

Intestinal transplantation –
An overview
(What you should know as a
non-intestinal transplant surgeon)

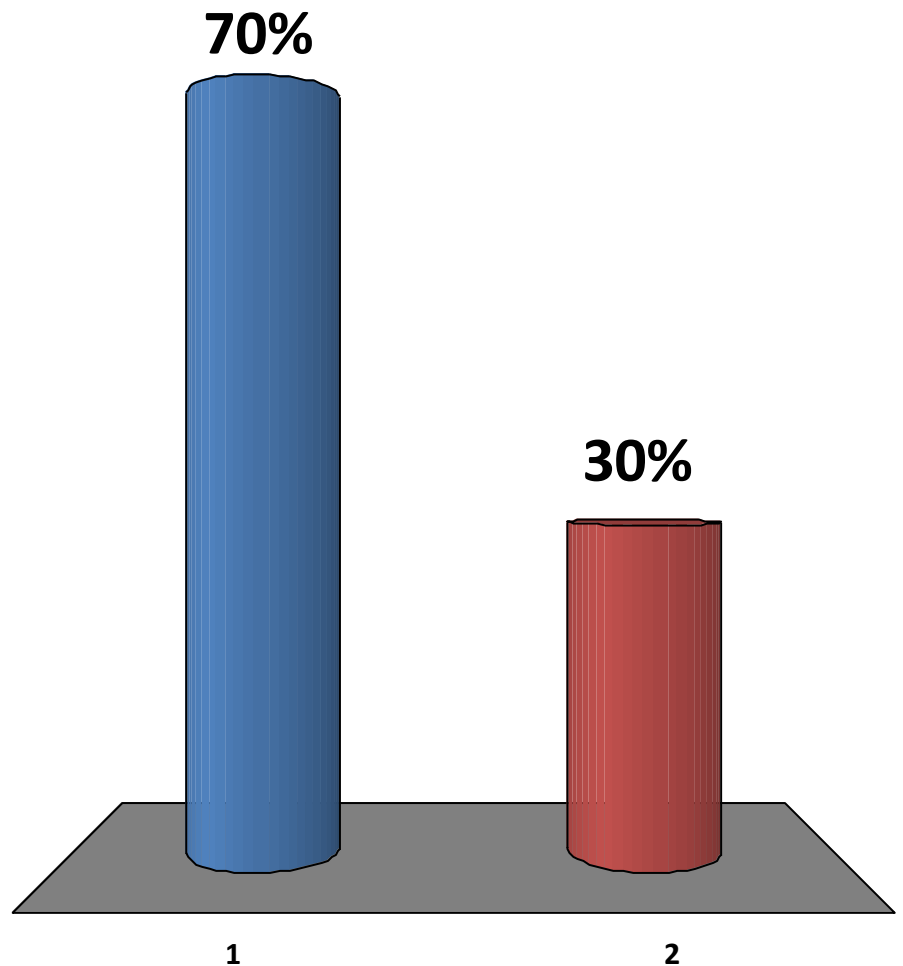
Wendy J. Grant, MD
Associate Professor of Surgery
Assistant Dean for Student Affairs
University of Nebraska College of Medicine

Disclosures

- No financial disclosures
- I am an intestinal transplant surgeon and believe that is indicated for those that need it
- I take care of intestinal rehabilitation patients

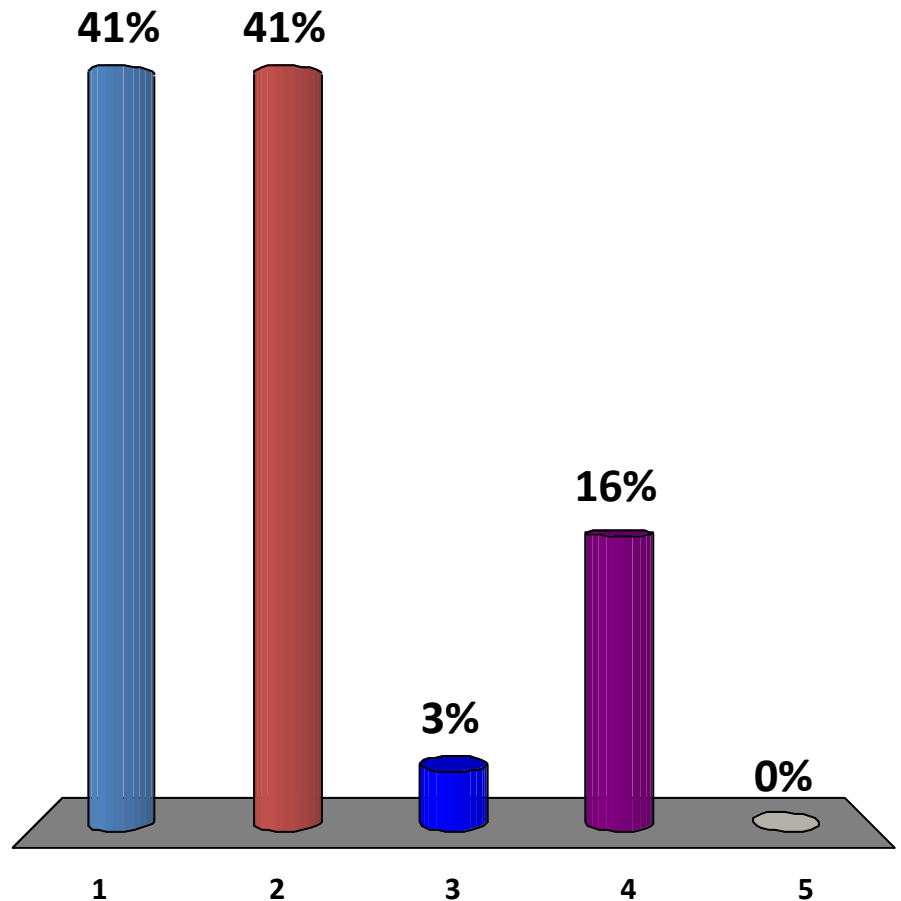
Does your institution perform intestinal transplants?

1. Yes
2. No



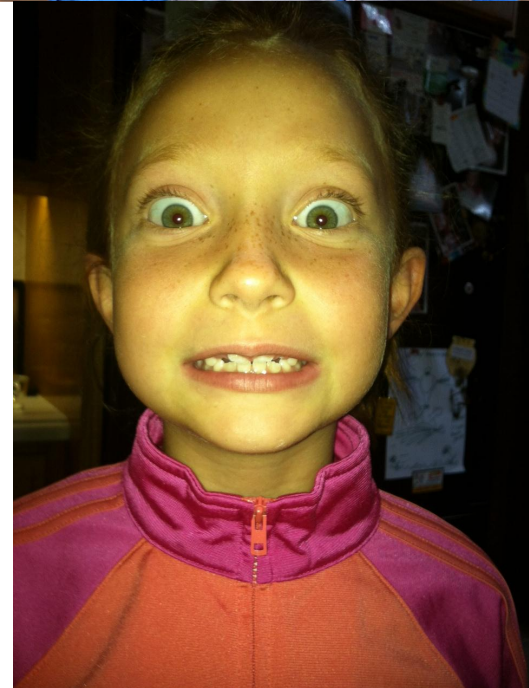
How many intestinal transplant recipient operations have you participated in?

