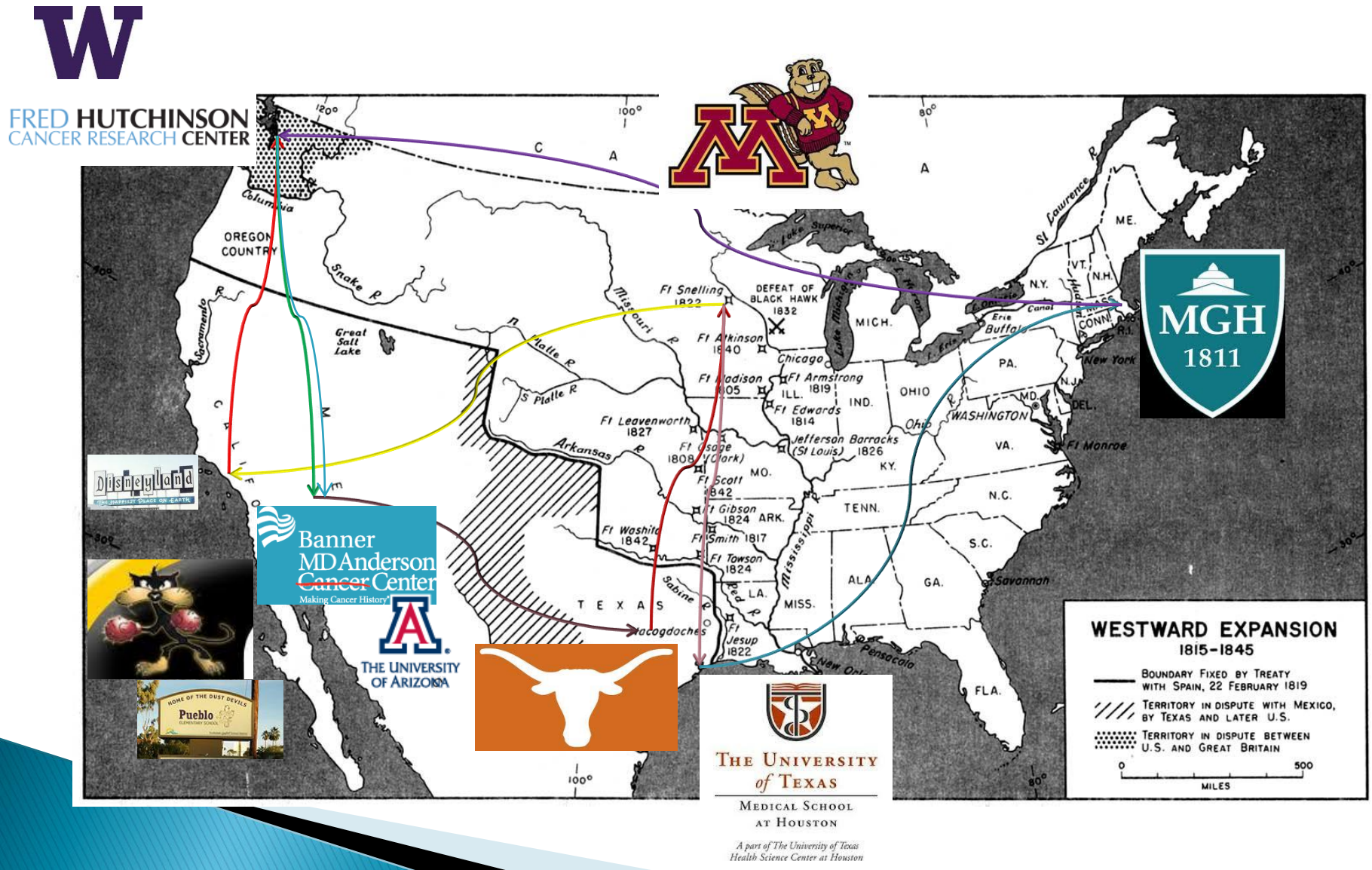
Oncologic Emergencies

Matthew Ulrickson, MD
Banner MD Anderson Cancer Center
July 26, 2022
Matthew.ulrickson@bannerhealth.com

Banner MD Anderson Cancer Center
Making Cancer History®

Where are you from?



Objectives

- Provide an overview of the diagnosis and management of common oncologic emergencies
- Help determine which situations are truly emergent
- Discuss the most common cancer types contributing to each presentation
- Help lower your pulse rate whenever you encounter these patients

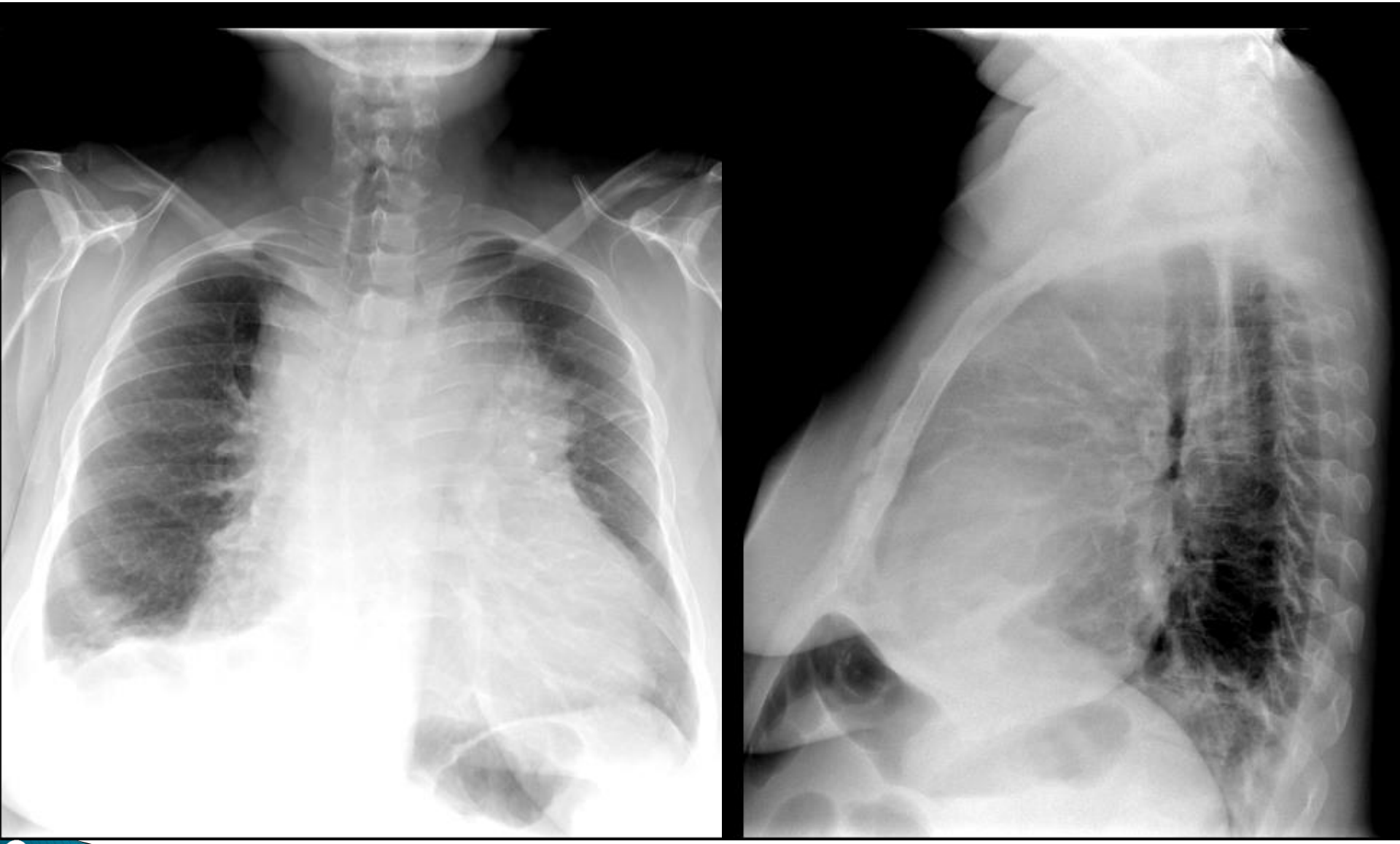
Oncologic Emergencies

- Is the situation truly emergent?
- Is the problem related to malignancy?
- Is the tumor sensitive to chemotherapy, radiation?
- What are the wishes of the patient and family?
  - https://depts.washington.edu/toolbox/dnr.html

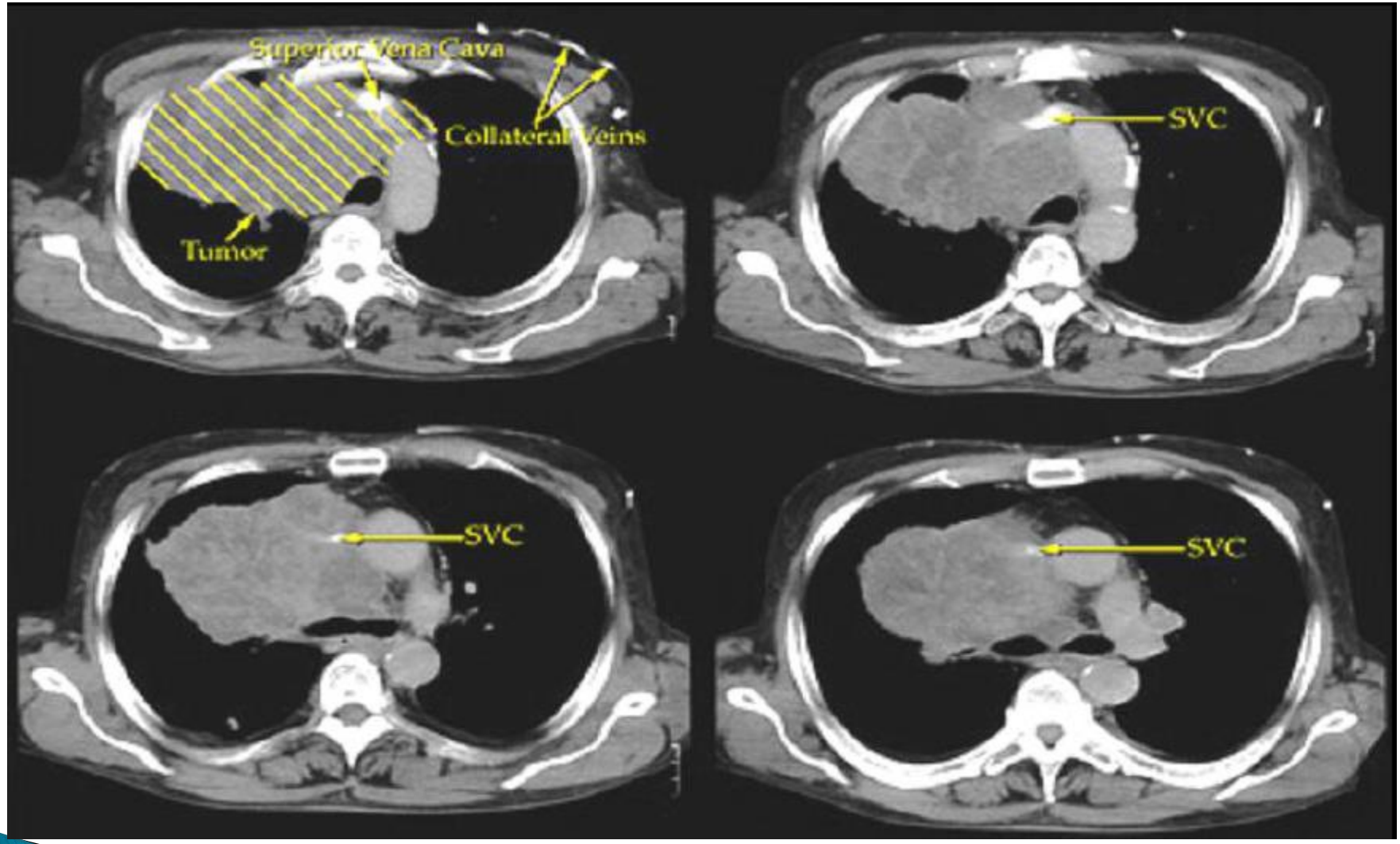
Case 1

- You are called to the ED at the VA to evaluate a 54yo woman with dyspnea, weight loss, and fevers for two weeks

