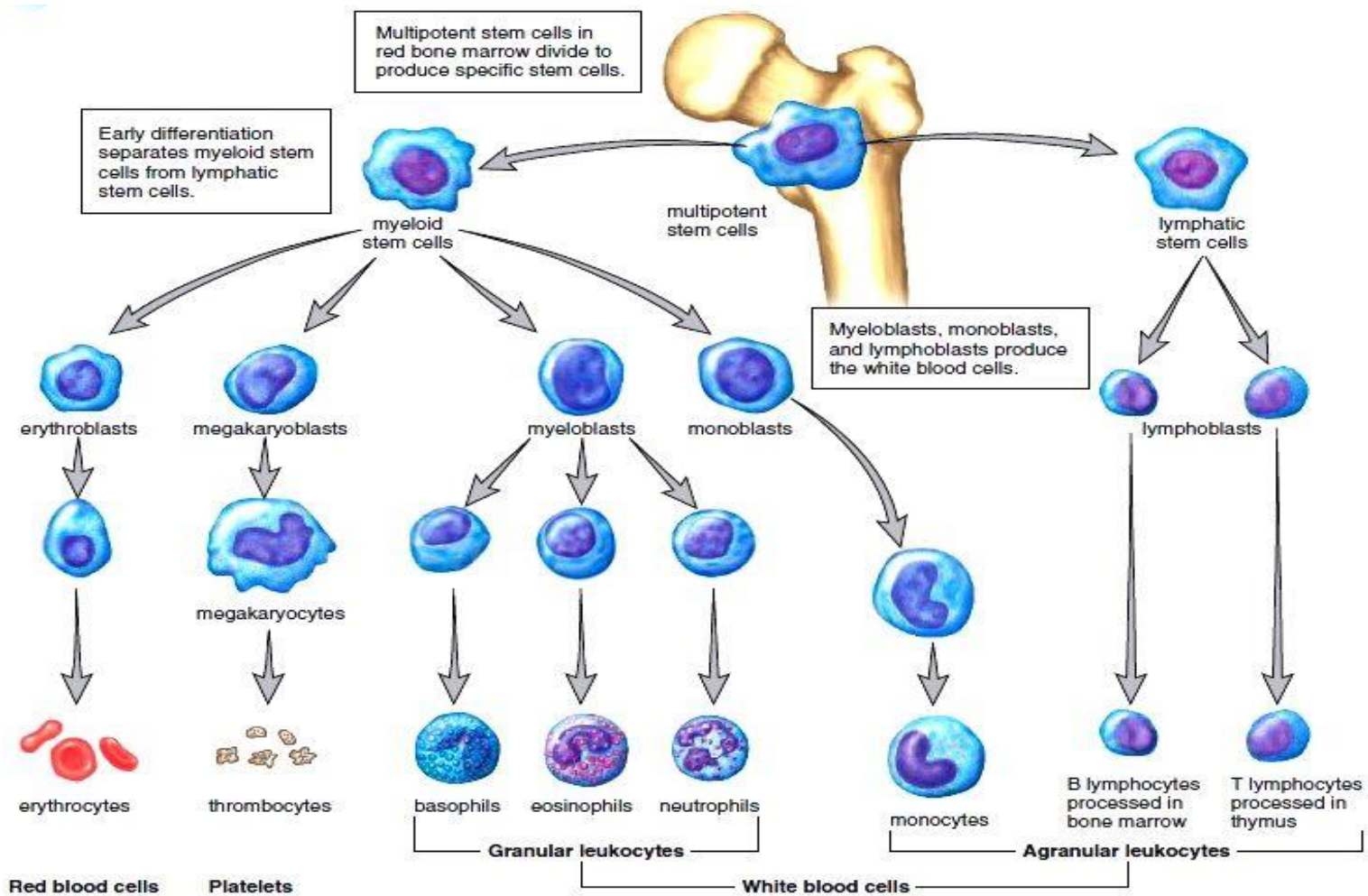
Hematopoiesis: blood cell production

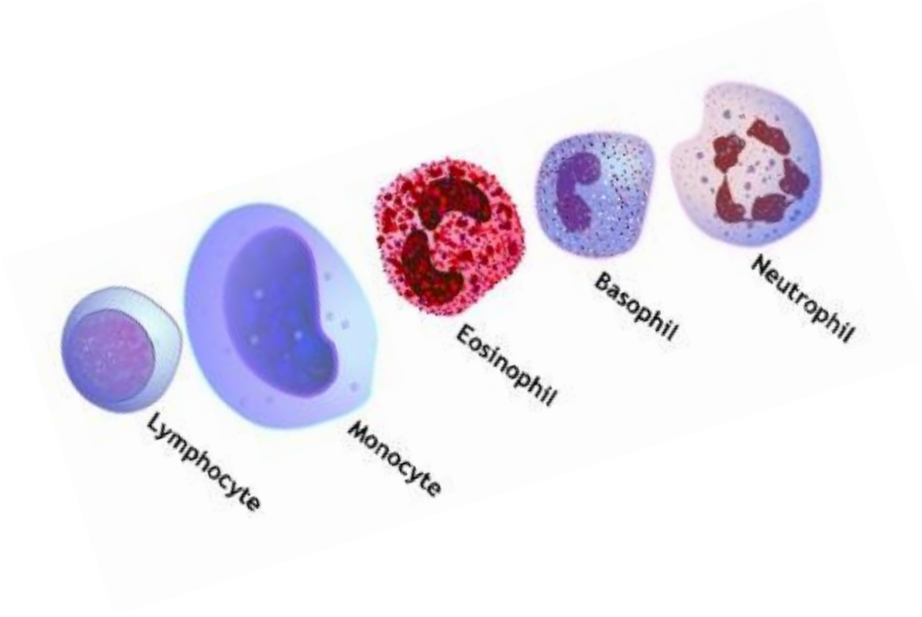


Complete Blood Count

Abbreviation	Test Name	Definition	Associated Disorders
WBC WBC Diff	White blood cells WBC differential Neutrophils Lymphocytes Monocytes Eosinophils Basophils	WBCs fight infection. The 5 different types of WBCs are listed to the left.	Infection, leukemia
RBC	Red blood cells	RBCs (with the help of hemoglobin) carry oxygen throughout the body	↓ Anemia, bleeding, malnutrition, kidney disease ↑ Polycythemia, heart and lung disease, dehydration
Hb or Hgb	Hemoglobin	Protein that carries oxygen	↓ Anemia, bleeding, malnutrition, cirrhosis, cancer ↑ Dehydration, polycythemia
Hct	Hematocrit	Amount of space in the blood that is occupied by RBCs	↓ Anemia, bleeding, malnutrition, cirrhosis, cancer
			↑ Dehydration, polycythemia, hemochromatosis
MCV	Mean corpuscle volume	Average size of the RBCs	Anemia, thalassemia, malnutrition
MCH	Mean corpuscle hemoglobin	Average amount of Hb in each RBC	Anemia, thalassemia, malnutrition
MCHC	Mean corpuscle hemoglobin concentration	Average amount of Hb in the RBCs compared to the average size of the RBCs	Anemia, thalassemia, malnutrition
RDW	Red cell distribution width	Amount of variation in size of the RBCs	Anemia, thalassemia, malnutrition
Plt	Platelet count	Platelets are sticky cells that help to form blood clots	Bleeding and clotting disorders
MPV	Mean platelet volume	Average size of the platelets	Bleeding and clotting disorders

White blood cells: infection-fighters

- White blood count: normal value 4,000-10,000
- Differential:
  - **Neutrophils**: 48-76%; also called granulocytes, polys
    - First cell to fight infection
    - **Absolute neutrophil count (ANC)**
      - "Neutropenia" when <500/uL
      - Can be low when undergoing treatment
  - **Lymphocytes:** 18-41%
    - Fight viral infections
  - **Monocytes:** 4-11%
    - Phagocytes: They ingest foreign material and remove dead cells
  - **Eosinophils:** 0-5%
    - Modulate allergic reactions and defend against some kinds of infection
  - **Basophils:** 0-1.5%
    - Appear in inflammatory reactions, especially allergic symptoms

