# General Hematology!

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OHSU GENERAL HEMATOLOGY

# Disclosures

- None

# Today

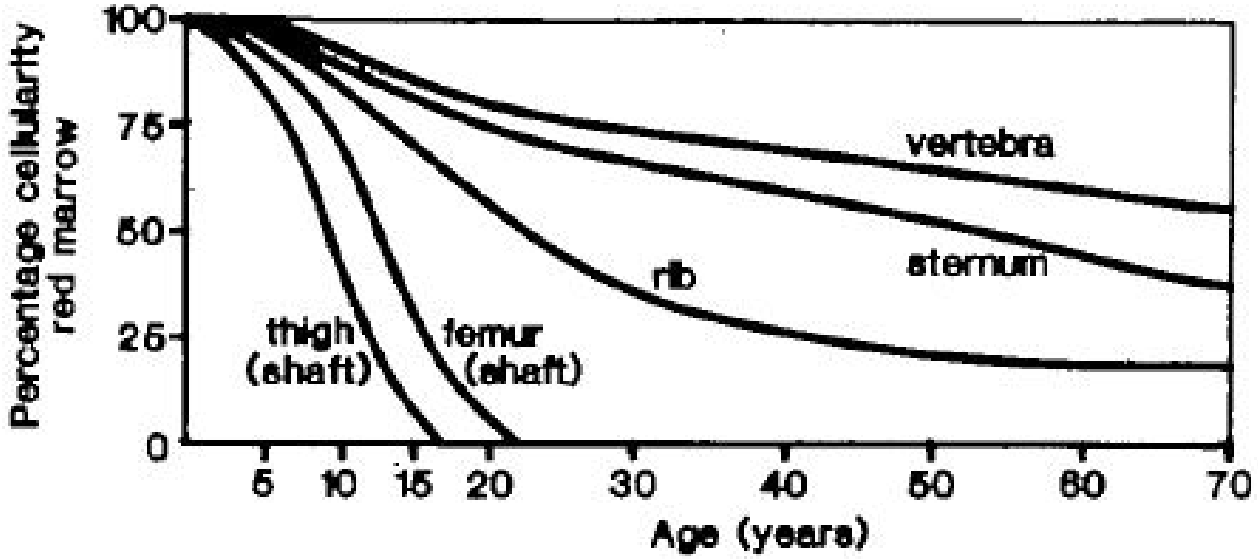
- Abnormal MRI signal
- TTP update

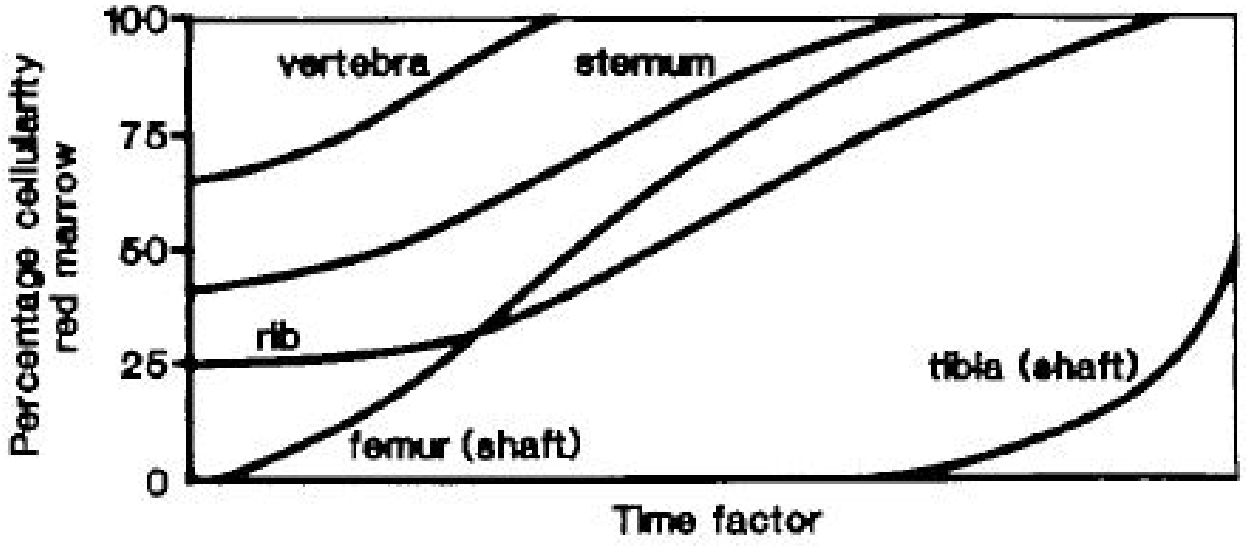
# Abnormal MRI Signal

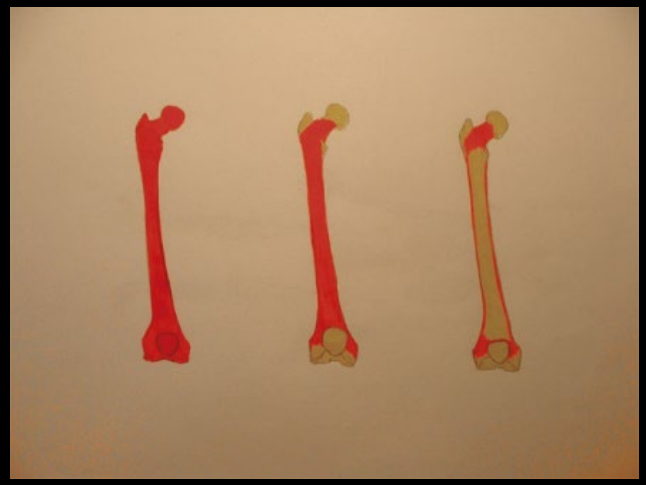
- Common issue
- Scary for patients
- Absolutely no guidance or consensus
- An approach

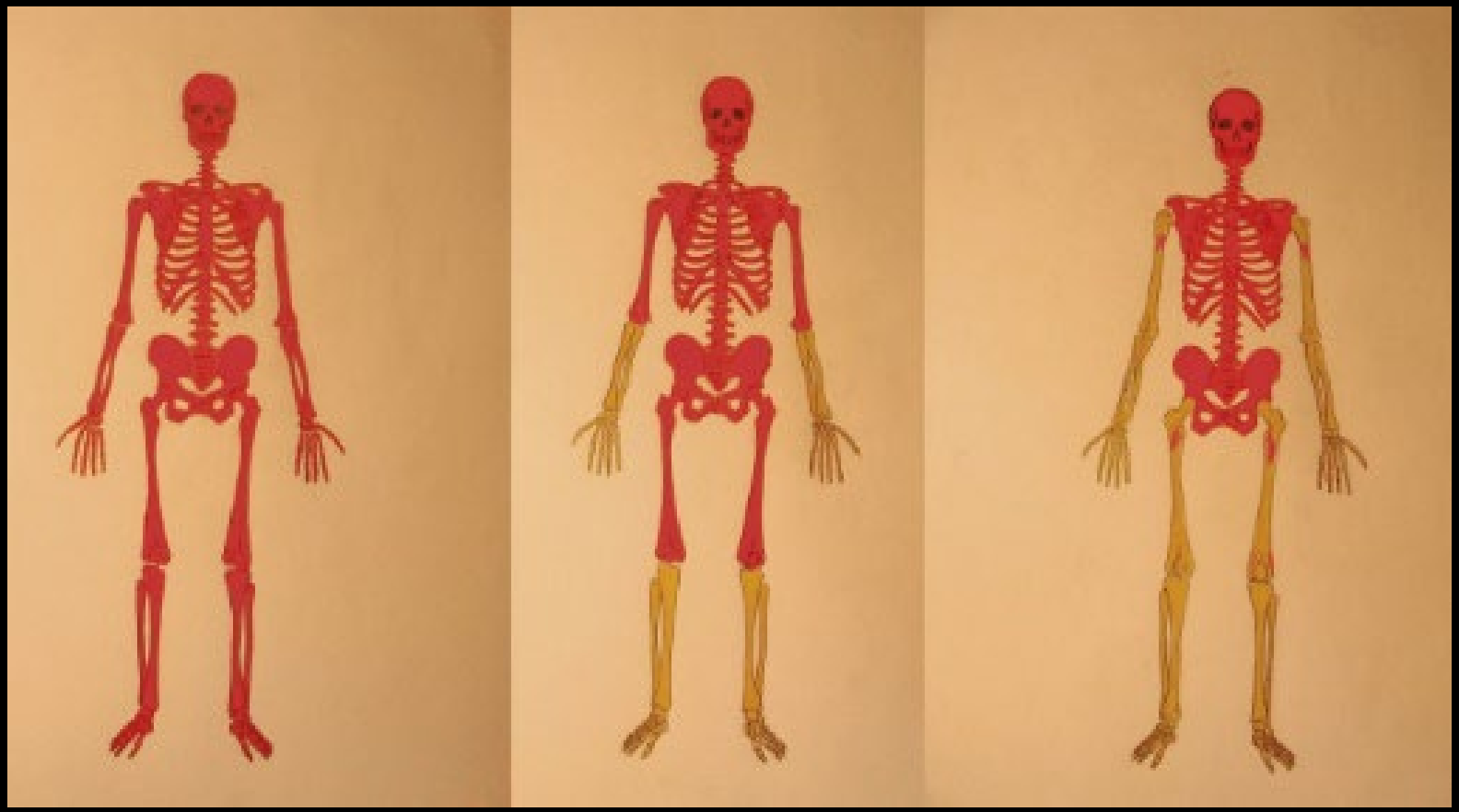
# Bone Marrow 101

- “Red marrow” produces blood
- Percent of red marrow decreases with age and replaced with fat “yellow marrow”
- Red and yellow marrow different on MRI


Percentage cellularity red marrow
100
75
50
25
0
vertebra
sternum
rib
thigh (shaft)
femur (shaft)
5
10
15
20
30
40
50
60
70
Age (years)


Percentage cellularity red marrow
100
75
50
25
0
vertebra
sternum
rib
tibia (shaft)
femur (shaft)
Time factor





# What can go Wrong?

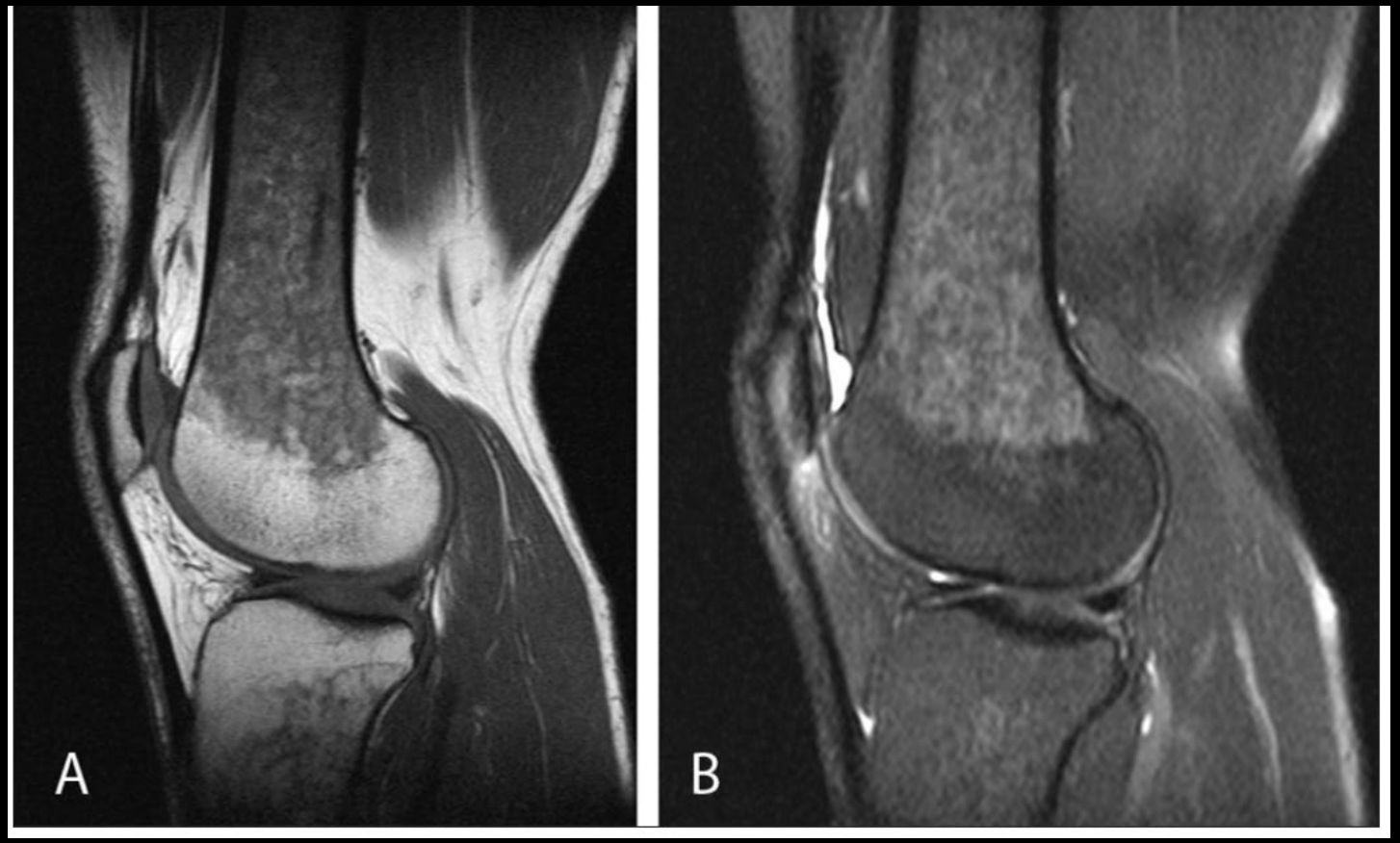
- Variation in regression of red marrow
- Physiological responses to physiologic stresses
- Bad things

