Focal and Segmental Glomerulosclerosis (FSGS) in Kidney Transplantation

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Outline

I-Introduction

- Epidemiology
- Classification of FSGS
- Pathogenesis
- FSGS variants
- FSGS in kidney transplantation

II-The Necker Hospital Experience

Epidemiology of FSGS on native kidney

Increasing frequency

***Children:**

20% 1990-1992 → **47% 1992-1996** *Gulati S et al. AJKD 1999*

***Adults:**

2.5% 1974 → **18.7% 1993** *D'Agati V et al. Kidney Int 1994*

4% 1974-1979 → **12.7% 1987-1993** *Haas M et al. AJKD 1995*

The most common cause of transplantation in children. *NAPRTCS 1997*

FSGS Classification

Secondary FSGS

Podocyte Genetic Disorders: Nephrin, Podocin, CD2AP, WT1…	**Nephron Reduction**
Podocyte Injury: HIV, Parvovirus B19, Pamidronate, IFNγ	**Others:** Obesity, Heart diseases

Primary FSGS

‘Complex Immune Disorder’

FSGS Classification

Secondary FSGS

Podocyte Genetic Disorders: Nephrin, Podocin, CD2AP, WT1…	**Nephron Reduction**
Podocyte Injury: HIV, Parvovirus B19, Pamidronate, IFNγ	**Others:** Obesity, Heart diseases

Primary FSGS

Pathogenesis

Primary FSGS: Pathogenesis of recurrence

*Circulating Vascular Permeability Factor :

-**Early recurrence of nephrotic syndrome after transplantation.** *Hoyer JR et al. Lancet 1972*

-**Serum from patients with recurrent FSGS infused in rats induced albuminuria.** *Zimmerman SW et al. Clin Nephrol 1984*

-**Occurrence of a transient nephrotic syndrome in newborn infants of women with FSGS.** *Lagrue G et al. Presse Med 1991*

-**Plasma exchange and/or immunoadsorption can induce remission.** *Dantal J et al. NEJM 1994*

Primary FSGS: Pathogenesis of recurrence

*T lymphocyte disorder?

-Vascular Permeability Factor and T-cell hybridomas from patients with FSGS. *Koyama A et al. Kidney Int 1991*

-Th2 profile?

- Increased IL-13 mRNA expression in PBMC from patients *Yap HK et al. JASN 1999*
- Overexpression of IL-13 in rat induce MCD. *Lai KW et al. JASN 2007*

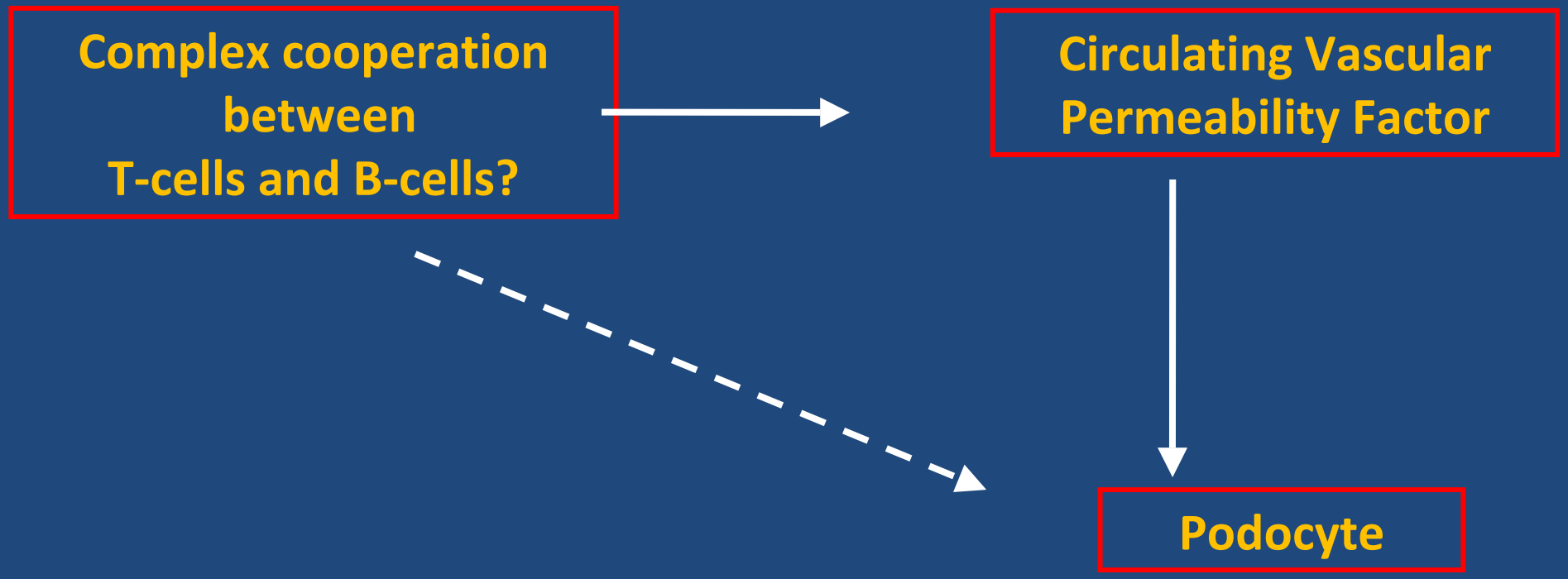
-$CD34^+$ stem cells of patients with INS induced albuminuria in a humanized mouse model. *Sellier-Leclerc AL et al, JASN 2007*

-But Calcineurin inhibitors, anti-CD3 and anti-CD52 have inconstant efficiencies

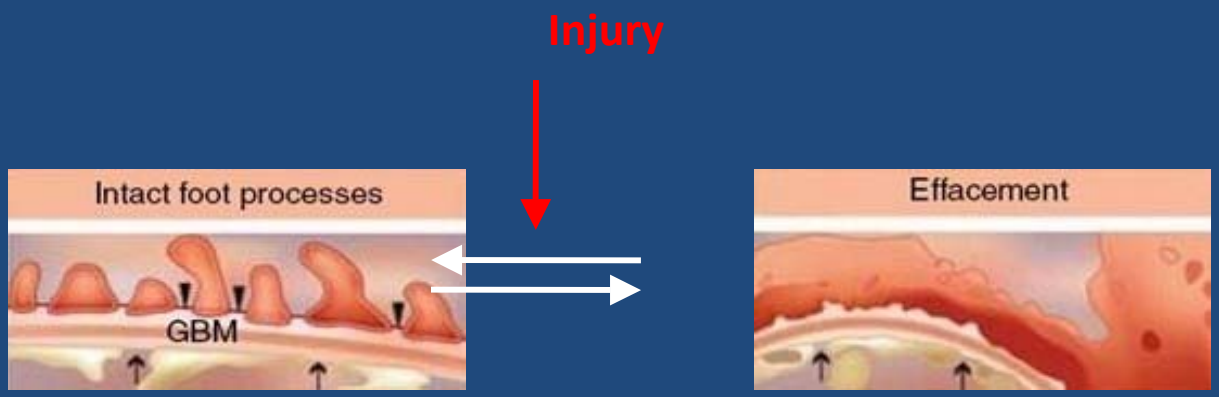
*B lymphocyte disorder?

-Inconstant efficiency of Rituximab.

