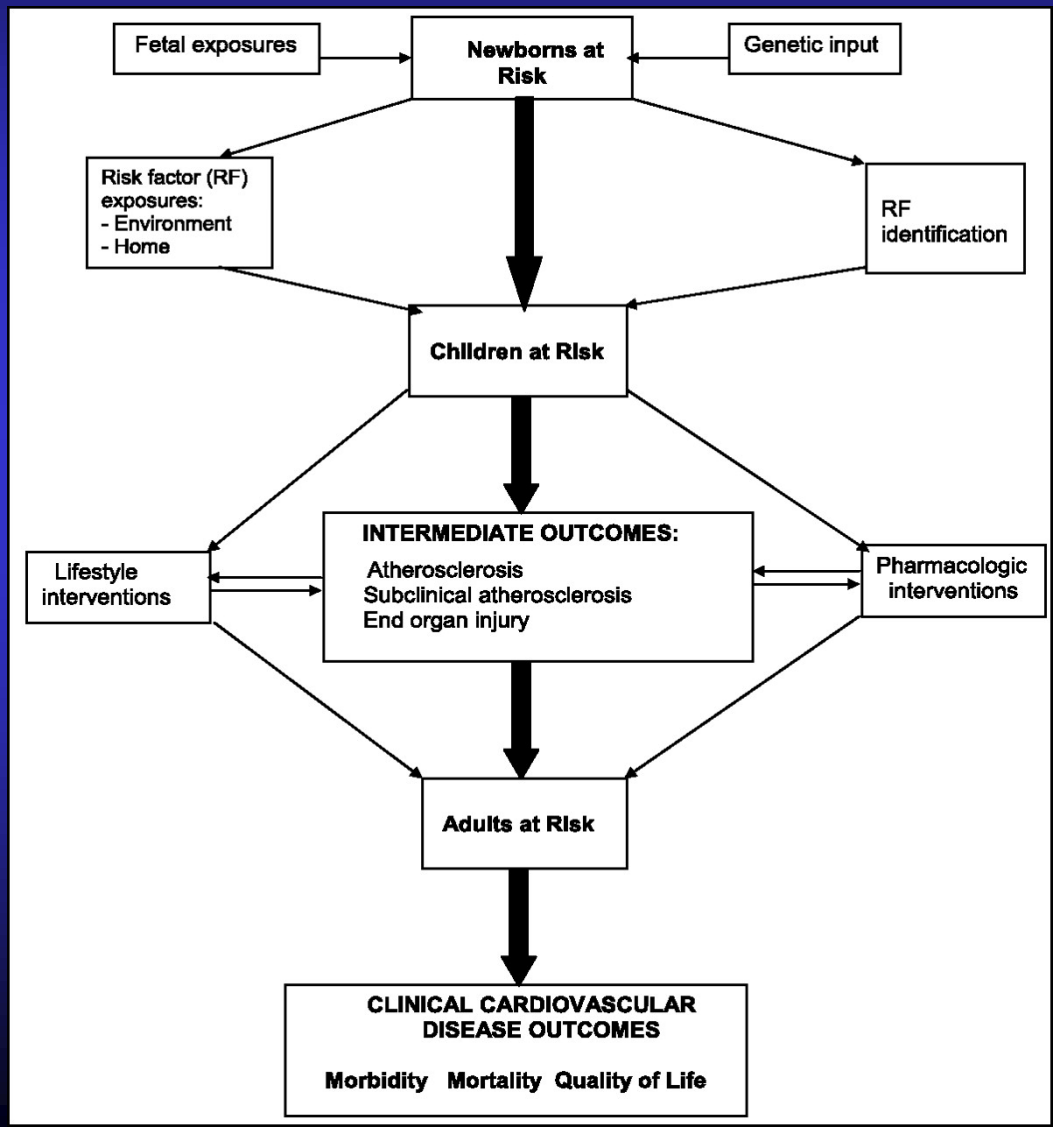
SYSTEMIC HYPERTENSION AND RENAL TRANSPLANTATION IN ARPKD

KEVIN E. C. MEYERS
PROFESSOR OF PEDIATRICS
THE CHILDREN'S HOSPITAL OF PHILADELPHIA
AND
THE UNIVERSITY OF PENNSYLVANIA

Children's Hospital of Philadelphia®

HYPERTENSION

CARDIOVASCULAR (CV) RISK FROM THE FETUS TO ADULT



Gidding S S et al. Pediatrics 2012; 129:e1311-e1319

HYPERTENSION

In ARPKD occurs pre and post transplant

The Hypertension Program is a multidisciplinary collaboration between the Divisions of Nephrology and Cardiology at Children's Hospital of Philadelphia (CHOP). CHOP's position as a national leader in hypertension and vascular disease enables us to provide the very best care.

HERE FOR YOU

This cutting-edge clinical outpatient consultation and screening program evaluates youth of all ages who have or are at risk for hypertension, especially secondary to a significant pediatric condition *(see list at right)*. The program is open to all patients within CHOP as well as those referred by outside clinicians.

The hypertension team includes:

- Kevin Meyers, MBBCh, and Amy Kogon, MD (Nephrology)
- Shobha Natarajan, MD (Cardiology)
- Melodee Mendoza, CRNP (Program Coordinator)

In conjunction with a clinic visit with Nephrology and often Cardiology, testing is tailored to the individual patient and can include the following:

- Ambulatory blood pressure monitoring
- Cardiac assessment: ECG, echocardiogram, exercise stress test
- Vascular risk assessment: pulse wave velocity in the aorta and carotid intima-media thickness

The hypertension clinic does not take the place of the child's primary healthcare team. Follow-up with the Hypertension Program is often required, but we are an added layer of service, delivering care in close collaboration and communication with the primary team.

WHAT RAISES A CHILD'S RISK FOR HYPERTENSION?

- Renal insufficiency/failure
- Renal artery stenosis
- Coarctation of the aorta
- Obesity
- Solid organ or bone marrow transplant
- Chemotherapy
- Prematurity
- Small for gestational age (SGA)
- Twin-twin transfusion syndrome
- ECMO
- Diabetes and other endocrine disorders
- Lupus erythematosus
- Sickle cell disease
- Vasculitis

We believe this list will grow as we gain understanding of pediatric hypertension.

Children's Hospital of Philadelphia

LEARN MORE OR MAKE A REFERRAL:
Ashley Kicsak, Program Administrator
215-590-2200

HYPERTENSION

- Neonates with large echogenic kidneys have ectasia of 60–90 % of the renal collecting tubules and generally have hypertension and decreased kidney function
- Neonates with hypertension are more likely to require mechanical ventilation

Guay-Woodford LM, Desomond RA (2003) ARPKD: the clinical experience in North America. Pediatrics 111:1072–1080
Sweeney WE Jr, Avner ED (2011) Diagnosis and management of childhood polycystic kidney disease. Pediatr Nephrol 26: 675–692