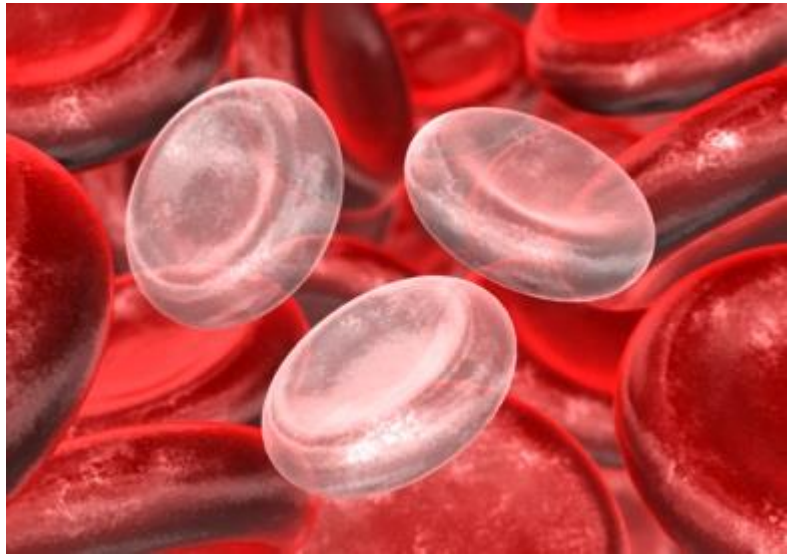


Red blood cells: oxygen-carriers

- **RBC**: number of red blood cells
  - ***4.7-6.1 million cells/microliter***
- **Hemoglobin**: protein molecule in the RBC that carries oxygen and delivers it throughout the body
  - ***12.5-16.3 g/dL***
- **Hematocrit:** percentage of total blood volume consisting of RBC
  - ***38-50%***
- **MCV:** mean corpuscular volume; average volume of a RBC
  - ***80-96 fl/red cell***