1. 0
2. 1-5
3. 5-10
4. >10
5. Too many to count

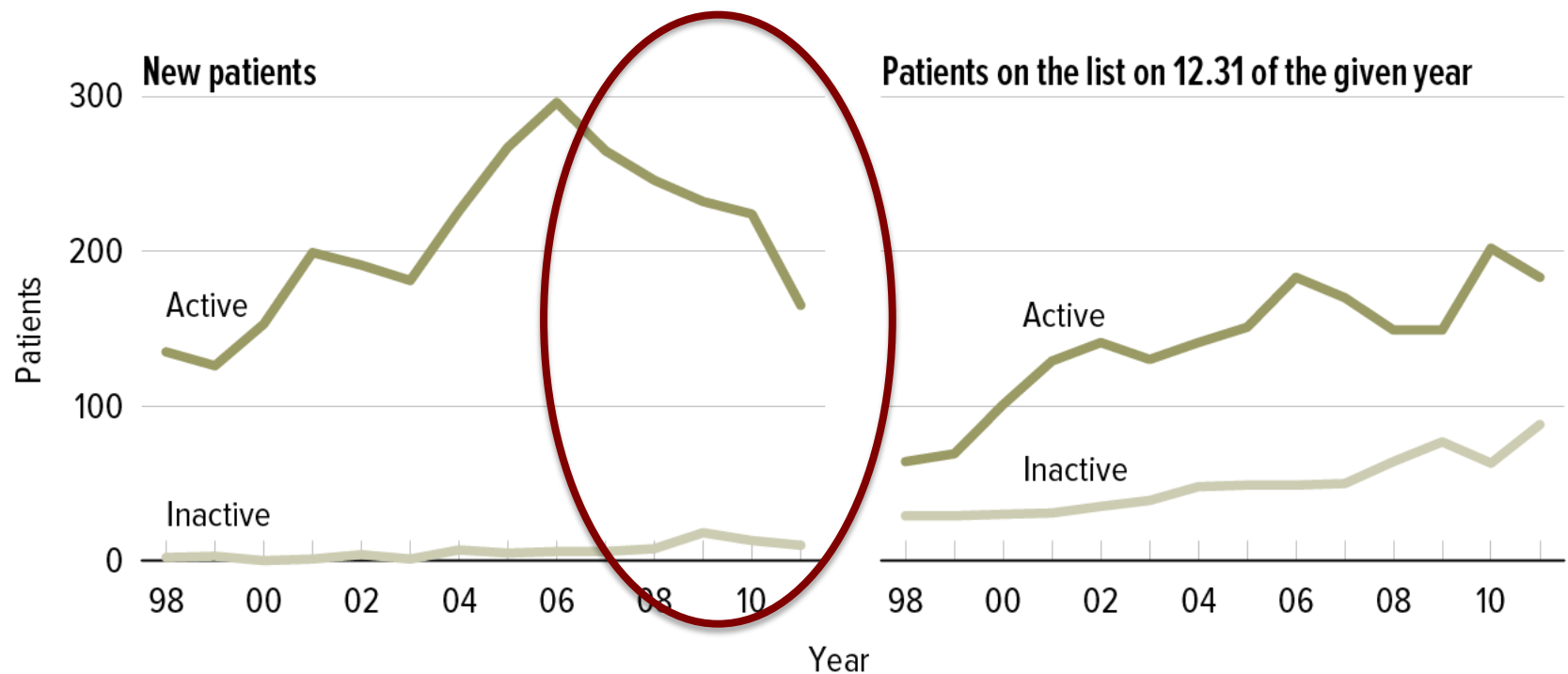


What will we talk about

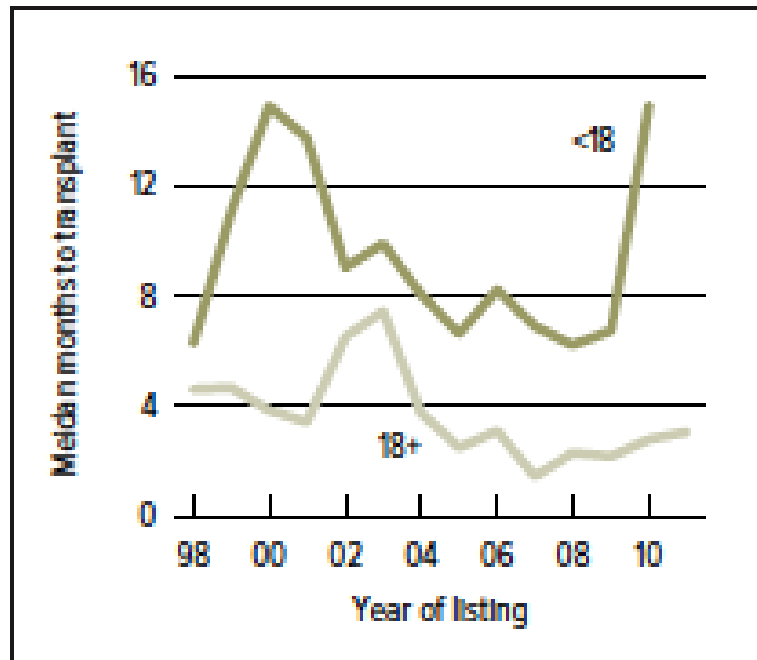
- Intestine transplant volumes
- Indications for transplant
- Isolated intestine
- Intestine with liver (and other bits)
- Allocation
- Patient survival
- Cases



IN 1.1 Patients waiting for an intestinal transplant



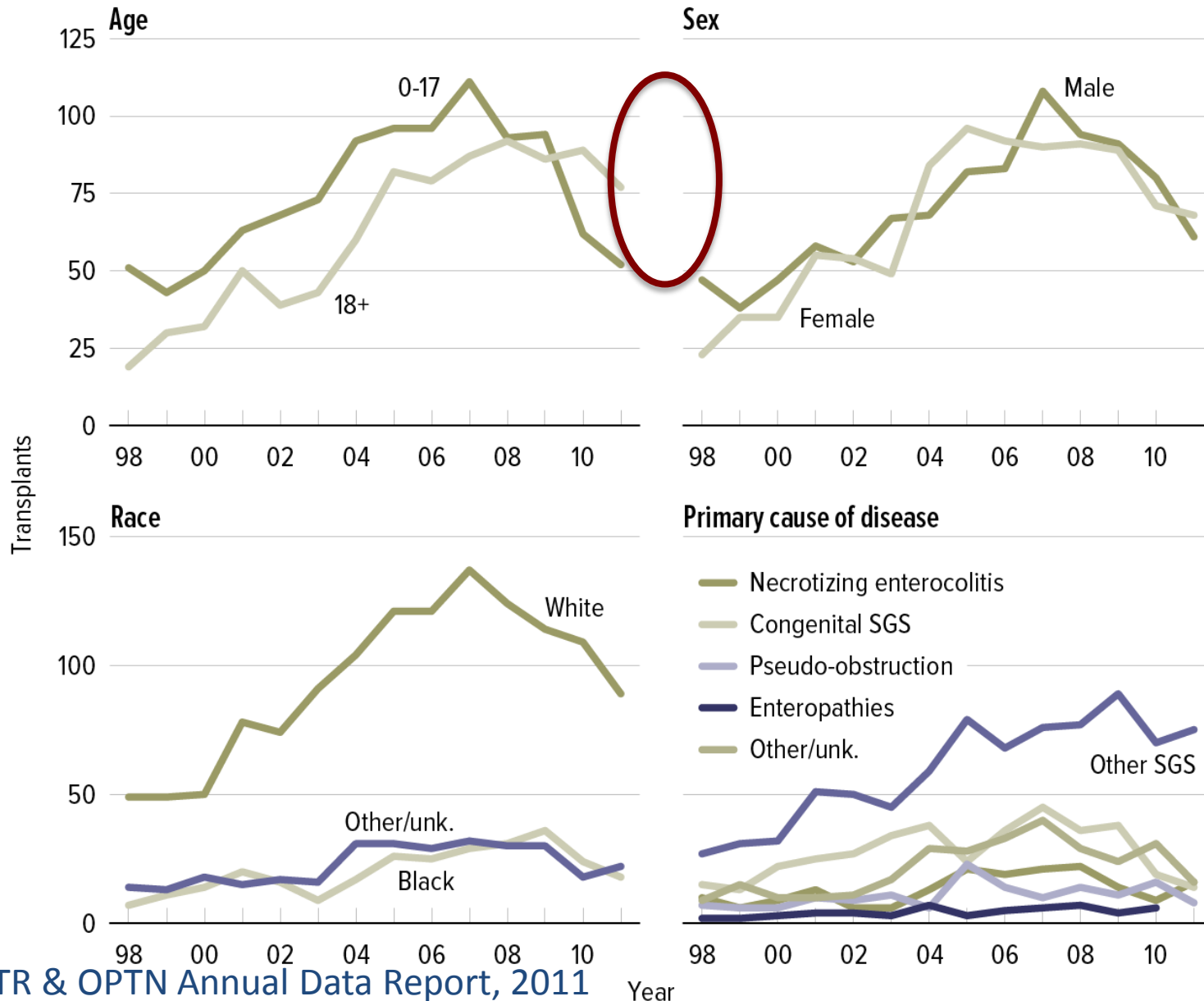
Transplant wait time



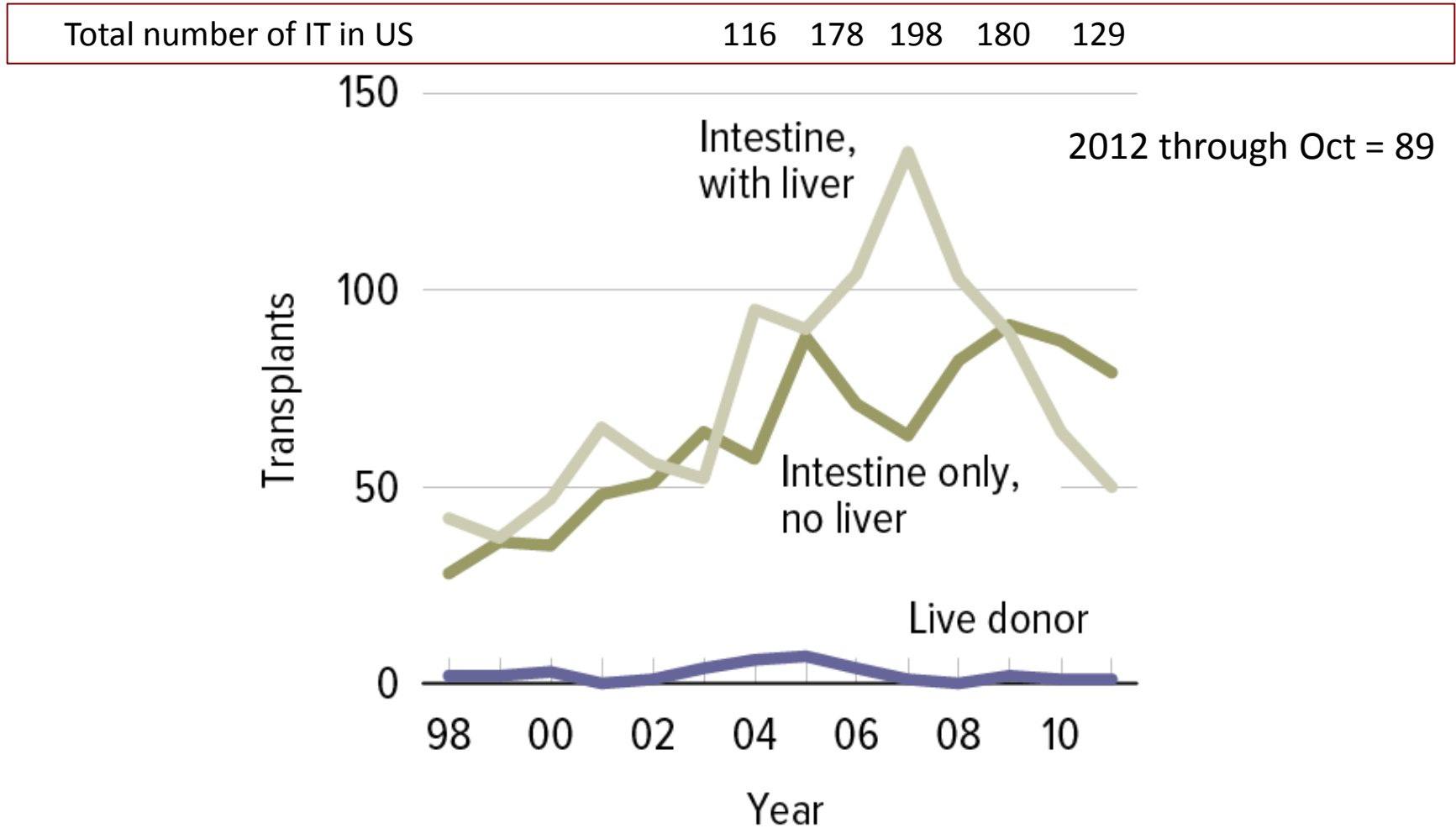
IN 1.7 Median months to intestinal transplant for wait-listed patients, by age

Patients waiting for a transplant, with observations censored at December 31, 2011; Kaplan-Meier method used to estimate time to transplant. If an estimate is not plotted for a certain year, 50% of the cohort listed in that year had not been transplanted at the censoring date. Only the first transplant is counted.

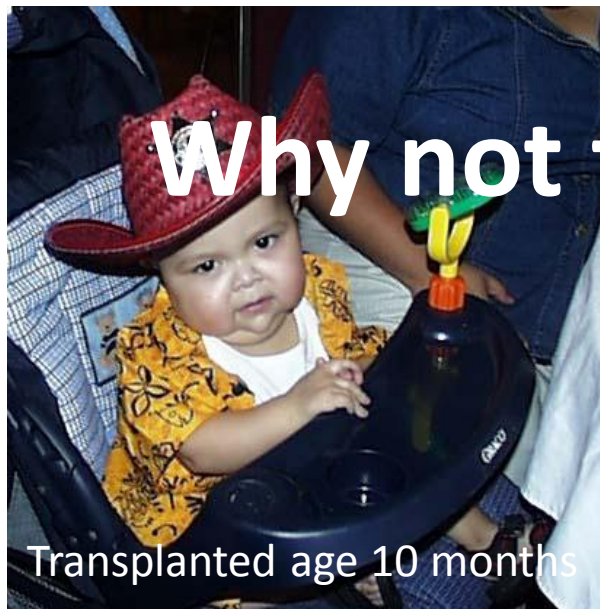
IN 3.2 Intestinal transplants



IN 3.1 Total intestinal transplants



Why not transplant?????



