Role of Plasma-Exchange in Recurrent FSGS After Kidney Transplant in Children

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Overview

- Case history
- When does, **r**ecurrence of **F**SGS **a**fter **t**ransplant (r-F-AT) occur ?
- How does (r-F-AT) Manifest ?
- Risk factors associated with (r-F-AT)
- Pathogenesis of recurrence of FSGS
- Diagnosis
- Treatment Modalities & Outcomes
- Studies in Adult & Pediatric Population

Case Study

Case Presentation

Case 1 : 11 years, Boy

2014

- Typhoid, incidental S.Creatinine 2mg%,
- Kidney size ≈ 6cm.
- Conservative management for 9 months

2015

- Creatinine = 9mg%, advised dialysis.
- Ayurvedic treatment for 2 years

2018 (FEB)

- Loss of consciousness, Anasarca, UOP (**N**)
- Urine protein 2+, Sr Creatinine 13mg%
- Initiated on MHD.
- Access : right IJV cuffed HD catheter
- MHD : Thrice weekly, 3 hours, 1-1.5 L UFG

Case 2 : 9 years, Girl

2017

- Anasarca,
- born out of 3° consanguineous marriage.
- Paternal uncle, elder sister : CKD
- Treated as SRNS with Tacrolimus & Steroid.

2020

- Azotemia, oliguria,
- Kidney biopsy : MCD
- initiated on MHD,
- Access : right IJV cuffed HD catheter.
- MHD : Thrice weekly, 3 hours, 1-1.5 L UFG
- Genetic testing : no pathogenic variants causative of reported phenotype

Transplant Prospects

	Case-1	Case – 2
Age at Tx/ Blood group	**14 years**, O+ve	**12 years**, B+ve
Native Kidneys at Presentation	RK : 5.8 x 2.8 cm LK : 6.2 x 2.9 cm (B/L ↑ echogenicity, CMD lost, multiple cysts in renal medulla)	RK : 5.0 x 2.1 cm LK : 4.8 x 2.7 cm (B/L ↑ echogenicity, CMD lost)
Primary Disease	**? Nephronopthisis/? CGN/? FSGS**	**Biopsy proven MCD/ unsampled FSGS**
Transplant date:	27 August 2018	4 January 2021
Donor / Age / Blood Group	Grandmother (maternal) / 55 yr /O+ve	Grandmother (maternal) / 52 yr/ O+ve
HLA / LCM	6/6 Mismatch, Negative	6/6 Mismatch, Negative

Transplant Surgery

	Case-1	Case – 2
Left Donor Nephrectomy	GFR : 57.1 ml/min/1.73m^2	GFR : 50 ml/min/ 1.73m^2
Anesthesia	General Anesthesia	
Warm ischemia time	3 mins 54 sec	7 mins 56 sec
Cold Ischemia time	**20 mins**	**25 mins**
Procedure	Left renal artery anastomosed to common iliac artery (end to side) Left renal vein anastomosed to common iliac vein (end to side) Ureteric implantation with DJ stent insitu.	
Post KT graft + vessel doppler	9.8 x 5.4 cm, Normal	10.8 x 5.2 cm, Normal

Immunosuppression Protocol

	Case-1	Case – 2
PreTx weight	23 kg	27 kg
Prior to Vascular anastomosis : Inj Methyl-Prednisolone 500mg		
Induction Used	**Thymoglobulin (ATG)**	**Grafalon (ATLG)**
Total Dose	150 mg	150 mg
Day 0	75 mg	100 mg
Day 2	75 mg	-
Day 6		50 mg
Maintenance	Prednisolone 20 mg/d Tacrolimus 5 mg/day Mycophenolate sodium : 360 mg/d	Prednisolone 20 mg/d Tacrolimus 5 mg/day Mycophenolate sodium : 360mg/d

Case -1, Highlights (Post KT)

POD	Tac Level	Hb (g%)	WBC (u/L)	Platelet (x 10^6 u/L)	Creatinine	Albumin	UPCR	Steroid (mg/d)	Tacrolimus (mg/d)	MMF-S (mg/d)	Weight (kg)
0								500 MPS	2.5	360	23
1	1.[illegible]			[illegible]	2.11	2.62	1.31	400 (IV Hydrocortisone)	2.5	360	23
2					0.8			200 (IV Hydrocortisone)	3	360	24
3		7.7	6700	1.65	0.7	2.59		200 (IV Hydrocortisone)	3	360	**24**
4	1.[illegible]			[illegible]	0.8	2.35		100 (IV Hydrocortisone)	3	360	**26**
5					1.[illegible]	2.48	10.6	30 (PO Prednisolone)	3	360	**27**
6		6.8	8150	2.45	**1.23**	2.41	2.4	30 (PO Prednisolone)	5	360	27
7				[illegible]	0.94	2.45	1.6	30 (PO Prednisolone)	5	360	27
8					0.8	2.59	1.3	30 (PO Prednisolone)	5	360	27
9		11	22600	3.56	0.8	2.54	0.8	30 (PO Prednisolone)	5	360	26

POD-3

1 kg Weight gain

S.Creatinine : 0.7 mg%

POD-5

4 kg Weight gain

S.Creatinine : 1.1 mg%

UPCR : 10.6

POD-9

1 kg Weight lost

S.Creatinine : 0.8 mg%

UPCR : 0.8

Case -2, Highlights (Post KT)

POD	Tac Level	Hb (g%)	WBC	Platelet	Creatinine (mg%)	Albumin (g%)	UPCR	Steroid (mg/d)	Tacrolimus (mg/d)	MMF-S (mg)	Weight (Kg)
0					3.17	3.3	Anuria	500 MPS	3	360	27
1					1.26			400 (IV Hydrocortisone)	3	360	30
2		6.4	6360	84000	0.64			300 (IV Hydrocortisone)	4	360	30
3					0.69	2.8		200 (IV Hydrocortisone)	4	360	30
4					1.05		5.95	35 (PO Prednisolone)	4	360	32
5		7.2	3930	1.51	**1.62**			30 (PO Prednisolone)	5	360	32
6 (post Plex)					1.22	2.8		250 MPS	5	360	32
7					1.05			250 MPS	5	360	32
8			7410	1.37	0.71	2.8	0.9	250 MPS	5	360	33

