The PREDNOS Study outcome

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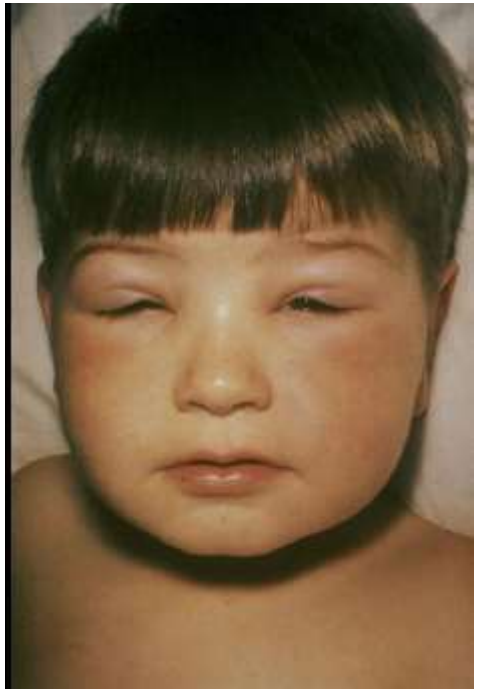
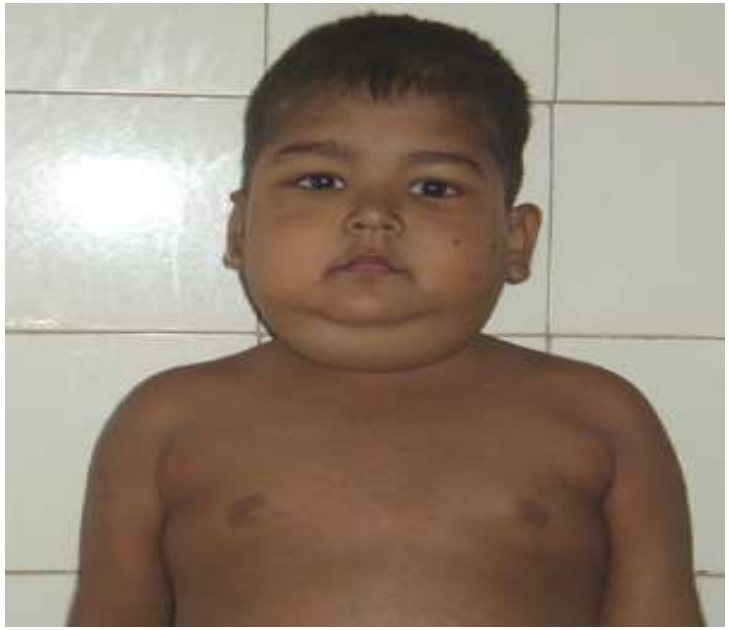
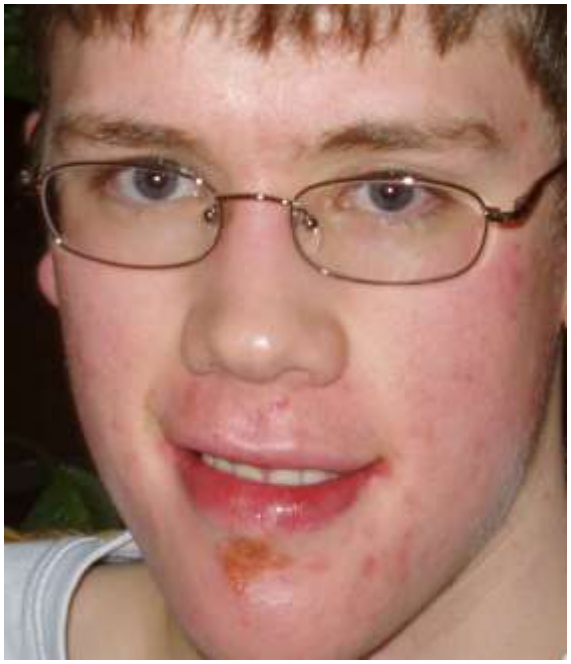
Steroid sensitive nephrotic syndrome

