

# **STEROID FREE PROTOCOLS**

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# STEROID FREE PROTOCOLS

- **WHEN WERE STEROIDS INTRODUCED INTO CLINICAL RENAL TRANSPLANTATION?**

# STEROID FREE PROTOCOLS

- HAMBURGER, ET AL *PRESS MED* 67:1771, 1959
  - **USE OF WHOLE BODY IRRADIATION**
- CALNE, R. *LANCET* 1:417, 1960
  - **AZATHIOPRINE INTRODUCED**
- GOODWIN, ET AL *J UROL* 89:13, 1963
  - **CORTICOSTEROIDS INTRODUCED**
- STARZL, ET AL *SURG, GYNEC & OBSTET* 124:301, 1967
  - **ANTI-LYMPHOCYTE SERUM INTRODUCED**

# STEROID FREE PROTOCOLS

- THE IMPETUS FOR ATTEMPTING TO MINIMIZE OR ELIMINATE STEROIDS IN THE RENAL TRANSPLANT IMMUNOSUPPRESSIVE REGIMEN ARE OBVIOUS:
- REDUCE OR ELIMINATE THE STEROID INDUCED ***SIDE EFFECTS*** ESPECIALLY GROWTH RETARDATION IN PEDIATRIC RECIPIENTS

# STEROID FREE PROTOCOLS

- REPORTS BEGINNING IN 1990's WITH CYCLOSPORIN MONOTHERAPY OR CYCLOSPORIN PLUS AZATHIOPRINE AND STEROID WITHDRAWAL > 3 MONTHS POST-TRANSPLANT WERE NOT UNIFORMLY SUCCESSFUL AND WERE ASSOCIATED WITH A SIGNIFICANT INCIDENCE OF ACUTE REJECTION EPISODES (ARE)

# STEROID FREE PROTOCOLS

- REPORTS BEGINNING IN 2000's WITH TACROLIMUS MONOTHERAPY OR CYCLOSPORIN AND MMF INDICATED AN INCREASED SUCCESS RATE AND *LIMITED OR NO ACUTE REJECTION EPISODES*

# STEROID FREE PROTOCOLS

- ODENSE, DENMARK (1994)
  - ATG (3 DOSES)
  - CYCLOSPORIN (DAILY)
  - MMF (AFTER 1995)
- STANFORD (2001)
  - ANTI-IL<sub>2</sub> RECEPTOR AB (8 DOSES)
  - TACROLIMUS
  - MMF
    - INTOLERANCE
      - < 6 MO AZATHIOPRINE
      - > 6 MO SIROLIMUS
- PITTSBURGH (2006)
  - ATG/CAMPATH (ONE DOSE)
    - 2 DOSES MP
  - TACROLIMUS
    - TWICE DAILY
    - @ 6 MO DAILY
    - @ 12 MO QOD

# STEROID FREE PROTOCOLS

- UC DAVIS (2007)
  - ATG (5 DOSES)
    - 3 DAILY DOSES MP
  - TACROLIMUS
    - TWICE DAILY
  - MMF
- SANTIAGO, CHILE (2007)
  - ANTI-IL<sub>2</sub> RECEPTOR AB (2 DOSES)
    - PREDNISON 6 DAYS
  - TACROLIMUS
  - MMF



