

Oncologic Problems: A Case-Based Approach

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Disclosure of Relationships

I have no real or apparent conflict of interest with the material in this presentation. I have no financial relationships to disclose.



Objectives

- Understand some of the more common problems in oncology
- Articulate a plan for management of the common oncologic problems utilizing a case-based approach

Case 1

- 72 y/o female with newly diagnosed Ann Arbor Stage II diffuse large B cell lymphoma presents with fever to ER. She completed her first cycle of chemotherapy one week ago. She had chills this evening, with a fever of 100.4° F. Presents per her oncologist's instructions
- She denies any cough, urinary frequency or urgency, N/V/D. No recent sick contact or recent travel history

Case 1

- History
 - PMH: HTN, Hypothyroidism
 - PSH: Appendectomy and hysterectomy
 - FH: Father-HTN, DM, CAD
 - SH: quit smoking 35 yrs ago, social drinker
 - ROS: (+) for fever and chills, (-) for cough, diarrhea, urinary symptoms

Case 1

- Exam

- Vitals: T-101.1°F , P- 96, R-16, SaO₂- 97% RA
- HEENT-No pallor/icterus, No palpable LN
- Port site clean, non-tenender, no erythema
- Resp-no rhonchi/rales, CTA
- CVS-R/R/R, no murmurs. DP 2+ b/l
- Abd-NT/ND, BS (+), no organomegaly
- Ext-no edema
- Neuro-A/Ox3, nonfocal

Case 1

- Labs
 - Hb 11.9
 - WBC 2.9, ANC 400
 - Platelets 230k
 - Chemistries normal
 - INR 1.1
 - Lactate 1.4

Case 1

- What is the diagnosis?
Febrile Neutropenia
- What is the next step?
- What Abx?
- What dose?

Febrile Neutropenia

- Definition—oral temperature $>101^{\circ}\text{F}$ (38.5°C), or two consecutive readings of >100.4 for $\geq 1\text{hr}$ with ANC <500 , or <1000 with predicted decline to $<500/\text{mm}^3$
- Despite major advances in prevention and treatment, remains one of the most concerning complications of cancer chemotherapy, and is a major cause of morbidity
- Success in management requires prompt recognition of, and reaction to, potential infection

Febrile Neutropenia

- Incidence...
 - 5% in solid tumors
 - 11% in some hematologic malignancies
 - Mortality is worse in patients with proven bacteremia
 - 18% in Gram-negative
 - 5% in Gram-positive

Febrile Neutropenia

- Over the last few decades a shift has occurred from Gram-negative bacteria to Gram-positive organisms
 - Of (+) blood cultures, about 70% are reported to be Gram-positive organisms
- An increase in antibiotic-resistant strains such as ESBL-producing Gram-negative bacteria, VRE, MRSA
- Increasing numbers of infections with fluconazole-resistant *Candida* strains (e.g. *Candida krusei* and *Candida glabrata*) also reported

Initial Management of Febrile Neutropenia

- Note presence of indwelling IV catheters
- Symptoms/signs of infectious focus
 - Respiratory tract
 - GI tract
 - Skin
 - Perineal region/GU discharge
 - Oropharynx
 - CNS

