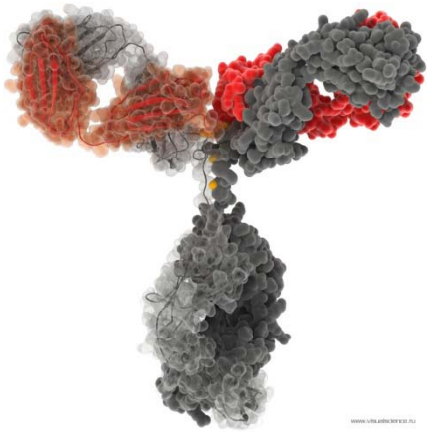


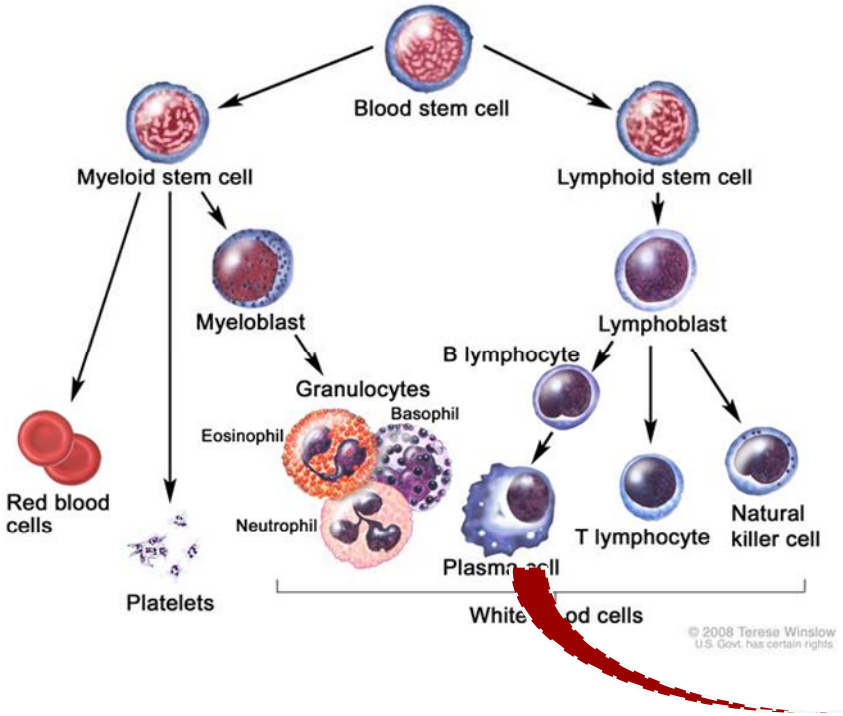
Aspectos clínicos y terapéuticos de las Gammapatías monoclonales

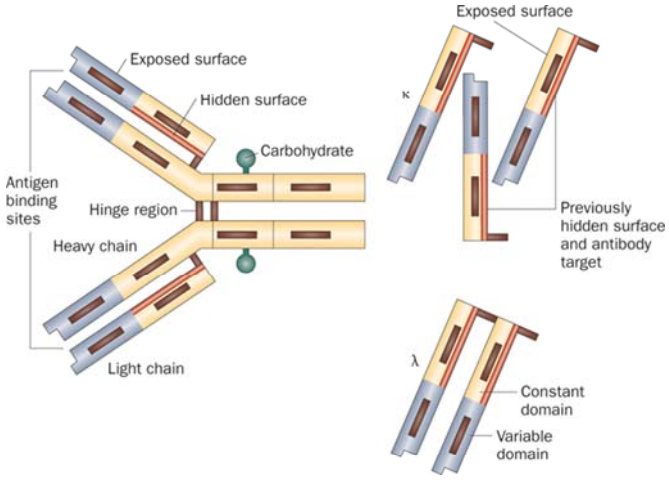
Miguel Perdiguero Gil
Nefrólogo Clínico
Hospital General y Universitario de Alicante.

Definición

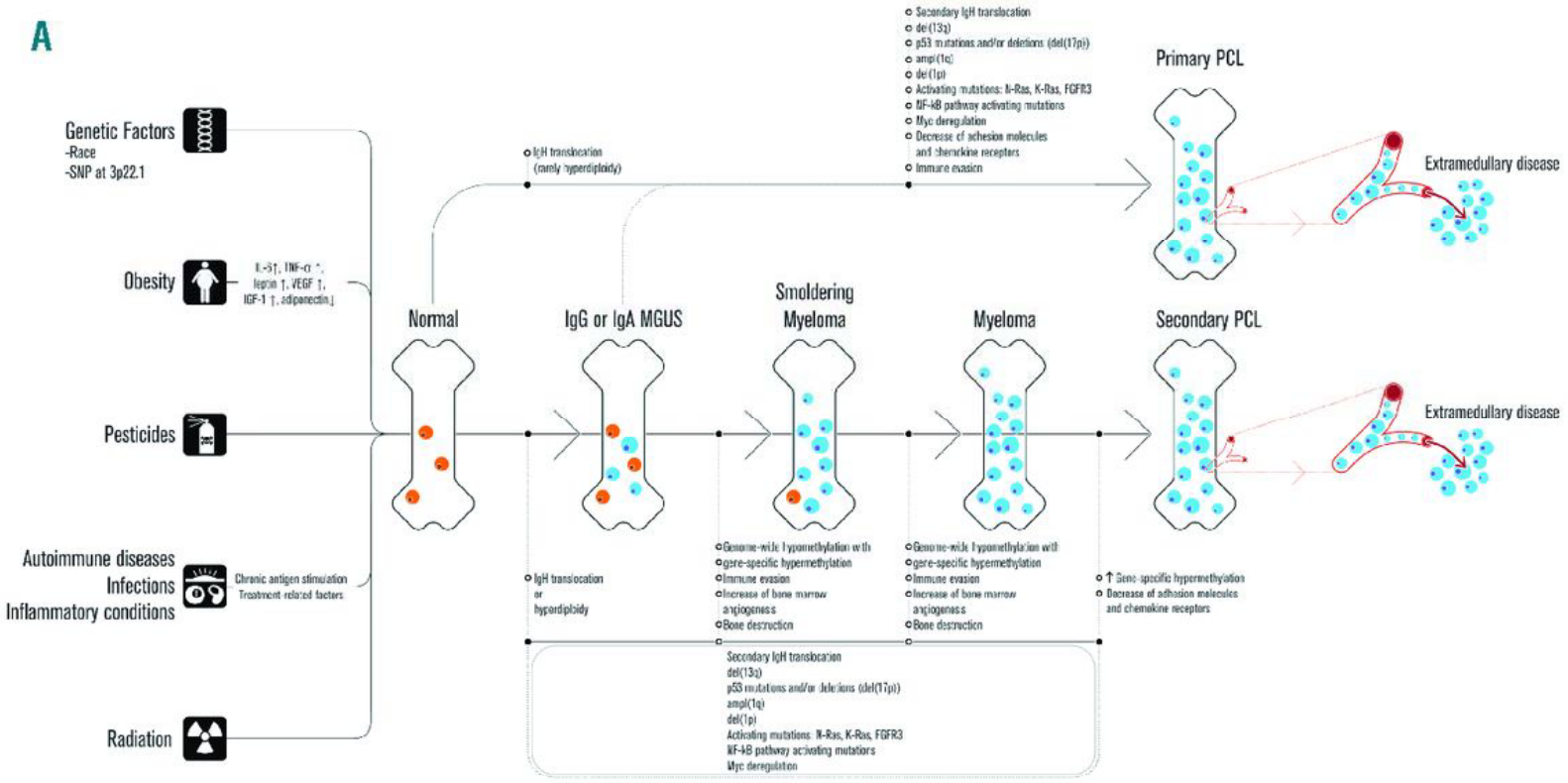
Paraproteinemia = Gammapatía monoclonal = Proteinemia monoclonal =**Discrasias células plasmáticas**…

-Grupo de enfermedades que se caracterizan por proliferación de un clon de células plasmáticas , que producen una *inmunoglobulina monoclonal* (completa o fracción).





Model for the mechanisms that contribute to the development and progression of MGUS. Obesity, exposure to pesticides, radiation exposure, and personal history of autoimmune diseases, inflammatory conditions and infections are associated with an increased ri...



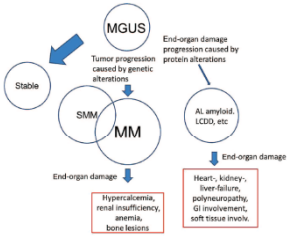
Niels W.C.J. van de Donk et al. Haematologica 2014;99:984-996

haematologica
the hematology journal

Differential diagnosis of monoclonal gammopathy of undetermined significance

Giampaolo Merlini[1,2] *and Giovanni Palladini*[1,2]

[1]*Amyloidosis Research and Treatment Center, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy; and* [2]*Department of Molecular Medicine, University of Pavia, Pavia, Italy*



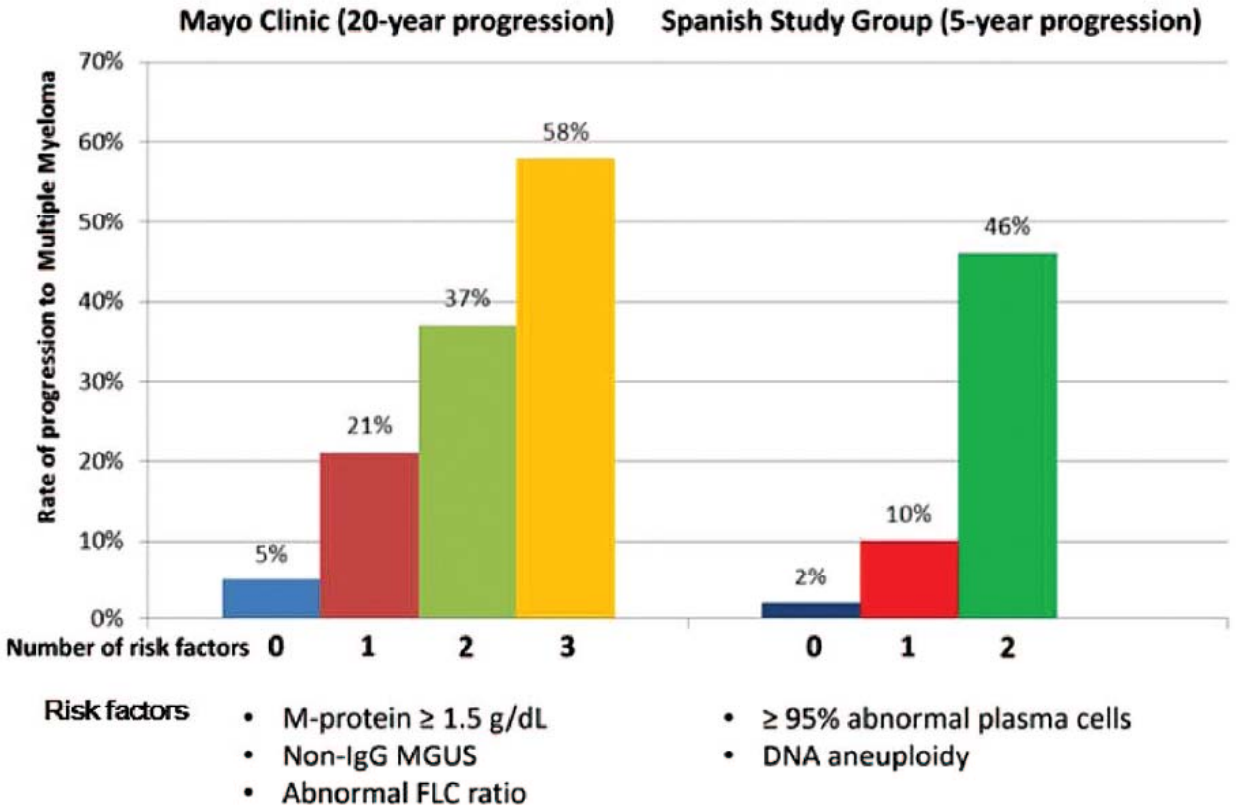
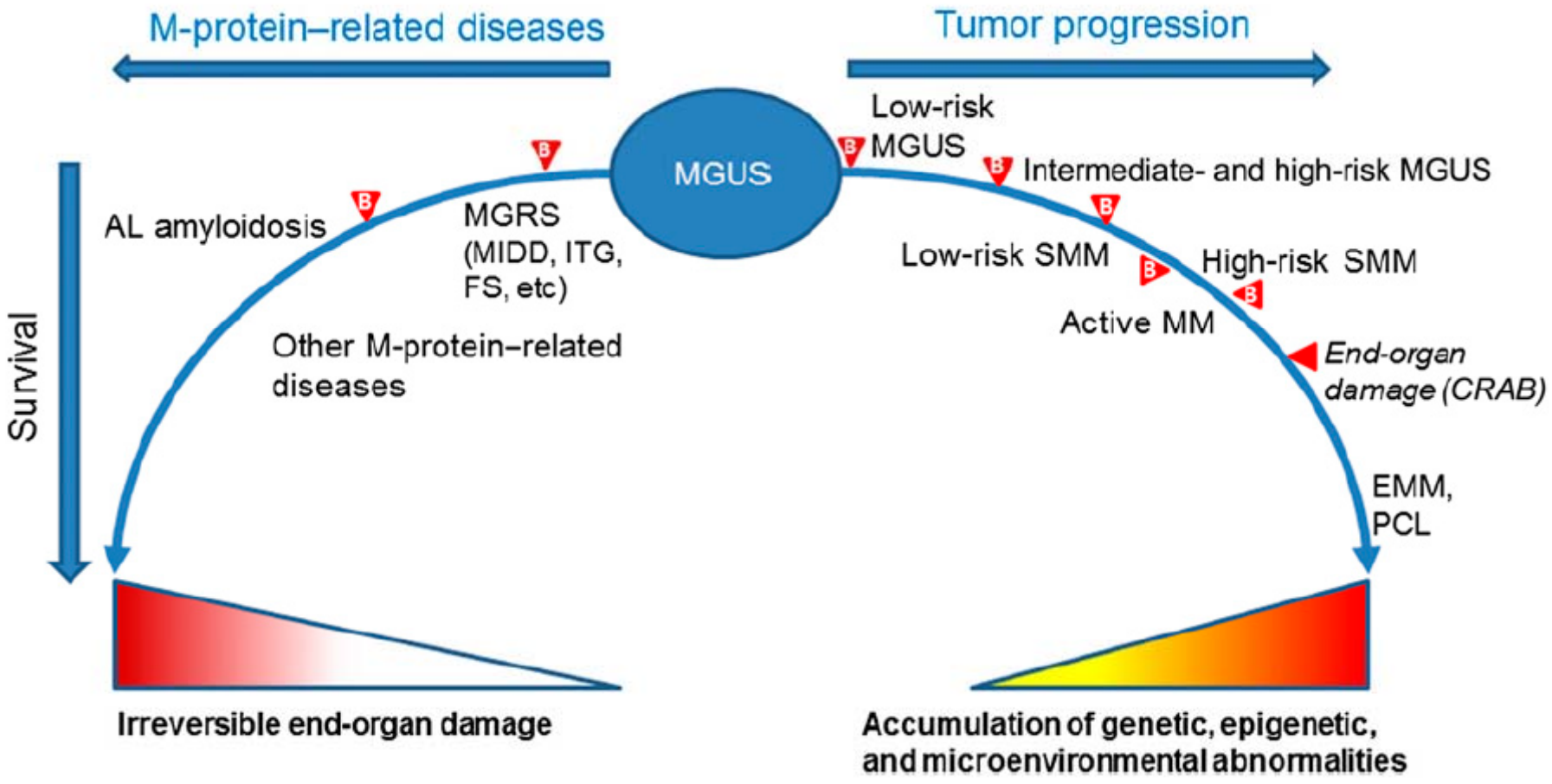


Figure 2. Risk-stratification schemes for MGUS according to the 2 major models. In the Mayo Clinic model, the following features are considered to be adverse risk factors: M-protein concentration ≥ 1.5 g/dL, non-IgG isotype, and an abnormal serum FLC ratio (normal reference, 0.26-1.65). Patients with 0, 1, 2, or 3 risk factors are considered low-, low-intermediate, high-intermediate, and high-risk, respectively. The Spanish model uses multiparametric flow cytometry of BM aspirates to differentiate aberrant from normal PCs. PCs characteristically express CD138 and intense (bright) CD38. The features of aPCs include decreased CD38 expression, expression of CD56, and the absence of CD19 and/or CD45. Risk factors for progression are ≥ 95% aPCs/BMPC and DNA aneuploidy.

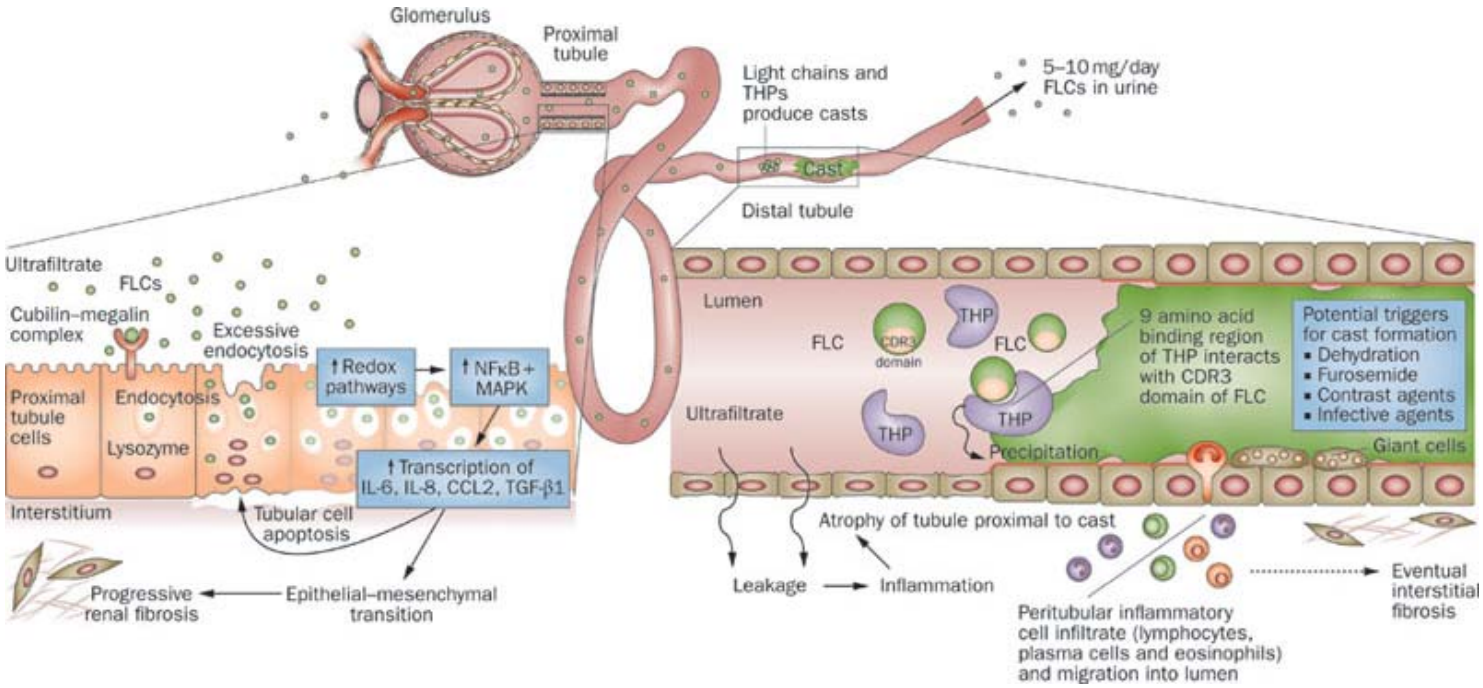
Determining the significance of MGUS

Giampaolo Merlini[1,2] [1]FONDAZIONE ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO POLICLINICO SAN MATTEO; [2]UNIVERSITY OF PAVIA



