Protein-Induced Injury and Protein Removal in Multiple Myeloma

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Multiple Myeloma

- Overall Survival has improved, but remains poor
  - Survival improved from 29.9 to 44.8 months between 1996 and 2006 (~50%)

    Hutchison et al, "Novel approaches for reducing free light chains in patients with myeloma kidney", Nature Reviews Nephrology 8, 234-243 (April 2012)
  - 1027 patients, between 1985 and 1998, median overall survival was 33 months
    - under 70yo survival 40.5 months, over 70yo survival 26.4 months

    Kyle et al, "Review of 1027 Patients With Newly Diagnosed Multiple Myeloma", Mayo Clinic Proceedings, January 2003, Volume 78, Issue 1

- AKI is a common complication of Multiple Myeloma
  - 40% pts have some AKI but usually moderate, 8% need dialysis

    Hutchison et al, "Novel approaches for reducing free light chains in patients with myeloma kidney", Nature Reviews Nephrology 8, 234-243 (April 2012)
  - 25% of MM pts have AKI when diagnosed with MM and 50% of MM pts will get AKI eventually, 10% of MM pts require dialysis

    Ludwig et al, "Reversal Of Acute Renal Failure By Bortezomib-Based Chemotherapy In Patients With Multiple Myeloma", Haematologica October 2007 92

- Often AKI is due to proteins, but there are other causes
  - Thrombotic microangiopathy, Hypercalcemia, Zolentronate toxicity
  - Let’s focus just on the protein diseases

Correlation between Renal Recovery and Improved Survival

- Median survival was 31.8 months in renal responders (Cr drops over 50%), and 11 months in non-responders

  Leung et al, "Improvement of cast nephropathy with plasma exchange depends on the diagnosis and on reduction of serum free light chains", Kidney International, Volume 73, Issue 11, 1 June 2008

- 39 pts, biopsy-proven MM kidney, ALL pts had chemotherapy PLUS dialysis or plasmapharesis
  - Median survival in pts on HD who did NOT recover renal function is 7.8 months
  - Median survival in pts on HD who recovered renal function is 42.7 months

  Hutchison et al, "Early reduction of serum-free light chains associates with renal recovery in myeloma kidney", J Am Soc Nephrol. 2011 Jun;22(6)

- 80% of patients with Cast nephropathy become dialysis dependant, median survival of dialysis dependant is 6 months

  Hutchison et al, Immunoglobulin free light chain levels and recovery from myeloma kidney on treatment with chemotherapy and high cut-off haemodialysis", Nephrol. Dial. Transplant. (2012)

- Median survival (in 2008) about 3yrs, but with AKI is less than 2 yrs

  Dimopoulos et al, "Pathogenesis and treatment of renal failure in multiple myeloma", Leukemia. 2008 Aug;22(8)

Multiple Myeloma Proteins

- Kappa are 21.6 kD monomers, Lambda are 45 dD dimers.
  - Light chains may also circulate as larger multimers, Multimers over 200 kD (so at least 10 chains)
  - Lambda light chain is worse, 2.4x higher rish of death

- Light chains are filtered through the glomerulus
  - As GFR drops the half life of FLC increases
  - Light chains half life 2-3hrs, but 2-3days in renal failure

- Not all Myeloma Proteins are Nephrotoxic
  - Small Study - 40 patients with Multiple Myeloma or AL Amyloidosis
  - Example patient withOUT AKI: kappa light chains
    - 50 gram/day proteinuria
    - Cr was NORMAL for 3 years of heavy proteinuria
  - Example patient with AKI: kappa light chains
    - 25 gram/day proteinuria
    - Cr was 9 mg/dL. Had tubular casts on renal biopsy

Solomon el al, "Nephrotoxic potential of Bence Jones proteins"
N Engl J Med. 1991 Jun 27;324(26):1845-51.

Types of Renal Injury

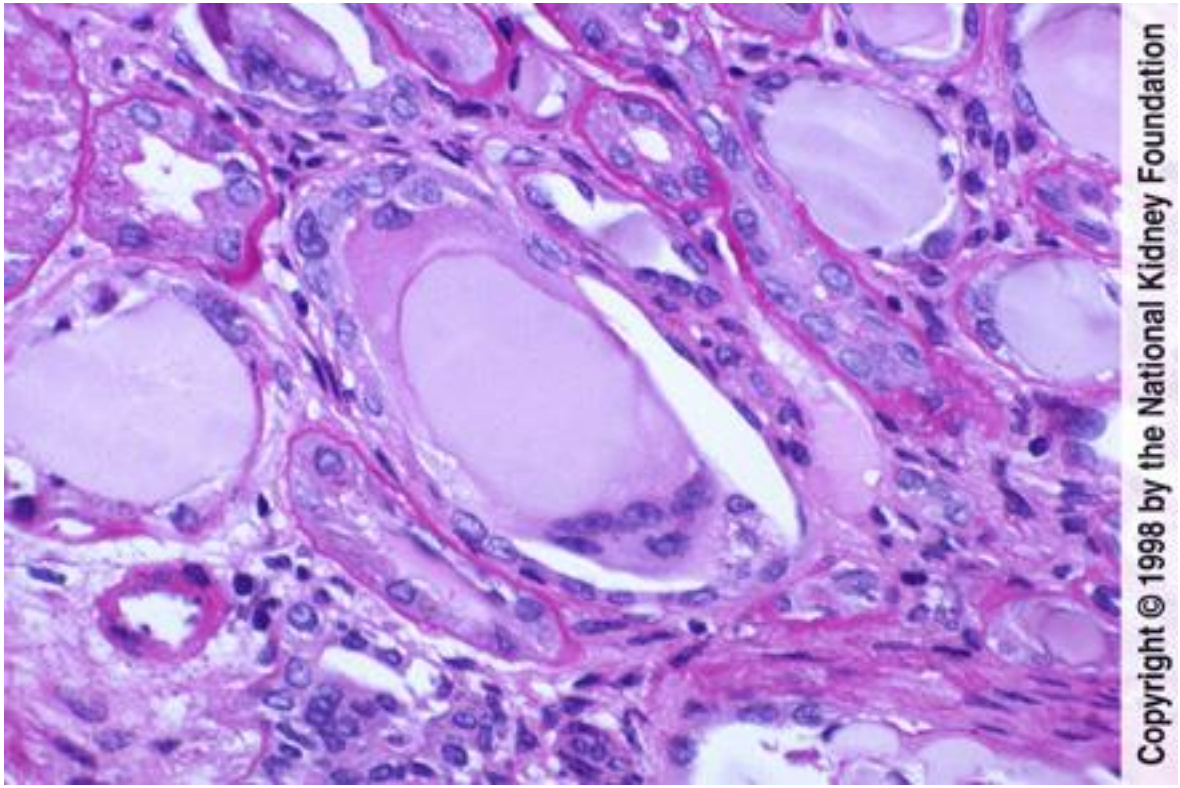
- Cast nephropathy
  - Light chains form casts in the ascending limb of the loop of Henle
  - Seen in 30% of patients
  - The CDR3 domain in the both Kappa and Lambda light chain binds to D8C on Uromodulin.
  - More common with light chains that have isoelectric point below 7.4