POD-2

3 kg Weight gain

S.Creatinine : 0.64 mg%

POD-4-5

5 kg Weight gain

S. Creatinine : 1.05 – 1.62 mg%

UPCR : 5.95

POD-8

6 kg Weight gain

S.Creatinine : 0.72 mg%

UPCR : 0.9

Plasmapheresis Prescription

	Case 1	Case 2
Why FSGS/ recurrence suspected?	Anasarca + UPCR : 10.6	Rising Creatinine, UPCR : 5.95
1st week of KT,	3 Sessions POD-5,7,9	1 Session POD – 6
Prescription	**1 volume exchange** **Replacement : Inj H. Albumin 20% + Crystalloids**	
1st 3 months post KT	Remission	After Discharge : POD - 14 **Once a week x 7 sessions** **Once in 10 days x 4 sessions**

Follow-Up, Case – 1, Post KT

Sept 2018

- 3 PlEx sessions in 1st week
- Well for 2 years

Sept 2020

- Sr Creatinine 3.8 mg% & UPCR 1.16,
- Graft biopsy (crescentic GN),
- 5 sessions of plasmapheresis.
- Sr Creatinine 2 mg%, Dipstick U. Prot 1+

Nov 2020

- COVID-19 Pneumonia
- Immunosuppression modified
- Rising Creatinine + Anasarca : MHD initiated.

Follow-Up, Case – 2, Post KT

Jan 2021

- 1 PlEx in 1st week
- 1 PLEx on POD-14

Feb 2021

- Once a week x 7 sessions
- Once in 10 days x 4 sessions

May 2021

- Sr Creatinine – 2 mg%
- UPCR 1 mg/mg
- Lost to Follow-up

Discussion

Incidence

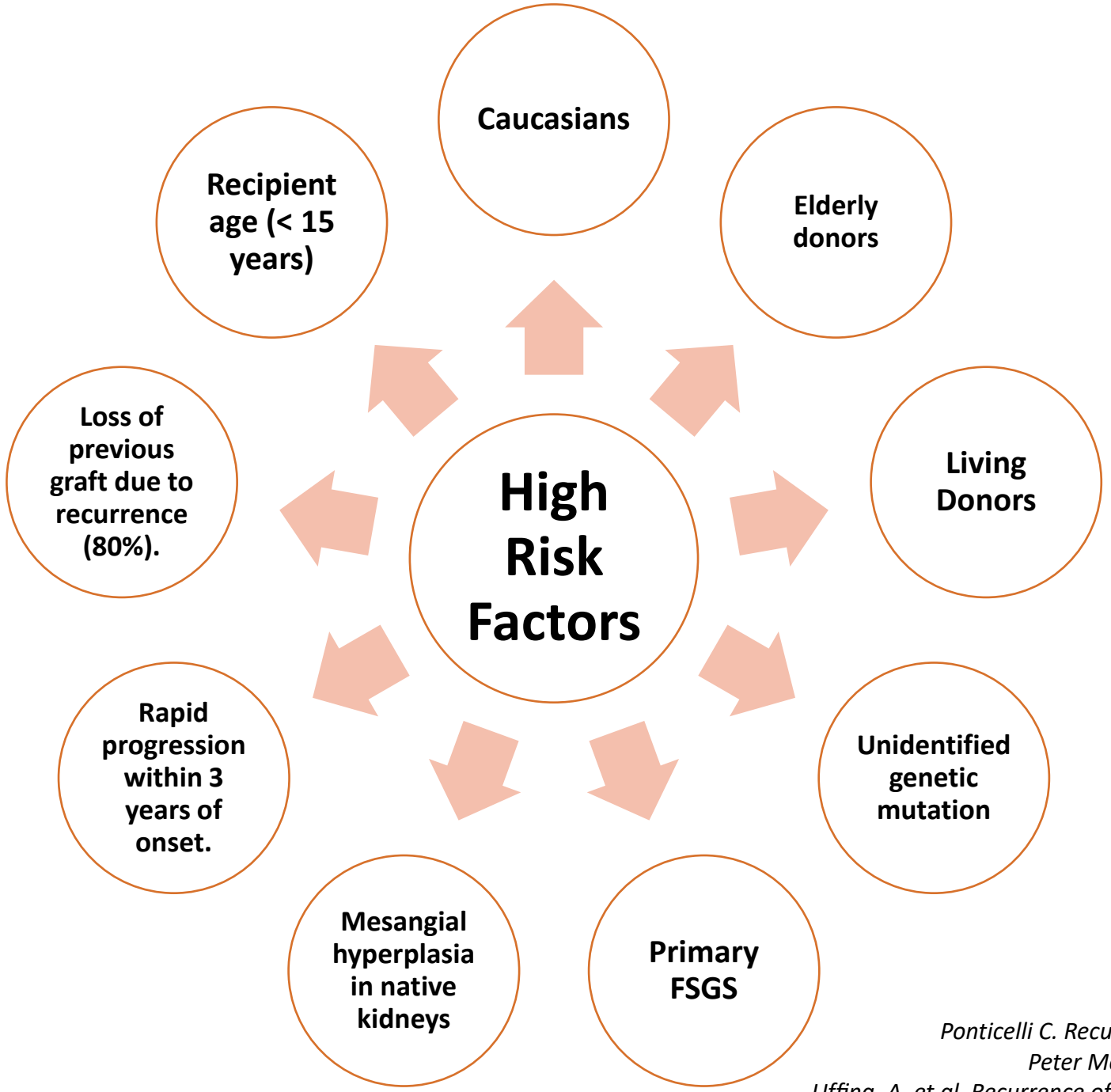
- Clinical Recurrence Rate : 20 – 30%
  - Adults : 10 – 15%
  - Children : 20 – 50%
- Graft loss in Recurrent FSGS : 40 – 50%