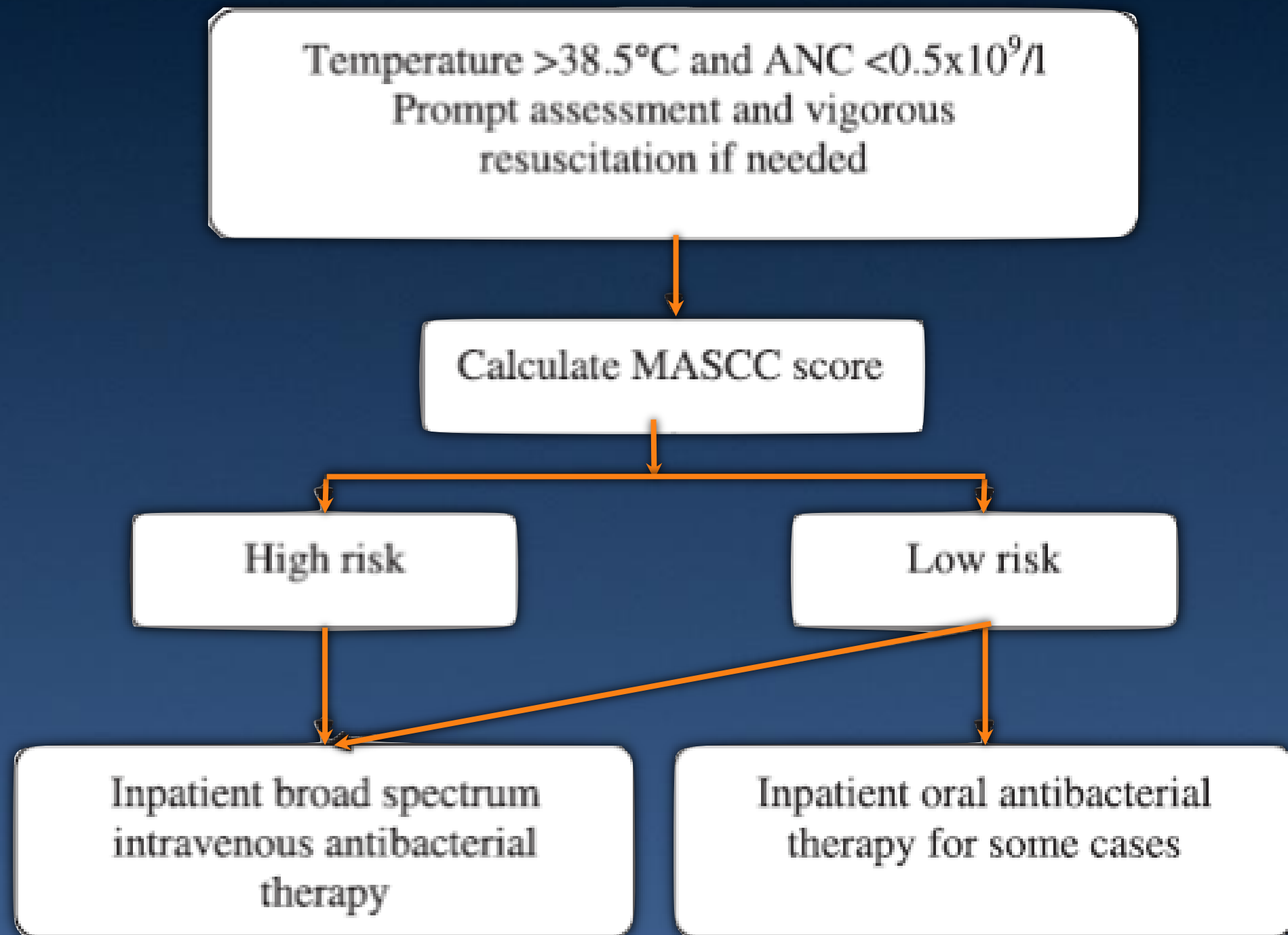
Initial Management of Febrile Neutropenia

- Check for previous positive microbiology reports
- Routine studies...
 - Labs to assess bone marrow, liver, renal function
 - Coagulation screen
 - C-reactive protein
 - Blood cultures (2 sets minimum) including one set from IV line
 - UA with culture
 - Sputum culture
 - CXR

Multinational Association for Supportive Care (MASCC) Score

Characteristic	Score
Burden of illness: no or mild symptoms	5
Burden of illness: moderate symptoms	3
Burden of illness: severe symptoms	0
No hypotension (systolic BP >90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor/Lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient at onset of fever	3
Age < 60 years	2

Low-risk cases are those scoring ≥ 21 . The serious medical complication rate in these is estimated to be 6% and mortality just 1%.



