# Management of renal failure in Myeloma (MM)

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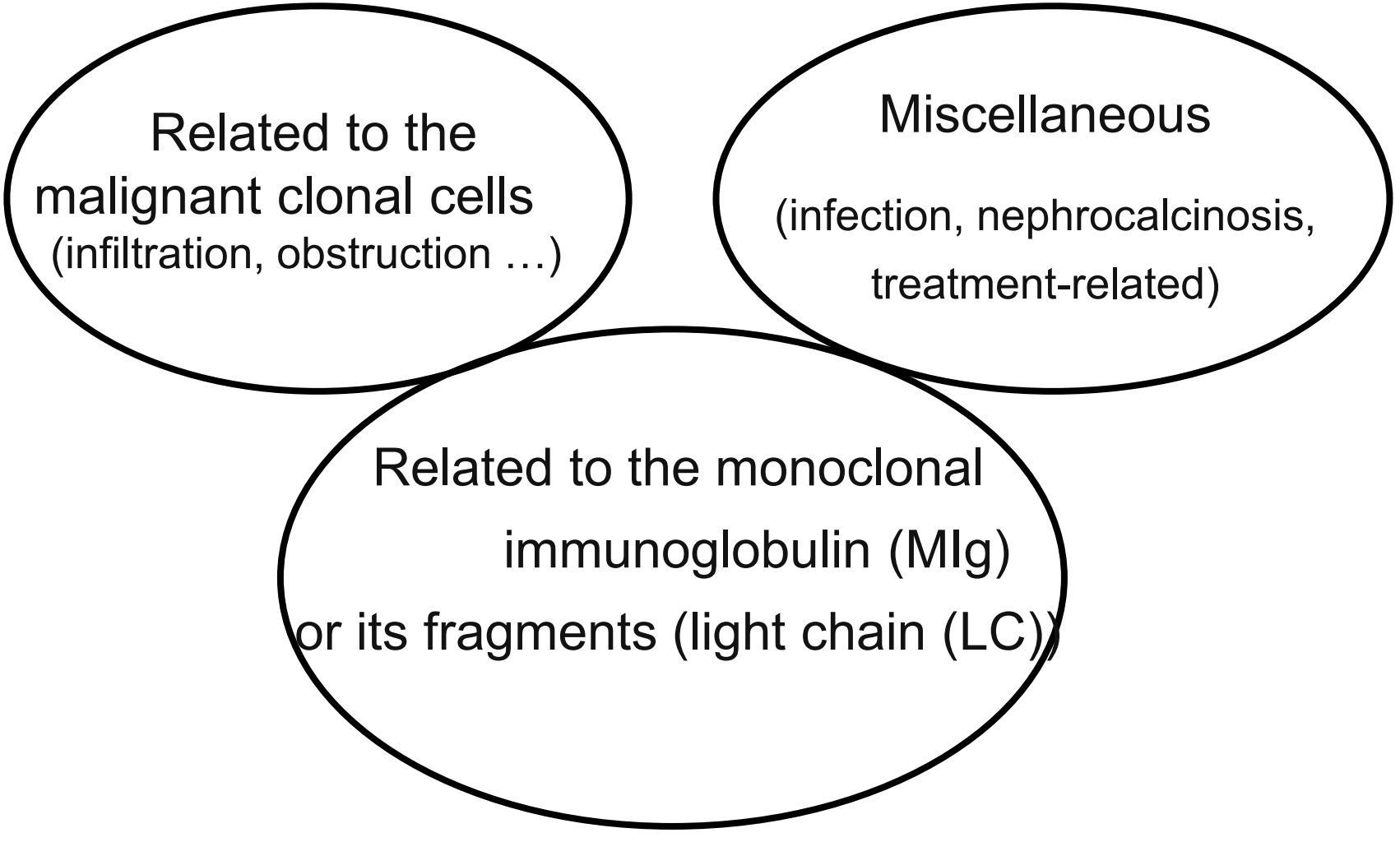
No disclosure to declare