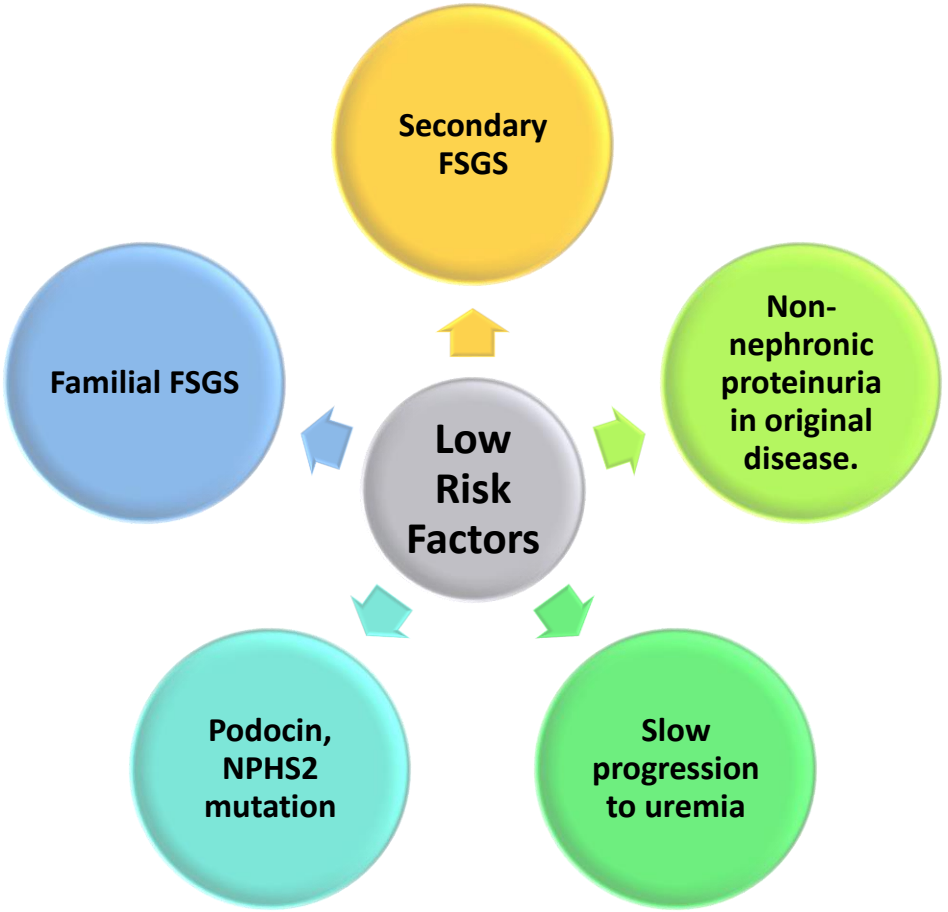
Senggutuvan P, et al. Recurrence of focal segmental glomerulosclerosis in transplanted kidneys: Analysis of incidence and risk factors in 59 allografts. Pediatr Nephrol. 1990;4:21–28.
Artero M, et al. Recurrent focal glomerulosclerosis: Natural history and response to therapy. Am J Med. 1992;92:375–383.
Fuentes GM, et al. Long term outcome of focal segmental glomerulosclerosis after pediatric renal transplantation. Pediatr Nephrol 2010; 25:529-34

When does, recurrence of FSGS after transplant (r-F-AT) occur ?

- Nephrotic-range proteinuria within hours after transplant (UPCR > 2mg/mg)
- 1st month of Transplantation, Median time : 6 – 14 days (13 days)
- FSGS that appears after 12 months after KT is not considered recurrent FSGS.

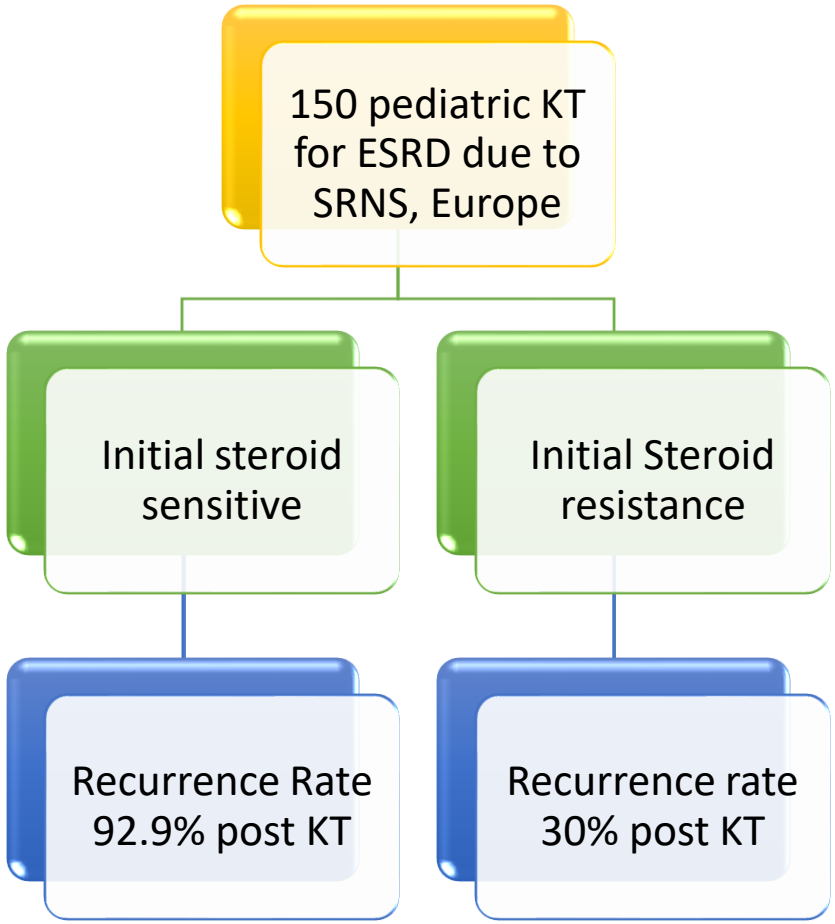
Feehally John, Comprehensive Clinical Nephrology, 6th Edition, Elsevier, 2019, 1240
Oxford Textbook of Clinical Nephrology, 4th Edition, Oxford University Press, 2016, 2503
Peter Morris, Kidney Transplantation Principles & Practice, 8th Edition, Elsevier, 2020, 639
Robert Schrier, Schrier's diseases of the kidney, 9th edition, Lippincott, 2013, 1494