# Variation in Regression

- Conversion may not be uniform
- Can be “speckled pattern”
- Usually recognized as normal variant

# Smokers

- Smoker have increase hematopiesis
  - Inflammation
  - Carbon monoxide
- Can see abnormal marrow MRI




Vanhoenacker, F et al 2016 Common Mistakes and Pitfalls in Magnetic Resonance Imaging of the Knee. *Journal of the Belgian Society of Radiology,* 100(1): 99, pp. 1–17, DOI: http://dx.doi.org/10.5334/jbr-btr.1206

# Obesity

- High WBC very common
  - Adipose cells secrete growth factors
  - WBC 10-18,000
- Can see reconversion
- Reverses with weight loss

# Exercise

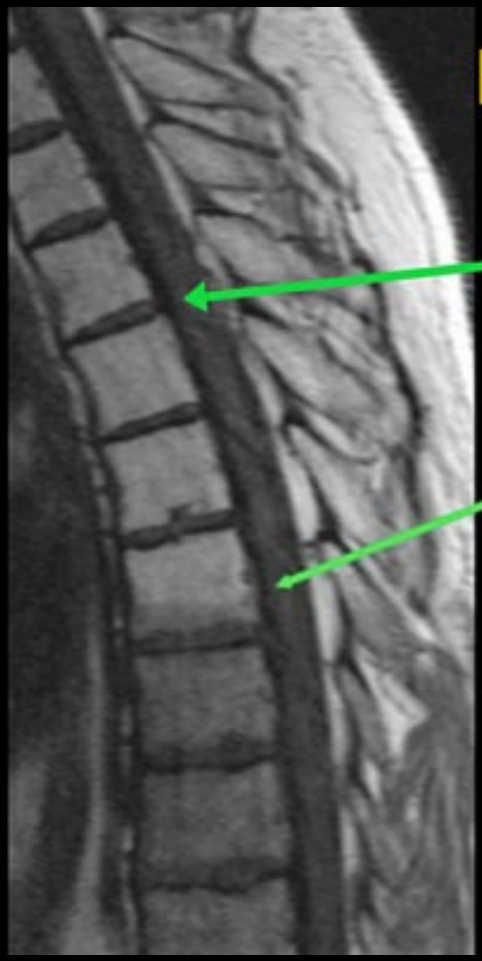
- Increased red cell turnover
  - Hemolysis
  - Iron deficiency
- Reconversion near joints
  - Also with DJD

# Anemia

- Can lead to a variety of abnormalities
- Iron/B12 deficiency
  - Increased reconversion
- Aplastic anemia
  - All fat
- Recent IV iron

# Radiation

- Radiation therapy can permanently destroy marrow
- Can be very remote
  - Childhood cancer
  - Adjuvant breast cancer

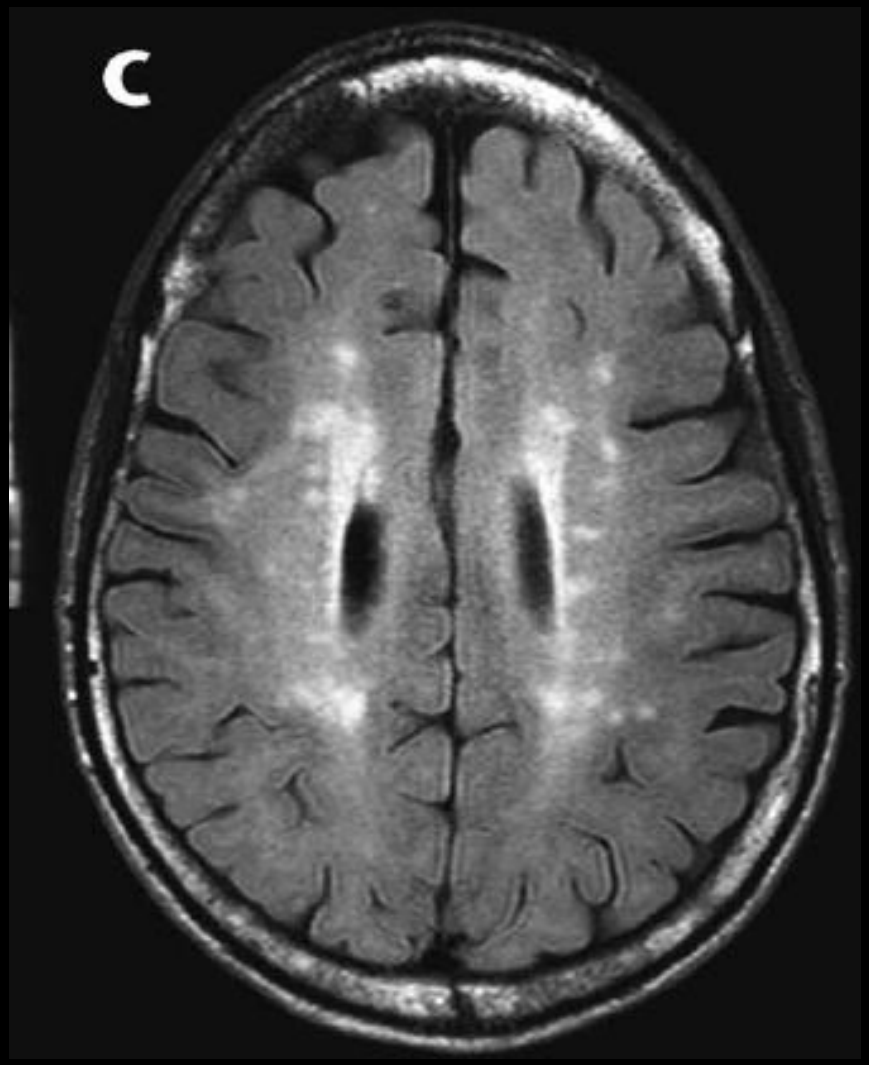


# POST RADIOTHERAPY CHANGES

Post RT, tumour/ normal marrow is replaced by fat which is high signal on T1

Sharp cut off in signal change where RT effect ends

RAD/ED ASIA
Radiology Education


C

# Bad Things

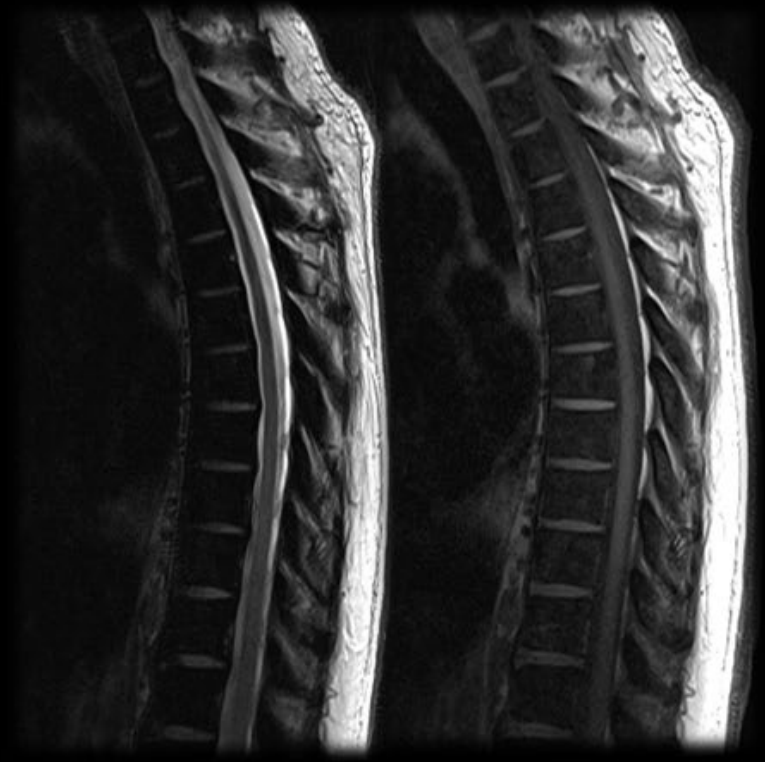
- Leukemia
- Marrow fibrosis
- Myeloma
- Lymphoma

# Leukemia

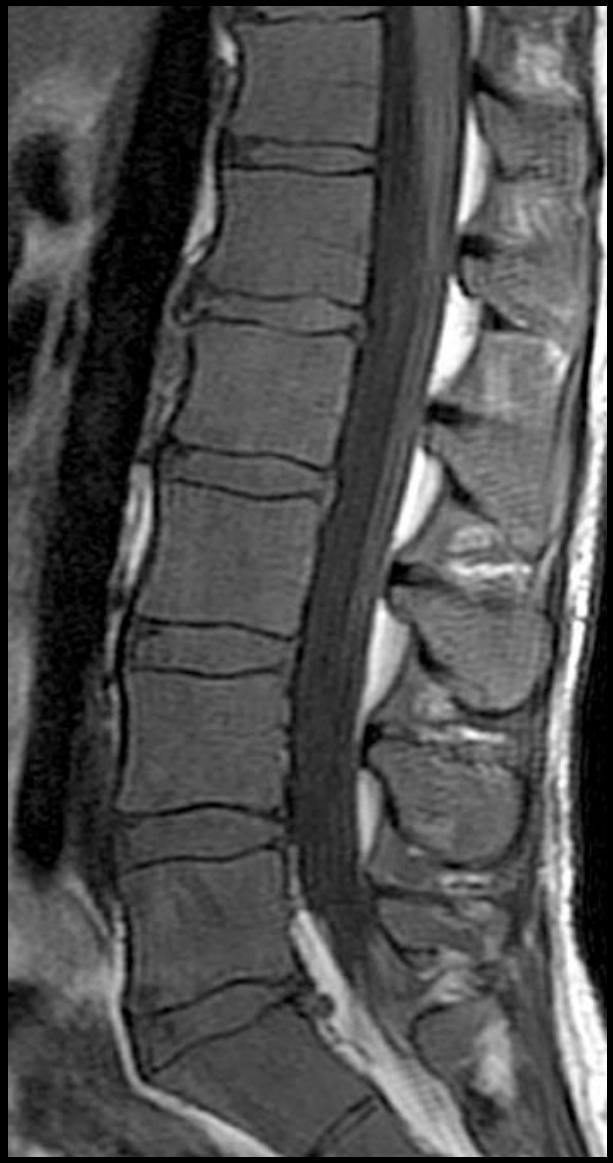
- Hypercellular – very abnormal MRI signal
- CBC always abnormal

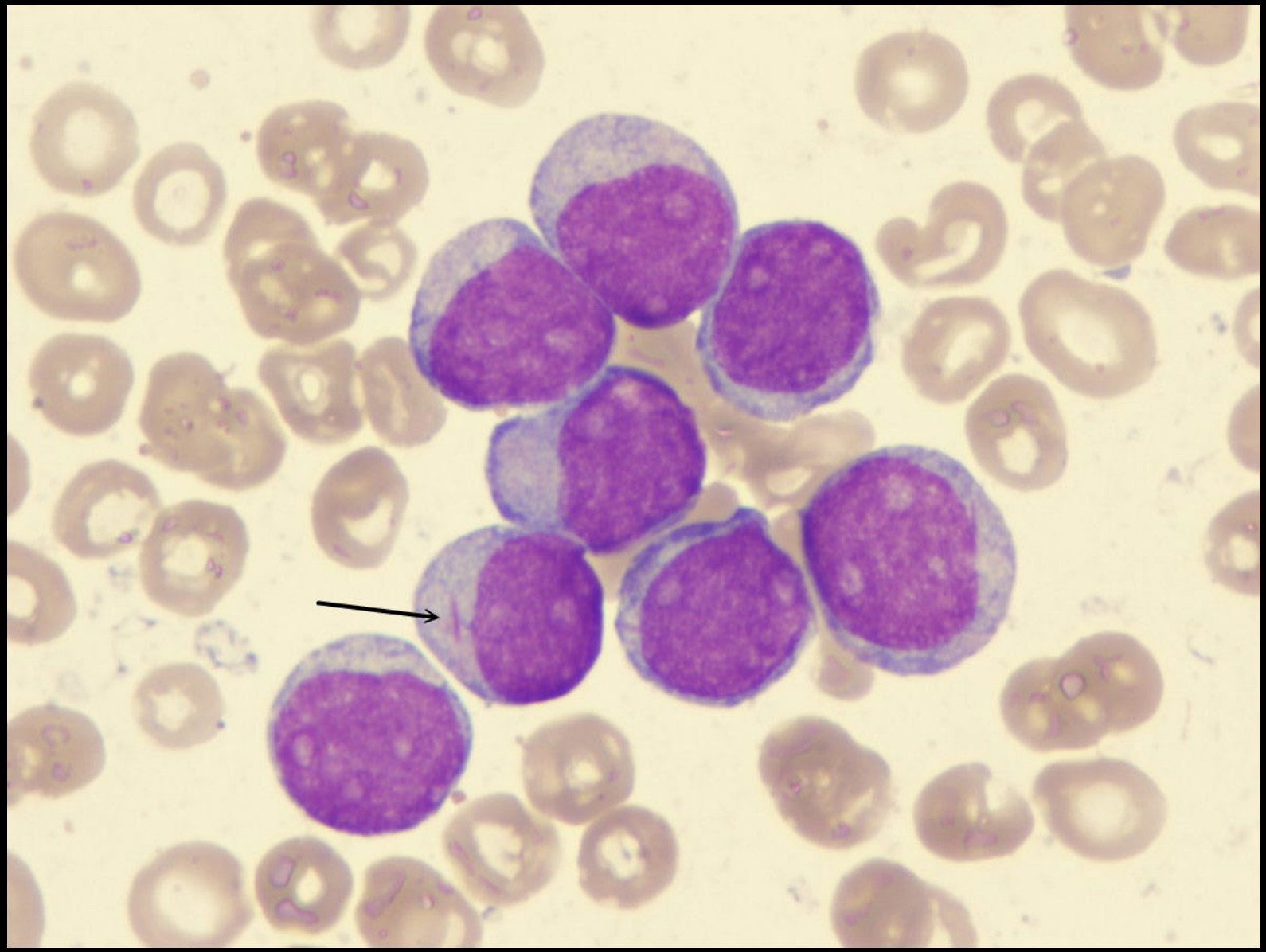
# Discussion

- Findings
  - Diffuse low signal of bone marrow
  - T1 bone marrow signal darker than intervertebral discs
- Differential
  - Leukemia
  - Chronic anemia
  - Myelofibrosis
  - Lymphoma
  - Multiple myeloma
  - Diffuse metastases
  - “Red” hematopoietic marrow



