Clinical Research Facility
Central Manchester University Hospitals
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Clinical trials in childhood steroid sensitive nephrotic syndrome: the PREDNOS studies

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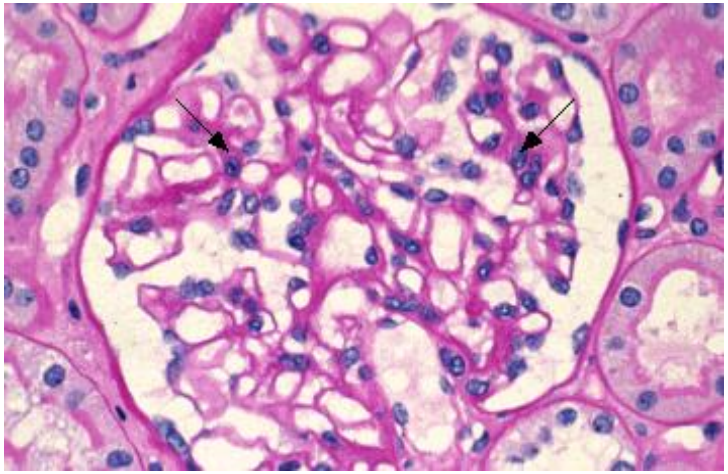
Nephrology for General Paediatricians Meeting, Southampton, July 2017

MANCHESTER 1824
The University of Manchester

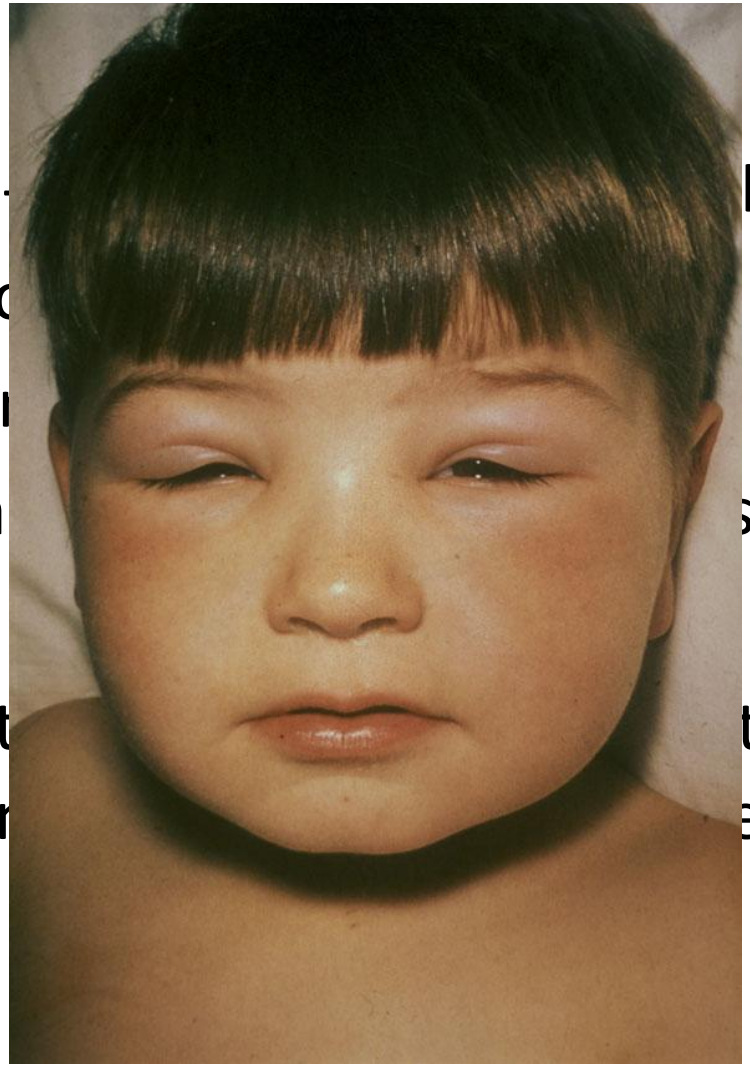
Supported by
MAHSC Manchester Academic Health Science Centre (MAHSC)
wellcome trust

