Reunion ampliada comitè de nefrología pediátrica

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Glomerulopatía por C3 y trasplante renal

Original Investigation

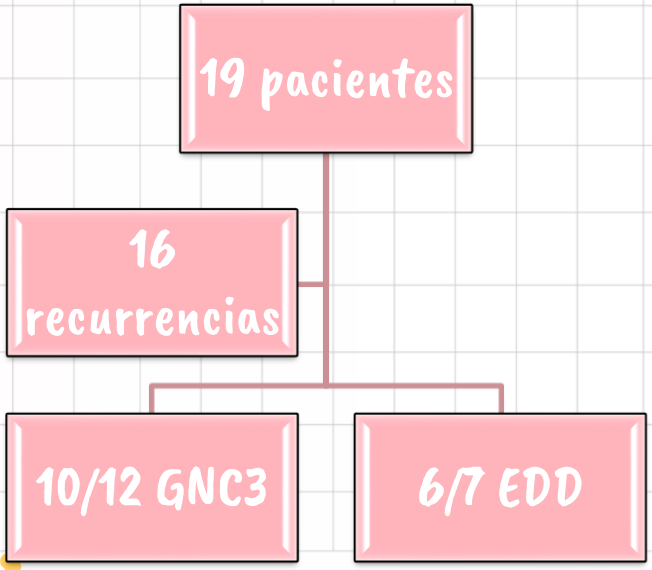
AJKD

Kidney Transplantation in C3 Glomerulopathy: A Case Series

Renu Regunathan-Shenk, Rupali S. Avasare, Wooin Ahn, Pietro A. Canetta, David J. Cohen, Gerald B. Appel, and Andrew S. Bomback

01 Método

19 pacientes con GC3 trasplantados desde 1999 – 2016 (12 GNC3 y 7 EDD) evaluados en el Centro de Enfermedades Glomerulares del Centro Médico de la Universidad de Columbia



- Seguimiento de 76 meses
- 14 recibieron Inmunosupresión previa

Table 1. Baseline Characteristics of C3G Patients Who Underwent Kidney Transplantation

ID	Sex	Age at Dx, y	Age at First Tx, y	Prior Immunosuppression	Tx Type	HLA Antigen Mismatch	Complement Abnormality or Genetic Mutation	Paraprotein Identified
C3GN1	M	12	21	Steroids, MMF, CNI, rituximab	LURT[a]	NA	*CD46* mutation	NT
C3GN2	M	18	23	Steroids, CYC, MMF, CNI	LRRT[a]	NA	NT	NT
C3GN3	M	12	28	Steroids, MMF, rituximab, eculizumab	LRRT	3 of 6	C3Nef	NT
C3GN4	M	36	39	None	LRRT[a]	NA	C3Nef	NT
C3GN5	M	35	41	Steroids, MMF	LURT	NA	NT	NT
C3GN6	F	18	19	None	LRRT	NA	NT	NT
C3GN7	F	26	28	Steroids	LRRT[a]	0 of 6	NT	NT
C3GN8	M	17	19	None	LRRT	NA	NT	NT
C3GN9	F	22	26	Steroids, CYC	DDRT	NA	None	NT
C3GN10	M	60	70	Steroids	DDRT	3 of 6	NT	IgGκ
C3GN11	M	22	23	Steroids, MMF, CNI	LRRT[a]	NA	C5Nef	No
C3GN12	M	33	38	None	LURT[a]	NA	NT	No
DDD1	F	43	47	Steroids	DDRT	0 of 6	Anti-CFH Ab, homozygous *CFHR5* deletion	IgGλ
DDD2	M	30	41	Steroids	LRRT	6 of 6	C3Nef	NT
DDD3	M	22	23	None	LRRT[a]	0 of 6	CFI deficiency, heterozygous *CFI* mutation	NT
DDD4	F	37	41	Steroids, CYC	LURT	2 of 6	C3Nef	IgGκ
DDD5	M	28	31	Eculizumab	LRRT[a]	3 of 6	NT	NT
DDD6	M	60	64	Steroids, CYC	DDRT	0 of 6	NT	No
DDD7	M	7	18	Steroids	LURT	NA	C3Nef	No

Abbreviations and definitions: Ab, antibody; C3G, C3 glomerulopathy, C3GN, C3 glomerulonephritis; C3Nef, C3 nephritic factor; C5Nef, C5 nephritic factor; *CD46*, the gene encoding membrane cofactor protein (MCP); CFH, complement factor H; CFI, complement factor I; CNI, calcineurin inhibitor; CYC, cyclophosphamide; DDD, dense deposit disease; DDRT, deceased donor renal transplant; Dx, diagnosis; LRRT, living related renal transplant; LURT, living unrelated renal transplant; MMF, mycophenolate mofetil, NA, data not available; NT, not tested; Tx, transplantation.
[a]Preemptive transplantation.