Primary FSGS: Pathogenesis of recurrence



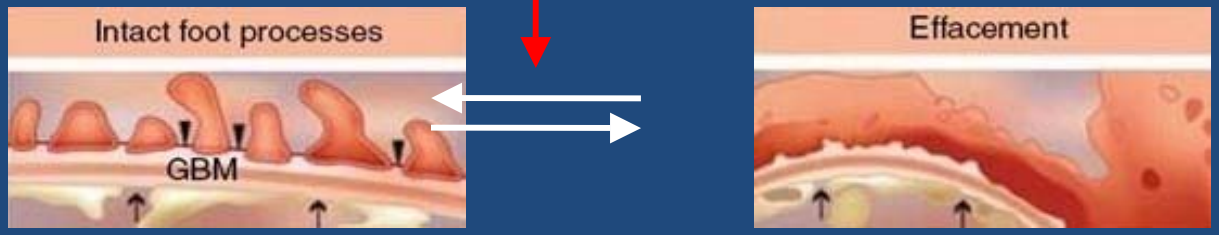
Primary FSGS: Pathogenesis of recurrence



Reversible step

Primary FSGS: Pathogenesis of recurrence

Injury



Sustained Injury

Irreversible Podocyte Stress

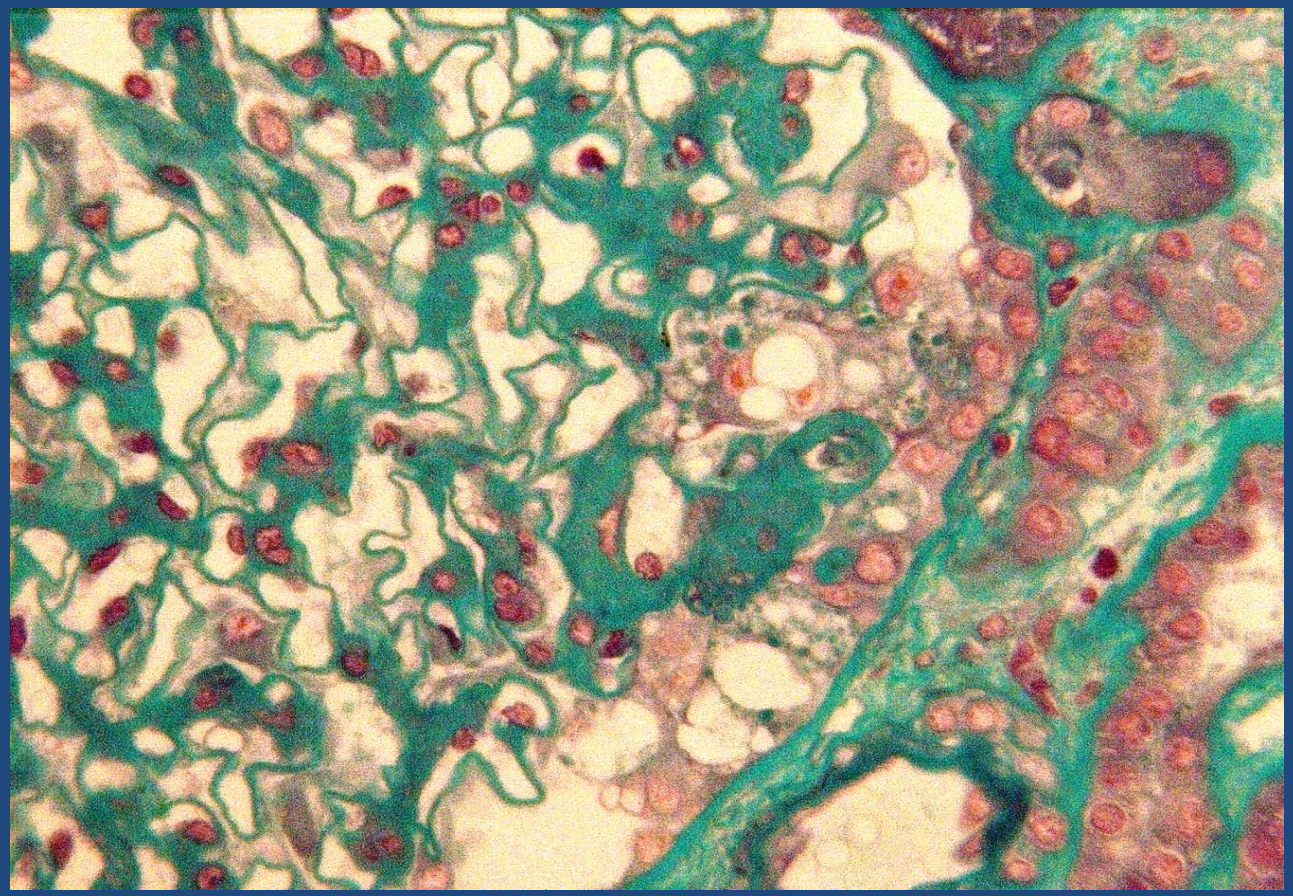
Proliferation

Collapsing

Podocyte detachment or apoptosis

Glomerulosclerosis

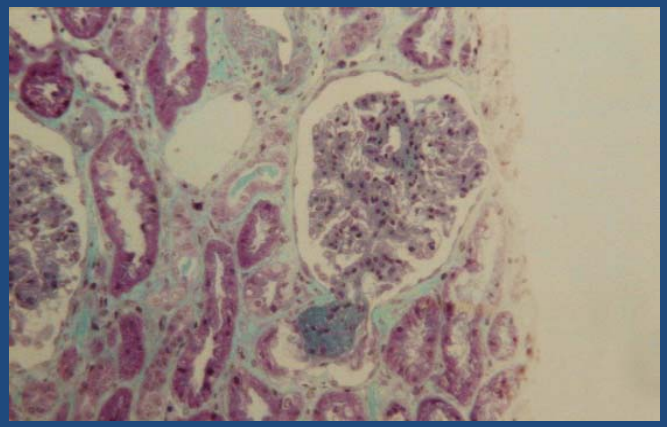
Primary FSGS: Pathogenesis of recurrence



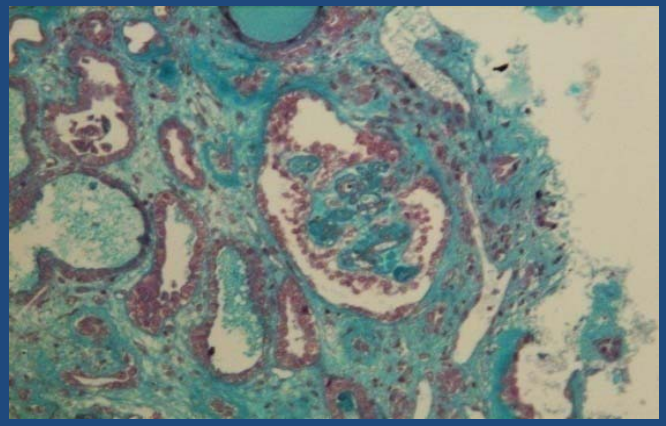
FSGS variants

The Columbia classification of FSGS variants

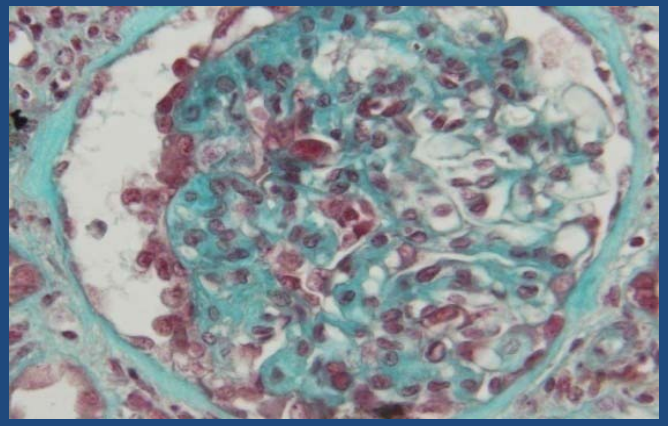
Tip (TIP)



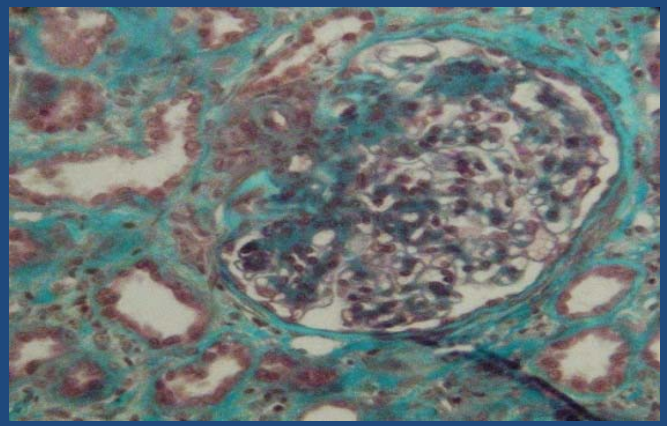
Collapsing (COL)