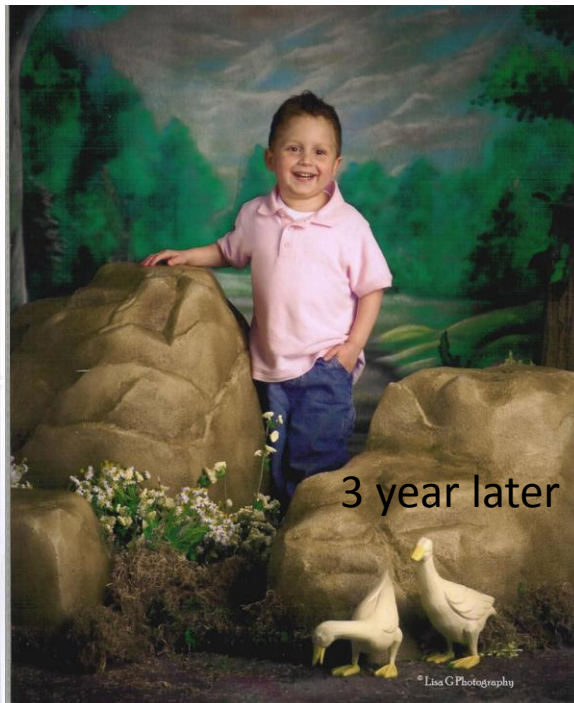
Transplanted age 10 months



Kindergarten graduation



Transplanted at age 15 months



3 year later



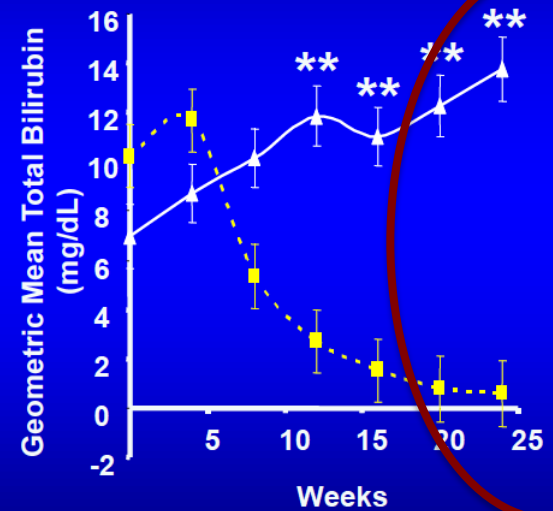
Prospective, Case Controlled Trial of 24 weeks of Intravenous Fish Oil in Children with Intestinal Failure Associated Liver Disease

Kara Calkins^{*1}, Stephen Shew², James Dunn², Douglas Farmer², and Robert Venick^{1,2}

¹Department of Pediatrics, ²Department of Surgery
University of California, Los Angeles

*Supported by NIH grant T32GM75776-6

BILIRUBIN



**p-value<0.

PROSPECTIVE FO COHORT

Satisfies Inclusion Criteria



FO

Omegaven™ 1 gm/kg/d IV
X 24 weeks or until death/transplant

RETROSPECTIVE SO COHORT

Satisfies Inclusion Criteria



SO

Intralipid™ 0.5 – 4 gm/kg/d
x 24 weeks or until
death/transplant

Hepatic Fibrosis Persists and Progresses Despite Biochemical Improvement in Children Treated With Intravenous Fish Oil Emulsion Mercer, David F.; Hobson, Brandy D.; Fischer, Ryan T.; Talmon, Geoffrey A.; Perry, Deborah A.; Gerhardt, Brandi K.; Grant, Wendy J.; Botha, Jean F.; Langnas, Alan N.; Quiros-Tejeira, Ruben E.

Journal of Pediatric Gastroenterology & Nutrition:POST ACCEPTANCE, 27 November 2012

	1				2		3				4		5			6	
age at biopsy (w)	43	52	99	131	14	41	8	34	40	67	8	38	11	19	47	28	83
length (cm)	67.5	73	80.5	84.5	50.5	65	54.6	69	71	77.5	46	63	58.5	62	73.5	62	75
weight (kg)	8.2	9.5	10.8	12	4.1	8.3	4.1	7.2	8.3	9.7	2.4	7.2	4.9	6.6	9	6.6	9.4
%enteral	15	0	0	16	0	70	0	0	15	47	0	25	30	35	35	94	86
%parenteral	85	100	100	84	100	30	100	100	85	53	100	75	70	65	65	6	14
Total bili (mg/dl)	0.4	1.7	0.4	0.4	3.4	0.4	6.5	0.4	0.3	0.3	17.4	0.6	4.4	0.3	0.4	0.4	0.7
Dir bili (mg/dl)	0.2	0.2	0.1	ND	ND	0.1	3.6	ND	ND	ND	10.4	ND	3.6	ND	ND	0.1	ND
AST (U/L)	75	107	95	39	58	56	142	28	53	27	52	83	105	94	129	36	70
ALT (U/L)	125	127	201	121	77	42	109	21	75	22	29	141	129	231	229	44	116
GGT (U/L)	196	96	31	35	107	23	ND	22	18	32	223	ND	139	159	122	20	44
alk phos (U/L)	185	231	260	164	548	271	475	251	257	310	673	348	510	385	557	401	251
Trig (mg/dl)	60	40	ND	17	59	53	96	41	28	50	90	37	67	34	ND	29	26
platelets	275	247	225	212	397	325	241	204	194	272	101	118	422	247	241	273	454
PT-INR	1.6	1.2	1.2	1.1	1.2	1.2	ND	1.2	1.1	1.1	102	1.1	1	1.2	0.9	1.4	1.2
albumin	2.3	2.9	3.2	3.2	3.6	2.1	2.3	1.8	3.5	2.3	2.6	3.1	3	2.5	3.3	3.1	3.1
time on FOE at biopsy (w)	11	20	off	off	6	off	1	27	33	off	1	31	0	9	36	20	75
steatosis	1	0	1	1	0	0	0	1	0	0	0	1	0	0	0	0	1
cholestasis	1	1	0	0	2	0	3	1	1	0	4	1	3	2	0	1	0
inflammation	0-1	1-2	0	0	0-1	0-1	2	1	1	1	1	0-1	1	0	0	2	0
fibrosis	3	3	3	3	2	2	0	2	3	3	1	2	1	2	2	2	1
ductal proliferation	no	yes	no	no	no	no	no	yes	no	no	yes	yes	no	yes	no	yes	no

Table 3. Summary of clinical, laboratory and pathological data for six study subjects. AST – aspartate aminotransferase; ALT – alanine aminotransferase; Alk phos – alkaline phosphatase; Trig – triglyceride; FOE – fish oil emulsion; ND – not done Percent enteral and parenteral calories are calculated based on an estimated need of 85 kCal/kg/d.



Retrospective Study of Central Venous Catheter Infections in Intestinal Rehabilitation Patients Using Ethanol Therapy or Alternative Therapy.

Heidi O'Connell¹, David Mercer¹, Teresa Barry³, Fedja Rochling¹, Laura Beerman², Brandy Hobson², Brandi Gerhardt¹, Jaime Carney¹

¹Department of Surgery- Intestinal Rehabilitation- University of Nebraska Medical Center, Omaha, ²The Nebraska Medical Center, Omaha. ³College of Nursing-Families and Health Systems, University of Nebraska Medical Center, Omaha.

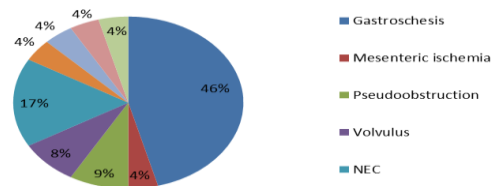
OBJECTIVE

Central venous catheter related infections (CVCI) are a significant cause of morbidity and mortality in patients with long term parental nutrition (PN) needs. Each CVCI generally results in a hospital stay and antibiotic therapy use, both of which have detrimental effects on the patient/family and increase costs of health care. The purpose of this study was to determine if ethanol lock therapy (compared to alternative therapy) decreased the incidence of CVC total infections per 1000 line days and total line insertions in Intestinal Rehabilitation patients who have long term PN needs. In addition, number and types of cultured organisms are examined.

METHODS

- Retrospective analysis of 25 patients
- Subjects used as their own controls, equal time period prior and post 70% ethanol therapy initiation
- Alternative therapies prior to ethanol therapy included saline, antibiotic, or heparin locks
- Inclusion criteria:
 - a) receiving parental nutrition via long term CVC,
 - b) enrolled in the University of Nebraska Medical Center IRP program,
 - c) using ethanol locks
 - d) the patients were served by home health agencies using standardized ethanol therapy protocol.
- Study variables include patient age, days with CVC, days with ethanol therapy, number of infections, the microbes cultured, new line insertions and patient anatomy.
- Statistical analysis was done in SPSS using paired t-tests.

Underlying Cause of Intestinal Failure



RESULTS

- Median age: 23 months old, (range 6 months to 82 years).
- most common cause of IF(44%) gastrostochsis,
- 48% of patients had less than 50cm of SB remaining
- Mean number of days on ethanol therapy was 406 days (13.5 months) (SD= 371).
- Most common organisms cultured during alternative and ethanol therapy: gram positive and gram negative organisms (15 and 6 respectively).

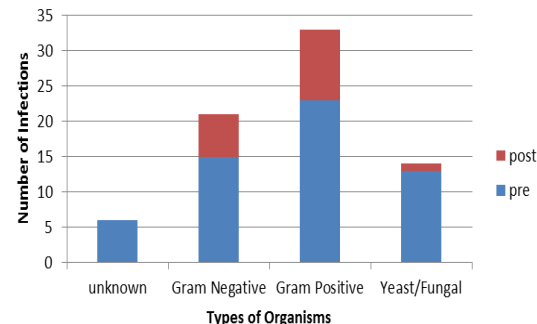
Table 1

Comparison of CVC Infections for pre-ethanol therapy and post ethanol therapy

	Pre-ethanol therapy Mean (SD)	Post-ethanol therapy Mean (SD)	p-value
CVC Infections	2.20 (2.57)	0.68 (1.41)	.012*
CVC Infections per 1000 line days	7.29 (8.74)	1.16 (2.07)	.002*
New Line insertions	4.88 (4.06)	3.56 (4.20)	.262

*p < .05.

