

*Minimizing Growth Suppression in  
Children with Steroid-sensitive  
Nephrotic Syndrome*



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# *Outline*



- Define steroid-sensitive nephrotic syndrome
- Disease course – relapse pattern
- Side effects of steroids
- Growth suppression data
- Strategies to prevent growth-suppression

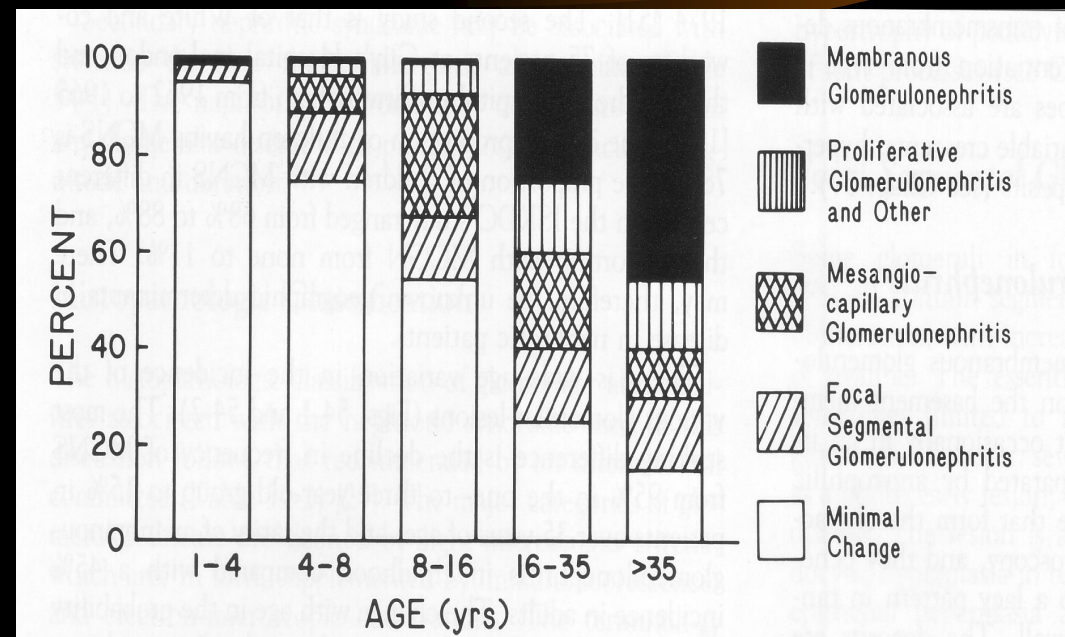
# *Definition*



- “Nephrotic Syndrome = clinical entity having multiple causes, characterized by high glomerular membrane permeability, manifested by massive proteinuria and lipiduria, ...in the absence of depressed GFR.” (G. Schreiner, 1963)
- Urinary excretion rates are usually  $>40$  mg/m<sup>2</sup>/hr in children, or  $>1$  g protein/g creatinine (random sample)

# Childhood Nephrotic Syndrome (NS)

- **Most common cause:** minimal change disease (MCD)
- **First line of therapy:** corticosteroids – daily followed by alternate day
- Many protocols