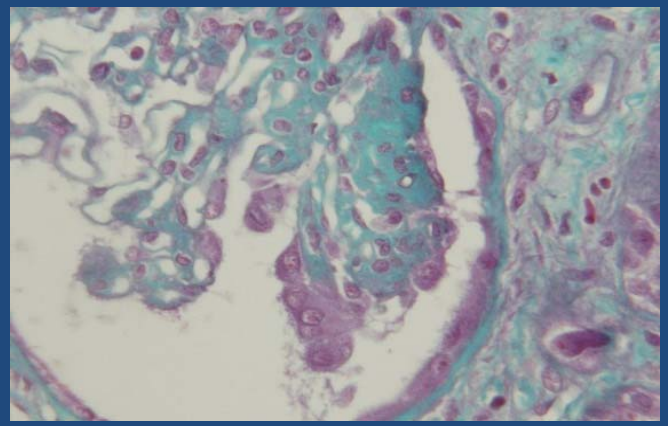
Cellular (CELL)



Perihilar (PH)



Not otherwise specified (NOS)



D'Agati VD et al. AJKD 2004

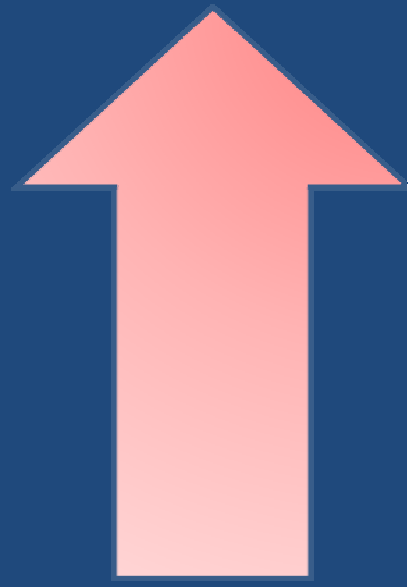
Prognosis of FSGS variants on native kidneys

- **TIP:**
  - **often steroid sensitive**
  - **rarely progress to ESRD.** *Stokes MB et al. Kidney Int 2004. Thomas DB et al. Kidney Int 2006*
- **COL :**
  - **severe prognosis**
  - **poor or even no response to treatment.** *Stokes MB et al. Kidney Int 2004. Thomas DB et al. Kidney Int 2006*
- **NOS, PH and CELL :**
  - **intermediate prognosis.** *Stokes MB et al. Kidney Int 2004. Thomas DB et al. Kidney Int 2006*

FSGS in kidney transplantation

FSGS in kidney transplantation

- **Recurrence after transplantation:**
  - Frequent (20-80%)
  - Poor graft surviving: 50-60% at five years
- **Risks factors:**
  - Recurrence on a previous graft
  - Young age at onset
  - Rapidity of evolution toward ESRD?
  - Mesangial proliferation?
  - Duration of HD before kidney transplantation?
  - Donor age?



The Necker Hospital experience

The Necker Hospital experience

1) Frequency, risk factor of recurrence and allograft survival rate

2) Pathological examination of recurrence

3) Therapeutic aspect of recurrence

The Necker Hospital experience

1) Frequency, risk factor of recurrence and allograft survival rate

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Frequency and risks factors for recurrence

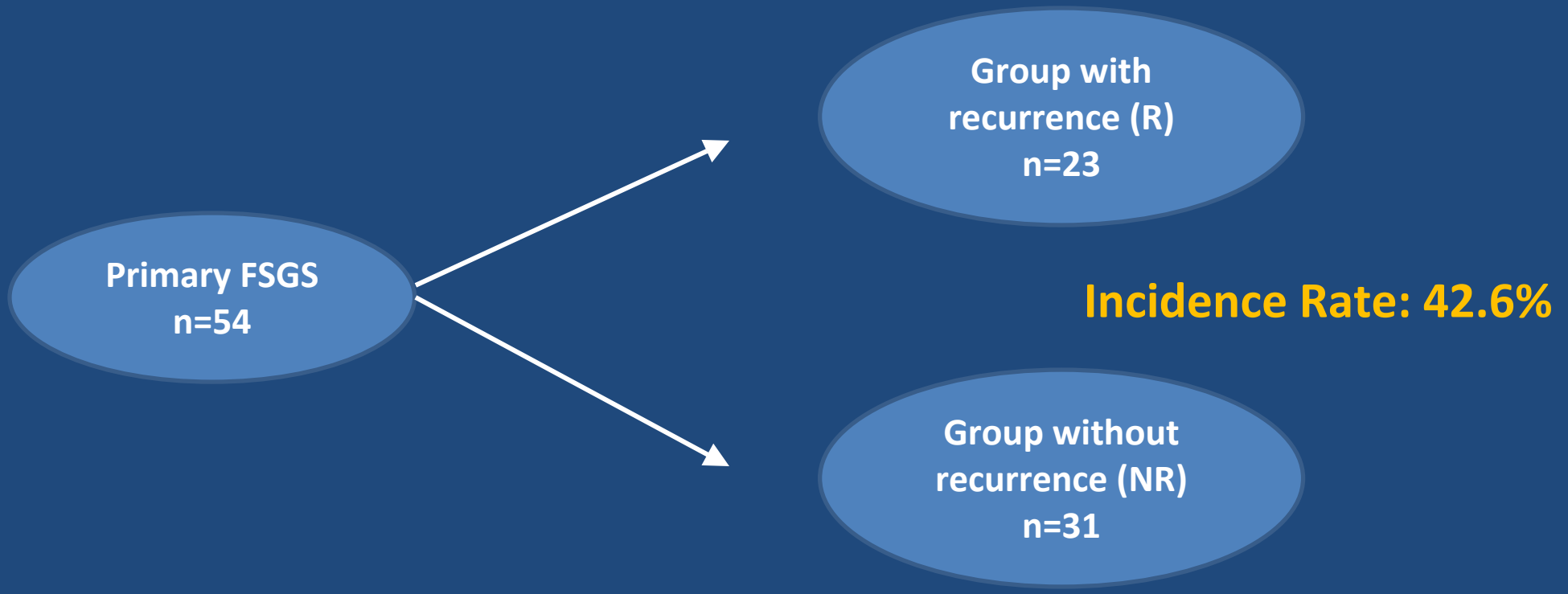
Material and methods:

*Patient with primary FSGS

*Period 1996-2006, n=875 kidney transplantation

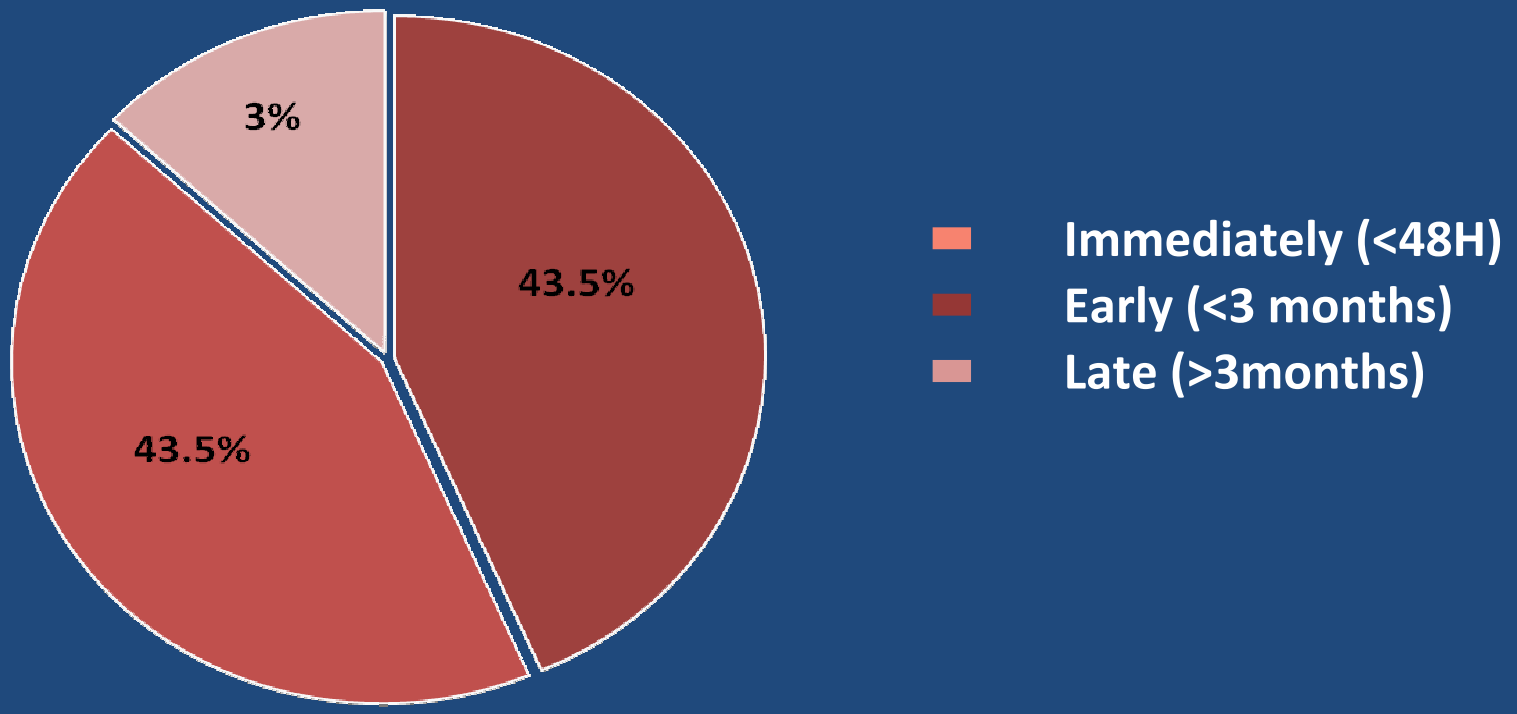
*Nephrotic range proteinuria without glomerular abnormality

Frequency and risks factors for recurrence



Incidence Rate: 42.6%

Delay of recurrence



Frequency and risks factors for recurrence

Recipients characteristics:

*Age at onset of proteinuria
*Sex
*Ethnical characteristics
*Recurrence on a previous graft
*Delay before ESRD
*Duration of hemodialysis
*Immunosuppressive drug during the post transplant course

Donors characteristics:

*Age
*Sex
*Cold ischemia
*HLA mismatch
*Creatinine level

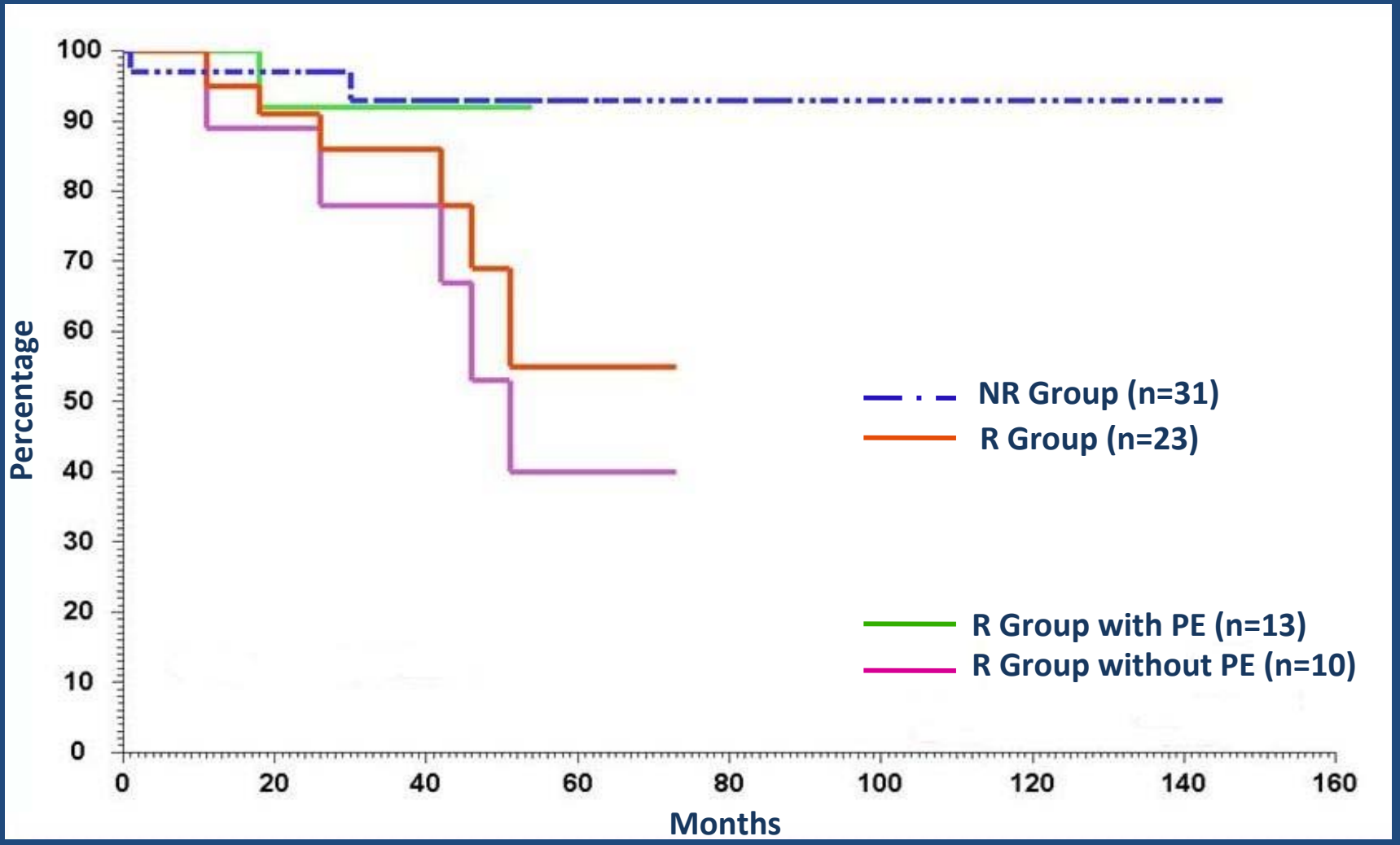
Risks factors for recurrence: univariate analysis

Characteristics	R group	NR group	P-value
Age at onset of proteinuria (years)	16.7±9.6	23.8±10.3	0.01
Recurrence on a previous graft	8/9	0/7	0.001
Delay before ESRD (years)	2.8±1.7	5±5	0.004
Duration of HD (years)	2.3±2.3	5±3.8	0.04
Donor age (years)	49.9 ±13.7	42.5±12.8	0.04

Risks factors for recurrence: multivariate analysis

Characteristics	R group	NR group	P-value
Recurrence on a previous graft	8/9	0/7	0.001
Delay before ESRD (years)	2.8±1.7	5±5	0.004
Duration of HD (years)	2.3±2.3	5±3.8	0.04

Allograft survival rate: Necker Cohort



The Necker Hospital experience

1) Frequency, risk factor of recurrence and allograft survival rate

2) Pathological examination of recurrence

3) Therapeutic aspect of recurrence

The Columbia classification of Focal Segmental Glomerulosclerosis and allograft risk of recurrence

Guillaume Canaud, Daniel Dion, Julien Zuber, Marie-Claire Gubler, Rebecca Sberro, Eric Thervet, Renaud Snanoudj, Marina Charbit, Rémi Salomon, Frank Martinez, Christophe Legendre , Laure-Hélène Noël et Patrick Niaudet.

