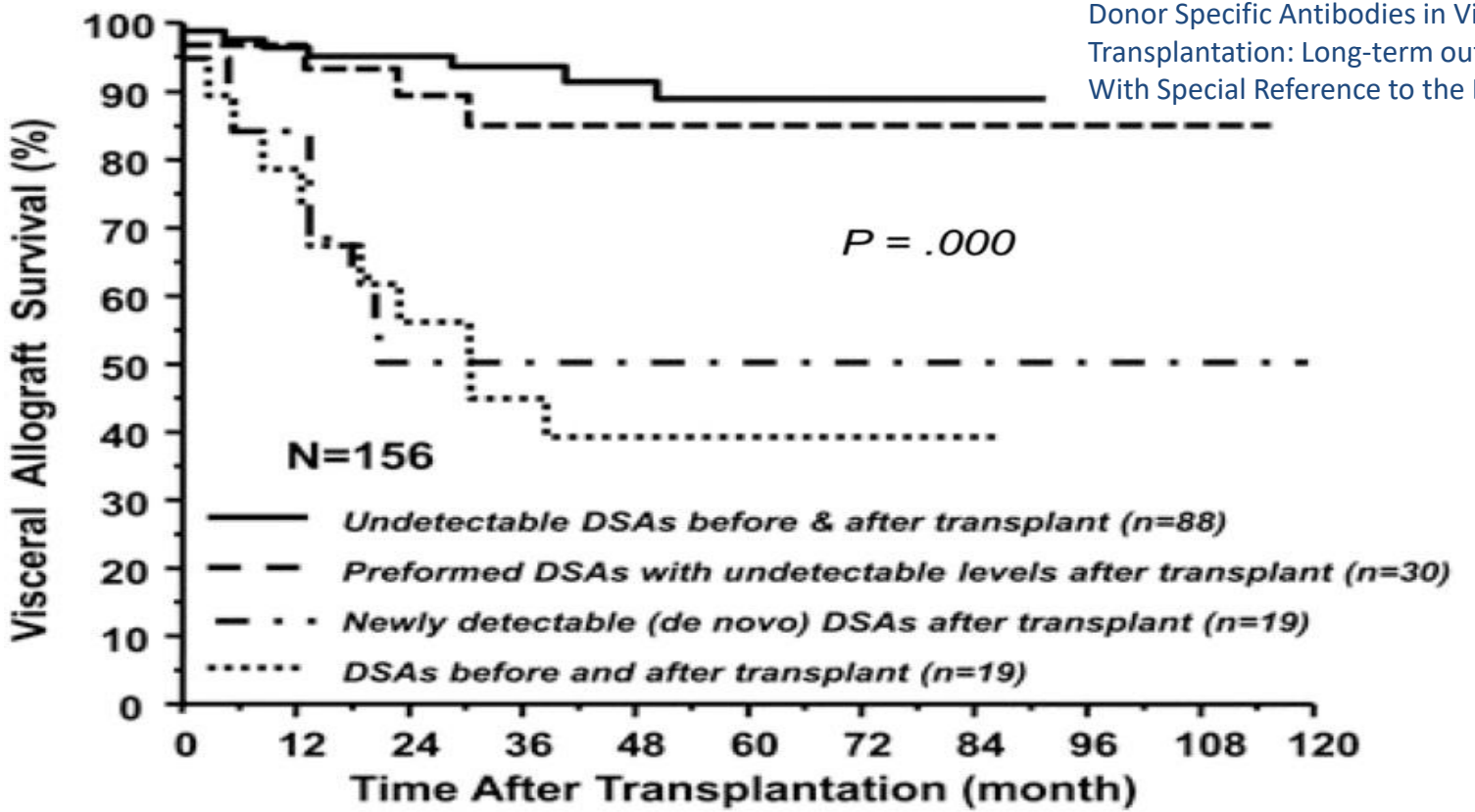
Values given are number (percentage).

Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation.
Abu-Elmagd KM; Kosmach-Park B; Costa G; Zenati M; Martin L; Koritsky DA; Emerling M; Murase N; Bond GJ; Soltys K; Sogawa H; Lunz J; Al Samman M; Shaefer N; Sindhi R; Mazariegos GV

Annals of Surgery. 256(3):494-508, 2012 Sep.
DOI: 10.1097/SLA.0b013e318265f310

Donor specific antibodies

Abu-Elmagd et al. Preformed and de novo Donor Specific Antibodies in Visceral Transplantation: Long-term outcome With Special Reference to the Liver



