Oncologic Emergencies

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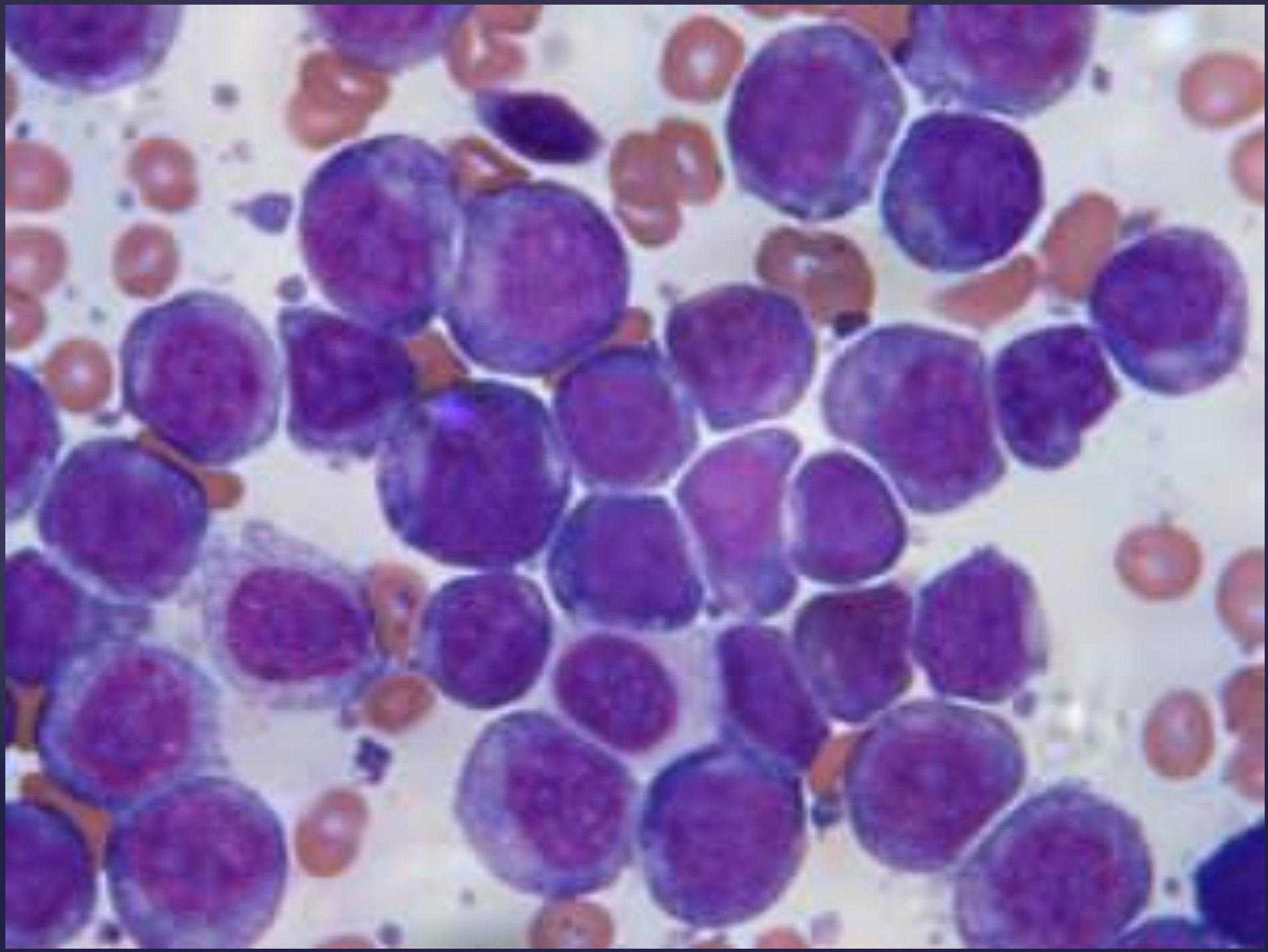
What constitutes an oncologic emergency?

- Complications arising from
  - Cancer
  - Paraneoplastic syndrome
  - Treatment of cancer

- Requires immediate attention and reversal

Outline

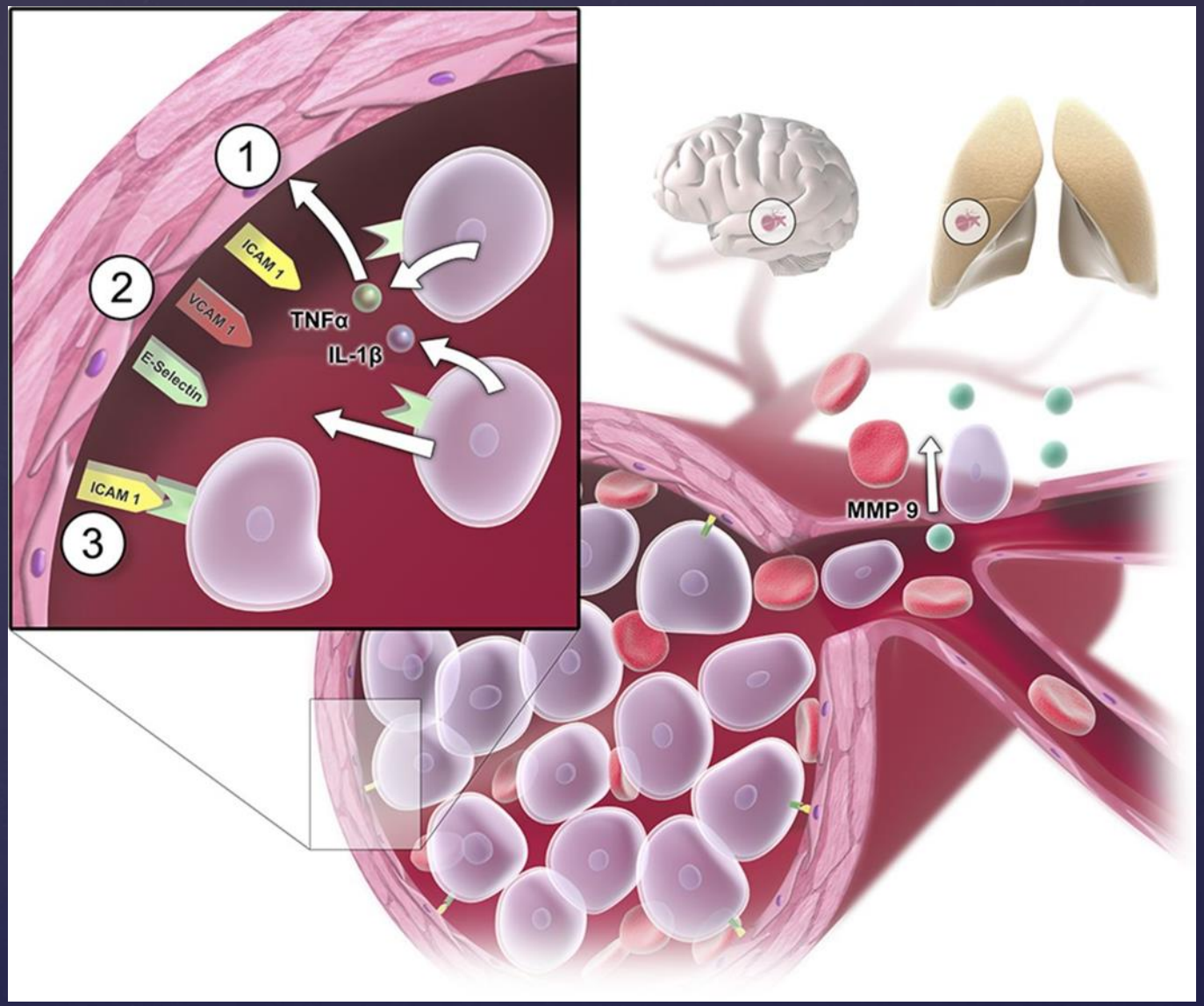
- Hyperleukocytosis
- Tumor lysis syndrome
- Disseminated intravascular coagulation
- Hypercalcemia
- Thrombotic thrombocytopenic purpura/HUS
- Hyperviscosity
- Spinal cord compression
- SVC Syndrome



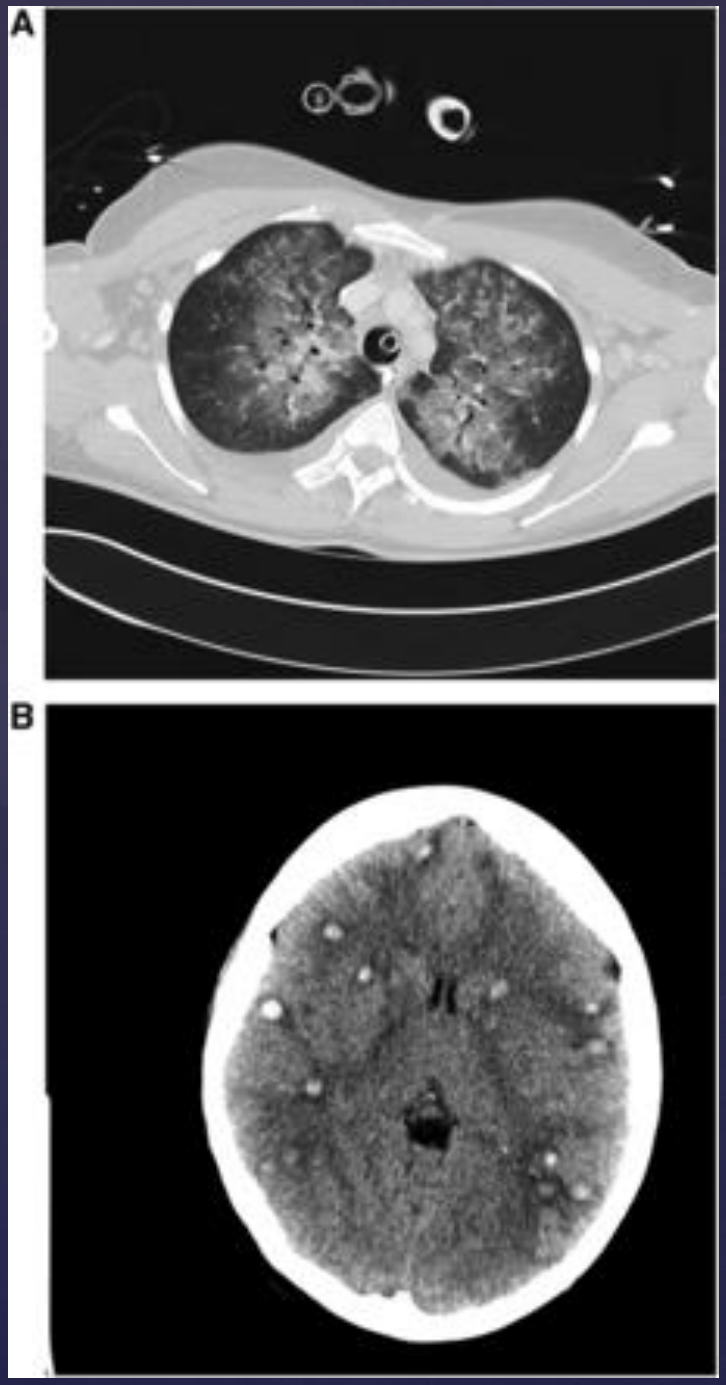
Hyperleukocytosis

- 5-20% of adults dx'd with AML
- 3 main complications of HL include:
  - Leukostasis
  - DIC
  - Tumor lysis syndrome
- Early mortality increased in AML patients with HL
- Shorter overall survival

