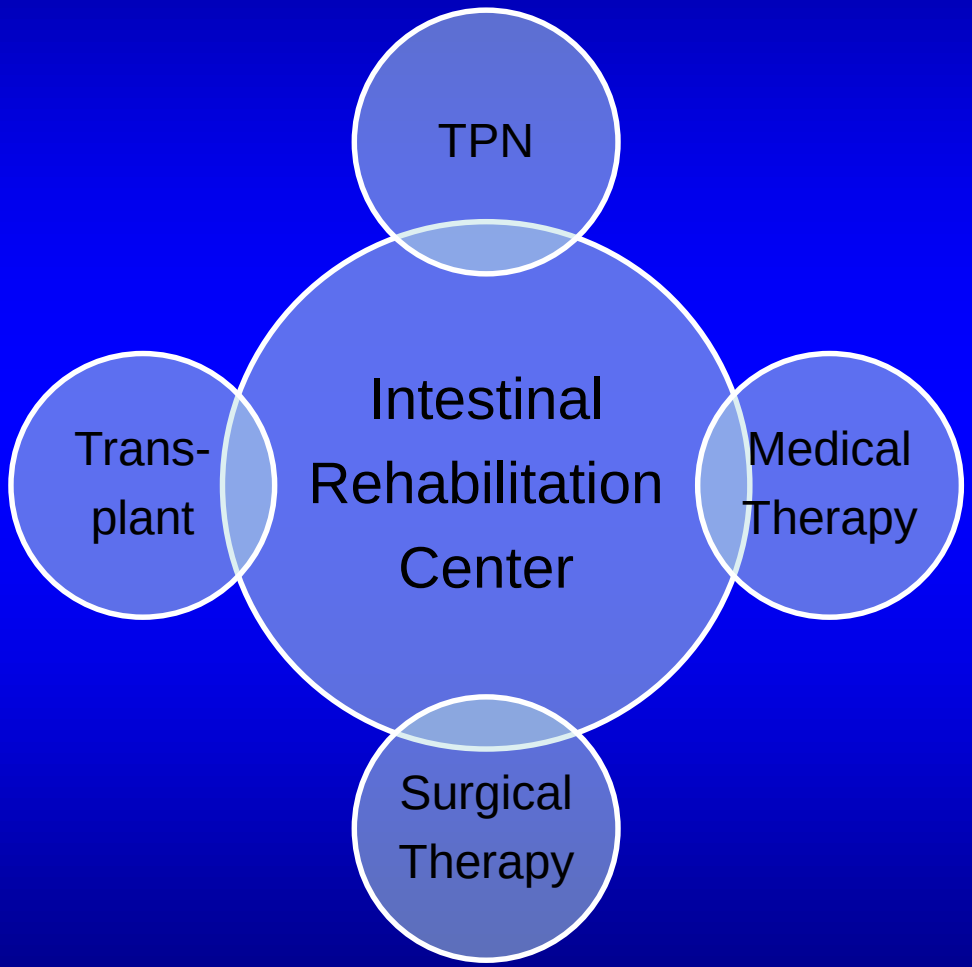
INTESTINAL FAILURE, REHABILITATION & TRANSPLANTATION: Indications, Techniques and Outcomes

Douglas G. Farmer, MD.
Professor of Surgery
Director, Intestinal Transplant Program
Dumont-UCLA Transplant Center
Los Angeles, CA

DISCLOSURES

- Peer-Peer Speakers Bureau for NPS Pharma
- All immunosuppressant drugs used in intestinal transplantation are OFF LABEL
- Most antibiotics used in intestinal transplantation are OFF LABEL


TPN
Trans-
plant
Intestinal
Rehabilitation
Center
Medical
Therapy
Surgical
Therapy

Short Bowel/Gut Syndrome

Short Bow  t Syndrome

DEFINITIONS

Intestinal Failure

Condition resulting “from obstruction, dysmotility, surgical resection, congenital defect, or disease associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balance”.

Intestinal Failure
Functional Causes

- Chronic Intestinal Pseudo-obstruction
- Adhesions
- Fistulae

Intestinal Failure
Mucosal Causes

- Microvillous inclusion disease
- Tufting enteropathy
- Congenital neuroendocrinopathy

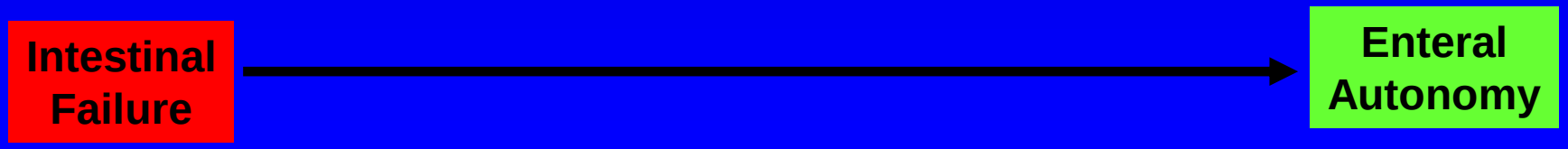
Intestinal Failure
Surgical Causes (ADULT)

- IBD
- Trauma
- Volvulus
- Mesenteric venous thrombosis
- Mesenteric arterial thrombosis
- Embolic phenomenon
- XRT
- Adhesions
- Fistulae
- Tumor (GIST, Desmoid; FAP)

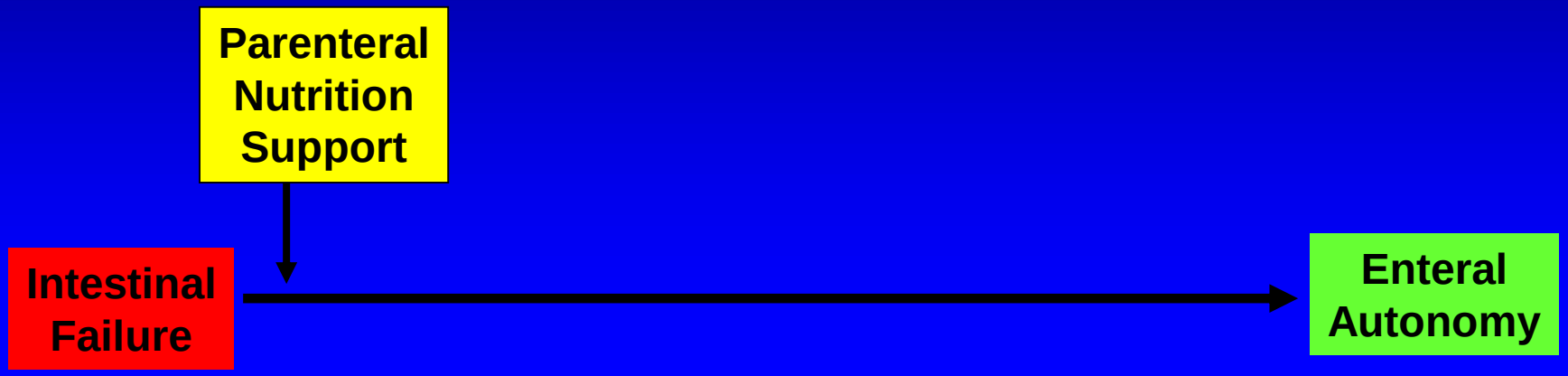
Intestinal Failure
Surgical Causes (CHILDREN)

- In utero volvulus
- JI atresia
- Gastroschisis
- Omphalocele
- Meconium ileus
- Hirschsprungs Disease
- NEC
- Post-Natal volvulus
- Pseudoobstruction

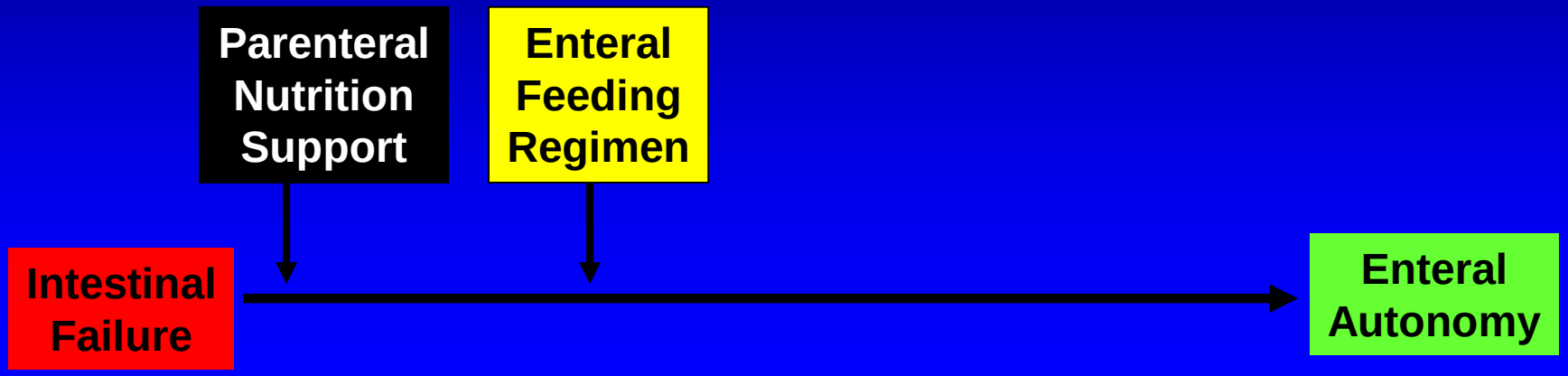
The Journey



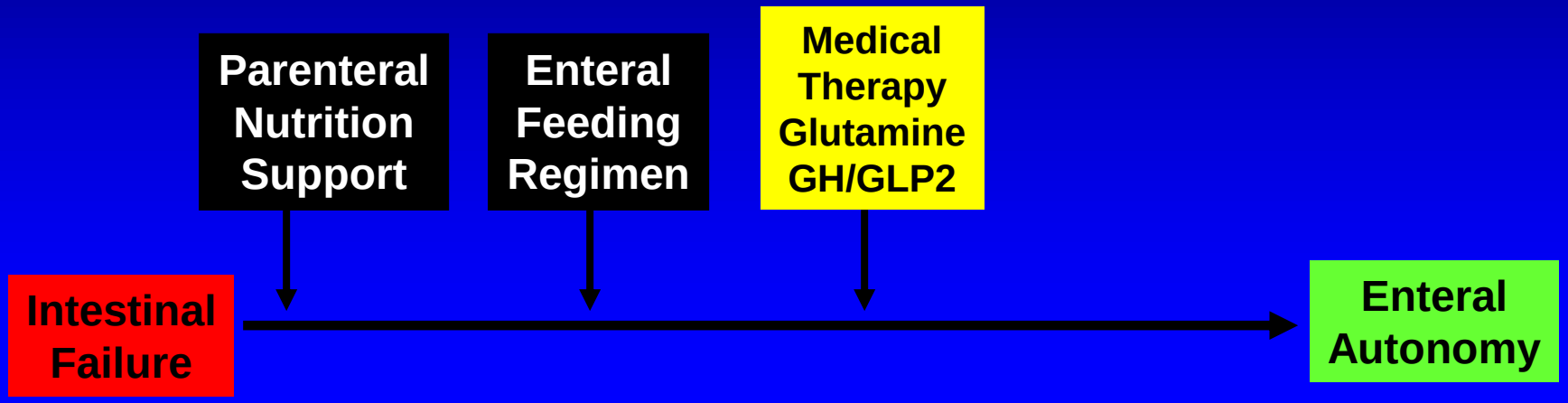
The Journey


Parenteral Nutrition Support
Intestinal Failure
Enteral Autonomy

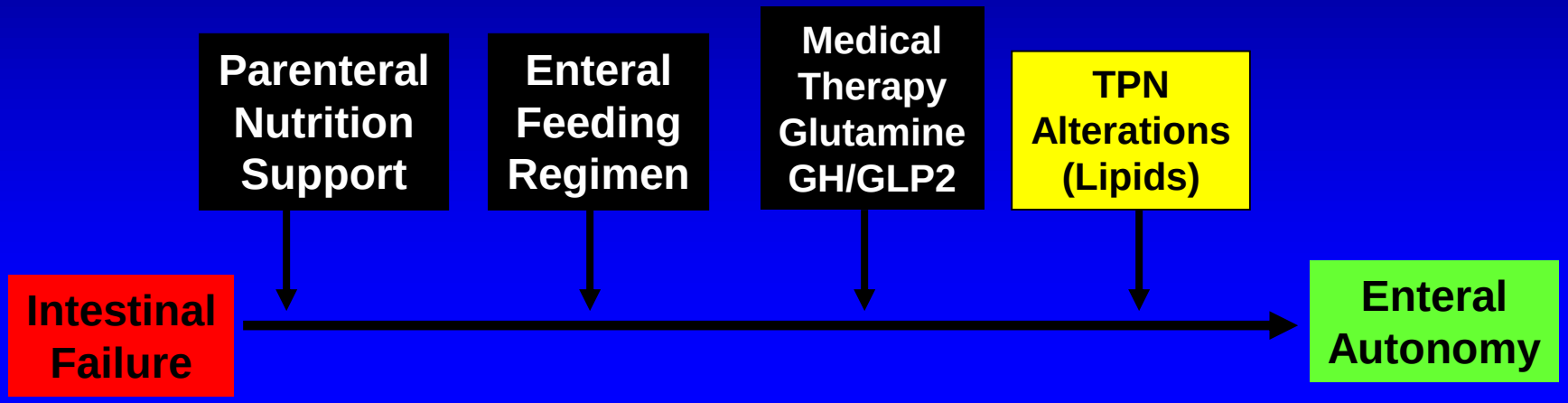
The Journey


Parenteral Nutrition Support
Enteral Feeding Regimen
Intestinal Failure
Enteral Autonomy