- Commonest childhood glomerular disease
  - Incidence 3 /100,000 children
  - More common in S Asians
- Heavy proteinuria, low albumin levels and generalised oedema
- Initial treatment is with high dose prednisolone therapy (variable course)
- 80% of children follow a relapsing course
  - One half of these have frequent relapses
- Much treatment related morbidity

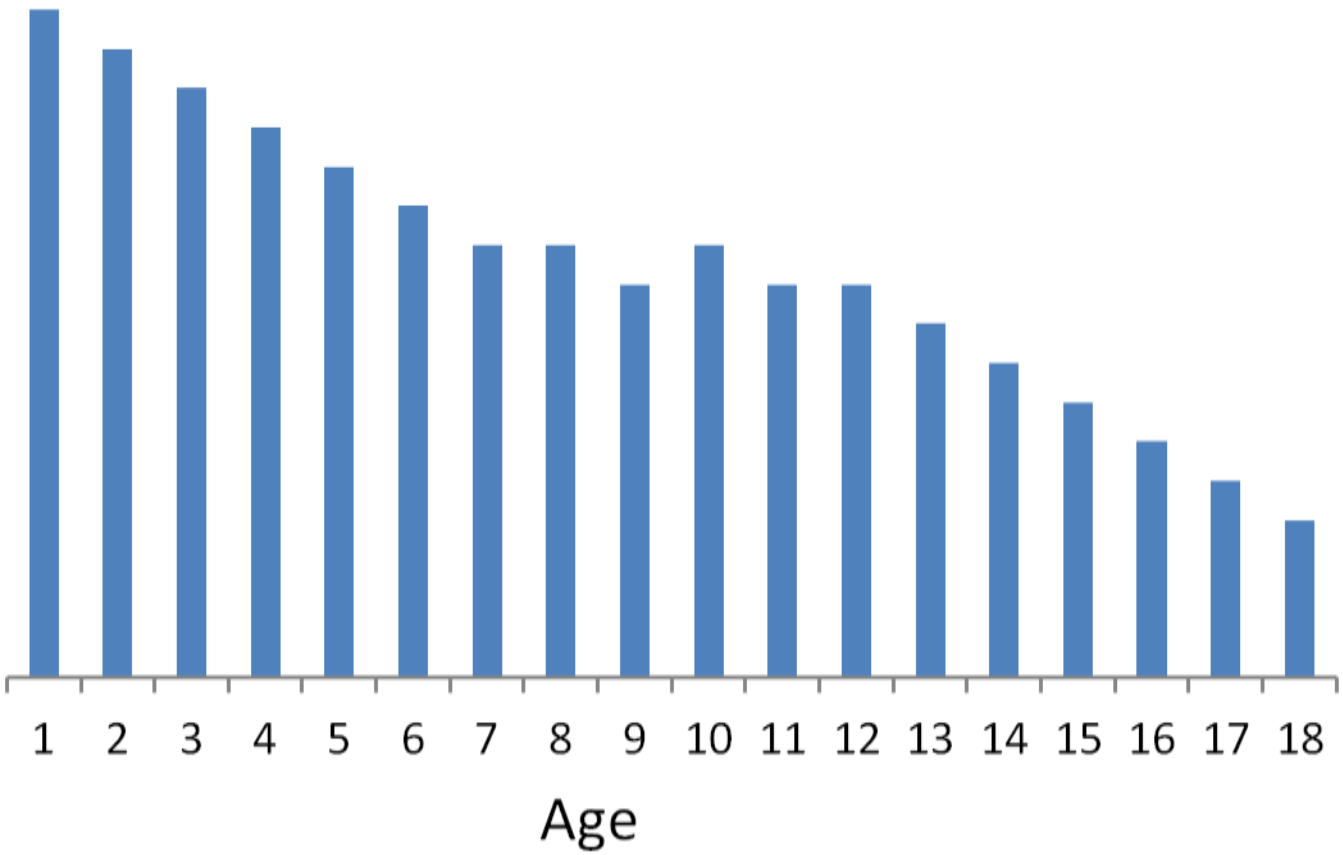


Adverse-effects of corticosteroids





Risk of relapses long term



ISKDC regimen

- Prednisone (Prednisolone) 60mg/m^2 (max 80mg) daily for 4 weeks followed by 40mg/m^2 (max 60mg) on alternate days for 4 weeks