Pathogenetic mechanisms in leukostasis



Christoph Röllig, and Gerhard Ehninger Blood 2015;125:3246-3252


A
B

Clinical

- Unexplained fever
- Fatigue
- Weight loss
- Bone pain
- Bruising/Bleeding
- Gum hypertrophy
- Hepatosplenomegaly
- AMS
- Hypoxia

Lab

- Abnormal CBC – Leukocytosis or pancytopenia
- Coagulopathy/DIC
- High LDH
- Peripheral smear

Management of HL

- *Definitive treatment*
- Hydroxyurea 1-3 g PO q 6 hours
- Leukopheresis

Leukoreduction Apheresis

- Rapidly removes excess leukocytes by mechanical separation
- Single round of leukopheresis reduced WBC by 10-70%
- Debate:

  -Majority of leukemic burden in marrow

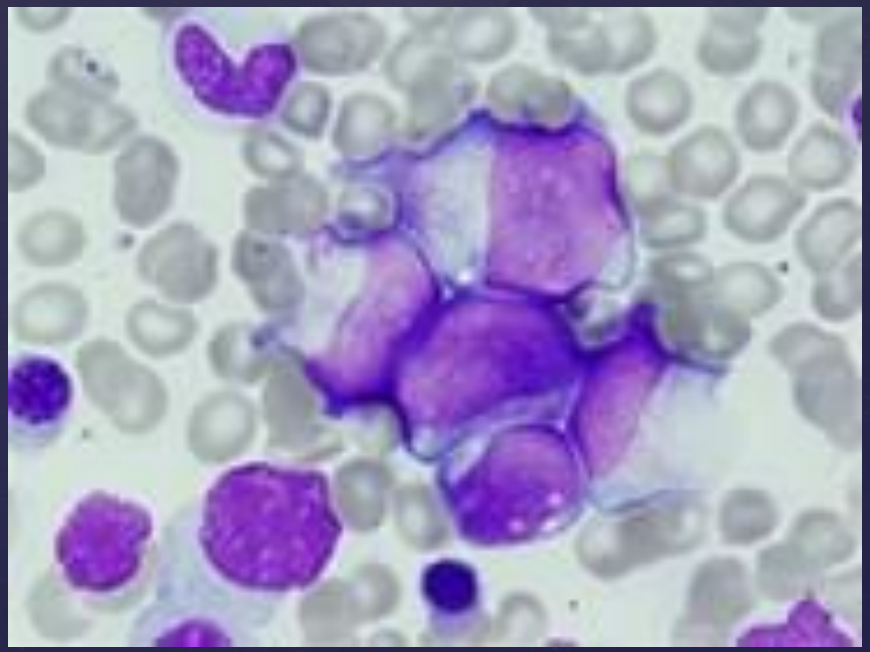
  -Beneficial clinical effect on early outcomes could not be shown consistently in clinical trials

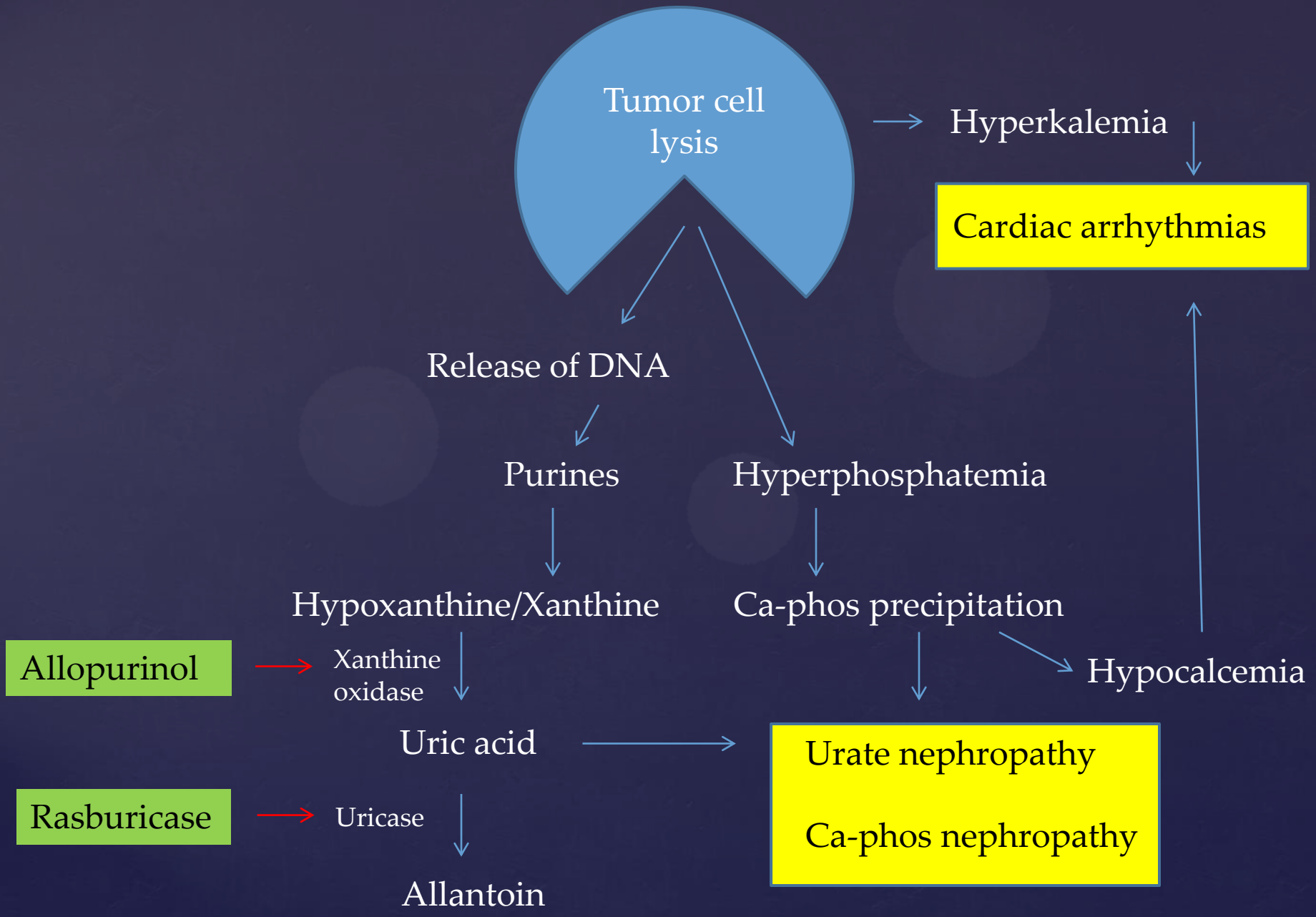
Leukoreduction Apheresis

- Contraindications
  - Hemodynamic instability
  - Coagulopathy
  - Cardiovascular comorbidites
- No evidence for clinical benefit in HL patients without leukostasis symptoms
- Given pros and cons, routine leukophoresis can not be routinely recommended.

Tumor Lysis Syndrome

- TLS is the most common oncologic emergency.
- Constellation of metabolic abnormalities resulting from either spontaneous or chemotherapy-induced tumor cell death




Tumor cell lysis
Hyperkalemia
Cardiac arrhythmias
Release of DNA
Purines
Hyperphosphatemia
Hypoxanthine/Xanthine
Ca-phos precipitation
Hypocalcemia
Allopurinol
Xanthine oxidase
Uric acid
Urate nephropathy
Ca-phos nephropathy
Rasburicase
Uricase
Allantoin

Risk factors for TLS

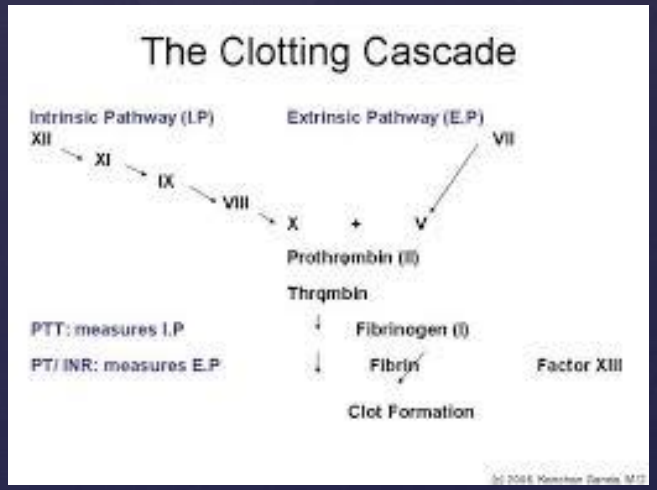
- Clinical
  - Large tumor burden with rapid cell turnover (acute leukemias, lymphomas)
  - Sensitivity of tumors to chemotherapy
  - Eldery/reduced GFR
  - Volume depletion
- Laboratory
  - Elevated LDH
  - Baseline hyperuricemia
  - Baseline renal dysfunction

Prophylaxis against TLS

- Aggressive hydration
- Prevent uric acid deposition into renal tubules
  - Urinary alkalinization
    - Target urine pH ≥ 7
  - Allopurinol
    - 300 mg daily to BID
  - Rasburicase

Disseminated Intravascular Coagulopathy

Loss of normal hemostatic control in response to sustained and systemic cell injury



