Oncologic Emergencies

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Objectives

- Provide an overview of the diagnosis and management of common oncologic emergencies
- Describe the first steps in management including the appropriate consultants to involve early in the care of the patient
- Help lower your pulse rate whenever you encounter these patients

Case 1

A 64-year-old woman presents to the ER with unintentional weight loss, back pain, fatigue, and difficulty walking for the past 2 days. There is no history of trauma.

She has a history of breast cancer treated 10 years ago with a mastectomy and chemotherapy and is currently in remission.

On exam: BP 110/72, HR 100, RR 18, Afebrile, 02 saturations 97% on RA. She has tenderness to palpation over the mid thoracic spine and upper lumbar spine. She has decreased sensation in a band starting at T7 level. Her arm strength is 5/5 but her legs are weak bilaterally and her patellar and ankle reflexes are brisk.

A PA and lateral chest x-ray and thoracic spine x-ray are reported as normal.

You are called to by the ED physician to admit this patient.

Which of the following is the most appropriate next step in management?

A. Stat Neurology consultation
B. Stat MRI of the C, T , L, and S spine
C. Stat dexamethasone 10 mg IV and stat MRI of spine, cord compression protocol
D. Stat MRI of spine, cord compression protocol

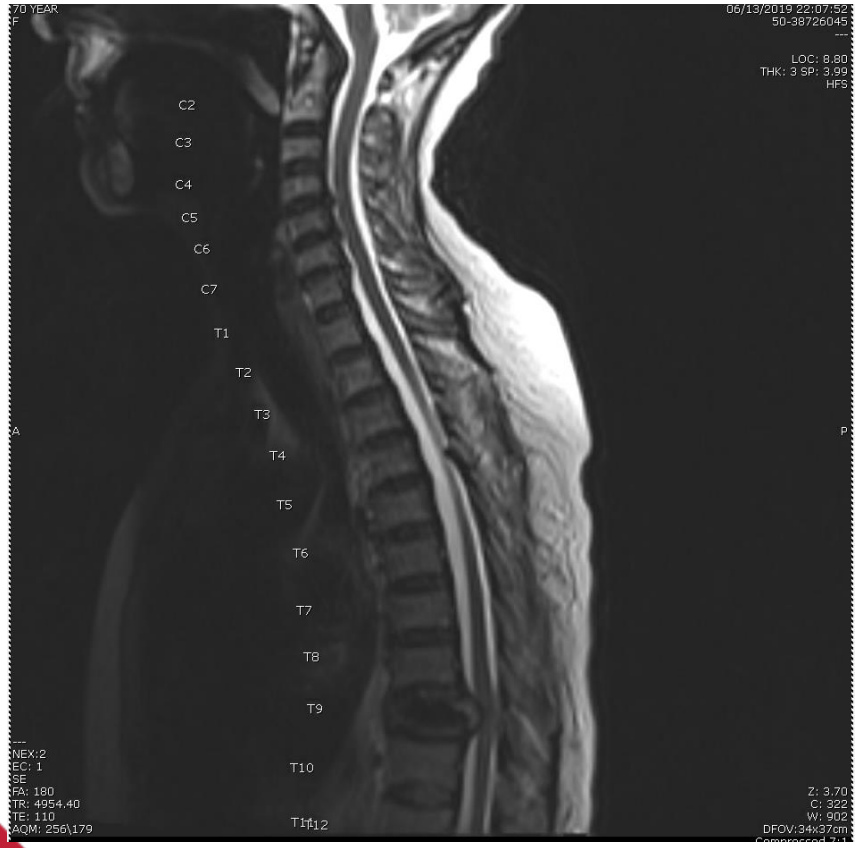
Spinal Cord Compression

- Clinical Presentation
  - Back pain (95%)
  - History of cancer = red flag
  - Weakness
  - Sensory level change
  - Bowel/Bladder dysfunction
- Physical Exam
  - Point tenderness over spinous processes
  - Motor weakness
  - Loss of sensation
  - Upper motor neuron signs (brisk reflexes)

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

Spinal Cord Compression

- Diagnosis:
  - Stat MRI of spinal cord compression protocol (20 minutes)
  - 70% of cases involve thoracic spine
  - 50% involve multiple levels



Spinal Cord Compression

- If neurologic compromise is evident, treatment should include
  - High dose steroids dexamethasone 10 -100 mg IV x 1 then 4-10 mg every 6 hours with taper over 2-3 days
  - Quick action with steroids may help prevent permanent paralysis
- Consult neurosurgery or ortho/spine surgery emergently for decompression/biopsy

The historical perspective

- Prior to 2005, the standard treatment of spinal cord compression from cancer was steroids and radiation therapy

- ***Patchell et al, Lancet, 2005***
- Randomized, non-blinded trial
- 50 pts randomized to surgery, then radiation therapy
- 51 patients randomized to radiation therapy alone
- Both treatment arms received 10 3 Gy fractions

- Primary Endpoint:
  - Ability to walk

- Secondary Endpoints:
  - Urinary continence
  - Functional status
  - Muscle strength
  - Need for opiates/steroids
  - Survival Time

Study stopped early

- Surgery group (n=50)
  - 84% (42/50) able to walk
  - Duration median 122 days
  - 62% (10/16) ***regained*** ability to walk
- Radiation group (n=51)
  - 57% (29/51%) able to walk
  - Duration median 13 days
  - 19% (3/16) ***regained*** ability to walk

Interpretation:

Direct decompressive surgery plus postoperative radiotherapy is superior to treatment with radiotherapy alone for patients with spinal cord compression caused by metastatic cancer.