Pérdida del injerto

9/19 PACIENTES (6/7 EDD Y 3/12 GNC3)

47%

Table 2. Treatment of Recurrence and Occurence of Graft Failure

ID	Dx of Recurrence	Rituximab	Eculizumab	TPE	Other Therapy	Graft Failure
C3GN1	True	No	Yes	No	Steroids	No
C3GN2	True	No	No	No	No	No
C3GN3	No	No	No	No	No	No
C3GN4	Probable	No	No	No	Steroids, ACTH	Yes
C3GN5	True	No	No	No	Increased MMF	No
C3GN6	True	No	No	No	No	Yes
C3GN7	True	No	No	No	Increased MPA	No
C3GN8	True	No	No	No	No	No
C3GN9	True	No	No	No	No	No
C3GN10	Probable	No	Yes	Yes	Switched from tacrolimus to belatacept	No
C3GN11	True	No	Yes	No	No	Yes
C3GN12	No	No	No	No	No	No
DDD1	True	Yes	No	Yes	Steroids and oral CYC	Yes
DDD2	Probable	No	Yes	No	No	Yes
DDD3	Probable	No	Yes	Yes	No	Yes
DDD4[a]	True	Yes	Yes	Yes	No	Yes
DDD5	No	No	No	No	No	Yes
DDD6	True	No	No	No	No	No
DDD7[b]	True	No	No	No	No	Yes
DDD7[c]	Probable	Yes	Yes	No	CDX-1135	Yes
DDD7[d]	True	No	Yes	No	No	No

Abbreviations and definitions: ACTH, corticotropin; C3GN, C3 glomerulonephritis; CDX-1135, experimental complement blocker; CYC, cyclophosphamide; DDD, dense deposit disease; Dx, diagnosis; MMF, mycophenolate mofetil; MPA, mycophenolic acid; probable recurrence, light microscopy pattern of membranoproliferative glomerulonephritis/mesangioproliferative glomerulonephritis/thrombotic microangiopathy with C3-dominant or codominant staining with suspicion of complement-mediated disease and exclusion of other causes; TPE, therapeutic plasma exchange; true recurrence, meets consensus criteria for C3 glomerulopathy of light microscopy pattern of membranoproliferative glomerulonephritis/mesangioproliferative glomerulonephritis with C3-dominant staining.

[a]DDD4 first biopsy.
[b]DDD7 first allograft.
[c]DDD7 second allograft.
[d]DDD7 third allograft.

- **Rituximab**: 3/ 3 pérdida del injerto
- **Eculizumab**: 7/5 pérdida del injerto

A pesar de la triple terapia inmunosupresora, el aumento o cambio en la misma la recurrencia de esta enfermedad es frecuente.

medical sciences

MDPI

Article

Treatment of C3 Glomerulopathy in Adult Kidney Transplant Recipients: A Systematic Review

Maria L Gonzalez Suarez [1,2,*], Charat Thongprayoon [2,*], Panupong Hansrivijit [3], Karthik Kovvuru [4], Swetha R Kanduri [4], Narothama R Aeddula [5], Aleksandra I Pivovarova [1], Api Chewcharat [6], Tarun Bathini [7], Michael A Mao [8], Arpita Basu [9] and Wisit Cheungpasitporn [1,2,*]

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Objetivo

Evaluar la eficacia de diferentes tratamientos para la recurrencia de GC3 en pacientes trasplantados