- Has been the 'gold standard' regimen against which all others have been compared

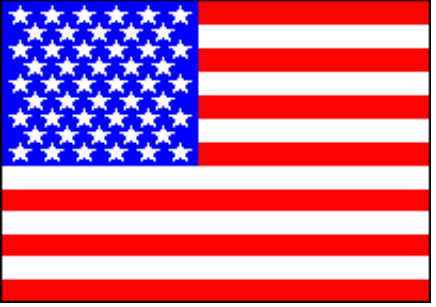
APN regimen

Prednisolone

60 mg/ m^2/day (max. 80 mg) for **<u>6 weeks</u>**

Followed by

40 mg/ m^2 alternate days for **<u>6 weeks</u>**



Variation in practice exists..

- Taper steroids at urinary remission 14%
- ISKDC regimen 13%
- ISKDC regimen followed by steroid taper 36%
- 12 week regimen (APN) 7%
- 12 week regimen followed by steroid taper 14%
- Other 15%

Lande *et al* Pediatr Nephrol 2000 14 766-769

Study details

- **Full Title**:–

  Long-term tapering versus standard prednisolone therapy for the treatment of the initial episode Of childhood nephrotic syndrome: national Multicentre randomised double blind trial

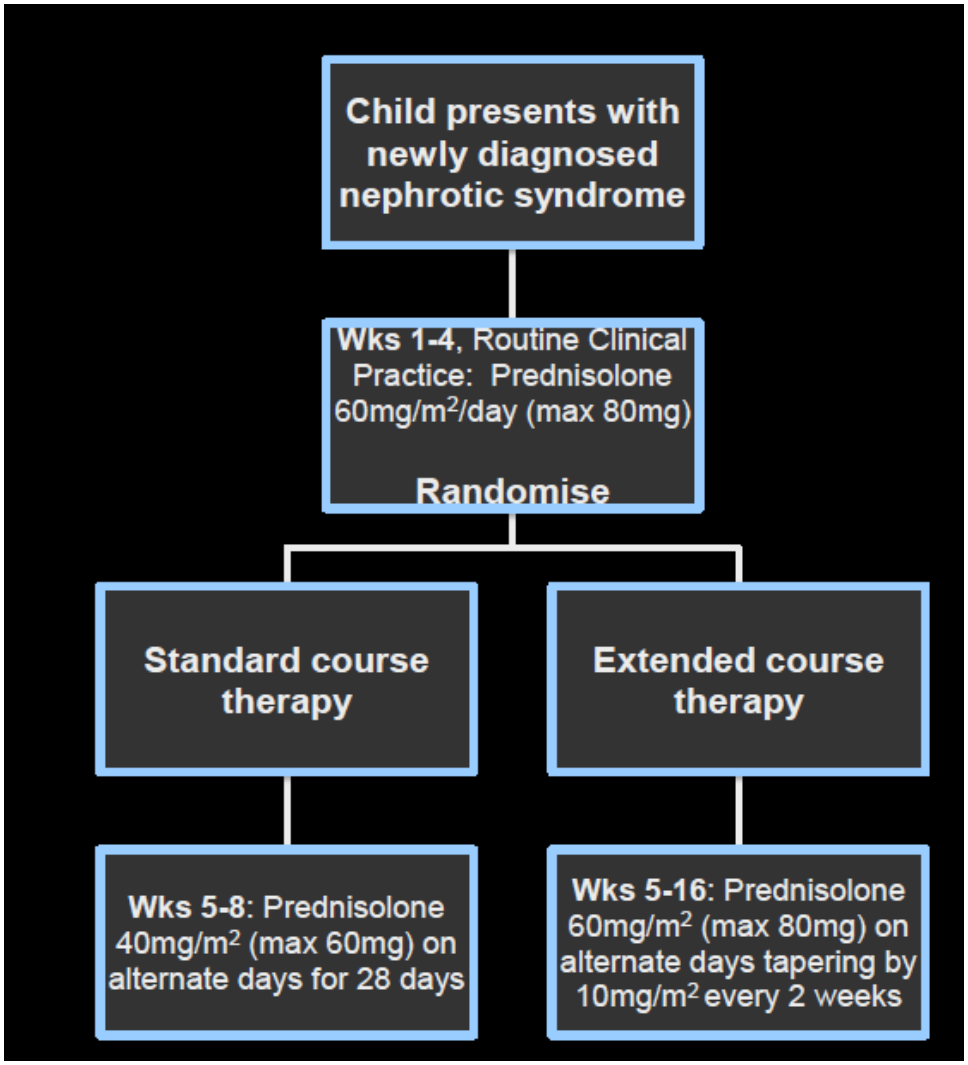
- **Short Title**:– PREDnisolone in NephrOtic Sydrome :The **PREDNOS** study