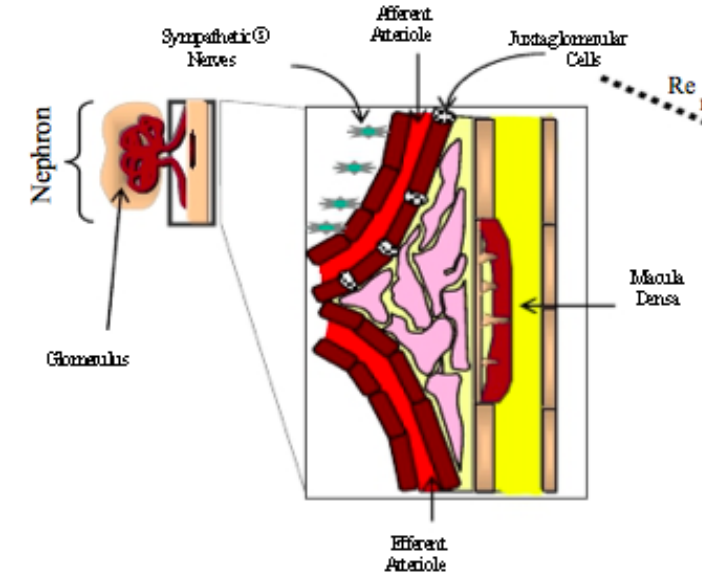
HYPERTENSION

- Beyond the neonatal period, hypertension occurs in two-thirds (2/3) of children
- Studies show that activation of the intra-renal renin-angiotensin-aldosterone system, without concurrent elevation in systemic angiotensin I and II levels, may play a role

Sweeney WE Jr, Avner ED (2011) Diagnosis and management of childhood polycystic kidney disease. Pediatr Nephrol 26: 675–692
Loghman-Adham M, Soto CE, Inagami T, Sotelo-Avila C. Expression of components of the renin-angiotensin system in ARPKD. The Journal of Histochemistry and Cytochemistry. 2005; 53:979–988
Goto M, Hoxha N, Osman R, Dell KM. The renin-angiotensin system and hypertension in ARPKD. Pediatric Nephrology. 2010; 25:2449–2457

HYPERTENSION

RAAS Diagram



Renin Secretion
- ↑ Macula densa signal
- ↓ Renal artery pressure/blood flow
- ↑ Sympathetic stimulation

ANGIOTENSINOGEN

Renin ⑦

ANGIOTENSIN I

Converting Enzyme ①

ANGIOTENSIN II

②

Adrenal Cortex → ↑ Aldosterone synthesis ⑥

Kidney, Intestine → Sodium/Water Reabsorption ⑤

CNS → Vasopressin → ↑ Blood Volume

CNS → Sympathetic Discharge

Peripheral Nervous System → ↑ Total Peripheral Resistance ⑤

Vascular Smooth Muscle → Vasoconstriction ④

Heart → ↑ Contractility ③④ → ↑ Cardiac Output

↑ Blood Pressure

HYPERTENSION

- Impaired urinary dilution with associated fluid retention
- Dysregulation of the collecting duct epithelial sodium channel may be contributing factors to ARPKD-related systemic HTN

Rohatgi R, Greenberg A, Burrow CR, Wilson PD, Satlin LM. Na transport in autosomal recessive polycystic kidney disease (ARPKD) cyst lining epithelial cells. J Am Soc Nephrol. 2003; 14:827–836.
Veizis IE, Cotton CU. Abnormal EGF-dependent regulation of sodium absorption in ARPKD collecting duct cells. American journal of physiology Renal physiology. 2005; 288:F474–F482.

HYPERTENSION

MANAGEMENT

- ACEi or ARB not both (aim - optimize blood pressure control, while minimizing further reduction in GFR in the context of chronic kidney disease (CKD))
- Avoid excess fluid intake (water)
- [Diuretics – Lasix]
- The recent multicenter ESCAPE trial in children with Chronic Kidney Disease stages 2–4 indicated that aggressive blood pressure control (target 24-hour mean arterial blood pressure below the 50th percentile for age, height and sex) may slow progression to end-stage renal disease; the specific target for ARPKD has not been established, however the same principles apply

Rohatgi R, Greenberg A, Burrow CR, Wilson PD, Satlin LM. Na transport in autosomal recessive polycystic kidney disease (ARPKD) cyst lining epithelial cells. J Am Soc Nephrol. 2003; 14:827–836.
Veizis IE, Cotton CU. Abnormal EGF-dependent regulation of sodium absorption in ARPKD collecting duct cells. American journal of physiology Renal physiology. 2005; 288:F474–F482

HYPERTENSION

STEPPED-CARE THERAPY

Step 1

Begin with the recommended initial dose of desired medication

If BP control is not achieved:

Step 2

Increase dose until desired BP target is reached, or maximum dose is reached

If BP control is not achieved:

Step 3

Add a second medication with a complementary mechanism of action

Proceed to highest recommended dose if necessary and desirable

If BP control is not achieved:

Step 4

Add a third antihypertensive drug of a different class

OR

Consult a physician experienced in treating childhood and adolescent hypertension

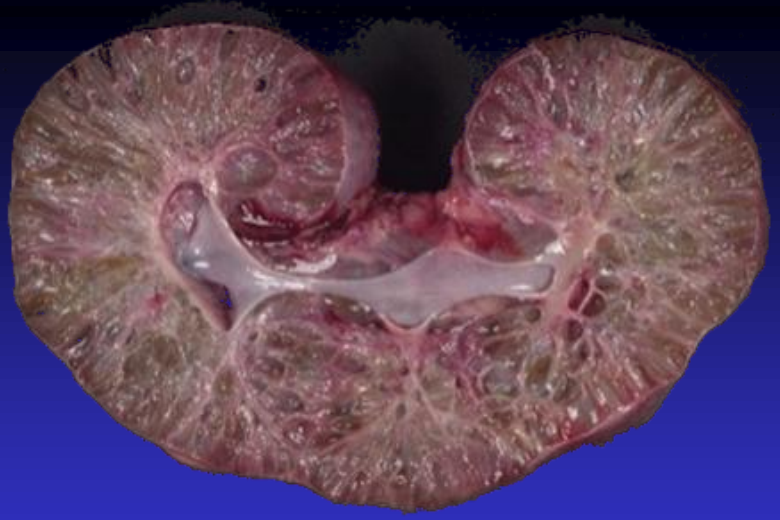
ARPKD CASE

- Prenatal diagnosis of enlarged polycystic kidneys
- NICU for 2 months
- Renal ultrasound revealed massive echogenic cystic kidneys measuring 10 cm and 10.7 cm, and diffuse hepatic biliary duct ectasia