Overview



- Steroid sensitive nephrotic syndrome
  - Overview
  - PREDNOS study
  - PREDNOS 2 study

Childhood idiopathic nephrotic syndrome

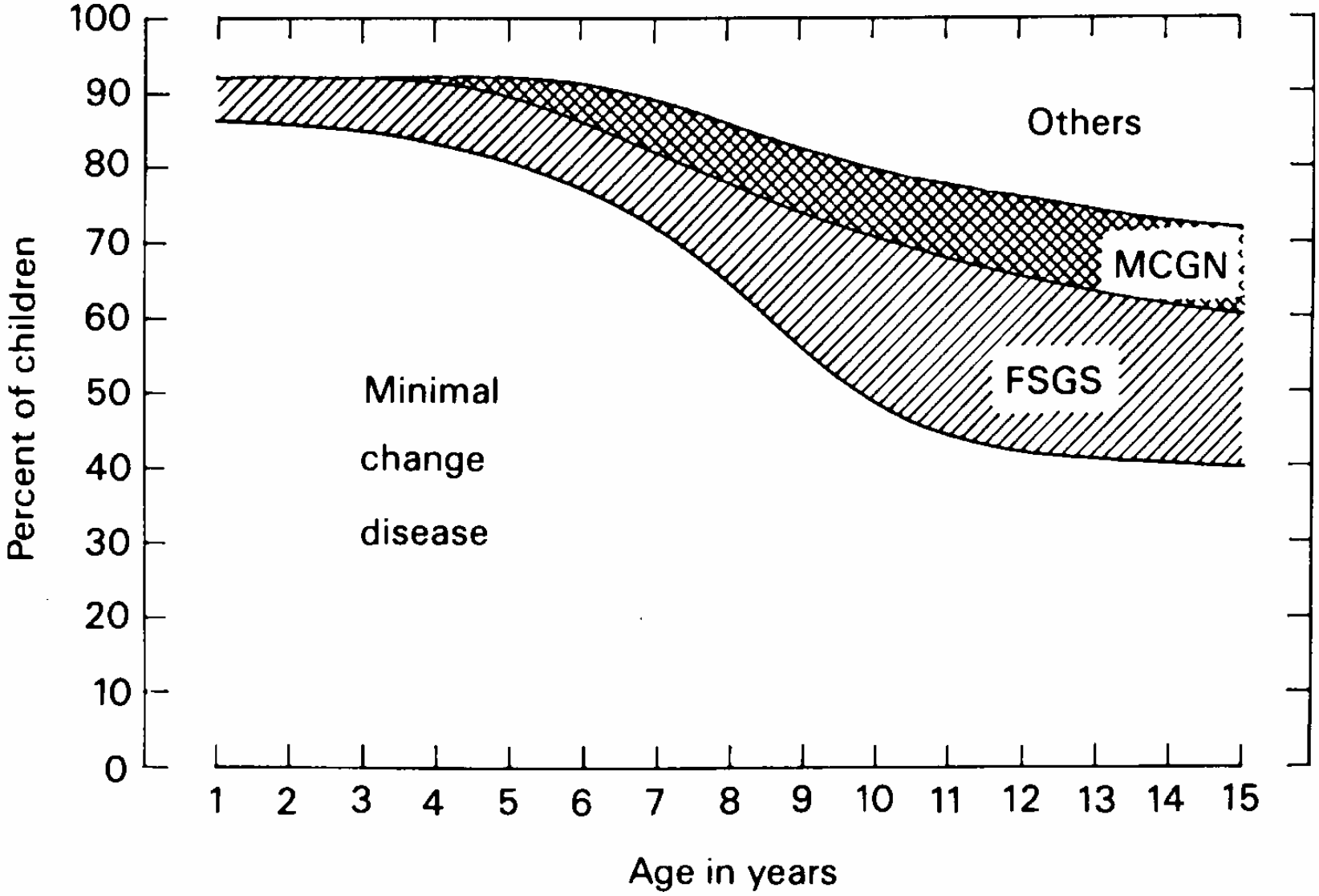


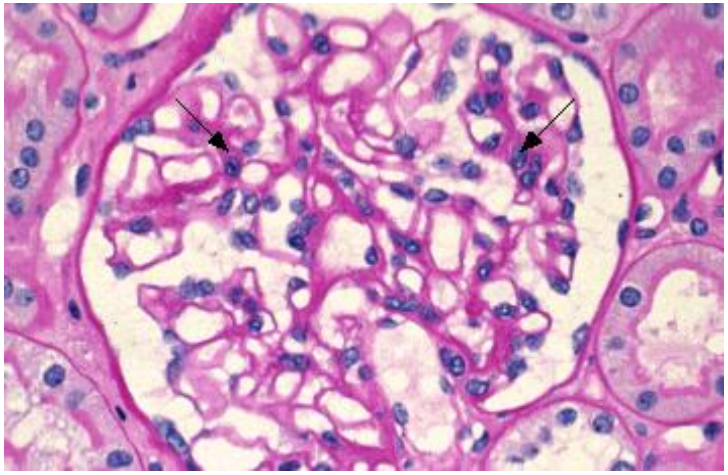
- Incidence 2- K
- Modal age c
- Twice as co
- 4-6 x increa sian population

- Acute onset th subsequent developmer e

Childhood idiopathic nephrotic syndrome

- Diagnosis based on clinical presentation, low plasma albumin and (very) heavy proteinuria
- Renal function generally normal
  - Transient increase in plasma creatinine in small proportion secondary to hypovolaemia
  - 25% have microscopic haematuria
- Blood pressure generally normal
  - 10-20% have transient hypertension secondary to hypovolaemia


100
90
80
70
60
50
40
30
20
10
0
Percent of children
Others
MCGN
FSGS
Minimal
change
disease
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Age in years



