era edta
LEADING EUROPEAN NEPHROLOGY

57TH ERA-EDTA CONGRESS
FULLY VIRTUAL
JUNE 6-9, 2020

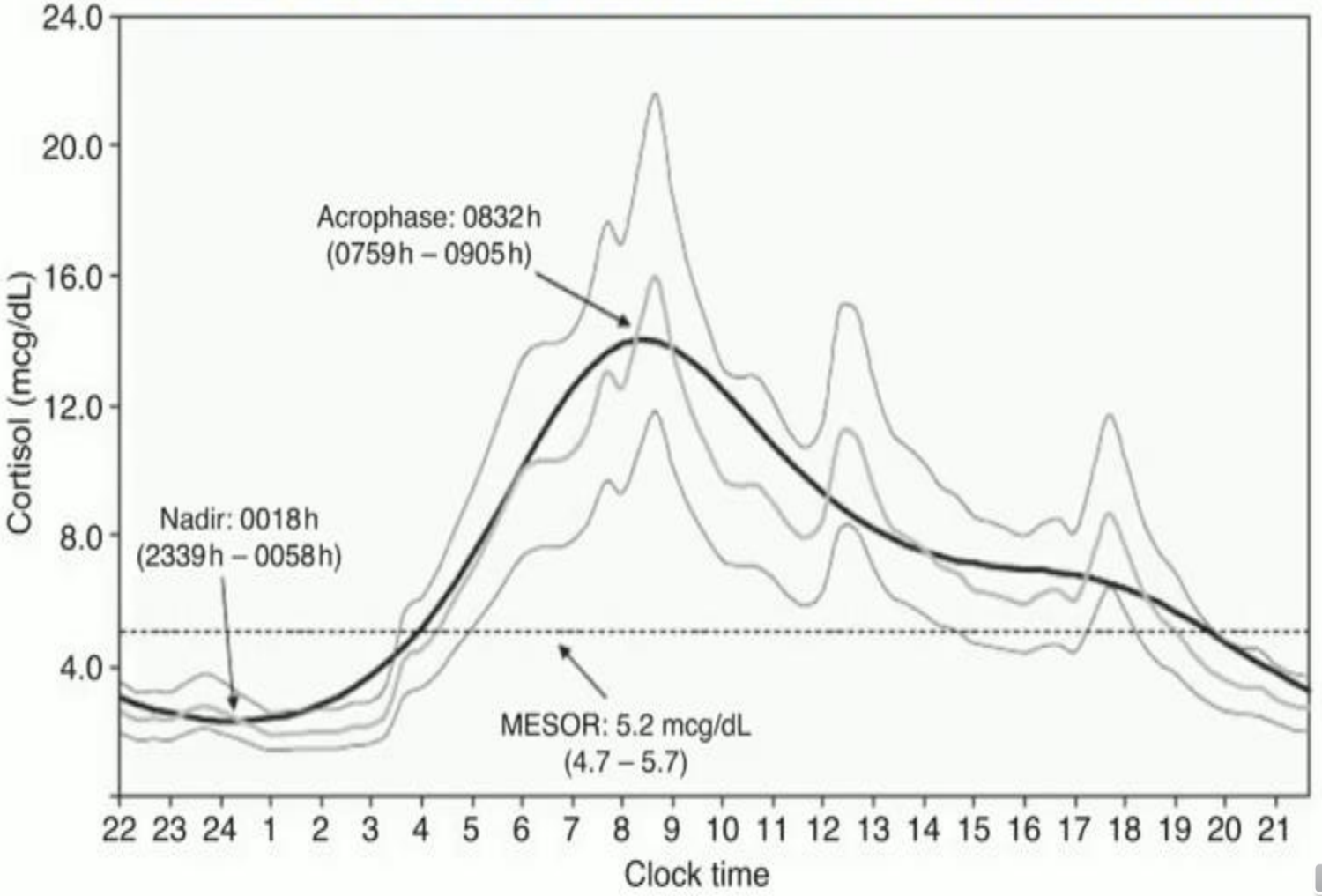
Corticosteroids as first treatment in MCD, FSGS and IgAN: when and how. Long- term side effects

Claudio Ponticelli

WWW.ERA-EDTA.ORG

Cortisol is secreted according to a circadian rhythm. In blood 80% of cortisol binds to transcortin.