Ponticelli C. Recurrence of FSGS after renal transplantation. Nephrol Dial Transplant (2010) 25:25-31.
Peter Morris, Kidney Transplantation Principles & Practice, 8th Edition, Elsevier, 2020, 639-40
Uffing, A. et al. Recurrence of FSGS after Kidney Transplantation in Adults. Clin. J. Am. Soc. Nephrol. 2020, 15, 247

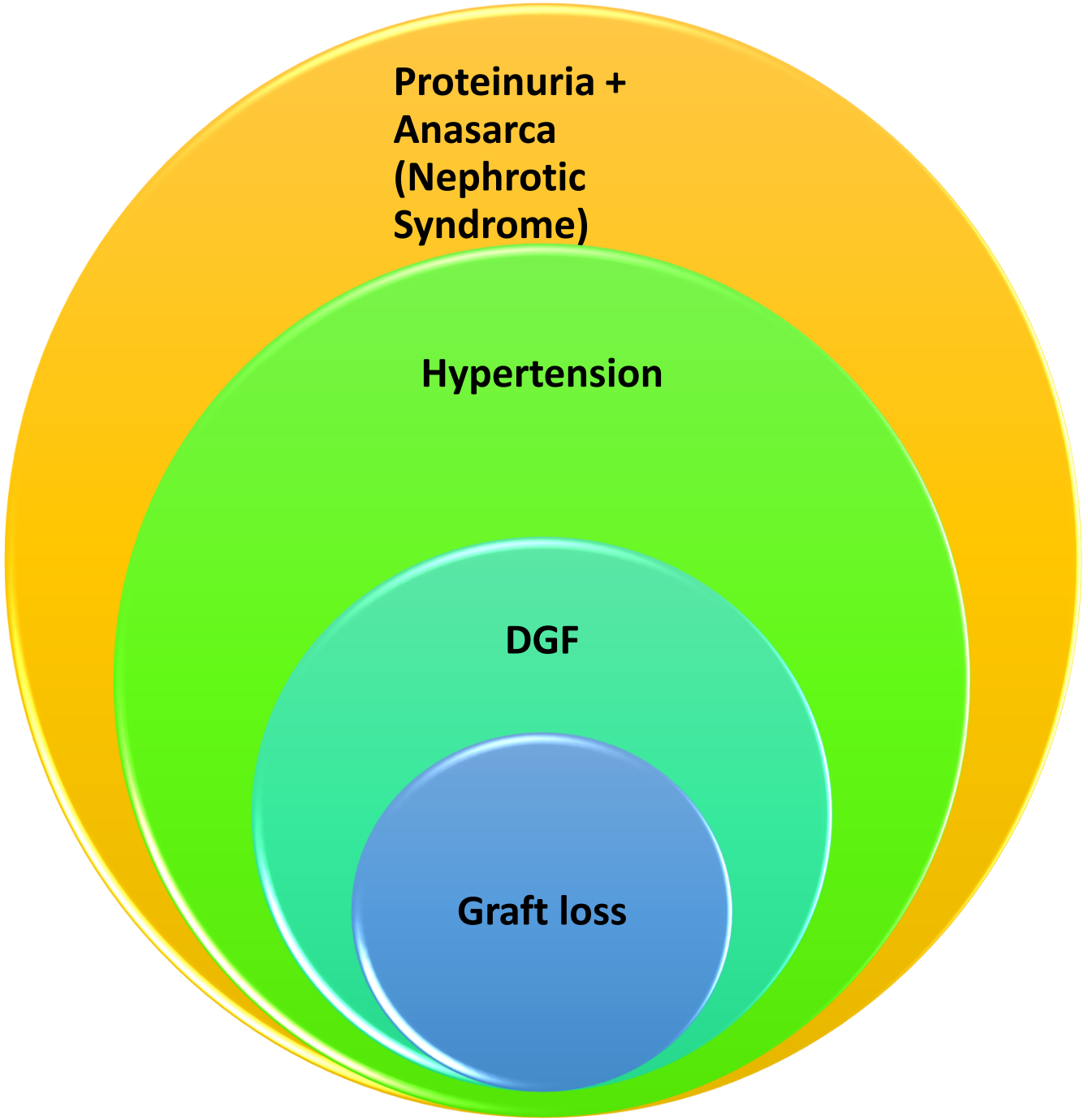
Native Steroid Responsiveness !!!



the incidence of recurrence after transplantation appears reduced in patients with steroid-resistant nephrotic syndrome (SRNS) due to monogenic disorders

Ding WY, et al. Initial steroid sensitivity in children with steroid-resistant nephrotic syndrome predicts post-transplant recurrence. J Am Soc Nephrol 2014; 25:1342-8

How does it Manifest ?