FSGS classification and allograft risk of recurrence in adults and infants

Material and methods:

*Biopsy proven idiopathic FSGS and evolution toward ESRD (excluding all secondary forms) including adults and children

*Biopsies performed:

- On native kidneys
- Transplanted kidney: screening biopsies at Month 3 and 12
- Transplanted kidney and Proteinuria Recurrence
- Transplanted kidney and Acute renal failure

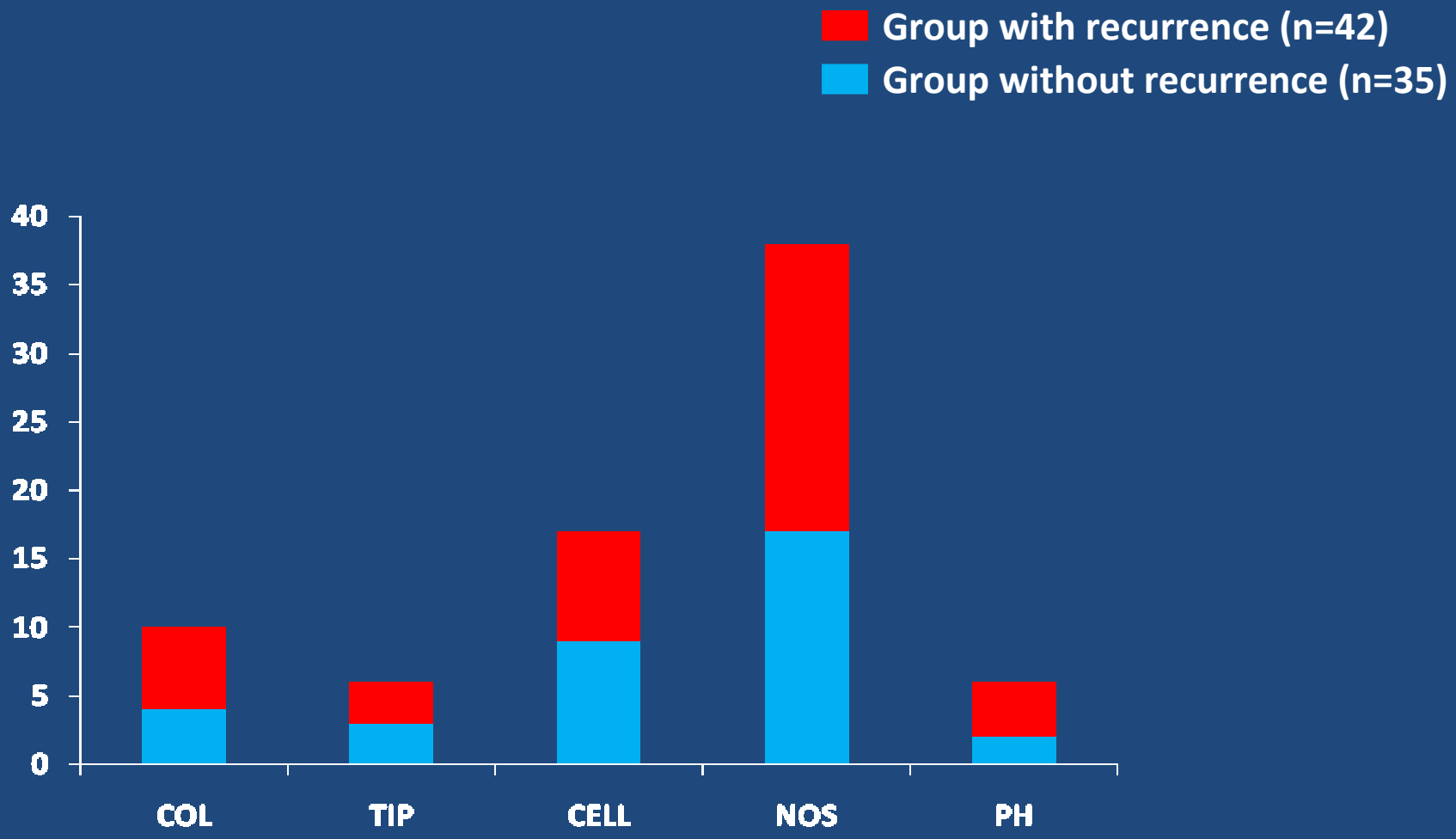
*Columbia classification for each biopsy, at least 15 serial sections

FSGS on natives kidney

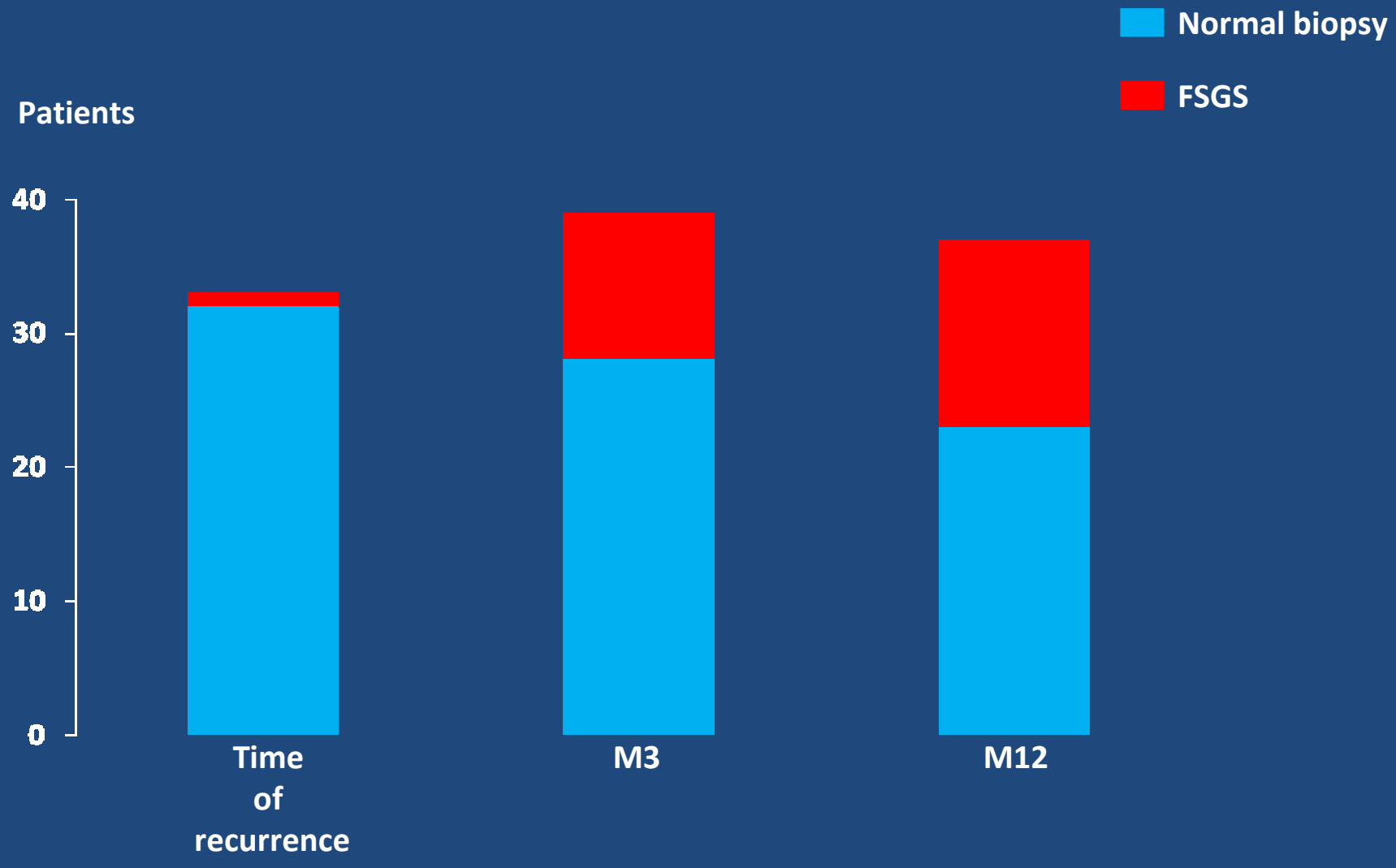
n=77 patients

Patients	Group with recurrence (n=42)	Group without recurrence (n=35)
NOS	21 (50%)	17 (48%)
CELL	8 (20%)	9 (26%)
COL	6 (14%)	4 (12%)
TIP	3 (7%)	3 (8%)
PH	4 (9%)	2 (6%)