Initial Management of Febrile Neutropenia

Febrile Neutropenia

- Treatment of Low Risk Patients
 - Inpatient oral antibiotics can be substituted for conventional IV antibiotics in some low risk patients (hemodynamically stable, no acute leukemia, evidence of organ failure, pneumonia, indwelling venous catheter, severe soft tissue infection)
 - Single-agent quinolones were not inferior to combinations (quinolone with amoxicillin plus clavulanic acid) but the latter are preferred given the rise in Gram-positive episodes

Febrile Neutropenia

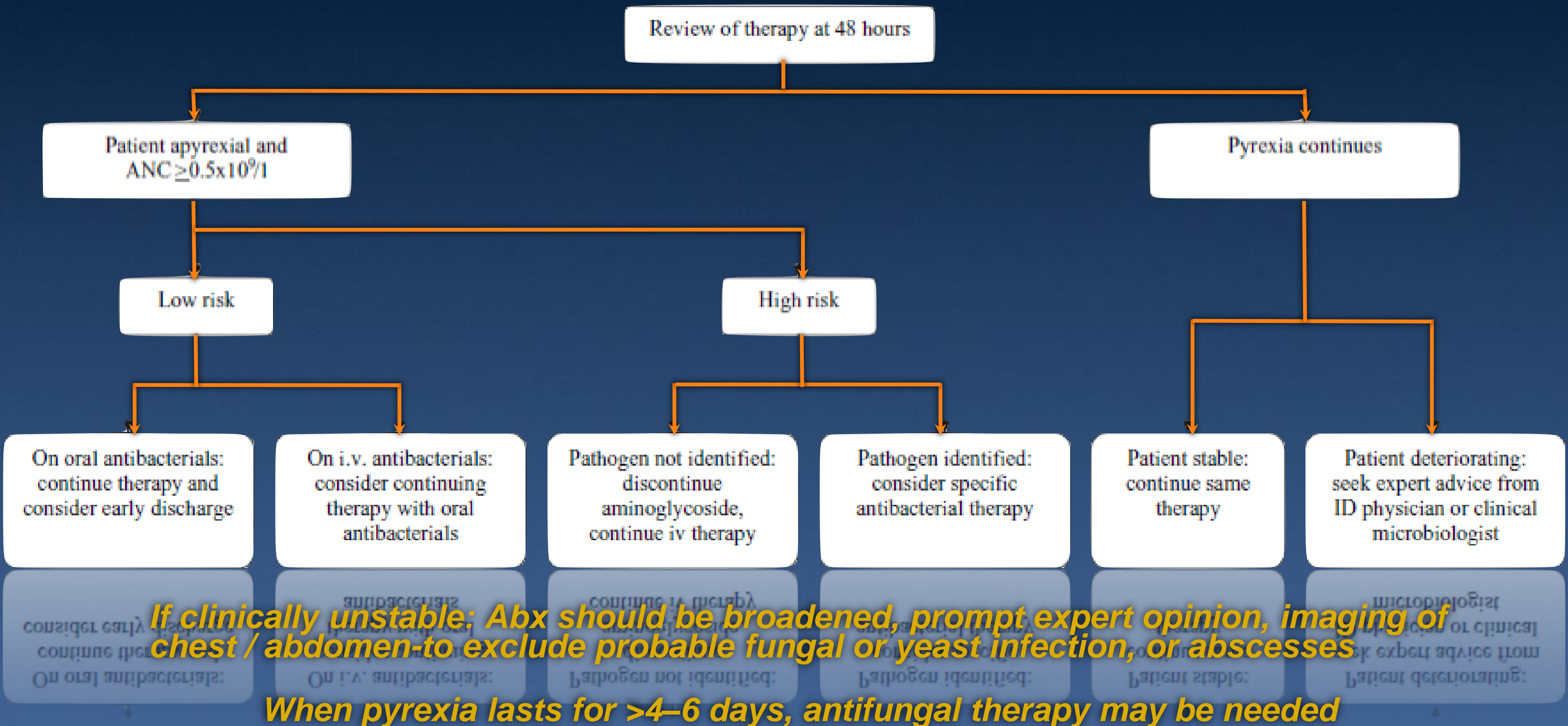
- Treatment of High Risk Patients
 - Patients at high risk should be admitted and treated with broad spectrum IV antibiotics
 - Local epidemiological bacterial isolate and resistance patterns are important in determining first-choice empirical therapy (coverage for MRSA or resistant gram-negative bacteria may be required)
 - A meta-analysis comparing monotherapy (e.g. an anti-pseudomonal cephalosporin like ceftazidime or a carbopenem) with combination therapy found equivalent efficacy

“Doctor, can I do this at home?”