Pathogenesis of recurrence of FSGS, Post KT

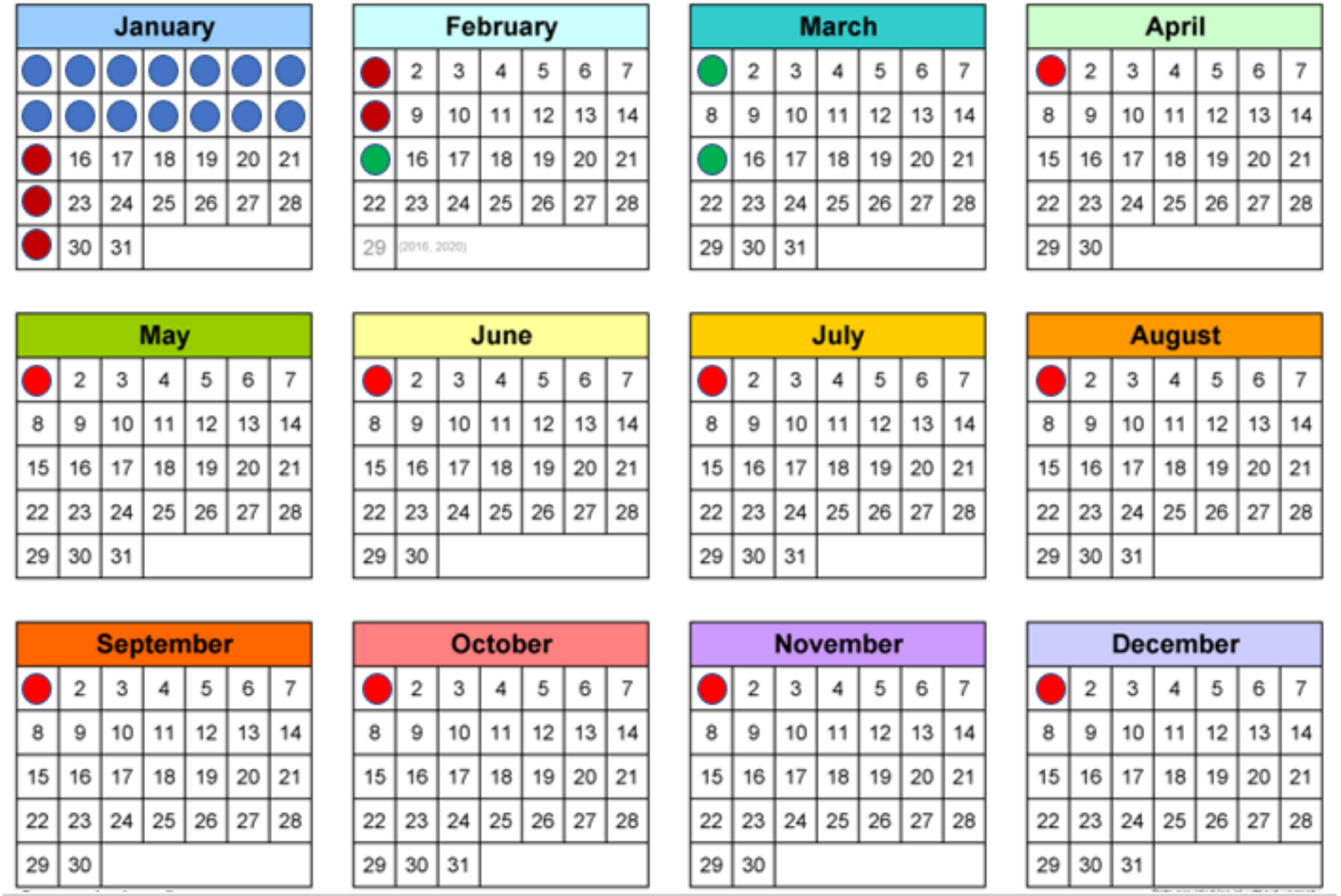
WHEN TO TEST?
PROGNOSTIC SIGNIFICANCE?

- FSGS Permeability factor (FPF)
- suPAR (blood/ urine)
- Panel of 7 antibodies (anti-CD-40)
- co-stimulatory protein B7-1 (CD-80)

Savin VJ, et al. Circulating factor in recurrent FSGS. N. Engl. J. Med, 1996; 334:878-883
Gallon L, et al. Resolution of recurrent FSGS after retransplantation. N Engl J Med. 2012;366(17):1648-49
Sharma M, et al. "The FSGS Factor:" enrichment and in vivo effect of activity from FSGS plasma. J Am Soc Nephrol, 1999; 10:552-561
Wei C, et al. Circulating Urokinase receptor as a cause of FSGS. Nat Med, 2011; 17:952-960
Winnicki, W, et al. Diagnostic & Prognostic value of suPAR in FSGS & Impact of detection method. Scientific reports. Natureresearch. 2019, 9:13783

Diagnosis : Monitoring UPCR

Daily
Weekly
Monthly

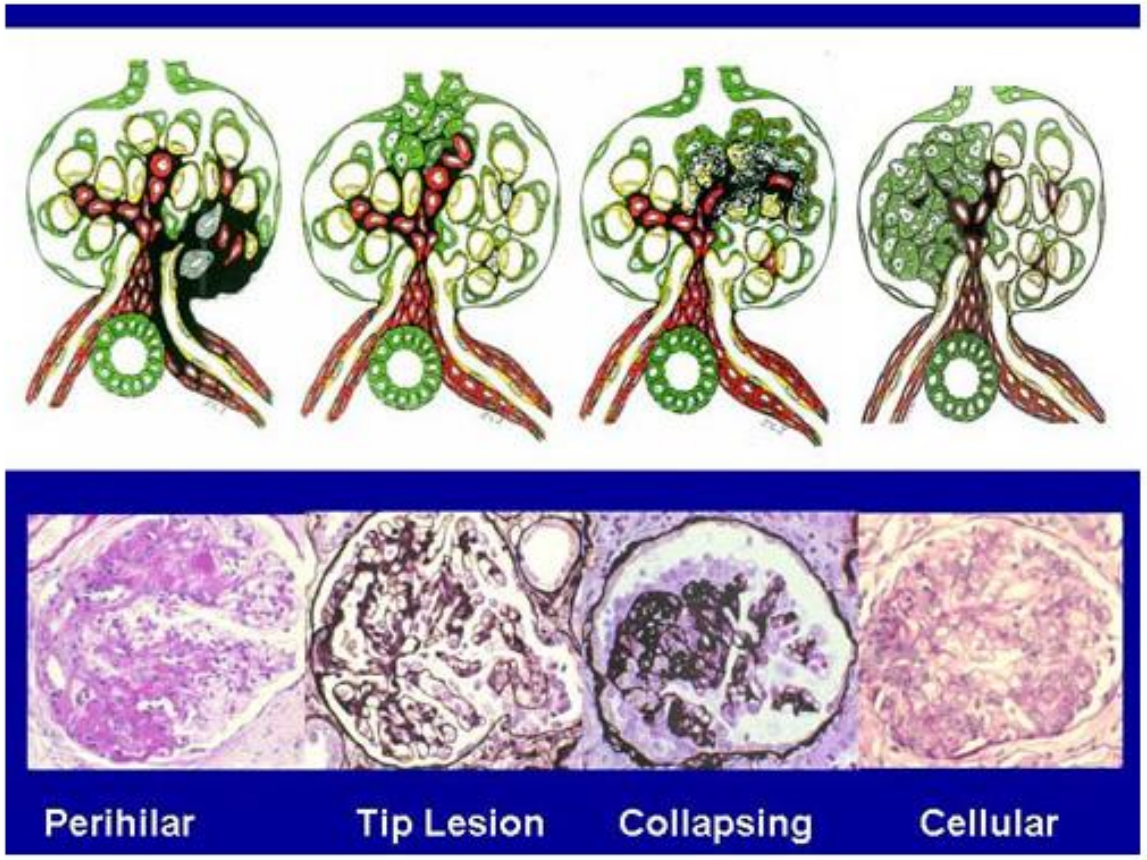


Uffing, A. et al. Recurrence of FSGS after Kidney Transplantation in Adults. Clin. J. Am. Soc. Nephrol. 2020, 15, 247
Ponticelli,C.Recurrence of focal segmental glomerularsclerosis (FSGS)after renal transplantation. Nephrol. Dial. Transplant. 2009, 25, 25–31

Biopsy Picture

Whether native kidney lesion recurs?
Prognosis based on histological type of recurrent FSGS?