http://headneckbrainspine.com/Case-335-discussion.php

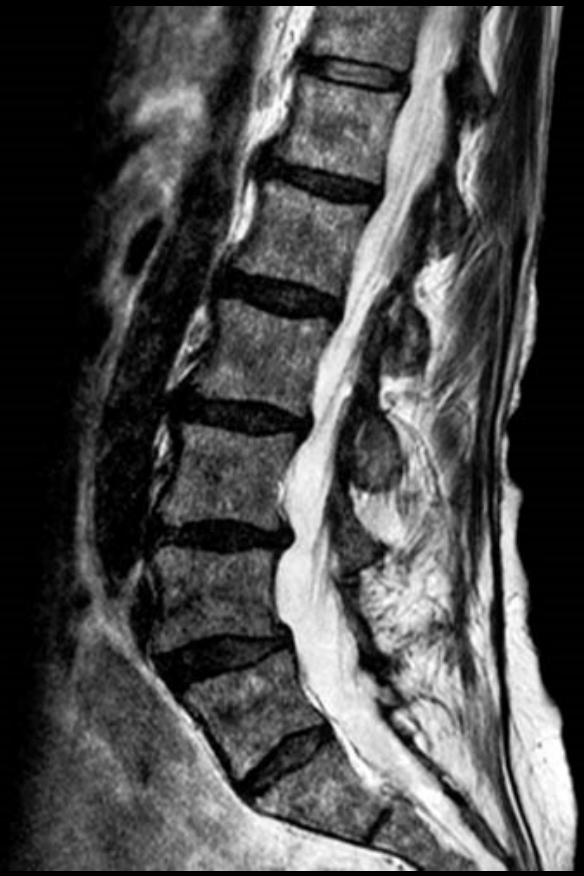


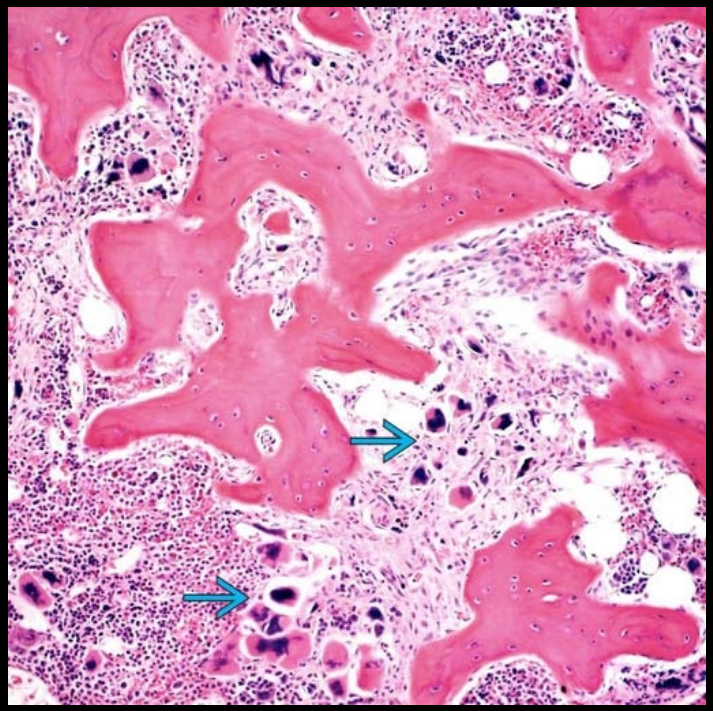


http://www.mog-eg.com/apps/photos/photo?photoid=38256199

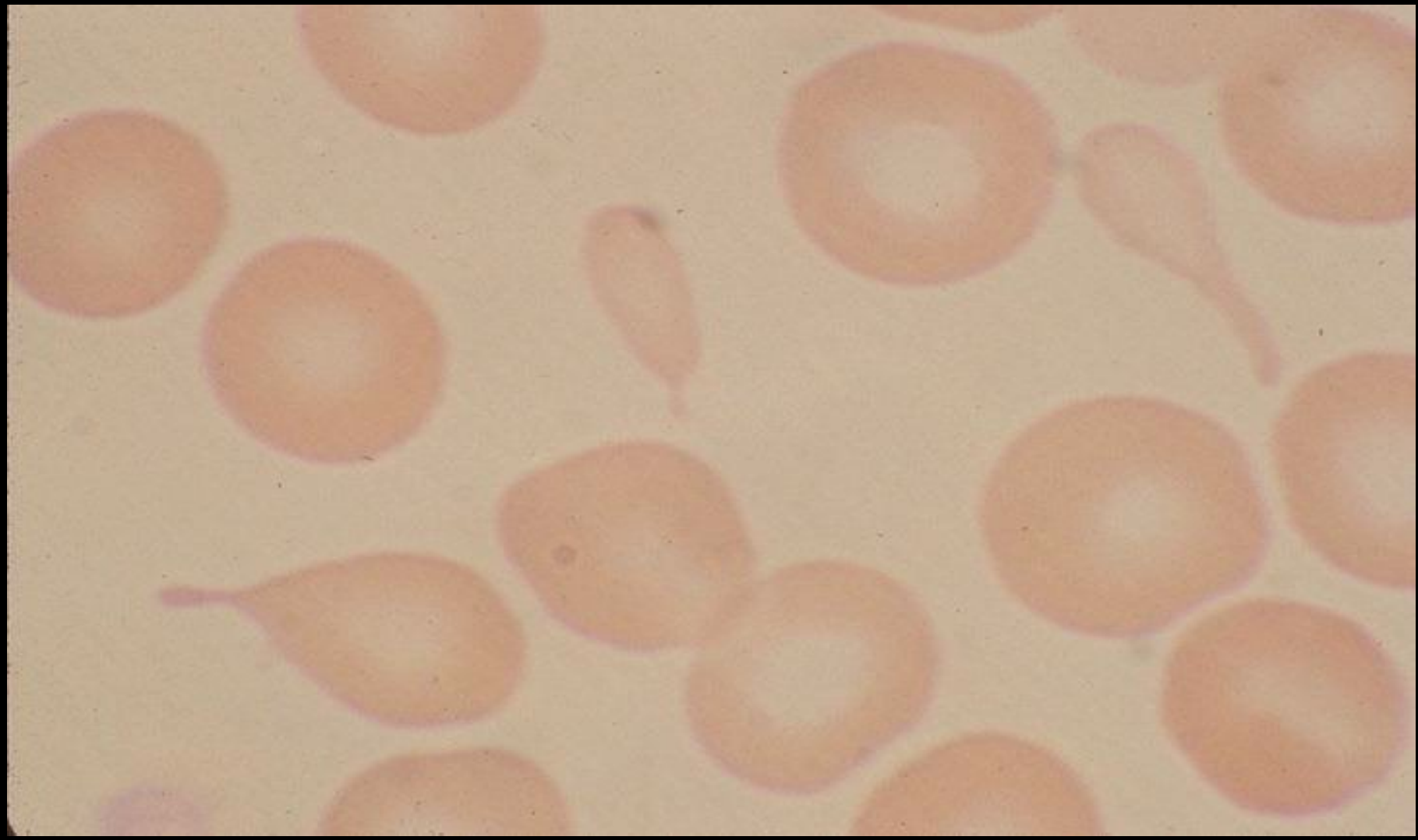
# Marrow Fibrosis

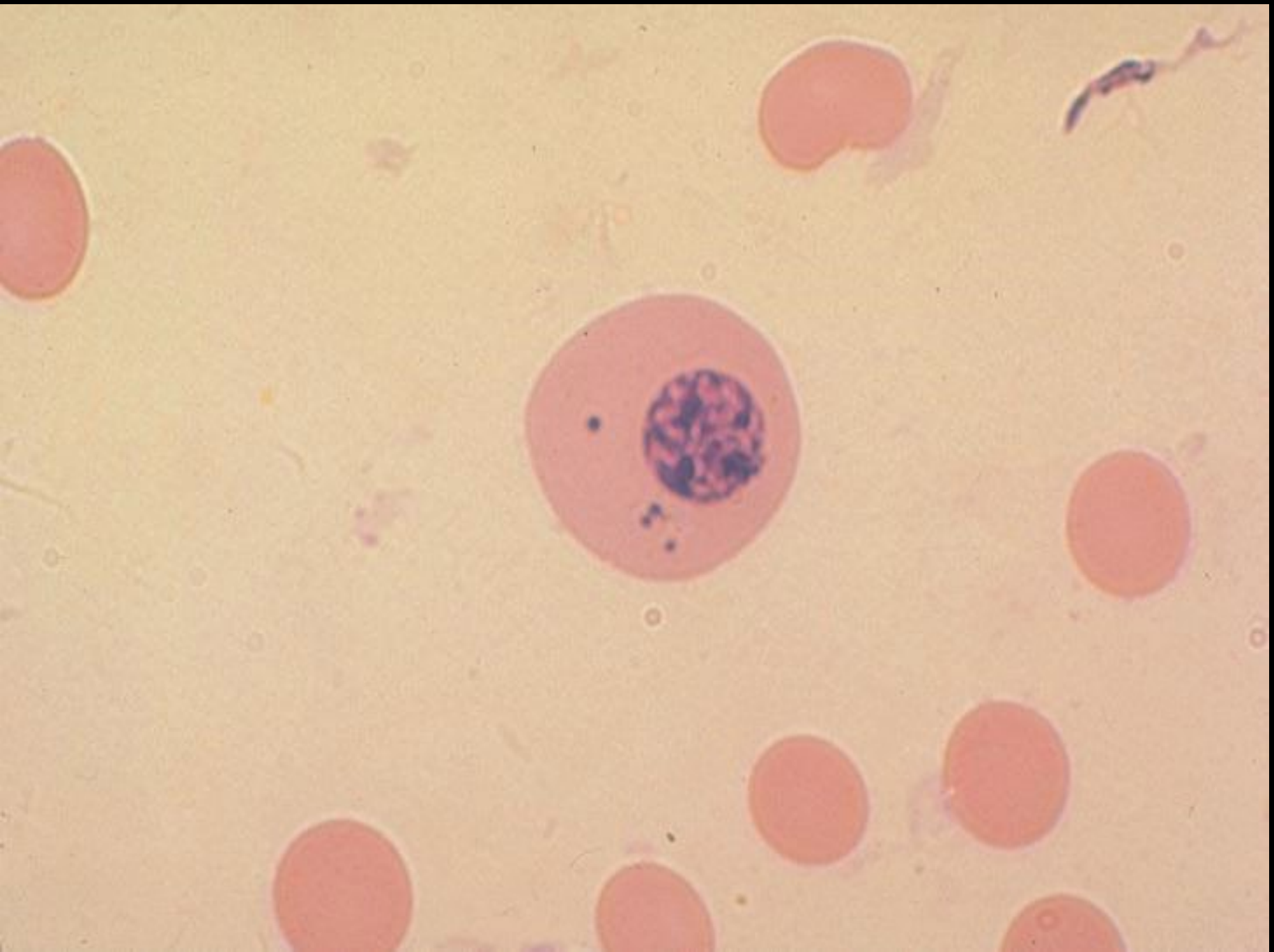
- Myelofibrosis
  - Myeloproliferative syndrome
- Secondary fibrosis
  - Lupus
  - Infections
  - Etc..
- CBC/smear abnormal