- Fanconi Syndrome
  - Light chains normally pass through Glomerulus are endocytosed by Proximal Tubule epithelial cells
    - Megalin/Cubilin receptors on epithelial cells bind the proteins
  - Large volumes of filtered light chains cause toxicity in the proximal tubule cells
    - Both kappa and lambda cause Fanconi
    - Isoelectric point of light chains does not affect PCT cell toxicity

- Amyloidosis
  - Light chains form beta-pleated sheets in blood vessel walls or interstitium or glomeruli
  - Usually lambda
  - Light chains are endocytosed in the glomerulus and form beta-pleated sheets in the lysosomes
    - Cause mesangial cells to become like fibroblasts

- Light chain deposition disease
- Monoclonal Ig Deposition Disease (MIDD)
  - Non-organized deposits in Tubule basement membrane, subendothelial in glomerular basement membrane, and/or in the mesangium
  - May be kappa or lambda

Cast Nephropathy



Tubule Obstruction causes injury **quickly**

- Measure obstruction in a single isolated Rat tubule
  - 12 rats, inject wax block into tubule, while it is still in living kidney

- After 1 day
  - Glomeruli look fairly normal but they lose brush border microvilli in PCT cells
  - **Downstream** of plug is severely damaged - cell necrosis and also some cell regeneration
  - Mild changes **Upstream** above the plug , but no necrosis

- After 1 week
  - GFR is 2/3 of normal
  - Glomeruli had PMN and lymphocyte infiltration
  - PCT cells lose height, microvilli

- After 1 month
  - GFR is 1/3 of normal
  - Glomerular **capillaries shrink**
  - Nephron shrinks, lose 29% of volume
  - Interstitium has fibrosis and many interstitial cells
  - Outer tubule and also Lumen diameter shrinks, cross-sectional size is 33% normal

Tanner et al, "Glomerular and proximal tubular morphology after single nephron obstruction", Kidney International, Volume 36, Issue 6, December 1989

Casts are formed by light chains binding to Uromodulin (Tamm-Horsfall Protein)

- Uromodulin
  - 616-amino acid protein, made from cells in the thick loop of Henle
  - 105 kDa, heavy glycosylation
  - Made by epithelial cells in thick ascending limb
  - Half life is 16 hours
  - Attaches to the apical membrane via phosphatidylinositol (GPI) proteins
  - Binding site on Uromodulin is a peptide fragment between residues 6 and 287

  - Copy of amino acids 225-233 is a competitive inhibitor (peptides AHWSGHCCL)
  - Complement peptide of amino acids 225-233 also blocks cast formation
    - Made from the complementary DNA of the DNA that encodes Amino acids 225-233
    - This complement peptide has an inverse hydropathic profile
    - Binds to Uromodulin, blocks cast formation

    Huang and Sanders, "Localization of a single binding site for immunoglobulin light chains on human Tamm-Horsfall glycoprotein", Journal of Clinical Investigation, 1997

- Light Chains
  - Kappa and lambda light chains contain a region CDR3
  - Forms a non-covalent bond to Uromodulin
  - A synthetic protein that replicates CDR3 will competitively inhibit
  - The CDRs (CDR1, CDR2, CDR3) are hyper-variable, but seem to have the same hydropathic signature

  Wei-Zhong et al, "Mapping the Binding Domain of Immunoglobulin Light Chains for Tamm-Horsfall Protein", American Journal of Pathology, May 2001 Volume 158, Issue 5

Light Chain Charge Affects Cast Formation

- Not all light chains form casts
  - Light chains with slightly different hydropathic signatures on CDR3 will be more or less prone to make casts.
  - Hydropathics, not the specific amino acids, are what determine the non-covalent binding and thus cast formation.
  - Changing the pH of urine between 5 and 8.5 will alter the LC-Uromodulin interaction

- Inject different types of kappa light chains into other rats

- Group 1: kappa light chains had pI=4.3, light chains are **anions** in urine
  - GFR fell 33%
  - Some Tubules had casts in TAL, CD (less than pI=5.2 group
  - These rats still excreted up to 200 mg/day of FLC in urine, rats survived 40 days

- Group 2: kappa light chains had pI=5.2, light chains are **anions** in urine
  - GFR fell 69%
  - Tubules had casts in TAL, CD, Foamy vacuoles in PCT cells
  - These rats excreted up to 60 mg/day of FLC in urine, Rats survived 15 days

- Group 3: kappa light chains had pI=6.7, light chains are **cations** in urine
  - GFR is unchanged
  - 5 of 8 rats had normal tubules, while other 3 rats had tubular cell regeneration - c/w injury recovery
  - These rats still excreted up to 150 mg/day of FLC in urine, and survived 40 days

Smolens et al, "Effect of chronic administration of different Bence Jones proteins on rat kidney", Kidney Int. 1986 Dec;30(6):874-82.

