Oncology Emergencies for the Non-Oncology PA

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Disclosures

Non-Declaration Statement:

The presenter has no relevant relationships with ineligible companies to disclose within the past 24 months.

Session Objectives

At the end of the session, the participant should be able to:

- Describe the pathophysiology and clinical presentation of:
  - Febrile Neutropenia
  - Spinal Cord Compression
  - Hypercalcemia of Malignancy
  - Tumor Lysis Syndrome
- Diagnose each of these common oncology emergencies using well-accepted criteria.
- Formulate a timely and effective initial management plan for each of these emergent situations.
- Appreciate the role of the PA in the early detection and management of oncology emergencies.

Oncologic Emergencies and Urgencies

Central Nervous System

- Spinal cord compression
- Brain metastases
  - Intracranial pressure
  - Seizures

Cardiothoracic

- Superior vena cava syndrome
- Pericardial effusion; tamponade
- Airway obstruction
- Massive hemoptysis
- Malignant pleural effusion

Gastrointestinal and urologic

- Bowel and urinary obstruction
- Biliary obstruction; cholangitis
- Malignant ascites

Paraneoplastic: metabolic

- Hypercalcemia of malignancy
- SIADH
- Hypoglycemia
- Lactic acidosis

Paraneoplastic: hematologic

- Thromboembolic events
- DIC
- Leukostasis
- Hyperviscosity Syndrome

Chemotherapy induced

- Febrile neutropenia
- Tumor Lysis Syndrome
- Diarrhea
- Cytokine release syndrome
- Anaphylactic hypersensitivity reactions

Oncology Emergencies: Overview

Events can be classified as:

Metabolic	• Hypercalcemia of malignancy • SIADH
Hematologic	• Hyperviscosity syndrome
Structural	• Spinal cord compression • Superior vena cava syndrome
Treatment-related	• Febrile neutropenia • Tumor lysis syndrome

Mercer-Falkoff A, Lacy J. (2013). Oncologic Emergencies. In Oncology in Primary Care, Rose MG, DeVita VT, Lawrence TS, Rosenberg SA (Eds).

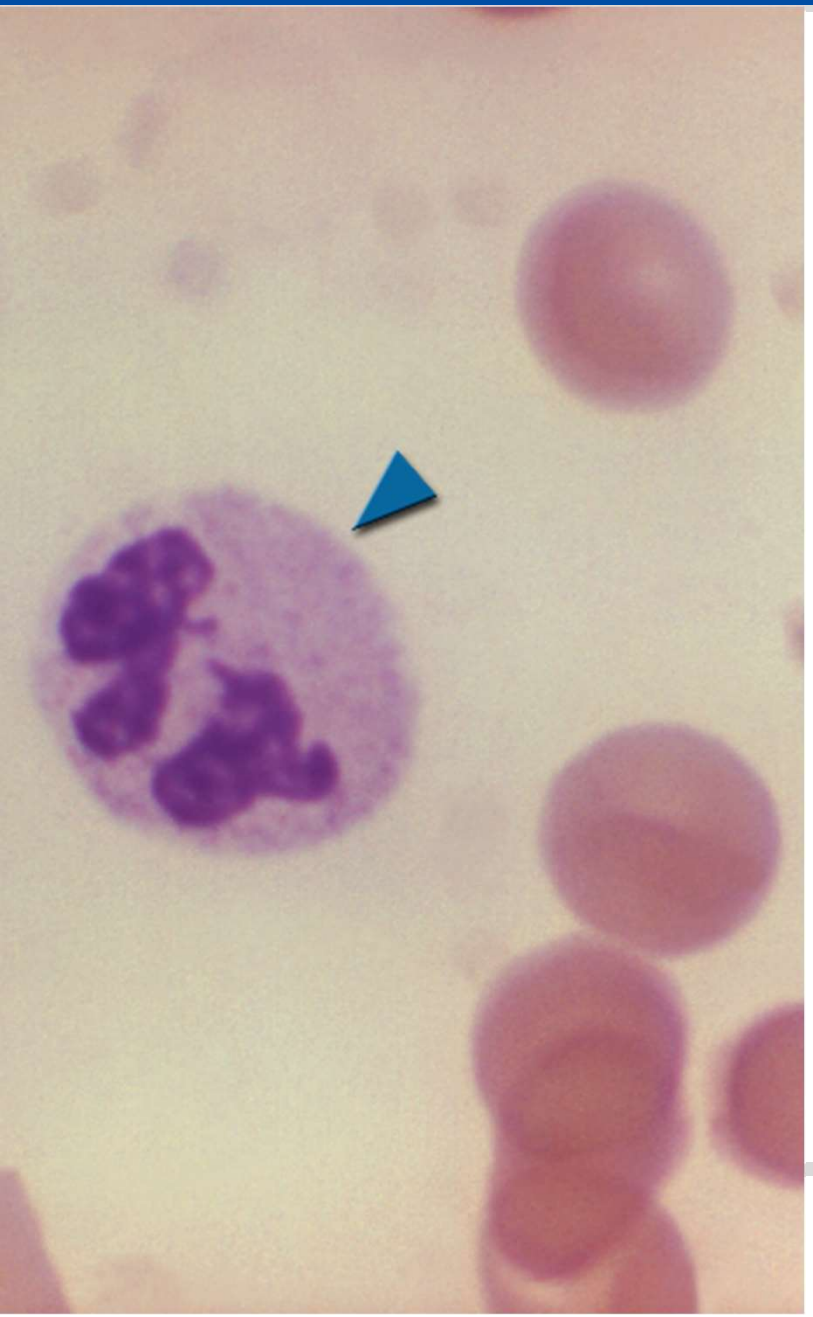
Case 1

- Patient: 32-year-old male
- 1:40 a.m.
- CC: “My oncologist told me to come to the emergency room”

- A 32-year-old male with a recent diagnosis of Non-Hodgkin’s Lymphoma presents to the ED with fever. He received his first cycle of chemotherapy (CHOP-R regimen) 8 days ago and tolerated it well.
- He has no symptoms and is annoyed when you try to elicit a review of systems stating he is only here because his oncologist’s office told him he must come to the ED.
- On physical exam you note temperature of 102F (orally) and pulse of 105. PE is otherwise normal.
- CXR is negative. CBC is pending.
- Patient wants to go home.