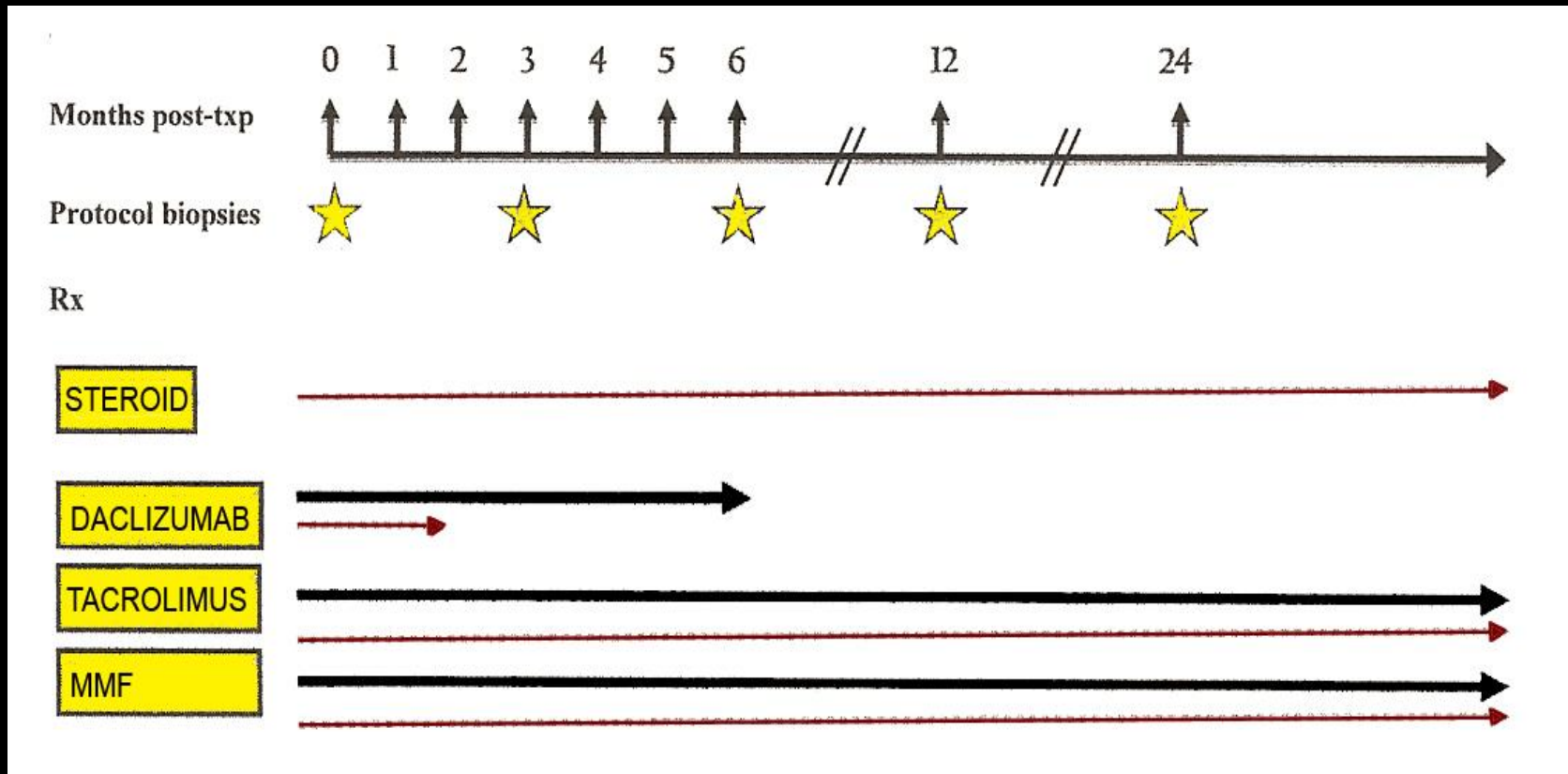
# STEROID FREE PROTOCOLS

## – RCT (*NAPRTCS*)

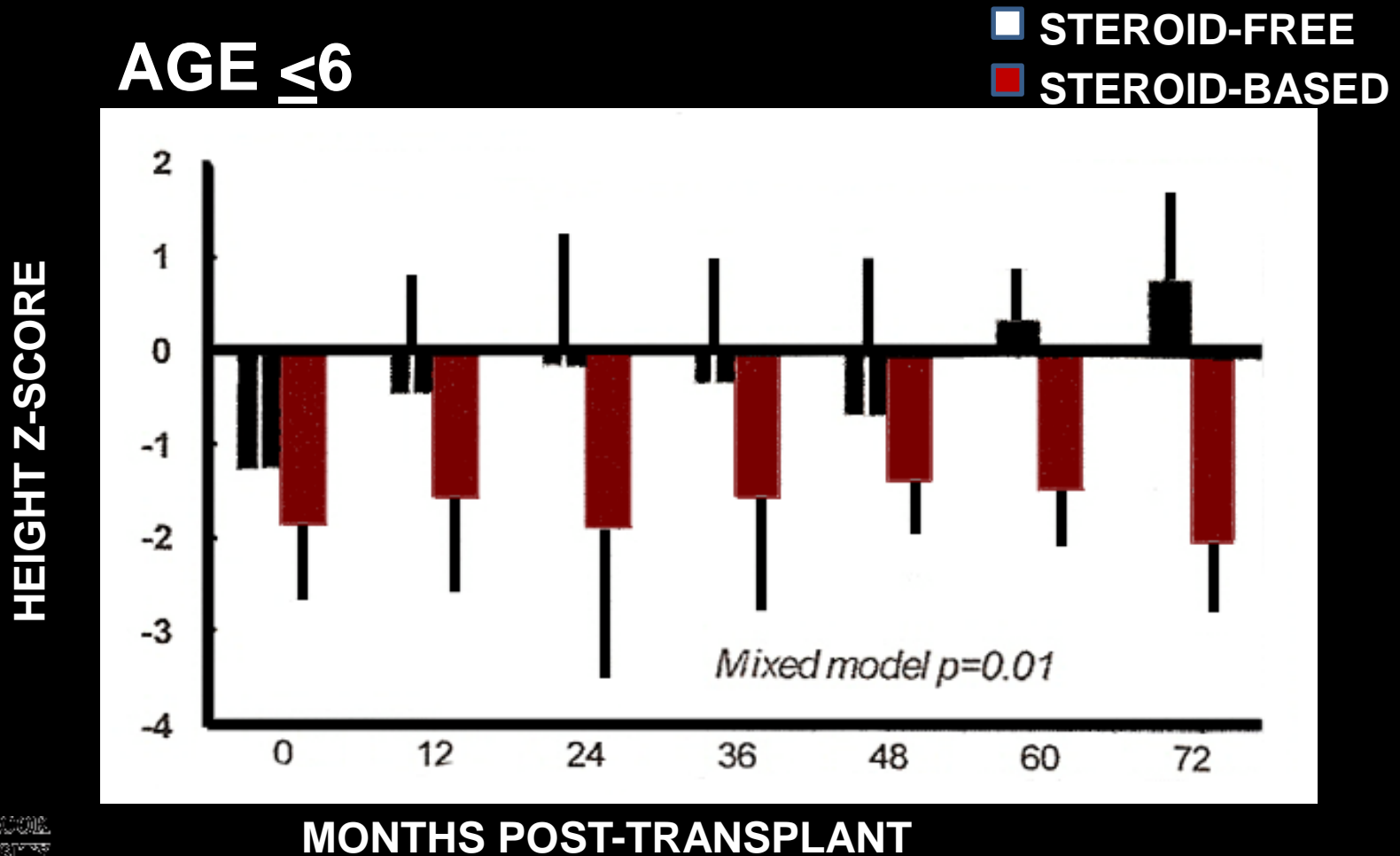
- ANTI-IL<sub>2</sub> RECEPTOR AB
- TACROLIMUS / CYCLOSPORIN
- SIROLIMUS
- STEROIDS
- @ 6 MONTHS THOSE WITH NO ACUTE REJECTION EPISODES WERE RANDOMIZED TO STEROID WITHDRAWAL OVER 6 MONTHS OR CONTINUATION OF MAINTENANCE STEROID THERAPY
- STUDY STOPPED BECAUSE OF A 6.9% INCIDENCE OF PTLD - ? IMMUNOSUPPRESSION WAS **TOO "ROBUST"**

BENFIELD ET AL AM J TRANSPLANT 10:81, 2010

# STEROID FREE PROTOCOLS



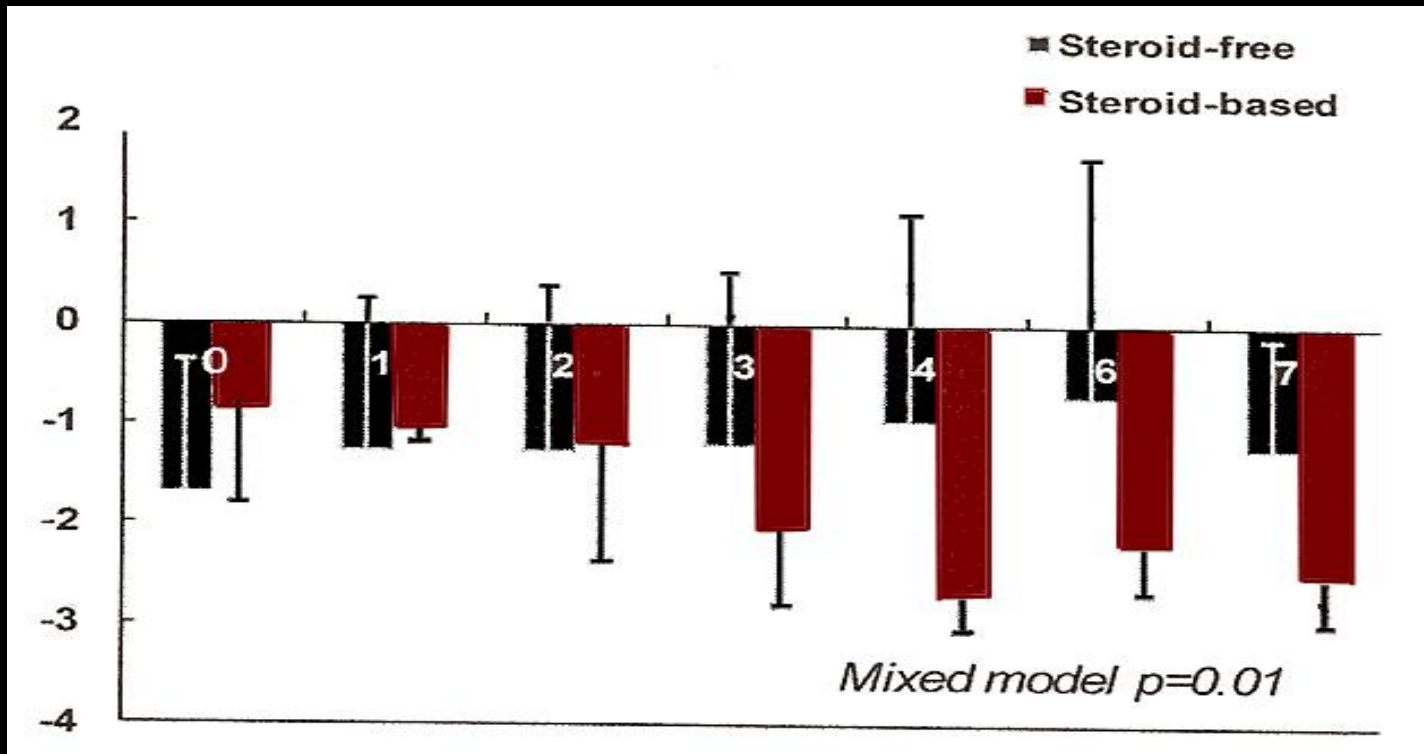
# STEROID FREE PROTOCOLS



# STEROID FREE PROTOCOLS

## AGE 6-12

HEIGHT Z-SCORE



MONTHS POST-TRANSPLANT

# STEROID FREE PROTOCOLS (TWIST STUDY)

- TAC/MMF/DAC (N=98) – STERIODS DISCONTINUED ON DAY 5 vs TAC/MMF/STR (N=98) – STEROID TAPER TO  $<10\text{mg}/\text{M}^2$
- AT 6 MONTHS SDS IMPROVED ( $\Delta 0.13$ ) IN SW GROUP ( $p < 0.005$ ) – **PRIMARY PRE-PUBERTAL RECIPIENTS**
- CLINICAL PARAMETERS SIMILAR EXPECT INCREASE INFECTION/ANEMIA IN TAC/MMF/DAC