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

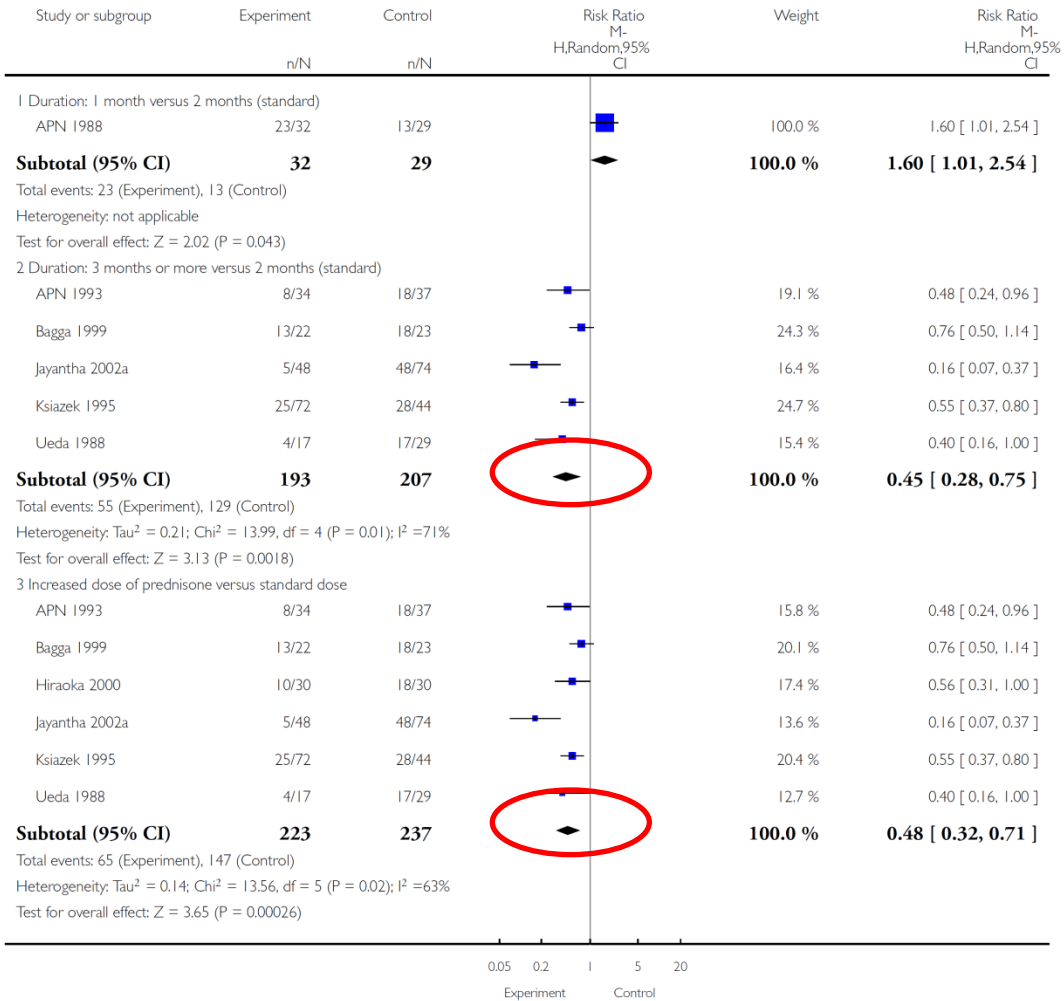
Treatment of the presenting episode

Analysis 1.1. Comparison 1 Steroid therapy in first episode of nephrotic syndrome: comparisons with ISKDC standard therapy, Outcome 1 Number of children relapsing by 6 months.

Review: Corticosteroid therapy for nephrotic syndrome in children