	Early	Late
Light Microscopy	Normal	Segmental lesion with endocapillary proliferation & foam cell accumulation → glomerular sclerosis, interstitial fibrosis
Electron Microscopy	Effacement of podocyte foot process	



Daphne H.T. Ijpelaar, Fidelity and Evolution of Recurrent FSGS in Renal Allografts. J Am Soc Nephrol 19: 2219 –2224

Treatment Modalities

- Therapeutic plasmapheresis ± Rituximab
    - Perioperative preventive plasmapheresis
- Protein- A Immunoadsorption ± Rituximab
- Rituximab
- Ofatumumab (refractory to rituximab)
- Steroids
- ACE or ARBs
- High dose cyclosporine ± Plasmapheresis & or Steroids
- Cyclophosphamide (in pediatric patients – 4 trials)
- Abatacept
- ACTH

Kumar J, et al. Rituximab in post transplant pediatric recurrent FSGS. Pediatr Nephrol 2013; 28:333-8
Wang CS, et al. Ofatumumab for the treatment of childhood nephrotic syndrome. Pediatr Nephrol 2017; 32:835 – 41
Cochat, et al. Recurrent Nephrotic Syndrome after transplantation: early treatment with plasmapheresis & cyclophosphamide. Pediatr Nephrol, 1993; 7:50-54

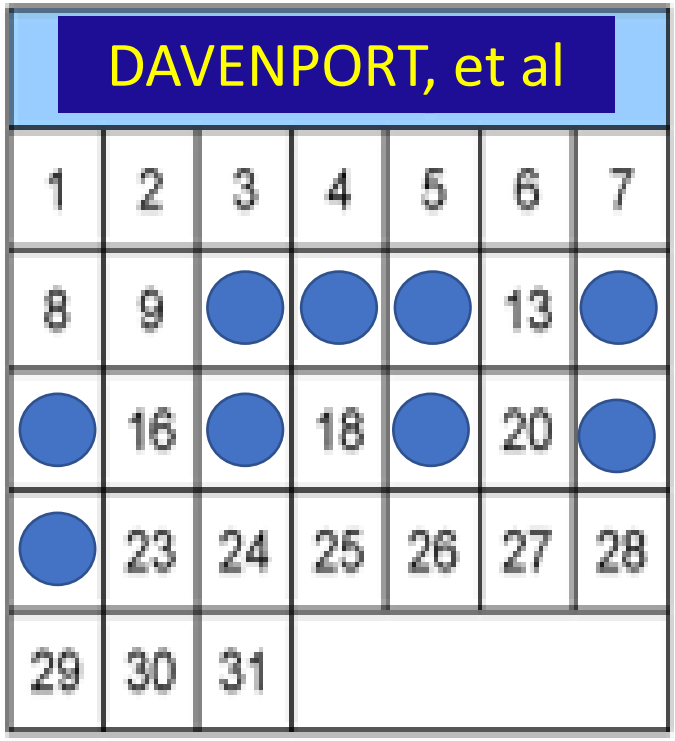
FSGS Protocol at Mattel Children's Hospital, UCLA

Identify High risk patient
LRDT (allow pretreatment & avoid ATN, so that CNI can be used)
ACEI/ARBs as tolerated

	Living Donor Graft Recipients	Deceased Donor Graft Recipients
PreTX PLEx :	10	
PostTx Plex :	3 (maybe extended)	10 PlEx (maybe extended)
CNI Used	Tacrolimus (BD/TID) (Trough level – 12- 15 ng/mL)	Cyclosporine (TID), (trough levels – 200 – 500 ng/mL)
PLEx	(1.5 volume with albumin, FFP (coagulopathic))	
Refractory to above ? Rituximab / Ofatumumab		

Gabriel Danovitch, Handbook of Kidney Transplantation, 6th edition, Lippincott Williams & Wilkins, 2017, 378.

Plasmapheresis Schedule



Davenport RD. Apheresis treatment of recurrent FSGS after kidney transplantation: re-analysis of published case reports and case series. J Clin Apheresis, 2001;16 : 175-178.
Vallianou, K.;et al. Therapeutic Options for Recurrence of Primary Focal Segmental Glomerulonephritis (FSGS) in the Renal Allograft: Single-Center Experience. J.Clin. Med. 2021,10, 373.
Bharati J, et al. Recurrent Focal Segmental Glomerulosclerosis after Kidney Transplant in Adults : A Report on Various Treatment Regimens. Indian J Transplant 2018; 12: 193-8.