Strategies for tolerance

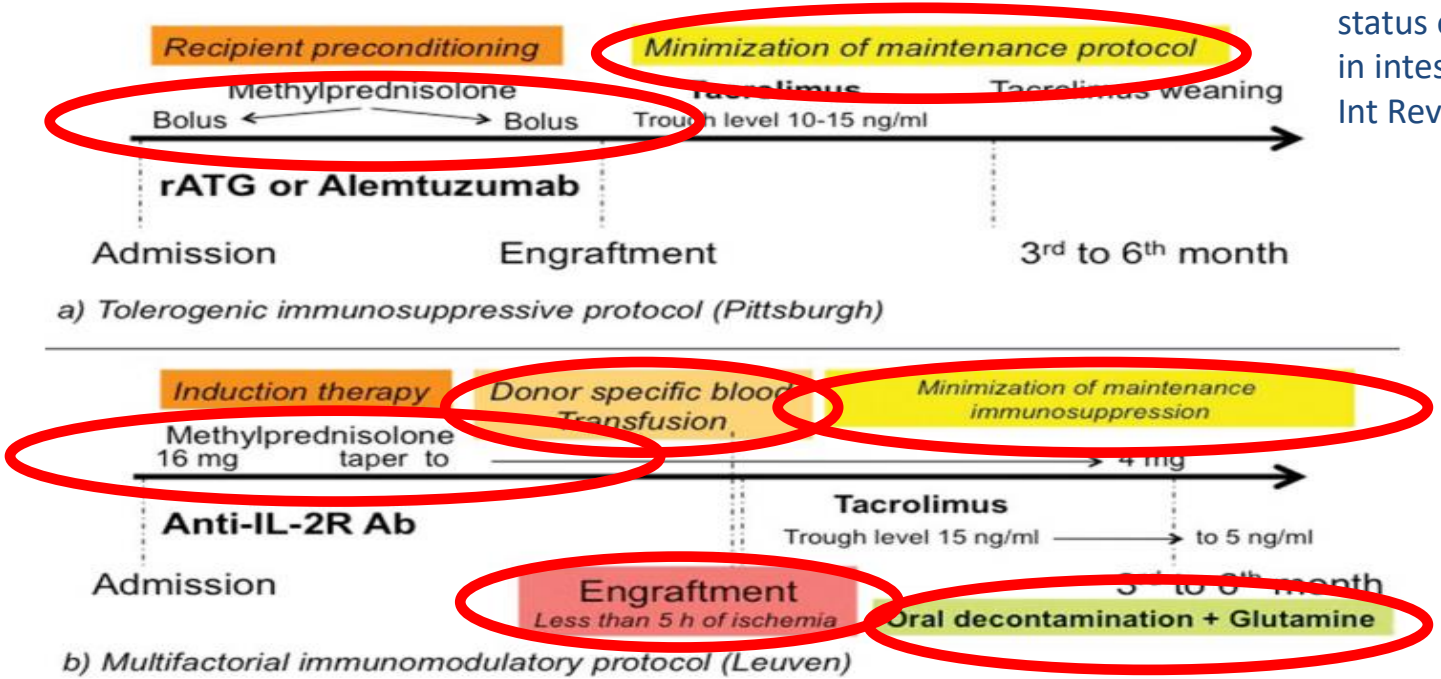


FIGURE 2. Comparison between the tolerogenic immunosuppressive protocol proposed by the Pittsburgh group and the multifactorial immunomodulatory protocol introduced by the Leuven group.

Meier D. et al. Current status o f Allograft Tolerance in intestinal Transplantation. Int Rev Immunol 2014

Immunosuppression strategy

- Leuven immunomodulatory protocol
  - Increase Treg
  - 92% 5 year graft survival
    - Strict donor selection
    - short cold-ischaemia time

Ceulemans LJ, Braza F, Monbaliu D, Jochmans I, De Hertogh G, Du Plessis J, Emonds MP, Kitade H, Kawai M, Li Y, Zhao X, Koshiba T, Sprangers B, Brouard S, Waer M, Pirenne J. The Leuven Immunomodulatory Protocol Promotes T-Regulatory Cells and Substantially Prolongs Survival After First Intestinal Transplantation. Am J Transplant. 2016 Oct;16(10):2973-2985

- Georgetown
  - Short cold-ischaemia time
  - Sirolimus
  - Monitoring and treatment of de novo DSA

Elsabbagh AM, Hawksworth J, Khan KM, Kaufman SS, Yazigi NA, Kroemer A, Smith C, Fishbein TM, Matsumoto CS. Long-term survival in visceral transplant recipients in the new era: A single-center experience. Am J Transplant. 2019 Jul;19(7):2077-2091.

- Similarity with inflammatory bowel disease

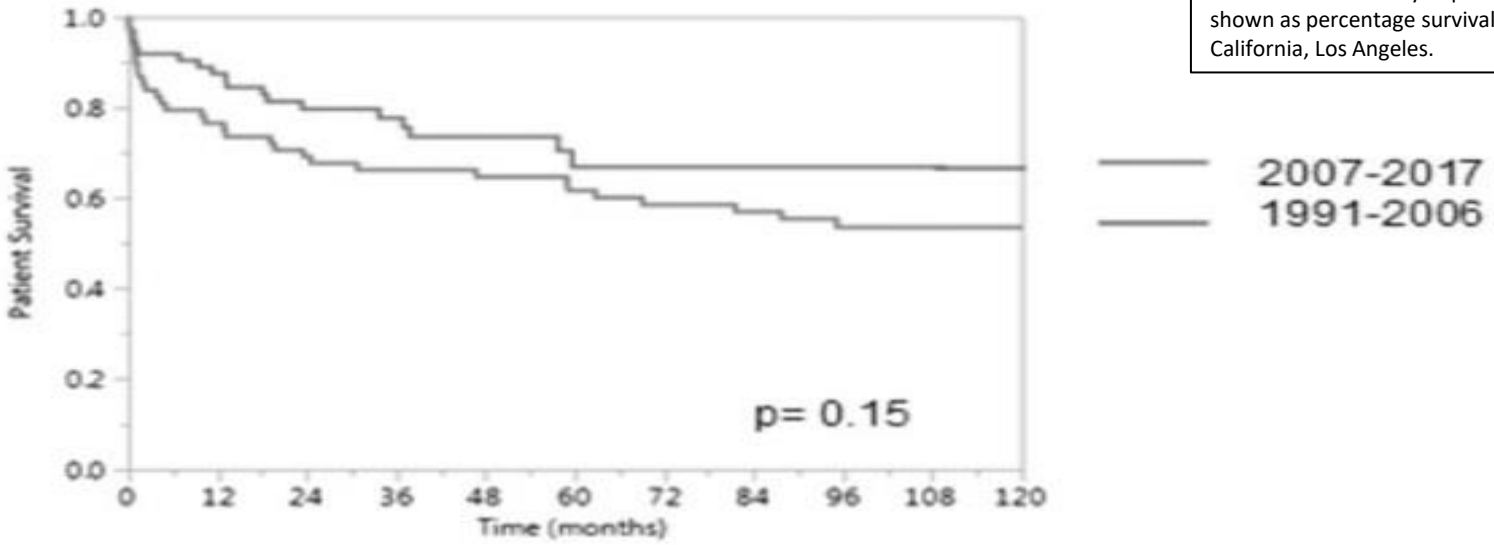
Kroemer A, Cosentino C, Kaiser J, Matsumoto CS, Fishbein TM. Intestinal Transplant Inflammation: the Third Inflammatory Bowel Disease. Curr Gastroenterol Rep. 2016 Nov;18(11):56

Long-term results of intestinal transplantation in children: survival after 10 years, intestinal function, quality of life.