BLOOD, 16 JANUARY 2014 • VOLUME 123, NUMBER 3

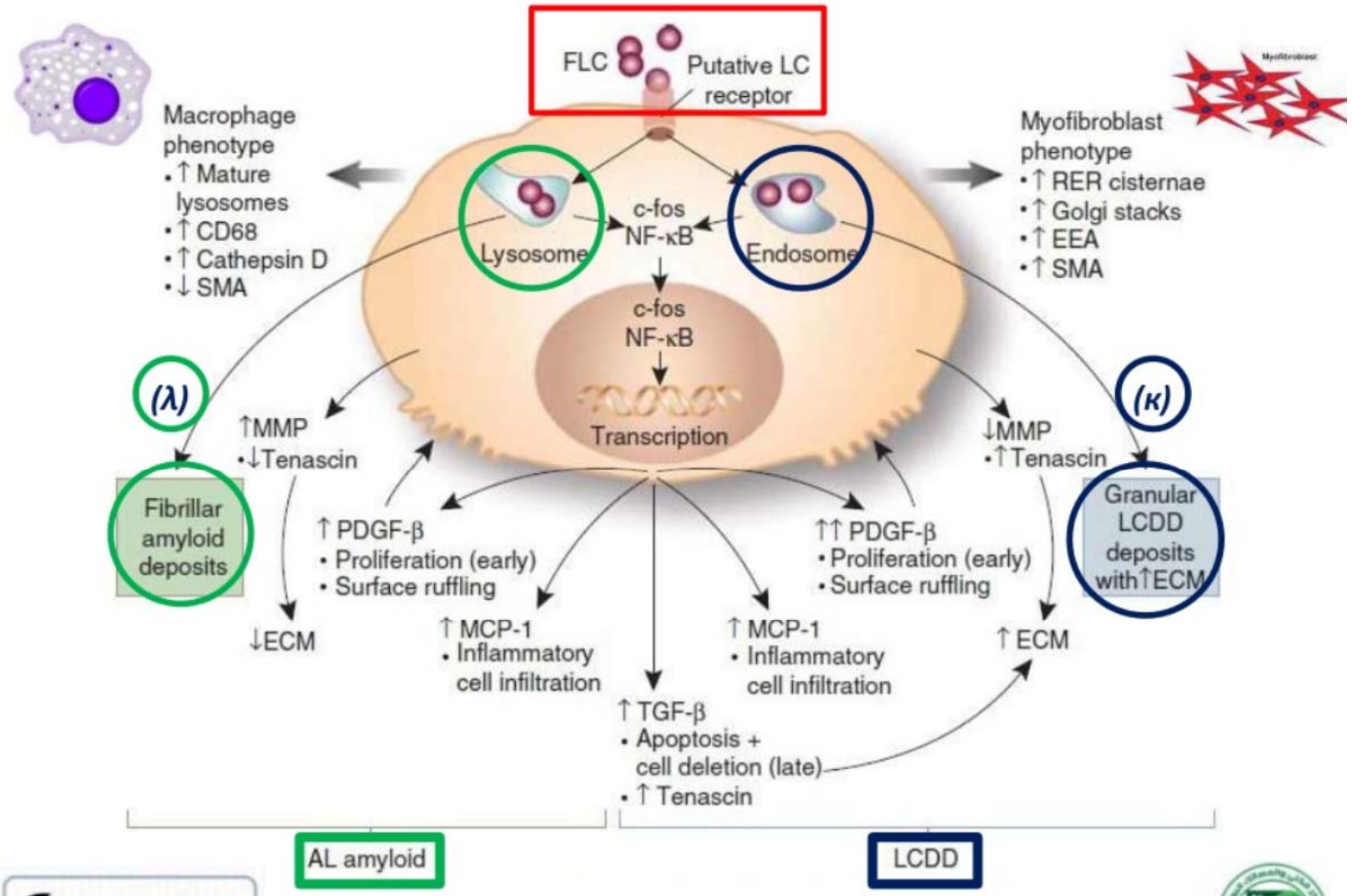
Figure 1 Mechanisms of FLC-induced acute kidney injury



Hutchison, C. A. *et al.* (2011) The pathogenesis and diagnosis of acute kidney injury in multiple myeloma
Nat. Rev. Nephrol. doi:10.1038/nrneph.2011.168

nature REVIEWS NEPHROLOGY

Interactions of FLCs with mesangial cells (MCs): AL amyloidosis (left) and light chain deposition disease (LCDD; right).



Kolitha Basnayake et al. Kidney Int (2011) 79, 1289–1301

Myeloma-related Kidney Disease

Nelson Leung and Samih H. Nasr

Table 2. Kidney Diseases of Multiple Myeloma

Common
Myeloma cast nephropathy
Acute tubular necrosis
AL amyloidosis
MIDD
Less common
LC Fanconi syndrome/proximal tubulopathy
PGNMID/MPGN with monoclonal deposits
Cryoglobulinemic glomerulonephritis
Immunotactoid glomerulonephritis
Fibrillary glomerulosclerosis
Rare
Plasma cell infiltration
Extramedullary hematopoiesis
Cryocrystaloglobulinemic glomerulonephritis
Membranous nephropathy
C3 nephropathy
IgA nephropathy
Anti-GBM disease

Advances in Chronic Kidney Disease, Vol 21, No 1 (January), 2014: pp 36-47

Clinicopathologic Correlations in Multiple Myeloma: A Case Series of 190 Patients With Kidney Biopsies

Samih H. Nasr, MD,[1] Anthony M. Valeri, MD,[2] Sanjeev Sethi, MD, PhD,[1] Mary E. Fidler, MD,[1] Lynn D. Cornell, MD,[1] Morie A. Gertz, MD,[3] Martha Lacy, MD,[3] Angela Dispenzieri, MD,[3] S. Vincent Rajkumar, MD,[3] Robert A. Kyle, MD,[3] and Nelson Leung, MD[3,4]

Table 3. Renal Characteristics at Kidney Biopsy

Characteristic	All Study Patients	Pure MCN	Pure Amyloid	Pure MIDD	*P* 3-Way Comparison	*P* MCN vs Amyloid	*P* MCN vs MIDD	*P* Amyloid vs MIDD
No. of patients	190	54	35	32				
Time from kidney disease onset to biopsy (wk)	3.0 (1.0; 12.0)	2.0 (1.0; 3.0)	12.0 (3.8; 41)	4 (1.0; 8.8)	<0.001[a]	<0.001[a]	0.01[a]	0.009[a]
24-h urine protein (g)	2.5 (1.3; 4.8)	2.3 (1.3; 4.1)	4.8 (2.7; 10)	2.8 (1.3; 5.1)	0.006[a]	0.002[a]	0.8	0.02[a]
24-h urine protein category								
<1 g	31/178 (17)	5/46 (11)	3 (9)	5/31 (16)	0.7			
1-3 g	72/178 (40)	25/46 (54)	7 (20)	13/31 (42)	0.006[a]			
≥3 g	75/178 (42)	16/46 (35)	25 (71)	13/31 (42)	0.004[a]			
Serum albumin (g/dL)	3.5 (3.0; 4.0)	3.6 (3.2; 4.0)	3.0 (2.4; 3.5)	3.5 (3.1; 4.0)	<0.001[a]	<0.001[a]	0.7	0.002[a]
Nephrotic syndrome	27 (14)	0 (0)	19 (54)	5 (16)	<0.001[a]	<0.001[a]	0.006[a]	0.002[a]
Percentage of urine protein that is albumin[b]	30.5 (8.0; 59)	6.0 (4.0; 11.0)	63.0 (57.5; 73.0)	53.0 (37.0; 64.0)	<0.001[a]	<0.001[a]	<0.001[a]	0.002
Urine protein composition category[b]								
>25% albumin	87/169 (51)	2/43 (5)	30/33 (91)	21/28 (75)	<0.001[a]	<0.001[a]	<0.001[a]	0.2
>50% albumin	62/169 (37)	0/43 (0)	28/33 (85)	14/28 (50)	<0.001[a]	<0.001[a]	<0.001[a]	0.005[a]
Microscopic hematuria	64/186 (34)	12/51 (24)	10/35 (29)	19/32 (59)	0.003[a]	0.6	0.002[a]	0.01[a]
Leukocyturia	49/185 (26)	11/51 (22)	5 (14)	8 (25)	0.6			
Serum creatinine (mg/dL)	3.2 (1.7; 5.5)	5.4 (3.8; 7.8)	1.3 (1.0; 2.0)	3.1 (2.0; 5.1)	<0.001[a]	<0.001[a]	<0.001[a]	<0.001[a]
Estimated GFR	18 (10; 38)	10 (7; 15)	50 (34; 66)	20 (11; 29)	<0.001[a]			
Requiring hemodialysis	38 (20)	20 (37)	3 (9)	7 (22)	0.008[a]	0.003[a]	0.2	0.18
Percentage glomeruli that are globally sclerotic	13 (0; 25)	10 (0; 25)	13 (5.2; 21.0)	14 (0.8; 38.3)	0.3			
Tubular atrophy/interstitial fibrosis score[c]	1.47 (1; 2)	1.31 (1; 2)	1.26 (1; 1)	1.91 (1; 3)	0.002[a]	0.5	0.003[a]	0.002[a]
Arteriosclerosis score[c]	1.28 (1; 2)	1.13 (0; 2)	1.31 (1; 2)	1.38 (1; 2)	0.4			

Note: Unless otherwise indicated, categorical values given as number (percentage); continuous variable as median (25th; 75th percentile) or mean (25th; 75th percentile).

Abbreviations: GFR, glomerular filtration rate; MCN, myeloma cast nephropathy; MIDD, monoclonal immunoglobulin deposition disease.

[a] $P < 0.05$.

[b] By urine protein electrophoresis.

[c] Mean; none = 0, mild = 1, moderate = 2, and marked = 3.

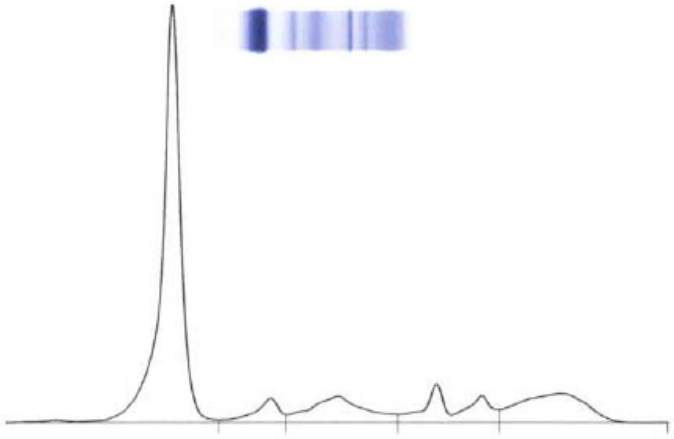
Table 1. Kidney Biopsy Findings

Pathologic Diagnosis	No. of Patients (%)
Paraprotein-associated renal lesions	
Myeloma cast nephropathy	62 (33)
Monoclonal immunoglobulin deposition disease	41 (22)
Amyloidosis	40 (21)
Fibrillary glomerulonephritis	2 (1)
Immunotactoid glomerulopathy	1 (0.5)
Light chain proximal tubulopathy	1 (0.5)
Interstitial infiltration by malignant plasma cells	2 (1)
Non–paraprotein-associated renal lesions	
Glomerular	
Diabetic glomerulosclerosis	9 (5)
Focal segmental glomerulosclerosis	5 (3)
Postinfectious glomerulonephritis	3 (2)
Membranous glomerulopathy	2 (1)
Minimal change disease	2 (1)
Membranoproliferative glomerulonephritis	1 (0.5)
Anti–glomerular basement membrane disease	1 (0.5)
Thin basement membrane disease	1 (0.5)
Smoking-related glomerulopathy	1 (0.5)
Tubulointerstitial	
Acute tubular necrosis	17 (9)
Chronic tubulointerstitial nephritis/ nephropathy	3 (2)
Acute interstitial nephritis	1 (0.5)
Oxalate nephropathy	1 (0.5)
Nephrocalcinosis	1 (0.5)
Vascular	
Arterionephrosclerosis	12 (6)
Thrombotic microangiopathy	1 (0.5)
Normal biopsy	3 (2)

Diagnóstico de la paraproteína

Serum protein electrophoresis (sPEP)

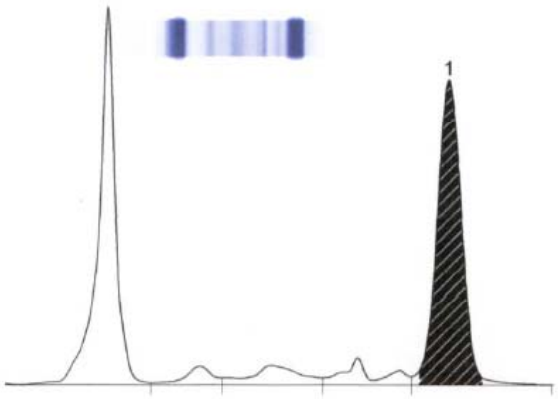
- Intended for the separation of human serum proteins
- Divides proteins in five major fractions:
  albumin, alpha-1, alpha-2, beta and gamma



Total Protein:	7.4	g/dl	T.P. Ref. Range:	6.00 - 8.30 g/dL
Fractions	Rel %	g/dl	Ref. %	Ref. g/dl
Albumin	60.2	4.45	55.1 - 65.7	3.75 - 5.01
Alpha 1	4.5	0.33	3.1 - 5.6	0.19 - 0.46
Alpha 2	10.6	0.78	8.0 - 12.7	0.48 - 1.05
Beta	10.4	0.77	8.5 - 12.8	0.48 - 1.10
Gamma	14.3	1.06	10.3 - 18.2	0.62 - 1.51

Diagnóstico de la paraproteína

sPEP provides quantitation of
the M-protein (m, monoclonal spike)



Total Protein: 10.1 g/dL T.P. Ref. Range: 6.0 - 8.3 g/dL

Fractions	Rel %	g/dl		Ref. %	Ref. g/dl
Albumin	40.3	4.07		55.1 - 65.7	3.75 - 5.01
Alpha 1	3.2	0.32		3.1 - 5.6	0.19 - 0.46
Alpha 2	6.0	0.61		8.0 - 12.7	0.48 - 1.05
Beta	5.3	0.54		8.5 - 12.8	0.48 - 1.10
Gamma	45.2	4.57	+	10.3 - 18.2	0.62 - 1.51
1	44.1	4.45			

sPEP can be normal in patients with oligo-secretory (~15-20%) on non-secretory myeloma (~1-3%)

Diagnóstico de la paraproteína

Urine Protein Electrophoresis (uPEP)

In monoclonal gammopathies, a proteinuria pattern may show a discrete band produced by monoclonal free light chains, or **Bence-Jones Proteinuria (BJP)**

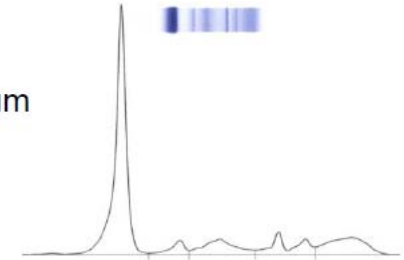
uPEP can provide quantification of M-protein

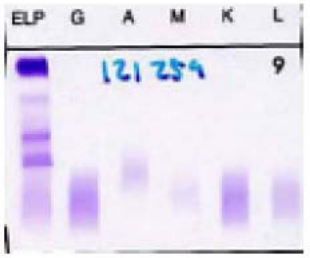
Diagnóstico de la paraproteina

Immunofixation Electrophoresis (IFE)

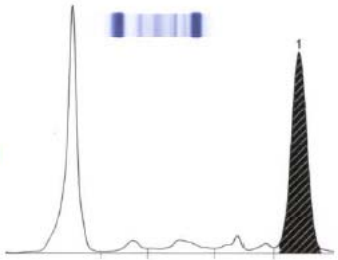
Serum IFE is **more sensitive than sPEP** for detection of M protein
Serum IFE provides characterization of M protein (heavy and light chain subclass)

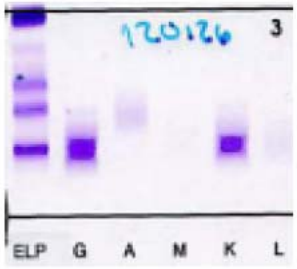
Normal serum





Monoclonal serum



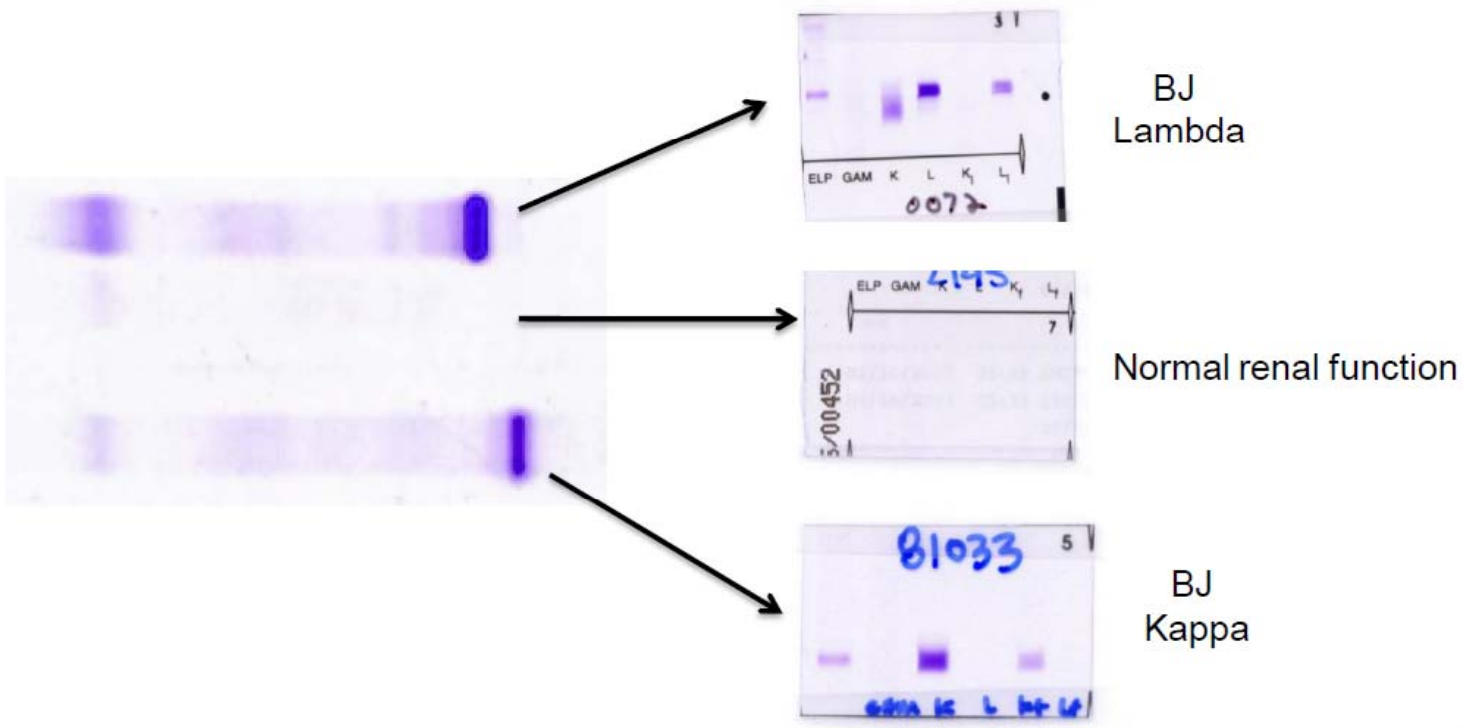


Serum IFE **does not** provide quantification of M-protein
Serum IFE can be normal in patients with non-secretory myeloma (~1-3%)

Diagnóstico de la paraproteína

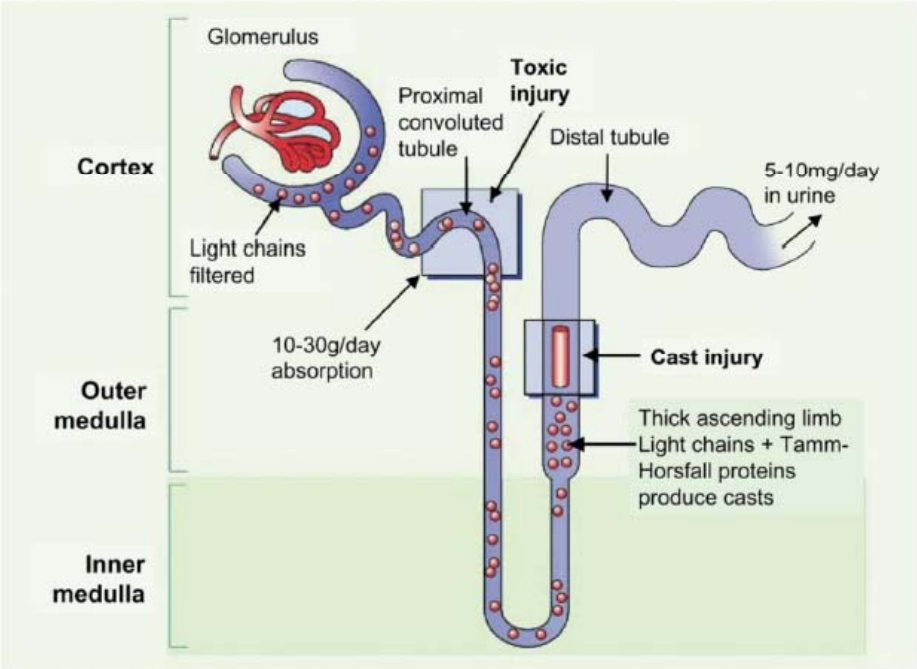
Urine IFE (uIFE)

