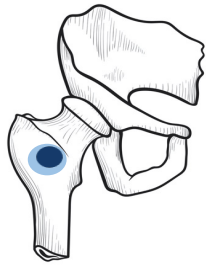
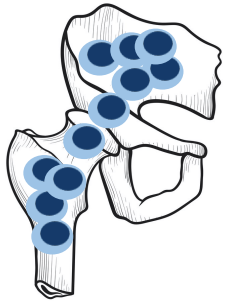
MULTIPLE MYELOMA Introductory Lecture

Plasma Cells and Antibodies

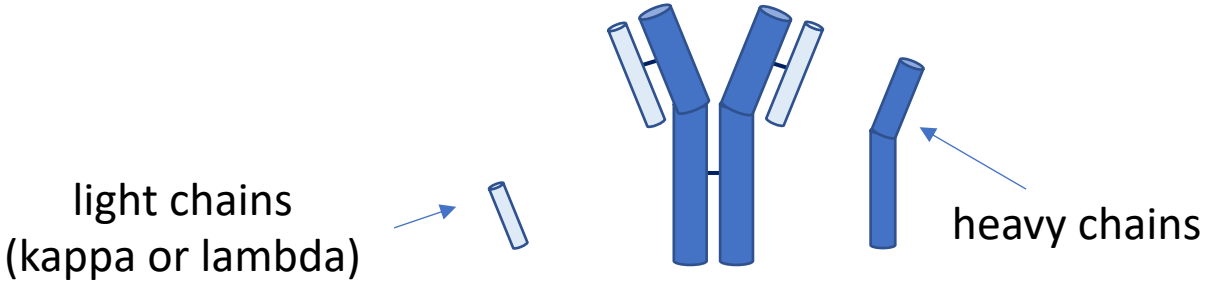
plasma cell neoplasm



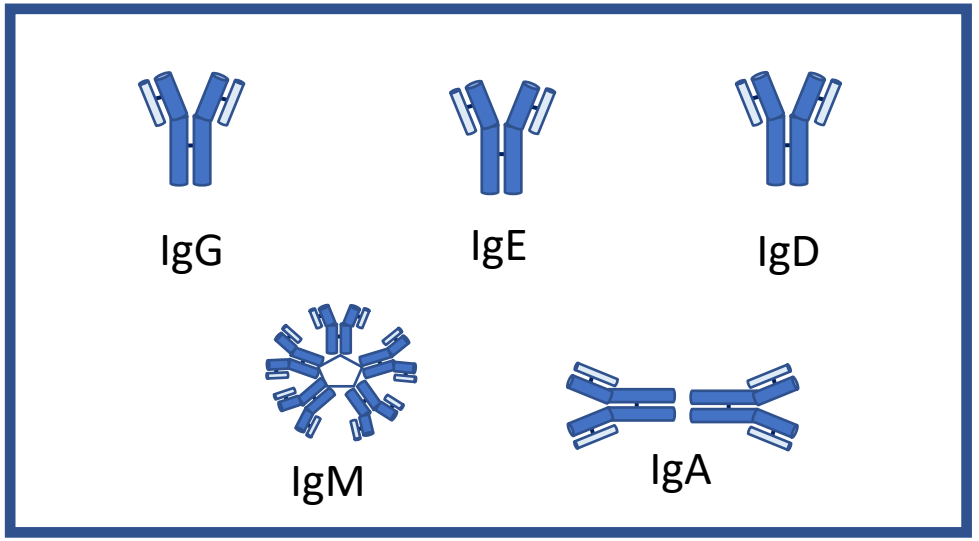
normal bone marrow



myeloma bone marrow

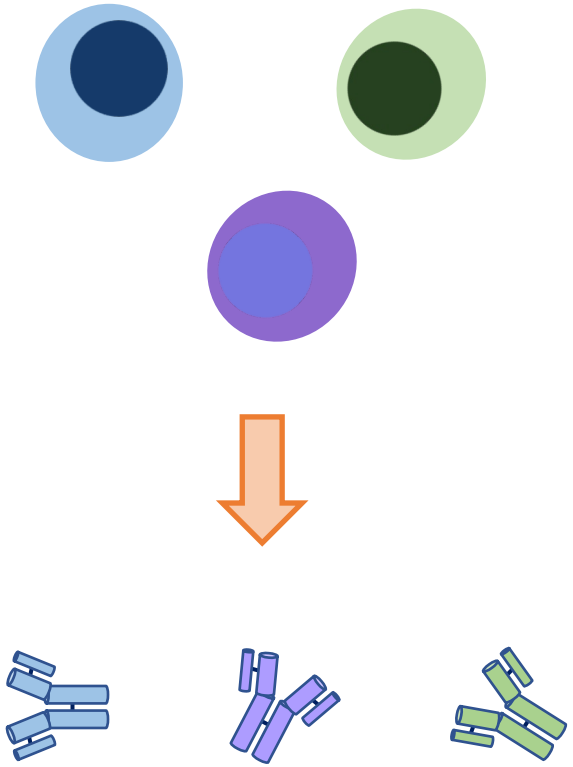


plasma cells produce antibodies



they can produce any type of antibody or just light chains

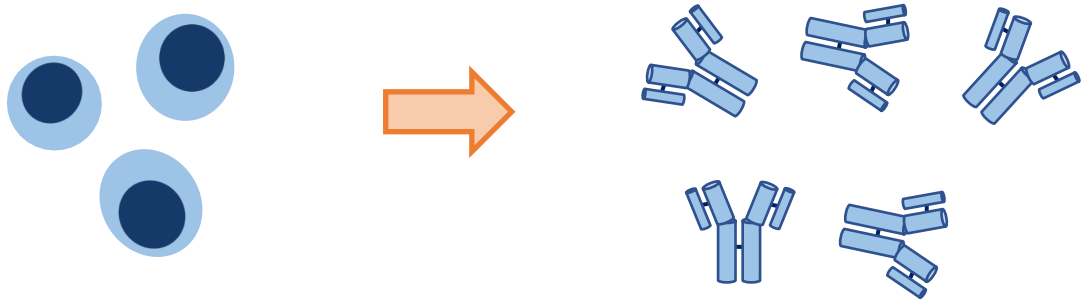
POLYCLONAL



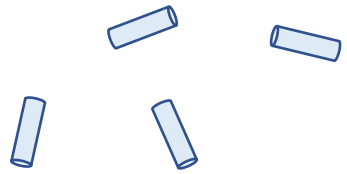
normally **polyclonal plasma cells** produce **polyclonal antibodies**

MONOCLONAL

multiple myeloma = **monoclonal population of plasma cells** → over-production of one type of **monoclonal antibody or light chain**



These monoclonal antibodies will have **EITHER kappa OR lambda** light chains



kappa

lambda

MULTIPLE MYELOMA Clinical Presentation

CRAB