Venick RS

Current Opinion in Organ Transplantation. 23(2):219-223, 2018 04.
DOI: 10.1097/MOT.000000000000051410.1097/MOT.0000000000000514

FIGURE 1 . Improved patient survival over the past decade at UCLA as calculated by Kaplan-Meier method. Survival is shown as percentage survival versus time. UCLA, University of California, Los Angeles.

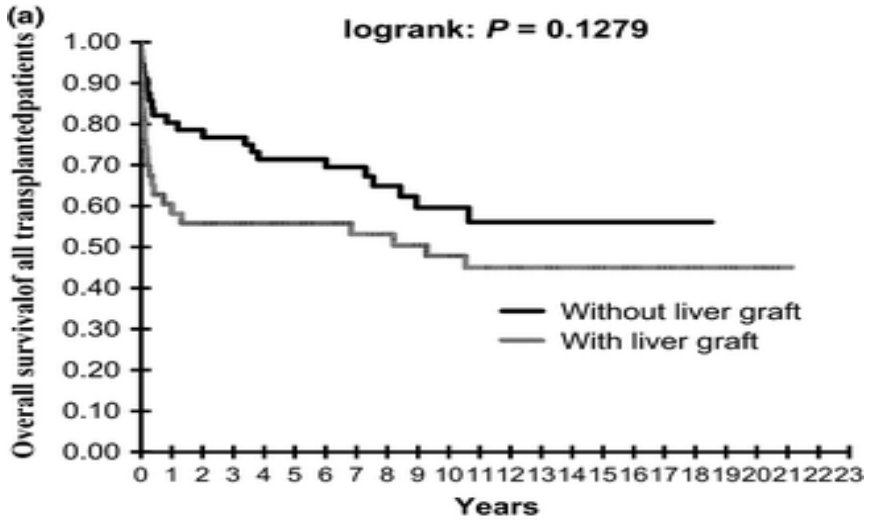


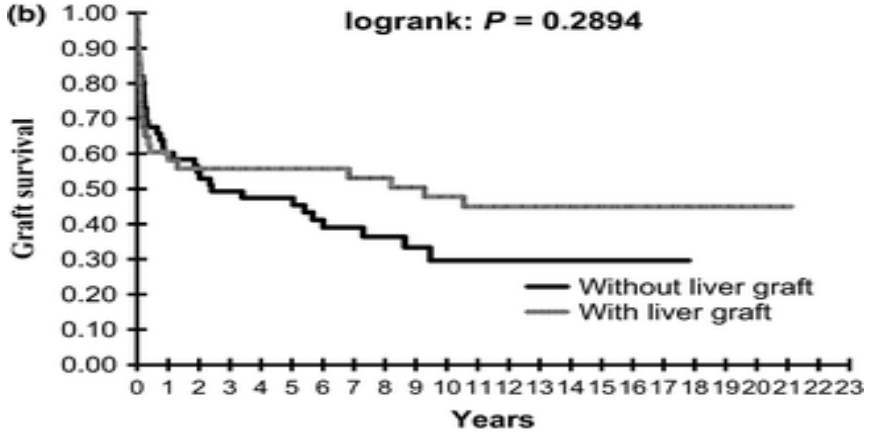
Time (years)	1	5	10
Patient Survival (%) 2007-2016	87	70	67

Very long term outcomes

Twenty-eight years of intestinal transplantation in Paris: experience of the oldest European center

Transplant International, Volume: 30, Issue: 2, Pages: 178-186,
First published: 27 November 2016, DOI: (10.1111/tri.12894)





Quality of life post transplant

- QoL is better after transplant than on PN

Ambrose T, Holdaway L, Smith A, *et al.* The impact of intestinal transplantation on quality of life. Clin Nutr. 2020 Jun;39(6):1958-1967

Pironi L, Baxter JP, Lauro A, et al.Assessment of quality of life on home parenteral nutrition and after intestinal transplantation using treatment-specific questionnaires. Am J Transplant. 2012;12(Suppl 4):S60–S66

- However, ongoing immunosuppression with SEs and ongoing risk of rejection means QoL gains for "pre-emptive" transplant are unknown
- Future population based studies with generic and specific tools are needed

Psychosocial aspects

- Good educational attainment/employment long-term post-ITx
- 1/3 have mental health problems
  - Depression, drugs, alcohol

Norsa L, Gupte G, Ramos Boluda E, *et al.* Life of patients 10 years after a successful pediatric intestinal transplantation in Europe. Am J Transplant. 2018 Jun;18(6):1489-1493

Courbage S, Canioni D, Talbotec C, *et al.* Beyond 10 years, with or without an intestinal graft: Present and future? Am J Transplant. 2020 Oct;20(10):2802-2812

- Ongoing need for psychosocial support


Future

Increasing indications

Review > Pediatr Transplant. 2017 Aug;21(5). doi: 10.1111/petr.12904. Epub 2017 Apr 9.

