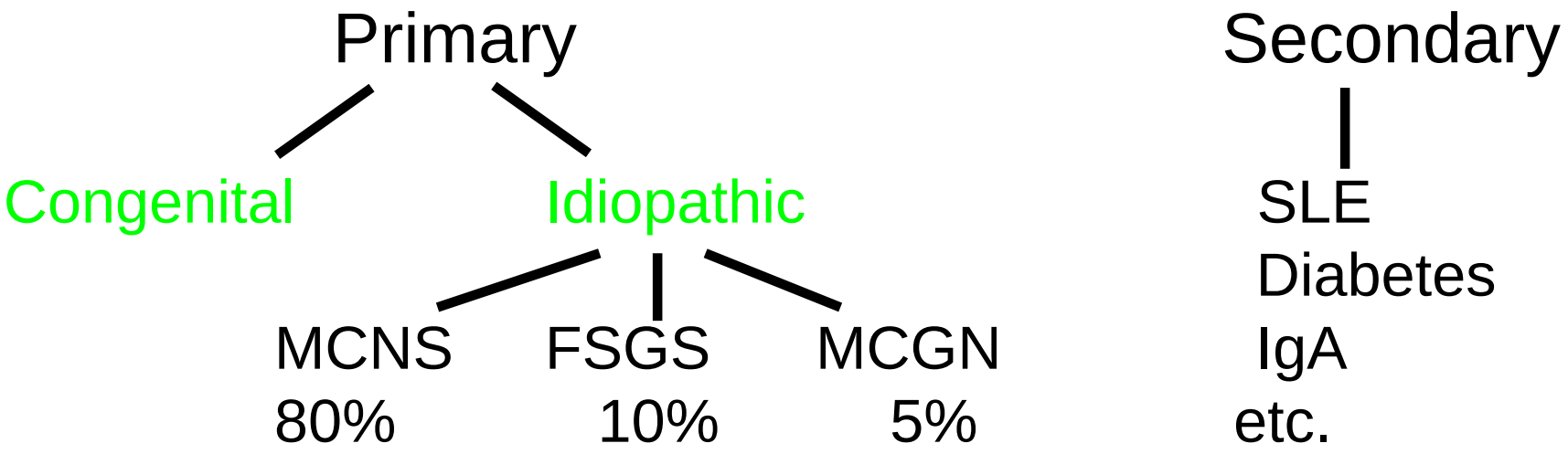
SDNS

SRNS

Gianni Celsi

Nephrotic syndrome



MCNS = minimal change nefros
FSGS = focal segmental glomerulosclerosis
MCGN = mesangiocapillary (membranoproliferative)glomerulonephritis

Clinical signs contradicting MCNS

- age < 1 or >12 y
- persistent hematuria
- red cell casts
- complement
- hypertension
- decreased renal function

Renal biopsy!!

Response to corticosteroids %

Histology	MCNS	FSGS	MCGN
Responders	93	21	7
Nonresponders	7	79	93

MCNS
%

SSNS	93	40 no relaps
		30 few relaps
		30 steroid dependent
SRNS	7	

SDNS

Recidiv under nedtrappning

Recidiv inom 2-3 veckor efter utsättning

Biopsi ?

Response to corticosteroids %

Histology	MCNS	FSGS	MCGN
Responders	93	21	7
Nonresponders	7	79	93

Recidiv

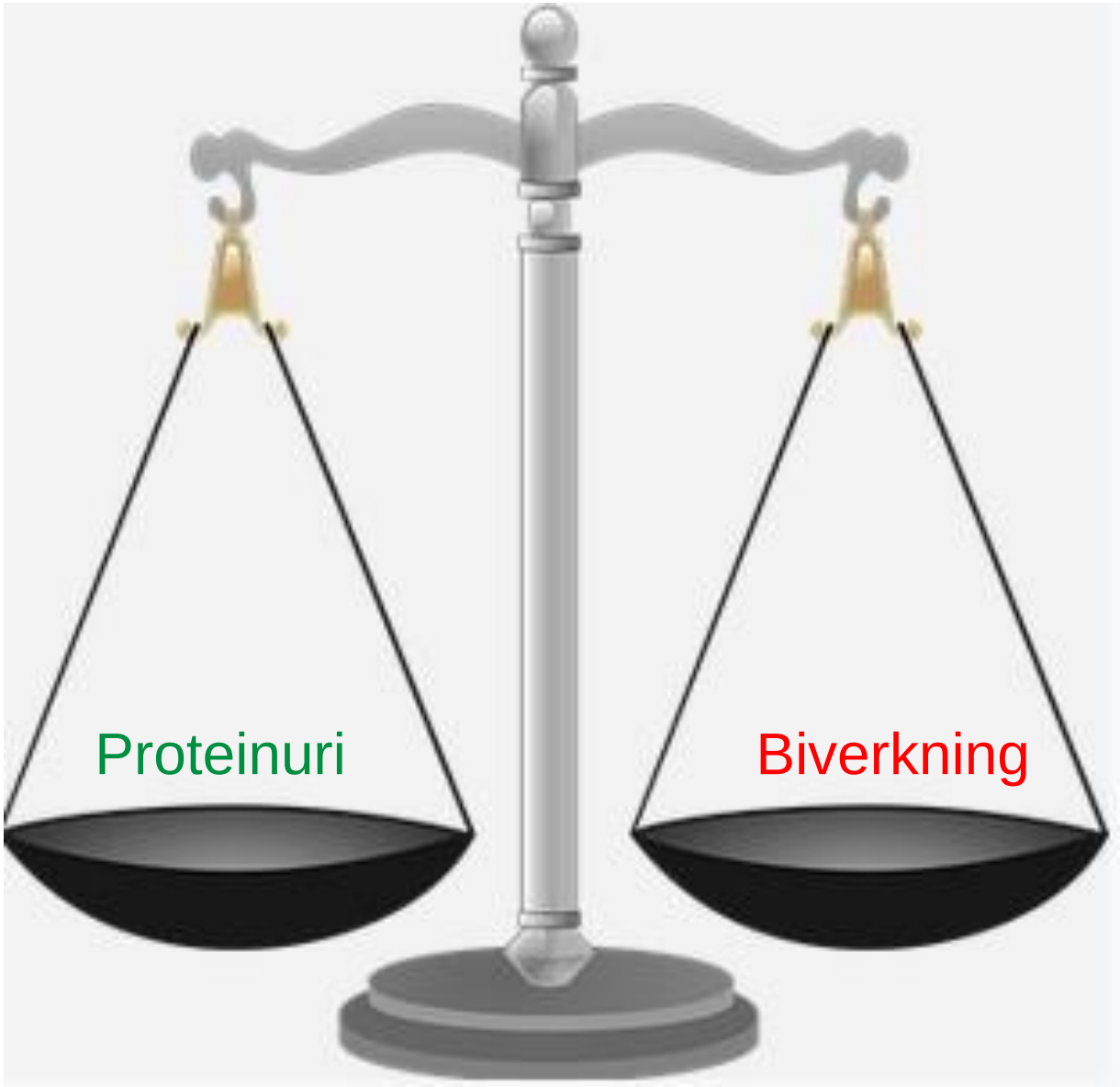
Nefrotisk proteinuri i 3 dagar

- utan feber

- med feber

BEHANDLING

KORTISON


Proteinuri
Biverkning

BIVERKNING

Tillväxt ??

