

The Answer, My Friend, is Flowing in the Blood: How to Monitor Treatment Response in Myeloma



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Disclosures

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Other: none

Mitigating Potential Bias

Not applicable

Objectives

1. List the indications for ordering an SPEP, UPEP, SFLC
2. Differentiate the types of myeloma based on SPEP, UPEP, SFLC results (M-protein myeloma, light chain myeloma, non-secretory myeloma)
3. Describe the concept of light chain escape in relapsed myeloma
4. List the definition for biochemical and clinical progressive disease in relapsed myeloma

Case

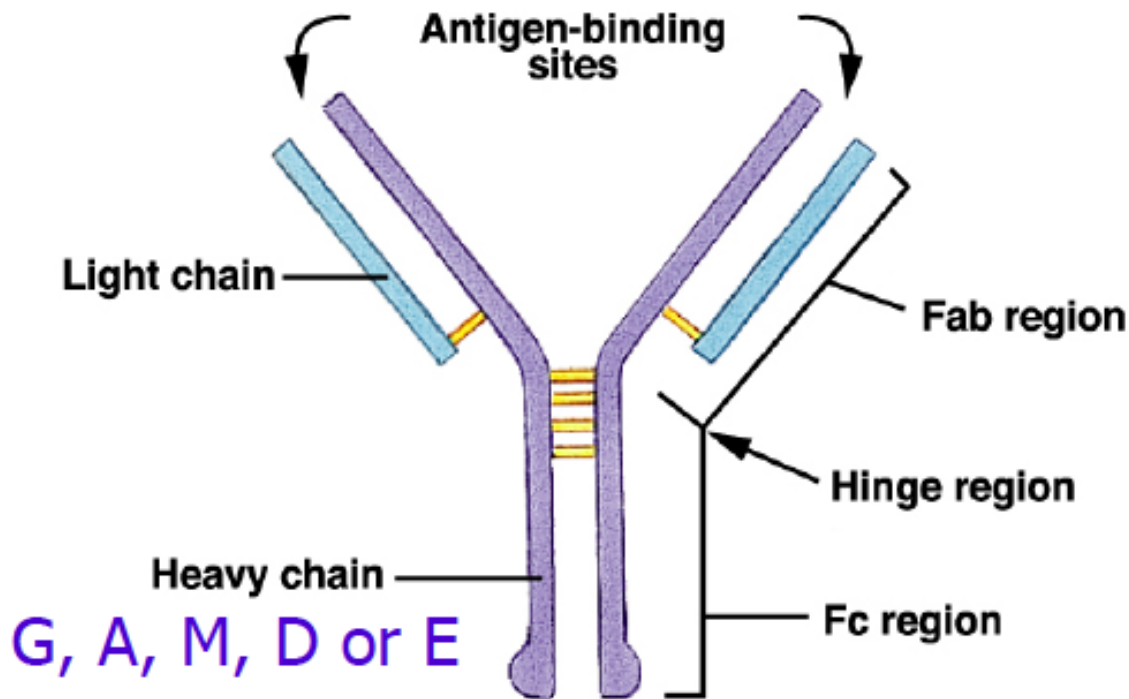
- 60 year old male
- Presented to ER with 1 month history of back pain and intermittent constipation
- Labs on admission to ER:
 - WBC 5.4 Plt 245 Hemoglobin 120 MCV 99.5
 - Creat 99 Ca²⁺ 3.45
- What to order?

Case

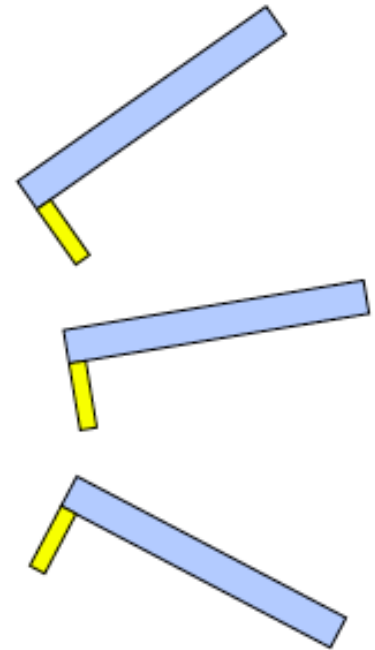
- **SPEP** – IgG kappa 81g/L monoclonal protein
- **UPEP** – monoclonal light chains present, type: kappa
- **SFLC**: Kappa light chain 186 mg/L; Lambda light chain 0.98 mg/L; K/L ratio 189
- Skeletal survey – multiple lytic lesions
- B2 microglobulin – 5
- Bone marrow – 30% plasma cells
- ISS-2 multiple myeloma

Definition of Monoclonal Protein

- Monoclonal immunoglobulin secreted by an abnormally expanded clone of plasma cells in an amount that can be detected by immunofixation of serum and/or urine/other fluids
- Also known as: M-protein, paraprotein, M-spike, M-component, M-band



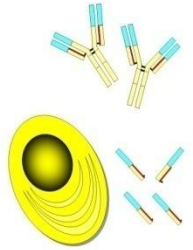
Intact immunoglobulin



Free light chains (FLC)

κ (kappa) or λ (lambda)