Triggers of DIC

-Sepsis/severe infection

-Trauma/burn/heatstroke

-Malignancy
-Solid tumors
-Acute leukemia

-Obstetrical conditions

-Amniotic fluid embolism

-Abruptio placentae

-HELLP syndrome

-Vascular abnormalities

-Kasabach-Merrit syndrome

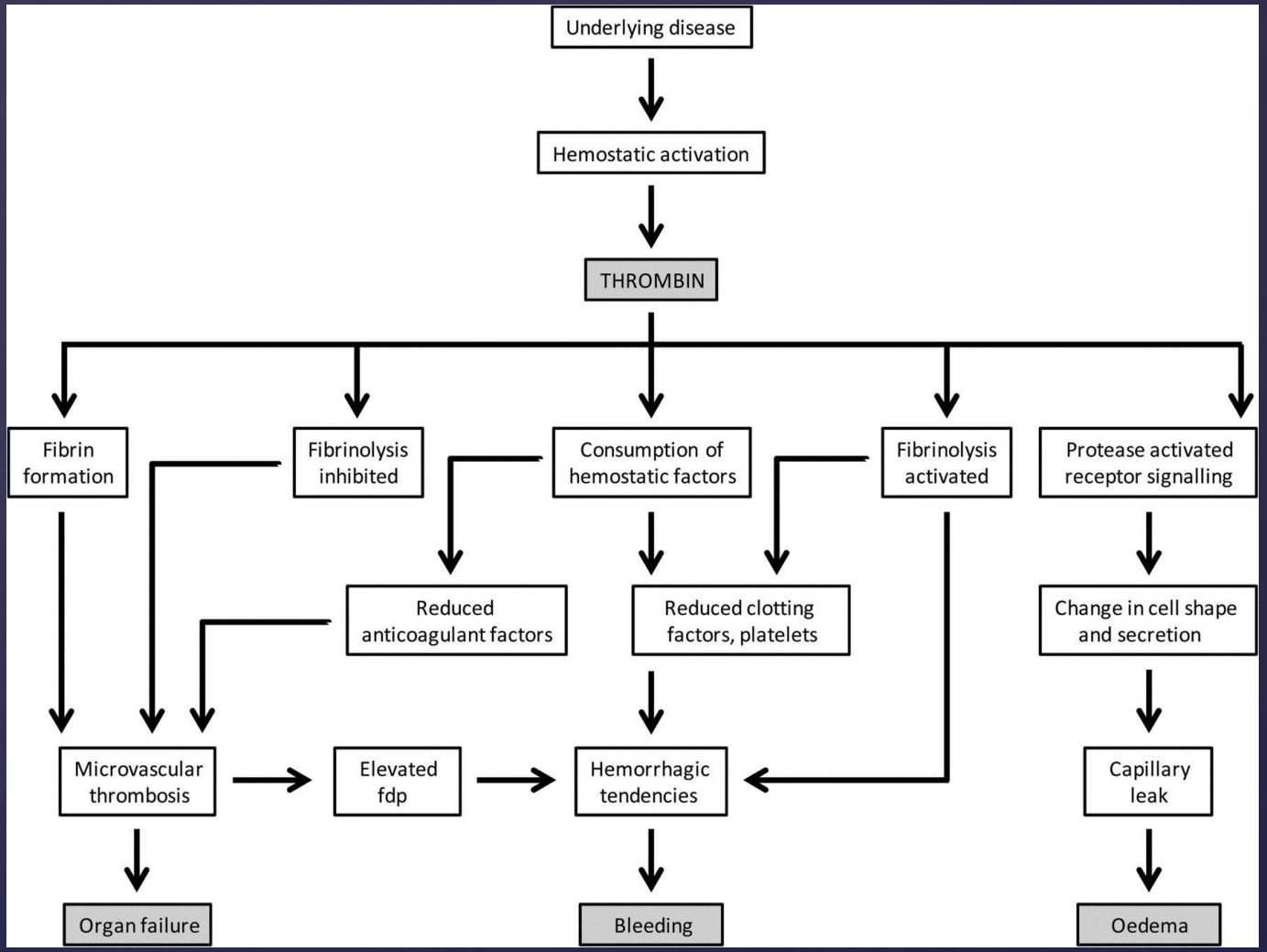
-Other vascular malformations

-Aortic aneurysms

-Severe allergic/toxic reactions

-Severe immunologic reactions (e.g., transfusion reaction)

Mechanisms in DIC



Cheng Hock Toh, and Yasir Alhamdi Hematology 2013;2013:286-291

Relevance of DIC

- Microvascular thrombosis
- Organ dysfunction
- Bleeding
- Increased mortality

Management of DIC

=

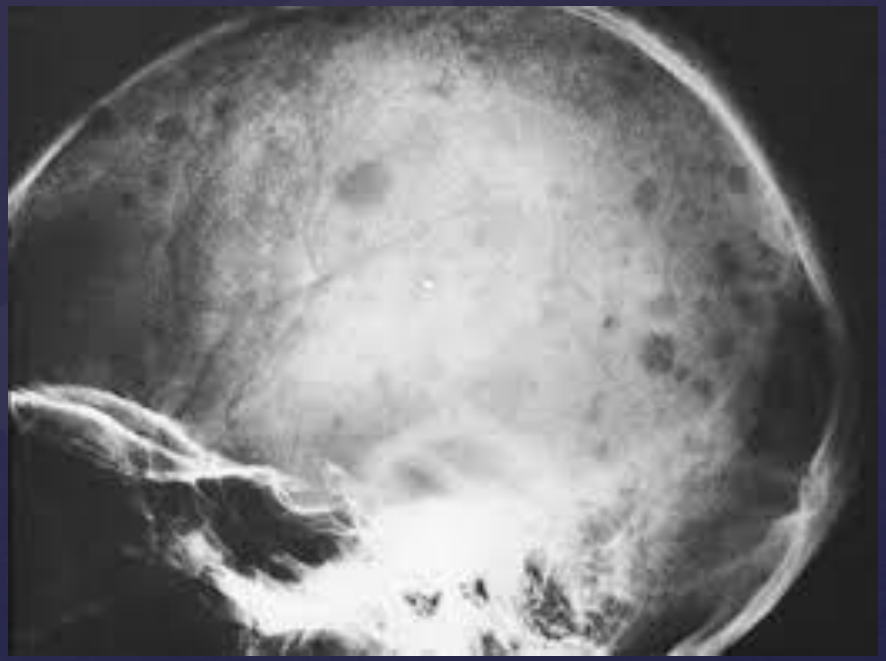
Treatment of underlying cause

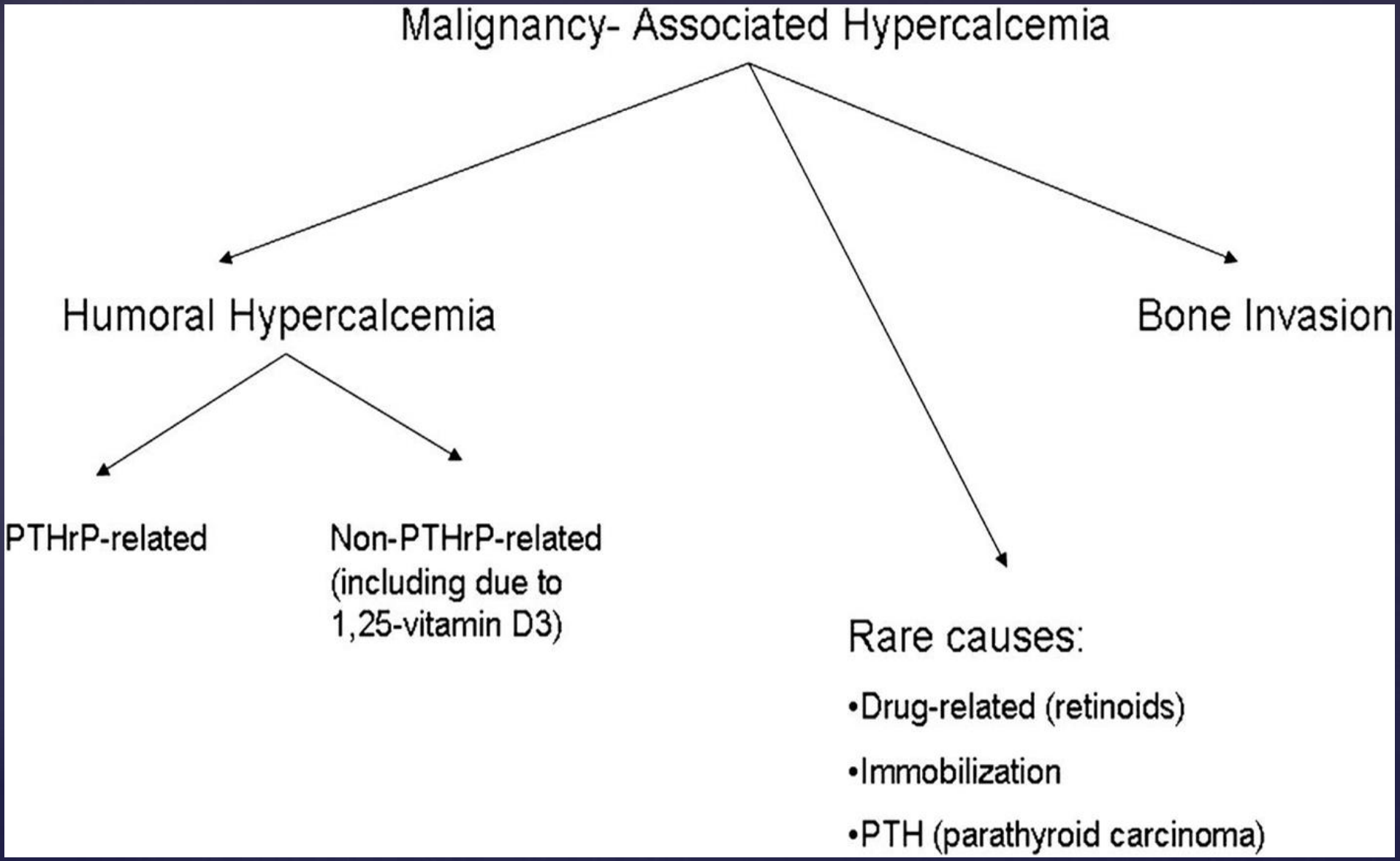
Management of DIC

- Blood product support
  - Platelets in the bleeding patient if $< 50 \times 10^9$/L
  - Fresh frozen plasma if bleeding and prolonged PT and PTT
  - Cryoprecipitate (2 pools) can be considered in patients with bleeding and fibrinogen levels less than 1.5 g/L
- Modulating profibrinolytic activity
  - Tranexamic acid
- Modulating thrombin generation
  - Heparin/LMWH
  - Antithrombin – controversial
  - APC – Prowess-SHOCK Trial showed no benefit

Hypercalcemia

- 20-30% of cancer patients
- Myeloma, lymphomas, cancers of prostate, lung, breast, and kidneys

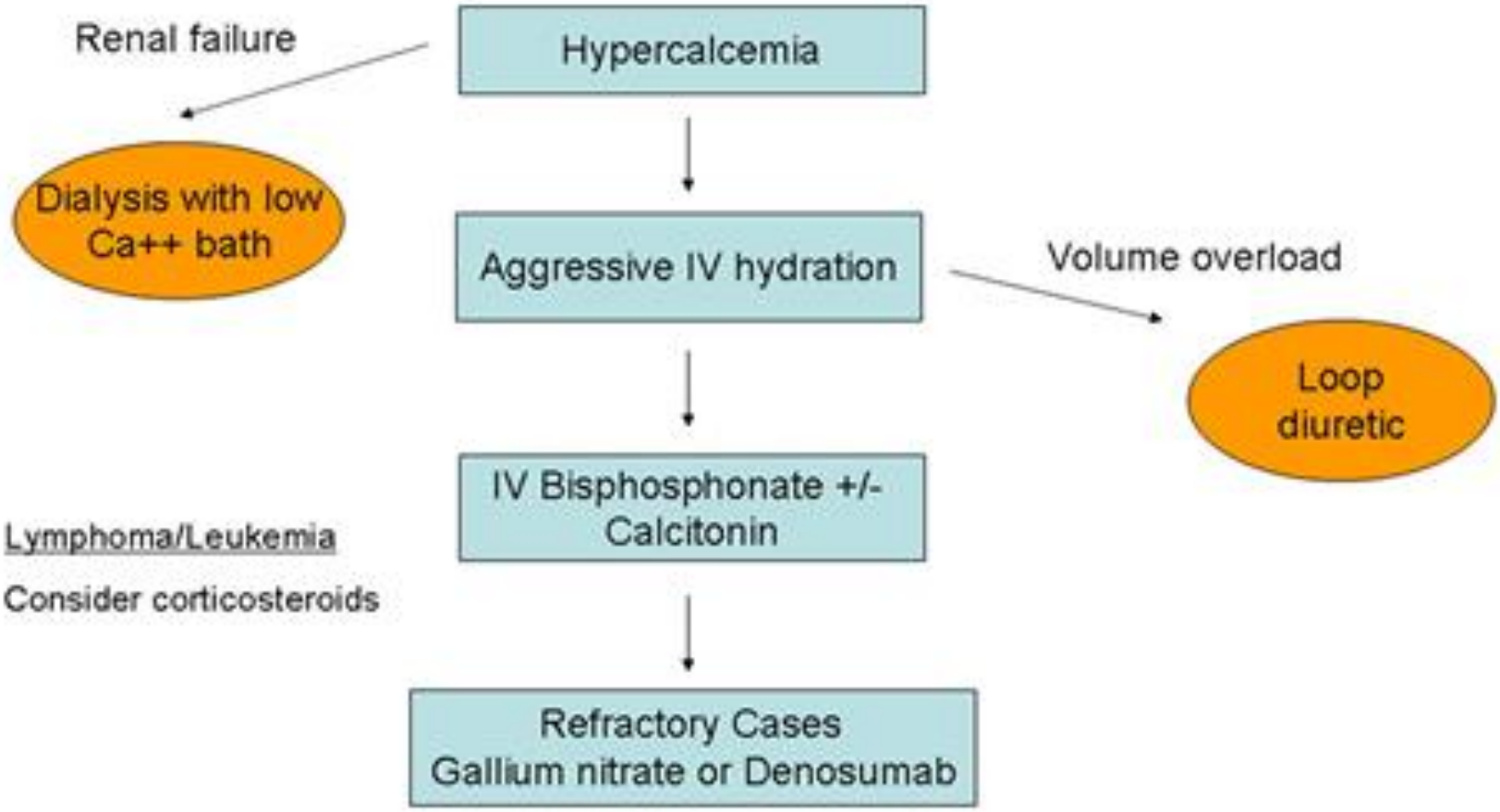



Malignancy- Associated Hypercalcemia
Humoral Hypercalcemia
Bone Invasion
PTHrP-related
Non-PTHrP-related
(including due to
1,25-vitamin D3)
Rare causes:
•Drug-related (retinoids)
•Immobilization
•PTH (parathyroid carcinoma)

Hypercalcemia: Symptoms

- N/V
- Constipation
- Decreased mental status
- Renal dysfunction

Treatment algorithm for malignancy-associated hypercalcemia.