Multivisceral transplantation for abdominal tumors in children: A single center experience and review of the literature

Eliza Lee [1], Nicole Hodgkinson [1], Rima Fawaz [2], Khashayar Vakili [1], Heung Bae Kim [1]

Case Reports > Transplant Proc. 2016 Mar;48(2):546-8. doi: 10.1016/j.transproceed.2016.01.014.

Case Report: Spleen-preserving Multivisceral Transplant for Peutz-Jeghers Syndrome

L Moulin [1], N Pedraza [1], J Padin [2], S Niveyro [3], G Tuhay [4], C Rumbo [5], P Barros Schelotto [1], A Crivelli [1], H Solar Muñiz [1], D Ramisch [1], G Gondolesi [6]

> Clin Transplant. 2018 Mar;32(3):e13186. doi: 10.1111/ctr.13186. Epub 2018 Jan 18.

Multivisceral transplant is a viable treatment option for patients with non-resectable intra-abdominal fibromatosis

Zhikai Chi [1], Richard S Mangus [2], Chandrashekhar A Kubal [2], Shaoxiong Chen [1], Jingmei Lin [1]

Innovations

American Journal of Transplantation 2016; 16: 1892–1900
Wiley Periodicals Inc.

doi: 10.1111/ajt.13693

Abdominal Wall Transplantation: Skin as a Sentinel Marker for Rejection

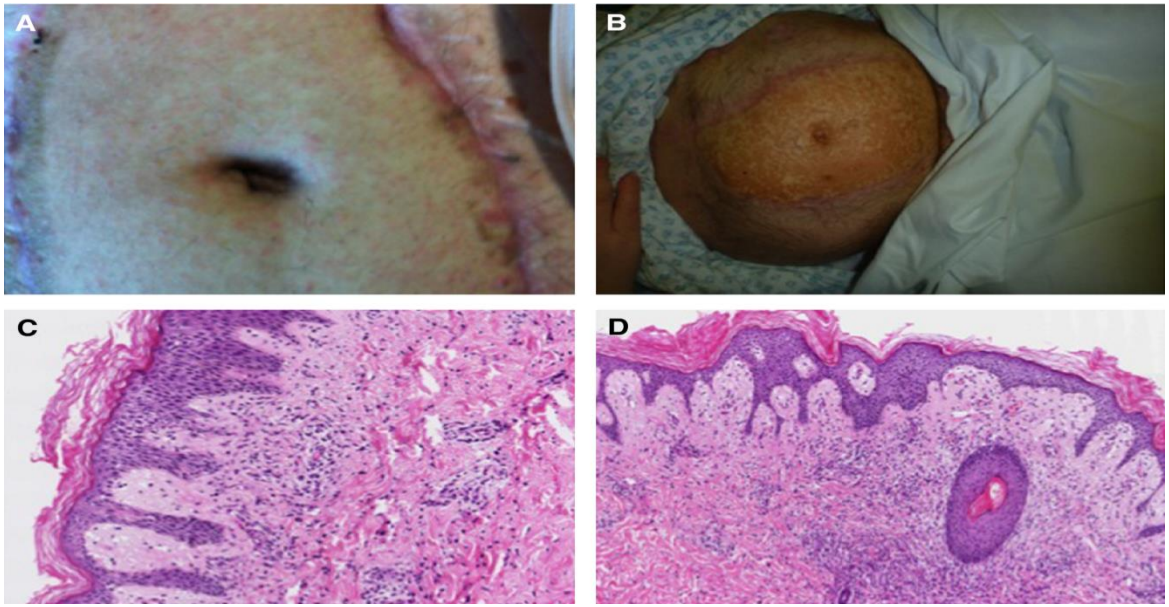
U. A. Gerlach[1,3,*], G. Vrakas[1], B. Sawitzki[4], R. Macedo[1], S. Reddy[1], P. J. Friend[1], H. Giele[2,†] and A. Vaidya[1,†]

Abbreviations: ACR, acute cellular rejection; AW, abdominal wall; AWTX, abdominal wall transplantation; CMV, cytomegalovirus; DSA, donor-specific anti-HLA antibody; GVHD, graft versus host disease; ITX, intesti-

Abdominal Wall Transplantation: Skin as a Sentinel Marker for Rejection

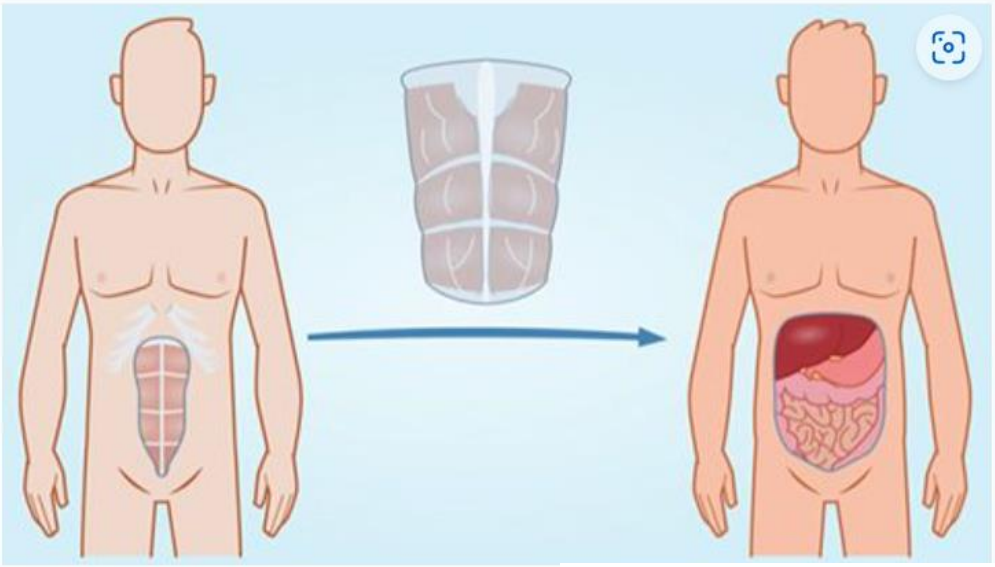
U. A. Gerlach ✉, G. Vrakas, B. Sawitzki, R. Macedo, S. Reddy, P. J. Friend, H. Giele, A. Vaidya