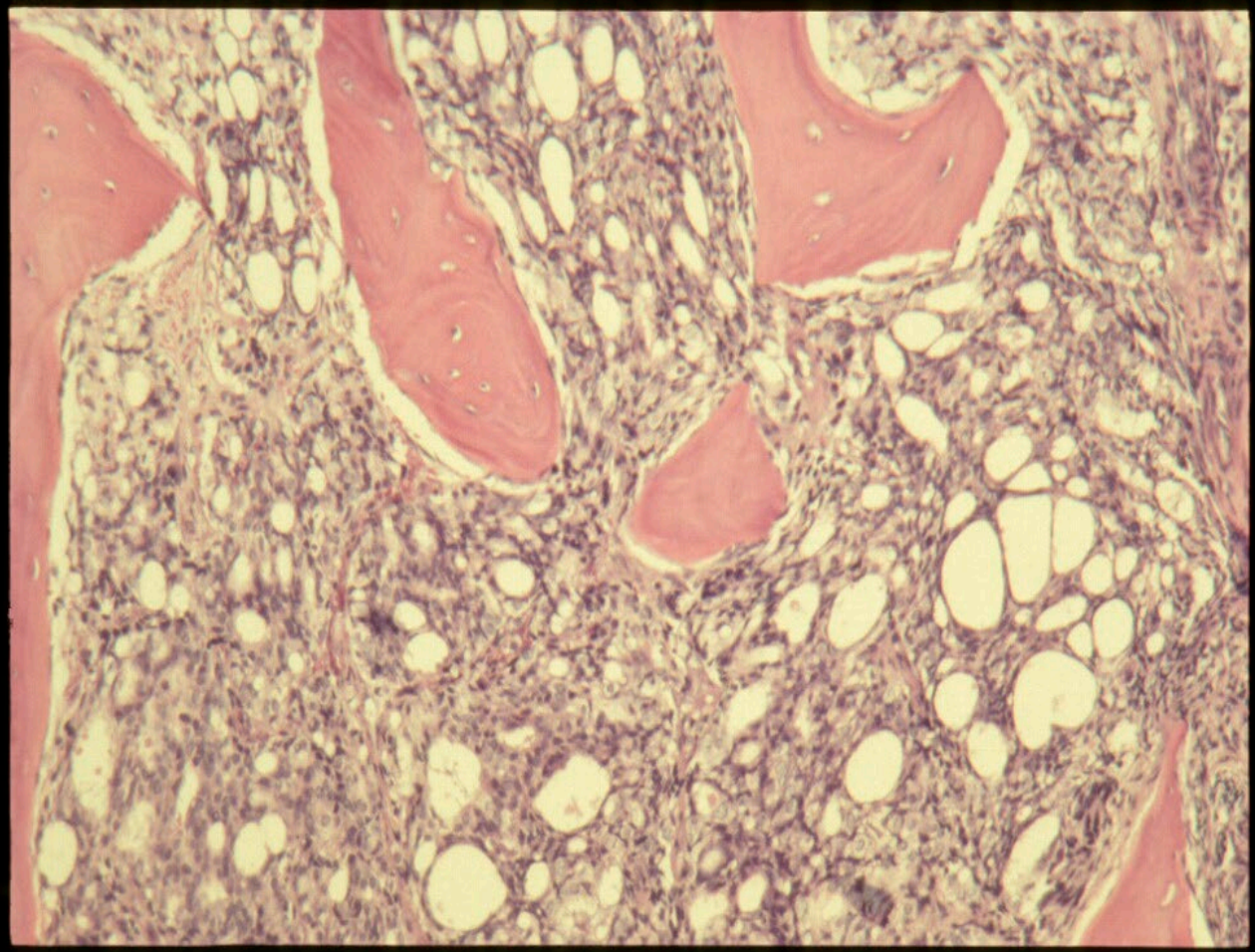




https://radiologykey.com/myelofibrosis/

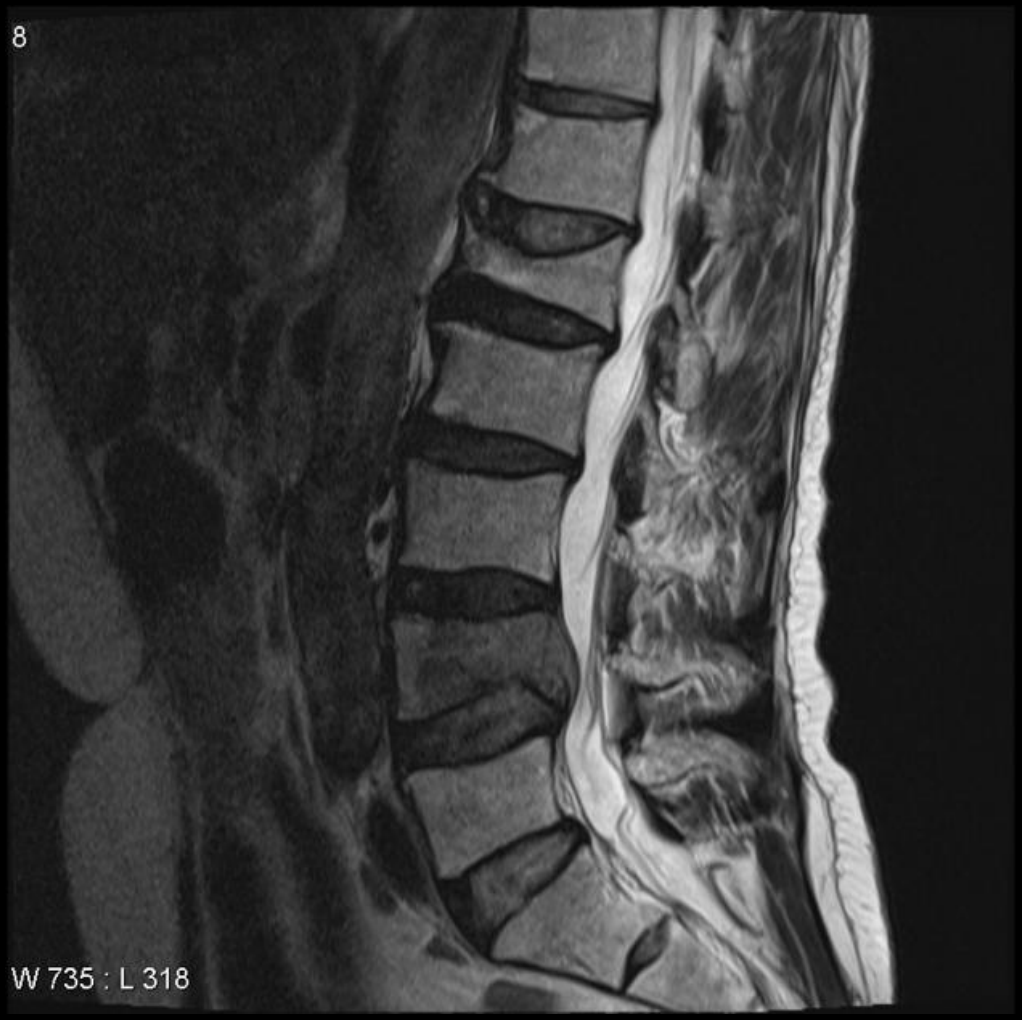






# Lymphoma

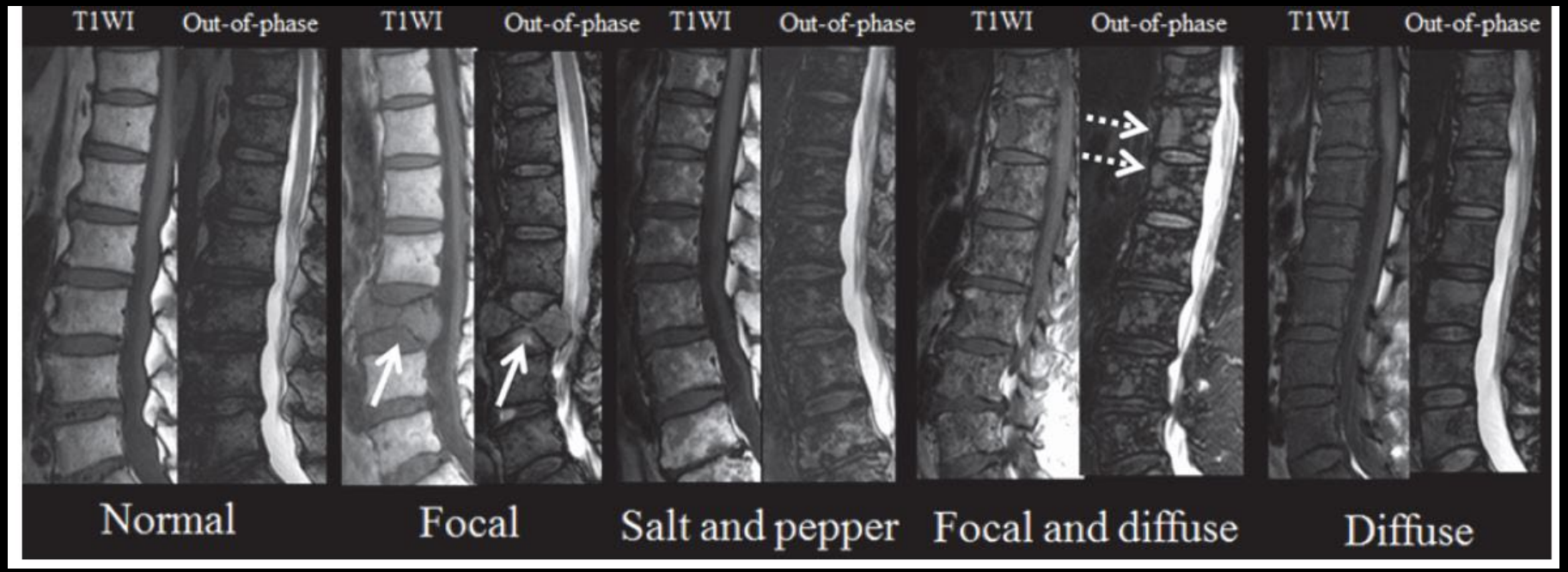
- Many types of lymphoma
- Marrow
  - Diffuse
  - Nodular
- Marrow only presentation unusual




https://radiopaedia.org/cases/lymphoma-of-the-spine-1

# Myeloma

- Two patterns
  - Diffuse infiltration of plasma cells
  - Plasmacytomas




PLOS ONE | DOI:10.1371/journal.pone.0116842 February 23, 2015

# OK How do I work up the patient?

# History

- Pattern of pain
  - Weeks vs year
- “B” symptoms
  - Night sweats
  - Weight loss
  - Fevers
- Smoker?
- Exercise?
- Job?

# Labs

- How far to go?
- Informal poll of my colleagues
  - Ranged from only a CBC to deep genomic sequencing of marrow

# Essential

- Complete blood count
- CMP
  - Renal (myeloma)
  - Total protein (myeloma)
- LDH?

# Almost Essential

- Myeloma work-up (age > 40)
- Serum protein electrophoresis
- Serum – not urine – free light chains

# Don’t do!

- Urine light chain
  - Not standardize
- UPEP
  - Not sensitive

# Our Data

- 1500 spine MRI
- 4% abnormal marrow signal
- 1 myeloma

- Spine 15:390, 2020

# When do I Marrow?

- Only if CBC or other testing suggest pathology
- Most are benign causes
- If in doubt – talk with radiologist!

# The Future

- Standardized reporting
- Standardized work-up!
- Research study going on

# Bottom Line

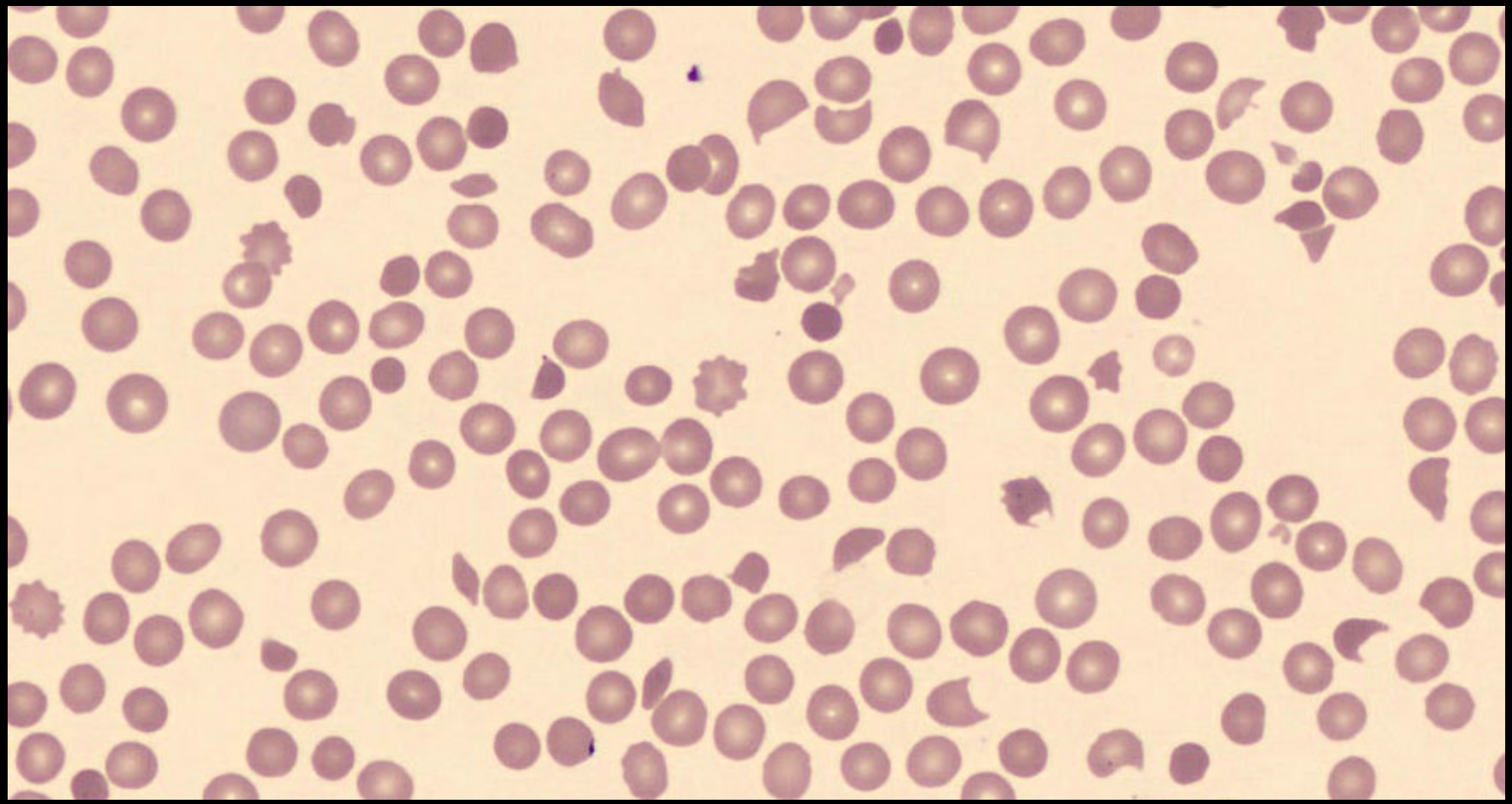
- Look at report
- Look at patient
- Look at labs