# STEROID FREE PROTOCOLS (TWIST STUDY)

- TWO YEAR FOLLOW-UP (WEBB ET AL TRANSPLANTATION 99:1178, 2015) REVEALED:
  - @ 1 YEAR STEROID WITHDRAWAL RECIPIENTS GREW BETTER ( $p=0.001$ )
  - @ 2 YEARS STEROID WITHDRAWAL RECIPIENTS NUMERICALLY BETTER ( $p=0.06$ ); HOWEVER, PREPUBERTAL RECIPIENTS GREW BETTER @ 2 YEARS ( $p=0.004$ )
  - PATIENT AND GRAFT SURVIVAL RATES, eGFR AND ADVERSE EVENTS SIMILAR IN BOTH GROUPS

# STEROID FREE PROTOCOLS

- 3 YEAR FOLLOW-UP OF NIAID SPONSORED RCT
  - 130 CHILDREN ENROLLED FROM 12 PEDIATRIC TRANSPLANT CENTERS
  - $\Delta$  Z-SCORE @ 3 YRS – ALL RECIPIENTS
    - - 0.99 (SF)
    - - 0.93 (SB)
  - $\Delta$  Z-SCORE @ 3 YRS - < 5 YRS OLD ( N= 27)
    - -0.43 (SF)
    - -1.14 (SB)
    - P= 0.019

# STEROID FREE PROTOCOLS

- **NIAID SPONSORED RCT**
  - BIOPSY-PROVEN ACUTE REJECTION @ 3 YRS SIMILAR IN **SF** (16.7%) & **SB** (17.1%) GROUPS
  - PATIENT SURVIVAL (100% IN BOTH GROUPS) AND GRAFT SURVIVAL SIMILAR IN BOTH GROUPS – SF (95%) & SB (90%)
  - SYSTOLIC BP AND CHOLESTEROL LEVELS LOWER IN THE SF GROUP

SARWAL ET AL AJT 12:2719, 2012



# STEROID FREE PROTOCOLS

- THE FAILURE TO DEMONSTRATE AN INCREASE IN THE “Z” SCORE IN RECIPIENTS >5 y/o RECEIVING THE SF PROTOCOL COMPARED TO THOSE RECEIVING THE SB PROTOCOL INDICATES THAT GROWTH FOLLOWING TRANSPLANTATION IS IMPACTED BY *FACTORS* OTHER THAN JUST CORTICOSTEROID ADMINISTRATION

## STEROID FREE PROTOCOLS

WHAT ARE  
THE VARIOUS  
STEROID  
FREE  
PROTOCOLS  
THAT HAVE  
BEEN  
UTILIZED?

- **COMPLETE AVOIDANCE**  
WITH EXTENDED  
INDUCTION
- **EARLY WITHDRAWAL** (<7  
DAYS) WITH INDUCTION
- **INTERMEDIATE  
WITHDRAWAL** (>7 DAYS  
BUT < 1 YEAR) WITH  
INDUCTION
- **LATE WITHDRAWAL** (> 1  
YEAR) WITHOUT  
INDUCTION

# STEROID FREE PROTOCOLS

- **WHAT ARE THE LONG-TERM OUTCOME DATA FROM INTERMEDIATE WITHDRAWAL PROTOCOLS?**

**KLARE ET AL TRANSPLANT INTERNATIONAL 25:276, 2012**

# STEROID FREE PROTOCOLS

- 74/81 (91%) PATIENTS TRANSPLANTED BETWEEN 1981 AND 2001 WERE WEANED OFF STEROIDS @ **4-6 MOS** WITH A MEAN FOLLOW-UP OF **8.5 YRS**
- GRAFT SURVIVAL @ 5, 10 AND 15 YRS WAS 92%, 71% AND 57%
- MEAN ADULT HEIGHT WAS  $-0.5 \pm 1.1$  SD AND  $-1.0 \pm 1.3$  SD WITH NORMAL ADULT HEIGHT IN 94% AND 80% FOR THE PREPUBERTAL AND PUBERTAL RECIPIENTS

KLARE ET AL TRANSPLANT INTERNATIONAL 25:276, 2012

# STEROID FREE PROTOCOLS

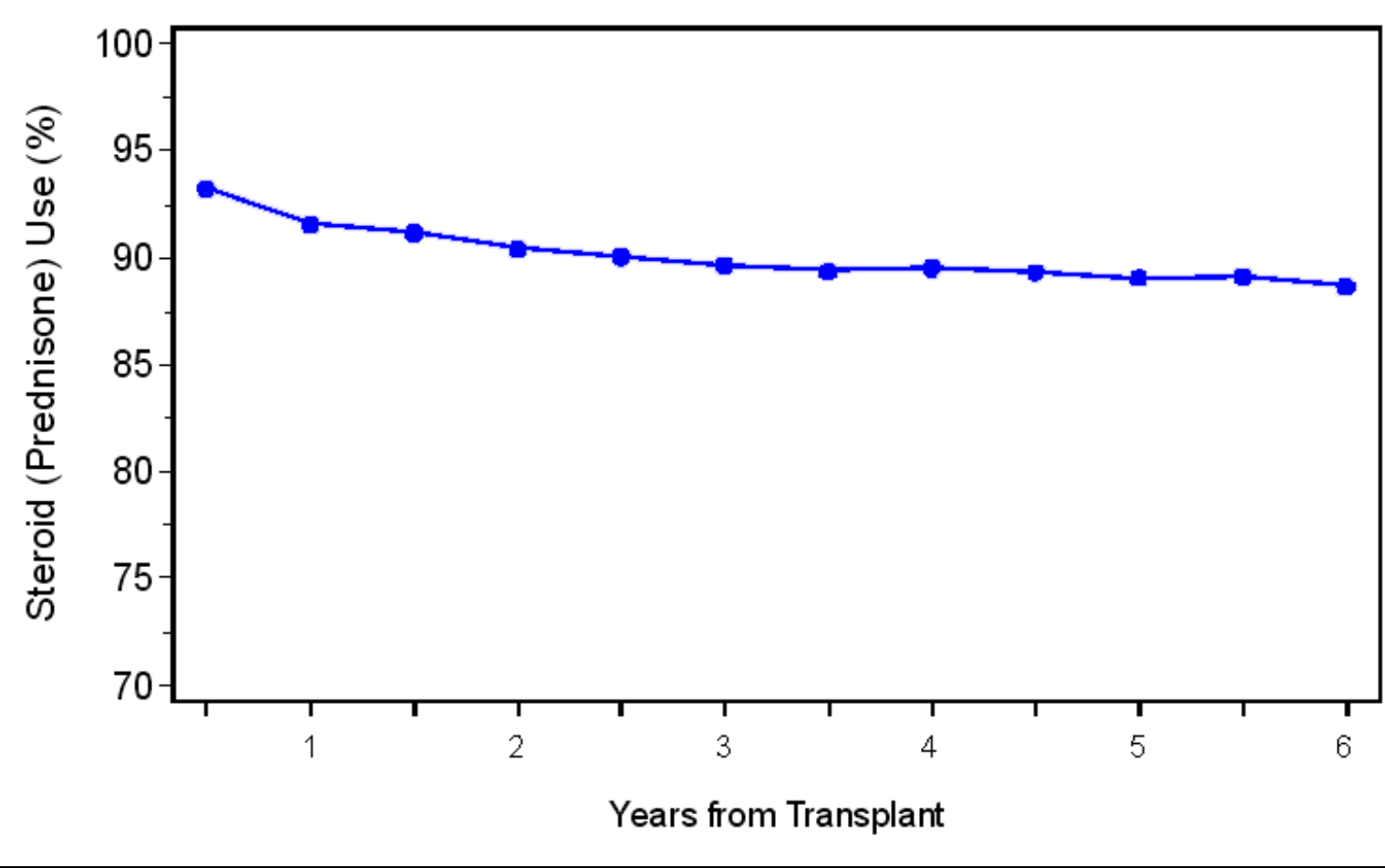
- **WHAT IS THE CURRENT STATUS OF THE USE OF STEROID FREE PEDIATRIC RENAL TRANSPLANT PROTOCOLS?**

# STEROID FREE PROTOCOLS

DOES THE INCIDENCE OF  
STEROID USE DECLINE  
FOLLOWING  
TRANSPLANTATION?