CRAB SYMPTOMS	MECHANISM
Hypercalcemia	Bone destruction Impaired renal clearance PTHrP
Renal Dysfunction	Light chain cast nephropathy Tubular toxicity Hypercalcemia/Hyperuricemia AL Amyloid
Anemia	Bone marrow replacement Low EPO (renal dysfunction)
Bone Lesions	Bone replacement/destruction

* CRAB symptoms need to be attributable to MM

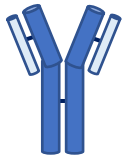
Other Symptoms

OTHER SYMPTOMS	MECHANISM
Frequent Infections	Hypogammaglobulinemia
Hyperviscosity	High concentration antibodies IgM > 3K, IgA > 5K, IgG > 7K
Neuropathy	Paraprotein nerve injury Drug effect
Coagulopathy	Inflammation Activation of pro-coagulant factors

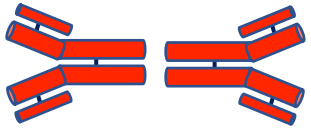
MULTIPLE MYELOMA Lab Tests

Quantitative Immunoglobulins

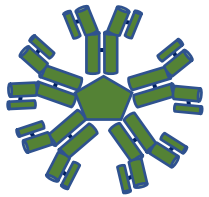
normally **polyclonal plasma cells** produce **polyclonal antibodies** that are present at normal ranges