Study details

- **Aim of Study**:–To compare an extended Course (16 week) tapering prednisolone regimen with the standard 8week ISKDC Regimen

- **Design** –Double blind placebo controlled RCT

Study details



PREDNOS

- **Primary end point**
  - Time to first relapse
- **Secondary end points**
  - Frequently relapsing and steroid dependent disease
  - Incidence of relapse
  - Frequency and severity of adverse effects
  - Total use of prednisolone over study period
  - Use of other immunosuppressive therapies
  - Behavioural change
  - Cost effectiveness

Early clinical course and randomisation

- Initial therapy with prednisolone 60mg/m^2 (max 80mg) daily
- Recommend use of non-soluble prednisolone tablets – crushers provided
- consent process once clear child is entering remission
  - consented and randomised in time to allow delivery of study medicines by Day 29

Study visit schedule

- Study visits at:
  - Weeks: 4 (start of randomised treatment), 8, 12, 16
  - Months: 5, 6, 8, 10, 12, 18, 24, 30, 36, 42 and 48

- Achenbach Child Behaviour Checklist and QALY (PedsQL and Child Health Utility-9D) questionnaires at:
  - Week 4
  - Months: 4,12, 24, 36 and 48

Mechanistic studies

- A single 10ml sample of blood will be collected for DNA extraction
  - GWAS to look for possible genetic loci associated with steroid sensitive nephrotic syndrome
    - Kleta / Bockenhauer UCL
  - DNA methylation studies
    - Ray / Lennon Manchester BRC

Health economic analysis

Objective: To measure the **cost-effectiveness** of long term tapering versus standard prednisolone therapy for the treatment of the initial episode of childhood nephrotic syndrome.