First published: 29 December 2015 | https://doi.org/10.1111/ajt.13693 | Cited by: 12



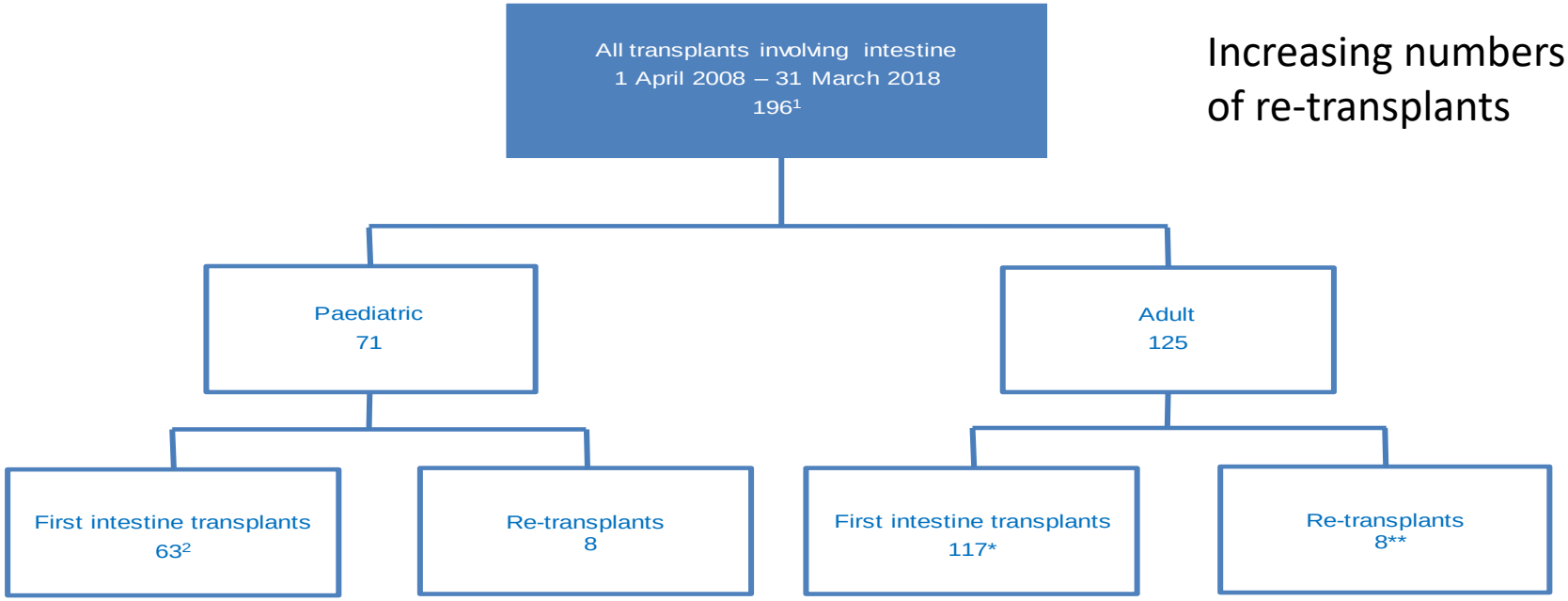
Acute rejection of the abdominal wall graft. (A) Macroscopic features of Banff type III rejection showed erythematous maculopapular rash on the entire abdominal wall graft, whereas the patients' native skin remained normal. (B) Macroscopically healing abdominal wall graft injury after antirejection treatment. (C) Histological features yielding Banff type II rejection: perifollicular chronic inflammatory cell infiltrate, overlying spongiosis, interface epidermal changes (spongiosis). (D) Histological features yielding Banff type III rejection: dermal perivascular infiltration, spongiosis and interface change, edema,

Non-vascularised rectus muscle fascia



Intestinal Rehabilitation & Transplant
ASSOCIATION

Figure 2.5 UK intestine transplants, 1 April 2008 to 31 March 2018



Increasing numbers of re-transplants

[1] Excludes one abdominal wall only transplant (October 2016)
[2] Includes one living donor liver and bowel transplant (June 2017)