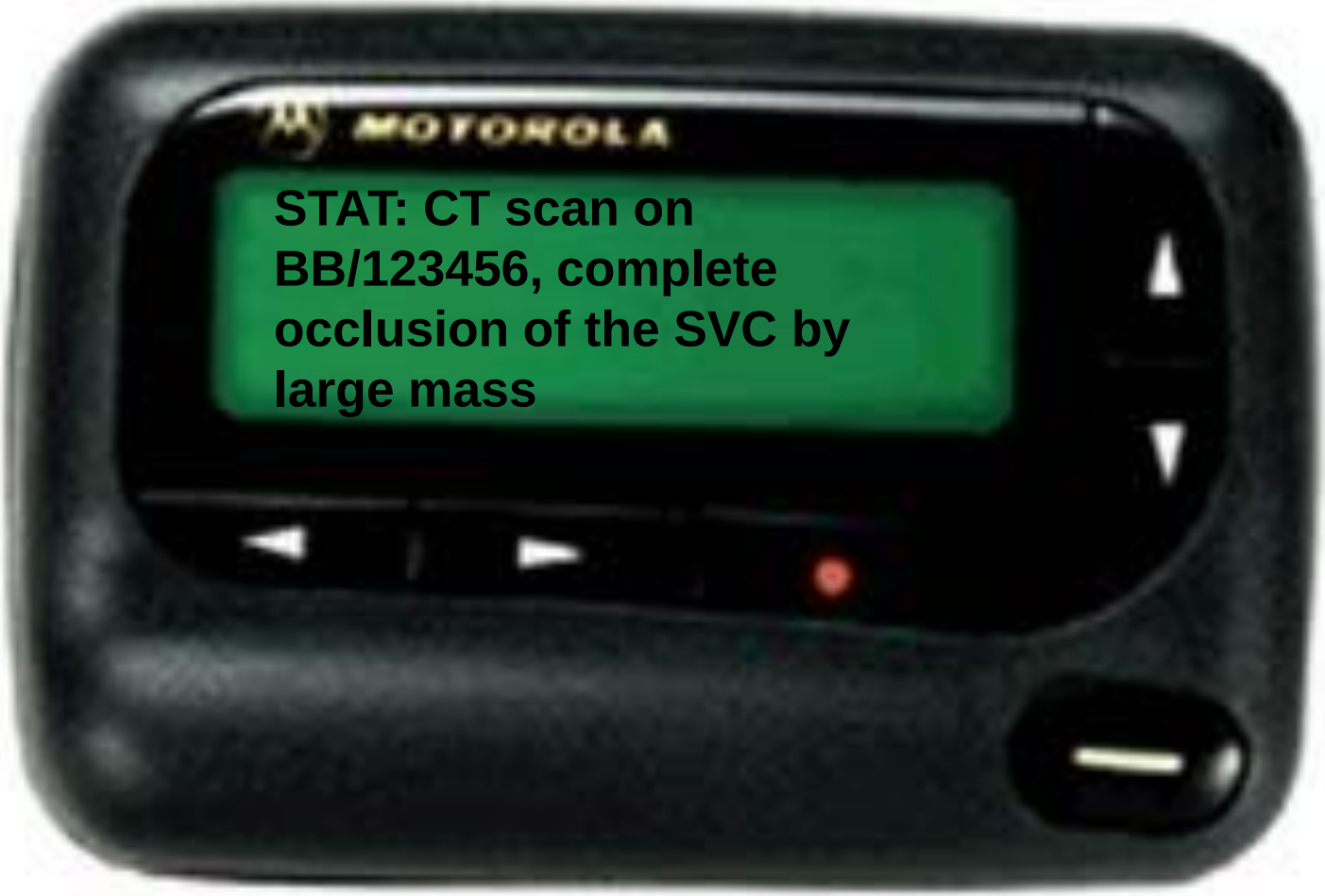
- Exam: BP 111/60, HR 110, RR 20
  - 2cm R axillary adenopathy, bilateral cervical adenopathy. No papilledema (do you know where an ophthalmoscope is in the hospital!)
  - Decreased breath sounds over left lung base, no stridor
  - No organomegaly
  - ALT 150, AST 23, LDH 620, Alk Phos 250, Uric Acid 6.5
  - CBC 3.5>12<95 ANC 2000



Banner
MD Anderson
Cancer Center
Making Cancer History®


Superior Vena Cava
Collateral Veins
Tumor
SVC
SVC
SVC

What do you recommend?



SVC Syndrome

- Which of the following do you recommend as a next best step?
- A) Radiation
- B) Vascular Stent
- C) Tissue Biopsy
- D) Chemotherapy
- E) Steroids

SVC Syndrome

- Which of the following do you recommend as a next best step?
- A) Radiation
- B) Vascular Stent
- C) Tissue Biopsy
- D) Chemotherapy
- E) Steroids

Biopsy in SVC Syndrome

Table 1. Surgical Procedure Performed

2 of the 4 were AF 5 of 13 were Abx

Type of Procedure	No. of Procedures*	Perioperative Complications	Intraoperative Complications	Postoperative Respiratory Complications	Significance
Cervical mediastinoscopy	32	4	1	3	NS
Medial sternotomy and resection	29	3	0	3	NS
Anterior mediastinotomy	20	4	1	3	NS
Thoracotomy and resection	12	1	1	0	NS
Thoracoscopy	8	2	1	1	NS
Cervical mediastinal exploration	6	2	0	2	NS
Extrathoracic lymph node biopsy	5	0	0	0	NS
Others	3	1	0	1	NS
Total	115	17	4	13	NS

* Some patients had more than one surgical procedure.

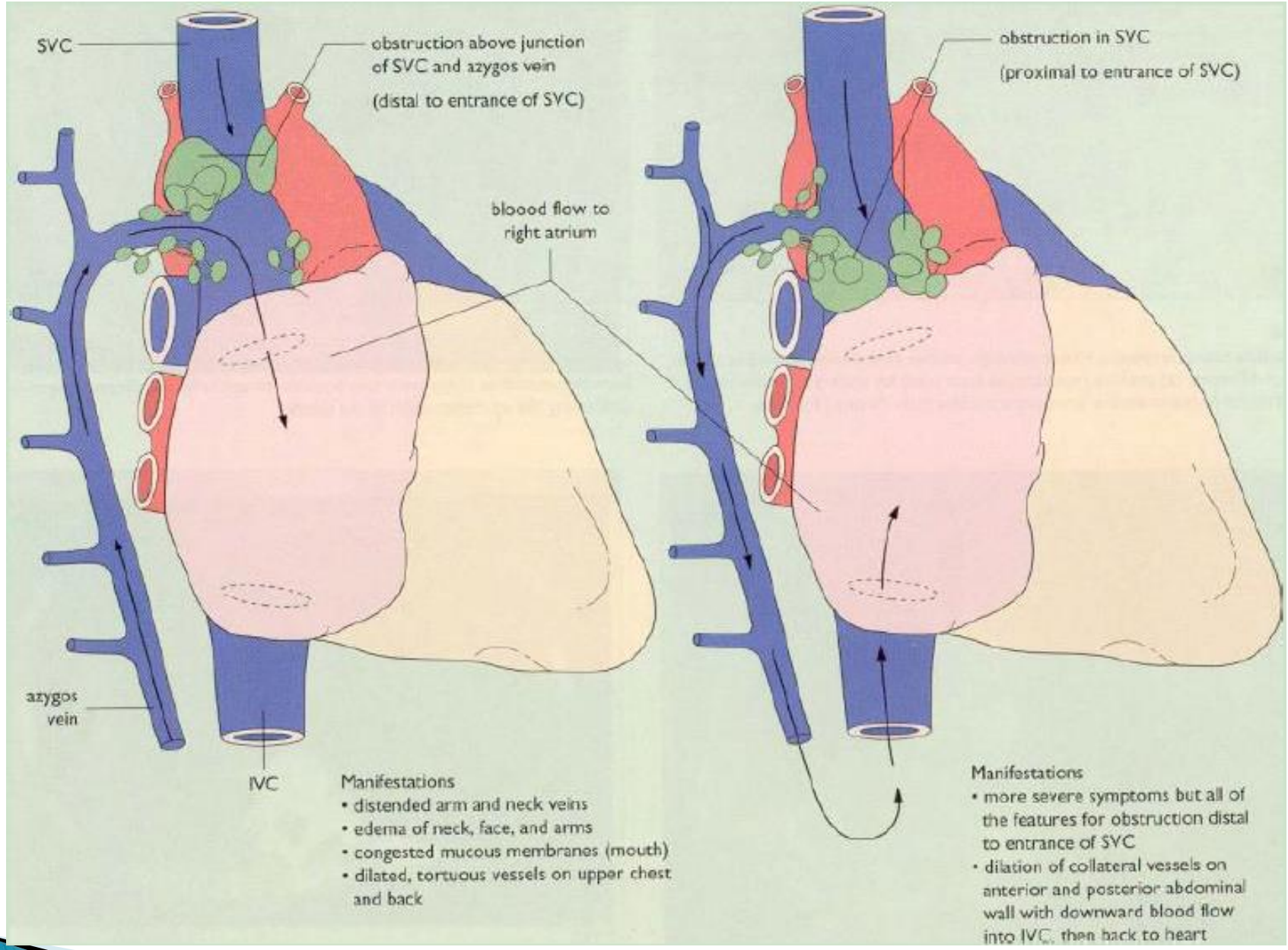
NS = not significant.

Bechard *Anesthesia* 2004

Intraoperative complications
(1) inability to ventilate or peak pressure >40 cm H2O
(2) severe pulmonary shunt (pulse oximetry <95% at FIO2 of 100%)
(3) hemodynamic instability (systolic BP <70 mmHg for 5 min or pulse rate <40 or >120 beats/min) necessitating treatment

Postoperative respiratory complications
occurring within 10 days after surgery and necessitating treatment
(1) Reintubation
(2) Noninvasive mechanical ventilation
(3) Bronchoscopy
(4) Inhalation therapy (racemic epinephrine, helium–oxygen mixture)
(5) Antibiotics

Dx: 31% lymphoma, 15% thymoma, 14% mets



Banner
MD Anderson
Cancer Center
Making Cancer History®

SVC Syndrome

- Physiology
  - Partial or complete obstruction of the SVC and collaterals
- Manifestations
  - Dyspnea, dysphagia, cough, stridor, papilledema, edema of upper torso/face, plethora, dilated venous collaterals (sometimes none of these)
  - Rare: hoarseness, syncope, HA, chest pain
- POC u/s may help with diagnosis (J Clin Ultrasound 2020 Apr 25. doi: 10.1002/jcu.22847)

SVC Syndrome

- Etiology
  - Malignant in 85-95% of cases
  - Benign
    - CVC/thrombus, pacemaker, infection (TB, histo)

Histology	% of cases	Total (%)
Lung carcinoma		79
Small cell	34	
Squamous cell	21	
Adenocarcinoma	14	
Large cell/other	11	
Lymphoma		14
Non-Hodgkin's lymphoma	13	
Hodgkin's lymphoma	1	
Other malignancy		6
Adenocarcinoma		
Kaposi's sarcoma		
Seminoma		
Granulocytic sarcoma		
Leiomyosarcoma		

Lymphoma

Lung

SVC Syndrome

- Immediate interventions:
  - Upright position (improve drainage), oxygen prn
  - Benefit of diuresis is questionable
  - Obtain necessary imaging
  - **Biopsy**
    - (FNA usually inadequate for lymphoma diagnosis)

  - Is this an emergency?