Cultured Organism Frequencies

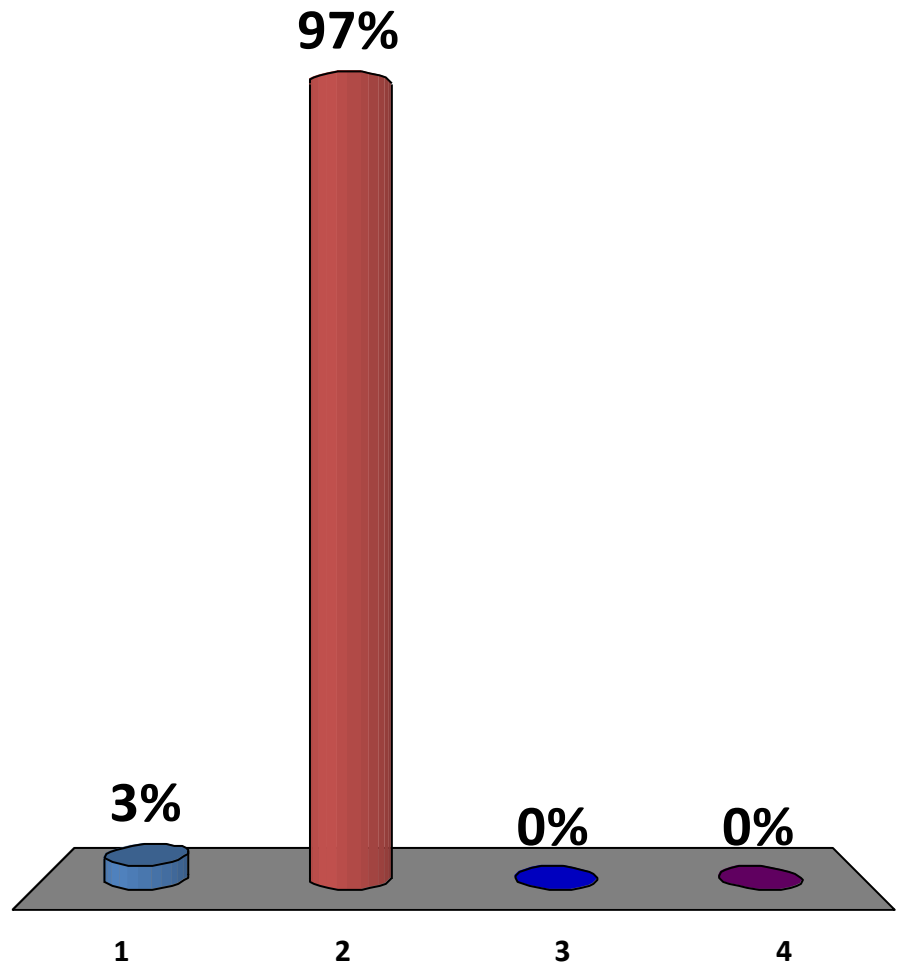


Conclusion and Future Directions

This is amongst the first known studies including both pediatric and adult patients using a standardized ethanol lock protocol. Compared with various alternative therapies, the use of 70% ethanol lock therapy significantly reduces the rate of CVCI per 1000 line days in IRP patients. Differences between groups for new line placements was not significant.

What is a STEP procedure?

1. Building stairs
2. Lengthening bowel
3. A dance
4. An app



International STEP Registry Data

HB Kim, MD

Boston Children's Hospital

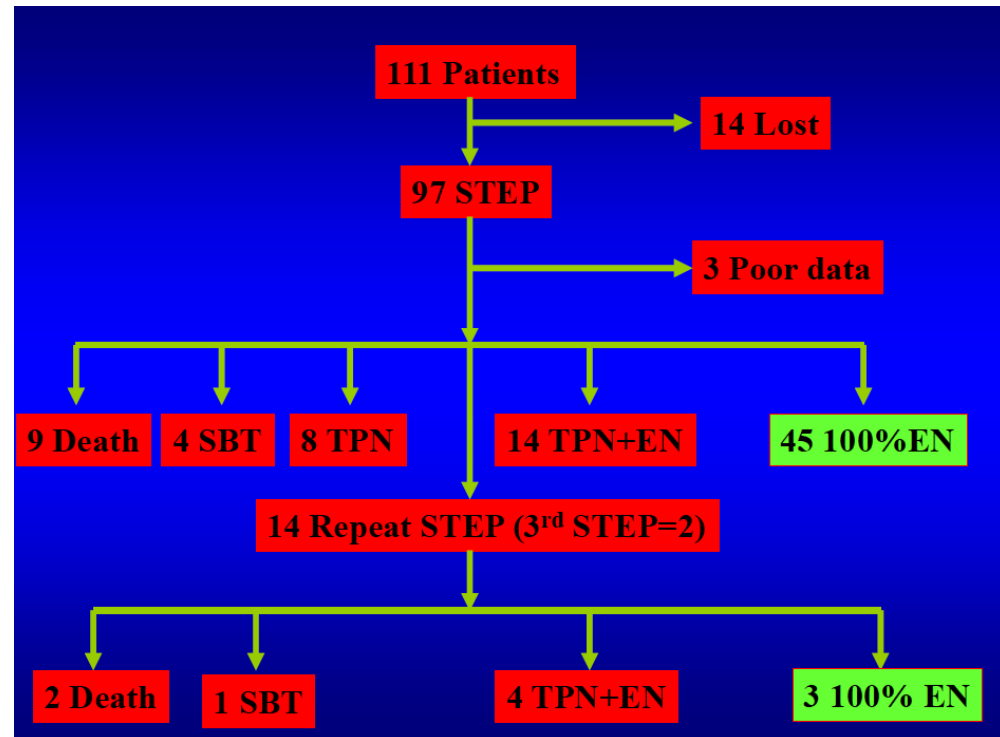
Pediatric Intestinal Failure and Rehabilitation
Symposium (PIFRS)

Chicago, IL 2010

STEP Registry

- 111 patients
- 9/2004 – 1/2010
- 50 worldwide centers

HB Kim, MD



UNMC IRP STEPs 01/06 to 08/11

Total STEPs		68 (50 patients)
Sex	Male	28 (52%)
	Female	24 (48%)
Gestational age (w)		33.5 +/- 2.9
Birth weight (g)		2308 +/- 802
Birth height (cm)		40.6 +/- 3.9
Diagnosis	NEC	8 (16%)
	Gastroschisis	28 (56%)
	Intestinal atresia	10 (20%)
	Volvulus	4 (8%)
Median length post initial surgeries (cm)		30 (10-175)

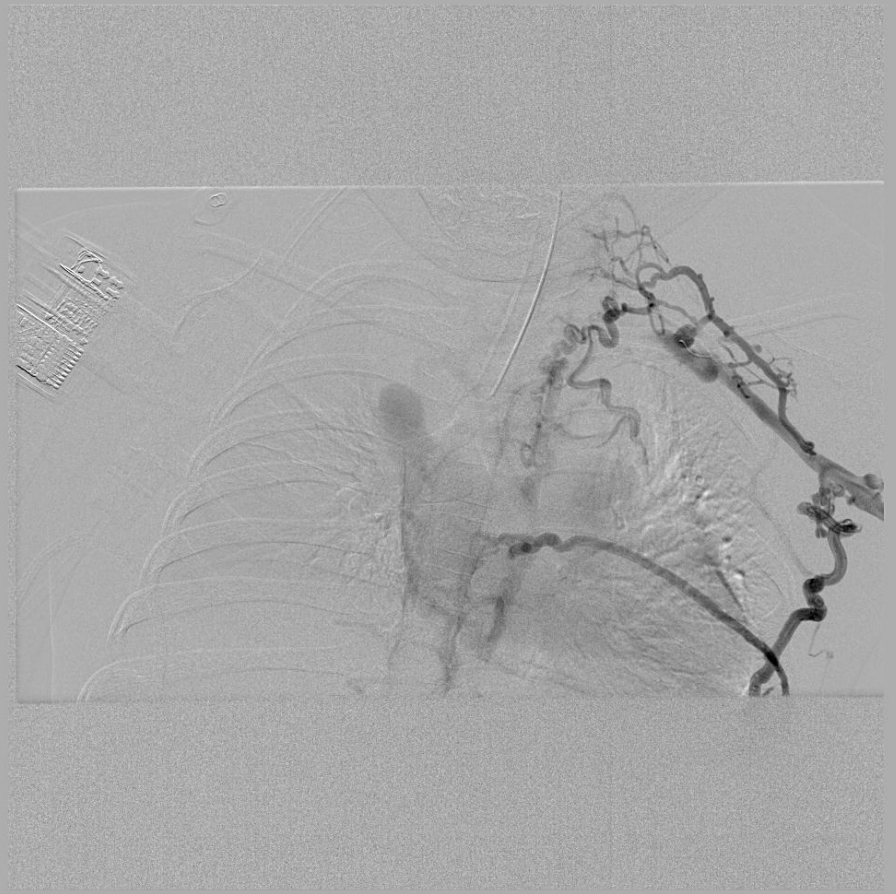
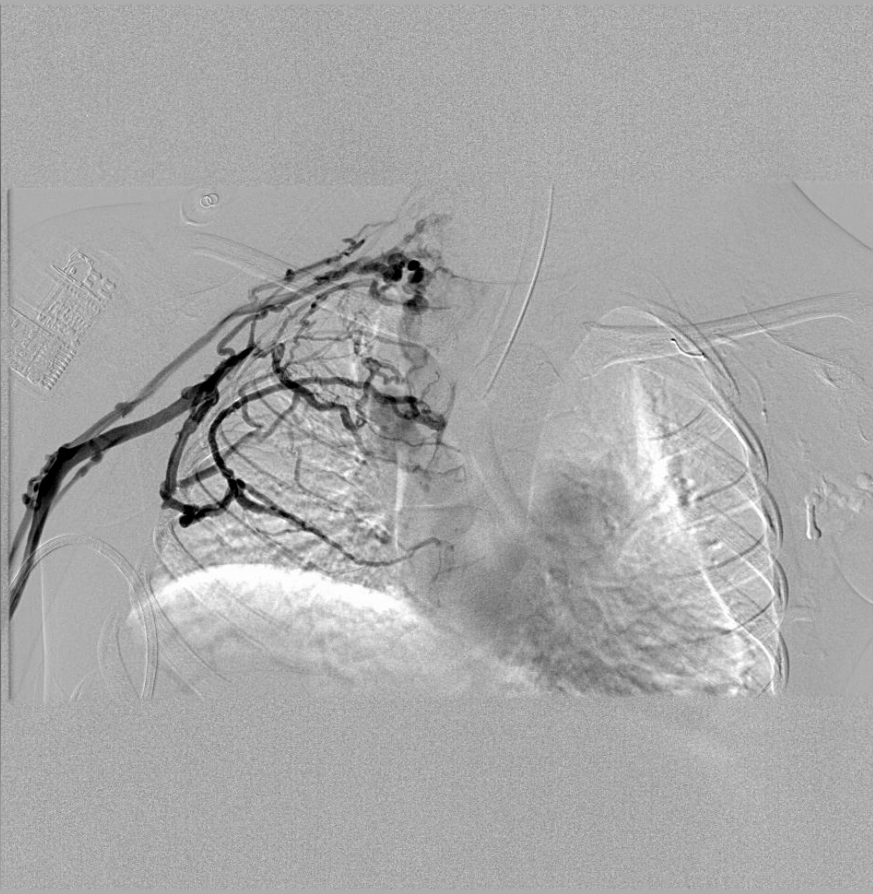
	Median (range)
Age (y)	1.0 (0.1–12.7)
Height (cm)	71 (46-140)
Weight (kg)	8.5 (3.1-32)
Length pre-STEP (cm)	51 (15-175)
Length post-STEP (cm)	87 (31-270)
Length gain	54% (5-130%)
OR Time (min)	115 (65-257)
Blood loss (ml)	0 (0-50)
Days to feeding	8 (5-44)
Days to discharge	14 (7-61)