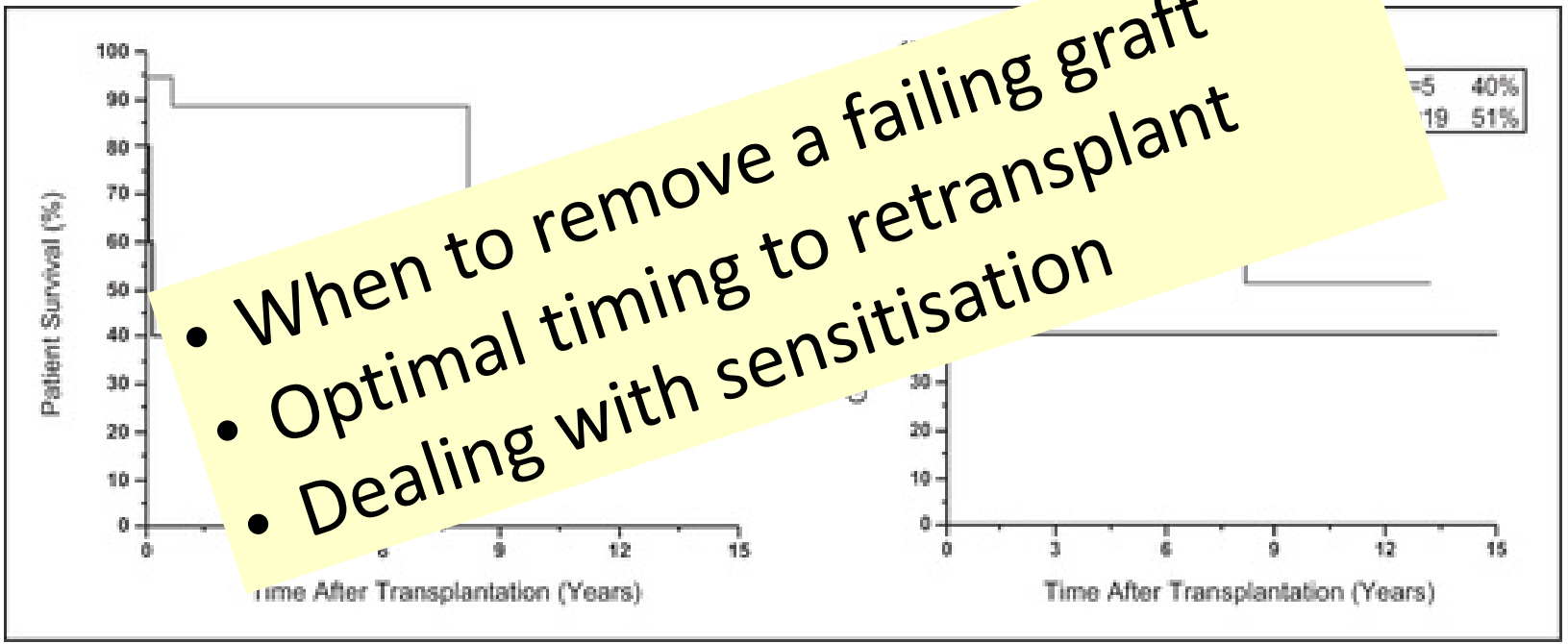
* Five of these transplants were super-urgent
** Two of these transplants were super-urgent

Source: Annual Report on Intestine Transplantation 2017/18, NHS Blood and Transplant

Intestinal re-transplantation: indications, techniques and outcomes

Ganoza, Armando; Celik, Neslihan; Mazariegos, George V

Current Opinion in Transplantation
Issue: Vol
2018, p 224-228



- When to remove a failing graft
- Optimal timing to retransplant
- Dealing with sensitisation

Improved patient and graft survival in the recent era with the introduction of rATG induction immunosuppression