# NAPRTCS GROWTH DATA

## STERIOD USE BY TIME SINCE TRANSPLANT



# STEROID USE POST-TRANSPLANT

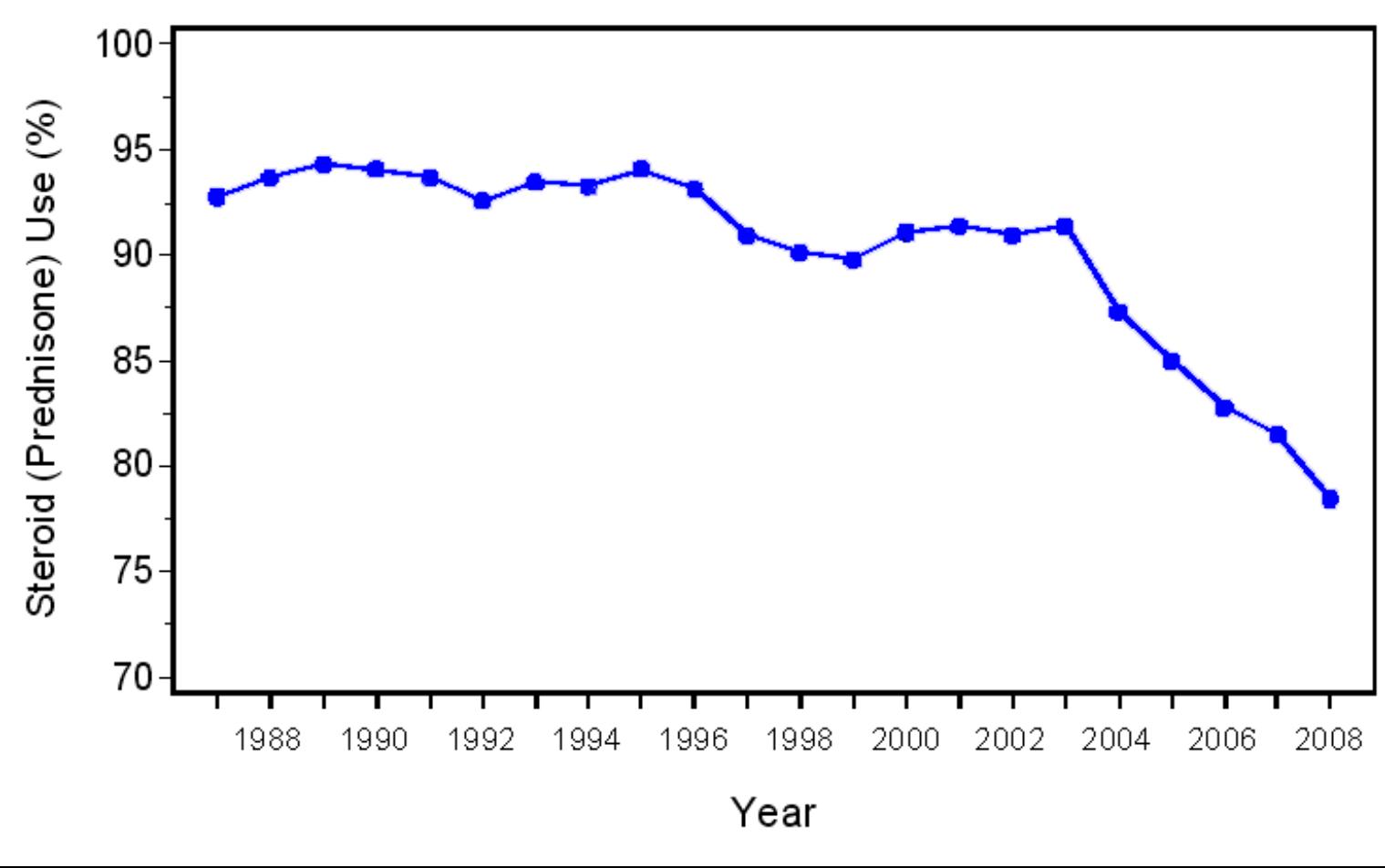
TIME	INCIDENCE
6 MONTHS	93%
3 YEARS	90%
5 YEARS	89%



# STEROID FREE PROTOCOLS

HAS INCIDENCE OF  
STEROID USE AT  
TRANSPLANTATION  
CHANGED DURING THE  
PAST TWO DECADES?

## STERIOD USE BY YEAR

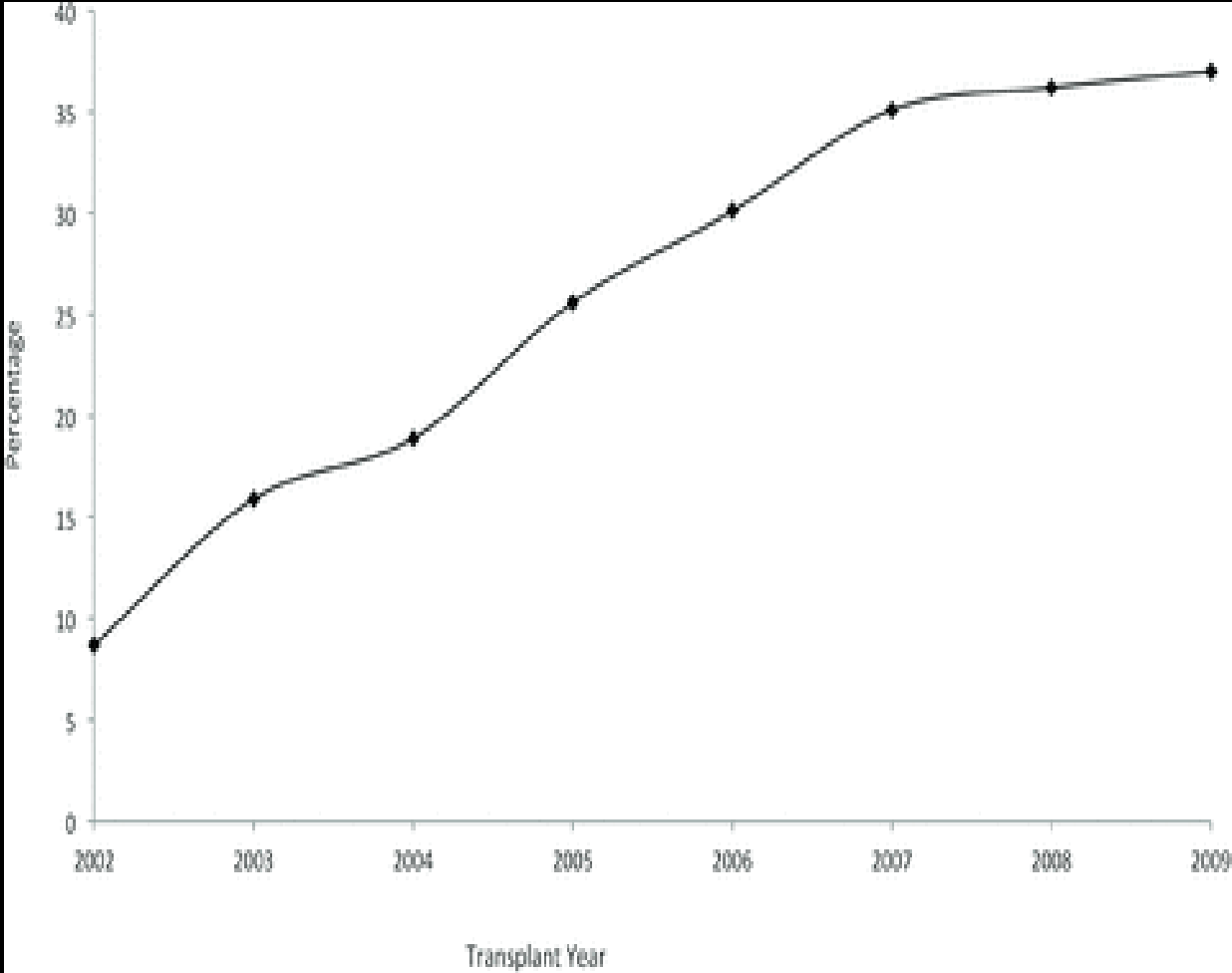


# STEROID FREE PROTOCOLS

- UNOS DATA OF **4627** PEDIATRIC RECIPIENTS FROM **2002 – 2009** INDICATED THAT STEROID AVOIDANCE PROTOCOLS – “NO STEROIDS @ TIME OF HOSPITAL DISCHARGE” – INCREASED FROM **8.7% IN 2002 TO 37% IN 2009**