So .. Who do we actually transplant?



- Dependence on TPN (intestinal failure) with
 - Advancing TPN-associated liver disease despite appropriate management
 - Thrombosis of ≥ 2 central veins
 - ≥ 2 episodes/yr severe sepsis especially fungemia despite appropriate management
 - Nonreconstructable GI tract

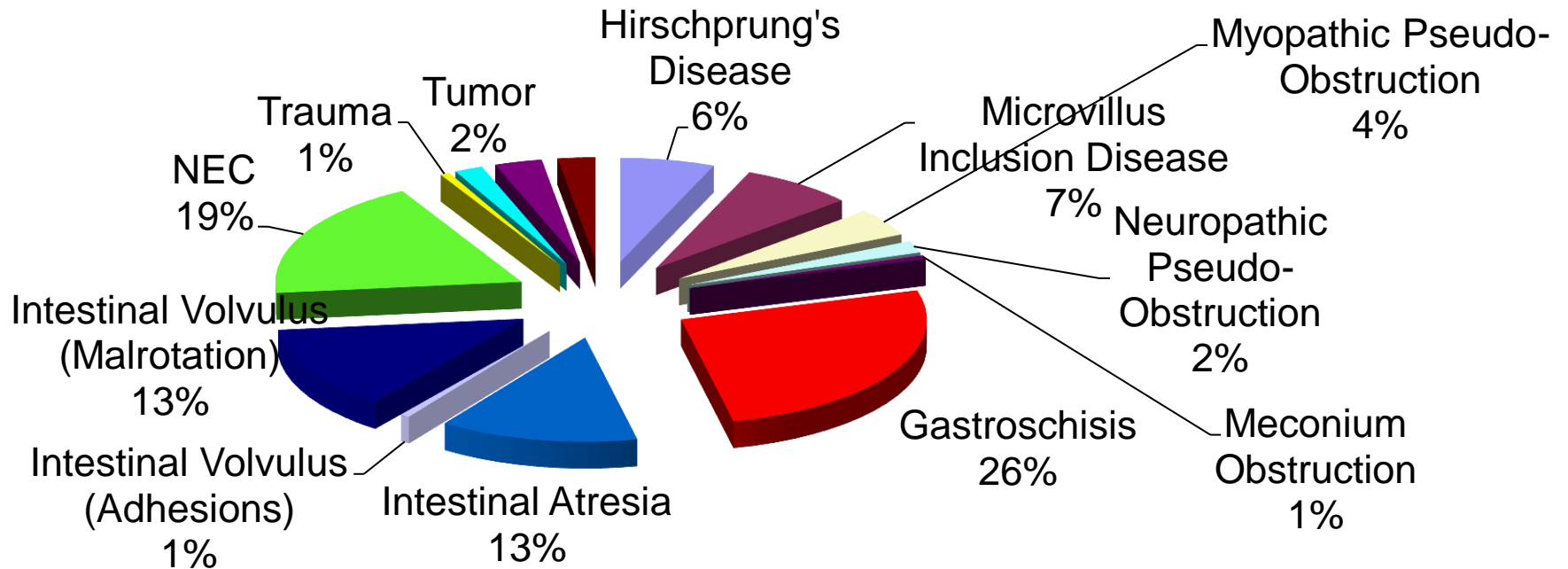
Loss of vascular access



Indications for intestinal transplant

- Loss of vascular access
- Advancing or advanced liver disease
- Repeated life threatening line infections despite optimal line management
- Non-reconstructable GI tract
- Uncontrollable fluid and electrolyte balance

Intestinal transplant diagnosis



Patient Evaluation

- Radiographic studies to define anatomy
 - Upper GI/ Small bowel series; barium enema
 - Ultrasound
 - Fistulogram, if present
- Lab work – Nutritional deficiency, liver disease
- Gastroenterologist
 - liver biopsy
 - endoscopy
- Surgeon
- Nurse coordinator
- Psychology
- Psychiatry
- Dietician
- Financial counselor



What will we talk about

- Intestine transplant volumes
- Indications for transplant
- Isolated intestine
- Intestine with liver (and other bits)
- Allocation
- Patient survival
- Cases

Isolated intestine

- Donor size
 - If all or most of native intestine in place can size match or go smaller
 - If most of native intestine gone and therefore loss of peritoneal domain need donor about 50% of size
- Donor characteristics
 - Hemodynamically stable
 - Nutrition
 - Bowel movements in recent days
 - Number
 - Character (not bloody)
 - CMV/EBV status
 - If patient not in dire straights can wait for CMV negative, but prophylaxis better and CMV not as big a problem as 10 years ago
- Procurement
 - No data showing better outcomes with HTK or SPS
 - Donor pretreatment with anti-lymphocyte preparation (Nebraska)
 - Pancreas
 - Technically feasible to procure pancreas and isolated intestine graft but aberrant anatomy and size must dictate this decision
 - Billing for pancreas if procured and discarded on backtable is controversial

Isolated intestine

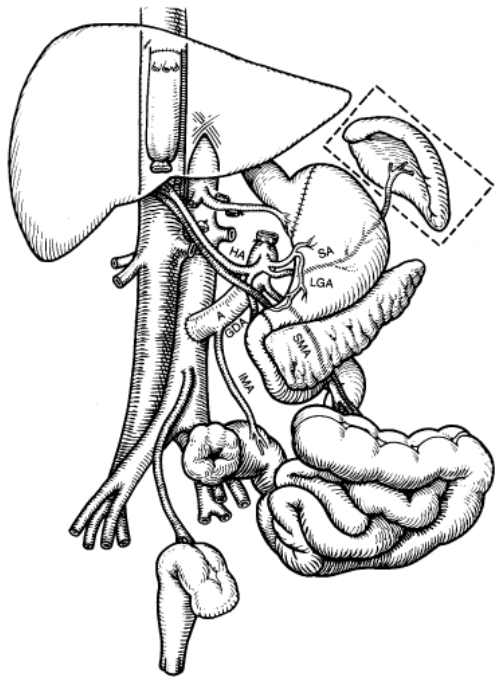
- Recipient operation
 - Arterial anastomosis to infrarenal aorta
 - Venous drainage into vena cava or portal system
 - Jejunojejunostomy
 - Ileocolostomy
 - Loop ileostomy (or end ileostomy if no colon)
- Ileostomy
 - Still no reliable serologic marker for rejection and infection so histology remains gold standard
 - Usually reversed after 6 months of clinical stability

Isolated intestine

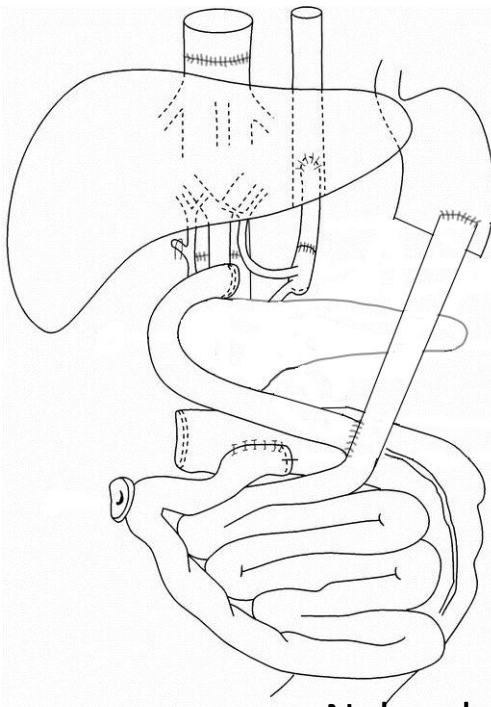


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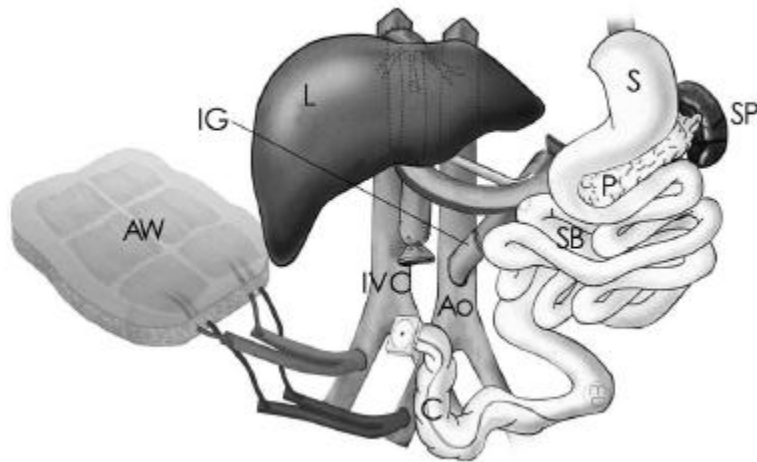
Original Pittsburgh