...can patients with low-risk febrile neutropenia be treated as an outpatient?

- One study closed due to poor accrual (Talcott, JA, et al.; Jour. Clin. Oncol. 2011) demonstrated no difference in outcomes for patients with low-risk febrile neutropenia treated as outpatients and compared with an inpatient cohort
- Seems reasonable for stable patients who...
 - Live close to facility
 - Are reliable and will call with changes
 - Can take fluids and nutrition po
 - Can follow-up as outpatients frequently (most centers qod)

Febrile Neutropenia



Febrile Neutropenia

- If ANC > 500 , patient is afebrile for 48 hours and blood cultures are negative, antibiotics can be discontinued
- If ANC ≤ 500 , patient is afebrile for 5–7 days, antibiotics can be discontinued except high-risk cases like acute leukemia or following high-dose chemotherapy, when antibacterials are often continued for up to 10 days or until ANC ≥ 500
- Patients with persistent fever despite neutrophil recovery should be assessed by an ID physician and antifungal therapy considered

Febrile Neutropenia

- Suggested inpatient empiric regimen...
 - Cefepime 1-2 gm IV every 12 hr
 - Vancomycin 15 mg/kg IV every 12 hr
 - If fungal infection suspected add Caspofungin 70 mg IV loading dose on day 1, then 50 mg IV daily
- Suggested outpatient empiric regimen...
 - Ciprofloxacin 500 mg po every 12 hr and Amoxicillin/clavulanic acid 875 mg po every 12 hr

Case 2

- A 26 y/o male is admitted to the hospital after recent diagnosis of AML for inpatient chemotherapy
- He is in normal health, and has no complaints
- He is scheduled to begin therapy with cytarabine and daunorubicin

Case 2

- History
 - PMH: Asthma
 - PSH: No surgeries
 - FH: Mother-asthma, hyperlipidemia
 - SH: smokes 3-4 cig/day for 5 years, drinks socially, no hx of IVDA
 - ROS: no complaints

Case 2

- Exam

- Vitals: T-98.6°F, P-78, BP-122/78, R-16, SaO₂-98% RA
- General- comfortable, in no distress
- HEENT- Pallor(+), No icterus, no pharyngitis
- Resp-CTA
- CV-RRR, no m/r/g
- Abd-no organomegaly, NT/ND, BS(+)
- Ext-no c/c/e
- Skin-no ecchymosis or purpura
- Neuro-A/Ox3, nonfocal

Case 2

- Labs
 - Hb 6.4gm
 - WBC 86,000
 - Platelets 70k
 - Na 145, K 5.0, BUN 24, Creat 1.6, LDH 720, Uric Acid 6.9

Case 2

- What is the most appropriate step before initiation of induction chemotherapy?
 - A. Administration of granulocyte colony stimulating factor
 - B. Administration of vancomycin
 - C. Aggressive IVF and allopurinol
 - D. Alkalinization of urine

Tumor Lysis Syndrome

- Etiology
 - Spontaneous or treatment induced lysis of malignant cells
 - Hyperkalemia, hyperuricemia, hyperphosphatemia, hypocalcemia, acute renal failure
 - Onset—within 1-5 days of induction chemotherapy
 - Highest risk—Acute leukemia and high grade lymphomas (less commonly associated with solid tumors)
 - Routine myeloid growth factor administration during induction chemotherapy—not recommended