NEHUS ET AL AM J TRANSPL 12:3441, 2012

# OUTCOMES OF STEROID-AVOIDANCE PROTOCOLS IN PEDIATRIC KIDNEY TRANSPLANT RECIPIENTS

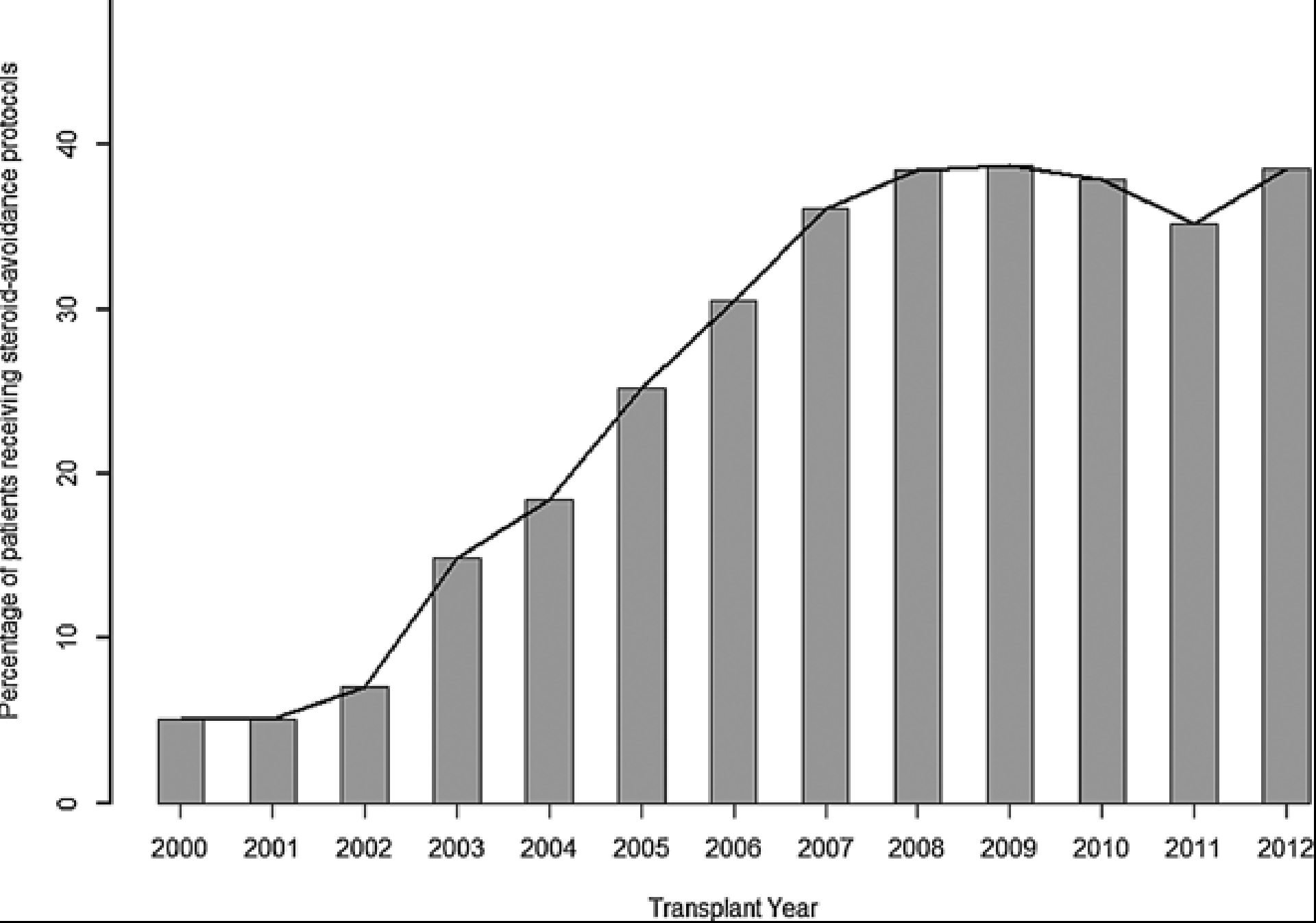


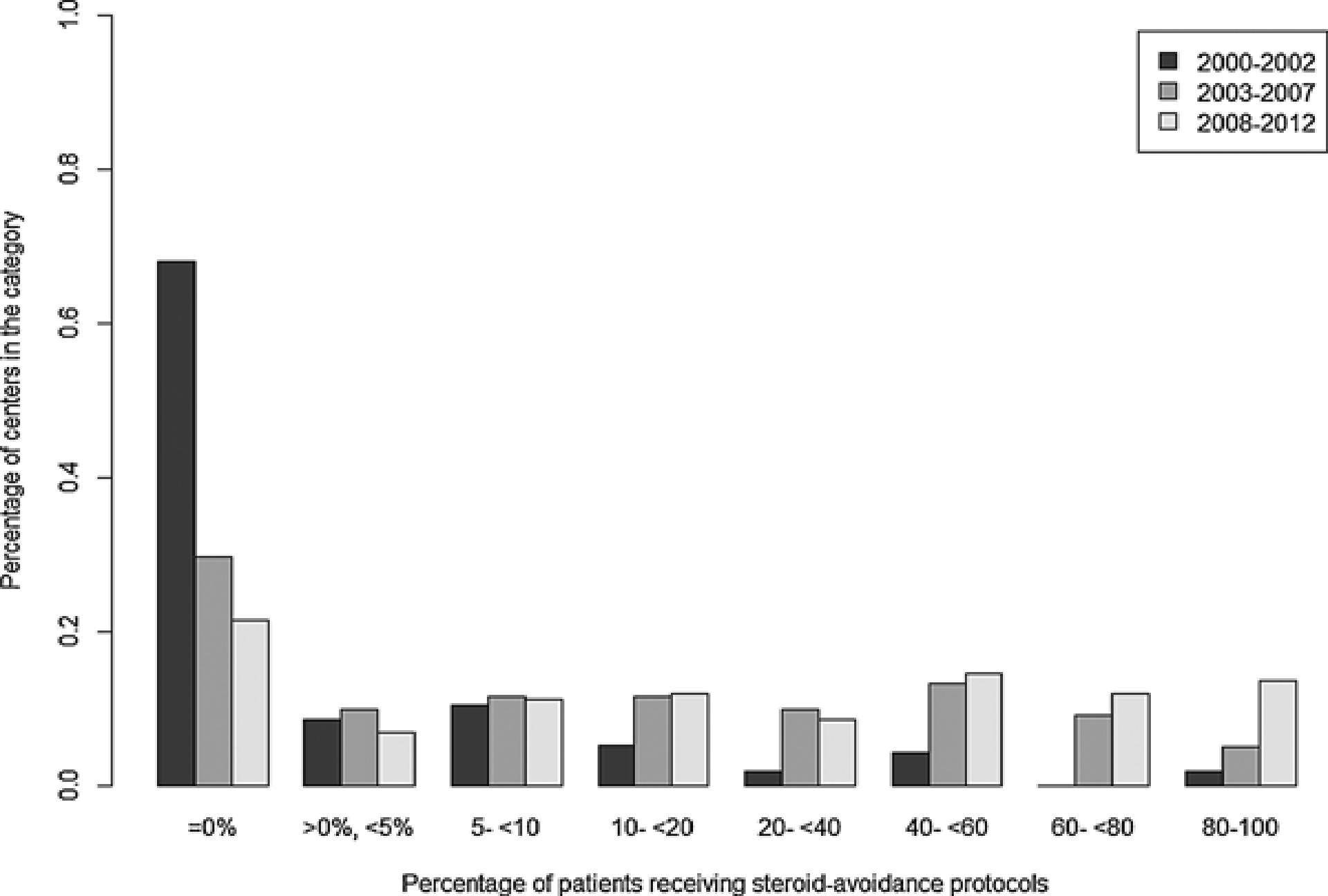
NEHUS ET AL AM J TRANSPLANT 12:3441, 2012

# STEROID FREE PROTOCOLS

- UNOS DATA OF **9494** PEDIATRIC RECIPIENTS @ **124** TRANSPLANT CENTERS BETWEEN **2000** AND **2012** INDICATED THAT **39%** OF THE CENTERS USED STEROID AVOIDANCE IN **<10%** OF DISCHARGED RECIPIENTS, **21%** IN **10-40%** OF DISCHARGED RECIPIENTS AND **40%** IN **>40%** DISCHARGED RECIPIENTS

NEHUS ET AL AM J TRANSPLANT 15:2203, 2015





# STEROID FREE PROTOCOLS

- WHAT WERE THE DEMOGRAPHIC AND CLINICAL PREDICTORS THAT A PEDIATRIC RECIPIENT WOULD NOT BE INCLUDED IN STEROID AVOIDANCE PROTOCOLS?



