IgA Nephropathy
Henoch Schonlein Nephritis

Kjell Tullus

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12 year old boy

- A few days into a respiratory infection
- Macroscopic haematuria
- Well in himself

Diagnosis?

1. Post infectious glomerulonephritis
2. Lupus nephritis
3. IgA nephropathy
4. Alport syndrome
5. Urinary tract infection

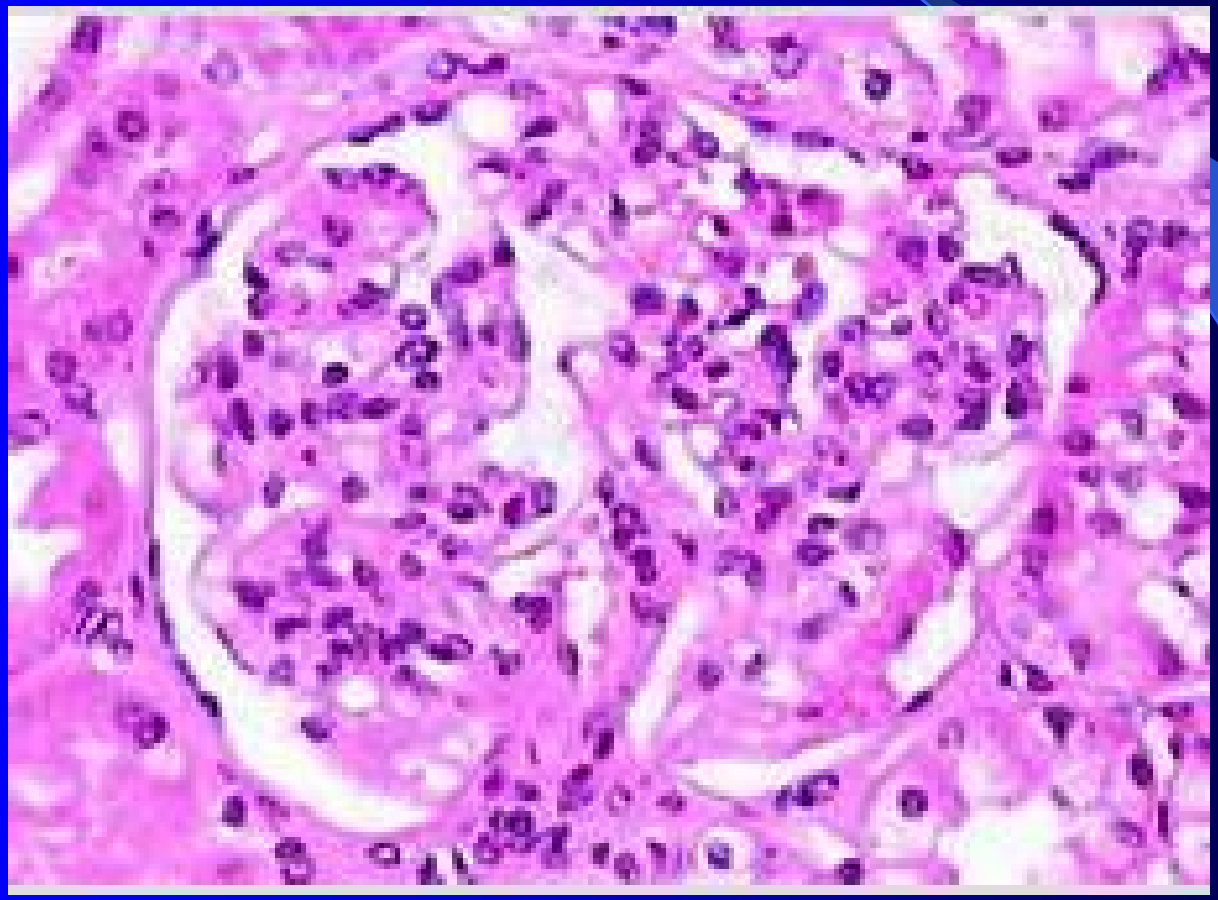
Data

- Urine 3+ blood, 3+ protein 2+ leucocytes
- (Urine culture negative)
- Creatinine 46
- C3 1.12
- BP 112/73
- No family history of kidney disease

Diagnosis?

1. Post infectious glomerulonephritis
2. Lupus nephritis
3. IgA nephropathy
4. Alport syndrome
5. Urinary tract infection