SVC Syndrome

- Tracheal obstruction or cerebral edema are the only true emergencies
  - Have you found the ophthalmoscope yet???

- **Tissue diagnosis** is most important
  - (sputum cytology, bronchoscopy, node biopsy, trans-thoracic needle biopsy, mediastinoscopy, VATS, etc)
  - Low risk even with general anesthesia

- Treatment
  - Chemotherapy for sensitive tumors, corticosteroids after biopsy while awaiting tissue diagnosis
  - Radiation for other tumors
  - Surgery or stent in selected cases

SVC Syndrome

- Biopsy (IR or Surgery)
- Most aren't truly emergent
- Steroids while waiting for pathology after biopsy usually ok (Onc consult)

Stone. Blood 2012. 119(10)

Case 2

- A 62yo man presents with fatigue, headaches, blurry vision, and epistaxis.
- He has generalized lymphadenopathy and a palpable spleen tip. Fundoscopic exam with enlarged retinal veins.
  - What is the thing called that you look in the eyes with?
- CBC 6.5>7.4<155
- Cr 1.4 Ca 9.1
- T Prot 8.4 Alb 2.2
- Head CT negative
- What do you suspect?

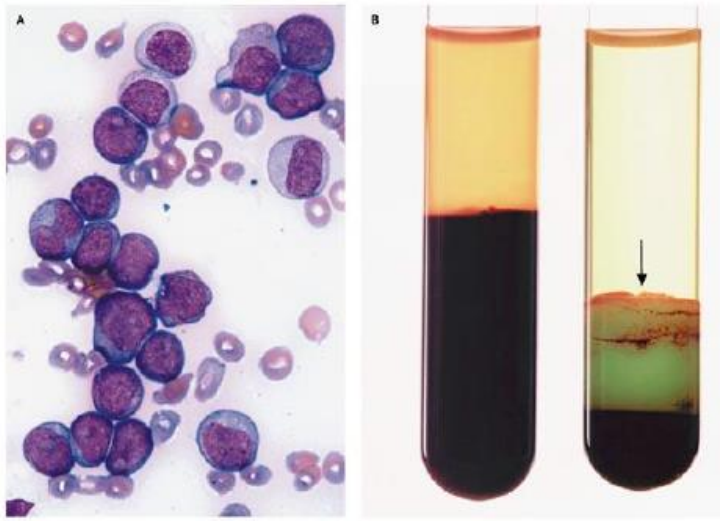
Hyperviscosity

- Increase in serum viscosity (above 4 cp) can cause sludging/microvascular insufficiency
  - Most commonly neurologic, pulmonary symptoms

- Waldenstrom Macroglobulinemia is a common cause due to IgM secretion (10-30% pts)
  - 80% IgM intravascular; therefore can remove with plasmapheresis(⇧viscosity with IgM above 4-5gm)
  - After reducing viscosity, then treat disease
    - chemotherapy and targeted agents for the lymphoplasmacytic lymphoma (LPL)

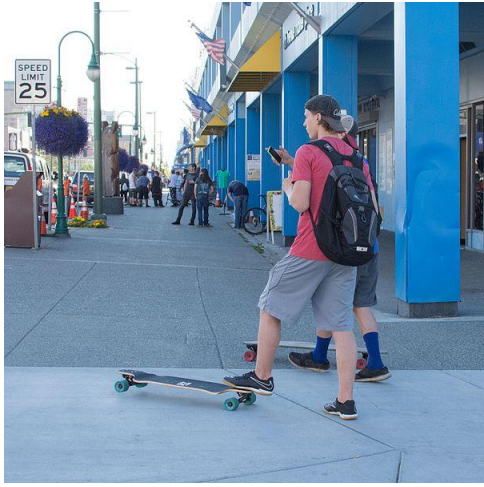
Leukostasis

- Can also cause hyperviscosity-like symptoms
  - Myeloid blast count >50k (AML)
  - Lymphoid blast count >400k (ALL)
  - Rare in CML, CLL, Leukemoid reaction
  - RBC transfusion increases viscosity, so delay until after cytoreduction if not urgent need
  - Preferable to start chemotherapy
    - Can temporize with leukapheresis

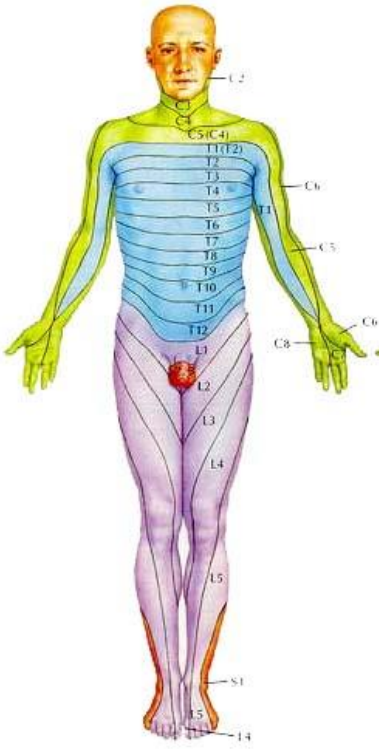


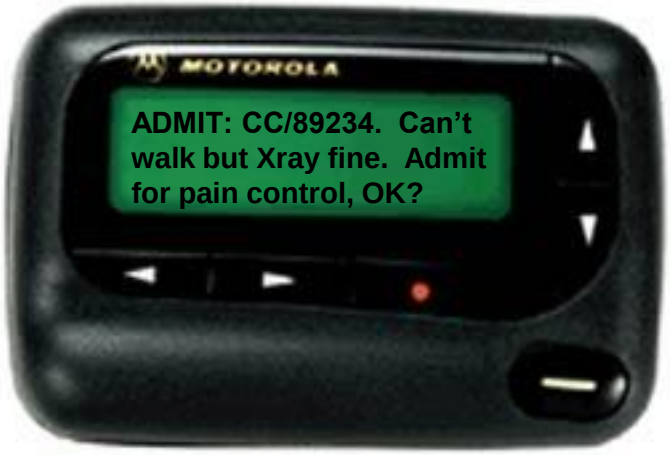
Mauro MJ NEJM 2003. 349:767

Case 3



- 22yo male presents to the ER with weight loss, back pain, dyspnea, fatigue, and difficulty walking. He ran into a wall three times while posting to TikTok.
- Exam: BP 110/72, HR 100, RR 18
  - Orthostatic
  - Back tender to palpation
  - Decreased sensation in a band starting at T5, LE weakness with 3/5 in BLE
  - Phone seems inseparable from his R hand, with 6+/5 grip strength noted. Thenar hypertrophy.
- Chest xray and Thoracic spine xray negative





- The ED physician calls to send him to the floor, where your team is busy admitting 4 new arrivals. You say:
- A) "Sure, as long as you put in some holding orders and swab for COVID"
- B) "How about an MRI?"
- C) "How about starting dexamethasone, then getting an MRI?"
- D) "I'm capped, save him for the night float"
- E) "Hydroxychloroquine"; works for everything

- MRI entire spine (cord compression protocol)
- Consider PSA, breast exam, CXR, SPEP as indicated if no prior diagnosis

Banner MD Anderson Cancer Center
Making Cancer History®

Epidural cord compression

- Compression of spinal cord by tumor extending from vertebral body or through foramina.
- Location
  - Thoracic (70%) > lumbar > cervical spine
- Manifestations
  - Pain (95%), weakness, sensory changes, bowel/bladder dysfunction
- PreTest Probability
  - Patient with known advanced malignancy and new back pain = MRI
  - Patient in your clinic tomorrow with new back pain – no MRI (usually)

Cord Compression

- Malignant in >90% of cases
  - Benign causes include trauma, DJD, osteoporosis and fracture, spinal stenosis, abscess
- Diagnosis
  - MRI
    - If cord compression is suspected, image the ENTIRE spine
    - >50% patients with multi-level involvement

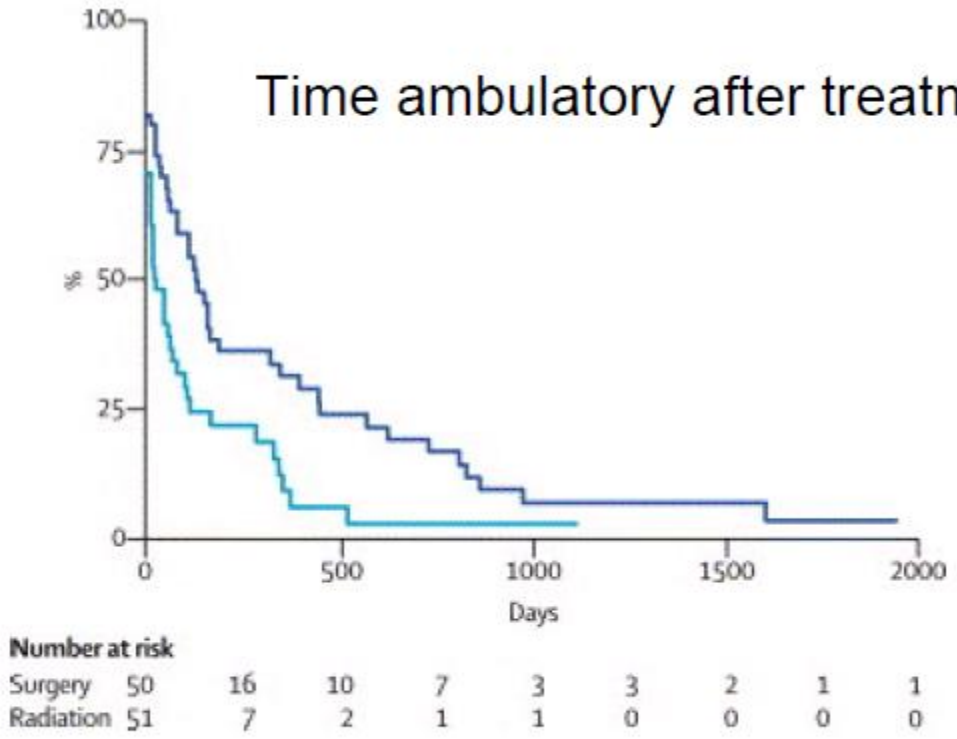
Histology	% of cases
Lung	18
Breast	13
Unknown primary	11
Lymphoma	10
Myeloma	8
Sarcoma	8
Prostate	6
Gastrointestinal tract	4
Renal	5
Other	17
Total Number of Cases	896

Cord Compression

- Treatment
  - Dexamethasone 10mg (some use 100mg) IV x 1 then 4mg IV q6hrs. Taper once compression resolved/XRT completed
  - Surgery then XRT vs Radiation alone
    - (Patchell et al. Lancet 2005. 366:643)
      - Primary endpoint, ability to walk
      - N=101
      - Had to be symptomatic (pain included)
      - Could not have been paraplegic for >48hrs
      - Tumor in one single area (could be multiple contiguous vertebrae)
      - Excluded 'very radiosensitive tumors'
        - Lymphoma, myeloma, leukemia