ISKDC – 1978, 1981

# *Types of Nephrotic Syndrome*



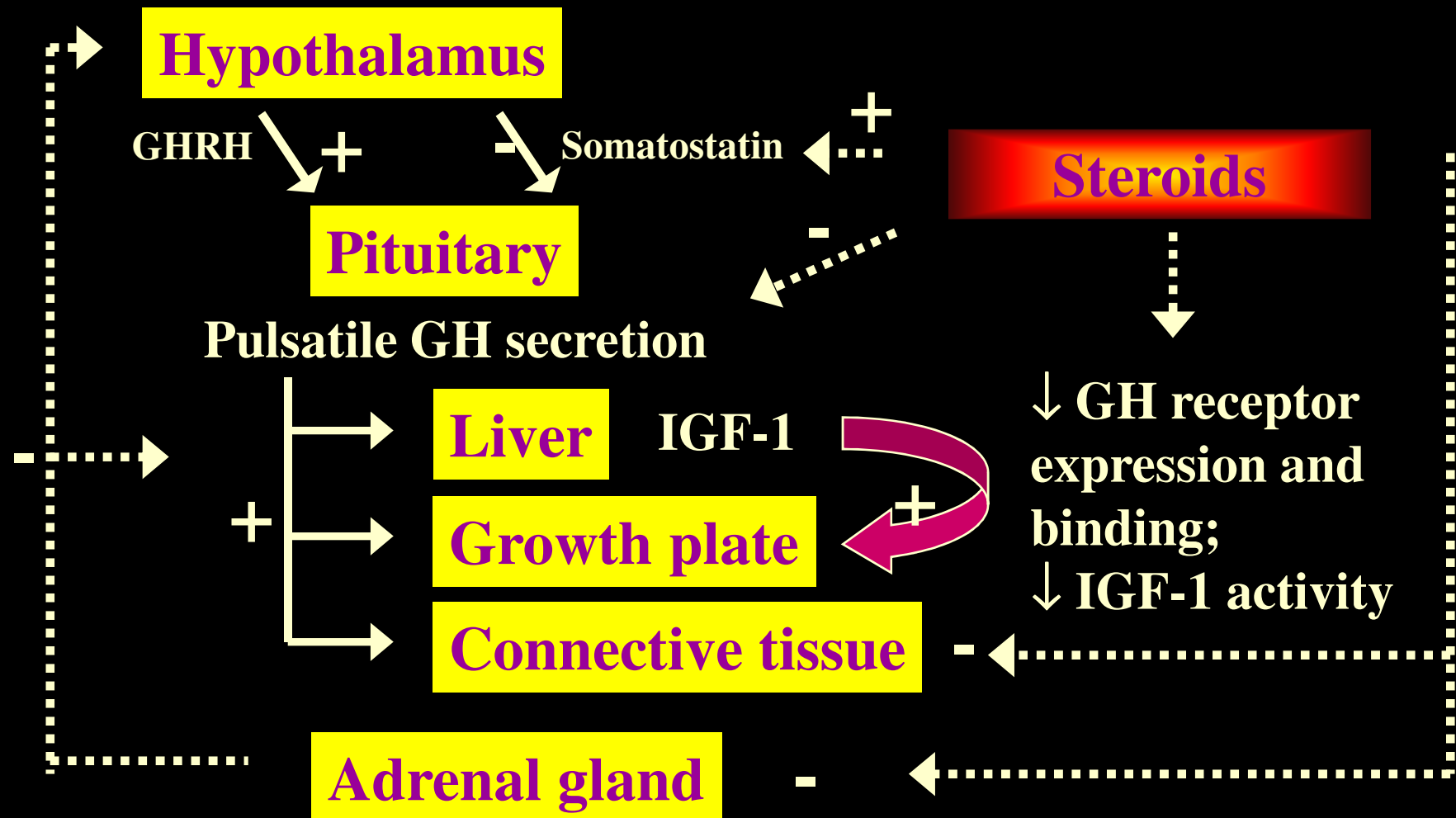
- Based on steroid sensitivity:
  - steroid-responsive (protein-free)
    - Infrequent relapsers (<2 in a year)
    - Frequent relapsers (2 in 6 months, or >3 in a year)
    - Steroid-dependent (within 1 month after steroids stopped or while on alternate day therapy)
  - steroid-resistant (no response after 4-6 weeks)

# *Systems Affected by Steroid Therapy*



- Gastro-intestinal (gastritis)
- Cardio-vascular (hypertension)
- Hematological (leukocytosis, immunosuppression)
- Neuro-psychological (psychosis, depression)
- Bone metabolism (osteoporosis)
- Skin and Eye (striae, cataracts)
- Glucose metabolism (diabetes, cushingoid body habitus)
- *Growth – suppression, leading to short stature*