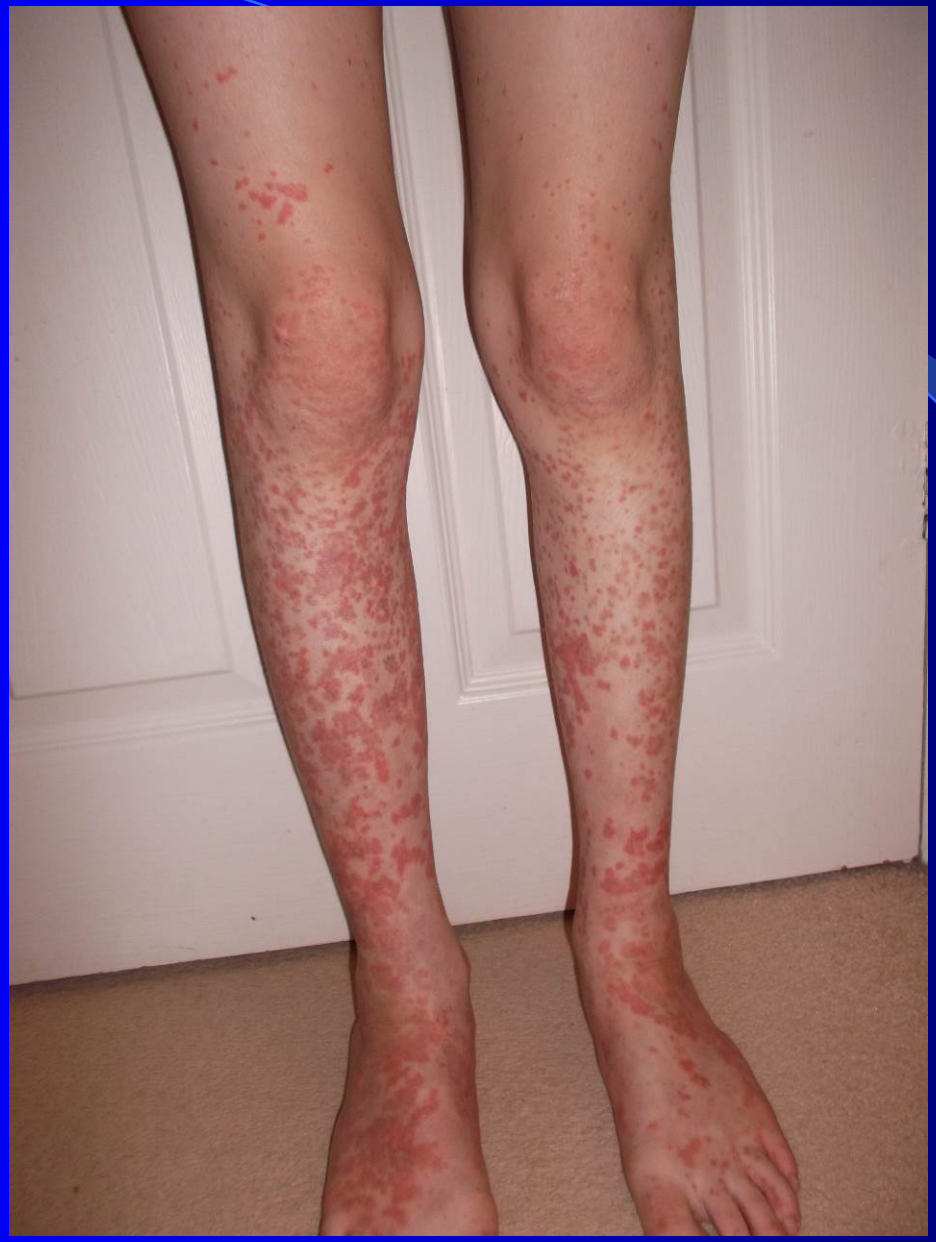
Kidney biopsy

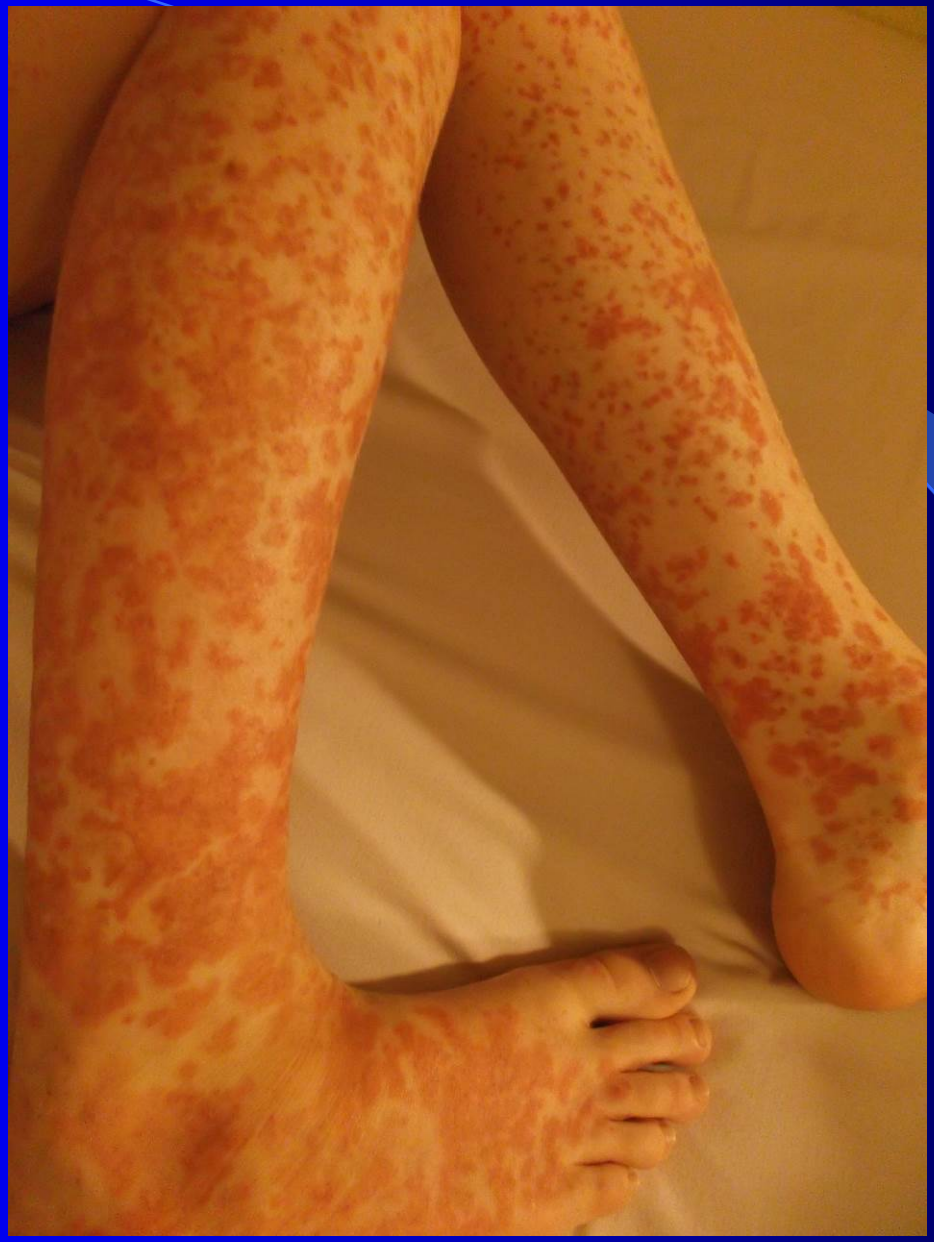



IgA nephropathy
Mesangial IgA deposit

12 year old girl

- A week after a throat infection developed rash
- Some stomach pain
- Swollen ankles





Laboratory tests

- Urine dipstick 3+ of blood and protein
- Urine albumin creatinine ratio 93-183-293 mg/mmol
- Serum albumin 39
- Creatinine 42-57-75

Kidney biopsy

- 24 glomeruli, none globally sclerosed
- The cortical area minimal irreversible chronic changes
- All glomeruli abnormal, diffuse mesangial proliferation
- 6 of the glomeruli show endocapillary proliferative lesions, 2 necrotizing lesions/segmental scars

- Immune mediated glomerulonephritis

- Diffuse deposition of mesangial IgA with some complement staining in the sclerosed tufts.

Is this two similar diseases or two rather different?

Comparison of primary IgA nephropathy and HSP nephritis

Table 2 | Comparison of primary IgA nephropathy and HSP nephritis

Clinical and histological features	Detection method	IgA nephropathy	HSP nephritis
Renal histology			
Crescents	Light microscopy	+/–	++
Glomerular tuft necrosis		+/–	++
Neutrophil infiltration		+/–	++
Mesangial IgA deposits	Immunofluorescence	+++	+++
IgA deposits along capillary walls		–	++
Subendothelial deposits	Electron microscopy	+/–	++
Clinical presentation			
Extrarenal symptoms	NA	+/–	+++
Age at onset	NA	Mostly >15 years	Mostly <15 years
Nephritic syndrome	NA	+/–	++
Nephrotic syndrome	NA	+/–	++
Disease course	NA	Continuous moderate activity with exacerbations	Repeated acute episodes
Renal outcomes			
Clinical remission	NA	30–50%	98%
CKD long after apparent complete remission	NA	–	+
ESRD	NA	20–40% after 20 years	1–3% in children, 30% in adults
Transplantation outcomes			
IgA deposit recurrence	Immunofluorescence	Frequent	Frequent
Graft loss at 5 years post-transplantation	NA	Rare	Rare
Graft loss at 10 years post-transplantation	NA	9.7%	7.5%

–, +/–, +, ++ and +++ indicate the relative likelihood of each clinical or histological feature occurring in a direct comparison of IgA nephropathy and HSP nephritis. Abbreviations: CKD, chronic kidney disease;

Davin, J.-C. & Coppo, R. (2014)
Henoch–Schönlein purpura nephritis in children
Nat. Rev. Nephrol.

Treatment guidelines for

IgAN and HSPN

should take into account the different pathophysiological mechanisms underlying these disorders which are in many ways similar but

differ in many relevant features

and lead to possible different outcomes.

Davin and Coppo, Ped Nephrol 2013;28:1897

The pathophysiology of IgAN and HSPN seems to be identical, with only quantitative differences…..

