Immunosuppression Minimization in Pediatric Kidney Transplantation

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William Harmon Disclosures

- I currently receive research support from:
  - National Institutes of Health (NIH)
  - Bristol Myers Squibb
  - Genzyme/Sanofi
- I receive honoraria from:
  - Springer
  - Up-To-Date
- I am an unpaid consultant to
  - Genzyme/Sanofi
  - Bristol Myers Squibb

ESRD in Children

- What are the options for treatment?
  - Conservative management
    - Too late
  - Regeneration
    - Too early
  - Chronic Dialysis
  - Kidney Transplantation

Chronic Dialysis

- Pro:
  - Technical problems have been alleviated
  - Rehabilitation has been enhanced with EPO and rhGH
  - Recurrent disease is irrelevant
  - Some progress is being made with nightly HD, making treatments less onerous on daily schedules

Chronic Dialysis

- Con:
  - Treatments do not correct uremia
    - Growth and development are inhibited
  - Treatments are always dependent on access
  - Treatments interfere with daily schedule
  - Recurrent treatments lead to shortened life-span and decreased graft survival
  - There has been no true technical break-through in over a decade

Kidney Transplantation

- Pro
  - Restores normal renal function
  - Provides best setting for growth and development
  - Has had multiple continuous improvements in past 3 decades
  - Has very low mortality rate
  - Children can have the best outcomes

Kidney Transplantation

- Cons
  - Is not a “cure”, requires continuous treatment and eventually fails
  - Chronic immunosuppressive medications have serious side effects
    - Infection, Cancer and Cardiovascular disease
  - Recurrent disease is possible
  - Success requires substantial adherence

How Do Children and Adults Differ?

- Children are generally smaller than adults
- Children will, on average, live longer than adults
- Children are constantly maturing: ie they are supposed to grow and develop
- Children's immune response is diminished early in life, but then becomes "average"

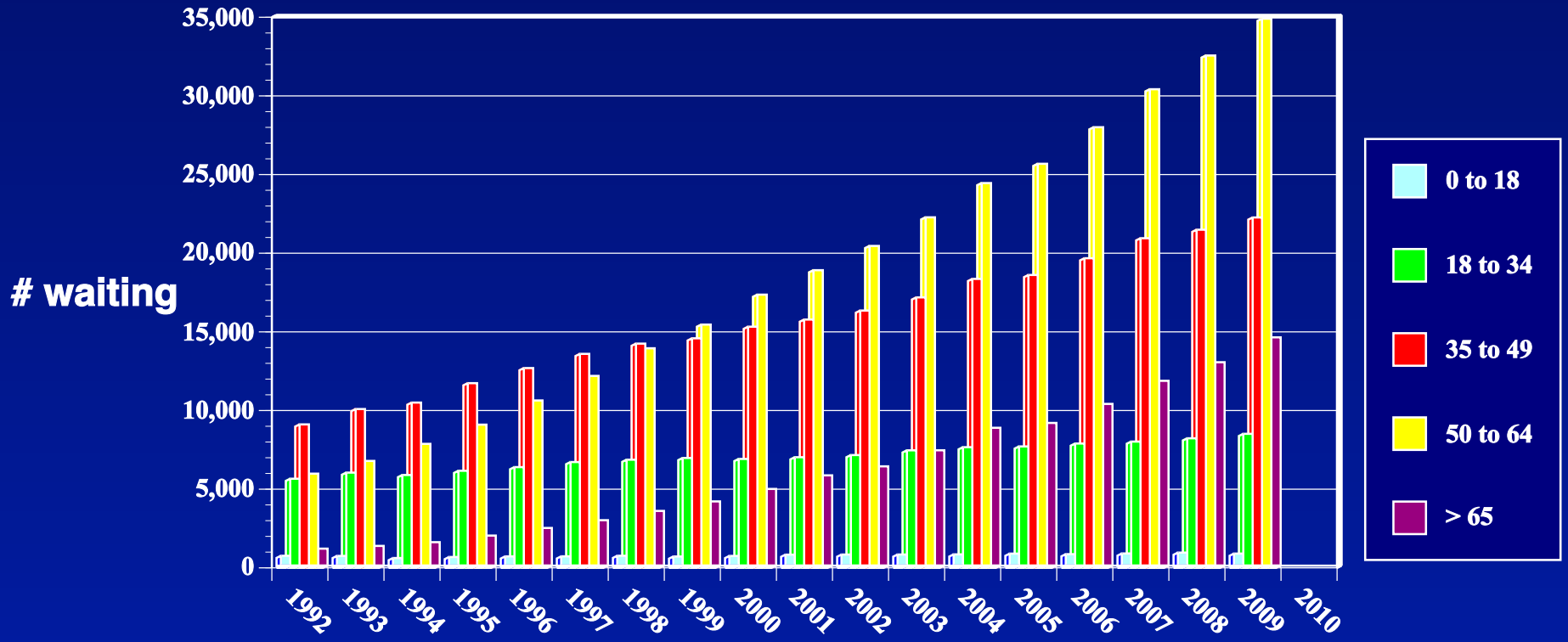
How Do Children and Adults Differ?

- Children are biologically naïve:
  - They are less likely previously to be sensitized
  - They are less likely previously to have been exposed to infections
- Children frequently have inherited or congenital causes for organ failure that won't recur in a transplanted organ
- Children are vulnerable and protected by society

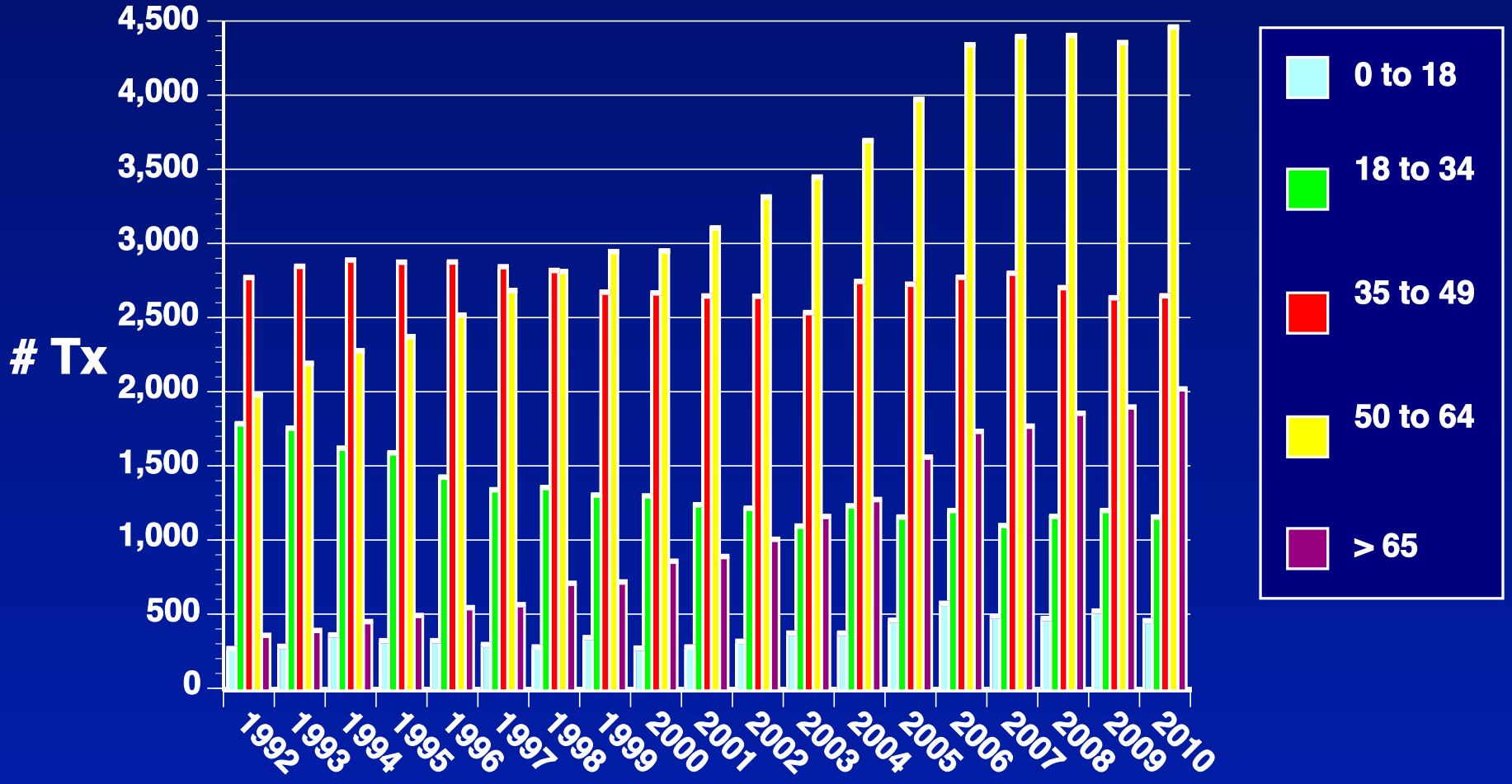
Outline

- Demographics of Chronic Kidney Disease and Transplantation in Children
- Recent experimental studies
- Current practices of renal transplantation in children
- Unresolved problems

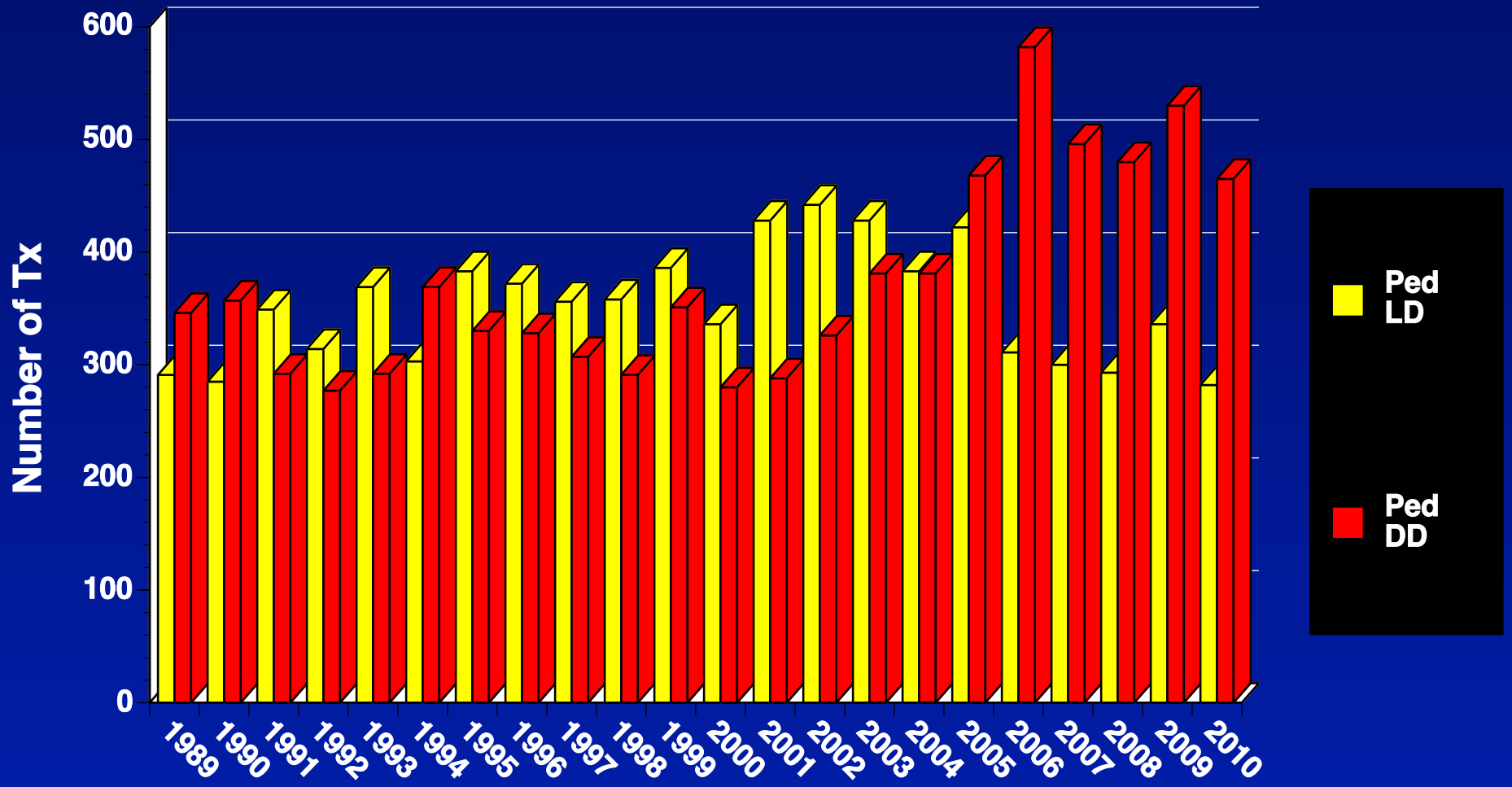
Waiting List by Age



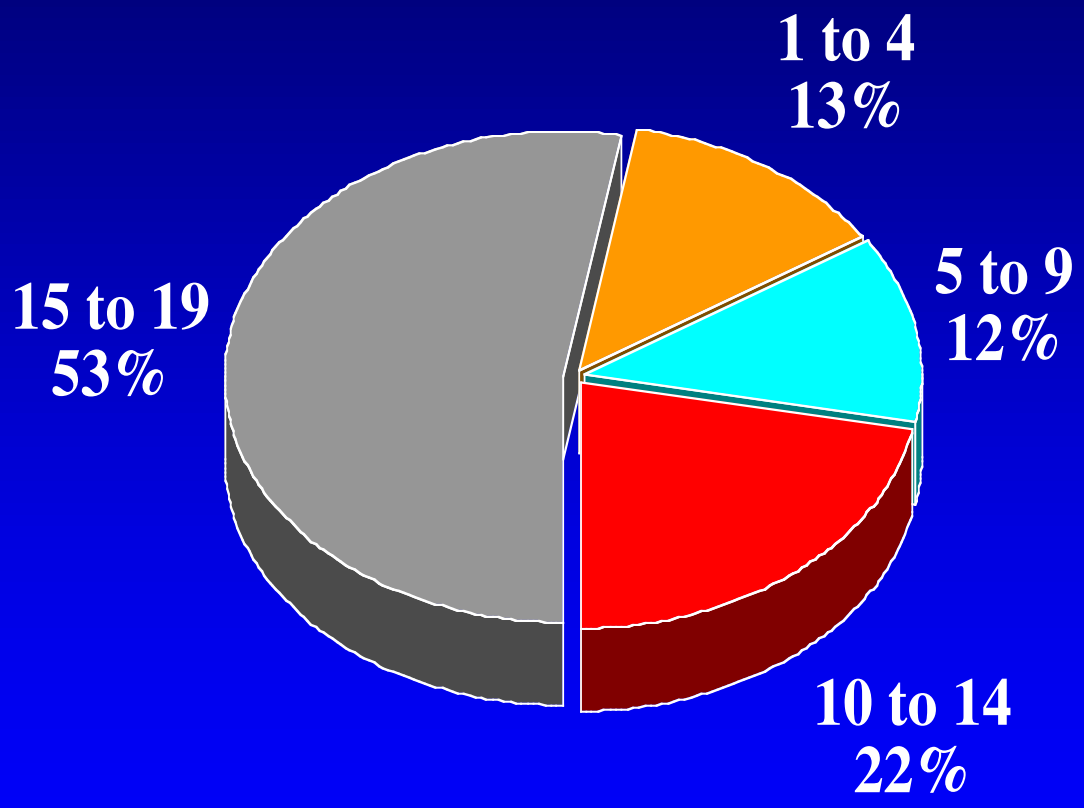
Deceased Donor Transplants by Age



Pediatric Living and Deceased Donor Kidney Transplants by Year



Annual renal transplants by recipient age



NAPRTCS

Demographics of pediatric renal transplant recipients by age

	0-1	2-5	6-12	13-17	>17
Male	68%	68%	60%	56%	54%
Female	32%	32%	40%	44%	46%
White	79%	65%	64%	60%	55%
AA	7%	14%	13%	18%	25%
Hispanic	10%	14%	16%	16%	13%
Other	4%	6%	6%	6%	6%