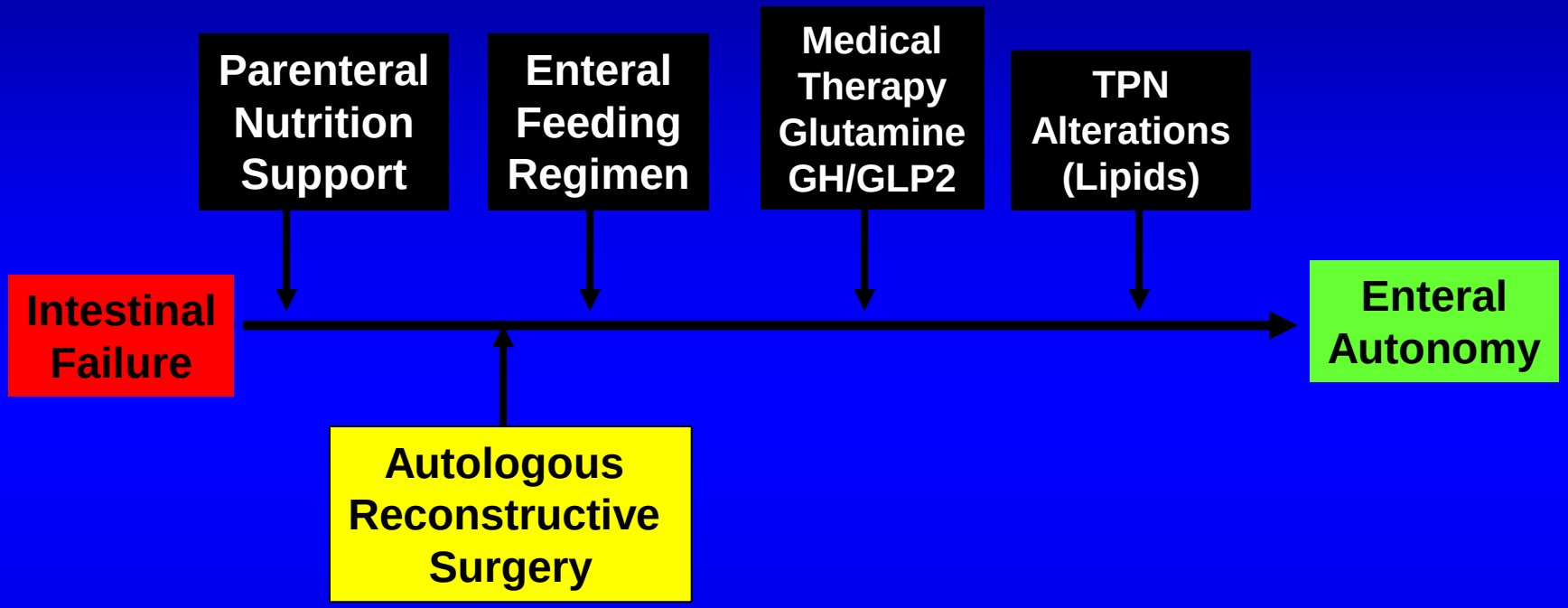
The Journey


Parenteral Nutrition Support
Enteral Feeding Regimen
Medical Therapy Glutamine GH/GLP2
Intestinal Failure
Enteral Autonomy

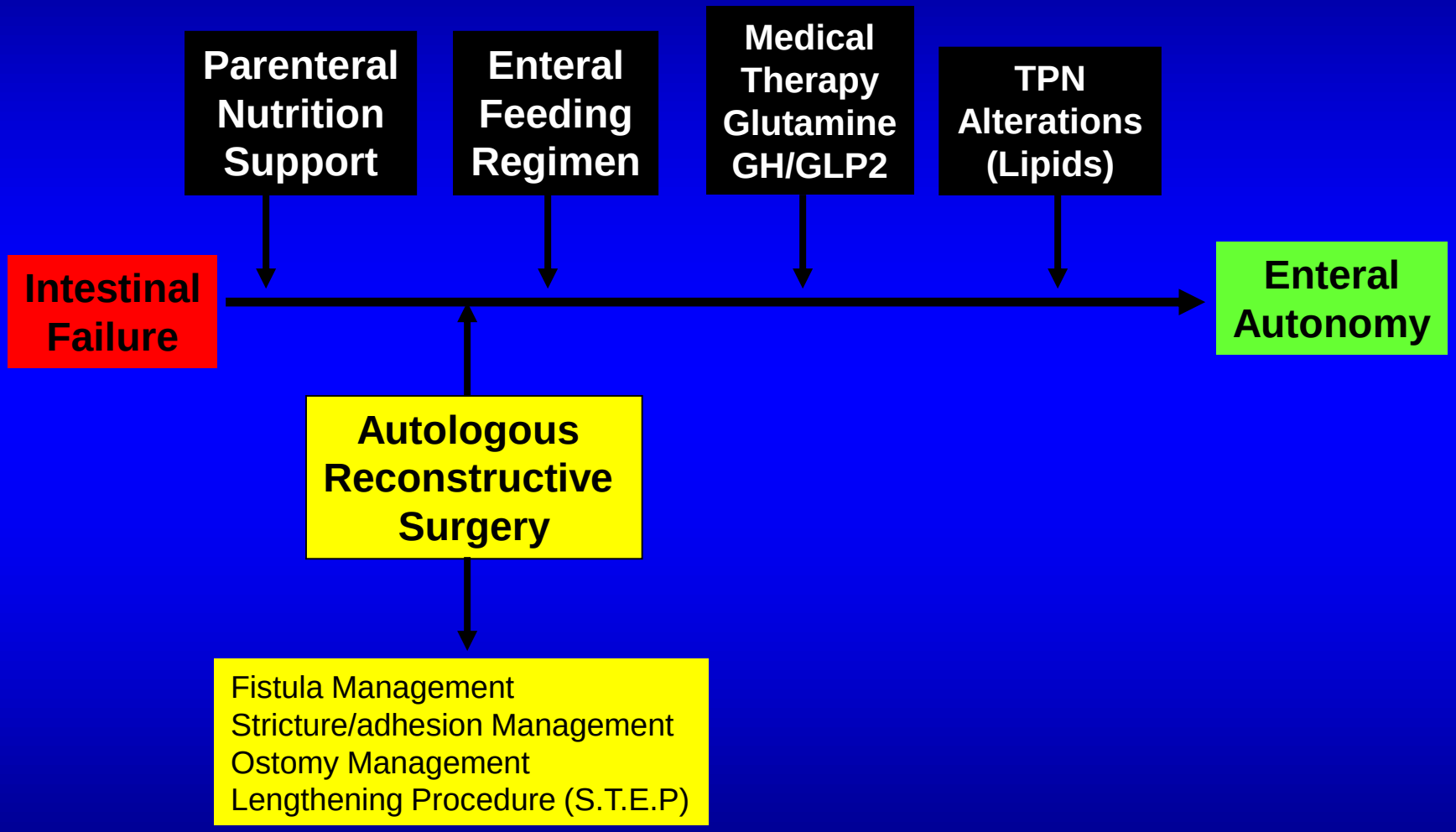
The Journey


Parenteral Nutrition Support
Enteral Feeding Regimen
Medical Therapy Glutamine GH/GLP2
TPN Alterations (Lipids)
Intestinal Failure
Enteral Autonomy

The Journey


Parenteral Nutrition Support
Enteral Feeding Regimen
Medical Therapy Glutamine GH/GLP2
TPN Alterations (Lipids)
Intestinal Failure
Enteral Autonomy
Autologous Reconstructive Surgery

The Journey


Parenteral Nutrition Support
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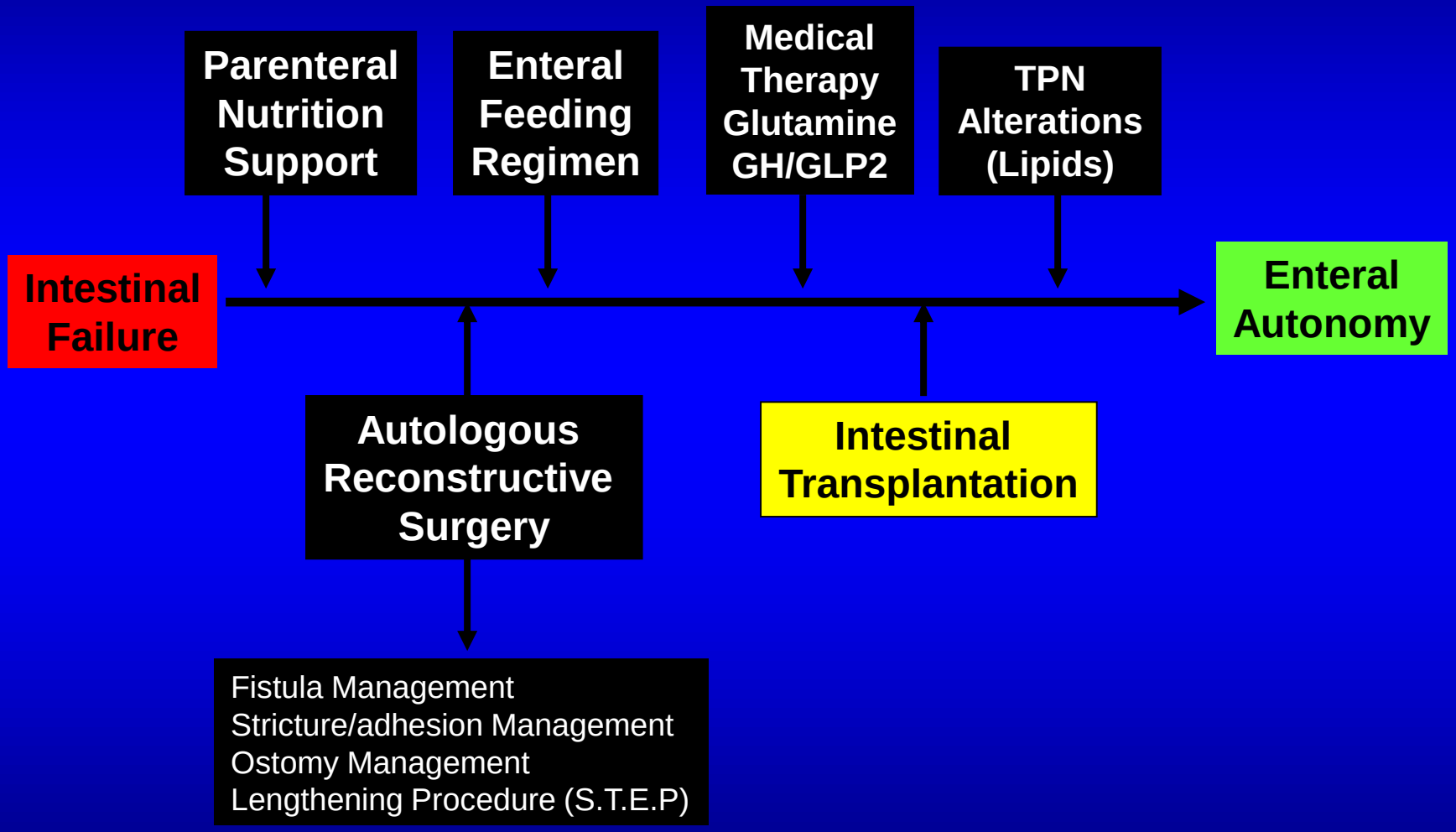
TPN Alterations (Lipids)
Intestinal Failure
Enteral Autonomy
Autologous Reconstructive Surgery
Fistula Management
Stricture/adhesion Management
Ostomy Management
Lengthening Procedure (S.T.E.P)

The Journey


Parenteral Nutrition Support
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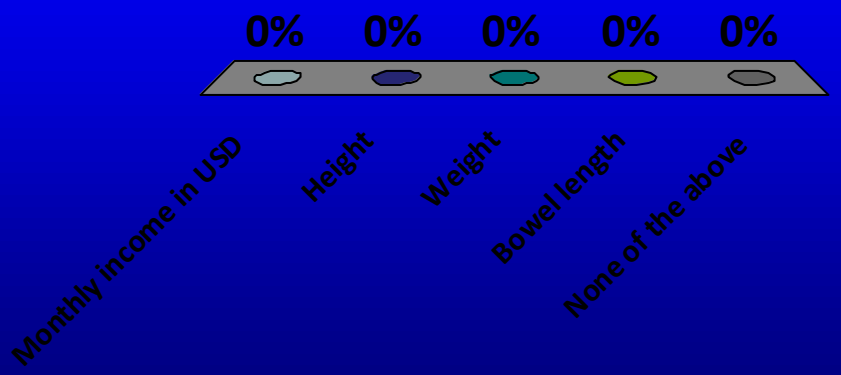
Medical Therapy Glutamine GH/GLP2
TPN Alterations (Lipids)
Intestinal Failure
Enteral Autonomy
Autologous Reconstructive Surgery
Intestinal Transplantation
Fistula Management
Stricture/adhesion Management
Ostomy Management
Lengthening Procedure (S.T.E.P)

Parenteral Nutrition Support

Predictor(s) of survival on TPN include:

A. Monthly income in USD
B. Height
C. Weight
D. Bowel length
E. None of the above



LONG-TERM PARENTERAL NUTRITIONAL SUPPORT AND INTESTINAL ADAPTATION IN CHILDREN WITH SHORT BOWEL SYNDROME: A 25-YEAR EXPERIENCE

RUBÉN E. QUIRÓS-TEJEIRA, MD, MARVIN E. AMENT, MD, LAURIE REYEN, RN, FAYE HERZOG, RN, MICHELLE MERJANIAN, MD, NANCY OLIVARES-SERRANO, MD, AND JORGE H. VARGAS, MD

Objective To analyze the outcome of children with short bowel syndrome (SBS) who required long-term parenteral nutrition (PN).