Övervikt

Osteoporos ??

Magkatarr

HPA

Katarakt

Hypertoni

Infektioner

1) Behandla recidiv

2) Minst 3 månader med prednisolon v.a.d. i nedtrappning dos

3) Hitta den lägsta effektiv dos

4) Utsättning??

5) Vid recidiv : - efter nedtrappning
öka till tidigare dos

- vid infektion
öka till varje dag

- utan infektion
vanlig behandling alt. iv

•Alkylating agents:

cyclophosphamide (dose of 2 mg/kg per day for 8 to 12 weeks (maximum cumulative dose of 168 mg/kg)

•Calcineurin inhibitors:

cyclosporine (initial dose of 4 to 5 mg/kg per day given in two divided doses) (conc: 100-200)

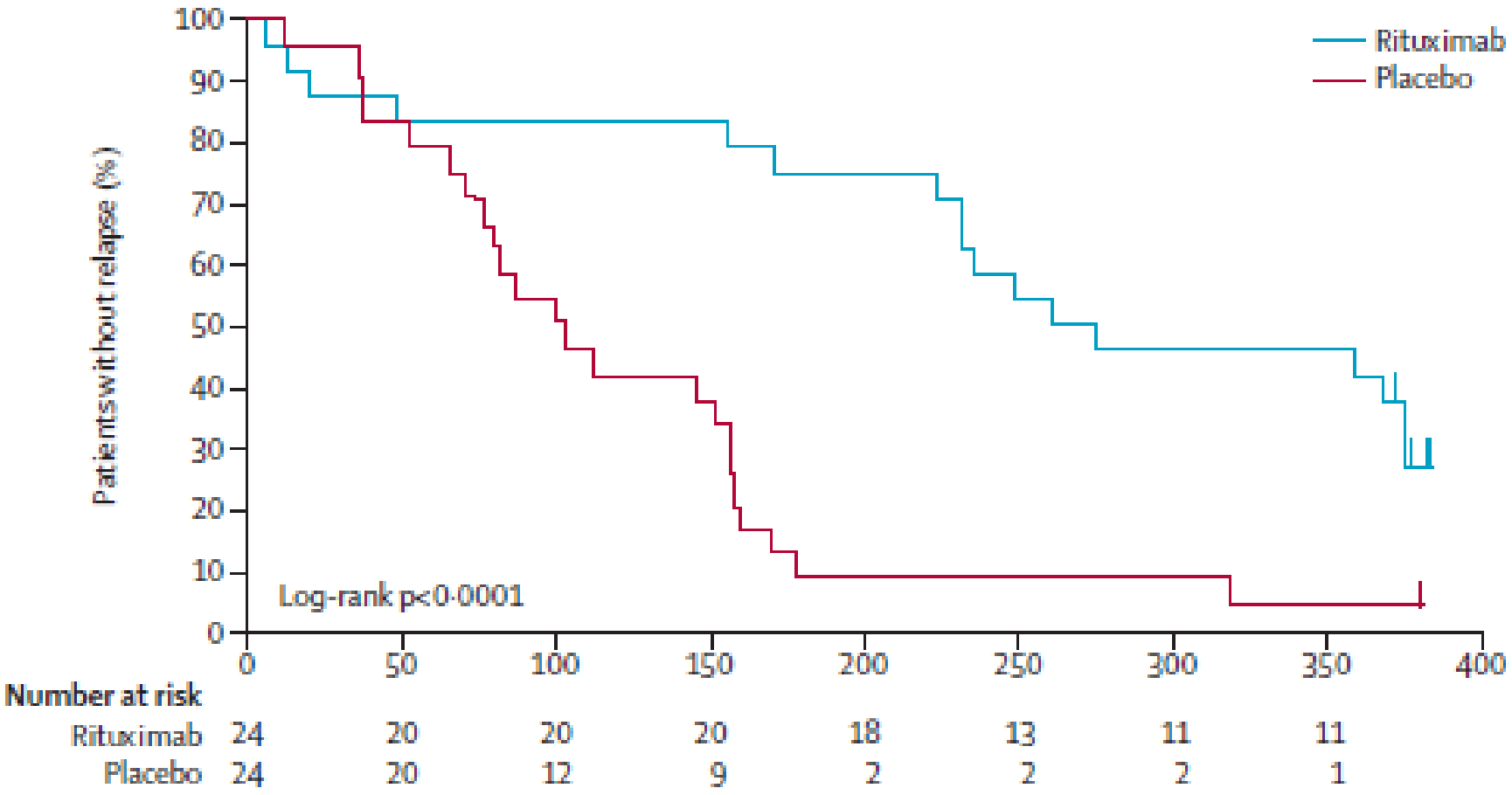
tacrolimus (initial dose of 0.1 mg/kg per day given in two divided doses) (conc: 4)

•MMF (initial dose of 1200 mg/m^2 per day given in two divided doses)