Chan and DeBono. Ther Adv Endocrinol Metab 2010



Synthetic corticosteroids

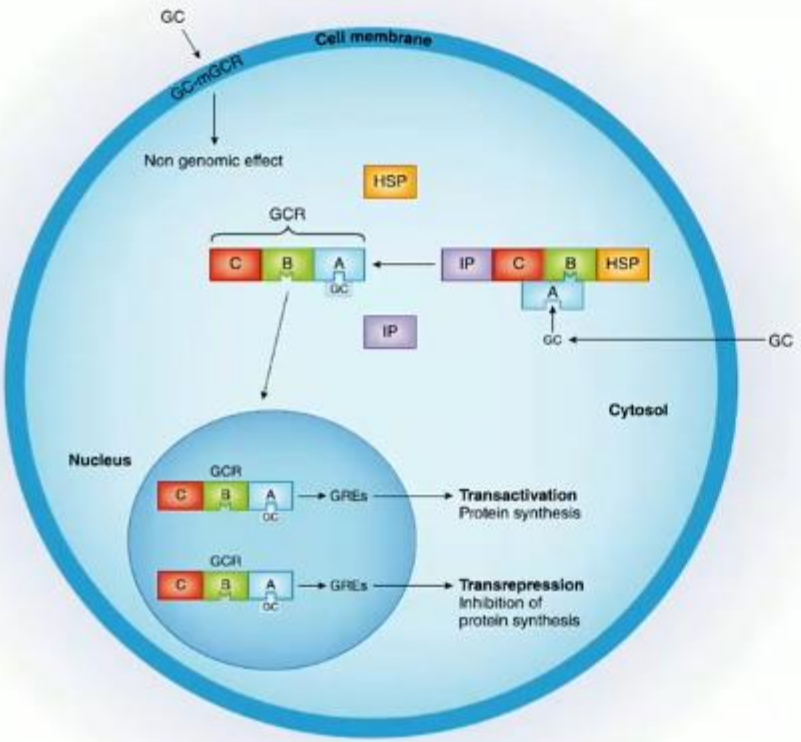
Their binding to transcortin is lower than cortisol, therefore their diffusion to tissues is higher and faster.

On the basis of their half-lives, synthetic CS are subdivided into:

short acting (prednisone, methylprednisolone, deflazacort) Half-life 60–200 min);

intermediate acting (parametasone, triamcinolone), Half-life 300 min;

long acting (desametasone, betametasone), Half-life 1-3 days .



Ponticelli C, Locatelli F CJASN 13,815,2018

GCs cross the cell membrane

57 ERA-EDTA CONGRESS FULLY VIRTUAL WWW.ERA-EDTA.ORG JUNE 6-9, 2020

In the cytoplasm GCs bind to GCRs that are part of a complex with imunophilins and HSP90

The binding to GCRs dissociates the complex, there is a conformational change of GCRs that become active

GC-GCRs enter the nucleus and bind to GC response elements (GRE)

Transactivation. **GCR-GRE activate anti-inflammatory genes**

Transrepression. **GCR-GRE repress transcription factors, NF-kB and AP-1**

Ponticelli C, Glassock RJ J Nephrol 32,851,2019

CS are metabolized by CYP450 enzymes

CYP450 Inhibitors	CYP450 Activators
GC accumulation	**GC depletion**
Old age	Children
Obesity	Malnutrition
Smoking	Biliary diversion
Grapefruit	Diarrhea
Liver disease	Anti-epileptic drugs
Imidazoles	Nafcillin
Macrolides	Oxacillin
Quinolones	Rifampicin
Non-dihydropyridine CCB	Rifabutin

CS side effects are time and dose dependent but are also influenced by individual factors

ACTH suppression	Cataract
Infection	Glaucoma
Psychiatric reaction	Peptic ulcer
Myopathy	Arterial hypertension
Osteoporosis	Acne, striae rubrae
Aseptic necrosis	Diabetes mellitus
Obesity	Impaired growth (children)

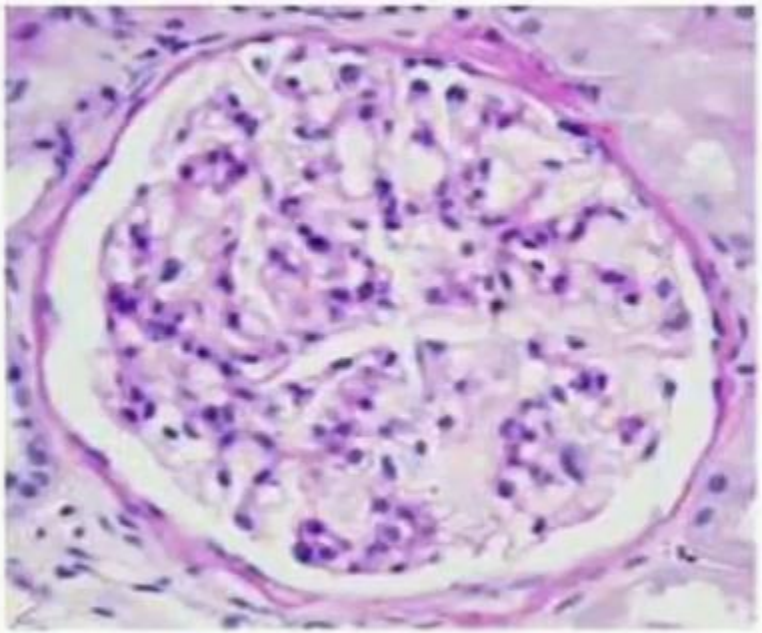
Prevention of steroid-related side effects

