

Multiple Myeloma: How does it affect organs?

Kara Cicero, MD MPH
University of Washington
Fred Hutchinson Cancer Center

July 27, 2024



1 “CRAB” Diagnostic Criteria

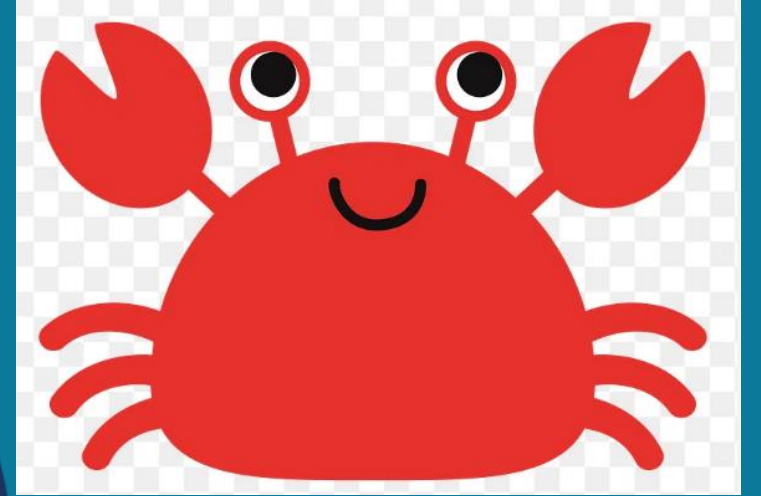
2 **R**enal Impairment

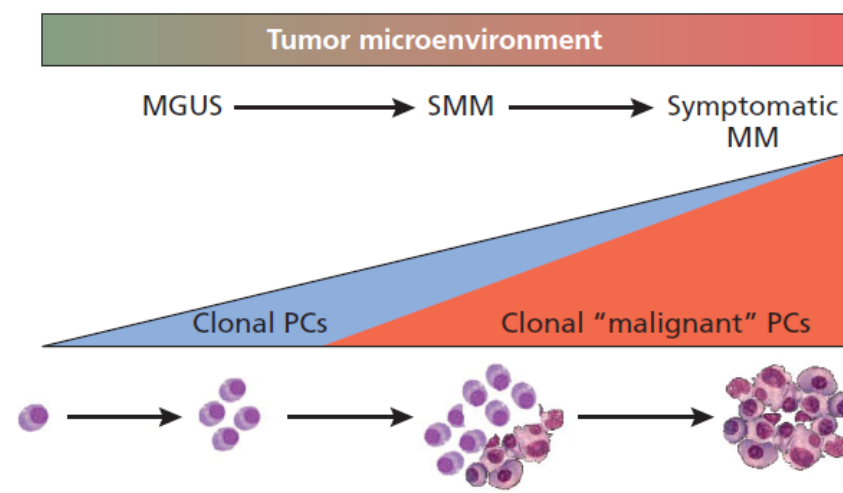
3 **A**nemia

4 **B**one Involvement

5 Elevated **C**alcium

CRAB?





Multiple Myeloma

Both criteria must be met:

- Clonal bone marrow plasma cells $\geq 10\%$ or biopsy-proven bony or extramedullary plasmacytoma
- Any one or more of the following myeloma defining events:
 - Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
 - Hypercalcemia: 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 minute or serum creatinine >177 μ mol/L (>2 mg/dL)
 - Anemia: hemoglobin value of >2 g/dL below the lower limit of normal, or a hemoglobin value <10 g/dL
 - Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT)
 - Clonal bone marrow plasma cell percentage $\geq 60\%$
 - Involved:uninvolved serum free light chain (FLC) ratio ≥ 100 (involved free light chain level must be ≥ 100 mg/L)
 - >1 focal lesions on magnetic resonance imaging (MRI) studies (at least 5 mm in size)

MULTIPLE MYELOMA

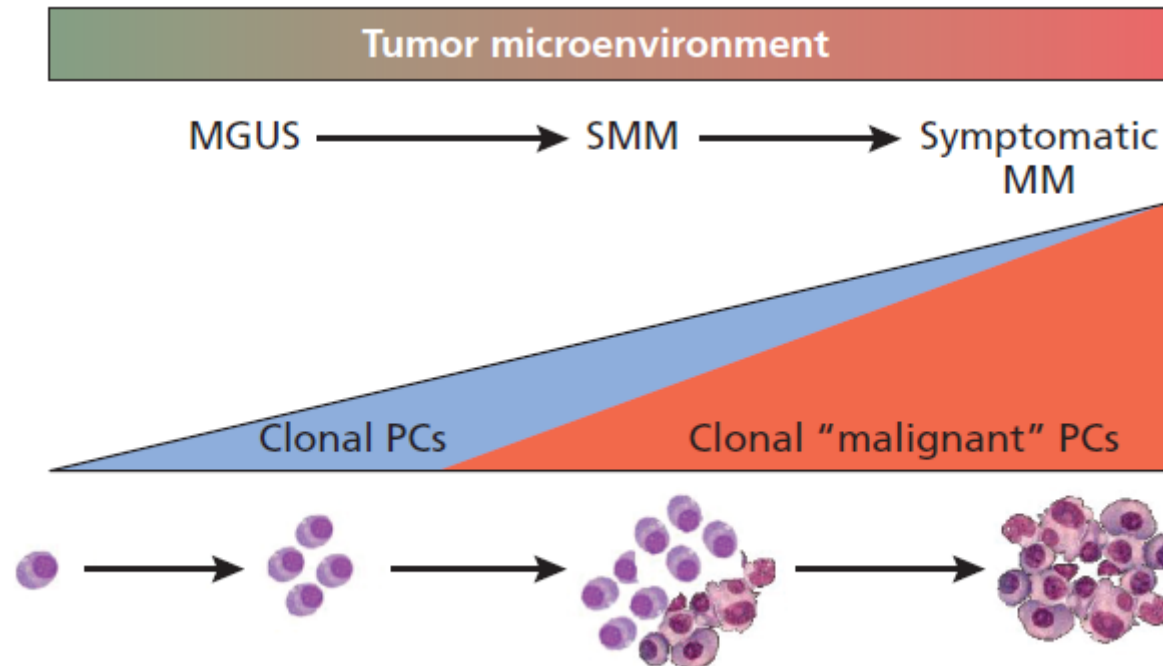
Calcium
Renal impairment
Anemia
Boney lesions



Monoclonal protein

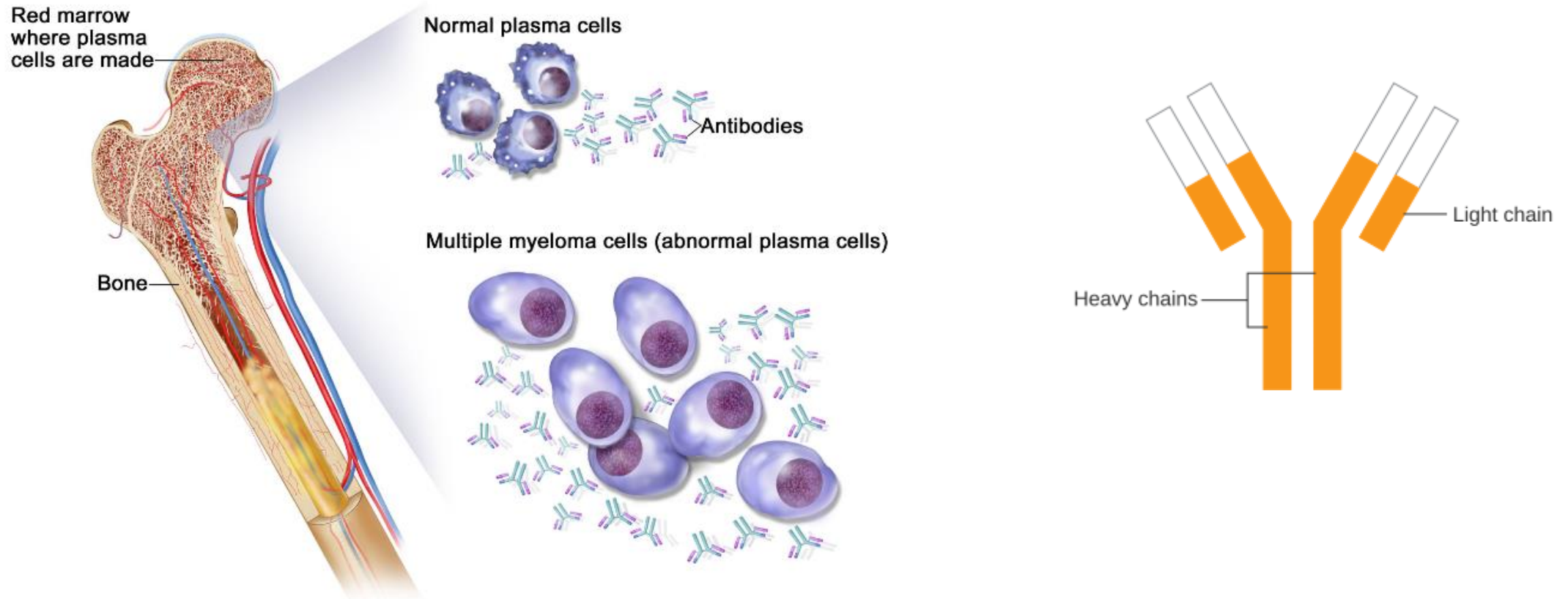


End-organ damage

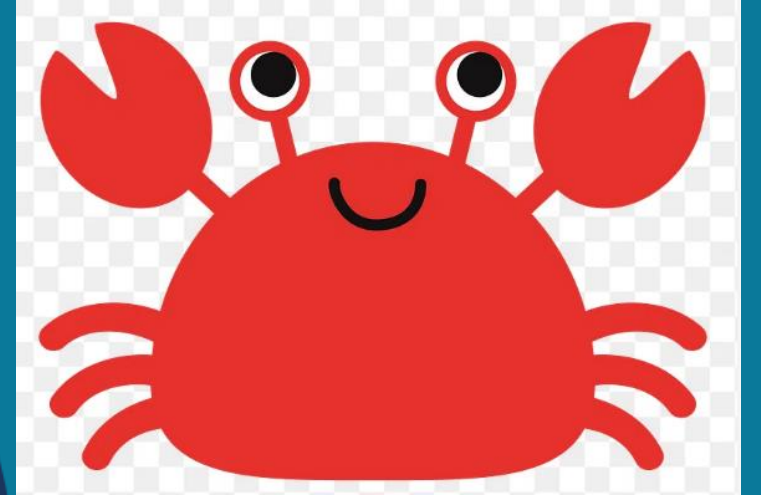


“CRAB”