ARPKD CASE

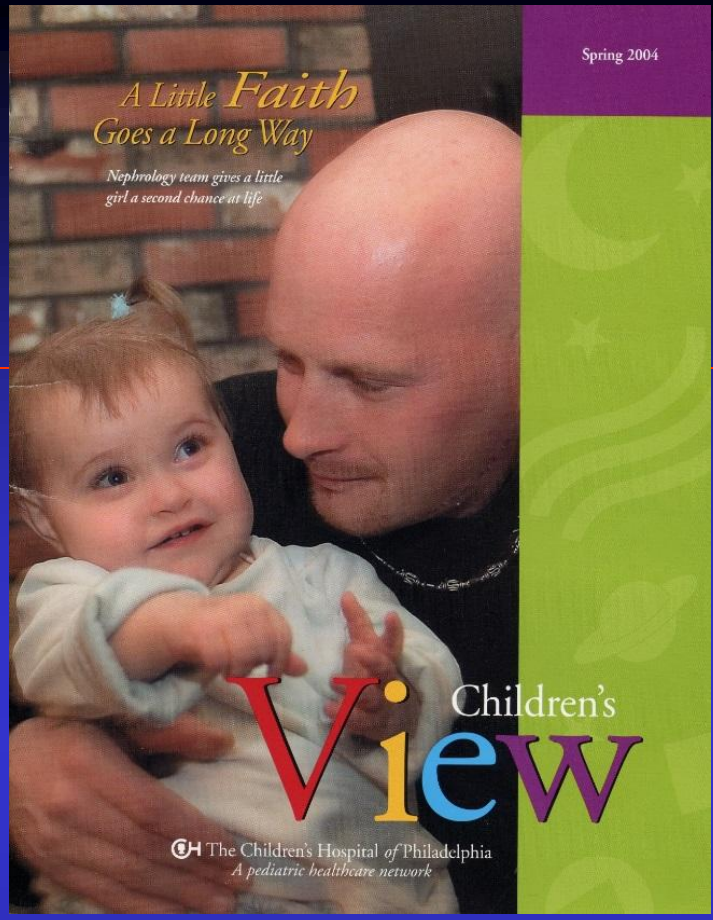
- Transferred to CHOP for uncontrolled hypertension and poor weight gain
- Discharged from CHOP at 3 months of age on multiple antihypertensive medications, including diuretics and NG feeds
- Unable to maintain normal electrolyte balance and stopped gaining weight.
- A gastro-jejunostomy tube was placed for feeding without improvement in growth

ARPKD CASE



- She underwent a left nephrectomy on 1/15/03 in an attempt to improve gastric emptying and weight gain
- Her post-operative course was uncomplicated, however, she gradually became more edematous and hyperkalemic
- She started hemodialysis

ARPKD CASE



- She received a LRD kidney transplant from her Father with a right native nephrectomy over 15 years ago and has done well. She is now a 16 year old but has CKD with hypertension and will require a second transplant in the future.

OBJECTIVES

- 1. To describe which persons with ARPKD might need a kidney transplant
- 2. To outline the preparatory process for kidney transplant in ARPKD
- 3. To review ARPKD kidney and kidney/liver transplants

WHICH CHILDREN WITH ARPKD NEED A KIDNEY TRANSPLANT

COMPLICATIONS & TREATMENT IN 50 PTS WITH FOLLOW-UP INFORMATION

	<1 Year (n = 17)	1–20 Years (n = 16)	>20 Years (n = 17)
ARPKD	17	14	11
Isolated congenital hepatic fibrosis	0	2	6
Kidney enlargement	9	7	4
Hypertension	7	4	6
Symptomatic kidney stone	1	2	3
Urinary tract infection	4	5	3
Renal insufficiency	8	3	3
ESRD	6	1	1
Dialysis	1	1	1
Kidney transplant	5	1	0
Splenomegaly	8	10	9
Hypersplenism	7	9	8
Variceal bleeding	6	8	6
Sclerosis/banding	5	7	5
Portosystemic shunt/ splenectomy	5	7	6
Cholangitis/hepatic abscess	1	4	5
Liver transplant	0	1	0
Mortality	6	4	2

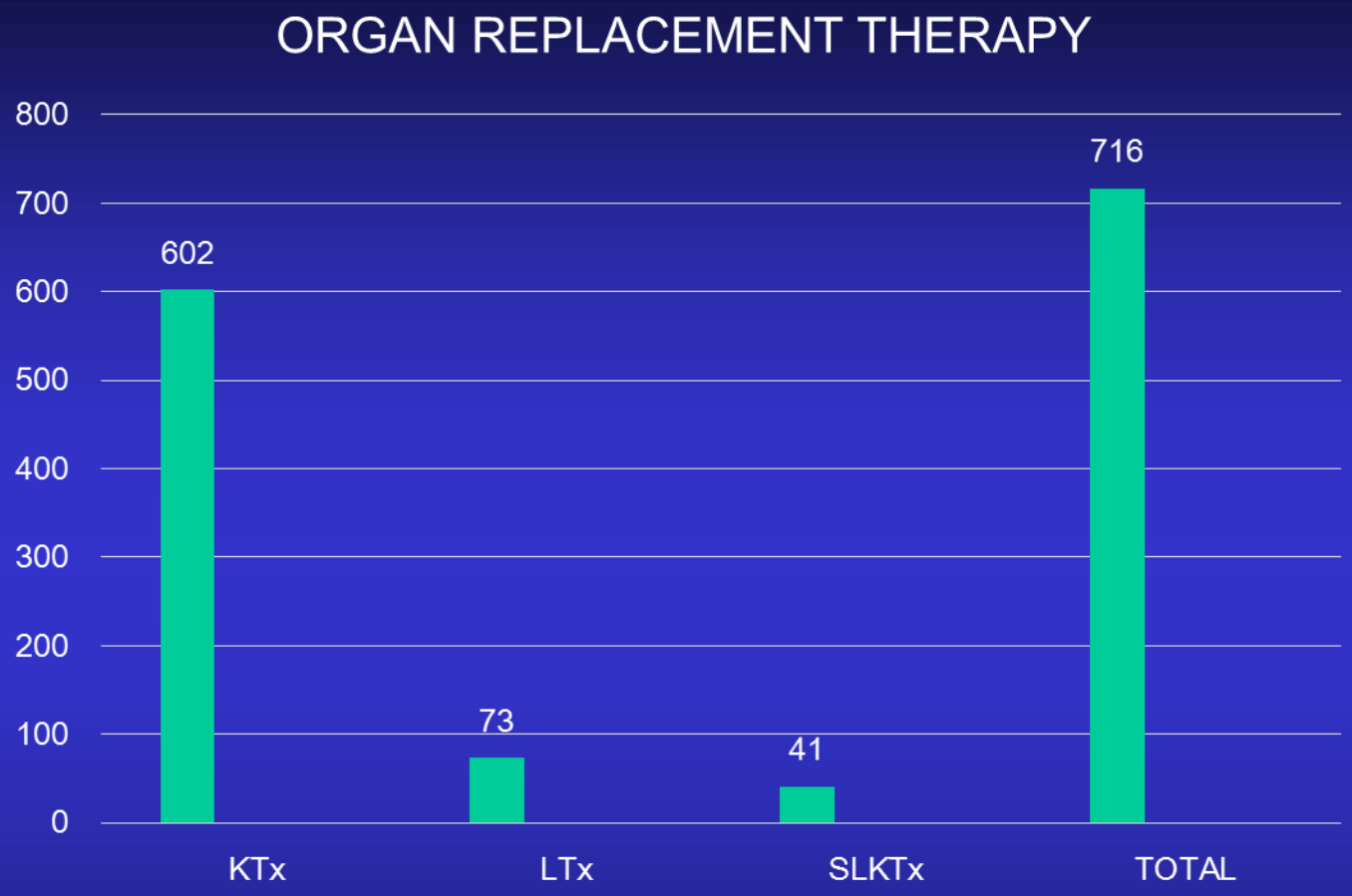
Adeva et al. Medicine 2006;85:1–21

RENAL REPLACEMENT THERAPY

At the age of 10 years:

- 60% of patients require kidney transplantation
- About 10% need liver transplantation
- Mainly sequential liver–kidney transplantation

TRANSPLANT



- In this cohort, the reason for liver replacement was Caroli syndrome in 29% and CHF in 71%
- Mortality after LTx was 23%, after KTx 10% and after SLKTx 12%
- It is of note that the overall mortality has improved in the recent decade

Wen JW, Furth SL, Ruebner RL. Kidney and liver transplantation in children with fibrocystic liver–kidney disease: data from the U.S. Scientific Registry of Transplant Recipients: Pediatr Transplant 2014; 18:726–732