Image credit: National Cancer Institute (photographer unknown)

Febrile Neutropenia: Definition



Fever

1 episode of temperature > 101 F (38.3 C)

or

temperature 100.4 F (38 C) > 1 hour

+

Neutropenia

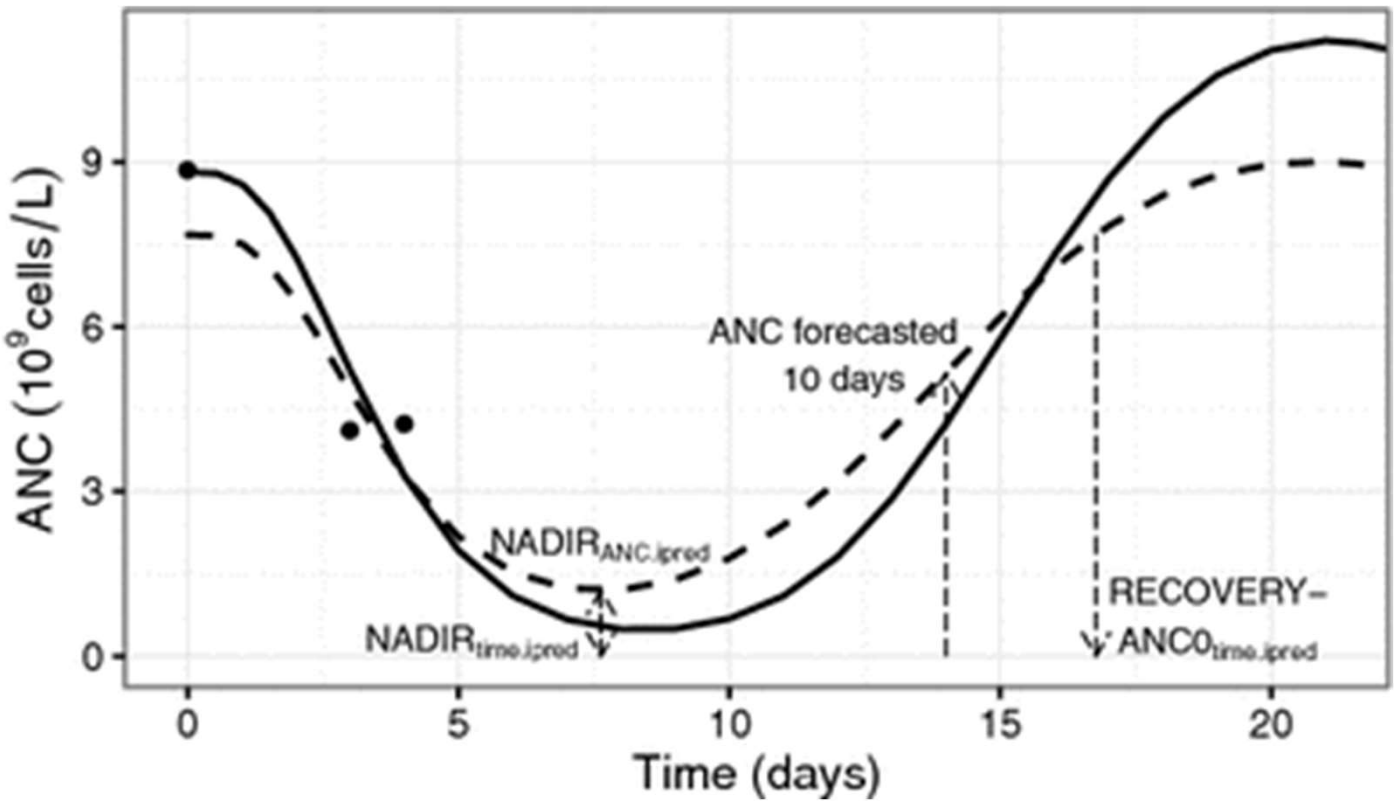
Absolute neutrophil count (ANC) < 500/mm^3

or

an expected ANC <500/mm^3 within 48 hours

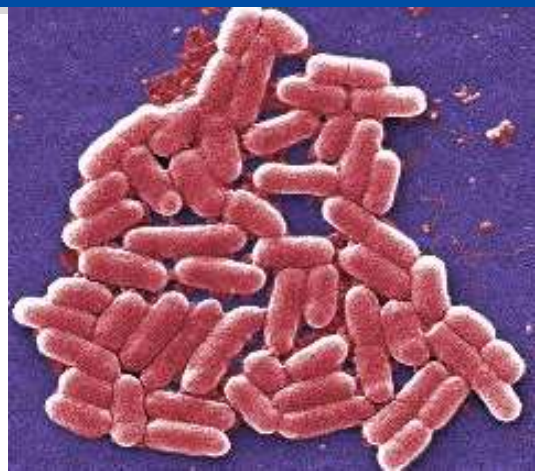
IDSA Guidelines: Clinical Infectious Diseases 2011; 52(4):e56–e93

Myelosuppression After Chemotherapy



Netterberg, I., Nielsen, E.I., Friberg, L.E. *et al.* Model-based prediction of myelosuppression and recovery based on frequent neutrophil monitoring. *Cancer Chemother Pharmacol* **80,** 343–353 (2017). https://doi.org/10.1007/s00280-017-3366-x

Febrile Neutropenia: Pathophysiology

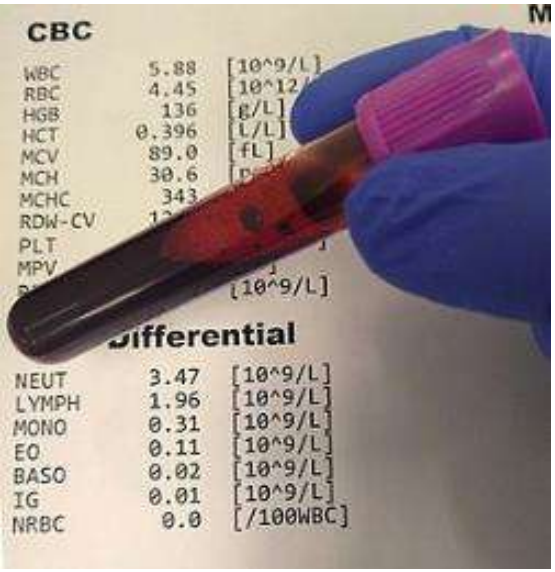


- Most common source of infection is patient's own flora.
  - Gram negative bacilli:
    - *Escherichia coli*, *Klebsiella* sp.
    - *Enterobacter* sp., *Pseudomonas*
  - Gram positive cocci:
    - Coag negative *Staph*, *Staph aureus* (including MRSA)
    - *Strep viridans*, Enterococcus
- Presumed origin of fever is bacteremia
  - but only 10-30% of blood cultures are positive.