Types of Myeloma

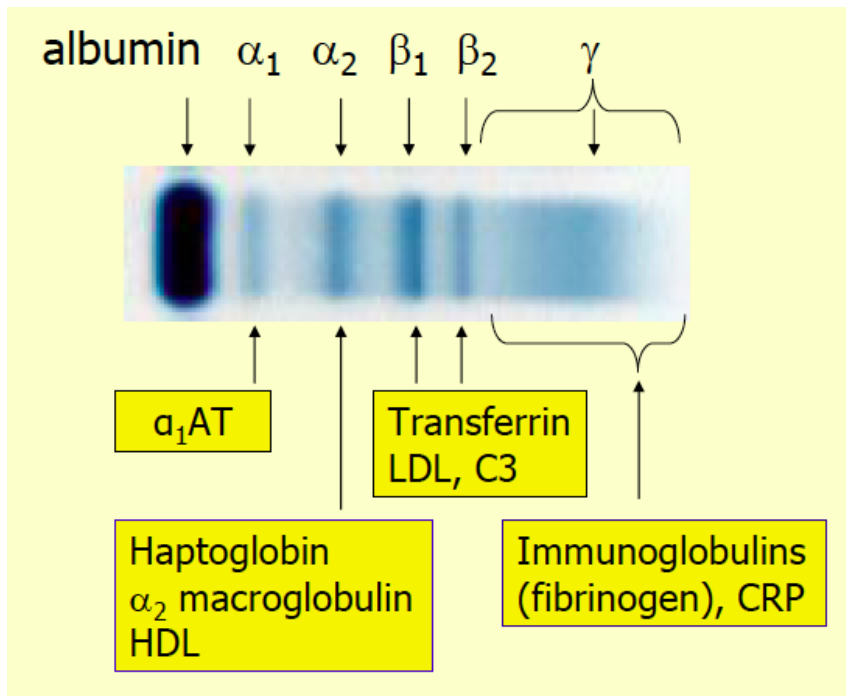


- **Intact immunoglobulin myeloma (~80%)**
 - Production of intact immunoglobulins (M-protein)
 - Commonly called myeloma
- **Light chain myeloma (~15-20%)**
 - Production of only light chains
 - Sometimes called light chain disease
- **Nonsecretory myeloma (~3%)**
 - M-protein is not present on SPEP, IFE, UPEP, uIFE, or SFLCR

When to order an SPEP?

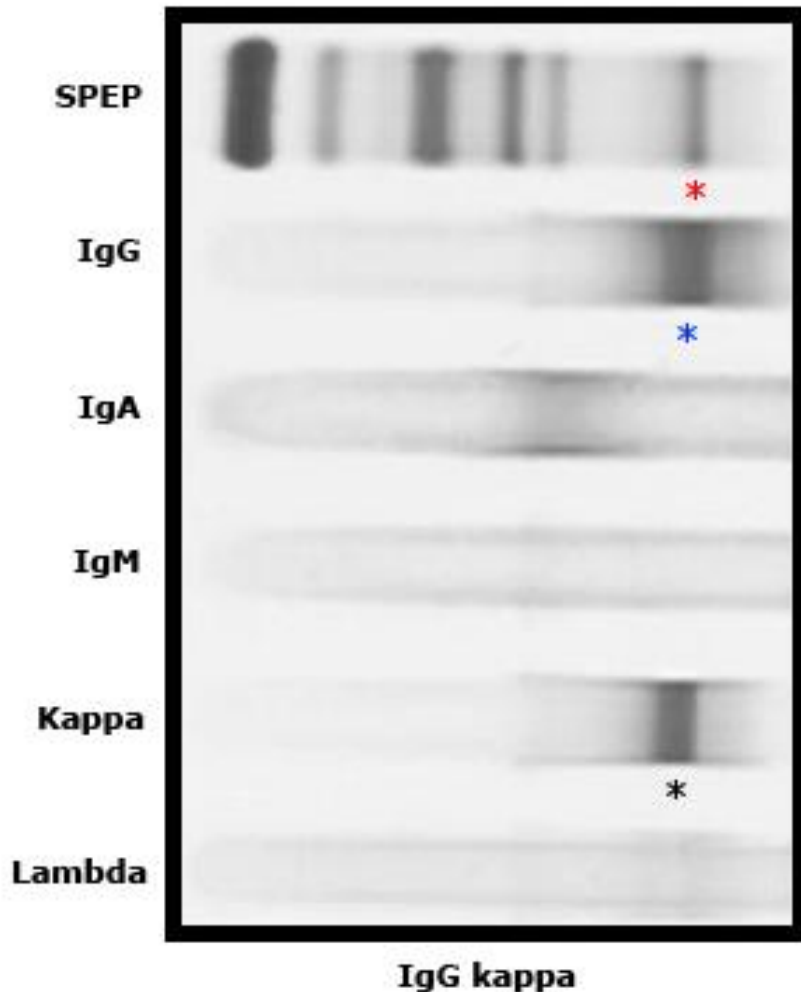
- 1. To diagnose myeloma**
2. For prognosis in MGUS and Smoldering Multiple Myeloma
- 3. To monitor**
 - Response assessment in “on treatment” patients
 - Progression and Relapse