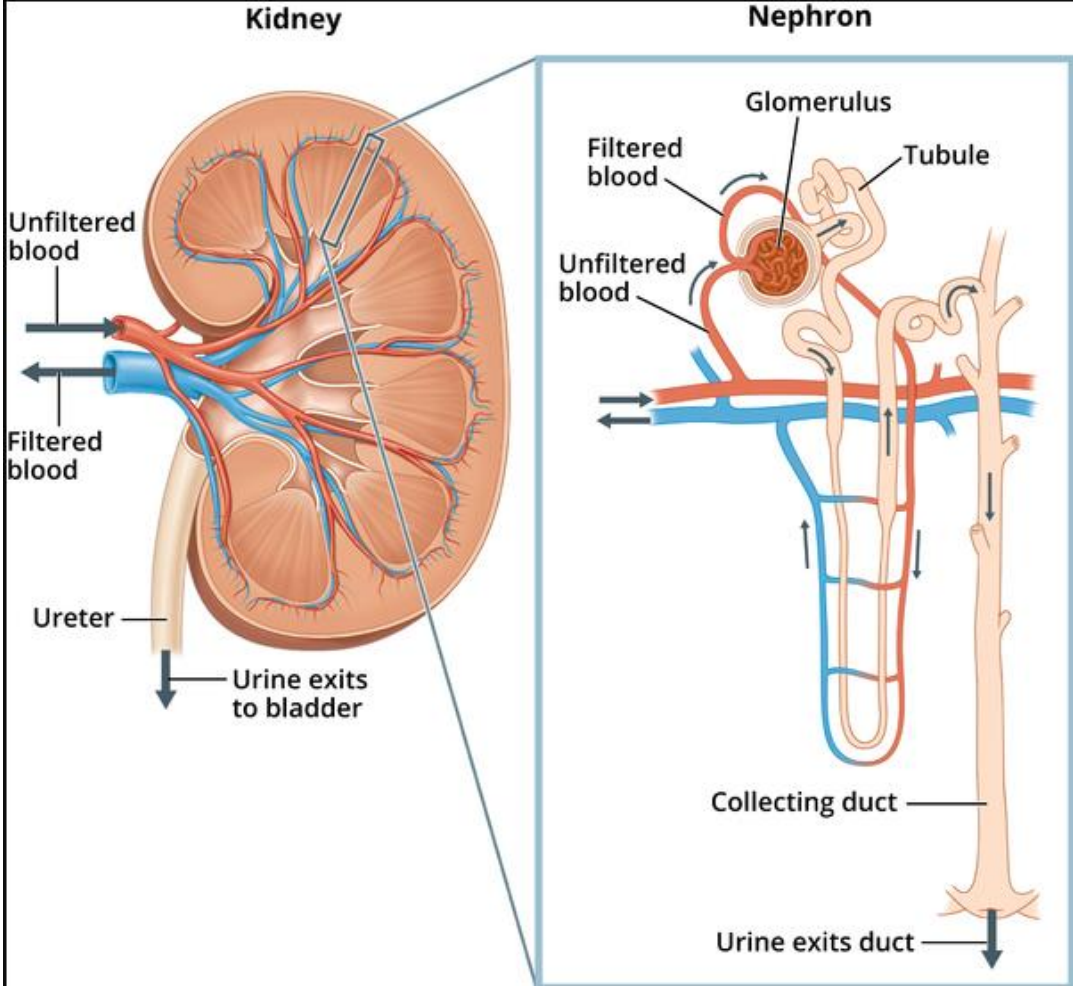
- Must be directly related to the monoclonal protein and/or underlying clonal plasma cells



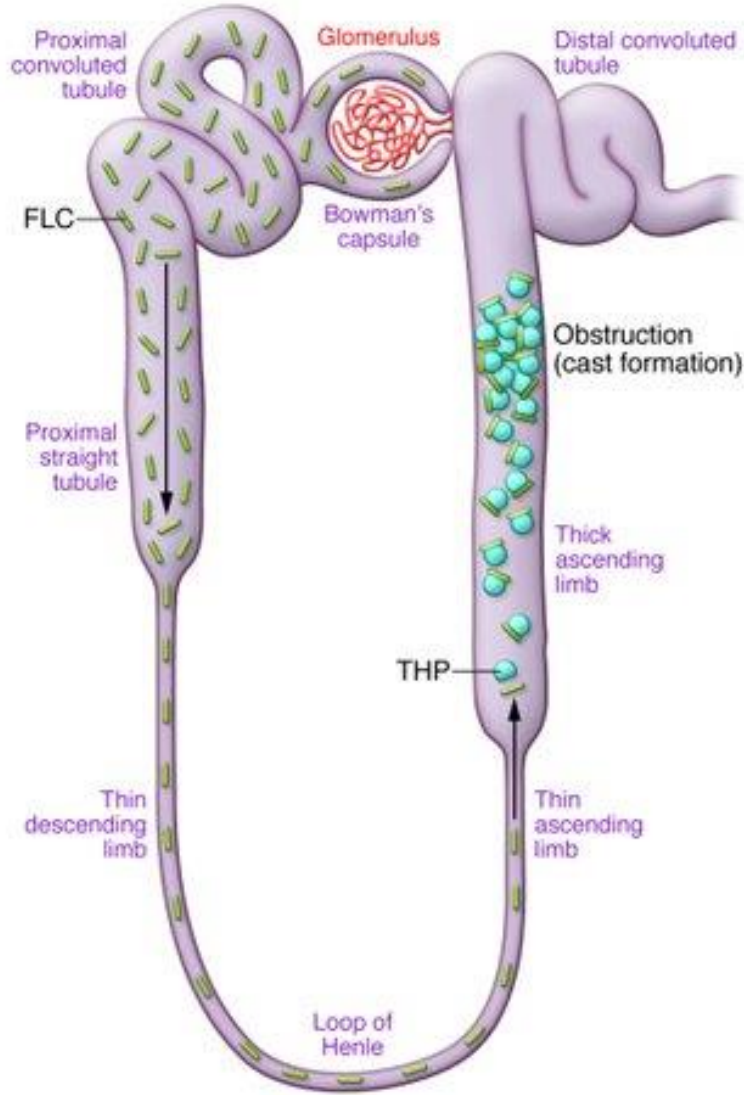
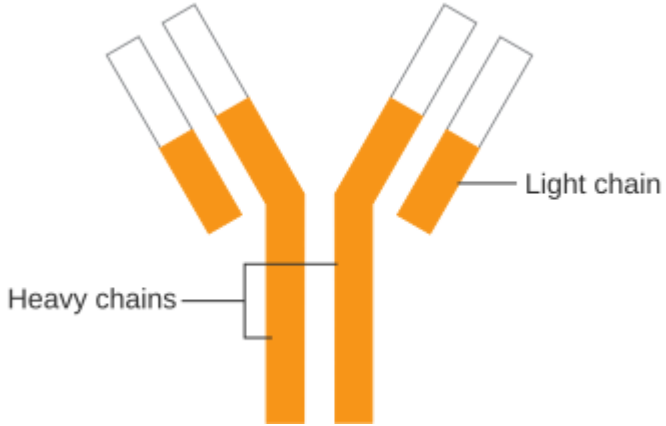
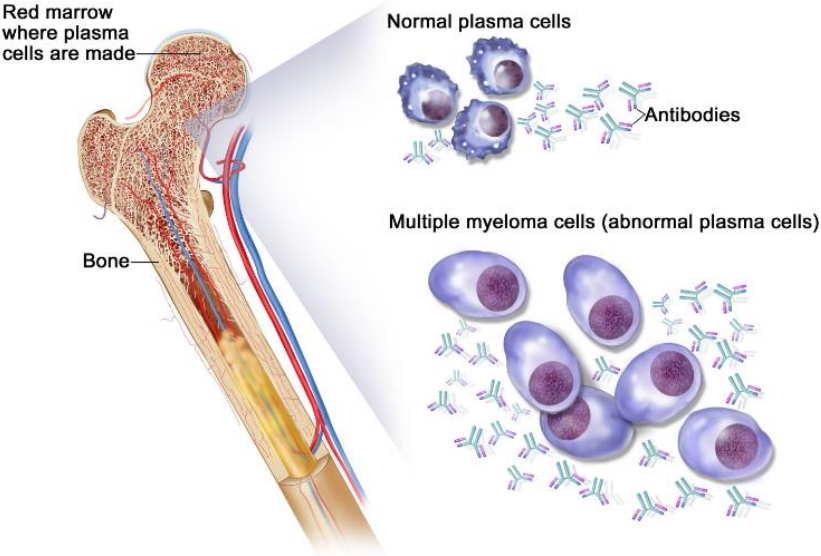
Renal Insufficiency:
Light Chain Cast
Nephropathy