Study design Retrospective analysis of children (n = 78) with SBS who required PN >3 months from 1975 to 2000. Statistics: univariate analysis, Kaplan-Meier method, and Cox proportional regression model were used.

Results We identified 78 patients. Survival was better with small bowel length (SBL) >38 cm, intact ileocecal valve (ICV), intact colon, takedown surgery after ostomy (all $P < .01$), and primary anastomosis ($P < .001$). PN-associated early persistent cholestatic jaundice ($P < .001$) and SBL of <15cm ($P < .01$) were associated with a higher mortality. Intestinal adaptation was less likely if SBL <15 cm ($P < .05$), ICV was removed, colonic resection was done (both $P < .001$), >50% of colon was resected ($P < .05$), and primary anastomosis could not be accomplished ($P < .01$). Survival was 73% (57), and 77% (44) of survivors had intestinal adaptation.

Conclusions SBL, intact ICV, intestinal continuity, and preservation of the colon are important factors for survival and adaptation. Adaptation usually occurred within the first 3 years. Need for long-term PN does not preclude achieving productive adulthood. Patients with ICV even with <15 cm of SBL and patients with SBL >15 cm without ICV have a chance of intestinal adaptation. *(J Pediatr 2004;145:157-63)*

OUTCOME PREDICTORS

SURVIVAL

- SMALL BOWEL LENGTH
- ILEOCECAL VALVE
- COLONIC RESECTION
- ENTEROSTOMA
- PN COMPLICATIONS
- PN LIVER DISEASE

ADAPTATION

- SMALL BOWEL LENGTH
- ILEOCECAL VALVE
- COLONIC RESECTION
- ENTEROSTOMA
- CHOLECYSTECTOMY
- #INFECTIONS
- TIME ON TPN

TPN Complications

Catheter Sepsis
Catheter Occlusion
Vascular thrombosis
Cholelithiasis
Liver Disease
Bone Disease
Nephrolithiasis
Renal Function
Death

Survival on TPN

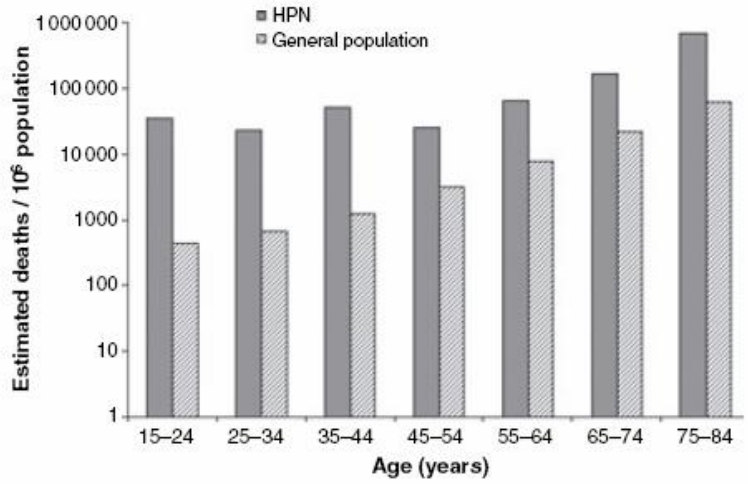


Figure 1. Mortality rates of patients receiving HPN compared with general population.

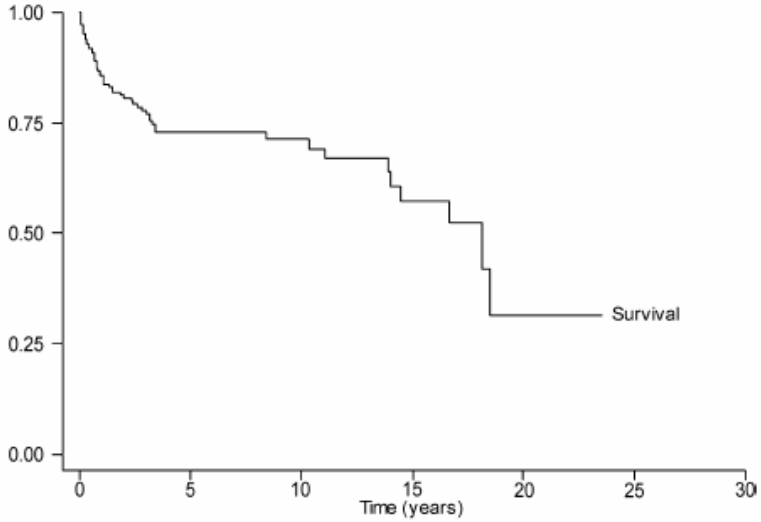


Figure 2. Kaplan–Meier plot of survival.

Aliment Pharmacol Ther 2006

Medical Therapies

Glutamine and Growth Hormone

"In the last decade, most IF research has been focused on exploring the potential of these substances as supportive IF treatment. However, clinical trials so far have ***not demonstrated reproducible or meaningful*** clinical benefits with the use of glutamine or growth hormone."

C. Tee, K. Wallis, S. Gabe, Clin Exp Gastro 2011

Glucagon-like Peptide-2

- Naturally occurring GI hormone
- Secreted by enteroendocrine L cells
  - Ileum and colon
  - Stimulators: fiber, SCFA, CHO, fat
- Trophic hormone
  - Enhances digestion
  - Enhances absorption
  - Increased mucosal mass
- Short half life: 7 minutes

Clin Exp Gastro 2011

Teduglutide (Gattex®)

- Modified GLP-2
  - Glycine substitution to prevent rapid inactivation by dipeptidyl peptidase IV (DPPIV)
  - Extends half life
  - Greater biologic potency
- NPS Pharma (Bedminster, NJ)
- FDA approval for SBS in December 2012

Glucagon-like Peptide 2 (GLP2)

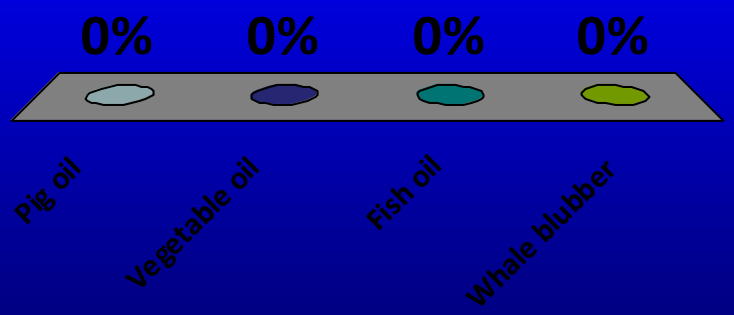
REF	N	OUTCOME
Gut 2011	83 (32 HD) (35 LD) (16 PD)	HD: no significant effect @ 20/24 wk LD: 16/35 RR (p=0.007) PD: 1/16 RR
CEG 2011 (unpublished extension study)	65 pt	LD: 75% sustained RR @ 1yr HD: 75% sustained RR @ 1yr PD-LD: 100% RR PD-HD: 28% RR
STEPS (unpublished Phase 3)	86	LD: 63% (27/42) RR @ 24 wk PD: 30% (13/43) RR @ 24 wk

HD= 0.1 mg/kg/d; LD 0.05 mg/kg/d; PD PLACEBO

TPN Alterations to Minimize Complications

Omegaven® is derived from?

A. Pig oil
B. Vegetable oil
C. Fish oil
D. Whale blubber



Fish Oil Emulsions
Omegaven®

Not US FDA Approved

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

Kara Calkins*[1], Stephen Shew[2], James Dunn[2], Douglas Farmer[2], and Robert Venick[1,2]

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

*Supported by NIH grant T32GM75776-6

Study Design

INCLUSION CRITERIA

- Clinical evidence of IFALD
- Direct bilirubin (DB) ≥ 2 mg/dL
- Expected Parenteral Nutrition (PN) course > 30 d
- > 2 weeks of age, < 18 years
- > 60% kcal from PN

EXCLUSION CRITERIA

- Inborn error of metabolism
- ECMO
- Seafood, egg or Omegaven™ allergy
- Liver disease other than IFALD
- Fatal chromosomal disorder
- Unable to obtain consent or tolerate laboratory draws

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

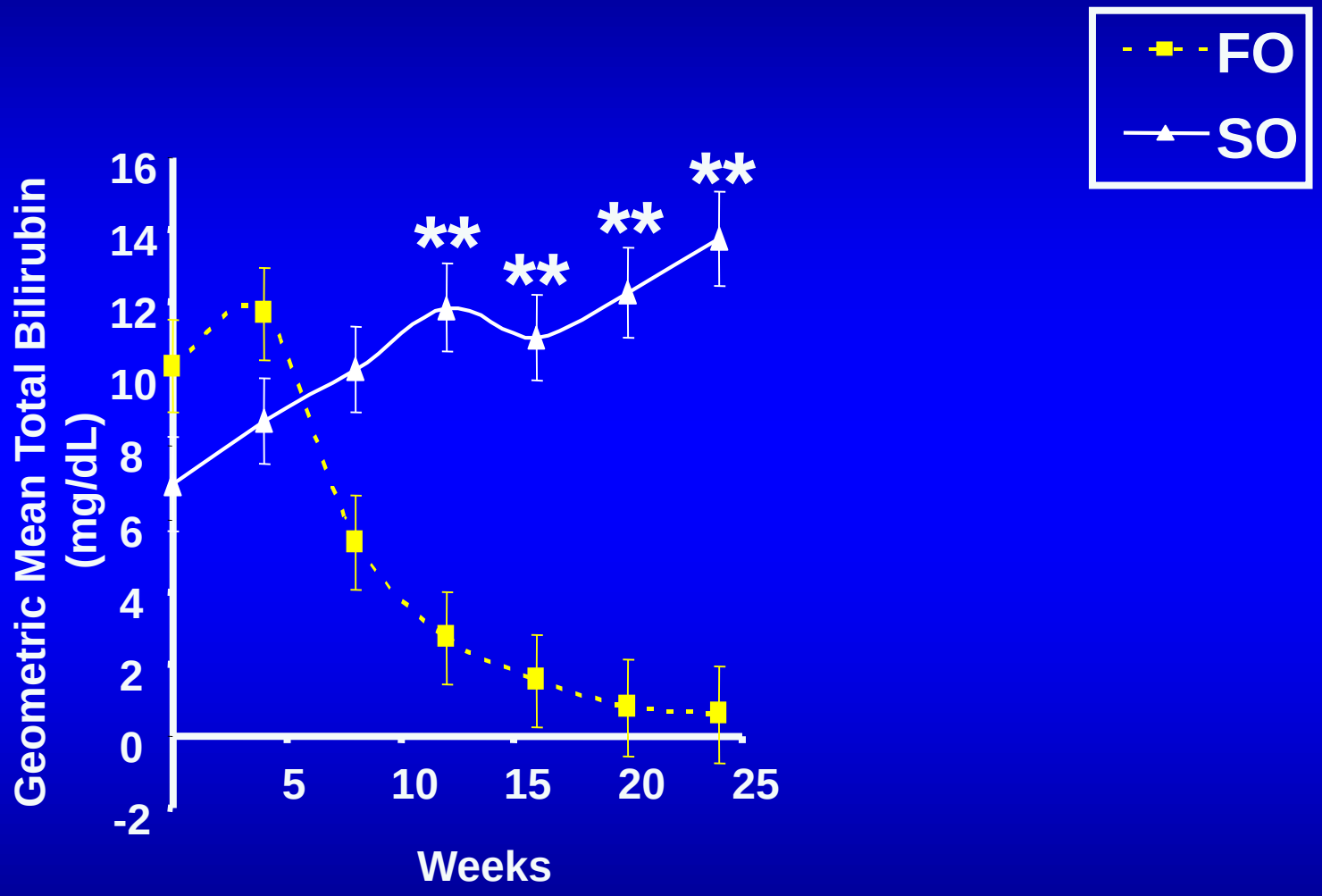
Demographics

	FO	SO	p-value
Age at Start of Study (d)	148.9±99.5	172±245.8	0.29
Age at End of Study (d)	282.7±119.4	324.8±250.5	0.66
Gestational Age (weeks)	33.8±4.2	34.0±3.8	0.90
Birth Weight (kg)	2.2±0.6	2.2±0.8	0.85
Male	3	13	0.12