Rituximab

1) 375 mg/m2 x 1

2) Upprepa behandling vid återfall



Lancet 2014; 384: 1273–81

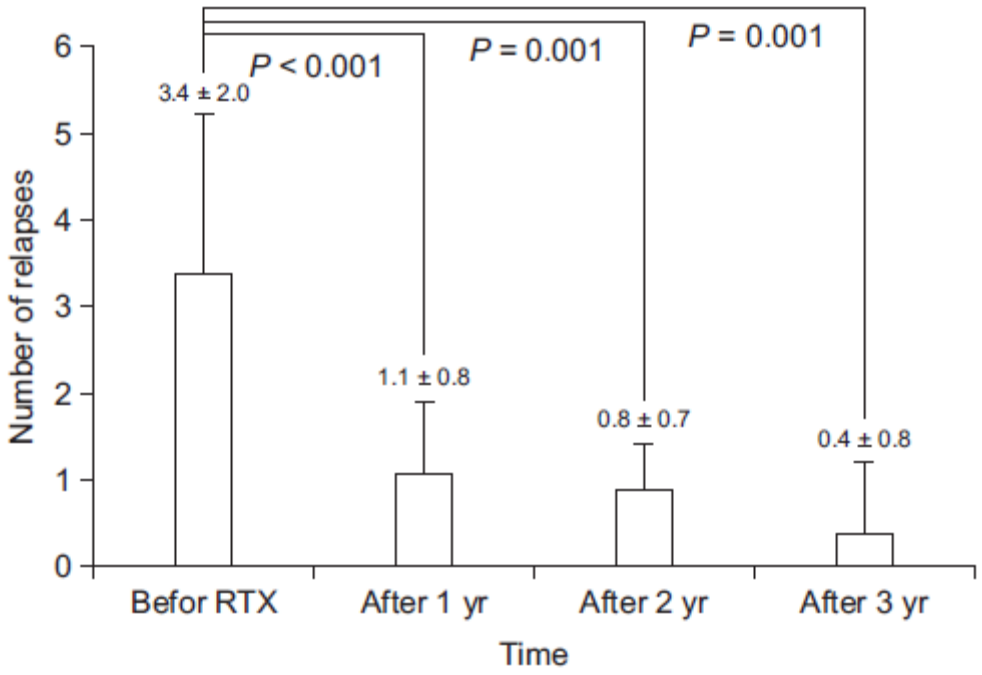


Figure 2. Relapse rates (mean ± 95% confidence interval) of nephrotic syndrome before and after rituximab (RTX) treatment.

	Rituximab (n=24)		Placebo (n=24)	
	Grade 3	Grade 4	Grade 3	Grade 4
Gastritis	1 (4%)	0	0	0
Gastroenteritis	1 (4%)	0	0	0
Gum infection	1 (4%)	0	0	0
Cellulitis	1 (4%)	0	0	0
Hypertension	1 (4%)	0	0	0
Respiratory disturbance	1 (4%)	0	0	0
Acute kidney failure	1 (4%)	0	0	0
Haemorrhagic cystitis	1 (4%)	0	0	0
Hyperuricaemia	0	1 (4%)	0	0
Hypoproteinaemia*	6 (25%)	0	6 (25%)	0
Adrenal insufficiency	1 (4%)	0	0	0
Nettle rash	1 (4%)	0	0	0
Lymphocytopenia	4 (17%)	0	4	0
Neutropenia	2 (8%)	2 (8%)	0	0
Increased aspartate aminotransferase	0	0	1 (4%)	0
Increased alanine aminotransferase	1 (4%)	0	2 (8%)	0
Increased γ-glutamyl transpeptidase	0	0	1 (4%)	0
Increased creatine phosphokinase	1 (4%)	0	0	0
Hypophosphataemia	0	0	1 (4%)	0

Data are n (%). *Not known to be a side-effect of rituximab and was probably caused by the original disease rather than by rituximab or placebo, because occurred at time of relapse in both groups; other adverse events were known to be caused by the study drug.

Table 5: Grade 3–4 adverse events

Lancet 2014; 384: 1273–81

Annualized cost of healthcare service	Cost of drug (US$)	Annualized healthcare Cost (US$)[a]
Study group		
Rituximab ($n = 10$)		
Total	71,476	197,031
Mean ± SD	7148 ± 1701	19,703 ± 1754
CNI ($n = 8$)		
Total	8655	189,857
Mean ± SD	1082 ± 431	23,732 ± 9835
Students t test (t)	9.7	1.21
P value	0.0001	0.24

Pediatr Nephrol
DOI 10.1007/s00467-017-3789-y

Steroid and immunosuppressant use at relapse immediately before assignment		
Ciclosporin, mycophenolate mofetil, and daily steroids	1 (4%)	0
Ciclosporin, mizoribine, and daily steroids	3 (13%)	3 (13%)
Ciclosporin and daily steroids	0	1 (4%)
Mycophenolate mofetil and daily steroids	0	1 (4%)
Mizoribine and daily steroids	1 (4%)	1 (4%)
Daily steroids with no immunosuppressant	1 (4%)	0
Ciclosporin, mycophenolate mofetil, and steroids on alternate days	2 (8%)	0
Ciclosporin, mizoribine, and steroids on alternate days	6 (25%)	4 (17%)
Ciclosporin and steroids on alternate days	2 (8%)	5 (21%)
Mycophenolate mofetil and steroids on alternate days	0	0
Mizoribine and steroids on alternate days	3 (13%)	3 (13%)
Steroids on alternate days with no immunosuppressant	1 (4%)	2 (8%)
Ciclosporin and mycophenolate mofetil, with no steroids	0	0
Ciclosporin and mizoribine, with no steroids	1 (4%)	1 (4%)
Ciclosporin, with no steroids	1 (4%)	2 (8%)
Mycophenolate mofetil, with no steroids	0	0
Mizoribine, with no steroids	2 (8%)	1 (4%)
No steroids or immunosuppressant	0	0

Lancet 2014; 384: 1273–81

Late steroid resistance

SRNS

Ingen effekt efter 4 veckor

Among patients who are not in remission after four weeks of daily steroid therapy:

3 pulses of methylprednisolone (1000 mg/1.73 m^2) every other day

LATE RESPONDERS

8 veckor utan respons

Biopsi
Genetisk analys

MCNC	60%
FSGS	30%
others	10%

Genetic forms of syndromic steroid-resistant nephrotic syndrome

Syndrome	Gene	Protein	Function	Transmission	Age at onset of proteinuria	Histology	Associated features
Denys-Drash syndrome	*WT1*	Wilms tumor protein	Podocyte development	AD	0 to 10 years	DMS	Male pseudohermaphroditism, Wilms tumor
Frasier syndrome	*WT1*	Wilms tumor protein	Podocyte development	AD	1 to 30 years	FSGS	Male pseudohermaphroditism, gonadoblastoma
Pierson syndrome	*LAMB2*	Laminin beta-2	Links GBM to podocyte cytoskeleton	AR	0 to 6 years	DMS	Microcoria, abnormal lens
Schimke syndrome	*SMARCAL1*	SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A-like protein 1	Chromatin bundling and gene transcription	AR	2 to 12 years	FSGS	Bone dysplasia, immune deficiency, ischemic cerebral lesions
Nail-patella syndrome	*LMX1B*	LIM homeodomain transcription factor 1, beta	Podocyte and GBM development	AD	10 to 70 years	FSGS	Hypoplastic nails and patellae, iliac horns
Charcot-Marie-Tooth disease	*INF2*	Inverted formin 2	Actin regulation	AD	10 to 45 years	FSGS	Neuropathy, deafness
Galloway-Mowat syndrome	*WDR73*	WD40 repeat-containing protein	Unknown	AR	5 to 15 years	FSGS	Microcephaly, intellectual disability, hiatal hernia, optic atrophy
Mitochondrial respiratory-chain disease	*MTTL1*	Mitochondrial tRNA leucine 1	Mitochondrial tRNA	Maternal	5 to 50 years	FSGS	MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like symptoms); diabetes mellitus; deafness
	COQ2	Polyprenyltransferase	Coenzyme Q10 biosynthesis	AR	0 to 2 years	FSGS	Encephalomyopathy, hypotonia, seizures, lactate acidosis
	COQ6	Ubiquinone biosynthesis monooxygenase COQ6	Coenzyme Q10 biosynthesis	AR	0 to 6 years	FSGS	Sensorineural deafness
	PDSS2	Decaprenyl diphosphate synthase, subunit 2	Coenzyme Q10 biosynthesis	AR	0 to 2 years	FSGS	Encephalomyopathy, hypotonia, seizures, lactate acidosis

AD: autosomal dominant; DMS: diffuse mesangial sclerosis; FSGS: focal segmental glomerulosclerosis; AR: autosomal recessive; GBM: glomerular basement membrane.

Genetic forms of isolated steroid-resistant nephrotic syndrome

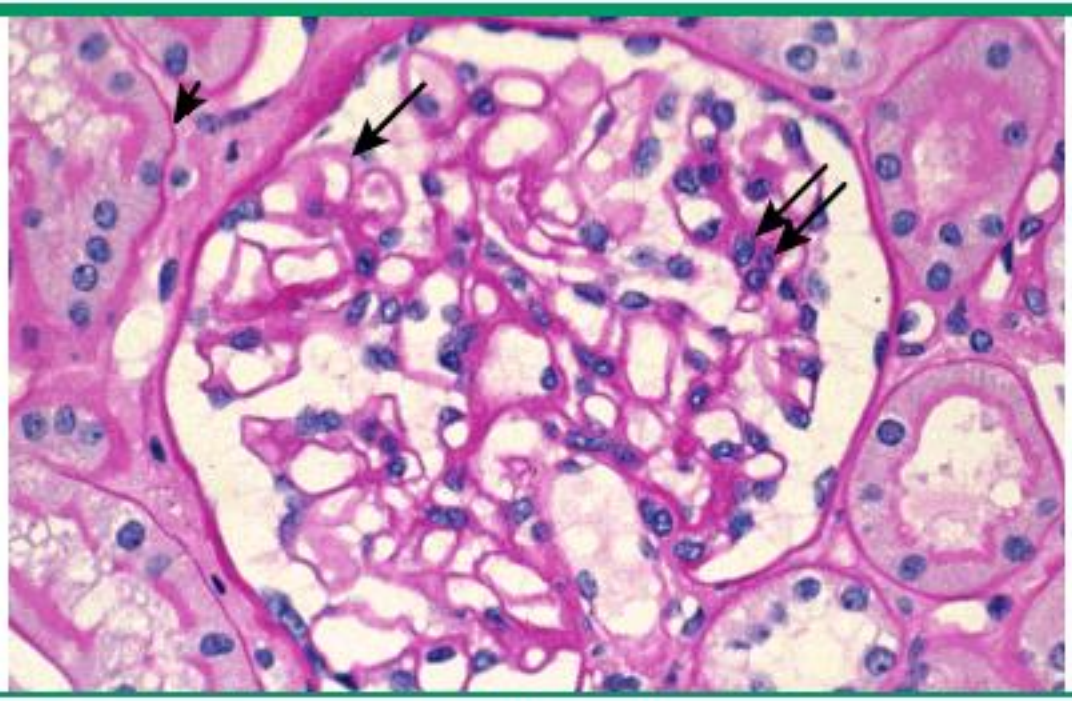
Gene	Protein	Protein function	Genetic transmission	Age at onset of proteinuria	Histology
NPHS1	Nephrin	Podocyte slit diaphragm protein	AR	0 to 10 years	MCD, FSGS
NPHS2	Podocin	Podocyte slit diaphragm protein	AR	0 to 40 years	MCD, FSGS
PLCE1	Phospholipase C epsilon-1	Podocyte differentiation, signalling protein	AR	0 to 8 years	DMS, FSGS
MYO1E	Myosin 1E	Actin function	AR	2 months to 9 years	FSGS
ADCK4	aarF domain-containing kinase 4	Podocyte cytoskeleton	AR	<1 to 21 years	FSGS
TTC21B	Intraflagellar transport protein IFT139	Trafficking regulation in the primary cilium	AR	9 to 30 years	FSGS
CRB2	Crumbs homolog 2 protein	Regulation of podocyte polarity	AR	9 months to 6 years	FSGS
CD2AP	CD-2 associated protein	Podocyte slit diaphragm protein	AR	1 year	FSGS
PTPRO	Receptor-type tyrosine-protein phosphatase O	Podocyte signaling	AR	5 to 14 years	MCD, FSGS
ACTN4	Alpha-actinin 4	Podocyte cytoskeleton	AD	3 to 54 years	FSGS
TRPC6	Transient receptor potential channel 6	Calcium channel	AD	2 to 75 years	FSGS
INF2	Inverted formin 2	Actin regulation	AD	5 to 72 years	FSGS
ARHGAP24	RHO GTPase-activating protein 24	Actin function	AD	<12 to 20 years	FSGS
ANLN	Anillin	Actin function	AD	9 to 69 years	FSGS
PAX2	Paired box protein 2	Kidney development	AD	7 to 68 years	FSGS

AR: autosomal recessive; MCD: minimal change disease; FSGS: focal segmental glomerulosclerosis; DMS: diffuse mesangial sclerosis; AD: autosomal dominant.