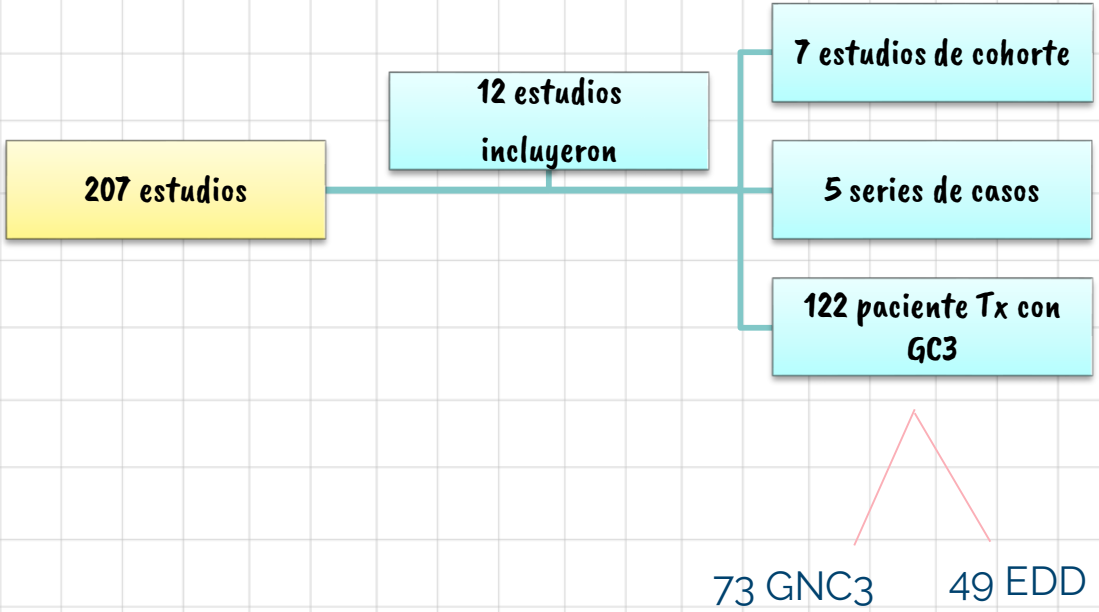


Table 1. Characteristics of the included studies in this systematic review of outcomes of KTx patients with C3GN.

C3GN among KTx Recipients														
Authors	**Type of Study**	**Patients (*n*)**	**Age at Time of Diagnosis/ Transplant, Median (Years)**	**Females (*n*)**	**Time to Dialysis or KTX, Median (Months)**	**Type of KTX**	**Complement Abnormality**	**Median Follow-Up (Months)**	**Median Time from KTx to Recurrence (Months)**	**Recurrence**	**Rituximab, Graft Failure (*n*)**	**Eculizumab, Graft Failure (*n*)**	**PLEX + Steroids, Graft Failure (*n*)**	**No Therapy for Recurrence, Graft Failure (*n*)**	**Graft Failure, Total (*n*)**
Regunathan-Shenk et al., 2019 [48]	Cohort	12	22	3	48	LRKTx, 7 LUKTx, 3 DDKTx, 2	CD46, 1 C3Nef, 2 C5Nef, 1 None, 1 Not done, 7	76	-	8, yes 2, probable2, no	0	3, 1 (1 treated with Eculizumab + PLEX)	1, 0	9, 2	3
Zand et al., 2014 [50]	Cohort	21	20.8	9	42.3	LKTx, 17 DDKTx, 4	-	73.9	28	14, yes 7, no	3, 2	0,0	1 + plus autologous peripheral stem cell transplant, 0 1 treated with steroids alone, 1	10, 0	7
Frangou et al., 2019 [71]	Cohort	17	46.7	4	-	LRKTx, 3 LUKTx, 3 DDKTx, 1	CFHR5, 17	157	37	3, yes 9, probable	0,0	0,0	2, 2	14, 3	5
Serra et al., 2018 [72]	Case series	3 (de novo)	66	1	-	DDKTx, 3	None, 2 Anti-CFH ab, 1	-	72	3 de novo	1, 1	0	0	2, 2	3
Wong et al., 2016 [73]	Case series	4 (familial)	26.5	2	-	DDKTx, 4	-	-	97	2, yes	0	0	0	2, 1	1
Alasfar et al., 2016 [74]	Cohort	5	37.4	3	-	DDKTx,1 LUKTx, 1	-	63.6	-	2, yes	0	1,0	0	1, 1	1
Jeantet et al., 2017 [75]	Cohort	9	-	-	-	-	-	-	1.5	9, yes	0	9, 2	0	0	2
Bomback et al., 2012 [32]	Case series	2	21	2	-	-	C3Nef, 2	-	2.5	2	-	2, 0 (1 treated with Eculizumab + PLEX, steroids)	1, 0	0	0

Abbreviations: KTX, kidney transplant; LKTx, living donor kidney transplant, LRKTx, living-related kidney transplant; LUKTx, living unrelated kidney transplant; DDKTx, deceased donor kidney transplant; PLEX, plasma exchange.

