UMC Utrecht

Monoclonal Gammopathy of Renal Significance: clinical and pathological aspects

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SKML meeting, February 13rd 2020

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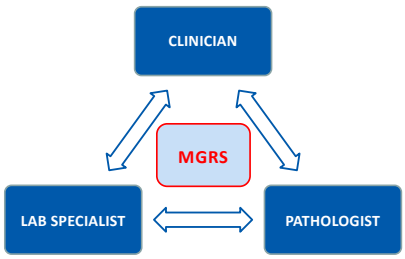
Take Home Message (1)



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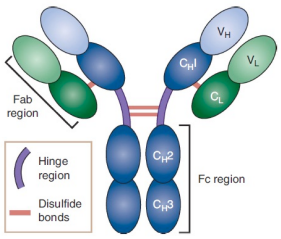
Immunoglobulin



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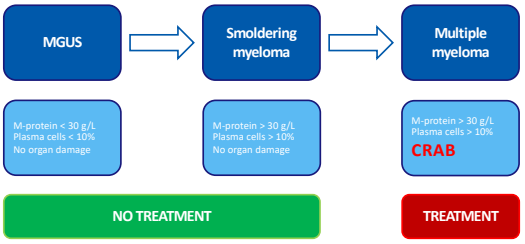

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HEMATLINE

Home

Titel: RICHTLIJN BEHANDELING MULTIPEL MYELOOM 2019

Initiatiefnemer: HOVON Myeloom werkgroep

Geautoriseerd door: Nederlandse Vereniging voor Hematologie

Autorisatiedatum: 25-06-2019

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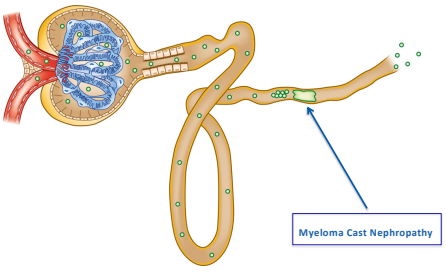
Myeloma Cast Nephropathy

Associated with high tumor burden



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MGRS → NEPHROPATHY → CKD/ESKD

M-protein < 30 g/L
Plasma cells < 10%

Monoclonal Gammopathy of Renal Significance

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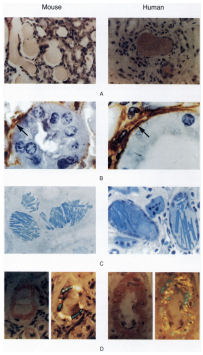
Pathophysiology of light chains in the kidney

Structure and biochemistry of light chains



- Light chain cast nephropathy
- Light chain deposition disease
- Light chain proximal tubulopathy
- AL amyloidosis

Solomon, NEJM 1991

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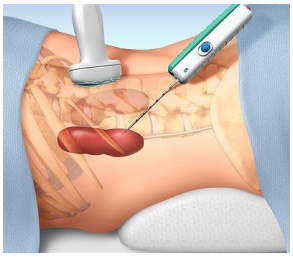
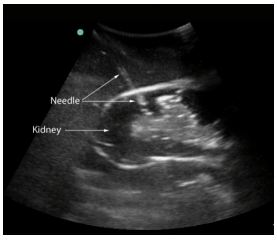
Kidney biopsy procedure





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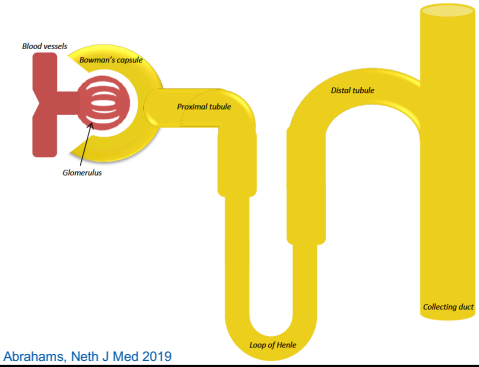
Compartments of the kidney