The Nephron

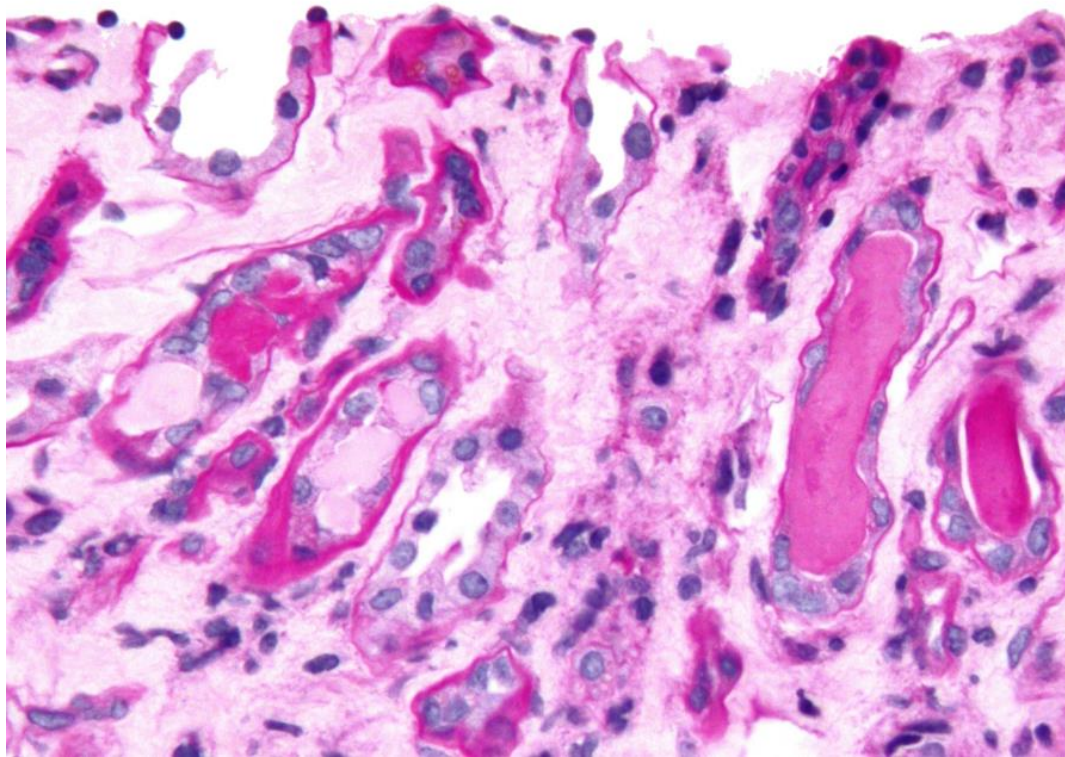


Light Chain Cast Nephropathy

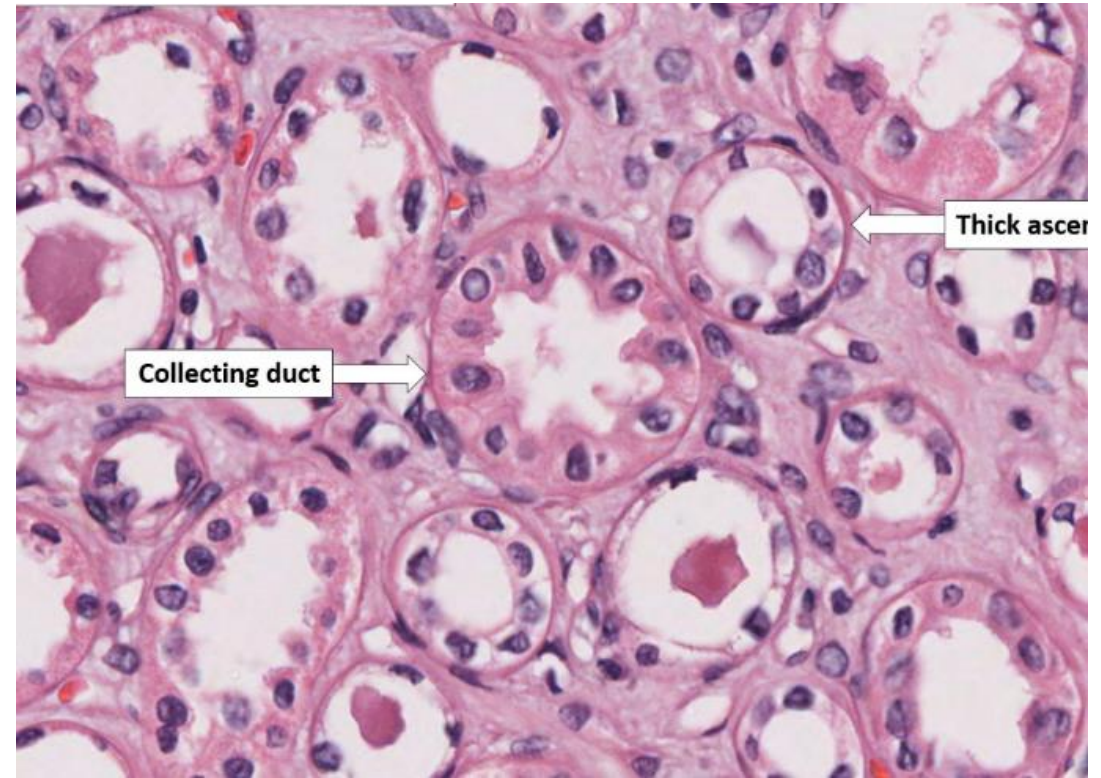


Light Chain Cast Nephropathy

Myeloma Kidney



Healthy Kidney



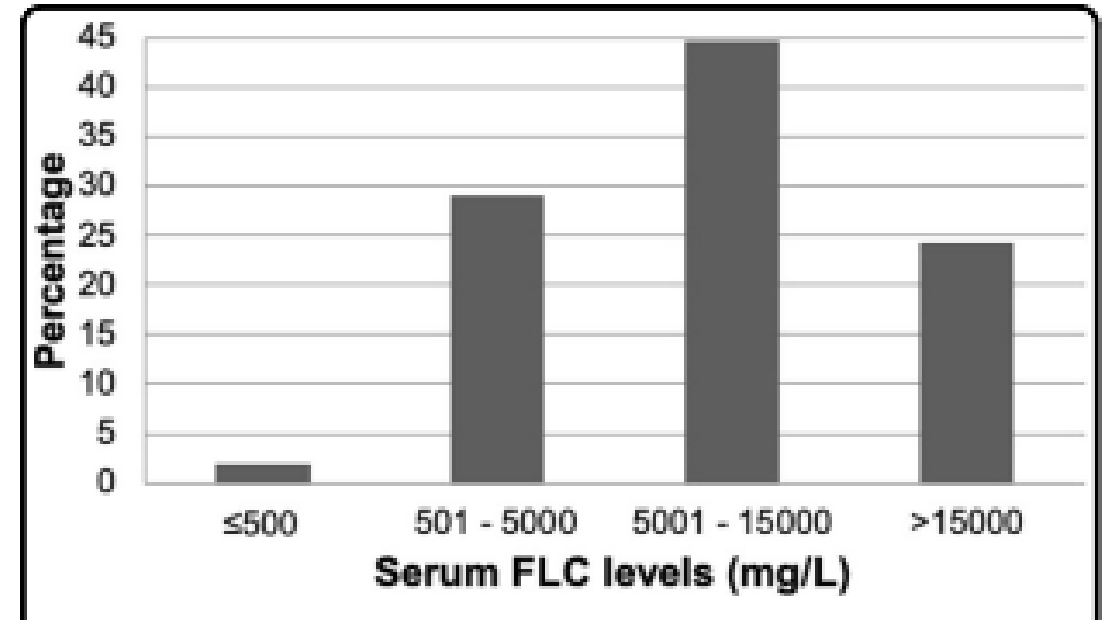
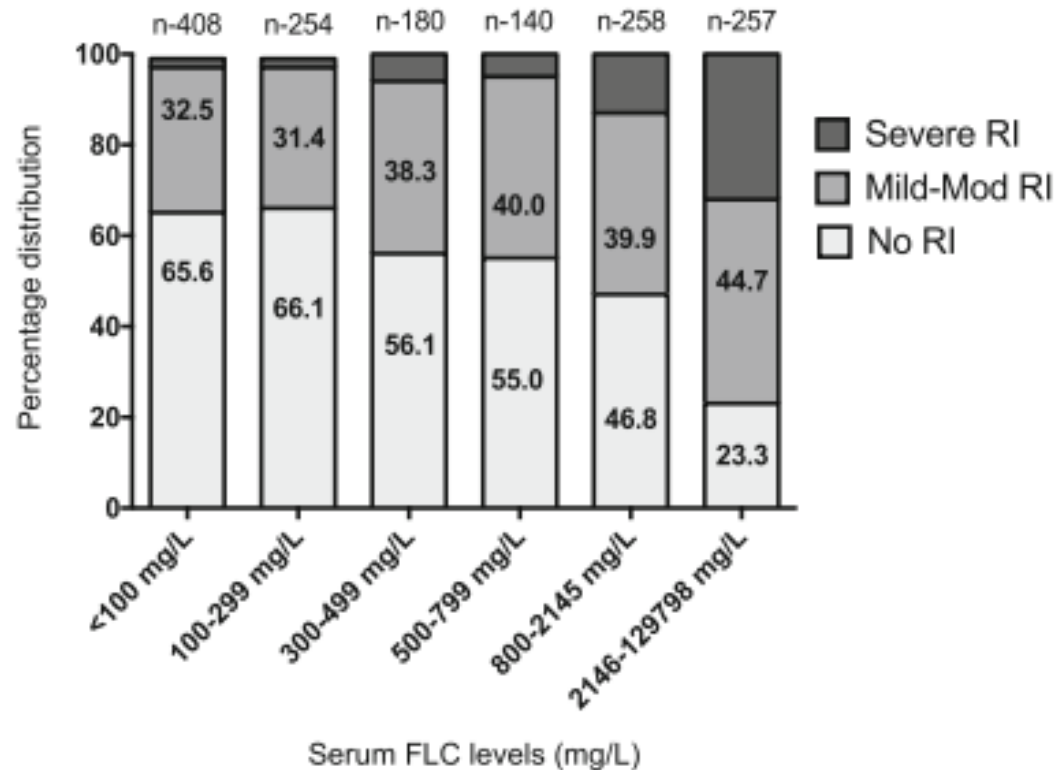
Clinical Manifestations of Kidney Injury

- Asymptomatic – found on routine labs / incidentally discovered
- Swelling
- Shortness of breath
- Frothy urine
- Anemia*
- Decreased urine output
- Nausea
- Loss of appetite
- Weakness & fatigue

Renal Impairment as a Myeloma Defining Event

- **eGFR <40 or Cr >2 due to light chain cast nephropathy**
- Other causes of AKI must be excluded, for example:
 - Dehydration
 - Diabetes
 - High blood pressure
 - Other plasma cell disorders (i.e. AL amyloidosis)
 - *Hypercalcemia**

Levels of involved FLC & Kidney Function



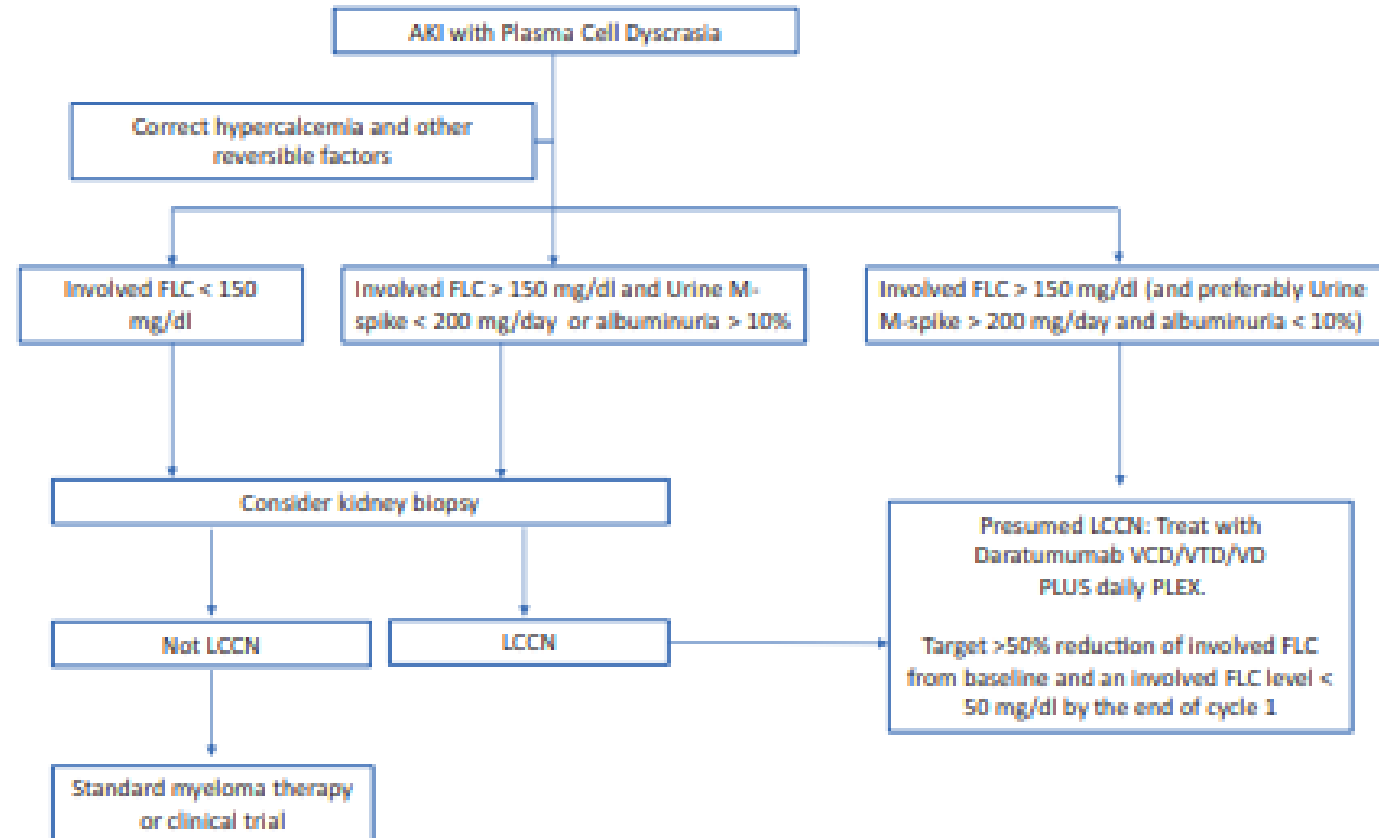
- Since mechanism of kidney impairment is based on excess FLC being cleared through the kidneys, the higher the involved FLC, the worse the renal impairment
- Rare to have light chain cast nephropathy with iFLC <50 mg/dL

Renal Impairment as a Myeloma Defining Event

Kidney Biopsy

- May be avoided if:
 - iFLC >150mg/dL (*higher the iFLC, greater the suspicion*)
 - Majority of proteinuria Bence Jones (<10% albuminuria)
 - No clear alternative etiologies for AKI
 - Not the only myeloma defining event necessitating treatment

Management of AKI with Plasma Cell Disorder



Treatment Considerations: Renal Insufficiency

- May be an emergency requiring hospitalization for immediate initiation of treatment
 - Rapid reduction of FLC imperative to renal recovery
 - At least 50-60% reduction in FLC; faster is better
 - Ideally <50 mg/dL by C1
- Plasma cell directed therapy – prevents FLC production
- Plasmapheresis (PLEX) – ??