NAPRTCS

Etiology of E.S.R.D. in children and adults

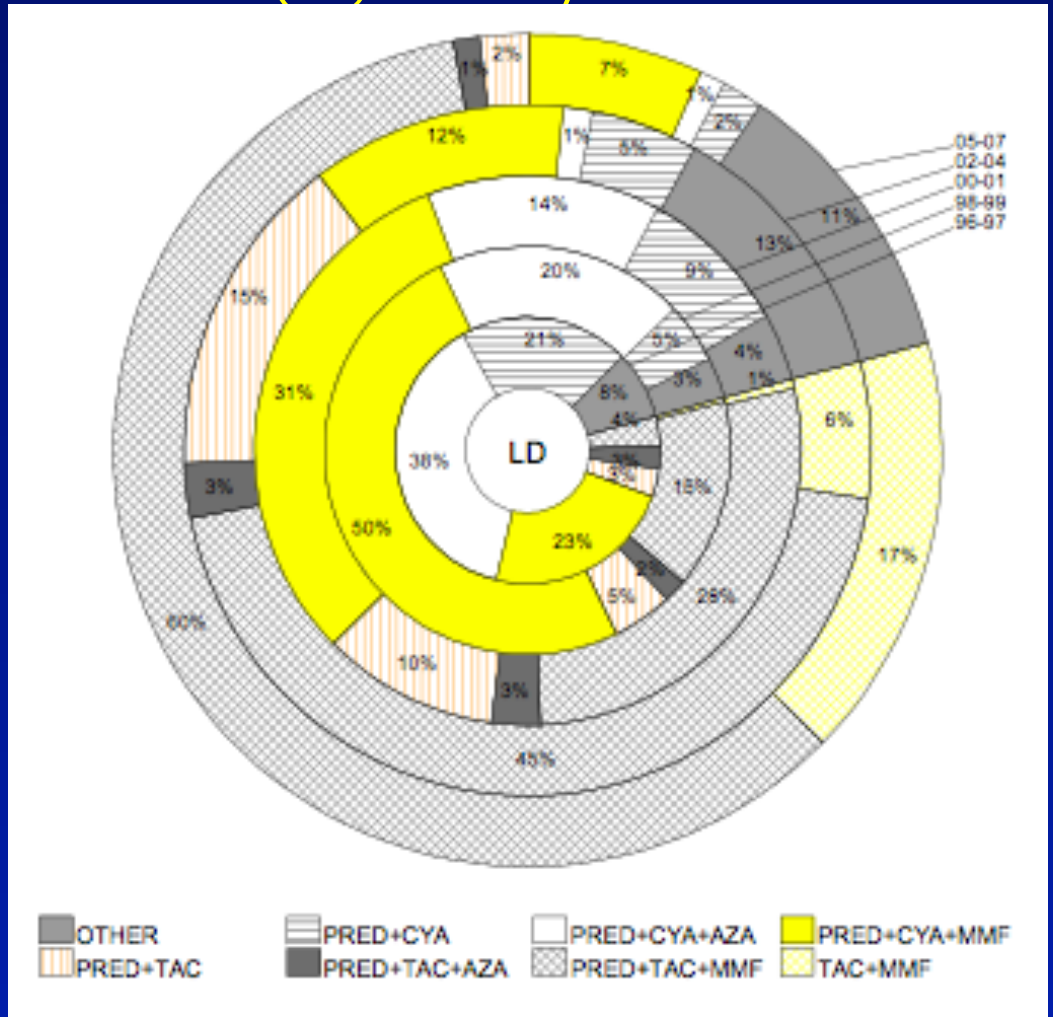
Etiology of ESRD in Children and Adults

Disease Category	Children (<18)*	Adults (20-64)+
Renal Dysplasia	17%	0.3%
Urologic	26%	4%
Other Congenital	15%	5%
FSGS	11%	2%
Other GN/Immunologic	14%	17%
Hypertensive Nephropathy	0%	22%
Diabetic Nephropathy	0.1%	40%

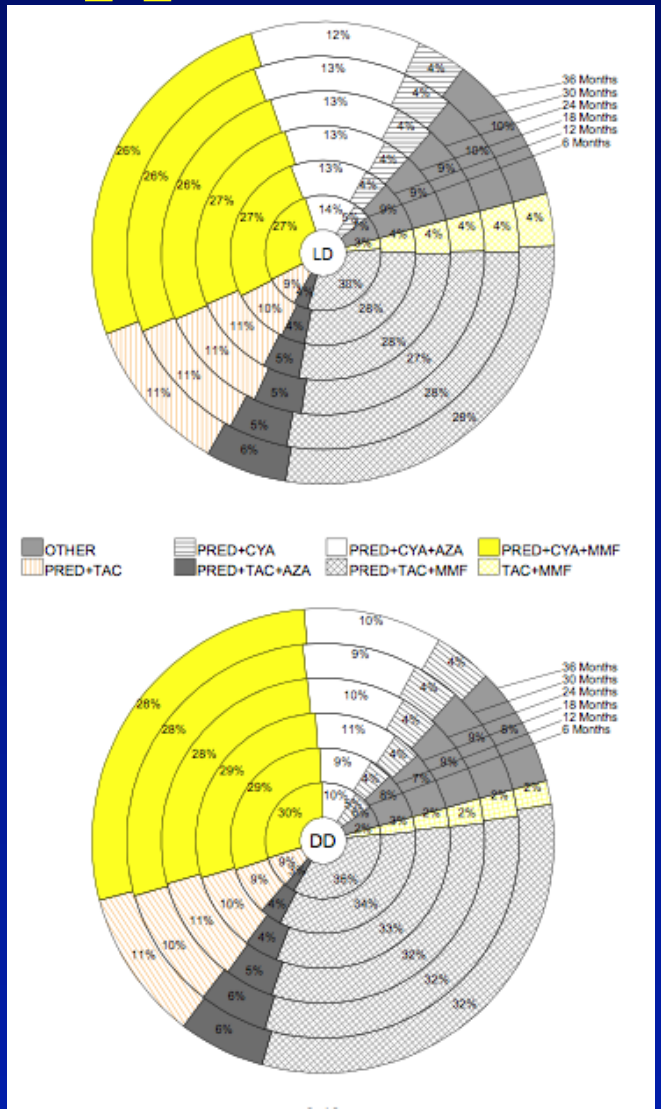
*Source: NAPRTCS

+Source: USRDS

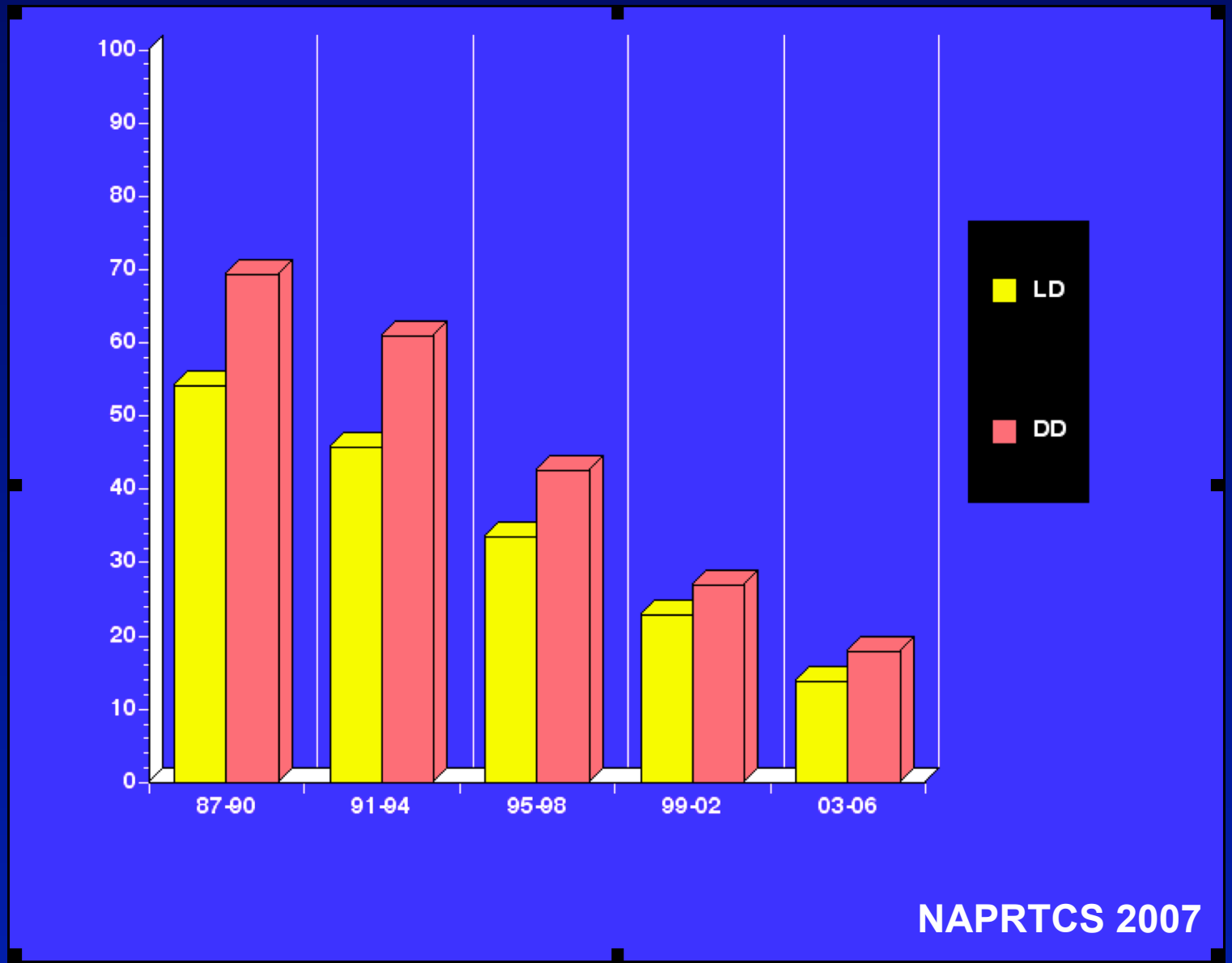
Pediatric Living Donor Kidney Transplant Immunosuppression @ Day 30



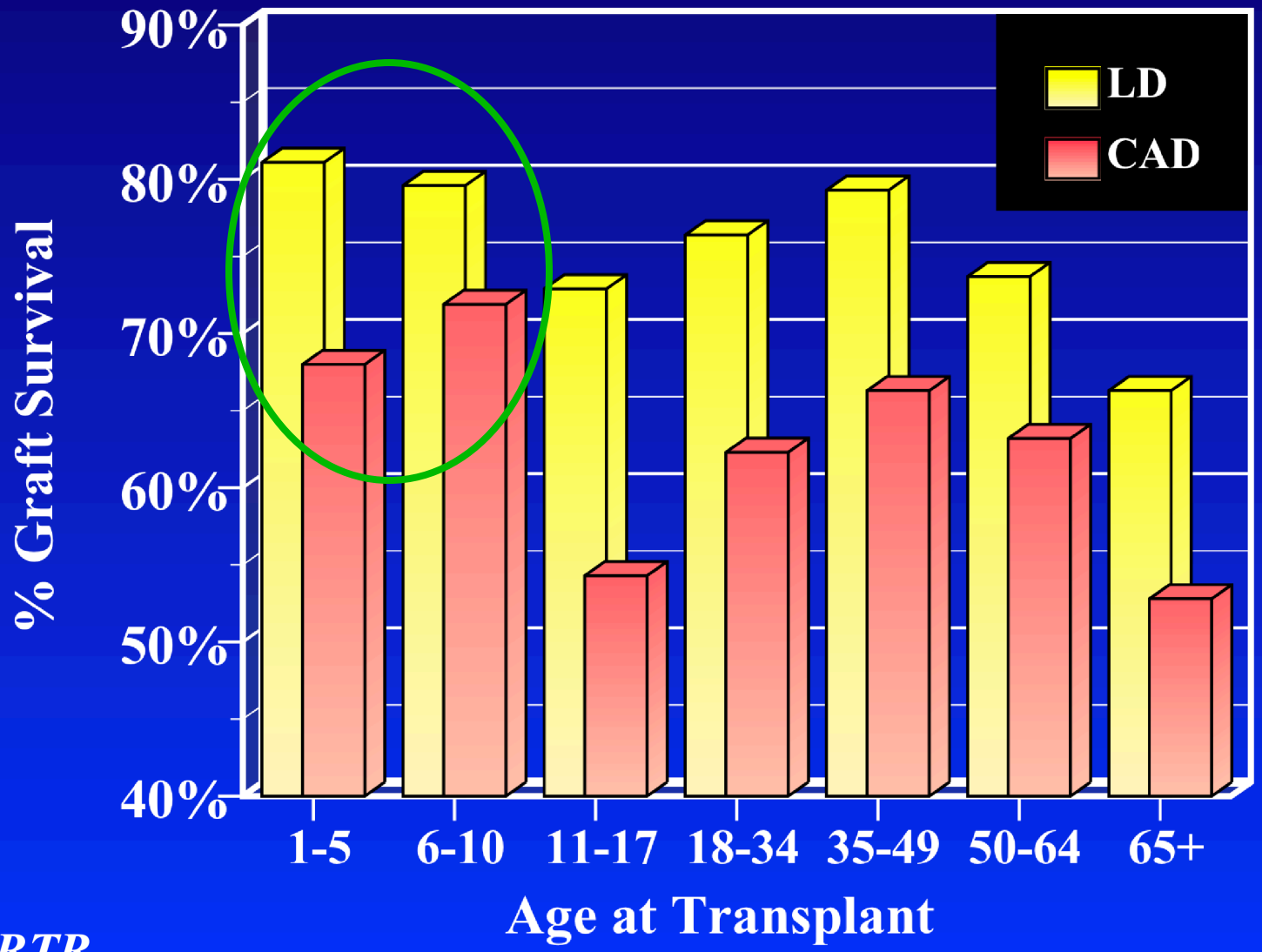
Pediatric Kidney Transplant Immunosuppression Follow-Up