THE PREPARATION PROCESS FOR KIDNEY TRANSPLANT IN ARPKD

STAGES OF CHRONIC KIDNEY DISEASE (CKD)

Stages	Description	GFR ($ml/min/1.73m^2$)
I	Kidney damage: N or ↓ GFR	greater than 90
II	Kidney damage: mild ↓ GFR	60-89
III	Kidney damage: moderate ↓ GFR	30-59
IV	Kidney damage: severe ↓↓ GFR	15-29
V	Kidney failure: ↓↓↓ GFR	less than 15 (or on dialysis)

EVALUATION FOR TRANSPLANT

- **RECIPIENT**
  - **Medical management of CKD**
    - **Nutrition**
      - **Ca/PO_4/Fluid/Calories/Acidosis**
      - **NGT/GT/GJT**
    - **Liver/GI**
      - **Hypersplenism/Portal HTN/Infection**
    - **Cardiovascular**
      - **HTN**
  - **Dialysis**
  - **Psychosocial evaluation**

EVALUATION FOR TRANSPLANT

- **DONOR**
  - **LRD or DD**
  - **Medical assessment**
  - **Psychosocial evaluation**

CHOP ARPKD CHILDREN WITH KIDNEY TRANSPLANTS AND REVIEW OF PUBLISHED LITERATURE

CHOP: KIDNEY TRANSPLANTS IN CHILDREN WITH ARPKD 2002

Patient	Age at Δ	Age at txp LRD/DD	FU (yrs)	Latest eGFR	Liver status
1.	Pre-birth	1.2 yrs LD	4.75 yr	54	LF;HS
2.	Pre-birth	10.8yrs DD	2.9 yr	90	LF;HS
3.	Pre-birth	13.4 yrs DD	2.25 yr	95	LF - mild
4.	Birth	15.1 yrs DD	2.2 yr	80	LF;HS
5.	Birth	15.6 yrs DD	1.9 yr	110	LF - mild

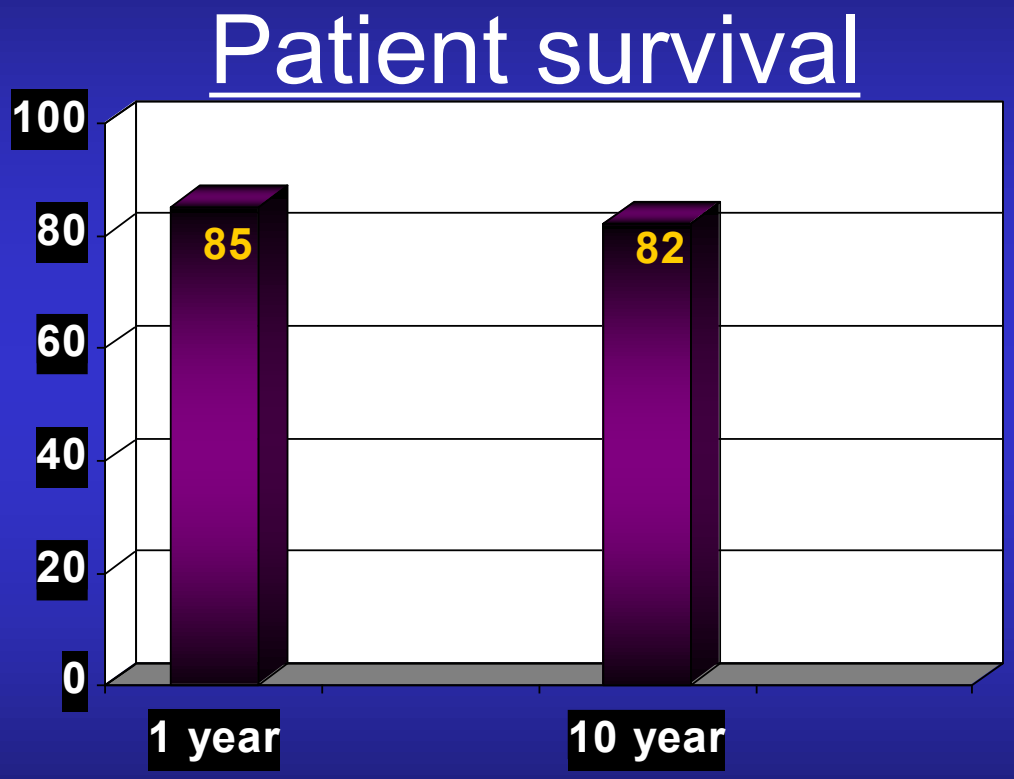
LF – liver fibrosis; PHTN – portal hypertension; HS - hypersplenism

CHOP: KIDNEY TRANSPLANTS IN CHILDREN WITH ARPKD 2018

ARPKD	Follow Up	Age at Txp	Current Age	Type	Ethnicity
1	TXF	1.6	31.7	LR	C
2	C	1.2	16.5	LR	C
3	TXF	10.8	24.3	LR	C
4	TXF	13.4	26.2	DD	AA
5	TXF	15.1	27.9	LR	C
6	TXF	15.6	28.1	DD	H
7	GL	10.4**		DD	
8	TXF	15.8	25.5	DD	C
9	C	12.2**	20.0	LD	C
10	C	2.7	8.8	LD	C
11	C	6.5	12.6	LD	C
12	C	2.3	7.8	LD	C
13	C	3.2	8.4	DD	AA
14	TXF	2.1	7.2	LD	C
16	C	17.4	20.5	LD	C
17	C	2.2	5.0	LD	C