Baseline GI Characteristics

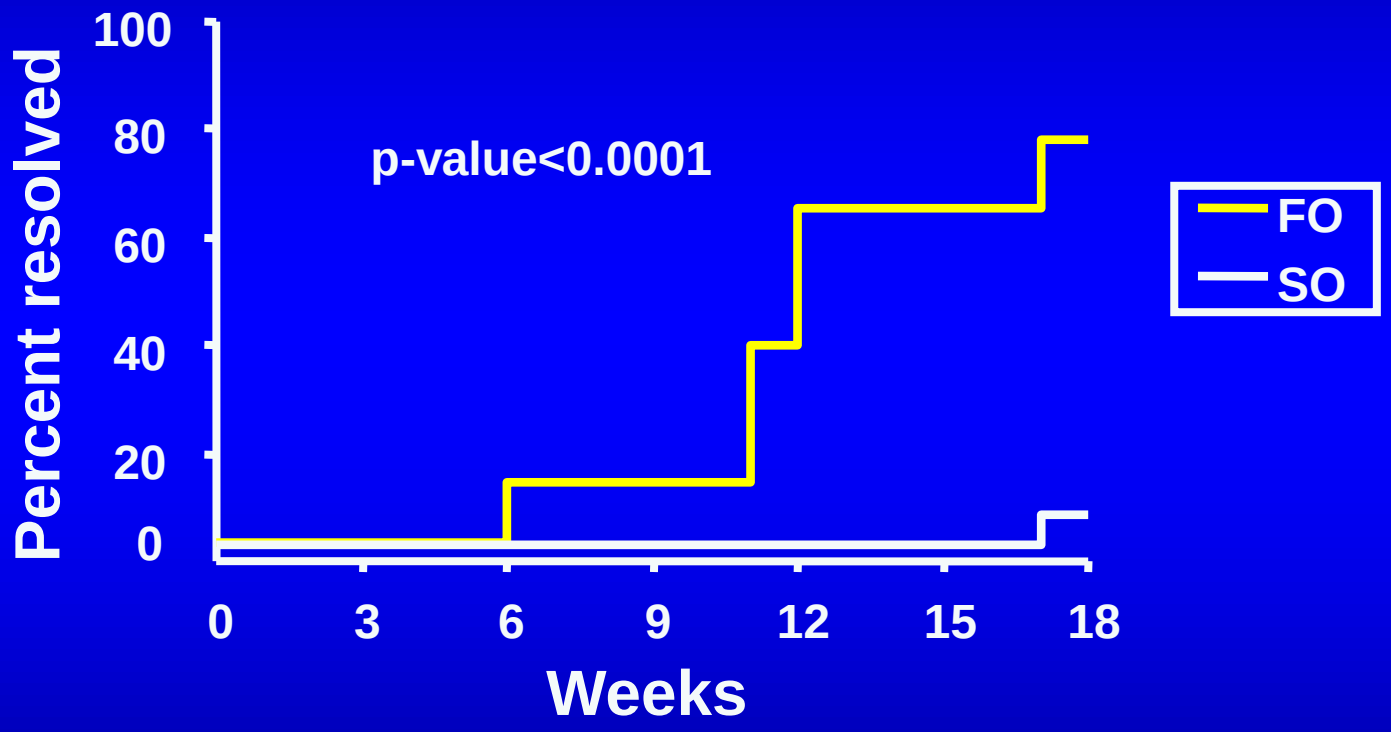
	FO	SO	p-value
GI diagnosis			0.37
gastroschisis	4	8	
NEC	2	4	
atresia	2	5	
Small bowel length (cm)	25±19	27±17.8	0.78
Ileocecal Valve	6	11	0.13
100% colon	7	11	0.69
Small bowel connected to colon	7	11	0.69

BILIRUBIN



**p-value<0.0001

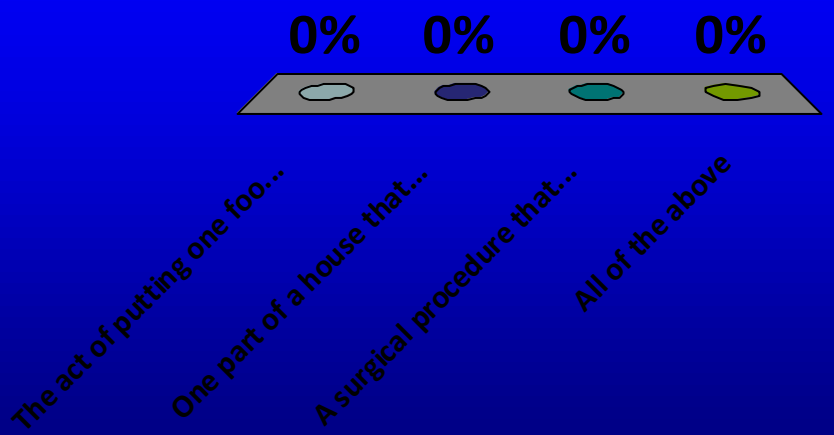
Time to Resolution of Cholestasis



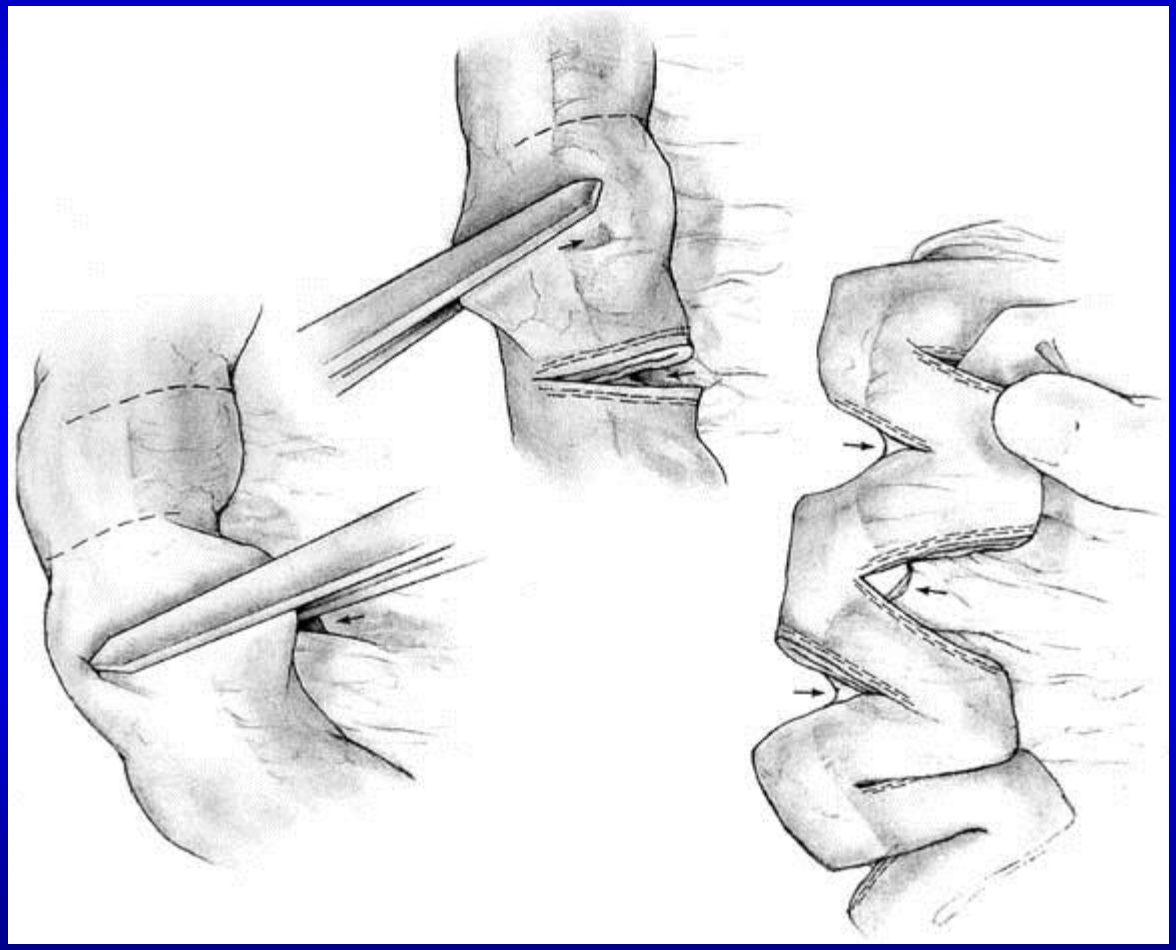
STEP

STEP means:

A. The act of putting one foot in front of the other
B. One part of a house that allows access to the upper floors
C. A surgical procedure that lengthens the intestine
D. All of the above

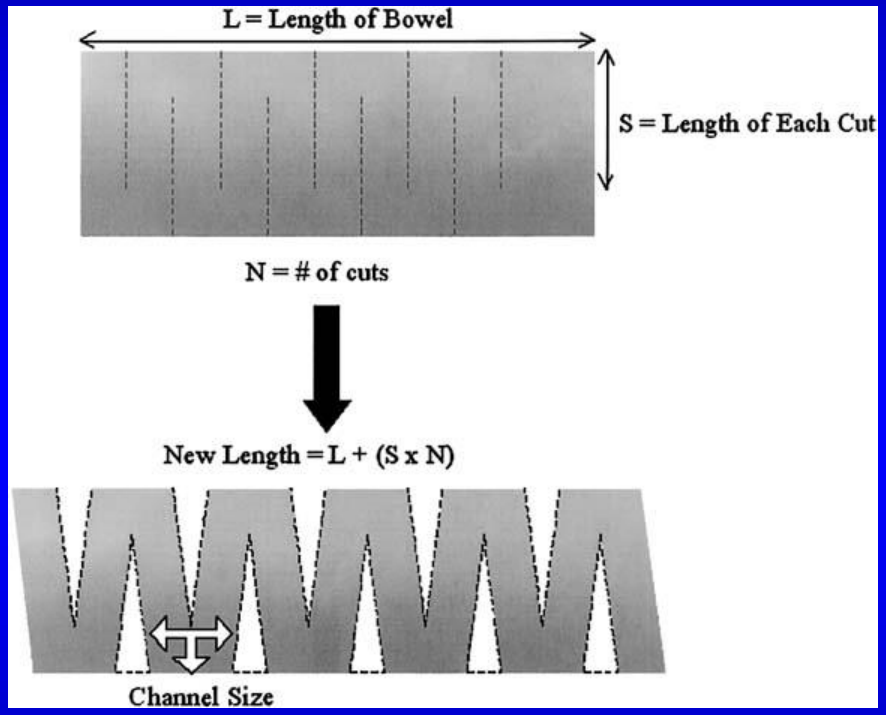


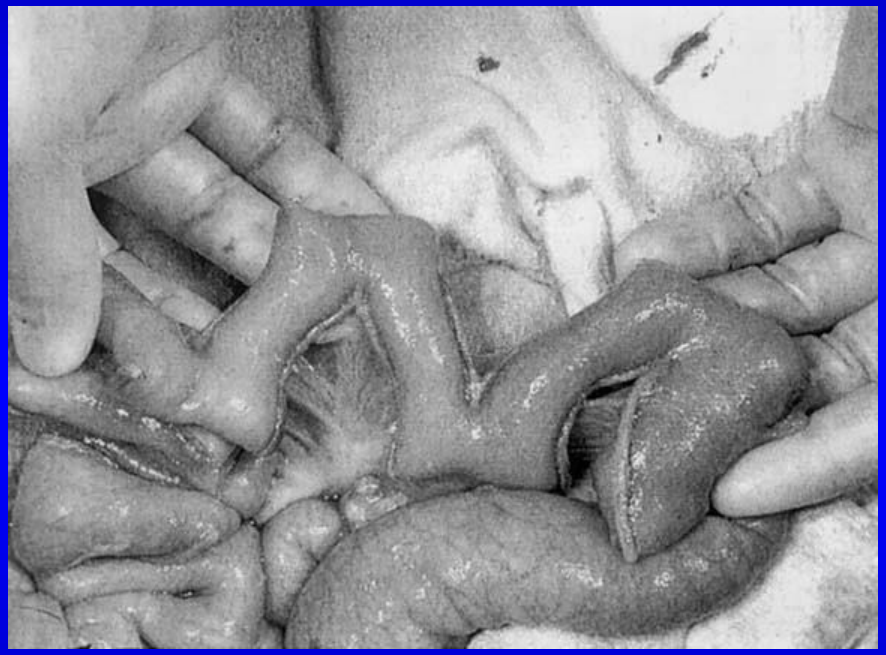
STEP



Kim et al., JPS 2003

STEP


L = Length of Bowel
S = Length of Each Cut
N = # of cuts
New Length = L + (S x N)
Channel Size



International STEP Registry Data

HB Kim, MD
Boston Children's Hospital

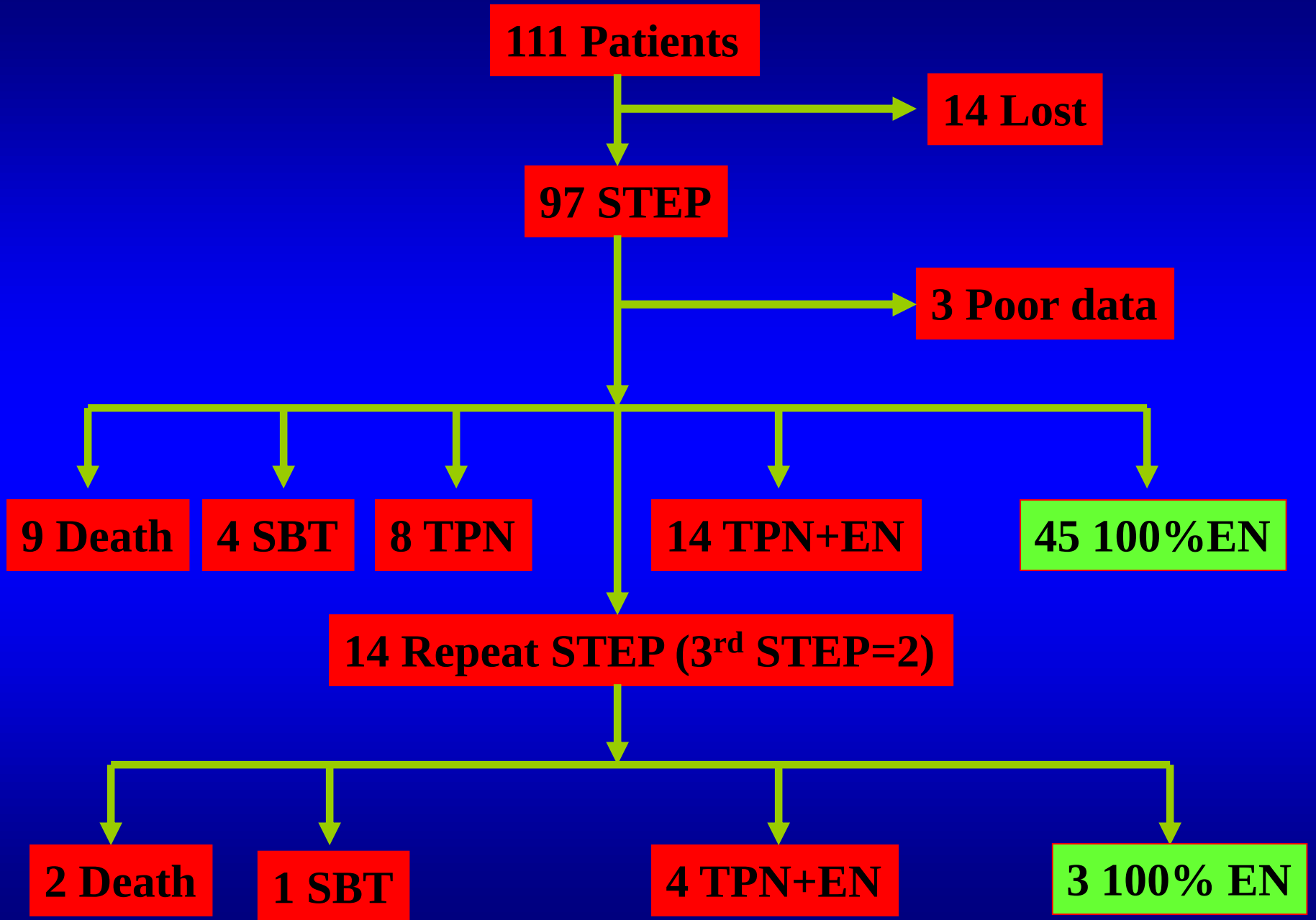
Pediatric Intestinal Failure and Rehabilitation Symposium (PIFRS)