# STEROID FREE PROTOCOLS

- UNKNOWN CENTER VARIABILITY
- \* HISTORY OF PREVIOUS TRANSPLANT (7 TIMES LESS LIKELY)
- HIGH PRA
- \* INDUCTION AGENT (PREFER LYMPHOCYTE DEPLETING AGENTS)
- DECEASED DONOR
- \* GLOMERULAR DISEASE
- AFRICAN-AMERICAN
- PRETRANSPLANT DIALYSIS
- LACK OF PRIVATE INSURANCE
- DELAYED GRAFT FUNCTION

# STEROID FREE PROTOCOLS

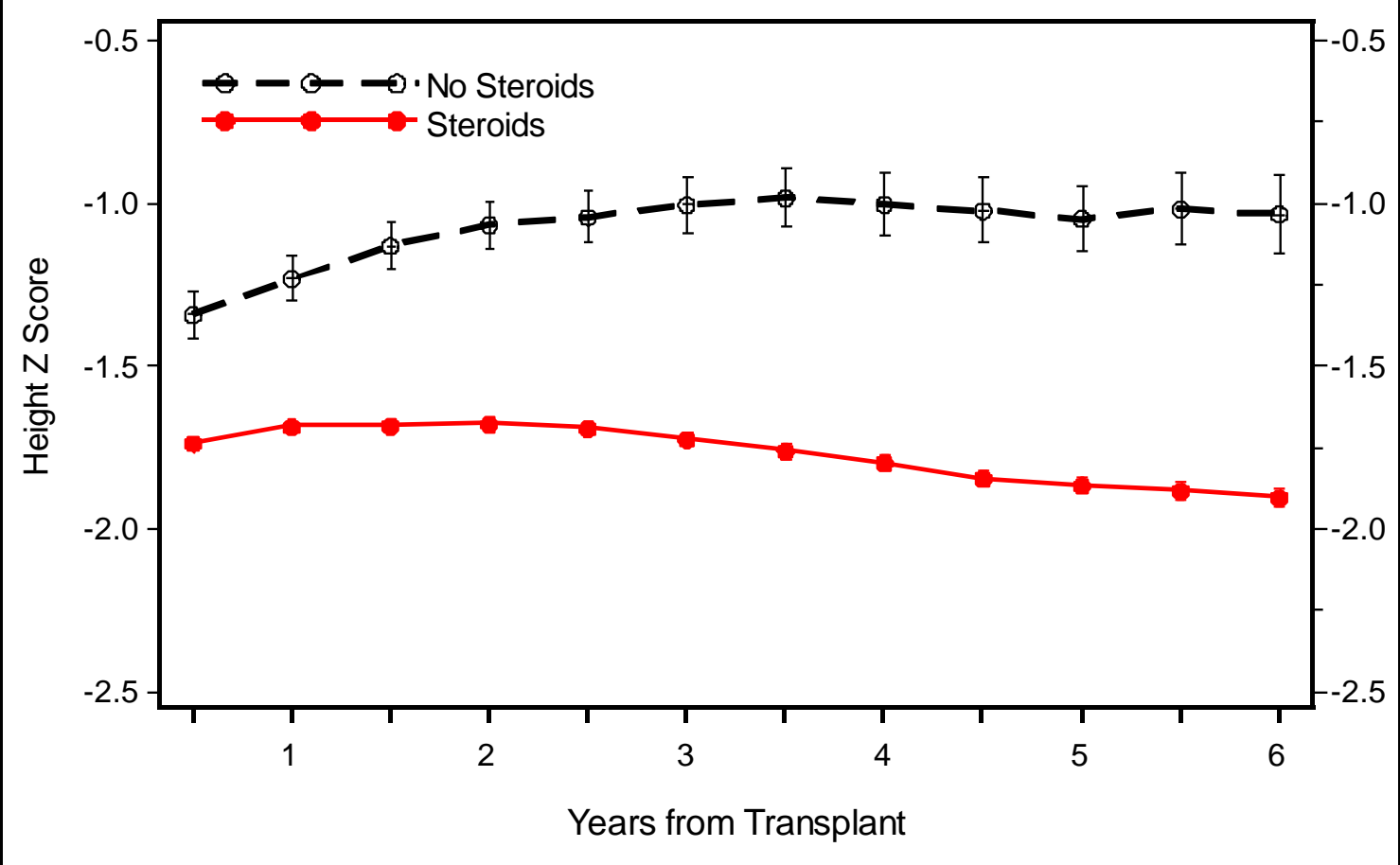
- **WHAT INDUCTION AGENTS HAVE BEEN UTILIZED IN THE STEROID FREE PROTOCOLS?**
  - **Anti-IL<sub>2</sub> RECEPTOR ANTIBODIES (Anti-CD<sub>25</sub>) :**  
**BASILIXIMAB, DACLIZUMAB**
    - STANFORD, CHILE AND NIH RCT PROTOCOLS
  - **Anti-LYMPHOCYTE GLOBULIN/THYMOGLOBULIN**
    - ODENSE AND ST LOUIS
  - **ALEMTUZUMAB**
    - PITTSBURGH, MOSCOW, PORTLAND & STONY BROOK