Acute Rejection Rates by Era



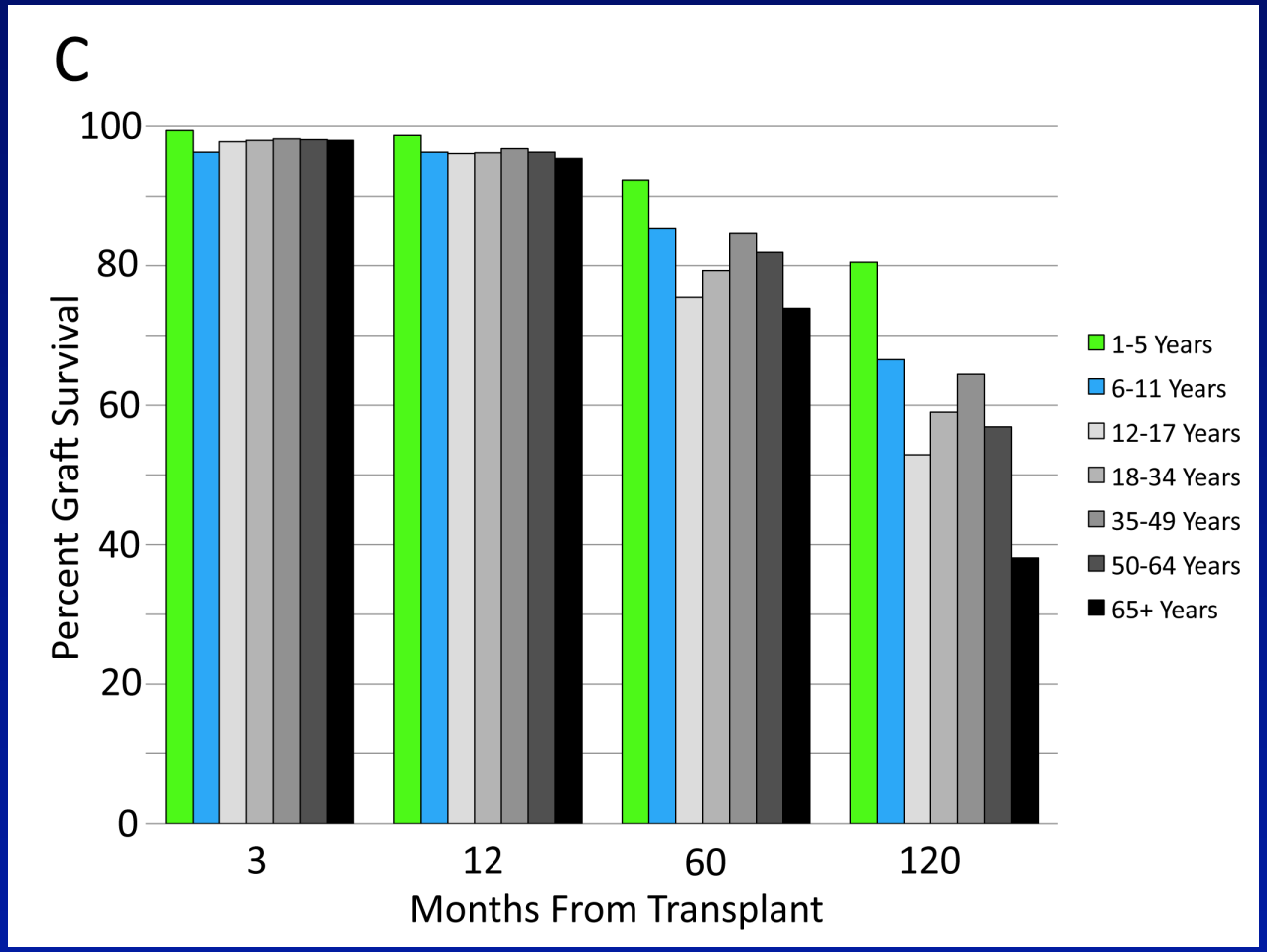
5-Year Graft Survival by Recipient Age



SRTR

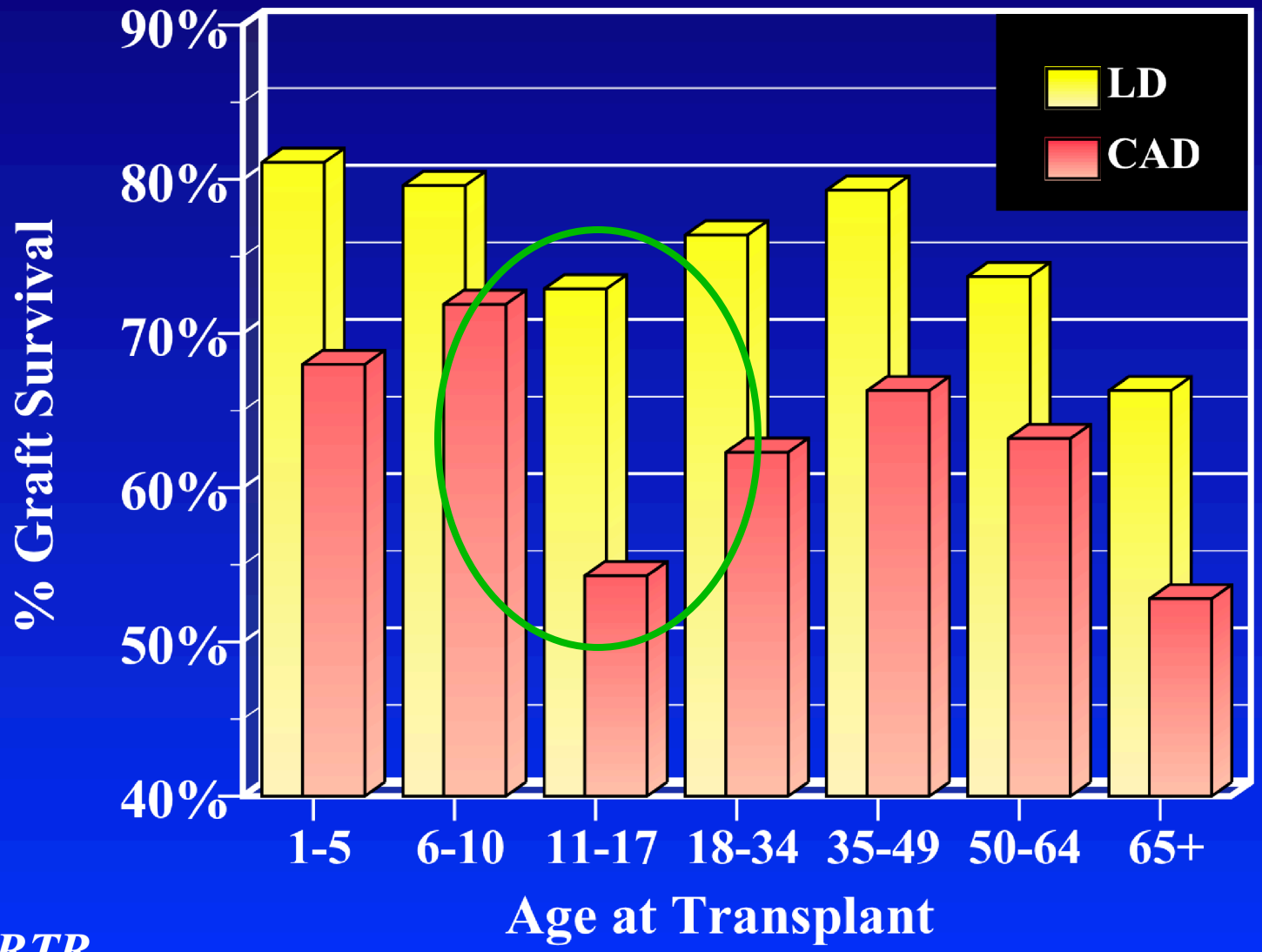
OPTN/SRTR 2002 Report, Table 5.8

Kidney Graft Survival by Age



Young children have the best long-term graft survival of all age groups

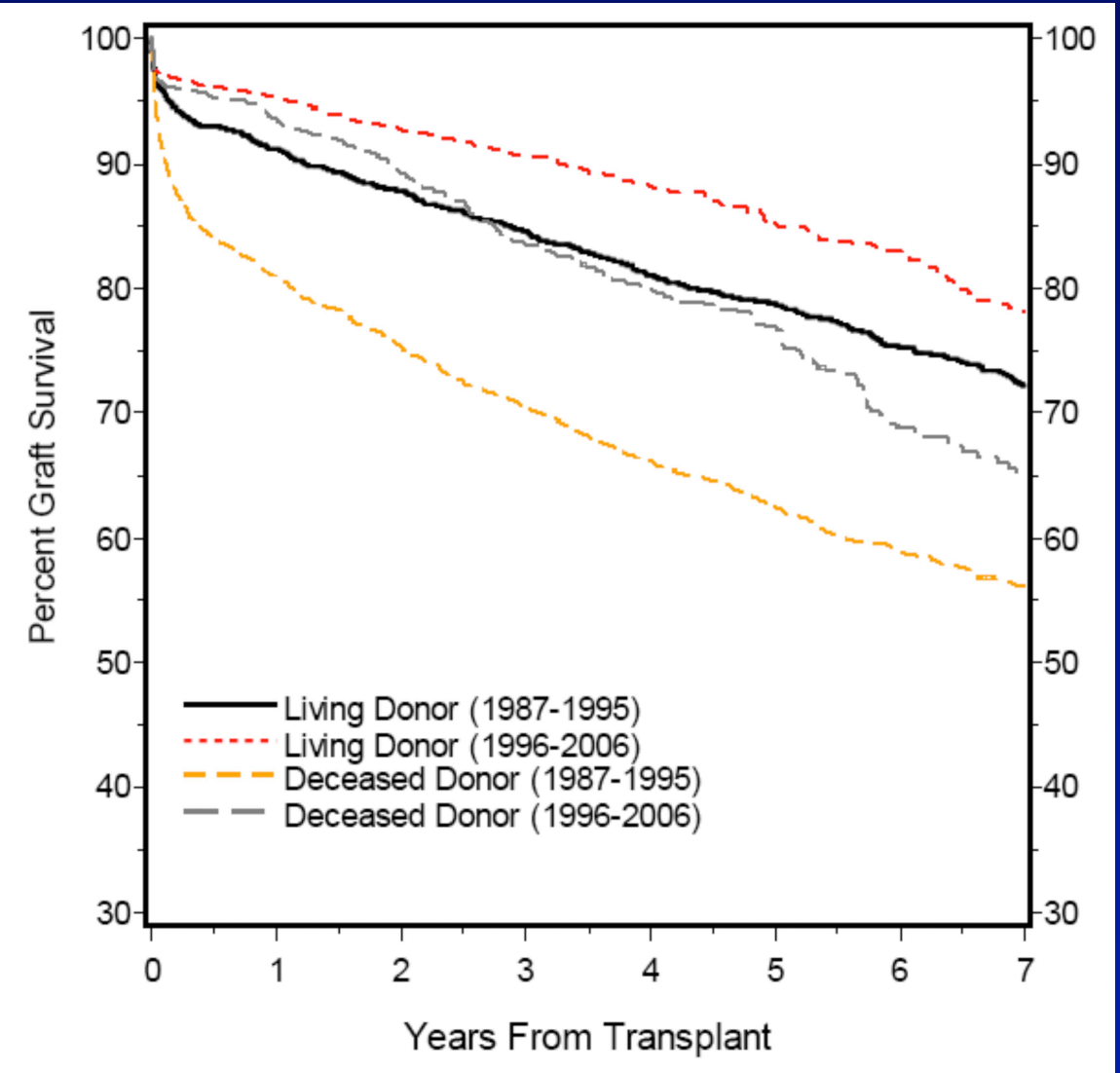
5-Year Graft Survival by Recipient Age



SRTR

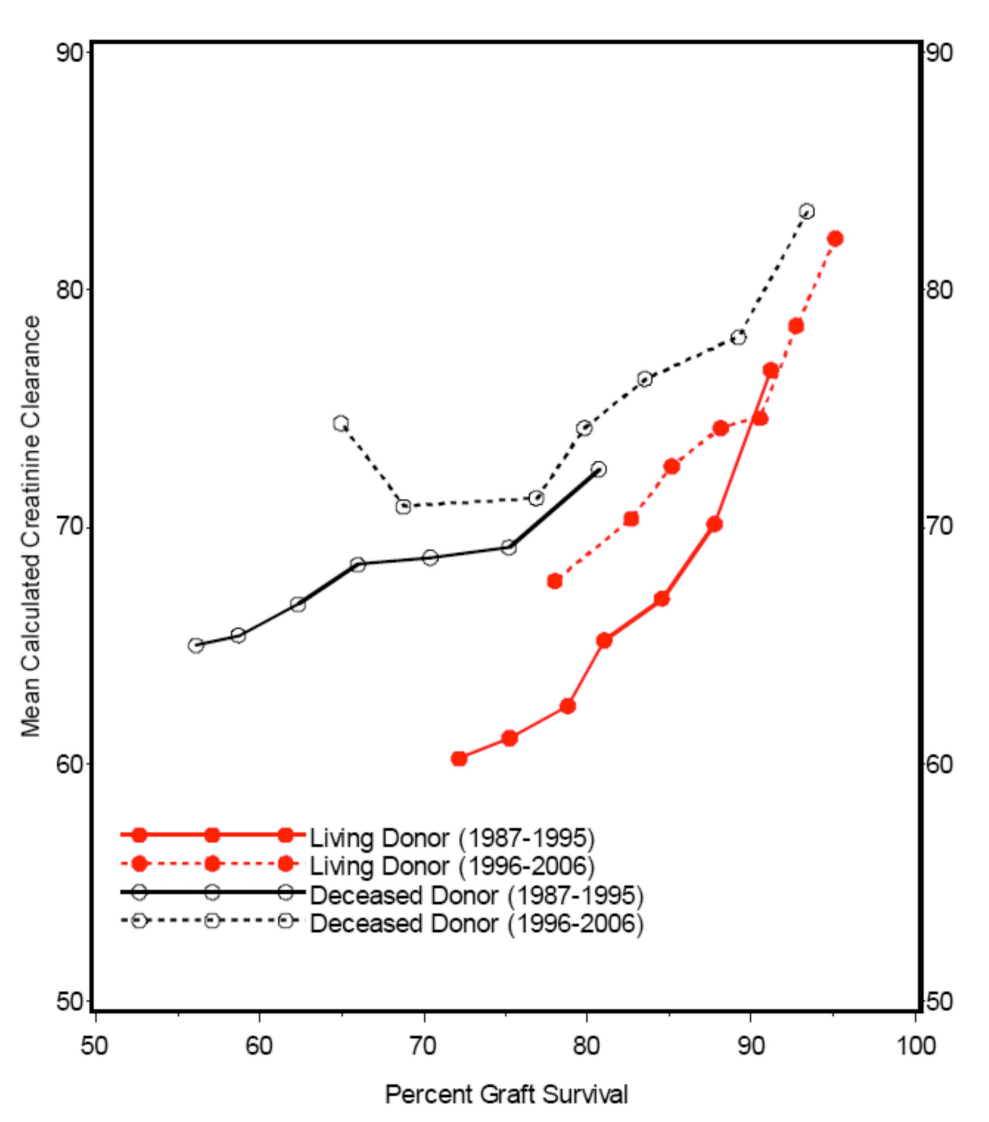
OPTN/SRTR 2002 Report, Table 5.8

Pediatric Kidney Transplant Survival



NAPRTCS 2007

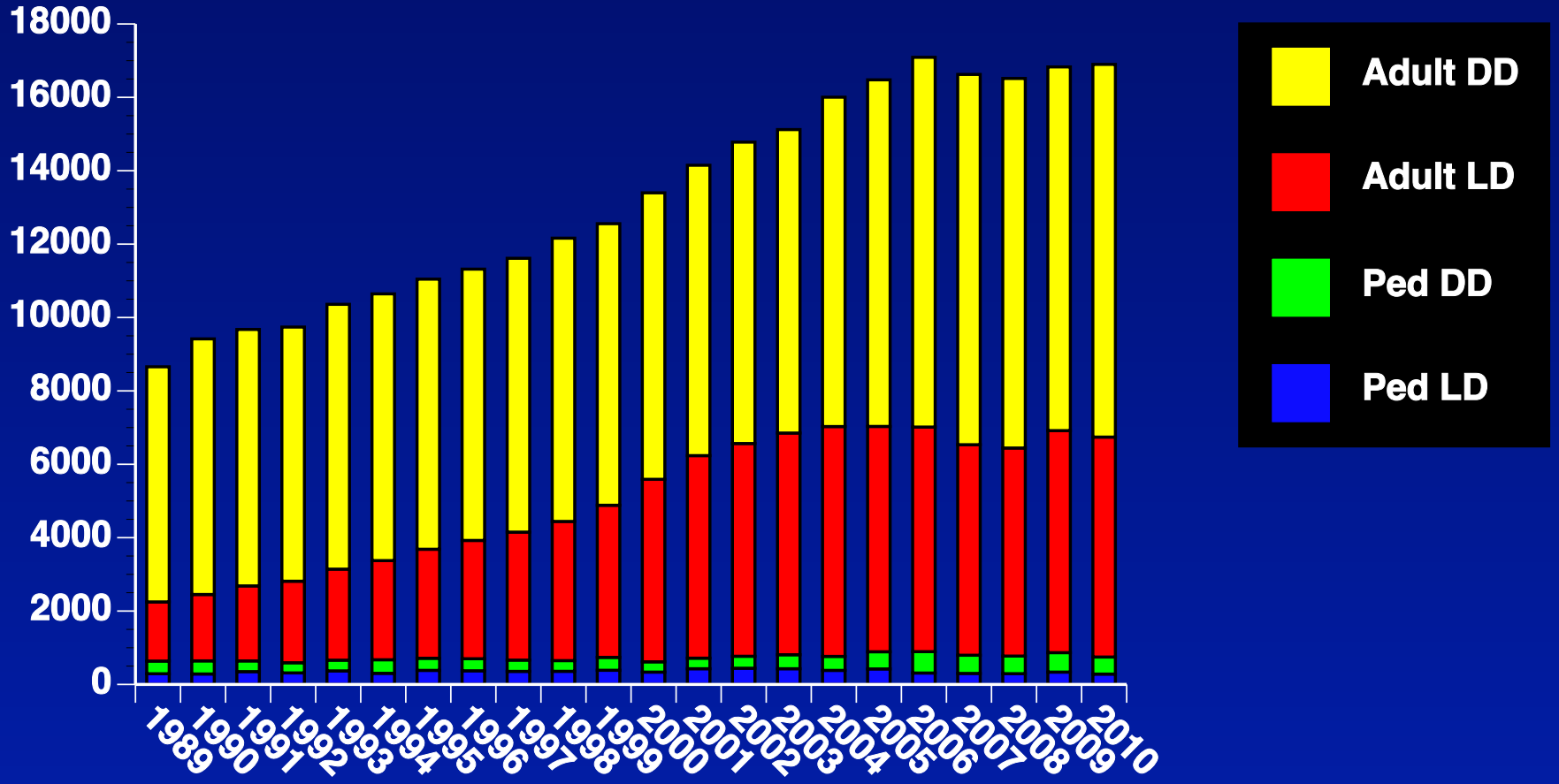
Graft Function and Survival at Annual Follow-up



Pediatric Kidney Transplant Outcomes

- As with adults, short-term outcomes of pediatric kidney transplants have improved and are excellent.
- Young children are low risk and have the best outcomes of all age groups.
- Adolescents are a high-risk age group.
- Long term outcomes have not improved and are particularly important for children because their mortality rates are low.
- GFR (graft function) deteriorates constantly.

Why do Pediatric Studies Require Multi-Center Study Groups?