OUTCOMES OF ARPKD

Clinical course of 164 neonatal survivors

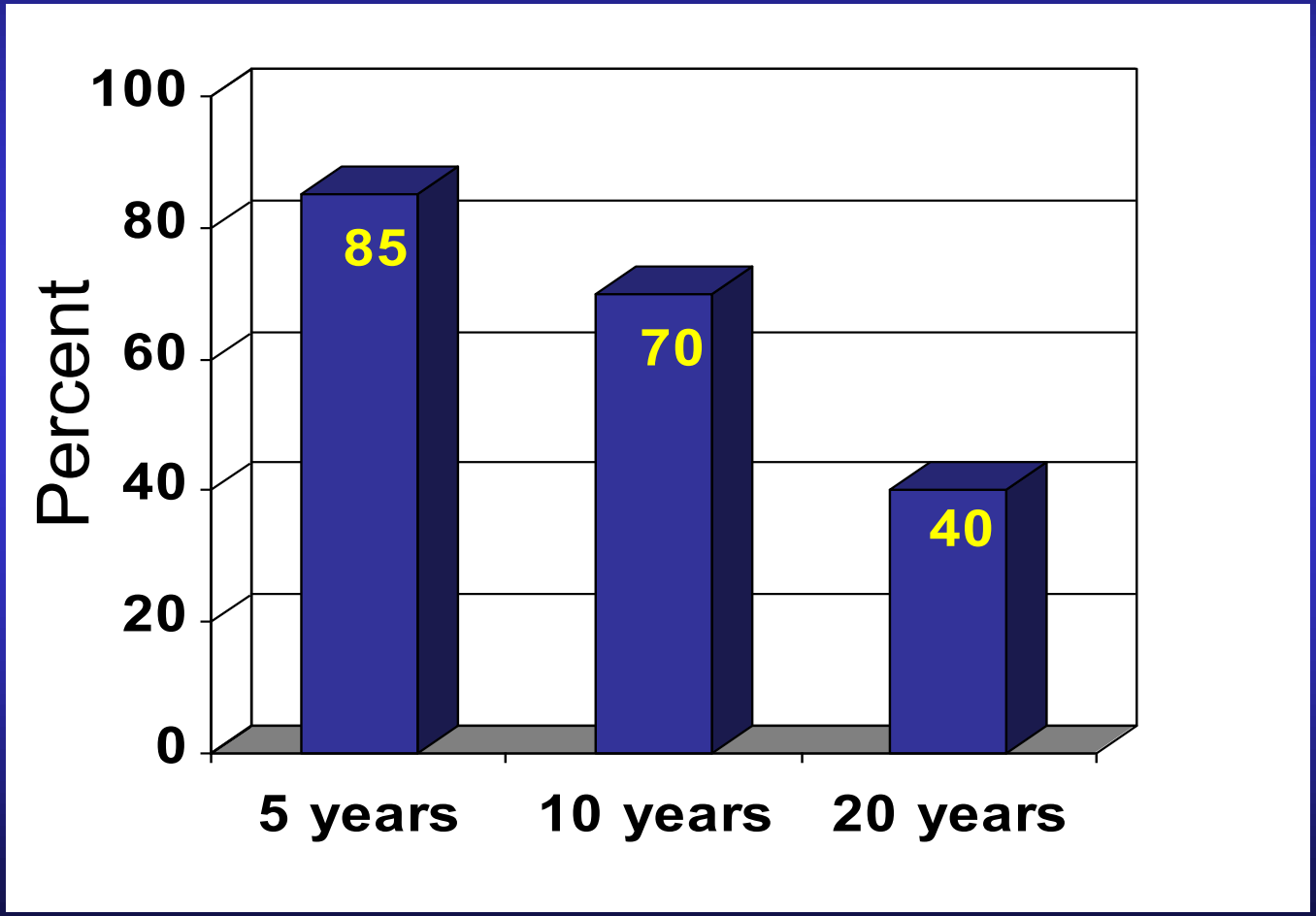


Chronic renal failure first detected at a mean age of 4 years

Bergmann et al Kidney Int. 2005 67:829-48

ACTUARIAL RENAL SURVIVAL

Clinical course of 164 neonatal survivors



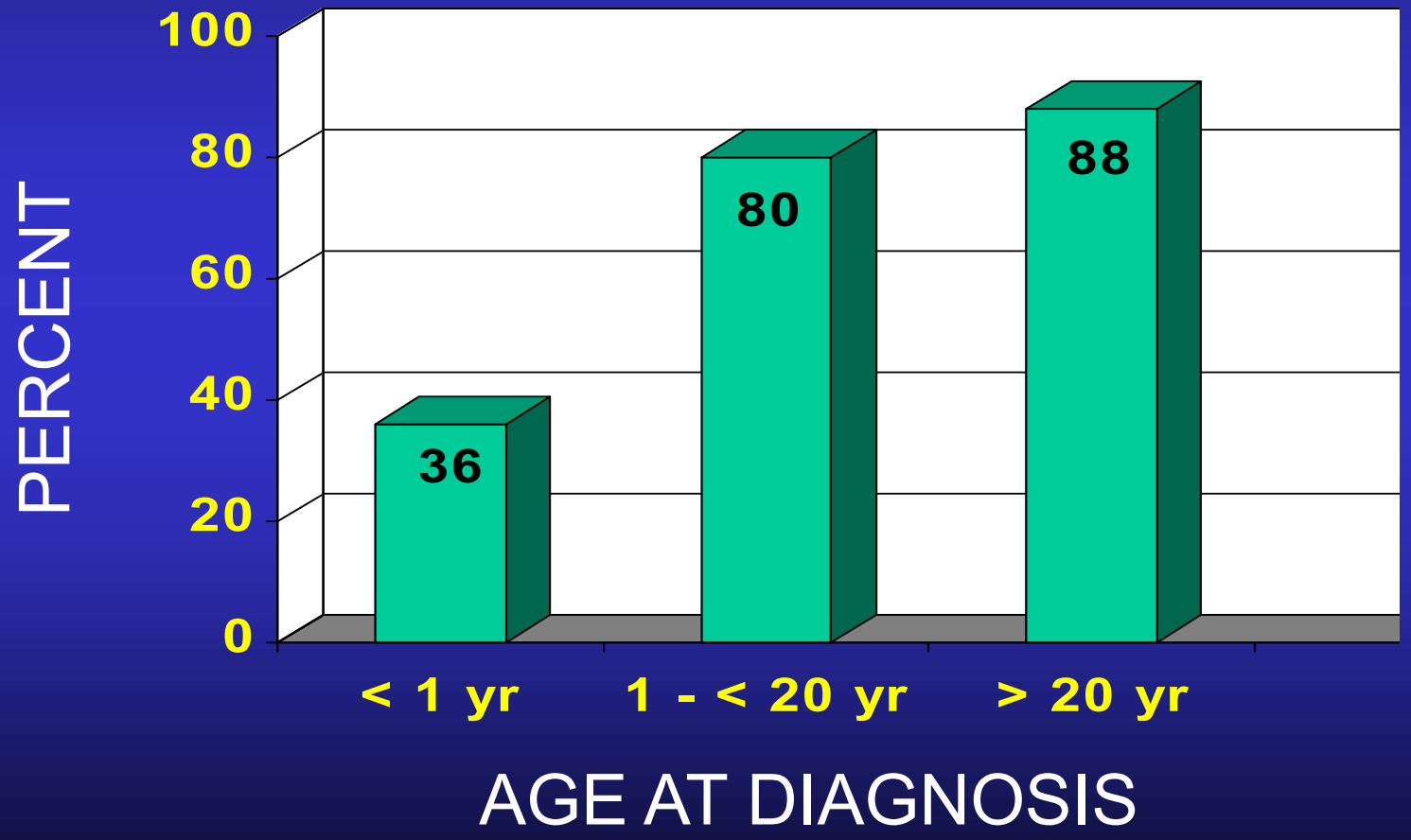
Bergmann et al Kidney Int. 2005 67:829-48