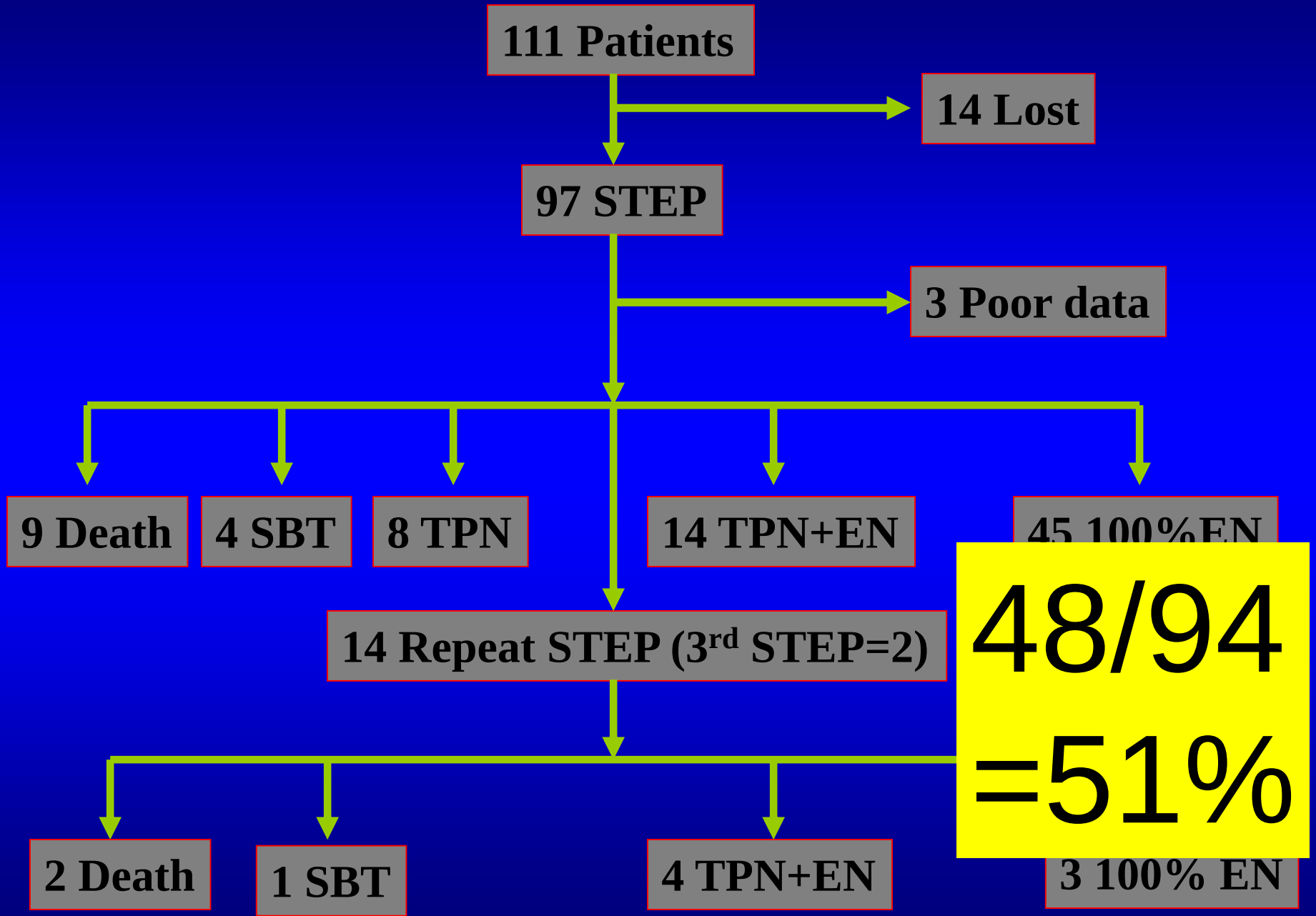
Chicago, IL 2010

STEP Registry

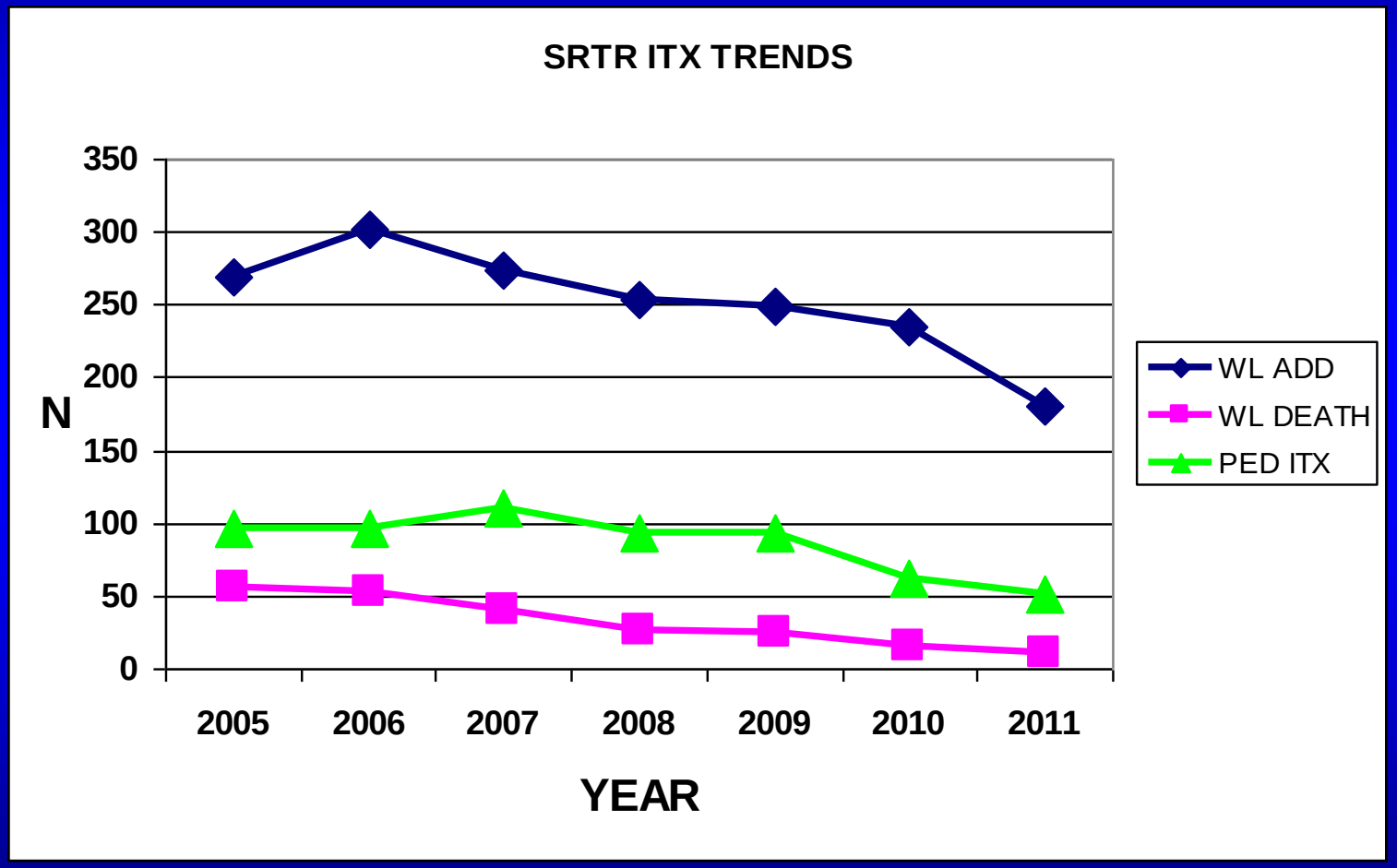
- 111 patients
- 9/2004 – 1/2010
- 50 worldwide centers

HB Kim, MD


111 Patients
14 Lost
97 STEP
3 Poor data
9 Death
4 SBT
8 TPN
14 TPN+EN
45 100%EN
14 Repeat STEP (3rd STEP=2)
2 Death
1 SBT
4 TPN+EN
3 100% EN


111 Patients
14 Lost
97 STEP
3 Poor data
9 Death
4 SBT
8 TPN
14 TPN+EN
45 100%EN
14 Repeat STEP (3rd STEP=2)
48/94
=51%
2 Death
1 SBT
4 TPN+EN
3 100% EN

EFFECT?


SRTR ITX TRENDS
350
300
250
200
150
100
50
0
N
2005
2006
2007
2008
2009
2010
2011
YEAR
WL ADD
WL DEATH
PED ITX

Transplantation

July. 28. 2009. 7AM. At UCLA
Mr. WanChao Wu had a small bowel
transplant by Dr. Farmer. & his team

Intestinal Transplantation Indications

Irreversible **Intestinal Failure** associated with one or more life-threatening complications:

- Liver Disease
- Loss Vascular Access
- Recurrent Catheter Sepsis
- Complex fluid and electrolyte management
- Non-reconstructible GI Tract