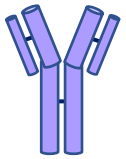
IgG = 80%



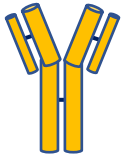
IgA = 15%



IgM = 5%

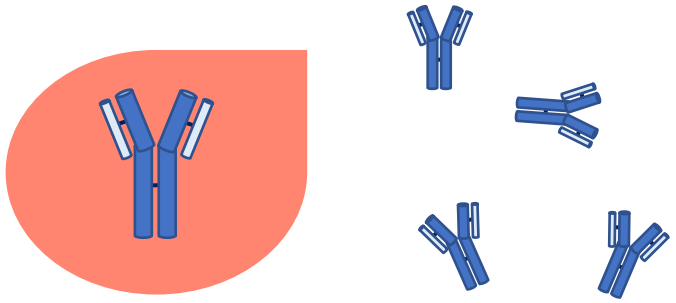


IgD = < 1%



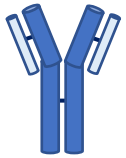
IgE = < 1%

In MM: a single monoclonal antibody population is over-produced, labs can show **high levels of a single antibody** and **low levels of uninvolved antibodies**

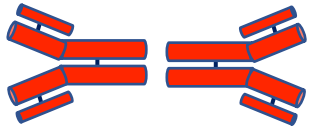


ex: serum IgG > 3,000 mg/dL (normal 700-1600 mg/dL)

subtype distribution



50% IgG



20% IgA

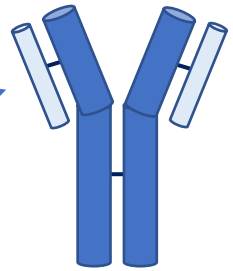
15% light chain

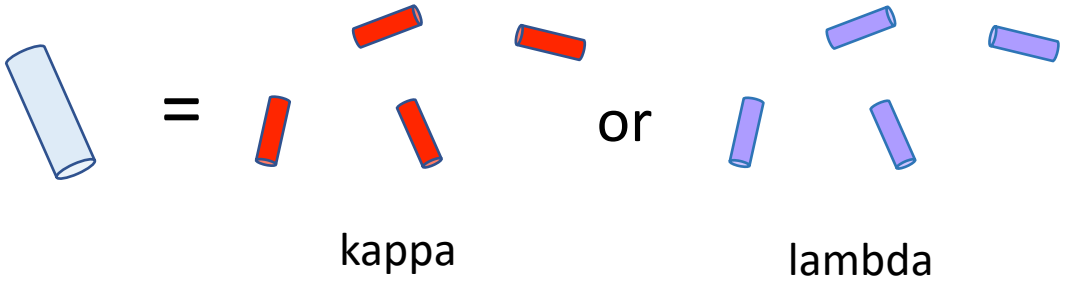
* Can be oligo or non-secretory

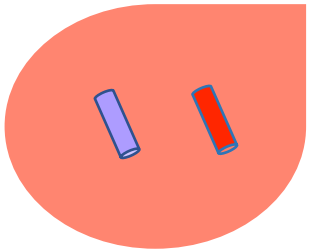
Free kappa/lambda Light Chain Ratio

In MM: monoclonal antibodies will have **EITHER kappa OR lambda** light chains

light chains
(kappa or lambda)

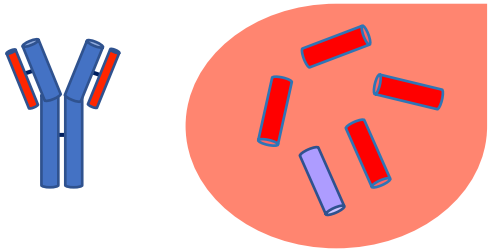






normal serum free K/L is around 1 (0.5-1.5)
(equal # of kappa and lambda)