Serum Protein Electrophoresis (SPEP)



- Serum protein migrate into bands based on their size and charge
- Limitations:
 - Not sensitive when M-protein is small
 - Cannot classify type of M-protein

Serum immunofixation



- Used to determine clonality
 - Monoclonal versus polyclonal
- Not able to quantitate the concentration of the M band
- Must be done in conjunction with the SPEP
 - Does not give the concentration of the M-protein

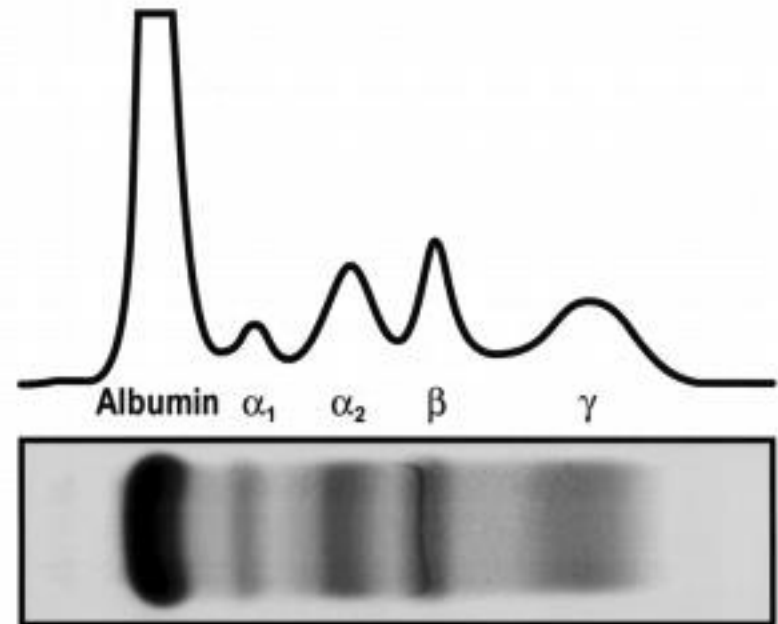
SPEP – interpretation

- Normal
 - No M protein present

RESULTS

SERUM MONOCLONAL PROTEIN INVESTIGATION

Serum Total Protein	61
Serum Albumin	34
No M protein present.	

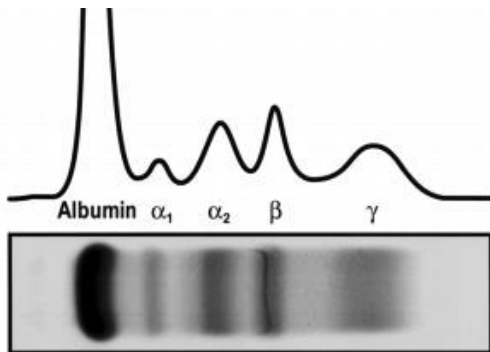


SPEP – interpretation

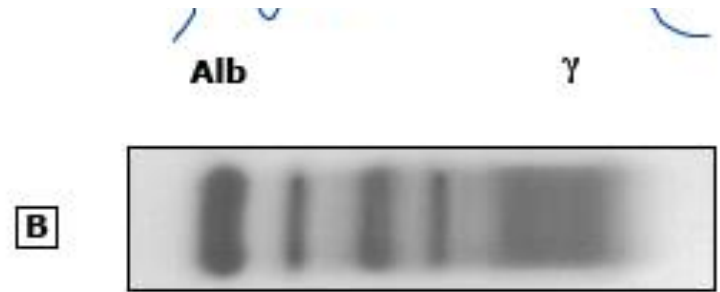
- Polyclonal gammopathy



	Flags	Results	Reference Range	Units	#
Total Protein (serum)	N	73	60 - 80	g/L	#
Protein Electroph-Serum					
Alb SerPI Elph-mCnc	N	42.8	38 - 54	g/L	
A1 Globulin SerPI Elph-mCnc	N	1.3	1 - 3	g/L	
A2 Globulin SerPI Elph-mCnc	N	6.7	5 - 9	g/L	
B-Globulin SerPI Elph-mCnc	N	8.9	6 - 11	g/L	
G-Globulin SerPI Elph-mCnc	A	13.3	5 - 12	g/L	
093-5 GDML		Polyclonal gammopathy.		g/L	
Protein Electroph-Urine		No light chains noted		g/L	