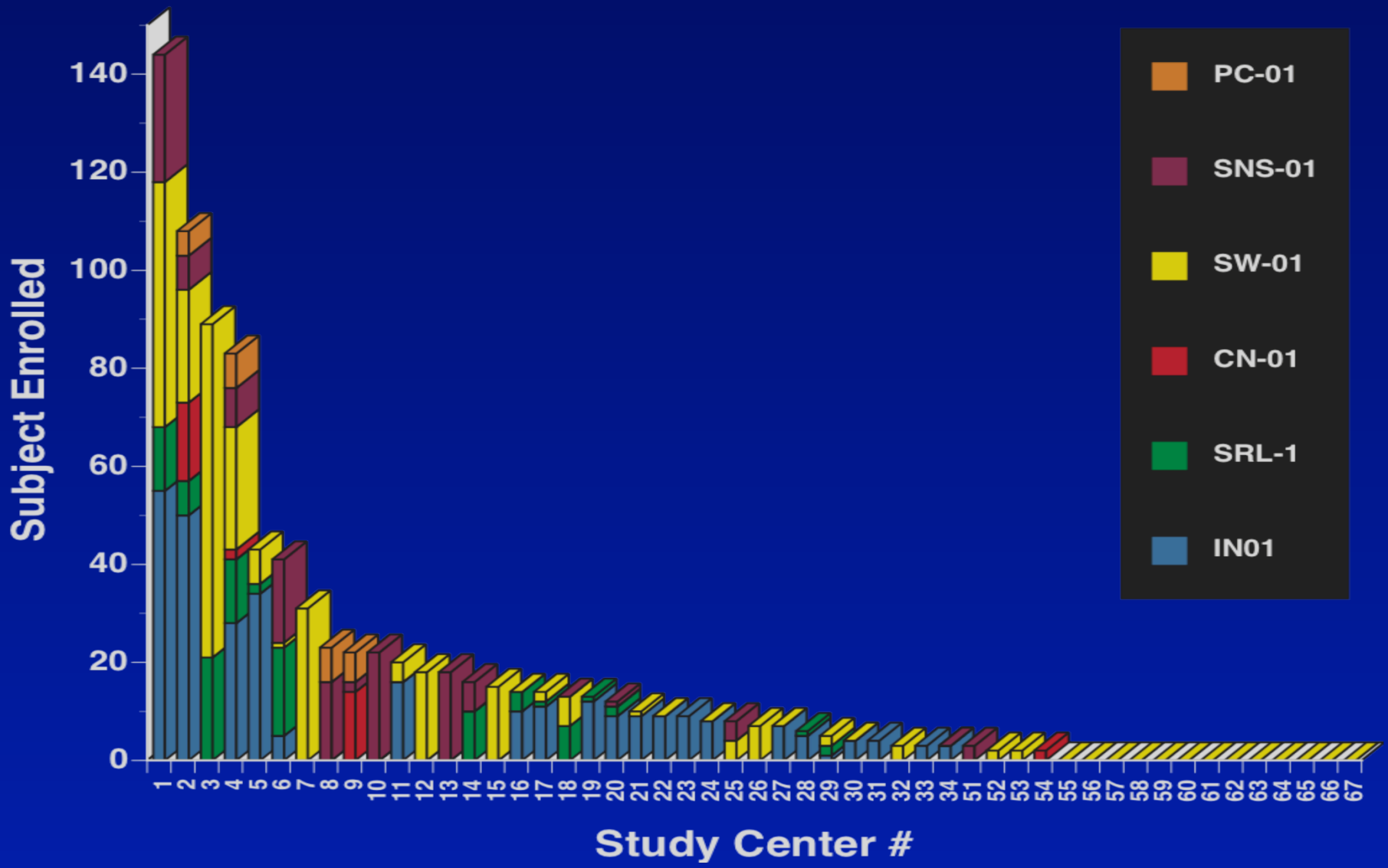
Two USA Pediatric Organizations

- CCTPT?
- CTOT-C?

What is CCTPT?

- Cooperative Clinical Trials in Pediatric Transplantation
  - Funded through NIAID
  - U-01 mechanism
    - Clinical trial
    - Mechanistic or other basic studies
  - Total funding $2.5M/year for 4-5 years for 2 centers
  - Began 1994 Ended 2008

NAPRTCS/CCTPT Transplant Studies



What is CTOT-C

- Clinical Trials in Organ Transplantation in Children
- U-01 to replace CCTPT, begin 3/08
- 4 Consortia Funded
  - 2 Kidney:
    - Harmon: 6 Center
    - Kirk: 3 Centers
  - 1 Lung: Sweet, 6 Centers
  - 1 Heart: Webber, 6 Centers

Pediatric Kidney Transplant Controlled Trials

Table 1. Recent randomized prospective multicenter trials in pediatric kidney transplantation.

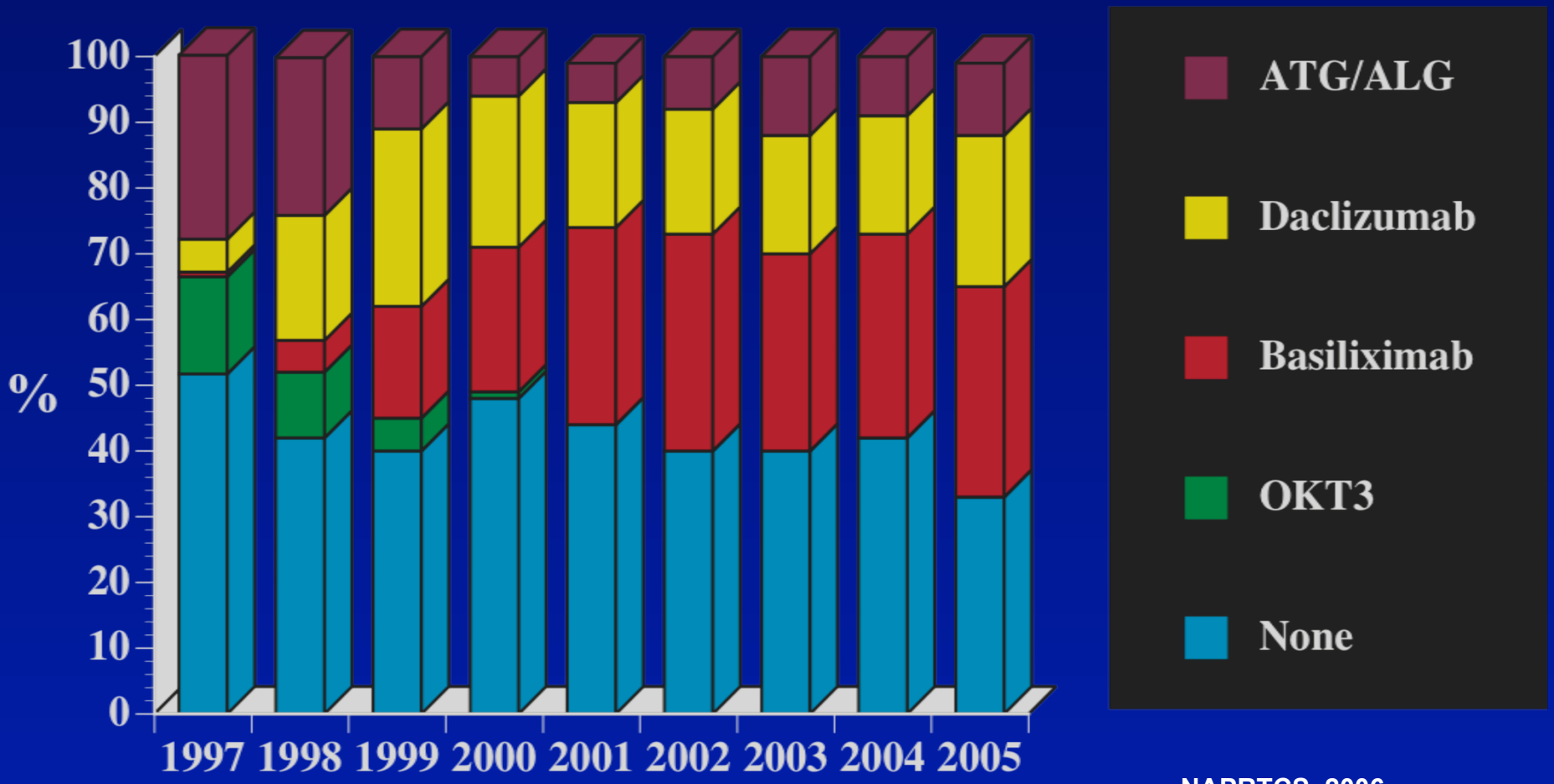
Trial name	Purpose	Reference group immunosuppression (n)	Study group immunosuppression (n)	Conclusion/ comments
IN01 [95]	Efficacy of OKT3 induction and double blind comparison of Neoral to Sandimmune	Cyclosporine A induction, oral cyclosporine, anti-metabolite, steroids (n=140)	OKT3 induction, oral cyclosporine, anti-metabolite, steroids (n=147)	No differences between groups in any parameters
SW01 [96]	Late steroid withdrawal	Basiliximab, tacrolimus, sirolimus, steroids (n=73)	Withdrawal of steroids after 6 months post-transplant (n=59)	Significantly better height velocity and graft survival in study group but study stopped early due to excessive PTLD in both arms
Late steroid withdrawal study [97]	Safety of late steroid withdrawal	Cyclosporine A, mycophenolate, steroids (n=21)	Withdrawal of steroids after 1-year post-transplant (n=21)	Significantly better catch up growth, less hypertension and less frequent dyslipidemia in the steroid withdrawal group
FDCC [98]	Basiliximab induction efficacy in children	Cyclosporine A, mycophenolate, steroids and placebo (n=92)	Basiliximab, cyclosporine A, mycophenolate, steroids (n=100)	No significant difference in acute rejection rates between the groups
TWIST [68]	Efficacy and safety of early steroid withdrawal	Tacrolimus, mycophenolate, steroids (n=98)	Tacrolimus, mycophenolate, steroids till day 4 only, 2 doses only daclizumab (n=98)	Significantly improved height growth in study group, more so in pre-pubertal.
SNS01	Efficacy and safety of steroid avoidance	Daclizumab 5 doses, tacrolimus, mycophenolate, steroids (n=65)	Daclizumab 9 doses, tacrolimus, mycophenolate (based on Stanford protocol; (n=65) [65, 69]	Study results not yet published

Pediatric Kidney Transplant Pilot Trials

Table 2. Other prospective multicenter trials in pediatric kidney transplantation.

Trial	Purpose	Immunosuppression (n)	Comments
Tricontinental study [64]	Efficacy and safety of mycophenolate mofetil suspension	Cyclosporine A, mycophenolate, steroids (n=100)	Drug well tolerated, low rate of withdrawal
CN01 study [99]	Pilot trial of calcineurin avoidance	Anti-IL2RmAb, sirolimus, mycophenolate, steroids (n=34)	Rates of graft survival and acute rejection similar to other protocols
FDCC subgroup study [100]	Compare fixed dose versus concentration controlled mycophenolate dosing	Cyclosporine A, mycophenolate, steroids (n=62)	Younger children (< 6) had numerically higher rates of leucopenia and diarrhea, but overall well tolerated
PC01?	Steroid Avoidance and CNI withdrawal	Campath Mycophenolate Tacrolimus to Sirolimus (n=35)	Generally successful with excellent function and histology
CTOTC-01	Monotherapy	Mycophenolate withdrawal to Sirolimus Monotherapy	In progress (4/7)
CCTPT-02?	Long-term impact of donor specific anti-HLA antibody development	Any	In progress (5/118)

Pediatric Renal Transplantation Induction Antibody Use

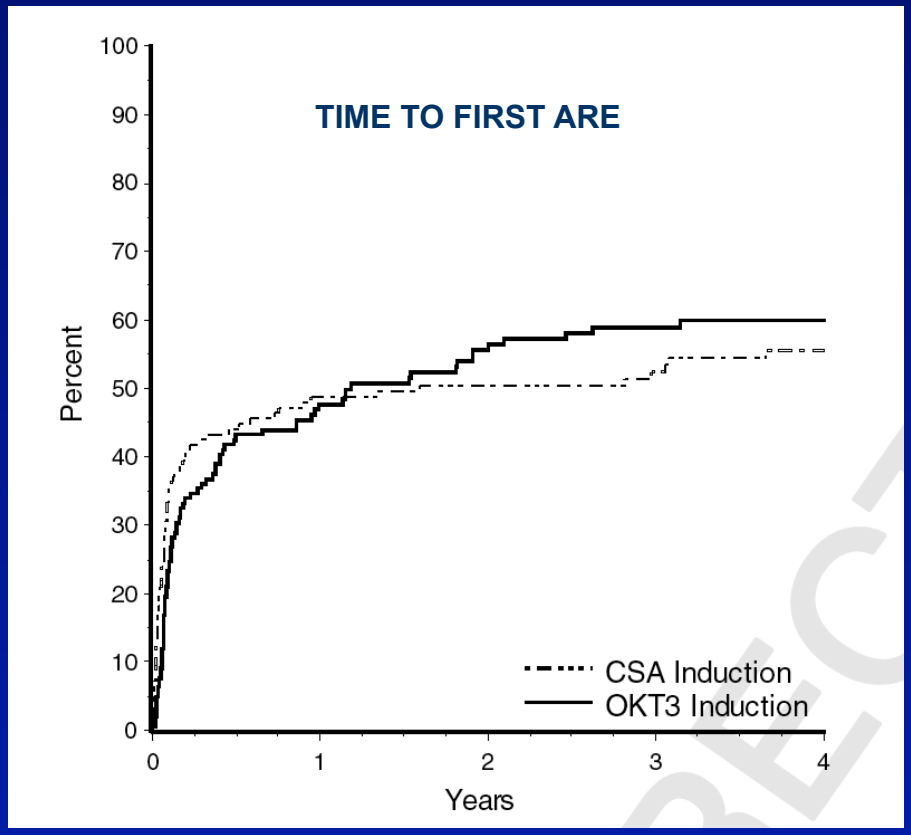


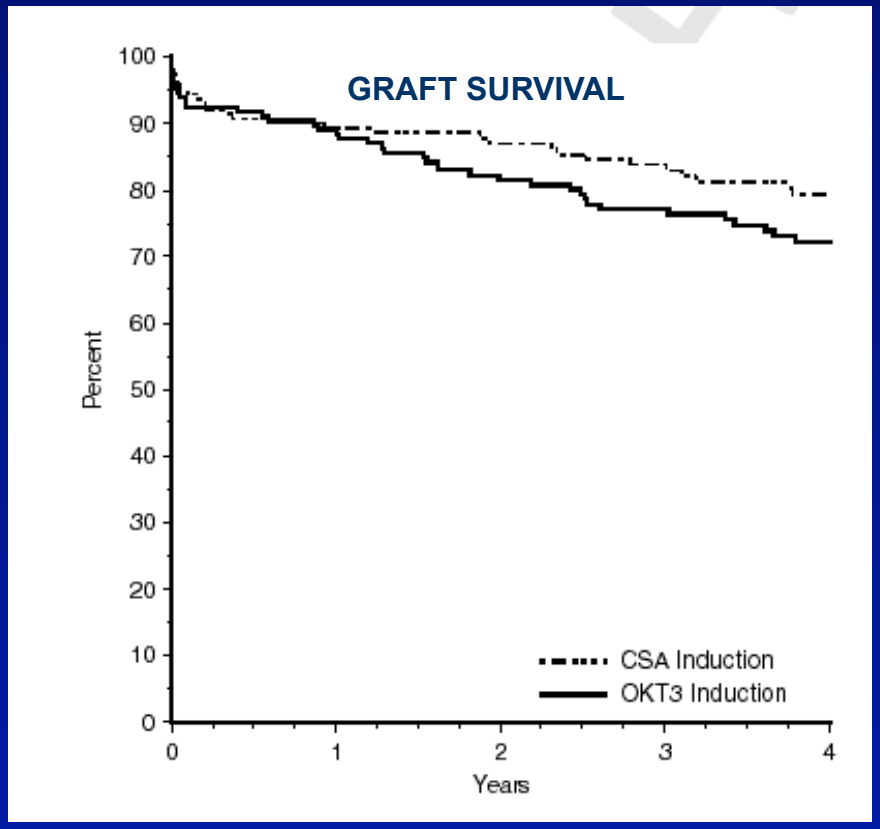
NAPRTCS, 2006

CCTPT IN-01 STUDY

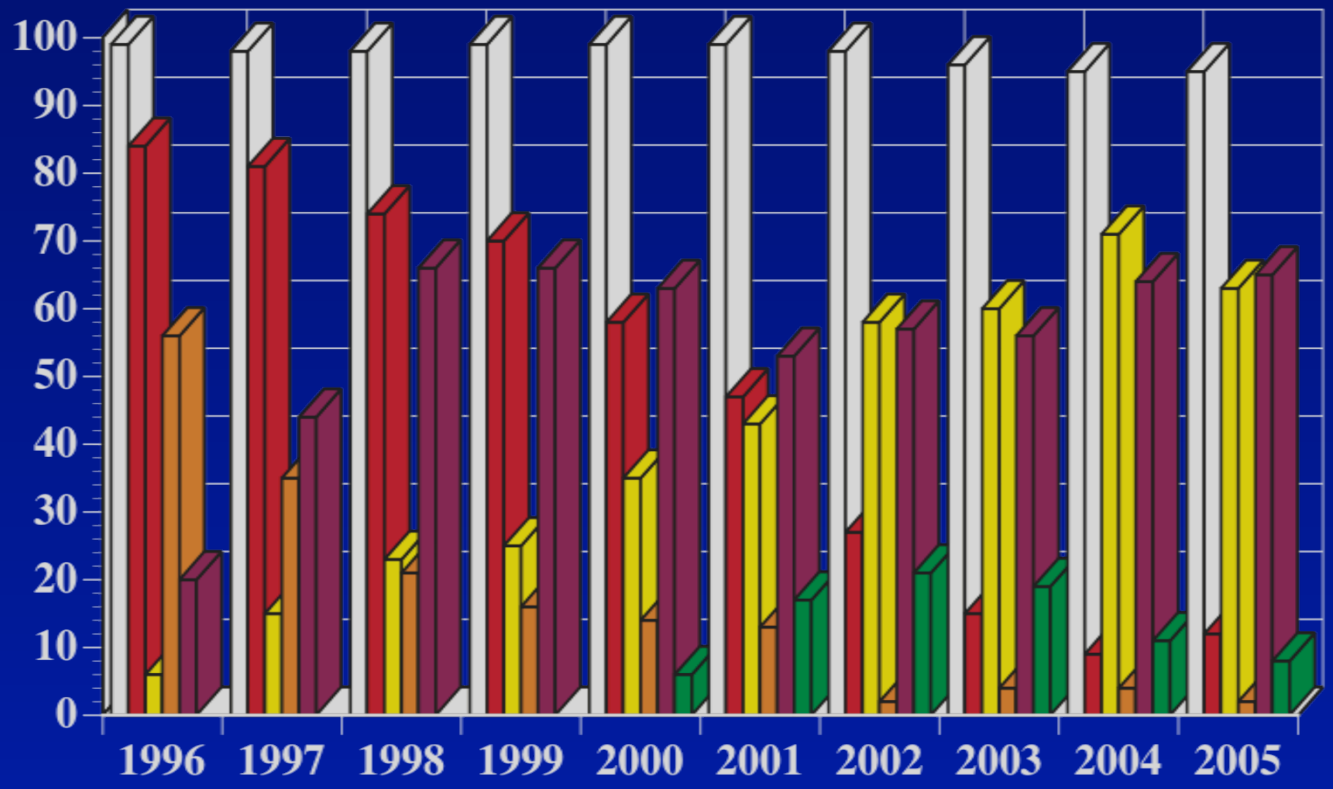
- Randomized, controlled trial
- 287 subjects enrolled
- OKT3 Induction vs IV Cyclosporine
- Maintenace Immunosuppression
  - Cyclosporine
  - Azathioprine/MMF
  - Corticosteroids