Intestinal Transplantation Graft Options

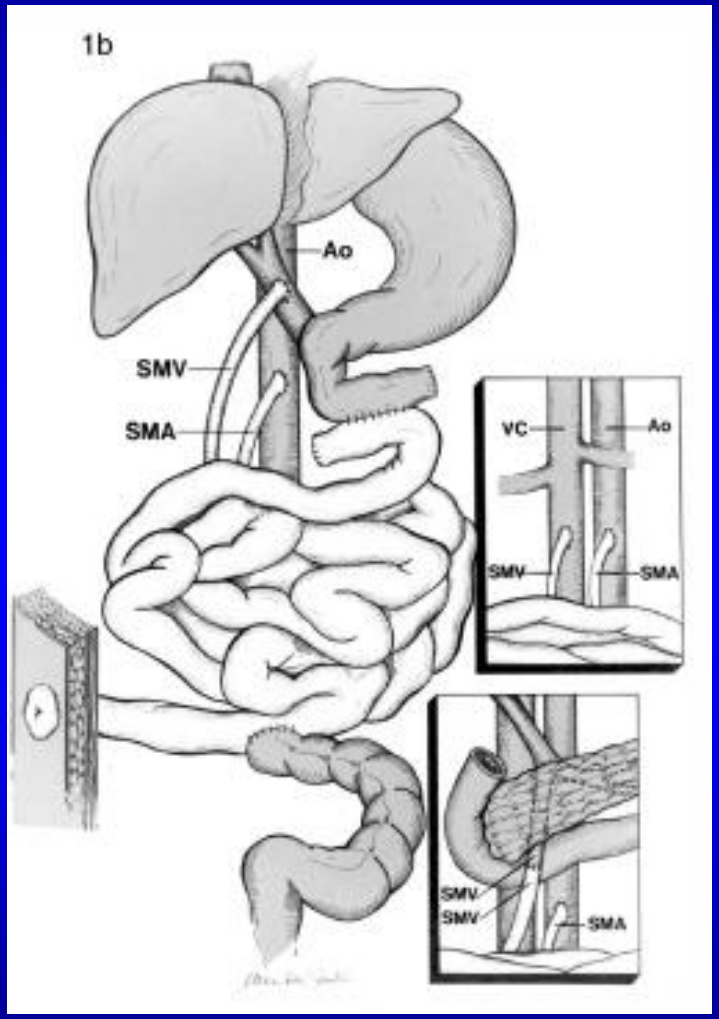
CORE OPTIONS

1. Isolated Intestine
2. Liver Intestine
3. Multivisceral
4. Modified Multivisceral
5. Isolated Liver

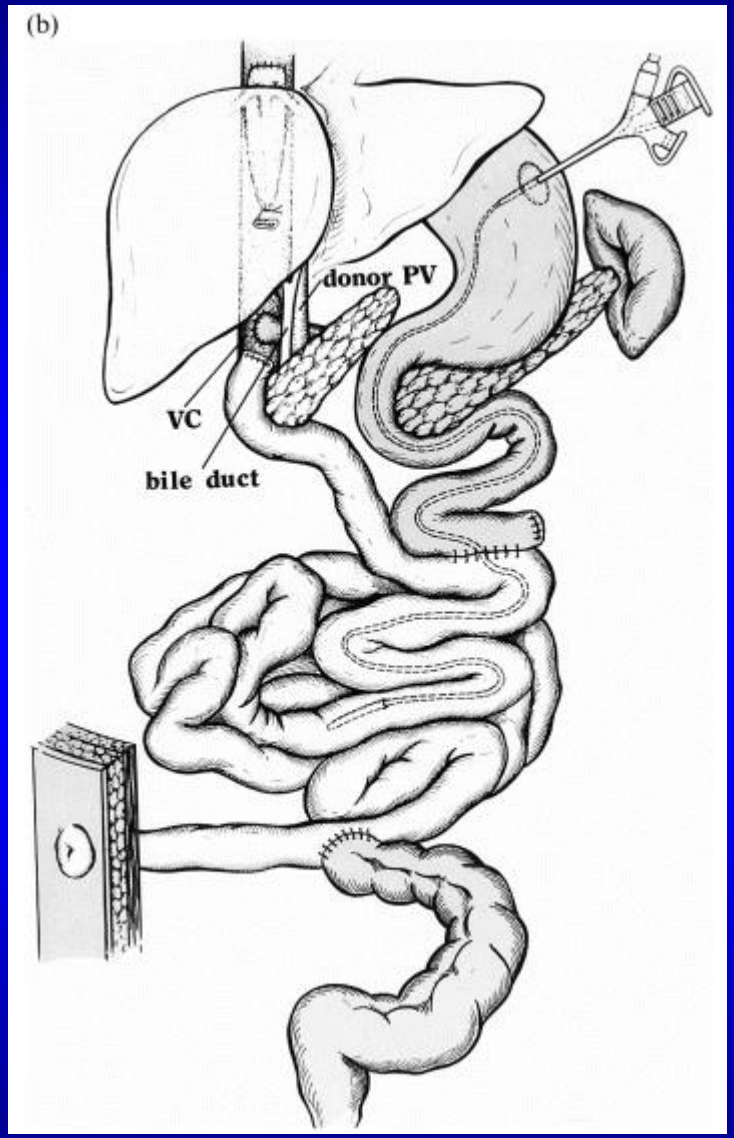
ACCESSORY OPTIONS

1. Stomach
2. Pancreas
3. Colon
4. Kidney

Isolated Intestine Implantation



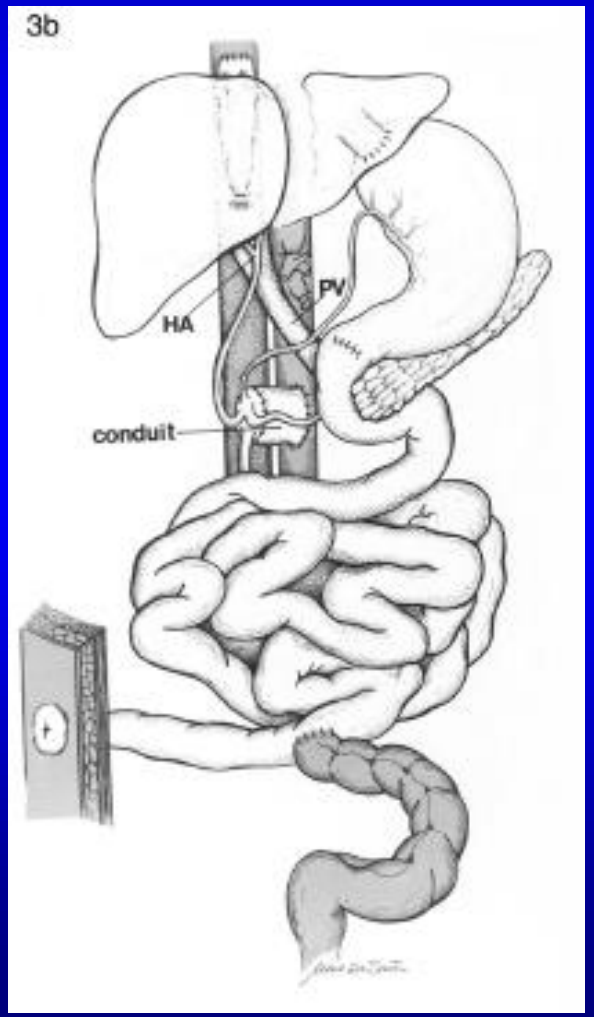
WJS 2002



COMBINED LIVER-INTESTINAL IMPLANTATION

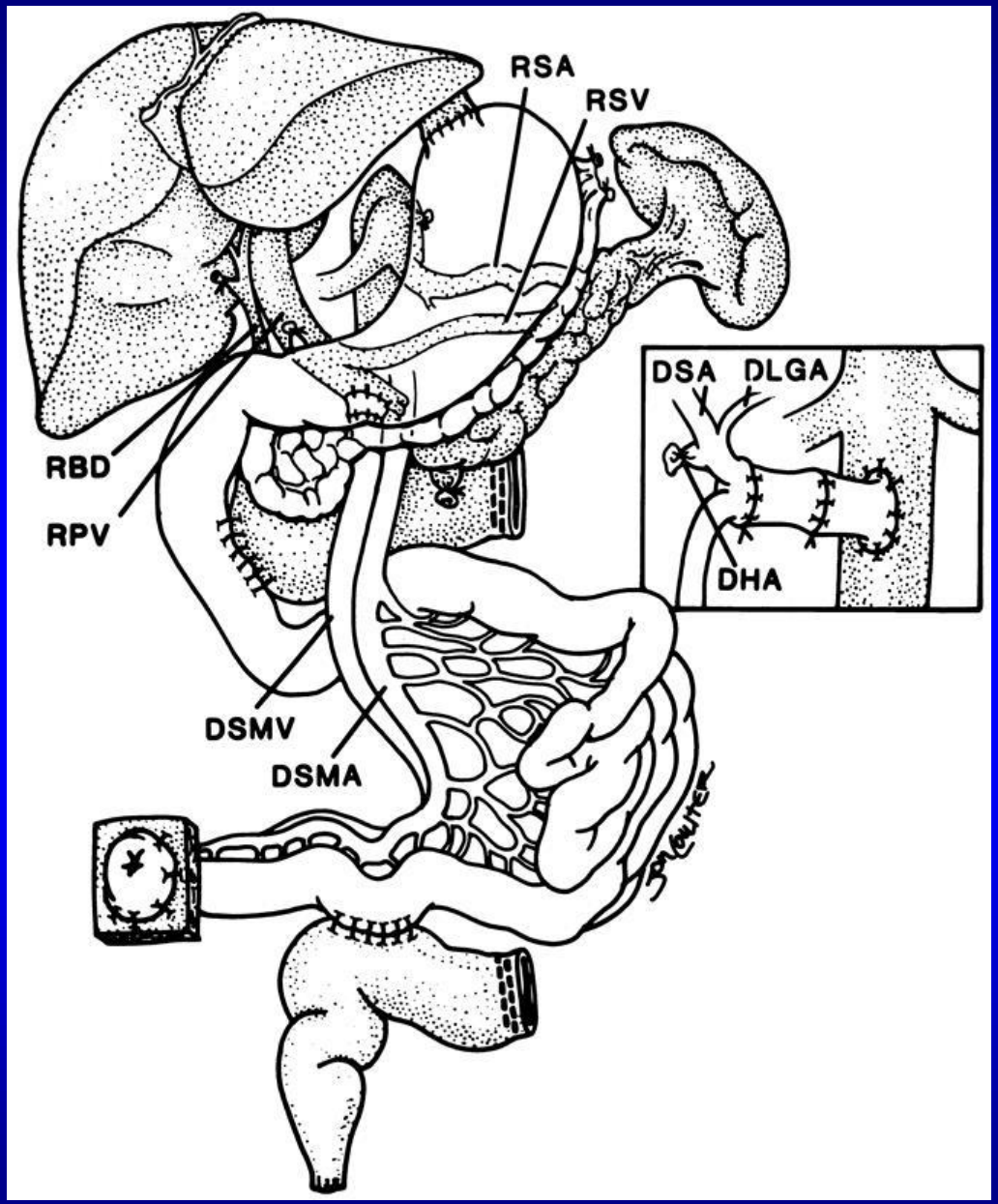
Miami Ped Transpl 1999

Multivisceral Implantation



WJS 2002

Modified Multivisceral Implantation



Ann Surg 2001

Pretransplant Predictors of Survival After Intestinal Transplantation: Analysis of a Single-Center Experience of More Than 100 Transplants

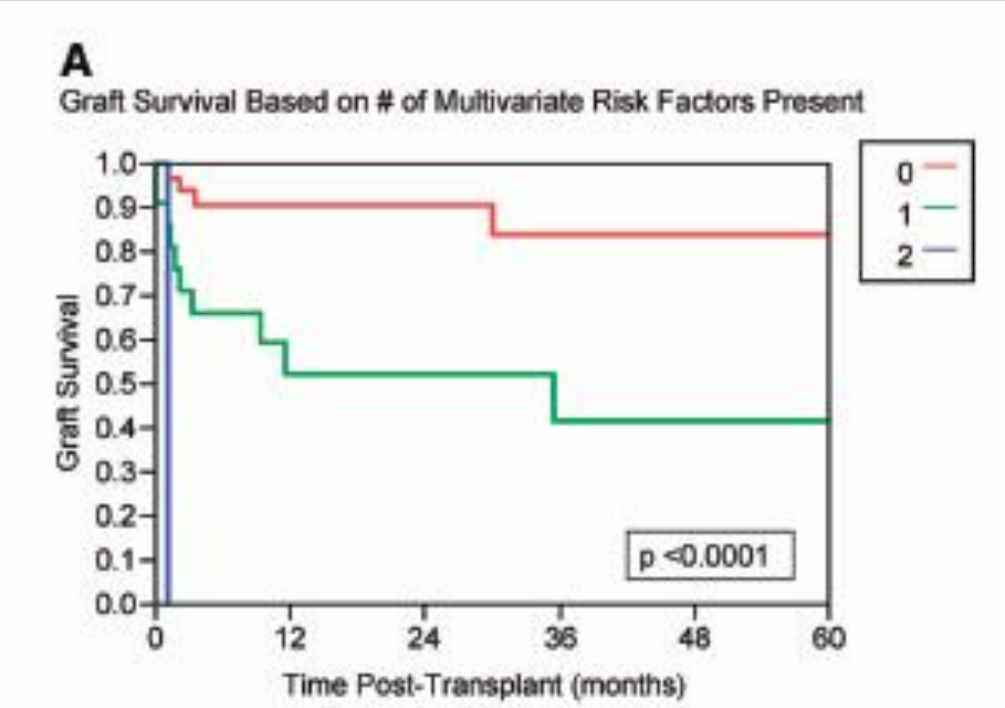
Douglas G. Farmer,[1,7] Robert S. Venick,[2] Joanie Colangelo,[1] Yvonne Esmailian,[1] Hasan Yersiz,[1] John P. Duffy,[1,3] Galen R. Cortina,[4] Kanela Artavia,[5] Khiet Ngo,[2,6] Suzanne V. McDiarmid,[2] and Ronald W. Busuttil[1]

Introduction. Outcomes after intestinal transplantation (ITx) have steadily improved. There are few studies that assess factors associated with these enhanced results. The purpose of this study was to examine peri-ITx variables and survival.
Methods. A review of a prospectively maintained database was undertaken and included all patients undergoing ITx from 1991 to 2010. The study endpoints were patient and graft survival. Data collection included 44 variables. Survival was computed using Kaplan-Meier methods. Univariate analysis was conducted (log-rank test) with significance set at *P* less than or equal to 0.20. Multivariate analysis of significant variables was conducted using model reduction by backward elimination variable selection method with significance set at *P* less than 0.05.
Results. Eighty-eight patients received 106 ITx. The majority of recipients were male, Latino, and children. The leading causes of intestinal and liver failure were gastroschisis and parenteral nutrition. Grafts transplanted were isolated intestine (24%), liver-intestine (62%), and multivisceral (14%). Overall 1- and 5-year patient and graft survival were 80% and 65%, and 74% and 64%, respectively. Significant univariate survival predictors were weight less than 20 kg, children, liver-inclusive allograft, panel reactive antibody less than 20%, absence of donor-specific antibody, negative crossmatch, warm ischemia time less than 60 min, absence of recipient splenectomy, interleukin-2 receptor antagonist induction, and era. Significant multivariate survival predictors were absence of donor-specific antibody, absence of recipient splenectomy, and liver-inclusive graft type.
Conclusion. This large, single-center ITx experience confirms a marked improvement in outcome over time. Several important factors were associated with survival, and these factors can potentially be adjusted before ITx. These findings should refocus future efforts on strategies to improve treatment and prevent graft loss.

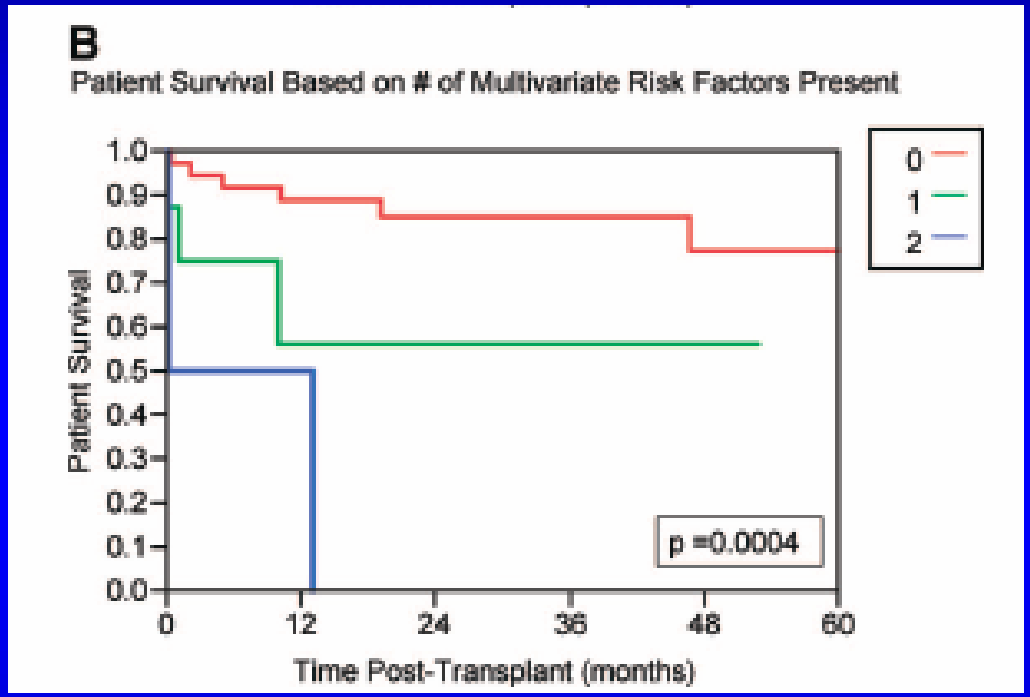
Keywords: Intestinal transplantation, Small bowel transplantation, Multivisceral transplantation, Outcomes.