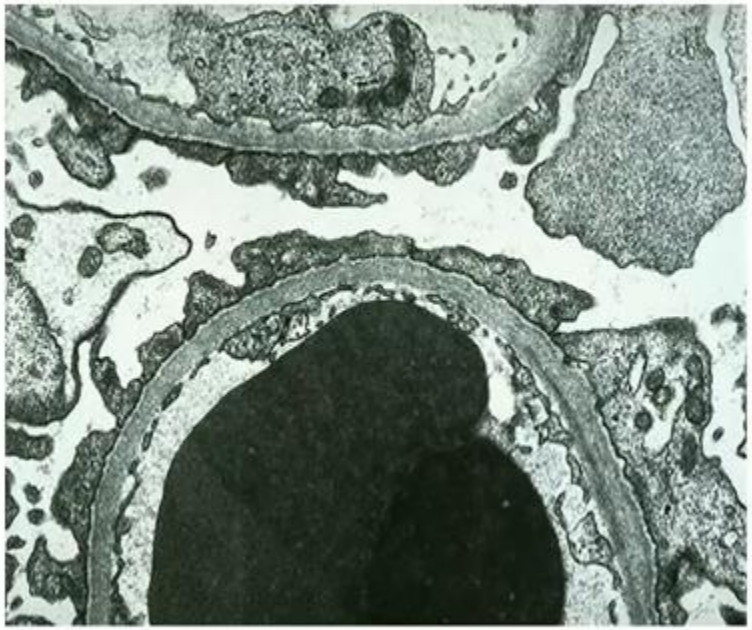
- Standard doses should be reduced in the elderly, smokers, and obese pts and also in case of recent infection, immunosuppressive therapy, and/or renal insufficiency.

- A short-acting CS should be given in a single morning dose between 8 and 9 a.m. Such a schedule mimicks the circadian rythm of cortisol.

- Low-calorie diet (obesity,diabetes), low sodium intake (edema, hypertension), physical activity (myopathy, obesity), avoiding cigarette (CVD, GI disease).

Minimal change disease (MCD)





Initial treatment (KDIGO 2012)

Children Prednisone should be given as a single daily dose of 60 mg/m^2/d, or 2 mg/kg/d, (max 80 mg/d) for 4 to 8 weeks, followed by alternate-day prednisone at 40 mg/m^2 (max 40 mg) to be continued for 2 -5 months with tapering of the dose.

Adults The initial dose of prednisone should be 1 mg/kg/d (max 80 mg/d max) or alternate-day single dose of 2 mg/kg (max 120 mg). If complete remission is not achieved before, the initial high-dose should be continued for a max of 16 weeks if well tolerated.

Relapse after remission

No Relapse	Infrequent relapses	Frequent relapses ≥ 2 in 6 months ≥ 4 in 12 months	Steroid dependence (Relapse within 2 weeks from steroid withdrawal)
20%	20%	30%	30%

Duration of initial treatment and relapses

- A meta-analysis showed that children given prednisone for only 8 weeks had a greater risk of relapse (60%) than children given long-term therapy (33%) with 1 month daily followed by 6 months of alternate-day prednisone.