ACTUARIAL RENAL SURVIVAL

TIME TO ESRD FROM DIAGNOSIS

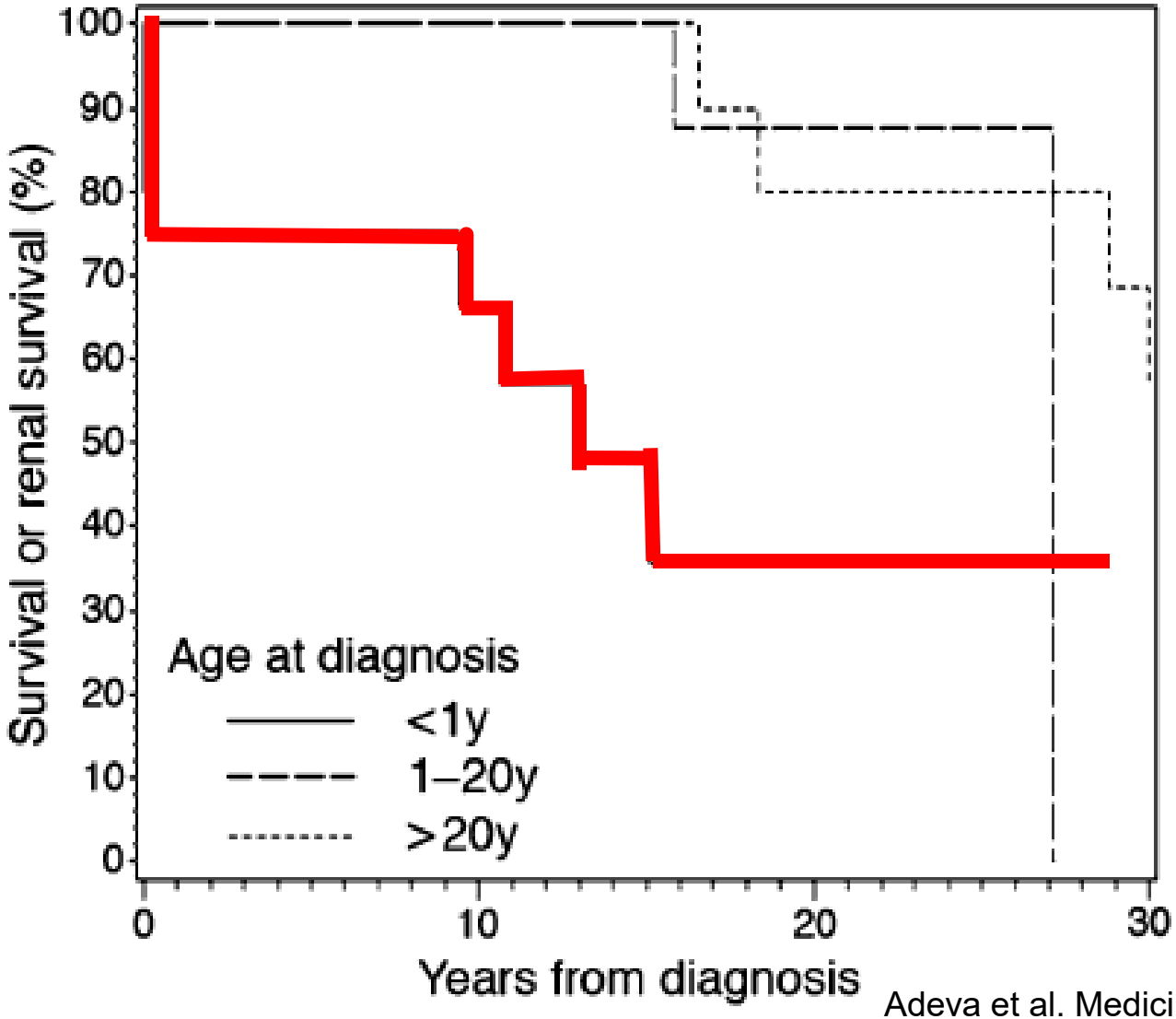
- From birth: 46% at 15 years [Kaplan et al 1989]
- From 1 month: 42% at 20 years [Bergman et al. 2005]
- From 1 month: 67% at 15 years [Roy et al 1993]
- From 1 year: 79% at 15 years [Kaplan et al 1989]