Mitchell H. Rosner, and Alan C. Dalkin CJASN 2012;7:1722-1729

CJASN

Thrombotic Thrombocytopenic Purpura

- Characterized by microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombosis
- Mortality rate of TTP without treatment ~ 80-90%

Acquired TTP

- Usually occurs in older children and adults
- Secondary to IgG autoantibody against ADAMTS13
- May be idiopathic or associated with mitomycin C, cyclosporin, tacrolimus, quinine, ticlopidine, clopidogrel, TBI, allogeneic BMT, solid organ txpt, or pregnancy/postpartum state

- In the U.S., ~1000 new cases diagnosed per year
- Most patients range in age from 20-60
- Slight female predominance – 3:2
- Relapses occur in ~1/3 of those who achieve remissions.

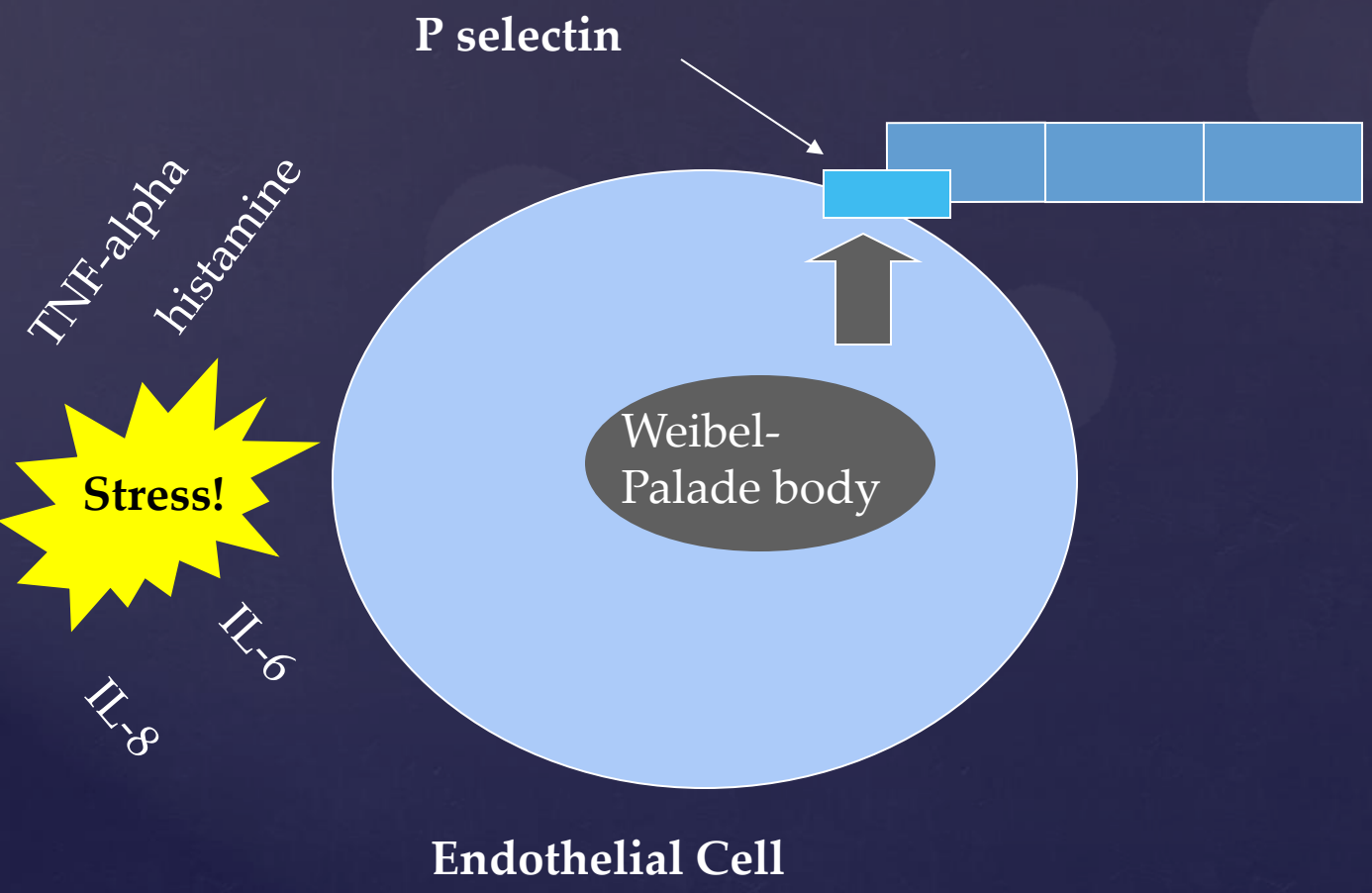
Pathophysiology of TTP

- vWF
- ADAMTS13
- Inhibitor of ADAMTS13

ADAMTS13

- "A disintegrin and metalloprotease with eight thrombospondin type 1 repeats"
- #13 a family of 19 distinct ADAMTS enzymes identified to date
- Encoded on chromosome 9q34
- Produced by the liver

Normal release of vWF into circulation



Sadler, et al. 2004. Hematology. 407-423.

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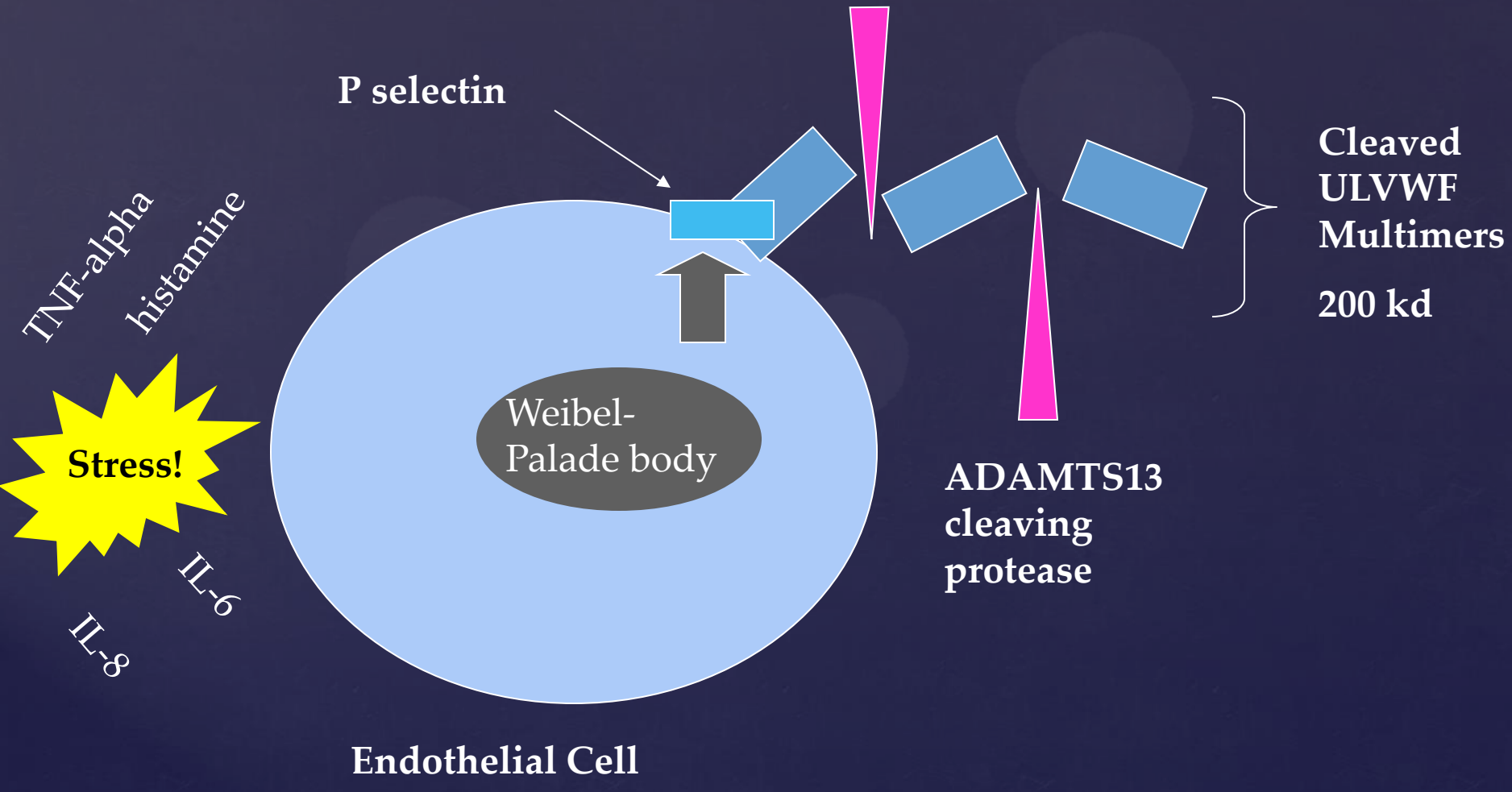