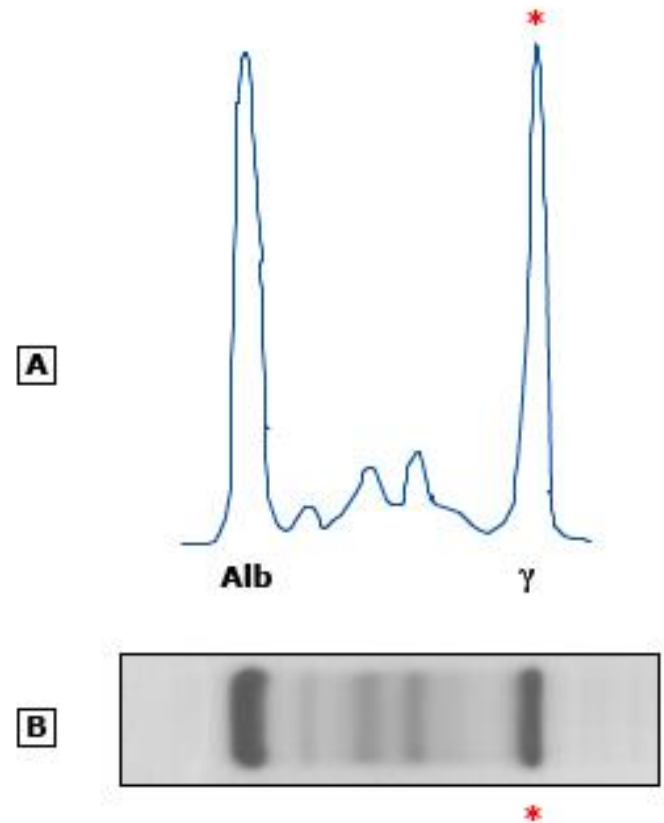
Normal



Polyclonal pattern

SPEP - Interpretation

- Monoclonal gammopathy



SPEP - Interpretation

RESULTS

REF

SERUM MONOCLONAL PROTEIN INVESTIGATION

Serum Total Protein	78
Serum Albumin	37
IgG	16.40*
IgA	0.36*
IgM	0.22*

Monoclonal Immunoglobulin PRESENT
 Class/type: Previous IgG / Kappa

Monoclonal Ig concentration: 14

NOTE: IgG, IgA and IgM results include normal and concentration when present.

Serum Electrophoresis

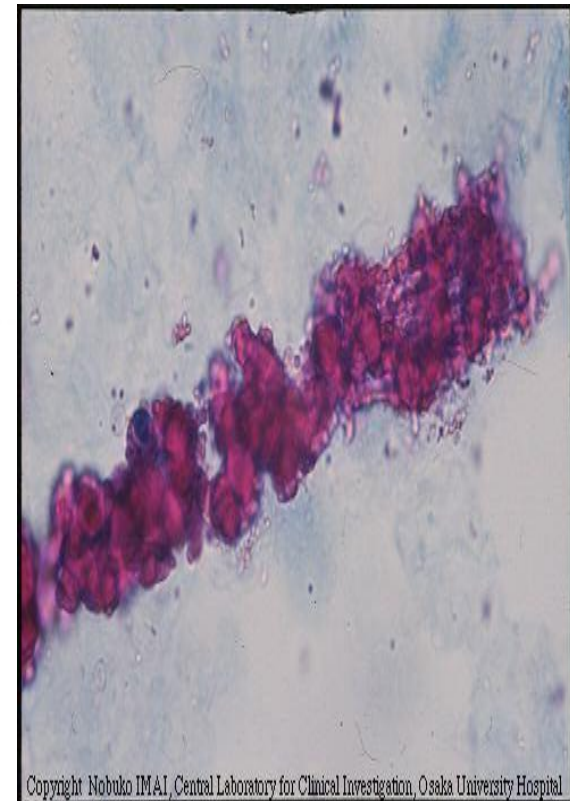
IGG		13.20	6.9 - 16.2	g/L
IGA	H	4.60	0.7 - 3.8	g/L
IGM		1.12	0.6 - 2.6	g/L
MONOCLONAL IMMUNOGLOBIN		present		

Beyond the SPEP

- If only SPEP is done – about 15% of myeloma /other disorders **WILL BE MISSED** because SPEP will be negative
- What can be done about this?
 - Urine Protein Electrophoresis (**UPEP**)
 - Serum free light chain ratio (**SFLCR**)

Urine Protein Electrophoresis (UPEP)

- 24 hour urine collection required
- **When to order?**
 - At diagnosis of myeloma
 - To monitor when urinary monoclonal protein present??
- **What is the alternative?**
 - Testing the serum for free light chains



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Serum free light chain ratio (SFLCR)

- **When to order?**
- **Diagnosis and monitoring**
 - Non-secretory, oligosecretory, light chain myeloma, and amyloidosis

- **Prediction of risk of progression for MGUS, smoldering myeloma, and plasmacytoma**

- **More sensitive than SPEP for monitoring for residual disease (required for stringent CR)**

RESULTS	REFERENCE	UNIT
FREE LIGHT CHAIN QUANTITATION		
Kappa Free Light Chain >4950.00*	3.3-19.4	mg/L
Lambda Free Light Chain 15.70	5.7-26.3	mg/L
Free Light Chain Ratio >315.29*	0.26-1.65	Ratio
This result should not be used in isolation for diagnosis or patient management, but rather interpreted in the context of clinical, morphologic and other laboratory findings. Please contact the laboratory with any unexpected or unexplainable results.		
Linearity limitations may affect accuracy at this detection level.		
KAPPA FREE LIGHT CHAIN [ABNORMAL] Low: 3.3 High: 19.4		53.22
LAMBDA FREE LIGHT CHAIN [ABNORMAL] Low: 5.7 High: 26.3		33.81
FREE LIGHT CHAIN RATIO [NORMAL] Low: 0.26 High: 1.65		1.57