Tasa de pérdida del injerto

33% después del eculizumab

01

02

42% después de la Plasmaferesis

81% después del rituximab

03

04

De estos 122/66 pacientes no Recibieron tto por Fr estable con una pérdida del injerto del **40%** (GNC3 32% y 53% EDD)

Pediatr Nephrol (2017) 32:1023–1028
DOI 10.1007/s00467-017-3619-2

ORIGINAL ARTICLE

C3 glomerulopathy and eculizumab: a report on four paediatric cases

Célia Lebreton[1] · Justine Bacchetta[1,2] · Frédérique Dijoud[2,3] · Lucie Bessenay[4] · Véronique Fremeaux-Bacchi[5] · Anne Laure Sellier-Leclerc[1]

Received: 1 June 2016 / Revised: 18 November 2016 / Accepted: 6 December 2016 / Published online: 24 February 2017

Reporte de 4 casos

Casos 1,2,3

3 pacientes (9-12-13 años) recibieron eculizumab por GC3 de sus riñones nativos con mejoría de la proteinuria y de la función renal en los tres casos.

Caso 4

Paciente 17 años con Dx GC3, con pérdida de su primer trasplante.
Estudio Genético sin mutación y Factor nefrítico c3 -.
Recibe su 2do Tx renal con recurrencia a los 6 meses postx

- Recibió eculizumab durante 5 meses por reactivación viral, rechazo humoral y nefritis por BK --→ SE SUSPENDE
- 3 meses después se reintroduce tto con una franca mejoría de la proteinuria y de la función renal

Conclusion

El eculizumab se puede retirar tras la remisión completa y reincorporar en casos de recaídas

Successful Use of Plasma Exchange to Prevent Recurrence of C3 Glomerulonephritis after Kidney Transplantation: A Case Report

Pipeleers L.[1], Sennesael J.[1], Massart A.[2], Geers C.[3], Goodship T.[4], Stordeur P.[5], Wissing K.M.[1]
[1]Universitair Ziekenhuis Brussel, Department of Nephrology and Hypertension, Brussels, Belgium, [2]Erasme Hospital ULB, Department of Nephrology, Dialysis and Renal Transplantation, Brussels, Belgium, [3]Universitair Ziekenhuis Brussel, Department of Pathology, Brussels, Belgium, [4]Newcastle University, Institute of Human Genetics, Newcastle upon Tyne, United Kingdom, [5]Erasme Hospital ULB, Department of Immunology, Brussels, Belgium

Background: Complement-mediated glomerulonephritis relapses in about 80% of patients with a history of disease recurrence in a previous graft. There is so far no efficient treatment to prevent recurrence.
Methods: Case report on the use of intermittent plasma exchange to prevent recurrence of C3 glomerulonephritis (C3GN) in a second kidney transplant, after loss of a previous graft due to disease recurrence.
Results: Our 26 year-old patient was initially diagnosed with type 1 membranoproliferative glomerulonephritis with isolated C3 deposits. She developed end stage renal disease and received a first kidney transplant in 2007. The post-transplant course was complicated by an early graft loss due to biopsy proven recurrence of C3GN (after 9 months). Persistent activation of the alternative complement pathway (low C3, high C3d and normal C4) was noted before, during and after transplantation. Thus far no underlying pathogenic mechanism has been found despite extensive evaluation of the complement pathway. Because of specific anti-HLA antibodies against more than 85% of the donor panel the patient was admitted to the Eurotransplant Acceptable Mismatch program. A second kidney transplantation was performed in January 2011. We combined standard triple immunosuppression with plasma exchange (40mL/kg body weight per treatment) at decreasing frequency, with a maintenance schedule of 1 exchange every two weeks after the first month. One year after transplantation no rejection has occurred and the patient maintains good graft function (creatinine 1.3 mg/dL) without signs of complement activation, microscopic hematuria and proteinuria. A protocol biopsy 3 months after transplantation showed no signs of disease recurrence on immunofluorescence and electron microscopy.
Conclusion: Prophylactic plasma exchange might correct the underlying pathogenic mechanism in patients with C3 glomerulonephritis, thereby preventing uncontrolled complement activation and recurrence of disease after kidney transplantation. Plasma exchange could be a cost-effective and widely available alternative to the recently developed C5 inhibitor Eculizimab in this indication.