# *Steroid-induced Growth Suppression - Mechanisms*




# *Impact of Short Stature*



- Body image
- Psychosocial adaptation
- Bone metabolism
- Pubertal development



# *Growth in Children with Nephrotic Syndrome*



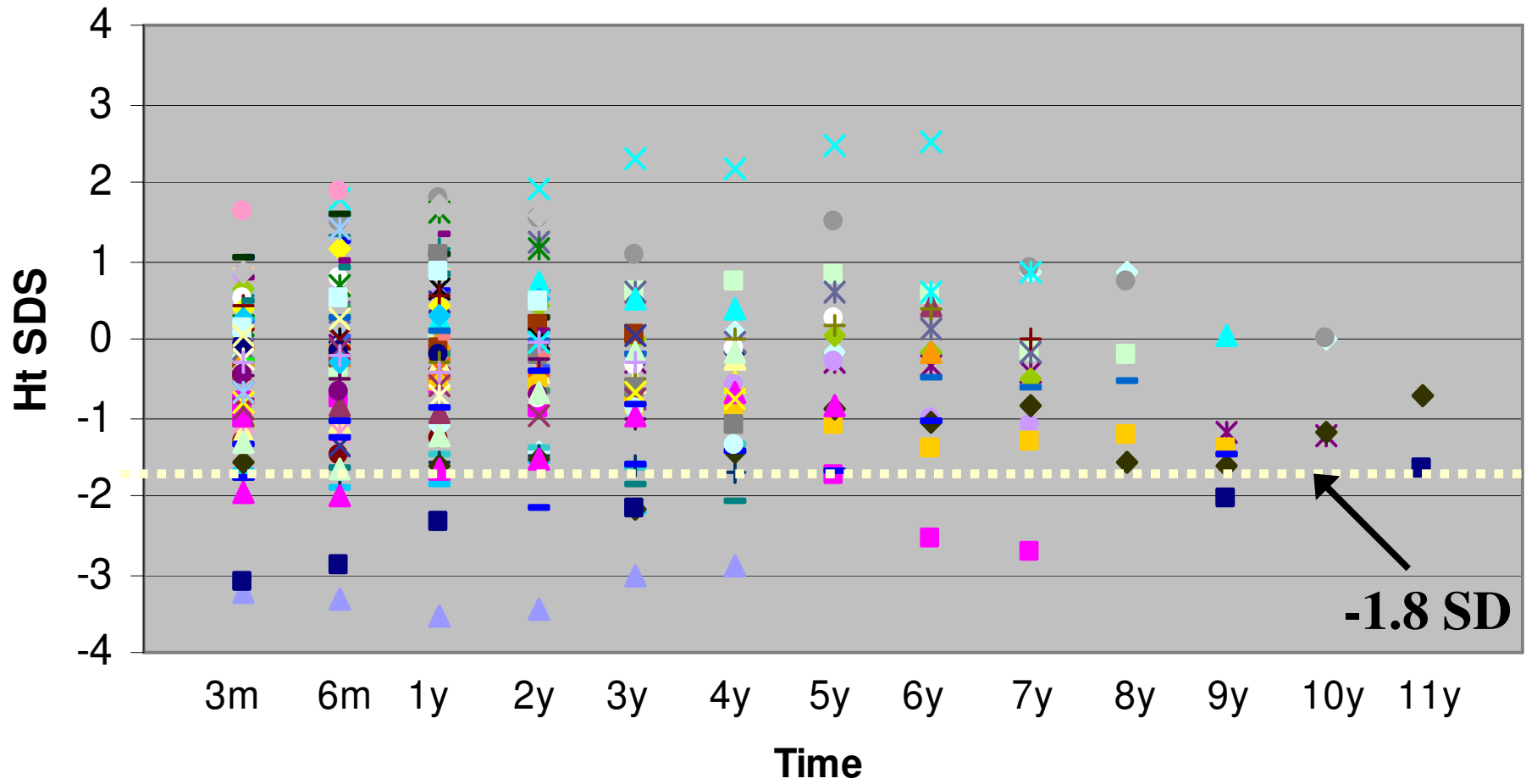
- Single center - Robert Wood Johnson Medical School, New Brunswick, NJ
- We sought to identify:
  - Degree of growth suppression caused by steroid therapy in children with NS, presumed to have MCD
  - Moment of “maximum impact”
  - Frequency of this adverse effect
  - Is this long-lasting?
- Patients with focal segmental sclerosis on biopsy, as well as those with other steroid-resistant forms of NS were **excluded**
- Data entered in GrowTrack v 1.0.6 Software (Genentech, Inc.)
- Standard deviation scores (SDS) for Ht (HtSDS) and GR (GRSDS), were calculated and compared with normal values for age and gender