Light Chain Charge Affects Ionic Levels In Tubule

- Collect Uromodulin from urine of humans with Multiple Myeloma
  - Inject into 37 rats
  - Different Light Chains Affect Ion Reabsorption in the Tubule
  - Light Chains from Patient 1 - Caused decreased chloride absorption
    - Increased Chloride concentration in the tubule
    - Formed casts in the tubule, aggregated with Uromodulin
  - Light Chains from Patient 2
    - Caused increased chloride absorption,
    - Lowered Chloride concentration in the tubule

Sanders et al, "Mechanisms of intranephronal proteinaceous cast formation by low molecular weight proteins", J Clin Invest. 1990 Feb;85(2):570-6

- Changing Ion Concentrations Further Affects Cast Formation
  - Uromodulin has an isoelectric point of 3.5, so in neutral solution, h
  - as a net negative charge
  - Light Chains and uromodulin are both anions so repel each other
  - If NaCl in the tubule increases, then the Na+ and Cl- ions can shield the charges on proteins, making them more net neutral and allows interaction

- Increasing NaCl in the tubule will if anything increase interaction between BJP and Uromodulin

Medications Also Affect Cast Formation

- Light Chains from 4 different Myeloma patients were injected into rats

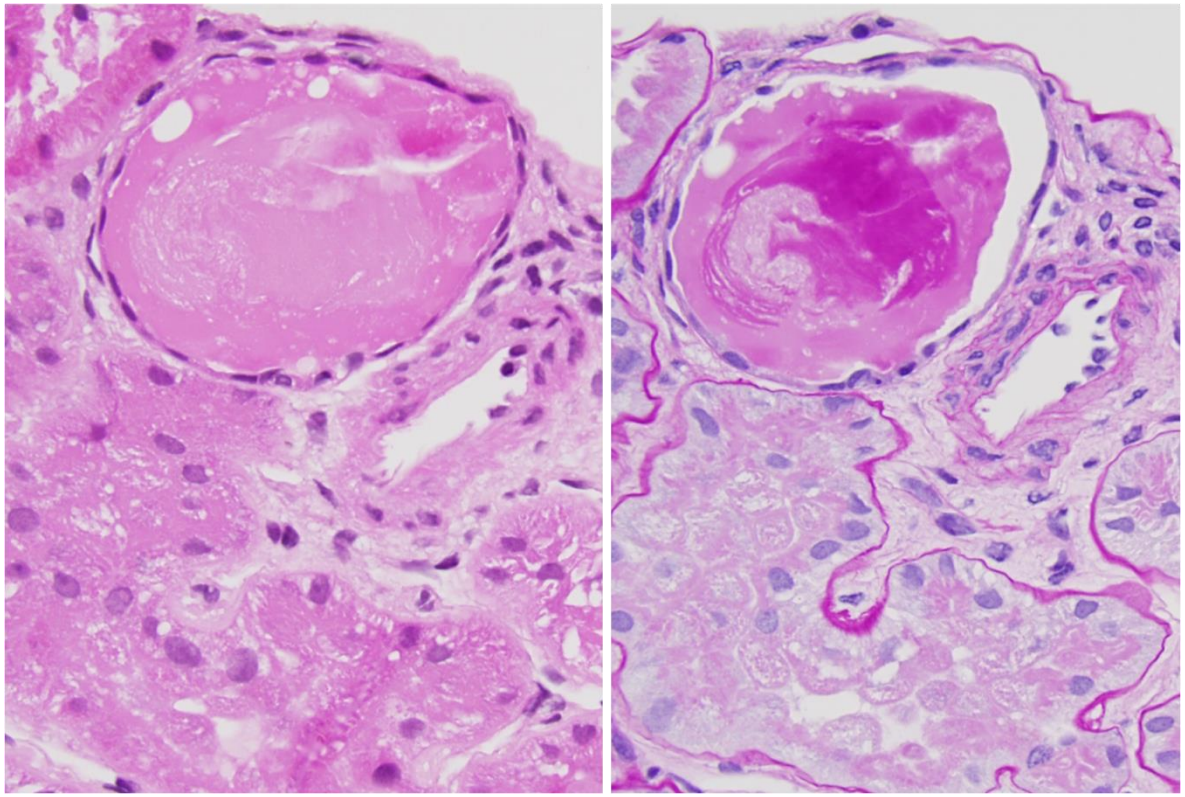
- Furosemide caused casts to form faster, in dose-dependant manner
  - It increased levels of NaCl in the tubule lumen
    - So it increased binding between Light Chains and Uromodulin
  - Furosemide also binds directly to Bence Jones proteins in vitro, but this is controversial
  - Furosemide binds at a different site than Uromodulin, so it is NOT a competitive inhibitor

- Colchicine reduces cast formation
  - Colchicine decreased secretion of Uromodulin 80%
  - Colchicine caused Uromodulin molecular weight to dropped 80 kD--> 60 kD
    - This was due to decreased carbohydrate in the Uromodulin glycoprotein
  - Rats given Colchicine and infused with Bence Jones proteins did not form casts

Sanders et al, "Pathobiology of cast nephropathy from human Bence Jones proteins", J Clin Invest. 1992 Feb; 89(2): 630–639.