Clinical TRANSPLAN
The Journal of Clinical and Translational Re

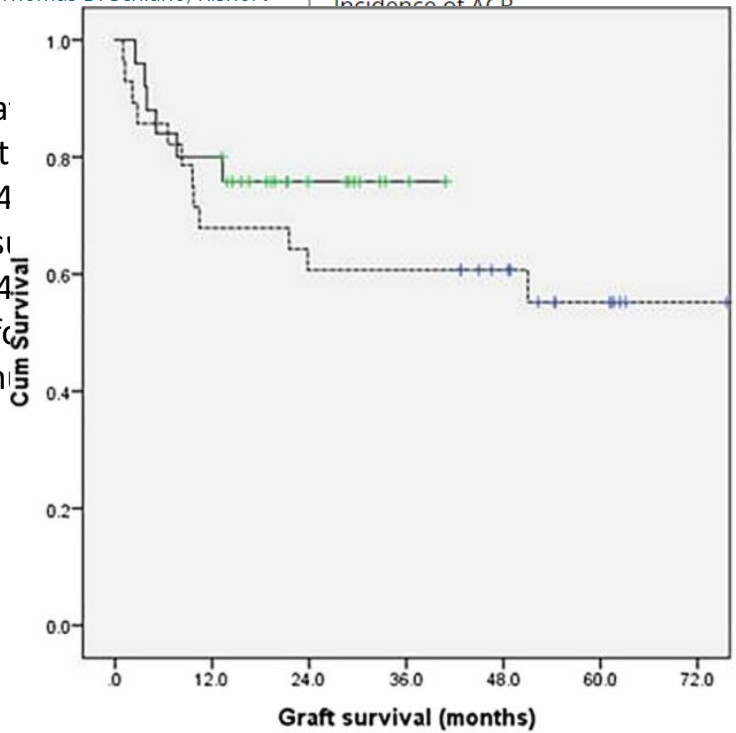
ORIGINAL ARTICLE | Full Access

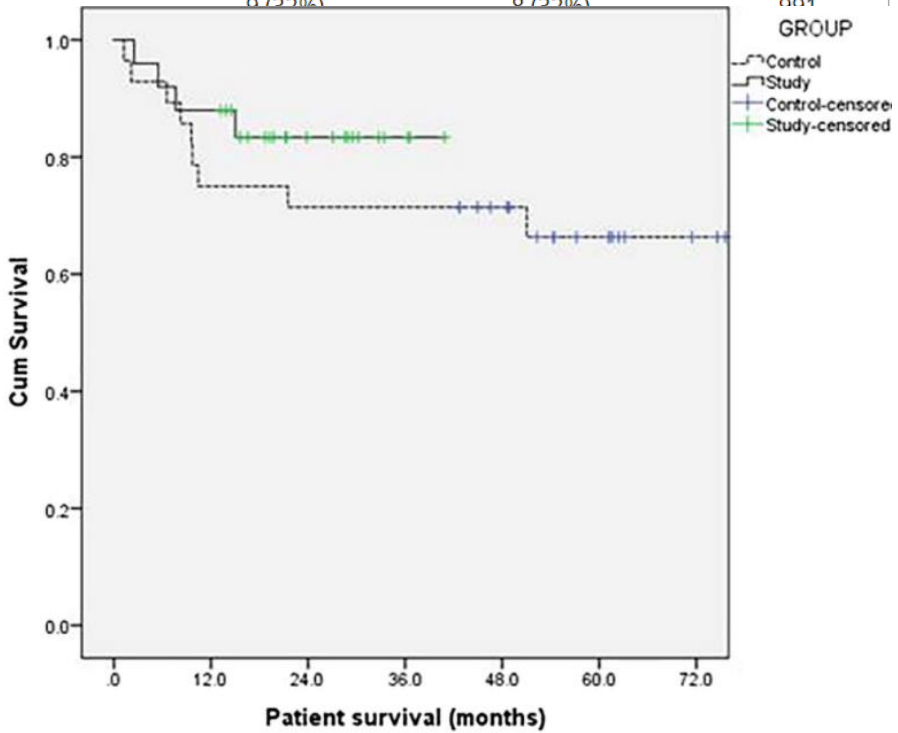
Routine surveillance endos
intestinal transplantation—

Jang I. Moon, Thomas D. Schiano, Kishore

	Control group (n = 28 grafts)	Study group (n = 25 grafts)	*P* value
Positive cross-match	4 (14%)	4 (16%)	.862
Incidence of ACR	9 (32%)	8 (32%)	.991

- Isola
- Cont
  2014
- No si
  2014
- Unifo
  imm





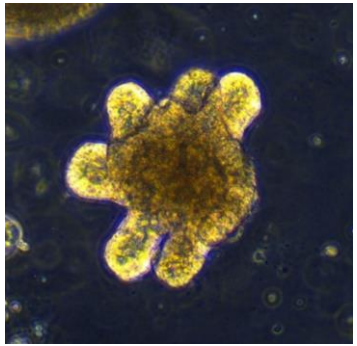
Non-invasive biomarkers

- Potential platforms for candidate biomarkers
  - Immunocyte dynamics
  - mRNA expression
  - miRNA expression
  - Metabolomics
  - Proteomics
  - Analysis of the gut microbiome

Metabolites. 2022 Jan; 12(1): 23.
Published online 2021 Dec 27. doi: 10.3390/metabo12010023
PMCID: PMC8780989
PMID: 35050145

The Proteomic Signature of Intestinal Acute Rejection in the Mouse

Mihai Oltean,[1,2,*] Jasmine Bagge,[2] George Dindelegan,[3,4] Diarmuid Kenny,[5] Antonio Molinaro,[6] Mats Hellström,[2] Ola Nilsson,[7] Carina Sihlbom,[5] Anna Casselbrant,[8] Marcela Davila,[9] and Michael Olausson[1]



Organoids

Intestinal organoids in infants and children. Sinobol Chusilp, Bo Li, Dorothy Lee, Carol Lee, Paisarn Vejchapipat, Agostino Pierro. Pediatric Surgery International (2020) 36:1–10

Advances in culturing intestinal and pluripotent stem cells have led to development of organoids

- Self-organising 3D structures with characteristics and physiological features of intestinal epithelium

- Used as a model for in vitro study of intestine

- Potential treatment short bowel syndrome
  - Have been instilled via rectum in mice and adhered to damaged colon – still present and generating epithelium after 25 weeks

Yui S, Nakamura T, Sato T et al (2012) Functional engraftment of colon epithelium expanded in vitro from a single adult Lgr5+ stem cell. Nat Med 18:618–623

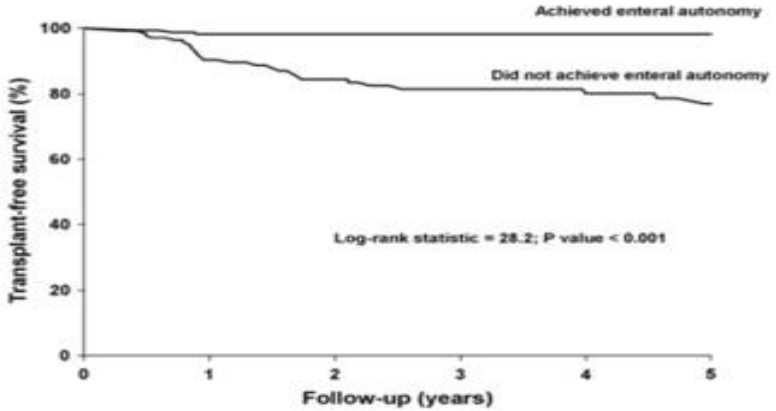
- Tissue-engineered small intestine developed from organoids
  - Contained smooth muscle and nerve components as well as epithelium
    - Potential in Hirschsprung's disease – tissue engineered small intestine with restored enteric nervous system

Workman MJ, Mahe MM, Trisno S et al (2017) Engineered human pluripotent-stem-cell-derived intestinal tissues with a functional enteric nervous system. Nat Med 23:49–59

- But, many other cells and structures of the intestine are not present

Survival

- Fullerton BS, Sparks EA, Hall AM, Duggan C, Jaksic T, Modi BP. Enteral autonomy, cirrhosis, and long term transplant-free survival in pediatric intestinal failure patients. J Pediatr Surg. 2016 Jan;51(1):96-100