# *Results*

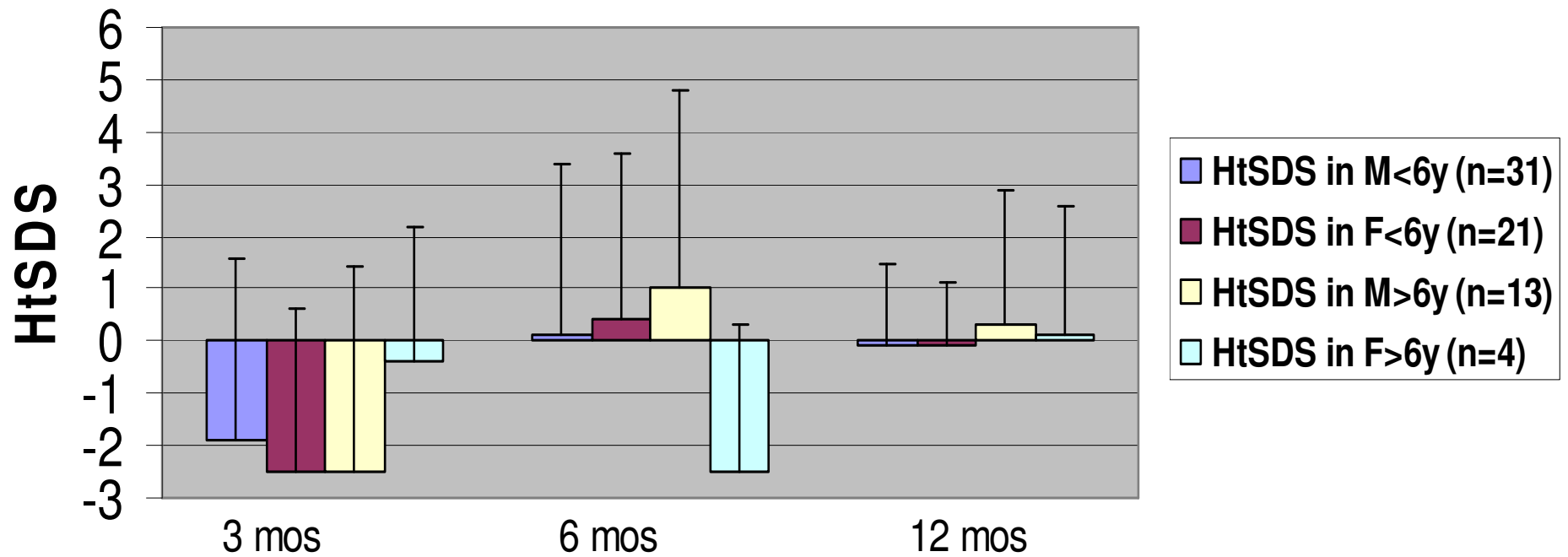


- 69 children with complete growth data
- 44 boys, 25 girls, M:F=1.8:1
- Age range 1-17.8 years
- Younger than 6 yrs of age 75.4%
- Older than 6 yrs of age 24.6%

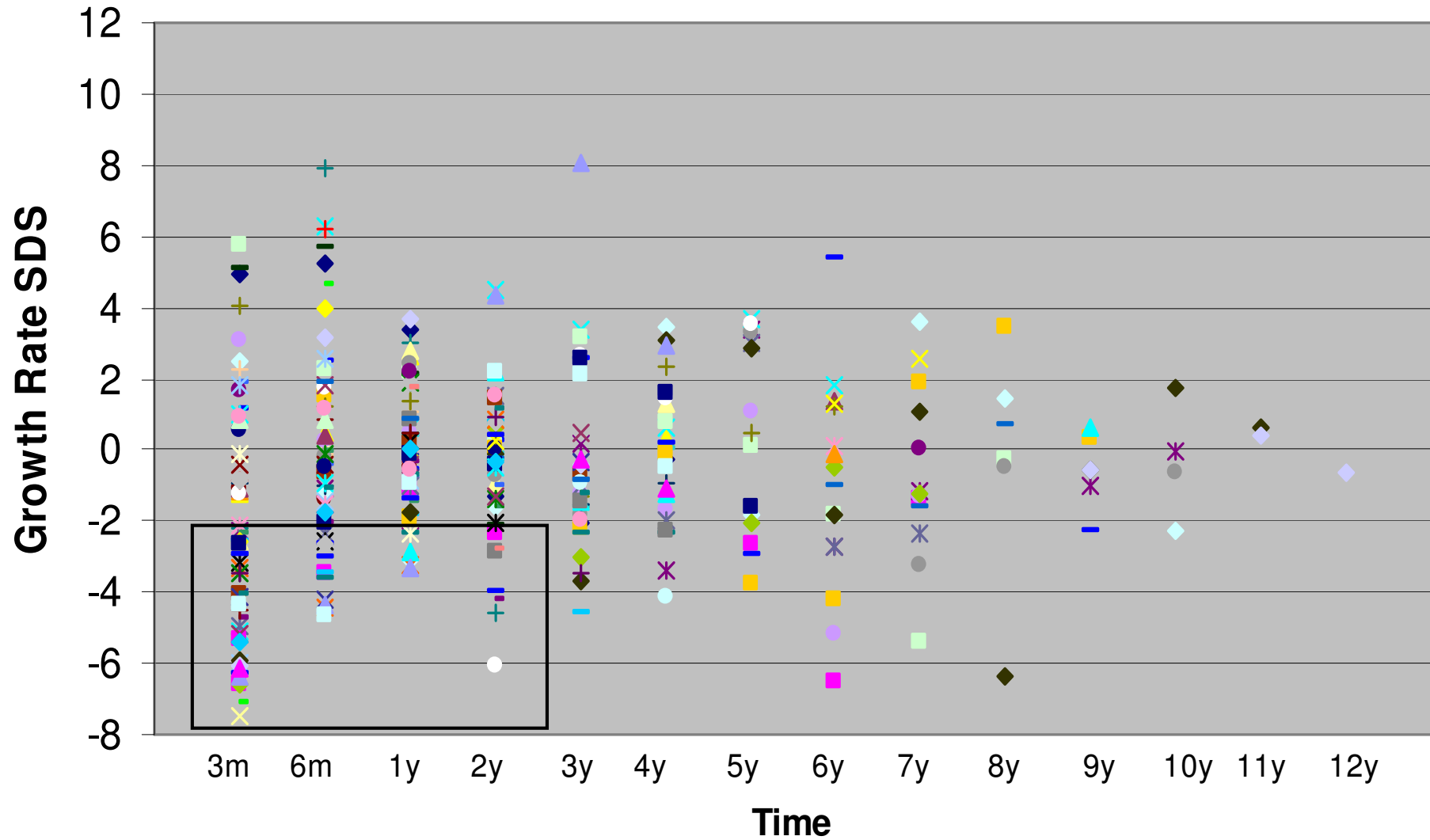
# Ht SDS in Children with Nephrotic Syndrome