(*Transplantation* 2010;90: 1574–1580)

XXIIth International Congress of the Transplantation Society
Vancouver, BC, August 2010



0 = No risk factors
1 = DSA+ OR non-Liver graft
2 – DSA+ AND non-liver graft



0 = No risk factors
1 = DSA+ OR splenectomy
2 – DSA+ AND splenectomy

The liver, spleen and preformed antibodies are important predictors of survival after intestinal transplantation: Analysis of a single center, 20 year experience

Douglas G Farmer, Robert S Venick, Laura Wozniak, Yvonne E Esmailian, Hasan Yersiz, Kanela Artavia, Laurie Reyen, Susan Ponthieux, Erin Core, Villy Hwang, Anna Zafar, Galen Cortina, Sue V McDiarmid, Ronald W Busuttil

Intestinal Transplant Program
Dumont UCLA Transplant Center

XIth International Small Bowel Transplant Symposium
Washington, DC, September 2011

Predictors of outcome after intestinal transplantation: An analysis of over 125 cases at a single center

Douglas G. Farmer, Laura J. Wozniak, Susan Ponthieux, Villy Hwang, Kanela Artavia, Elizabeth A. Marcus, Vatche G. Agopian, Ali Zarrinpar, Sue V. McDiarmid, Ronald W. Busuttil, Robert S. Venick

Intestinal Transplant Program
Dumont UCLA Transplant Center

XIIIth International Small Bowel Transplant Symposium
Oxford, UK, June 2013

Introduction

- Intestinal transplantation (ITx) has had remarkable advancement over the past 2.5 decades.
  - 80-90% 1-year survival has been reported
- Outcomes are still limited by rejection and infection.
  - Medium term survival still lags (5-yr 40-50%)
- Few large studies are available to analyze factors that affect long-term results.

AIM

- Review a large, single center experience
- Perform an analysis of factors (including pre-transplant, operative, and post-transplant variables) that impact outcome.

Materials & Methods

- Retrospective analysis of prospectively maintained database
- Single center experience
- IRB approved
- Include all ITx recipients from 1991 - 2012
- Endpoints
  - Patient death
  - Graft loss

VARIABLES

DEMOGRAPHIC	PRE-TRANSPLANT CHARACTERISTICS	LABORATORY DATA	PERI-OPERATIVE DATA	POST-OPERATIVE
AGE	GI DIAGNOSIS	TOTAL BILIRUBIN	GRAFT TYPE	Ventilator time
AGE GROUP	GI ANATOMY	CONJUGATED BILIRUBIN	COLD ISCHEMIA TIME	ICU time
GENDER	ILEOCECAL VALVE STATUS	ALANINE AMINOTRANSFERASE	WARM ISCHEMIA TIME	Hospital length
ETHNICITY	CENTRAL VENOUS CATHETER HISTORY	ASPARTATE AMINOTRANSFERASE	TOTAL ISCHEMIA TIME	Acute Rejection
HEIGHT	CENTRAL VENOUS CATHETER INFECTION HISTORY	GGT	DONOR SPLEEN MANAGEMENT	Chronic Rejection
WEIGHT	OPERATIVE HISTORY	ALBUMIN	RECIPIENT SPLEEN MANAGEMENT	Reoperations
	TIME ON TPN	FIBRINOGEN	ESTIMATED BLOOD LOSS	Nutrition data
	DEGREE OF LIVER DISEASE	INTERNATIONAL NORMALIZATION RATIO	TIME ON WAIT LIST	PTLD
	MELD/PELD SCORE	PLATELET COUNT	ABDOMINAL WALL MANAGEMENT	CMV Viremia
	LOCATION	ABO GROUP	IMMUNOSUPPRESSION REGIMEN	EBV Viremia
	MECHANICAL VENTILATION	EBV SEROLOGY		Infectious enteritis
	RENAL REPLACEMENT THERAPY	CMV SEROLOGY		
	CREATINE CLEARANCE			
	DONOR SPECIFIC ANTIBODIES			
	HLA CROSSMATCH STATUS			
	PANEL REACTIVE ANTIBODIES			

Materials & Methods

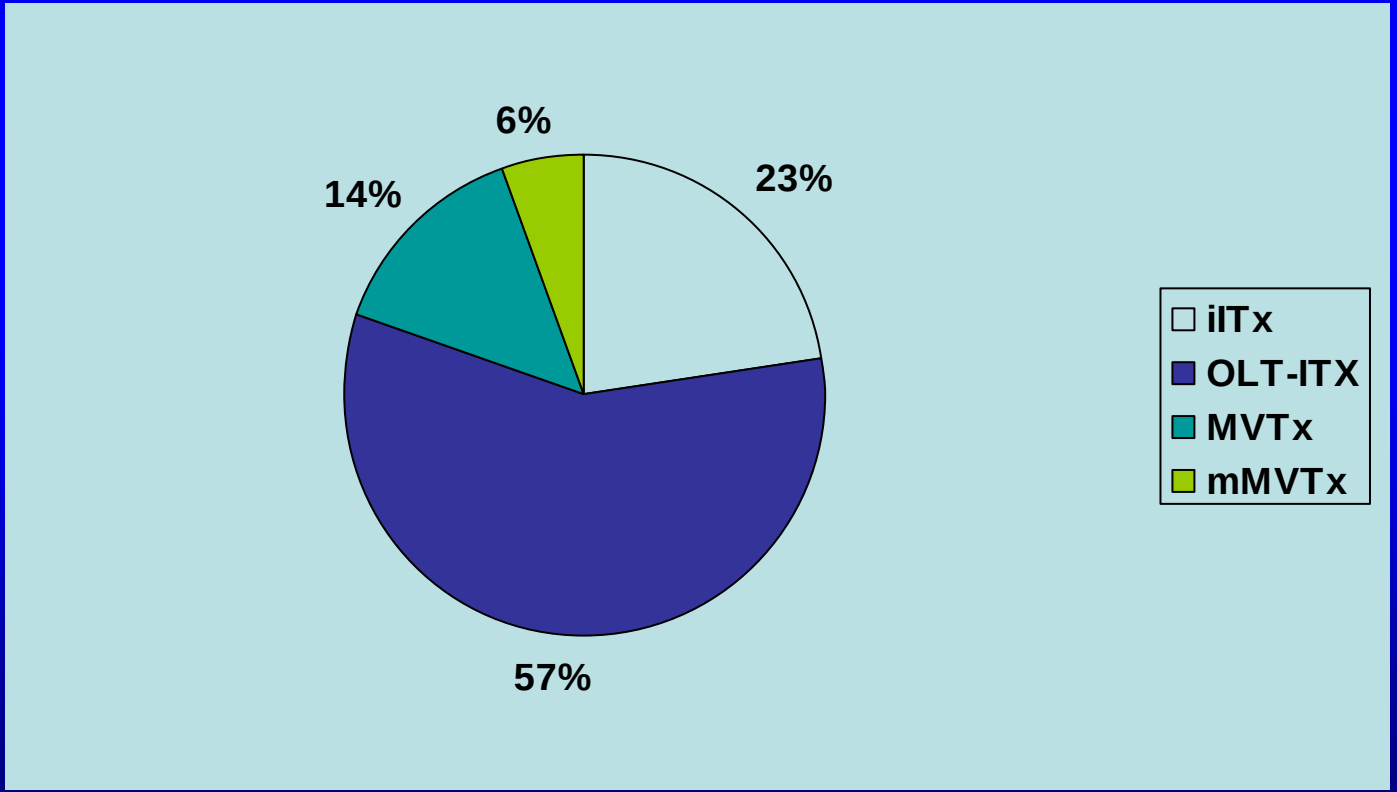
- Primary endpoints: Survival
  - Calculated using Kaplan-Meier method
- Univariate analysis
  - Log-rank test (categorical)
  - Cox proportional hazard model (continuous)
- Multivariate analysis
  - Backward elimination variable selection method

Results

- 127 ITx were performed in 104 patients
  - 72% children
  - 13.5 ± 15.5 yrs old
  - Actual MELD/PELD 15 ± 11
  - Adjusted MELD/PELD 34 ±10
  - 43% hospitalized (24% ICU)
  - cGFR 110 ± 58 ml/min/1.73m^2

- 115 ITx
  - 7 kidney inclusive
  - 11colon inclusive
  - 0 stomach inclusive

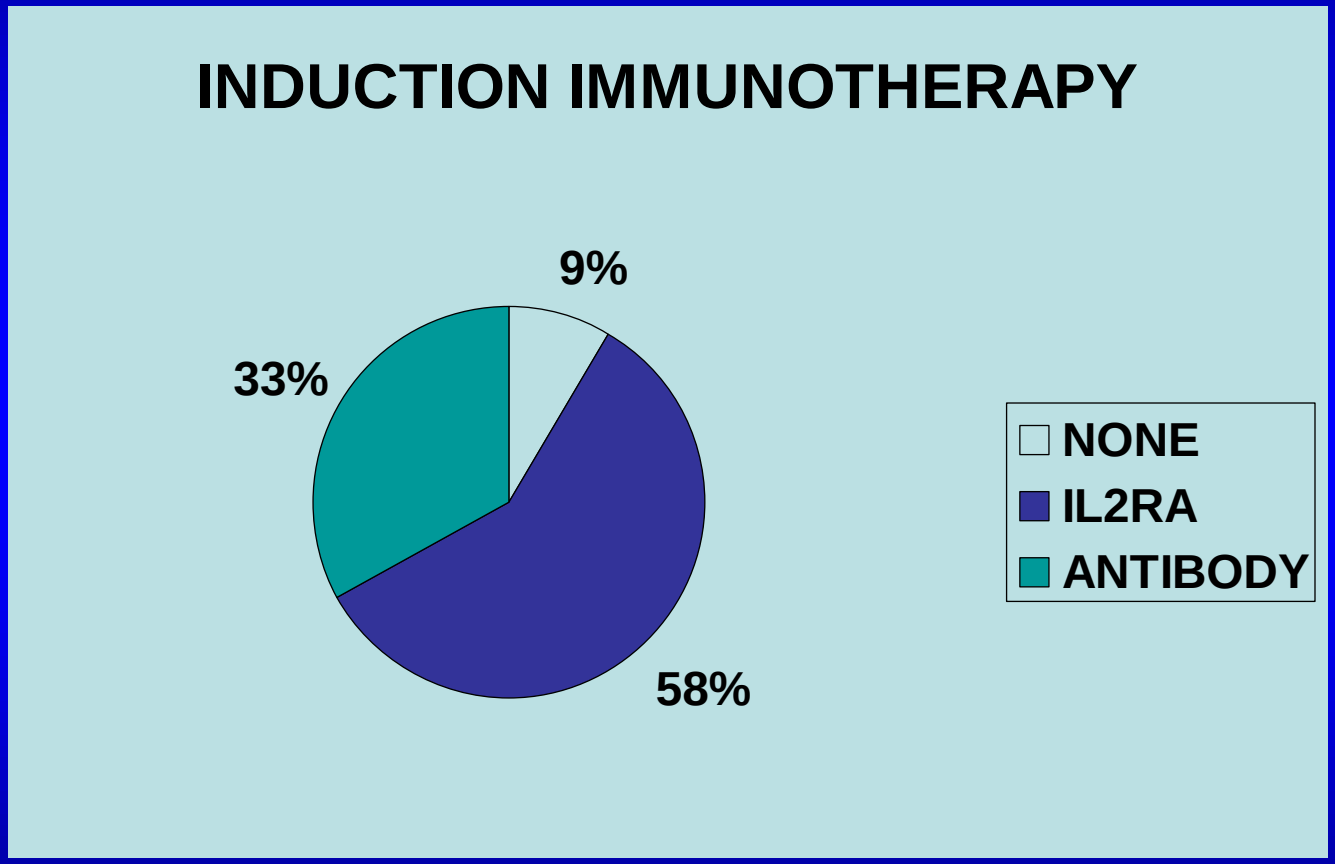
Results



Results

- Total ischemia time: 7.5 ± 2.0 hrs
- 24% required native splenectomy
- 40% had donor spleen transplanted and removed >1 hr post reperfusion