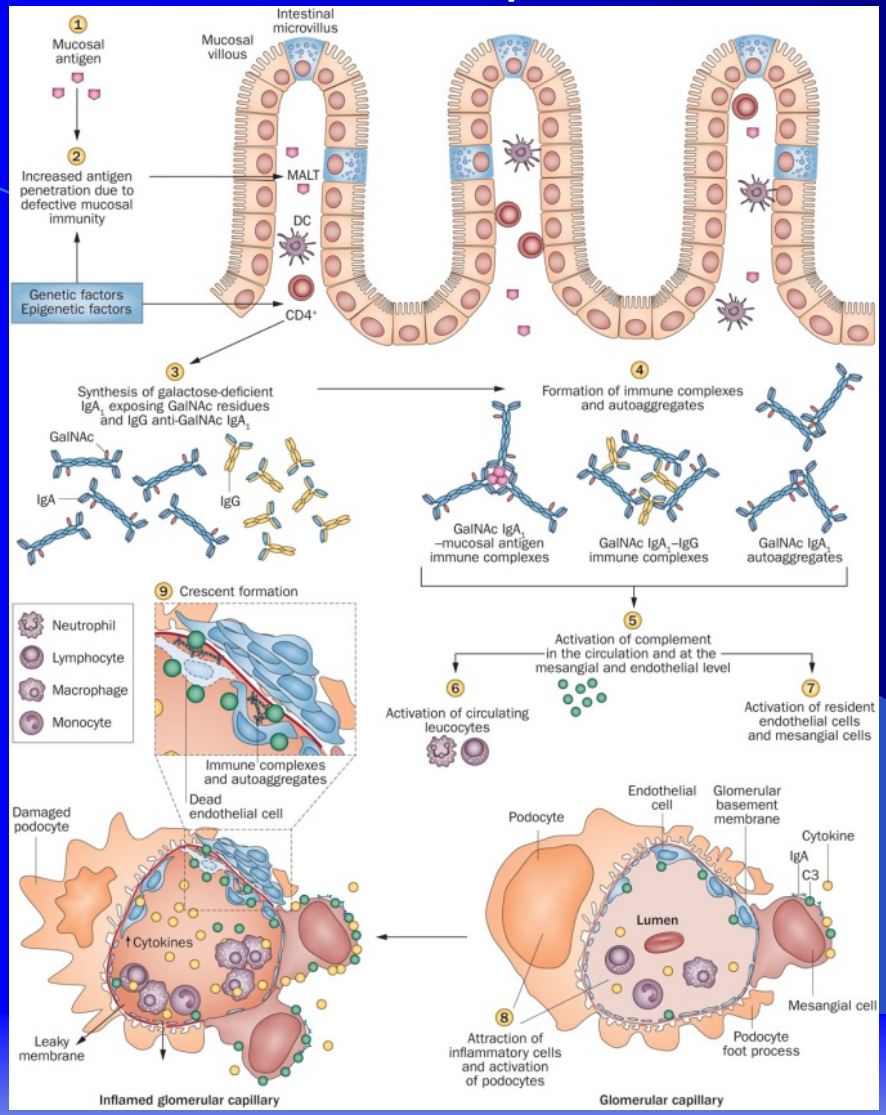
Pohl, Ped Nephrol 2015;30:245

My opinion

- Very different clinical behaviour
- Thus likely to respond differently to treatment

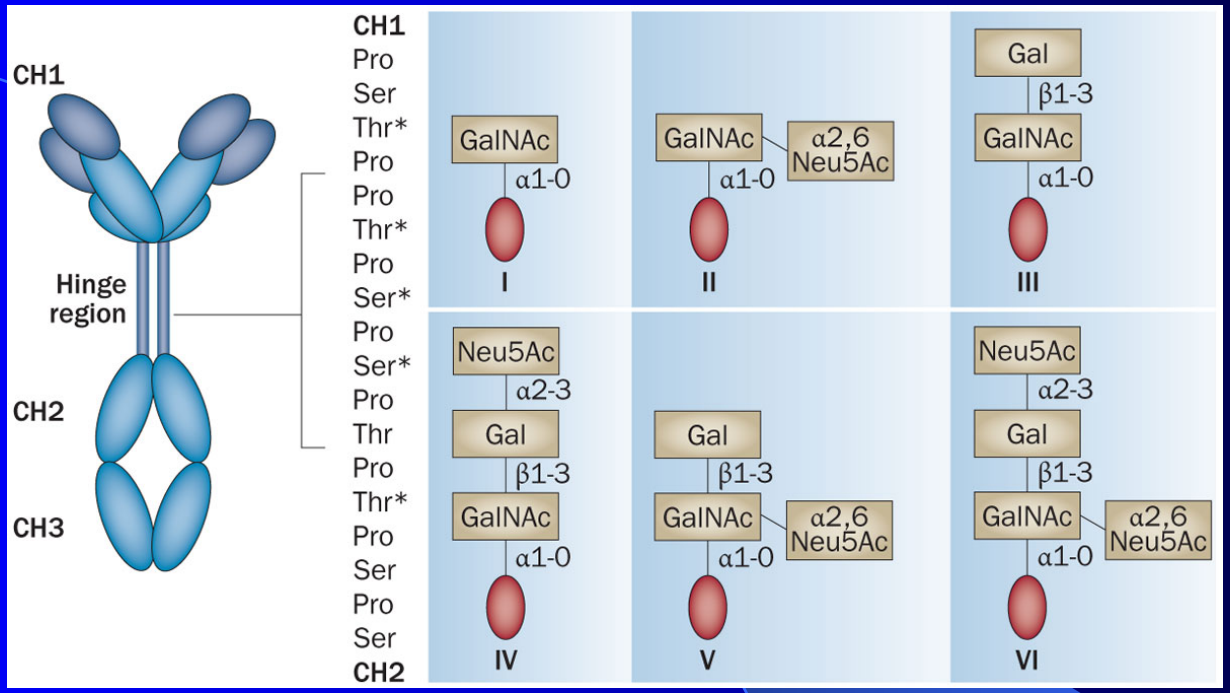
Aetiology

Figure 1 Pathogenesis of Henoch–Schönlein purpura nephritis



Davin, J.-C. & Coppo, R. (2014) Henoch–Schönlein purpura nephritis in children *Nat. Rev. Nephrol.*

Figure 2 Human IgA_1 *O*-glycosylation sites and galactosylation patterns



Davin, J.-C. & Coppo, R. (2014) Henoch–Schönlein purpura nephritis in children
Nat. Rev. Nephrol. doi:10.1038/nrneph.2014.126

Immune system reactants involved in the pathogenesis of HSP nephritis

Table 3 | Immune system reactants involved in the pathogenesis of HSP nephritis

Reactant*	Details	Reference(s)
Circulating IgA molecules	Galactose-deficient IgA_1 Autoaggregated galactose-deficient IgA_1 IgG antibodies to galactose-deficient IgA_1 IgG–IgA_1 circulating immune complexes IgA_1–soluble CD89 complexes	34,35 77 63 76 69
Receptors for IgA_1	Myeloid FcαRI (also known as CD89) Transferrin receptor (also known as CD71) on mesangial cells	68 129
Cytokines‡	IL-17 (increased ratio of IL-17:T_{REG} cells), TNF, IL-1β, IL-2, IL-6, IL-8, TGF-β, VEGF, TWEAK, low IFN-γ and IL-12, increased IL-4 (imbalance of T_H1:T_H2)	130
Mesangial cell receptors§	C3, FcγRI, TNF, TGF-β, PDGF-RB, IL-1, IL-6, IFN-γ, fibronectin receptor, integrins, angiotensin II receptor, CD71, EGF, TLR-3, TLR-4, chemokines	78,79
Products of mesangial cells	Cytokines: TNF, IL-1β, IL-6, TGF-β Chemokines: IL-8, RANTES, MCP-1 Prostanoids, angiotensin II, nitric oxide, reactive oxygen species	78

*This list is not exhaustive; the most relevant reactants are shown. ‡Produced by endothelial cells and/or infiltrating blood mononuclear cells. §Activated by specific ligands released in the mesangium.
Abbreviations: C3, complement protein C3; EGF, epidermal growth factor; FcαRI, IgA fragment crystallizable receptor; FcγRI, IgG fragment crystallizable receptor; HSP, Henoch–Schönlein purpura; IFN, interferon; MCP-1, monocyte chemotactic protein 1; PDGF-RB, platelet-derived growth factor-receptor β polypeptide; RANTES, regulated upon activation normal T cell expressed and secreted; TGF-β, transforming growth factor-β; T_H, T-helper; TLR, Toll-like receptor; TNF, tumour necrosis factor; T_{REG}, T regulatory; TWEAK, TNF-like weak inducer of apoptosis; VEGF, vascular endothelial growth factor.