Zimmer A, Freifeld AG. *J Oncol Pract* 2019;15:19-24.

Image credit: *E. coli* 0157:H7; Public Health Image Library (photographer Janet Haney Carr)

Febrile Neutropenia: Work-up



- CBC with differential leukocyte count
- Comprehensive metabolic panel; hepatic transaminase enzymes; total bilirubin
- 2 sets of blood cultures
  - from all lumens of all catheters *and* from a peripheral vein
  - If no catheter or central line, then collect from 2 separate peripheral vein sites

- Ask about history of medication allergy
- **Start empirical antibiotics asap, then proceed to rest of work-up**
- DO NOT take a rectal temperature

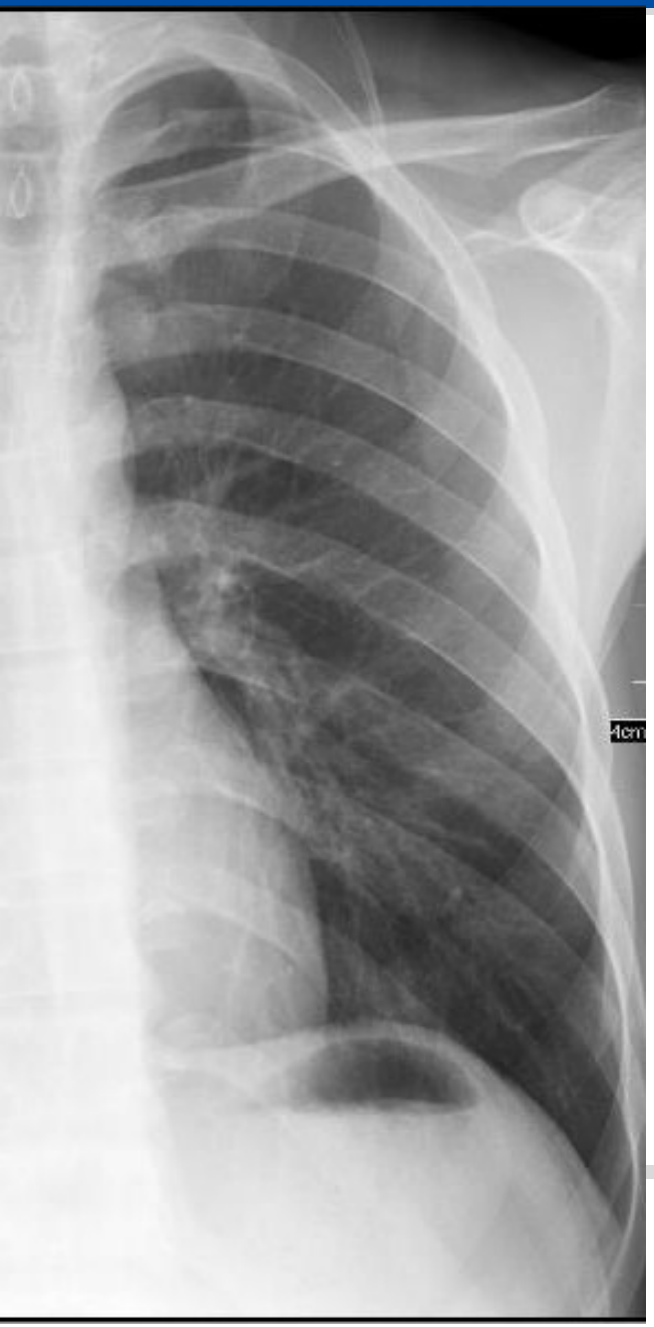
IDSA Guidelines: Clinical Infectious Diseases 2011;52(4):e56–e93

Febrile Neutropenia: Work-Up

- Thorough HISTORY
  - Mucositis symptoms: mouth pain, difficulty swallowing, diarrhea
  - Medications: steroids, fluroquinolones, immunosuppressive drugs
  - Type of chemo regimen: cycle; when last given
  - Receipt of G-CSF: filgrastim (Neupogen); PEGylated filgrastim (Neulasta)
  - Special considerations: CLL or splenectomized patient

- Thorough PHYSICAL EXAM
  - Patients don't show usual signs of infection
  - Examine the oral mucosa, teeth and gums
  - Examine catheter sites
  - Examine sinuses and ears
  - Examine genital and perianal area
  - NO DIGITAL RECTAL EXAM

Febrile Neutropenia: Work-up



- Culture specimens from other sites, as indicated
  - Urine
  - Skin lesions
  - Stool (if diarrhea or abdominal pain)
  - CSF (if suspected meningitis)
  - Respiratory specimens (if productive cough)
    - Influenza, RSV, and COVID-19
- Chest radiograph, PA and lateral study
  - CXRs are usually negative
  - IDSA: CXR only if patient has respiratory signs and/or symptoms

IDSA Guidelines: Clinical Infectious Diseases 2011;52(4):e56–e93

Febrile Neutropenia: Risk Stratification

- Anticipated long duration of neutropenia (> 7 days)
- ANC ≤ 100 cells/mm^3 or Rapid decline in ANC
- Hemodynamically unstable
- Skin break down; mucositis
- Intravascular catheter infection
- Significant co-morbidity:
  - HTN, PNA, new abdominal pain, neurologic changes
- Hepatic or renal dysfunction

- Anticipated short duration of neutropenia (< 7 days)
- Few co-morbidities; no hepatic or renal dysfunction
- Reliable patient; good support system
- Patients with solid tumors tend to be in the low-risk group