Casts Are Not Homogenous

- Different tubules in the same slide contain cast material with different appearance
  - Artifact of slide preparation?
  - More uromodulin on the downstream end?
  - Different pH or other chemical conditions?



Proximal Tubule Injury – Fanconi and more

Light Chains are freely filtered

- However, charge (due to isoelectric point) affects filtration
  - 23 Multiple Myeloma patients (14 kappa, 9 lambda)
  - 24hr urine collection
  - Negative correlation between pI and Cr clearance of light chains - Higher pI had lower Clearance
  - Increase in clearance for pI at 5.0 or below
    - FLC with net negative charge (isoelectric point < 5.1)

Coward et al, "The Importance of Urinary Immunoglobulin Light Chain Isoelectric Point (Pi) in Nephrotoxicity in Multiple Myeloma", Clinical Science Feb 01, 1984, 66 (2)

Light Chains are Endocytosed in Proximal Tubule

- Light Chains bind to Cubulin/Megalin receptor complex on Proximal Tubule Cells
  - Megalin has a transmembrane domain, it can internalize a ligand by itself
  - Cubulin does not have an internal domain
  - Megalin knockdown mice have reduced levels of cubulin synthesis
  - Dent's disease, CLCN5-deficiency, causes Megalin deficiency, Imerslund-Grasbeck syndrome causes Cubulin deficiency

- Megalin/Cubulin will non-specifically bind to many proteins including
  - Both kappa and lambda light chains, alpha-microglobulin, beta-microglobulin, Cytochrome C, Insulin, PTH, many peptide hormones
  - Saturable, reversible, consistent with receptor kinetics

- Blocking Cubulin/Megalin stops protein uptake into epithelial cells
  - Fluorescent tag light chains from human Multiple Myeloma patients
  - Protein is taken up by PCT cells from Sprague-Dawley rats
  - Anti-cubulin and anti-megalin antibodies from rabbits prevent binding of the tagged light chains to PCT cells

    Klassen et al, "Light chains are a ligand for megalin", Journal of Applied Physiology 1 January 2005 Vol. 98 no. 1

- siRNA that megalin or cubilin causes partial, not complete, effect of reducing endocytosis
  - Silencing both megalin and cubulin causes 85% inhibition
  - Not 100%, so there is another pathway. Maybe pinocytosis

    Li et al, "Silencing megalin and cubilin genes inhibits myeloma light chain endocytosis and ameliorates toxicity in human renal proximal tubule epithelial cells", American Journal of Physiology - Renal Physiology Published 8 July 2008 Vol. 295 no. 1

Endocytosed Light Chains Cause Cell Injury

- Endosomes fuse with lysosomes
  - Lysosomal proteases (Cathepsin B) degrade proteins
  - Proteins resistant to the proteolysis will accumulate and crystallize
  - Activates NFkB, and MAPK (mitogen-activated protein kinases) which leads to downstream activation of IL-6, IL-8, TGF-B1, and CCL2(CC-motif chemokine 2, AKA monocyte chemo attractant protein)
  - Interferes with Na-cotransporters so inhibits PCT reabsorption of Amino Acids, Phos, Glc, and so these spill into the urine.

- Not all light chains will produce Fanconi
  - Study K Light Chain in a specific Multiple Myeloma patient with Fanconi
  - Crystals are resistant to proteolysis
  - Crystals contain a 107 Amino Acid fragment in the variable domain
  - Specific peptide sequences in V region determine whether these FLC develop PTC lesions
  - Hydrophobic residues at positions 30 and 94 are required for Fanconi crystallization

  - Clone the VkJk gene from this patient in mice
  - The mice had impairment of urate, phosphate, and CC16 (Clara Cell Secretory protein 16) tubule reabsorption

Christophe Sirac et al, "Role of the monoclonal κ chain V domain and reversibility of renal damage in a transgenic model of acquired Fanconi syndrome", Blood 2006 108

Treatment Options

- Chemotherapy
- Bone Marrow Transplant
- Mechanical Filtration

Chemotherapy Improves Renal Outcomes

Prospective Trial of **High Dose** Dexamethasone

- 41 patients, all with newly diagnosed Multiple Myeloma and AKI (Cr over 2)
  - At start of the trial, 10 pts were on dialysis
- All treated with high dose Dexamethasone, IV fluids, Alkalinization
- 73% of all pats had improvement of renal function (Cr below 2), median time to reversal was 1.9 months
- **After treatment only 8 of the 10 pts got off dialysis**
- Small mortality change

Kastritis et al, "Reversibility Of Renal Failure In Newly Diagnosed Multiple Myeloma Patients Treated With High Dose Dexamethasone-Containing Regimens And The Impact Of Novel Agents", Haematologica April 2007

Retrospective - pts with AKI due to MM

- 68 patients got Bortezemib+Doxorubicin+Dex
- 72% had renal recovery, mean GFR improved 20.5-->48.4
- But only 3/9 pts on dialysis got off dialysis

Hutchison et al, "Novel approaches for reducing free light chains in patients with myeloma kidney“ Nature Reviews Nephrology 8, 234-243 (April 2012)

Chemotherapy Improves Renal Outcomes

Benefits of Bortezemib

- 24 patients, with Multiple Myeloma and renal failure, and 23 were on dialysis.
- All patients got Bortezemib and various other agents (Dex, Thalidomide, Doxorubicin,.....)
- 3 of 23 patients recovered renal function and got off dialysis

Chanan-Khan et al, "Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: a multicenter retrospective study", Blood 2007 109