Spinal Cord Compression Summary

- Give high dose dexamethasone early
- Diagnose with MRI cord compression protocol
- Consult Neurosurgery or Ortho Spine for decompression and biopsy if needed

Case 2

A 24-year-old woman with stage IV Burkitt Lymphoma is admitted for urgent treatment with R-hyper-CVAD chemotherapy.

On physical exam: BP 120/70, HR 90, RR 26, afebrile, 02 saturation 95% on RA. She has hepatosplenomegaly on examination. The rest of the exam is unremarkable.

Laboratory studies:

Sodium: 140 mEq/L (136-145 mEq/L)
Potassium: 5.9 mEq/L (3.5-5.0 mEq/L)
Chloride: 110 mEq/L (98-106 mEq/L)
C02: 14 mEq/L (23-28 mEq/L)

Laboratory studies continued:

BUN: 20 mg/dL (8-20 mg/dL)
Creatinine: 2.4 mg/dL (baseline 0.7 mg/dL)
Phosphorus: 9.0 mg/dL (3-4.5 mg/dL)
Calcium: 4.7 mg/dL (9-10.5 mg/dL)
Uric acid: 20 mg/dL (2.4-5.8 mg/dL)

In addition to IV fluid infusion, which of the following is the most appropriate management for this patient?

A. Alkalinization of the urine
B. Acidification of the urine
C. Allopurinol
D. Rasburicase

Tumor Lysis Syndrome (TLS)

- Release of intracellular contents **spontaneously** or **due to chemotherapy** causing metabolic derangements

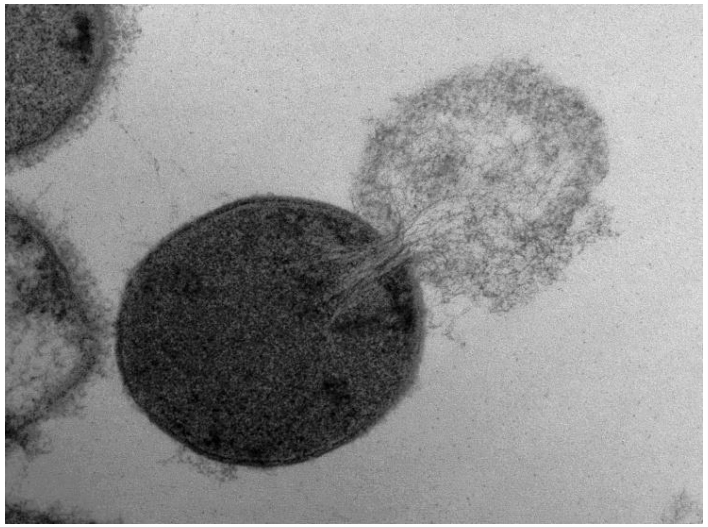


Image: Daniel Nelson, UMD

- Metabolic derangements
  1. Potassium ↑
  2. Uric acid (cellular purines) ↑
  3. Phosphorus ↑
  4. Hypocalcemia ↓ due to hyperphosphatemia binding calcium

Tumor Lysis Syndrome (TLS)

- Most common cancer types:
  - Leukemia
  - High grade lymphoma (Burkitt)
  - Small cell lung cancer
- High risk features:
  - Tumor > 10 cm
  - LDH > 2x ULN
  - >25K leukemic cells
  - Pre-existing CKD

J Clin Oncol. 2008 Jun1;26(16):2767-78.

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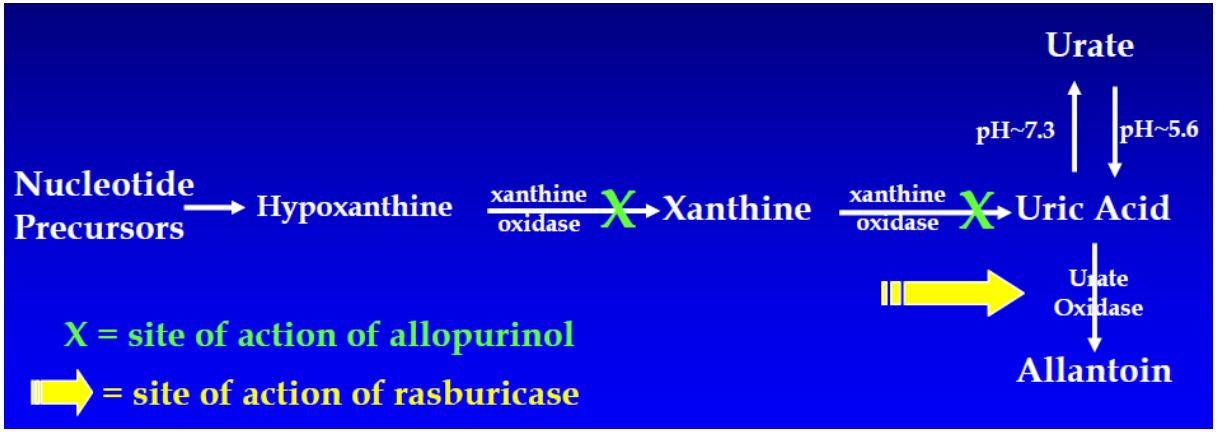
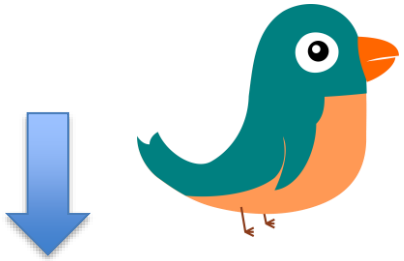
- Cairo-Bishop Laboratory Definition (*at least 2 of 4*):
  1. Uric acid > 6.5-8 (or 25% **above** baseline)
  2. Potassium > 6 (or 25% **above** baseline)
  3. Phosphorus > 6.6 (or 25% **above** baseline)
  4. Calcium < 7 (or 25% **below** baseline)
- Clinical consequences of TLS
  - Acute kidney injury (urate crystals)
  - Cardiac Arrhythmia
  - Seizure