PLEX in for Light Chain Cast Nephropathy

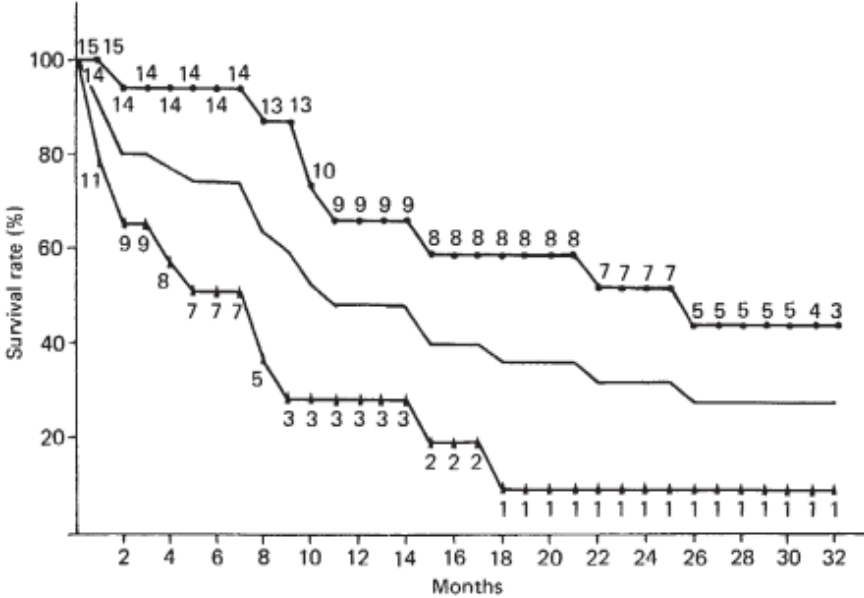


Fig. 3. Survival rate of both patient groups calculated by the Cutler and Edever outcome method. Group I vs. Group II, $P < 0.01$. Symbols are: (●—●) Group I; (▲—▲) Group II; (—) cumulative.

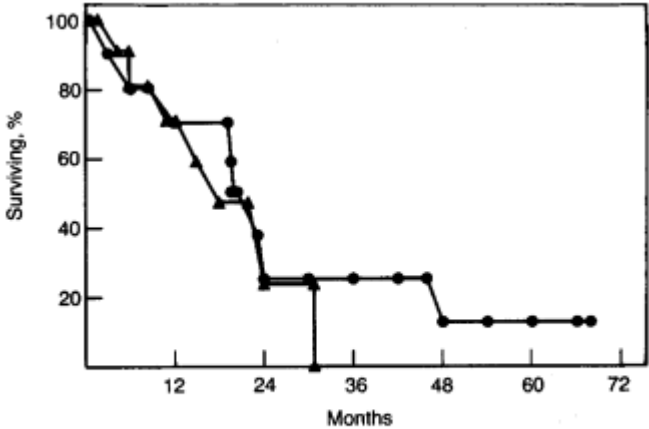
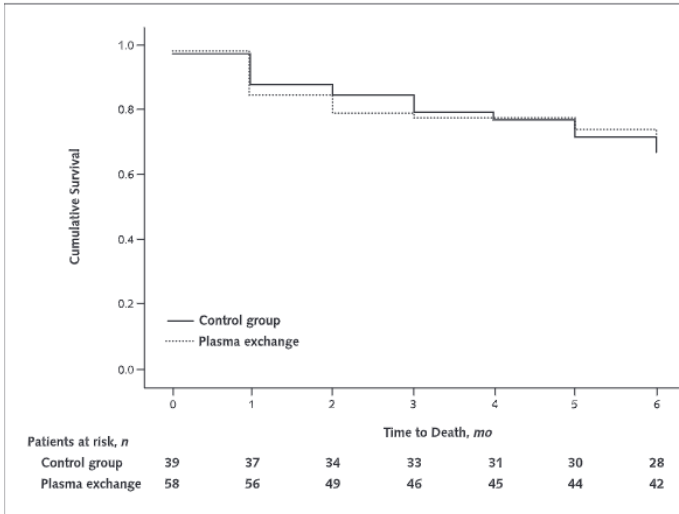


Fig 4.—Comparison of survival rates for patients treated with plasma-pheresis (lines with triangles, n = 11) and a control group (lines with circles, n = 10).

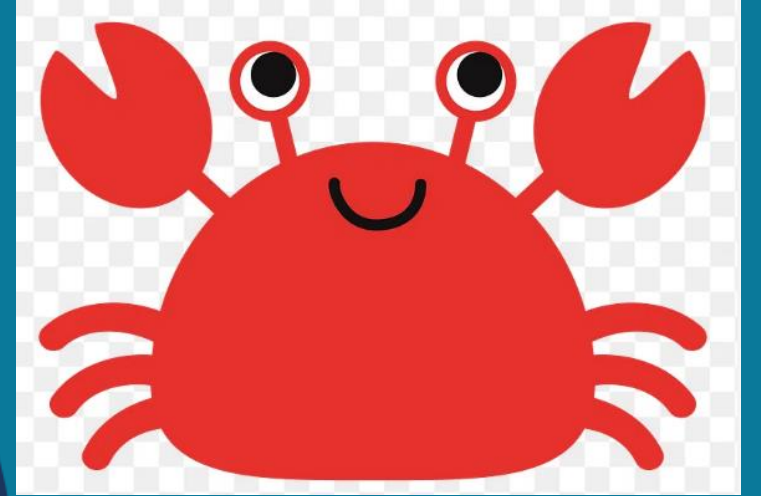


Patients at risk, n	0	1	2	3	4	5	6
Control group	39	37	34	33	31	30	28
Plasma exchange	58	56	49	46	45	44	42

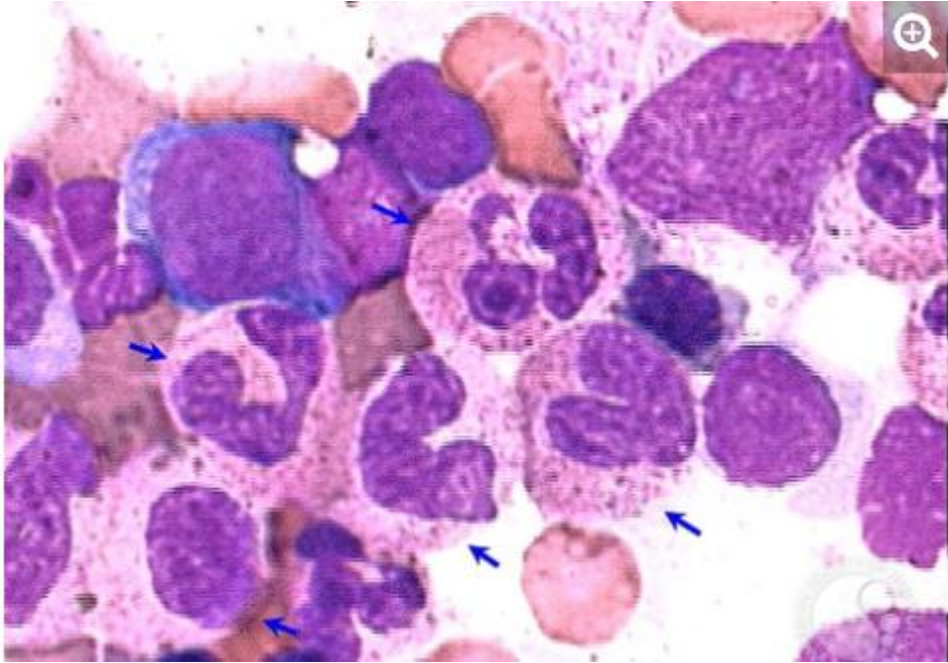
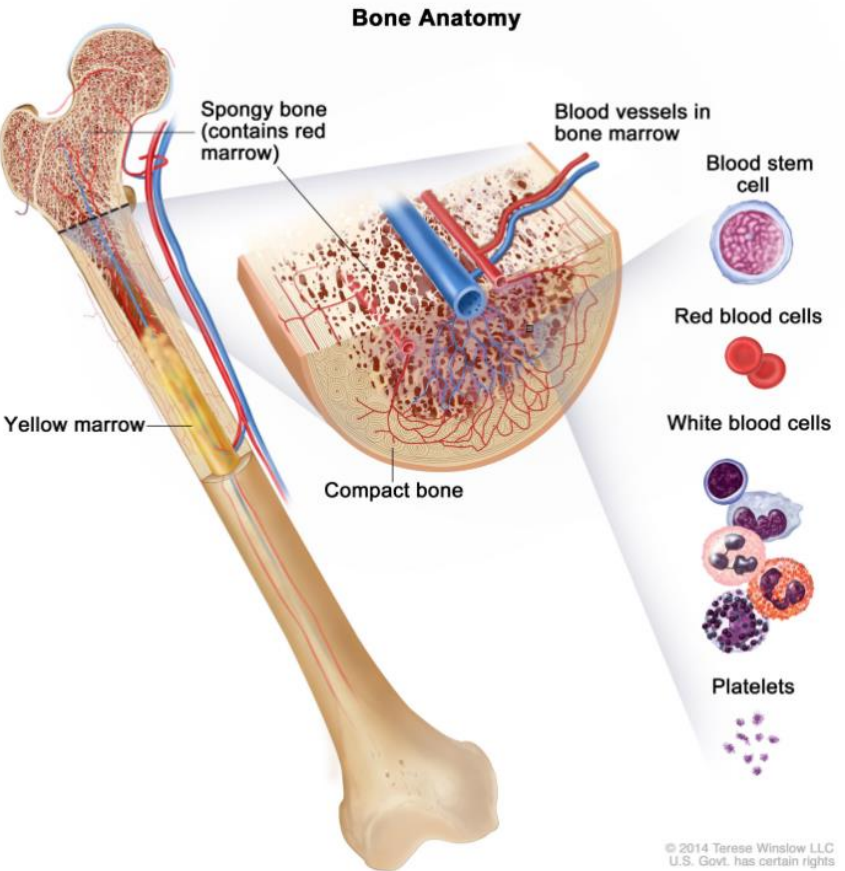
Treatment Considerations: Renal Insufficiency

- May be an emergency requiring hospitalization for immediate initiation of treatment
 - Rapid reduction of FLC imperative to renal recovery
 - At least 50-60% reduction in FLC; faster is better
 - Ideally <50 mg/dL by C1
- Plasma cell directed therapy – prevents FLC production
- Plasmapheresis (PLEX) – controversial
 - Mixed results in terms of efficacy, but low risk procedure

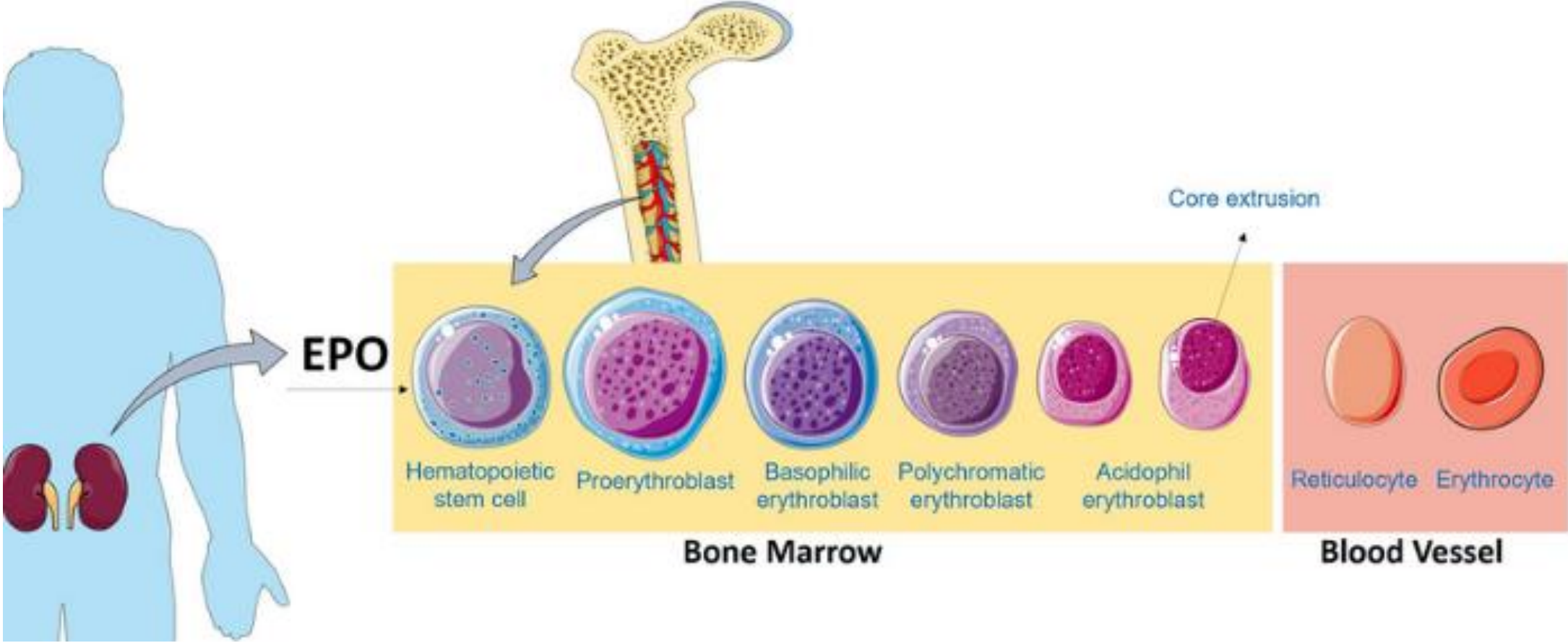
Anemia



Hematopoiesis



RBC Production



Anemia = Decreased Red Blood Cells

Parameter
Hemoglobin (g/dL)
Hematocrit (%)
RBC count ($\times 10^6$ /microL)
MCV (fL)
MCH (pg)
MCHC (g/dL)
RDW (%)
Reticulocyte count ($\times 10^3$ /microL or $\times 10^9$ /L)
Platelet count ($\times 10^3$ /microL)
WBC count ($\times 10^3$ /microL)