Back on their feet

- Surgery median duration 122 days
- Radiation median duration 13 days



Other Outcomes

- Patients who entered treatment unable to walk
  - Surgery/radiation: 62% were ambulatory after treatment
  - Radiation alone: 19% ambulatory

	Radiation group (n=51) median	Surgery group (n=50) median	Relative risk*	95% CI*	P*	Significant predictors**
Maintenance of continence	17 days	156 days	0·47	0·25–0·87	0·016	Surgery RR=0·51 (0·29–0·90) Baseline Frankel Score RR=0·56 (0·3–0·73)
Maintenance of ASIA score	72 days	566 days	0·28	0·13–0·61	0·001	Surgery RR=0·30 (0·14–0·62) Stable Spine RR=0·43 (0·22–0·83) Cervical Spinal Level RR=0·49 (0·26–0·90) Baseline Frankel Score RR=0·65 (0·46–0·91)
Maintenance of Frankel score	72 days	566 days	0·24	0·11–0·54	0·0006	Surgery RR=0·26 (0·12–0·54) Stable Spine RR=0·39 (0·20–0·75) Cervical Spinal Level RR=0·53 (0·74–0·98) Baseline Frankel Score RR=0·62 (0·44–0·88)
Survival time	100 days	126 days	0·60	0·38–0·96	0·033	Surgery RR=0·60 (0·40–0·92) Breast Primary Tumour RR=0·29 (0·13–0·62) Lower Thoracic Spinal Level RR=0·65 (0·43–0·99)

*Based on a Cox model with all covariates included. **Based on a Cox model with only significant predictors included (stepwise selection).

Patchell, Lancet 2005

Modified Tokuhashi Score

Ann R Coll Surg Engl 2012; **94**: 28–33 and *Spine* 1990. **15**:1110-1113

Original study suggested aggressive interventions for score ≥9 and less invasive if ≤5.

Feature	Score 0	Score 1	Score 2
Performance status	KPS 10–40%)	KPS 50–70%	KPS 80–100%
# Extraspinal bone mets	≥3	1–2	0
# vertebral body mets	≥3	1–2	0
Visceral Mets	Unresectable	Resectable	None
Primary Tumor	Lung/ Stomach	Kidney/liver/ uterine	Thyroid, prostate, breast, rectal
Spinal cord palsy	Complete	Incomplete	None

There are 9 score models for this same question

Cord Compression

- Empiric steroids as soon as suspicious
- Diagnose with MRI (even if pain alone with no neuro symptoms and suspicious)
- Decompression (Neurosurgery/Ortho, RadOnc)
  - Surgery better than radiation alone in selected patients

Case 4

- 24yo woman with stage IV Burkitt Lymphoma is admitted for urgent treatment with R-hyper-CVAD
- Exam: BP 120/70, HR 90, RR 26
- Hepatosplenomegaly
- Cr 2.4 (baseline 0.7), CO2 14, Uric acid 20, Potassium 6.4, Ionized Ca 1.9, Phosphate 9.0
- Diagnosis?

Tumor Lysis Syndrome

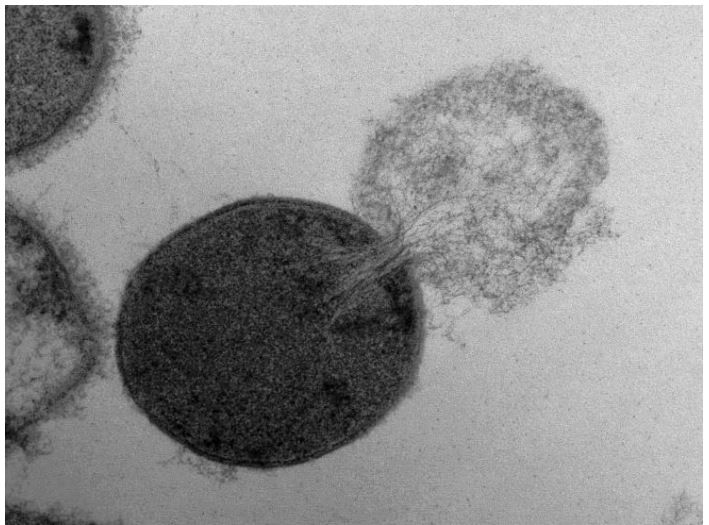
- Metabolic derangements associated with tumor necrosis (spontaneous or due to chemo)
  - Release of cellular purines, phosphate, potassium
- Hyperuricemia with acidemia induces crystal formation and obstructive uropathy
- Etiology: Lymphoma, Leukemia, Small cell lung,
- High risk features: tumor >10 cm, LDH > 2x ULN, leukemic cells > 25k/uL, pre-existing renal failure.

(*JCO* 2008;26:2767)

TLS Diagnosis

- **Cairo-Bishop laboratory definition**
  - At least <u>two</u> of the following:
    - Uric acid > 6.5-8 mg/dL or >25% above baseline
    - K > 6 mEq/L or > 25% above baseline
    - Phos > 6.5mg/dL or > 25% above baseline
    - Ca < 7mg/dL or < 25% below baseline
- **Clinical tumor lysis**: lab tumor lysis plus
  - Cr 50% above baseline
  - Arrhythmia (hyperK, hypoCa)
  - Seizure (from hypocalcemia)

Image: Daniel Nelson, UMD

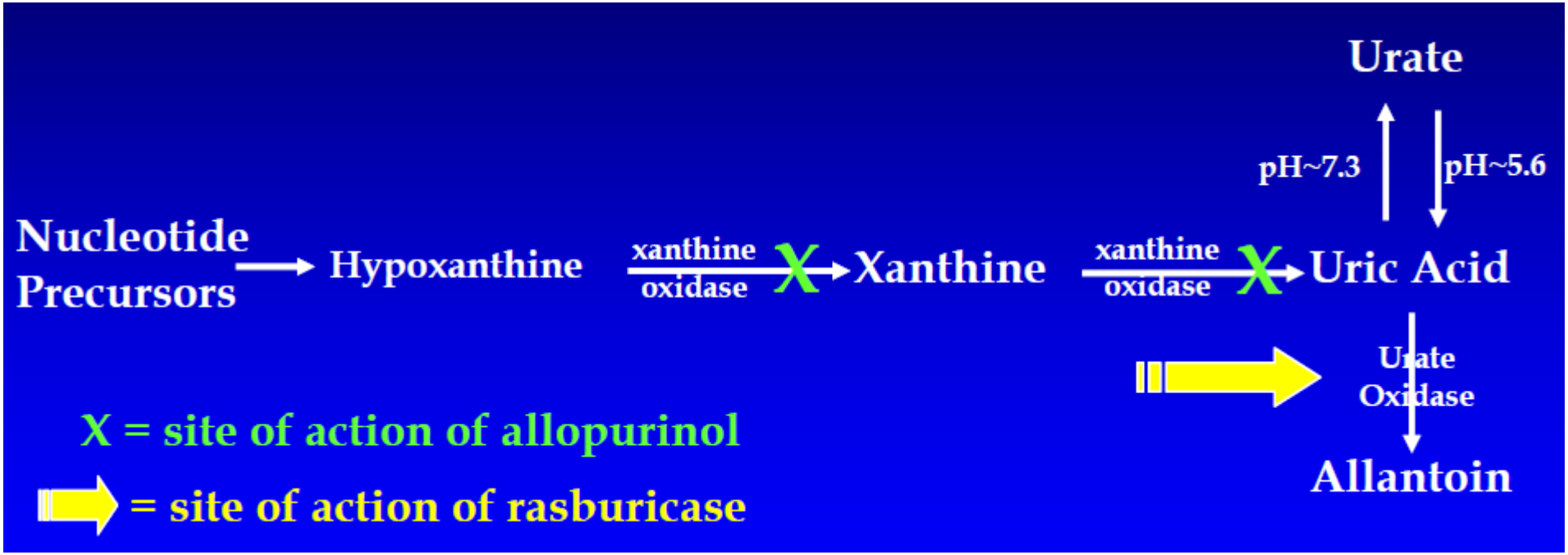


TLS prevention and Treatment

- **Prophylaxis**
  - Hydration: 0.9% NS (No potassium in IVF). Goal UOP 80-100 mL/hr (in high risk I usually start at 200cc/hr as long as no cardiac concerns)
  - Allopurinol: allopurinol 300mg PO daily

- **Treatment** (as above plus:)
- Electrolyte abnormalities:
  - Use caution prior to repleting for hypocalcemia
    - (Ca x PO4 >60 increases risk of precipitation)
  - Severe cases may require hemodialysis.
  - Loop diuretics can assist with uric acid excretion when patient no longer hypovolemic.
- *I have never, but you can consider alkalinizing the urine with goal urine pH of 7 if uric acid is >8mg/dL and phosphate is not >6.5mg/dL.
  - (alkalinization makes uric acid more soluble – but phosphate less soluble, so may trigger precipitation esp when Ca x PO4 is >60mg/dL. With rasburicase available, alkalinization is **rarely** indicated)

TLS Treatment



- – **Rasburicase**: (recombinant urate oxidase enzyme) for selected high-risk patients (uric acid >10), treat with 3-6mg IV x 1
  - may repeat after 8 hours in rare cases, esp if uric acid remains >8.5mg/dL
  - Caution: agent can cause hemolysis in G6PD deficient patients.
- Check level 6 hours after dose: **Note well**: Uric acid samples taken after administration of rasburicase must be collected in chilled heparin tubes, kept in ice, and run within 4 hours of collection as the enzyme will continue to be active within the tube and cause spuriously low results (Use *RASBURICASE* uric acid level order).

Aggressive IVF can often avoid need for rasburicase in borderline cases and increase value

Case Continued

- Patient was managed aggressively with control of her electrolyte abnormalities and her Cr improved without dialysis
- She completed 8 cycles of hyper-CVAD, entered remission, and was cured

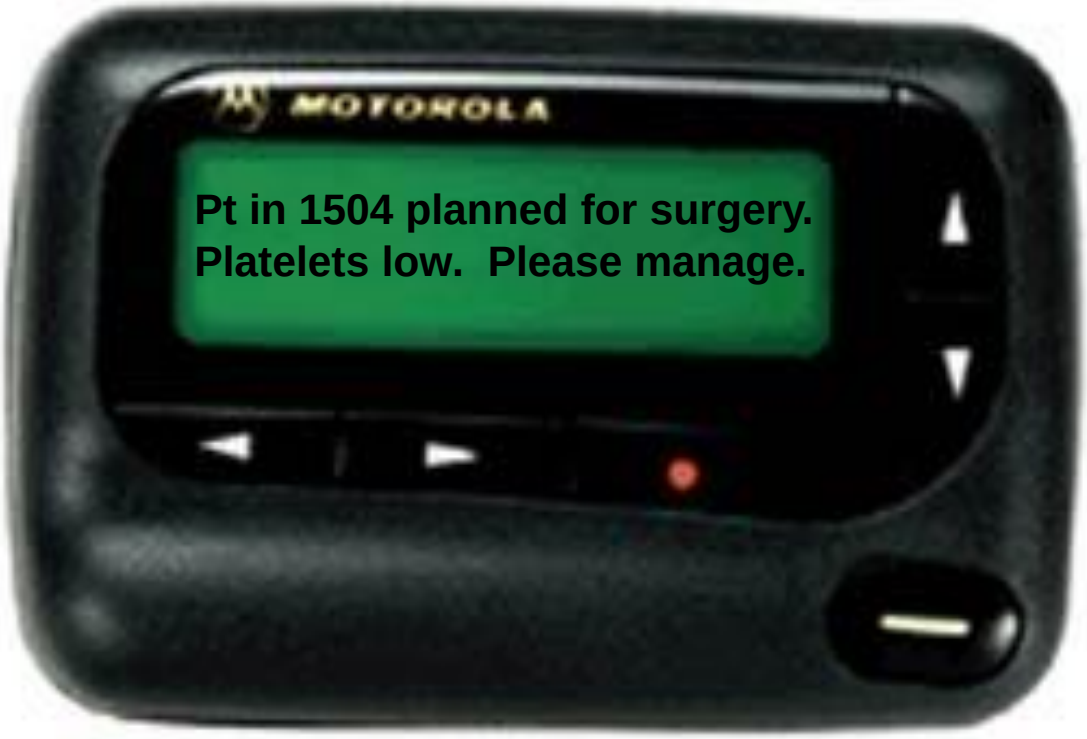
Case 5

- 36yo woman with no PMHx presents with RUQ abdominal pain, nausea/vomiting, and jaundice.
- No bleeding or bruising, no fevers