Tumor Lysis Syndrome

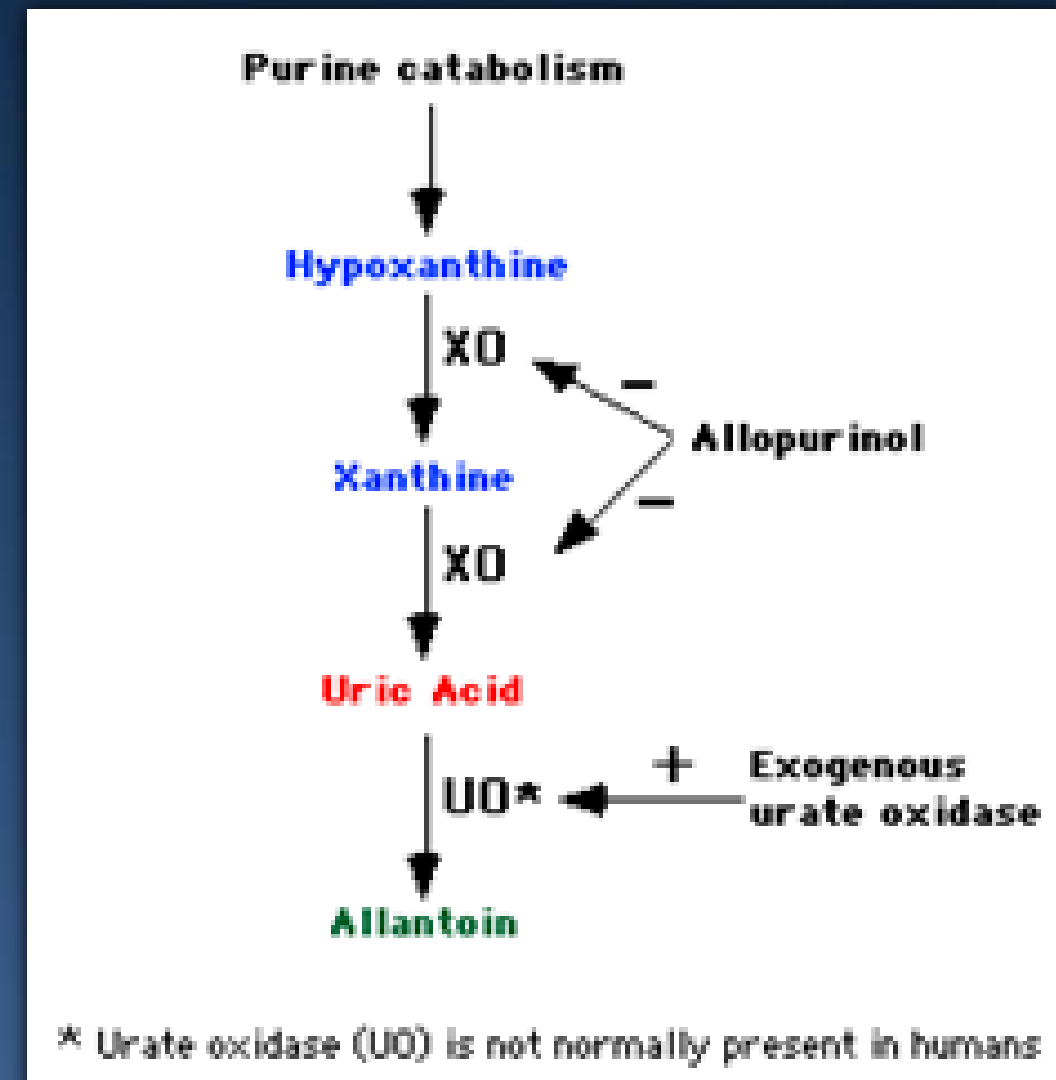
- Risk factors...
 - High leukocyte count
 - Bulky disease
 - High pretreatment LDH levels or uric acid levels
 - Compromised renal function
 - Concomitant use of nephrotoxic agents

Tumor Lysis Syndrome

- Prevention...
 - Vigorous hydration
 - Allopurinol 300-900 mg/day
 - Ideally 2 days before cytotoxic therapy
 - Role of urinary alkalization is controversial
 - In patients with hyperphosphatemia, increased risk of tissue deposition of calcium phosphate
 - Vigorous hydration with saline is likely as effective

Tumor Lysis Syndrome

- Rasburicase (Elitek[®])—Rapidly lowers uric acid by oxidizing it to allantoin which is water soluble



* Urate oxidase (UO) is not normally present in humans

Allantoin

Case 3

- 60 y/o male presents to ER with shortness of breath. SOB has progressively got worse over the last month. Also has nonproductive cough, facial swelling and difficulty swallowing. Has not seen a doctor for many years
- Denies any fevers, chills, chest pain, leg swelling, recent weight gain

Case 3

- History
 - PMH: HTN, hyperlipidemia
 - PSH: Cholecystectomy
 - FH: HTN, CAD, DM
 - SH: 45 pack year smoking history, drinks socially
- Medications
 - HCTZ 25 mg daily
 - Aspirin 81 mg daily
 - Fish oil daily
- ROS: (+) for SOB, cough, dysphagia, weight loss, facial swelling