  Hodson et al Cochrane Database Syst Rev 2005;(1)CD001533

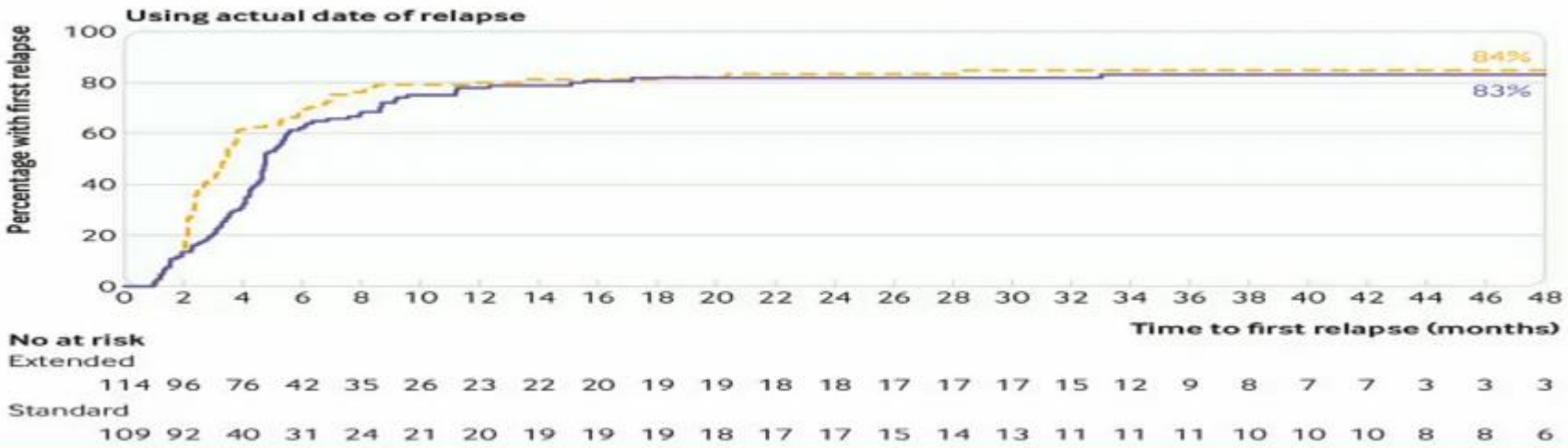
- Instead, two RCTs and a meta-analysis reported no difference in relapses between treatments of 8-12 weeks and longer treatments for 4-6 months

  Sinha et al KI 2015;87:217 - Yoshikawa et al KI 2015;87:225 - Hahn et al Cochrane Database 2015;(3)CD001533

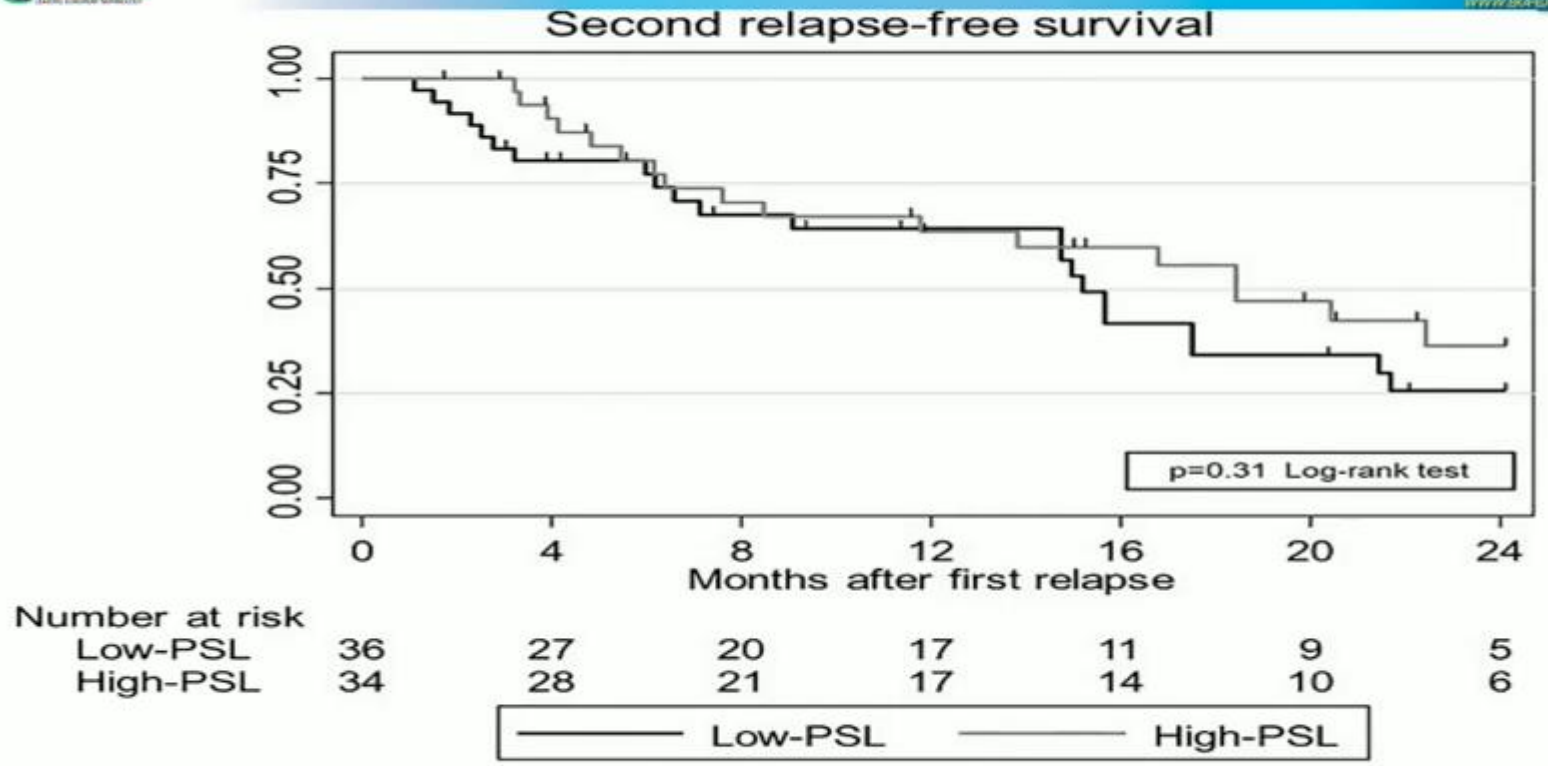
Tapering vs standard steroid therapy in children with INS