Comparison: 1 Steroid therapy in first episode of nephrotic syndrome: comparisons with ISKDC standard therapy

Outcome: 1 Number of children relapsing by 6 months



NIHR Health Technology Assessment programme funded project

PREDNOS

237 participants recruited by 7th October 2014

Total recruitment time 38 months

Results available Sept 2017

ISKDC re

Total 8 w

Then pla

2w

2w

2w

2w

2w

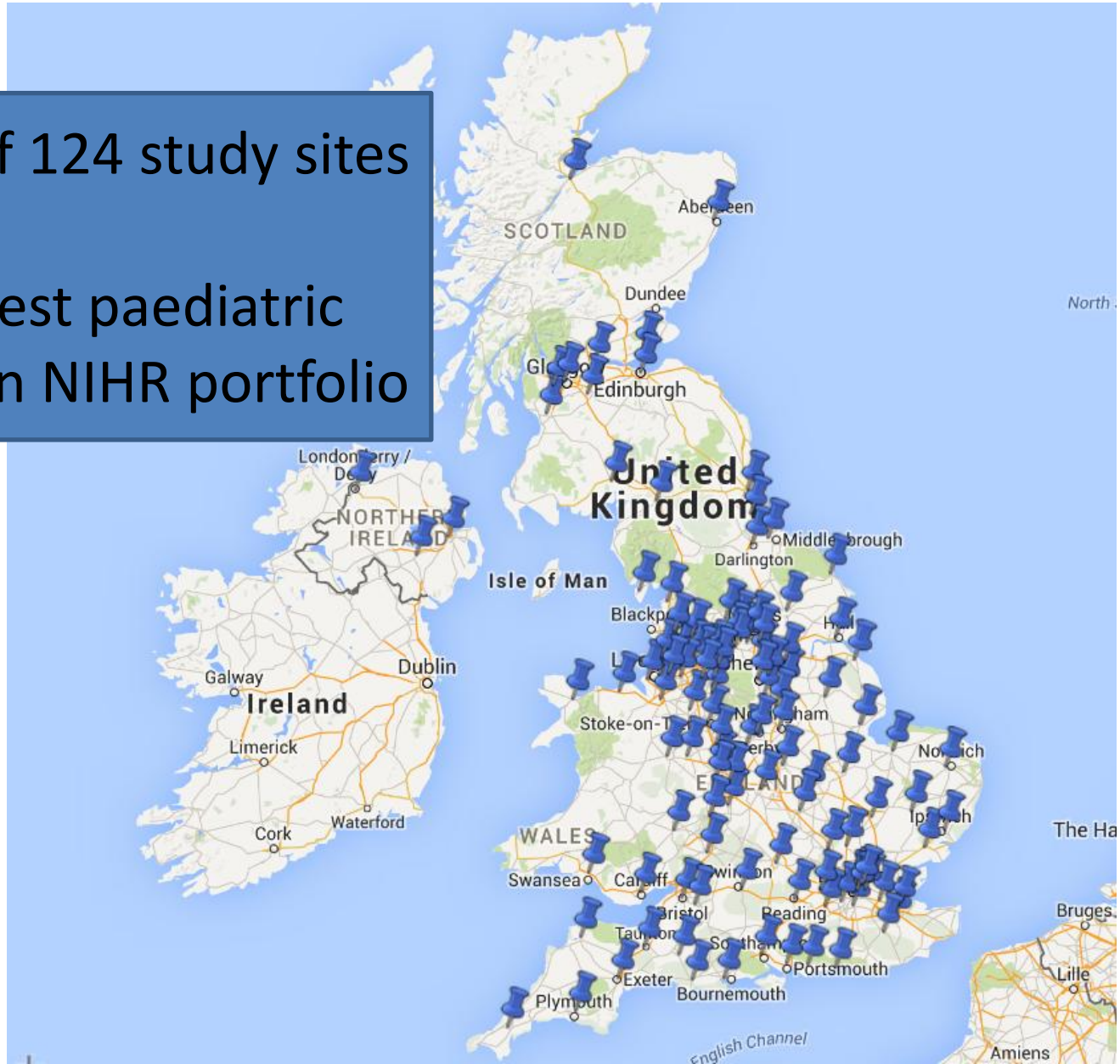
First patient randomised 2nd August 2011