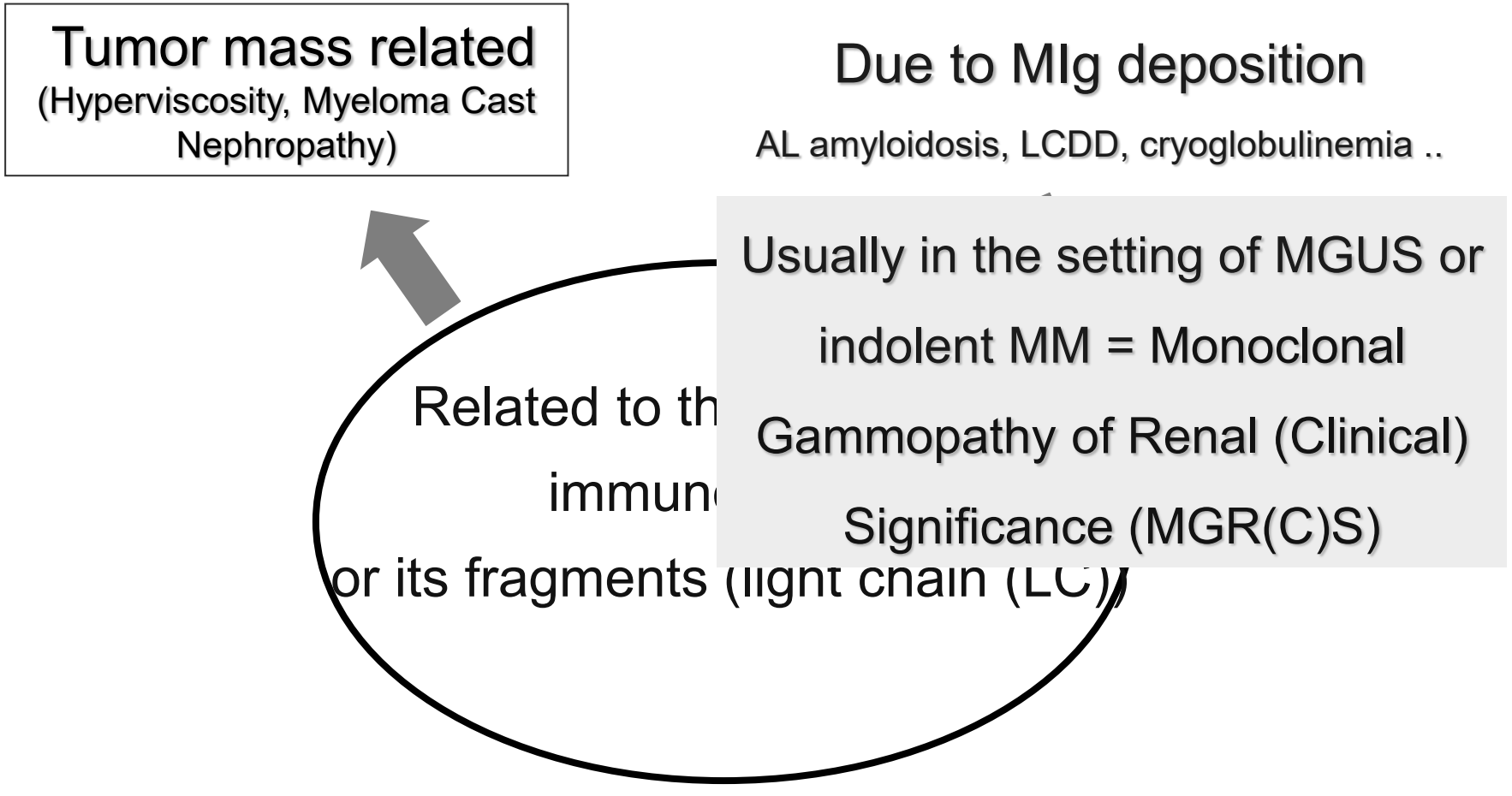
Management of renal failure in MM

# Renal manifestations of Myeloma



Management of renal failure in MM

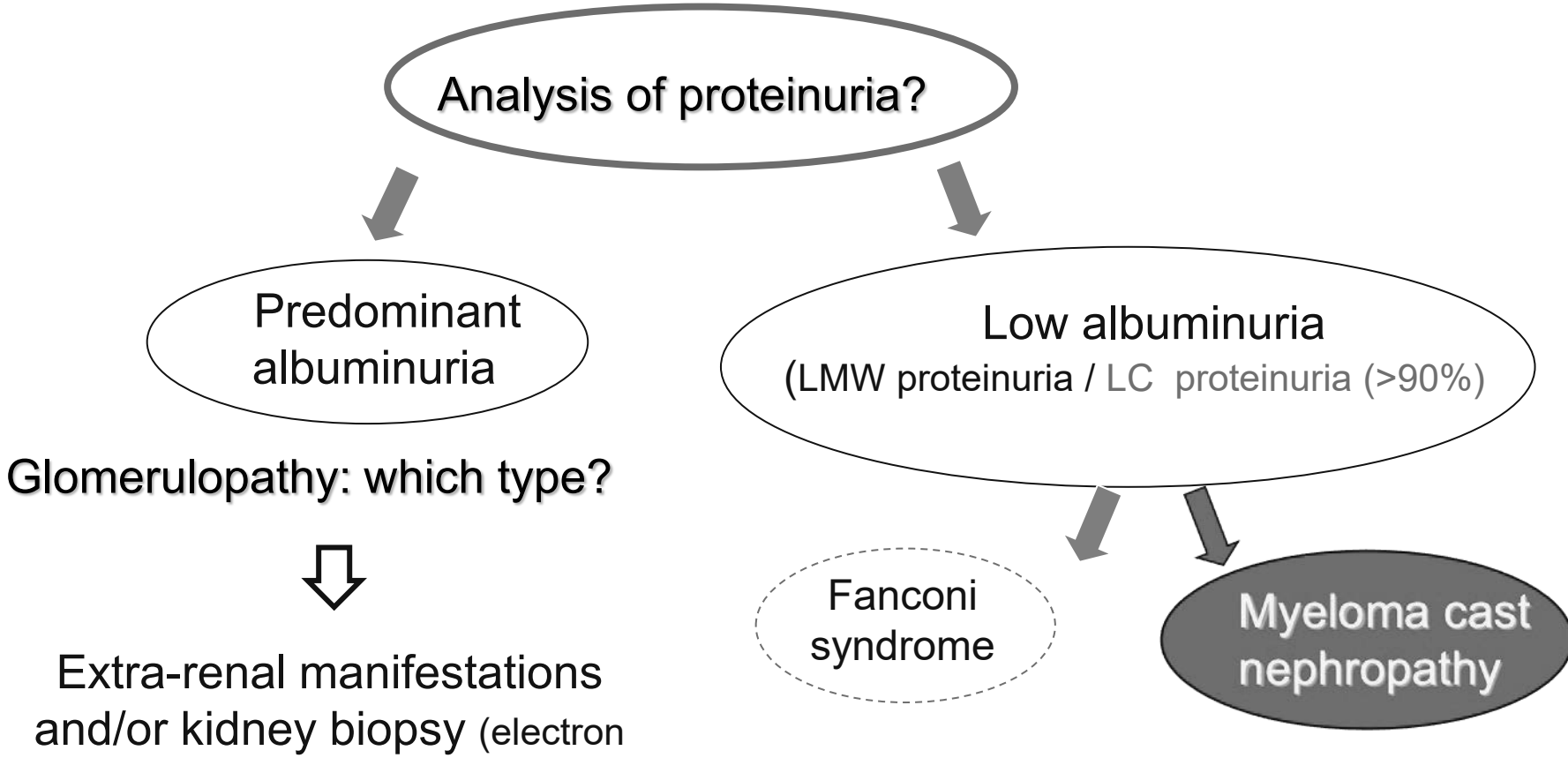
# Renal manifestations of myeloma



# Management of renal failure in MM

## Renal manifestations of Myeloma

## Diagnosis



Management of renal failure in MM

# Myeloma Cast Nephropathy (MCN)

Renal failure at any time in MM: ~ 50% of patients

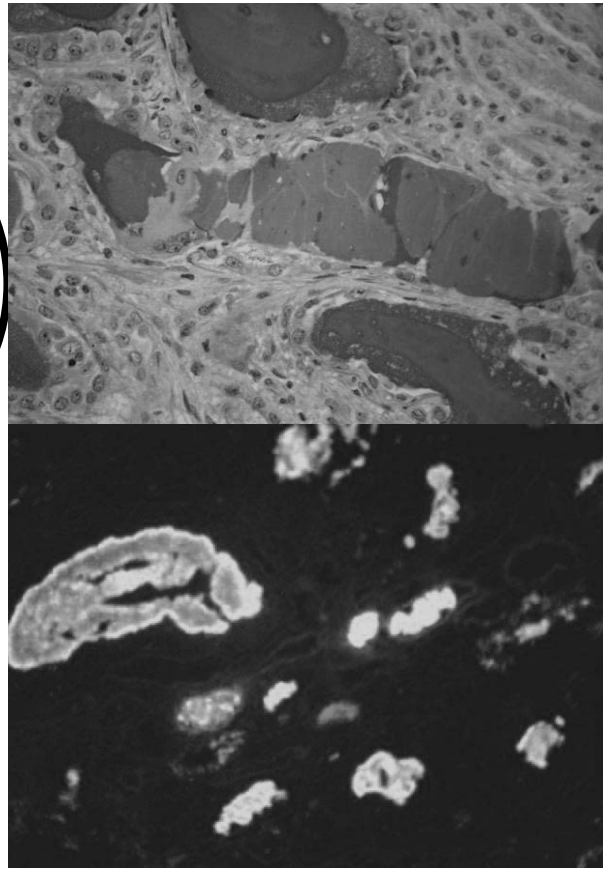
~ 75% of MM patients with renal failure = MCN

Intra-tubular precipitation of monoclonal LC with uromodulin

Urinary LC flow
(serum level of the pathogenic LC)

LC intrinsic nephrotoxicity
hydrophobicity, electric charge, glycosylation …

extrinsic factors
favorizing FLC and uromodulin interaction: acidic urine, calcium, **reduced tubular flow whatever its cause** (dehydration, RAS blockers, NSAIDs)



Management of renal failure in MM

# Myeloma Cast Nephropathy (MCN)

## Clinical presentation: Acute kidney injury (AKI)

Underlying high tumor mass MM

Often inaugural

Frequent precipitating factors: infection, dehydration
hypercalcemia, NSAIDs