FSGS

Focal segmental glomerulosclerosis

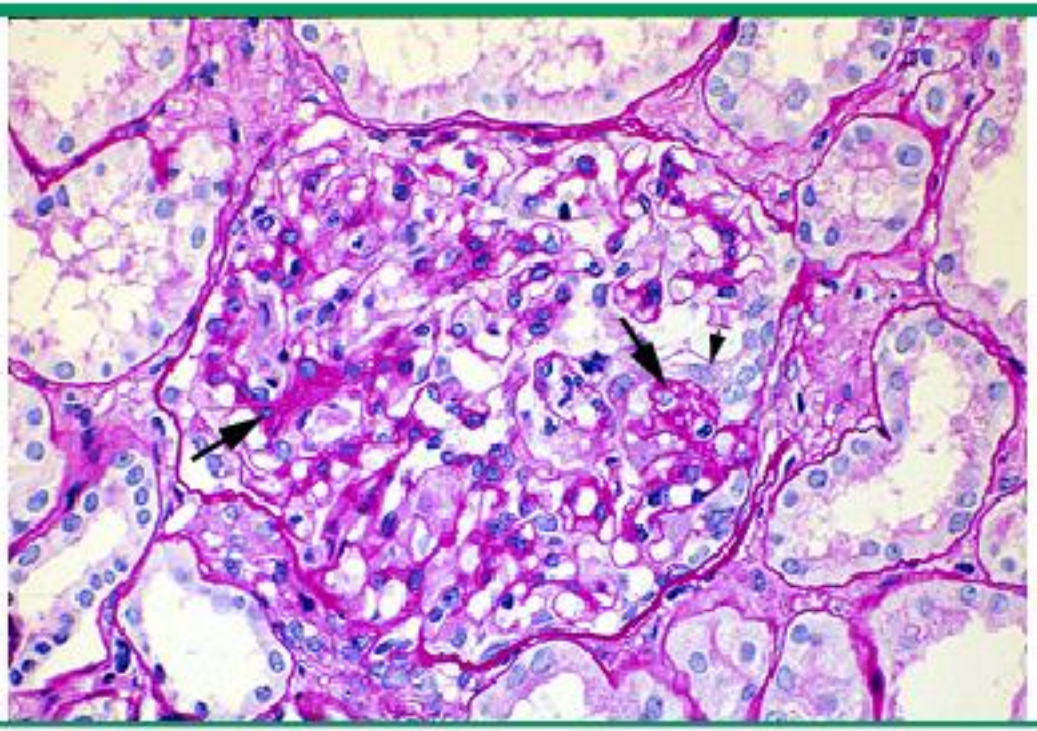
Normal glomerulus



Light micrograph of a normal glomerulus. There are only 1 or 2 cells per capillary tuft, the capillary lumens are open, the thickness of the glomerular capillary wall (long arrow) is similar to that of the tubular basement membranes (short arrow), and the mesangial cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).

Courtesy of Helmut G Rennke, MD.

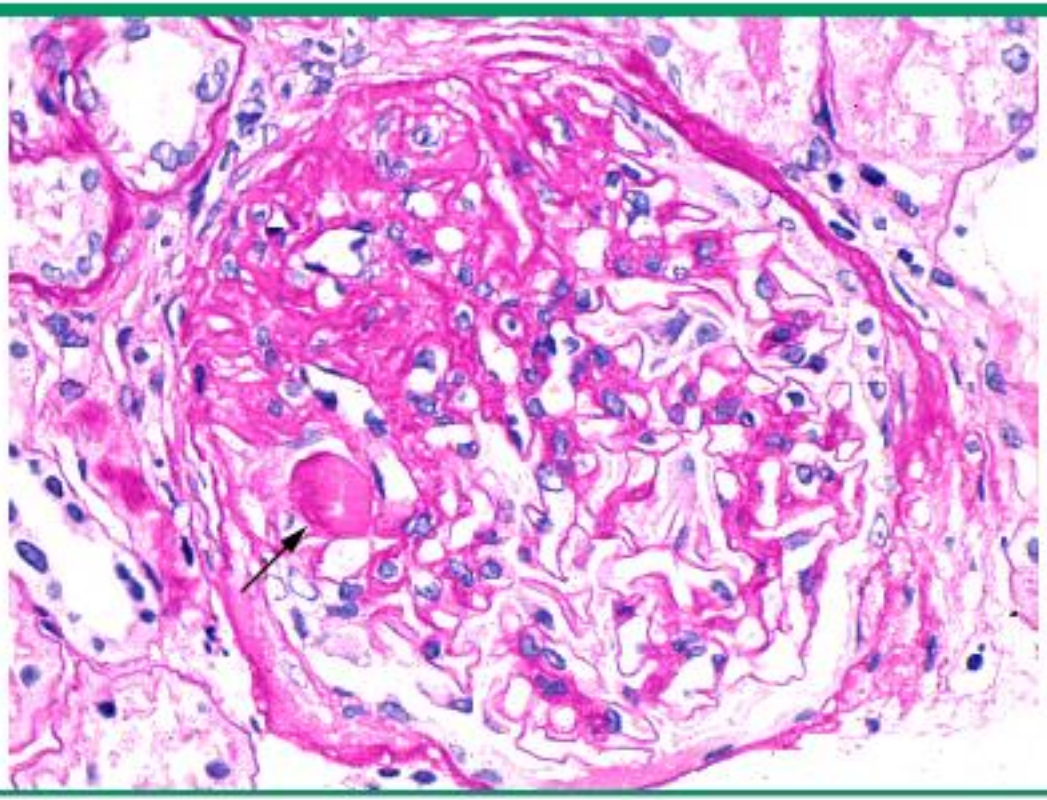
Mild FSGS



Light micrograph shows early changes in focal glomerulosclerosis with segmental capillary collapse (arrows) in areas of epithelial cell injury (small arrowhead).

Courtesy of Helmut Rennke, MD.