Nebraska



Current Pittsburgh



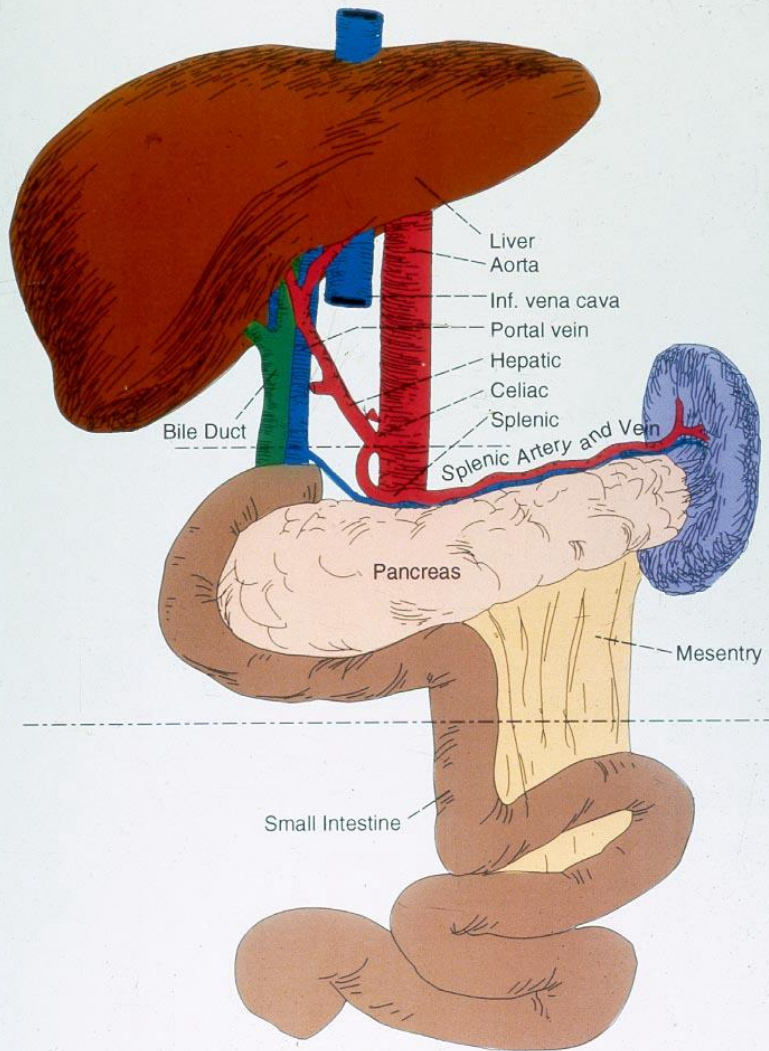
Miami

Intestine with liver and other bits

- Donor size
 - Liver and spleen usually enlarged so gives extra room
 - Regardless usually need donor smaller than recipient
- Donor characteristics
 - Same as isolated intestine
- Procurement
 - All organs en-bloc from stomach to colon, depending on what organs are being transplanted
 - Thoracic aortic conduit with preservation of celiac and superior mesenteric arteries
 - En-bloc kidneys can be procured depending on size of donor
 - Patch of aorta can be used to oversew aorta below SMA

Intestine with liver and other bits

- Recipient operation variations
 - Removal or preservation of foregut (duodenum, pancreas, spleen)
 - Partial gastrectomy
 - Caval replacement or piggy back
- GI reconstruction
 - Roux-en-y gastrojejunostomy when foregut removed
 - Jejunojunctionostomy when foregut preserved



Liver and other bits



Technical complications

- Isolated small bowel
 - Venous thrombosis
 - Hypovolemia, kinking, hypercoaguable states
 - Arterial thrombosis
 - Technical
- Liver small bowel
 - Vascular complications relatively uncommon
- Bowel perforation
 - Anastomotic
 - Trauma
 - Ischemia

Post operative management

- Aggressive use of take back/wash outs looking for perforations and peritonitis
- Diligent surveillance for blood stream infections and low threshold for line removal and changes
- Alprostodil for 7 days
- Initiation of enteral feedings when ileus resolves – usually within first 7-10 days
- Vivonex or similar formula to start to decrease risk of chylous ascites and effusions



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3.11 **INTESTINAL ORGAN ALLOCATION.** The following policies apply to intestinal organ allocation which may include the stomach, small and/or large intestine or any portion of the gastro-intestinal tract as determined by the medical needs of individual candidates.

3.11.1 Degree of Medical Urgency. Each candidate shall be assigned one of the following status codes which correspond to the medical condition of the candidate.

Status 7 A candidate listed as a Status 7 is temporarily inactive; however, the candidate continues accruing waiting time up to a maximum of 30 days. Candidates who are considered to be temporarily unsuitable transplant candidates are listed as Status 7.

Status 1 A candidate listed as a Status 1 has liver function test abnormalities and/or no longer has vascular access through the subclavian, jugular or femoral veins for intravenous feeding, or has other medical indications that warrant intestinal organ transplantation on an urgent basis.

Status 2 All candidates awaiting intestinal organ transplantation who do not meet the criteria for Status 1 will be classified as Status 2.

From intestine allocation

3.11.4 Combined Intestine-Liver Allocation. For combined intestine-liver allocation, the liver must first be offered:

- according to the liver match run
- sequentially to **each** potential liver recipient (including all MELD/PELD potential recipients) through national Status 1A and 1B offers.

The liver may then be offered to combined liver-intestine potential recipients sequentially according to the intestine match run.

3.6 ALLOCATION OF LIVERS.

Adult Donor Liver Allocation Algorithm

Combined Local and Regional

1. Status 1A candidates in descending point order
2. Status 1B candidates in descending order

Local and Regional

3. Candidates with MELD/PELD Scores ≥ 35 in descending order of mortality risk (MELD) scores, with Local candidates ranked above Regional candidates at each level of MELD score

Local

4. Candidates with MELD/PELD Scores 29-34 in descending order of mortality risk scores (probability of candidate death)

National

5. Liver-Intestine Candidates in descending order of Status and mortality risk scores (probability of candidate death)

Local

6. Candidates with MELD/PELD Scores 15-28 in descending order of mortality risk scores (probability of candidate death)

Regional

7. Candidates with MELD/PELD Scores 15-34 in descending order of mortality risk scores (probability of candidate death)

3.11.4.2 Combined Liver-Intestinal Organs from Donors 0-10 Years of Age.

For donors 0-10 years of age, offers will be made using the liver match run with candidates prioritized as follows:

Combined Local and Regional

1. Pediatric Status 1A Liver and Liver-Intestine Candidates (age 0-17) in descending point order

National

2. Pediatric Status 1A Liver and Liver-Intestine candidates (age 0-11) in descending point order
3. Pediatric Status 1A Liver-Intestine candidates (age 12-17) in descending point order

Local

4. Adult Status 1A Liver and Liver-Intestine candidates in descending point order

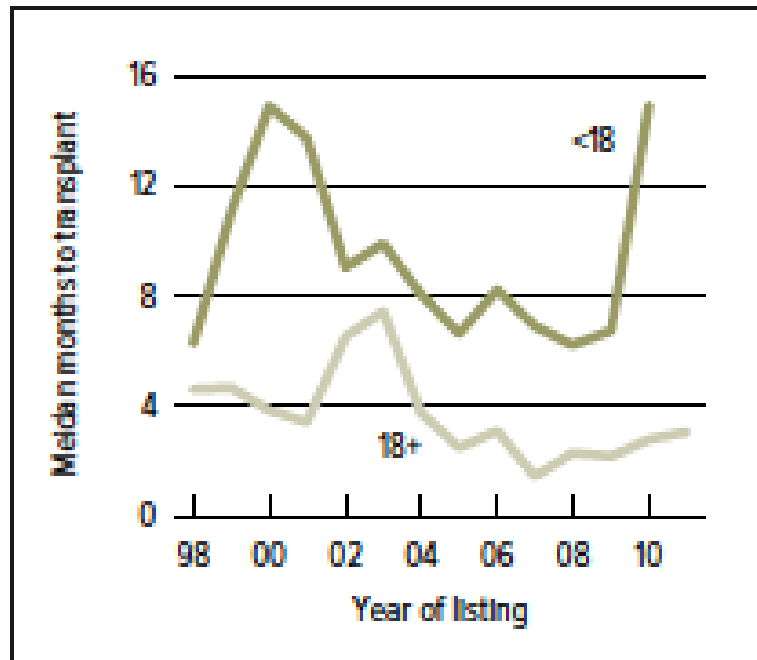
Regional

5. Adult Status 1A Liver and Liver-Intestine candidates in descending point order

Combined Local and Regional

6. Pediatric Status 1B Liver and Liver-Intestine candidates (age 0-17) in descending point order
7. Pediatric Liver and Liver-Intestine candidates (age 0-11) by PELD greater than 20