SFLC vs UPEP

- FLC more sensitive than UPEP
- More prognostic information available from SFLC
 - Predicts MRD negativity
 - Persistent abnormal SFLC had poorer progression free survival and overall survival
- In patients with measurable disease on SFLC, we are using this to monitor over UPEP

Blood 2016 :blood-2016-07-726778; doi:10.1182/blood-2016-07-726778

DSM requisition

HISTORY AND CLINICAL IMPRESSION REQUIRED:	SPECIMEN ID #
FLOW CYTOMETRY	
<i>REASON FOR TESTING MUST BE PROVIDED ABOVE (EXCEPTION PB48)</i>	
<input type="checkbox"/> CD4/CD8 subsets (EDTA)..... PB48 <input type="checkbox"/> Enumeration Panel (T, B & NK cells) (EDTA)..... PBEN <input type="checkbox"/> Paroxysmal Nocturnal Hemoglobinuria (EDTA)..... PNH <input type="checkbox"/> Oxidative Burst (HSC only) (EDTA)*..... OBRT <input type="checkbox"/> Hereditary Spherocytosis (EDTA)..... HSFC	<input type="checkbox"/> Immunophenotyping Peripheral Blood (EDTA) PBFC <input type="checkbox"/> Immunophenotyping Bone Marrow (Heparin)..... BMFC <input type="checkbox"/> Immunophenotyping Lymph Node LNFC <input type="checkbox"/> Immunophenotyping Fluid FLFC <input type="checkbox"/> Immunophenotyping Fine Needle Aspirate FNFC <input type="checkbox"/> Immunophenotyping Tissue TSFC
*PRIOR ARRANGEMENT WITH LABORATORY REQUIRED	
ST. BONIFACE HOSPITAL TESTS	HEALTH SCIENCES CENTRE TESTS
Systemic Autoimmune Disease <input type="checkbox"/> ANA SCREEN ANA <input type="checkbox"/> dsDNA DNA <input type="checkbox"/> ENA (includes the following group of 6 antigens) <input type="checkbox"/> SSA (Ro) SSA <input type="checkbox"/> SSB (La) SSB <input type="checkbox"/> JO-1 JO1 <input type="checkbox"/> Scl-70 SCL <input type="checkbox"/> Sm SM <input type="checkbox"/> Sm/RNP RNP <input type="checkbox"/> Centromere B CENB <input type="checkbox"/> Hep2 HEP2	Protein Quantitation (Serum) <input type="checkbox"/> IgG IGG <input type="checkbox"/> IgA IGA <input type="checkbox"/> IgM IGM <input type="checkbox"/> IgG Subclasses IGG5 <input type="checkbox"/> Complement C3 C3 <input type="checkbox"/> Complement C4 C4 <input type="checkbox"/> Rheumatoid Factor (RF) RF <input type="checkbox"/> Free Light Chain Ratio FLCH <input type="checkbox"/> CT Esterase Inhibitor CEI
Rheumatoid Arthritis <input type="checkbox"/> Cyclic Citrullinated Peptide CCP	
Celiac Disease <input type="checkbox"/> CELIAC Panel (includes Tissue Transglutaminase IgA & IgG and Endomysial IgA as required) GLUG <input type="checkbox"/> ONLY Tissue Transglutaminase IgG TTG	Monoclonal Gammopathy Investigation (includes M peak and immunoglobulin levels when applicable) <input type="checkbox"/> SERUM PE <input type="checkbox"/> Initial <input type="checkbox"/> Follow-up <input type="checkbox"/> URINE PEU <input type="checkbox"/> Initial <input type="checkbox"/> Follow-up
Inflammatory Bowel Disease <input type="checkbox"/> Saccharomyces Cerevisiae (IgG & IgA) ASCA <input type="checkbox"/> IFA Neutrophil Cytoplasmic Ab (does not include MPO and PR3) IFNC	



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Patient Information		Ordering Physician (stamp if available)		
Last Name: As per MHSC Card		Please include Physicians Surname, First Initial & Address		
First Name: As per MHSC Card				
PHIN:	MHSC:	Physicians After-Hours Contact # for Critical Results:		
DOB: YYYY MM DD	Gender:			Phone #:
Address:				Chart #:
Payment Agency Responsibility: The Minister requires that one of the following boxes be marked by the requisitioning physician at the time the tests are ordered:		CC: Physician Name: Address: Phone #: () Fax #: ()		
<input type="checkbox"/> MB <input type="checkbox"/> WCB <input type="checkbox"/> Other (specify):		<input type="checkbox"/> Cash <input type="checkbox"/> Cheque Receipt #:		

Manitoba Health requires that a medical practitioner who requisitions tests on this form shall specify individual tests and shall not requisition tests in non-specific blocks such as "C.B.C.", "Liver Profile", or "Thyroid Profile". A laboratory shall not perform tests that are requisitioned in non-specific blocks.