Webb et al BMJ 2019;365:11800

In a RCT 237 children with a first episode of NS were randomized to 16 weeks of prednisolone (total dose 3150 mg/m^2) or to 8 weeks of prednisolone (total dose 2240 mg/m^2). The time to first relapse and the incidence of frequent relapses (53% vs 50%) or steroid-dependence (42% vs 44%) were similar.



Ozeki T et al PLoSOne 2018; 13:e0199228



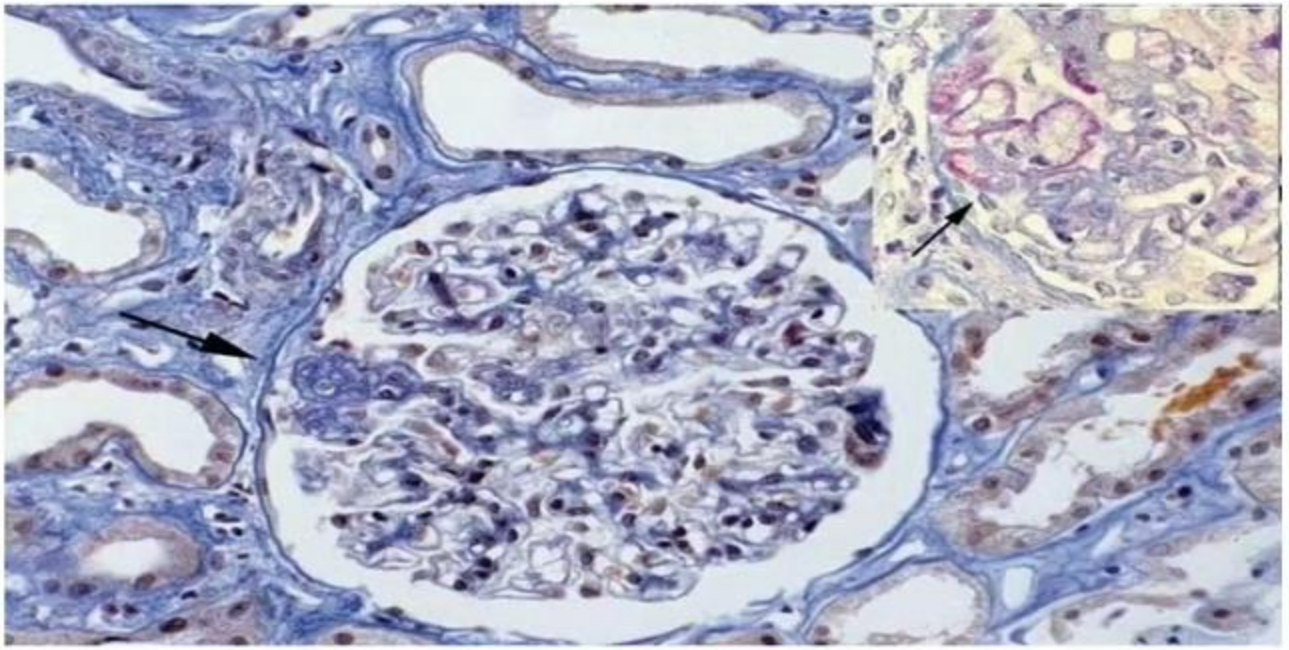
In a retrospective study, <u>adults</u> in CR given Prednisone dose <10 mg/day, had a similar risk of relapse at 2 yrs than those given higher dose (>20 mg/day)