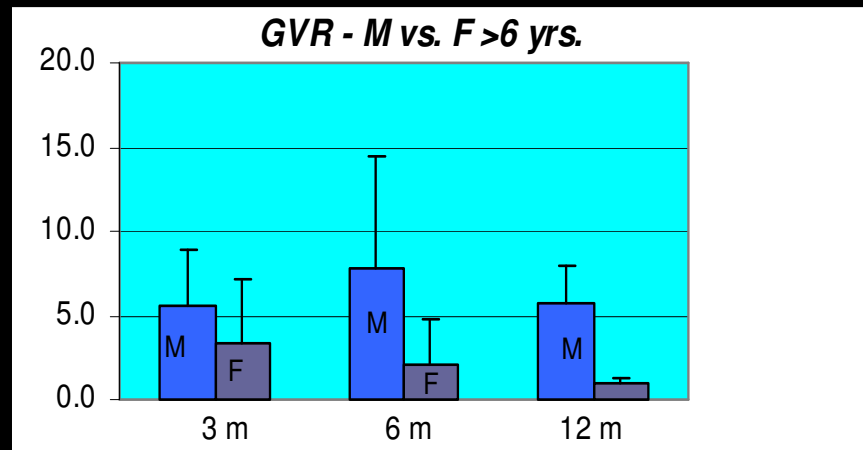
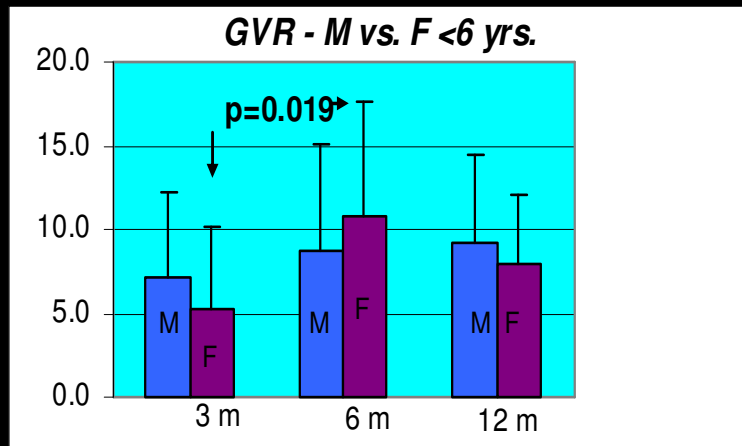
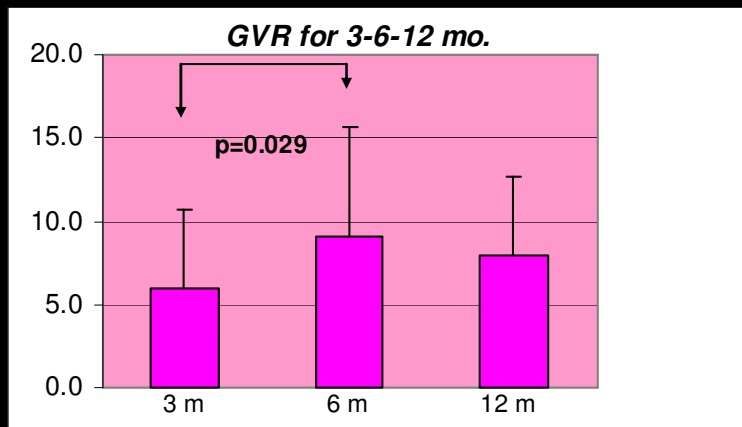
## HtSDS in Children with Nephrotic Syndrome