FSGS on natives kidney

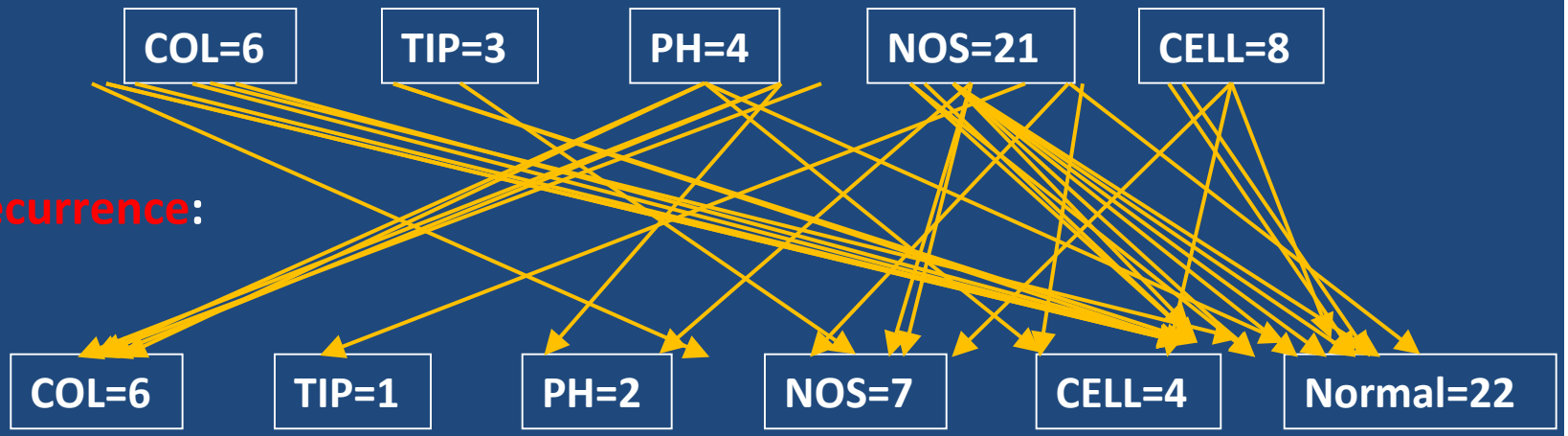


Serial Transplant biopsies after proteinuria recurrence



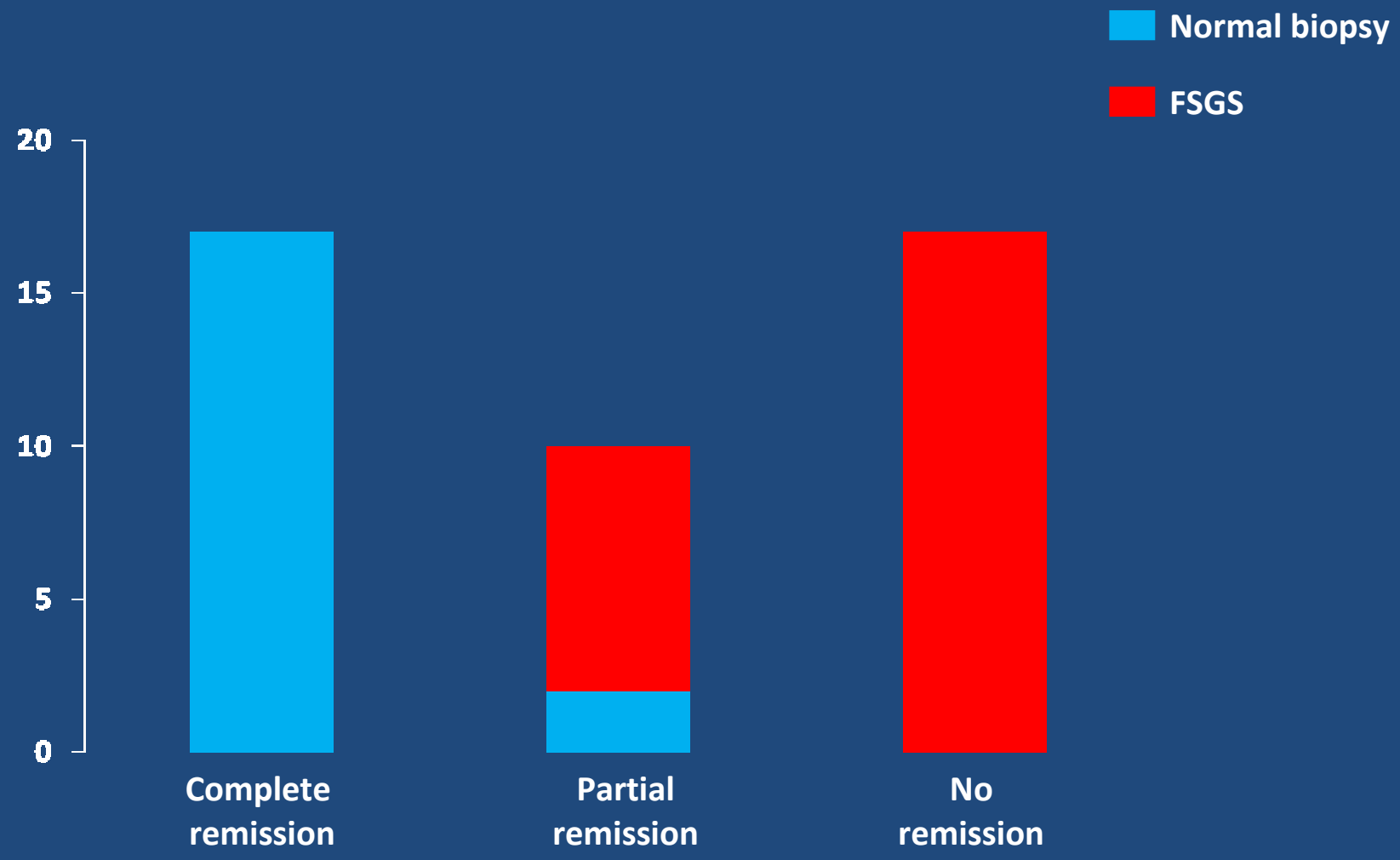
Transplant biopsies and Columbia classification

FSGS variants on native kidneys of patients affected with recurrence:



FSGS variants of recurrence:

Proteinuria remission and histological finding



FSGS variants and recurrence

Fidelity and Evolution of Recurrent FSGS in Renal Allografts

Daphne H.T. IJpelaar,* Alton B. Farris,† Natascha Goemaere,‡ Kerstin Amann,§ Roel Goldschmeding,‖ Tri Q. Nguyen,‖ Evan Farkash,† Marius C. van den Heuvel,¶ Emile de Heer,* Jan A. Bruijn,* Robert B. Colvin,† and Ingeborg M. Bajema*

Table 3. Recurrence classification

Types of Recurrence	*n*	Patient
I. Fidelity to native disease		
type X FSGS → type X FSGS	11	1, 2, 3, 4, 4[a], 5, 6, 10, 13, 14[d], 16
II. Fidelity to native disease after MC intermediate[b]		
type X FSGS → MC → type X FSGS	4	11, 12, 17, 18
III. Lack of fidelity to native disease[c]		
type X FSGS → type Y FSGS		
early (<1 yr)	2	15, 19
late (>1 yr)	2	7, 8
IV. Less than 1 mo of follow-up	2	1[a], 9