Minimal change disease

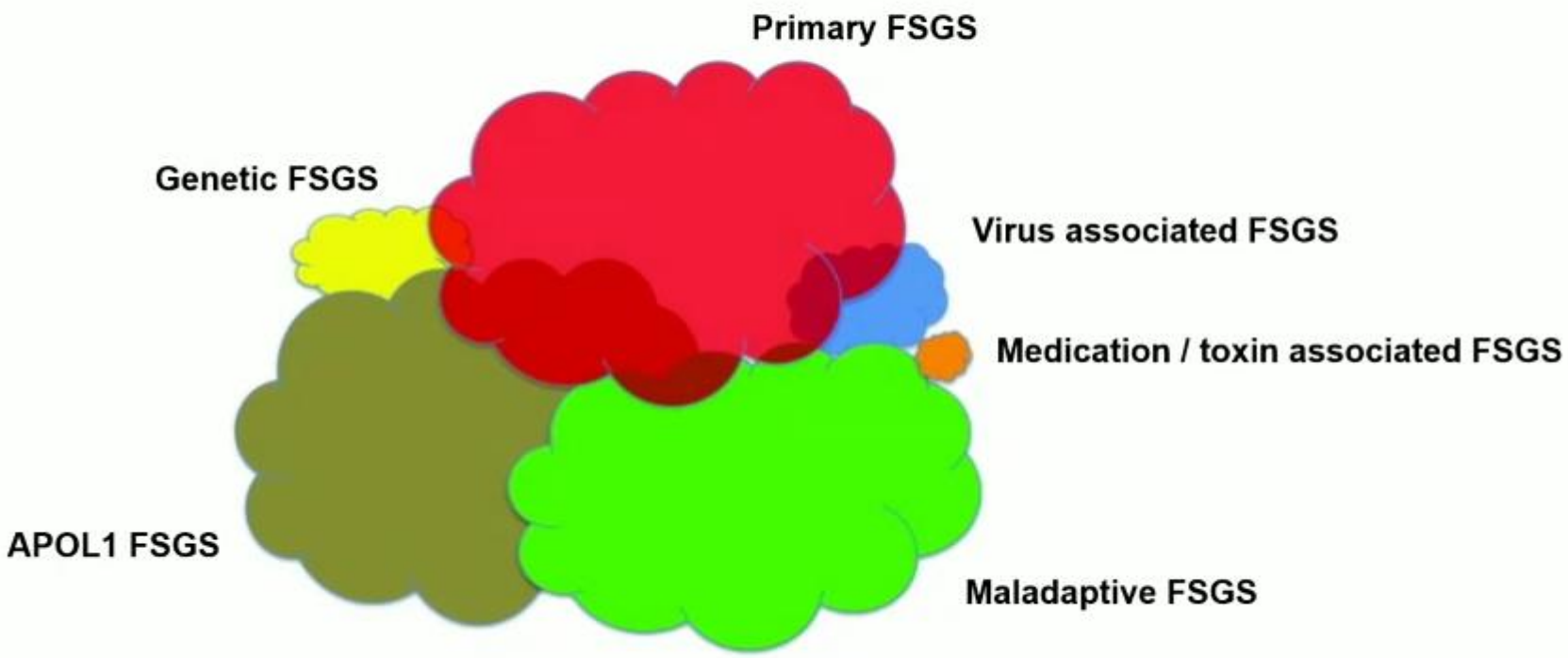
- CS represent the mainstay for initial treatment both in children and adults.
- In adults the response to CS is lower and the initial treatment should be longer
- It seems that a long-term duration of CS for initial treatment does not prevent relapse in children
- A correct use of CS may reduce side effects, but in many steroid-dependent pts alternative treatments are required

Focal segmental glomerular sclerosis

It is a histological term to indicate that some, but not all, glomeruli (Focal) have a partial sclerosis of the tuft (Segmental)



Rosenberg, Kopp: FSGS .CJASN 12,502,2017



KDIGO guidelines

-On the basis of observational studies the initial treatment of primary FSGS should be based on Prednisone 1 mg/kg/d for at least 4 weeks. In no response high-dose prednisone may be continued for a max of 16 weeks.

-CNI are the drugs of choice for treating pts with steroid-resistance or steroid-intolerance.

NEW STUDIES PUBLISHED

Primary or Maladaptive FSGS ?