Production

- Vitamin deficiencies: B12, folate, iron
- Bone marrow infiltration / dysfunction: multiple myeloma, MDS
- Decreased epo levels: kidney disease
- Chronic inflammation
- Infection
- Congenital disorders
- Medications

Destruction

- Autoimmune hemolysis
- Shearing: heart valves, micro-thromboses
- Splenic sequestration
- Congenital disorders
- Medications

Loss

- Bleeding

Anemia in Myeloma

Production

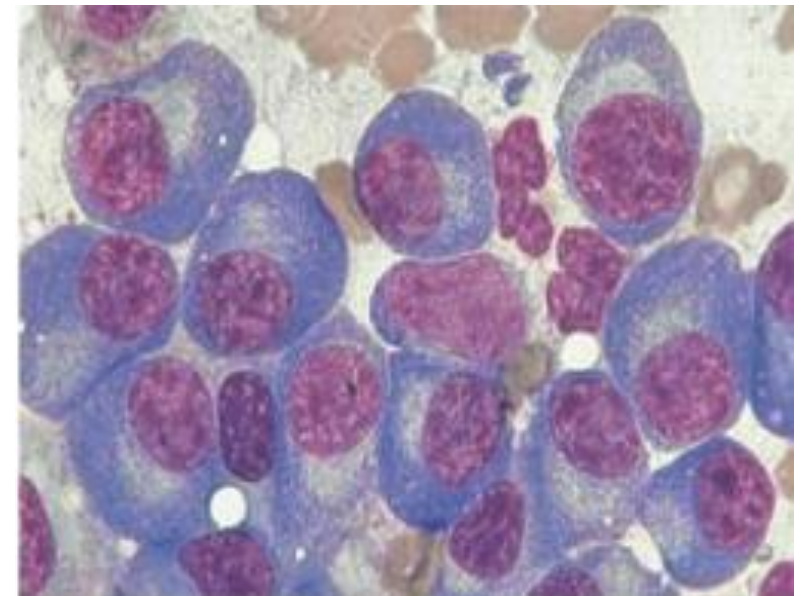
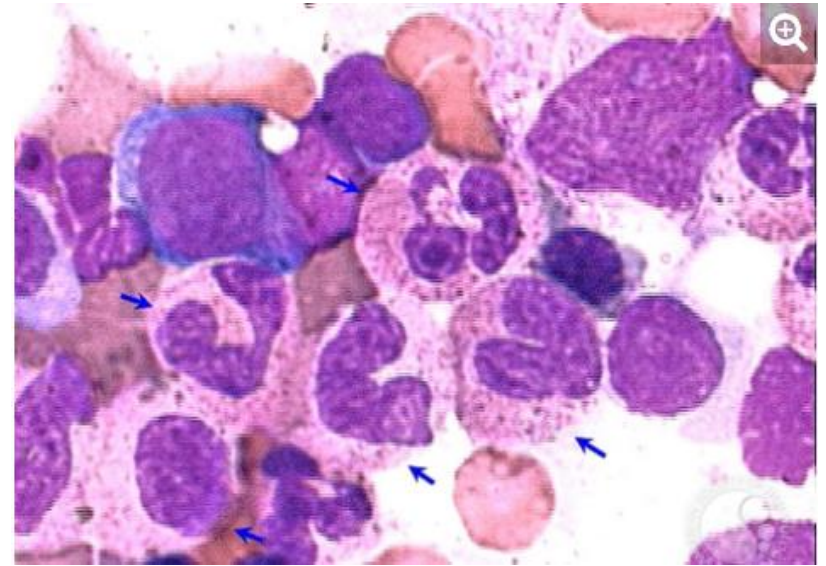
- Vitamin deficiencies: B12, folate, iron
- **Bone marrow infiltration / dysfunction: multiple myeloma, MDS**
- **Decreased epo levels: kidney disease**
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Destruction

- Autoimmune hemolysis
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Loss

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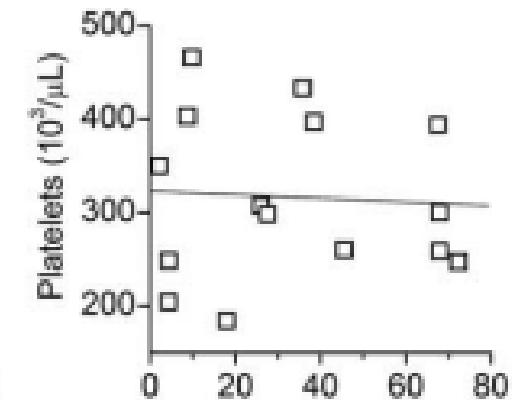
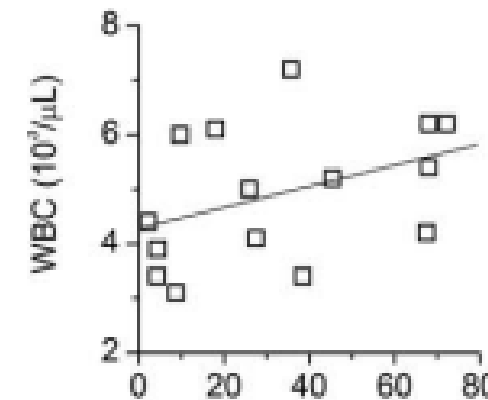
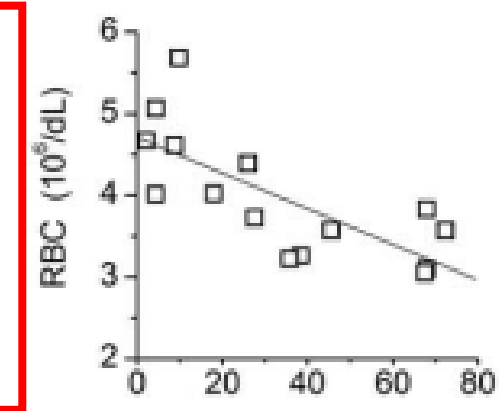
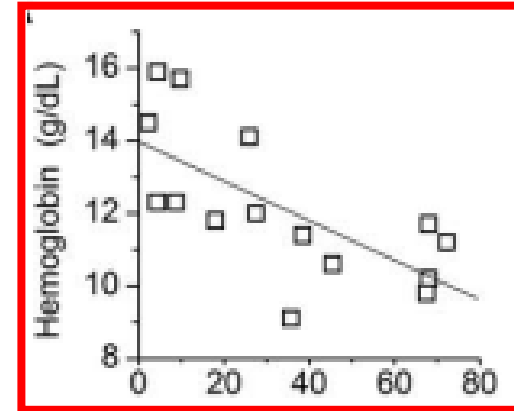


Clinical Manifestations of Anemia

- Fatigue & weakness
- Lightheadedness
- Palpitations
- Shortness of breath
- Headaches
- Pallor

Anemia as a Myeloma Defining Event

- Hgb <10 or Hgb >2 below lower limit of normal due to the underlying clonal plasma cells
- Other causes of anemia must be excluded:
 - Labs: iron/ferritin, B12, folate, TSH, haptoglobin, epo
 - BMbx

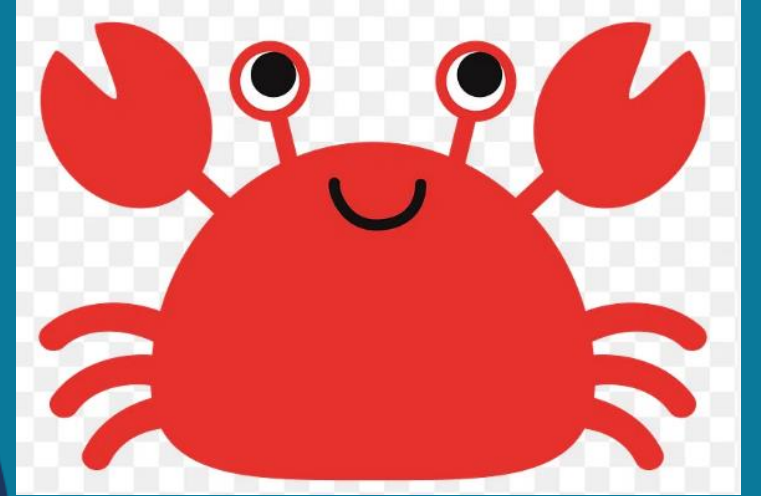


Marrow Infiltration by Multiple Myeloma (%)

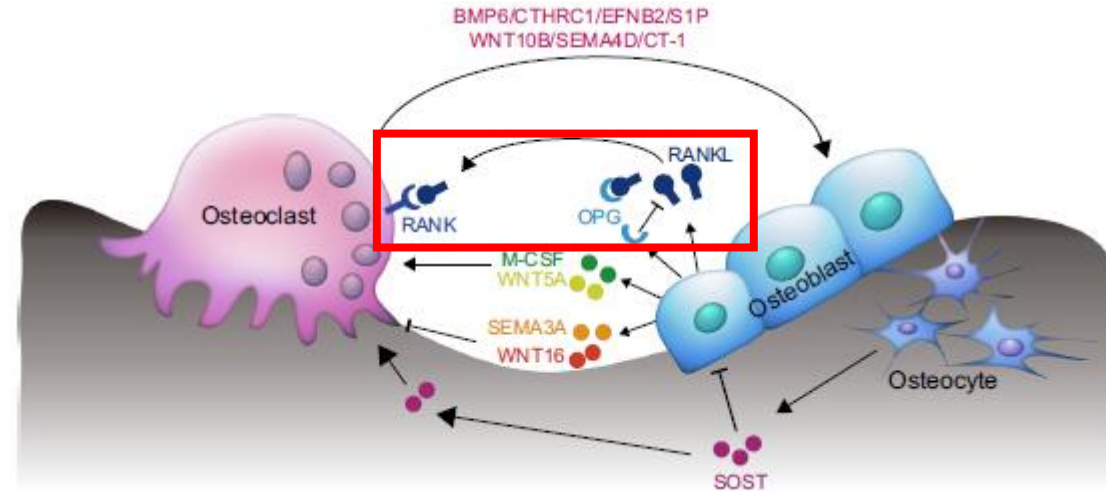
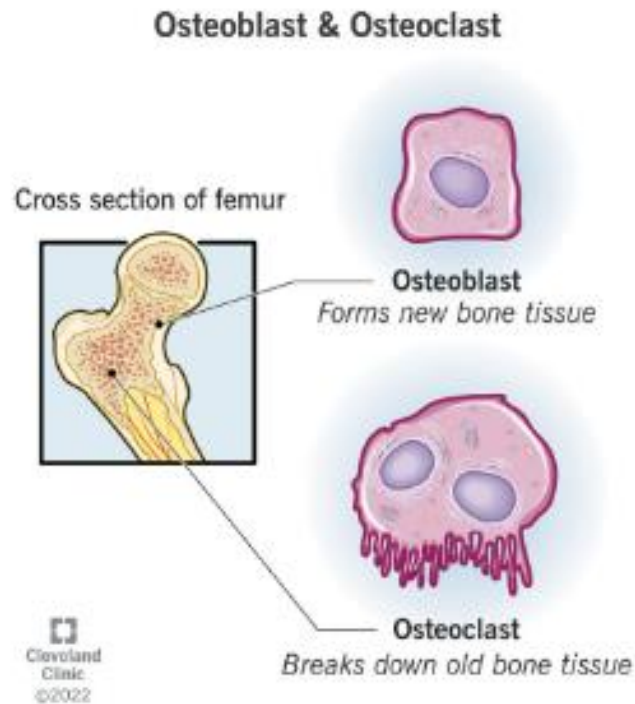
Treatment Considerations: Anemia