Case 3

- Exam

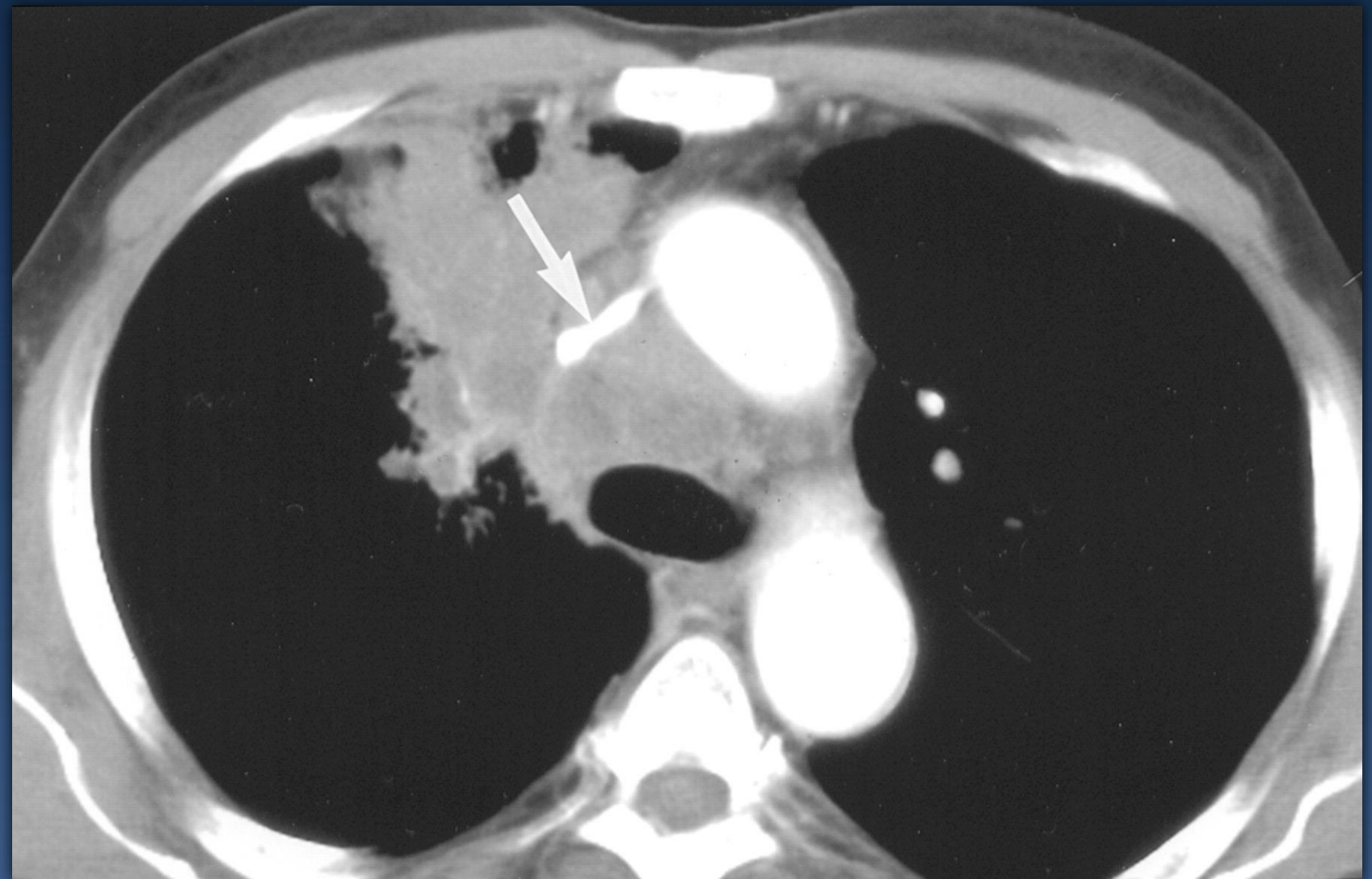
- Vitals: T-99°, P-86, BP-102/63, R-18, SaO₂-96%
RA
- General-appears cachectic, in no acute distress, face edematous with distended neck veins
- CV-RRR, no m/r/g, 2+ DP pulses b/l
- Resp- ↓BS b/l, no wheeze, rhonchi
- Abdomen-soft/ nontender / nondistended / BS(+)
- Extremities- No edema, cyanosis, clubbing
- Neuro- A/Ox3, speaks appropriately and normal strength