Characterization of BJ protein (kappa or lambda light chain)
uIFE is **more sensitive than uPEP** for detection of BJ protein



Diagnóstico de la paraproteína

Daily production of FLCs is ~500mg/day
Kidneys can metabolize ~30 times the normal production of FLC



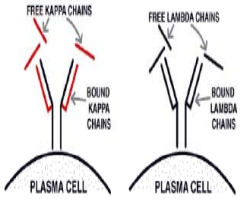
Comprehensive Clinical Nephrolog by Johnson RJ, Feehally J

Diagnóstico de la paraproteína

Free light chains

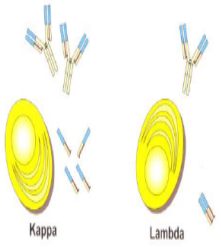
Immunoglobulin molecules consist of 2 identical heavy chains linked to 2 identical light chains (kappa or lambda)

- Majority of light chain in serum exists bound to heavy chain
- Low levels of FLC are found in serum of normal individuals



In serum, kappa FLC exists predominantly as monomer and lambda FLC as a dimer

- Resulting in a **differential renal filtration rate**
- Half life of kappa: 2-3 hours; lambda: 4-6 hours
- Serum kappa FLC concentrations are ~50% lower



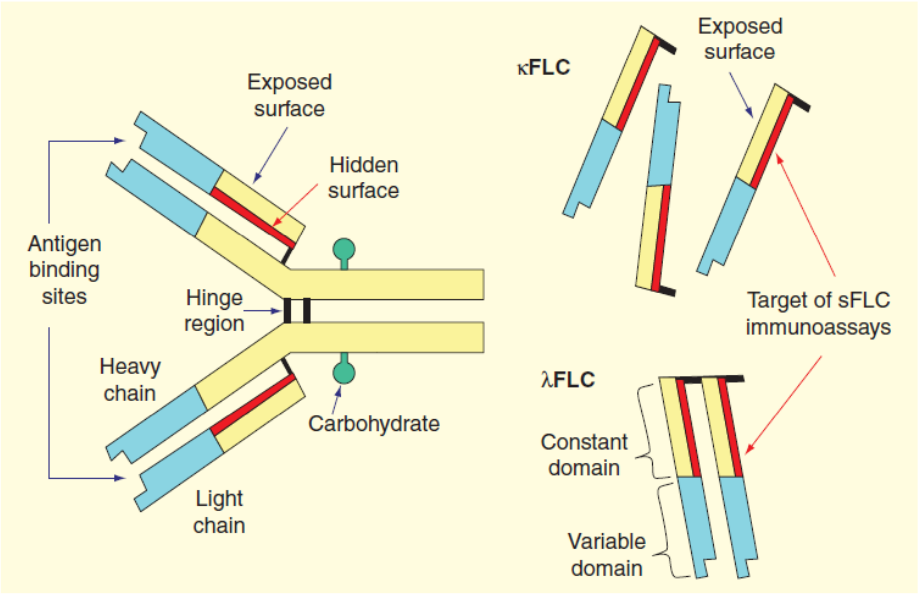
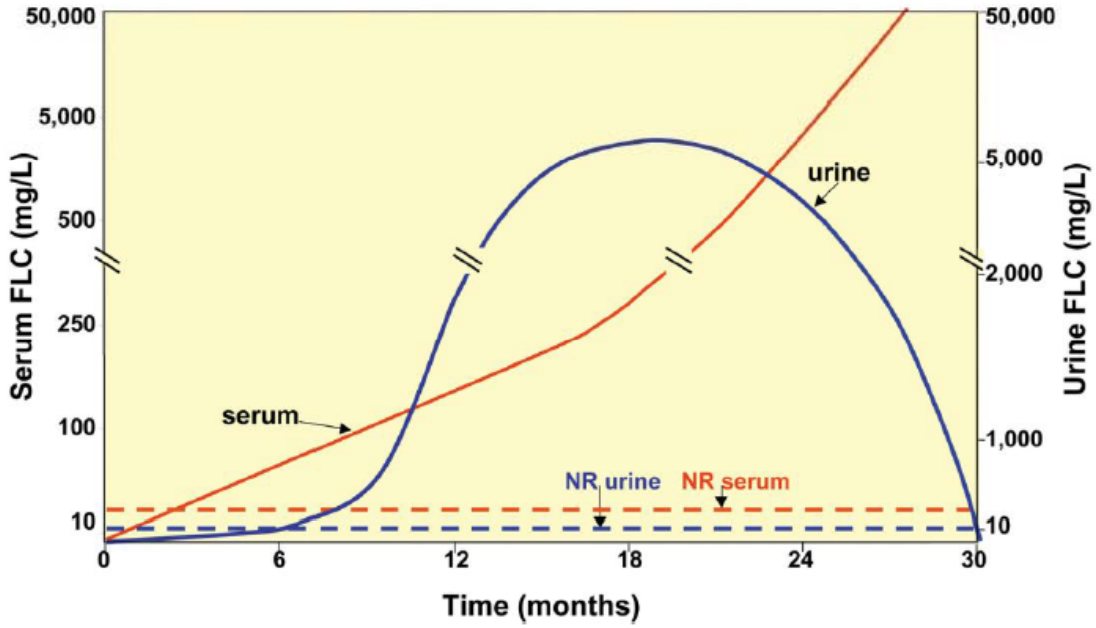


Figure 1. An antibody molecule showing the heavy and light chain structure, together with free κ and λ free light chains.
FLC: Free light chain.
Reproduced with permission from [201].

Diagnóstico de la paraproteína

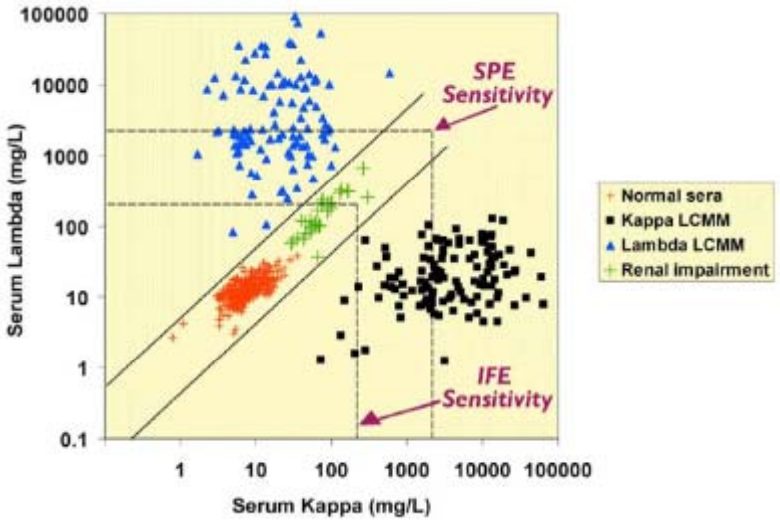
Serum is preferable to urine for assessing FLC concentrations



Comprehensive Clinical Nephrology by Johnson RJ, et al.

International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders

A Dispenzieri[1], R Kyle[1], G Merlini[2], JS Miguel[3], H Ludwig[4], R Hajek[5], A Palumbo[6], S Jagannath[7], J Blade[8], S Lonial[9], M Dimopoulos[10], R Comenzo[11], H Einsele[12], B Barlogie[13], K Anderson[14], M Gertz[1], JL Harousseau[15], M Attal[16], P Tosi[17], P Sonneveld[18], M Boccadoro[6], G Morgan[19], P Richardson[14], O Sezer[20], MV Mateos[3], M Cavo[17], D Joshua[21], I Turesson[22], W Chen[23], K Shimizu[24], R Powles[25], SV Rajkumar[1] and BGM Durie[26] on behalf of the International Myeloma Working Group[27]



Ratio 0.26-1.65

> 1.65 CL kappa clonal.
< 0.26 CL lamda clonal.

Table 3 Four hundred and twenty-eight patients with urinary monoclonal protein detected by immunofixation electrophoresis[20]

Laboratory test	*% abnormal*
Serum immunofixation electrophoresis	93.5
Serum protein electrophoresis	80.8
Serum FLC κ/λ ratio	85.7
Serum immunofixation electrophoresis or FLC ratio	99.5

Leukemia (2009) 23, 215–224

International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders

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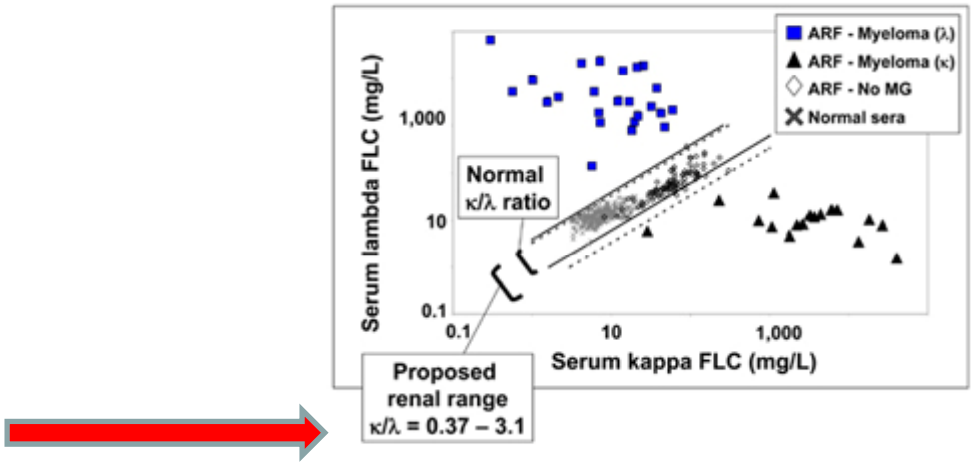
En gammapatías monoclonales asociadas con insuficiencia renal severa (las reducciones en la tasa de filtración glomerular (GFR) tienen como consecuencia un resultado en orina más reducido.

- Por este motivo, las concentraciones de cadenas ligeras libres en orina no reflejan las concentraciones en suero ni la producción.
- Con insuficiencia renal, suben las concentraciones kappa y lambda pero el ratio κ/λ queda habitualmente en los límites normales.



Leukemia (2009) 23, 215–224

El riñón en las discrasias de células plasmáticas

- GMSI
  - Pico Monoclonal en suero < 3g/dL
  - Plasmacitosis clonal en médula ósea < 10%
  - **NO** daño orgánico y **NO** enfermedad linfoproliferaiva asociada.

- **Mieloma**
  - Proteina Monoclonal en sangre u orina
  - Plasmacitosis clonal en médula ósea > 10% o plasmacitoma
  - Daño orgánico "CRAB": increased **c**alcium level, kidney (**r**enal) failure, **a**nemia, and destructive **b**one lesions.

- **GMSR**
  - Pico monoclonal en sangre u orina
  - Plasmacitosis clonal en médula ósea < 10%
  - **Daño renal** asociado a **B-cell dyscrasia**
    - **Afectación no está relacionada con prolipereción celular**
    - **Depósito monoclonal de inmunoglobilinas.**

Haematologica June 2014 99: 984-996;

Table 3. Diagnostic evaluation for MGUS.

Medical history and physical examination
Emphasis on symptoms and findings that may suggest underlying MM, WM, AL amyloidosis, or M-protein related disorders
Blood
Complete blood count with differential
BUN, creatinine, total protein, CRP
LDH, calcium, phosphate
Beta-2 microglobulin and albumin
Serum protein electrophoresis, immunofixation, serum free light chain analysis
Quantitative tests for IgG, IgA, and IgM
Urine
24-hour urine collection for electrophoresis and immunofixation
24-hour urine for total protein
Bone marrow[#]
Biopsy for histology
Aspirate for:
Morphology
Immunophenotyping
Cytogenetic analysis by FISH* focused on del(17p13), del(13q), del(1p21), ampl(1q21), t(11;14), t(4;14), and t(14;16) (only in patients suspected of having a malignant plasma cell disorder)
Imaging[#]
IgA and IgG: Radiographic skeletal survey including skull, pelvis, vertebral column, and long bones†
IgM: CT scan of chest, abdomen and pelvis to detect organomegaly and lymphadenopathy
DXA: assessment of bone mineral density, especially when other risk factors for osteoporosis are present
Additional investigations, which may be useful under certain circumstances
Lumbar puncture (cell counts, chemistry, cytology, immunophenotyping): suspicion of leptomeningeal involvement
MRI: evaluation of cord compression or painful area of the skeleton (suspicion of soft tissue plasmacytomas arising from bone)
CT, MRI, or ^{18}F-FDG-PET/CT: suspicion of extramedullary plasmacytomas
Survey for evaluation of AL amyloidosis
Bleeding time, APTT, PT
Cryoglobulins, Coombs test (cold autoantibody)
Serological tests for hepatitis C virus: type II cryoglobulinemia
IgM anti-myelin-associated glycoprotein activity: peripheral neuropathy
Serum viscosity, fundoscopy: symptoms of hyperviscosity

Time to redefine Myeloma

Guy Pratt,[1,2] Stella Bowcock,[3] Andrew Chantry,[4] Gordon Cook,[5] Graham Jackson,[6] Maggie Lai,[7] Eric Low,[7] Nicola Mulholland,[8] Roger Owen,[9] Neil Rabin,[10] Karthik Ramasamy,[11] John A Snowden,[12] Matthew Streetly,[13] Ashutosh Wechalekar,[14] Kwee Yong[10] and Jenny Bird[15]

British Journal of Haematology, 2015, **171,** 1–10

Table I. The new IMWG definition of multiple myeloma (Rajkumar *et al*, 2014). Changes from the previous 2003 (International Myeloma Working Group 2003) definition are highlighted in bold.

Definition of multiple myeloma

Clonal bone marrow plasma cells **≥10% or biopsy-proven bony or extramedullary plasmacytoma*** and any one or more of the following myeloma-defining events or any one or more of the following biomarkers of malignancy:

Myeloma-defining events:

Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder as follows:

- Hypercalcaemia: serum calcium >0·25 mmol/l (>1 mg/dl) higher than the upper limit of normal or >2·75 mmol/l (>11 mg/dl)
- Renal insufficiency: **creatinine clearance <40 ml per min† or serum creatinine >177 μmol/l (>2 mg/dl)**
- Anaemia: haemoglobin value of >20 g/l below the lower limit of normal or a haemoglobin value <100 g/l
- Bone lesions: one or more osteolytic lesions on skeletal radiography, **CT, or PET-CT‡Any one or more of the following biomarkers of malignancy:**

- **Clonal bone marrow plasma cell percentage* ≥60%**
- **Involved:uninvolved serum free light chain ratio§ ≥100**
- **>1 focal lesion on MRI studies¶**

Definition of smouldering multiple myeloma

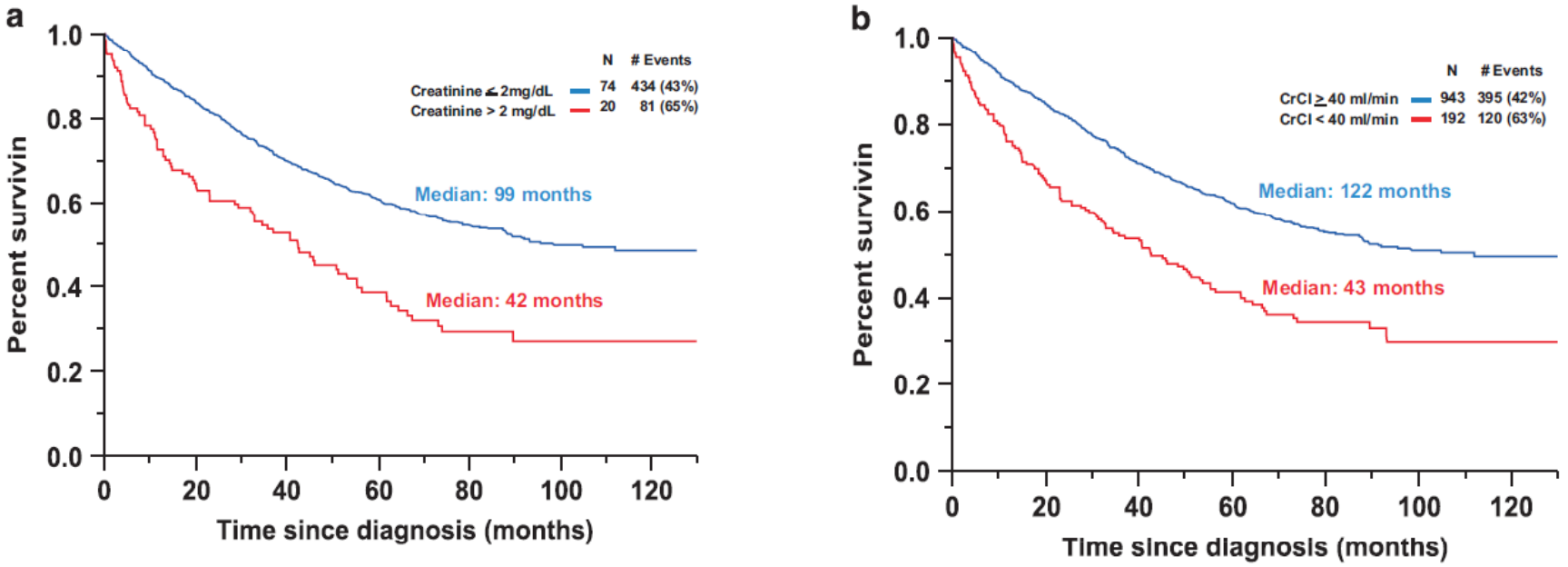
Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/l or urinary monoclonal protein ≥500 mg/24 h and/or **clonal bone marrow plasma cells 10–60%**
- Absence of myeloma defining events **including biomarkers of malignancy** or amyloidosis

Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma

WI Gonsalves, N Leung, SV Rajkumar, A Dispenzieri, MQ Lacy, SR Hayman, FK Buadi, D Dingli, P Kapoor, RS Go, Y Lin, SJ Russell, JA Lust, S Zeldenrust, RA Kyle, MA Gertz and SK Kumar

1135 patients with NDMM seen between 1 January 2003 and 31 December 2010.