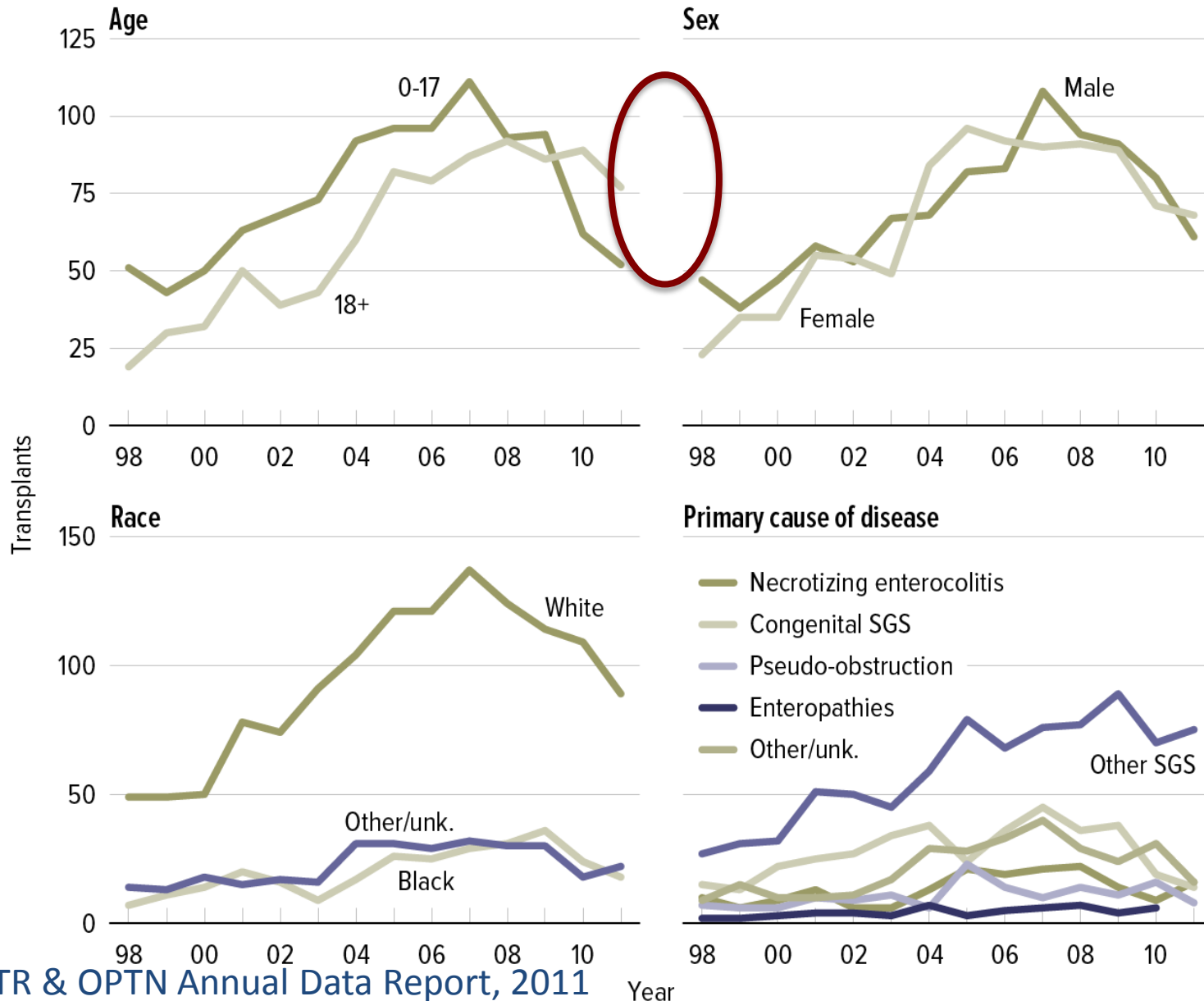
Transplant wait time



IN 1.7 Median months to intestinal transplant for wait-listed patients, by age

Patients waiting for a transplant, with observations censored at December 31, 2011; Kaplan-Meier method used to estimate time to transplant. If an estimate is not plotted for a certain year, 50% of the cohort listed in that year had not been transplanted at the censoring date. Only the first transplant is counted.

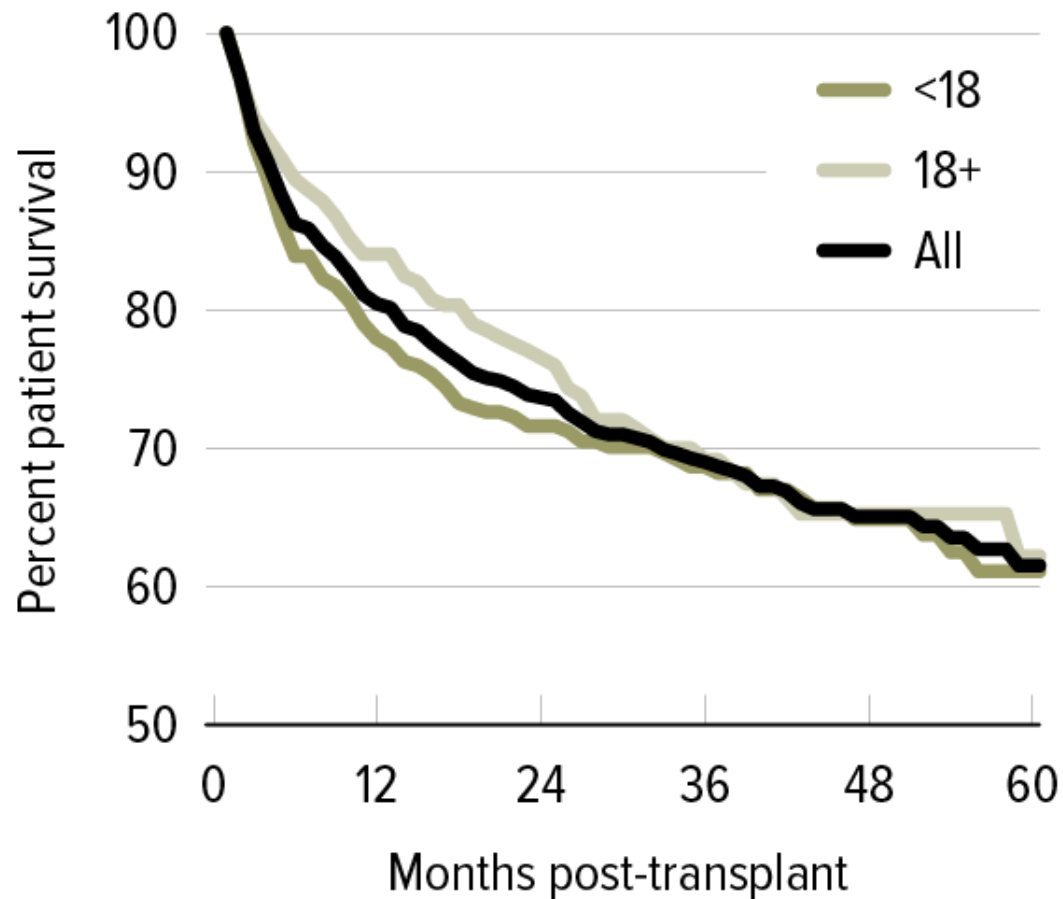
IN 3.2 Intestinal transplants

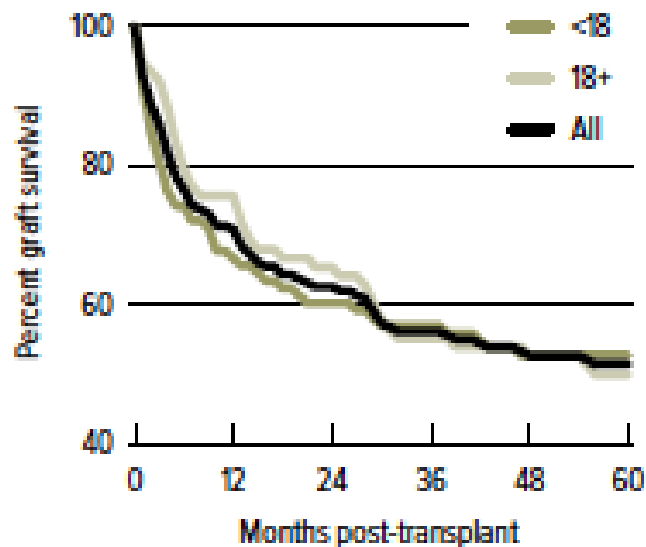


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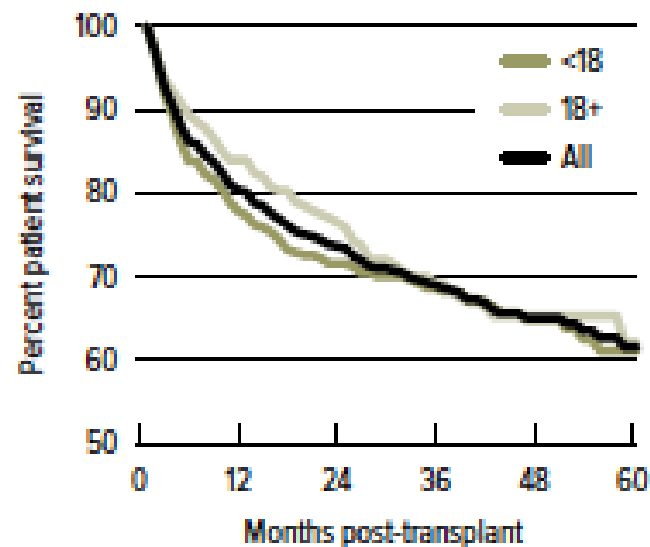
IN 4.4 Patient survival among intestinal transplant recipients, 2002–2006, by age: deceased donors





IN 4.3 Graft survival among intestinal transplant recipients transplanted in 2006, by age: deceased donors

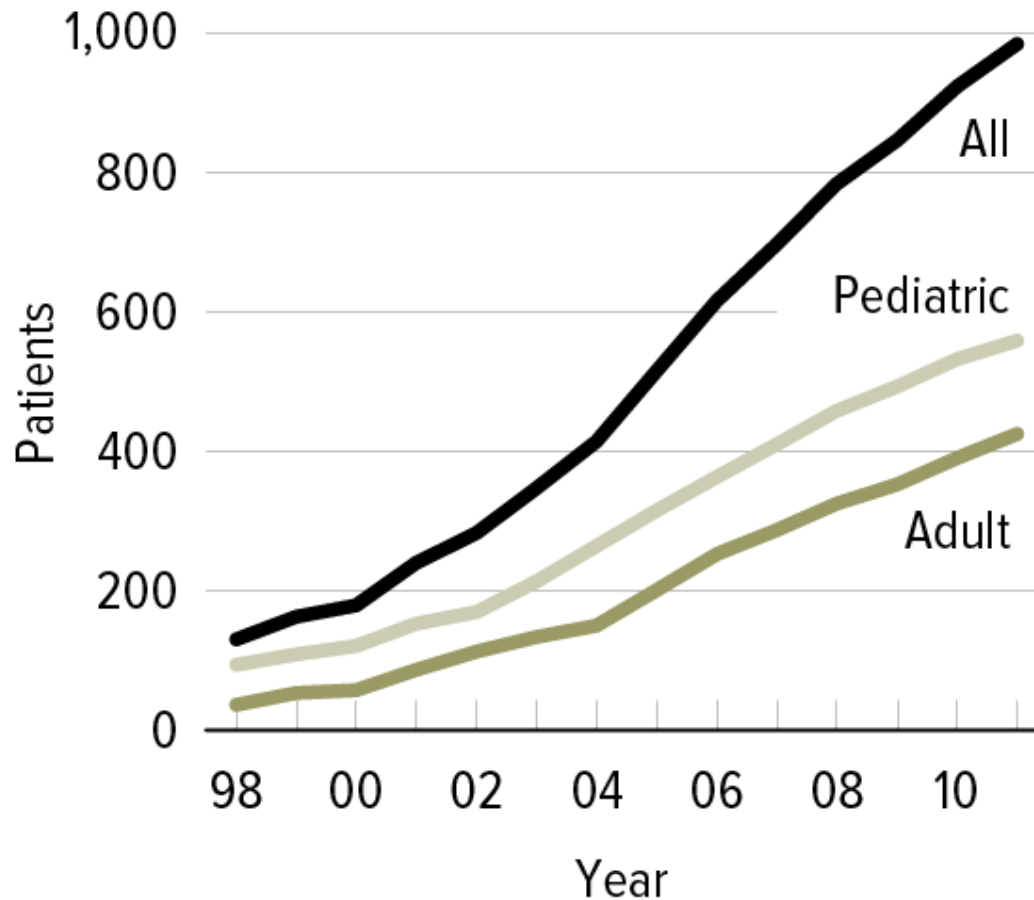
Graft survival estimated using unadjusted Kaplan-Meier methods.