Therapies for recurrent focal segmental glomerulosclerosis in adults: Comparison of various studies

Study	Patients	Remission (%)	Schedule and dosing
Plasmapheresis/PLEX			
Artero *et al.*[23]	6	50	Daily for 3 days, then 3 days/week (total of 9 sessions)
Ponticelli *et al.*[27]	3	100	Variable; 3 days/week × 2 weeks, then 2 days/week × 8 weeks, 2 days/month and continue based on response
Canaud *et al.*[28]*	10	100	3 days/week × 3 weeks, then 2 days/week × 3 weeks, then 1 day/week × 6 weeks, then 2 days/month × 8 weeks, then 1 day/month × 16 weeks
Deegens *et al.*[13]	13	85	18-58 sessions, daily × 3 days, then based on response
Hickson *et al.*[7]	8	75	Pre-Tx PLEX (days−5, −3, and−1): 3; Post-Tx PLEX (daily × 3-7 days, then 3 days/week × 4-12 weeks, then weekly/monthly/stop): 5
Present study	2	50	3 days/week × 2 weeks, then based on response
Plasmapheresis/PLEX + rituximab (combined)			
Rodríguez-Ferrero *et al.*[29]	3	0	RTX 375 mg/m^2 q week × 4 doses
Garrouste *et al.*[20]	19 (13^)	63.1 (50^)	RTX 375 mg/m^2 q week (1-4 doses)
Tsagalis *et al.*[30]	4	100	RTX 2 doses, 1 g 2 weeks apart after stable proteinuria with PLEX, repeat same after1 year
Yabu *et al.*[31]	4^	0	RTX 2 doses 1 g 2 weeks apart in 1 patient, 375 mg/m^2 weekly × 4 doses in 1 patient, 375 mg/m^2 weekly × 6 weeks in 2 patients
Present study	6	83.3	RTX (375 mg/m^2) single dose after 7-10 PLEX sessions
RAAS blockade			
Artero *et al.*[23]	9§	55.6	Captopril up to 150 mg/day, Enalapril up to 20 mg/day
Moroni *et al.*[17]	10#	40	Enalapril up to 40 mg/day
Freiberger *et al.*[24]	1	100	Ramipril 10 mg/day, Aliskiren 300 mg/day, candesartan 64 mg/day
Bansal *et al.*[25]	1	100	Telmisartan 120 mg/day
Present study	5	80	Telmisartan up to 80 mg/day, Ramipril up to 20 mg/day

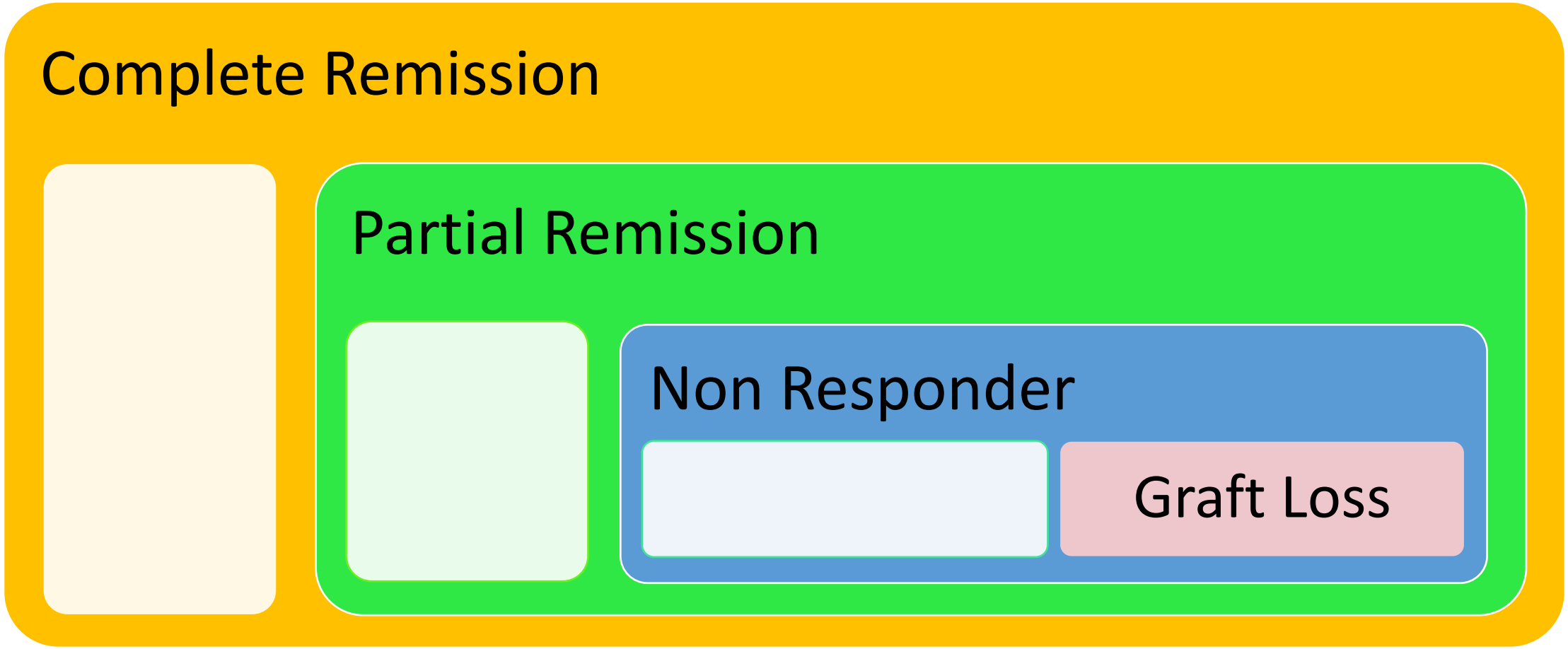
Bharati J, et al. Recurrent Focal Segmental Glomerulosclerosis after Kidney Transplant in Adults : A Report on Various Treatment Regimens. Indian J Transplant 2018; 12: 193-8

KDIGO Guidelines – April 2020

Level of Evidence	Guideline
1B : Recommend	**Not to exclude candidate with primary FSGS** from Kidney Transplantation. The risk of recurrence should be considered & discussed with candidate.
Not graded	**Loss of a prior graft due to recurrent FSGS** indicated a **high risk** of recurrence upon subsequent transplantation & this factor should be a major consideration in **determining candidacy**
2C : Suggest	**Genetic testing** (eg, podocin & nephrin gene mutations, among others) be performed in children & young adults with a clinical course consistent with genetic FSGS to **inform the risk of recurrence.**
2D : Suggest	**Avoid routine use of pre-transplant PLEx or Rituximab** to reduce the risk of recurrent FSGS.