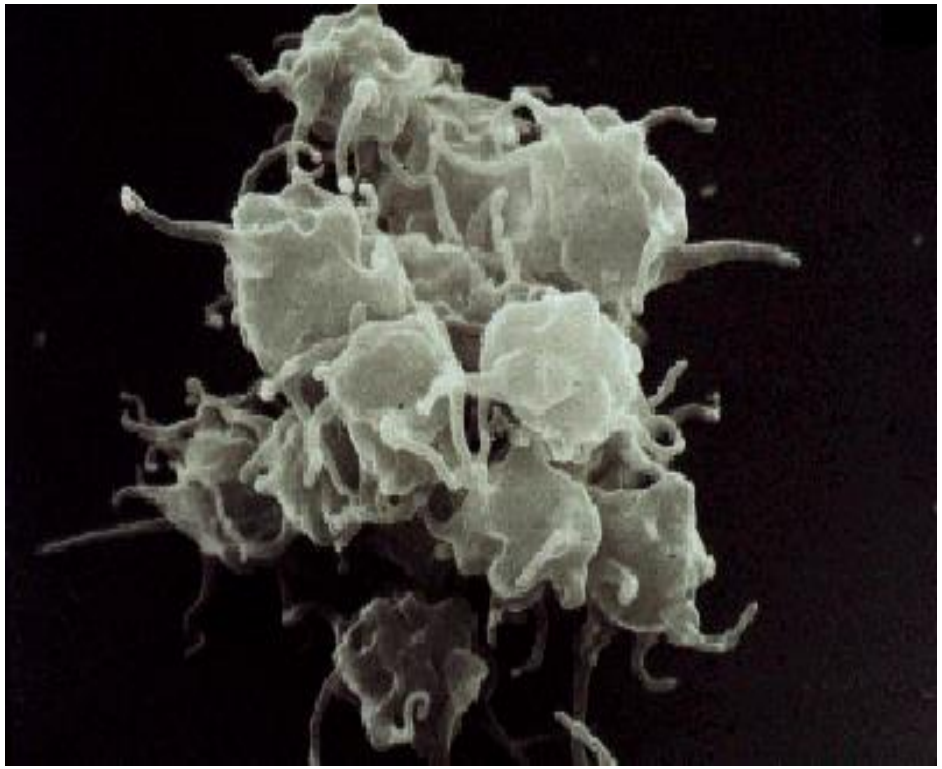
Anemia

- Anemia can be caused by:
  - Bone marrow infiltration by the LPL/WM cells
  - Increased levels of **hepcidin**
    - Produced by WM cells and blocks iron absorption in the gut
  - Hemolysis of RBC due to cold agglutinins
- Anemia work-up:
  - Iron, TIBC, Ferritin
  - Iron Saturation= Iron/TIBC
  - Intravenous iron infusions for iron deficiency can delay chemotherapy



Platelets: help clot your blood

- Platelets (also called thrombocytes): ***150,000-350,000***
  - Can be reduced in WM
  - Platelet function can be affected by Ibrutinib



Normal Blood Counts

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
CBC With Differential/Platelet					
WBC	5.7		x10E3/uL	4.0-10.5	01
RBC	5.27		x10E6/uL	4.10-5.60	01
Hemoglobin	15.4		g/dL	12.5-17.0	01
Hematocrit	46.1		%	36.0-50.0	01
MCV	84		fL	80-96	01
MCH	29.2		pg	27.0-34.0	01
MCHC	34.9		g/dL	32.0-36.0	01
RDW	13.7		%	11.7-15.0	01
Platelets	266		x10E3/uL	140-415	01
Neutrophils	47		%	40-74	01
Lymphs	46		%	14-46	01
Monocytes	6		%	4-13	01
Eos	1		%	0-7	01
Basos	0		%	0-3	01
Neutrophils (Absolute)	2.6		x10E3/uL	1.8-7.8	01
Lymphs (Absolute)	2.6		x10E3/uL	0.7-4.5	01
Monocytes(Absolute)	0.4		x10E3/uL	0.1-1.0	01
Eos (Absolute)	0.1		x10E3/uL	0.0-0.4	01
Baso (Absolute)	0.0		x10E3/uL	0.0-0.2	01
Immature Granulocytes	0		%	0-1	01
Immature Grans (Abs)	0.0		x10E3/uL	0.0-0.1	01

So, what do we look at?

- Are you anemic?
  - *Anemia is the most common reason WM patients begin therapy*
    - Criteria to treat: Hemoglobin < 10.0 g/dL
- Are your platelets normal?
  - Criteria to treat: Platelets < 100,000
- Is your white blood count normal?
  - Is WBC elevated or low?
    - What is the ANC?
  - Is the differential normal?
    - Are the lymphocytes elevated?

Chemistry panel

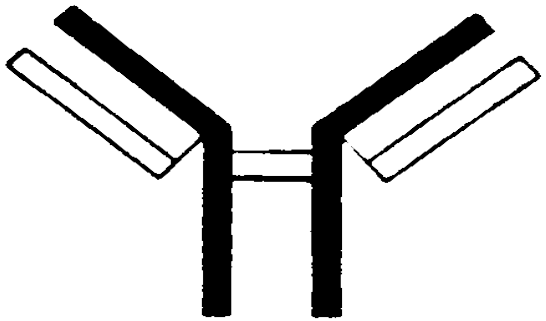
- Electrolytes
  - Sodium, potassium
- Kidney function
  - BUN, creatinine
- Liver function
  - ALT, AST
- Protein
  - ***Globulin: Predictor of the IgM***
  - ***Total Protein-albumin =Globulin***