Benefits of Bortezemib

- 8 Multiple Myeloma patients, 7 new diagnosis and 1 with relapsed Myeloma
- No renal biopsies, Mean Cr at start of treatment was 9.05
- All patients treated with Bortezemib
- 5 of 8 patients had renal recovery, Cr dropped to 2.1 at 41-71 days
- After followup of 15.9 months, 4 patients died, 2 of those who had renal recovery, and of the 4 survivors, 3 had renal recovery and 1 did not have renal recovery

Ludwig et al, "Reversal Of Acute Renal Failure By Bortezomib-Based Chemotherapy In Patients With Multiple Myeloma", Haematologica October 2007 92

Mechanical Filtration is Controversial, Lower Grade, Sometimes Recommended

Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH), UK Myeloma Forum

Consider physical methods of removing free light chains from the blood (plasma exchange, large pore haemofiltration) within the context of a clinical trial(Grade C2)

European Myeloma Network Guidelines, 2015

Therapeutic plasma exchange (TPE) has been suggested to impact the outcome of the renal failure, but its role remains controversial

International Myeloma Working Group, 2016

The use of high-cutoff hemodialysis membranes in combination with antimyeloma therapy can be considered (grade B)

International Myeloma Working Group recommendations for global myeloma care, 2013

benefit for plasmapheresis has so far not been proven. In addition, the use of special dialysis membranes and long-term dialysis for the removal of serum free light-chains is not yet established.

If Proteinemia is Bad, is Removing Proteins Good?

- Positive Trials
  - Johnson et al 1990 – Plasmapheresis or not – Positive
- Dose-Dependent Improvement (baseline mortality if the effective control group)
  - Hutchison 2011
  - Hutchison et al, 2009 - High Cut-Off Dialyzers
  - Hutchison et al, 2012 - High Cut-Off Dialyzers
  - Zucchelli et al 1988 – Hemodialysis vs Peritoneal Dialysis
- Inconclusive (often no control group)
  - N Leung et al 2008 – Plasma Exchange with/without Cast Nephropathy
  - Gerth et al 2016 – High Cut-Off Dialyzers vs Conventional HD – Positive but Confounders
- Negative
  - Clark et al 2005 – Dialysis vs no dialysis – Negative
- Pending or incomplete trials
  - EuLITE - European trial of free light chain removal by extended haemodialysis in cast nephropathy
  - MERIT - MyEloma Renal Impairment Trial
- Things to Watch for
  - Is there a control?
  - Did both groups get the same chemotherapy
  - Was AKI/CKD biopsy-proven Myeloma Kidney

Compare Plasma Exchange to No Exchange - Positive

- 21 patients with Multiple Myeloma and AKI
  - 16 patients got biopsies
  - 12 patients on dialysis at start of trial
  - All patients got chemotherapy (Melphalan/Prednisone 7d cycle every 6wks), PO bicarb, IV NS, lasix (!)

- Group 1: Chemotherapy only
  - 10 patients, mean initial Cr 8.25, 5 patients on HD at the start
  - 5 of 10 patients improved Cr, mean Drop of 3.8 md/dL
  - 5 of 9 patients making urine dropped Urine Prot over 50%
  - **No patients got off dialysis** - all patients of dialysis at start remained on dialysis

- Group 2: Chemotherapy and Plaxma Exchange
  - 11 patients, mean initial SCr 9.95, 7 patients on HD at the start
  - Plasma Exchange for 1-4wks (mean 7.9 sessions, replace mean 48.6 mL/kg with 5% albumin and NS)
  - 4 of 11 patients improved Cr, mean Drop of 7 mg/dL
  - 4 patients ended up on chronic HD, 3 of 7 patients got off dialysis
  - 5 of 7 patients making urine dropped Urine Prot over 50%

- Plasma exchange associated with
  - **Larger drop in free light chains, More recovery from dialysis**
  - No huge difference, although N is tiny

Johnson et al, "Treatment of Renal Failure Associated With Multiple Myeloma – Plasmapheresis, Hemodialysis, and Chemotherapy" Arch Intern Med. 1990

Lower Free Light Chains is Always Better – Dose-Dependent Improvement

- Retrospective Study - 39 pts, all had biopsy-proven MM kidney
  - Average GFR 9
  - Median serum FLC 420 mg/dL
  - ALL got chemotherapy PLUS dialysis or plasmapharesis
  - 26 of 39 pts (66%) had some renal recovery
  - 24 pts were on HD at start of trial, and 15 of 24 (62%) got off dialysis

- Day 12
  - 8 of 8 pts who had 75% reduction in FLC had renal recovery
  - 9 of 12 pts who had 50-74% reduction in FLC had renal recovery
  - 4 of 5 pts who had 25-49% reduction in FLC had renal recovery
  - 3 of 5 pts who had 25-49% reduction in FLC had renal recovery