# STEROID FREE PROTOCOLS

**WHAT IS THE IMPACT OF  
STEROID AVOIDANCE ON  
HEIGHT Z-SCORE IN  
TRANSPLANT RECIPIENTS?**

# NAPRTCS GROWTH DATA

## MEAN $\pm$ SE) BY STANDARDIZED HEIGHT SCORE (STERIOD USE

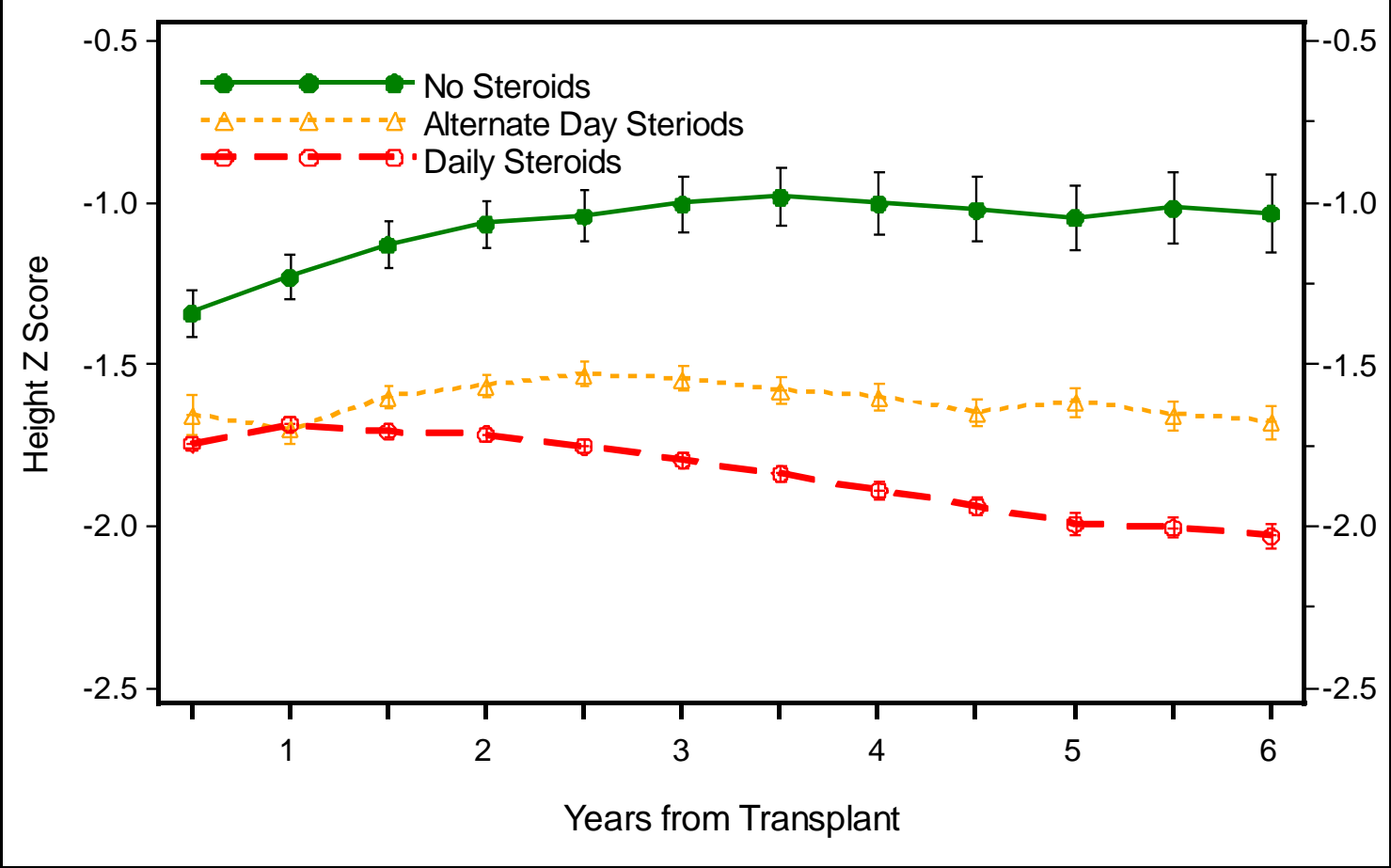


# STEROID FREE PROTOCOLS

**WHAT IS THE IMPACT OF DAILY STEROIDS, ALTERNATE DAY STEROIDS AND STEROID AVOIDANCE ON HEIGHT Z-SCORE IN TRANSPLANT RECIPIENTS?**

# NAPRTCS GROWTH DATA

## STANDARDIZED HEIGHT SCORE (MEAN $\pm$ SE) BY STEROID SCHEDULE



# STEROID WITHDRAWAL, MINIMIZATION OR AVOIDANCE

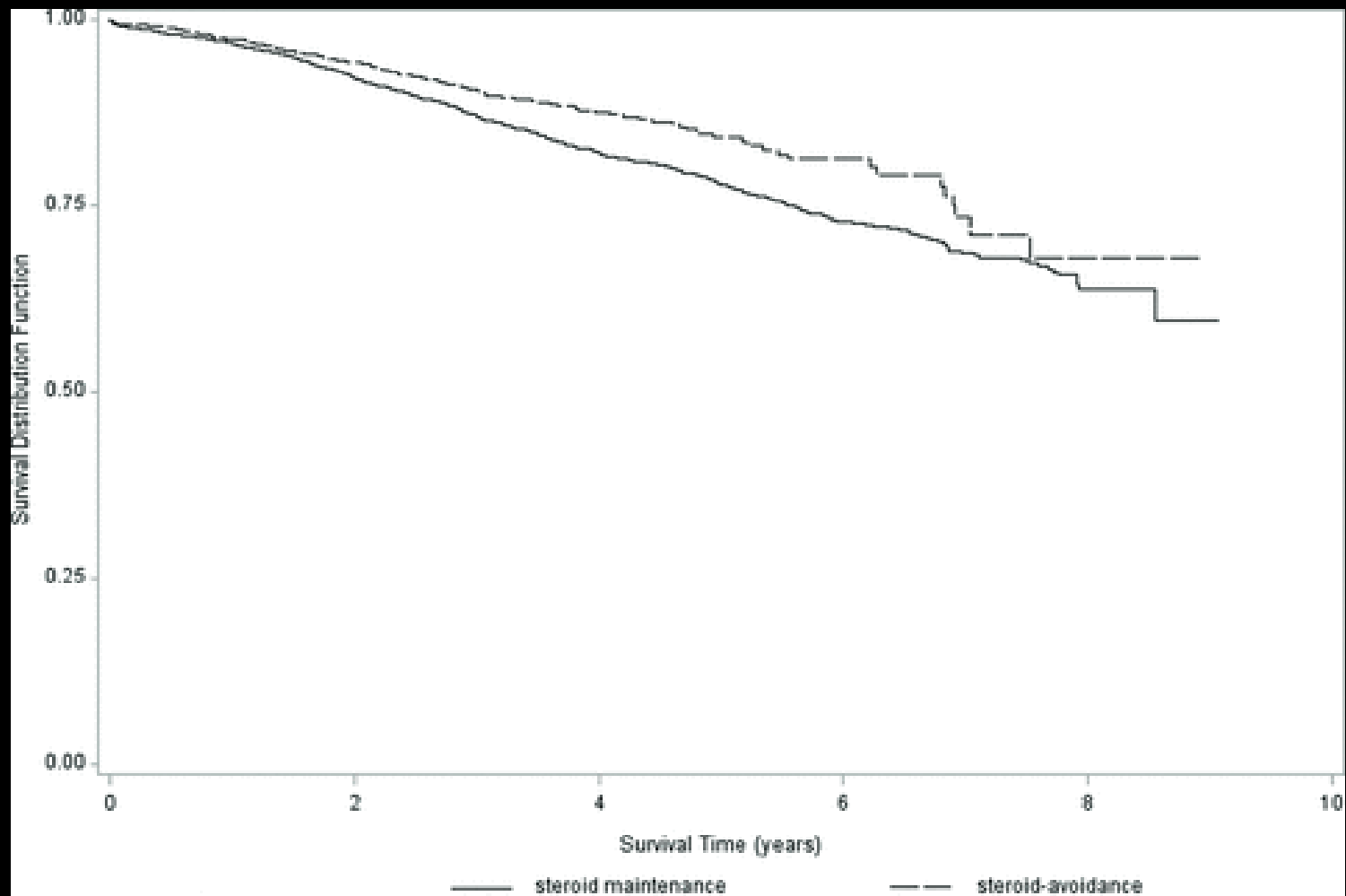
- ARE THERE SPECIFIC RISKS TO STEROID AVOIDANCE, WITHDRAWAL OR MINIMIZATION?

# STEROID FREE PROTOCOLS

- **“STEROID AVOIDANCE APPEARS SAFE WITH REGARD TO GRAFT REJECTION AND LOSS IN PEDIATRIC KIDNEY TRANSPLANT RECIPIENTS OF LOW IMMUNOLOGIC RISK” (NEHUS ET AL AM J TRANSPLANT 12:3441, 2012 – 1296/4627 PEDIATRIC PATIENTS DISCHARGED WITHOUT MAINTENANCE STEROIDS BETWEEN 2002 AND 2009 IN UNOS DATABASE)**



# OUTCOMES OF STEROID-AVOIDANCE PROTOCOLS IN PEDIATRIC KIDNEY TRANSPLANT RECIPIENTS



NEHUS ET AL AM J TRANSPLANT 12:3441, 2012

# STEROID FREE PROTOCOLS

- “ELIMINATION OF STEROIDS (EARLY OR LATE) DOES NOT INCREASE THE RISK OF ACUTE REJECTION OR CAUSE LONG-TERM DETERIORATION OF GRAFT FUNCTION” (**GREYDA PEDIATR NEPHROL 28:2107,2013**)

# STEROID FREE PROTOCOLS

- 3 YEAR RESULTS OF MULTICENTER RTC OF STEROID AVOIDANCE ( **SARWAL ET AL AM J TRANSPLANT 12:2719, 2012**)
  - NO DIFFERENCE IN BIOPSY PROVEN REJECTION (16.7% - **SF** vs 17.1% **SB**)
  - NO DIFFERENCE IN GRAFT SURVIVAL (95% - **SF** vs 90% - **SB**) (p=0.30)
  - PATIENT SURVIVAL 100% IN BOTH ARMS

# STEROID FREE PROTOCOLS

- DO STEROID FREE PROTOCOLS INCREASE THE INCIDENCE OF DISEASE RECURRENCE FOLLOWING TRANSPLANTATION?