CCTPT IN-01 STUDY





Pediatric Renal Transplant Immunosuppression @ 30 Days



NAPRTCS, 2006

Research proposals

- Decrease or eliminate toxic medications
  - Diminish toxic effects without adversely affecting outcome
- Immunologic monitoring
- Mechanistic studies
- Is there something we can do for adolescents?

Which immunosuppressives should we eliminate?

- Corticosteroids:
  - Cushingoid appearance, obesity
  - Hypertension, Hyperlipidemia
  - Steroid diabetes
  - Aseptic necrosis, Osteoporosis
  - Growth failure

Which immunosuppressives should we eliminate?

- Calcineurin inhibitors
  - NEPHROTOXICITY
  - Neurotoxicity, hepatotoxicity
  - Hypertension, hyperlipidemia
  - Cosmetic issues
  - Steroid diabetes
  - ?PTLD risk

Recent Studies

- NAPRTCS/CCTPT Steroid Withdrawal (SW-01)
- NAPRTCS/CCTPT Calcineurin Inhibitor Avoidance (CN-01)
- CCTPT Steroid Avoidance Protocol (SNS-01)
- NAPRTCS/CCTPT Campath Induction (PC-01)

NAPRTCS/CCTPT SW-01

- Randomized, controlled, double-blind trial of steroid withdrawal
- Primary LD or CD recipients
- Initial Immunosuppression: αIL-2r, Pred, Rapa, FK/CyA for 6 months
- Biopsy at 6 months: Randomize if no rejection
- Randomize to Taper to 0 vs Daily Low Dose

NAPRTCS/CCTPT SW-01

- 274 of 300 Patients enrolled by August, 2004
- Enrollment closed August, 2004 for PTLD rate

SW-01 Results

- 274 Subjects enrolled
- Acute rejection rate 13.8%
- Subjects who had steroids withdrawn had:
  - *Lower* rate of late acute rejection
  - *Same* 3-year patient and graft survival
  - *Possibly better* growth rate

  Than the control group

PTLD in SW-01

- Rate was:
  - 12% in 0-5 year olds
  - 7% in 6-10 year olds
  - 3% in 11-17 year olds
  - 0% in >17 year olds
- Prophylaxis and enhanced observation were not prescribed by original protocol
- Most patients treated by decreasing immunosuppression alone

Our conclusions from SW-01

- This was first controlled trials demonstrating that steroid withdrawal is possible in children
- We have left withdrawal group on CNI + Rapa and have weaned control group off of steroids
- IL2r antibody, steroids, CNI and Rapamycin are too immunosuppressive in at-risk population
- Pediatric immunosuppression trials must include strategies for PTLD avoidance

CN-01 Study Design

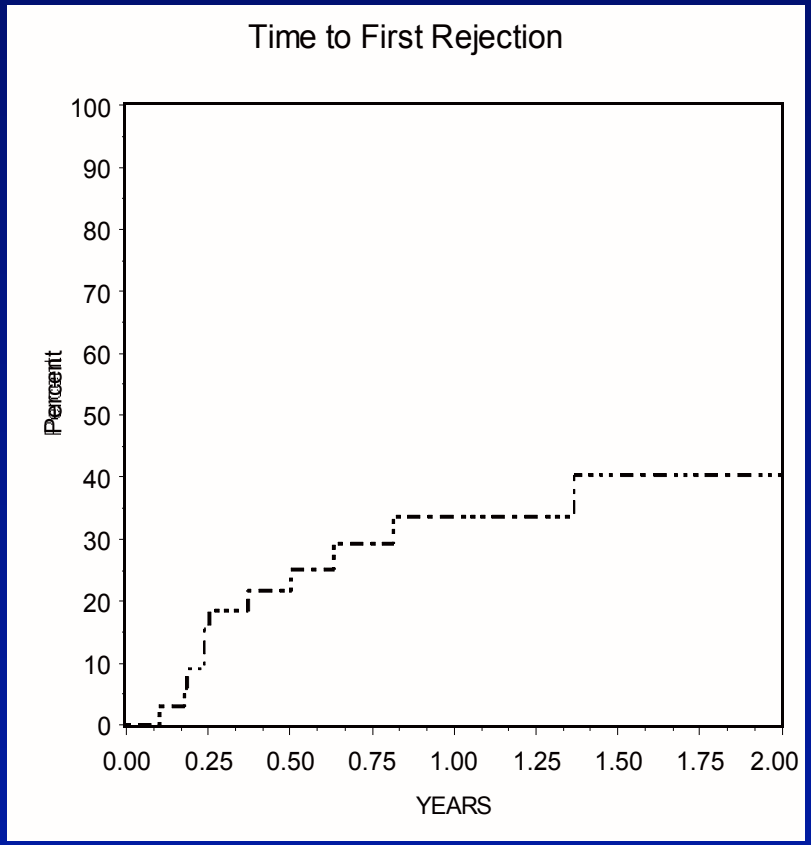
- Single-arm pilot trial of calcineurin inhibitor avoidance
- 35 pediatric living donor kidney transplants
- 4 Centers
- CCTPT oversight
- Primary objective: To determine if rejection risk is sufficiently low to permit use of this protocol in children: Acute rejection rate at 6 months

CN-01 Clinical Protocol

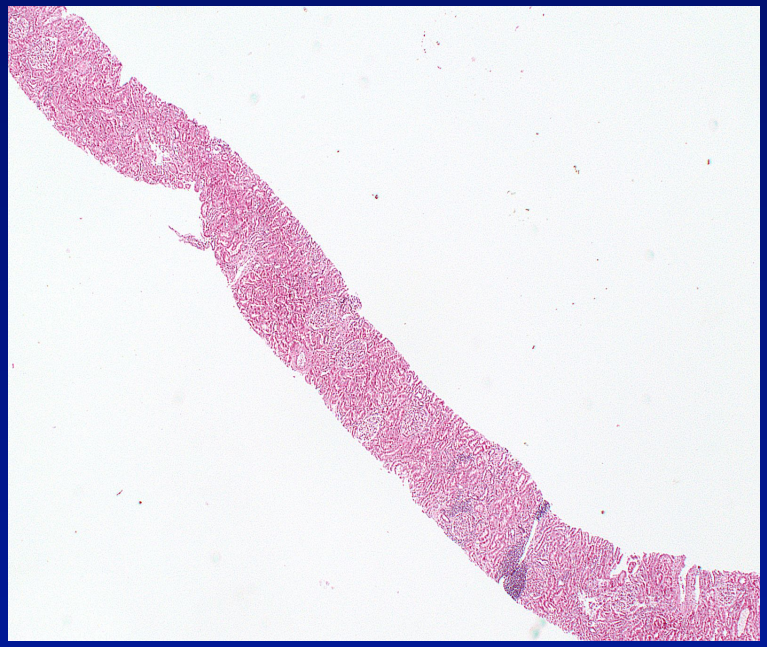
- Eligibility: 1st or 2nd Living donor transplant
- Immunosuppression
  - Daclizumab 5 doses
  - Sirolimus to target levels (25 -> 15 ng/ml), dosage bid
  - MMF at 1,200 mg/M^2/day, divided bid
  - Prednisone tapered to QOD dose
- Biopsies at 0, 3, 6, 12 months
- Mechanistic studies

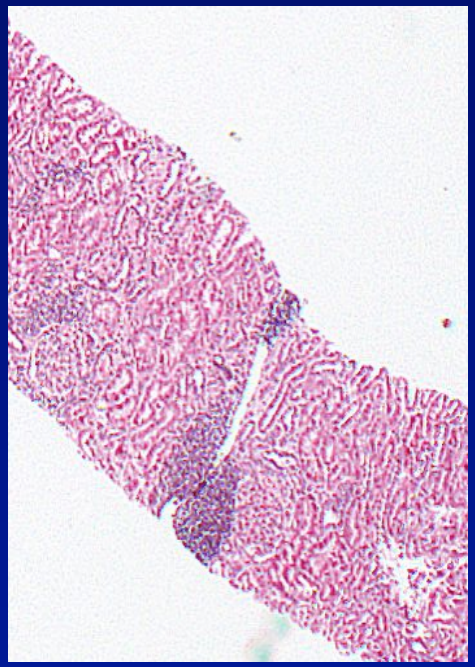
Acute Rejections

- 11/33 subjects had 14 ARE
  - 11 acute cellular
  - 2 acute/chronic
  - 1 acute cellular/vascular
- 14 treated with pulse steroids
  - 3 received antibody Rx
  - 2 converted to FK



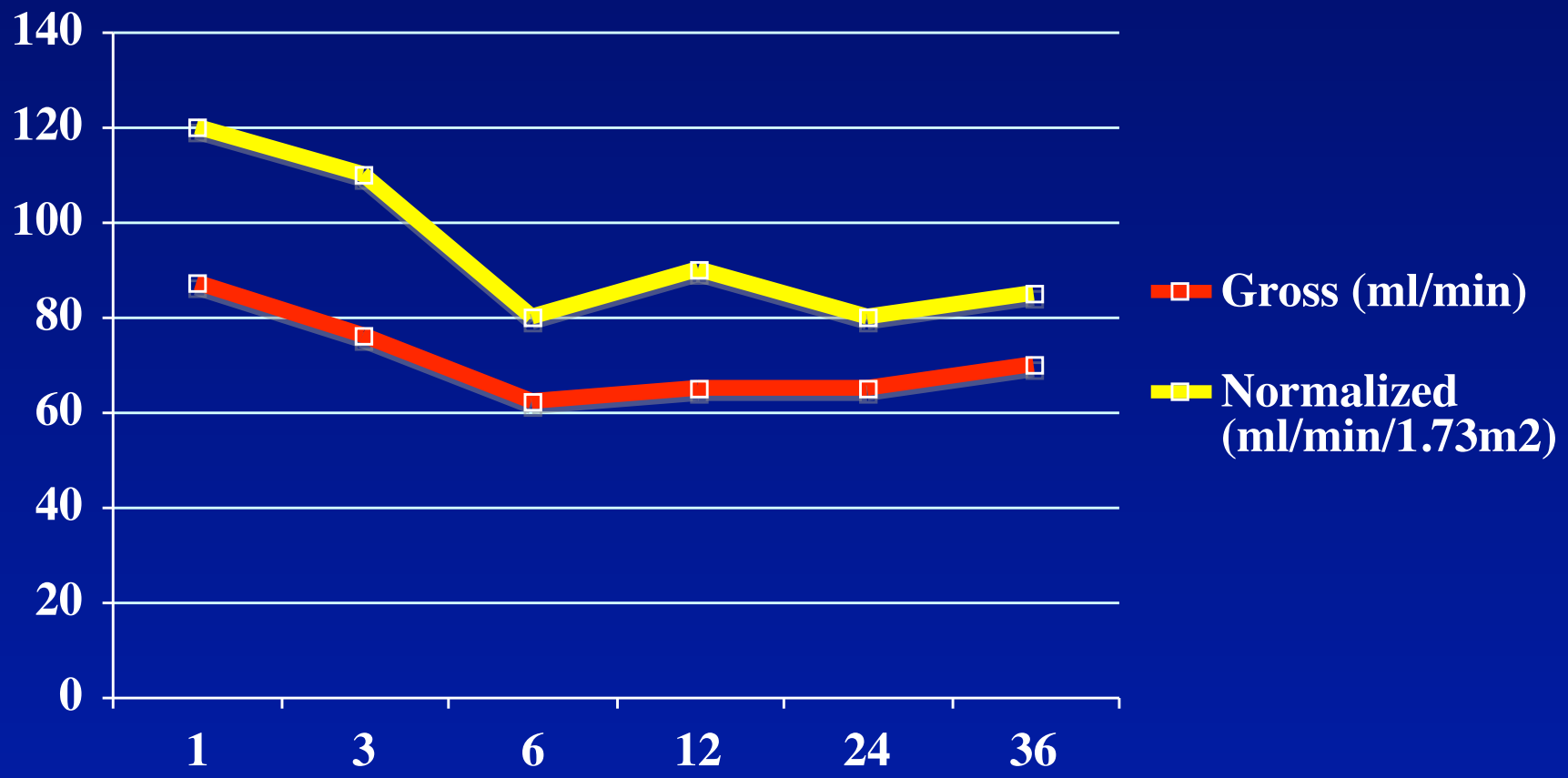
Surveillance Biopsies





- Many of the infiltrates were not associated with tubulitis or vasculitis and resolved spontaneously

Measured GFR



CN-01 Summary

- This calcineurin inhibitor avoidance protocol resulted in excellent short-term patient and graft survival and GFR
- The acute rejection rate was high
  - More robust induction might be beneficial
- Complications included some cases of lymphocele and poor wound healing. Also, GI disturbance was frequent.