Superchem			
Tests	**Results**	**Ref. Range**	**Units**
Total Protein	5.6	5.0–7.4	g/dL
Albumin	3.3	2.7–4.4	g/dL
Globulin	2.3	1.6–3.6	g/dL
A/G Ratio	1.4	0.8–2.0	
AST (SGOT)	28	15–66	IU/L
ALT (SGPT)	88	12–118	IU/L
Alk Phosphatase	68	5–131	IU/L
GGT	4	1–12	IU/L
Total Bilirubin	0.3	0.1–0.3	mg/dL
BUN	28	6–31	mg/dL
Creatinine	1.0	0.5–1.6	mg/dL
BUN/Creatinine Ratio	**28 (HIGH)**	**4–27**	
Phosphorus	3.8	2.5–6.0	mg/dL
Glucose	114	70–138	mg/dL
Calcium	9.1	8.9–11.4	mg/dL
Corrected Calcium	9.3		
Magnesium	1.6	1.5–2.5	mEq/L
Sodium	141	139–154	mEq/L
Potassium	3.9	3.6–5.5	mEq/L
Na/K Ratio	36	27–38	
Chloride	105	102–120	mEq/L
Cholesterol	203	92–324	mg/dL
Triglyceride	**410 (HIGH)**	**29–291**	**mg/dL**
Amylase	592	290–1125	IU/L
Lipase	132	77–695	IU/L
CPK	114	59–895	IU/L
Comment			
Hemolysis 1+ and Lipemia 1+ No significant interference.			

Immunoglobulins

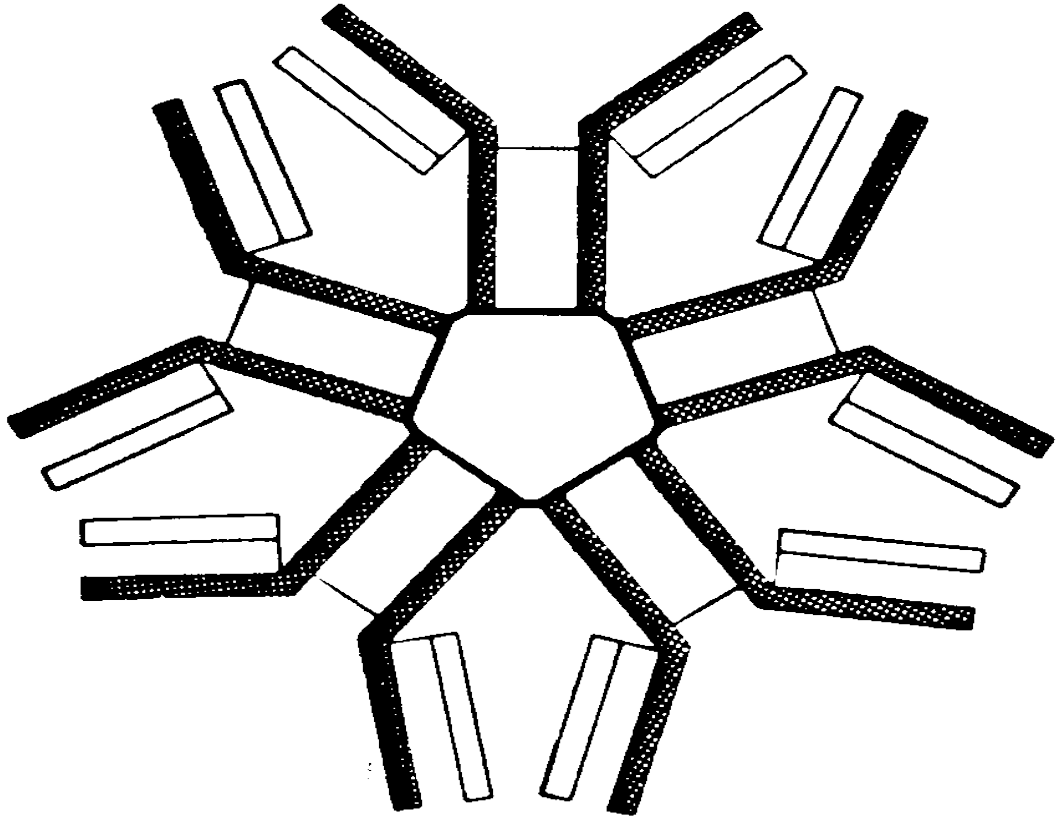
- A large y-shaped protein produced by plasma cells that functions as an antibody to neutralize pathogens such as bacteria and viruses
  - ***IgG***: most abundant immunoglobulin in adult human (***500-1500 mg/dL)***
    - Protects against viral and bacterial infections
    - Levels are often low in WM
  - ***IgA***: found in the mucous membranes, especially those lining the respiratory and gastrointestinal tracts.
    - Levels are low in WM patients
  - ***IgM***: largest of the immunoglobulins; first antibody to respond to an antigen
    - IgM is overproduced by the WM cells