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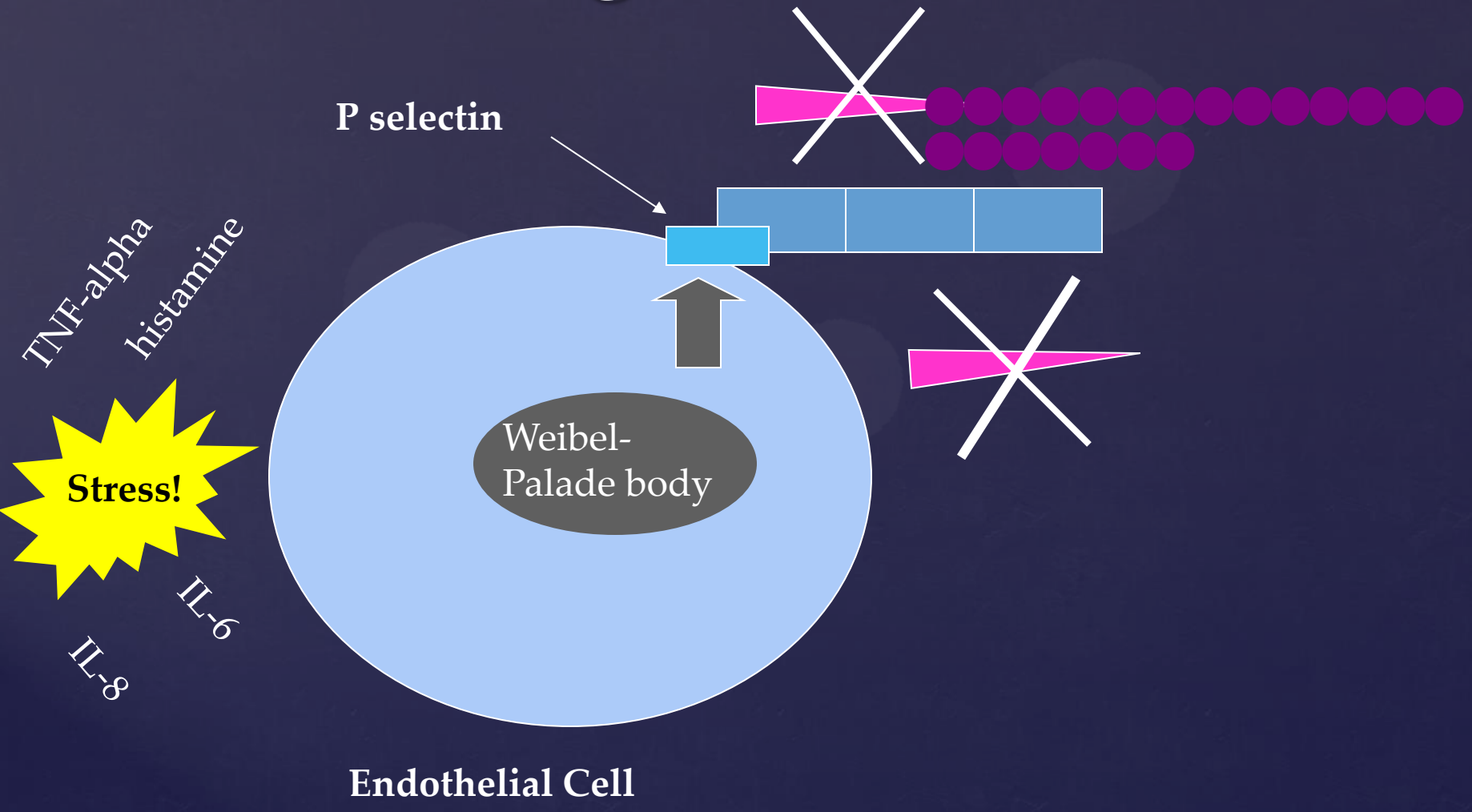
ADAMTS13 inhibitors: no cleavage of ULVWF



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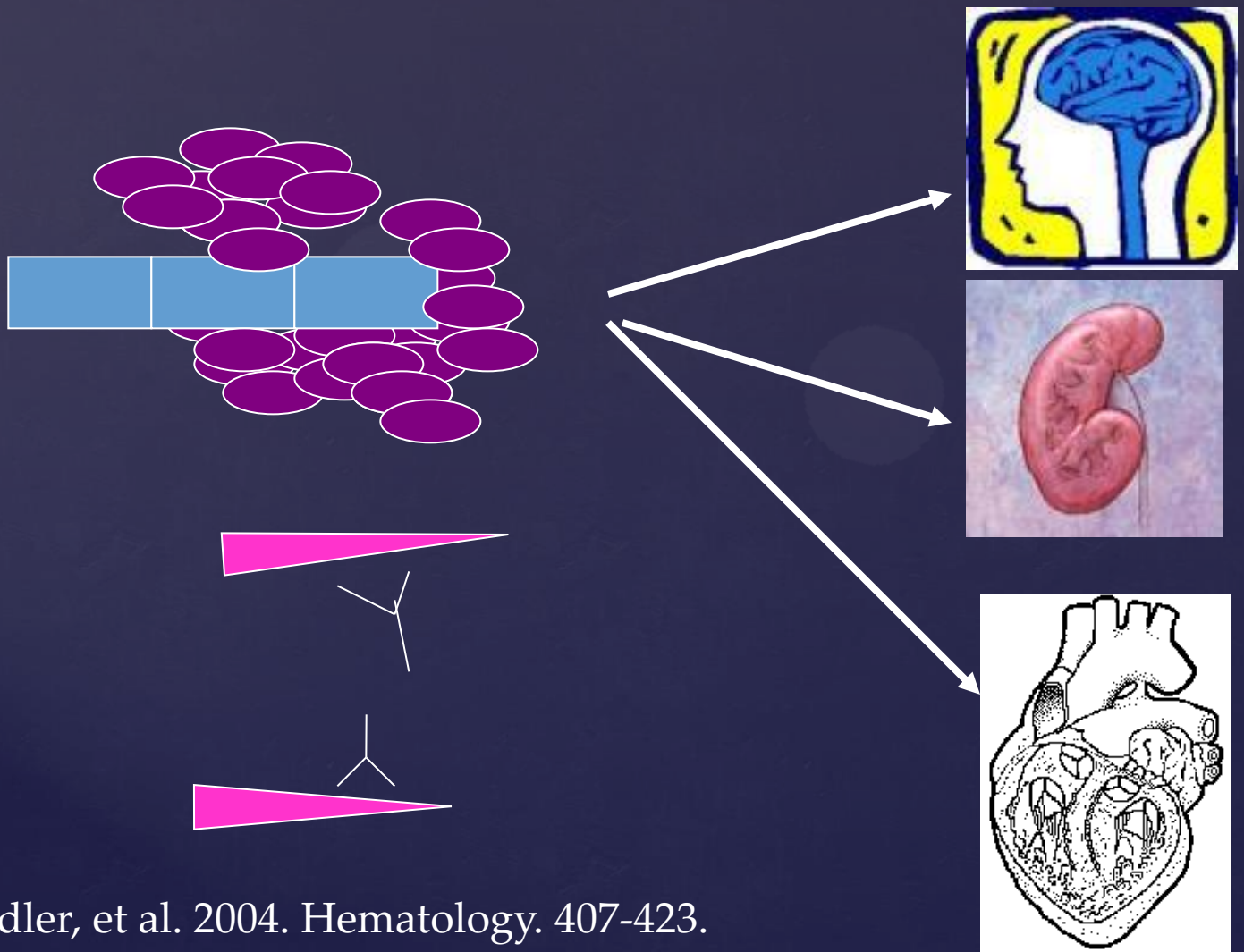


Sadler, et al. 2004. Hematology. 407-423.

Absence of ADAMTS13: ULvWF predominance

- ULvWF adheres to platelets and causes platelets to aggregate
- ULvWF has greater binding affinity to platelets than smaller vWF, possibly secondary to more effective exposure of gp1bα
- ULvWF may detach from endothelial cells in the presence of fluid shear stress/increasing torque generated by platelet adherence to ULvWF and embolize to downstream microvessels resulting in organ ischemia