CCTPT: Steroid Avoidance SNS-01

Steroid No Steroid (SNS): Controlled trial to test Stanford Steroid Avoidance Pilot

- 120 Primary LD and CD primary transplants
- Randomized at entry
- Group 1: αIL-2r x 6 months, FK, MMF
- Group 2: αIL-2r x 2 months, FK, MMF, low dose Pred
- Outcomes: Rejection, growth, etc
- 1-2 year

CCTPT: SNS-01

- Enrollment closed 8/2006
  - 130 recipients from 12 sites
- Results
- Acute rejection rate is ~20% in experimental and control groups
  - Patient and graft survival is excellent
  - Growth rate not yet improved in experimental group

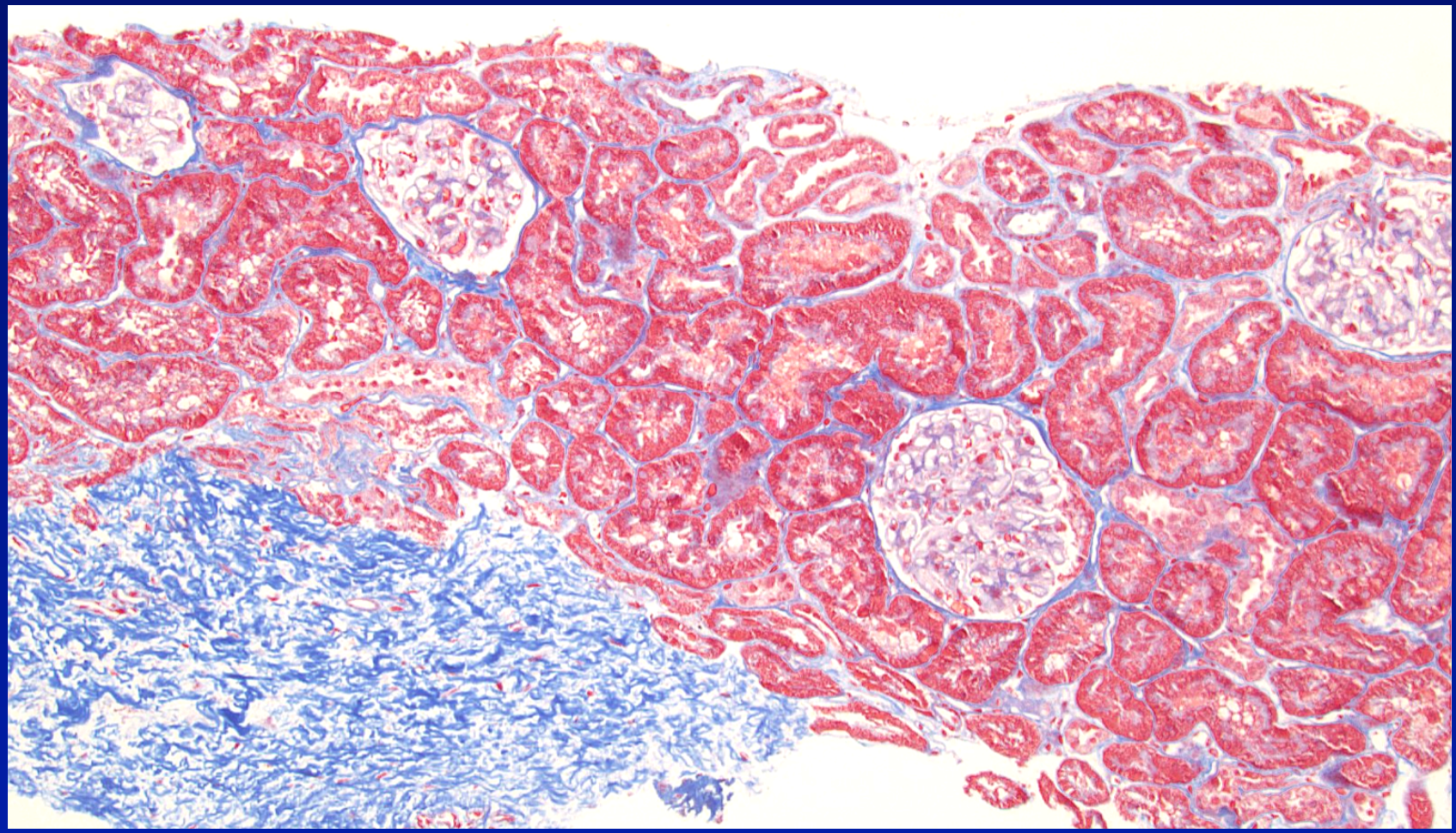
CCTPT: Campath Induction PC-01

- 35 patients in a pilot trial from 4 sites
- Campath 1-H induction (2 doses)
- MMF and FK for 2-3 months
- Convert FK to Rapa after 2-3 months
- Steroid Avoidance and CNI withdrawal
- Protocol biopsies and mechanistic studies

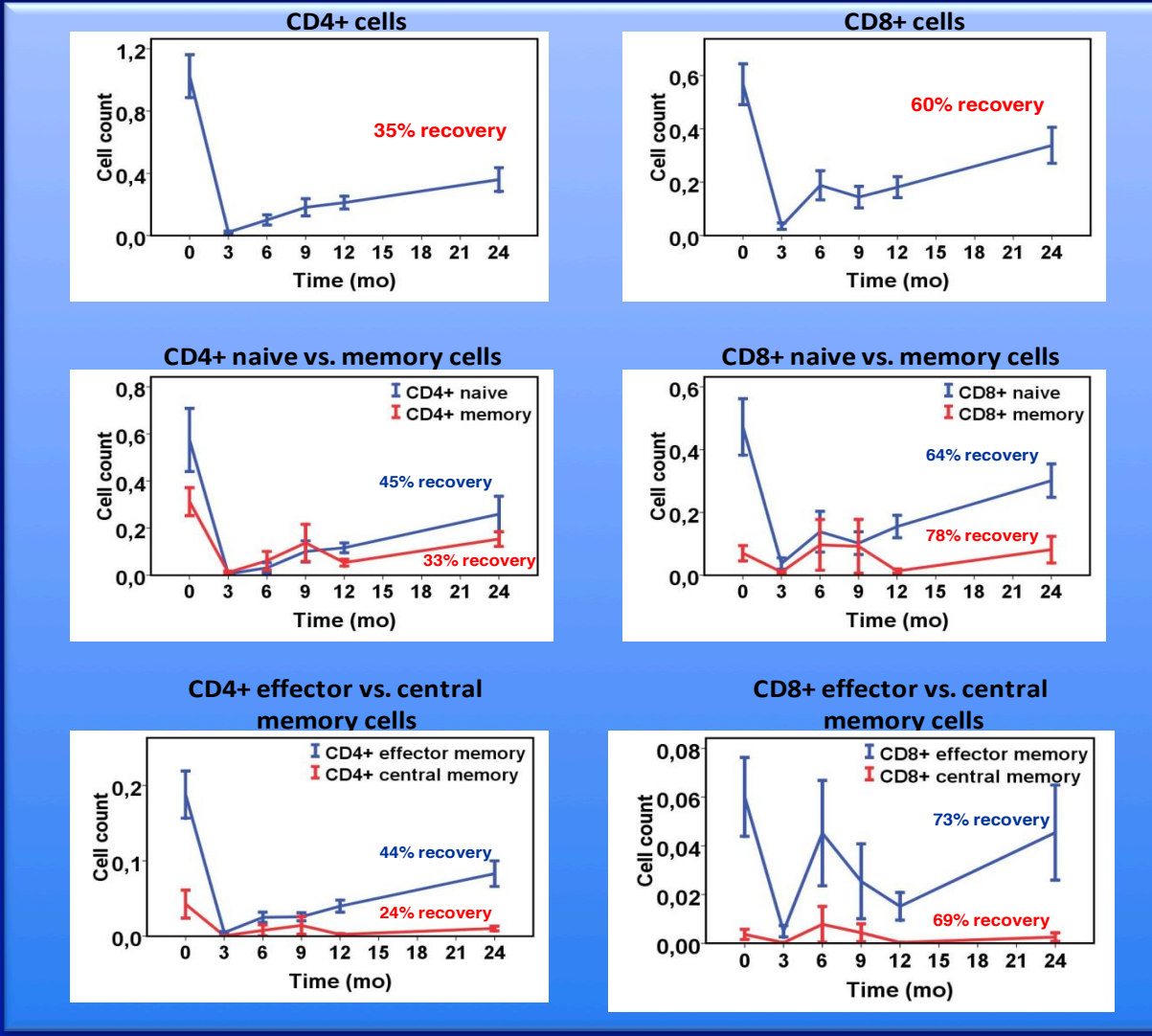
PC-01 Results

- 35 Subjects enrolled
  - 1-year follow-up
    - 6 Acute Rejections (17%)
      - 4 with Clinical Acute Rejection
      - 2 with Sub-clinical Acute Rejection
    - 2 Gaft losses: Recurrent FSGS and non-adherence
    - No deaths, no serious infections
    - No PTLD
    - Most important complication is leukopenia

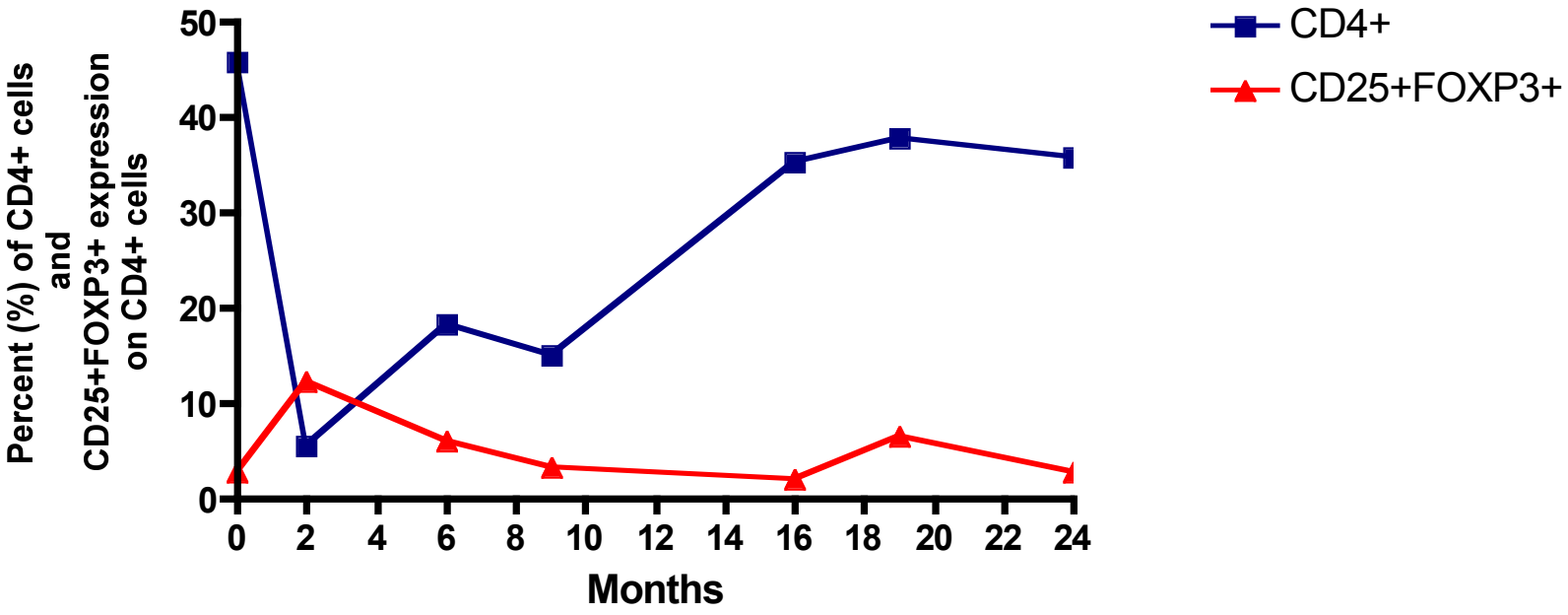
CCTPT: Campath Induction PC-01



T Cell Recovery After Alemtuzumab in Children



Percent of circulating Tregs in peripheral blood



Comparison between Pediatric and Adult Data

Pediatric

- Profound depletion of both CD4+/CD8+ T cells.
- CD4+ T cells recovered at ~18 months post-tx.
- CD8+ T cells return to baseline at 6 months.
* **Depletion of both memory and naïve T cells with quicker recovery of naïve T cells.**
* **Memory T cells spared were mostly effector (Tem) in comparison to central memory (Tcm).**

Adult

- Profound depletion of both CD4+/CD8+ T cells.
- CD4+ T cells still reduced at 15 months post-tx.
- CD8+ T cells return to baseline at 6 months.
* **CD4+ Memory T cell (mostly Tcm) spared in comparison to naïve counterpart.**

Wood, K. *Transplanatation* 2006
Remuzzi, G. *J Am Soc Nephrol* 2007

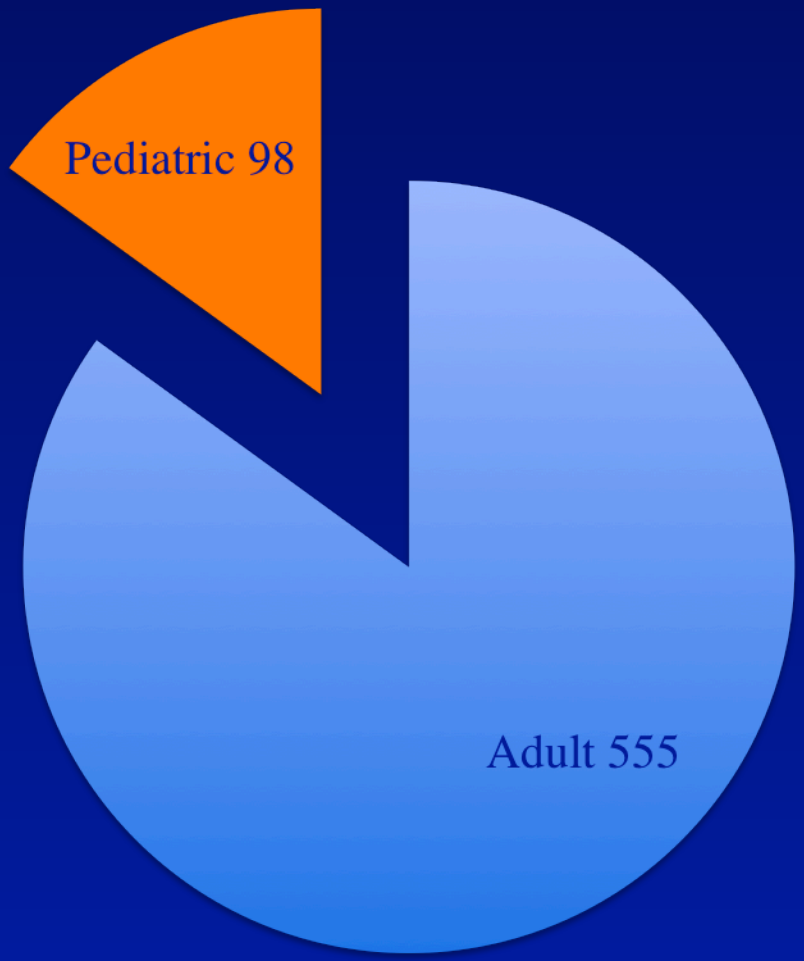
Extension of PC-01: CTOTC-01

- 10 subjects from PC-01
  - Stable at 2 years post transplant
  - No ARE
  - < 5% anti-HLA antibody
  - Normal GFR
  - No CAN
- Taper MMF gradually to monotherapy with Sirolimus

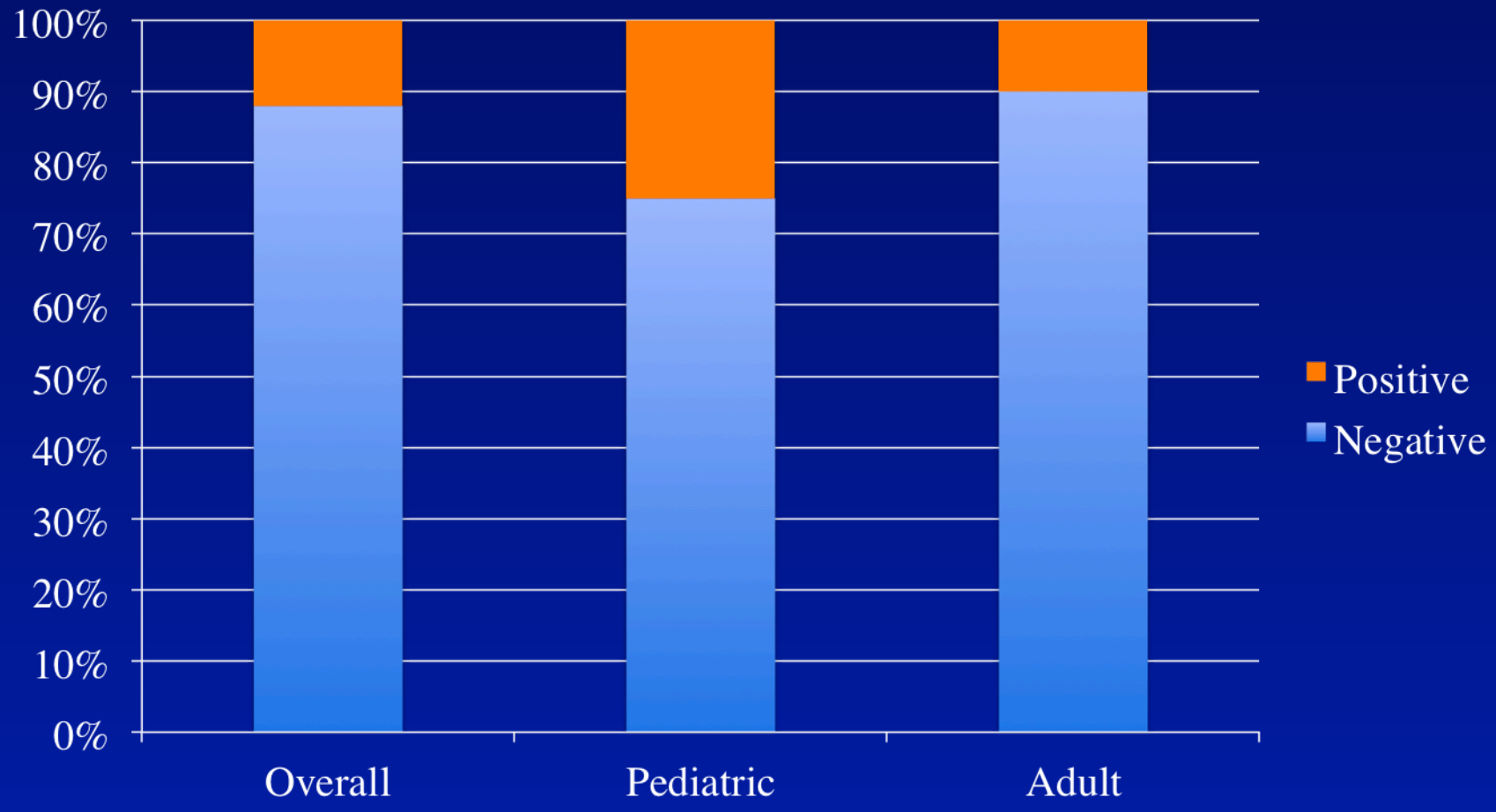
CTOT/CCTPT-02

- Combined adult/pediatric study to measure incidence of anti-HLA antibody production in unsensitized kidney transplant recipients
- 18 centers involved
- 694 subjects enrolled, 653 evaluated
- 79 subjects developed anti-HLA antibodies