Dr Shankar and team, City General Hospital, Stoke on Trent

Participating sites

Total of 124 study sites

Largest paediatric study in NIHR portfolio



Recent studies

http://www.kidney-interr

see commentary

Extendin
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children

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see clinical trial on pages 217 and 225

clinical trial

New lessons from randomized trials in steroid-sensitive nephrotic syndrome: clear evidence against long steroid therapy

Peter F. Hoyer[1]

The best initial therapy for steroid-sensitive nephrotic syndrome (SSNS) in children is subject to ongoing debate. Systematic reviews and meta-analyses have concluded that at least 3 months and up to 7 months of treatment would reduce the number of relapses by 30%. But summarizing small underpowered studies cannot eliminate the basic flaws in design. Two well-powered randomized prospective trials now come to the opposite conclusion, and these results should impact the management of children with SSNS.

Kidney International (2015) **87,** 17–19. doi:10.1038/ki.2014.354

in a
ths
of illness in
syndrome

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ics, All India Institute of

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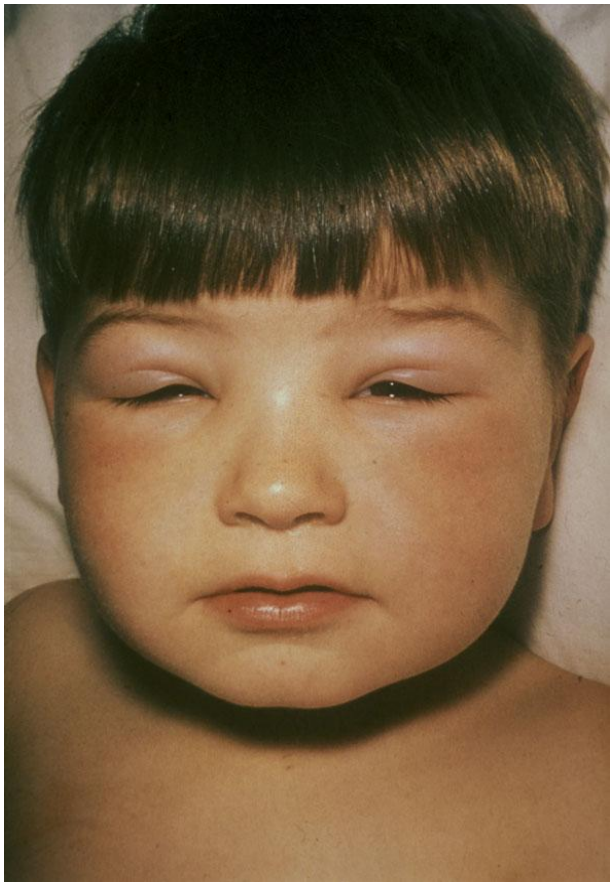
Corticosteroid therapy for nephrotic syndrome in children: 2015 update