- CBC 10.5>7 <12
- INR 1.2, PTT 30
- LDH 1,059
- Cr 1.7, TBili 4.8
- Albumin 3.6

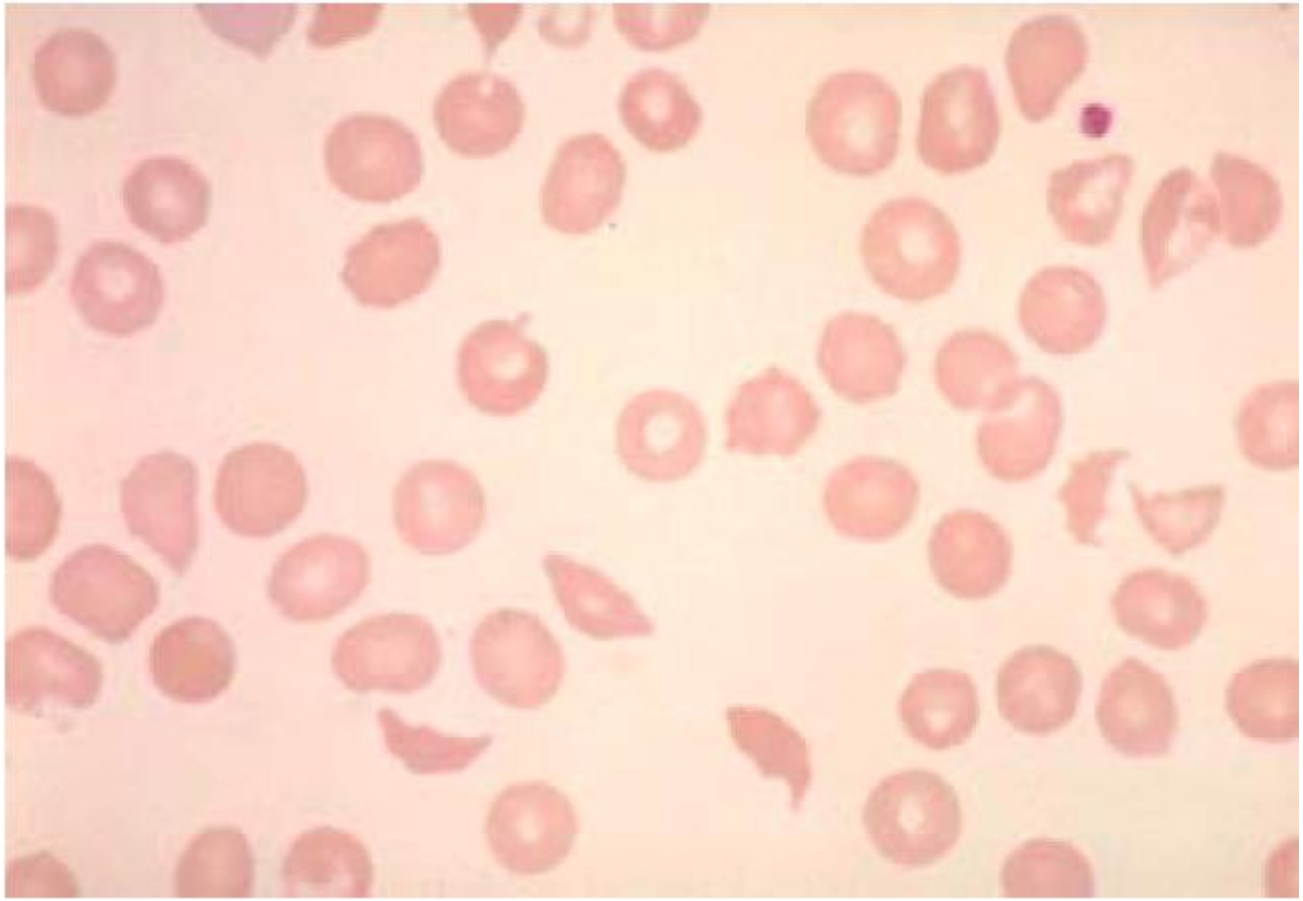
- Abdominal ultrasound reveals pericholecystic fluid and mild gallbladder wall thickening
- She is planned for cholecystectomy

Next Steps?


MOTOROLA
Pt in 1504 planned for surgery.
Platelets low. Please manage.

CellaVision allows viewing of PB smear from any computer

Peripheral Smear

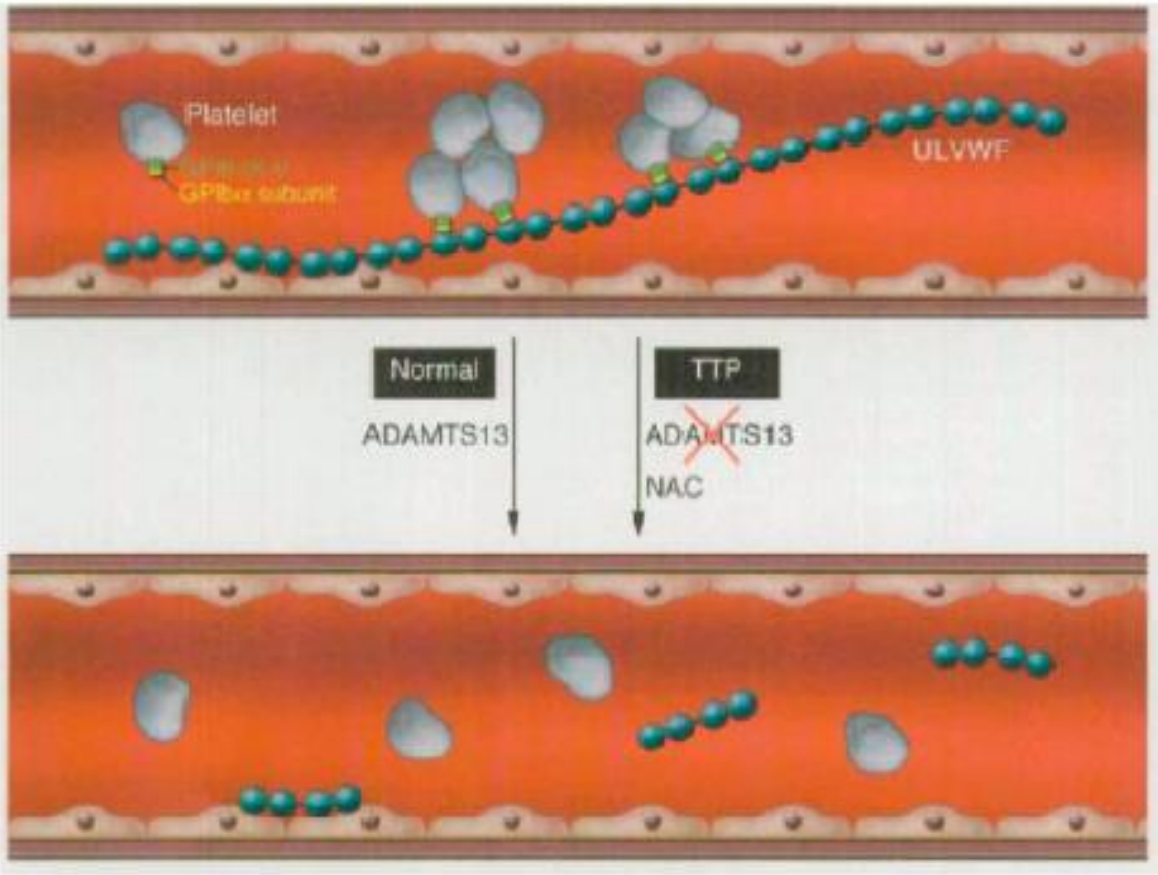


Thrombotic Thrombocytopenic Purpura (TTP)

- Thrombocytopenia and microangiopathic hemolytic anemia (MAHA) are only requirements to suspect diagnosis
- Treat with emergent plasma exchange (large bore pheresis line)
  - Replace the ultralarge vWF with normal spectrum of vWF
  - UL vWF is more adhesive than shorter vWF
  - Platelets bind to vWF
- Many cases are autoimmune (inhibitor against ADAMTS13) – steroids can be helpful
- Confirm diagnosis with ADAMTS13 activity level with reflex to inhibitor

TTP Physiology

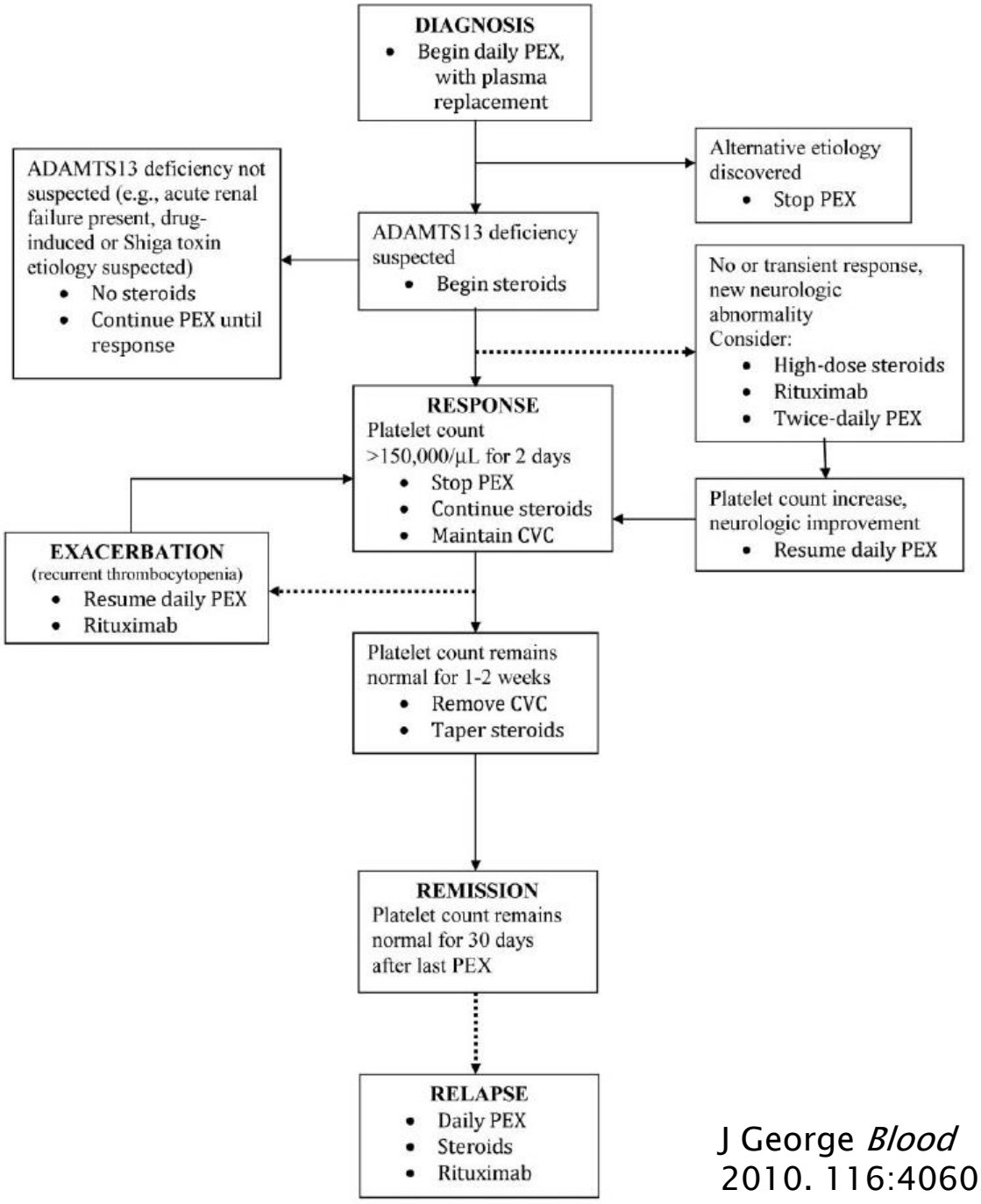
- Early plasma exchange decreases mortality from 90% to 15%



JCI 2011. 121:522.