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IgA Nephropathy treatment

KDIGO

Antiproteinuric and antihypertensive therapy

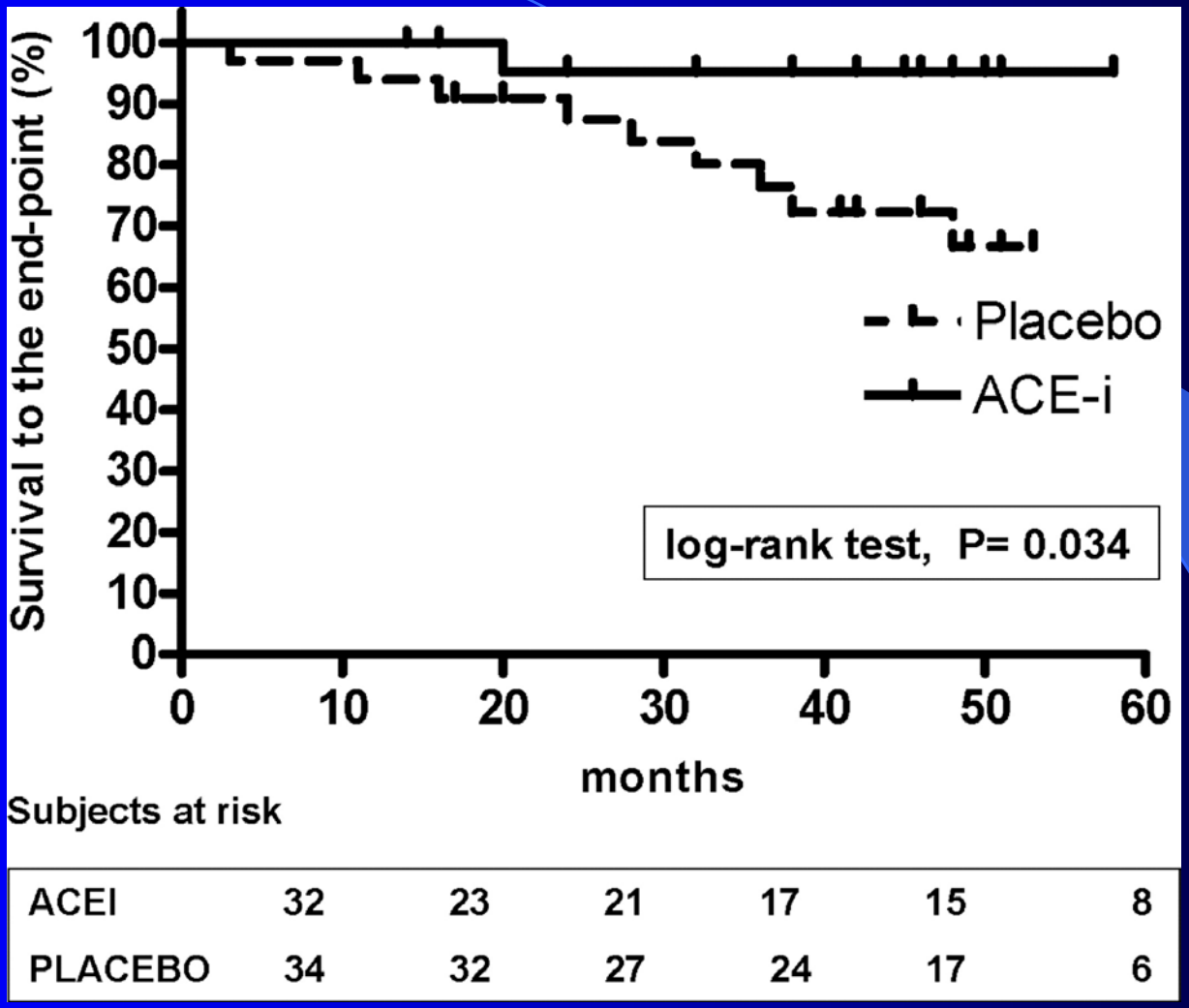
- We recommend long-term **ACE-I or ARB** treatment when proteinuria is >1 g/d, (*1B*)
- We suggest ACE-I or ARB treatment if proteinuria in children, between 0.5 to 1 g/d per 1.73 m^2 (*2D*)
- We suggest the ACE-I or ARB be titrated upwards as far as tolerated to achieve proteinuria <1 g/d. (*2C*)
- Blood pressure treatment goals of <130/80 mmHg in patients with proteinuria <1 g/d, and <125/75 mmHg when initial proteinuria is >1 g/d (*Not Graded*)

ACE inhibitor treatment

- 32 ACEi and 34 placebo
- Median follow-up 38 month
- Primary end point 30% decrease in creatinine clearance
- Nine patients in the placebo group vs one in treatment group experienced a secondary end point (incl. also proteinuria) p=0.034