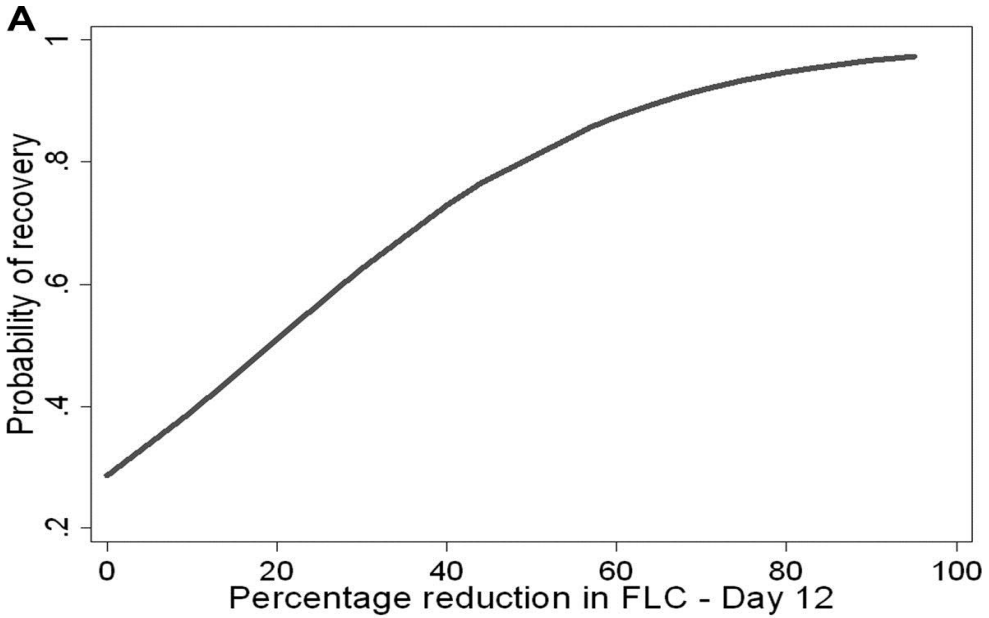
- Day 21
  - 13 of 14 pts who had 75% reduction in FLC had renal recovery

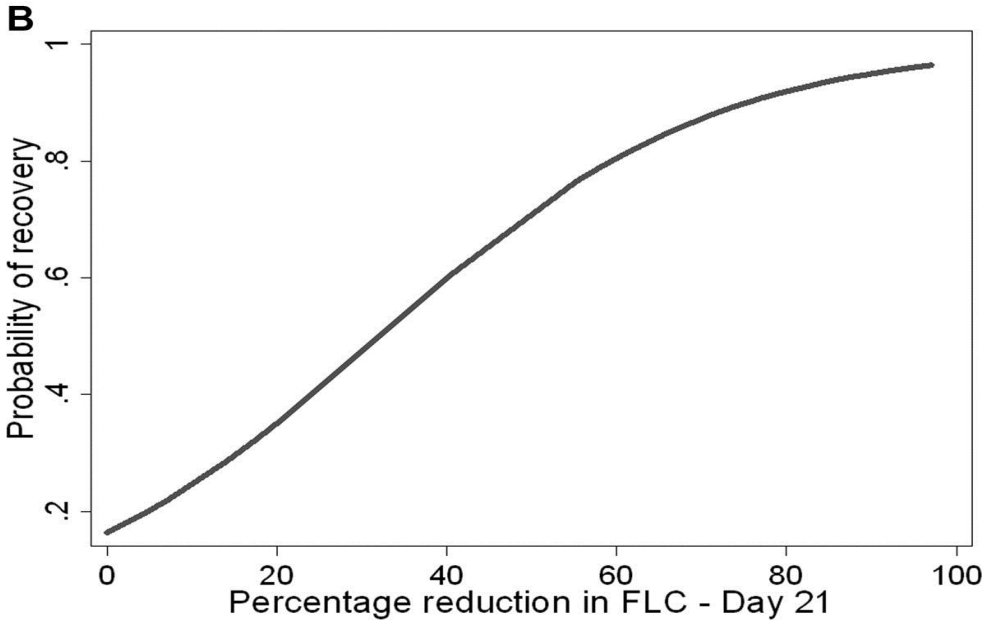
- Linear mapping between percent reduction in FLC at day 12 and 21 and survival.
  - No specific threshold, more reduction is always better
  - No real difference between dialysis or plasma exchange

- Renal Recovery is Important For Survival
  - Median 7.8 months if NO renal recovery, 42.7 months with recovery

Hutchison et al, "Early reduction of serum-free light chains associates with renal recovery in myeloma kidney“ J Am Soc Nephrol. 2011 Jun;22(6)

Lower Proteins are *Always* Better?





- No Minimum threshold for mortality after diagnosis of MM
- What about MGUS?
  - Median serum FLC 420 mg/dL
  - 30% reduction will grop below 300 mg/dL

Hutchison et al, "Early reduction of serum-free light chains associates with renal recovery in myeloma kidney", J Am Soc Nephrol. 2011 Jun;22(6):1129-36

High-cutoff Dialysis leads to renal recovery -Dose-Dependent Improvement

- 19 patients with Multiple Myeloma and requiring dialysis, with cast nephropathy on renal biopsy
  - All got Chemo, 7 got Cyclophosphamide/Dex, 14 got Thalidomide/Dex.
  - 6 patients had chemo interrupted (usually due to infection)

- 13 of the patients with uninterrupted Chemotherapy and Dialysis
  - All 13 became dialysis independant
  - 8hrs of HD daily x5 days then 8hrs Q48hr x12 days, thern 6hrs TIW
  - Several types of dialyzers (Braun Hi-PeS 18, Gambro HCO 1100, Toray BG 2.1, Idemsa, Nikkiso, ASahi)
  - Gambro HCO 1100 dialyzer, 2 dialyzers in series, had best clearance. Filter had protein cutoff of 45 kD. Serum FLC clearance between 10 and 40 mL/min
- No control group

- Longer dialysis sessions caused more FLC removal from serum.
  - 60% of pats removed 100% of FLC when HD 4hrs TIW
  - 91% of patients had 100% serum clearance if 12hr/day
    - But, FLC levels rebounded within 1-2 days

Hutchison et al, "Treatment of Acute Renal Failure Secondary to Multiple Myeloma with Chemotherapy and Extended High Cut-Off Hemodialysis", CJASN April 2009 vol. 4 no. 4 745-754

Rapid Reduction of Free Light Chains Improves Chance of Renal Recovery – Dose-Dependent Improvement