Costs- of medications, hospital visits, consultation, admission etc

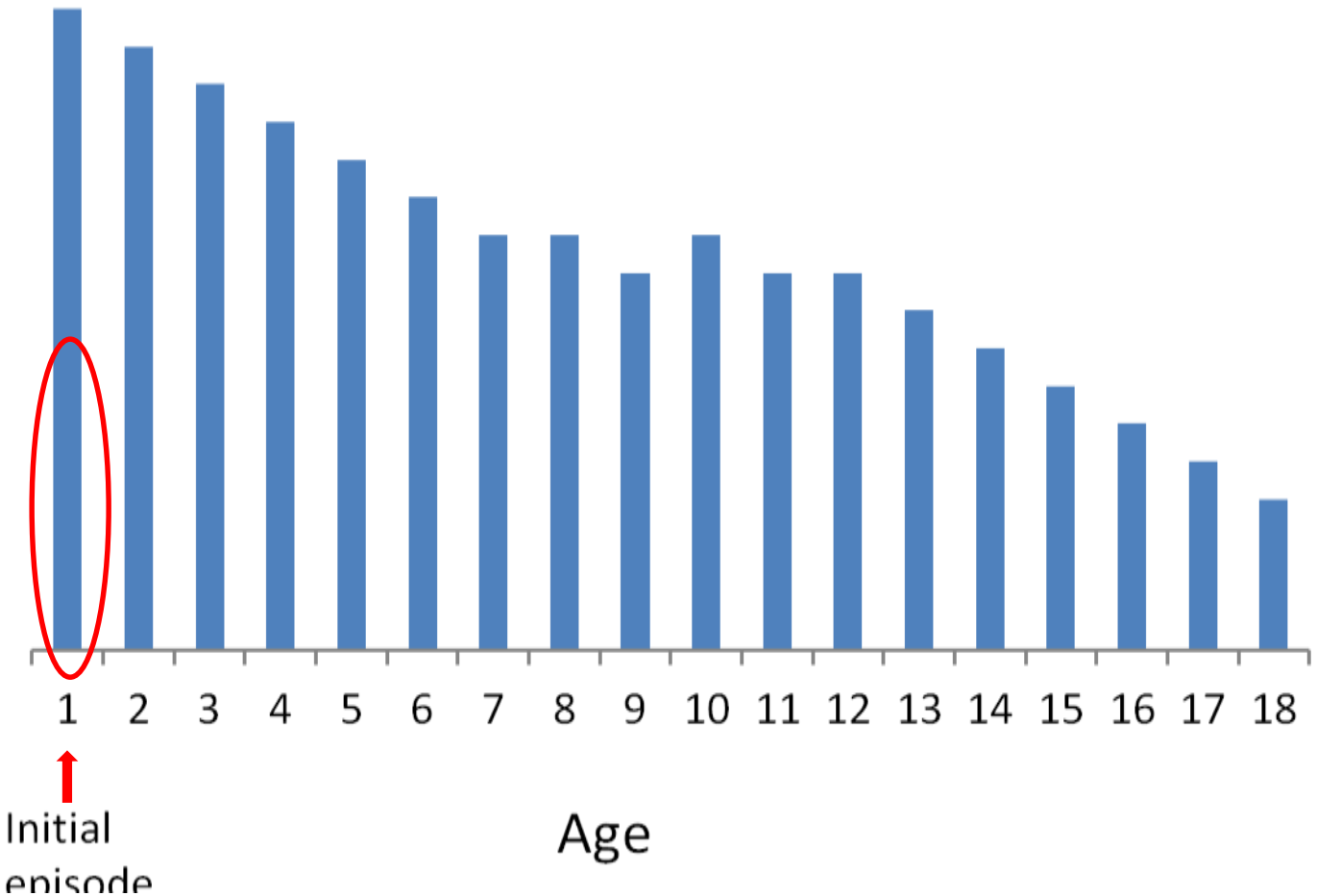
Assessed by- Paed Quality of Life inventory (Ped QL) and Child Health Health Utility (CHU-9D) questionnaires

Results: Presented using 'cost per Quality-Adjusted Life Year (QALY)' gained (primary analysis) and cost per 'relapse of proteinuria' (secondary analysis)

Outcomes

- **Achenbach Child Behaviour Checklist (ACBC)-** used to assess behaviour change as a potential adverse effect of steroids

Risk of relapses long term



Results

- 86 UK centres, Aug 2011-Oct 2014
- 237 recruits;

  118 standard course (SC)

  119 Extended course (EC)
- First few weeks-14 (SC 9, EC 5)withdrawn (steroid resist)
- Later- 30 out of study (15 consent withdrawn, 11 lost for fu, 4 withdrew)
- Total-44 (19%) withdrawn (20 SC, 24 EC)
- Data analysed for 223(237-14), SC 109, EC 114

Results

- Mean age at randomisation 4.9 years
- 65% Male, 20% South Asian
- Mean BMI %tile 87.5%, pred 58.2mg/sqm/day
- 86 (39%) of 223 pts didn't complete their course of study meds (i.e. relapses during study period mainly SC)-50% SC, 28% EC
- 79 relapses (first 12 weeks), SC 50, EC 29
- Good adherence-only 13% missed doses
- >90% fu rates

Results

- 179 recruits reported relapse
- SC 88/109 (81%), EC 91/114 (80%)
- Time to first relapse-*ns* between SC and EC
- Ethnicity and age-*ns* effect on outcome
- 0-15 relapses per recruit
- 8 in SC gp and 9 in EC had 10 or more relapses
- Mean no. of relapses, development of FRNS/SDNS or needing second line agents between gps-*ns*

Results

- Total steroid received SC 5475 mg, EC 6674 mg
- 67 SAEs in 46 recruits (21%)-

  SC-39 SAEs in 27 recruits (25%)