# Growth Rate SDS in Children with Nephrotic Syndrome



# Growth Velocity Rate (GVR) in Children with NS



# *Long-term Linear Growth in Children with SD or FR Nephrotic Syndrome*

- 56 children (37 M, 19 F) followed-up for  $10.5 \pm 3.1$  yrs
- SD = 42, FR = 14
- Average growth loss was  $0.66 \pm 0.89$  SD
- 2 patients fell below -2SD
- 23 reached final height with loss of:
  - $0.92 \pm 0.8$  HtSDS from the onset of disease ( $p=0.001$ )
  - $0.68 \pm 0.7$  HtSDS from predicted target height ( $p=0.001$ )
- Correlated with steroid dose – higher risk if more than 6 months
- Growth velocity rate lower in younger children,  $<4$  yrs

**Emma F, et al. *Pediatr Nephrol* 18:783-8, 2003**

*So far ...*



- Reviewed the impact of steroids on growth
- How can we minimize exposure to steroids?
  - Lower the frequency of relapse
  - Lower the initial dose of steroids
- *Can we tailor the therapy?*



# *Tailor Therapy*



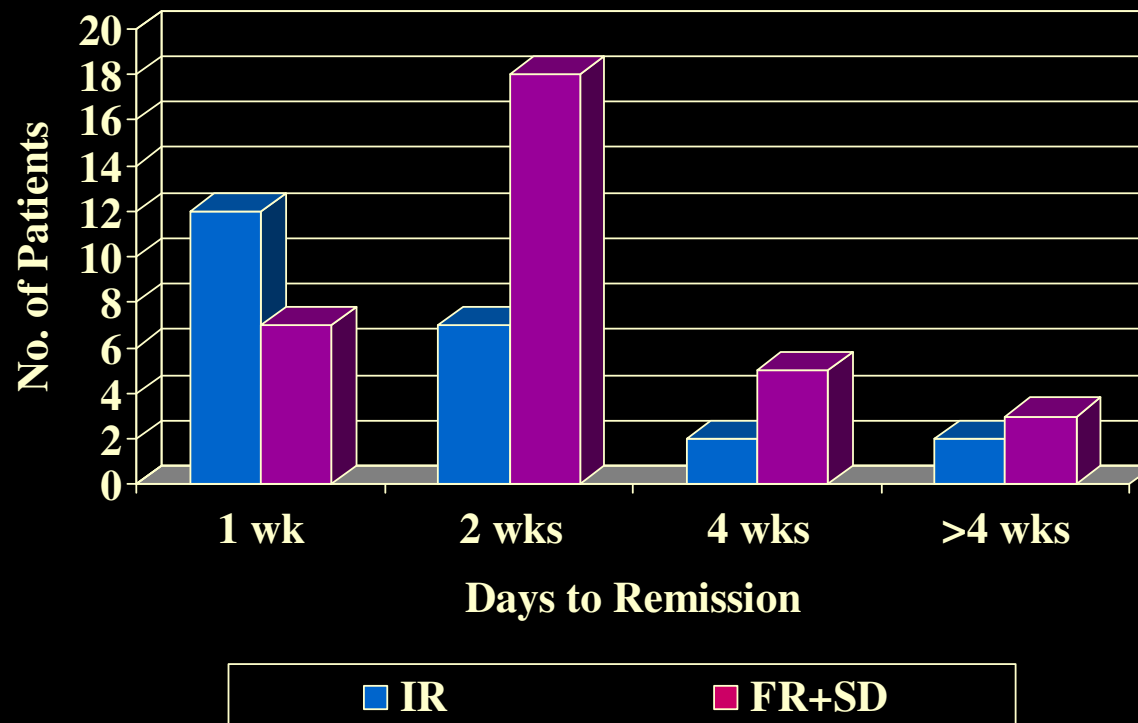
- Arbeitsgemeinschaft für Pädiatrische Nephrologie published in 1998, in Lancet, the finding that 6 weeks of daily steroids + 6 weeks of alternate day steroids appear to reduce the relapse rate – larger cumulative steroid dose
- Niaudet and Habib in 1994 introduced cyclosporine in the treatment of NS, as steroid-sparing agent.
- No sustained remission, additional side effects
- *Segregate according to “days to remission” ?*