Amaador, Abrahams, Neth J Med 2019

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3D scan of glomerulus

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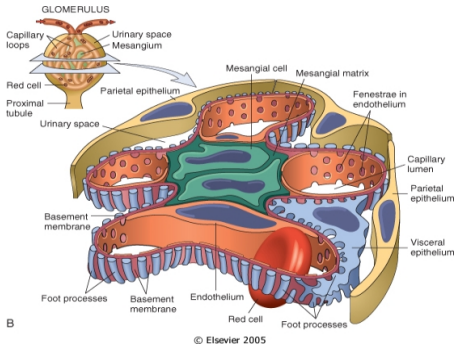
Schematic overview of glomerulus



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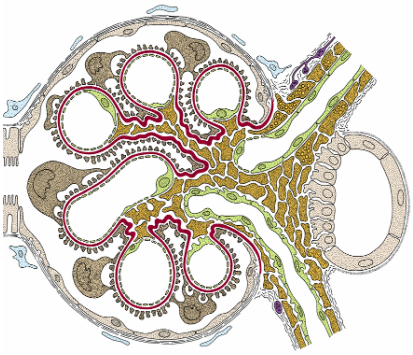
Normal glomerulus



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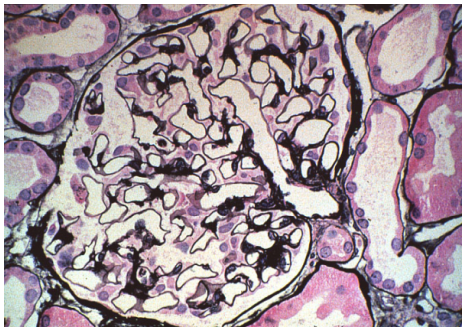
Normal glomerulus



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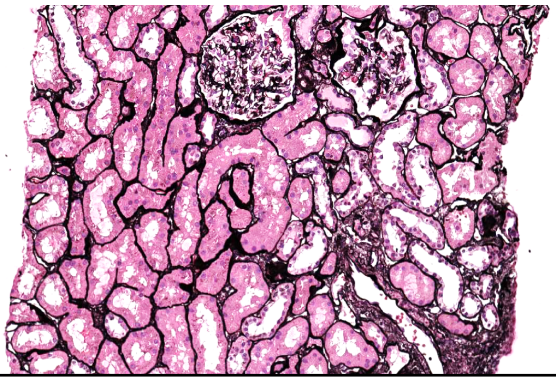
Normal histology of cortex



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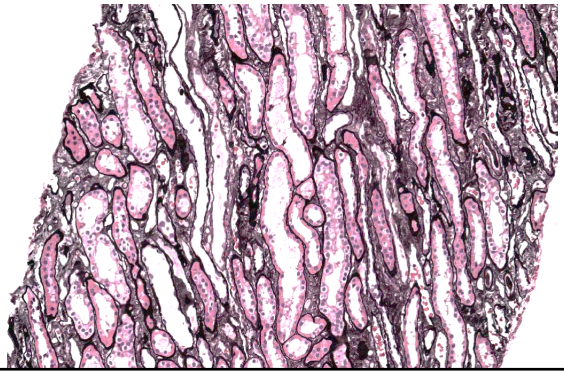
Normal histology of medulla



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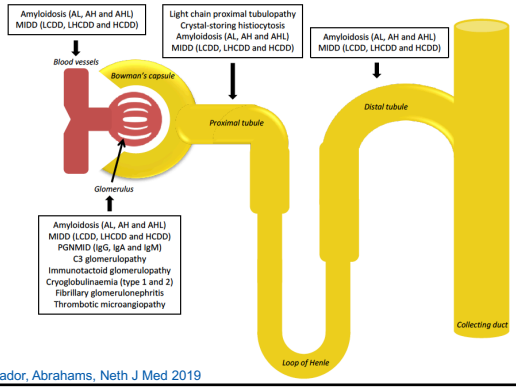
Localization of paraprotein-related kidney diseases