  EC-28 SAEs in 19 recruits (17%) p=0.1

Study drug related-SC 6/39, EC 6/28

- Admission for Rx or haemodyn complication
- Bacterial infection needing abs-SC 4 and EC 7
- One unrelated accidental death

Results

- Most common AEs-increased appetite, poor behaviour, cushingoid, excess hair, abdo pain

AEs

AEs	First 16 weeks			By 24 months		
	Total %	Sc %	EC %	Total %	SC %	EC %
Increased appetite	87	87	86	94	94	93
Poor behaviour	83	90	76	87	93	82
Cushingoid facies	67	66	68	72	71	73
Hypertrichosis	26	23	30	39	38	39
Abdominal pain	26	28	25	45	47	43

Results

- At 16 weeks, 6,12 and 24 months-*ns* difference in between gps with respect to AEs
- Except poor behaviour, lower in EC group
- No differences in ACBC scores
- Cost effectiveness analysis- EC therapy is associated with a mean increase in health benefit (0.0162 additional QALYs) and cost saving (£4369 vs. £2696)

Discussion

- EC offers no clinical benefit over SC

No significant difference between gps in terms of-

- Time to first relapse
- Number of relapses
- Risk of developing FRNS/SDNS
- Need for second line agents

EC cheaper & more effective in QALY terms

Discussion

- 80.3% recruits relapsed (179/223) over median fu period of 37 months
- FRNS; 50% with SC, 52% with EC
- Minor increase in bacterial infection needing admission in EC group

Poor behaviour (parentally reported)-

- More common in SC group
- Achenbach Child Behaviour Checklist (ACBC)- No difference

Discussion

- Ethnicity, age and gender made no difference
- No major effect on blood pressure
- Height Z scores increased following initial fall during first 16 weeks in both gps
- Weight Z score remained constant
- BMI Z score decreased over time

Strength of study

- Design and strength of study
- 20% Asian and 14% other non-white ethnic gp
- Nationwide, DGHs, tertiary units took part
- Well run, great cooperation
- Pilot study-design of study

Weakness of study

- Study drug-tablet, crushed form only
- Younger kids not recruited (mean age 4.9 yrs)
- Placebo tasted bit different
- Multiple observers (many centres)
- No formal ophthalmological review
- No regular blood tests
- Bone mineral density not measured

Economic evaluation

EC group recruits-

- Lower rate of hospital admission
- Shorter duration of hospital stay
- Fewer hospital emergency visits
- Fewer outpatient and GP visits

EC regimen cheaper by £1673/recruit !

Cost effective

Economic evaluation

- Compares costs and effects
- Effects are measured using QALYs (CHU-9D)
- Costs are offset against difference in effects
- Both are simultaneously considered
- Joint density of cost and effect difference is the focus of economic evaluation

Analysis- EC group is cheaper and produces more QALYs

Conclusion

*Extending the duration of prednisolone beyond two months ISKDC regimen does **NOT** result in reduction in the time of first relapse, number of recruits developing FRNS or SDNS or the total dose of prednisolone administered.*

No difference in steroid induced AEs

Cost analysis-EC is cheaper and more effective in QALY terms

PREDNOS 3

- Is prednisolone 30 mg/m^2 daily until remission as effective in the treatment of relapses in idiopathic steroid-sensitive nephrotic syndrome as a convention dose of 60 mg/m^2?

- Does waiting for 5 days of heavy proteinuria compared to the standard of starting steroids on the third day reduce the annual cumulative steroid dose with equivalent efficacy?

Study rationale

- Optimal duration of prednisolone therapy at disease presentation remains uncertain
  - ISKDC initially proposed 8 week regimen
  - Number of studies have suggested that longer duration therapy may be beneficial in reducing the subsequent relapse rate
  - Safety and cost-effectiveness of this approach is not well documented
  - Cochrane group recommended that a further study be conducted
- PREDNOS should help definitively answer these questions
  - Based on successful pilot NEPHROTIC study
  - Largest and only blinded study ever conducted
  - Strong focus on adverse effects of therapy
  - Formal health economic analysis