Supplement to Transplantation November 27, 2012, Volume 94 Number 10S

Reporte de caso sobre el uso de plasmaféresis intermitente para prevenir la recurrencia de GNC3 en un segundo trasplante renal.

Pacte de 26 años en su segundo trasplante, recibe una combinación esquema inmunosupresor estándar + plasmaferesis (2 recambios semanales a partir del primer mes) para prevenir la recurrencia

Un año después del trasplante el paciente mantiene una buena función del injerto, sin signos de activación del complemento, hematuria microscópica y proteinuria

Las normas KDIGO recomiendan

1. No excluir candidatos con MPGN del trasplante renal; sin embargo, el riesgo de recurrencia debe ser considerado y discutido con el candidato (1B)

2. Recomiendan investigar una causa infecciosa, autoinmune o mediada por paraproteínas antes del trasplante para guiar el tratamiento e informar el riesgo de recurrencia (1C)

3. Sugieren tratar la causa de MPGN antes del trasplante, incluida la EDD y GNC3 (2C).

4. Sugieren que los candidatos con C3G se evalúen en busca de causas genéticas o adquiridas para la desregulación de la vía alternativa del complemento para guiar el tratamiento e informar el riesgo de recurrencia (2C)

Qué hacemos...

Cuadro situación

Original Investigation

AJKD

Kidney Transplantation in C3 Glomerulopathy: A Case Series

Renu Regunathan-Shenk, Rupali S. Avasare, Wooin Ahn, Pietro A. Canetta, David J. Cohen, Gerald B. Appel, and Andrew S. Bomback

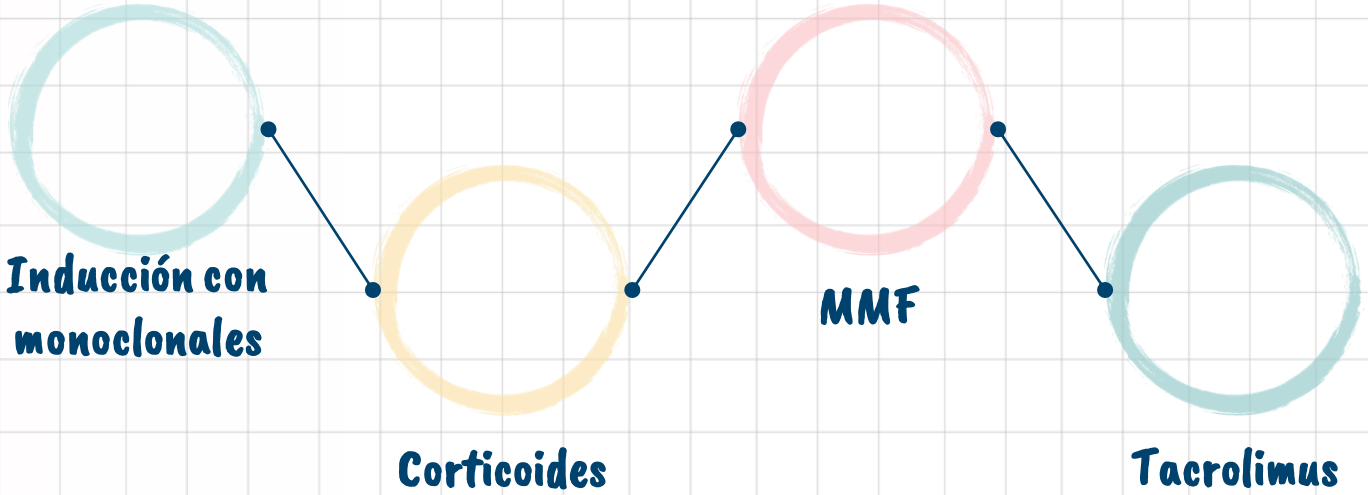
Rationale & Objective: C3 glomerulopathy (C3G), a form of glomerulonephritis associated with dysregulation of the alternative complement pathway, occurs either as dense deposit disease (DDD) or C3 glomerulonephritis (C3GN). Few

in patients with DDD (6 of 7) than in patients with C3GN (3 of 12), occurred at a median time of 42 months posttransplantation, and was attributed to recurrent disease in half the failures. A rare genetic variant or autoantibody

Complete author and article information provided before references.