Treatment

- Platelet transfusion?
  - Minimize
  - Likely ok if required to get line placed



J George *Blood* 2010. 116:4060

Questions

AEQUANIMITAS

Thou must be like a promontory of the sea, against which, though the waves beat continually, yet it both itself stands, and about it are those swelling waves stilled and quieted.

Marcus Aurelius.

I say: Fear not! Life still
Leaves human effort scope.
But, since life teems with ill,
Nurse no extravagant hope:
Because thou must not dream, thou need'st not then despair

Matthew Arnold, Empedocles on Etna.

["Aequanimitas," *Aequanimitas*, p. 3]

Sir William Osler, 1889

I

AEQUANIMITAS[1]

To many the frost of custom has made even these imposing annual ceremonies cold and lifeless. To you, at least of those present, they should have the solemnity of an ordinance—called as you are this day to a high dignity and to so weighty an office and charge. You have chosen your Genius, have passed beneath the Throne of Necessity, and with the voices of the fatal sisters still in your ears, will soon enter the plain of Forgetfulness and drink of the waters of its river. Ere you are driven all manner of ways, like the souls in the tale of Er the Pamphylian,[2] it is my duty to say a few words of encouragement and to bid you, in the name of the Faculty, God-speed on your journey.

I could have the heart to spare you, poor, careworn survivors of a hard struggle, so "lean and pale and leaden-eyed with study;" and my tender mercy constrains me to consider but two of the score of elements which may make or mar your lives—which may contribute to your success, or help you in the days of failure.

In the first place, in the physician or surgeon no quality takes rank with imperturbability, and I propose for a few minutes to direct your attention to this essential bodily virtue. Perhaps I may be able to give those of you, in

- Matthew.ulrickson@bannerhealth.com
- @MattUlricksonMD

Banner MD Anderson Cancer Center
Making Cancer History®

Case 3

- 55yo man with a prior history of treated non-small cell lung cancer (NSCLC) you see in clinic with weight loss, fatigue, and dyspnea for two weeks
- Exam: BP 90/60, HR 130, RR 38
  - Crackles and dullness at both lung bases, LE edema, hepatomegaly, JVP 15cm H2O

What do you suspect?

Cardiac Tamponade

- Impairment of diastolic filling by fluid/tissue in pericardium
- Rate of fluid accumulation is most important determinant of severity of symptoms

- Symptoms
  - Dyspnea, tachycardia, hypotension, elevated JVP, increased pulsus

Pulsus Paradoxus

Also can be seen in severe obstructive lung disease

- Exaggerated decrease in Systolic BP with inspiration (10–12mmHg is <u>normal</u> (6+/- 3))
- To Measure:
  - 1. Find a manual BP cuff (don't tell the patient you are watching their breathing)
  - 2. Stop cuff when first Korotkoff sounds heard
    - Notice that the sounds come and go

      INHALE EXHALE INHALE EXHALE INHALE
      I I I I I I I I   I I I I I I
  - 3. Gradually decrease the cuff pressure 2mmHg at a time
    - Wait a few respirations at each level to confirm sounds come and go
  - 4. Once sounds continually present, record and take difference (Step 2 – Step 4)

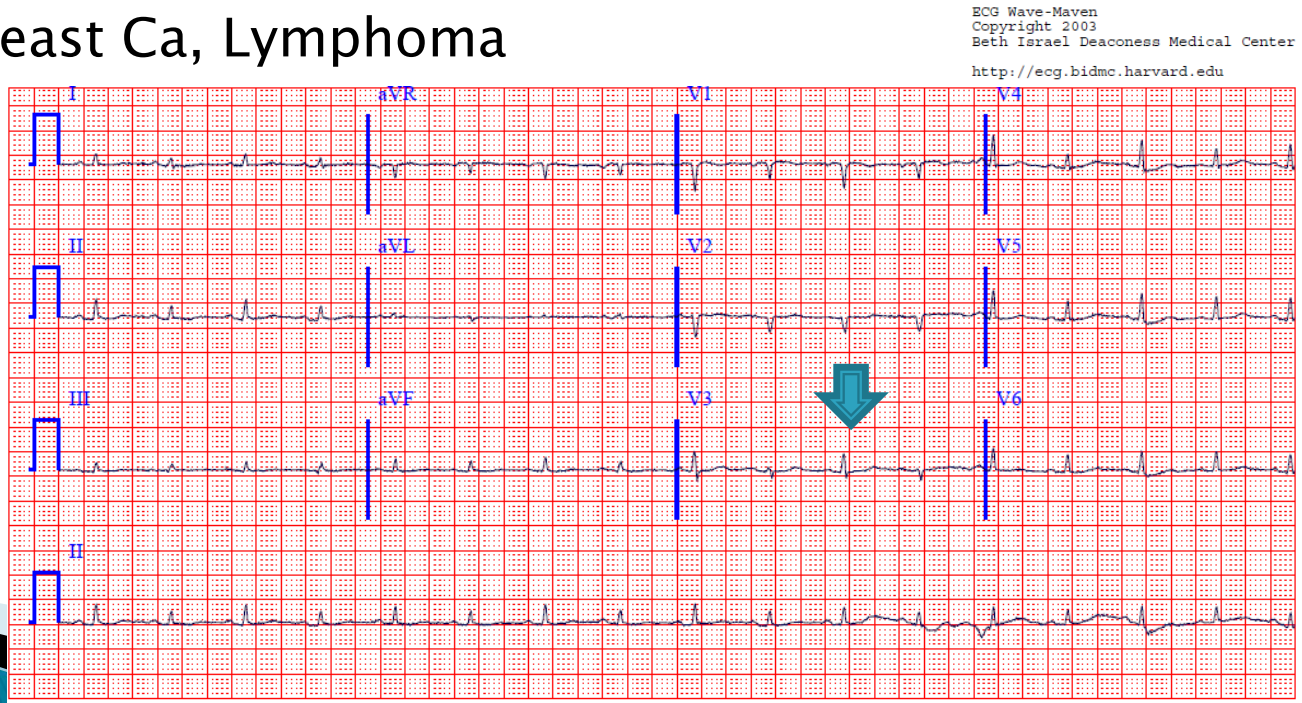
    INHALE EXHALE INHALE EXHALE INHALE
    I I I I I I I I I I I I I I I I I I I I I I I I I I I I I I I I I
  - 5. When sounds disappear completely, this is DBP, which is not significantly influenced in tamponade

    INHALE EXHALE INHALE EXHALE INHALE

Cardiac Tamponade

- Diagnosis
  - CXR: pleural effusion, increased cardiac silhouette, widened mediastinum
  - Echo: RA/RV diastolic collapse
  - Cardiac Cath: equalization of pressures
- Etiology
  - Most common malignancies:
    - Lung Ca, Breast Ca, Lymphoma

EKG: low voltage, electrical alternans, may have ST elevations in pericarditis pattern



Cardiac Tamponade

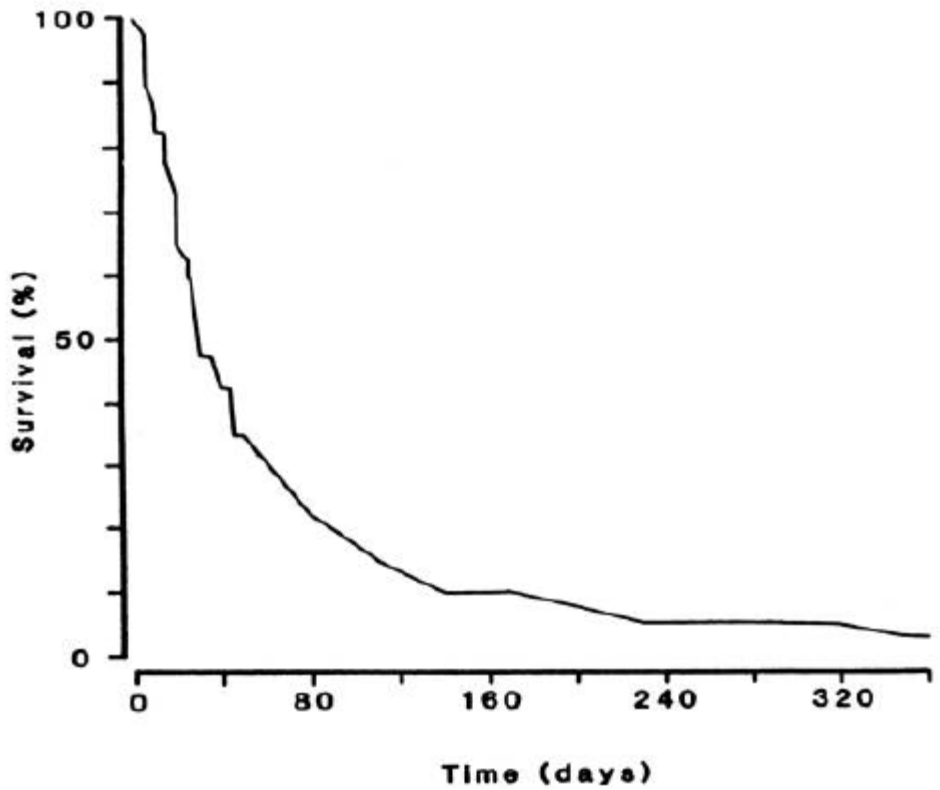
- Treatment
  - O2, IVF (no diuresis even if CHF symptoms/pleural effusions), pressors if needed
  - Pericardiocentesis, emergently if unstable
    - Drain may remain in situ
  - Chemotherapy can transiently control ~70% of malignant cases
  - Pericardial window or pericardiectomy
  - Sclerosis with bleomycin, minocycline rarely used

Cardiac Tamponade

- IVF and BP support as needed
- Check pulsus
- STAT Echo (Cardiology)
- Drain Fluid (If suspect malignant, Onc)