IDSA Guidelines: Clinical Infectious Diseases 2011;52(4):e56–e93

Febrile Neutropenia: Empiric Antibiotic Therapy

- Administer antibiotics within 1 hour of initial presentation
- Broad gram-negative and anti-pseudomonal β-lactam agent

- Monotherapy: (normal renal function dosing)
  - Cefepime 2g IV every 8 hours
  - Imipenem-cilastatin 500 mg IV every 6 hours
  - Piperacillin-tazobactam 4.5 grams IV every 6-8 hours

- For immediate-type hypersensitivity reaction to penicillin:
  - Aztreonam + vancomycin
  - Ciprofloxacin + clindamycin

IDSA Guidelines: Clinical Infectious Diseases 2011;52(4):e56–e93

Febrile Neutropenia: Management

- Consider adding:
  - Aminoglycosides, fluoroquinolones, and/or vancomycin if:
    - Evidence of hypotension or pneumonia
    - Antimicrobial resistance is suspected or proven
  - Add vancomycin if:
    - Suspected catheter-related infection
    - Suspected soft-tissue infection
    - Suspected or proven MRSA
    - Known colonization with MRSA
    - Prior prophylaxis with ciprofloxacin
    - In case of severe mucositis
      - risk of overwhelming infection with *Strep viridans*

IDSA Guidelines: Clinical Infectious Diseases 2011;52(4):e56–e93

Febrile Neutropenia: Management

- Continue antibiotic treatment:
  - For at least the duration of neutropenia
  - Until ANC $\geq$ 500 cells/mm^3
  - Adjust regimen according to cultures and sensitivities

IDSA Guidelines: Clinical Infectious Diseases 2011;52(4):e56–e93

Febrile Neutropenia: Other Considerations

- Granulocyte-Colony Stimulating Factor (G-CSF)
  - i.e., filgrastim and pegfilgrastim
  - Prophylactic use:
    - After cycle of chemotherapy before neutropenia develops
    - Good evidence to support use in patients with high-risk of developing FN
  - Therapeutic use:
    - Less evidence supporting use in FN
    - Shortens duration of neutropenia by 2 days on average
    - However, no survival advantage

J Natl Compr Canc Netw 2020;18(1):12–22. doi: 10.6004/jnccn.2020.0002

Febrile Neutropenia: Other Considerations

- According to NCCN recommendations, patients with FN who have:

received/ are receiving filgrastim	• Continue receiving filgrastim
received pegfilgrastim	• Should not receive additional G-CSF
not received prophylactic G-CSF	• Evaluate risk factors: • infection-related complications or poor clinical outcome

J Natl Compr Canc Netw 2020;18(1):12–22. doi: 10.6004/jnccn.2020.0002

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In a patient with febrile neutropenia, empiric antibiotics are started after blood cultures are collected and before a physical exam is completed.

True

False

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Case 2

- Patient: 68-year-old male
- CC: “I’m having trouble walking up stairs.”

- A 68-year-old male with a history of prostate cancer treated 1 year ago presents to the ED c/o 2-3-day history of upper back pain. Pain is “below the shoulder blades.” It is currently 8/10 severity, with a progressive onset and getting worse. The pain radiates around his chest “like a belt.” Nothing makes it better. Sneezing and lying in bed make it worse. He’s not sure if it’s related, but he started having trouble walking up the stairs this afternoon, so his wife made him come to the ED. He denies history of trauma.
- Social History is positive for a 48-pack-year history. He quick smoking cigarettes 3 years ago.

Image credit: National Cancer Institute (photographer Daniel Sone)

Spinal Cord Compression: Pathophysiology

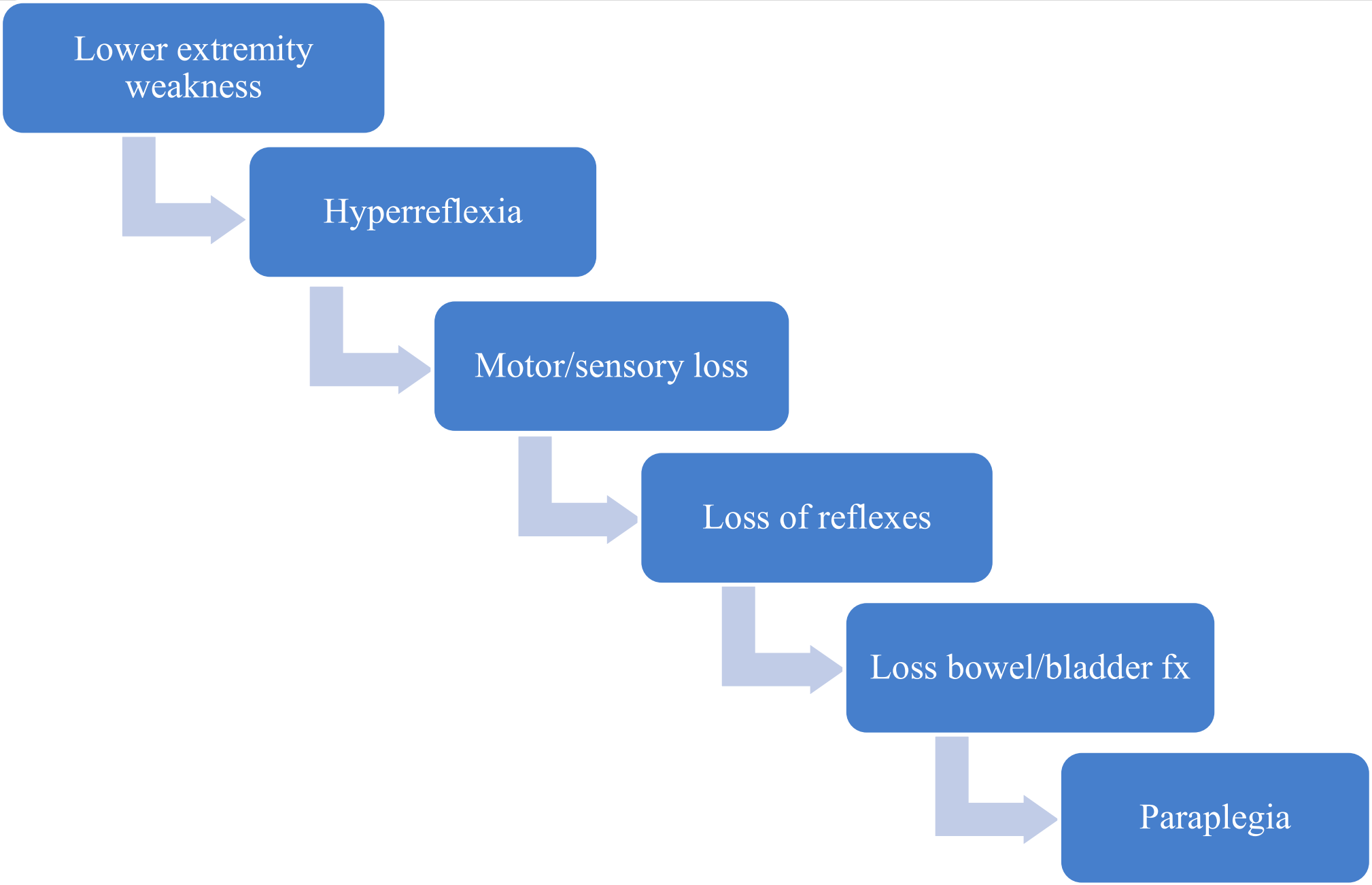
- Definition: Compression or displacement of the spinal cord by metastatic or locally advancing tumor