Citation: Blood Cancer Journal (2015) **5**, e296; doi:10.1038/bcj.2015.20

Riñón del mieloma

- 15-40 % de los pacientes presentarán afectación renal
- En el momento del diagnóstico el el 30-40% tienen la Cr elevada.
  - Un 20% > 2mg/dl
  - Un 2-5% requieren diáisis en el diagnóstico
- El 10 % requerirán tratamiento dialítico

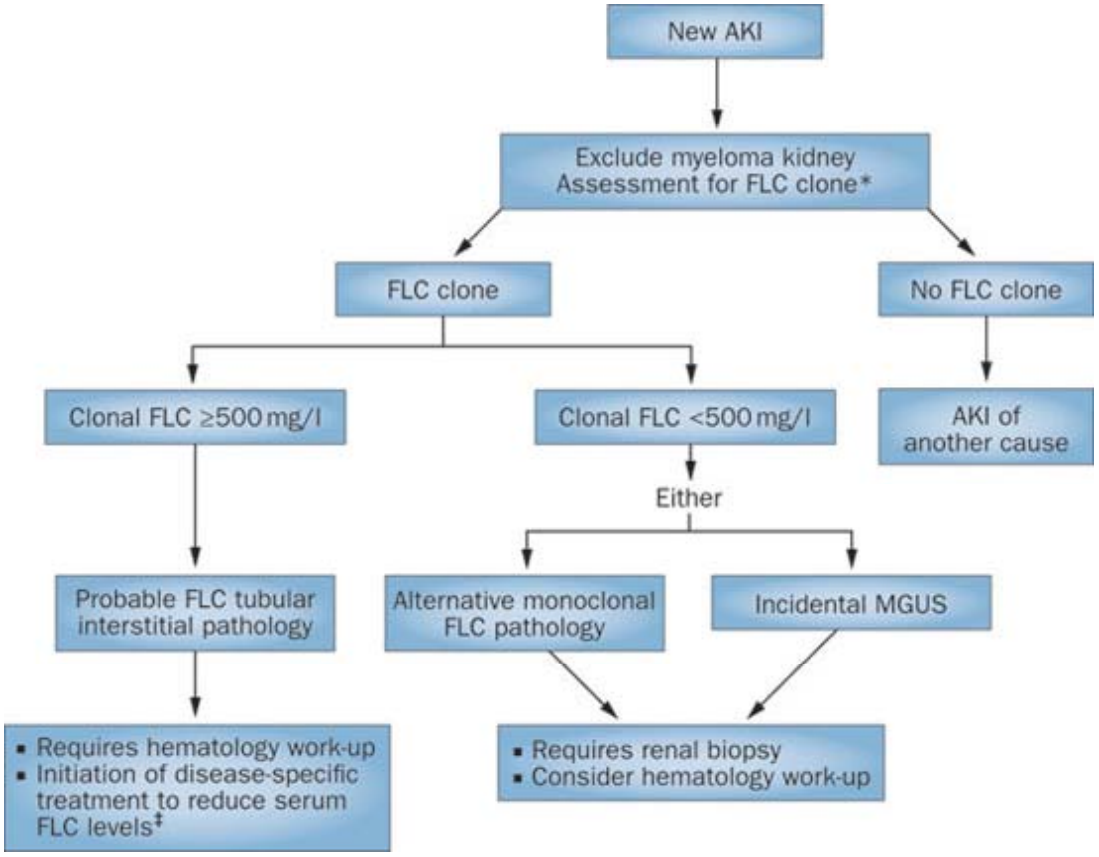
Nephrol Dial Transplant (2012) 27: 3713–3718

Riñón del mieloma

- **Necesidad de Biopsia**:
  - FRA con CLL monoclonales > 500 mg/dl y sin albuminuria no se requería biopsia
  - Si Proteinuria fundamentalmente a expensas de albúmina, descartar amiloidosis.
    - PAAF grasa o biopsia glándula salival
    - Biopsia renal
  - Si ERC previa la biopsia será necesaria.

Nephrol Dial Transplant (2012) 27: 3713–3718

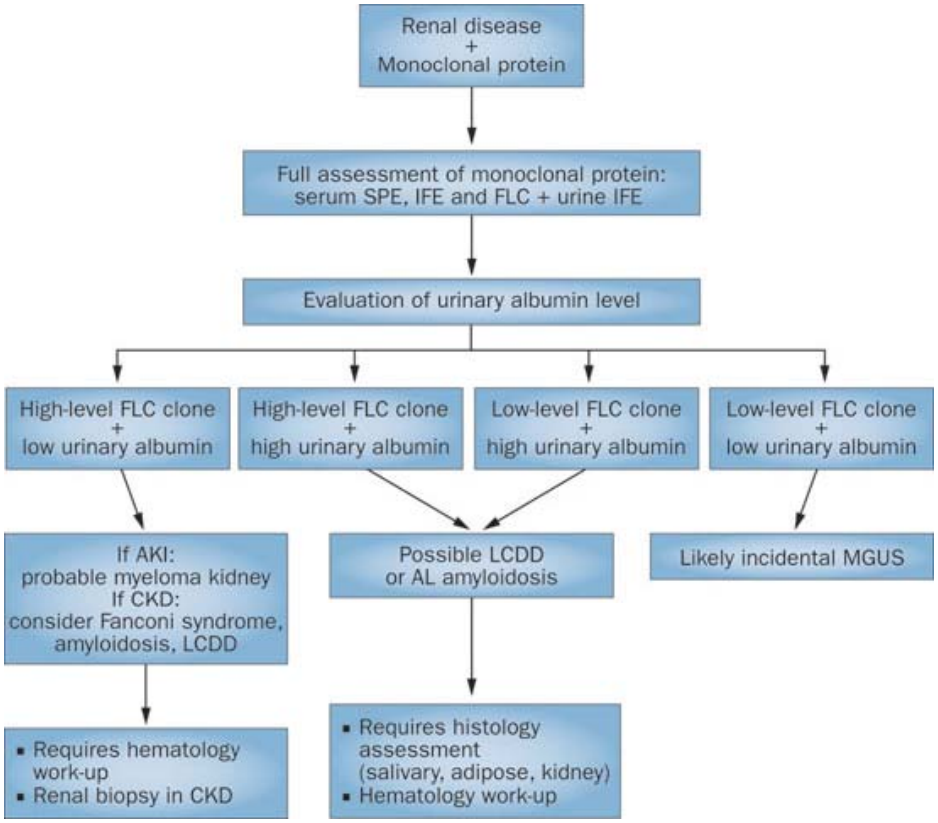
Figure 2 Screening algorithm for monoclonal disease in AKI



Hutchison, C. A. *et al.* (2011) The pathogenesis and diagnosis of acute kidney injury in multiple myeloma
Nat. Rev. Nephrol. doi:10.1038/nrneph.2011.168

nature REVIEWS NEPHROLOGY

Figure 3 Diagnostic approach to a patient with renal disease and a monoclonal protein



Hutchison, C. A. *et al.* (2011) The pathogenesis and diagnosis of acute kidney injury in multiple myeloma *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2011.168

nature REVIEWS NEPHROLOGY

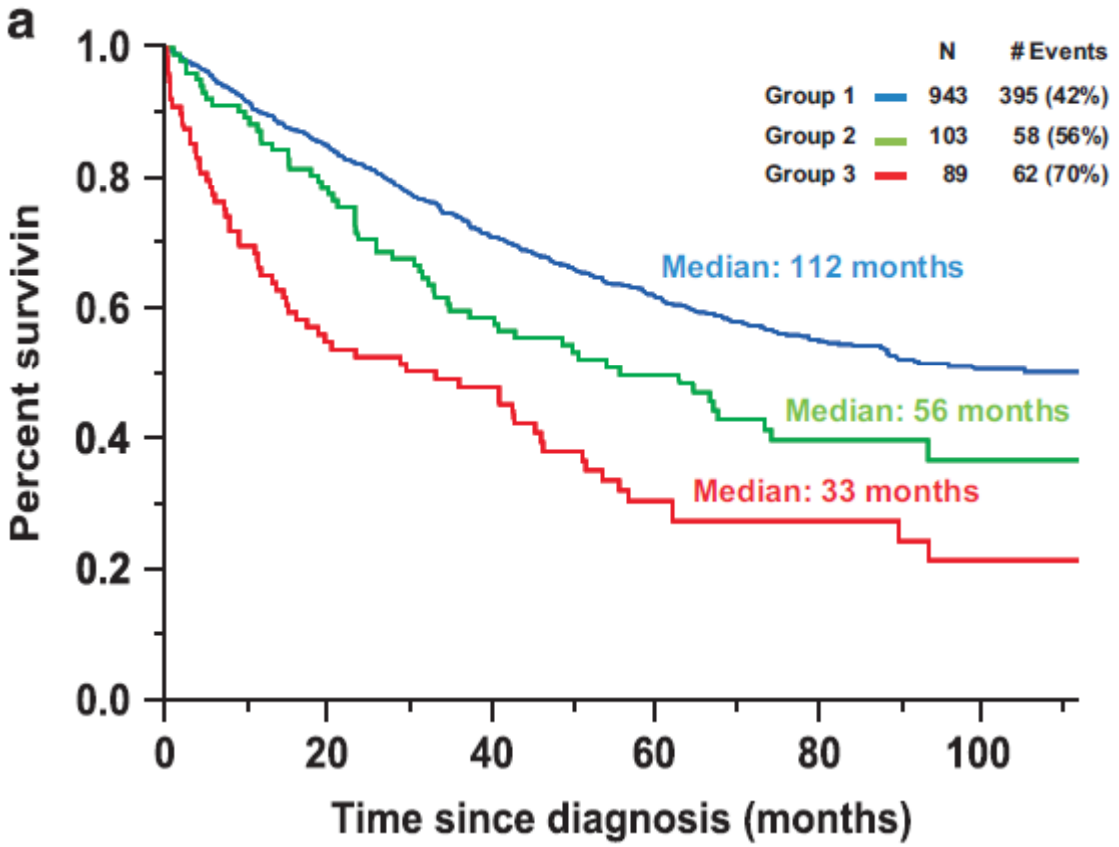
Riñón del mieloma

- **Objetivos del tratamiento:**
  - Eliminar o prevenir las condiciones agravantes
  - Reducir la exposición renal a la presencia de CLL
    - Inhibir su síntesis mediante quimioterapia
    - Eliminación de las cadenas libres circulantes
  - Inhibir la interacción de las cadenas ligeras libres con la proteína de Tam-Hofstall

Nephrol Dial Transplant (2012) 27: 3713–3718

Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma

WI Gonsalves, N Leung, SV Rajkumar, A Dispenzieri, MQ Lacy, SR Hayman, FK Buadi, D Dingli, P Kapoor, RS Go, Y Lin, SJ Russell, JA Lust, S Zeldenrust, RA Kyle, MA Gertz and SK Kumar



group 1, CrCl>40 at diagnosis.

group 2,CrClo< 40 at diagnosis but improved to > 40 after therapy.

group 3, CrClo< 40 at diagnosis and remained <40 after therapy

Citation: Blood Cancer Journal (2015) **5**, e296; doi:10.1038/bcj.2015.20

Riñón del mieloma

- **Objetivos del tratamiento**:
  - Eliminar o prevenir las condiciones agravantes
    - Evitar deshidratación
    - Evitar nefrotóxicos (AINES)
    - Tratar la hipercalcemia (Bifosfonatos/Zolendronato)
    - Tratar la acidosis
    - Evitar los diuréticos de asa
    - Evitar contrastes

Nephrol Dial Transplant (2012) 27: 3713–3718

Myeloma Kidney: Improving Clinical Outcomes?

Richard Haynes, Nelson Leung, Robert Kyle, and Christopher G. Winearls

Table 2. Innovations in Therapy for Multiple Myeloma

Year	Therapy	Comment
1962	Melphalan–prednisolone	The first therapy to show improved survival. Mainstay of treatment for more than 30 years.
1996	ASCT	Improves survival, although uncertainty remains optimal timing. High transplant-related mortality in renal failure.
1999	Thalidomide	Improves survival compared with melphalan–prednisolone alone. Use limited by adverse effects in renal impairment.
2001	Free light chain assay	Improves detection and monitoring of treatment of monoclonal plasma cell disorders.
2003	Bortezomib	Improves survival in those with relapsed disease. Now a first-line option.
2003	Tandem ASCT	Improves survival in those not achieving a very good partial response with single ASCT.
2005	Lenalidomide	Improves survival in those with relapsed disease. Now a front/first-line option.
2008	High cutoff dialysis	Improves free light chain FLC removal from plasma (not serum strictly—it is clotted). Trials are underway to investigate whether this improves renal prognosis.
2010	Zoledronic acid	In addition to chemotherapy, improves survival.
2010	Carfilzomib	Second-line proteasome inhibitor, with activity in bortezomib-resistant disease.

Abbreviation: ASCT, autologous stem cell transplantation.

Advances in Chronic Kidney Disease, Vol 19, No 5 (September), 2012: pp 342-351

Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma

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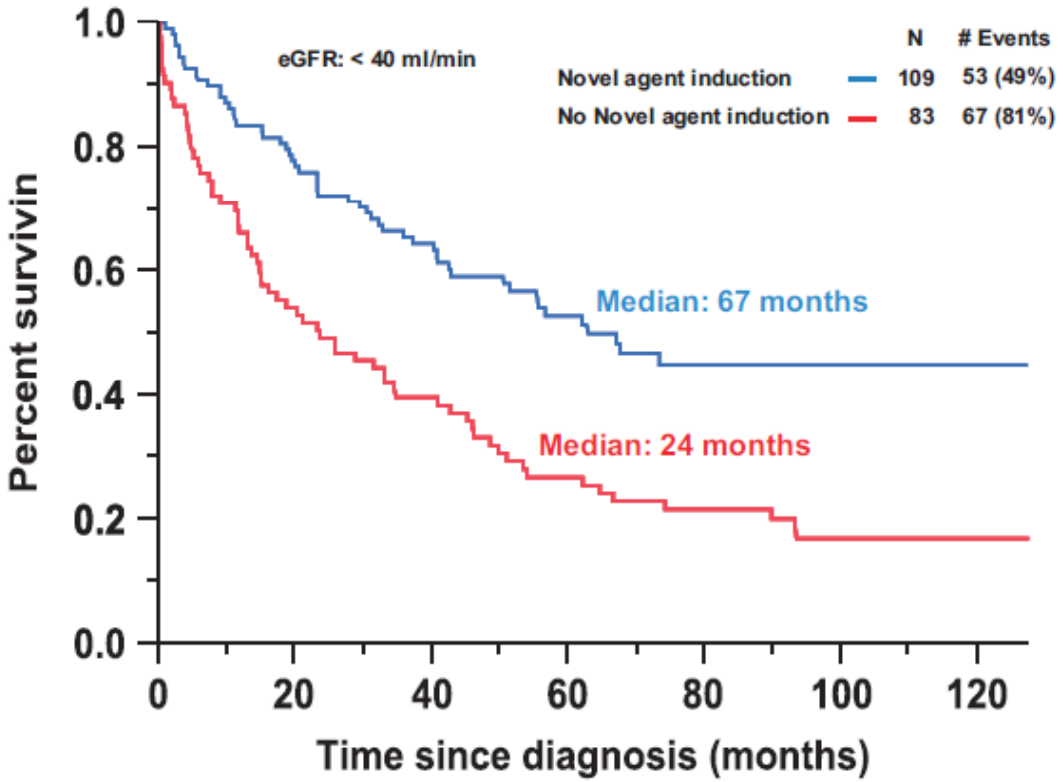

Figure 2. Kaplan-Meier plot comparing overall survival between patients with an estimated creatinine clearance of < 40 ml/min based on the presence or absence of a novel agent induction regimen.

Citation: Blood Cancer Journal (2015) **5**, e296; doi:10.1038/bcj.2015.20

Early Reduction of Serum-Free Light Chains Associates with Renal Recovery in Myeloma Kidney

Colin A. Hutchison,* Paul Cockwell,* Stephanie Stringer,* Arthur Bradwell,†‡ Mark Cook,§ Morie A. Gertz,‖ Angela Dispenzieri,‖ Jeffrey L. Winters,¶ Shaji Kumar,‖ S. Vincent Rajkumar,‖ Robert A. Kyle,‖ and Nelson Leung**

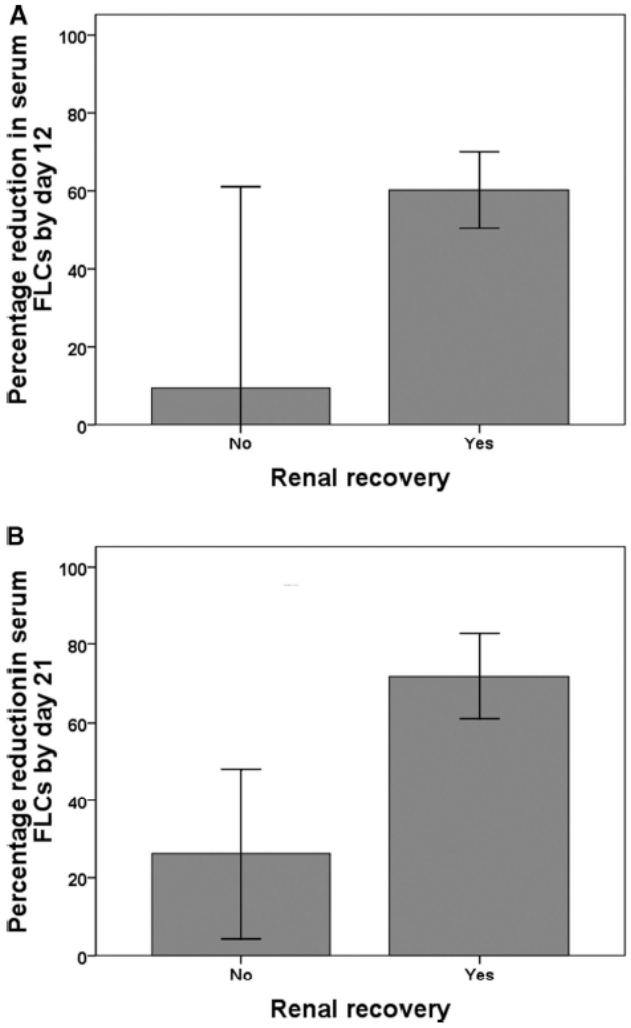

Figure 1. Renal recovery associates with an early reduction in serum FLC concentrations. By day 12 (A) and by day 21 (B).

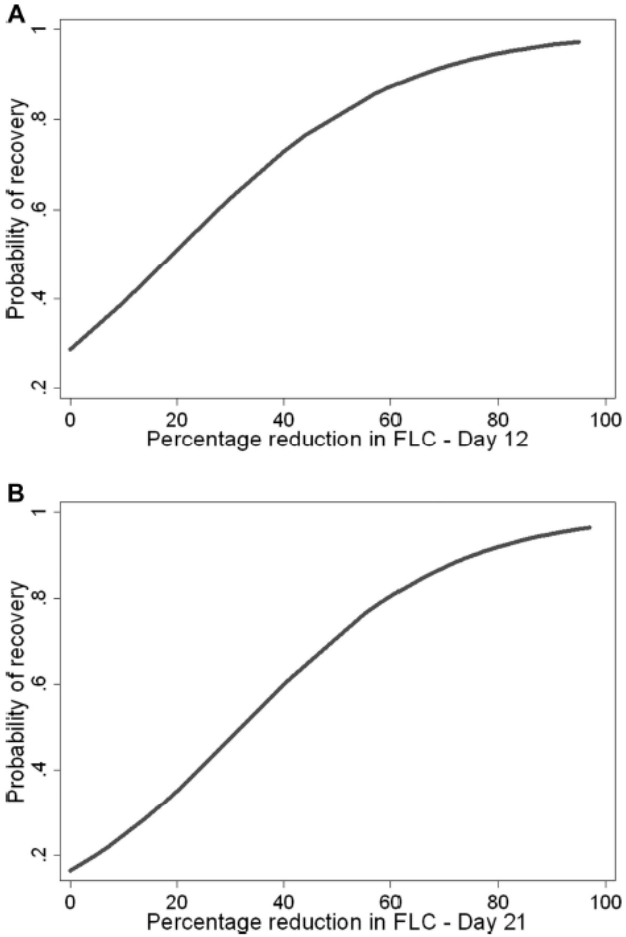

Figure 2. The relationship of reduction in serum FLCs and renal recovery is linear in patients with myeloma kidney. To enable a renal recovery rate of 80%, a 60% reduction in FLC levels by day 21 is required. Probability plot of renal recovery in relation to serum FLC reductions at days 12 (A) and 21 (B).

J Am Soc Nephrol 22: 1129–1136, 2011.