IN 4.4 Patient survival among intestinal transplant recipients, 2002–2006, by age: deceased donors

Percent patient survival using unadjusted Kaplan-Meier methods. For patients with more than one transplant during the period, only their first transplant is considered.

IN 4.5 Recipients alive & with a functioning intestinal transplant on June 30 of the year



CASES

26 year old woman with Gardner's syndrome. Total abdominal colectomy then enterocutaneous fistulas associated with desmoid tumors.

- Underwent total enterectomy leaving duodenal stump as a blind end
- Gastrojejunostomy tube for drainage of the foregut
- Aspiration pneumonia at time of last operation requiring ECMO for 14 days and prolonged course in ICU with MSOF
- TPN dependent
- Lives independently, only pain meds are for GT exit site
- 2 line infections in 8 months
- No loss of vascular access
- Liver synthetic function intact



THE NEBRASKA MEDICAL CENTER
23-Mar-11
04:16:33

24, F
GRANT WENDY J
GRANT WENDY J
3376708
Upper Gastrointst w Sm Bowel
4142-1-13



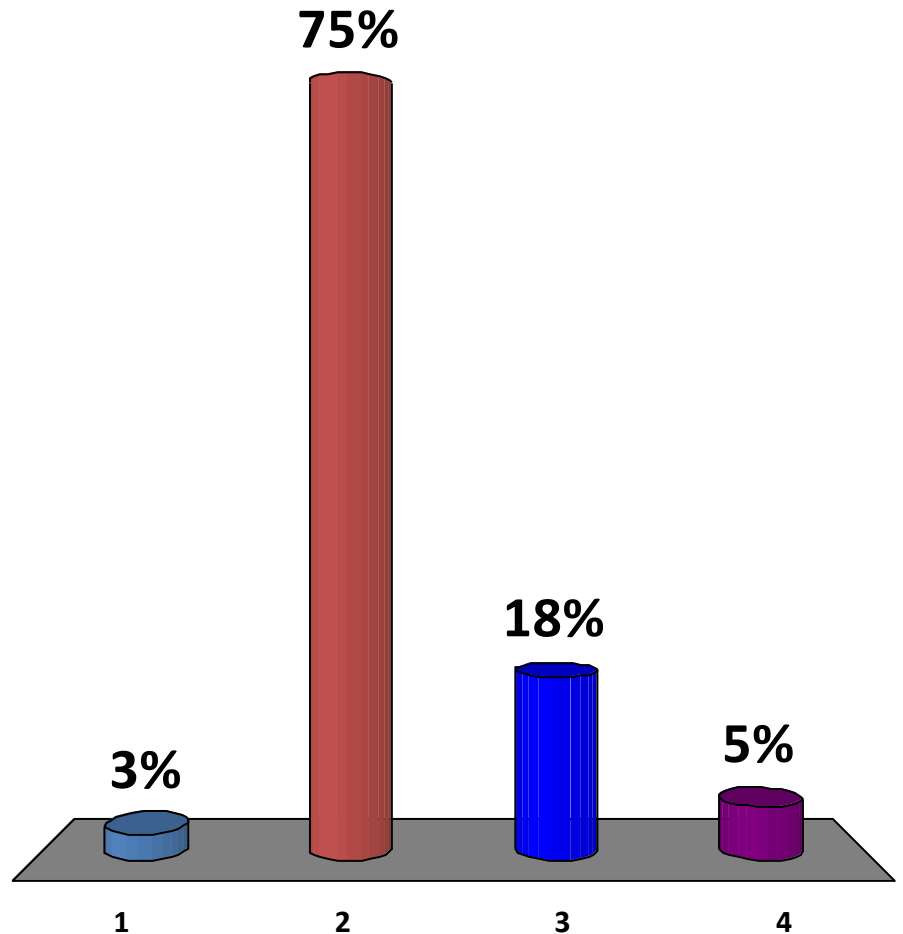
GAMMA H1
EDGE BP2
Medium
14"
111 kV
320 mA
8.1 ms

DCF CA
SHUTTERS
DR:Single

W2: 386
W1: 16

What would you offer her

1. Hospice
2. Isolated small bowel transplant
3. Ongoing TPN
4. Combined liver and small bowel transplant



What we did

- Listed for isolated small bowel transplant
- Transplanted 2 months later
- Post-transplant course unremarkable
 - Off TPN in 2 weeks
 - No rejection or infection
 - Maintenance immunosuppression of tacrolimus, mycophenolate and steroids
 - Allowed to leave Nebraska 6 weeks post-operatively



5 Ileostomy



4 Small Bowel

So we thought we were really smart
(or lucky)

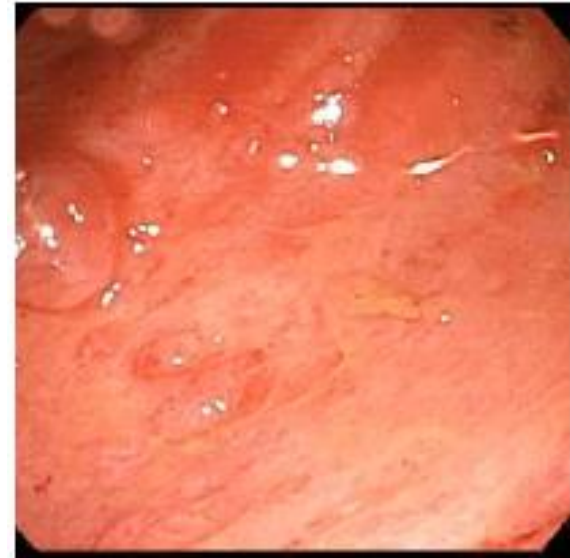
- 6 weeks later she has labs and tacrolimus was undetectable ...
- She denied missing any medications so dose was increased
- Presented 2 weeks later with diarrhea



4 Small Bowel: Small bowel graft



1 Proximal small bowel graft



6 Small Bowel: Small bowel graft

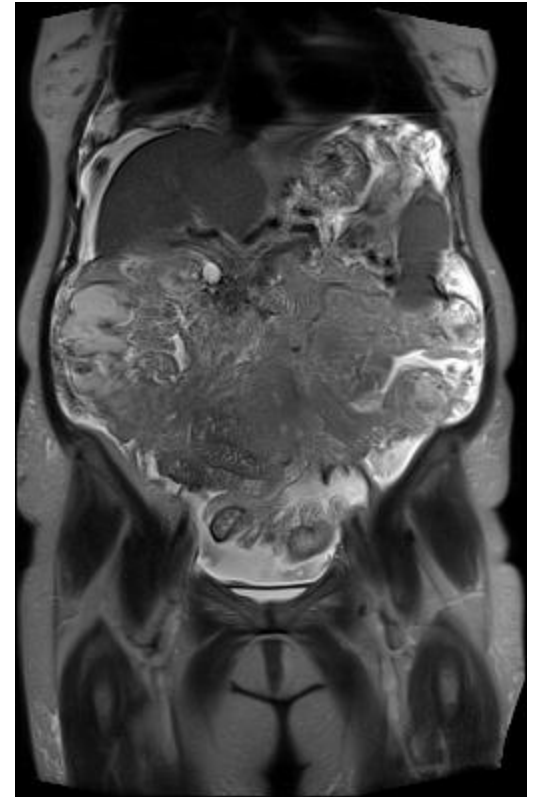
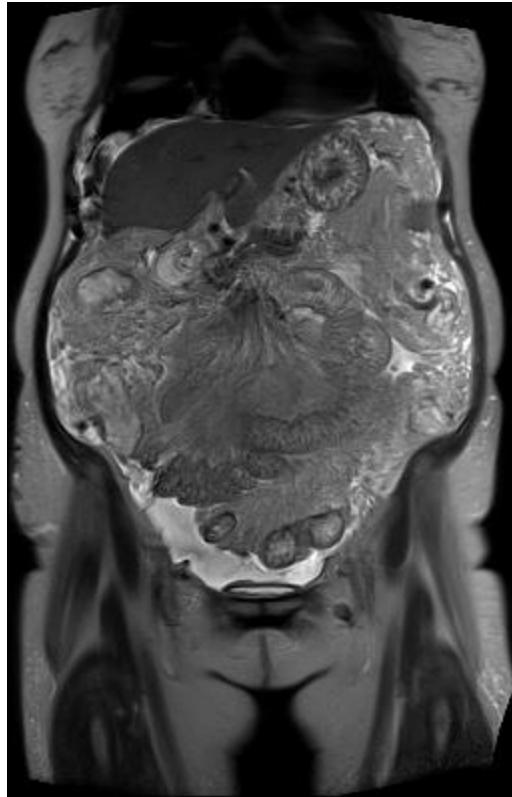


Rejection

- Presented to local emergency room
- Local physician was willing to communicate with us and plan was made
- Steroids were given and biopsy arranged for the following morning
- Phone communication - the distal graft looked “terrible”, more steroids were given and patient was transferred to Nebraska
- Repeat endoscopy confirmed findings of denudation and sloughing, consistent with severe rejection
- Thymoglobulin therapy started

53 year old woman with hepatitis C, small bowel resections due to Crohn's disease leaving 180cm small bowel, renal failure on dialysis for past 2 weeks, JAK-2 mutation

- Cirrhosis confirmed on biopsy and imaging
- Required TPN for the past month, but up until that point was enterally independent
- Living functional life until 10 weeks ago
- Has been on and off anti-coagulation over the past 5 years
- Renal failure thought to be due to hepatorenal
- MELD 39+



T2 weighted images – dark is fluid – notice NO DARK in mesentery

What would you offer this patient?

1. Hospice
2. Isolated liver transplant
3. Liver and small bowel transplant
4. Combined liver and kidney transplant
5. Combined liver, small bowel and kidney transplant
6. Isolated small bowel transplant

What we did

- Listed for liver/small bowel transplant
- Supportive care
- After 10 days on the list developed multisystem organ failure and died while awaiting organs



Summary

- Intestinal transplant volume transiently decreasing
- Survival satisfactory in the short term, steady for the long term
- Multi-disciplinary management of intestinal failure is essential and can help some patients avoid intestinal transplantation
- Cannot ignore concrete indications and we should try and prevent these from happening

So, what should you know

- Patients with intestinal transplants are susceptible to rejection
- Rejection should be diagnosis of exclusion, especially in first few months following transplant
- Early endoscopy with biopsy and communication with intestinal transplant center is highly recommended

So, what should you know

- If rejection is not the problem, viral infections are a serious problem
- Aggressive hydration and even TPN are necessary during recovery
- Viral infections make intestinal transplant recipients susceptible to rejection