IgG



Molecular weight: 150,000

IgM



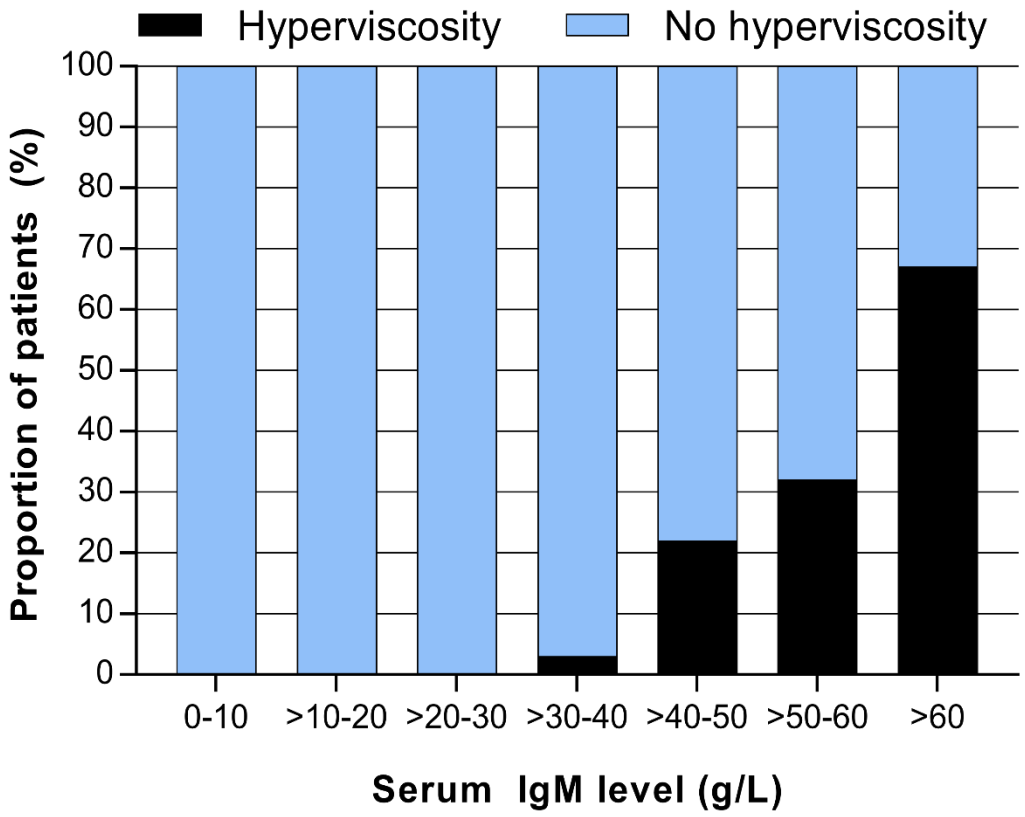
- Molecular weight: 900,000

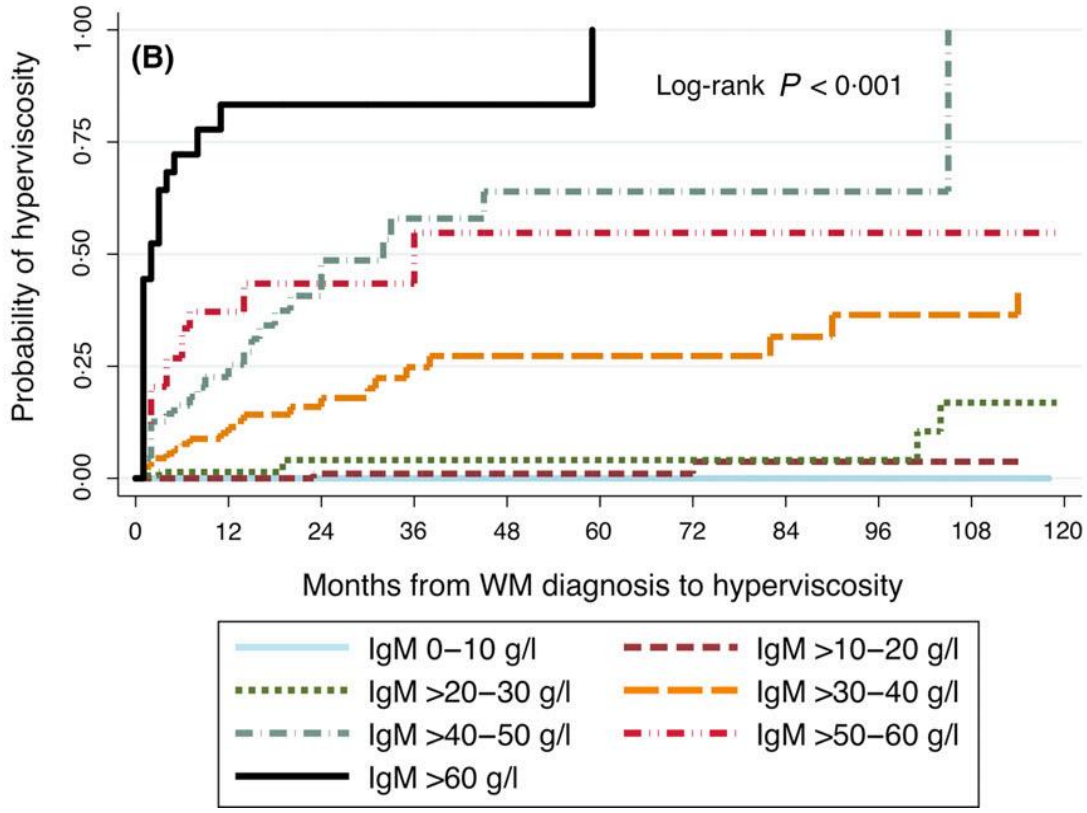
Hyperviscosity & IgM Level

- Accumulation of IgM in blood increases serum viscosity (i.e. blood thickness)
- Increases the risk of bleeding at blood vessels in the eye and/or brain
- **Symptoms**: blurry vision, headaches, nosebleeds, mental fog
- Can be identified by fundoscopic examination
- Occurs in patients with a serum IgM >3,000 mg/dL
- Patients with a serum IgM >6,000 mg/dL are at high risk
  - Median time to development of symptomatic HV was 3 months
  - Treatment may be indicated for these patients even if asymptomatic