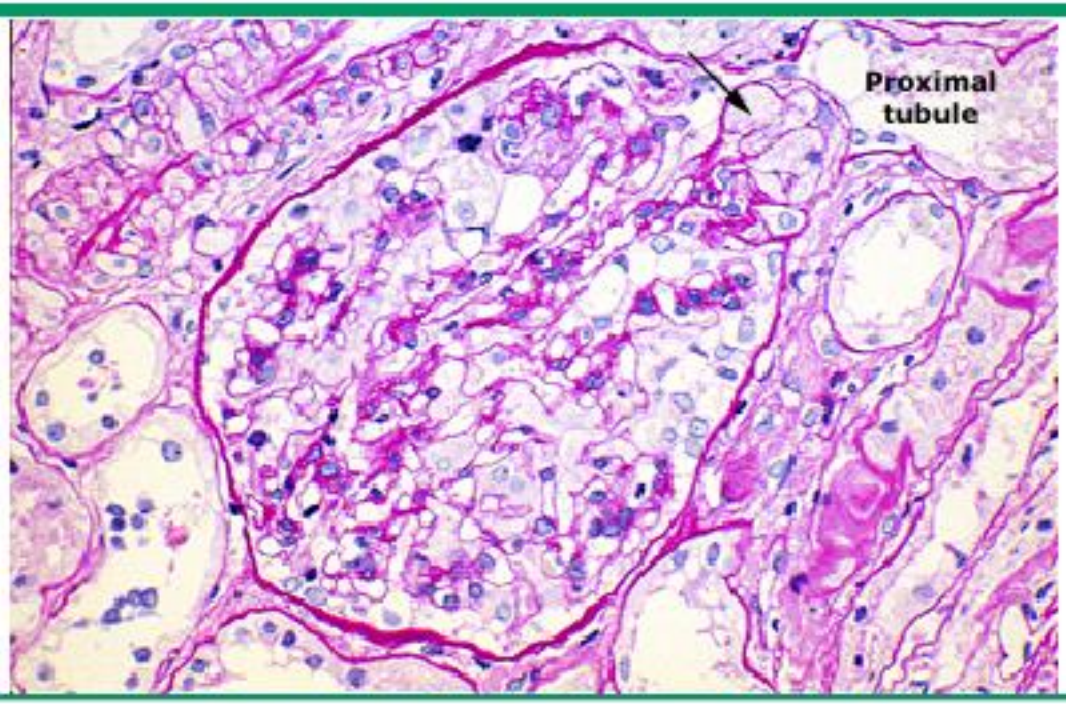
Moderate FSGS



Light micrograph in focal segmental glomerulosclerosis shows a moderately large segmental area of sclerosis with capillary collapse on the upper left side of the glomerular tuft; the lower right segment is relatively normal. Focal deposition of hyaline material (arrow) is also seen.

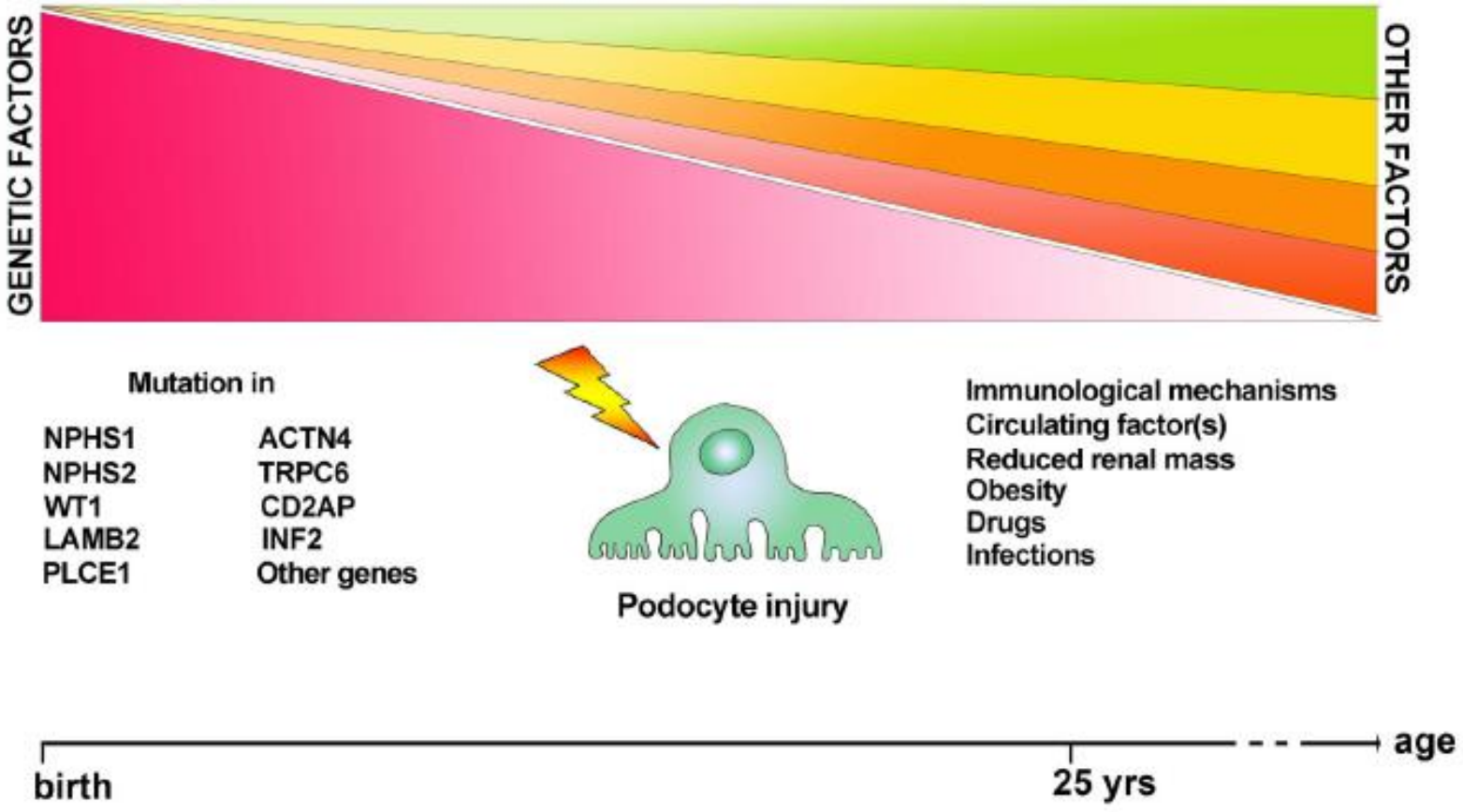
Courtesy of Helmut Rennke, MD.

Tip lesion in early FSGS



Light micrograph shows a tip lesion (arrow), which is considered to be an early change in primary focal segmental glomerulosclerosis. This lesion is characterized by epithelial cell injury and foam cell accumulation; note the enlarged cells with foamy cytoplasm in the lumen of the affected capillary. The lesion occurs at the "tip" of the glomerulus near the beginning of the proximal tubule.

Courtesy of Helmut Rennke, MD.