Riñón del mieloma

- **Reducir la presencia de CLL**

  - Inhibir su síntesis mediante quimioterapia.
    - Se deber ser rápido en el inicio del tratamiento, no esperar incluso a tener la PMO.
      - Dosis altas de dexametasona 40 mg día (4/5)
      - Protocolos basados en Dexa mas Bortezomib
        - » Induccion de apoptosis en clones mielomatosis
        - » Inhibición NF-kB en el riñon

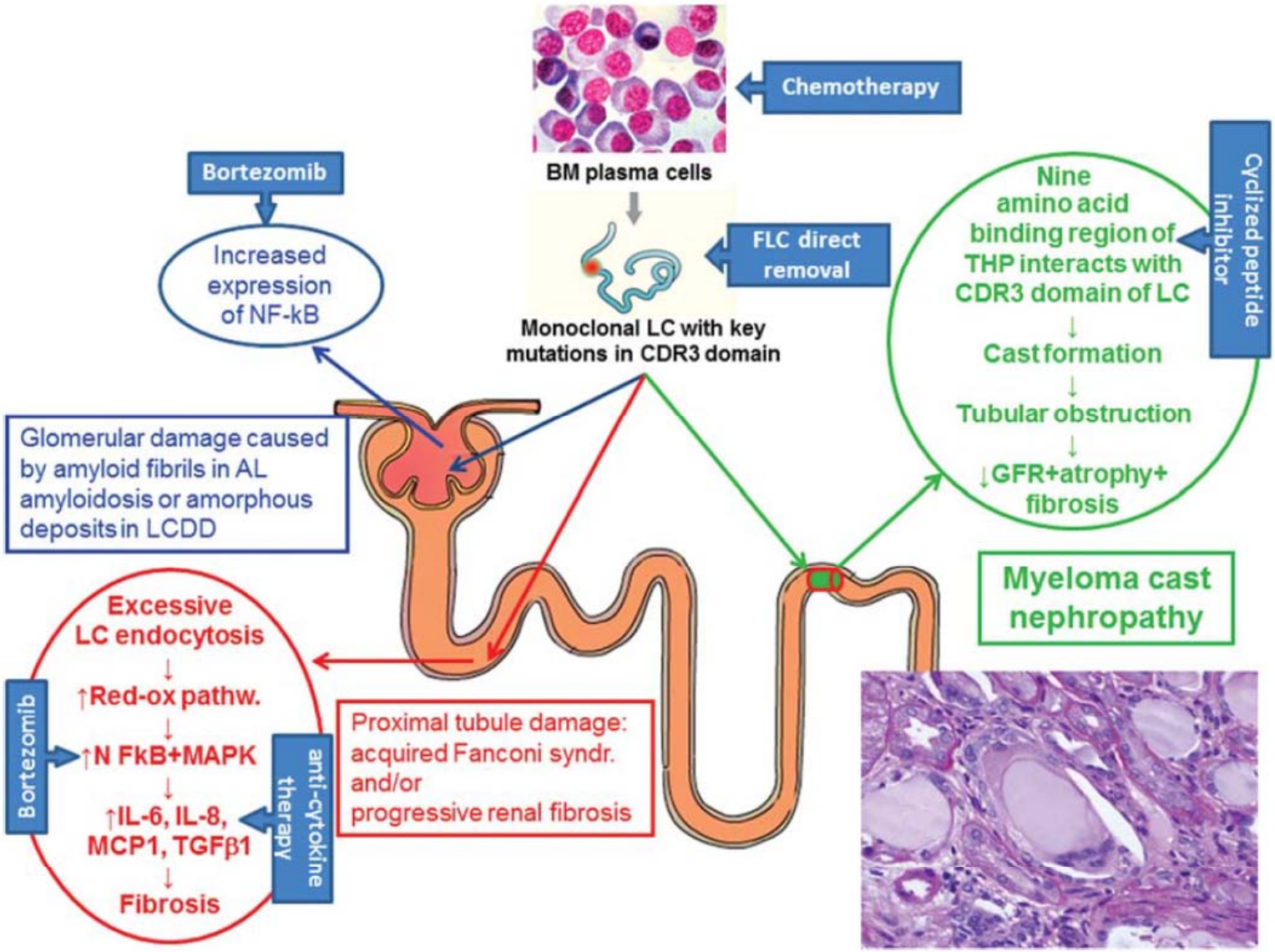

Fig. 1. Mechanisms of FLCs-induced kidney injury. Clonal bone marrow (BM) plasma cells may produce high amounts of FLCs. The light chains may target the glomerulus, as observed in AL amyloidosis and LCDD. High concentrations of FLCs in the ultrafiltrate can cause direct injury to PTCs resulting in acquired Fanconi syndrome and/or progressive renal fibrosis. In the distal tubules, FLCs can bind to a consensus sequence on THP and co-precipitate to form casts. These casts results in tubular atrophy and lead to progressive interstitial inflammation and intratubular giant cell formation surrounding the casts (as shown in the kidney biopsy). Virtually all key actors of the light chain-mediated kidney damage can now be targeted by effective drugs or procedures (callouts).

Management of myeloma-associated renal dysfunction in the era of novel therapies

Expert Rev. Hematol. 5(1), 51–68 (2012)

Table 3. Summary of renal response in multiple myeloma patients treated with various newer anti-myeloma regimens.

Study (year)	Regimen type	Renal response	Ref.
Kastritis *et al.* (2007)	Dexamethasone	73% of patients showed renal reversal	[109]
	Dexamethasone with thalidomide and/or bortezomib	80% of patients showed renal reversal. 85% reversal of RI occurred in patients with MM responding to treatment, in contrast to 56% reversal of RI in patients with resistant MM	
Matsue *et al.* (2010)	Dexamethasone and/or thalidomide in dialysis patients	25% of patients showed complete response 42% of patients showed PR 67% of patients became dialysis independent	[111]
Dimopoulos *et al.* (2009)	Bortezomib plus dexamethasone	59% of patients showed renal response, including 30% having complete renal response with two out of nine patients becoming dialysis independent	[110]
Li *et al.* (2009)	Bortezomib plus dexamethasone	Reversal of RI occurred in ~39% of patients, with a 50% reduction in serum creatinine level seen in ~33% of patients. In 13 out of 15 patients, MM response was associated with improvement of renal function	[72]
Ludwig *et al.* (2010)	Bortezomib–doxorubicin–dexamethasone regimen	MM response was shown in 72% of patients, while renal response was shown in 62% of patients	[73]
Morabito *et al.* (2010)	Bortezomib-based regimen	41% of patients showed renal reversal 21% of patients became dialysis independent	[69]
Chanan-Khan *et al.* (2007)	Bortezomib-based regimen	75% overall response rate and four out of 20 patients became dialysis independent	[70]
Roussou *et al.* (2008)	Bortezomib-based regimen	50% renal improvement and 85% of patients showed a decrease in serum creatinine	[71]
Dimopoulos *et al.* (2010)	Lenalidomide plus dexamethasone	25% of patients achieved a complete renal response, while 16% achieved a minor renal response	[86]
Roussou *et al.* (2010)	Conventional chemotherapy plus dexamethasone	Improvement of RI in 59% of patients	[112]
	IMiD-based regimens	Improvement of RI in 79% of patients	
	Bortezomib and dexamethasone	Improvement of RI in 94% of patients	
Tosi *et al.* (2004)	Thalidomide	Reversal of renal function in 12 out of 15 patients whose MM was responsive to treatment	[50]
Tosi *et al.* (2010)	Thalidomide plus dexamethasone as induction therapy prior to autologous SCT	82% renal improvement in patients achieving PR versus only 37% in patients failing to achieve PR	[103]

IMiD: Immunomodulatory drug; MM: Multiple myeloma; PR: Partial response; RI: Renal impairment; SCT: Stem cell transplantation.

Tasas de respuesta renal 60-80%

Novel approaches for reducing free light chains in patients with myeloma kidney

Colin A. Hutchison, Joan Bladé, Paul Cockwell, Mark Cook, Mark Drayson, Jean-Paul Fermand, Efstathios Kastritis, Robert Kyle, Nelson Leung, Sonia Pasquali and Christopher Winearls on behalf of the International Kidney and Monoclonal Gammopathy Research Group

Table 4 | Dose modification of chemotherapeutic agents in patients with renal impairment

Drug	Degree of renal impairment	Dose adjustment
Thalidomide	Any	Not required
Lenalidomide	Mild renal impairment (creatinine clearance 50–80 ml/min)	25 mg (full dose) every 24 h
Lenalidomide	Moderate renal impairment (creatinine clearance 30–49 ml/min)	10 mg every 24 h
Lenalidomide	Severe renal impairment (creatinine clearance <30 ml/min)	15 mg every 48 h
Lenalidomide	Severe renal impairment (requiring dialysis)	15 mg three times per week
Bortezomib	Any	Not required

Hutchison, C. A. *et al. Nat. Rev. Nephrol.* **8**, 234–243 (2012)

High-dose glucocorticoids improve renal failure reversibility in patients with newly diagnosed multiple myeloma

Ulas Darda Bayraktar,* Sean Warsch, and Denise Pereira

One-fifth of the newly diagnosed multiple myeloma (MM) patients present with renal failure (RF) [1–3]. Glucocorticoids (GCs) may improve RF in MM by (1) rapid reduction of paraprotein production, (2) lessening inflammation and fibrosis in renal parenchyma, and (3) decreasing serum calcium level. We hypothesized that lower dose GCs may be less effective in restoring renal function and retrospectively compared the RF reversibility between the newly diagnosed MM patients who were treated with GCs equivalent to ≥160 mg DX over 4 days (high-dose GC group, $n = 16$) versus those who were treated with <160 mg (low-dose/no GC group, $n = 8$). There was no difference in age, baseline calcium, and creatinine levels between the two groups. Renal function was restored in seven patients in the high-dose GC group (44%) and in none of the patients in the low-dose/no GC group ($P = 0.026$). The only other factor found to impact the RF reversibility was the delay of GC initiation. Four and 1 patients developed a severe infection in the high- and low-dose/no GC groups, respectively. The use of higher dose GCs in the newly diagnosed MM patients who present with RF increases the likelihood of renal function restoration.

Division of Hematology/Oncology, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida
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Conflict of interest: Nothing to report.
Published online 15 November 2010 in Wiley Online Library

Tras diagnostico de FRA por MM 4 dosis de Dexametsona 40 mg día

Riñón del mieloma

- **Reducir la exposición a CLL**
  - Eliminación de las cadenas libres circulantes.
    - Plasmaféresis.
      - Síndrome hipreviscosidad (IgM)
      - Crioglobulinemia tipo I asociada
    - Aféresis con filtro de alto poro > 45 KD
    - Inmunoadsorción
  - Recuperación FR entre 50-80 % de lo pacientes tras un mes de tratamiento.

Annals of Internal Medicine | ARTICLE

Plasma Exchange When Myeloma Presents as Acute Renal Failure

A Randomized, Controlled Trial

William F. Clark, MD; A. Keith Stewart, MD; Gail A. Rock, MD; Marion Sternbach, MD; David M. Sutton, MD; Brendan J. Barrett, MD; A. Paul Heidenheim, MA; Amit X. Garg, MD; David N. Churchill, MD; and the Canadian Apheresis Group

Background: Two small, randomized trials provide conflicting evidence about the benefits of plasma exchange for patients with acute renal failure at the onset of multiple myeloma.

Objective: To assess the effect of 5 to 7 plasma exchanges on a composite outcome in patients with acute renal failure at the onset of multiple myeloma.

Design: Randomized, open, controlled trial, stratified by chemotherapy and dialysis dependence, conducted from 1998 to 2004.

Setting: Hospital plasma exchange units in 14 Canadian medical centers.

Participants: 104 patients between 18 and 81 years of age with acute renal failure at the onset of myeloma.

Intervention: Study participants were randomly assigned to conventional therapy plus 5 to 7 plasma exchanges of 50 mL per kg of body weight of 5% human serum albumin for 10 days or conventional therapy alone. Ninety-seven participants completed the 6-month follow-up.

Measurements: The primary outcome was a composite measure of death, dialysis dependence, or glomerular filtration rate less than 0.29 $mL \cdot s^{-2} \cdot m^{-2}$ (<30 mL/min per 1.73 m^2).

Results: At enrollment, the plasma exchange and control groups were similar for dialysis dependence, chemotherapy, sex, age, hypercalcemia, serum albumin level, 24-hour urine protein level, serum creatinine level, and Durie–Salmon staging. The primary composite end point occurred in 33 of 57 (57.9%) patients in the plasma exchange group and in 27 of 39 (69.2%) patients in the control group (difference between groups, 11.3% [95% CI, −8.3% to 29.1%]; $P = 0.36$). One third of patients in each group died.

Limitations: The study was small, used a composite outcome, and did not use renal biopsy as an inclusion criterion. Recruiting physicians were blinded to treatment allocation but not to treatment thereafter.

Conclusions: In patients with acute renal failure at the onset of multiple myeloma, there is no conclusive evidence that 5 to 7 plasma exchanges substantially reduce a composite outcome of death, dialysis dependence, or glomerular filtration rate less than 0.29 $mL \cdot s^{-2} \cdot m^{-2}$ (<30 mL/min per 1.73 m^2) at 6 months.

Ann Intern Med. 2005;143:777-784. www.annals.org
For author affiliations, see end of text.
ClinicalTrials.gov identifier: NCT00120263.

Efficient Removal of Immunoglobulin Free Light Chains by Hemodialysis for Multiple Myeloma: *In Vitro* and *In Vivo* Studies

Colin A. Hutchison,*† Paul Cockwell,*† Steven Reid,‡ Katie Chandler,‡ Graham P. Mead,‡ John Harrison,* John Hattersley,§ Neil D. Evans,§ Mike J. Chappell,§ Mark Cook,‖ Hermann Goehl,¶ Markus Storr,¶ and Arthur R. Bradwell‡**

*Departments of *Renal Medicine and ‖Hematology, Queen Elizabeth Hospital, QEMC, ‡The Binding Site Ltd., Birmingham, and †Divisions of Medical Sciences and **Immunity and Infection, Medical School, University of Birmingham, Birmingham, and §School of Engineering, University of Warwick, Coventry, United Kingdom; and ¶Gambro Dialysatoren GmbH & Co. KG, Hechingen, Germany*

J Am Soc Nephrol 18: 886–895, 2007.

Class	Make	Model	Membrane Material	Surface Area (m^2)	Molecular Cutoff in Blood (kD)	Mean Reduction in FLC (%)		Mean FLC Concentration in UF (%)	
						κ	λ	κ	λ
High flux	B. Braun	Hi-PeS 18	PES	1.8	10	54	39	17	12
	Asahi	APS-1050	PS	2.1	10[b]	71	65	30	18
	Nikkiso	FLX 8GWS	PEPA	1.8	10[b]	68	45	12	11
	Idemsa	200 MHP	PES	2.0	10[b]	67	59	21	16
Super flux	Toray	BK-F 2.1	PMMA	2.1	20[c]	88	73	0.1	0.2
	Toray	BG 2.1	PMMA	2.1	20[c]	71	41	0.1	0.1
High cutoff	Gambro	HCO 1100	PAES	1.1	45[c]	96	94	62.5	90

[a]FLC, free light chains; PAES, polyarylethersulfone; PEPA, polyester polymer alloy; PES, polyethersulfone; PMMA, polymethyl methacrylate; PS, polysulfone; UF, ultrafiltrate.
[b]This is an approximate size because manufacturers' data were not available.
[c]Obtained from manufacturer.

Cantidad de CL eliminadas también depende de….

- Concentración inicial en suero.
- Tiempo de diálisis.
- Flujo de baño.
- Superficie del dializador.
- QT eficaz.

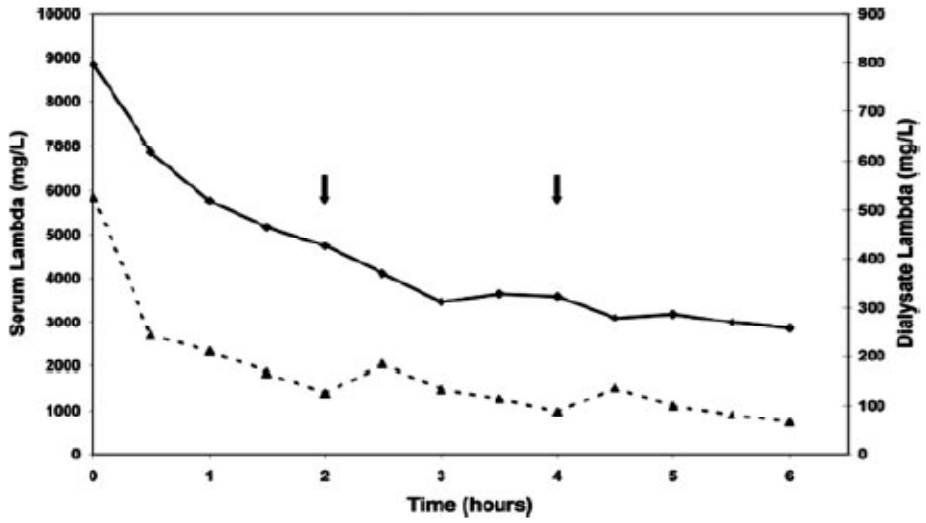
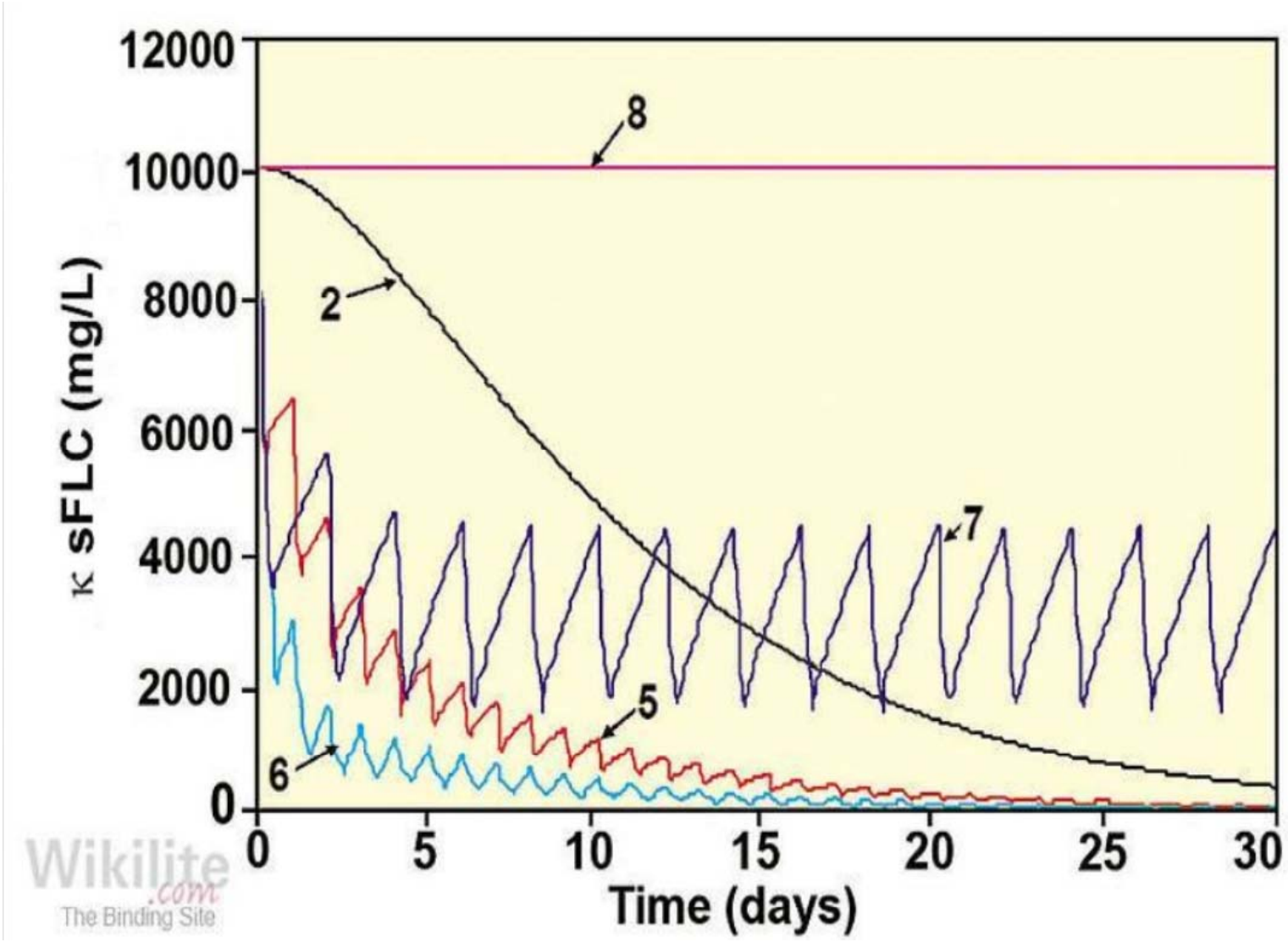


Figure 2. Serum (◆) and dialysate (△) λ FLC concentrations during a 6-h hemodialysis session using Gambro HCO 1100 dialyzers (patient 6). Arrows indicate use of a new dialyzer.