- Retrospective trial - 67 patients, 16 centers in 9 countries
  - 50% of patients had renal biopsy, main diagnosis was cast nephropathy
  - All patients got chemo - Bortezomib and/or Thalidomide
  - 97% of patients had some dialysis

  - 48% got over 6hr HD
  - Gambro HCO 1100. It has small surface area, 1.1 m2 so often 2 dialyzers in series

- After dialysis - 63% patients became dialysis INdependant
  - Linear relationship between amount of decline in FLC and probability of dialysis independance
  - Patients with High-Cut-Off Dialysis within 7 days had a better chance of becoming dialysis independant

- Dialysis without chemo will have limited benefit
  - Dialysis does not remove the cells, only the proteins
  - Multiple Myeloma has high rate of FLC production

Hutchison et al, "Immunoglobulin free light chain levels and recovery from myeloma kidney on treatment with chemotherapy and high cut-off haemodialysis" Nephrol. Dial. Transplant. (2012)

Compare Hemodialysis with Peritoneal Dialysis

Dose-Dependent Improvement

- 29 patients with AKI and MM between 1980 and 1986
  - Rapid rise of Cr over 5.0, 17 pts had renal biopsy, and all but 1 showed cast nephropathy
  - Initially treated with 0.5-**1.5** grams lasix, 2-5L IV NS, PO bicarb
  - All patients in both groups got chemo: IV Methylpred, then PO Prednisone and PO Cyclophosphamide

- Group I: Plasma Exchange plus optional Hemodialysis
  - Plasma exchange daily x5 days, each session replaces 3-4L plasma with NS+Albumin+FFP
  - 13 of 15 patients **also** got Hemodialysis TIW, 4-5hrs

  - During first 2 months: 11 of 13 patients had renal recovery, 1 patient died
  - During first year: 66% survival (53% at 2 years)

- Group II: Peritoneal dialysis
  - 11 of 14 patients got intermittent Peritoneal dialysis - 40 Liters every other day for 10 days

  - During first 2 months: 2 of 11 patients had renal recovery, 5 patients died
  - During first year: 28% survival at 1 year

- This just compares dialysis modalities
  - **Hemodialysis may be better than PD**

Zucchelli et al, Controlled plasma exchange trial in acute renal failure due to multiple myeloma, Kidney International - June 1988

Plasma Exchange only helps if Cast Nephropathy - Inconclusive

- Retrospective study, 40 patients total
  - 9 patients were on HD at start of study, 1 started HD during study, 2 started HD after study
  - Plasma exchange either daily or QOD. Usually 5 plasma exchanges, with albumin replacement, and occasionally FFP.
  - Variable chemo regimens, but only 85% got chemo during the plasma exchange period
  - NO Control Group

- 28 of 40 patients had renal biopsy
  - 18 of 28 had pure cast nephropathy
  - Other biopsy diagnoses included Cast Nephropathy with Light Chain Deposition Disease (2pts), Pure Light Chain Deposition Disease (3pts), ATN (3 pts), Diabetic Nephropathy (1 pt), Amyloid (1pt)

- 18 of 40 patients had renal response - defined as 50% decrease in creatinine and dialysis independence
  - Median survival was 31.8 months in renal responders, and 11 months in non-responders
  - No patients with just Light Chain Deposition Disease responded
  - Half of patients with CN and Light Chain Deposition Disease responded

- In Pure cast nephropathy (18 patients)
  - 9 had over 50% drop in FLC, and 7 of these 9 had renal recovery
  - 5 had less than 50% drop in FLC, and 0 of these 5 had renal recovery

- Renal recovery depended on >= 50% drop in FLC ONLY in patients with pure Cast Nephropathy
  - But patients without cast nephropathy seemed to be sicker

N Leung et al, "Improvement of cast nephropathy with plasma exchange depends on the diagnosis and on reduction of serum free light chains", KI, 1 June 2008

High Cutoff Dialysis vs Normal Dialysis - Inconclusive

- 59 MM patients with new AKI on dialysis
  - No patients on HD prior to myeloma
  - "almost all“ patients had Biopsy proven cast nephropathy

- Intervention Group: 42 patients got High Cutoff dialysis
  - 5x per week, 6 hrs/session, Gambro 1100 or Theralite filter
  - **76%** got "novel" chemo of (Bortezemib lenalidomide) and chemo started same day as HD
  - 64% of pts had renal recovery (27/42) - Took average of 36 days to reach FLC <= 1000mg/L
  - 69% pts survived to 1 year

- Control Group: 17 patients got conventional dialysis
  - 3x per week, 4hrs/session, FMC filters
  - **23.5%** got "novel" chemo of (Bortezemib lenalidomide) AND chemo started avg 4 days after HD
-
  - 29.4% of pts had renal recovery (5/17), Took average of 14 days to reach FLC <= 1000mg/L
  - 47.1% pts survived to 1 year

- More patients in intervention group got first-line chemotherapy
  - Chemo regimens were different and that is important

Gerth et al, "Impact of High-Cut-Off Dialysis on Renal Recovery in Dialysis-Dependent Multiple Myeloma Patients: Results from a Case-Control Study", 2016

Plasma Exchange Does Not Help - Negative

- 14 Canadian centers, 1998-2003
  - All patients had Cr > 2.3 (mean eGFR 14.8 in test group, 13.3 in control)
  - No biopsies
  - All patients got chemo: Melphalan+Prednisone or VAD=Vincristine/Adriamycin/Dexamethasone
  - 43 of 97 total patients started dialysis while in the trial - 24 in plasma exchange group and 19 in control

- Group I: 61 patients got plasma exchange
  - 5-7 exchange procedures over 10 days, exchange 50mL/kg with 5% albumin and NS
  - 10 of the 24 patients requiring hemodialysis became dialysis independant.