Coppo et al JASN 2007:18:1880-88

Survival without the combined end point



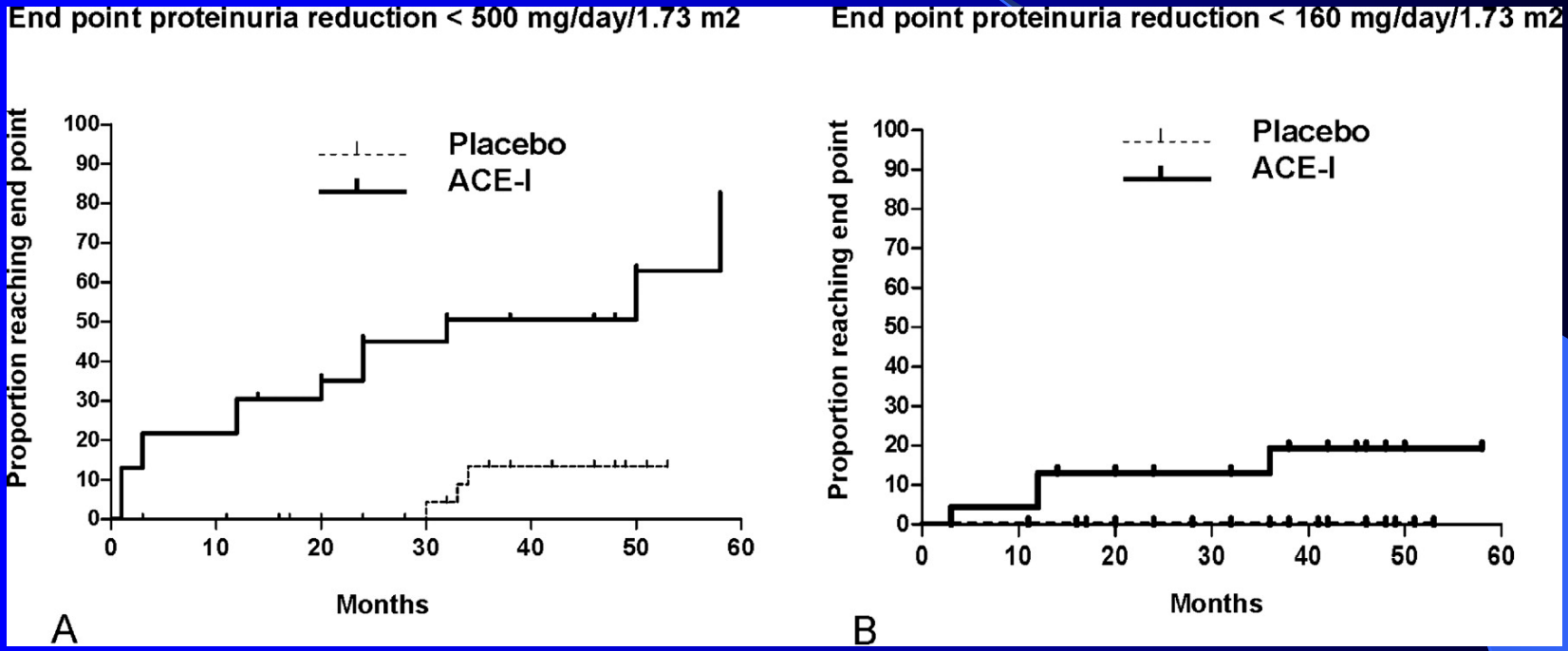
Subjects at risk

ACEI	32	23	21	17	15	8
PLACEBO	34	32	27	24	17	6

Coppo R et al. JASN 2007;18:1880-1888

JASN

ACEi vs placebo in IgA nephropathy



Coppo R et al. JASN 2007;18:1880-1888

JASN

Corticosteroids

- Patients with persistent proteinuria ≥1 g/d, despite 3–6 months of optimized supportive care and GFR >50 ml/min per 1.73 m^2, receive a 6-month course of corticosteroid therapy. (*2C*)

Table 2 Effective corticosteroid regimens in IgA nephropathy

Table 2 | Effective corticosteroid regimens in IgA nephropathy*

Reference	Country	Corticosteroid regimen
Pozzi *et al.* (2004)[64] (1999)[65]	Italy	Intravenous methylprednisolone 1 g per day for 3 consecutive days at the beginning of months 1, 3, and 5, plus oral prednisone for 6 months (0.5 mg/kg every other day)
Manno *et al.* (2009)[66]	Italy	Oral prednisone for 6 months (1 mg/kg per day for 2 months, then reduced by 0.2 mg/kg per day per month)
Lv *et al.* (2009)[67]	China	Oral prednisone for 6–8 months (0.8–1 mg/kg per day for 2 months, then reduced by 5–10 mg every 2 weeks)

*Comparison of the corticosteroid dosages used in three trials that showed a benefit of corticosteroids (versus supportive therapy) on the progression of IgA nephropathy.

Floege, J. & Feehally, J. (2013) Treatment of IgA nephropathy and Henoch–Schönlein nephritis *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2013.59

Immunosuppressive agents (cyclophosphamide, azathioprine, MMF, cyclosporine)

- **Not treating with corticosteroids combined with cyclophosphamide or azathioprine (*2D*)**
- **Not using immunosuppressive therapy in patients with GFR <30 ml/min per 1.73 m^2 unless there is crescentic IgAN with rapidly deteriorating kidney function (*2C*)**
- **We suggest not using MMF in IgAN. (*2C*)**

MMF in IgAN

- 52 patients 7-70 years old
- Treated with Lisinopril and Omega-3
- Persistent raised proteinuria
- Randomised to MMF or placebo
- Studied planned to 12 month

Hogg et al AM J Kid Dis 2015;Jul 21

MMF in IgAN Outcome

- Trial terminated early; 44 completed 6 month of treatment
- No difference found between groups regarding proteinuria.
- No improvement of proteinuria in MMF group.

Hogg et al AM J Kid Dis 2015;Jul 21

Other treatments

- We suggest using ***fish oil*** in the treatment of IgAN with persistent proteinuria ≥1 g/d, despite 3–6 months of optimized supportive care (*2D*)
- We suggest not using ***antiplatelet agents*** to treat IgAN. (2C)
- We suggest that ***tonsillectomy*** not be performed for IgAN. (*2C*)

Omega-3 fatty acids and alternate day prednisone

- Moderate to severe proteinuria in children with IgAN
- Three arms (treatment for two years):
  - Prednisone (weaning doses 60-30 mg/m^2 eod) (n=33)
  - O3FA 4g/d (N=32)
  - Placebo (n=31)

Hogg et al CJASN 2006;1:467-74

Protocol

- Endpoint eGFR <60% of baseline
- 73% completed the study
- Mean age 21-24 (+/-10years)
- ***Enalapril 2.5mg-40mg was given for hypertension***
- Groups comparable at baseline except that O3FA group had higher proteinuria

Results

- No difference between the groups was found!

- Problems:
  - Short study
  - Different baseline values
  - Small study

Japanese studies

- Several Japanese studies using one out of two schemes

1. Combinations of many drugs influencing the coagulation system and immunosuppressing drugs
   - Warfarin
   - Axathioprine
2. Moderate dose every other day steroids

Severe childhood IgA nephropathy

- Randomised trial
- New diagnosis, diffuse mesangial proliferation
- <15 years old
- No previous treatment
- At least 10 gloms on biopsy

Yoshikawa et al CJASN 2006;1:511-7

Protocol

- Two groups
  - Prednisolone, azathioprine (2mg/kg) , warfarin (Thrombotest 30-50%) and dipyridamole 5mg/kg/day
  - Prednisolone 2mg/kg/day for two weeks, weaning over 12 weeks to 1mg/kg eod
- ***ACEi and ARB treatment forbidden***
- 40 patients in each group
- Two year study

End points

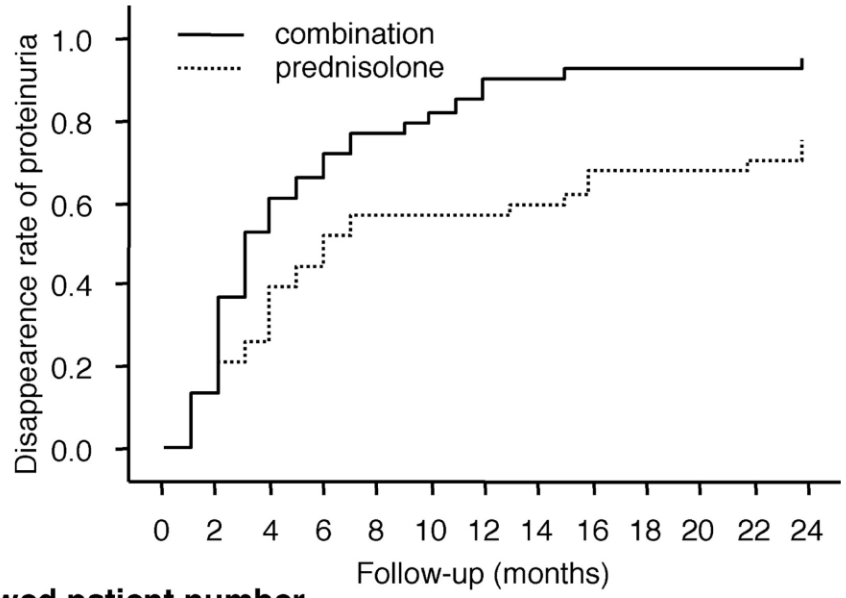
- Primary - disappearance of proteinuria
- Secondary
  - Decrease in proteinuria
  - Change in number of sclerosed glomeruli
  - Adverse effects