Case 3

- Labs
 - Chemistries normal
 - Hb 12.9
 - WBC 4.6, platelets 167k

Case 3

Imaging



Case 3

- What is the diagnosis?
Superior Vena Cava Syndrome
- What is the next step?

Superior Vena Cava Syndrome

- Etiology
 - SVC syndrome is characterized by gradual, insidious compression/obstruction of the superior vena cava
 - Easy to compress as SVC has a thin wall and low intravascular pressure and is surrounded by rigid structures
 - The low intravascular pressure also allows for the possibility of thrombus formation, such as catheter-induced thrombus
 - The subsequent obstruction to flow causes an increased venous pressure, resulting in interstitial edema and retrograde collateral flow

Superior Vena Cava Syndrome

- Causes
 - More than 90% of patients have an associated malignancy as the cause
 - Infectious causes (syphilis, tuberculosis) have decreased because of improvements in antibiotic therapy
 - Thrombosis from central venous instrumentation (catheter, pacemaker, guidewire)

Superior Vena Cava Syndrome

- Causes
 - Bronchogenic carcinoma accounts for more than 80% of cases
 - Lymphomas account for about 15%
 - Even when treated with radiation, only 10% of these patients are alive 30 months after presentation
 - Patients with superior vena cava syndrome due to a malignant cause survive only 30 days without radiation

Superior Vena Cava Syndrome

- Evaluation
 - The diagnosis of superior vena cava syndrome is often made on clinical grounds alone, combining clinical presentation with a history of thoracic malignancy
- Imaging
 - Plain radiography
 - Venography
 - CT chest

Superior Vena Cava Syndrome

- Management
 - Attention to the ABCs is essential
 - Stabilize the airway and consider steroids
 - If cerebral/airway edema is present, consider diuretics
 - Endovascular shunts are increasingly used, as are thrombolytics if a thrombotic cause is present
 - After a tissue diagnosis, radiation and chemotherapy may be initiated

Superior Vena Cava Syndrome

- Complications
 - Total superior vena cava obstruction
 - Fortunately, this is rare
 - Potential causes include indwelling catheters
 - Thrombolysis must be considered
 - Airway compromise is unusual but may result from extrinsic compression of the superior vena cava or the trachea by the tumor mass

Superior Vena Cava Syndrome

- Prognosis
 - The prognosis for relief of symptoms is good with radiation therapy
 - Symptoms usually decrease within 1 month of the onset of radiation therapy
 - However, the ultimate prognosis is associated with underlying malignancy
 - If not associated with malignancy, prognosis is excellent

Case 4

- A 62 year old female was brought to the ER by neighbor who found her confused
- Had been acting strange over last two weeks, with occasional hallucinations, increased somnolence, progressively worsening anorexia, weight loss, and constipation
- Diagnosed 4 years ago with stage II right breast infiltrating ductal carcinoma
 - Treated with mastectomy, adjuvant chemotherapy, then placed on anastrozole

Case 4

- History
 - PMHx: Breast Ca, HTN
 - SH: denies tobacco, alcohol, or drugs
 - Meds: Anastrozole, HCTZ
 - Family Hx: Mother died of breast Ca at age 55
 - ROS: weight loss, fatigue, back pain, depression

Case 4

- Exam

- Vitals: T- 98.6°, BP-100/70, P- 75/min, Pox-99%RA
- General: lethargic, not in distress
- HEENT: dry mucous membranes, anicteric sclera
- CNS: A/O x 1, confused; unable to follow simple commands; minimally verbal; No focal signs
- Chest: CTA b/l, No crackles, No wheezing
- Heart: RRR, No m/r/g
- Abdomen: Soft, NT, ND, +BS
- Osteo: tender in ribs bilat, No CVA tenderness; pain over spinous processes L2-4
- Extremities: No C/C/E

Case 4

- Labs
 - Electrolytes normal
 - BUN 31, Creat 1.3
 - UA: SG > 1.024, 3+ ketones, no bacteria or WBC on microscopic exam

Case 4

- Any other labs?
 - Ca 17
- What is the diagnosis?
 - Malignant Hypercalcemia
- Malignancy must be ruled out in patients that present with a very high calcium and no other obvious cause...