# *Predictors of Frequent Relapses in NS*



- Mishra et al. J Trop Pediatr 2013; 59:343-349
  - 60% relapse (150 – 1 year) – **young age** and **longer time to remission** predicts frequent relapsing course
- Harambat et al. Pediatr Nephrol 2013; 28:631-638
  - 70% FR/SD (120 – 6.7 years) – **longer time to remission** predicts use of steroid-sparing agents
- Sureshkumar et al. Pediatr Nephrol 2014; 29:1039–1046
  - 66% relapse (129 – 1 year) – **male, young age, short time to first relapse** predicts FR

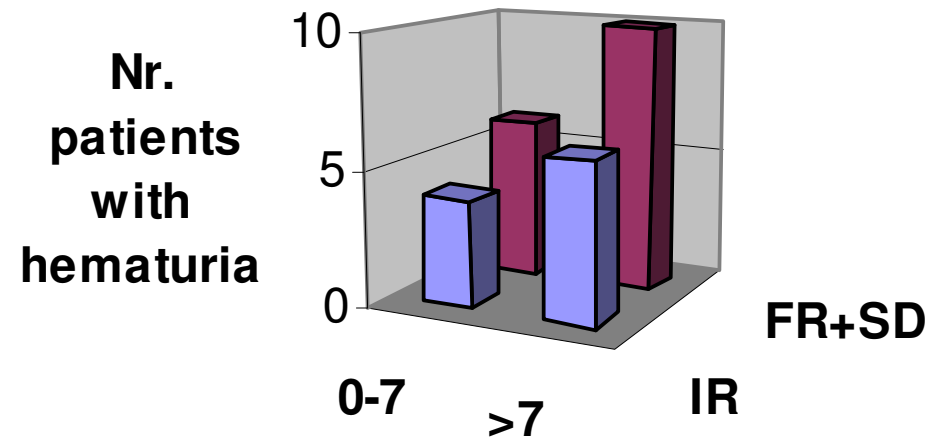
# *Distribution Based on Days to Remission*



Constantinescu et al, Pediatrics 2000; 105:492-495

# *Disease Course in Patients with Hematuria*

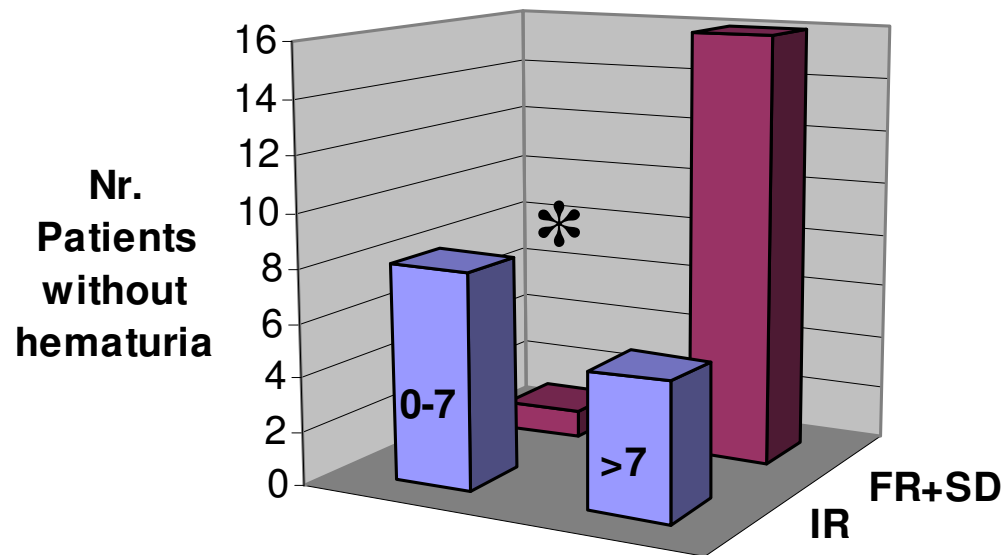
**Relapse pattern vs. Days to  
remission**



**Constantinescu et al, Pediatrics 2000; 105:492-495**

# *Disease Course in Patients without Hematuria*

Relapse Pattern vs. Days to remission



**Predicts**  
*infrequent*  
**relapsing**  
**course**

\*  $p < 0.05$

# *MDR-1 Gene Polymorphism*



- *MDR-1* encodes for P-glycoprotein-170, a biological barrier
- Up-regulated *MDR-1* gene expression correlates with a poor response to steroids
- *MDR-1* polymorphism studies – in NS, **TT genotype associated with a delayed response to steroids and a FR course**

Wasilewska, A, et al. *Pediatr Nephrol* 22:44-51, 2007

# *Our Approach to Minimize Exposure to Steroids*



- Establish the diagnosis of nephrotic syndrome
- Determine if hematuria is present at the onset
- Start steroid therapy
- Parents call first day urine is protein-free
- With hematuria, steroids 6 wks QD + 6 wks QOD
- Without hematuria AND response in >1 wk, therapy for 6 wks QD + 6 wks QOD
- **Without hematuria AND response in <1 wk**, therapy only for 4 wks QD + 4 wks QOD
- No response in 4 wks - kidney biopsy