LIKELIHOOD OF BEING ALIVE WITHOUT ESRD 20 YEARS AFTER THE DIAGNOSIS



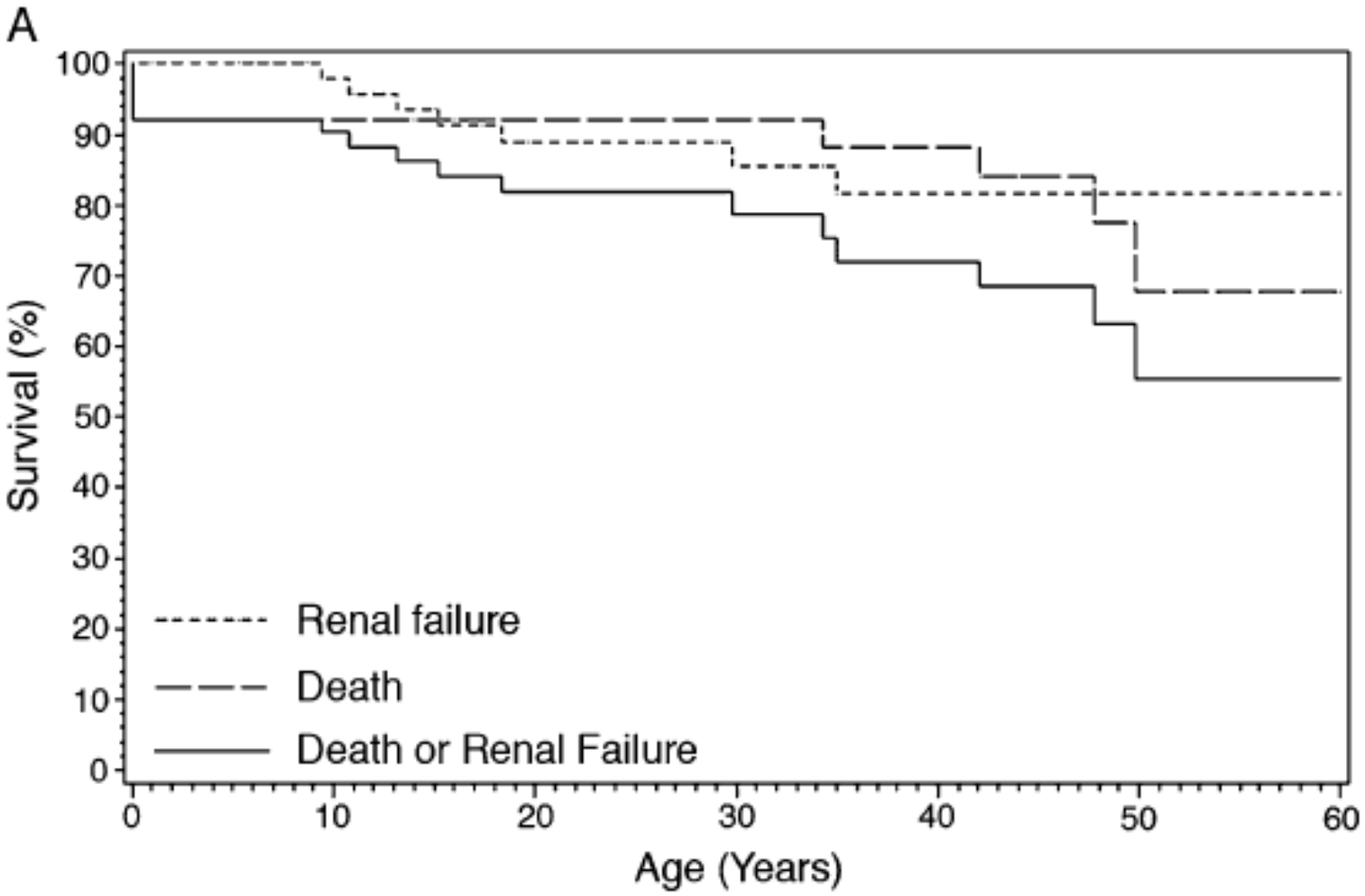
Adeva et al. Medicine 2006;85:1–21

Likelihood of being alive without ESRD 20 years after diagnosis



Adeva et al. Medicine 2006;85:1–21

Survival and renal survival for the ARPKD cohort



Adeva et al. Medicine 2006;85:1–21

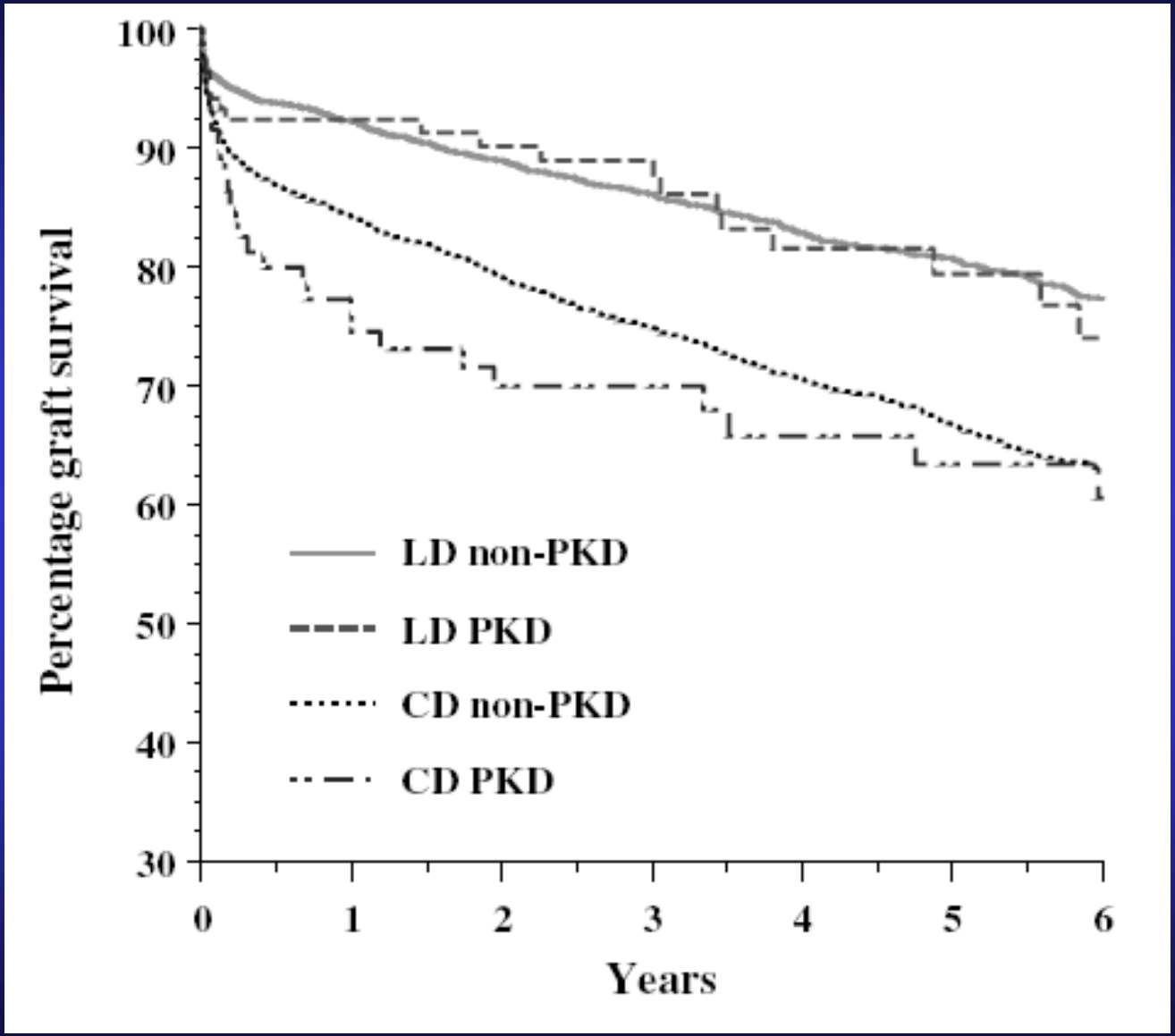
NEONATAL NEPHRECTOMY DIALYSIS & KIDNEY TRANSPLANT

		Neonatal						Nephrectomy (Nx)		Peritoneal dialysis		Transplantation (Tx)				Hepatic involvement		
Patient	Gender	Gestational age (weeks)	Birth weight (kg)	Prenatal diagnosis	Oligo-hydramnios	Neonatal ventilation	Pneumothorax	Age at Nx (months)	Weight Nx (kg)	Peritonitis	Peritoneal leak	Age at Tx (months)	Weight at Tx (kg)	Donor (L = living; C = cadaveric)	Graft loss	Clinical sign of periportal fibrosis	Portal hypertension	Cholangitis
1	F	41	3.5	Yes	Yes	Yes*	Yes	0.7	3.6	No	Yes§	17.6	9.9	L	No	Yes	Yes	Yes
2	M	38	4.1	Yes	Yes	Yes	No	33.0	16.2	No	No	33.0	16.2	L	Yes†	No	No	No
3	M	36	3.9	No	No	Yes	Yes	9.0	8.2	Yes	Yes	27.9	15.8	L	No	No	No	No
4	M	40	3.1	No	No	Yes‡	Yes	4.5	4.5	No	Yes	13.6	9.7	L	No	Yes	Yes	No
5	M	43	3.6	Yes	No	No	Yes	9.0	8.6	Yes	No§	13.7	9.6	L	No	Yes¶	Yes	Yes
6	M	38	3.6	Yes	Yes	Yes*	Yes	1.5	4.1	Yes	Yes	67.0	20.2	L	Yes	Yes	Yes	No
7	F	38	3.2	No	Yes	No	No	38.0	12.0	No	No	41.9	13.8	C	Yes	Yes	Yes	Yes
8	M	37	4.0	No	No	Yes	No	6.0	6.9	No	No	30.6	11.6	C	No	Yes	Yes	No
9	M	35	4.9	Yes	No	Yes*	No	0.1	4.8	No	Yes	12.9	9.5	L	No	No	No	No
10	M	41	3.2	Yes	Yes	No	Yes	1.0	3.6	No	Yes	Awaiting				No	No	No

*Patient on ventilation at time of nephrectomy, †deceased, ‡ chronic obstructive pulmonary disease (COPD), §conversion to hemodialysis due to poor ultrafiltration, ¶liver transplantation.

Sarawal et al. Pediatric Transplantation 2007

GRAFT SURVIVAL RATE



North **A**merican **P**ediatric **R**enal **C**ollaborative **T**rial**S** (NAPRCTS) registry data

Davis et al. Pediatric Transplantation 2003

COMPLICATONS

- GRAFT THROMBOSIS
- REJECTION
- GROWTH
- PTLD
- CARDIOVASCULAR (HTN)
- INFECTION*
- LIVER*

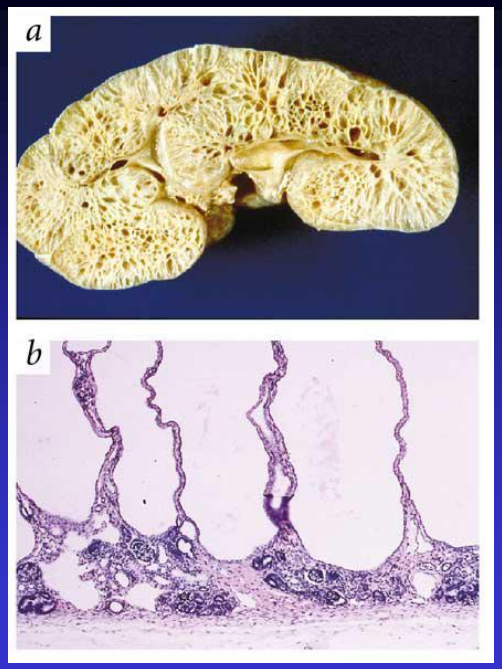
MORBIDITY AND MORTALITY FROM CHF AFTER RENAL TRANSPLANTATION FOR ARPKD

Complications of CHF occurred in 79% with kidney transplants for ARPKD

Mortality related to CHF occurred in 29% (5 pts)