Tratamiento con hemodiálisis del fracaso renal agudo en el mieloma múltiple con filtros de alto poro (*high cut off*)

Guillermo Martín-Reyes[1], Remedios Toledo-Rojas[1], Álvaro Torres-Rueda[1], Eugenia Sola-Moyano[1], Lourdes Blanca-Martos[1], Laura Fuentes-Sánchez[1], M. Dolores Martínez-Esteban[1], M. José Díez-de los Ríos[2], Alicia Bailén-García[3], Miguel González-Molina[1], Isabel García-González[4]

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[4] Servicio de Anatomía Patológica. Hospital Regional Universitario Carlos Haya. Málaga

Nefrologia 2012;32(1):35-43

Tratamiento con hemodiálisis larga con filtros de alto *cut-off* en la nefropatía por cilindros del mieloma: nuestra experiencia

Josefa Borrego-Hinojosa[1], M. Pilar Pérez-del Barrio[1], M. del Mar Biechy-Baldan[1], Enoc Merino-García[1], M. Carmen Sánchez-Perales[1], M. José García-Cortés[1], Esther Ocaña-Pérez[2], Patricia Gutiérrez-Rivas[1], Antonio Liébana-Cañada[1]

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Nefrologia 2013;33(4):515-23

Bortezomib-based therapy combined with high cut-off hemodialysis is highly effective in newly diagnosed multiple myeloma patients with severe renal impairment

Beatrice Anna Zannetti,[1] Elena Zamagni,[1] Marisa Santostefano,[2] Lucia Barbara De Sanctis,[2] Paola Tacchetti,[1] Elena Mancini,[2] Lucia Pantani,[1] Annamaria Brioli,[1] Raffaella Rizzo,[2] Katia Mancuso,[1] Serena Rocchi,[1] Annalisa Pezzi,[1] Enrica Borsi,[1] Carolina Terragna,[1] Giulia Marzocchi,[1] Antonio Santoro,[2] and Michele Cavo[1]*

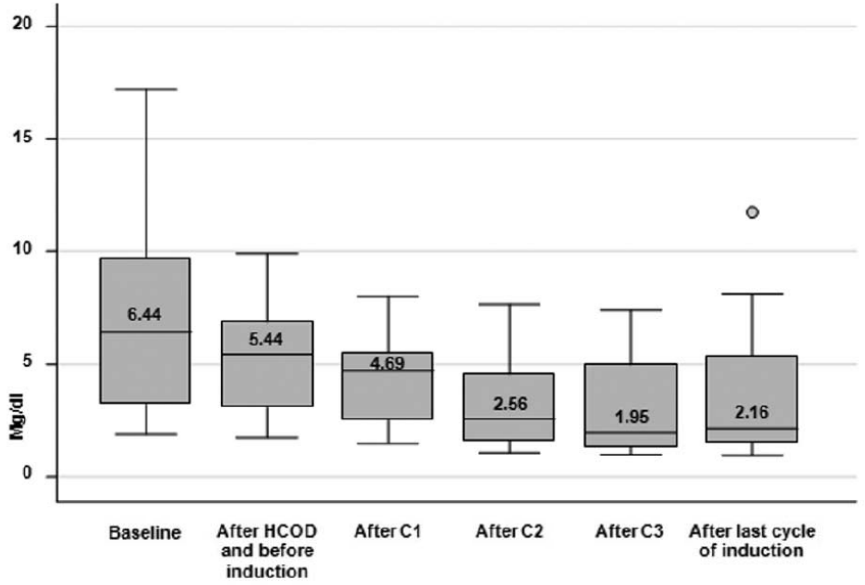


Figure 1. Serum creatinine reduction throughout cycles of induction treatment

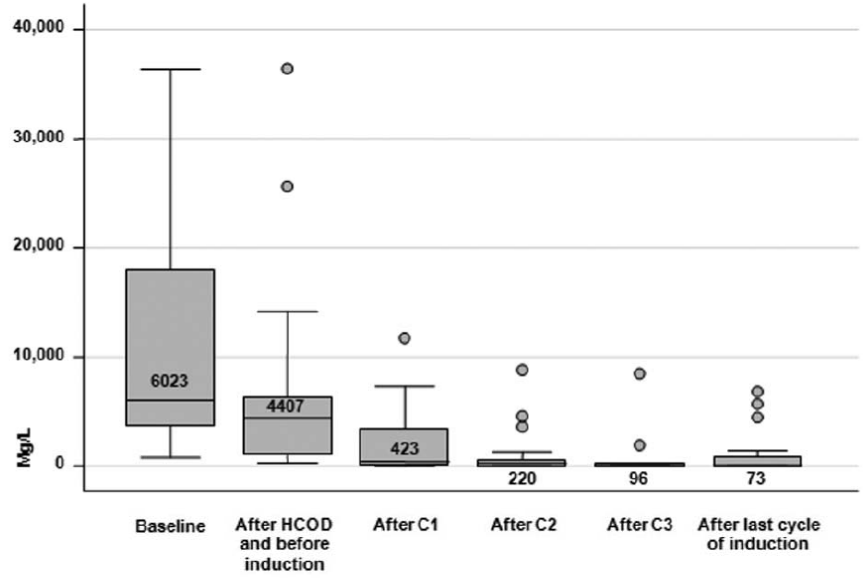


Figure 2. DeltaFLC reduction throughout cycles of induction treatment

Seminars in Dialysis

Is High Cut-Off Hemodialysis Effective in Myeloma Kidney?

Kevin W. Finkel
Section of Nephrology, Division of Renal Diseases & Hypertension, UTHealth Science Center at Houston, The University of Texas MD Anderson Cancer Center, Houston, Texas

To date, all trialswith HCO-HD membranes have been conducted without appropriate control groups.
The studies only report reduction in FLC concentrations with HCO-HD in combination with chemotherapy.
We currently do not know whether HCO-HD offers any additional benefit over current chemotherapeutic regimens.
Randomized controlled trials proving the benefit of adding HCO-HD to
patients with cast nephropathy treated with current chemotherapy will be necessary before its routine use can be recommended. **(EuLITE) (MYRE)**

Therefore, until the results of these trials are known, the answer to the question is “No.”

Seminars in Dialysis—Vol 27, No 3 (May–June) 2014 pp. 234–236

Riñón del mieloma

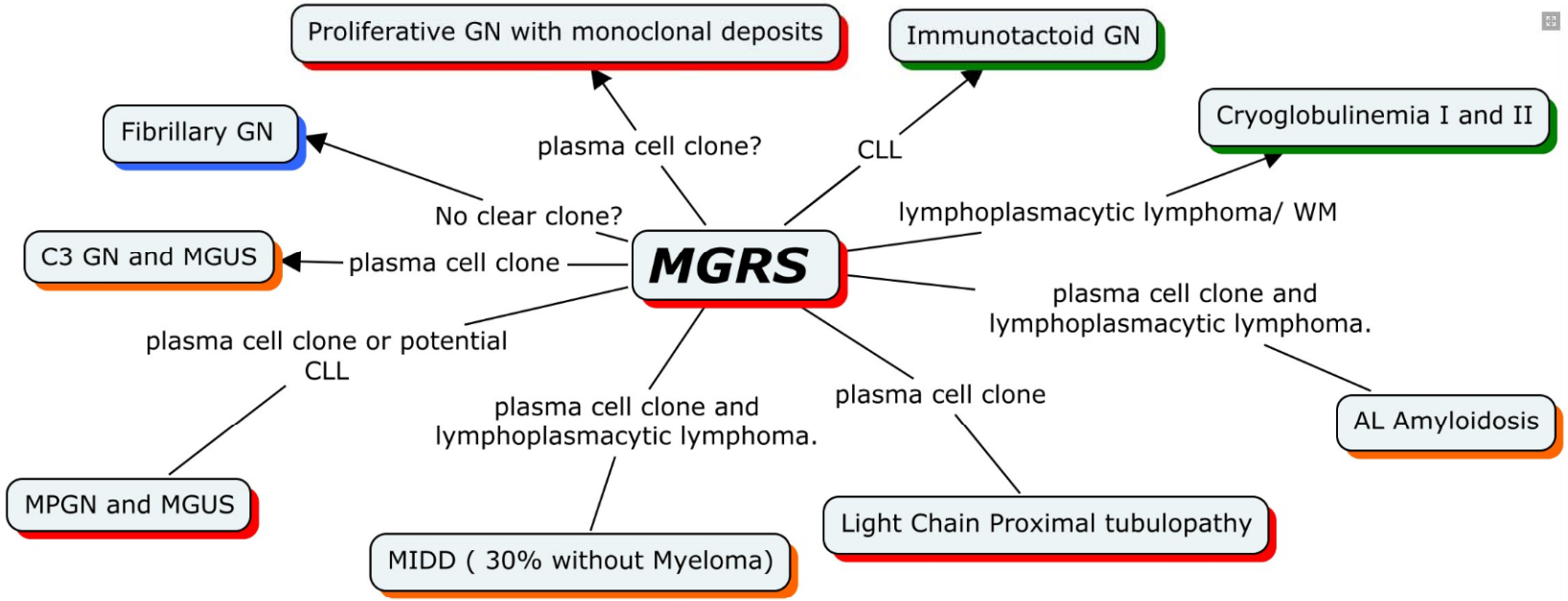
- Reducir la exposición a CLL
  - Aféresis con filtro de alto poro > 45 KD o >65KD
    - Preguntas.
    - ¿A todos los pacientes con FRA?
      - » ¿Qué nivels de FG?
    - ¿ Solo a los que requieren HD en el diagnóstico?
    - ¿ Son todas las CLL iguales?
    - ¿ Otras patologías renales diferentes de riñón del Mieloma?

Gammapatías monoclonales de significado renal

- Agrupa todas las alteraciones causadas por un inmunoglobulina monoclonal secretadas por un clon no maligno de Celulas B
  - No cumplen criterios de Mieloma
  - Alteraciones hematológicas se engloban dentro de la GMUS
- Están relacionadas con alta morbi-mortalidad
- Se requieren un alto índice de sospecha
- Rápido diagnóstico es crucial en el pronóstico

Diagnosis of monoclonal gammopathy of renal Significance.
Frank Bridoux1, Nelson Leung2,3, Colin A. Hutchison4 et all, Kidney Int 2015

La GMSR no es un enfermedad.



Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant

BLOOD, 22 NOVEMBER 2012 • VOLUME 120, NUMBER 22

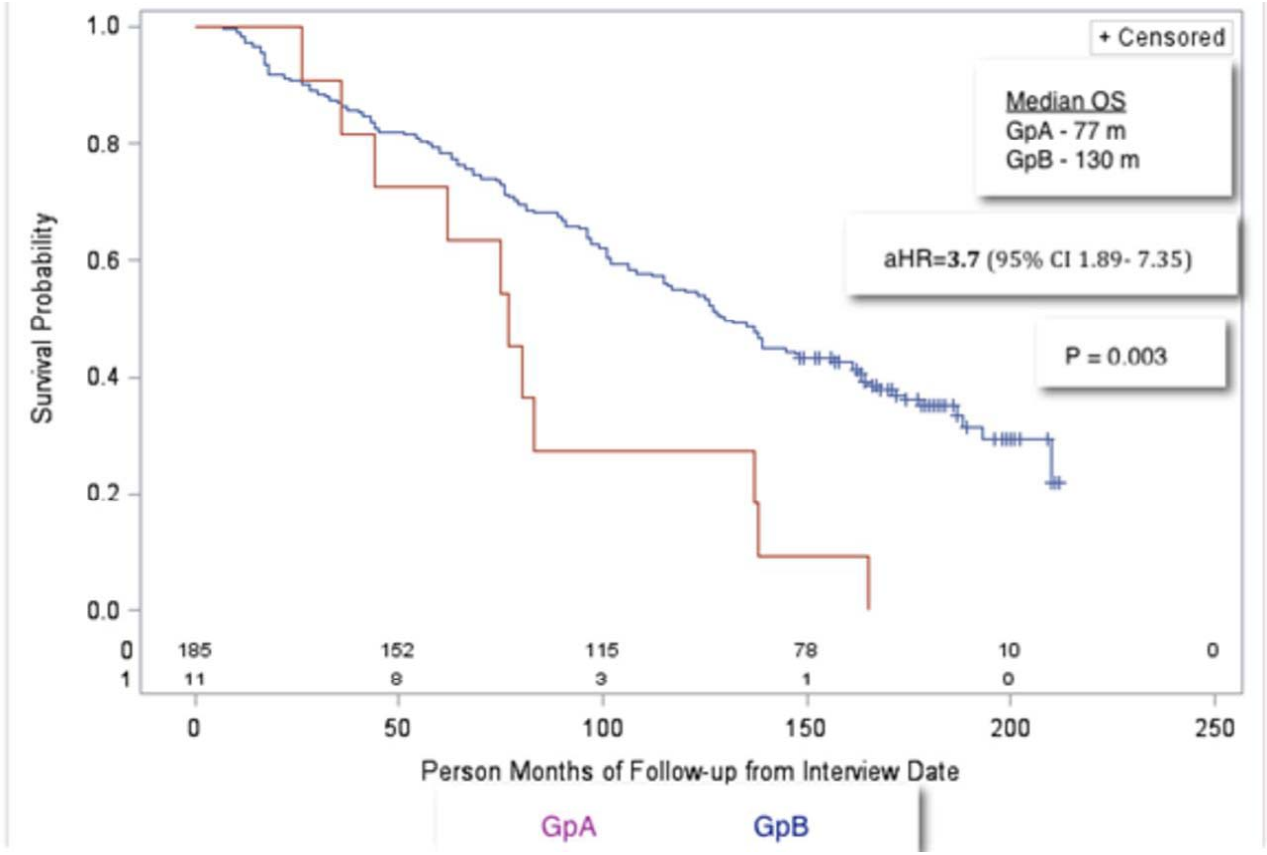
GMSR

- Solo el 8% de las Amiloidosis AL tiene criterios de MM en el diagnostico.
- La particularidades estructurales y no su cantidad condicionan la patología.
- La consideración de no malignidad ha condicionado su tratamiento hasta ahora.
- **MGUS no es igual a MGSR**

Diagnosis of monoclonal gammopathy of renal Significance.
Frank Bridoux1, Nelson Leung2,3, Colin A. Hutchison4 et all, Kidney Int 2015

Long Term Survival of Monoclonal Gammopathy of Renal Significance (MGRS): An Analysis of Nhanes III

Median over all survival between two groups:.



Mohammed Shaik, and Anas Al-Janadi Blood 2014;124:4849

GMSR

- La estrategia terapéutica se debe basar en el trastorno subyacente.
- La rápida reducción del componente monoclonal se ha demostrado efectiva
- En ausencia de supresión adecuada de la proteína monoclonal previamente al trasplante asegura su recurrencia dentro del primer año del mismo.

GMSR

- Prevalencia:

33,994 NHANES III subjects from the NHANES III database:

  - Prevalence of clinical MGRS (defined as renal insufficiency with no other obvious reason but MGUS) is 6% amongst patients with MGUS.

Shaik, M., & Al-Janadi, A. (2014). Long Term Survival of Monoclonal Gammopathy of Renal Significance (MGRS): An Analysis of Nhanes III. *Blood*,*124*(21), 4849-4849.

GMSR: Clasificación

- **Glomerular:**
  - Depósitos organizados
    - Fibrilares
      - Amiloidosis AL
      - Gn fibrilar
    - Microtubulares
      - Gn crioglobulinémica tipo I
      - Gn Inmunotactoide
  - Depósitos no organizados
      - Gn membranoproliperativa con depósitos monoclonales de Igs
      - Enfermedad por depósito de cadenas ligeras
      - Enfermedad por depósito de cadenas pesadas
      - C3 Glomerulonefritis

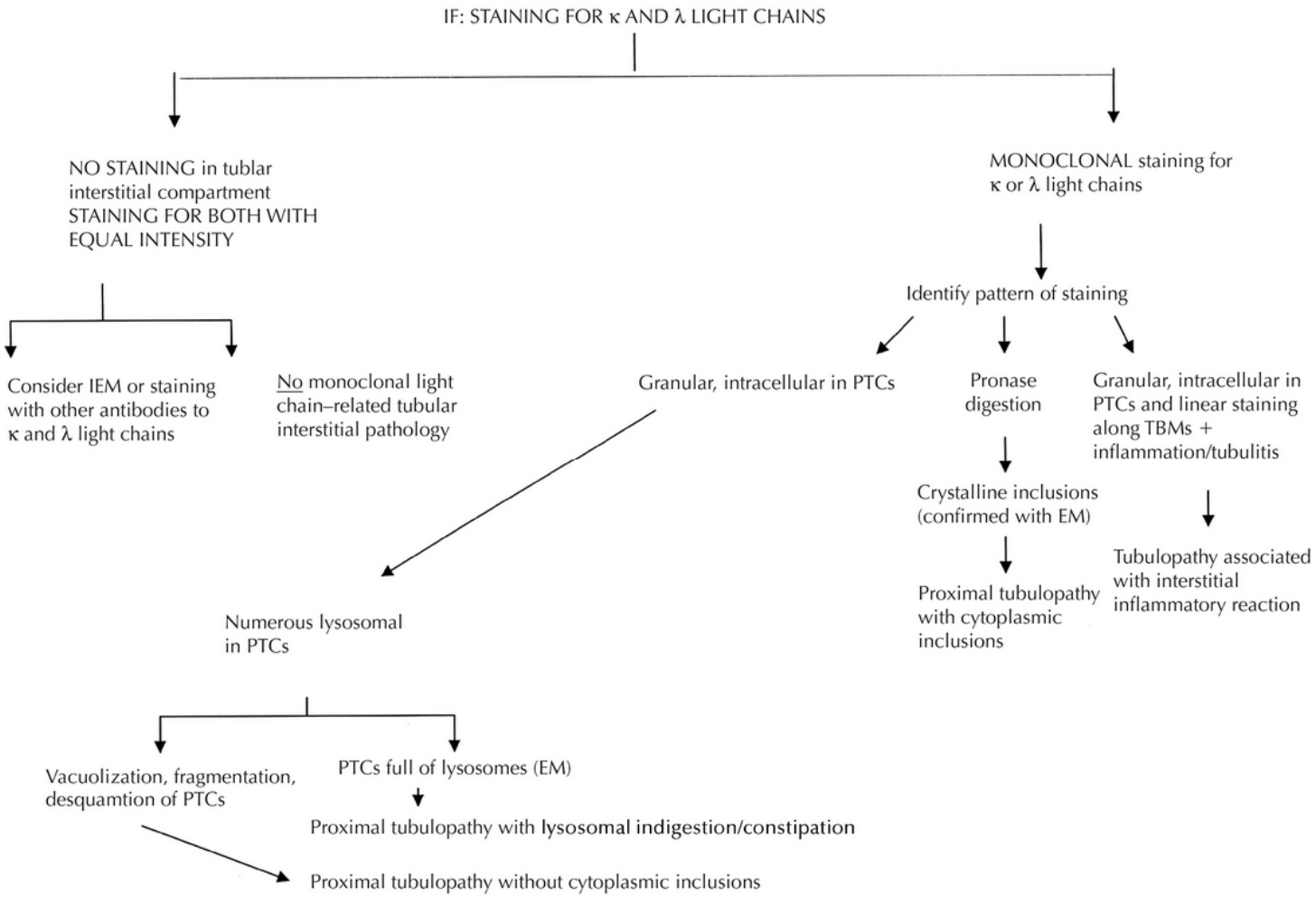
GMSR: clasificación

- **Tubular**:
  - Light Chain fanconi syndrome
  - Tubulopatía proximal sin cristales
  - Histicoitosis con depósito de cristales.