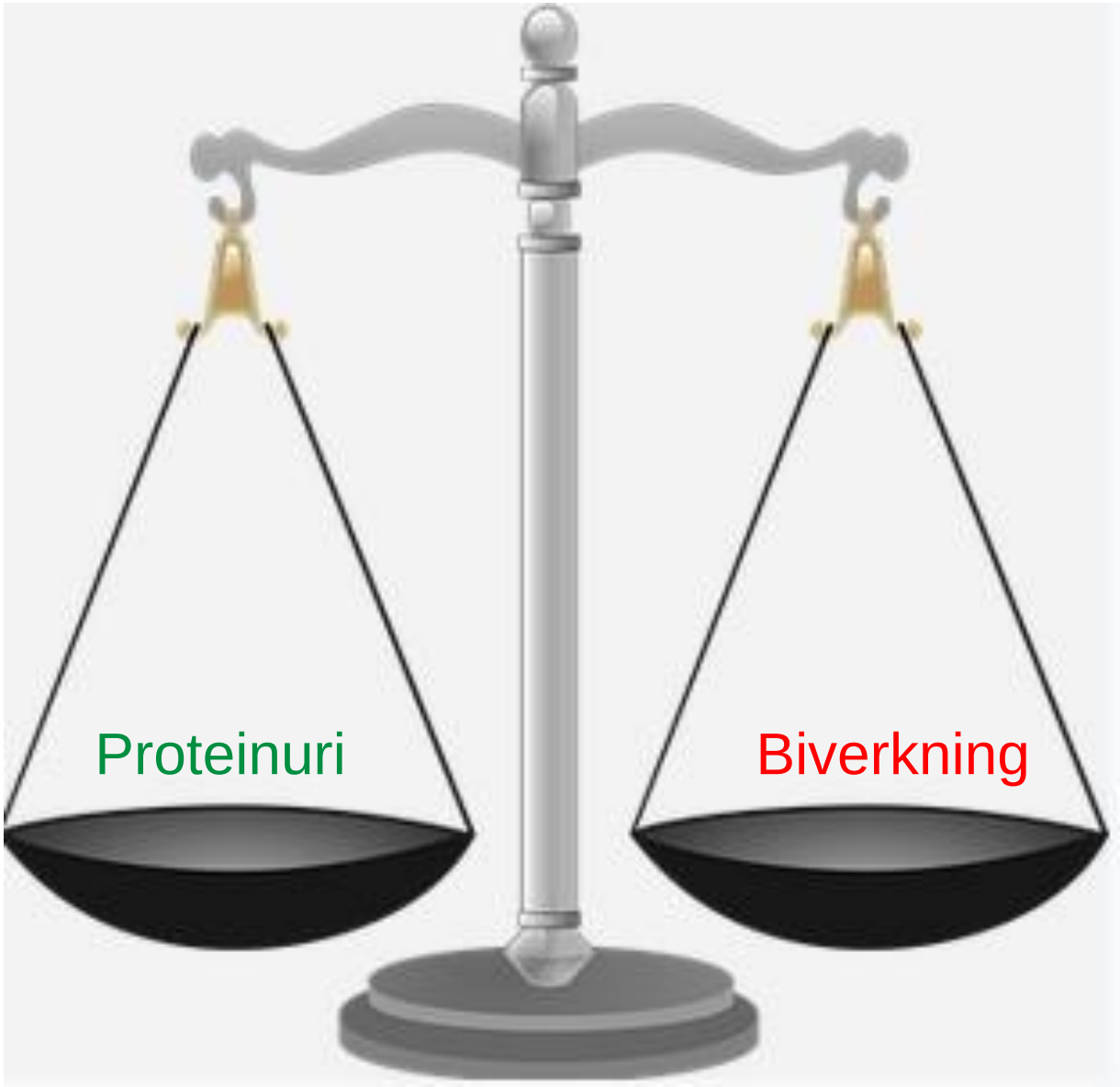

GENETIC FACTORS
OTHER FACTORS
Mutation in
NPHS1
NPHS2
WT1
LAMB2
PLCE1
ACTN4
TRPC6
CD2AP
INF2
Other genes
Podocyte injury
Immunological mechanisms
Circulating factor(s)
Reduced renal mass
Obesity
Drugs
Infections
birth
25 yrs
age

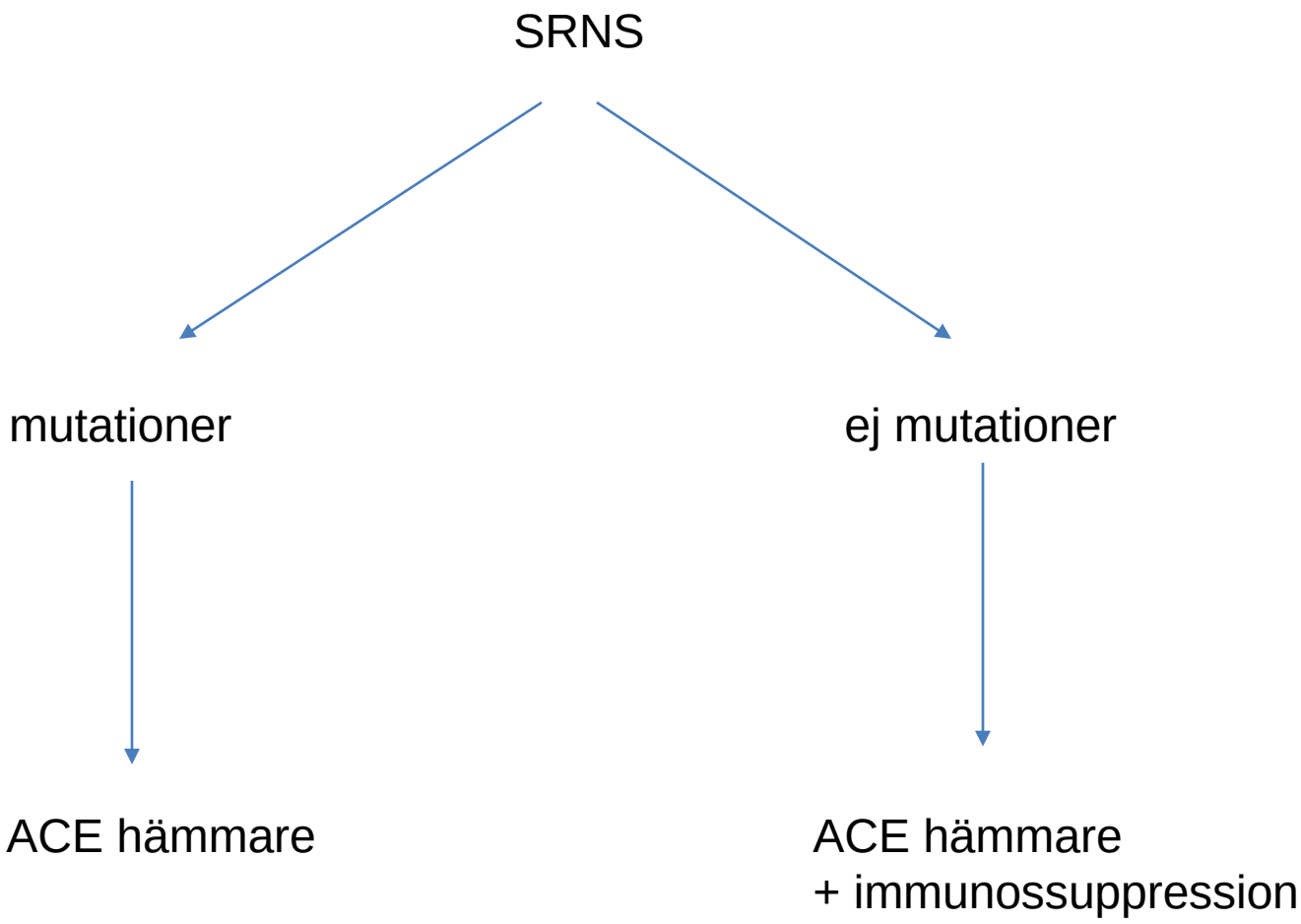
Risk för terminal njursvikt : 50 % (ej remission)