Results

- 39 patients in each group completed the study
- Primary endpoint (free of proteinuria)
  - 92.3% in combination group
  - 74.4% in Prednisolone group
  - P=0.00003

Results

Figure 2. Disappearance of proteinuria as defined by urinary protein excretion



Followed patient number

combination	40	39	39	39	39
prednisolone	40	40	40	40	39

Yoshikawa, N. et al. Clin J Am Soc Nephrol 2006;1:511-517

CJASN

Results (2)

- Number of sclerosed glomeruli
  - Unchanged in combination group
  - Increased in Prednisolone group (3.1 – 14.6%)

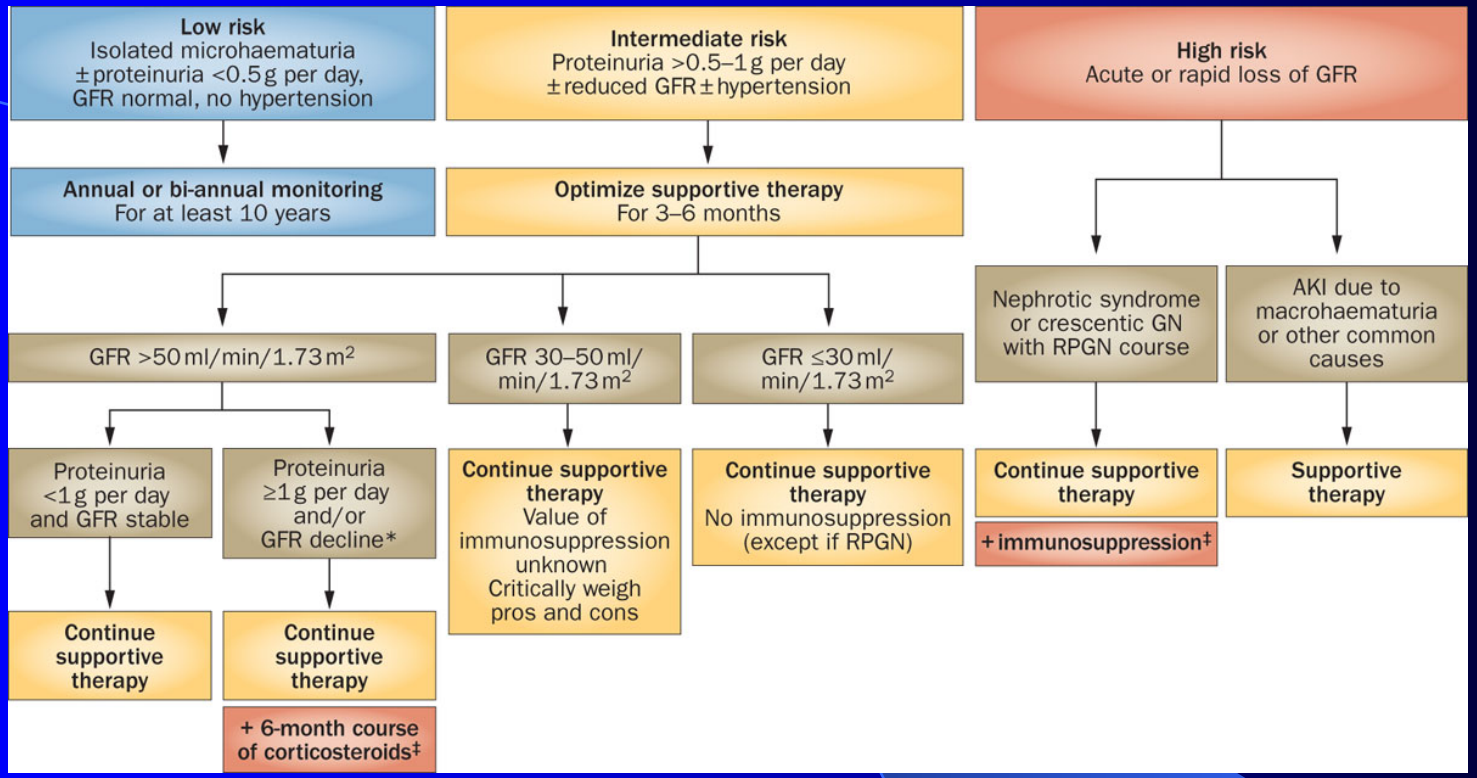
Adverse effects

Adverse Effect	Combination (n = 40)	Prednisolone (n = 40)
Hypertension	0	5 (12.5%)
Glucosuria	0	3 (7.5%)
Aseptic necrosis of femur	1 (2.5%)	1 (2.5%)
Glaucoma	2 (5.0%)	2 (5.0%)
Cataract	0	2 (5.0%)
Headache	3 (7.5%)	0
Leukopenia	4 (10.0%)	0
Bleeding	1 (2.5%)	0
Anemia	1 (2.5%)	0
Elevation of transaminase concentration	2 (5.0%)	1 (2.5%)

Comments

- Hugely difficult to get enough patients in this kind of studies
- The Japanese multidrug cocktail seems best, but I am not sure that any of us wants to use it.

Figure 1 Suggested treatment algorithm for patients with primary IgAN depending on their initial presentation



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HSP nephritis

Different principles

- Treat the crescentic/rapidly progressive nephritis
- Treat the disease and the inflammation
- Treat the important symptoms
  - Blood pressure
  - Proteinuria
- In HSP treat to protect from later severe nephritis

Crescentic nephritis

- No evidence base
- Many of us gives the “full treatment”
  - Steroids
  - Plasma exchange
  - Immunosuppressive agent
    - MMF
    - Rituximab
    - Cyclophosphamide
    - Azathioprine
- Outside of this talk

Table 4 | Treatment of HSP nephritis

Type of treatment	Evidence	
	Randomized clinical trials	**Nonrandomized studies**
Oral steroids	Oral prednisone does not prevent the development of nephritis[17]	No effect of prednisone alone on existing nephritis (retrospective studies)[25,36,122,123]
Other immunosuppressive drugs or combination	In children, no advantage of cyclophosphamide (used without prednisone) over placebo[109] In adults, no advantage of cyclophosphamide plus methylprednisolone pulses followed by oral prednisone versus the steroid schema alone[111] In patients with nephrotic-range proteinuria, 1 year of treatment with ciclosporin is not inferior to methylprednisolone pulses followed by 4 months prednisone[110]	Advantage of methylprednisolone pulses followed by prednisone versus prednisone alone (prospective study with historical controls)[116] Favourable effect of immunosuppressive drugs in patients receiving several agents (retrospective studies and one prospective study)[45,118–121]
ACE inhibitors	NA	Efficacy of ACE inhibitors in moderately severe proteinuria (retrospective study)[131]
Plasma exchange	NA	Favourable effects of plasma exchange in patients with very severe clinical and histological features (retrospective study)[114,115]

Abbreviations: ACE, angiotensin-converting enzyme HSP, Henoch–Schönlein purpura; NA, not available.