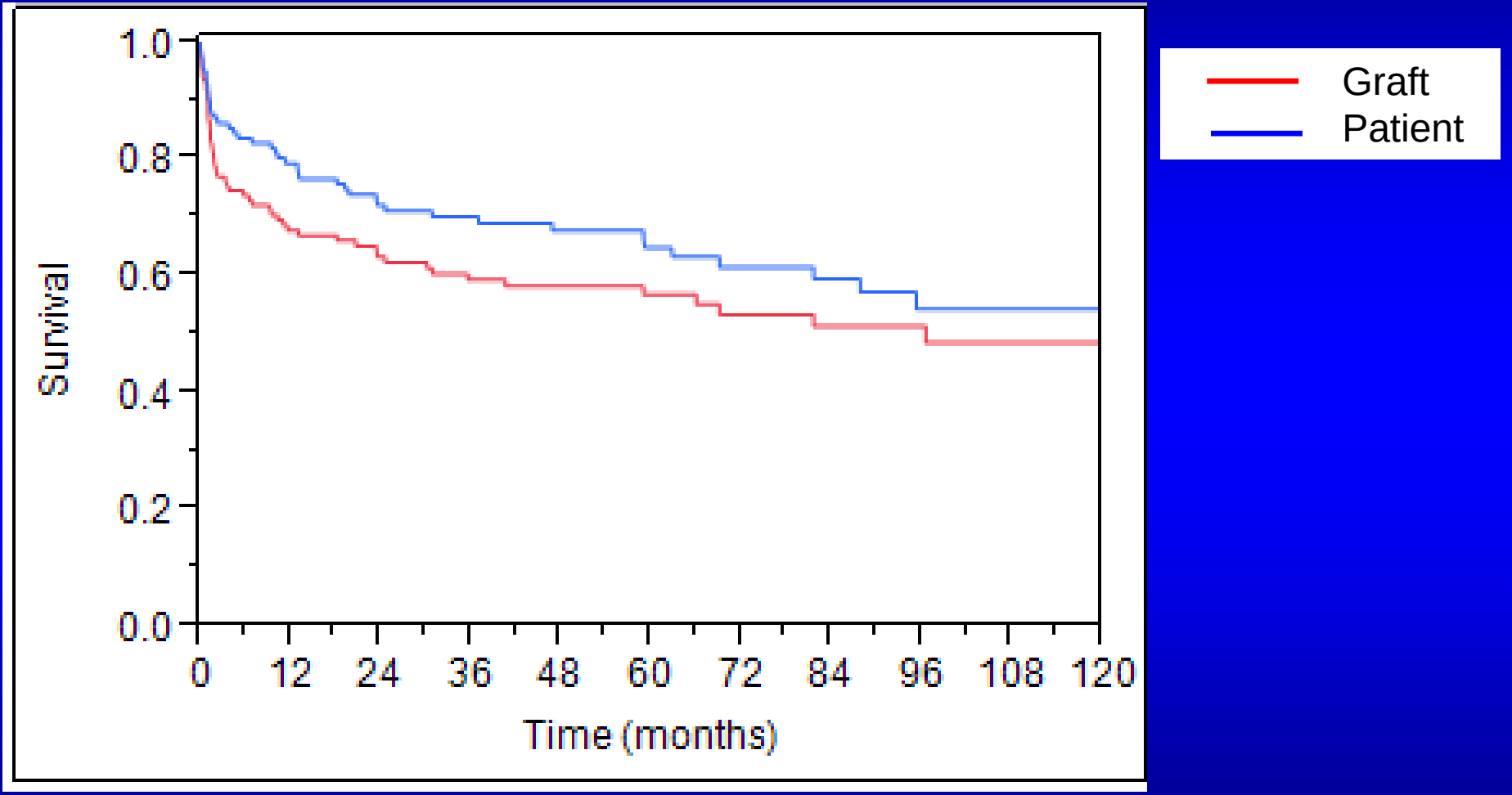
Results



Results

- Acute Rejection
  - 42% without ACR
  - Median 1 ACR/graft
- Chronic Rejection: 11 pt (9%)
  - 3.4 ± 2.4 yrs post-ITx
- GVHD: 3 pt (2.4%)
- Tissue invasive CMV Dz: 8 pt (6%)
- PTLD: 14 pt (11%)
- Infectious Enteritis: 76 pt (60%)

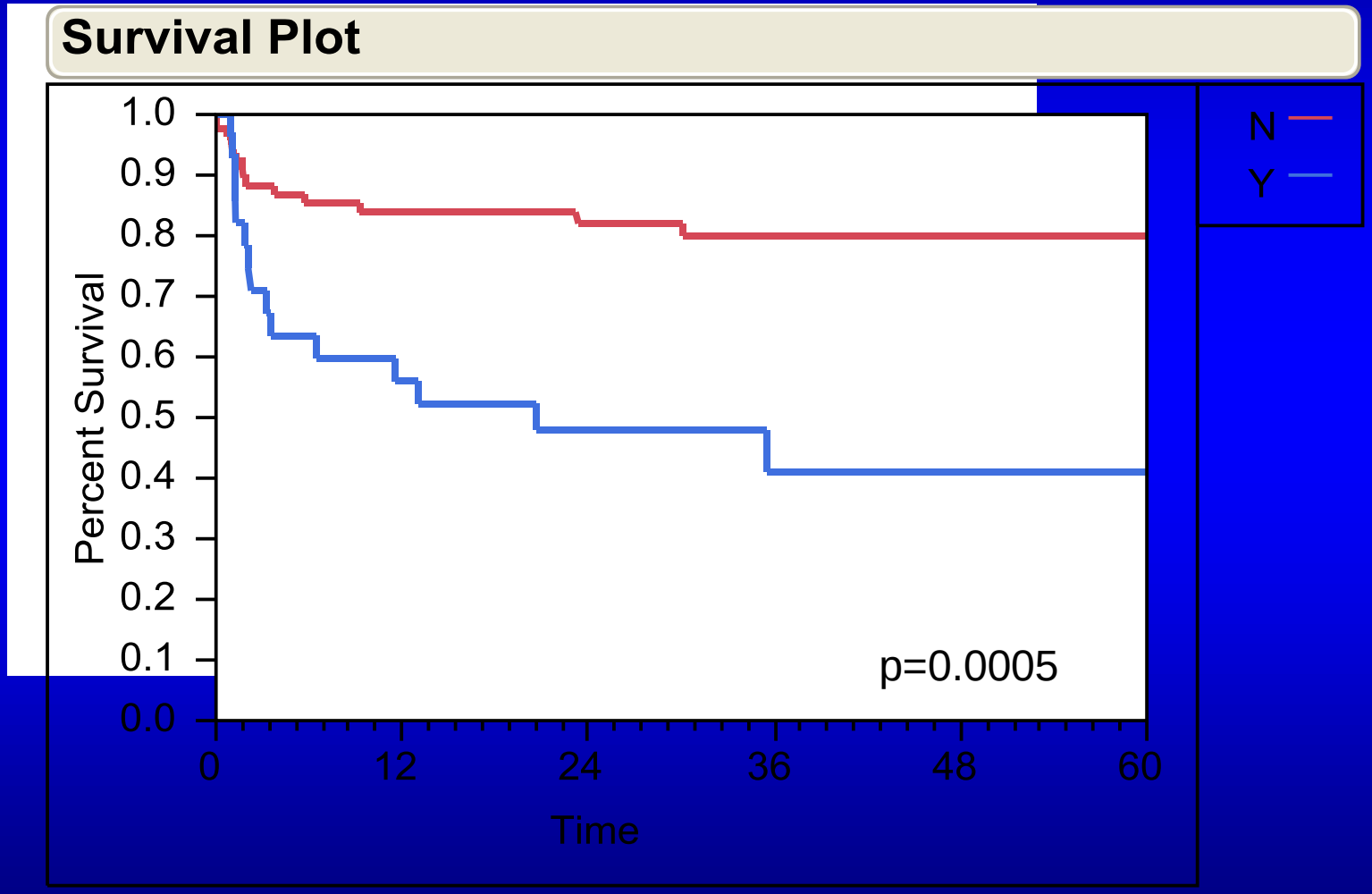
Graft and Patient Survival



Univariate Analysis Graft

FACTOR	VARIABLE A	VARIABLE B	HR	P VALUE
ERA	PRE-2000	POST-2000		0.07
INDUCTION		IL2RA		
ITX TYPE	NON-LIVER INCLUSIVE	LIVER INCLUSIVE		0.04
PRA	>20%	<20%		0.05
DSA+	YES	NO		0.09
T-XM+	YES	NO		0.05
WEIGHT	>20KG	<20KG		0.03
AGE GRP	ADULT	CHILD		0.05
WIT	>60 MIN	<60 MIN		0.002
SEVERE ACR	YES	NO		0.0005
INTUBATION	> 7 DAYS	<7 DAYS		0.07

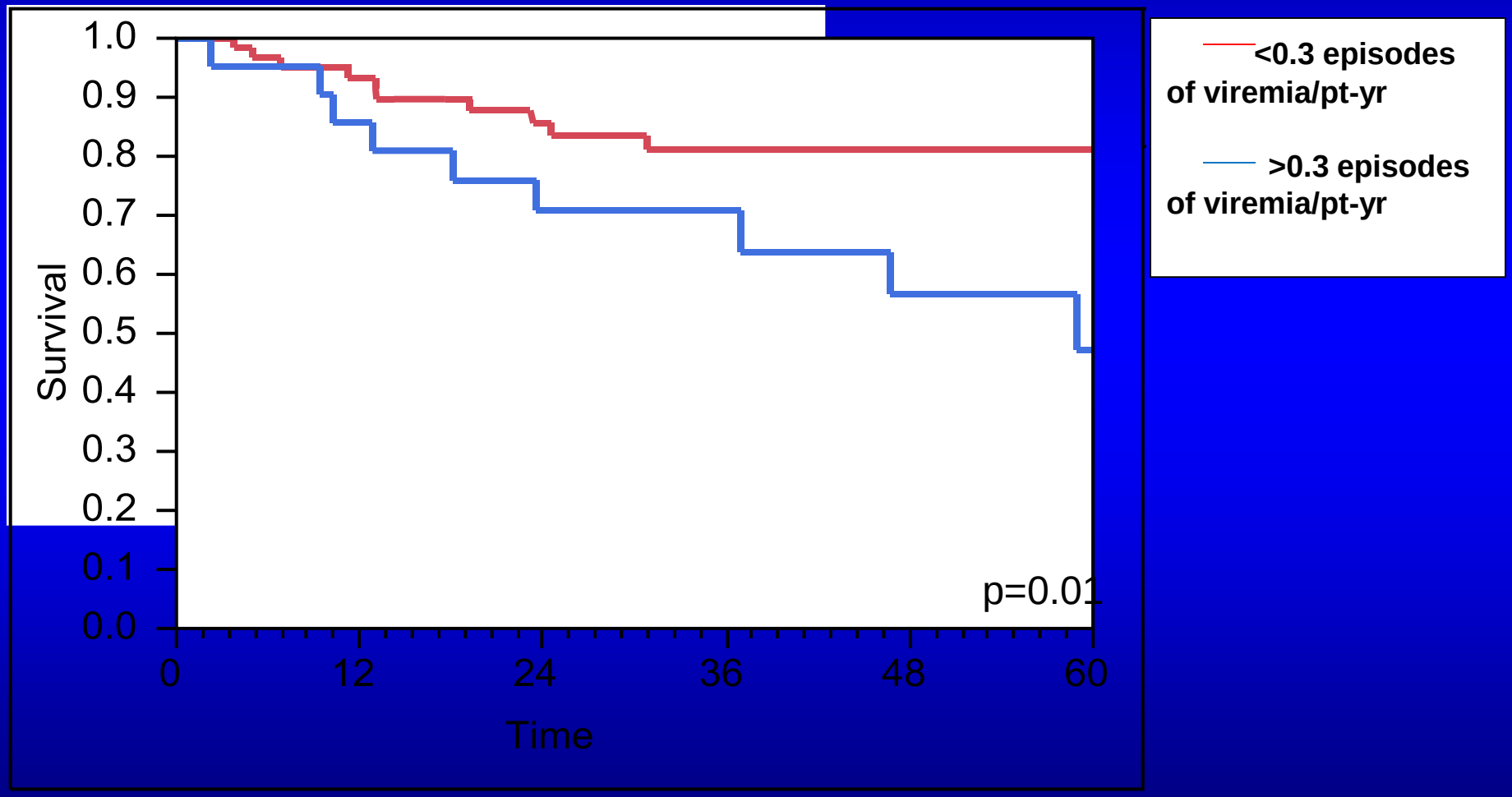
Graft Survival Based on Severe ACR (Y/N)



Univariate Analysis Patient

FACTOR	VARIABLE A	VARIABLE B	HR	P VALUE
TX #	RE-TX	1º TX		0.15
LOCATION	HOSPITAL	HOME		0.10
PRA	>20%	<20%		0.10
DSA+	YES	NO		0.14
T-XM+	YES	NO		0.19
DONOR SPLEEN	REMOVED	TX-THEN REMOVED		0.07
RECIPIENT SPLENECTOMY	YES	NO		0.006
WIT	>60 MIN	<60 MIN		0.0006
ERA	<2000	>2000		0.001
CIT	>10 HR	<10 HR		0.01
M/PELD	>16	<16		0.03
INDUCTION	IL2RA	NON-ILRRA		0.01

Patient Survival Based on CMV Viremia



CONCLUSIONS

CONCLUSION 1

- TPN therapy required for all
- Long-term TPN management appropriate in some case
- Emphasize PN weaning
- Minimize PN associated complications

CONCLUSION 2

- Fish oil based lipid formulations appear to be safer in short-term for infants and children with early IFALD
- No long-term data
- Other emulsions in development

CONCLUSION 3

- Medical consideration should be given to the use of GLP2 analog in select patients
- Close monitoring and follow-up required
- End point of therapy remains to be determined
- Cost analysis needed

CONCLUSION 4

- Surgical options should be considered in all
- STEP best applied to patients with
  - dilated small bowel segments
  - Dependent on PN for 25-75% of calories
  - Absence of advanced hepatic fibrosis/cirrhosis

CONCLUSION 5

- Reserve transplantation for patients who
  - Fail with adaptation
  - Develop 1 or more life-threatening TPN complications
  - Careful patient selection, operative planning
  - Choose the correct organs!

XIV INTERNATIONAL SMALL BOWEL TRANSPLANT SYMPOSIUM

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Thank You!