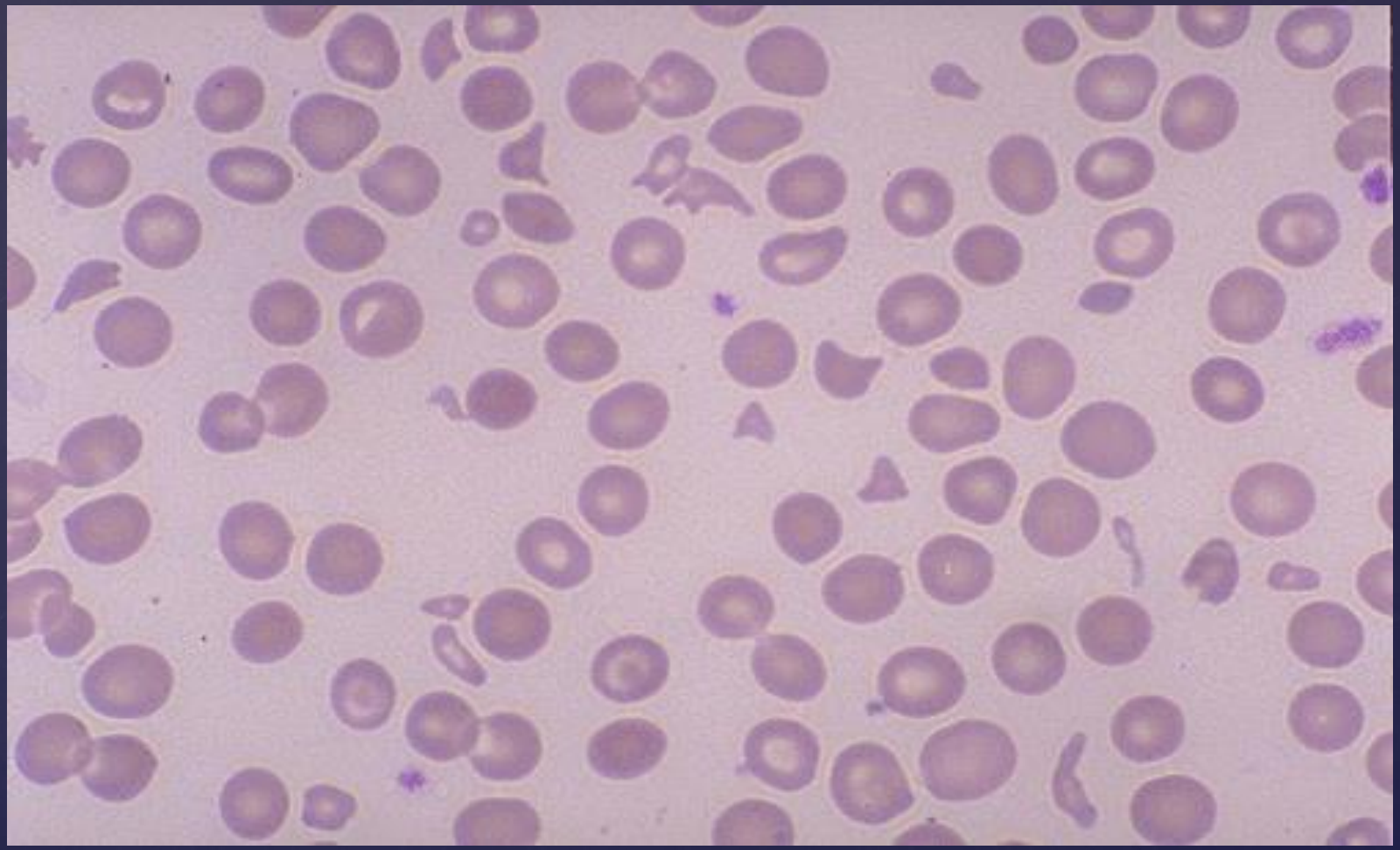
Classic TTP pentad

1. Neurologic abnormality
2. Renal failure
3. Thrombocytopenia
4. Microangiopathic hemolytic anemia (MAHA)
5. Fever

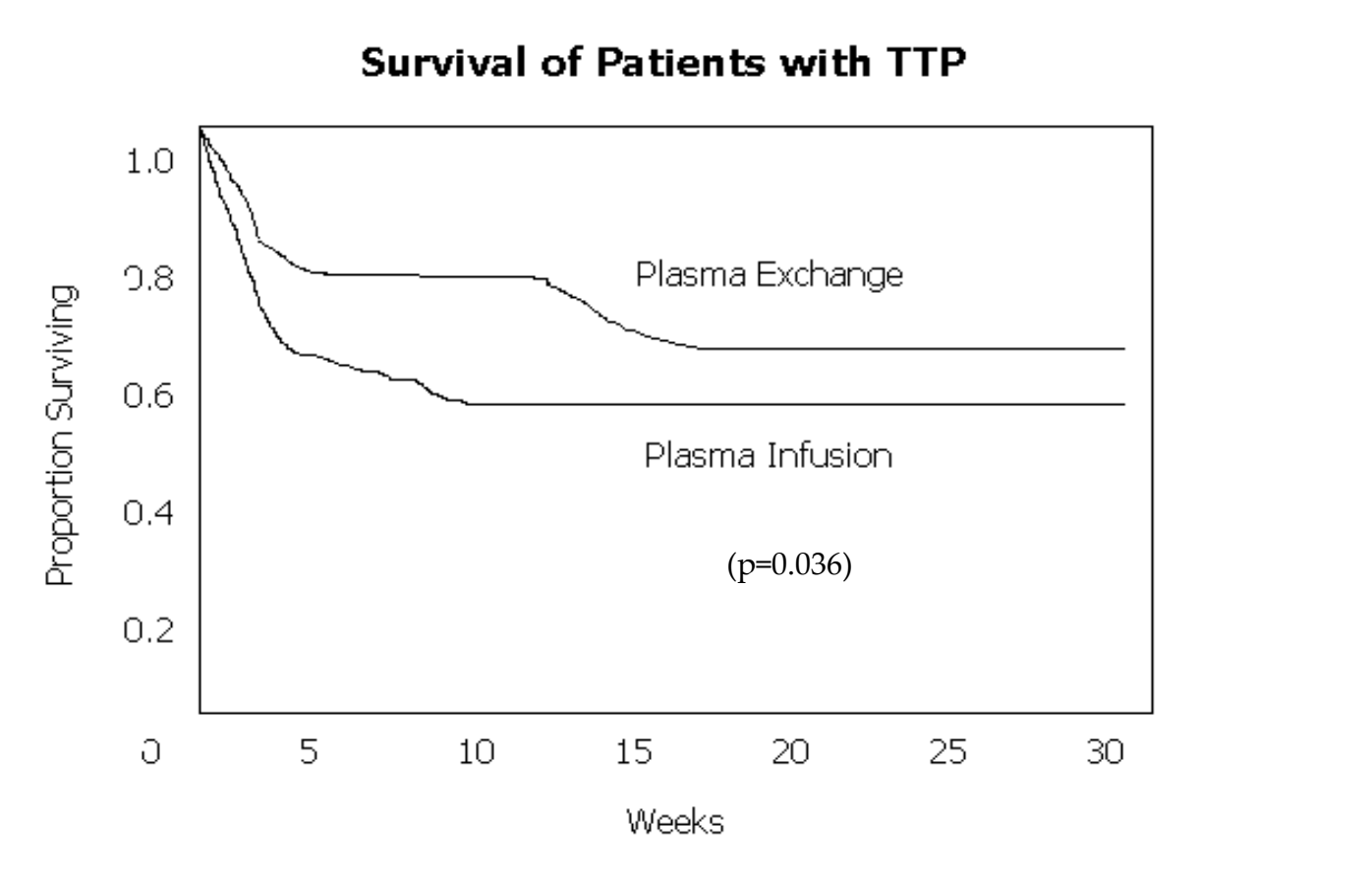
Amorosi et al. 1966. Thombotic thrombocytopenic purpura: report of 16 cases and review of the literature. Medicine (Baltimore). 45: 139-159.

Laboratory Findings

- Thrombocytopenia (often <20K)
- Increased LDH secondary to lysis and diffuse organ ischemia
- RBC fragmentation (e.g. schistocytes and helmet cells) due to passage of RBCs through microvessels that are partially occluded by plt aggregates



Comparison of plasma exchange with plasma infusion in the treatment of TTP



Rock et al. 1991. Comparison of plasma exchange with plasma infusion in the treatment of TTP. *NEJM*. 325 (6): 393-397.

Comparison of plasma exchange with plasma infusion in the treatment of TTP

Conclusions:

1. Plasma exchange is superior to plasma infusion in the treatment of TTP, both at the end of the first cycle of tx and after six months.
2. The significantly lower death rate when plasma is exchanged suggests a possible role for the removal of some plasma constituent in addition to the supply of fresh plasma.

Rock et al. 1991. Comparison of plasma exchange with plasma infusion in the treatment of TTP. *NEJM*. 325 (6): 393-397.

Plasma Exchange

- No defined schedule
- Performed on a daily basis until platelet count reaches ~150 (also monitor for normalization of Hb, LDH, and any clinical abnormalities at diagnosis), then taper
- If response to initial treatment is poor, may need intensification of plasma volume exchange (1.5 vs. 1.0 or bid treatment) or initiation of immunosuppressive agents

Glucocorticoids

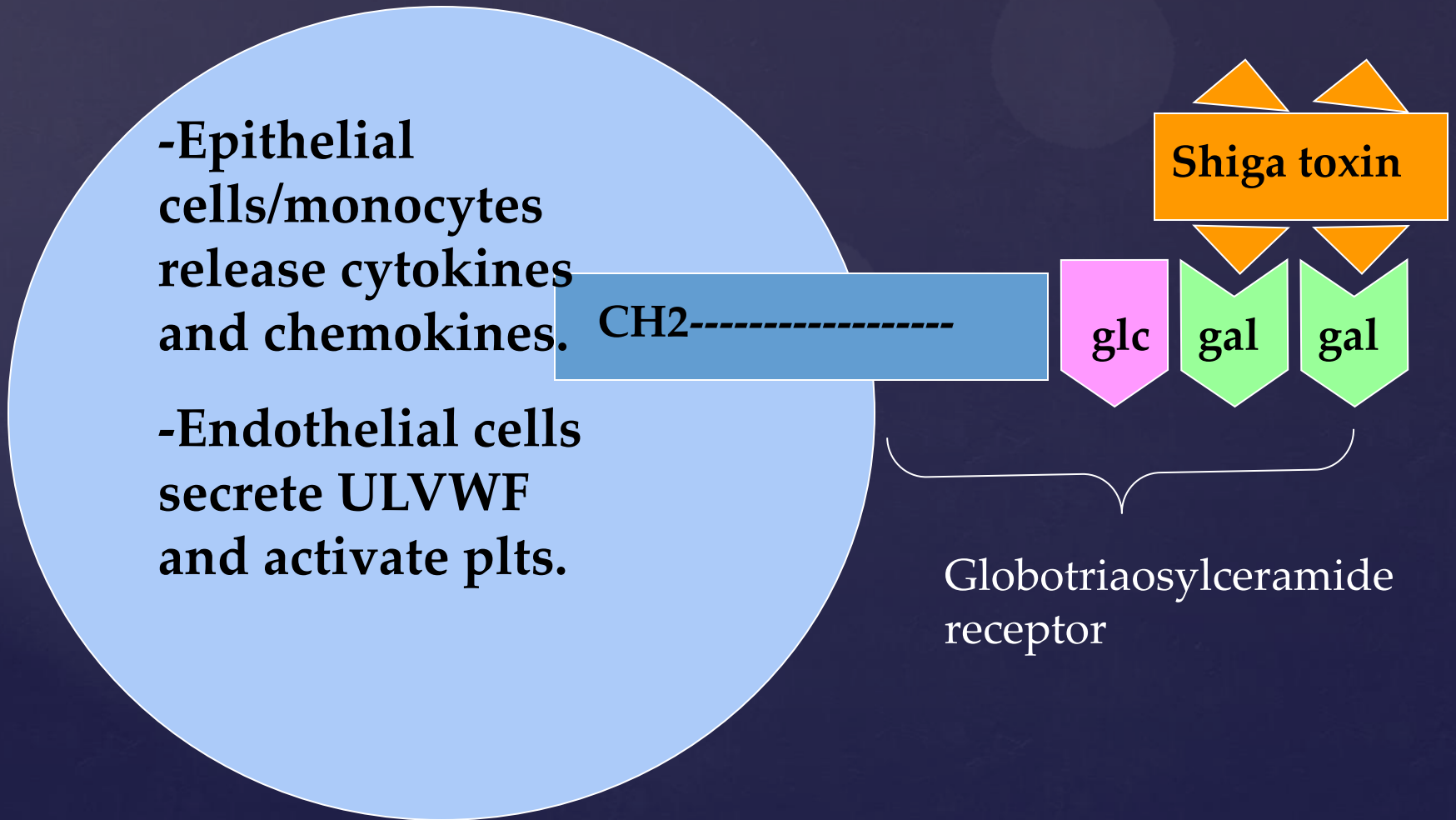
- Prednisone 1 mg/kg/d or Methylprednisolone 125 mg IV bid
- Suppresses production of ADAMTS13 autoantibodies by inducing lymphocytic apoptosis

Acquired HUS

- Occurs in 9-30% of children about a week after an episode of bloody diarrhea precipitated by ingestion of enterohemorrhagic bacteria that produce the shiga toxin (e.g. *e.coli* 0157:H7 and *shigella dysenteriae*)
- Sources include contaminated milk, cheese, or meat
- Common in Buenos Aires, Argentina, and Calgary, Canada

Moake et al. 2002. Thrombotic Microangiopathies. *New England Journal of Medicine*. 347 (8): 589-600.

Role of Shiga Toxin, Cytokines, uLVWF, and Cellular Injury



HUS - Treatment

- Plasma Exchange

- Supportive
  - IVF's
  - RBC transfusions
  - Dialysis if appropriate

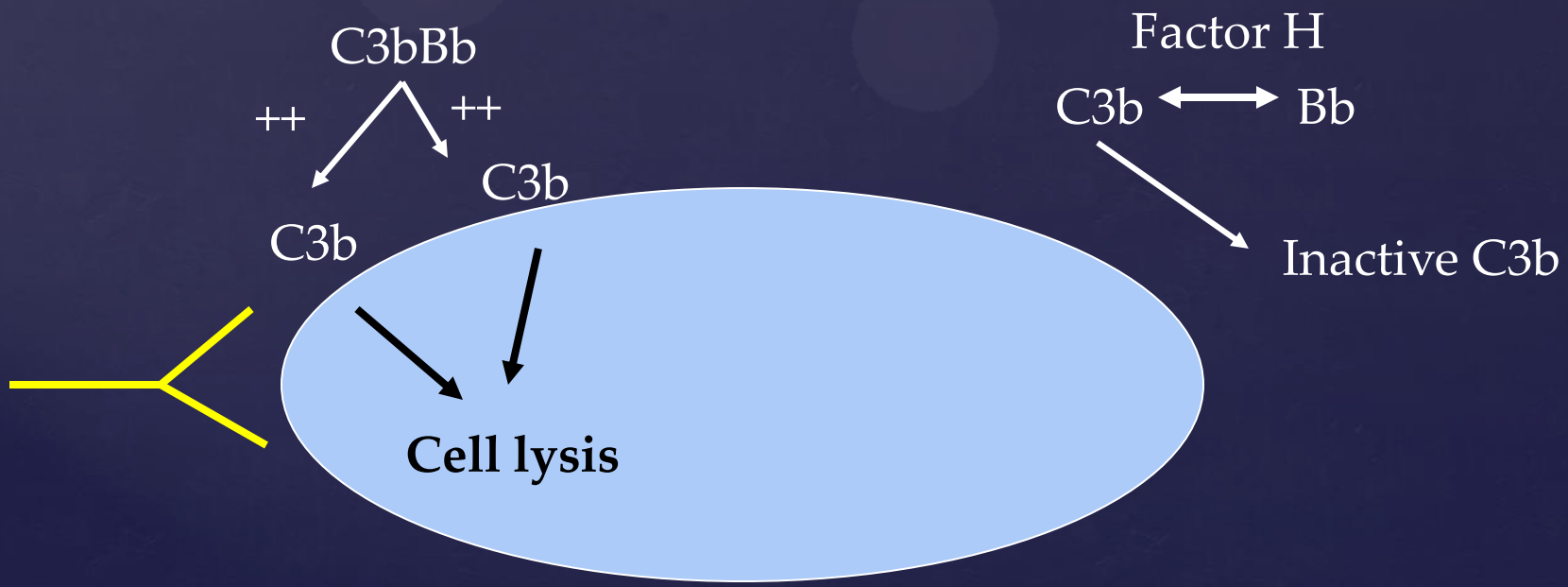
Atypical HUS

- Accounts for 5-10% of HUS
- Mortality rate ~50% vs 3-5% for typical, acquired HUS
- About 50% relapse, and over 33% require long-term dialysis; 16% who receive kidney allografts lose function of graft within 1 mo.