- *Correct any other reversible underlying causes of anemia!*
- Plasma cell directed therapy – eliminates infiltration of plasma cells crowding out the bone marrow
- Erythropoietin stimulating agents
 - Epoetin
 - Darbepoetin
- RBC transfusions

Bone Involvement: Lytic Lesions

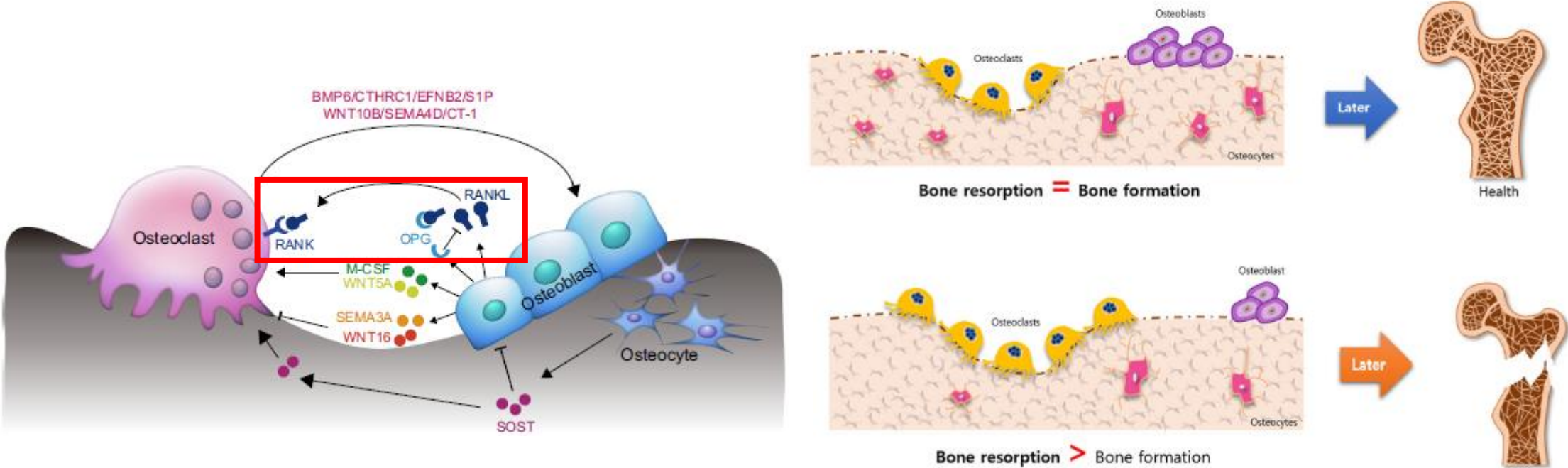


Normal Bone Physiology



- Osteoblasts express RANKL -> binding of RANK to RANKL stimulates osteoclast activation
- OPG, decoy receptor of RANKL, inhibits binding of RANK to RANKL