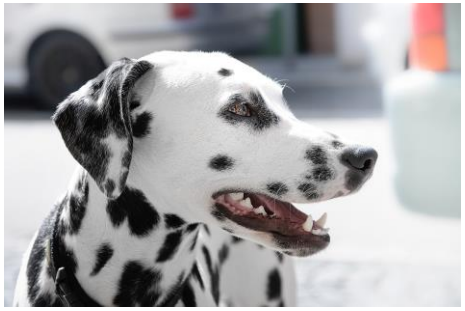
Allopurinol and Rasburicase



Has Urate Oxidase Enzyme!

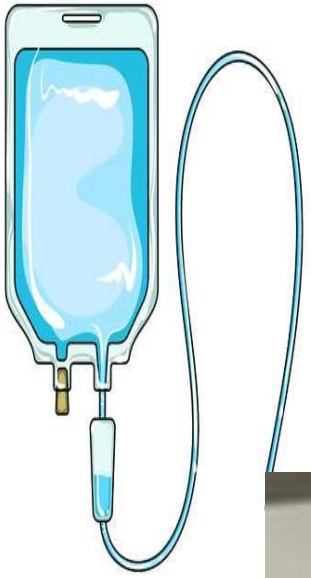


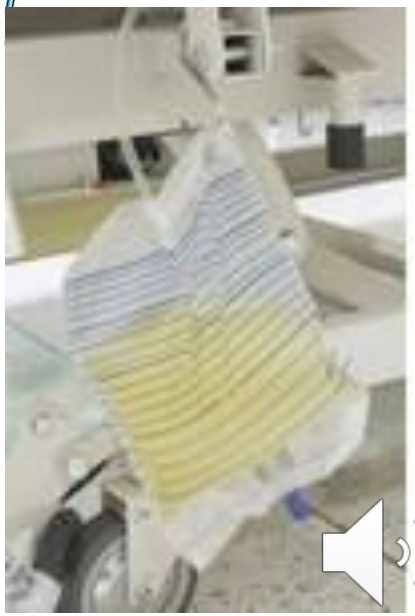
No Urate Oxidase Enzyme…



Tumor Lysis Syndrome Prevention

- **TLS *Prevention***
  - **Hydration:** 0.9% NS at 200 cc/ hour
    - ***No potassium*** in IVF!
    - Monitor closely for fluid overload in patients with CHF or CKD
  - **Goal urine output 80-100 mL/hour**
  - **Start Allopurinol 300mg PO daily**





TLS Treatment

1. Hyperuricemia
   - Rasburicase ***if uric acid > 10 mg/dL and/or low GFR***
   - Repeat uric acid must be sent in special chilled heparin tube on ice, and run as "rasburicase uric acid value" to avoid spuriously low value
   - Use with caution in G6PD deficient patients (hemolysis)
   - Urine alkalinization may improve solubility of uric acid but **worsens calcium phosphate solubility** and can promote calcium phosphate tissue deposition

2. Hypocalcemia
   - Use caution when repleting calcium
   - Calculate the Ca x Po4 product and if >60 can increase risk of precipitation

3. Hyperkalemia
   - Continuous cardiac monitoring
   - Labs q 6 hours stat
   - EKG, usual medical therapy
   - Hemodialysis if refractory to medical management

Tumor Lysis Syndrome Summary

- Suspect TLS based on tumor type and electrolyte derangements seen
- Know importance of fluids and how to manage the electrolyte derangements
- Understand indication for rasburicase
- Consultation nephrology if need help with hyperkalemia or possible need for dialysis

Case 3

A 60-year-old man with acute myelogenous leukemia (AML) develops an acute fever to 38.5^{0}C 7 days after completing induction chemotherapy. His peripheral blood WBC count is 1 (x10^{3}/mm^{3}) and differential with 50% neutrophils.