# Thrombotic Microangiopathy

- Key diagnostic features
  - Microangiopathic hemolytic anemia
    - Schistocytes
    - Hemolysis
  - Thrombocytopenia
  - High LDH
  - End organ damage

# The Pentad of TTP: Dead, Dead, Dead

- Thrombocytopenia
- MAHA
- Mental status changes: only seen in 40-50%
- Renal insufficiency: most often mild
  - Proteinuria most common
- Fevers: 20%



# Other Abnormalities

- LDH elevations (>2-3x nl)
- Myocardial involvement
- Pulmonary involvement
- Gastrointestinal involvement
  - Pancreatitis

# Pitfalls in Diagnosis

- Classic pentad most often not present
- Thrombocytopenia may be mild (20-60,000/ul)
- Neurological defects vague
- Diagnosis not thought of

## PLASMIC Score

| Parameter | Result | Score |
|---|---|---|
| Platelet count | <30K | 1 |
| Creatinine | <2.0 | 1 |
| INR | <1.5 | 1 |
| MCV | <90 | 1 |
| Presence of hemolysis variable | Either:<br>-Retic>2.5%<br>-Undetectable hapto-globin or<br>-iBili>2 mg/dL | 1 |
| Abscence of active cancer | | 1 |
| No prior stem cell or organ transplant | | 1 |

| PLASMIC score | Probability of TTP[a] | Management |
|---|---|---|
| <5 | Low: <5% | Close observation<br>Consider alternative diagnoses<br>Send ADAMTS13 testing if no alternative cause identified |
| 5 | Intermediate: 5–25% | Send ADAMTS13 testing<br>Obtain expert consultation<br>Consider plasma infusion<br>TPE if no other cause identified |
| >5 | High: 60–80% | Send ADAMTS13 testing<br>Obtain expert consultation<br>Immediate TPE if high clinical suspicion for TTP |

Abbreviations: TMA, thrombotic microangiopathy; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura.
[a]Quantitative risk estimates based on approximate probabilities observed in the PLASMIC derivation and validation cohorts.[16]

# ADAMTS 13 Levels

- Levels may guide therapy
- <5% and inhibitor
  - More severe disease but lesser risk of death
  - Strong role for immunosuppression esp if relapses
- <5% and no inhibitors
  - Congenital?
- 5-50%
  - Many diseases
- Normal
  - Think aHUS

# Therapy

- Steroids
- Plasma exchange
- Caplacizumab (?)
- Immune globulin (??)
- Vincristine
- Rituximab
- Splenectomy

# Steroids

- Seems to play a role in TTP therapy
- Usually 60-120 mg prednisone
- Slow taper when patients responds
- Some patients steroid sensitive

# Plasma Exchange

- Key factor in outcome
  - 2 RCT
- Start with 1.5 plasma volume exchange for at least 5 days
- Follow LDH
- Taper when LDH normal
- Plasma infusion until exchange
  - 1 unit/4-6 hours

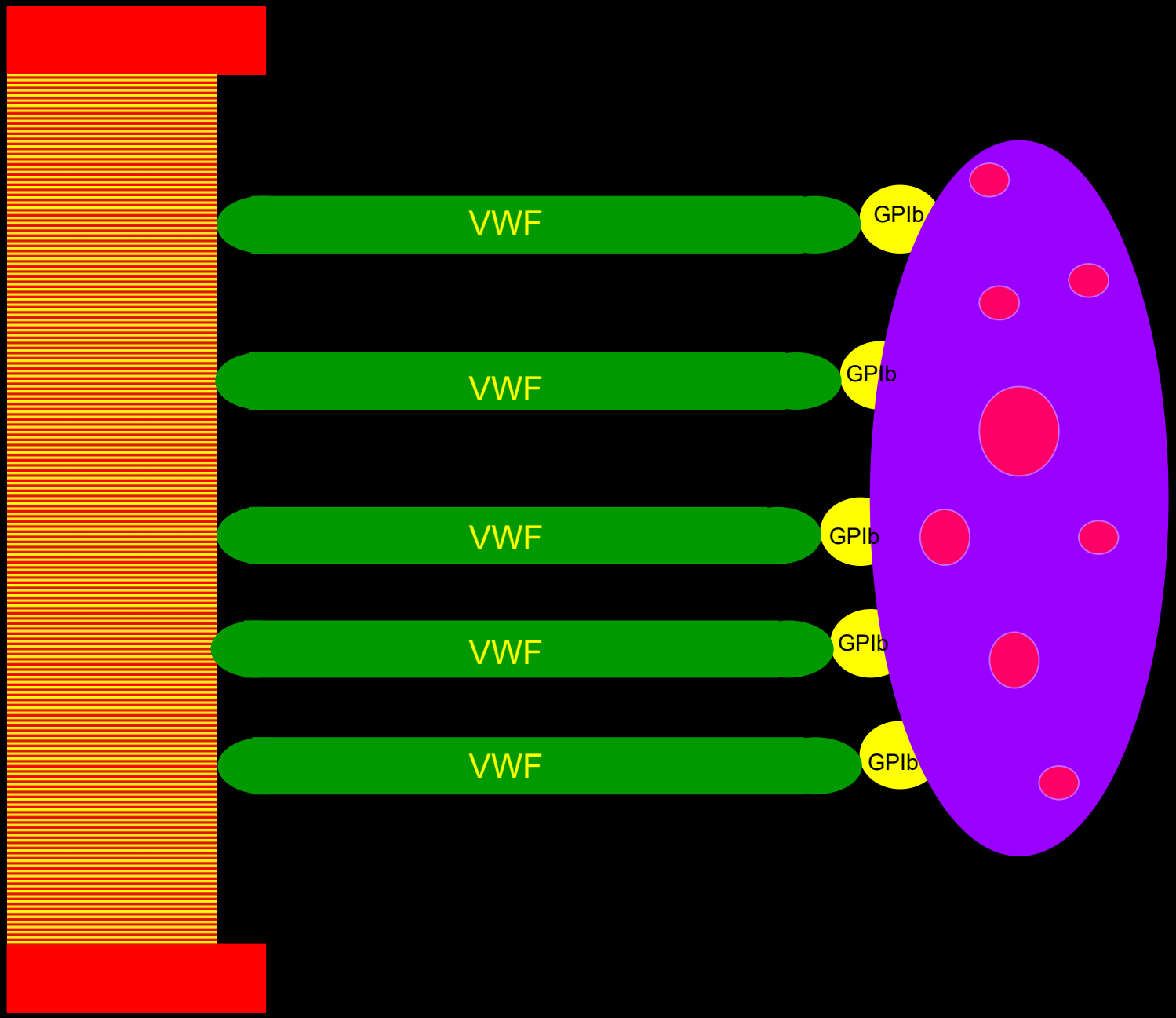
# Caplacizumab

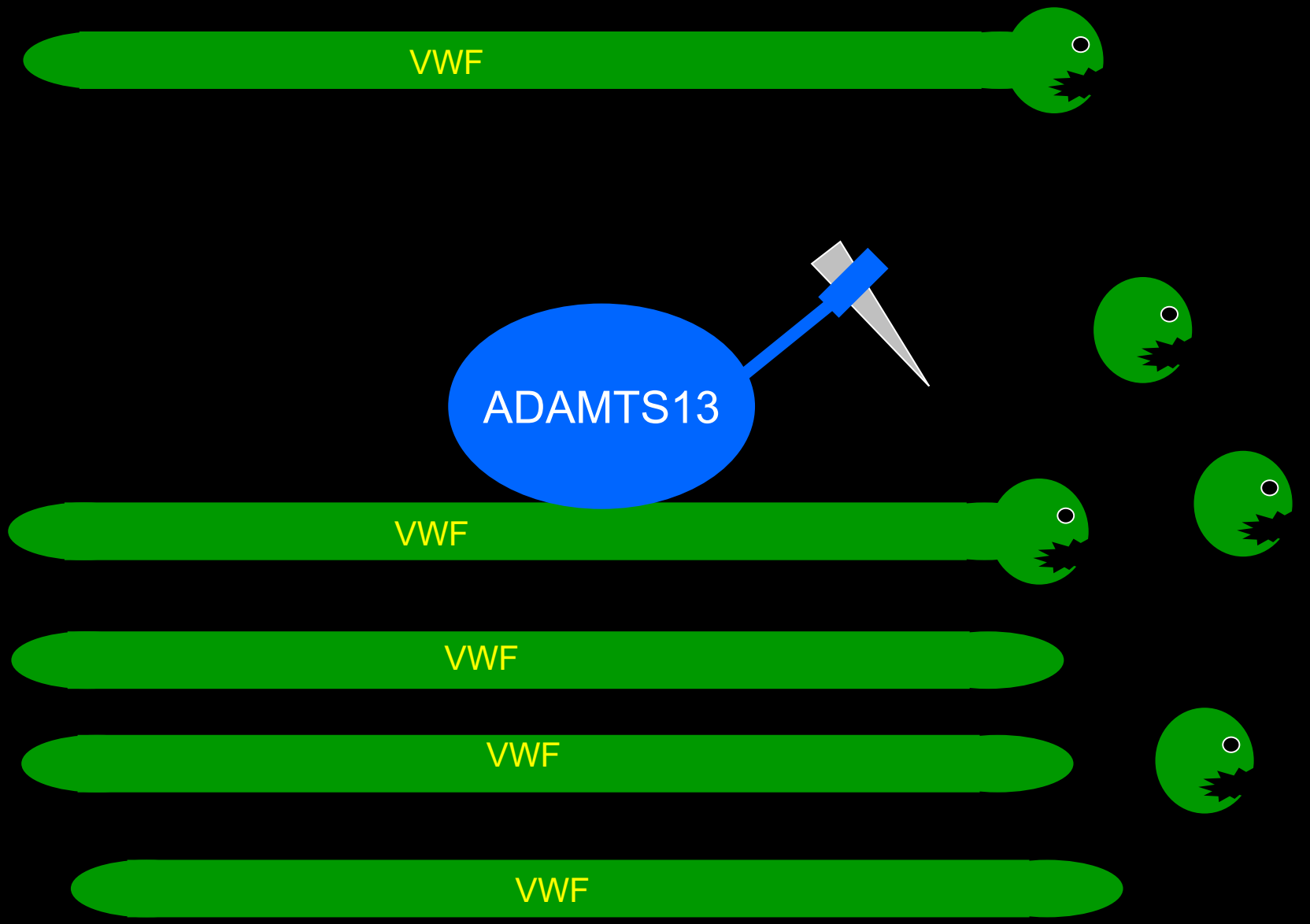
- Block VWF from binding platelets
- Decreases LOS and ICU stays
- Started at diagnosis and given until ADAMTS13 > 10%

# TTP: Role of Von Willebrand's Factor

- VWF mediates binding of platelets to endothelium
- VWF synthesized as giant molecule and is cleaved to a large molecule
- Metalloprotease is responsible for cleaving VWF
  - ADAMTS13