- Possible Etiologies:
  - Tumor grows into vertebral foramina
  - Tumor destroys cortical bone causing a compression fracture
  - Tumor metastasizes to the meningeal membranes

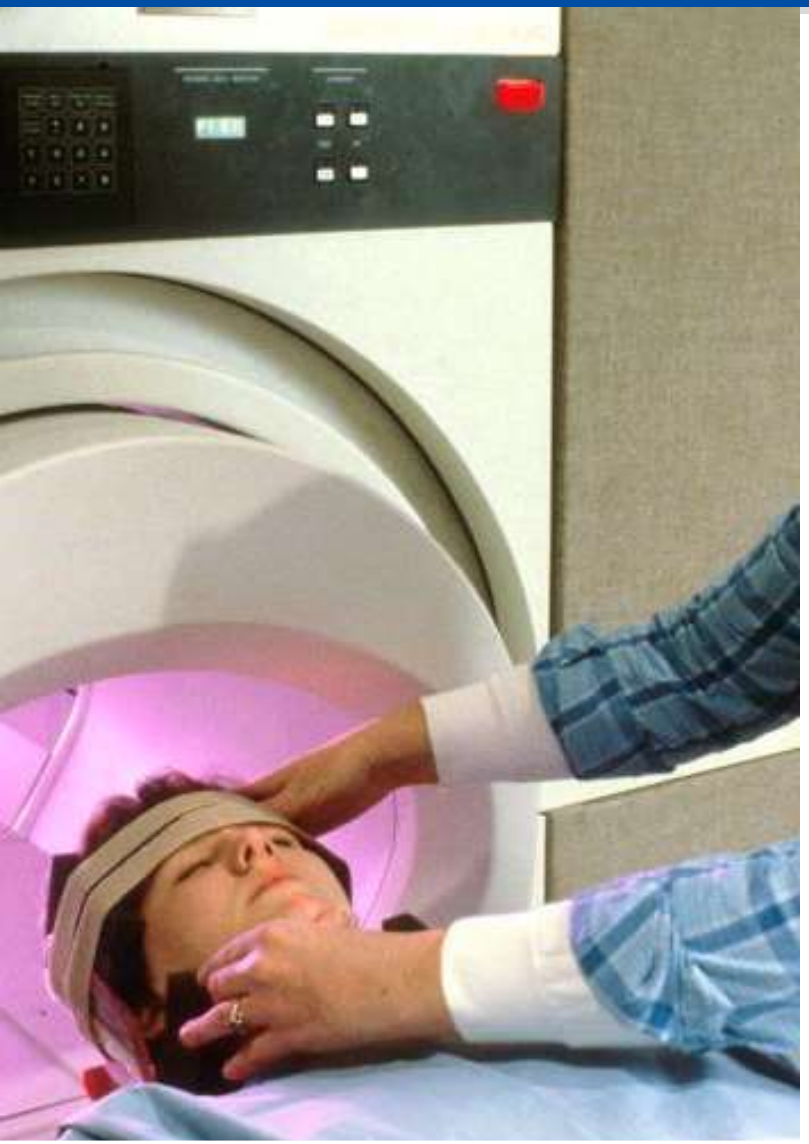
- Results in spinal cord infarction

- Mostly associated with breast, prostate, lung CA

Spinal Cord Compression: Presentation



Spinal Cord Compression: Work-up



- Complete neurological exam
  - Evidence of neurological deficits
- Assess for urinary retention and need for foley catheterization
- MRI of cervical, thoracic and lumbar spine