* ratio can be slightly abnormal in CKD/AKI

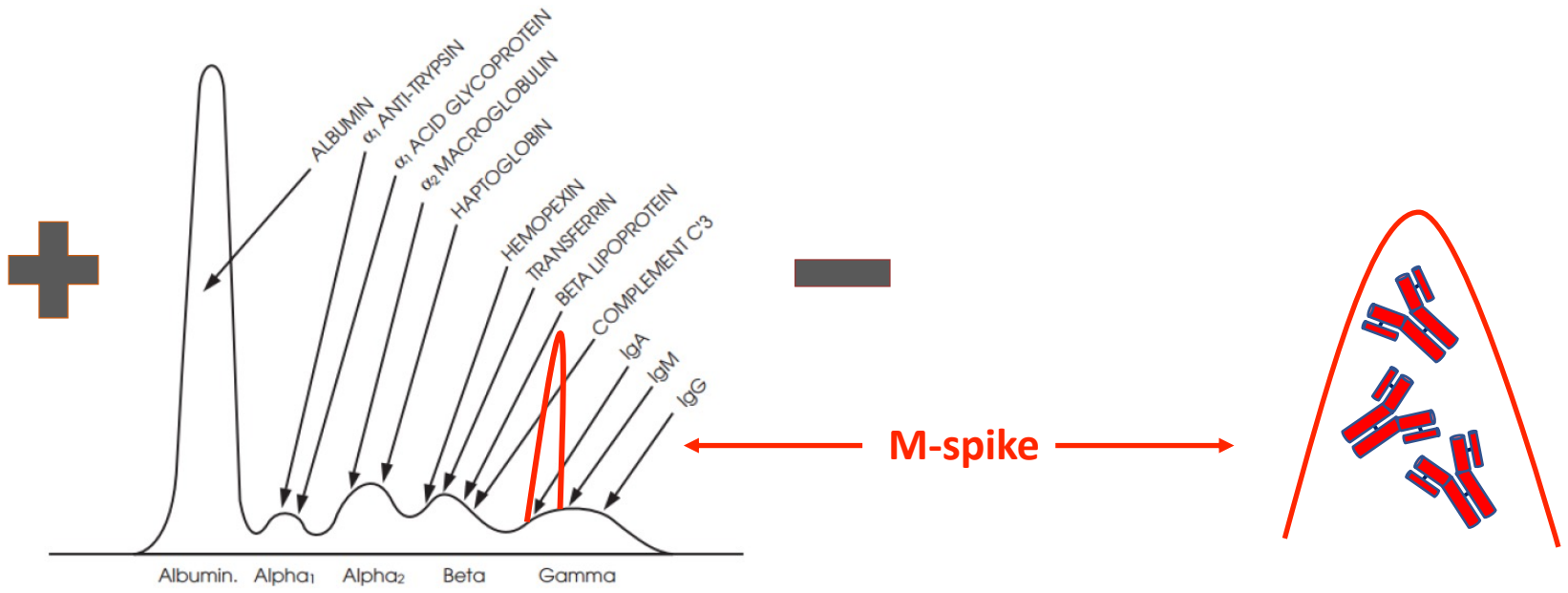


In MM: monoclonal population with either lambda or kappa free light chains → serum free K/L ratio > 3

* K/L >100 = now diagnostic of MM

Serum Electrophoresis

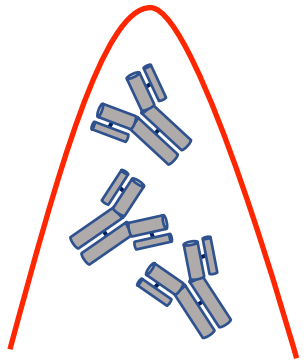
Innate charges on serum proteins cause them to migrate at different speeds through a charged electrophoresis gel



If there is a monoclonal antibody being produced there will be a big **monoclonal spike = "m-spike"** in the gamma band of the gel because there is a lot of Ig X with charge X migrating at the same speed through the gel and accumulating in one area of the gel

*can have spikes in other bands of the gel due to increased production of acute phase reactants… this is not diagnostic of MM

Serum Immunofixation



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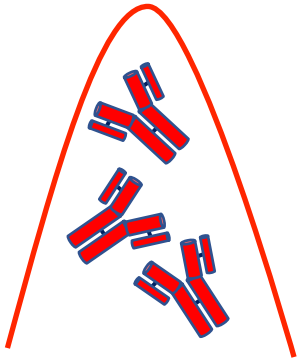

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Serum electrophoresis = IF monoclonal protein

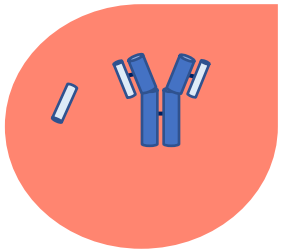
tells you ***if*** there is a monoclonal protein present = **"m-spike"**