Amaador, Abrahams, Neth J Med 2019

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Case 1

- Male, 58 yrs
- Progressive CKD (serum creatinine 110 → 214 µmol/L in 3 yrs)
- Proteinuria > 1 gr/24h
- No active sediment
- M-protein: **IgG-κ**, not to quantify
- FLC: **free κ 1450 mg/L**, free λ 19.5 mg/L, κ-λ **ratio 74**

- Kidney biopsy:

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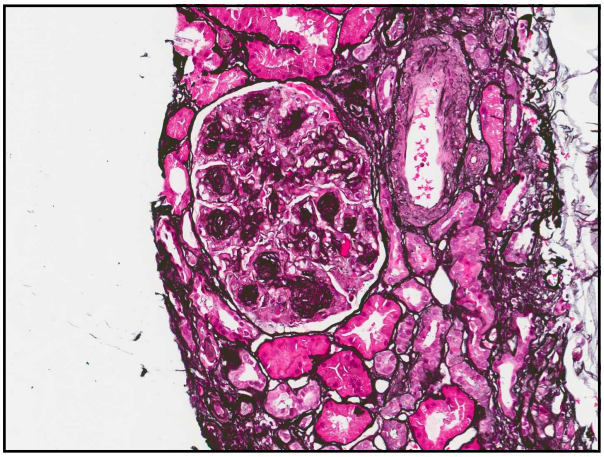

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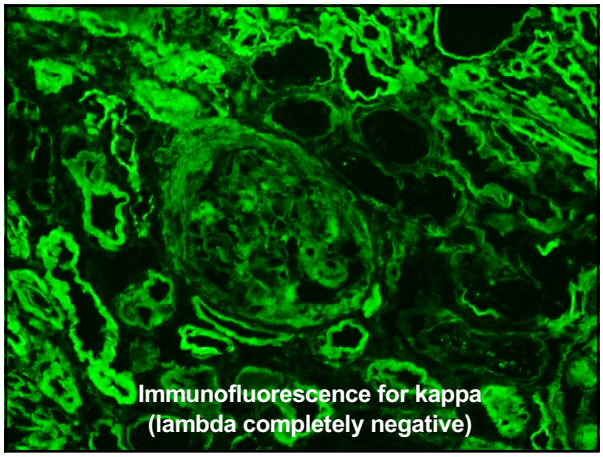

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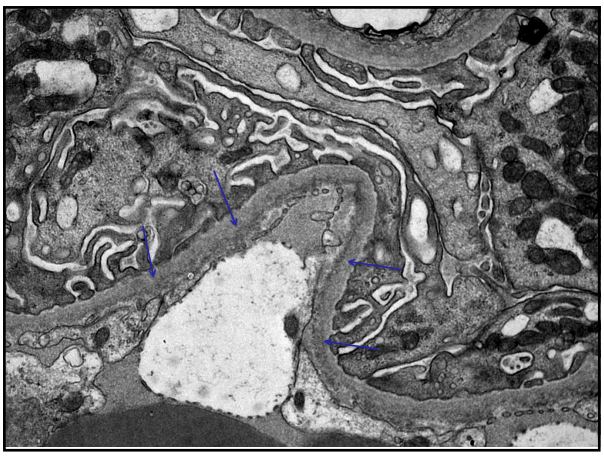

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Diagnosis case 1

Kidney biopsy with **light chain deposition disease (LCDD)**

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Case 2

- Female, 37 yrs
- Persistent proteinuria since pregnancy → 3.6 gr/24h
- Normal kidney function
- No active sediment
- M-protein: **IgG-κ**, not to quantify
- FLC: **free κ 20,26 mg/L**, free λ 12,48 mg/L, κ-λ ratio 1.62

- Kidney biopsy:

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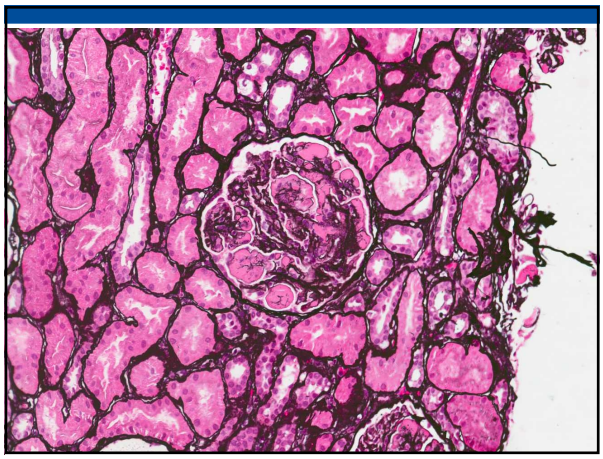

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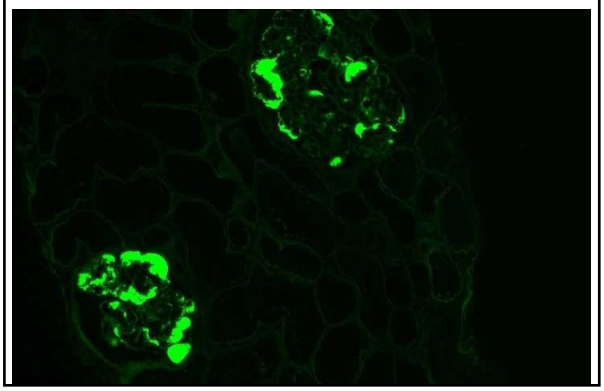
Immunofluorescence for IgG (IgA and IgM negative)



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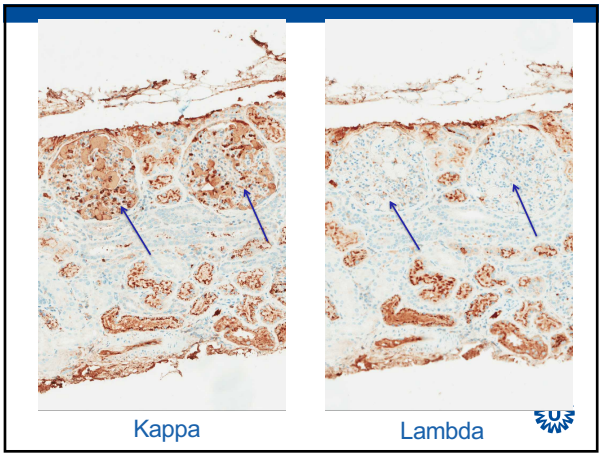

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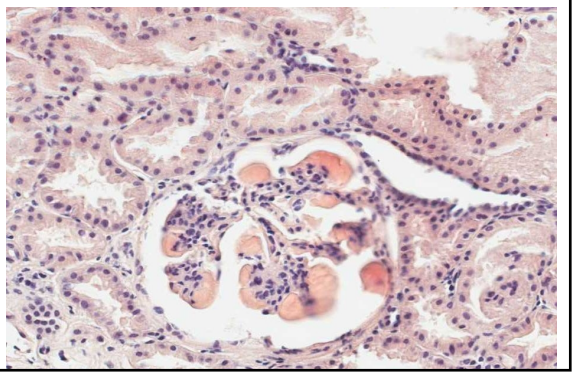
Congo red stain is negative



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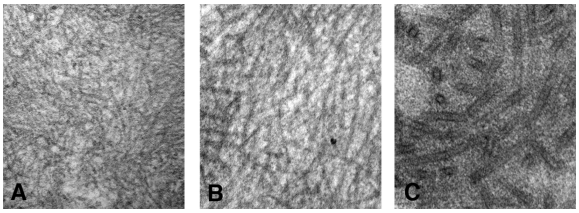
Electron microscopy for analysis of amorphous deposits



A	B	C
Amyloidosis	Fibrillary glomerulonephritis	Immunotactoid glomerulopathy
Disorderly arranged fibrils	Disorderly arranged fibrils	Microtubuli
8-12 nm	10-30 nm	30-50 nm