Implications for practice

Prolongation of prednisolone therapy beyond two to three months in the initial episode of SSNS does not reduce the risk of relapse in studies at low risk of bias whether the same total dose of prednisone is used for short and long durations or whether the total dose of prednisone is increased with longer durations of treatment.

The results of a further well designed study evaluating different durations and therefore total doses of prednisone are awaited (PREDNOS Study 2013).

Clinical course following first episode of SSNS



- 10-20% have no further relapses
- 30% have infrequent relapses
- 50% develop frequently relapsing* or steroid dependent+ disease requiring alternative therapies

* >4 relapses per year
+ 2 relapses on or within 14 days of stopping AD steroids

ISKDC relapse treatment

- Prednis(ol)one
  - 60mg/m^2 until urinary remission (3 days zero or trace proteinuria)
  - then 40mg/m^2 alternate days for 28 days
- Infrequent relapses treated with repeated courses
- Multiple relapses increase risk of steroid related adverse events

Steroid sparing treatments – the prevention of disease relapses

- Alternate day prednisolone
- Levamisole
- Alkylating agents
  - cyclophosphamide and chlorambucil
- Calcineurin inhibitors
  - ciclosporin and tacrolimus
- Purine inhibitors
  - mycophenolate mofetil
- Anti- B cell therapies
  - rituximab

Evolution of PREDNOS 2 - URTI and relapses

- Around 50% of relapses are preceded by an URTI
- If URTI develops, around 50% chance of a relapse developing
- It seems logical that URTI is pivotal and attempts to ameliorate the URTI driven process are appropriate

Pre-emptive treatment of relapses

Gulati *et al*. Clin J Am Soc Nephrol 2011; 6: 63-69

- 100 children - FRNS on AD prednisolone (32 on levamisole)
- At time of development of URTI randomised to 7 days of
  - **daily prednisolone** at same dose
  - **Remained on AD prednisolone**
- URTI defined as
  - Fever >38, rhinorrhoea, cough, diarrhoea
- Incidence of URTI-related relapse reduced
  - Relapse rate reduced by 0.7/y (95%CI 0.3-1.1: $p<0.01$)

Unanswered questions

- Utility of this approach in Western nations
  - Different pattern of URTI – less fever, diarrhoea etc.
- Utility in children receiving other therapies
  - ciclosporin, tacrolimus, MMF, cyclophosphamide, rituximab +/- AD prednisolone?
- Cost-effectiveness
- Adverse-effect risk?
  - Particularly effect on behaviour