Image source: National Cancer Institute

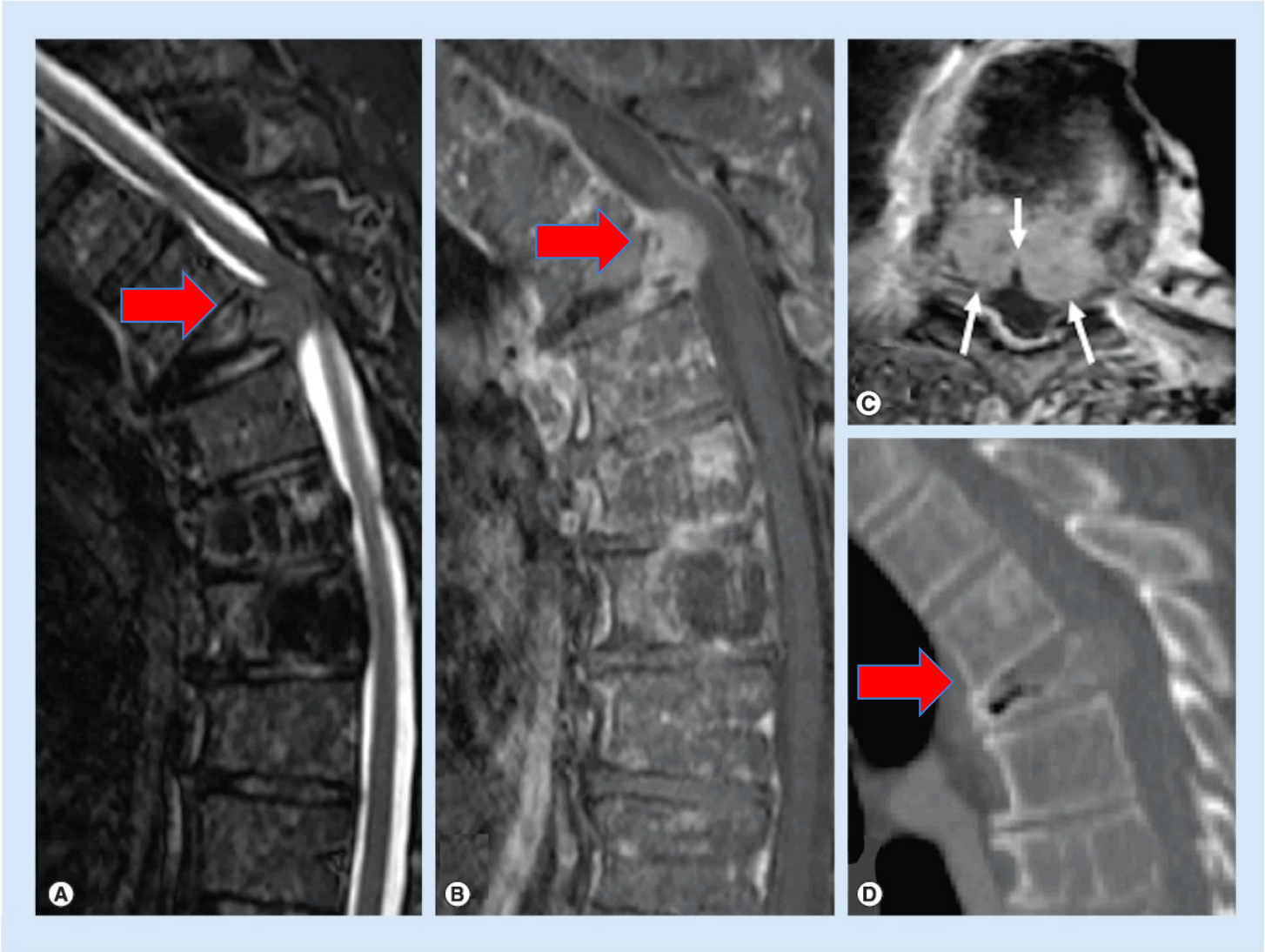


Figure 11. Pathologic fracture with spinal cord compression. **(A)** Sagittal short tau inversion recovery image reveals a collapsed vertebral body with a large epidural mass compressing the spinal cord; **(B)** sagittal and **(C)** axial contrast-enhanced fat-suppressed turbo spin echo T_1-weighted images highlight the neoplastic tissue that involves the anterior epidural space. Axial image depicts the 'draw-curtain sign' (arrows), a sign indicative of neoplastic epidural involvement. **(D)** Sagittal reformatted CT image demonstrates the lytic pattern of neoplastic growth also at other vertebral levels.

Distefano D, Cianfoni A. Imaging of spinal cord compression. *Imaging in Medicine.* 2014; (6)1. www.openaccessjournals.com/articles/imaging-of-spinal-cord-compression-11440.html#a1