Correspondence to R. Regunathan-Shenk (rshenk@mfa.gwu.edu)

Esquema de inmunusupresión



En resumen...

01

Todos los trabajos reportados utilizaron eculizumab ante la recurrencia

02

No hay nada escrito sobre su uso preventivo

03

Nuestro planteo es No utilizar eculizumab de forma preventiva y estar atento a la recurrencia y asi iniciar tratamiento

04

Como sospechar la recurrencia

- Monitero de la funcion renal
- proteinuria
- Dosaje de C3
- Bx renal

preguntas

1. Alguno utilizaria timoglobulina ?
2. Otra sugerencia respecto a la inmunosupresión?
3. Utilizarían plasmaferesis de forma preventiva para evitar la recurrencia?

Factores de riesgo de recurrencia

Abstract# A41

Biological Markers to Predict Recurrence of C3 Glomerulopathies After Renal Transplantation. M. Le Quintrec,[1,2] M. Rabant,[3] M. Marinozzi,[2] M. Buchler,[4] C. Mousson,[5] F. Bridoux,[6] C. Legendre,[7] M. Delahousse,[1] V. Fremeaux-Bacchi.[8,2] *[1]Nephrology and Renal Transplanttaion, Foch Hospital, Suresnes, France; [2]UMRS 872, Cordeliers Center Research, Paris, France; [3]Anatomopathologie, Necker Hospital, Paris; [4]Nephrology and Renal Transplantation, Hopital Bretonneau, Tours, France; [5]Nephrology and Renal Transplantation, CHU, Dijon, France; [6]Nephrology and Renal Transplantation, CHU, Poitiers, France; [7]Renal Transplantation, Necker Hospital, Paris, France; [8]Immunology Laboratory, HEGP, Paris, France.*

C3 glomerulopathies (C3G) (Dense Deposits Disease (DDD) and glomerulonephritis with isolated C3 deposits (GNC3)) and MPGN type I are complement-mediated diseases. After renal transplantation, recurrence is common and responsible for graft loss.

Aim: Identify risk factors for recurrence and graft outcome in particular the role of alternative pathway consumption and complement deposits (C3d, C5b9) in graft.

Methods: Patients with MPGN type I or C3G on native kidney with renal transplantation were selected from 8 Transplant Units. All patients had complement investigations (C3 and sC5b9 plasma levels, C3 Nef and genetic screening) and C5b9 and C3d staining on biopsies. Clinical recurrence was defined by proteinuria (>1g/g), renal failure (creatinine >30% of baseline), positive C3 deposits and absence of other nephropathy on graft biopsy.

Results: Fifty seven patients were selected, with DDD (n=16), MPGN type I (n=21) or GNC3 (n=20). Mean age at diagnosis, ESRF, and renal transplantation was 23, 30 and 38 years old. Graft survival was significantly lower in patients with clinical recurrence than in those without recurrence (p=0.05). MPGN type I recurred more frequently than DDD (HR: 3.19 (1.39-7.30), p=0.0069. After renal transplantation, low plasmatic C3 and high soluble C5b9 are associated with the higher recurrence risk compared normal plasmatic C3 (HR= 3.20, p=0.031) and normal sC5b9 (HR 11.54, p=0.0001). Positif C3Nef was not associated with recurrence risk (p=0.6). C5b9 staining was positive in 76% patients with clinical recurrence (n=13/17) and in all who lost their graft du to recurrence (n=7).

Conclusion: Persisting uncontrolled pathways activation (low C3 and sC5b9) and C5b9 staining in C3G/MPGN type I after RT are predict markers for severe recurrence.

C3 bajo
C5b9 aumentado

Después de Tx renal

La recurrencia se definio

Proteinuria > 1gr
Alteración de la función renal (aumento de la Cr >30% de su valor basal)
Depósitos de C3 y C5b9 en la BR en ausencia de otra nefropatía


HOSPITAL INTERZONAL DE AGUDOS ESPECIALIZ
PEDIATRIA " SOR MARIA LUDOVIC

Gracias!