Proximal Tubulopathies Associated With Monoclonal Light Chains

The Spectrum of Clinicopathologic Manifestations and Molecular Pathogenesis

Guillermo A. Herrera, MD



IF: Immunofluorescence
IEM: Immunoelectron microscopy
EM: Electron microscopy
PTCs: Proximal tubular cells
TBMs: Tubular basement membranes

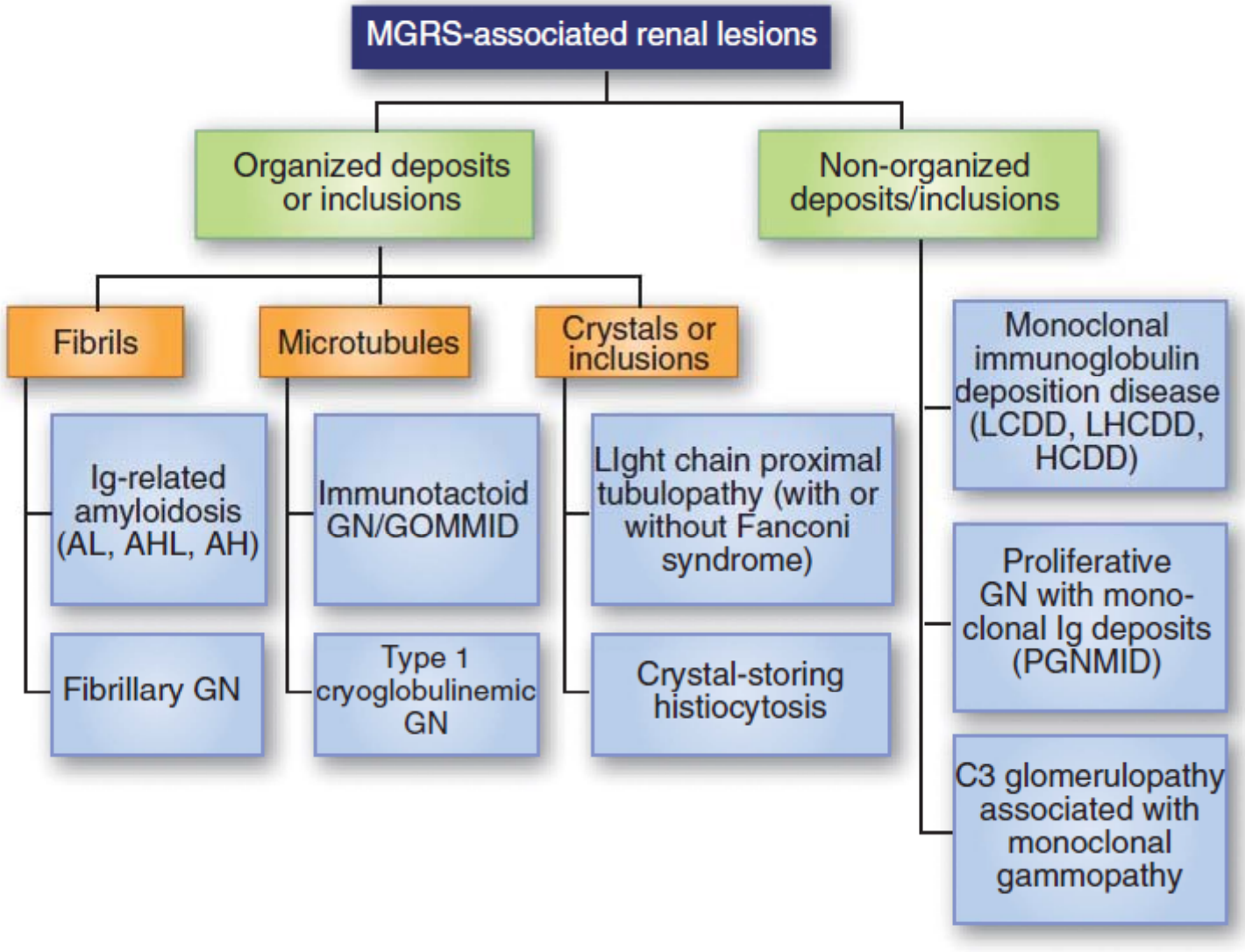


Figure 2 | Diagram of MGRS-associated renal lesions.

Diagnosis of monoclonal gammopathy of renal Significance.
Frank Bridoux1, Nelson Leung2,3, Colin A. Hutchison4 et all, Kidney Int 2015

GMSR

- D. organizados
  - Fibrilares
    - Amiloidosis AL

- Enfermedad sistémica

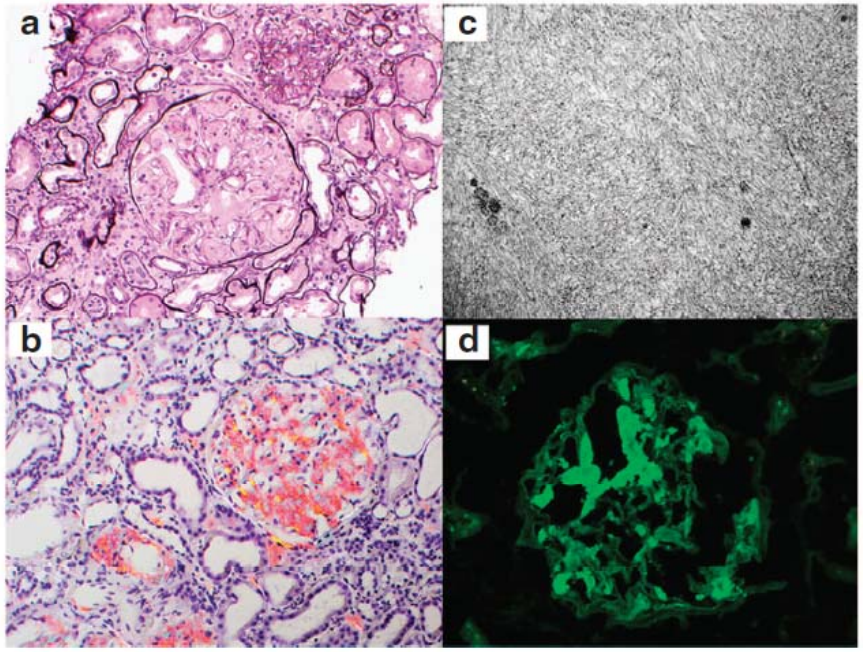


Figure 3 | Pathology of renal Ig–related amyloidosis. (**a**) There is global marked mesangial and segmental glomerular capillary wall deposition of acellular non-argyrophilic amyloid deposits (silver stain, X200). (**b**) By definition, amyloid deposits should be Congo-red positive. The figure shows extensive glomerular and vascular and focal interstitial Congo-red positive amyloid deposits, which produce anomalous colors (yellow/orange/green) when viewed under polarized light (X200). (**c**) On high magnification at the ultrastructural level, amyloid fibrils appear haphazardly oriented and measure between 7 and 14 nm in diameter (electron microscopy, X46,000). (**d**) On immunofluorescence, amyloid deposits appear smudgy and show light chain restriction. The figure shows global mesangial and segmental glomerular capillary wall staining for lambda (X400). Staining for kappa was negative (not shown). Ig, immunoglobulin.

Diagnosis of monoclonal gammopathy of renal Significance.
Frank Bridoux1, Nelson Leung2,3, Colin A. Hutchison4 et all, Kidney Int 2015

GMSR

- D. organizados
  - Fibrilares no AL
    - GN Fibrilar

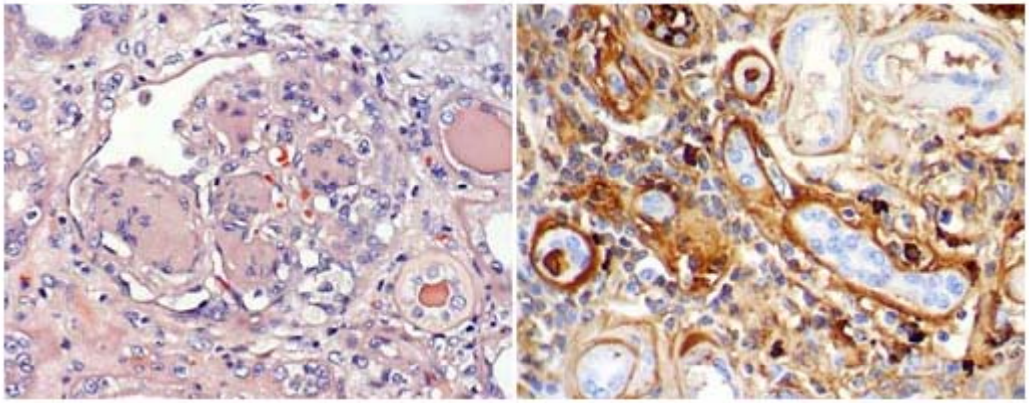


Figura 7. Izquierda: Tinción con rojo congo en la que no hay evidencia de depósitos de amiloide (también observado con luz polarizada - imagen negativa no mostrada), X400. Derecha: Inmunotinción con anticuerpos anti-Kappa demostrando depósitos de estas cadenas ligeras en membranas basales tubulares e intersticio; también se evidenciaron estos depósitos en los nódulos glomerulares, X200.

Diagnosis of monoclonal gammopathy of renal Significance.
Frank Bridoux1, Nelson Leung2,3, Colin A. Hutchison4 et all, Kidney Int 2015

GMSR

- D.organizados
  - Microtubulares
    - **Gn crioglobulinémica tipo I**

- S Nefritico, ERC
- GNMP/endcaopilar
- Microtombos
- Dp C3,C4, C1Q
- Afectación sistémica

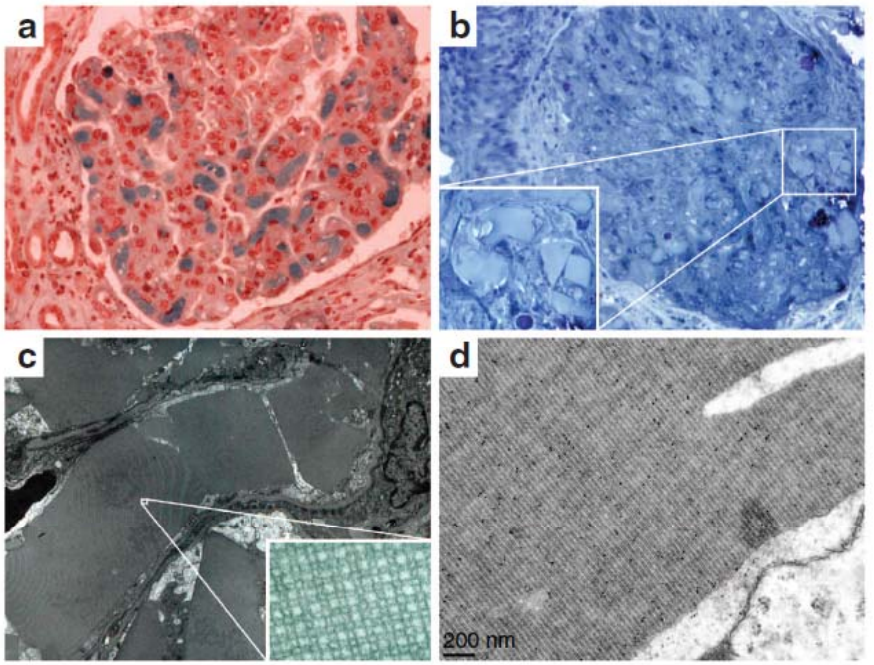


Figure 5 | Pathology of type I cryoglobulinemic glomerulonephritis. Kidney biopsy from a 65-year-old male patient with IgA lambda type I cryoglobulinemia. (**a**) Global endocapillary hypercellularity with numerous hyaline thrombi in glomerular capillary lumens (green light trichrome stain, X312). (**b**) The toluidine blue-stained semithin sections revealed crystalline inclusions within glomerular capillary lumens (X312, and insert X1000). (**c**) By electron microscopy (X2500), subendothelial deposits and hyaline thrombi were highly organized with a remarkable 'grid-like' appearance on higher magnification (insert, X100,000). (**d**) Immunoelectron microscopy, anti-human lambda light-chain gold conjugate (X60,000). Numerous gold particles specifically decorated crystalline glomerular thrombi. Similar staining was observed with the anti-alpha conjugate, whereas no significant staining was seen with anti-gamma, anti-μ, and anti-kappa conjugates (not shown).

Diagnosis of monoclonal gammopathy of renal Significance.
Frank Bridoux1, Nelson Leung2,3, Colin A. Hutchison4 et all, Kidney Int 2015

GMSR

- D. organizados
  - Microtubulares
    - **Inmunotactoide**

- Proteinuria, SN, ERC, microhematuria ,HTA
- GN mesangial
- Ig1, k>L, C3, C4 y C1q
- C3 bajo 3%

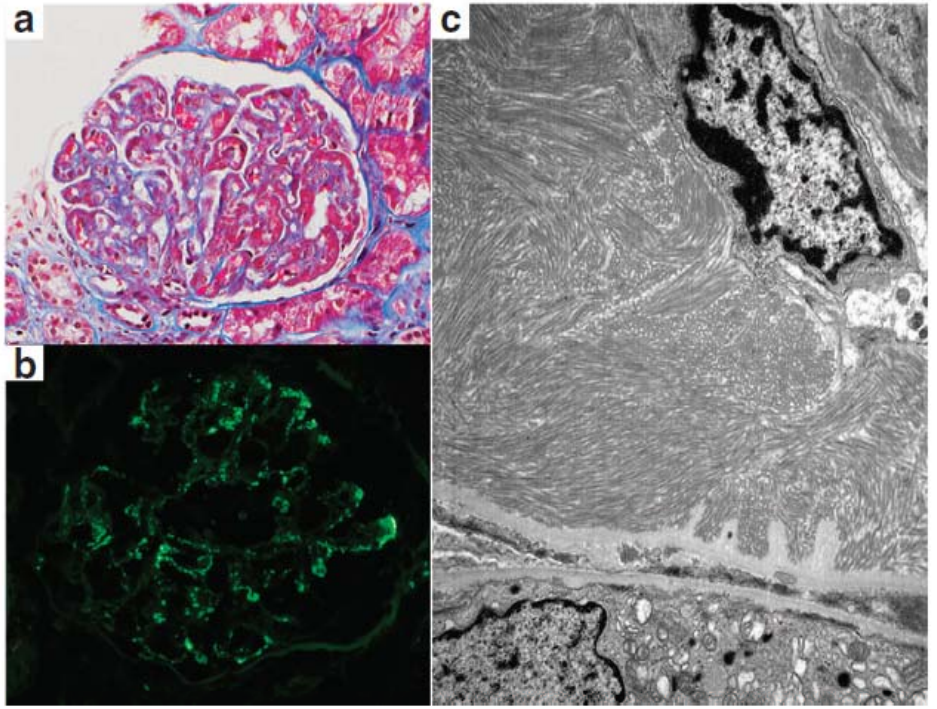


Figure 4 | Pathology of immunotactoid glomerulopathy. (**a**) The glomerulus shows global glomerular capillary wall thickening and mesangial expansion by red-staining immune deposits (trichrome stain, X400). (**b**) In this case of immunotactoid glomerulopathy with a predominantly membranous pattern of injury, there is coarsely granular global glomerular capillary wall and segmental mesangial staining for IgG (X400). Similar glomerular staining for lambda was seen, with negative staining for kappa (not shown). (**c**) Electron microscopy in a different case exhibits large subendothelial and mesangial deposits composed of large microtubules (mean 52 nm) with hollow centers, which are organized in parallel arrays (X9700).

Diagnosis of monoclonal gammopathy of renal Significance.
Frank Bridoux1, Nelson Leung2,3, Colin A. Hutchison4 et all, Kidney Int 2015

GMSR

- Inclusiones
  - LC tubulopatía proximal

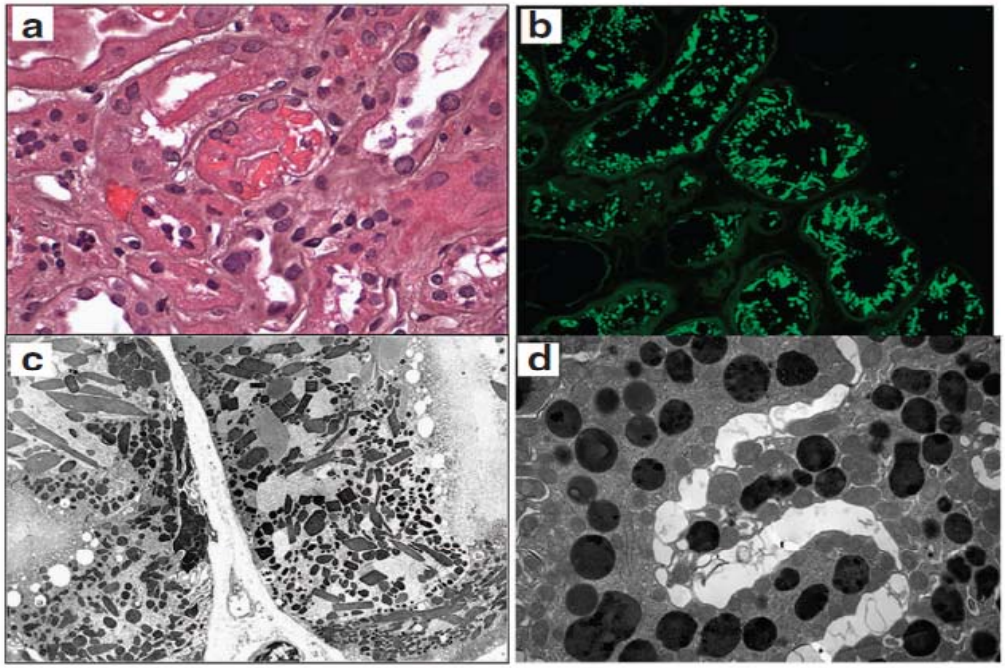


Figure 6 | Pathology of light-chain proximal tubulopathy. (**a**) Large rod-shaped hypereosinophilic crystals are seen within the cytoplasm of some proximal tubular cells. (H&E, X600). (**b**) By immunofluorescence performed on pronase-digested, paraffin-embedded tissue, proximal tubular crystals stain strongly for kappa (as shown) with negative lambda (not shown). The intracellular crystals failed to stain for kappa or lambda on standard immunofluorescence on frozen tissue (not shown). (**c**) Ultrastructurally, the proximal tubular cells are loaded with electron dense light-chain crystals with rod, rhomboid, or rectangular shapes. The crystals are present predominantly free within the cytoplasm (not membrane-bound). The proximal tubular brush borders appear intact (X1850). (**d**) In this case of light-chain proximal tubulopathy, the proximal tubular cells are filled with large election dense phagolysosomes, without crystals (electron microscopy, X9700). H&E, hematoxylin and eosin.

GMSR

- Cristales
  - **Crystal storing hysticitosis**

- Tubulopatía /ERC
- GNMPo Endocapilar
- Afectación cutánea
- Hipocomplementemia

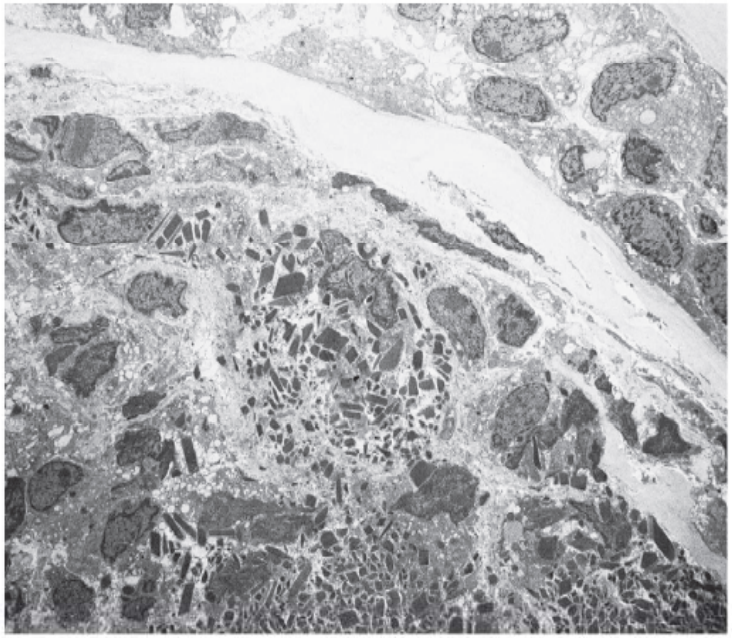


Figure 7 | Pathology of crystal-storing histiocytosis. The figure shows numerous light-chain crystals with rod, needle, or rhomboid shapes, within the cytoplasm of interstitial infiltrating histiocytes. The tubule depicted in the upper portion of the image does not exhibit intracytoplasmic or intraluminal crystals (electron microscopy, X1850).