Survival in malignant hypercalcemia

- (except for myeloma) Median: 60 days



Ralston et al. Ann Int Med 1990. 112:499

Banner MD Anderson Cancer Center
Making Cancer History®

Case 4

- 85yo male with a history of multiple myeloma recently stopped therapy after entering a remission. His wife calls you while you are covering calls for the clinic.
  - Worsening rib pain
  - Previously functional, his wife reports that he is more confused and lethargic

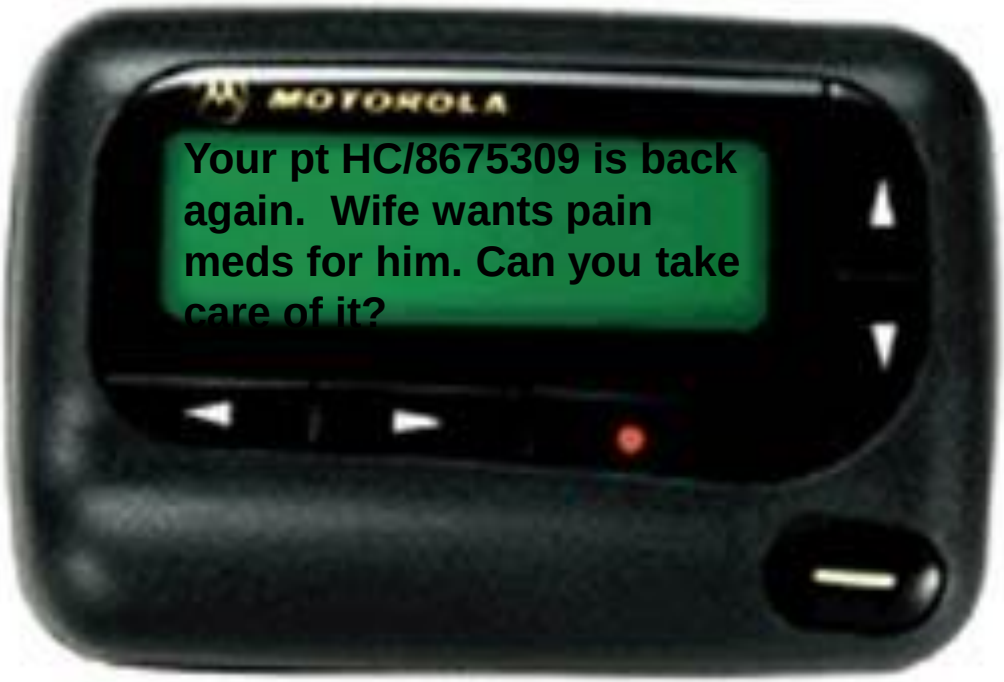
You advise him to present to ED for evaluation

- CBC: 11.1>32%<325 ANC 8000
- Lytes: Na 134, Cr 1.3, LFTs WNL
- CXR: Normal
- No sensory loss or other neurologic changes.
- Due to the negative evaluation, they send the patient home for outpatient management

- What else should they have checked?

The next day

- Patient returns home from ED at 1am; the next afternoon he is brought back to the ED by EMS with worsening confusion and pain



The next day

- Patient returns home from ED at 1am; the next afternoon he is brought back to the ED by EMS with worsening confusion and pain

- Serum Calcium = 14.2 (Alb 3.2)

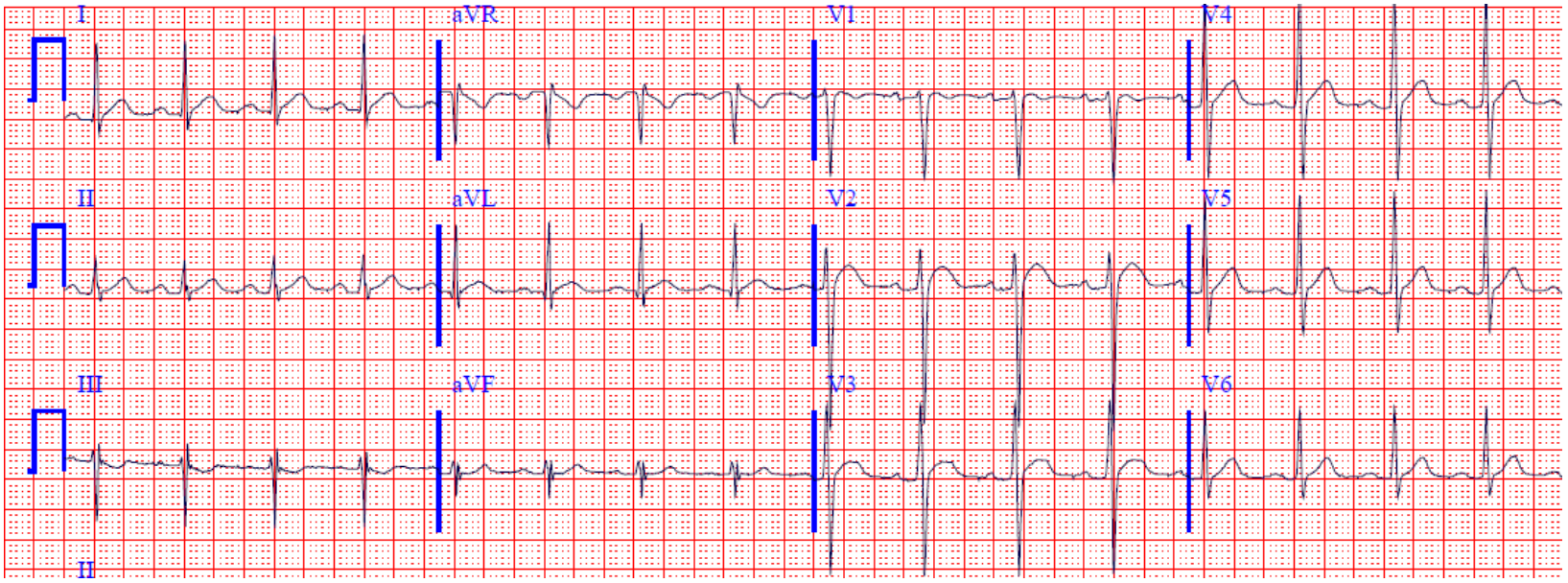
Hypercalcemia

- Occurs in 10-20% of patients with cancer
- Malignancy most common cause inpatient (hyperPTH most common in clinic)
  - NSCLC, Breast Ca, Myeloma
  - **15% of patients with hypercalcemia AND malignancy have a **separate** cause for the hypercalcemia
    - PTH, thiazide, milk-alkali, granuloma, hyperthyroid, etc
- Physiology
  - PTHrP
  - Increased 1,25 Vit D (lymphoma)
  - Increased bone breakdown (bony lesions)

Histology	% who develop hypercalcemia
Breast	19-30%
Lung	10-35%
Multiple myeloma	20-30%
Head and neck	5-24%
Renal	17%

Hypercalcemia

- Symptoms
  - Nausea, emesis, polyuria/ polydipsia, confusion/ somnolence, psychosis, pain, hyporeflexia, constipation, AKI, bradycardia, ECG changes
    - Prolonged PR, short QT, wide T



Banner MD Anderson Cancer Center
Making Cancer History®

Hypercalcemia

- Treatment
  - Treat underlying malignancy
  - Hydration (~3-7 liters in 24-36hrs)
  - Hydration (Goal UOP >75cc/hr)
  - Hydration
  - Diuretics (furosemide or other loop)
  - Bisphosphonate
  - Dialysis if necessary
  - Calcitonin can help slightly for a few days
    - NOT nasal; must be SQ

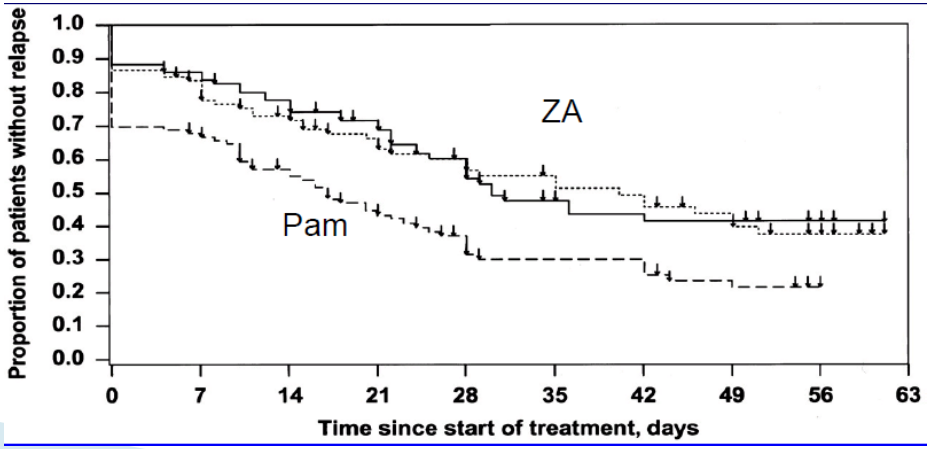
Algorithm for management of hypercalcemia

Calcium level	Symptoms	Therapy
<12 mg/dl (3.0 mM)	None	Observation, or hydration followed by observation
<12 mg/dl (3.0 mM)	Present	Hydration, Bisphosphonate
12-14 mg/dl (3.0-3.5)	Present	Hydration, Bisphosphonate
>14 (>3.5)	Present	Hydration, Bisphosphonate
>14 (3.5)	Severe	Hydration, loop diuretics, calcitonin, bisphosphonate Alternatives; plicamycin, gallium nitrate, prednisone phosphate, dialysis

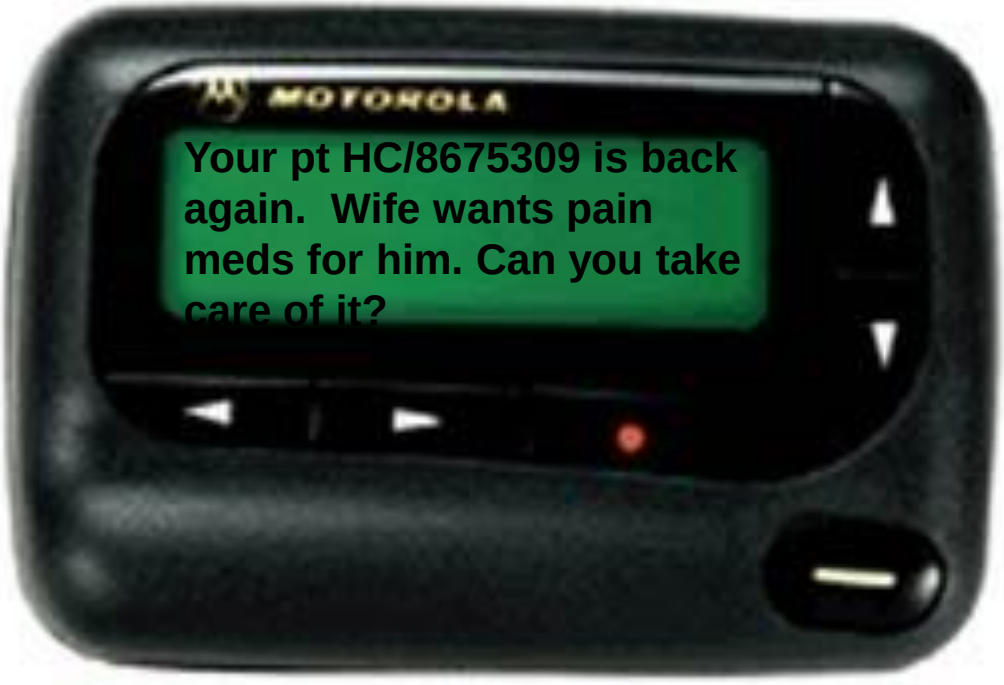
Bisphosphonates

- With first infusion, can cause ‘acute phase’ symptoms: fever, nausea, pain
  - Usually does not recur with later infusions
- Zoledronic acid 4mg or Pamidronate 90mg
  - May cause hypocalcemia in vit D deficiency
  - Rarely osteonecrosis of the jaw
  - Onset of benefit in 24-48hrs
  - Duration of effect 30-40 days
  - If CrCl <30,
    use pamidronate

JCO 2001. 19:558



- Hydration
- Bisphosphonates if symptomatic
- Identify cause (History, PTH, PTHrp, 1,25 VitD)
- Consider furosemide, calcitonin, HD



Banner MD Anderson Cancer Center
Making Cancer History®

Case 6

- 24yo with new diagnosis of AML was treated with idarubicin and cytarabine 10 days ago. He has had some intermittent diarrhea since discharge. He felt febrile at home, so presented to the ED per advice of his oncologist.