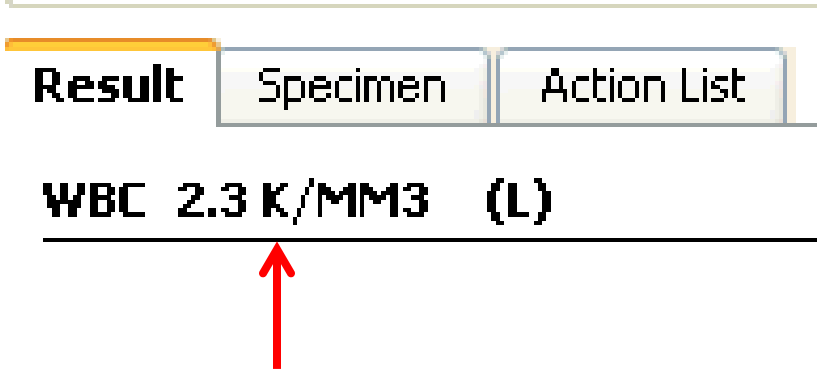
What is his absolute neutrophil count (ANC)?

A 5
B 50
C 500
D 5000
E 50%

Calculating ANC

2.3 x 1000 = 2300 x 0.81 = 1863

WBC	2.3 L
RBC	2.87 L
HGB	8.3 L
HCT	26.9 L
MCV	94
MCH	28.9
MCHC	30.9 L
RDW-CV	19.6 H
RDW-SD	67.0 H
Platelet	174
MPV	12.0
telet Estimate	Normal
f Type	SCAN
Immature Granulocyte % (IG%)	2.2 * H
Immature Granulocyte # (IG#)	0.0
Segs	81



Definition Neutropenic Fever

- Fever:
  - Single oral temperature of ≥ 101°F (38.3°C)
  - Temperature ≥ 100.4°F (38.0°C) over 1 hour

- Neutropenia:
  - ANC < 500 cells/mm^3
  - Expected ANC < 500 cells/mm^3 within the next 48 hours

Chemotherapy Induced Neutropenia

Relationship Between Neutrophil Count and Infection

- Risk of infection increases as the absolute neutrophil count falls below 1000/mm^3
- Risk of infection is related to
  - degree or depth of neutropenia
  - duration of neutropenia
  - rate at which neutropenia occurs

Severe neutropenia
ANC < 100

Bodey et al. *Ann Intern Med.* 1966;64:328-340.

Classification

- Initial neutropenic fever
  - Typically coincides with neutrophil nadir
  - Standard protocol – concern for bacterial infection
- Persistent neutropenic fever
  - Fever despite 4-7 days of empiric antibiotic therapy
  - Complex management – concern for fungal infection
- Recrudescent neutropenic fever
  - Fever that recurs following initial response
  - Wide differential

Case 3 continued:

60-year-old man with AML is admitted for induction chemo. PICC line placed on admission. Develops neutropenia on HD#12 and fever to 38.6^{0}C on HD#15. Patient notes some chills but no other complaints. Exam unremarkable other than P108. CXR negative. Blood cultures are ordered.

What is the most likely source for his infection?

A Bacterial Translocation

B PICC line

C Pneumonia

D Urinary tract

E Intra-abdominal abscess

Etiology / Microbiology

Infectious (~30%)

- ***Bacterial translocation***
  - Intestinal
  - Oropharyngeal
- Community-acquired
  - Respiratory viruses
- Healthcare-associated
  - MDR organisms, C.diff
  - CLABSI, CAUTI
- Opportunistic
  - Herpes virus reactivation
  - Fungal

Non-infectious

- Underlying malignancy
- Blood products
- Tumor lysis
- Hematoma
- Thrombosis
- Phlebitis
- Atelectasis
- Viscus obstruction
- Drug fever
- Myeloid reconstitution

Clinical Evaluation

- Symptoms and signs of inflammation may be minimal or absent in the severely neutropenic patient
  - Cellulitis with minimal to no erythema
  - Pulmonary infection without discernable infiltrate on radiograph
  - Meningitis without pleocytosis in the CSF
  - Urinary tract infection without pyuria
  - Peritonitis - abdominal pain without fever or guarding

Sickles, Arch Intern Med 1975; 135;715-9

Case 3 continued:

60-year-old man with AML admitted for induction chemo. PICC line placed on admission. Develops neutropenia on HD#12 and fever to 38.6^{0}C on HD#15. Patient notes some chills but no other complaints. No recent antibiotic use. Exam unremarkable other than P108. CXR negative. Blood cultures performed.

What is the next best step in management?

A Observe off antibiotics

B Start levofloxacin

C Start cefepime

D Start vanco + cefepime

E Start vanco + cefepime + gentamicin

Initial Neutropenic Fever

- Empiric antibiotics:
  - *Pseudomonas* and *Streptococcus* coverage
    - INPT: Cefepime OR Zosyn OR Meropenem
      - ➢ +/- Aminoglycoside (severe sepsis, significant risk for resistance)
      - ➢ +/- Vancomycin
    - OUTPT: Augmentin + Cipro

- Bacterial etiology:
  - Gram-negative organisms
    - *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella*
  - Gram-positive organisms
    - Coag neg *Staph,* Viridans *Streptococcus,* MRSA *Corynebacterium jeikeium*

Empiric Vancomycin: 6 reasons to use "up front"

- Hemodynamic instability or other evidence of severe sepsis
- Positive blood culture for gram-positive bacteria, before final identification and susceptibility testing is available
- Clinically suspected serious catheter-related infection (eg, chills or rigors with infusion through catheter and cellulitis around the catheter entry/exit site)
- Skin or soft-tissue infection at any site
- Colonization with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, or penicillin-resistant *Streptococcus pneumoniae* (see text)
- Severe mucositis, if fluoroquinolone prophylaxis has been given and ceftazidime is employed as empirical therapy

Case 3 continued:

60-year-old man with AML admitted for induction chemo. PICC line placed on admission. HD#12 neutropenia.