Pediatric Subjects in CTOT/CCTPT-02

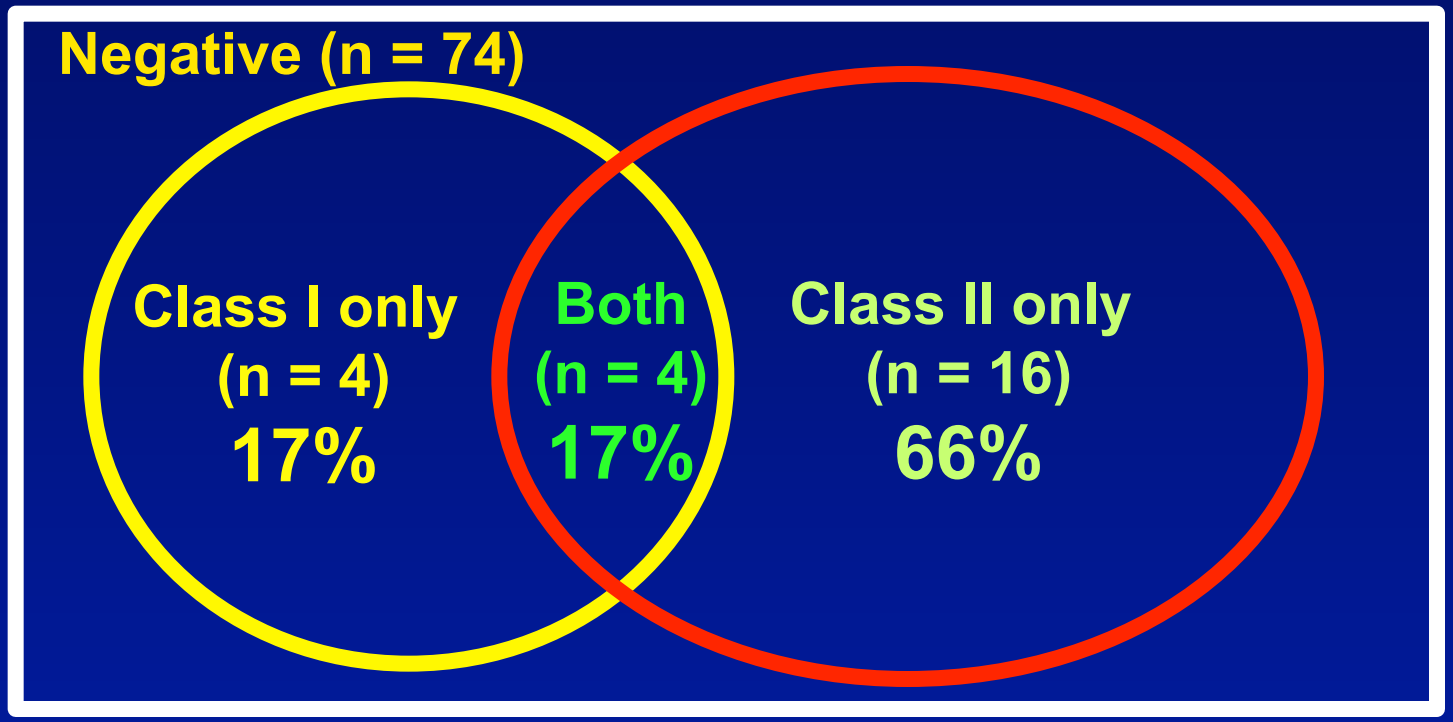


De Novo anti-HLA Antibody



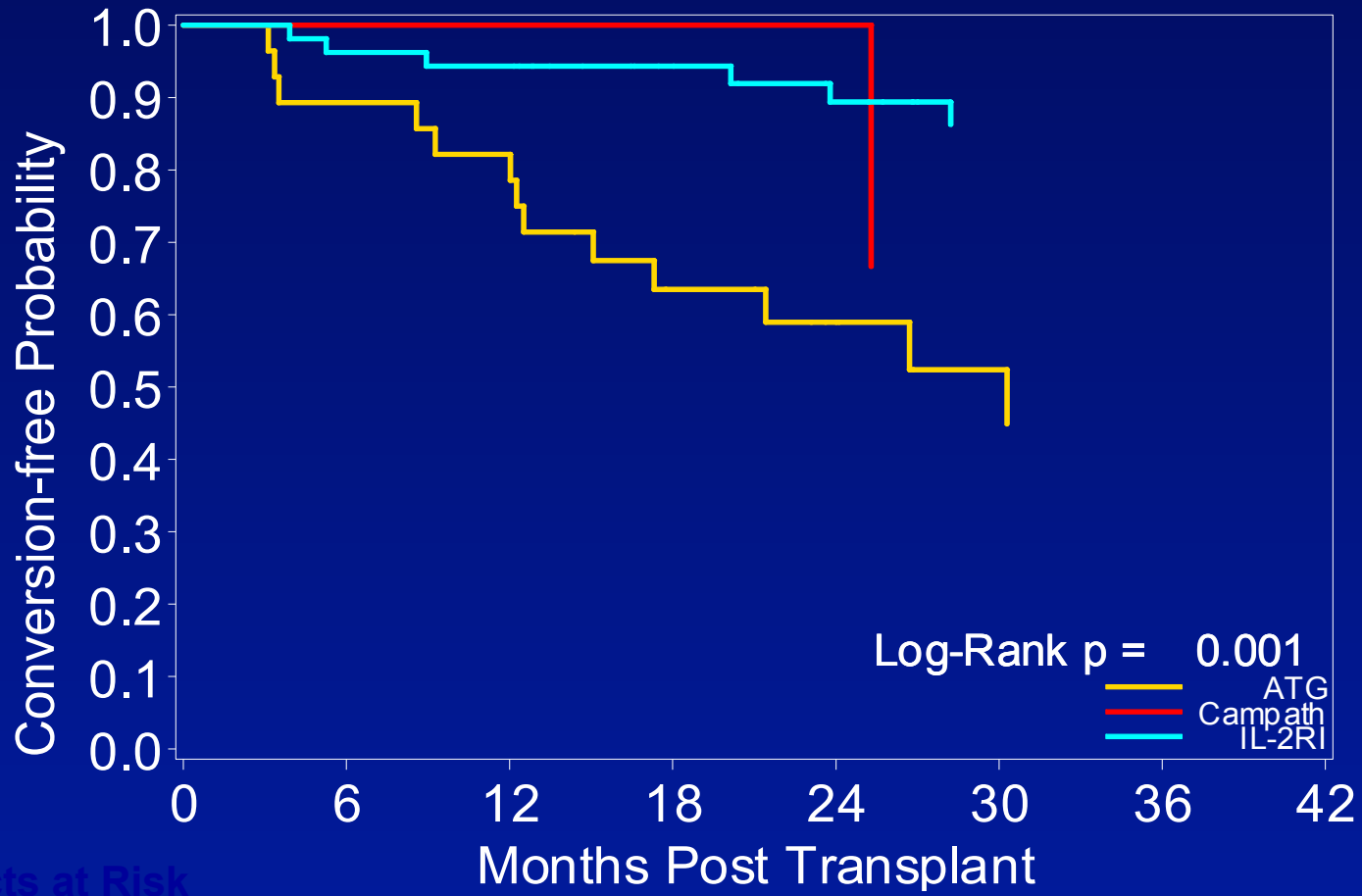
HLA Conversion by Class

n = 98



Induction Agent and HLA Ab Production

Conversion-free Survival

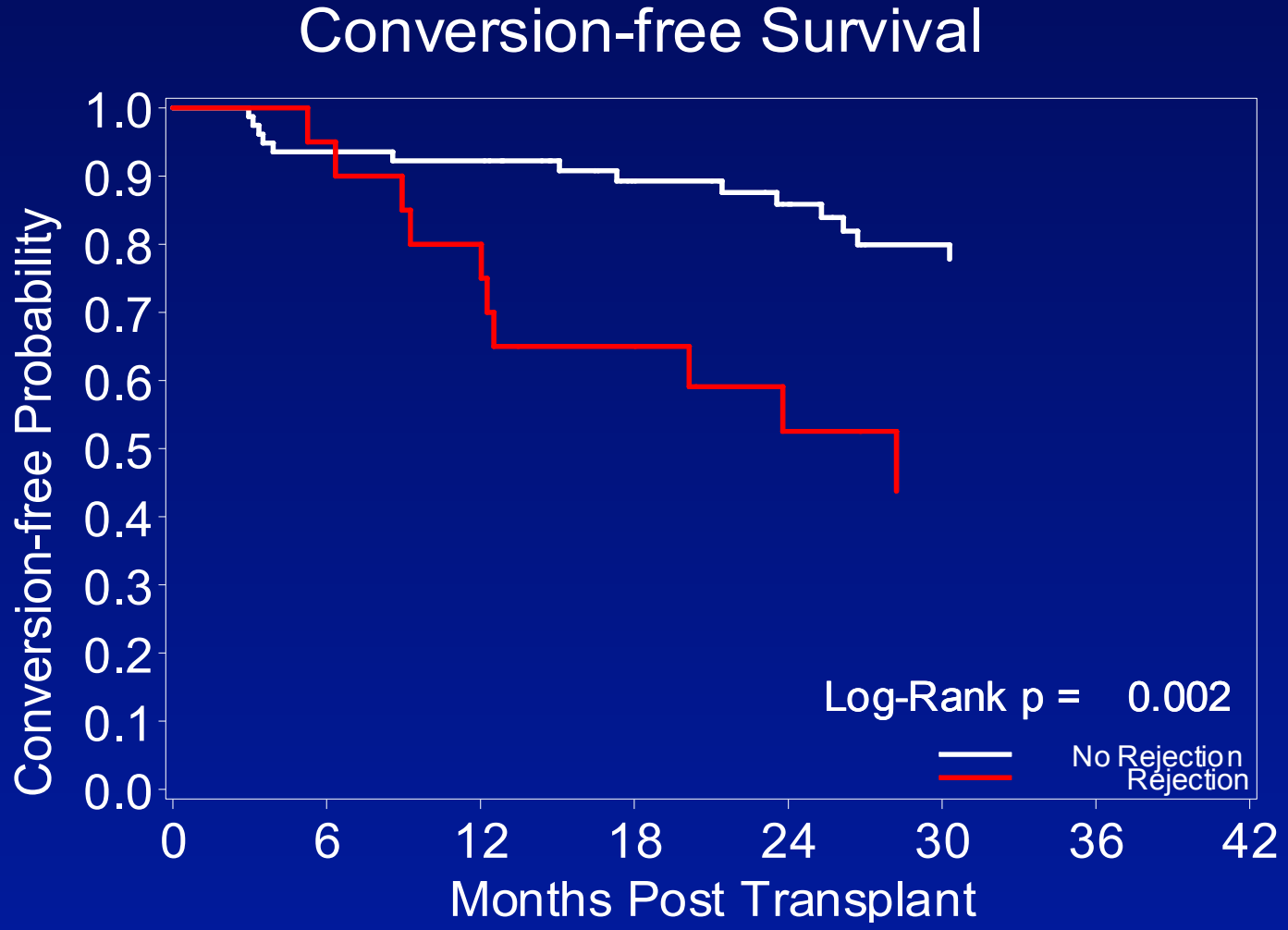


Subjects at Risk								
ATG	28	25	23	15	11	7	2	0
Campath	3	3	3	3	3	2	0	0
IL-2RI	54	51	50	41	34	28	8	2

Induction and Anti-HLA Antibody Production

	Odds Ratio (95% CI)	*P*
Age	0.93(0.80-1.07)	0.288
No IL-2 RI vs. IL-2 RI	5.74 (1.97-16.72)	0.001

Acute Rejection and HLA Ab Production



Subjects at Risk								
No rejection	78	72	71	56	47	38	10	2
Rejection	20	19	16	12	8	5	0	0

Acute Rejection and HLA antibody

	HLA Ab Positive (n=24)	HLA Ab Negative (n=74)	*P*
Acute rejection, n(%)	10 (42%)	10 (14%)	0.003
Cellular, n(%)	9 (38%)	10 (14%)	0.016
Antibody-mediated, n(%)	4 (17%)	0 (0%)	0.003

	Acute rejection among HLA Ab positives (n=10)
Rejection ***before*** Ab conversion	2 (20%)
Time before conversion (mo)	- 6.3 ± 2.3
Rejection ***after*** Ab conversion	8 (80%)
Time after conversion (mo)	+ 4.0 ± 4.3

Minimization the Pediatric Organ Transplant Recipient

- Infants and young children can have the best outcome of kidney transplantation of any age group
- Infants and young children undergoing kidney transplantation have unique conditions
- Infants and young children may be the ideal candidates for minimization protocols
- Monotherapy with Tacrolimus or Sirolimus

What Have We Accomplished?

- Multiple studies have accomplished steroid avoidance or withdrawal in pediatric kidney transplantation (SW-01, SNS-01, TWIST, Pittsburgh monotherapy, PC-01)
- Some pediatric kidney transplant recipients can be withdrawn from CNIs and perhaps reach monotherapy
- Prior to CCTPT young children had the worst outcomes of all kidney transplant recipients; now they have the best

Conclusions

- Successes during past two decades
  - Overall early graft survival benefit
  - Marked improvement in success in young children
  - Reduction in ARE
  - Growth delay overall is not as severe
  - Steroid avoidance is possible
- Remaining challenges
  - Opportunistic viral infections
  - CNI/Steroid toxicities
  - CAN
  - Adherence to multi-drug protocols
  - Cost of chronic immunosuppression
  - Recurrent disease
  - Racial differences in outcome

What Are the Most Important Barriers to Successful Organ Transplantation in 2013?

What Are Current Barriers to Success of Organ Transplants

- Children are at high risk for chronic viral infections, especially EBV
- Chronic Graft Loss continues and results in need for re-transplantation
  - CAN has not been defined or treated
- Recurrent disease has not been addressed
- Adolescents currently lose transplants at accelerated rate: Biology vs Adherence?
- African Americans have unacceptably high rates of graft loss and we don't know why

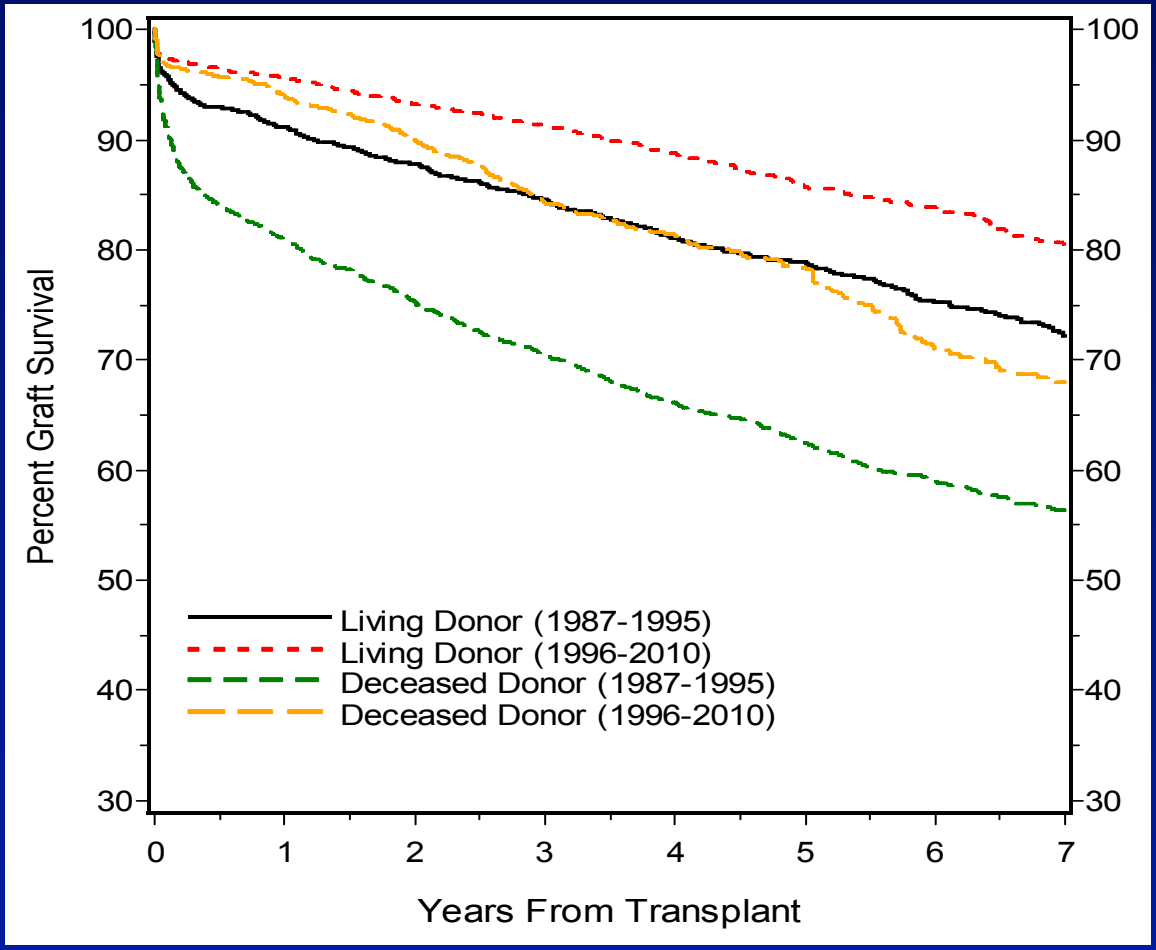
Viral Infections

- Viruses and treatments:
  - CMV: Valganciclovir prohylaxis and treatment
  - EBV: ? Valganciclovir, surveillance, IS modulation
  - Polyomavirus: Surveillance, IS modulation, ? meds
- Pediatric-specific problem of Donor +/ Recipient -