Lytic Lesions in Myeloma



Balance of RANKL vs. OPG determines bone resorption vs. formation

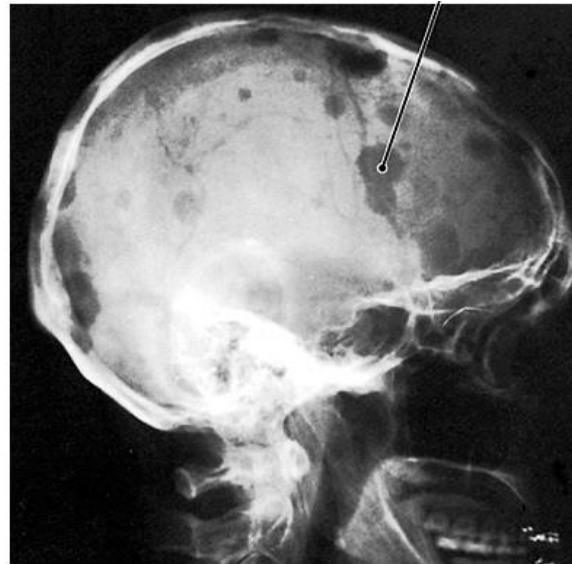
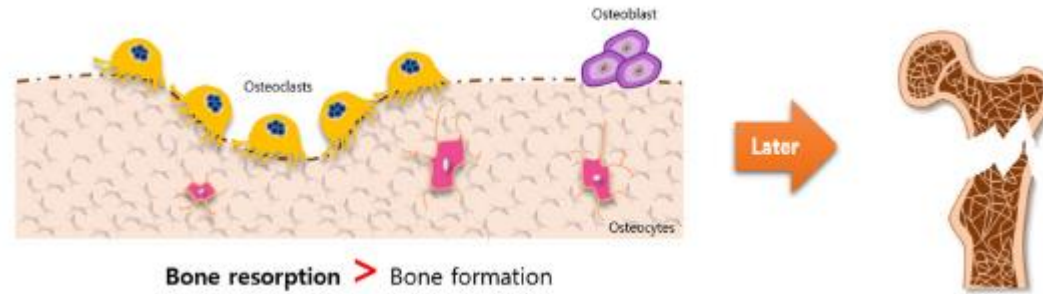
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    graph LR
      A[Myeloma cells over-produce inflammatory signals] --> B[1. Upregulate RANKL  
2. Suppress osteoblastic differentiations]
      B --> C[Enhanced bone resorption]
  
```

Teramachi, et al., *Journal of Bone & Min Metabolism*, 2023

Images: Chang, et al., *Exper & Mol Medicine*, 2019; Han, et al., *Bone Research*, 2018

Lytic Lesions in Myeloma



Clinical Manifestations of Bone Involvement

- Bone pain
 - Often precipitated by movement
 - Less common at night, though can occur with change in position
 - Usually involves central skeleton rather than extremities
- Pathologic fractures
 - Neurologic complications
 - Cord compression – emergency!
 - Radiculopathy
- Loss of height – due to vertebral collapse

Bone Lesions as a Myeloma Defining Event

- One or more osteolytic lesion(s) $\geq 5\text{mm}$
 - **If only one lytic lesion, then clonal bone marrow plasma cells must be $\geq 10\%$**
 - **Multiple lytic lesions (confirmed plasmacytomas) with BMPC $< 10\%$ and no other MDE = macrofocal myeloma**
- Other causes of lytic lesions must be ruled out if indeterminate – bone biopsy
 - E.g. other malignancies, benign lesions
 - If without significant BMPC involvement but suspecting macrofocal myeloma
- Other bone abnormalities on imaging in absence of lytic lesions are *not* considered a myeloma defining event
 - E.g. osteoporosis, compression fractures, FDG avidity on PET
 - Exception: 2+ focal lesions $\geq 5\text{mm}$ on MRI = myeloma defining event

First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial

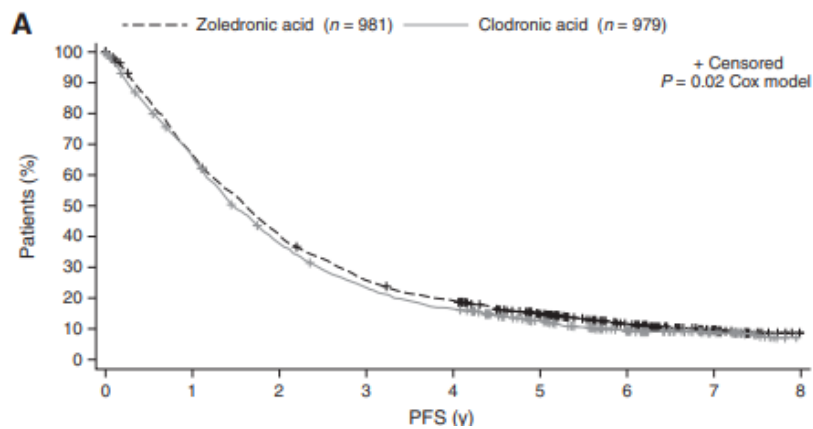


Gareth J Morgan, Faith E Davies, Walter M Gregory, Kim Cocks, Sue E Bell, Alex J Szubert, Nuria Navarro-Coy, Mark T Drayson, Roger G Owen, Sylvia Feyler, A John Ashcroft, Fiona Ross, Jennifer Byrne, Huw Roddie, Claudius Rudin, Gordon Cook, Graham H Jackson, J Anthony Child, on behalf of the National Cancer Research Institute Haematological Oncology Clinical Study Group

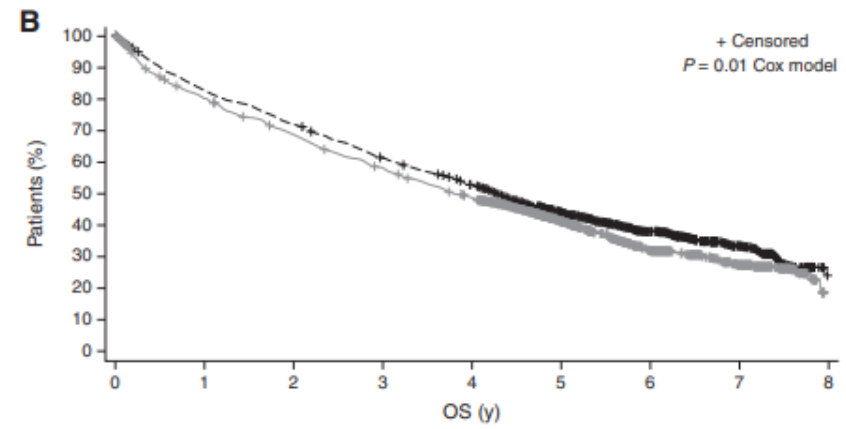
	Intensive pathway			Non-intensive pathway		
	Zoledronic acid (n=555)	Clodronic acid (n=556)	p value	Zoledronic acid (n=426)	Clodronic acid (n=423)	p value
CR, VGPR, or PR	432 (78%)	422 (76%)	0.43	215 (50%)	195 (46%)	0.18
CR or VGPR*	200 (36%)	193 (35%)	0.63	85 (20%)	60 (14%)	0.018
CR*	78 (14%)	69 (12%)	0.42	39 (9%)	27 (6%)	0.13

CR=complete response. PR=partial response. VGPR=very good partial response. *Exploratory analyses.

Table 5: Response rates after induction therapy (intention-to-treat population)



Median PFS: 19 vs. 18 mo