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Different principles

- Treat the crescentic rapidly progressive nephritis
- Treat the disease and the inflammation
- Treat the important symptoms
  - Blood pressure
  - Proteinuria
- In HSP treat to protect from later severe nephritis

Summary

- We do not know how to treat HSP nephritis!
- No solid data exist
- “Problem”: the highly variable outcome in untreated children

Table 1 Predictors of long-term renal outcome in HSP

Table 1 | Predictors of long-term renal outcome in Henoch–Schönlein purpura

Factor	Symptoms	Outcome
Initial renal symptoms[15,32]	Nephrotic and nephritic syndrome	CKD >50%[15]
	Nephrotic syndrome	CKD 40%[15]
	Nephritic syndrome	CKD 15%[15]
	Heavy non-nephrotic proteinuria	CKD 15%[15]
	Haematuria and/or minimal proteinuria	CKD <5%[15]
	Nephrotic syndrome persisting <3 months	ESRD 0%[32]
	Nephrotic syndrome persisting >3 months	ESRD 41%[32]
Renal symptoms during follow-up	GFR <70 ml/min/1.73 m^2 at 3 years*	ESRD 100%[26]
Initial symptoms versus increasing proteinuria during follow-up	Mean follow-up proteinuria (g per day)	ESRD RR 1.78, $P<0.01$[31]
	Severely impaired versus normal GFR at onset	ESRD RR 3.83, $P=0.20$[31]
	Nephrotic versus minimal proteinuria at onset	ESRD RR 4.74, $P=0.17$[31]

*Univariate analysis of predictors related to renal survival that used dialysis therapy as an end point; GFR was calculated using the Schwartz formula. Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; RR, relative risk. Reproduced and modified with permission from the American Society of Nephrology © Davin, J. C. *Clin. J. Am. Soc. Nephrol.* **6**, 687–689 (2011). http://cjasn.asnjournals.org/.

Davin, J.-C. & Coppo, R. (2014) Henoch–Schönlein purpura nephritis in children *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2014.126

KDIGO guidelines

- Based very much on adult experience
- Draws strong parallels to IgA nephropathy
- Many critical voices

Henoch-Schönlein purpura nephritis

- Children with
  - persistent proteinuria, >1 g/d per 1.73 m^2,
  - after a trial of ACE-I or ARBs, and
  - GFR >50 ml/min per 1.73 m^2,
- be treated the same as for IgAN with a 6-month course of corticosteroid therapy (*2D*)

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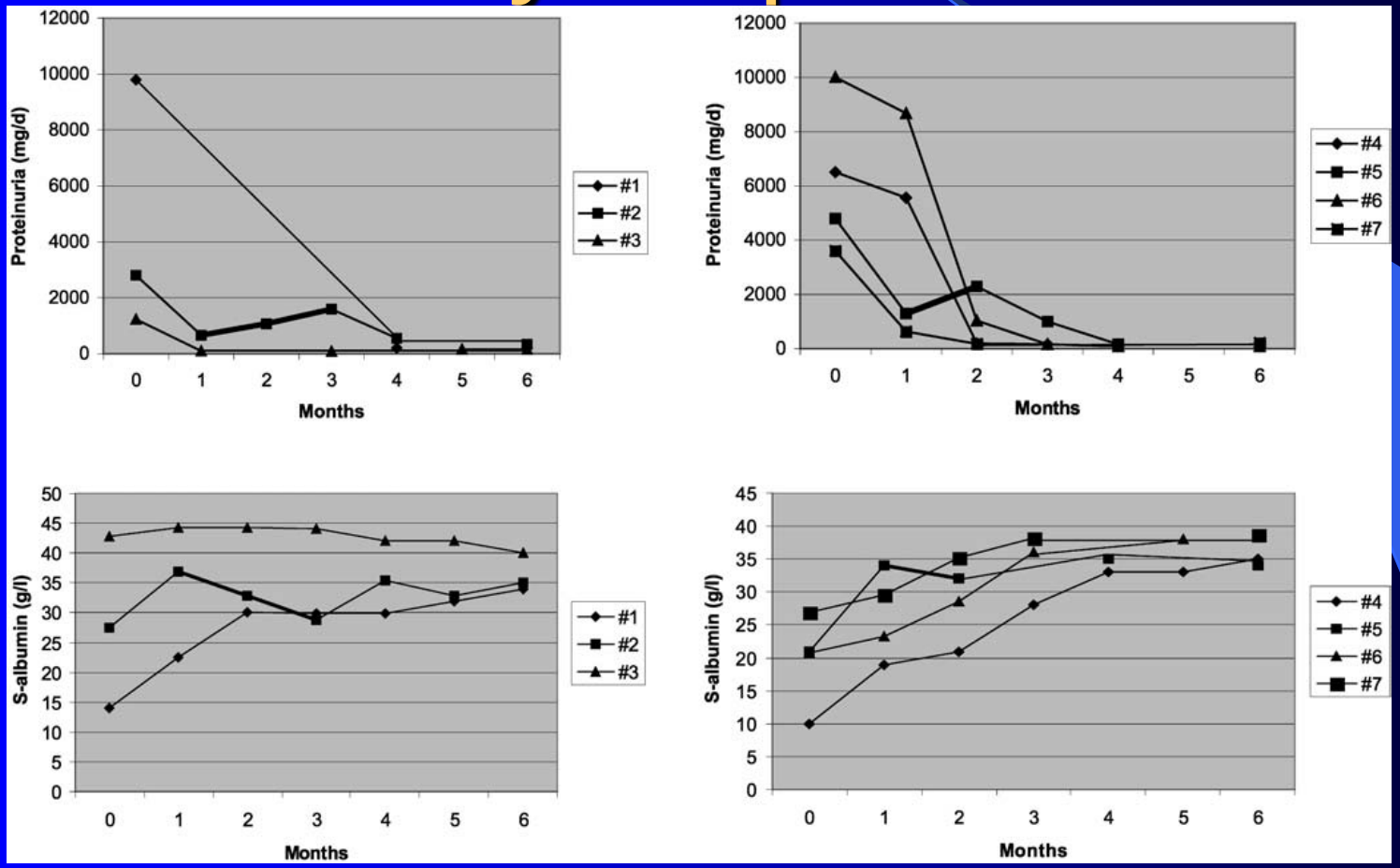
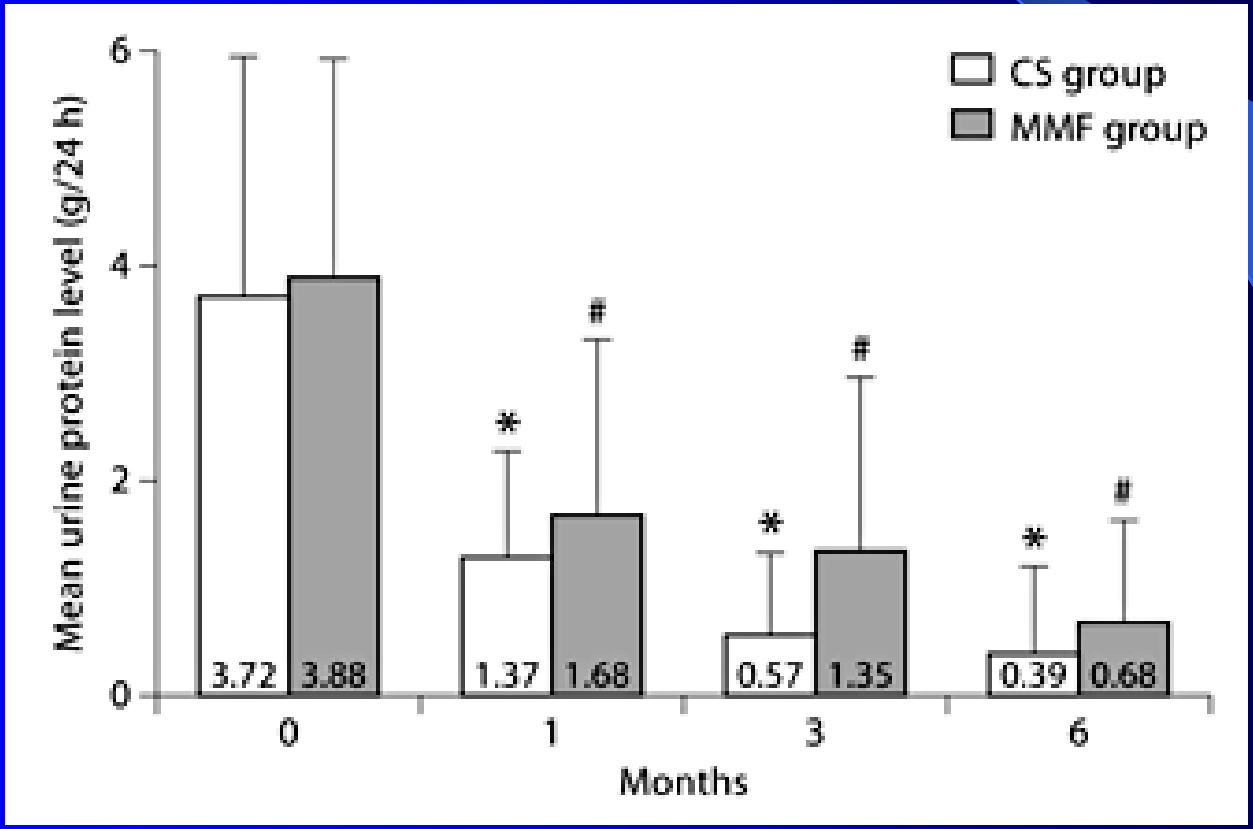
Seven children treated with cyclosporin