Ijpelaar DH., et al. JASN 2008

The Necker Hospital experience

1) Frequency, risk factor of recurrence and allograft survival rate

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Therapeutics options: Review

	n	Treatment	Remission
Laufer J, 1988	2	9 PE	Complete then relapse
Ingulli E, 1990	3	CsA	-1 complete then relapse -1 partial
Cochat P, 1993	3	Steroids +10 PE 2months + Cyclophosphamide	-Complete then relapse in 1 case
Dantal J, 1994	8	ATG+CsA+steroids+IA	-7 complete then relapse in all cases
Dall'Amico R, 1999	11	15 PE + Cyclophosphamide	-7 Complete
Cheong HI,2000	6	10 PE + Cyclophosphamide+ CsA IV	-3 complete -3 partial
Salomon R, 2003	16	CsA IV+PE in 4 cases	-14 complete -2 partial
Raafat RH, 2004	16	Oral CsA + PE in 7 cases	-11 complete -2partial
Deegens JK, 2004	13	PE at time recurrence	-7 complete -4 partial
Valdivia P, 2005.	10	17 PE+ Losartan	-6 complete -3 partial

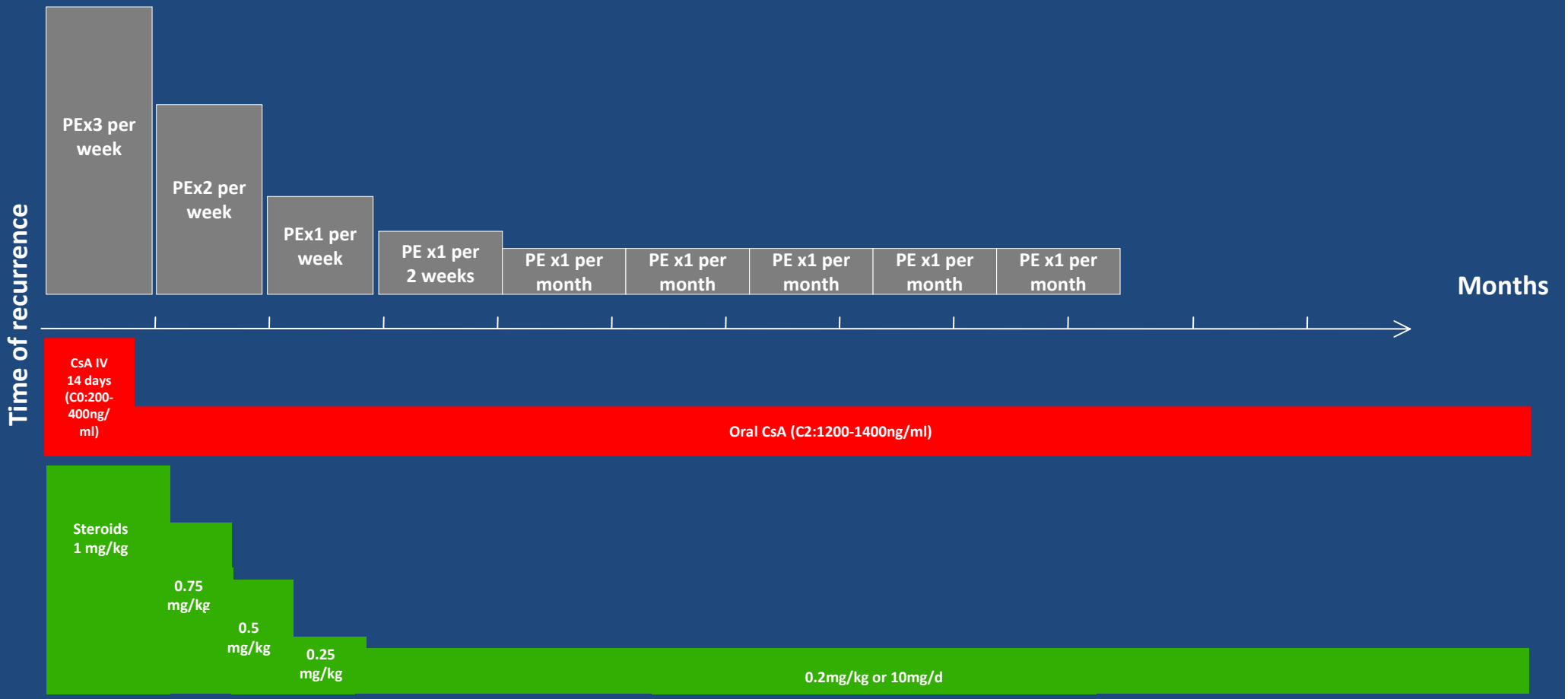
American Journal of Transplantation 2009; 9: 1–6
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.02580.x

Intensive and Prolonged Treatment of Focal and Segmental Glomerulosclerosis Recurrence in Adult Kidney Transplant Recipients: A Pilot Study

Guillaume Canaud, Julien Zuber, Rebecca Sberro, Virginie Royale, Dany Anglicheau, Renaud Snanoudj, Khaled Gaha, Eric Thervet, François Lefrère, Marina Cavazzana-Calvo, Laure-Hélène Noël, Arnaud Méjean, Christophe Legendre, Frank Martinez.

Therapeutic Strategy



Patients characteristics

Table 1: Patient characteristics according to proteinuria recurrence (p = ns)

	Patients with recurrence						Patients without recurrence					
Patients	Gender	Ethnicity	Age at onset of proteinuria	Delay to ESRD (years)	Duration of HD (years)	Donor	Gender	Ethnicity	Age at onset of proteinuria	Delay to ESRD (years)	Duration of HD (years)	Donor
1	M	African	26	7	1	LRD	M	Caucasian	16	3	0.8	DD
2	M	Caucasian	19	5	3.3	DD	M	Caucasian	18	4.5	2.1	DD
3	F	Caucasian	32	2	0	LRD	M	African	19	2.6	4	LRD
4	M	African	15	2.6	3	DD	F	African	15	4	2.8	DD
5	F	African	3	19	1	DD	M	African	32	8	1.6	DD
6	M	Caucasian	54	7	2	DD	F	Caucasian	7	7	4	DD
7	M	African	6	28	2	DD	M	Caucasian	6	12	2	LRD
8	M	Caucasian	12	3	5.8	DD	F	African	12	9	3.2	DD
9	M	African	11	5	8	DD						
10	M	African	18	2	2	DD						
Mean			19.6	8.1	2.8				15.6	6.2	2.5	
SD			14.8	8.6	2.4				8.1	3.3	1.2	

Results

Table 3: FSGS recurrence and treatment characteristics

Patient	Previous graft	Day of recurrence	Proteinuria at time recurrence (g/day)	Delay to remission (day)	Proteinuria month 3 (g/day)	Proteinuria month 12 (g/day)	Ioexhol GFR at 1 year (mL/min)	Follow-up after remission (months)	Total of PE sessions
1	0	2	4	18	0.05	0.05	86	21	25
2	0	12	5.4	24	0.1	0.1	58	19	25
3	0	55	7.1	28	0.3	0.3	75	16	25
4	0	1	7.9	29	0.15	0.07	84	18	25
5	0	2	5.6	18	0.20	0.05	94	17	25
6	0	4	7.7	20	0.22	0.1	41	14	25
7	0	4	22	10	0.3	0.05	61	16	25
8	2	1	8.7	23	0.04	1	85	15	39
9	0	1	40	33	0.05	0.1	56	13	25
10	0	1	12	26	0.2	0.1	45	9	25
Mean		8.3	12.0	22.9	0.16	0.19	68.5	15.8	
SD		16.8	11.1	6.7	0.09	0.29	18.6	3.3	