AKI featured by:

- predominant LC proteinuria (> 90%)
- high serum free kappa or lambda (FLC) LC level

Pathogenic clonal sFLC >500 mg/l + low urinary albumin excretion
(urine albumin/total protein ratio <10% + urine albumin/creatinine <30 mg/mmol)

⇨ diagnosis of MCN likely, histological confirmation not required

If sFLC < 500 mg/L and/or significant albuminuria,
kidney biopsy to be considered

# Management of renal failure in MM: MCN

## Treatment of AKI due to MCN = an emergency

### *Treatment strategy*

*Decrease concentration and precipitability of urinary LC:*

Urgent symptomatic measures

(vigorous IV rehydration with saline/alkaline fluid & correction of precipitating conditions: infection, hypercalcemia, nephrotoxic drugs…)

*Reduce LC production (and intrarenal inflammation)*

- High-dose steroids (Dexamethasone 40 mg/day, D 1-4)
- Chemotherapy based on agents without renal elimination

⇨ Current reference: Bortezomib + Dexamethasone (BD)

*Rapidly remove circulating nephrotoxic LCs*

Plasma exchanges? High-cutoff hemodialysis?

## Potential renal recovery

Management of renal failure in MM: MCN

## Best chemotherapeutic regimen for renal recovery ?

Are triplet regimens superior to the standard BD doublet

(as suggested by small retrospective series) ?

- **Myre randomized study** *(Bridoux et al. JCO 2020)*

BD *vs.* BD + cyclophosphamide (C-BD) in NCM pts (n=186) not requiring HD

- Slight higher efficacy of C-BD in reducing pathogenic LC

- not sufficient to counterbalance the deleterious renal effects of adverse events (severe infections)

⇨ No difference in renal response rates

At 3 mths, cumulative incidence of renal response (eDFG ≥ 40 ml/min/1.73 $m^2$)
: 44.6% (BD) vs 51% (C-BD) (p=0.46)

# Management of renal failure in MM: MCN

## Best chemotherapeutic regimen for renal recovery ?

A triplet may compromise renal recovery, because of increased risk of infection, hemodynamic instability and drug toxicity

**Careful assessment of the efficacy/toxicity balance & Indications adapted to patient frailty**

- Bortezomib-dexamethasone doublet = still the reference treatment, especially in frail patients.
- In fit patients, a triplet regimen may be considered, best combination to be defined.