VWF
VWF
VWF
VWF
VWF
GPIb
GPIb
GPIb
GPIb
GPIb


VWF
GPIb
VWF
GPIb
VWF
GPIb
VWF
GPIb
VWF
GPIb


VWF
ADAMTS13
VWF
VWF
VWF
VWF

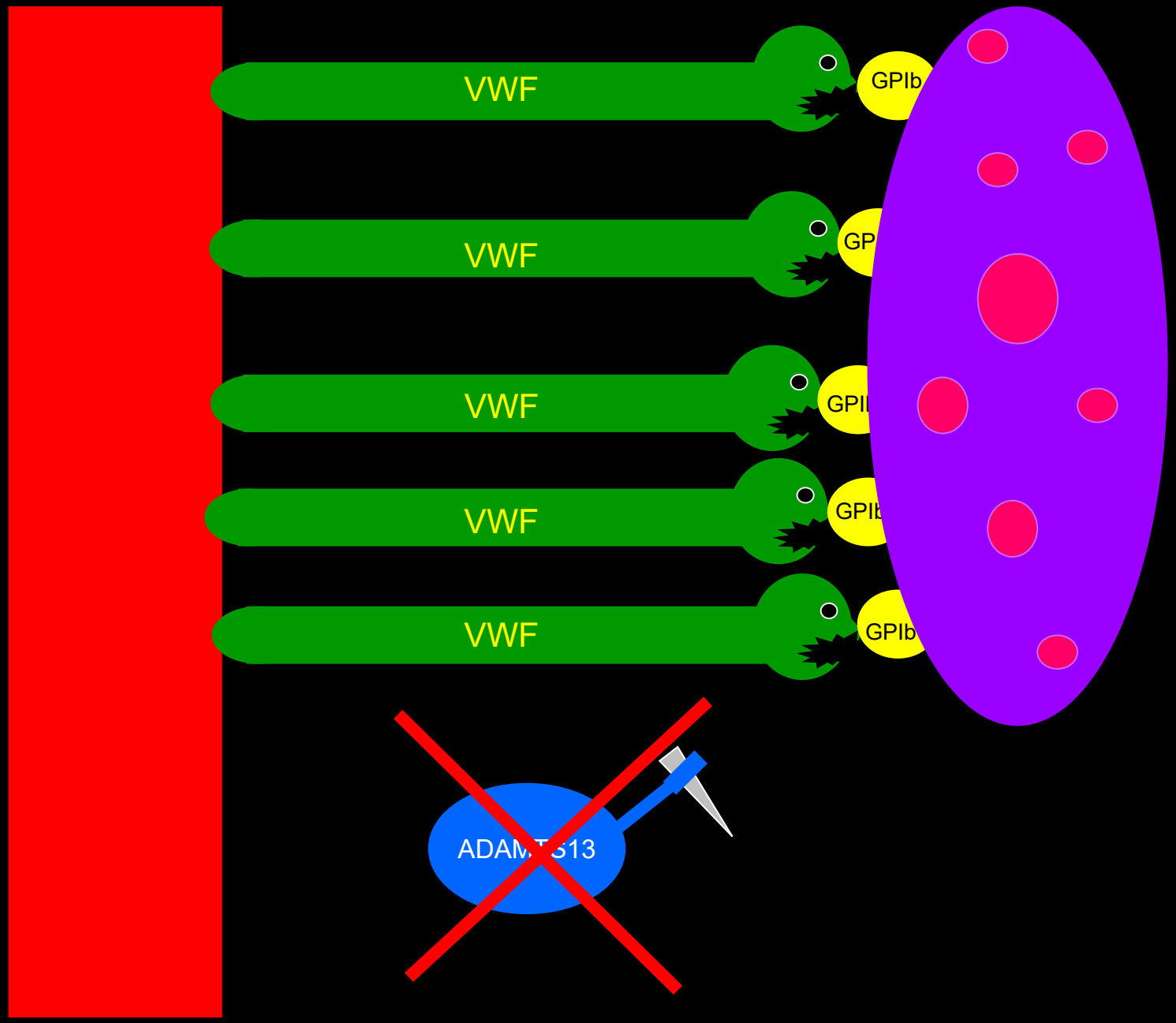
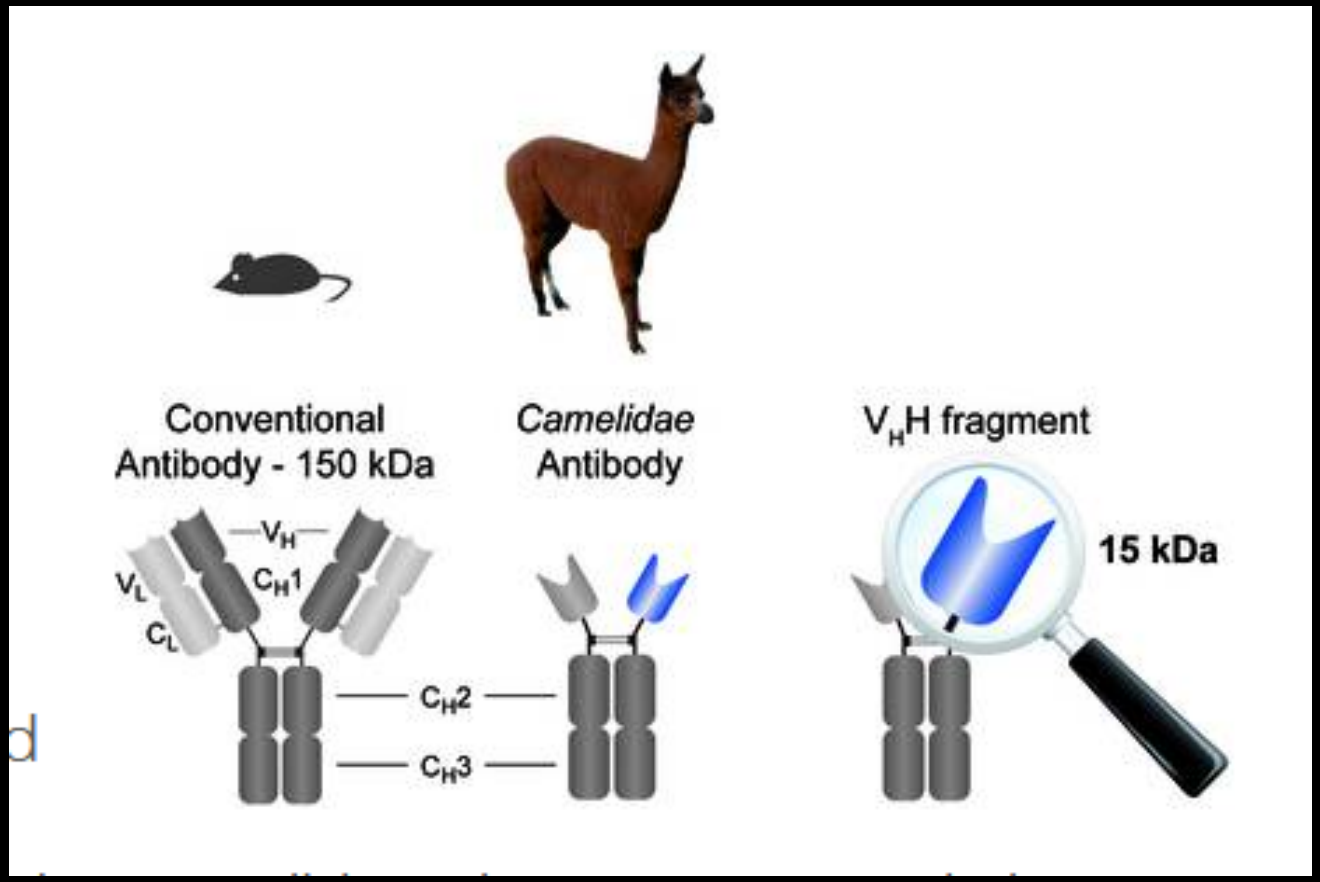
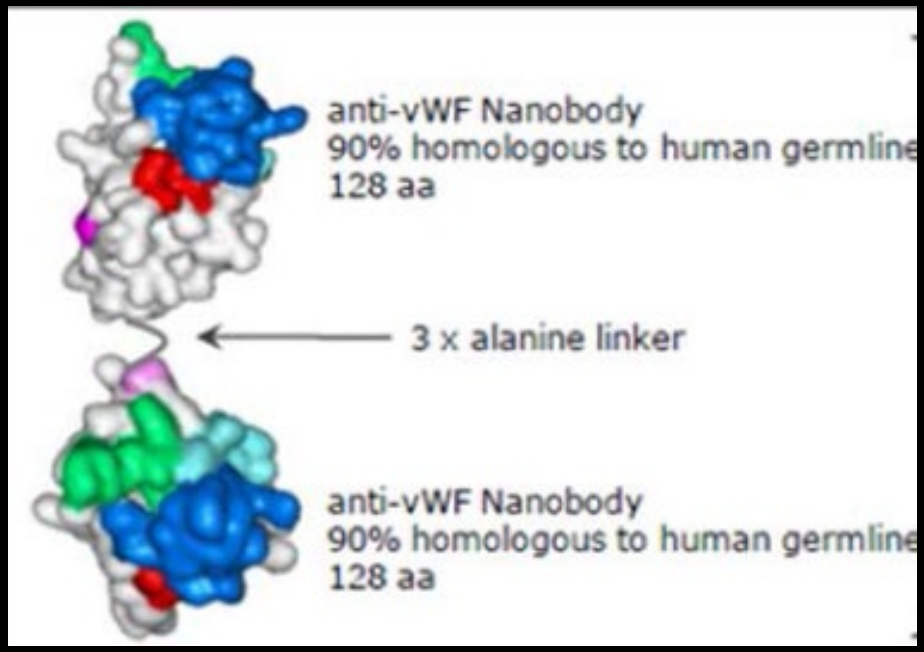
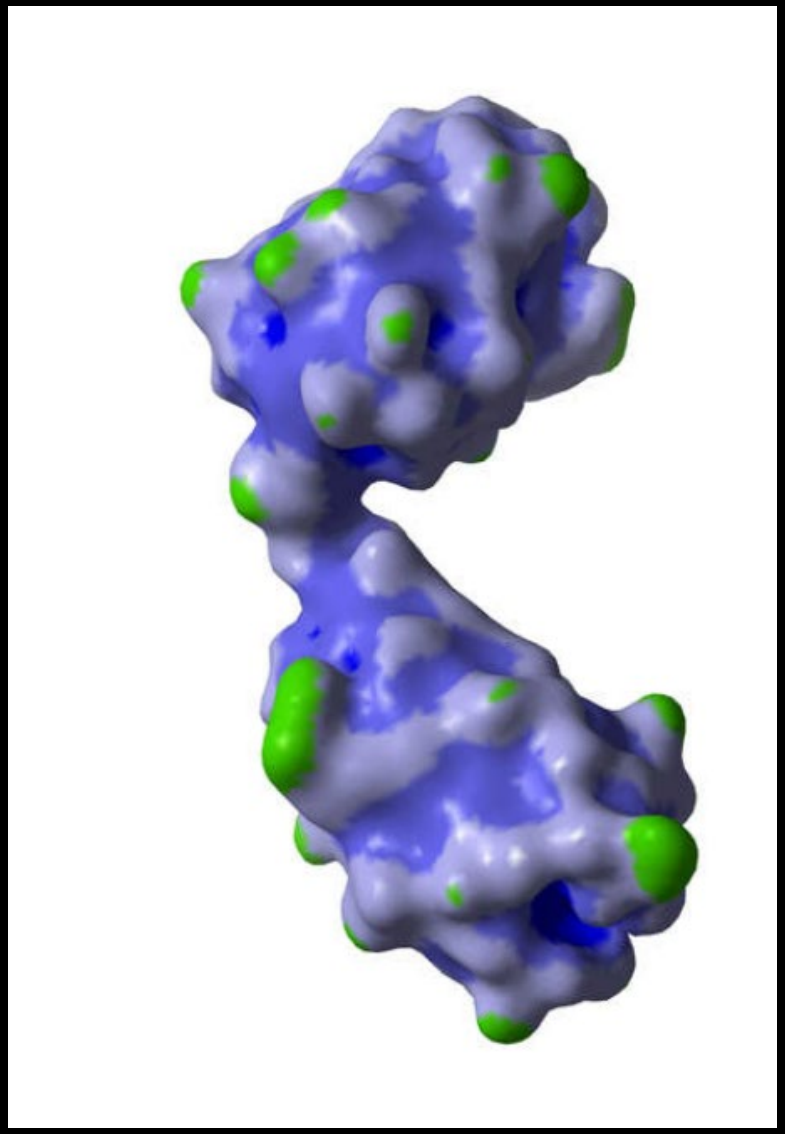
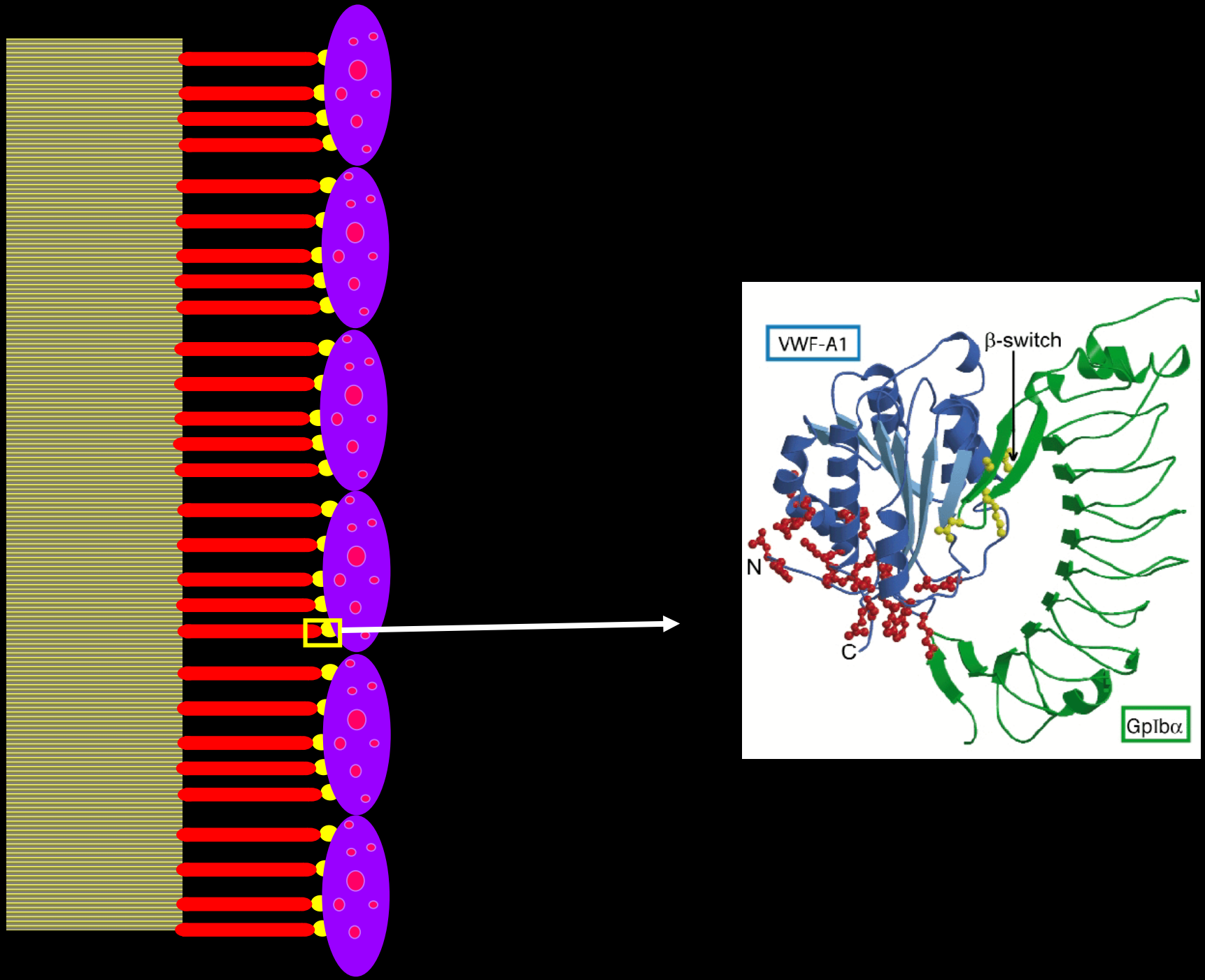