Alpers, JASN 2008

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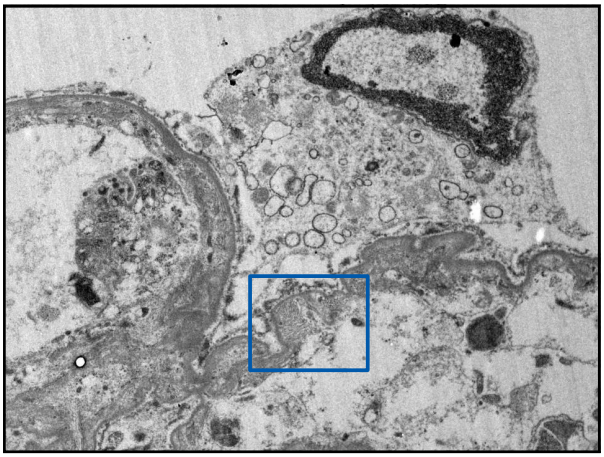

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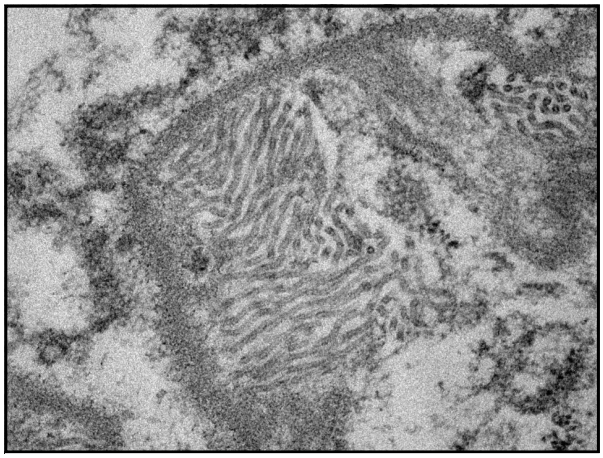

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Diagnosis case 2

Kidney biopsy with **immunotactoid glomerulopathy**

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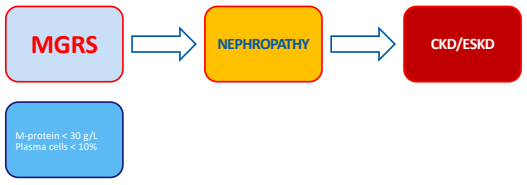

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blood

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

CME Article

Natural history and outcome of light chain deposition disease

Rabya H. Sayed,[1,2] Ashutosh D. Wechalekar,[1] Janet A. Gilbertson,[1] Paul Bass,[2] Shameem Mahmood,[1] Sajitha Sachchithanantham,[1] Marianna Fontana,[1] Ketna Patel,[1] Carol J. Whelan,[1] Helen J. Lachmann,[1] Philip N. Hawkins,[1] and Julian D. Gillmore[1]

[1]National Amyloidosis Centre and [2]Centre for Nephrology, Division of Medicine, University College London, London, United Kingdom

BLOOD, 24 DECEMBER 2015 • VOLUME 126, NUMBER 26

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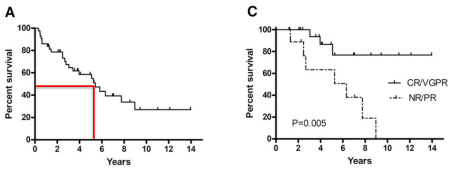
Renal survival depends on clonal respons



53 patients
Median renal survival 5.4 yrs
62% of patients required dialysis

Key Points

- Deep clonal responses to chemotherapy are associated with improved renal and overall outcomes in patients with light chain deposition disease.
- Deep clonal responses should be targeted, even in patients with advanced chronic kidney disease from light chain deposition disease.