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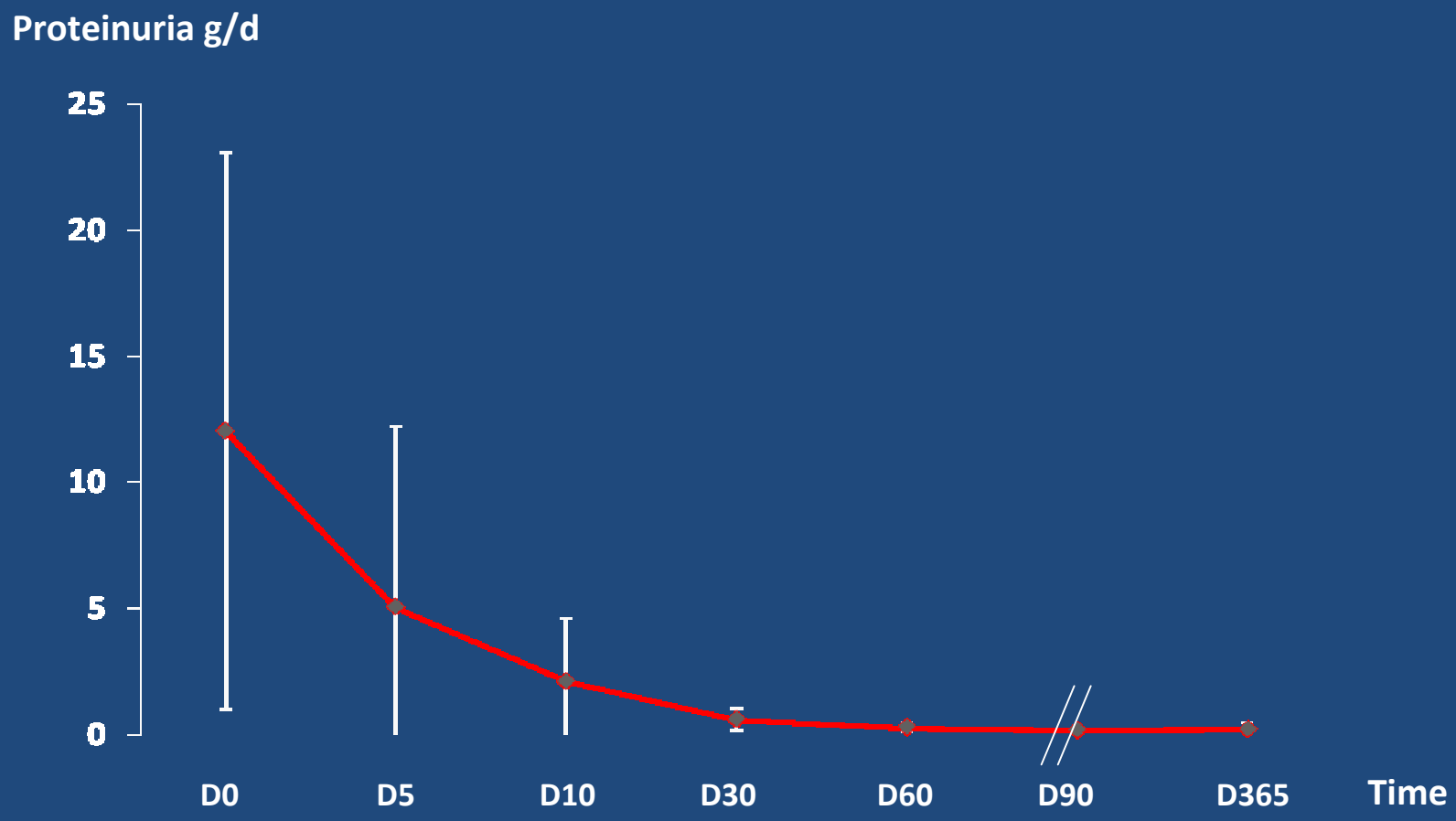
Proteinuria evolution after treatment



Historical control group

100% complete remission at 3 months
90% complete remission at one year

Table 2: Patients treated for FGGS recurrence during the1997–2005 time period (control group)

Patients	Treatment	Histological finding	Outcome	Proteinuria remission
1	CsA IV	FSGS on M12	Return on dialysis on M24	No
2	Cyc + PE	Normal kidney on light microscopy	Last follow-up M80	Complete and sustained
3	FK + PE	Normal kidney on light microscopy	Last follow-up M47	Complete and sustained
4	Steroids + FK	FSGS on M12	Last follow-up M52	No
5	CsA IV + PE	FSGS on M18	Return on dialysis on M36	No
6	Steroids + PE	Normal kidney on light microscopy	Last follow-up M61	Partial
7	CsA oral +PE	FSGS on M6	Return on dialysis M24	No
8	Steroids + PE	FSGS M12	Return on dialysis on M34	No
9	CsA oral + PE	Normal kidney on light microscopy	Last follow-up M92	Partial
10	CsA IV + PE	FSGS on M6	Return on dialysis on M6	No
11	CsA IV + PE	Normal kidney on light microscopy	Last follow-up M55	Complete and sustained
12	PE + Cyc + Rituximab	FSGS on M12	Return on dialysis M18	No
13	CsA IV	FSGS on M9	Return on dialysis on M48	No
14	CsA oral + PE	FSGS M18	Return on dialysis on M40	No
15	PE + Steroids + FK	FSGS M24	Return on dialysis on M24	No
16	FK+ PE	Normal kidney on light microscopy	Last follow-up M60	Complete and sustained
17	PE + Steroids + Rituximab	Normal kidney on light microscopy	Last follow-up M38	Partial
18	PE + Steroids	Normal kidney on light microscopy	Last follow-up M85	Complete and sustained
19	CsA IV + PE	FSGS on M24	Return on dialysis on M48	No

Cyc = cyclophosphamide; FK = tacrolimus.

Historical control group

100% complete remission at 3 months
90% complete remission at one year

42% partial remission
27% complete remission

Table 2: Patients treated for FGGS recurrence during the1997–2005 time period (control group)

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3	FK + PE	Normal kidney on light microscopy	Last follow-up M47	Complete and sustained
4	Steroids + FK	FSGS on M12	Last follow-up M52	No
5	CsA IV + PE	FSGS on M18	Return on dialysis on M36	No
6	Steroids + PE	Normal kidney on light microscopy	Last follow-up M61	Partial
7	CsA oral +PE	FSGS on M6	Return on dialysis M24	No
8	Steroids + PE	FSGS M12	Return on dialysis on M34	No
9	CsA oral + PE	Normal kidney on light microscopy	Last follow-up M92	Partial
10	CsA IV + PE	FSGS on M6	Return on dialysis on M6	No
11	CsA IV + PE	Normal kidney on light microscopy	Last follow-up M55	Complete and sustained
12	PE + Cyc + Rituximab	FSGS on M12	Return on dialysis M18	No
13	CsA IV	FSGS on M9	Return on dialysis on M48	No
14	CsA oral + PE	FSGS M18	Return on dialysis on M40	No
15	PE + Steroids + FK	FSGS M24	Return on dialysis on M24	No
16	FK+ PE	Normal kidney on light microscopy	Last follow-up M60	Complete and sustained
17	PE + Steroids + Rituximab	Normal kidney on light microscopy	Last follow-up M38	Partial
18	PE + Steroids	Normal kidney on light microscopy	Last follow-up M85	Complete and sustained
19	CsA IV + PE	FSGS on M24	Return on dialysis on M48	No

Cyc = cyclophosphamide; FK = tacrolimus.

Conclusion

-Still mysterious, frequent and associated with a poor allograft survival

-Risks factors: recurrence on a previous graft, rapidity of evolution toward ESRD, duration of HD

-The Columbia classification is of no help in predicting the risk of recurrence

-We might talk about proteinuria recurrence instead of FSGS recurrence

-An intensive and prolonged treatment induce complete and sustained proteinuria remission

Thanks!

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Thank you for your attention!