# STEROID FREE PROTOCOLS

- 6 OF 17 (35.3%) OF PEDIATRIC KIDNEY TRANSPLANT RECIPIENTS FAILING STEROID FREE IMMUNOSUPPRESSION DID SO AS A RESULT OF DISEASE RECURRENCE @ 5 YEARS – NO CONTROL GROUP INCLUDED IN THE ANALYSIS (SUTHERLAND ET AL TRANSPLANTATION 87:1744, 2009)

# STEROID FREE PROTOCOLS

- CHAVERS ET AL (**PEDIATR TRANSPLANT 16:704, 2012**) COMPARED GRAFT LOSS FROM RECURRENCE OF 25 @ RISK RECIPIENTS RECEIVING A RAPID (6 DAYS) STEROID DISCONTINUATION (**RSD**) PROTOCOL WITH 18 @ RISK HISTORICAL CONTROLS @ 3 YEARS POST-TRANSPLANT. THERE WAS **ONE** GRAFT LOST FROM RECURRENCE IN THE **RSD** GROUP AND **4** IN THE CONTROL GROUP

# STEROID FREE PROTOCOLS

- THEREFORE “THERE ARE LIMITED AND INCONCLUSIVE DATA REGARDING THE IMPACT OF STEROID FREE PROTOCOLS ON THE INCIDENCE OF RECURRENCE OR GRAFT LOSS RESULTING FROM RECURRENT DISEASE “(**GREYNA PEDIATR NEPHROL 28;2107,2013**)

# STEROID FREE PROTOCOLS

- WHAT % OF **STEROID AVOIDANCE** RECIPIENTS @ DISCHARGE ARE PRESCRIBED STEROIDS @ 6 MO (**14.3%**) AND 1 YEAR POSTTRANSPLANT (**21.1%**)?
- WHAT % OF RECIPIENTS DISCHARGED **WITH STEROIDS** HAVE THEM DISCONTINUED @ 6 MO (**6.2%**) AND 1 YR (**9.3%**) POSTTRANSPLANT?

NEHUS ET AL AM J TRANSPLANT 15:2203, 2015



# STEROID FREE PROTOCOLS

- WHAT IS THE LONG-TERM (>5 YRS) IMPACT OF STEROID AVOIDANCE OR EARLY STEROID WITHDRAWAL ON:  
*Δ HEIGHT SDS, GRAFT SURVIVAL, ACUTE REJECTION EPISODES AND GLOMERULAR FILTRATION RATE (e OR m GFR)?*

# STEROID FREE PROTOCOLS

## ■ ***Δ HEIGHT SDS***

### ■ DELUCCHI ET AL (CHILE) (**5 YEARS**)

- $1.4 \pm 0.4$  (SW) vs  $1.1 \pm 0.3$  (SC) ( $p < 0.02$ )

### ■ WAREJKO AND HMIEL (ST LOUIS) (**10 YEARS**)

- 0.79 @ 5 YEARS

### ■ WHITTENHAGEN ET AL (ODENSE) (**15 YEARS**)

- -1.7 to -1.1 @ 5 years ( $p = 0.007$ )
- -2.1 to -0.9 @ 5 years in  $< 5$  y/o ( $p = 0.02$ )

# STEROID FREE PROTOCOLS

## ■ **GRAFT SURVIVAL**

- TAN ET AL (PITTSBURGH) (**4 YEARS**)
  - 85.4%
- DELUCCHI ET AL (CHILE) (**5 YEARS**)
  - 90% (SW) AND 96% (SC) (p=ns)
- WAREJKO AND HMIEL (ST LOUIS) (**10 YEARS**)
  - 93% @ 5 YEARS
- WITTENHAGEN ET AL (ODENSE) (**15 YEARS**)
  - 81% @ 5 YEARS AND 63% @ 10 YEARS

# STEROID FREE PROTOCOLS

## ■ ACUTE REJECTION EPISODES

- TAN ET AL (PITTSBURGH) (**4 YEARS**)
  - 0%, 2.4%, 4.8%, 4.8% @ 1, 2, 3, 4 YEARS
- DELUCCHI ET AL (CHILE) (**5 YEARS**)
  - BIOPSY PROVEN 11% (SW)/ 17.5% (SC) (p=ns) - 5YR
- WAREJKO & HMIEL (ST LOUIS) (**10 YEARS**)
  - 9% BIOPSY PROVEN
- WITTENHAGEN ET AL (ODENSE) (**15 YEARS**)
  - 9% FIRST YEAR 14% SUBSEQUENTLY

# STEROID FREE PROTOCOLS

- **GLOMERULAR FILTRATION RATE**  
(ml/min/1.73m<sup>2</sup>)
  - TAN ET AL (PITTSBURGH) (**4 YEARS**)
    - 95.0±21.7 @ 3 YEARS
  - DELUCCHI ET AL (CHILE) (**5 YEARS**)
    - 80.6±27.8 (SW) vs 82.6±25.1 (SC) @ 5 YEARS  
(p=ns)
  - WAREJKO & HMIEL (ST LOUIS) (**10 YEARS**)
    - eGFR 59.3±11.5 & mGFR 64.2±8.5 @ 3 YEARS

# STEROID FREE PROTOCOLS

- **WHAT ARE THE CLINICAL ADVANTAGES TO STEROID FREE IMMUNOSUPPRESSION?**
  - **IMPROVED GROWTH**
  - **DECREASED CUSHINGOID FACIES**
  - **IMPROVED LIPID PROFILE**
  - **IMPROVED GLYCEMIC CONTROL**
  - **IMPROVED BLOOD PRESSURE CONTROL**

# STEROID FREE PROTOCOLS

- DOES STEROID AVOIDANCE IMPROVE CARDIOVASCULAR (**CV**) RISK FACTORS?
  - MIDWEST PEDIATRIC NEPHROLOGY CONSORTIUM STUDIED **CV** RISK FACTORS IN **70** STEROID AVOIDANCE RECIPIENTS OVER A **3** YR PERIOD AND COMPARED THE OUTCOMES TO A GROUP OF MATCHED CONTROLS ON CHRONIC CORTICOSTEROIDS

WEAVER ET AL PEDIATR TRANSPLANT 20:59, 2016

# STEROID FREE PROTOCOLS

- @ 12 MONTHS POST TRANSPLANT THERE WAS A STATISTICALLY SIGNIFICANT **DECREASE** IN **LEFT VENTRICULAR MASS INDEX (LVMI)** (p=0.014)
- @ 2 YEARS POST TRANSPLANT THERE WAS STATISTICALLY SIGNIFICANT **DECREASE** IN THE PREVALANCE OF **LEFT VENTRICULAR HYPERTROPHY (LVH)** (p=0.012)

WEAVER ET AL PEDIATR TRANSPLANT 20:59, 2016



# STEROID FREE PROTOCOLS

## ■ CONCLUSIONS:

- STEROID FREE PROTOCOLS HAVE **NO** DELETERIOUS EFFECT ON:
  - **PATIENT SURVIVAL**
  - **GRAFT SURVIVAL**
  - **BIOPSY PROVEN ACUTE REJECTION EPISODES**
- STEROID FREE PROTOCOLS IMPROVE GROWTH *SDS* PRIMARILY IN RECIPIENTS <5 YEARS OF AGE
- SIDE EFFECTS OF STEROIDS ARE MINIMISED BY STEROID FREE PROTOCOLS

# STEROID FREE PROTOCOLS

- THE 2009 **KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES (KDIGO)** GUIDELINES RECOMMENDED THAT STEROIDS CAN BE DISCONTINUED DURING THE FIRST WEEK POST-TRANSPLANT IN PATIENTS WITH **LOW** IMMUNOLOGIC RISK

KDIGO CLINICAL PRACTICE GUIDELINES FOR THE CARE OF KIDNEY TRANSPLANT RECIPIENTS AM J TRANSPLANT 9:S1, 2009