Sayed, Blood 2015

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CJASN Clinical Journal of the American Society of Nephrology

CJASN ePress. Published on January 4, 2016 as doi: 10.2215/CJN.06290615

Article

Trends in Survival and Renal Recovery in Patients with Multiple Myeloma or Light-Chain Amyloidosis on Chronic Dialysis

Alexandre Decourt, Bertrand Gondouin,* Jean Christophe Delanziere,† Philippe Brunet,* Marion Sallée,* Stephane Burtey,* Bertrand Dussol,* Vadim Ivanov,‡ Regis Costello,§ Cecile Couchoud,‖ and Noemie Jourde-Chiche**

1459 patients with MG on dialysis
18% ALA, 23% LCDD, 59% MCN
Median FU 13.1 months
Renal recovery in 9.1% of patients

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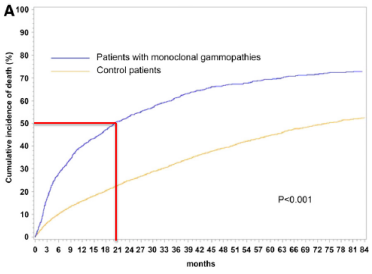
Survival of patients with MG on dialysis is poor



Decourt, CJASN 2016

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blood

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Treatment of B-cell disorder improves renal outcome of patients with monoclonal gammopathy–associated C3 glomerulopathy

Sophie Chauvet,[1-3] Véronique Frémeaux-Bacchi,[2,4] Florent Petitprez,[5] Alexandre Karras,[1] Laurent Daniel,[6] Stéphane Burtey,[7] Gabriel Choukroun,[8] Yahsou Delmas,[9] Dominique Guerrot,[10] Arnaud François,[11] Moglie Le Quintrec,[12] Vincent Javaugue,[13,14] David Ribes,[15] Laurence Vrigneaud,[16] Bertrand Arnulf,[17] Jean Michel Goujon,[14,18] Pierre Ronco,[19] Guy Touchard,[13,14] and Frank Bridoux[13,14]

BLOOD, 16 MARCH 2017 • VOLUME 129, NUMBER 11

French cohort of 201 C3 GP patients
50 patients had also monoclonal Ig
66% male, median age 65 yrs
sCreat 158, eGFR 37 ml/min
Proteinuria 3.1 gr/24h, NS in 43%

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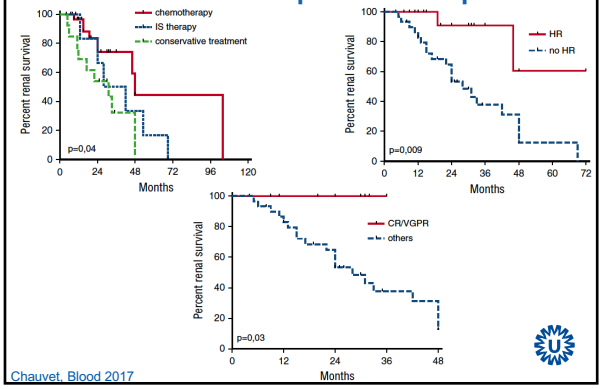
Renal survival depends on respons



Chauvet, Blood 2017

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When to consider MGRS

- **Renal symptoms** → clinical manifestations depend on affected segment of nephron
  - Renal impairment
  - Proteinuria/nephrotic syndrome
  - Hematuria
  - Hypertension
  - Proximal tubular dysfunction
- **M protein**
- No other obvious cause for renal symptoms
- C3 glomerulopathy and TMA

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Diagnostic evaluation

Renal disease
- History
- RR, edema
- **Lab**: creat, albumin, lipids, CBC, Ca, glucose, bicarb, PO_4, uric acid
- **Urine sediment**
- **Urinalysis**: creat, total protein, albumin, glucose, PO_4, uric acid, pH
- **24h urine**: creat, total protein, Bence Jones

M protein testing
- Serum protein electrophoresis
- Urine protein electrophoresis
- Serum and urine immunofixation
- **Serum free light chain assay**
- Total IgM, IgA, IgG