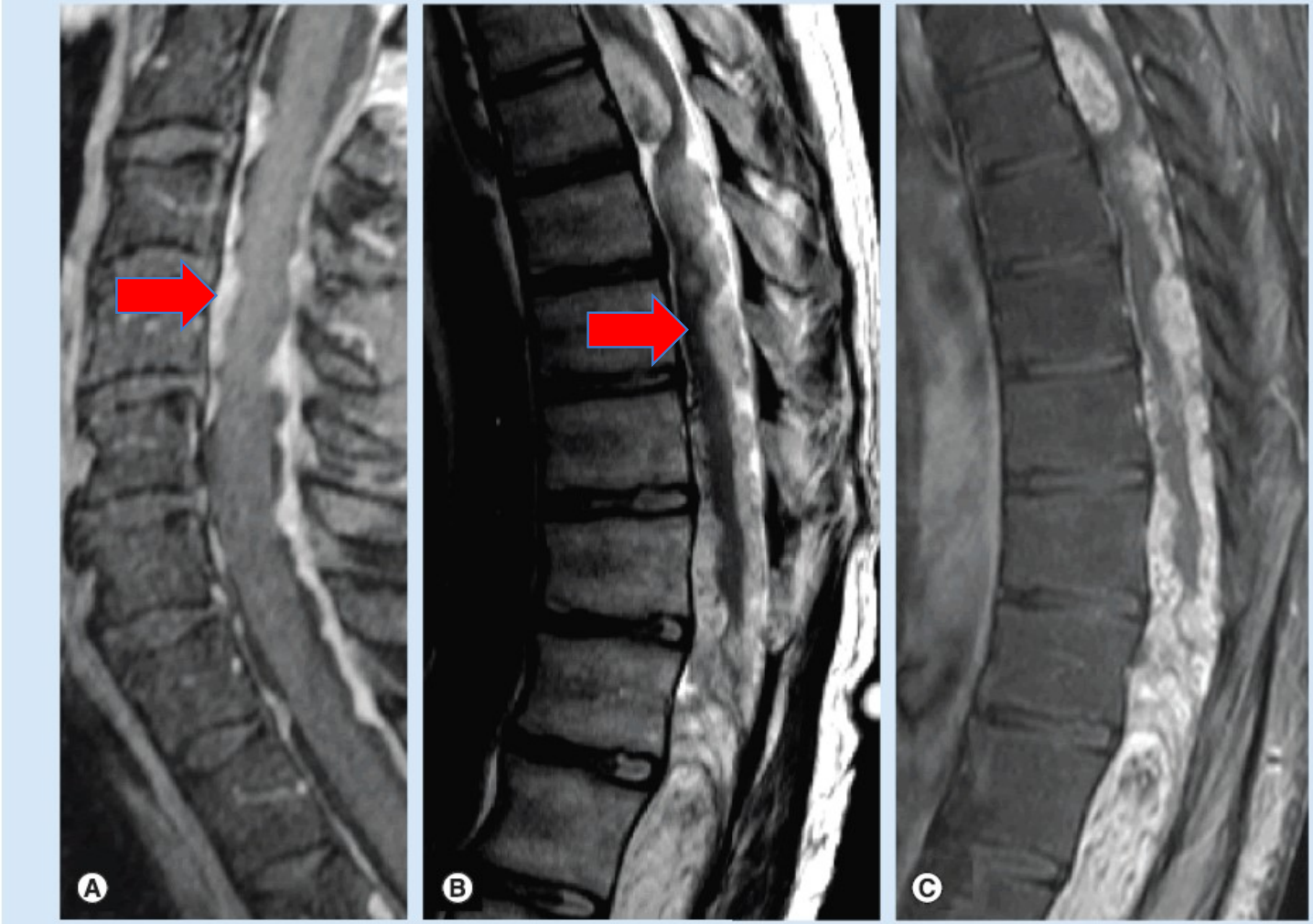


Figure 24. Two cases of meningeal metastasis. **(A)** A turbo spin echo fat-suppressed enhanced T_1-weighted image shows dural nodular-enhancing deposits compressing the spinal cord, in this patient with primary lung cancer. **(B & C)** Sagittal turbo spin echo T_2-weighted and fat-suppressed enhanced T_1-weighted images show extensive bulky subarachnoid leptomeningeal carcinomatosis, compressing the spinal cord, from a myxopapillary ependymoma.

Distefano D, Cianfoni A. Imaging of spinal cord compression. *Imaging in Medicine.* 2014; (6)1. www.openaccessjournals.com/articles/imaging-of-spinal-cord-compression-11440.html#a1

Spinal Cord Compression: Initial Management

- Dexamethasone 10 mg IV bolus x 1
  - then 16 mg daily by mouth in divided doses (i.e., 4 mg PO every 6 hours). Taper once definitive treatment starts.
  - Start steroids before you get an MRI
- Assess need for pain management and DVT prophylaxis
- Consult:
  - Medical Oncology
  - Neurology
  - Neurosurgery
  - Radiation Oncology

Lawton AJ, et al. Assessment and Management of Patients with Metastatic Spinal Cord Compression. *J Clin Oncol*. 2019;37(1): 61-71.

Spinal Cord Compression: Definitive Treatment

External Beam RT

- Lymphoma and multiple myeloma respond well
- Prostate and breast CA respond well
- Responsiveness of other solid tumors vary

Chemotherapy

- Lymphoma and multiple myeloma respond well

Surgery

- Prior spinal irradiation
- Unknown primary

  10% of spinal cord compression occurs with no known cancer diagnosis
- Spinal instability
- Compression fracture/bony impingement on cord

Lawton AJ, et al. Assessment and Management of Patients with Metastatic Spinal Cord Compression. *J Clin Oncol*. 2019;37(1): 61-71.

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Text **ALEXANDRIAGA831** to **37607** once to join

Which of the following signs or symptoms increase clinical suspicion for spinal cord compression?

Able to rise from a chair

No prior cancer diagnosis

Pain that radiates down the legs

Saddle anesthesia

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Case 3

- Patient: 65-year-old female
- CC: Partner states patient is very confused.

- A 65-year-old female with a history of metastatic squamous cell lung cancer is brought to clinic by her partner and son. The patient has become increasingly sleepy and confused over the last 3 days. The partner also mentions that the patient has frequently complained of nausea and constipation over the last 1-2 weeks.
- Chemotherapy has not been effective.

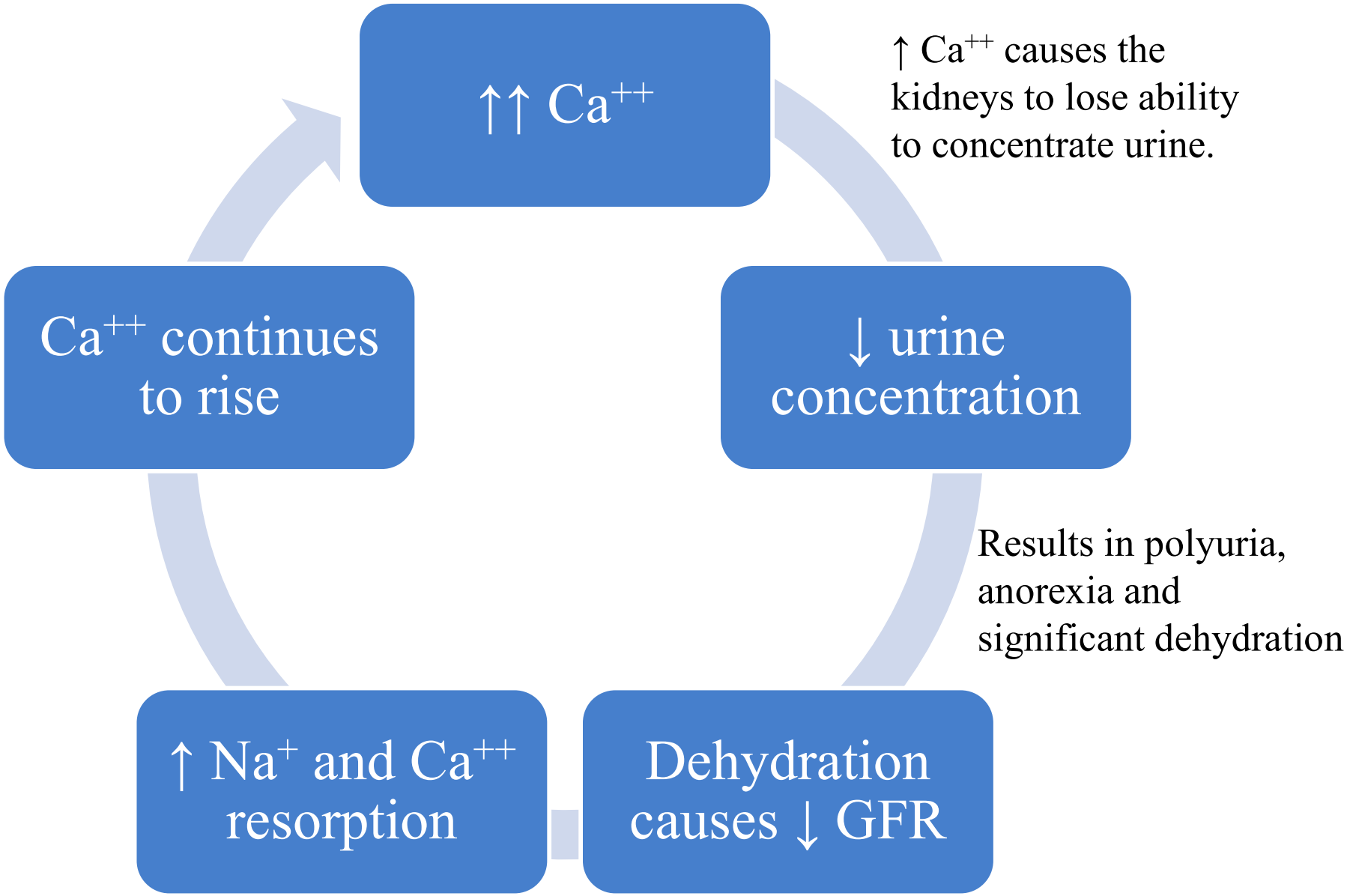
Image credit: National Cancer Institute (photographer Rhoda Baer)