VWF
VWF
VWF
VWF
VWF
GPIb
GP
GPI
GPIb
GPIb
ADAMTS13


Photo Credit: Nathaniel Young

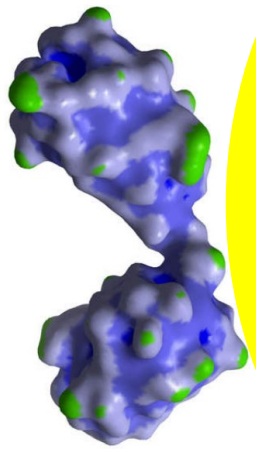

Conventional
Antibody - 150 kDa
Camelidae
Antibody
VHH fragment
15 kDa
VH
CH1
VL
CL
CH2
CH3


anti-vWF Nanobody
90% homologous to human germline
128 aa
3 x alanine linker
anti-vWF Nanobody
90% homologous to human germline
128 aa




VWF-A1
β-switch
N
C
GpIbα

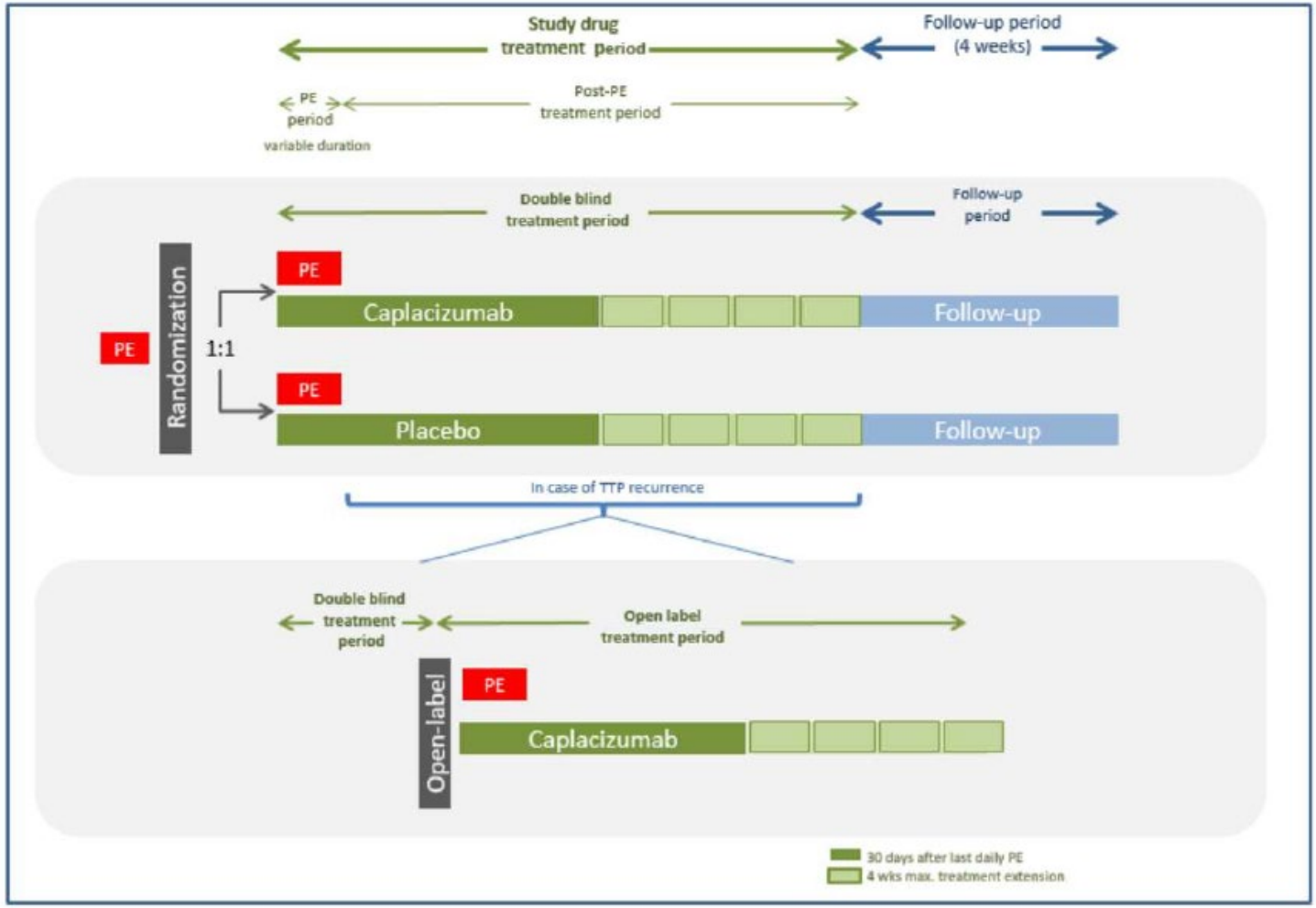
R
G
D



R
G
D

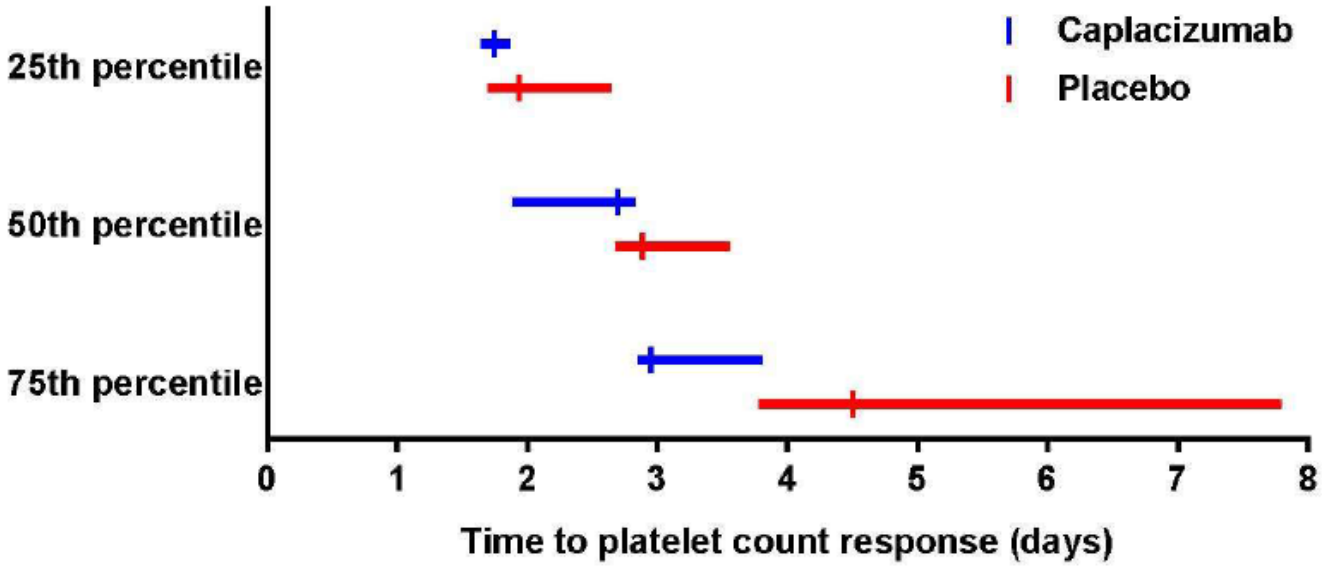
# HERCULES

- DBRCT N = 145
- Caplacizumab 10mg IV before plex then 10mg sq for 30 days
  - Could be extend by 28 days if ADAMTS13 < 10% at the end of 30 days
- Primary Endpoint Plts > 150,000
- NEJM 380:335-46, 2019


Study drug
treatment period
Follow-up period
(4 weeks)
PE
period
variable duration
Post-PE
treatment period
Double blind
treatment period
Follow-up
period
Randomization
PE
1:1
Caplacizumab
Follow-up
PE
Placebo
Follow-up
In case of TTP recurrence
Double blind
treatment
period
Open label
treatment period
Open-label
PE
Caplacizumab
30 days after last daily PE
4 wks max. treatment extension

# Results

- Cap resulted in greater plt response (1.55)
- Relapses (after treatment ended)
  - C: 9 (12%) P: 28 (38%)
- Days of Plex (mean/median)
  - C: 5.8/5 P: 9.4/7.0 (-3.6/2.0)
- Hospital days
  - C: 9.9/9.0 P: 14.4/12.0 (-4.5/3.0)
- ICU Days
  - C: 3.4/3.0 P:9.7/5.0 (6.4/2.0)


25th percentile
50th percentile
75th percentile
Caplacizumab
Placebo
0
1
2
3
4
5
6
7
8
Time to platelet count response (days)

# Other Endpoints

- Deaths C:1 P:3
- Serious Bleeding C:11% P:1%
  - One patient treated with VWF
- More minor bleeding
  - Gums/nose

# ADAMTS13

- 1 week after end of plex 57% still had ADAMTS13 < 10%
- 24% still low after trial ended
- Low levels predicted relapse

***Table 2. Integrated efficacy endpoints of the randomized subjects from the Phase II TITAN and Phase III HERCULES studies***

| Efficacy endpoints | Caplacizumab (N=108) | Placebo (N=112) |
|---|---|---|
| **Primary endpoint** | | |
| Time to platelet count response[a]: caplacizumab vs. placebo | | |
| Platelet count normalization ratio (95% CI) | 1.65 (1.24-2.20) | |
| P value | 0.0006 | |
| **Secondary endpoints** | | |
| *The proportion of subjects with at least one of the events below while on DB/SB study drug treatment – no. (%)* | 14 (13.0) | 53 (47.3) |
| TTP-related death | 0 | 4 (3.6) |
| major thromboembolic event[b] | 8 (7.4) | 14 (12.4) |
| TTP recurrence (exacerbation)[c] | 6 (5.6) | 39 (34.8) |
| P value | <0.0001 | |
| *TTP recurrence during the entire study period[c] – no. (%)* | 19 (17.6) | 39 (34.8) |
| P value | 0.0040 | |
| *Refractory to treatment[d] – no. (%)* | 0 | 7 (6.3) |
| P value | 0.0089 | |
| *Mortality rate – no. (%)* | | |
| During the DB/SB treatment period | 0 | 4 (3.6) |
| P value | 0.0477 | |
| During the entire study period | 1 (0.9)[e] | 5 (4.5)[f] |
| P value | 0.1086 | |
| *Number of days of Plasma Exchange during the DB/SB treatment period[g] – Mean (± Standard Deviation)* | 6.5 (4.5) | 10.4 (7.7) |

[a] TITAN: Response was defined by recovery of platelets count ≥150,000/µL. This response had to be confirmed at 48 hours after the initial

# Conclusion

- Caplacizumab raised the platelet count quicker, lower the rate of relapse, and saved resources

# Good

- Clearly reduced intensity of care
- Did reduce relapses
  - Higher incidence of late relapses
- Suggestive reduction of deaths/thrombosis

# Bad

- Daily therapy for 30-58(?) days
- Need for addition therapy if ADAMTS13 is still low
- Expensive
- Incremental gain
- Studies low use of rituximab

# Caplacizumab

- We use
  - Severe disease (neuro changes)
  - Refractory cases

# Other Therapies

- IVIG: not effective
- Vincristine: classic drug for resistance disease
  - 2 mg day 1, 4, 7, 10
- Rituximab – lessens relapses
  - + Antibodies

# Pre-emptive Therapy

- Check ADAMTS13 q3-6m in remission
- If < 10% - rituximab

# Work-Up of TM

- Pre-treatment
  - ADAMTS13 levels and inhibitors
  - C3 and C4
- Consider congenital TTP
  - Very low ADAMTS13
  - No inhibitor
- Consider aHUS
  - ADAMTS13 normal
  - Family history of aHUS
  - Progressive disease – esp renal

# The Nightmare Call

- “I have a pregnant patient who I think has TTP”

# DDx

- Gestational thrombocytopenia
- Immune thrombocytopenia
- Microangiopathic hemolytic anemias
- HELLP syndrome
- Other bad pregnancy things
- Hypersplenism

# Pregnancy Thrombocytopenia

- Very common
  - 1-2% of pregnancy
- Drop in platelet count normal
  - Increase M-CSF
  - Increase platelet turn-over

# Gestational Thrombocytopenia

- Most common
- Counts slowly fall during pregnancy
- Nadir 50,-70,000/ul
- No harm to child or mom
- Normal counts outside of pregnancy

# Immune Thrombocytopenia

- Relativity common
- Severe thrombocytopenia 1st trimester
- Can be exacerbation of ITP or *de novo*
- Mother presents with mucocutaneous bleeding
- Small risk child can have low counts due to passage of antibody

# ITP: Diagnosis

- Clinical diagnosis!!!
- No other blood abnormalities
  - Review blood smear
- No suspect drugs
- Patient otherwise healthy
- No value in antibody test
- Bone marrow only for uncertain cases

# Microangiopathic Hemolytic Anemias

- TTP most common in 2nd trimester
- Thrombocytopenia + hemolysis + end organ damage
- Plasmapheresis is treatment of choice
  - Can control disease throughout pregnancy
- Post-partum HUS
  - Devastating syndrome
    - ~ 100% renal failure untreated