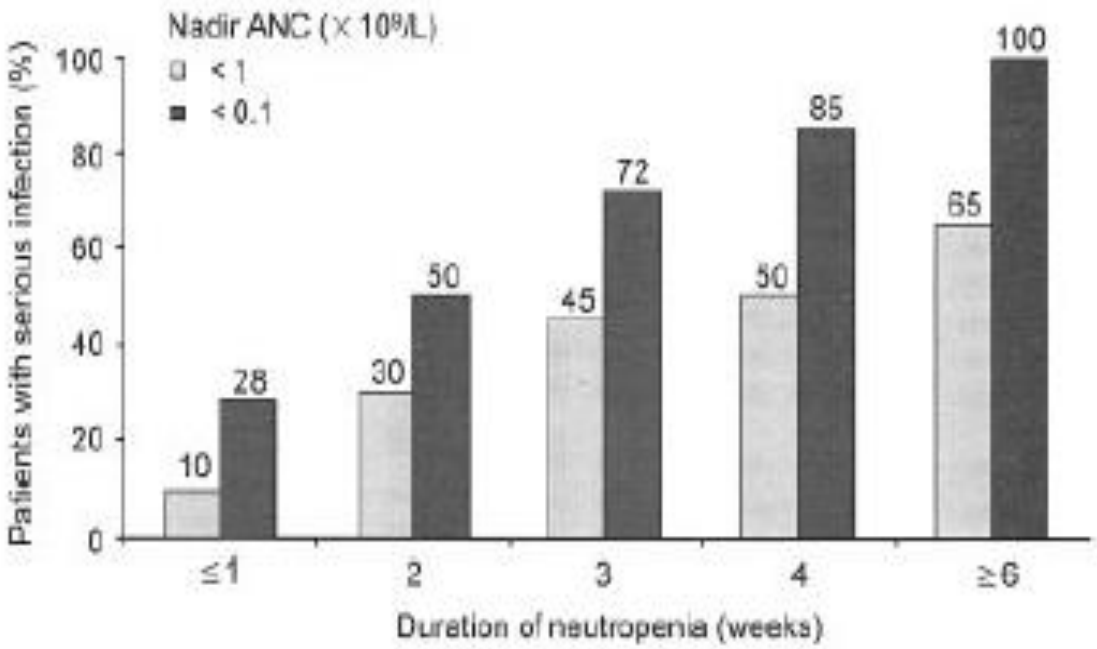
- Exam: Temp 39.5 BP 110/64 HR 90
- He otherwise looks and feels well
- Next step?

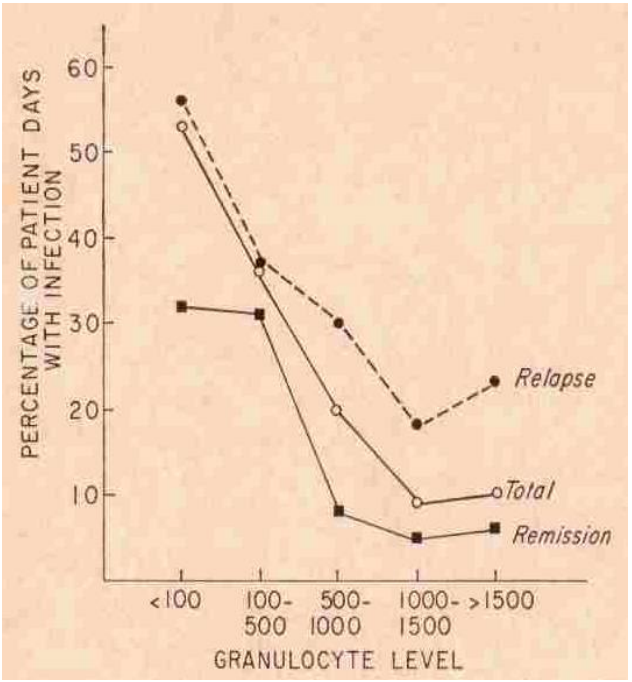
- CBC: 0.1>25%<15k ANC 0
- How do you treat him?

Public Domain
https://commons.wikimedia.org/w/index.php?curid=1685144

Banner MD Anderson Cancer Center
Making Cancer History®

Depth and Duration



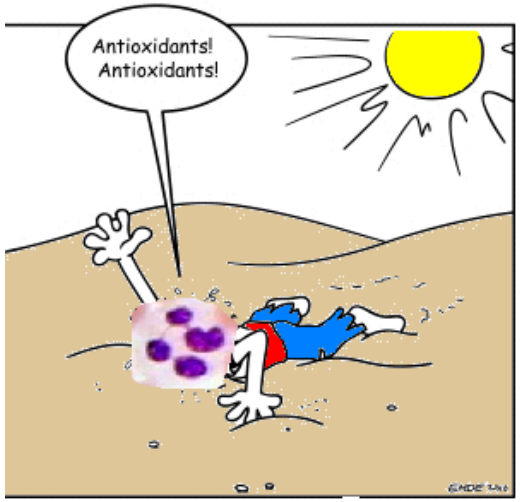


The risk of infection in patients with neutropenia correlates with both the depth and duration of the neutropenia
(Bodey et al. *Ann Int Med* 1966, 2:328 and Viscoli, *Clin Inf Ds* 2005).

Banner MD Anderson Cancer Center
Making Cancer History®

Definitions

- Fever
  - single oral temperature >38.3°C (101°F) or >38.0°C (100.4°F) that persists for 1 hour
- Neutropenia
  - ANC <500 cells/mm^3
  - ANC <1000 cells/mm^3 and expected to nadir below 500 cells/mm^3



Evaluation and Etiology

Physical Examination	Testing
Orthostatic vital signs	CBC with differential
Evaluate for sinus tenderness	Blood cultures x 2 (either one culture from each central line lumen or one central culture and one peripheral) Urine culture (UA is an unreliable screen during neutropenia)
Examine CVC site	Chest x-ray
Thorough skin exam	Review prior culture and resistance data
Perineal exam (no digital rectal exam)	Other imaging as directed by symptoms

Thorough evaluation for source should be undertaken

Type of infection	No. (%) of infections	
	In patients with hematological malignancy	In patients with solid tumor
Pneumonia	93 (38)	99 (26)
Bloodstream	88 (35)	74 (20)
Urinary tract	27 (11)	85 (22)
Skin and soft tissue	17 (6)	65 (17)
Gastrointestinal	16 (6)	38 (10)
Other	12 (4)	17 (5)
Total	253 (100)	378 (100)

NOTE. This survey was conducted September 2001–February 2002; data are from [3].

Yadegarynia, *Clin Inf Ds* 2003

Treatment

- Empiric cefepime (ceftazidine) **2gm q8hrs**
  - PCN-allergic: Aztreonam 2gm q8hrs

- No trial has ever shown improved outcome with empiric addition of vancomycin in febrile neutropenia (so, direct use as clinically indicated)

Special Situations

- Duration of neutropenia >20 days (higher risk of gram negative bacteremia)
  - Consider adding empiric gentamicin
- Past history of frequent cephalosporin exposure (increased risk of resistant gram-negatives)
  - Consider adding gentamicin OR use carbapenem
- Potential or witnessed aspiration (risk for anaerobic infection)
  - Consider adding clindamycin OR use carbapenem
- Clinical tunneled line infection
  - Add empiric vancomycin
- Severe mucositis (possible *S. viridans* bacteremia)
  - Consider adding 72hr trial of empiric vancomycin
- For patients with resistant colonizing organisms on rectal/nasal swab or prior culture:
  - MRSA or PCN-resistant S. pneumonia: consider 72hr trial of empiric vancomycin
  - VRE: consider empiric linezolid or daptomycin
  - Non-albicans candida species: consider adding amphotericin product
  - Prior mold (aspergillus, fusarium): consider adding voriconazole
  - Resistant pseudomonas, stenotrophomonas, enterobacter: consider empiric gentamicin

Vitamin Vanco

- If a patient is placed on an empiric trial of vancomycin, the following “endpoints” should be assessed at 72hrs:
  - Presence of gram positive organisms on blood culture
  - Presence of clinical catheter tunnel infection
  - Clinical response to vancomycin (e.g., patient becomes afebrile after vancomycin was instituted)
- If none of the above are true, consider stopping vancomycin at that time

Persistent febrile neutropenia (>72hrs)

- F/N on antibiotics for >72hrs without identified source of infection
  - Consider Infectious disease consult
  - Probability of invasive fungal infection increases after 3-5 days of persistent fever (without other identified focus) in high-risk patients
    - allogeneic SCT patients
    - neutropenia >20 days
    - patients known to be colonized with mold or fluconazole-resistant yeast, who have not yet received antifungals other than fluconazole – amphotericin B (or other appropriate agent) should be started.
    - In patients not known to be colonized with the above pathogens, the risk of invasive fungal infection and need for additional therapy should be determined with the aid of the following risk factors:
      - History of invasive fungal infection prior to transplantation
      - History of culture negative febrile neutropenia during previous chemotherapy
      - History of ongoing steroid therapy or steroid therapy prior to transplantation
      - Underlying hematologic malignancy (particularly when not in remission)
      - Allogeneic transplantation (with cord blood recipients at highest risk)
      - Duration of neutropenia > 20 days
      - Age > 40
      - Prior history of CMV disease

- In Patients without risk factors, or if neutropenia is expected to resolve within three days – additional diagnostic testing (eg CT Chest to look for invasive aspergillosis, CT abdomen with contrast to evaluate for hepatic candidiasis, and/or CT sinuses) can be performed prior to initiating empiric antifungal therapy. Biopsy of abnormalities seen by CT imaging and/or BAL is strongly encouraged to help establish a microbiologic diagnosis to allow more specific antimicrobial therapy.

- **Empiric Management of Septic Shock:**
- For patients with signs of septic shock (i.e. hemodynamic instability), empiric antibiotics should be ordered and administered immediately (<1hr from time of evaluation) since the time to antibiotic receipt is a strong predictor of outcomes. If the patient is diagnosed with sepsis and neutropenia in the clinic, antibiotics should be started prior to transfer to the hospital for further management. (after blood cultures drawn)

- In the absence of empiric treatment, mortality in severely neutropenic patients with gram-negative bacteremia approaches 40%
  - Schimpff et al. *NEJM* 1971. 284:1061, Klastersky *Am J Med* 1986. 80:2.
- Over 50% of neutropenic patients present with fever as the only symptom of infection
  - (Klastersky *J Cancer Clin Onc* 1988. 24:S35)

- **<u>Antibiotics do not cure infections, neutrophils do</u>**