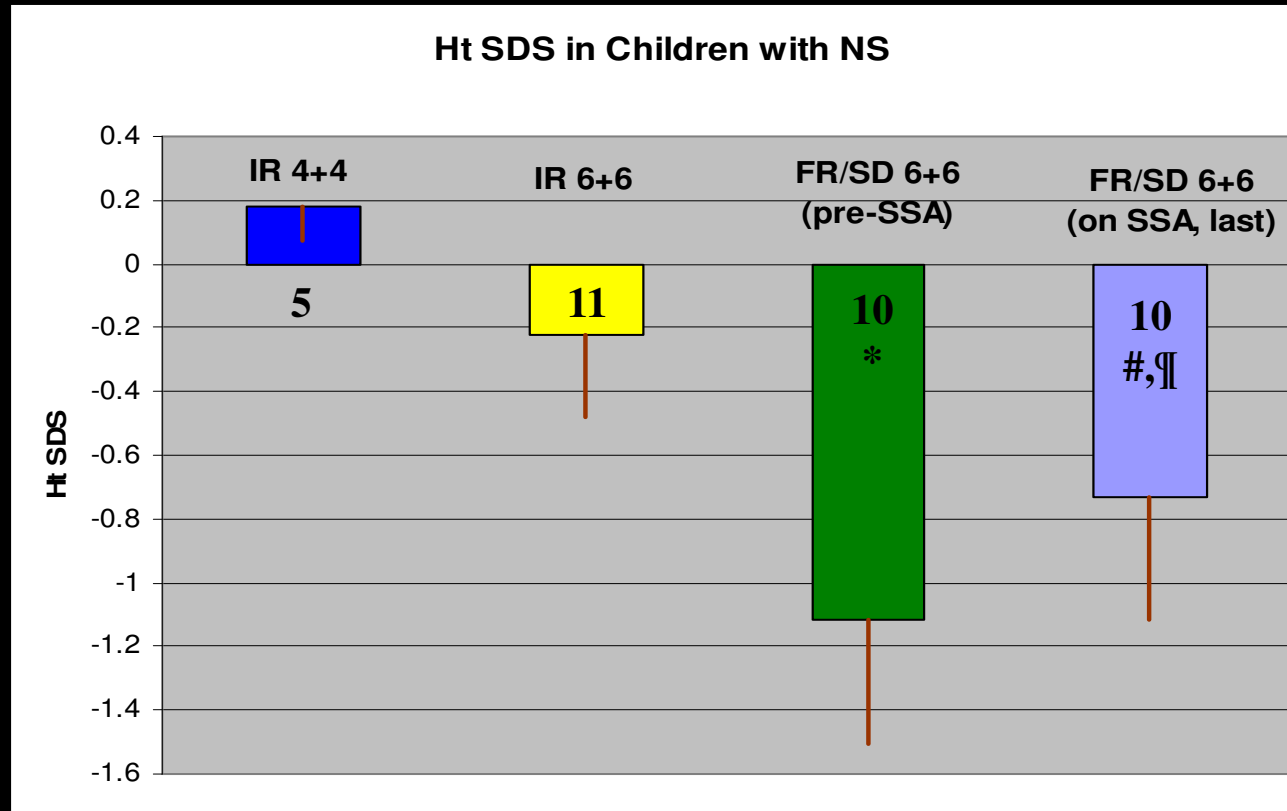
# *Our Data*



- 2006 – present: 60 children with steroid-sensitive NS
- 26 with complete growth records
- 34 – either recently diagnosed, incomplete records, or lost to follow-up
- Relapse pattern noted (IR, FR/SD)
- Initial steroid course (4+4 or 6+6)
- Ht SDS at the last visit



# *Ht SDS - A Function of Relapse Pattern and Steroid Dose*



SSA = patient receiving steroid-sparing agent (tacrolimus or cyclosporine)

\*  $p = 0.039$  between IR 4+4 and pre-SSA

#  $p = 0.0000133$  between pre-SSA and last visit on SSA

¶  $p = 0.29$  between IR 4+4 and FR/SD 6+6 at last visit on SSA

# *Conclusions*



- Steroids have growth-suppression potential
- Attempts needed to minimize the exposure
- Change in daily dose is not recommended
- Cumulative dose can be decreased by predicting the infrequent relapsing pattern based on:
  - response within one week and,
  - the absence of hematuria.
- Prospective studies needed