Serum immunofixation = WHAT monoclonal protein

uses antibodies to characterize ***what*** the monoclonal protein is (is it IgG kappa or IgA lambda, etc)

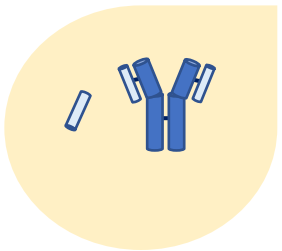
Electrophoresis + Immunofixation

electrophoresis + **immunofixation** can be obtained from serum or urine



blood

SPEP/SIFE



urine

UPEP/UIFE

* 24H urine collection preferred

MULTIPLE MYELOMA Diagnosis

Spectrum of Disease

	MGUS Monoclonal Gammopathy of Unknown Significance	Smoldering Myeloma	Multiple Myeloma
M-spike	< 3 g/dL	> 3 g/dL	> 3 g/dL
% plasma cells in bone marrow	< 10%	> 10% (< 60%)	> 10%
CRAB symptoms	NO	NO	YES
SUMMARY	Low [monoclonal protein] Asymptomatic	High [monoclonal protein] Asymptomatic	High [monoclonal protein] Symptomatic

SLIM CRAB

Diagnosis = Bone marrow > 10 % or Extramedullary plasmacytoma with any SLIM-CRAB features

SLIM CRAB	
S = Sixty	**60% plasma cells in bone marrow**
Li = Light Chains	**Free kappa/lambda ratio > 100**
M = MRI lesions	**> 1 focal bone lesion on MRI at least 5 mm (different than lytic lesion)**
CRAB Symptoms	**Present**

MULTIPLE MYELOMA Staging

Revised International Staging System

International Staging System	Labs	Median Survival
I (- high risk features)	B2 MG < 3.5 mg/L Albumin > 3.5 g/dL	Not reached
II	Not I or III	83 months
III (+ high risk features)	B2 MG > 5.5 mg/L	43 months
High Risk Features	High LDH FISH: del(17p), t(4;14), t(14;16)	

MULTIPLE MYELOMA Treatment

Principles of Treatment

1. Everyone who can get an auto-SCT should
2. No standard induction therapy
3. Triplet/Quadruplet therapy > Doublet therapy

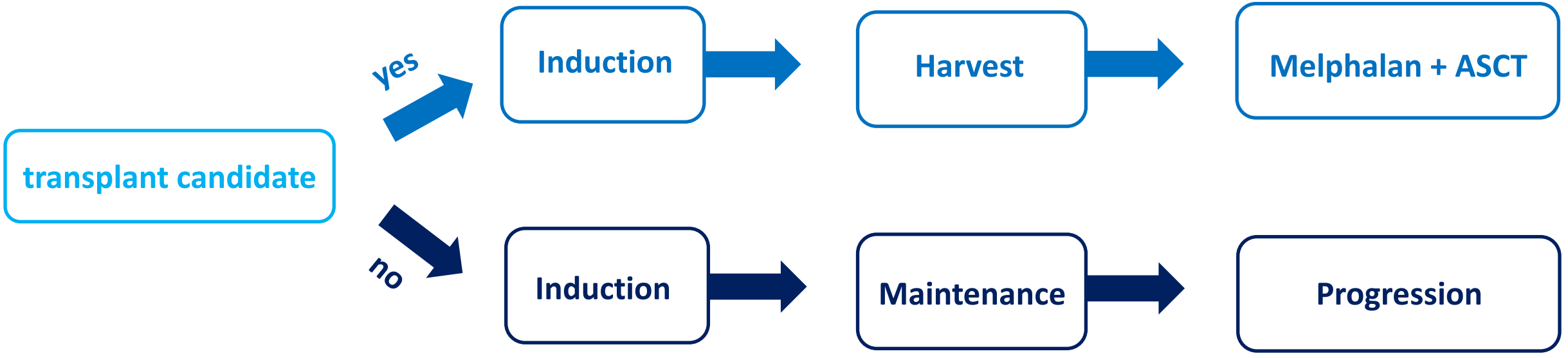
Auto-SCT

Contraindications:

- Age > 75
- ECOG >3
- Co-morbidities

Indications:

- Everyone who can get one, should
- Can get more than one
- When in remission



Non-Chemotherapy MM Agents	Drugs	Side Effects
Steroids	Prednisone Dexamethasone	
Proteasome Inhibitors **"ZOMIB"**	Bortezomib/Velcade (IV/SC) Carflizomib (IV) Ixazomib (PO)	Neuropathy HSV reactivation Thrombocytopenia N/V
Immune Modulators **"IDOMIDE"**	Thalidomide Lenalidomide/Revlimid (PO) Pomalidomide (PO)	Renal dosing VTE Myelosuppression Secondary malignancy
Monoclonal AB **"UMAB"**	Daratumumab (IV) = anti-CD38 Elotuzumab (IV) = anti-SLAMF7	
Histone Deacetylase Inhibitors **"INOSTAT"**	Panobinostat (PO) Ricolinostat (PO)	
BCL2 Inhibitor	Venetoclax = in t(11;14)	
Selective Inhibitor Nuclear Export	Selinexor	GI side effects (N/V, etc)

Common Non-chemotherapy Regimens

VRD +/- Dara

- Velcade (Bortezomib)
- Revlimid (Lenalidomide)
- Dexamethasone

CyBorD +/- Dara

- Cyclophosphamide
- Velcade (Bortezomib)
- Dexamethasone

RD +/- Dara

- Revlimid (Lenalidomide)
- Dexamethasone
- Daratumumab

* Can be followed by single/doublet agent maintenance therapy

Common Chemotherapy Regimens

(V) DPACE

- +/- Velcade
- Dexamethasone
- Cisplatin
- Adriamycin
- Cyclophosphamide
- Etoposide

(V) DCEP

- +/- Velcade
- Dexamethasone
- Cyclophosphamide
- Etoposide
- Cisplatin

* Avoids cardiotoxic adriamycin

* Chemotherapy used for rapid debulking
  Ex: severe symptoms, visceral crisis, bridge to transplant

Cellular Therapy

Cellular Therapies	Mechanism of Action
CarT	**Chimeric Antigen Receptor T Cells = engineered T cells that can recognize cancer antigens** **Notable Side effects: Cytokine Release Syndrome, Neurotoxicity** Ex: BCMA = B-cell maturation antigen in MM
Bispecific Antibodies	**Dual antibodies that can recognize a MM antigen and a T cell antigen simultaneously** Ex: Antibody to BCMA and CD3
Antibody-Drug Conjugates	**Antibody conjugated to a cytotoxic agent** Ex: anti-BCMA antibody conjugated to microtubulin poison

*** Many of these therapies are not yet FDA approved and can be administered only as part of a clinical trial**

Selecting a Regimen

VRD +/- Dara
- Velcade (Bortezomib)
- Revlimid (Lenalidomide)
- Dexamethasone

CyBorD +/- Dara
- Cyclophosphamide
- Velcade (Bortezomib)
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RD +/- Dara
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(V) DPACE
- +/- Velcade
- Dexamethasone
- Cisplatin
- Adriamycin
- Cyclophosphamide
- Etoposide

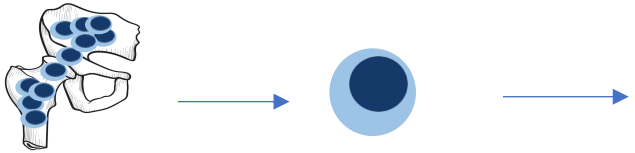
(V) DCEP
- +/- Velcade
- Dexamethasone
- Cyclophosphamide
- Etoposide
- Cisplatin

1. Tolerability	2. Side Effects	3. Onset of Action	4. Transplant Eligibility	5. Approval
Consider Age/ECOG * Doublet > triplet if older/weaker (ex: RD +/- Dara)	**Bortezomib/velcade =** * Neuropathy * HSV reactivation (viral ppx) **Lenalidomide/revlimid =** * Renally dosed * VTE (aspirin ppx)	DCEP/DPACE faster than VRD/RD	Pre-Transplant: * No melphalan (too cytotoxic)	* Certain therapies not FDA approved, or only approved after progression on other standard therapies