Malignant Hypercalcemia

- Signs and Symptoms...
 - Insidious and often non-specific
 - Anxiety, depression, cognitive dysfunction
 - Anorexia, constipation, abdominal pain, pancreatitis (rare), dehydration
 - Polyuria, polydipsia
 - Nephrolithiasis less frequent than in primary hyperparathyroidism
 - CKD if long standing untreated hypercalcemia
 - CV: Short QT interval, supraventricular and ventricular arrhythmias

Malignant Hypercalcemia

- Incidence
 - Occurs in 10 to 20% of patients with cancer
 - Both solid tumors and leukemias
- Most common: breast, lung, myeloma

Malignant Hypercalcemia

- Diagnosis...
 - Clinical symptomatology with
 - History of cancer
 - Risk factors for cancer
 - Suppressed PTH
 - Check PTHrP to confirm malignant hypercalcemia
 - High PTHrP may predict response to bisphosphonates

Malignant Hypercalcemia

- Intravenous hydration with isotonic saline
 - ***Volume, Volume, Volume!!!***
- Forced diuresis/calciuresis with furosemide (after rehydration)
 - Lower serum calcium
- Administration of bisphosphonates

Malignant Hypercalcemia

- Treatment
 - Calcitonin: interferes with osteoclast maturation
 - Works the fastest (onset within hours, duration 2-4 days)
 - Bisphosphonates: (pamidronate, zoledronate)
 - Interferes with osteoclast activity, cytotoxic to osteoclasts
 - Inhibits calcium release from bone
 - Other treatment options:
 - HD (last resort, if can't tolerate volume expansion and/or rapid correction of hypercalcemia needed)

Malignant Hypercalcemia

- Bisphosphonates
 - More potent than calcitonin
 - Maximum effect occurs in 2 to 4 days
 - Trend toward use of IV zoledronic acid in the acute situation (compared to pamidronate)
 - Both are nephrotoxic
 - Zoledronic acid more potent than pamidronate and is administered over a shorter period of time (15 minutes vs. 2 hours)

Malignant Hypercalcemia

- Prophylactic Use
 - Pamidronate use in patients with known lytic lesions
 - Less episodes of hypercalcemia
 - Less pathologic fractures
 - Less pain
 - Less spinal cord compression
 - Less need for radiation or surgery
 - Risk of Osteonecrosis of the jaw

References

- Escalante, CP. Causes and management of superior vena cava syndrome. *Oncology* (Huntingt) 1993; 7:61.
- Parish, JM, Marschke, RF Jr, Dines, DE, Lee, RE. Etiologic considerations in superior vena cava syndrome. *Mayo Clin Proc* 1981; 56:407.
- Rowell, NP, Gleeson, FV. Steroids, radiotherapy, chemotherapy and stents for superior vena caval obstruction in carcinoma of the bronchus: a systematic review. *Clin Oncol (R Coll Radiol)* 2002; 14:338
- [Bessmertny O, Robitaille LM, Cairo MS](#); Rasburicase: a new approach for preventing and/or treating tumor lysis syndrome.; *Curr Pharm Des.* 2005;11(32):4177-85.
- [Cervantes A and Chirivella J](#); Oncological Emergencies.; *Annals of Oncology* 2004;15 Suppl 4: iv 299-306
- J. de Naurois, I. Novitzky-Basso, M. J. Gill, F. Marti Marti, M. H. Cullen and F. Roila; Management of febrile neutropenia: ESMO Clinical Practice Guidelines, *Annals of Oncology* 21 (Supplement 5): v252–v256, 2010
- Shiber J, Fontane E, Oncologic emergencies; *Emer. Med. Rept.*, 2014 (Aug); online version at <https://www.ahcmedia.com/articles/118670-oncologic-emergencies>.