KDIGO Clinical Practice Guideline on Evaluation & Management of Candidates for Kidney Transplantation, April 2020, Volume 104, Number 4S

Outcomes


Complete Remission
Partial Remission
Non Responder
Graft Loss

The role of plasma exchange in treating post-transplant focal segmental glomerulosclerosis: A systematic review and meta-analysis of 77 case-reports and case-series

Abdullah Kashgary[1,2,5], Jessica M. Sontrop[3,4,5], Lihua Li[4,5], Ahmed A. Al-Jaishi[4,5], Zainab N. Habibullah[1,5]

r-F-AT treated with Plasma-exchange, 1985 – 2012, 21 countries

678 citations, 77 [34 case reports (45) + 43 case series(378)]

423 patients with r-F-AT.

Median **TIME** to r-F-AT – 4 days, Median **AGE** at r-F-AT – 17 years

71 % of patients achieved full (Proteinuria <0.5g/d) or partial remission (Proteinuria 0.5 – 3.5 g/d) after treatment with plasma exchange

*Kashgary, A, et al. The role of plasma exchange in treating post-transplant focal segmental glomerulosclerosis : A systematic review & meta-analysis of 77 case reports & series. BMC Nephrol **2016**, 17, 104*

European Society of Pediatric Nephrology survey on current practice regarding recurrent focal segmental glomerulosclerosis after pediatric kidney transplantation

Antonia Bouts[1] | Floor Veltkamp[1] | Burkhard Tönshoff[2] | Marina Vivarelli[3] |

"20 Question" (Open & MCQs) Survey – ESPN members
20th Dec 2017 to 12th March 2018
(59/391) Nephrologists, 31 countries
807 FSGS Patients underwent KT
r-F-AT in 241 (30%)
Variation of current practice of treatment of FSGS & its recurrence post KT.

*Bouts, A et al, Members of the Working Group "Transplantation", Ïdiopathic Nephrotic Syndrome"of the European Society of Pediatric Nephrology. European Society of Pediatric Nephrology survey on current practice regarding recurrent focal segmental glomerulosclerosis after pediatric kidney transplantation. Pediatr Transplant. **2019**. 23:e13385*

Therapeutic Options for Recurrence of Primary Focal Segmental Glomerulonephritis (FSGS) in the Renal Allograft: Single-Center Experience

Kalliopi Vallianou *, Smaragdi Marinaki, Chrysanthi Skalioti, Sophia Lionaki, Maria Darema,

Retrospective Analysis, 1993 – 2019
Laiko General Hospital, Athens, Greece
26 out of 46 Patients with primary FSGS, had RECURRENCE (r-F-AT)
Use of PLEx (Prophylactic + in Recurrence), Immunoadsorption, Rituximab, Abatacept, ACTH (Tetracosactide)

Vallianou, K.;et al. Therapeutic Options for Recurrence of Primary Focal Segmental Glomerulonephritis (FSGS) in the Renal Allograft: Single-Center Experience. J.Clin. Med. ***2021****,10, 373.*

Recurrence of FSGS after Kidney Transplantation in Adults

Audrey Uffing,[1,2] Maria José Pérez-Sáez,[1,3] Marilda Mazzali,[4] Roberto C. Manfro,[5] Andrea Carla Bauer,[5]

Retrospective, TANGO Study, 15 KT centers, Jan 2005- Dec 2015
57 out 176 patients of idiopathic FSGS had recurrence (r-F-AT)
Plasmapheresis ± rituximab was associated with complete remission (21%), partial remission (36%), and no response (43%)

*Uffing, A. et al. Recurrence of FSGS after Kidney Transplantation in Adults. Clin. J. Am. Soc. Nephrol. **2020**, 15, 247*

Recurrence of Focal Segmental Glomerulosclerosis after Kidney Transplantation in Adults

CJASN
Clinical Journal of American Society of Nephrology

Post-Transplant Glomerular Disease Project (TANGO)

Observational Multicenter International

2005 to 2015

Kidney transplant recipients
n = 11,742

Risk Factors for recurrence

	Hazard Ratio
Old age	1.37 *per decade (1.09-1.56)*
White race	2.14 *(1.08-4.22)*
BMI	0.89 per Kg/m² *(0.83-0.95)*
Native kidney nephrectomy	2.76 *(1.16-6.57)*

Recurrence of FSGS

32% *(n = 57)* → 39% *(22 of 57)*

Recurrent FSGS

Graft loss
Median IQR: 5 years

Response to treatment of recurrent FSGS

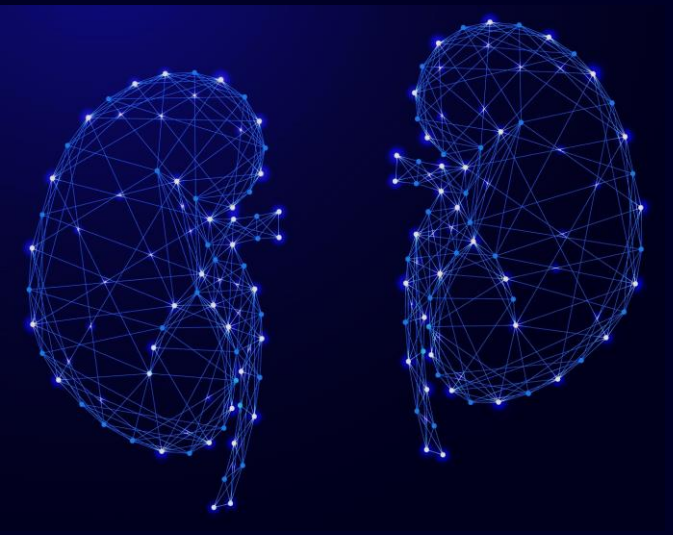
81% *(n = 61)*

Plasmapheresis ± Rituximab were the most frequent treatments

Complete Remission	Partial Remission	No Response
21% *(n = 13)*	36% *(n = 22)*	43% *(n = 26)*

Conclusions: Idiopathic FSGS recurs post-transplant in one-third of cases, increas by five-fold the risk of graft loss. Response to treatment significantly improves outcomes b achieved in only half of the cases.

Audrey Uffing, Maria José Pérez-Sáez, Marilda Mazzali, et al. ***Recurrence of Focal Segmental Glomerulosclerosis after Kidney Transplantation in Adults.*** CJASN doi: 10.2215/CJN.08970719. Visual Abstract by Edgar Lerma, MD, FACP, FASN



THANK-YOU