De Vriese et al JASN 29,759.2018

Primary FSGS

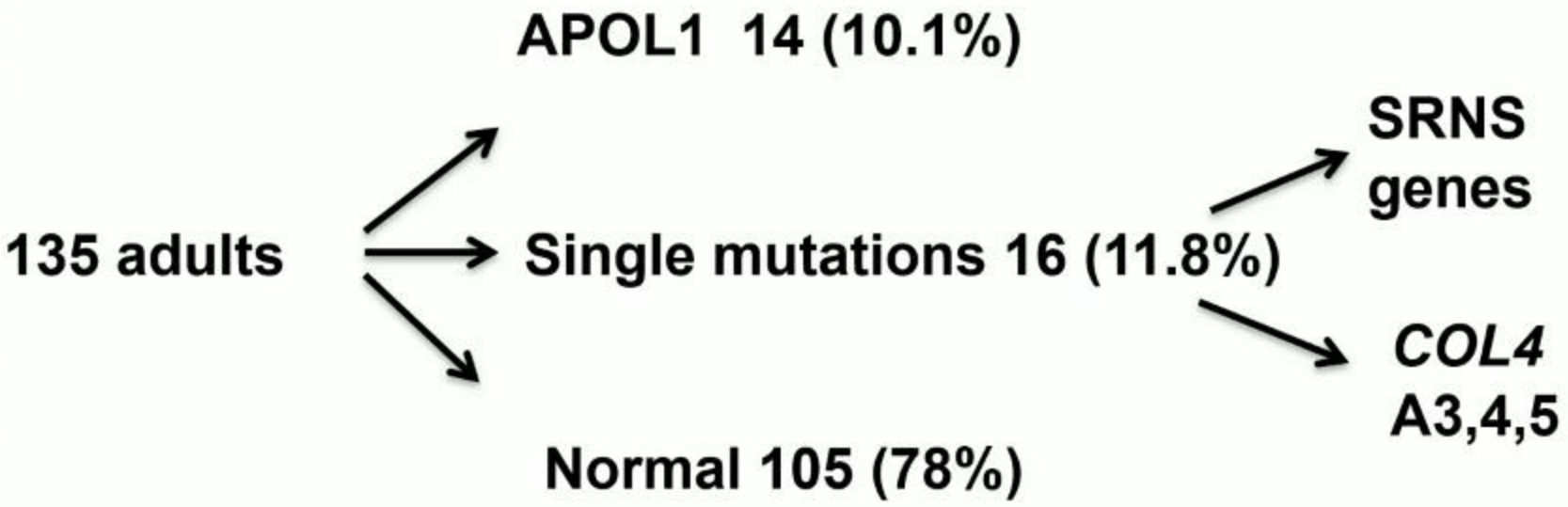
Pts have a nephrotic syndrome with proteinuria > 3.5 g/day, albuminemia <3.0 g/dl and edema. The natural course of the FSGS is ominous in most patients with NS. FSGS lesion is characterized by segmental sclerosis. There is diffuse foot process effacement on EM.

Adaptive FSGS

Proteinuria is often < 3.5 g/day, albuminemia is normal, foot process effacement is segmental, and progression is slow.

Mutation analysis in adults with steroid-resistant FSGS

Gribouval et al Kidney Int 94:2013; 2018



When is genetic analysis useful ?

De Vriese et al JASN 29,759.2018

1) Children and adolescents (Risk of mutation inversely related to age).

2) Pts with steroid resistant FSGS.

3) Pts with extrarenal manifestations.

4) Pts with family history of renal or extrarenal manifestation.

5) Candidates to kidney transplant (no risk of recurrence if FSGS is caused by genetic mutation).

Rovin B et al Kidney Int. 95,281,2019

In adults, a minimum duration of 16 weeks of high-dose CS as first-line therapy for FSGS was felt to be controversial, given its potential toxicity. However, data to support alternative therapies are insufficient.

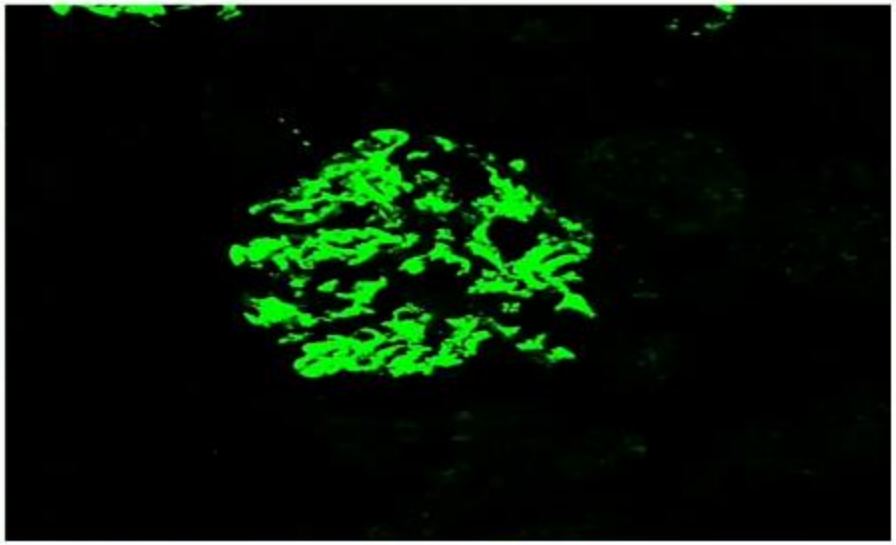
The recommendation for CNIs and MMF as second- and third-line treatments should be maintained.