Accounted for 80% deaths (4/5 pts)

Am J Transplant. April 2002

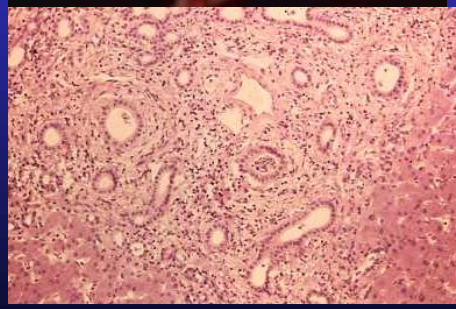


CLD

Liver Transplant

CKD → Kidney Transplant ↔ Liver Transplant

Liver Transplant



DUAL KIDNEY–LIVER TRANSPLANT IN ARPKD

Current guidelines regarding listing for combined kidney-liver transplantation (CKLT) are in the context of end-stage liver disease due to hepatocellular dysfunction, for which listing for CKLT is recommended when estimated glomerular filtration rate is <30 mL/min/1.73 m^2 .

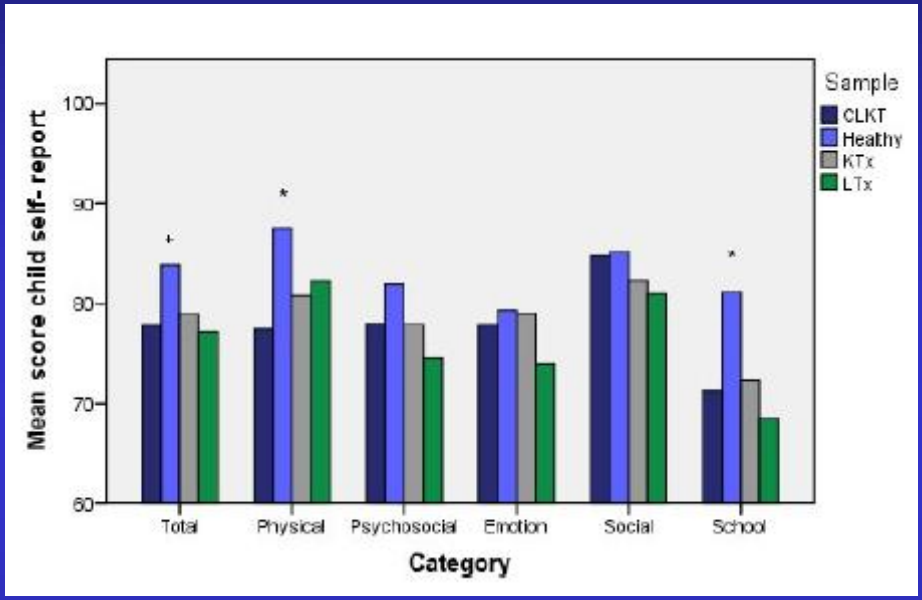
Khan K, Schwarzenberg SJ, Sharp HL, Matas AJ, Chavers BM. Morbidity from congenital hepatic fibrosis after renal transplantation for autosomal recessive polycystic kidney disease. Am J Transplant. 2002;2(4):360–365
Charlton MR, Wall WJ, Ojo AO, et al; International Liver Transplantation Society Expert Panel. Report of the first international liver transplantation society expert panel consensus conference on renal insufficiency in liver transplantation. Liver Transpl. 2009;15(11):S1– S34 doi:10.1002/lt.21877

DUAL KIDNEY–LIVER TRANSPLANT IN ARPKD

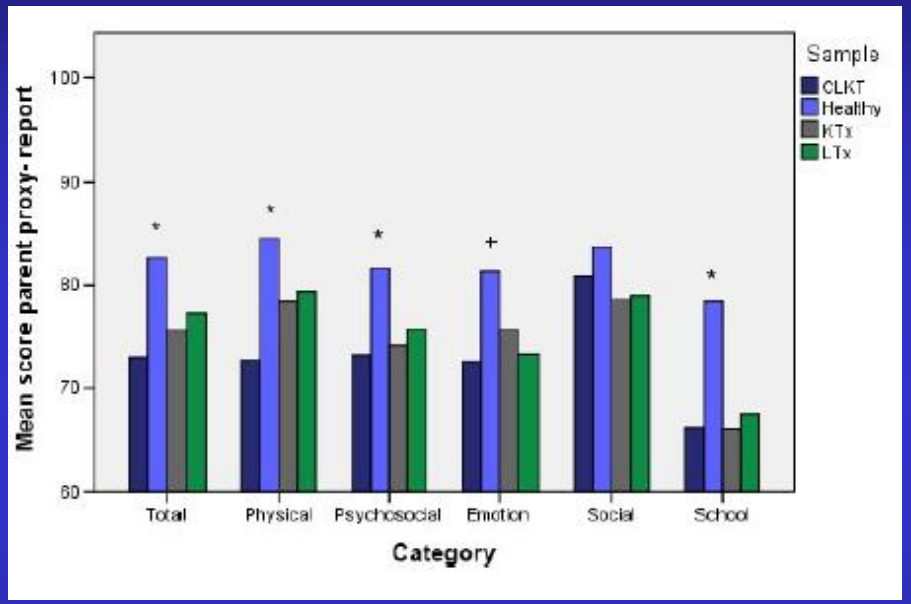
- Whereas survival after KTx in ARPKD is in the order of other underlying kidney diseases, the mortality after KTx is in 60–80% related to ascending cholangitis.
- The immunosuppression after KTx may increase the risk for cholangitis. Therefore, SLKTx should be considered for patients with ESRD and liver disease, especially with Caroli syndrome or a history with cholangitis.
- A recent report from Hamburg [Brinkert] and duplicated in Essen [Hoyer] show excellent survival rates after SLKTx, justifying this strategy in a subgroup at risk.

Telega G, Cronin D, Avner ED. New approaches to the autosomal recessive polycystic kidney disease patient with dual kidney–liver complications. Pediatr Transplant 2013; 17:328–335
Brinkert F, Lehnhardt A, Montoya C, et al. Combined liver–kidney transplantation for children with autosomal recessive polycystic kidney disease (ARPKD): indication and outcome. Transpl Int 2013; 26:640–650

HEALTH RELATED QOL AFTER COMBINED KL TRANSPLANT



Child self- report PedsQL 4.0 of all four (CLKT, LTx, KTx, and healthy) groups. Mean scores for each subscale and each sample for the child self- report; *P*<.01*, *P*<.05+ ; significant difference indicates the comparison between the CLKT sample and the selected group



Parent proxy- report PedsQL 4.0 of all four (CLKT, LTx, KTx, and healthy) groups. Mean scores for each subscale and each sample for the parent proxy- report; *P*<.01*, *P*<.05+ ; significant difference indicates the comparison between the CLKT sample and the selected group

Schmaeschke et al. Pediatric Transplantation 2107