HEMATOLOGY	MICROBIOLOGY
<input type="checkbox"/> Hemoglobin <input type="checkbox"/> Hematocrit <input type="checkbox"/> RBC <input type="checkbox"/> Indices <input type="checkbox"/> Platelet <input type="checkbox"/> WBC <input type="checkbox"/> WBC Differential <input type="checkbox"/> Reticulocytes <input type="checkbox"/> ESR	Please indicate source where applicable: <input type="checkbox"/> Throat C&S <input type="checkbox"/> Urine C&S <input type="checkbox"/> Ear C&S <input type="checkbox"/> L or <input type="checkbox"/> R <input type="checkbox"/> Eye C&S <input type="checkbox"/> L or <input type="checkbox"/> R <input type="checkbox"/> Other C&S, Source: <input type="checkbox"/> Synovial Fluid, Source: <input type="checkbox"/> MRSA Culture, Source: <input type="checkbox"/> VRE Culture, Source:
<input type="checkbox"/> INR/Prothrombin Time <input type="checkbox"/> Ferritin <input type="checkbox"/> Folate <input type="checkbox"/> Iron <input type="checkbox"/> Iron TIBC <input type="checkbox"/> Vitamin B12 <input type="checkbox"/> Malaria	GENITAL SAMPLES: <input type="checkbox"/> Chlamydia, Source: <input type="checkbox"/> Cervix for GC <input type="checkbox"/> GC Other than Cervix, Source: <input type="checkbox"/> Vagina (Trichomonas, Yeast) <input type="checkbox"/> Gram Stain/Vaginal BV <input type="checkbox"/> Cervix Culture <input type="checkbox"/> Urethral Culture <input type="checkbox"/> Vaginal C&S <input type="checkbox"/> Vag/Anorectal for GBS
CHEMISTRY	STOOL/URINES
<input type="checkbox"/> Sodium <input type="checkbox"/> Potassium <input type="checkbox"/> Chloride <input type="checkbox"/> CO2 <input type="checkbox"/> BUN/Urea <input type="checkbox"/> Creatinine <input type="checkbox"/> Fasting Glucose <input type="checkbox"/> HbA1C <input type="checkbox"/> Random Glucose <input type="checkbox"/> Glucose 2-Hr PC <input type="checkbox"/> GTT (non-pregnancy)	<input type="checkbox"/> Stool for Occult Blood <input type="checkbox"/> Urinalysis Complete <input type="checkbox"/> Urinalysis Stick ONLY <input type="checkbox"/> Urine Albumin/Creatinine Ratio <input type="checkbox"/> Urine Microalbumin <input type="checkbox"/> 24-Hr Ur Creatinine <input type="checkbox"/> 24-Hr Ur Creatinine Clearance* <input type="checkbox"/> 24-Hr Ur Protein <input type="checkbox"/> 24-Hr Ur Other (Specify) Total Volume: *Height: *Weight:
<input type="checkbox"/> Alk. Phosphatase <input type="checkbox"/> ALT <input type="checkbox"/> AST <input type="checkbox"/> Amylase <input type="checkbox"/> Bilirubin Total <input type="checkbox"/> Calcium <input type="checkbox"/> CK <input type="checkbox"/> GGT <input type="checkbox"/> LDH <input type="checkbox"/> Lipase <input type="checkbox"/> Magnesium <input type="checkbox"/> Phosphate <input type="checkbox"/> Uric Acid <input type="checkbox"/> Total Protein <input type="checkbox"/> Albumin <input type="checkbox"/> Globulin	SYNOVIAL FLUID
LIPIDS <input type="checkbox"/> Fasting <input type="checkbox"/> Random <input type="checkbox"/> Cholesterol <input type="checkbox"/> Triglycerides <input type="checkbox"/> HDL Cholesterol <input type="checkbox"/> LDL Cholesterol <input type="checkbox"/> Cholesterol/HDL Ratio <input type="checkbox"/> CEA <input type="checkbox"/> PSA Total	<input type="checkbox"/> Cell Count Source: <input type="checkbox"/> Crystals
<input type="checkbox"/> Protein Electrophoresis - serum <input type="checkbox"/> Protein Electrophoresis - urine	SEMEN ANALYSIS

Case

- Started on induction chemotherapy with CyBorD x 4 cycles. Plan for autologous stem cell transplant
- Monthly zoledronic acid
- What to order prior to each cycle of CyBorD?

- **Day 1 - CBC and retic, full biochemistry, SPEP, FLC**
- **Day 15 – CBC and retic (only required for cycle 1,2)**

Case

- After 4 cycles of CyBorD
 - M-protein undetectable, FLC normal
 - Proceeds to autologous SCT, started on lenalidomide maintenance post-transplant
- Monitoring monthly with CBC, biochemistry, SPEP, FLC
- TSH, urine Alb:Creat ratio required every 3 months
- **Why order the FLC??**

Standard IMWG Response criteria

Stringent Complete Response (sCR)

Meets criteria for CR
AND

Normal FLCR
AND

No BM clonal plasma cells

Complete Response (CR)

No M protein in serum or urine by IFE **AND**

No evidence of plasmacytoma **AND**

PC <5%

Normalization of FLCR (if light chain only)

Very Good Partial Response (VGPR)

M protein detectable on IFE but not on SPEP **OR**

90% reduction in serum M protein **AND**

Urine M protein <100mg/24hrs

90% reduction in FLC

Lancet Oncol 2016; 17: e328–46

Standard IMWG Response criteria

Partial Response (PR)