HD#15 Tm 38.6^{0}C. Exam: P108, lethargic/confused. CXR negative. Patient started on vanco + cefepime + gent. HD#17 still febrile 38.3^{0}C x 2d, but mental status back to baseline. D15 and D16 BCxs remain negative.

What is the next best step in management?

A Stop vancomycin

B Change cefepime to imipenem

C Switch to linezolid, imipenem, tobramicin

D Add micafungin

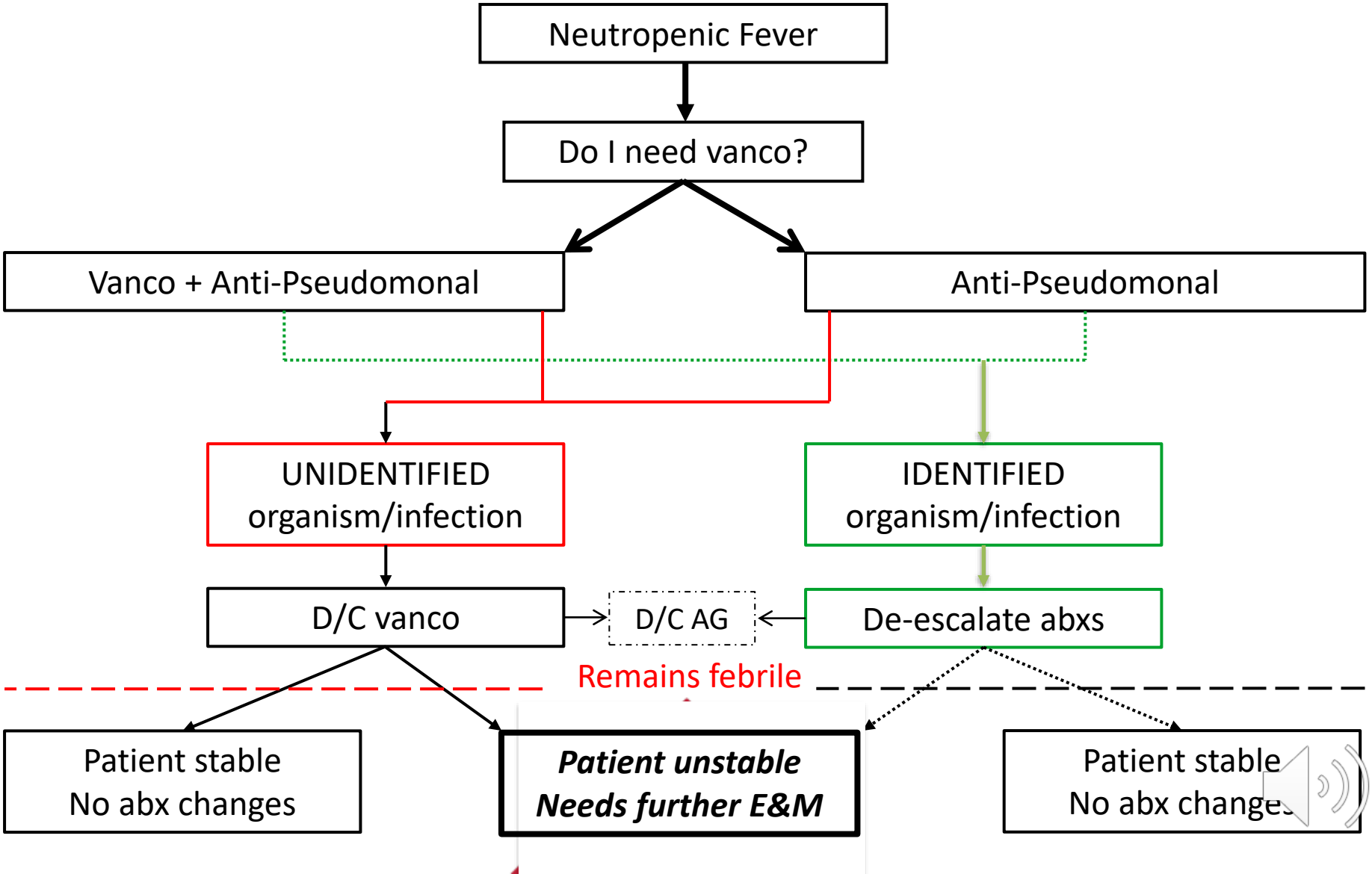
E Continue current regimen

Antimicrobial Modification

18. If vancomycin or other coverage for gram-positive organisms was started initially, it may be stopped after 2 days if there is no evidence for a gram-positive infection (A-II).