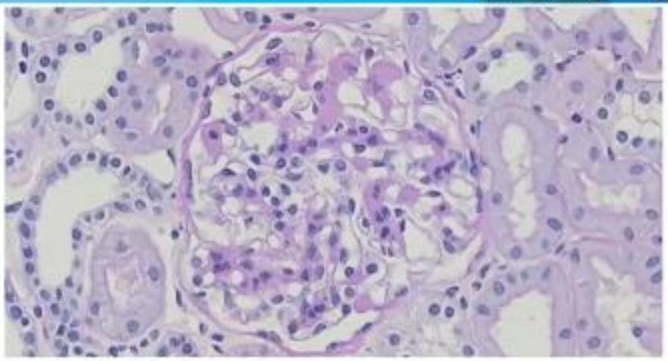
FSGS

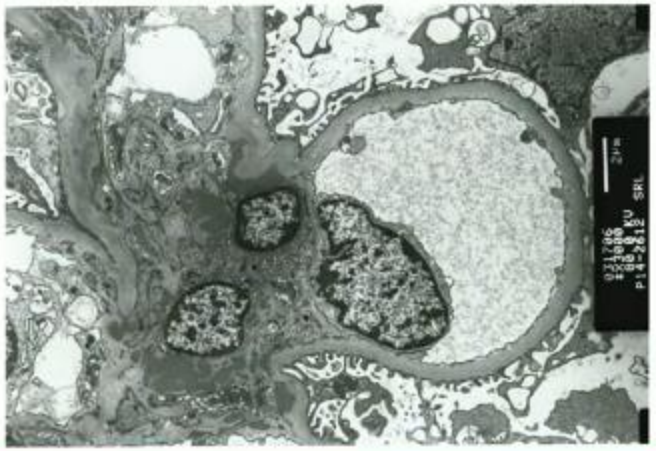
- FSGS is a histologic pattern of different diseases.
- It is important to separate primary from maladaptive FSGS
- Some 40% pts with primary FSGS may enter complete remission with a prolonged administration of steroids.
- Genetic analysis is required in true steroid-resistant cases

IgA nephropathy

It is an autoimmune disease caused by Abs directed against polymeric hypogalactosylated IgA1 in mesangium.







KDIGO recommendations

On the basis of three RCTs the KDIGO suggested a six month course of high-dose oral or intravenous CS in patients with persistent proteinuria despite 3-6 months of renin angiotensin system inhibitors (RASi) treatment.

GCs in IgAN

A large retrospective study (VALIGA) confirmed the superiority of steroids over symptomatic treatment, especially in proteinuric pts (Tesar V et al JASN 2015;26:2248).

Two RCTs from Germany (Rauen et al NEJM 2015; 373(23): 2225) and China (Lv et al JAMA. 2017;318:432) reported that in pts with IgAN and different levels of GFR steroid treatment may increase the probability of remissions but it caused a higher risk of adverse events

New published studies

STOP trial. Separate analysis of 2 treatments

Rauen T et al JASN 2018;29:317

Group A

GFR ≥ 60 ml/min. Steroids alone
Full clinical remission: 11 (20%) pts given CS vs 3 (6%) pts on supportive care (*P*=0.02).
A similar number of pts with side effects in steroid monotherapy and controls (12 vs 14).

Group B

GFR 30-59 ml/min. Steroids + Cyc and AZA
Remissions did not differ between IS combination and controls (11% vs 4% *P*=0.30).
More pts with combined IS had side effects (17 vs 6).
1 death in IS and 1 in controls.

Steroids for IgAN. A metaanalysis

Lin Y et al Am J Nephrol 2018;47(6):385-394.

- A metaanalysis of 12 RCTs involving 1,057 pts found that CS significantly prevented the decline in renal function (relative risk 0.42,p < 0.001) and reduced proteinuria (mean -0.58 g/day) in pts with IgAN.

- The results were not influenced by steroids' dose (≤30 or > 30 mg/day), duration (≤ 8 or > 8 months), or serum creatinine (< 1.10 or ≥1.10 mg/dL).

- However, steroids increased the risk of side effects

IgA Nephropathy

- RCTs and Meta-analyses reported that steroid therapy may increase the probability of achieving remission of proteinuria.
- With one exception (Pozzi et al JASN 15:157,2004) all the available studies have a too short-term follow-up to assess the possibility of altering the long-term outcome of IgAN.
- Many studies pointed out that steroid terapy was loaded by side effects, but in some studies the use of steroids was not correct.

Conclusions

- CS remain the cornerstone initial treatment in MCD, iFSGS, IgAN.
- CS have a narrow therapeutic index.
  Attention is needed in handling other drugs and side effects.
- Short-acting CS, single morning administration, and hygienic measures can reduce the side effects.
- A careful selection of pts and appropriate adjustment of the doses may improve the efficacy and safety of corticosteroids.

Claudio Ponticelli

Corticosteroids as first treatment in MCD, FSGS and IgAN: when and how. Long term side effects