Bortezomib-dexamethasone + monoclonal anti-CD38 antibody = future backbone of chemotherapy for optimizing renal recovery in MCN?

# Rapidly removing circulating nephrotoxic LCs

## Plasma exchanges?

- No benefit of plasmapheresis in a randomized trial *(Clark et al, 2005)*
- Renal response rates of up to 75% in recent retrospective series

## High-cutoff hemodialysis (HCO-HD)?

- Highly efficient removal of both kappa and lambda LC with High Cut-Off dialyzers.

- In pioneering retrospective studies, intensive HCO-HD + novel anti-myeloma agents = HD independence rate #60% (vs #30% with conventional HD)

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# Randomized comparison of HCO-HD and standard dialysis The MYRE and EuLite trials

*(Bridoux et al. JAMA, 2017, Hutchinson et al. Lancet Oncol. 2019)*

Noticeable differences in design

i) *Randomization*: upfront in EuLite, after pre-inclusion phase in MYRE to randomize only pts still requiring HD

ii) *HD schedule*: different in EuLite (highly intensive in HCO group only). Same intensive but tolerable HD dose for all pts in MYRE.

iii) *Chemo regimen*: triplet In EuLite, BD doublet in MYRE

- At 6 months,

in the HCO groups of both studies, HD independence rate # 60%

In control groups, - 60% in EuLite

- 35% in MYRE (p= .04)*

- Good tolerance profile of HCO-HD and similar OS in the two groups of the MYRE study.
- High rate of SAE (severe infections) and higher mortality in the HCO group of EuLite.

*In the MYRE study, HD withdrawal rates were not significantly different at 3 months (primary endpoint)

Management of renal failure in MM: MCN

# HCO-Hemodialysis a relevant therapeutic option?

- **Rationale is still pertinent:**

  - HCO-HD constantly and rapidly reduces pathogenic sFLC
  - Renal recovery unlikely with current chemo regimens alone in all newly-diagnosed pts and even more in pts with MCN at myeloma relapse

- **With novel regimens introducing monoclonal anti-CD38 antibodies?**

  - Place of extracorporeal treatment to be re-evaluated through dedicated phase II trials (more realistic than large phase III trials)

- **Indication based on assessment of renal prognosis with kidney biopsy?**

  - High risk of End Stage Renal Disease (numerous casts on biopsy): HCO + chemotherapy
  - Lower risk: chemotherapy alone

# Renal response and prognosis

- Crucial to early assess hematologic response by serial sFLC measurements
  - increased probability of renal response if ≥90% reduction in sFLC level

  - for pts requiring dialysis, involved sFLC level < 500 mg/L after the first cycle of chemotherapy = independent factor of renal recovery.

- Goal = to reach a stable eGFR value ≥40 ml/min/1.73m$^2$

  particularly in young patients otherwise eligible for HDT/ASCT

- Life expectancy of MM pts on chronic dialysis still < 2 years

  Renal transplantation increasingly considered in selected young pts, without high-risk cytogenetics, who achieved sustained negative MRD

# Management of renal failure in MM: Conclusions

**MCN** is the main but not the sole cause of AKI

Monitoring and characterization of proteinuria mandatory during follow-up of any monoclonal gammopathy

**MCN** still associated with high morbidity and mortality

***Prevention*** : Patient (and physician) education

Avoid dehydration and any precipitating factor

***Early diagnosis*** +urgent symptomatic measures including high dose steroids

***Optimizing the efficacy/toxicity balance of chemotherapy***

By combining a Bortezomib-Dex-based regimen with a monoclonal anti-CD38 antibody?

***Serial sFLC measurements*** to assess the hematologic response

***Collaboration between nephrologists and hematologi***

particularly to better define the place of kidney biopsy, hemodialysis and renal transplantation.

Thank you for your attention