Vancomycin can cause nephrotoxicity especially with trough levels > 15.
Synergistic nephrotoxicity with vancomycin in combination with aminoglycosides.

Management Algorithm



Neutropenic Fever: Early Management Summary

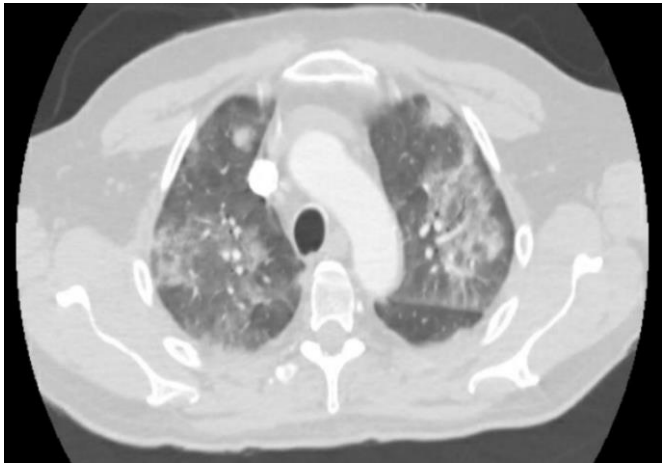
- Initial choice should include coverage for Pseudomonas and Strep
- Vancomycin is NOT routinely indicated except in 6 circumstances
- De-escalate empiric therapy after 48-72 hours
- If organism is isolated, narrow therapy. No need to double cover Pseudomonas if sensitive to monotherapy.
- If clinical worsening
  - Aggressive diagnostics
  - Modify antibiotics to cover for resistant organisms
  - Start anti-fungal therapy
- The ID consultant is your friend

Case 4

A 70-year-old man is diagnosed with a left parietal scalp melanoma, at least 1.3 mm in depth, no ulceration. He underwent wide local excision and sentinel lymph node biopsy. The final pathology revealed 7.1 mm depth and 1/3 lymph nodes involved. PET/CT showed no evidence of metastatic melanoma.

He received cycle 1 of adjuvant pembrolizumab.

Approximately 2 weeks later he was admitted to the hospital with acute hypoxic respiratory failure and a blistering skin rash. He had no fever or leukocytosis.

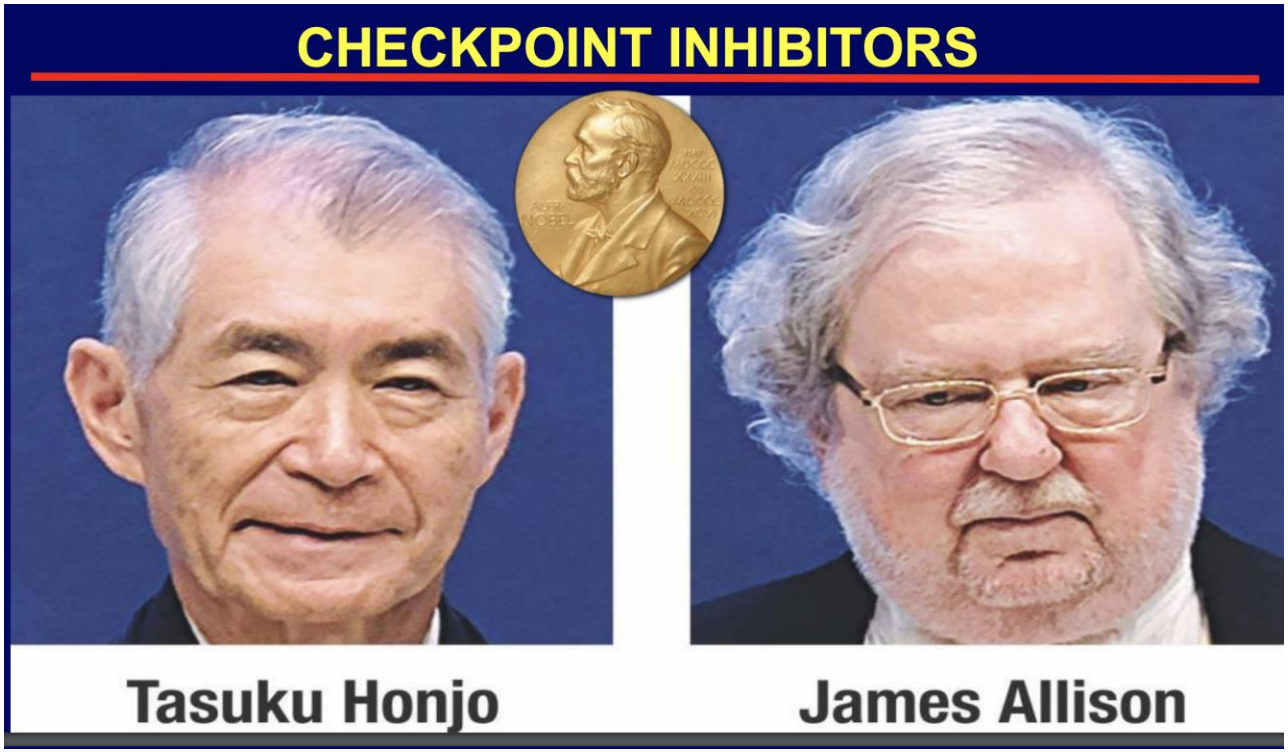


In addition to oxygen and broad-spectrum antibiotic therapy which of the following is the next most appropriate step in management?