Chronic Allograft Nephropathy in Children

- Chronic Allograft Nephropathy (CAN) is the major limiting factor in pediatric kidney transplantation.
- Etiology of CAN:
  - Immunologic
  - Non-Immunologic

Pediatric Kidney Transplant Graft Survival by Source and Era

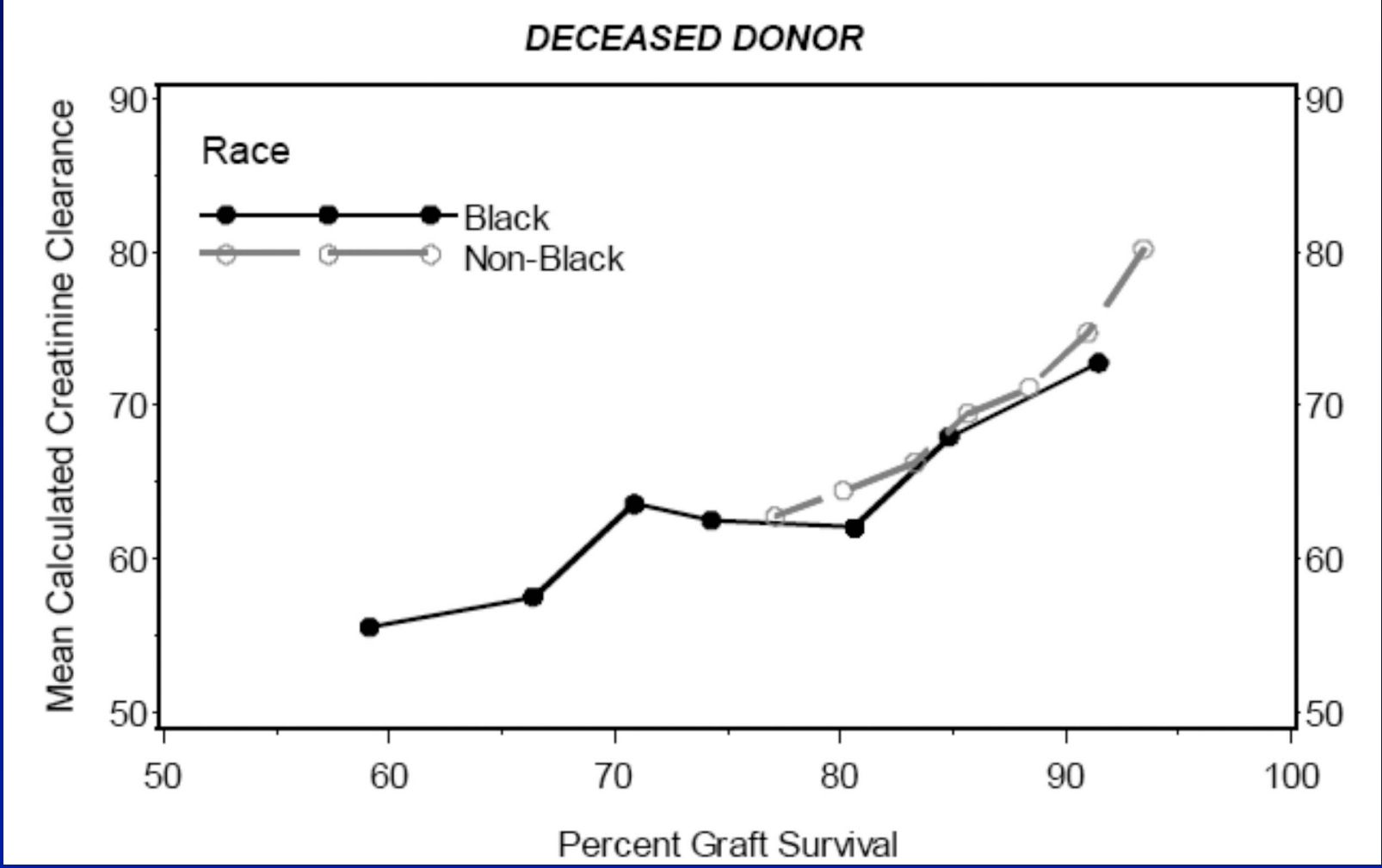


NAPRTCS 2010

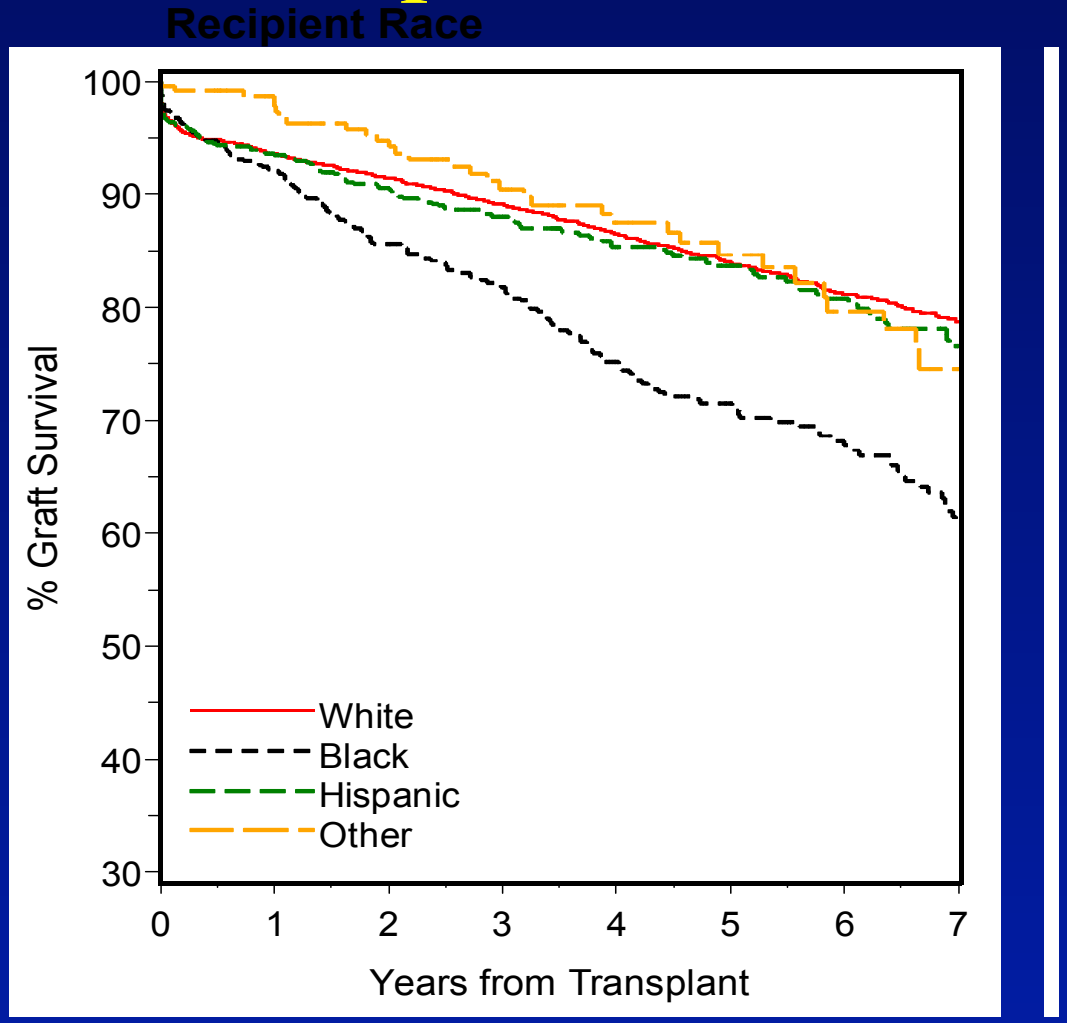
Immunologic Causes of CAN

- Insufficient Immunosuppression
  - Chronic Immunosuppression is inadequate
  - Late acute rejections
  - Race
  - Immunosuppression adherence
  - ?Pubertal changes

CAN and Race

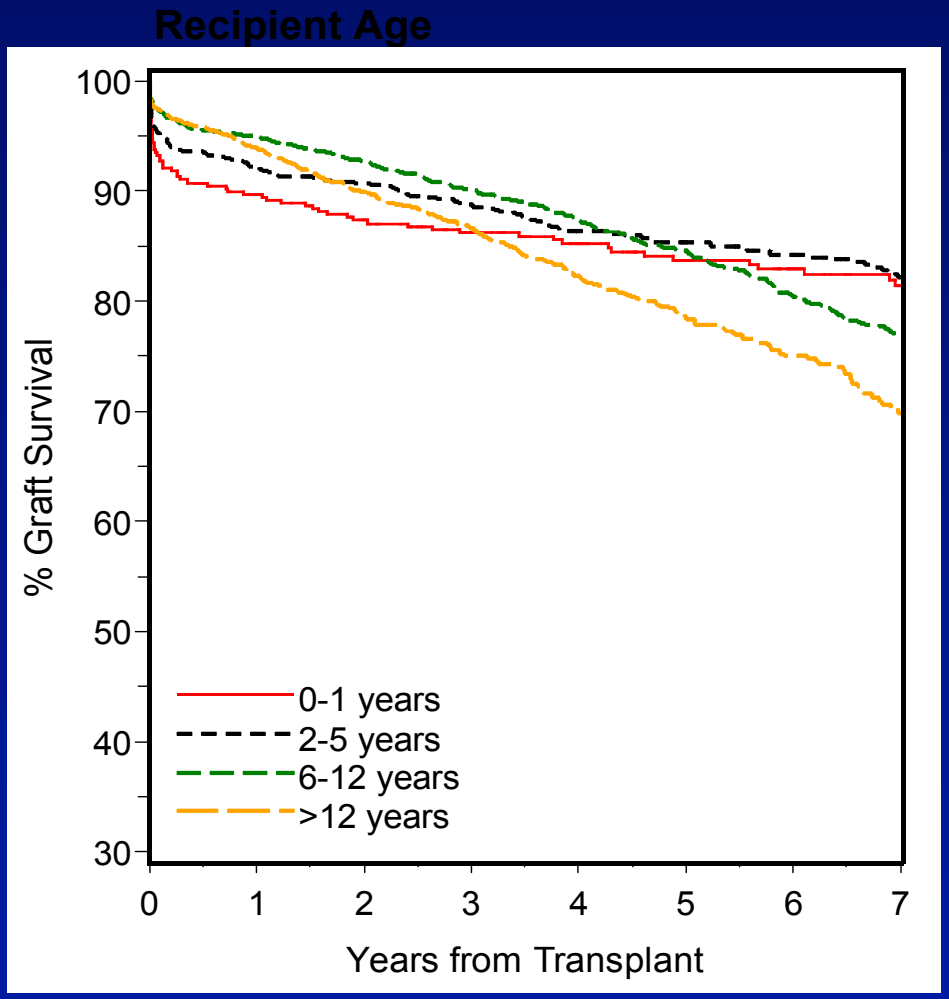

DECEASED DONOR
Race
Black
Non-Black
Mean Calculated Creatinine Clearance
Percent Graft Survival
90
80
70
60
50
50
60
70
80
90
100

Pediatric Kidney Graft Survival by Recipient Race



NAPRTCS 2010

Pediatric Kidney Transplant Graft Survival by Recipient Age



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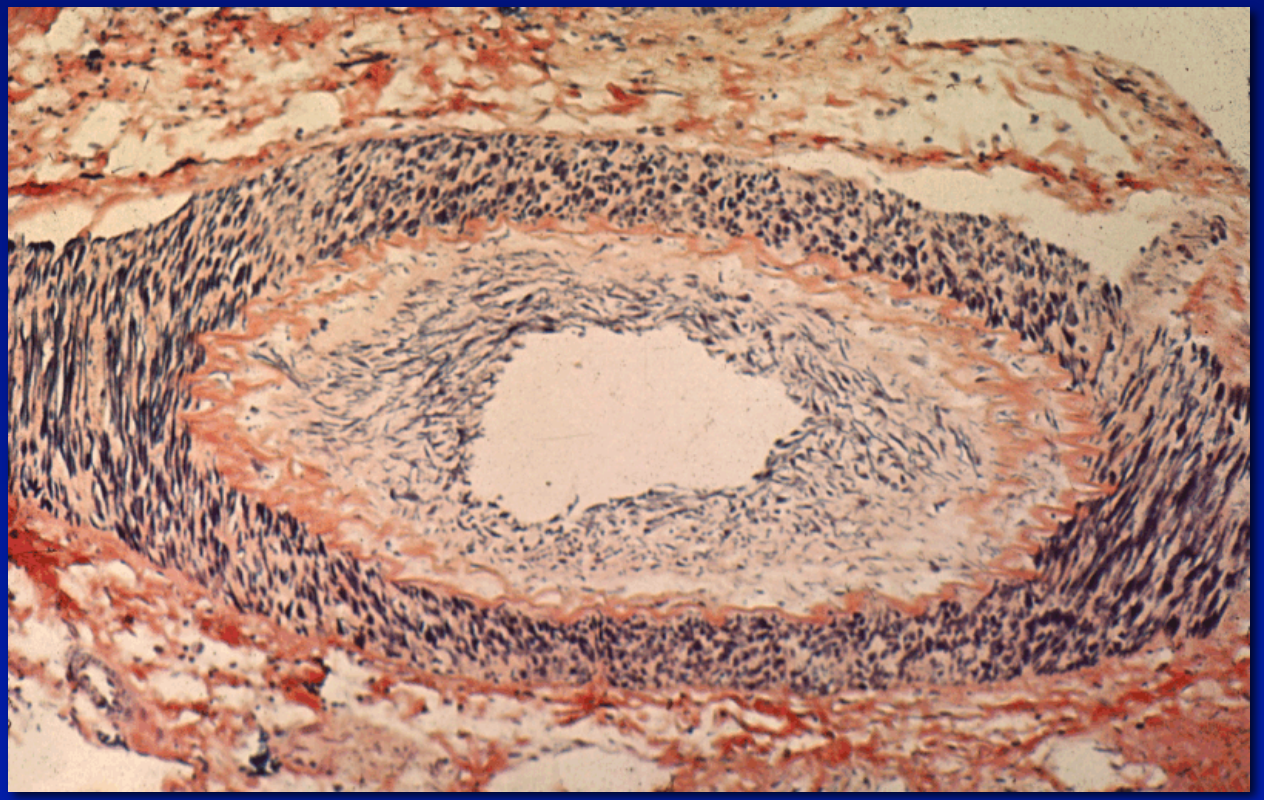
Chronic Allograft Nephropathy

- Calcineurin Inhibitor Toxicity



Medication Adherence

- Rejection is an inevitable consequence of failure of adherence to immunosuppression protocol
- Solution to failure of IS adherence
  - Change adolescent behavior
  - Change immunosuppression delivery
  - Promise of belatacept

Recurrent Disease after Kidney Transplantation

- Atypical HUS: Eculizumab or Liver/ Kidney transplantation
- Oxalosis: Liver/Kidney transplantation
- FSGS: ???? Current approaches do not address pathophysiology
- Diabetes: Islet cell or Kidney/Pancreas transplantation

Conclusions

- Kidney Transplantation is currently the best treatment for children with ESRD and is likely to remain so for the foreseeable future
- Outcomes in kidney transplantation are continually improving
- Long-term consequences of kidney transplantation need increased attention

Conclusions

- Resolution of current barriers to successful transplantation require better understanding of their etiologies
- Application of new treatments requires careful pediatric trials
- Children are naïve to many viruses
- Children are more easily sensitized by transplantation than adults