Noris, et al. 1999. Hypocomplementemia discloses genetic predisposition to HUS and TTP: role of factor H abnormalities. J Am Soc Nephrol. 10:281-93.

aHUS

- Due to a regulatory protein defect in the alternative complement pathway
- Results in excessive activation, endothelial damage, platelet activation, thrombus formation



aHUS

- If suspicion for aHUS, begin plasma exchange but if no improvement after 3-5 days, may be unresponsive → eculizumab

- Eculizumab
  - Recombinant humanized monoclonal antibody that target C5
  - Blocks cleavage of C5 and prevents formation of membrane attack complex

Hyperviscosity

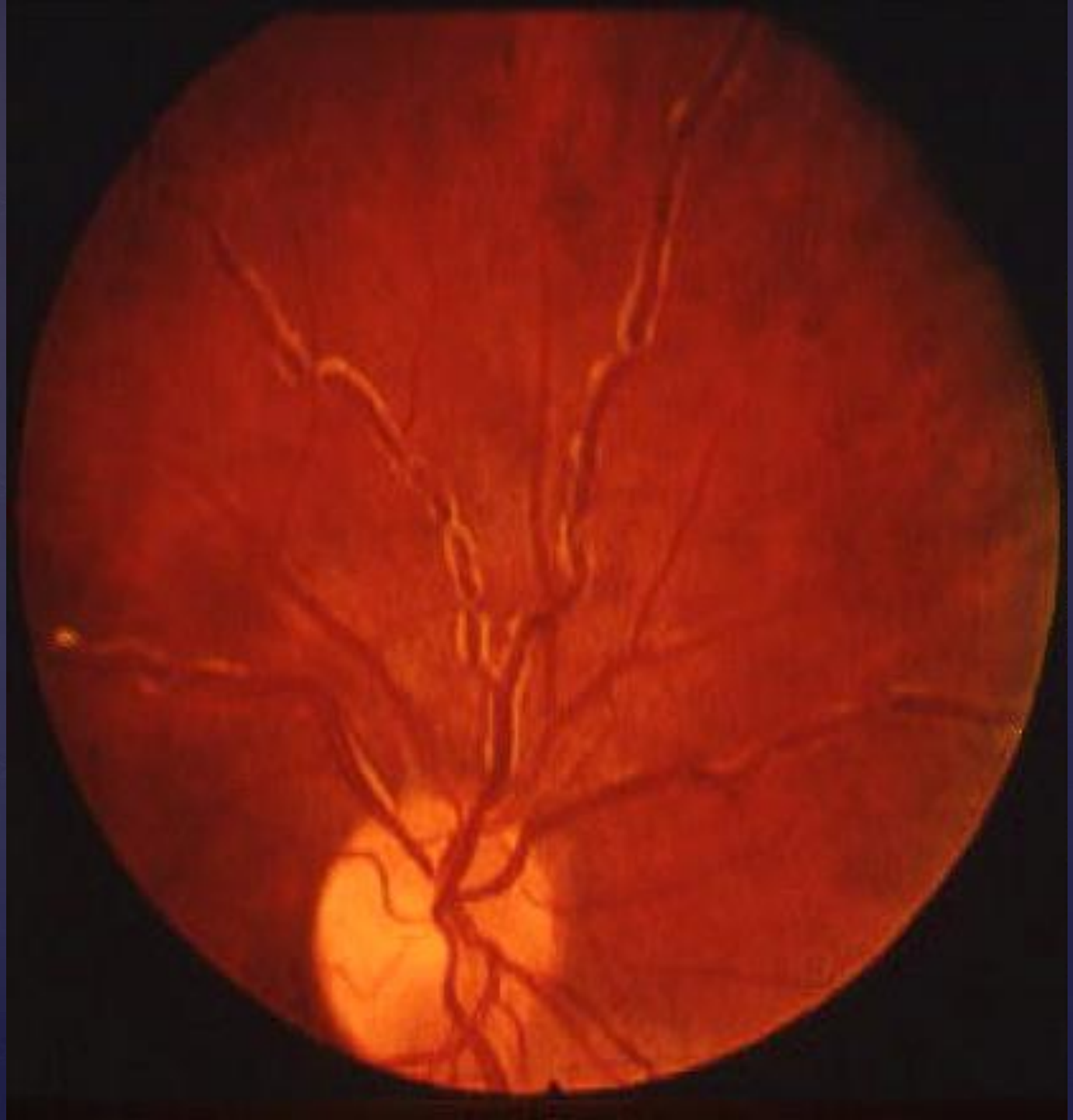
- Increased serum viscosity resulting from increased serum Ig's

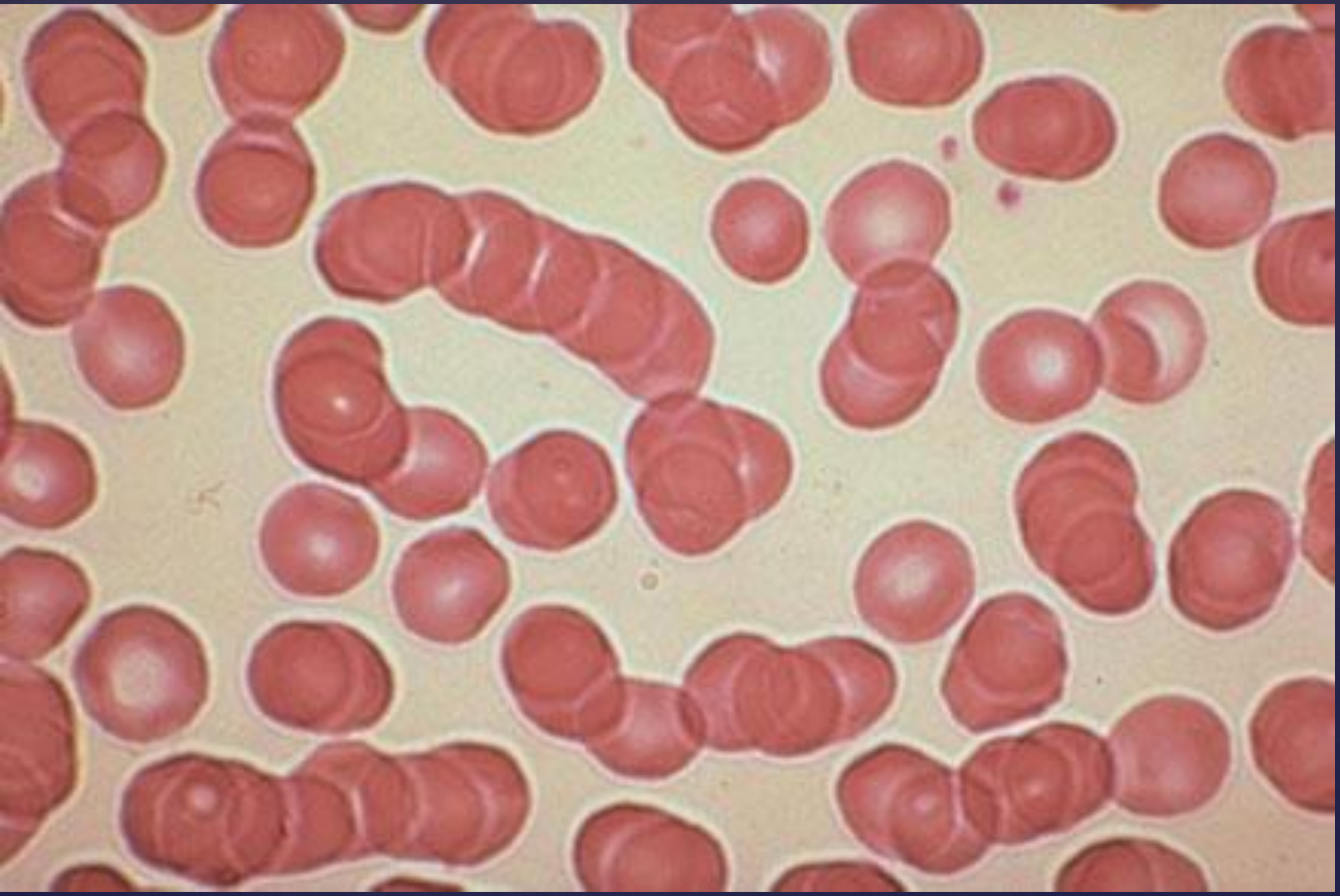
- Waldenstrom's macroglobulinemia/myeloma

- Symptoms
  - Typically occur when serum viscosity >5 cp
  - Mucosal bleeding*
  - CNS symptoms
  - Cardiopulmonary symptoms