Median OS: 52 vs. 46 mo

Treatment Considerations: Bone Involvement

Plasma cell directed therapy

- Eliminates myeloma cells -> re-establishes homeostasis of bone remodeling
- Direct anabolic activity of proteasome inhibitors & daratumumab
- Consider RT if rapid treatment necessary

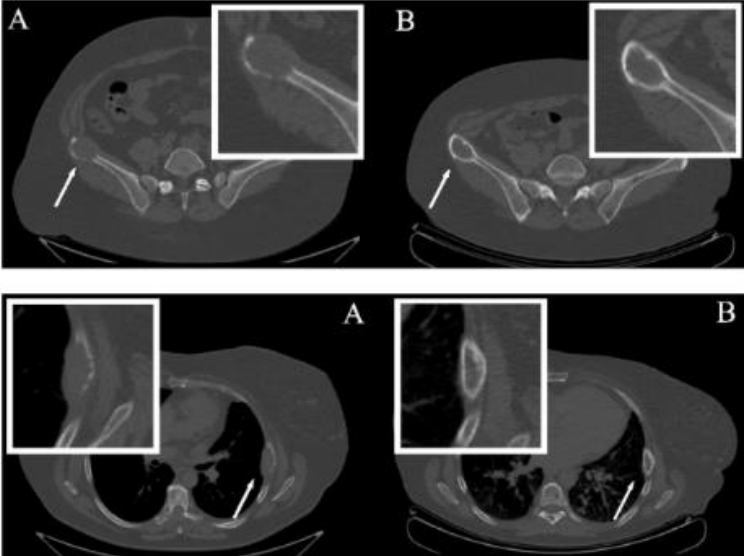
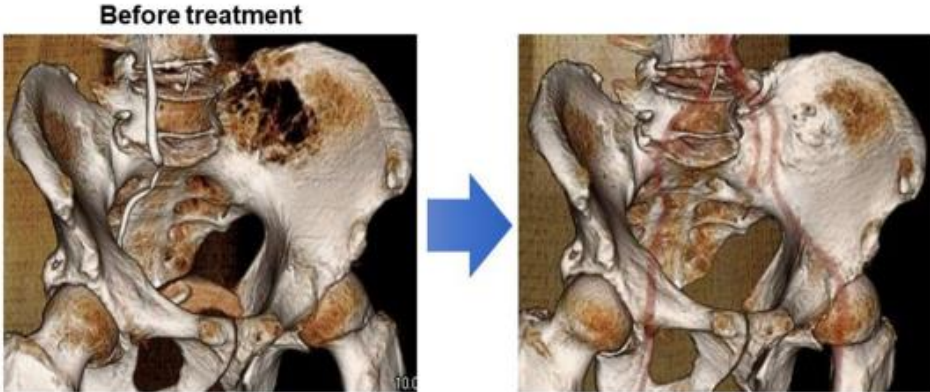
Bone modifying agents

- Zoledronic acid (zometa) x2 years – SOC as part of myeloma treatment, regardless of bone involvement
 - Reduces skeletal-related events
 - ??antimyeloma effects
- Denosumab - does not need to be renally adjusted
 - Non-inferior to zometa for reduction of skeletal-related events

Treatment Considerations: Toxicities of Bone Modifying Agents

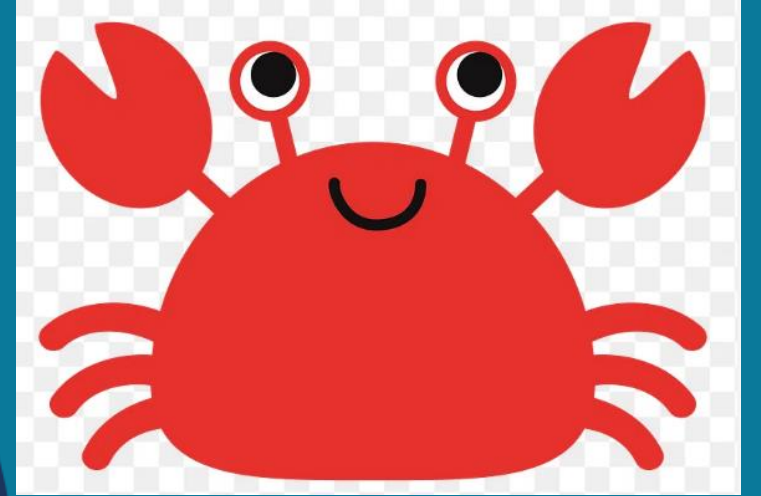
- Osteonecrosis of jaw
 - Dental clearance before starting!
- Severe hypocalcemia (denosumab > zoledronic acid)
- Bisphosphonates
 - Flu-like symptoms
 - Ocular symptoms
 - AKI, proteinuria
- Denosumab
 - Bone pain
 - Nausea, diarrhea
 - Shortness of breath
 - Rebound fractures

Bone Involvement: Before & After Treatment

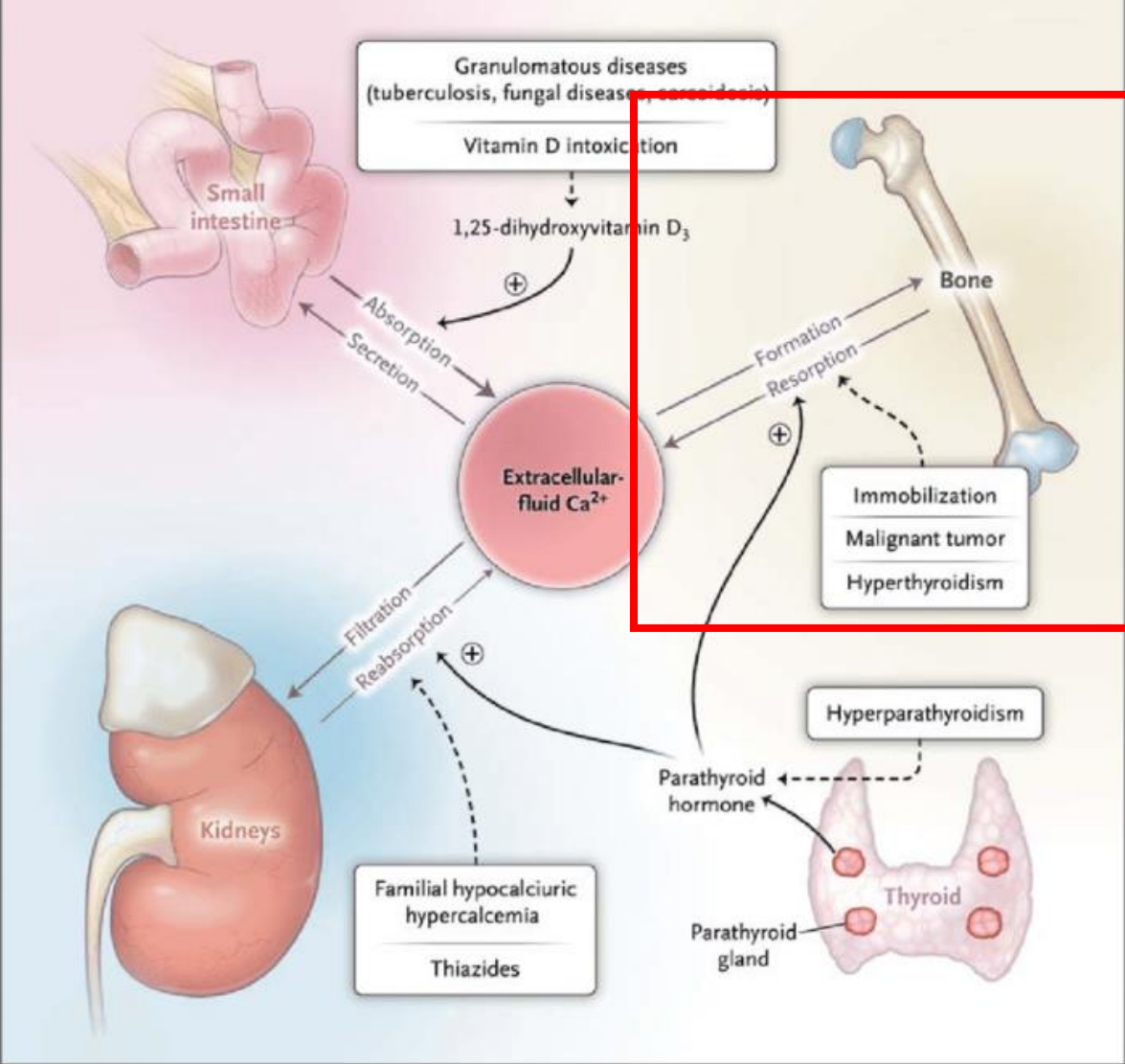


Images: Teramachi, et al., *Journal of Bone & Min Metabolism*, 2023; Hinge, et al., *Haematologica*, 2016

Elevated Calcium

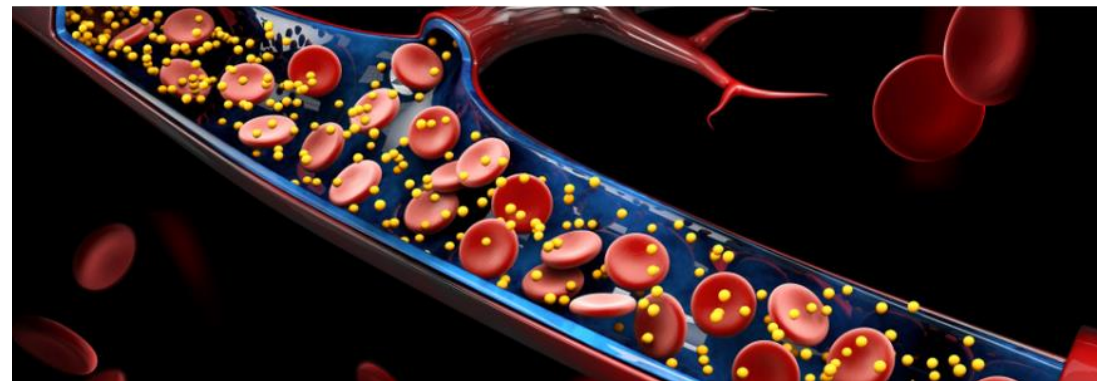
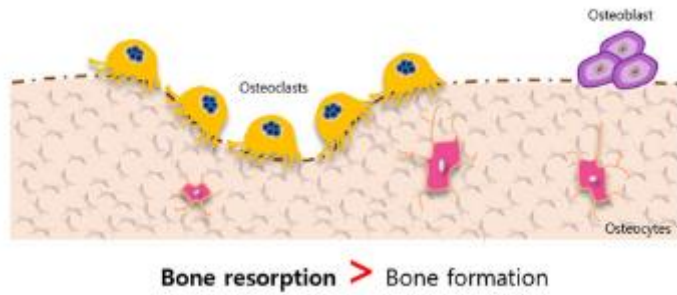


Normal Calcium Balance



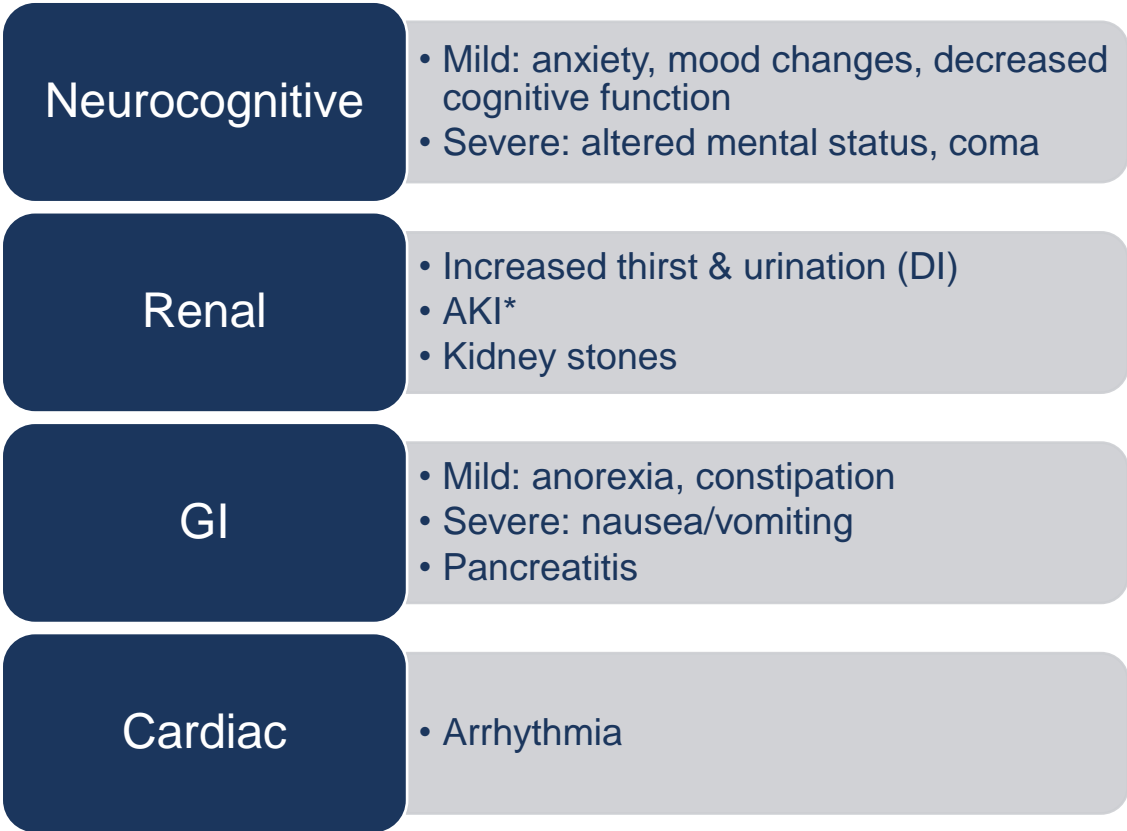
98% calcium stored within bones

Elevated Calcium in Myeloma



Clinical Manifestations of High Calcium

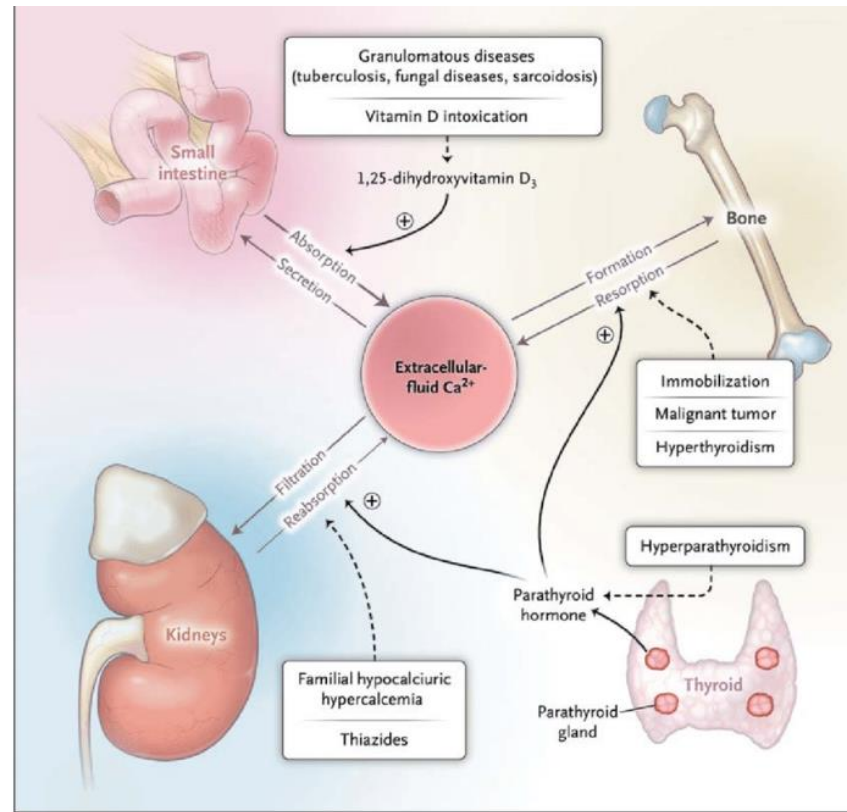
- Symptom severity based on both degree of elevation as well as rapidity of increase



Severe hypercalcemia =
emergency

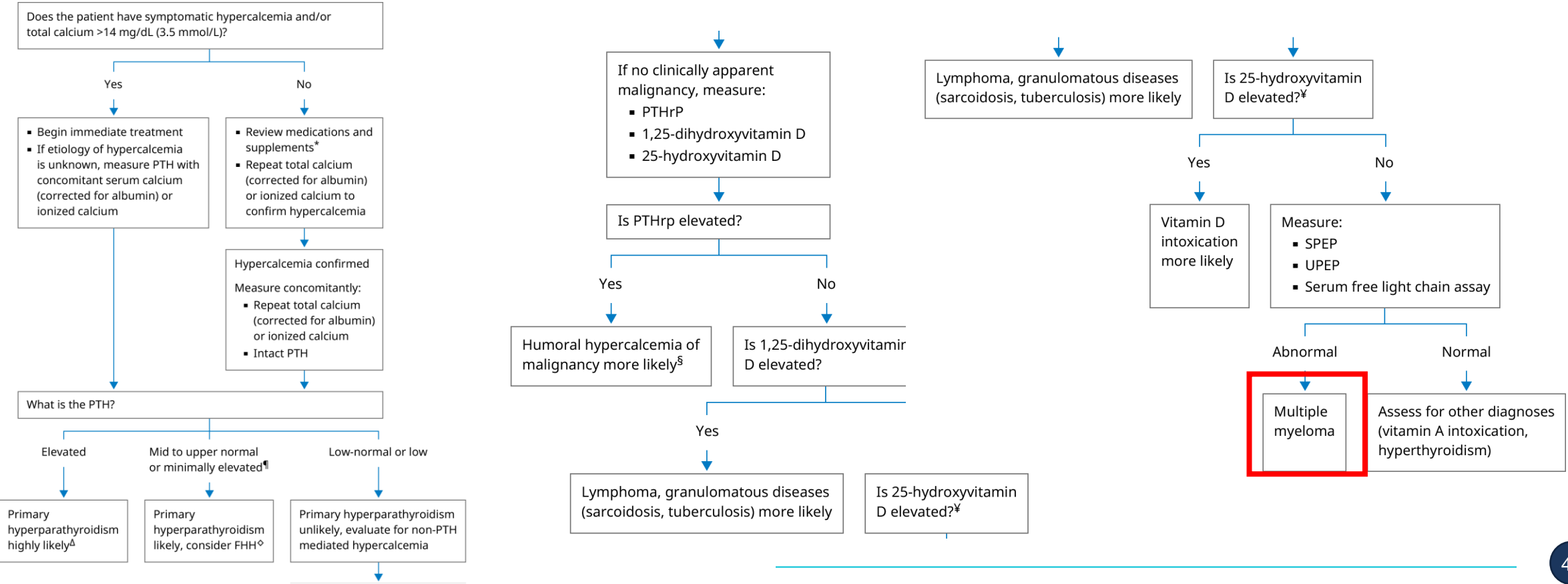
Hypercalcemia as a Myeloma Defining Event

- **Ca >11 mg/dL or >1 mg/dL above upper limit of normal due to the underlying clonal plasma cells**
- Other causes of hypercalcemia must be excluded:



Hypercalcemia as a Myeloma Defining Event

- **Ca >11 mg/dL or >1 mg/dL above upper limit of normal due to the underlying clonal plasma cells**
- Other causes of hypercalcemia must be excluded:



Treatment Considerations: Hypercalcemia

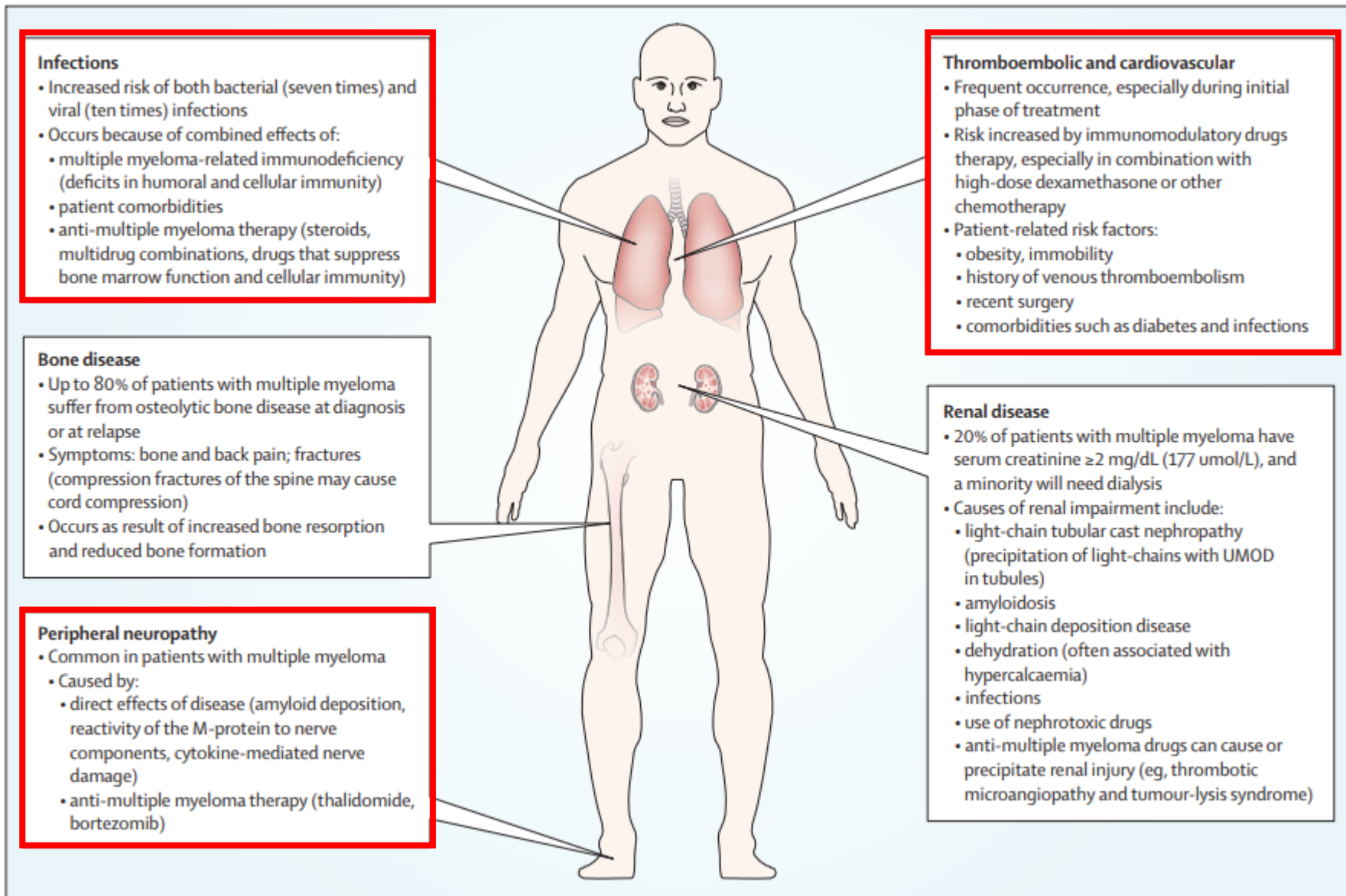
- Symptomatic / severe hypercalcemia = emergency
 - IV hydration +/- diuretics
 - Calcitonin
 - Inhibits osteoclasts
 - Eliminates Ca through kidneys
 - Zoledronic acid or denosumab*
 - Bisphosphonates:
 - Inhibits osteoclast-mediated bone resorption, arrests osteoclast development, osteoclast apoptosis
 - Decreases osteoblast apoptosis
 - Denosumab* - effective in hypercalcemia refractory to bisphosphonates
 - Antibody against RANKL
 - iHD
- Plasma cell directed therapy – restores bone homeostasis

MULTIPLE MYELOMA

Calcium
Renal impairment
Anemia
Boney lesions



Beyond CRAB?



Thank you!