- Lymphadenopathy, hepatosplenomegaly

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Monoclonal FLC detection

Table 3. *Overview of methods for monoclonal FLC detection*

	Serum protein EP	Urine protein EP	Serum IF	Urine IF	sFLC assay
Quantitative or qualitative	Semi-quantitative	Semi-quantitative	Qualitative	Qualitative	Quantitative: independent measurement of κ and λ FLC + calculation of a κ/λ ratio
FLC detection limit (sensitivity)	500-2000 mg/l	20-50 mg/l	150-500 mg/l	20-50 mg/l	κ: 1.5 mg/l λ: 3 mg/l
Advantages	Inexpensive; Easy to perform.	Inexpensive; Easy to perform.	10X more sensitive than serum PE.	-	Valuable as prognostic factor; Valuable for monitoring response to therapy.
Disadvantages	Low sensitivity for detection of low levels M-proteins, FLCs in particular.	FLCs in urine only when tubular reabsorptive capacity is overwhelmed; 24-hour urine collection required; Identification of monoclonal FLCs is a subjective interpretation of EP results; Difficult interpretation of EP results in concentrated urine or proteinuria.	-	FLCs in urine only when tubular reabsorptive capacity is overwhelmed 24-hour urine collection required.	More expensive; FLC assays are not accurate and measurements results are not equivalent between different methods; Assay reactivity of monoclonal and polyclonal κ and λ FLC in specific disease groups needs improvement.

Amaador, Abrahams, Neth J Med 2019

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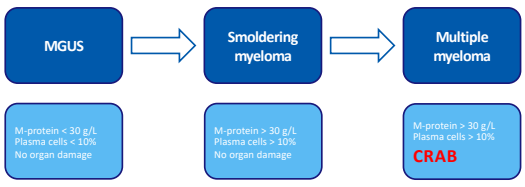
Hematologic work up

- BM biopsy and aspiration
- Low dose whole body CT/ CT neck/thorax/abdomen
- Abdominal fat aspiration if AL amyloidosis is suspected



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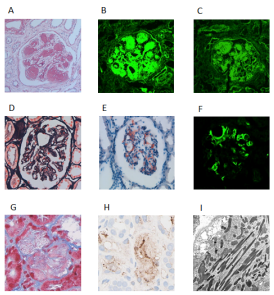
KIDNEY BIOPSY IS THE KEY



- Light microscopy
- Immunofluorescence
- Immunohistochemistry
- Electron microscopy
- Laser microdissection-mass spectrometry

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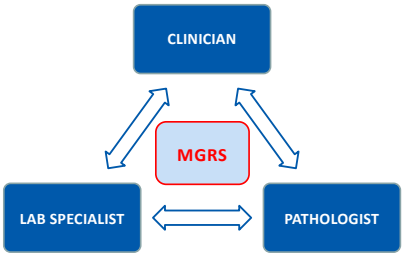
Take Home Message (1)



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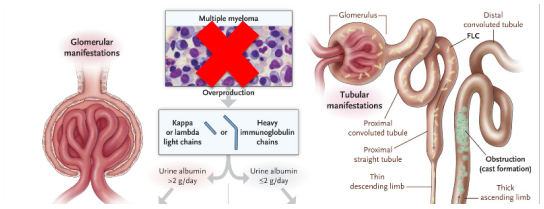
After the kidney biopsy…



… treatment of the clone

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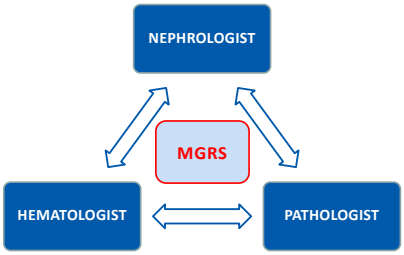
Take Home Message (1)



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Goals of treatment

- **Preserve or improve organ function**
  - Not to prevent progression of the B-cell clone
- Achieve (near) complete disappearance of the underlying B-cell clone/M-protein = **complete hematologic remission**
- NB: **no evidence-based recommendation**

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Treatment depends on

- Type of underlying clone in the bone marrow
  - B-cell clone with **IgM M-protein**
  - Plasma cell dyscrasia with **IgG, IgA, or LCs only**
- Renal metabolism and potential renal toxicity of therapy
- Presence of neuropathy in the patient