Gustine et al, BJH 2017

Serum IgM & Hyperviscosity Risk





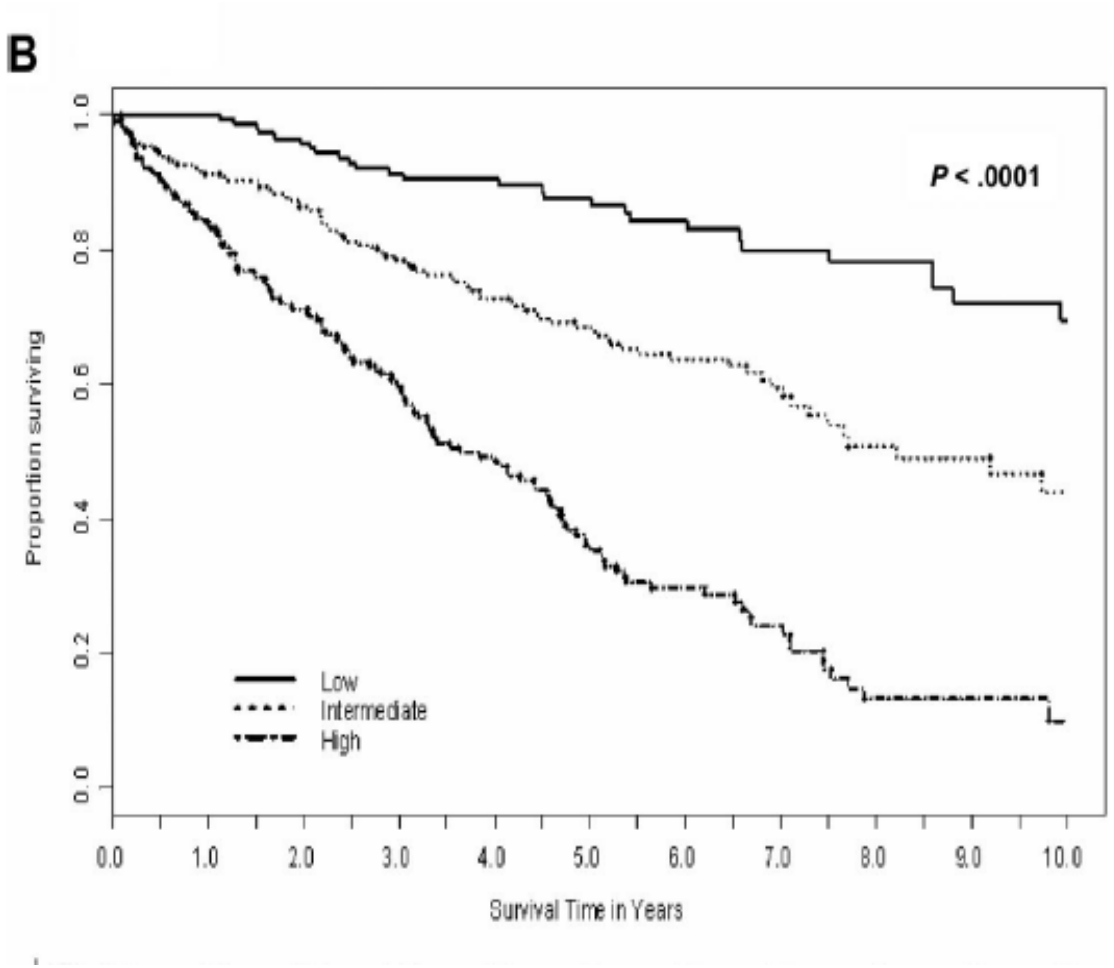
IPPS: International Prognostic Scoring System for Waldenstrom's Macroglobulinemia

- Prognostic Variables before treatment for WM:
  - Age >/= 65 y
  - Hemoglobin </= 11.5 g/dL
  - Platelets </= 100k
  - B2-microglobulin > 3mg/L
  - IgM level > 7,000 mg/dL

Stratum	Score
Low Risk	0-1 (except age)
Medium Risk	Age or 2
High Risk	>/= 3

- *Morel et al. Blood, 2009*

Survival after first treatment initiation: based on IPPS



Mutational analysis

- **MYD88 mutation:** present in 95% of WM patients
- **CXCR4 mutation:** present in 40% of WM patients
  - Associated with higher serum IgM levels and increased risk for HV
- Mutational analysis can be done on peripheral blood but results are less accurate, especially in a previously treated patients

Take Home Points

- Labs are an important part of your evaluation for WM
- Trends in labs are generally more important than any one value
- Anemia the most common symptom of WM and the criteria to treat for most patients
- Risk of hyperviscosity is significantly increased with an IgM > 6,000 mg/dL

In thanks

Bing Center for Waldenstrom's Macroglobulinemia Clinical Team

Jorge J. Castillo, Toni Dubeau, Kirsten Meid, and Joshua Gustine

As well as…

Steven Treon, Christopher Patterson, Zachary Hunter, Lian Xu, Jiaji Chen, Xia Liu, Robert Manning, Philip Brodsky, Nicholas Tsakmaklis, Maria Demos & Gloria Chan