A. Consult pulmonary for a stat bronchoscopy
B. Start high dose corticosteroids
C. Perform a skin biopsy of the blistering skin rash

Nobel prize winners in 2018 for Medicine

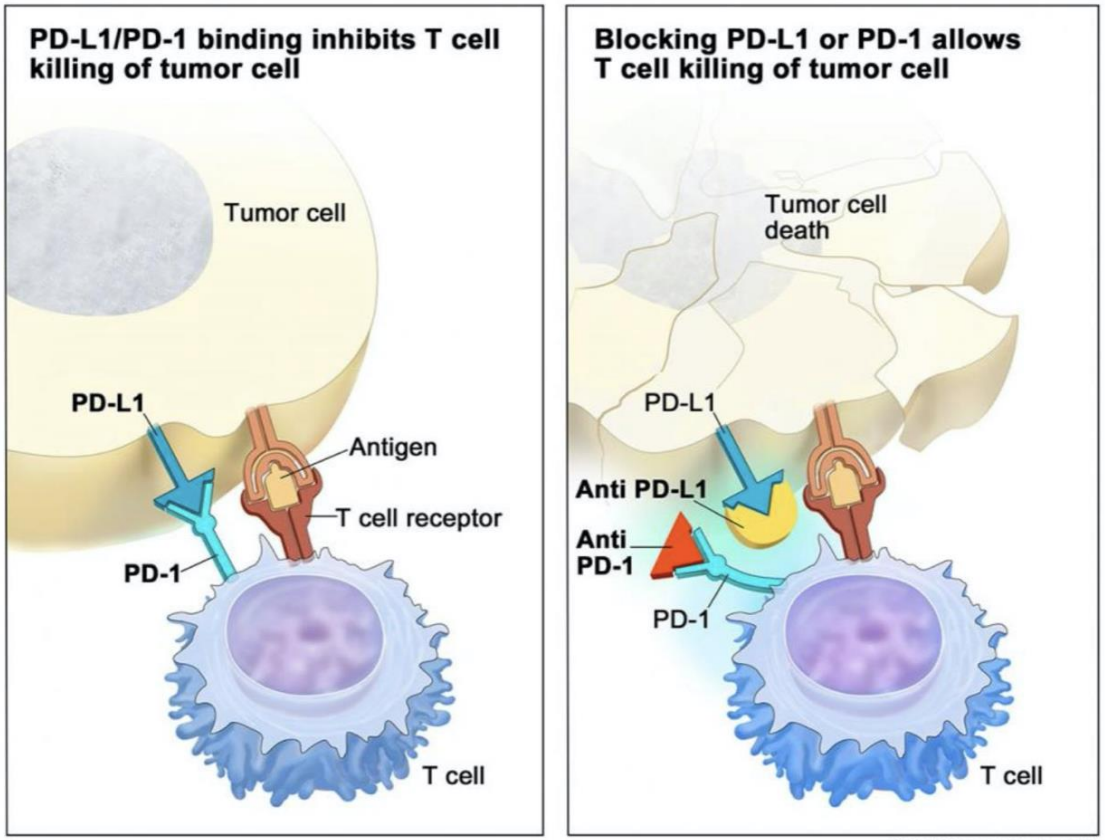
Honjo, a professor in the Department of Immunology and Genomic Medicine at Japan's Kyoto University Graduate School of Medicine, discovered PD-1 on the surface of immune cells in 1992 and later demonstrated that the protein inhibited immune response. His research eventually led to the development of Keytruda (pembrolizumab) and Opdivo (nivolumab), both of which were approved for the treatment of advanced melanoma in 2014