Ronkainen et al Ped Nephrol 2003;18:1138

53 children with HSPN
MMF/low dose pred vs. full dose prednisolone



Ren P, Am J Nephrol 2012;36:271

Different principles

- Treat the crescentic rapidly progressive nephritis
- Treat the disease and the inflammation
- Treat the important symptoms
  - Blood pressure
  - Proteinuria
- In HSP treat to protect from later severe nephritis

Henoch-Schönlein purpura nephritis KDIGO

- Children with HSP nephritis and persistent proteinuria, >0.5–1 g/d per 1.73 m^2, are treated with ACE-I or ARBs. (*2D*)

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How I do it

- If signs of active disease; increasing creatinine and high proteinuria then
  - Biopsy
  - Steroids
  - MMF or tacrolimus
- Later in a more chronic phase
  - ACE inhibitor
  - Fish oil (reluctantly)

Different principles

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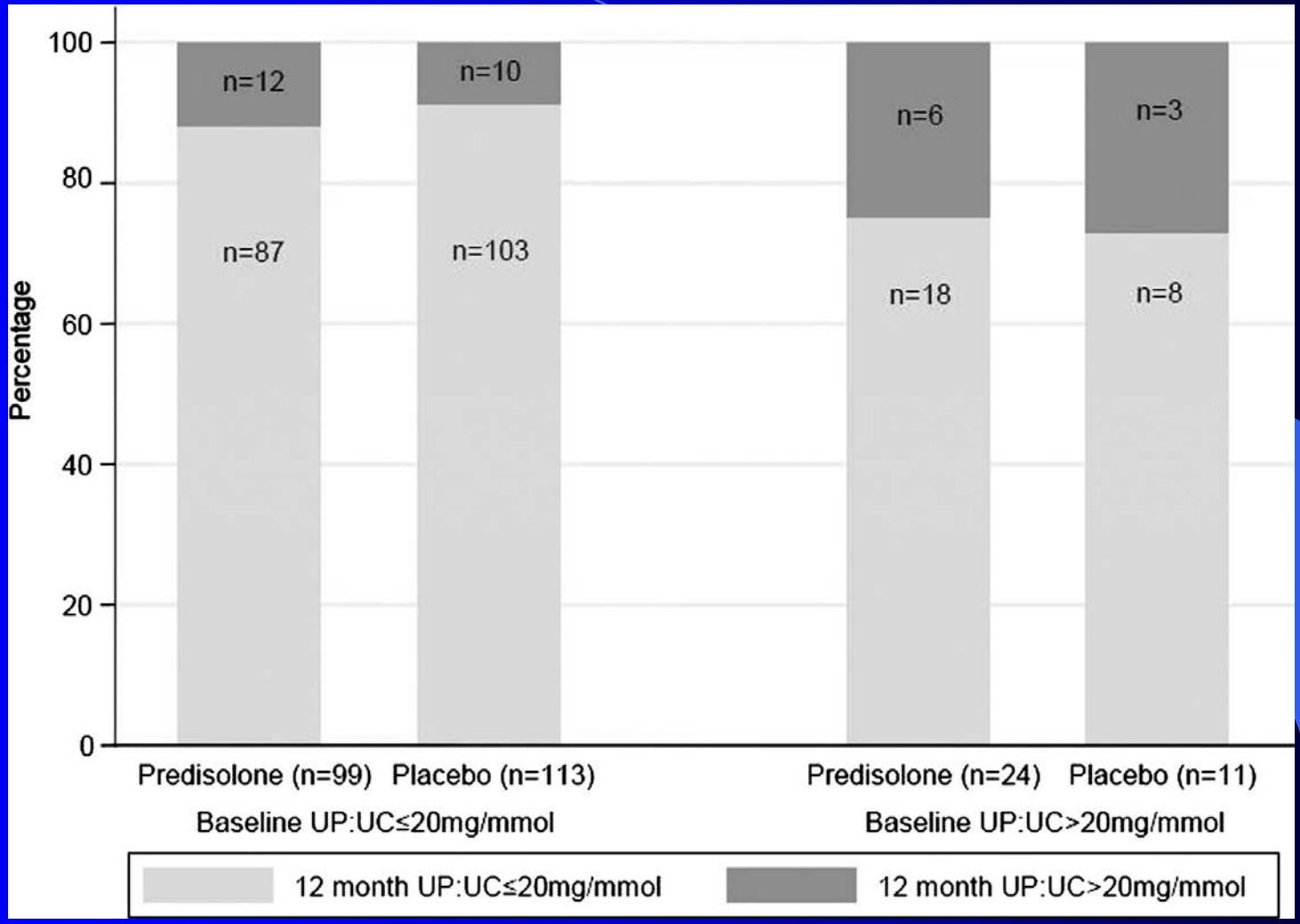
Steroids in HSP

- 181 children received prednisolone
- 172 children received placebo
- Pred dose
  - 2mg/kg/day for 7 days
  - 1mg/kg/day for 7 days
- 19/145 and 15/145 showed proteinuria at 12 month follow-up, NS

Dudley, Arch Dis Child 2013;98:756-763

Albuminuria at baseline and 12 months



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ADC

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Nat. Rev. Nephrol. doi:10.1038/nrneph.2014.126

Summary

- IgAN and HSPN share similarities but are different in their acuteness
- Treatment should be guided by how acute the disease is
- Good scientific support for ACE inhibitor
- Very limited support for any other treatment