GMSR

- D. no organizados
  - **MIDD**
    - **LCDD**
    - **LHDCDD**
    - **HCDD**

- Proteinuria, SN Microhematuria, HTA
- G Nodular
- Afectación sistémica
- C3 bajo en IgG1 y 3

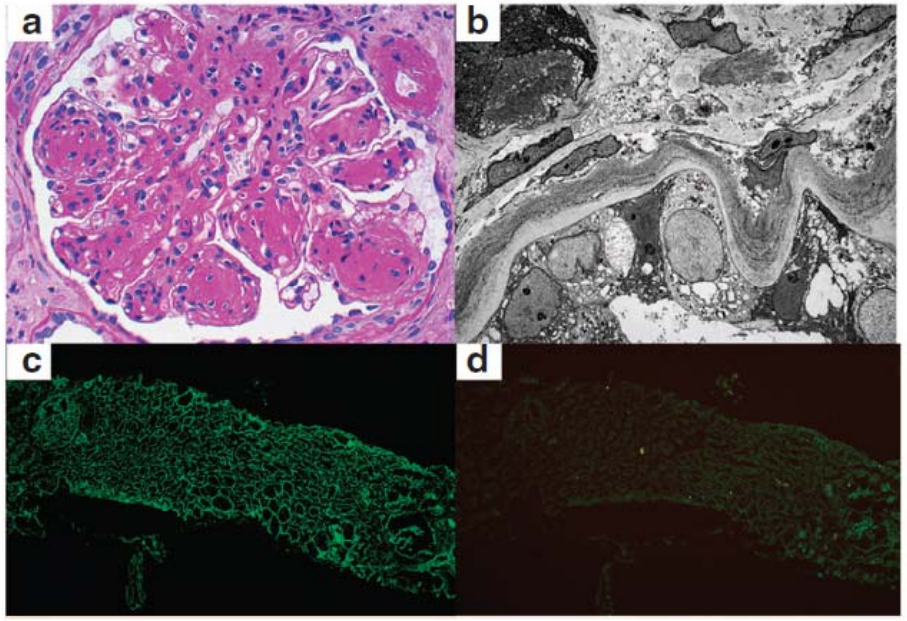


Figure 8 | Pathology of renal monoclonal immunoglobulin deposition disease. (**a**) The glomerulus shows nodular mesangial sclerosis, which is seen in most but not all cases of MIDD. The nodules are PAS-positive similar to the nodules of diabetic glomerulosclerosis (PAS, X400). (**b**) The diagnostic ultrastructural finding in MIDD is finely granular electron dense deposits involving the outer aspect of the tubular basement membranes (as seen in this figure) and the inner aspect of the glomerular basement membranes (not shown) (electron microscopy, X2400). (**c** and **d**) In this case of LCDD kappa type, immunofluorescence reveals diffuse linear glomerular and tubular basement membranes staining for kappa (**c**) with negative staining for lambda (**d;** X100 for **c** and **d**). LCDD, light chain deposition disease; MIDD, monoclonal immunoglobulin deposition disease. PAS, periodic acid–Schiff.

GMSR

- Depósitos no organizados
  - **Gn proliferativas con depósitos monoclonales de Igs**

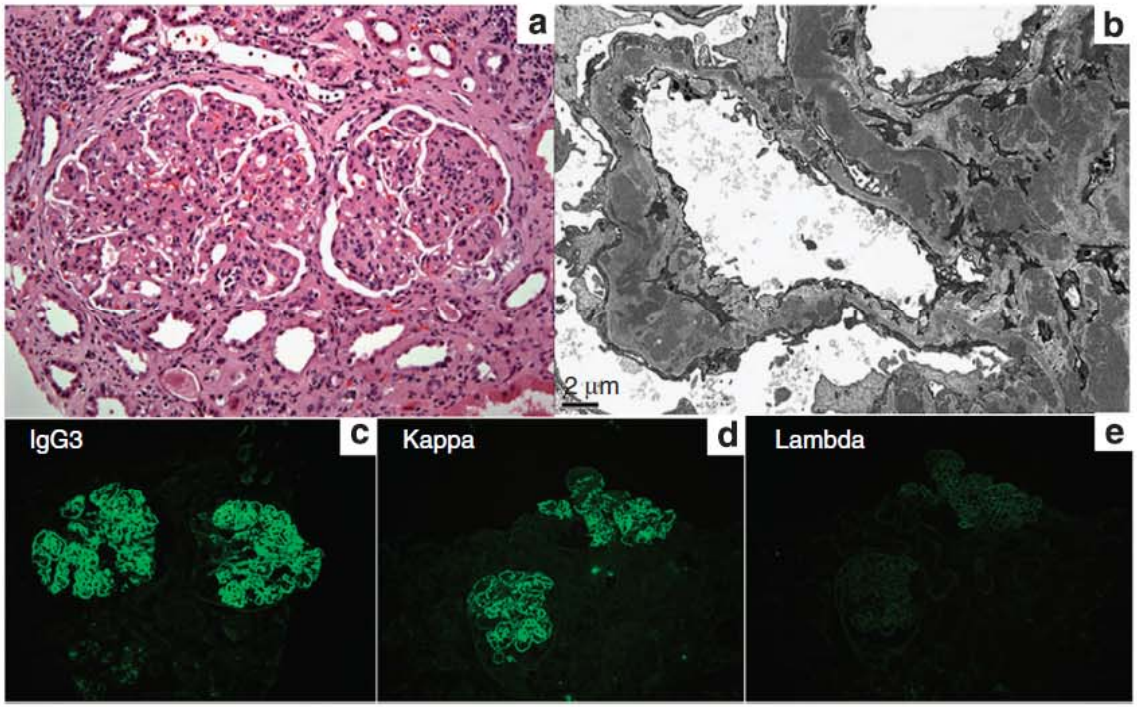


Figure 9 | Pathology of proliferative glomerulonephritis with monoclonal IgG deposits. (**a**) Glomeruli exhibit marked global mesangial and segmental endocapillary hypercellularity (H&E, X200). (**b**) On electron microscopy, there are large mesangial, intramembranous, and subepithelial deposits, together with segmental duplication of the glomerular basement membrane. The electron dense deposits appear granular (without substructure; X6000). (**c–e**) Glomeruli in this case of PGNMID show bright global mesangial and glomerular capillary wall

GMSR

- Depósitos no organizados
  - Gn proliferativas con depósitos monoclonales de Igs

  – Proteinuria, SN Microhematuria, HTA, ERC
  – GNMP, endocapilar, Gn membranosa, Gn mesangial
  – Depósitos granulares mesangiales IG montípica IgG3, k>L
  – Depósitos de C3 y C1Q
  – Sin afectación extrarrenal
  – Pico monoclonal se detectcata solo en 10-30%
  – Pude parecer hipocomplementemia

Diagnosis of monoclonal gammopathy of renal Significance.
Frank Bridoux1, Nelson Leung2,3, Colin A. Hutchison4 et all, Kidney Int 2015

GMSR

- Depósitos no organizados
  - GN C3 con Gammapatía monoclonal

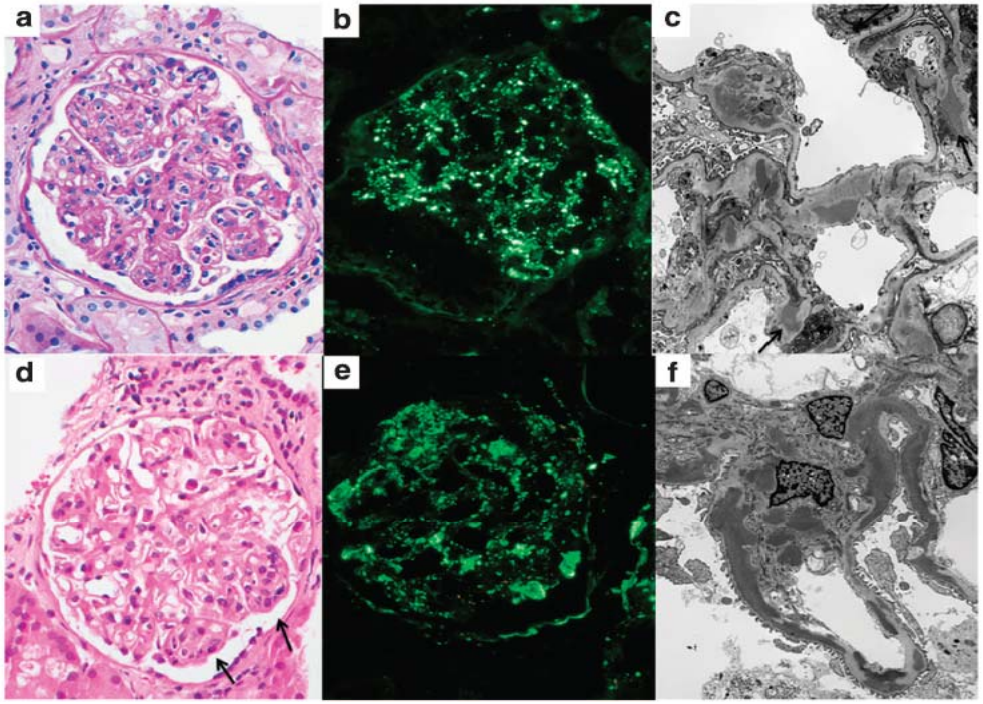


Figure 10 | Pathology of C3 glomerulopathy. a–c are from a 69-year-old patient with IgG lambda MGRS and C3 glomerulonephritis. Complement pathway workup showed CFH risk polymorphism (Y402H). On light microscopy, the glomerulus shows marked global mesangial and segmental endocapillary hypercellularity with intracapillary infiltrating lymphocytes, monocytes, and some neutrophils (**a**; PAS, X200). On immunofluorescence, there is global granular mesangial and glomerular capillary loop staining for C3 (**b**, X200). Glomeruli were negative for IgG, IgA, IgM, kappa, and lambda in this case (not shown). Ultrastructurally, there are large electron dense mesangial deposits and scattered subepithelial deposits (arrows; **c**, X7830). **d–f** are from a 59-year-old male with IgG kappa MGRS and dense deposit disease. Complement pathway workup was positive for FH autoantibody. The glomerulus depicted shows global mesangial hypercellularity and segmental occlusion of peripheral capillaries by endocapillary hypercellularity and influx of inflammatory cells (arrows). The glomerular basement membranes appear segmentally thickened (**d**; H&E, X200). Immunofluorescence highlights global granular to semilinear glomerular capillary wall and mesangial C3 deposits, with linear staining of Bowman's capsule (**e**; X200). The defining feature of dense deposit disease is 'sausage-like' thickening of the glomerular basement membranes by highly electron dense intramembranous deposits. Large rounded mesangial electron dense deposits are also seen (**f**; X6000). CFH, complement factor H; H&E, hematoxylin and eosin; MGRS, monoclonal gammopathy of renal significance; PAS, periodic acid–Schiff.

C3 Glomerulonephritis Associated With Monoclonal Gammopathy: A Case Series

Ladan Zand, MD,[1] Andrea Kattah, MD,[1]* Fernando C. Fervenza, MD, PhD,[1] Richard J.H. Smith, MD,[2] Samih H. Nasr, MD,[3] Yuzhou Zhang, PhD,[2] Julie A. Vrana, PhD,[3] Nelson Leung, MD,[1] Lynn D. Cornell, MD,[3] and Sanjeev Sethi, MD, PhD[3]*

Am J Kidney Dis. 62(3):506-514. © *2013*

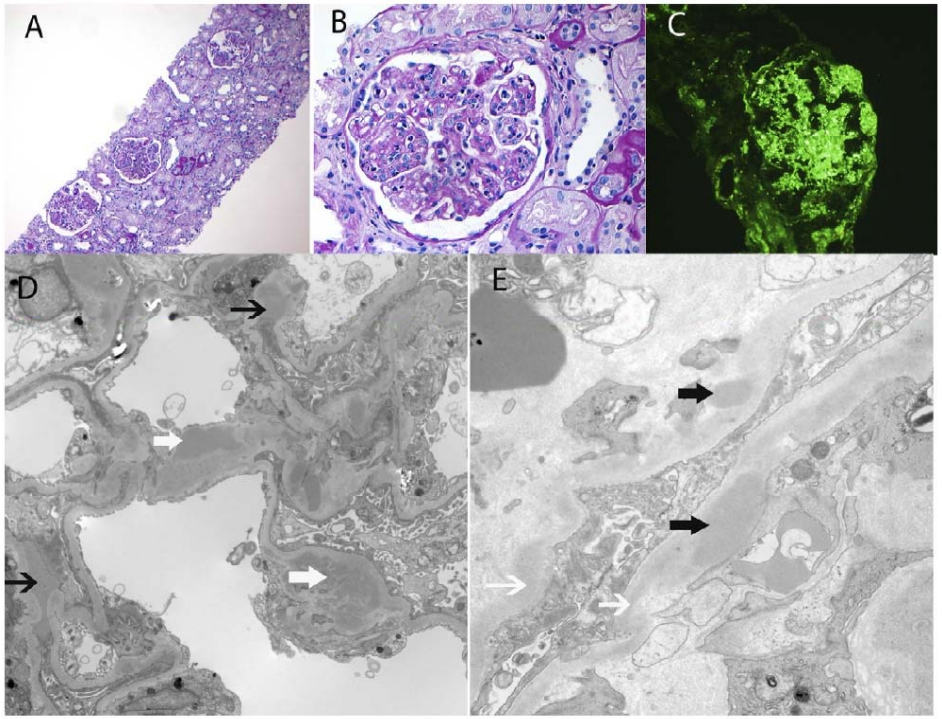


Figure 1. Representative light, immunofluorescence, and electron microscopy in patient 4 with C3 glomerulonephritis with monoclonal gammopathy. (A, B) Light microscopy shows a membranoproliferative pattern of injury. (Periodic acid–Schiff stain; original magnification, [A] ×10, [B] ×40.) (C) Immunofluorescence studies show bright C3 in the mesangium and along capillary walls. (Original magnification, ×40.) (D, E) Electron microscopy shows mesangial deposits (thick white arrows), subendothelial deposits (thick black arrows), subepithelial deposits (thin black arrows), and intramembranous deposits (thin white arrows). (Original magnification, [D] ×7,830, [E] ×17,900.)

- Gn C3 es un glomerulopatía en la que existe un disregulación del complemento
- La MGUS actuaría como disparador en la disrregulación del complemento
- El tratamiento está por definir.
- Se requiere un alto índice se sospecha

GMSR

- Se pueden asociar otros factores biológicos o actividad como anticuerpo de la paraproteína.

  – POEMS: Secreción de VEGF y MAT
  – GN MP por Lamda monoclonales diméricas que se comportan como autoanticuerpos frente al Facto H del complemento
  – Gn Membranosa por actividad cruzada de IgGk3 frente al receptor de la PLA2

Diagnosis of monoclonal gammopathy of renal Significance.
Frank Bridoux1, Nelson Leung2,3, Colin A. Hutchison4 et all, Kidney Int 2015

GMSR: Diagnóstico

- Biopsia renal: Identificar el depósito y la organización de los mismos.
  - Inmunofluroscencia o inmunohistoquímica
    - Kappa, lambda e Igs isotipos
  - M. E.
  - InmunoME
  - Análisis mediante microsisección laser o espectrofotometría de masas

  - **Importancia del Patólogo Motivado**

GMSR: Diagnóstico

- Evaluación Hematológica:
  - EEF en S y O.
  - IEF en S y O.
  - Determinación de cadenas ligeras libres en S y Orina.
  - Punción médula ósea
    - Citometria de flujo
    - Fish
  - Biopsia de ganglio linfático. (IgM)

  - **Importancia del Hematólogo Motivado.**

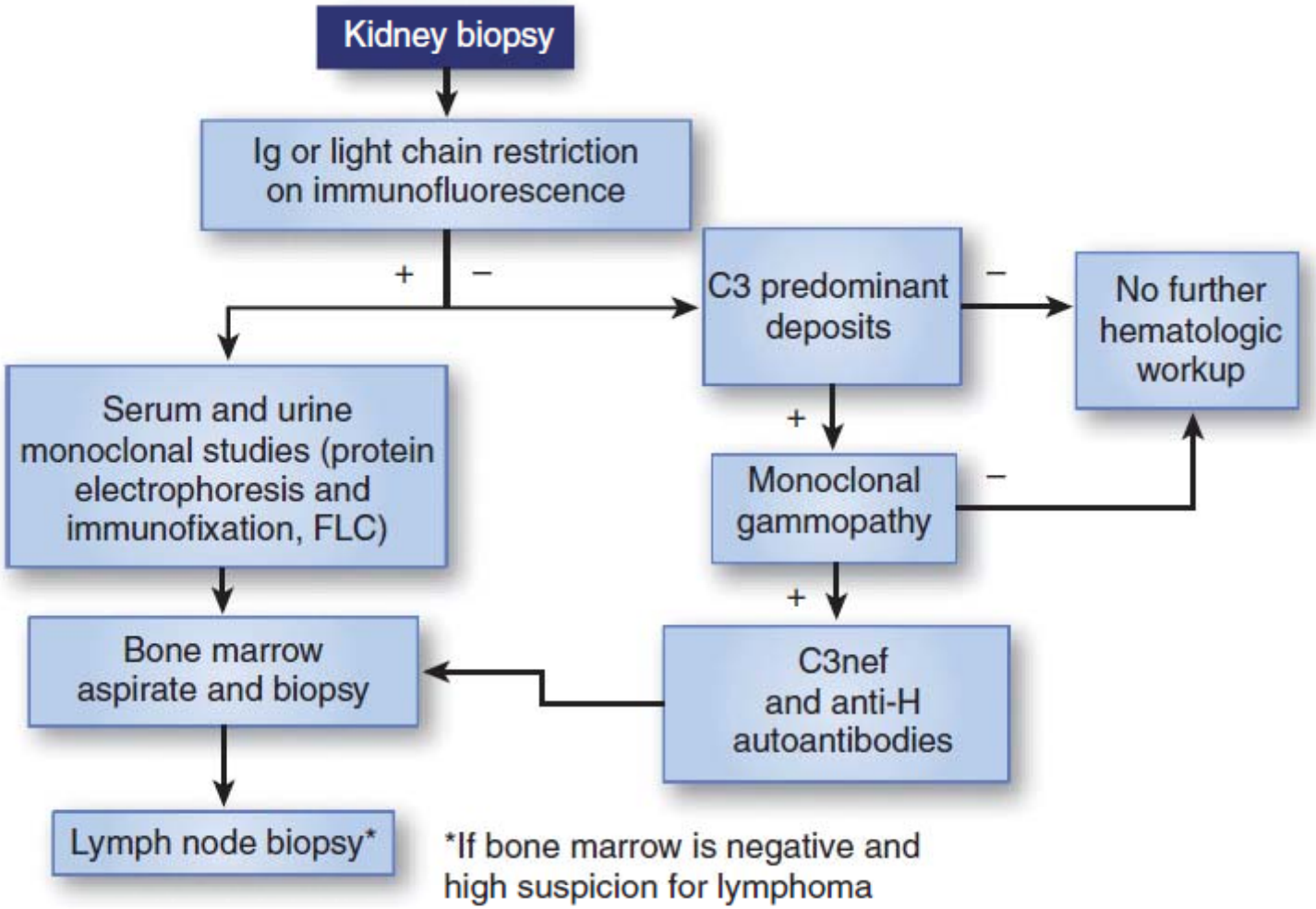


Figure 1 | Proposed algorithm for hematologic workup in patients with MGRS. MGRS, monoclonal gammopathy of renal significance; FLC, serum-free light chain assay.

Diagnosis of monoclonal gammopathy of renal Significance.
Frank Bridoux1, Nelson Leung2,3, Colin A. Hutchison4 et all, Kidney Int 2015

How I treat monoclonal gammopathy of renal significance (MGRS)

Jean-Paul Fermand,[1] Frank Bridoux,[2] Robert A. Kyle,[3] Efstathios Kastritis,[4] Brendan M. Weiss,[5] Mark A. Cook,[6] Mark T. Drayson,[7] Angela Dispenzieri,[3] and Nelson Leung,[3,8,9] on behalf of the International Kidney and Monoclonal Gammopathy Research Group

[1]University Hospital Center St. Louis, Paris, Ile de France, France; [2]Department of Nephrology and Transplantation, University Hospital Center Poitiers, Poitiers, France, [3]Division of Hematology, Mayo Clinic, Rochester, MN; [4]Department of Clinical Therapeutics, Alexandra Hospital, University of Athens, School of Medicine, Athens, Greece; [5]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; [6]Department of Laboratory Medicine and Pathology, and Departments of Hematology, and [7]Department of Immunity and Infection, University of Birmingham, Birmingham, UK; [8]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; and [9]Centre National de Référence Amylose AL , Poitiers, France

- No hay pautas claras de tratamiento establecido.
- Balance entre pronostico vital y pronóstico renal
- Estrategias:
    - Inhibición del depósito
    - Remoción del os depósitos
    - Tratamiento basado en el control del clon de célula plasmáticas.
        - Ciclofosfamida > Melfalan
        - Thalidomida > lenalidomida
        - Bortezomib
        - Autotrasplante (Amiloidosis AL)
- Seguimiento: Respuesta hematológica (cadenas ligeras)

- Tratamiento ERC
    - Trasplante renal

BLOOD, 21 NOVEMBER 2013 • VOLUME 122, NUMBER 22