# Pregnancy TTP

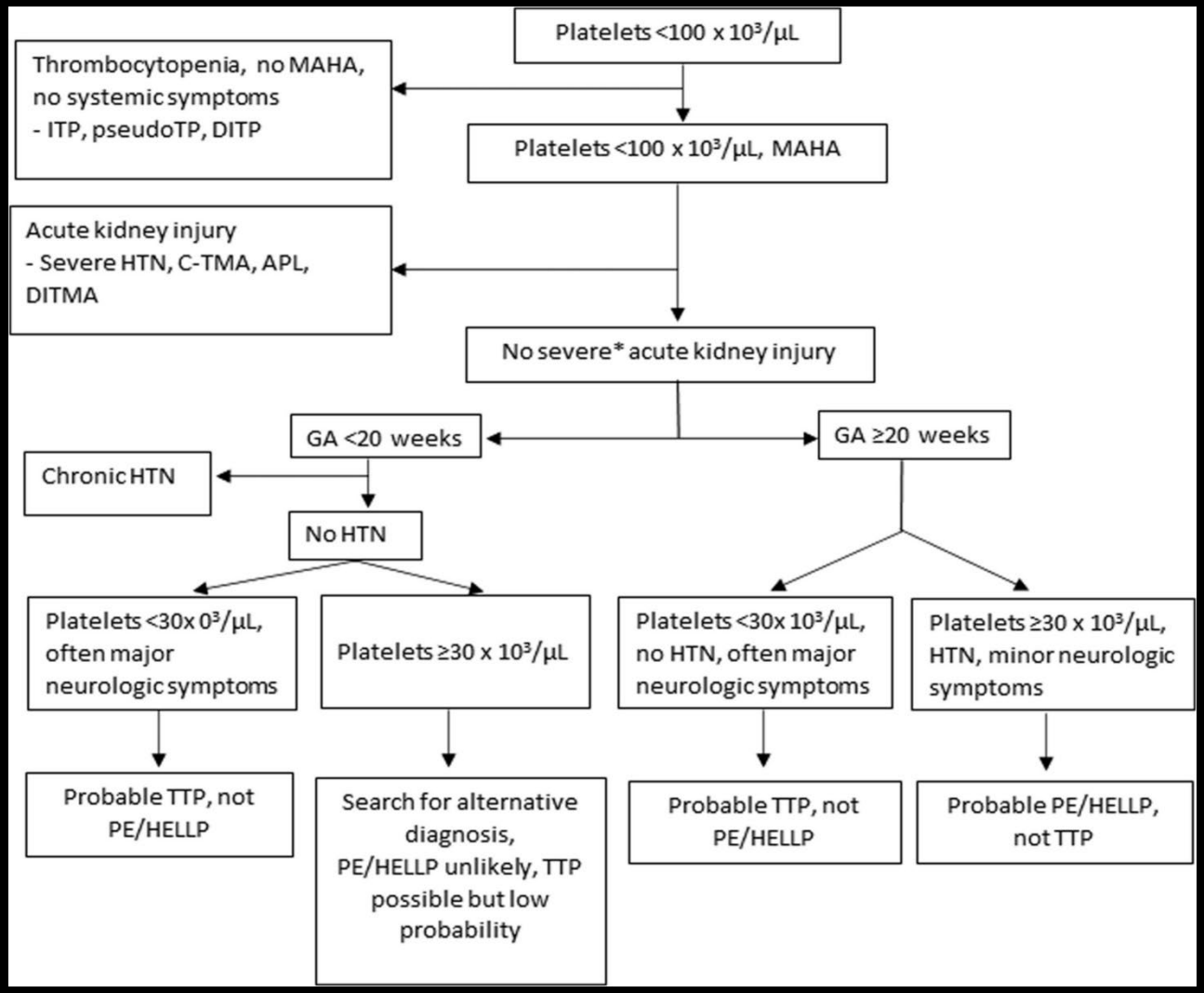
- Tx: Plasma exchange daily and then taper
- May need to do throughout pregnancy
- Risk of recurrence with next pregnancy is ~30%
- Can be presentation of congenital TTP

# HELLP syndrome

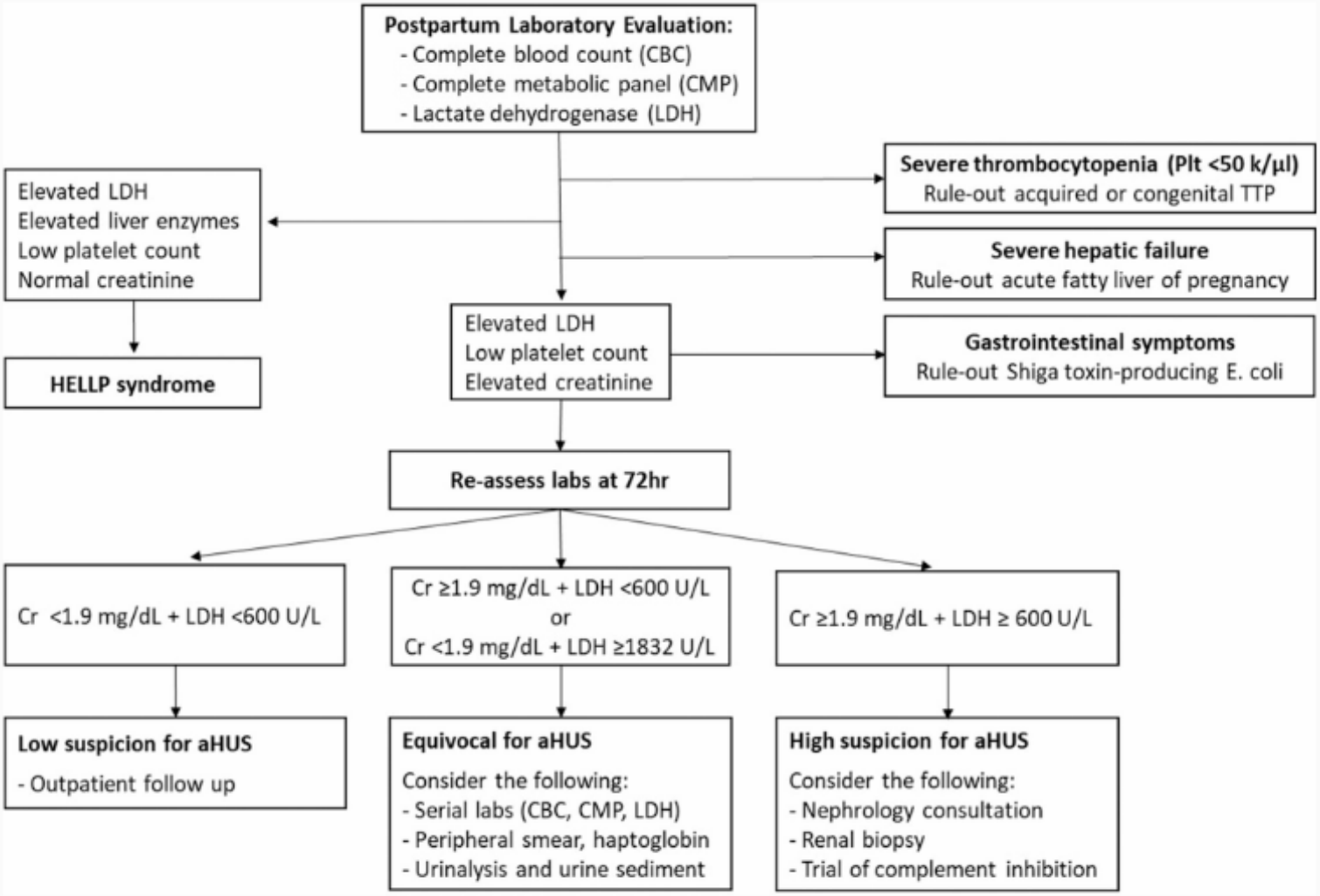
- Usual late in pregnancy
- Early HELLP seen with APLA syndrome
- Requires ending of pregnancy

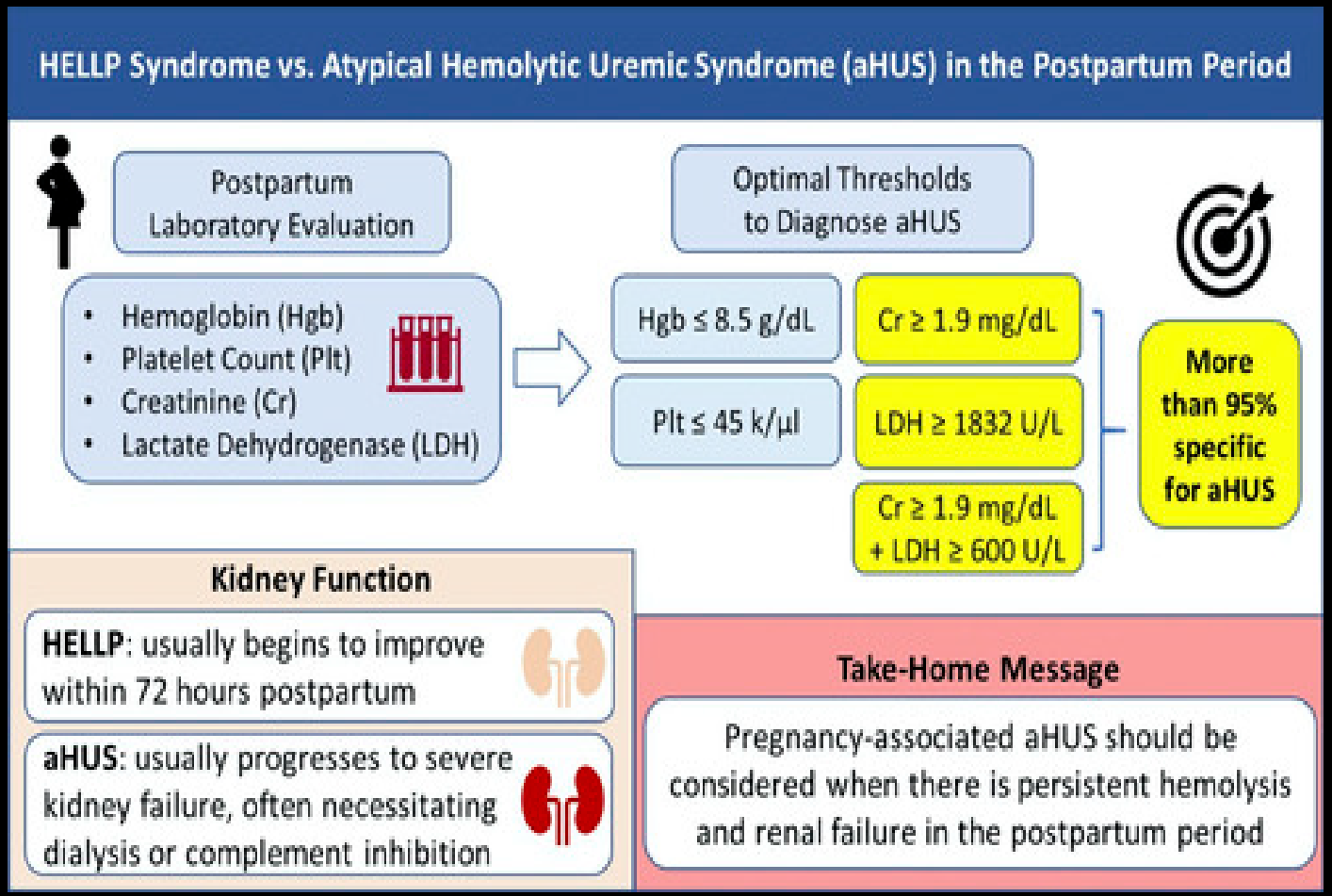
# How to Differentiate

- HELLP can have renal disease and schistocytes
- HELPP can persist post-partum
- Can see liver involvement in TTP and rarely aHUS
- All can have HTN




American Journal of Hematology, First published: 23 August 2021, DOI: (10.1002/ajh.26328)


Postpartum Laboratory Evaluation:
- Complete blood count (CBC)
- Complete metabolic panel (CMP)
- Lactate dehydrogenase (LDH)
Severe thrombocytopenia (Plt <50 k/µl)
Rule-out acquired or congenital TTP
Elevated LDH
Elevated liver enzymes
Low platelet count
Normal creatinine
Severe hepatic failure
Rule-out acute fatty liver of pregnancy
Elevated LDH
Low platelet count
Elevated creatinine
Gastrointestinal symptoms
Rule-out Shiga toxin-producing E. coli
HELLP syndrome
Re-assess labs at 72hr
Cr <1.9 mg/dL + LDH <600 U/L
Cr ≥1.9 mg/dL + LDH <600 U/L
or
Cr <1.9 mg/dL + LDH ≥1832 U/L
Cr ≥1.9 mg/dL + LDH ≥ 600 U/L
Low suspicion for aHUS
- Outpatient follow up
Equivocal for aHUS
Consider the following:
- Serial labs (CBC, CMP, LDH)
- Peripheral smear, haptoglobin
- Urinalysis and urine sediment
High suspicion for aHUS
Consider the following:
- Nephrology consultation
- Renal biopsy
- Trial of complement inhibition




Richard M. Burwick. Hypertension. Differentiating Hemolysis, Elevated Liver Enzymes, and Low Platelet Count Syndrome and Atypical Hemolytic Uremic Syndrome in the Postpartum Period, Volume: 78, Issue: 3, Pages: 760-768, DOI: (10.1161/HYPERTENSIONAHA.121.17311)

# Talk

- Abnormal MRI marrow
  - Rare to be an issue
- TTP – still vexing