- Group II: 43 patients NO plasma exchange
  - 7 of the 19 patients requiring hemodialysis became dialysis independant.

- **NO statistical difference** between plasma exchange and non-plasma exchange in primary outcomes (death, dialysis dependance at 6 mos or eGFR below 30 at 6 mos)
  - But, 95% confidence intervals were wide
  - Approx 1/3 pts in each group died

- Subgroup analysis – more renal recovery with plasma exchange
  - This lumped outcomes, so if patients died with renal recovery, that is still considered a failure.

Clark et al, "Plasma Exchange When Myeloma Presents as Acute Renal Failure: A Randomized, Controlled Trial", Ann Intern Med. 2005

Incomplete or Pending Trials

- EuLITE - European trial of free light chain removal by extended haemodialysis in cast nephropathy
  - Prospective, random, open-label, multicenter
  - All patients get Bortezemib, Doxorubicin, Dexamethasone
  - Group 1: (intervention) Extended Dialysis with Gambro 1100 HCO dialyzers
    - 6hrs of HD on non-Bortezemib days
  - Group 2: (control) Regular dialysis with Gambro 1100 HCO dialyzers
    - 4hrs sessions TIW
  - Primary endpoint is GFR > 15 and independance from dialysis, Secondary Endpoint is FLC levels

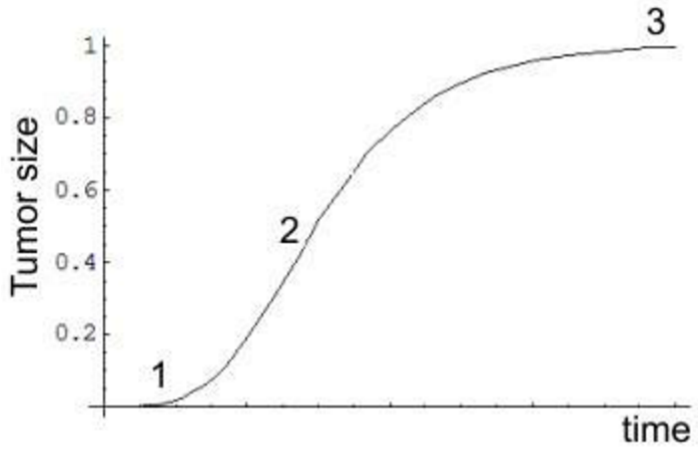
- MERIT - MyEloma Renal Impairment Trial - CLOSED
  - Randomised controlled trial
  - Plasma exchange Multiple myeloma and acute renal failure.
  - Planned 286 patients, closed after only recruiting 90 patients

Open Question:
How Much Dialysis Does Each Patient Need?

- Proteins rebound from interstitial space (like Urea rebound)
- Cells remain in Plasma and Bone Marrow
  - Does protein removal affect protein synthesis rate or cell growth rate?

We Can Simulate the Protein Removal

- Cell Growth follows a Gompertzian function
  - Sigmoid curve, slow-fast-slow
  - Exponential function with exponentially-decaying exponent
    - Why does growth slow? Resource constraints? Some feedback? Answer is not clear
  - Total protein synth rate is stable and constant when it approaches asymptotic limit
  - The initial concentration of protein is the same in plasma and interstitial compartments
  - Synthetic rates among these patients ranged from 1.5 to 34 pg/myeloma cell per day (mean, 14.5+9.6)



$$y(t) = a\mathrm{e}^{-b\mathrm{e}^{-ct}}$$

Sullivan PW, Salmon SE, "Kinetics of tumor growth and regression in IgG multiple myeloma", J Clin Invest 1972 Jul;51(7):1697-708

- Dialysis removes proteins, not the cells. So, synthetic capacity is unchanged

We Can Simulate the Protein Removal

- Protein volume of distribution includes interstitial space
  - Protein rebound after HD, similar to Urea rebound
  - Diffusion back into vascular space follows Fick's first law
    - Flux is proportional to gradient

$$J = -D \cdot \frac{dc(x)}{dx} \qquad \text{(Unit: D: cm}^2\text{/sec;} \quad \text{J: number/cm}^2\text{/sec)}$$

- Part of a larger physiologically-based pharmacokinetic model (PBPK)
  - Simplified model for monoclonal antibodies
  - One body compartment and vascular space

$$\frac{dC_p}{dt} = \frac{Input}{V_p} + f_d \cdot Q_{CO} \cdot \left(\frac{C_t}{K_P} - C_p \right) / V_p$$

$$\frac{dC_t}{dt} = f_d \cdot \frac{Q_{CO}}{V_t} \cdot \left(C_p - \frac{C_t}{K_P} \right) - \frac{C_t}{V_t} \cdot CL_T$$

  - Yanguang Cao, William J. Jusko, "Applications of minimal physiologically-based pharmacokinetic models", J Pharmacokinet Pharmacodyn. 2012 Dec; 39(6): 711–723 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3539784/

Demo

www.dawsondean.com/hdSim.html

- The Permeability coefficient used is actually a value for anti-CD3 antibody, called hu12F6mu. This will change for every antibody and protein
  - I see no study that measures the value for this for kappa or lambda
- Assume no extrarenal metabolism of light chains
- Initial Values can be changed. I used typical values from Myeloma studies

Kyle et al, “Review of 1027 Patients With Newly Diagnosed Multiple Myeloma”, Mayo Clinic Proceedings, January 2003, Volume 78, Issue 1

Future Work

- Retrospective study of MM patients
  - Derive a Physiologically-based pharmacokinetic model (PBPK) for Myeloma
  - Empirically derive permeability coefficient

Questions?

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