Tx for HVS: Plasmapheresis

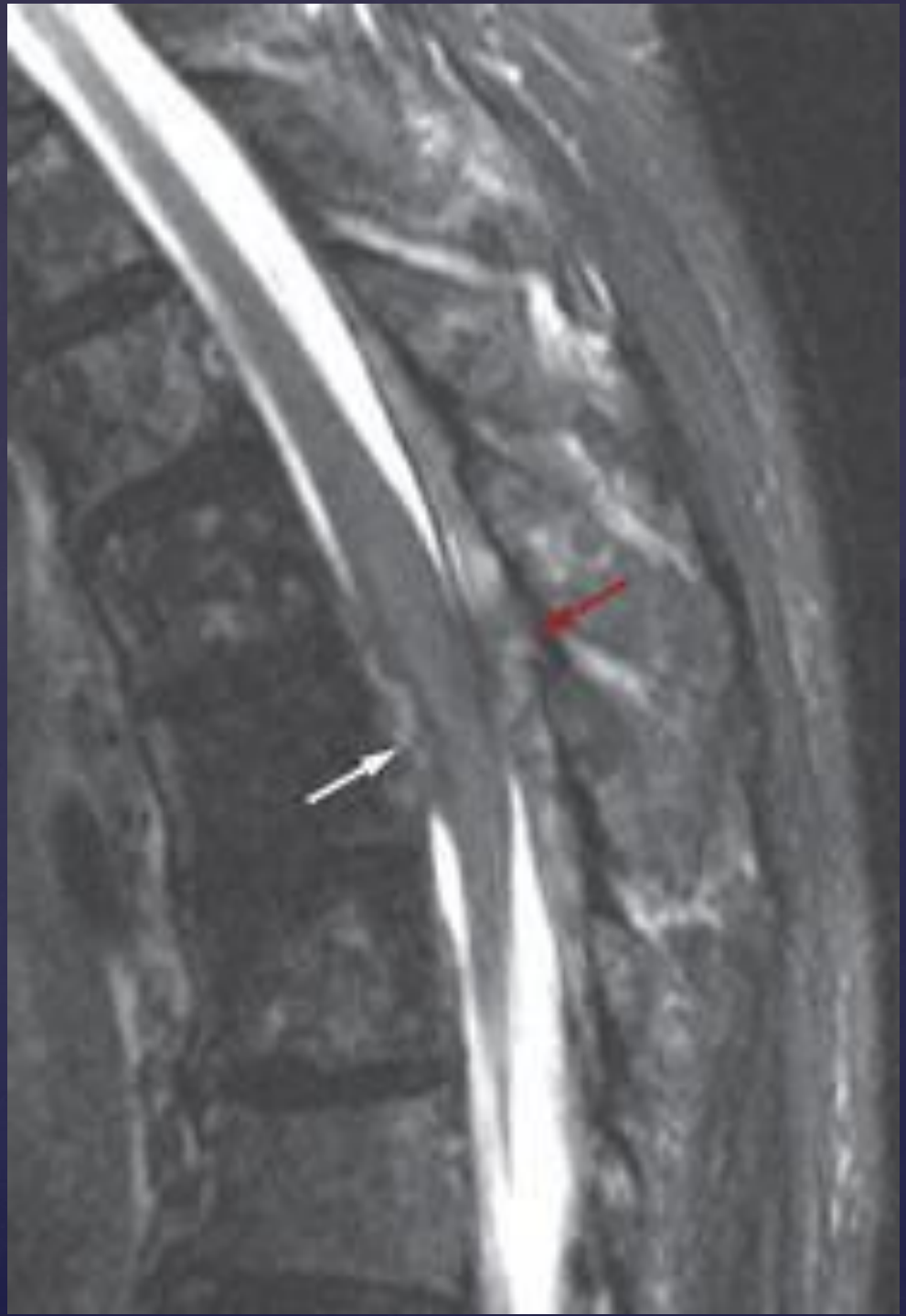
- Effective short-term treatment for HVS in WM
- A relatively small reduction in IgM concentration has a significant effect on lowering serum viscosity.
- Bleeding is the most common sign of HVS
- Urgent plasmapheresis should be carried out for patients experiencing visual symptoms to reduce the likelihood of blindness from retinal hemorrhages/retinal detachment.
- Plasma exchange reduces plasma viscosity approximately 20% to 30% per session.





Epidural Spinal Cord Compression

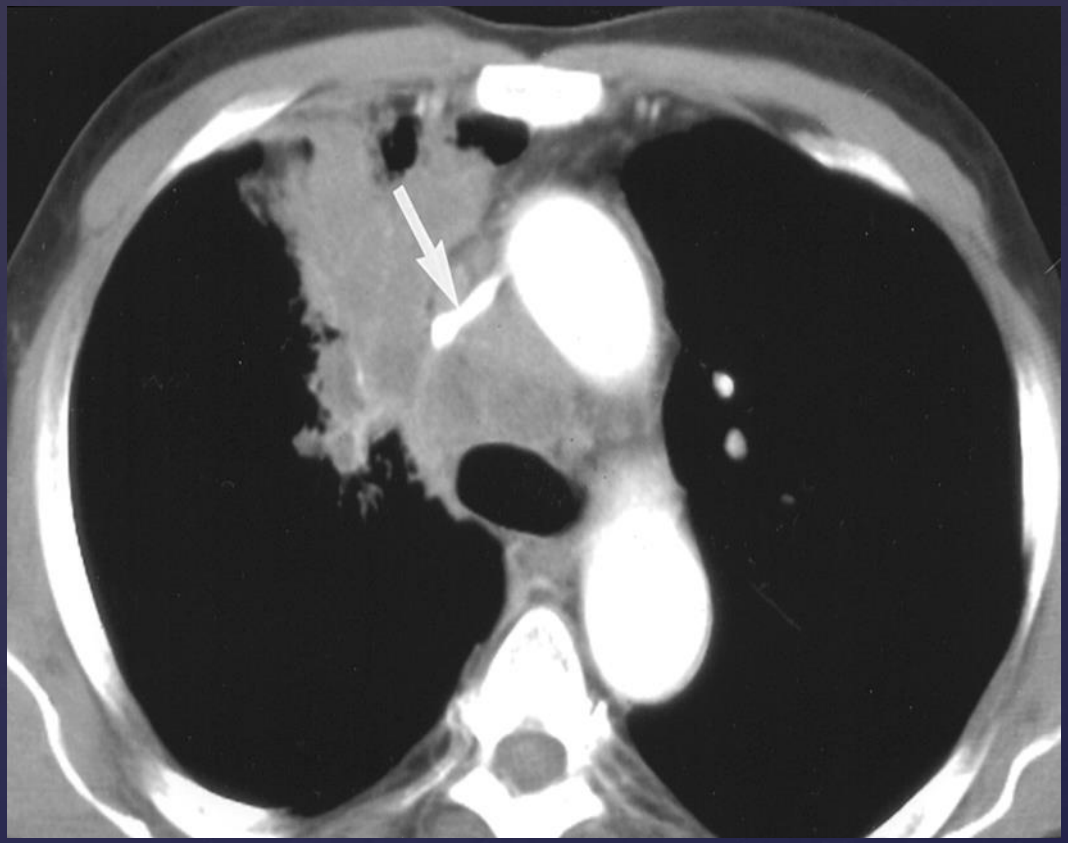
- Major complications include pain and irreversible loss of neurologic function
- Goals of therapy
  - Pain control
  - Preservation of neuro function



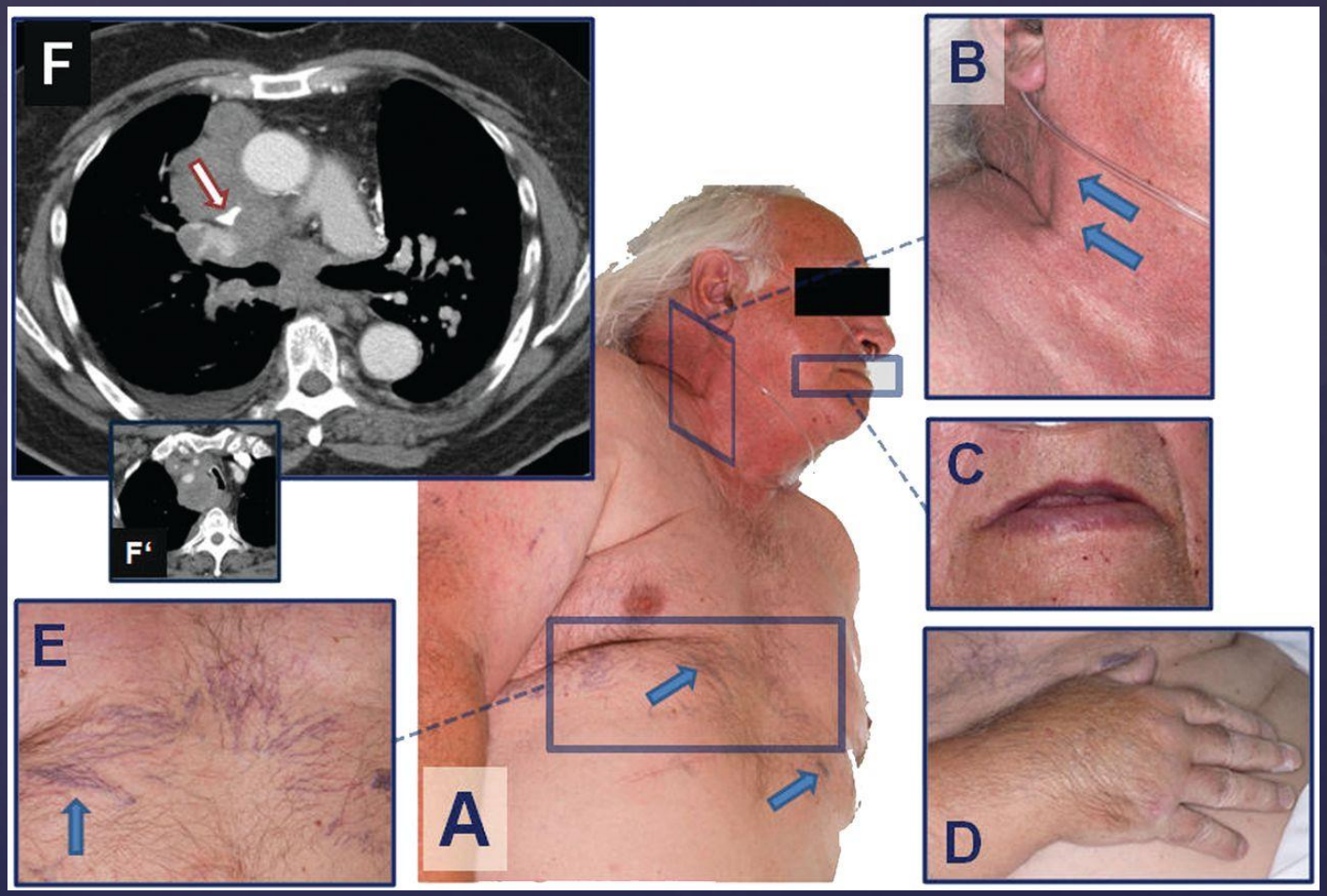
ESCC - Therapy

- Symptomatic Tx
  - Glucocorticoids
  - Opioids
  - Aggressive bowel regimen
- Definitive Tx
  - Assess spinal stability – Spine Instability Neoplasia Score
  - Surgery -> RT
  - +/-Chemotherapy

Superior vena cava syndrome



Typical clinical findings in a patient with superior vena cava syndrome



A: Plethora

B: Distended jugular veins

C: Cyanosis

D. Swelling hand/arm

E. Collateral circulation

F. Compression of SVC/tracheal compression

Philipp M Lepper et al. Respir Care 2011;56:653-666

SVC syndrome - Mechanism

- SVC surrounded by relatively rigid structures (sternum, trachea, right bronchus, aorta)
- Extends ~6-8 cm, from inominate veins to right atrium
- SVC syndrome causes by neoplastic invasion of venous wall with associated thrombus or by extrinsic compression

- Prompts collateral venous return through:
  - -Azygous venous system
  - -Internal mammary venous system
  - -Long thoracic venous system

- Develops in 5-10% of patients with right sided intrathoracic mass lesions

- Majority of cases due to bronchogenic cancer; 10-15% due to lymphoma

- Prognosis depends on underlying histology of tumor, presence of laryngeal and/or cerebral edema

- Symptoms often absent until obstruction near complete
  - -Dyspnea
  - -Facial and arm swelling
  - -Chest pain
  - -Dysphagia
  - -Change in vision
  - -Head fullness, headache

Treatment of SVC syndrome

Supportive

- Elevation of head
- Oxygen
- Corticosteroids
- Diuretics

Definitive Treatment

- ✓ Chemotherapy
- ✓ Radiation
- ✓ Stenting, particularly while bx being pursued

The End