Complications	Supportive Care
Hypercalcemia **mild <12, moderate 12-14, severe >14 mg/dL**	Tx = IVF [200-300 cc/hr], steroids Calcitonin = short term correction: 4u/kg BID x 48H Bisphosphonates/RANKL AB = long term correction: pamidronate, zoledronic acid, denosumab
Hyperuricemia **severe >10**	PPx = allopurinol [300 mg QD, renally dose] Tx = rasburicase (only give if uric > 10, G6PD negative)
ID Prophylaxis **check HIV, Hepatitis prior to Tx**	Acyclovir if on proteasome inhibitor (bortezomib) UTD Vaccinations PCP ppx if neutropenic
Bone Lesions **lytic**	Tx = consider RT, surgery PPx = bisphosphonate (pamidronate, zoledronic), RANKL AB (denosumab)
Thrombosis **including PVT**	Low risk: No ppx Mod risk: aspirin 81 mg (receiving dex) High risk: consider LMWH (receiving dex + doxorubicin)
Hyperviscosity **viscosity > 4-6 CP**	Sx = CNS (HA, vision, dizziness, coma, CHF, etc) Rare! More common w/ larger Ig like IgM > IgA > IgG Dx = viscosity doesn't correlate with symptoms Tx = plasmapheresis (only if sx)

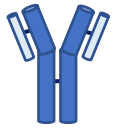
MULTIPLE MYELOMA Reference Handout

MM Pathology



monoclonal plasma cell neoplasm

→ monoclonal antibodies or light chains

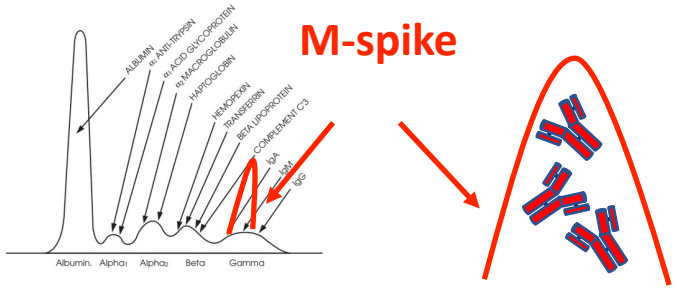


Antibody (IgG > IgA > IgM)

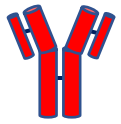
Light chain (kappa or lambda)

MM Work Up

1. **Serum/Urine Protein Electrophoresis**
   is there a monoclonal protein
   m-spike > 3 g/dl



2. **Serum/Urine Immunofixation**
   what is the monoclonal protein
   IgG > IgA > IgM = common



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3. **Free Light Chains**
   is there a monoclonal light chain
   Kappa / Lambda > 3

MM Symptoms

CRAB SYMPTOMS	MECHANISM
Hypercalcemia	Bone destruction Impaired renal clearance PTHrP
Renal Dysfunction	Light chain cast nephropathy Tubular toxicity HyperCa/Hyperuricemia AL Amyloid
Anemia	Bone replacement Low EPO
Bone Lesions	Bone destruction

OTHER SYMPTOMS	MECHANISM
Infections	Hypogammaglobulinemia
Hyperviscosity	High concentration antibodies IgM > 3K, IgA > 5K, IgG > 7K
Neuropathy	Paraprotein nerve injury Drug effect
Coagulopathy	Inflammation Activation of pro-coagulant factors

MM: Spectrum of Disease

	MGUS Monoclonal Gammopathy of Unknown Significance	Smoldering Myeloma	Multiple Myeloma
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MM Diagnosis

BMB > 10 % plasma cells or extramedullary plasmacytoma with SLIM-CRAB

SLIM CRAB	
S = Sixty	60% plasma cells in bone marrow
Li = Light Chains	Free kappa/lambda ratio > 100
M = MRI lesions	MRI lytic lesions
CRAB Symptoms	Present