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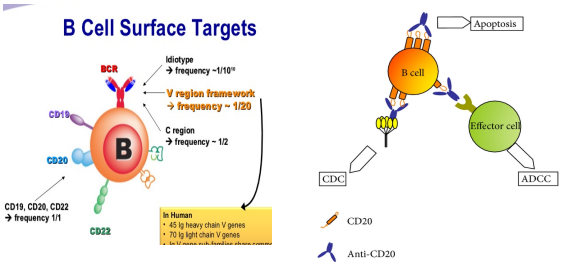
IgM M-protein

- B-cell NHL ≈ 17%
  - CD20 expression present: add Rituximab



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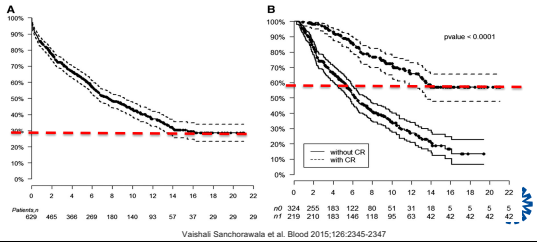
MGRS and IgA, IgG, LCs only

- Plasma cell clone (CD20 negative)
- Most data on AL amyloidosis: **survival** dependent on hematologic response



Vaishali Sanchorawala et al. Blood 2015;126:2345-2347

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Autologous stem cell transplantation

- Stem cell apheresis
- High dose melphalan → myeloablative
- "Rescue" therapy with stored stem cells

- Side effects: severe mucositis, pancytopenia (8 days), neutropenic fever, fatigue
- **Treatment related mortality: 0.8%**
- Morbidity mostly reversible, recovery 2-3 months

- Admission in hospital: 3 weeks or ambulatory
- Revalidation program recommended afterwards

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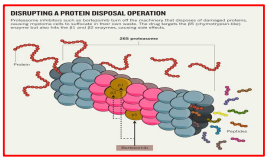
Proteasome inhibitors

- Interfere with the regulation of protein synthesis by turning off the machinery that disposes damaged proteins



- **Bortezomib** SC: day 1,4,8,11 / 3 weeks
- **Carfilzomib** IV: day 1,2,8,9,15,16 / 4 weeks
- **Ixazomib** PO (only in combination treatment with lenalidomide): day 1,8,15 / 4 weeks

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MGRS and IgA, IgG, LCs only

Eligible autologous SCT

- 3-4 courses **bortezomib**-dexa (+ cyclophosphamide)
- Stem cell apheresis
- High dose Melphalan with stem cell rescue = autologous SCT

Ineligible autologous SCT

- 6-8 courses **bortezomib**-dexa (+ cyclophosphamide)
- Alternative for bortezomib = lenalidomide

Cure?

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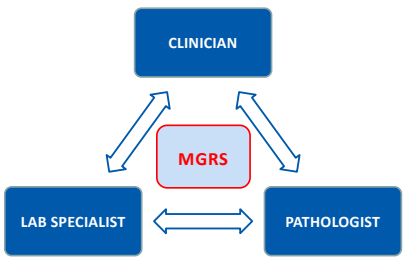
Take Home Message (1)



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Take Home Message (2)

- **In MGRS anti-clone directed therapy is indicated**
- **Goal: deep and longlasting hematologic remission**
- Choice of therapy will depend on
  - Type of clone
  - Eligibilty for autologous SCT
  - Side effects
  - *Scarce literature support*

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Benelux MGRS Working Group

- Dr MC Minnema, internist-hematologist UMCU
- Dr NWCJ van de Donk, internist-hematologist VUmc
- Dr AJ Croockewit, internist-hematologist Radboud UMC
- Dr TQ Nguyen, nephropathologist UMCU
- Dr AD Dendooven, nephropathologist UZ Antwerpen
- Dr JFM Jacobs, immunologist Radboud UMC
- Dr B Sprangers, internist-nephrologist UZ Leuven
- Prof dr J Wetzels, internist-nephrologist Radboud UMC
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REVIEW

Monoclonal gammopathy of renal significance (MGRS): histopathologic classification, diagnostic workup, and therapeutic options

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Thank you

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