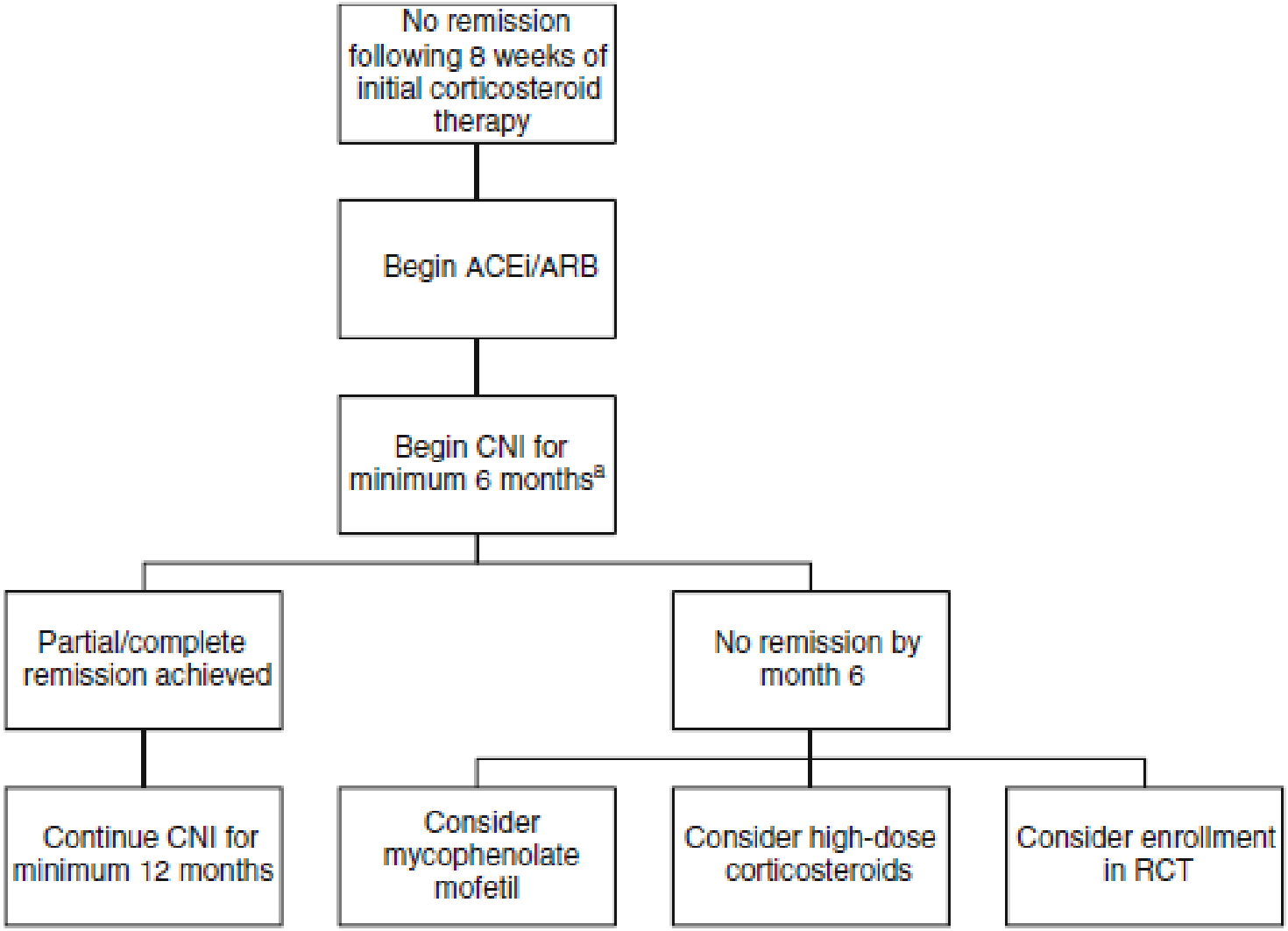
FSGS: 90 % bra njurfunktion efter 5 år (i remission)

Risk för terminal njursvikt : 50 % (ej remission)
MUTATIONER

FSGS: 90 % bra njurfunktion efter 5 år (i remission)
EJ MUTATIONER


Proteinuri
Biverkning


SRNS
mutationer
ej mutationer
ACE hämmare
ACE hämmare
+ immunossuppression


No remission following 8 weeks of initial corticosteroid therapy
Begin ACEi/ARB
Begin CNI for minimum 6 months[a]
Partial/complete remission achieved
No remission by month 6
Continue CNI for minimum 12 months
Consider mycophenolate mofetil
Consider high-dose corticosteroids
Consider enrollment in RCT

Behandling

Late responders
-Long term prednisolon
-iv pulsar

6-12 månader med

-Ciklosporin : 30 % ej proteinuri
- 40 % mindre proteinuri

-Takrolimus: (konc 4-6) samma effekt, mindre biverkningar

-Enalapril : 0.6 mg/kg 50% minsking av albuminuri

-Cyklophosphamide : ej bättre än kortison

Table 2 | Primary and secondary outcomes

Primary (6-month) outcome	Tacrolimus, 63	Cyclophosphamide, 61	*P*-value
Remission	52 (82.5)	28 (45.9)	<0.001
Complete	33 (52.4)	9 (14.8)	<0.001
Partial	19 (30.1)	19 (31.1)	0.90
Treatment failure	11 (17.4)	33 (54.1)	<0.001
Nonresponse	10	23	
Withdrawal of therapy	1	10	
>1 serious infection	0	8	
Declining GFR[a]	1	2	

Kidney International (2012) 82, 1130–1135

STEG 2
(ej respons)

-MMF
-+Takrolimus
-+ hög dos prednisolon (0.5 mg/kg/dag)

- respons 20-60%

-Rituzimab
-+ MMF
-+Takrolimus
-+ låg dos prednisolon