MM: Work Up

1. Bone marrow biopsy
2. Skeletal survey
3. Uric acid/G6PD
   LDH
   Albumin
   B2 microglobulin

MM: Staging/Prognosis

International Staging System	Labs	Median Survival
I (- high risk features)	B2 MG < 3.5 mg/L Albumin > 3.5 g/dL	Not reached
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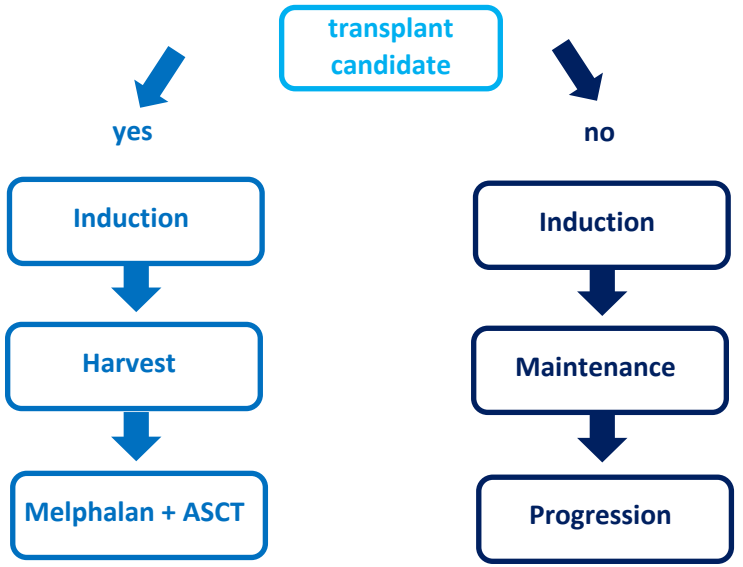
High Risk Features	High LDH FISH: del(17p), t(4;14), t(14;16)	

MM: Drug Classes

DRUG CLASS	DRUGS
Steroids	Prednisone Dexamethasone
Proteasome Inhibitors	Bortezomib/Velcade (IV/SC) Carflizomib (IV) Ixazomib (PO)
Immune Modulators	Lenalidomide/Revlimid (PO) Pomalidomide (PO)
Monoclonal AB	Daratumumab (IV) = anti-CD38 Elotuzumab (IV) = anti-SLAMF7
Histone Deacetylase Inhibitors	Panobinostat (PO) Ricolinostat (PO)
BCL2 Inhibitor	Venetoclax = in t(11;14)
Selective Inhibitor Nuclear Export	Selinexor

MM: Principles of Treatment

1. Everyone who can get an auto-SCT should
2. No standard induction therapy
3. Triplet therapy > doublet therapy



Regimen Selection

1. Tolerability (Age, ECOG)
Consider doublet > triplet if older/poor ECOG

2. Side Effects
Bortezomib (neuropathy, HSV re-activation)
Lenalidomide (renal dosing, VTE)

3. Onset of Action
CyBorD faster than VRD

4. Transplant Eligibility
No melphalan pre-transplant

4. FDA Approval

MM: Common Regimens

VRD +/- Dara
- Velcade (Bortezomib)
- Revlimid (Lenalidomide)
- Dexamethasone

CyBorD +/- Dara
- Cyclophosphamide
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(V) DPACE
- +/- Velcade
- Dexamethasone
- Cisplatin
- Adriamycin
- Cyclophosphamide
- Etoposide

(V) DCEP
- +/- Velcade
- Dexamethasone
- Cyclophosphamide
- Etoposide
- Cisplatin

MM: Management of Complications

Complications	Supportive Care
Hypercalcemia **mild <12, moderate 12-14, severe >14 mg/dL**	Tx = IVF [200-300 cc/hr], steroids Calcitonin = short term correction: 4u/kg BID x 48H Bisphosphonates/RANKL AB = long term correction: pamidronate, zoledronic acid, denosumab
Hyperuricemia **severe >10**	PPx = allopurinol [300 mg QD, renally dose] Tx = rasburicase (only give if uric > 10, G6PD negative)
ID Prophylaxis **check HIV, Hepatitis prior to Tx**	Acyclovir if on proteasome inhibitor (bortezomib) UTD Vaccinations PCP ppx if neutropenic
Bone Lesions **lytic**	Tx = consider RT, surgery PPx = bisphosphonate (pamidronate, zoledronic), RANKL AB (denosumab)
Thrombosis **including PVT**	Low risk: No ppx Mod risk: aspirin 81 mg (receiving dex) High risk: consider LMWH (receiving dex + doxorubicin)
Hyperviscosity **viscosity > 4-6 CP**	Sx = CNS (HA, vision, dizziness, coma, CHF, etc) Rare! More common w/ larger Ig like IgM > IgA > IgG Dx = viscosity doesn't correlate with symptoms Tx = plasmapheresis (only if sx)