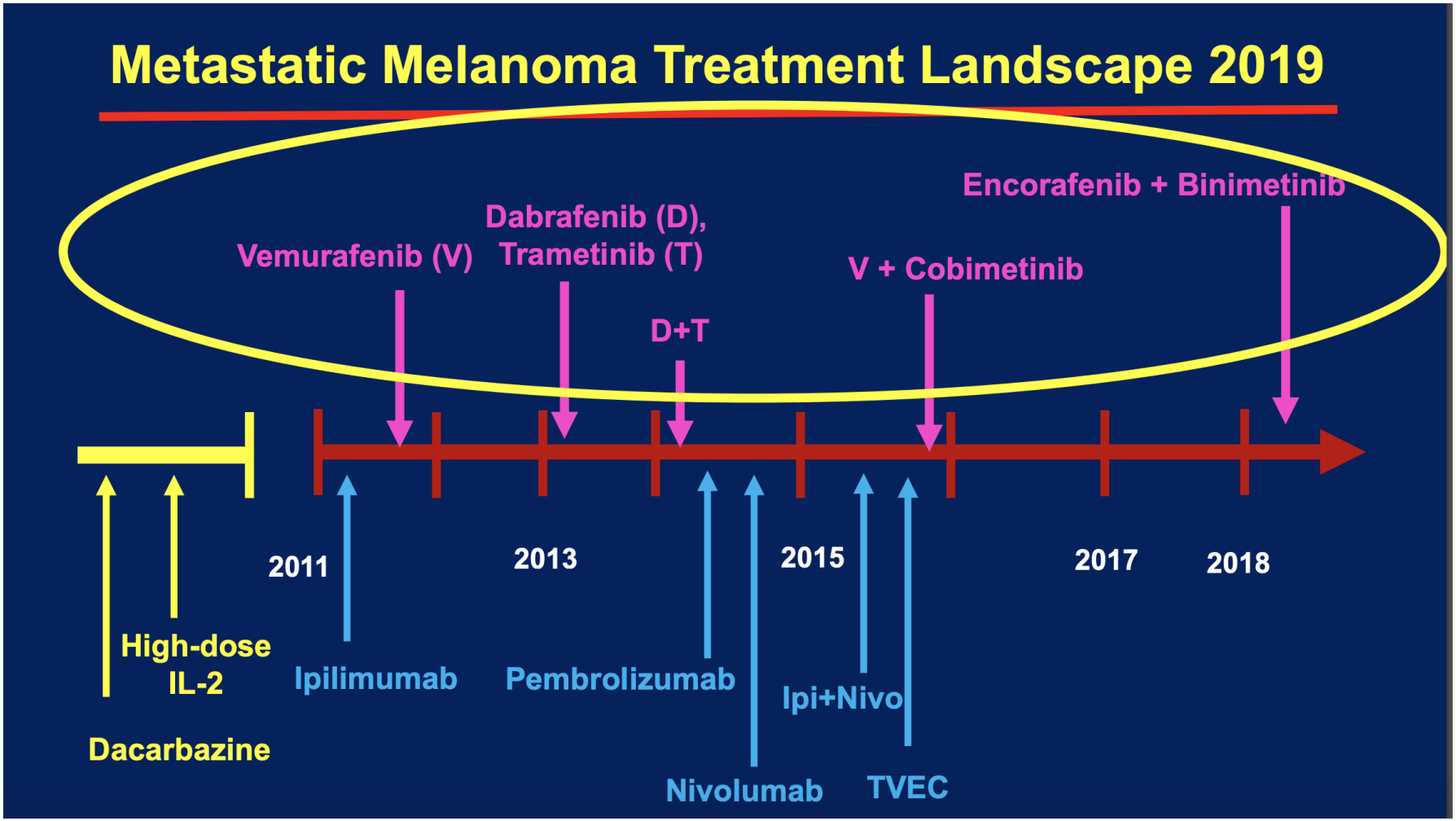


Allison, chair of Immunology and executive director of the Immunotherapy Platform at The University of Texas MD Anderson Cancer Center, is best known for his work in T-cell response mechanisms and his discovery that blocking the signaling of the immune checkpoint protein CTLA-4 improved antitumor immune responses. His research led to the development of Yervoy (ipilimumab), the first FDA-approved immune checkpoint inhibitor. The agency approved Yervoy the treatment of advanced melanoma in 2011.

Pembrolizumab (Keytruda): Anti-PD-1 monoclonal antibody (immune checkpoint inhibitor)

MOA: highly selective anti-PD1 monoclonal antibody, which inhibits programmed cell death by binding to PD1 receptor on T cells to block PD1 ligands from binding. This also reverses T-Cell suppression and induces an antitumor response




Metastatic Melanoma Treatment Landscape 2019
Encorafenib + Binimetinib
Dabrafenib (D),
Trametinib (T)
Vemurafenib (V)
V + Cobimetinib
D+T
2011
2013
2015
2017
2018
High-dose
IL-2
Dacarbazine
Ipilimumab
Pembrolizumab
Ipi+Nivo
Nivolumab
TVEC

Immune Checkpoint Inhibitors: Side Effects

Immune Checkpoint Inhibitor	Target	Indicated Treatment	Adverse effects (% frequency)
Ipilimumab	CTLA-4	Melanoma	**Diarrhea (27-41%)** **Colitis (7-15%)** **Rash (19-34%)** Neurological (5%) **Endocrinopathy (8-38%)** **Hepatic (4-24%)**
Nivolumab	PD-1	Melanoma, NSCLC, RCC, HCC, Hodgkin's lymphoma, SCC of Head/Neck, Urothelial carcinoma, Colorectal Cancer	**Diarrhea (8-16%)** Colitis (1%) Pulmonary (2-5%) **Rash (9-15%)** **Endocrinopathy (7-11%)** **Hepatic (3-11%)** Renal (2%)
Pembrolizumab	PD-1	Melanoma, NSCLC, Hodgkin's lymphoma, SCC of Head/Neck, Urothelial carcinoma, Gastric cancer, solid tumors with high satellite instability or mismatch-repair deficiency	**Diarrhea (7-19%)** Colitis (1-4%) Pulmonary (5%) **Rash (9-16%)** **Endocrinopathy (15-23%)** Hepatic (2%)

Immunotherapy Summary Slide

- Recognize the immunotherapy drugs to treat cancer by name and disease treated
- Understand the side effects of these drugs occur by immune activation and be on the lookout for these side effects
- Start empiric steroids quickly in patients admitted with colitis and pneumonitis and consult with their oncologist quickly