50% reduction in serum M protein **AND**

90% reduction in urine M protein (or <200mg/24hr)
AND

50% reduction in size of plasmacytoma (if present)

50% reduction in FLC

Minimal Response

>25 but <49% reduction in M protein **AND**

50-89% reduction in urine M protein **AND**

50% reduction in size of plasmacytoma (if present)

Stable Disease

Not meeting criteria for response or progressive disease

Lancet Oncol 2016; 17: e328–46

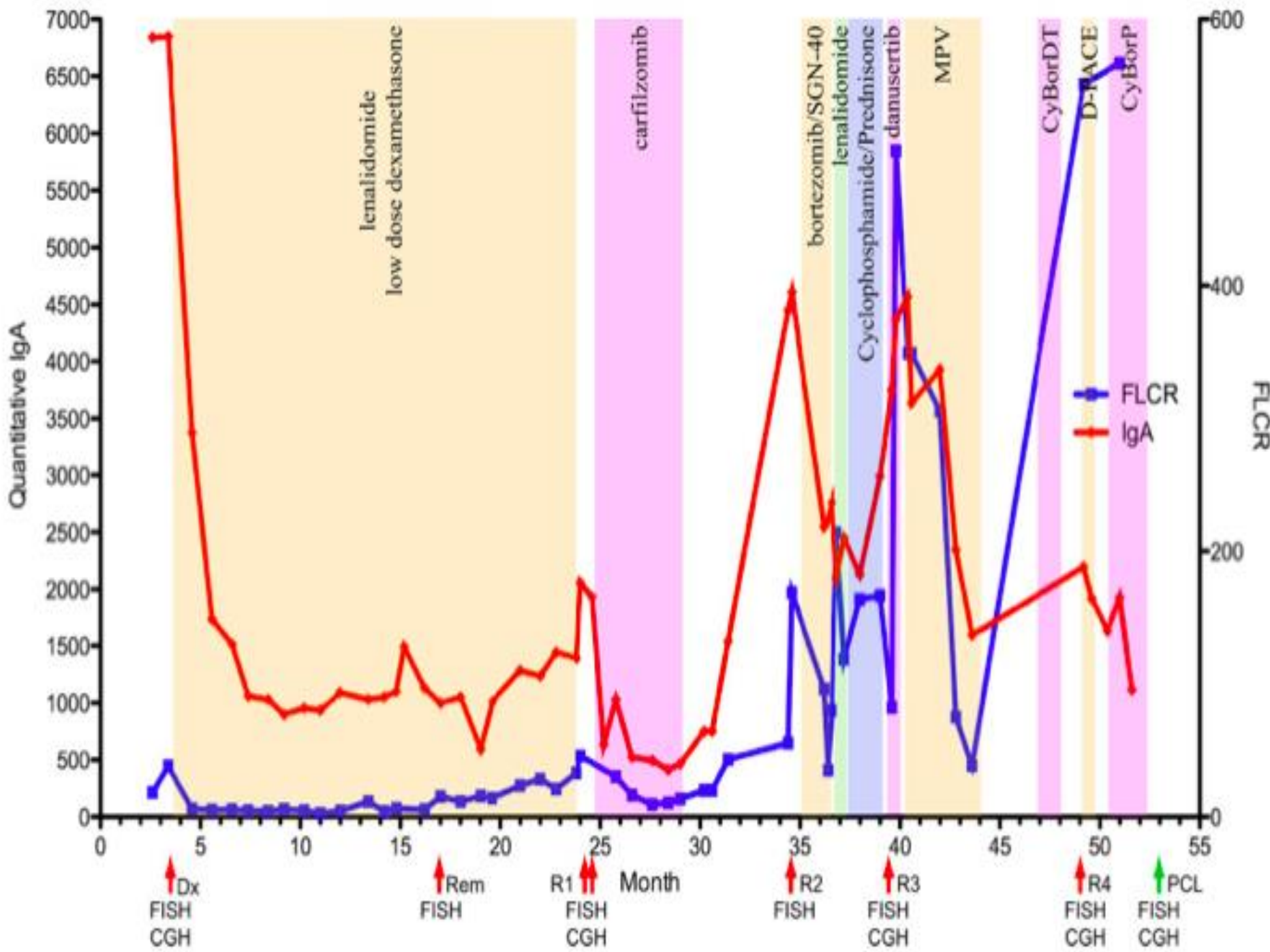
Case

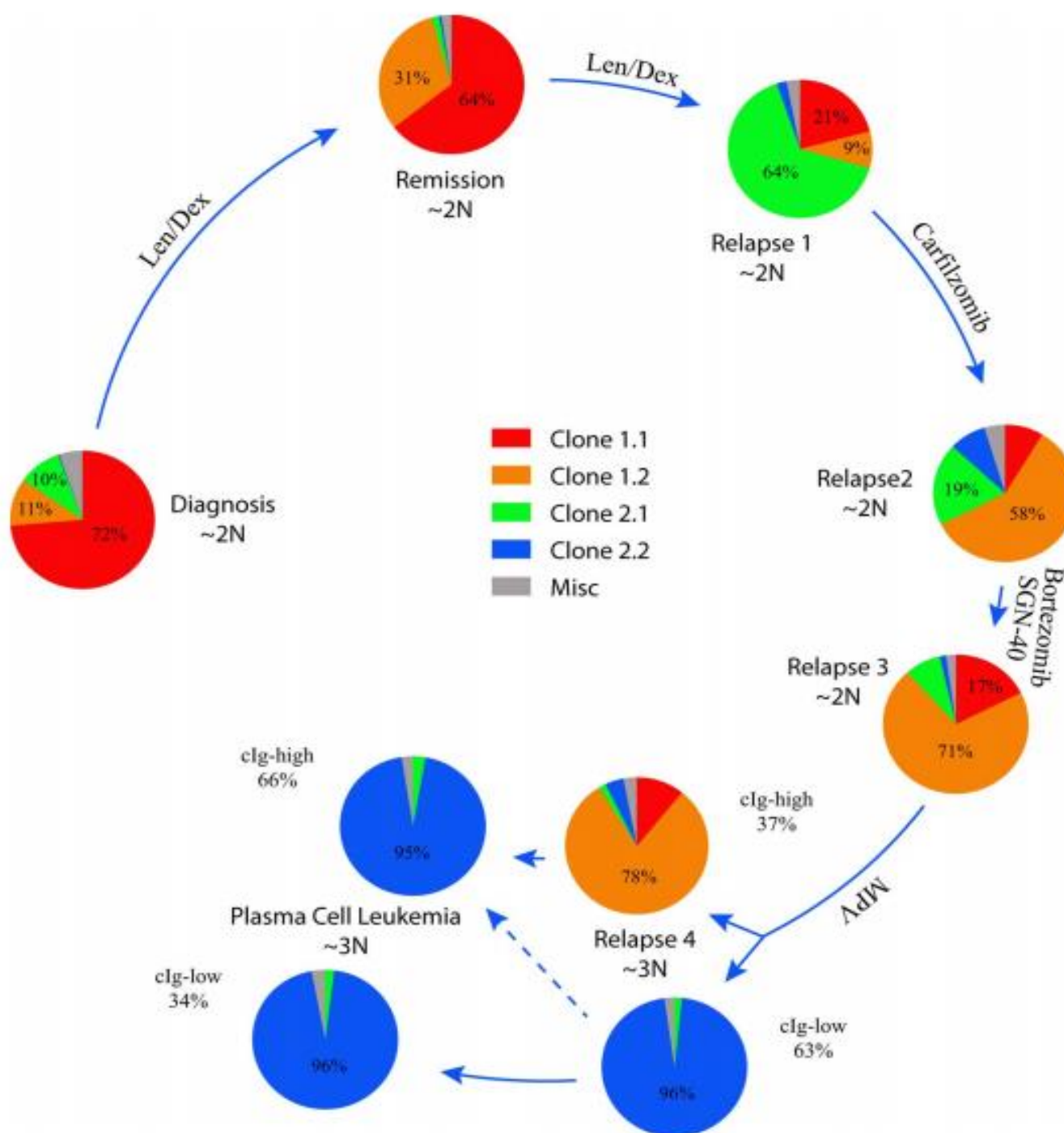
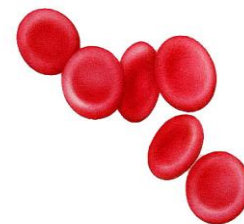
- 2 years later....
- Presents with severe back pain and calcium of 3.30
- CT lumbar spine shows soft tissue mass at L2-L3, no spinal cord compression
- SPEP – remains negative

- What next?

Case

- SFLC
 - kappa light chain 45,000
 - lambda light chain 7.11
 - ratio 6329
- UPEP
 - Monoclonal free light chains present, type: previous kappa
- What's going on?!?





Keats et al. Blood 2012; 120: 1067-76

IMWG Progressive Disease

- Increase by 25% from lowest confirmed response in any of the following:
 - Serum M-protein (absolute increase ≥ 5 g/L)
 - Urine M-protein (absolute increase of ≥ 200 mg/24 hours)
 - Bone marrow plasma cell percentage
 - >10 percent increase
 - Difference in the kappa and lambda FLC levels
 - FLC ratio must be abnormal **and**
 - absolute change must be >100 mg/L)

Lancet Oncol 2016; 17: e328–46

IMWG Clinical Relapse

- New soft tissue plasmacytoma or definite increase in size of existing plasmacytoma
- New bone lesions
- Hypercalcemia (Calcium > 2.8mmol/L)
- Decrease in hemoglobin by 20g/L (not related to therapy or other causes)
- Rise in serum creatinine above 177 umol/L or eGFR <40
- Hyperviscosity related to the paraprotein

Lancet Oncol 2016; 17: e328–46

Case

- Clinical relapse confirmed
 - Light chain escape
- Treated with lenalidomide/dexamethasone
 - Option of adding carfilzomib, ixazomib

Take Home Messages

1. Obtain monthly SPEP, SFLC for patients who are on treatment
2. UPEP at baseline
3. Biochemical progression/relapse should be addressed by hematologist within next 2-4 weeks
4. Clinical relapse requires CRAB features and needs be addressed ASAP – please contact us directly via paging
5. Please inform hematologist if less than PR is seen in on treatment patients