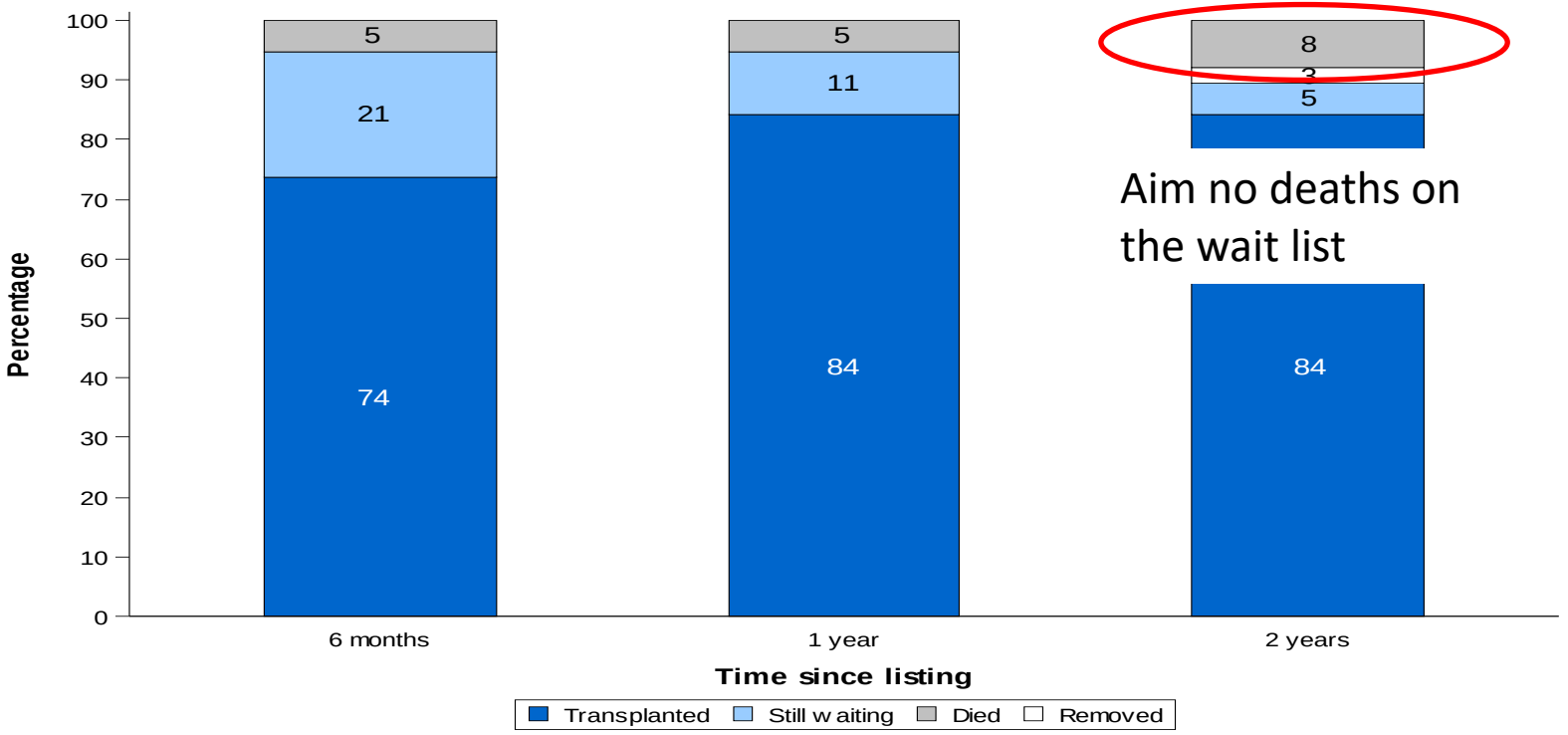


Aim 100% survival in intestinal failure

Aim all patients wean from long-term PN

NHS
Blood and Transplant

Figure 2.3 **Post-registration outcome for 38 elective registrations for an intestine transplant made in the UK, 1 April 2014 - 31 March 2016**



Source: Annual Report on Intestine Transplantation 2017/18, NHS Blood and Transplant

Intestinal Rehabilitation & Transplant
ASSOCIATION

VISION

- Excellent physical and emotional health for all people with intestinal failure through rehabilitation and transplantation.

MISSION

- Optimize the lives of intestinal failure patients worldwide through innovative nutritional, medical, psychosocial, surgical and transplant research and therapies.
- Maintain global leadership through a multidisciplinary approach to intestinal failure, rehabilitation and transplantation.
- Advance the support for all professionals working in the field of intestinal transplantation and rehabilitation with regard to education, policy, research and advocacy.

VALUES

- **Excellence:** Promoting innovative clinical, basic and translational science through multidisciplinary teamwork.
- **Collaboration:** Working closely with patients, IRTA members, scientific societies, health organizations, and governments.
- **Advocacy:** supporting the patient's voice in speaking as a unified influence in issues of concern to the IF and Intestinal transplant community.
- **Integrity:** Acting on the highest standards of ethical practice.

Intestinal transplantation

- Increasing patient survival in recent years
- Improved QoL post ITx compared to PN
- Long-term graft survival remains a challenge

- Intestinal rehabilitation outcomes are good in terms of survival
- Many intestinal failure survivors remain on long-term PN

  - New indications to improve patient selection and timing
  - Improve long-term graft survival with tolerogenic immunosuppression strategies, biomarkers and understanding of chronic rejection
  - “Pre-emptive” transplantation

  - Psychosocial support for ITx recipients needed
  - Patient empowerment and equity of access

  - Strong, active, international IRTA


SAVE the DATE
18th Congress of the Intestinal Rehabilitation and Transplant Association (CIRTA)
Intestinal Rehabilitation & Transplant ASSOCIATION
a section of TTS The Transplantation Society
UI Health
UIC
CIRTA XVIII
CHICAGO
JUNE 30 - JULY 3, 2023


Thank-you
jhind@nhs.net