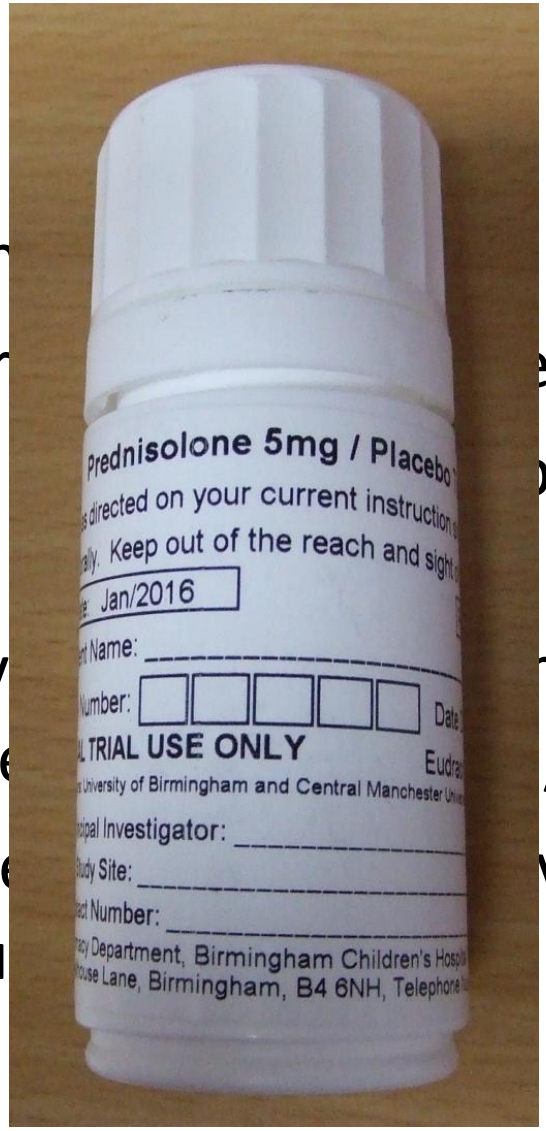
PREDNOS 2: Primary study objective

- To determine whether a six day course of oral prednisolone given at the time of URTI reduces the incidence of first URTI-related relapse

NIHR Health Technology Assessment programme funded project

PREDNOS 2

- 300 UK children [illegible] lapses in past 12m)
- On any long-ter [illegible] essive regimen
- Randomised to [illegible] placebo arm at study entry
- When URTI dev [illegible] mmence child on 6 days of daily pre [illegible] /m2) or placebo
- Repeated with e [illegible] velops over 12 month follow-u [illegible]



NIHR Health Technology Assessment programme funded project

PREDNOS 2

- URTI defined as the presence of at least 2 of the following *for at least 24 hours*:
  - sore throat
  - ear pain/discharge
  - runny nose
  - cough (dry/barking)
  - hoarse voice
  - fever >37^{O}C (measured using tympanometric electronic thermometer)

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PREDNOS 2

- Primary end-point – development of URTI-related relapse
- Secondary end points – relapse rate, cumulative prednisolone dose, adverse events (particularly behavioural), escalation / de-escalation of background immunosuppressive therapy
- Quality of Life Assessment
- Formal Health Economic Analysis (Frew, Birmingham)
- DNA sampling

Recruitment

New sites welcome to join study

- First participant recruited 19.3.13
- Total 285 participants recruited
- 116 sites set-up
- 64 have recruited participants
- Further sites currently in set-up

Funding extension

- Rate of recruitment slower than anticipated
- Number of participants completing study without URTI greater than anticipated
- Event rate (URTI-related relapse following first URTI) lower than anticipated

- Further funding to increase number of participants to 360 by April 2018
  - **We need the on-going help of Wessex centres to achieve this**

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Corticosteroid therapy for nephrotic syndrome in children: 2015 update

Four RCTs from emerging countries have shown that daily prednisone administered during an intercurrent infection reduces the risk of relapse. A further well designed RCT is currently assessing this intervention in European children, where the pattern of intercurrent infections may be different (PREDNOS 2 Study 2014).


PREDNOS 2 NEEDS
YOU"

Conclusions

- The PREDNOS studies have illustrated
  - Large scale multicentre paediatric studies in District Hospitals are entirely deliverable in the UK
    - Great willingness of DGH paediatricians to participate

- PREDNOS studies are answering clinically important questions
  - Results likely to influence future UK (and international) practice
  - Translation into changes in patient care could take place over a very short time period

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Acknowledgements

- NIHR HTA for funding the studies
- NIHR MCRN and CRN
- University of Birmingham Clinical Trials Unit
- Birmingham Children's Hospital Clinical Trials Pharmacy
- All Principal Investigators and teams
- Children who have participated and their families

Thank you

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