Hypercalcemia of Malignancy: Pathophysiology

- Bone resorption by activated osteoclasts with release of Ca^{++} from bone matrix

- Three mechanisms:
  - Secretion of PTHrP (PTH-related protein)
    - Seen in squamous cell cancers, renal, bladder, endometrial, lymphoma
    - Poor prognosis; resistant to treatment
  - Bone metastases with local release of osteolytic factors
    - Seen in diseases predisposed to metastasize to bone: breast, prostate; myeloma
    - Responds better to treatment
  - Elevated Serum Calcitriol
    - Hodgkin's lymphoma and some Non-Hodgkin's lymphomas

Hypercalcemia of Malignancy: Pathophysiology



Hypercalcemia of Malignancy: Presentation

Cardiovascular	• HTN • Digoxin sensitivity
GI	• Anorexia • Nausea/Vomiting/Abdominal pain • Constipation/Obstipation
Renal	• Polyuria • Nocturia
Neurologic	• Lethargy → Somnolence → Coma • Confusion

Hypercalcemia of Malignancy: Work-up

Obtain:

- Comprehensive Metabolic Panel
- 1,25-hydroxyvitamin D

Classification of Hypercalcemia		
	Corrected Calcium	**Ionized Calcium**
Mild	< 12 mg/dL	5.6-8 mg/dL
Moderate	12-14 mg/dL	8-10 mg/dL
Severe	> 14 mg/dL	10-12 mg/dL

When ionized calcium is not available, calculate the Corrected Calcium

Total calcium mg/dL + 0.8 x (4.0– serum albumin g/L)

Hypercalcemia of Malignancy: Initial Management

- Management considerations:
  - Degree of hypercalcemia
  - Acuity of Ca^{++} increase
- Asymptomatic patients with mild or moderate chronic hypercalcemia may not need immediate treatment.

For severe hypercalcemia in a patient with no cardiac or renal disease:

- Vigorous hydration with isotonic saline (i.e., 0.9% NaCl)
  - IVNS at 200-250 mL/hr for 3-4 hours (if tolerated)
    - Maintain urine output 100-150 mL/hour
  - Restores GFR and promotes excretion of Na^{+} and Ca^{++}
  - Monitor volume and electrolyte status closely

Hypercalcemia of Malignancy: Management

Severe hypercalcemia

- Calcitonin
  - Initial dose 4 iu/kg (intramuscularly or subcutaneously)
  - Repeat serum calcium in 4-6 hours
  - If calcium decreases, can repeat every 12 hours
  - Acts rapidly (12-24 hours)
  - Can be given before hydration
  - Not nephrotoxic; safe in renal failure

  - Disadvantage: rapid tachyphylaxis (rapid decrease in drug effectiveness)
  - Total duration 24-48 hours

Hypercalcemia of Malignancy: Management

Bisphosphonates

- Osteoclast Inhibitors
    - Onset of action is 48 hours
    - Calcium nadir in 7-10 days
  - zolendronic acid (Zometa) 4 mg IV over > 15 minutes

    OR
  - pamidronate (Aredia) 60-90 mg IV over > 2 hours

- Adverse Events:
  - Nephrotoxicity/nephrotic syndrome
  - Unusual fractures
  - Osteonecrosis of the jaw

Case 4

- Patient: 40-year-old female admitted to Oncology unit
- Rapid Response Team called

- The patient is a 40-year-old female with newly diagnosed Burkitt's lymphoma. She was admitted urgently yesterday with a 25cm abdominal mass. On admission, patient reported that the mass doubled in size from 1 week ago. She complained of abdominal pain, N/V. Admission labs: WBC = 15K; LDH = 8000. Chemotherapy was started yesterday afternoon.
- Overnight a substantial decrease in urine output was noted.
- During work rounds a code is called.

Image credit: National Cancer Institute (photographer Daniel Sone)

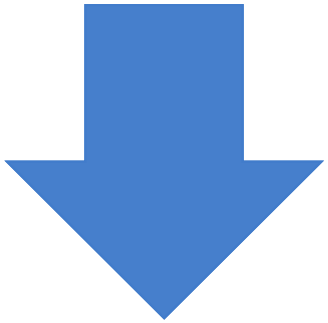
Tumor Lysis Syndrome

- Treatment-induced Metabolic Emergency
  - Lysed tumor cells rapidly dump intercellular contents into the blood stream faster than the body can eliminate them.
  - This is almost always in the setting of effective chemotherapy.
- Leads to renal failure, and if left untreated, to death.

Tumor Lysis Syndrome: Pathophysiology

Destructive metabolic cascade

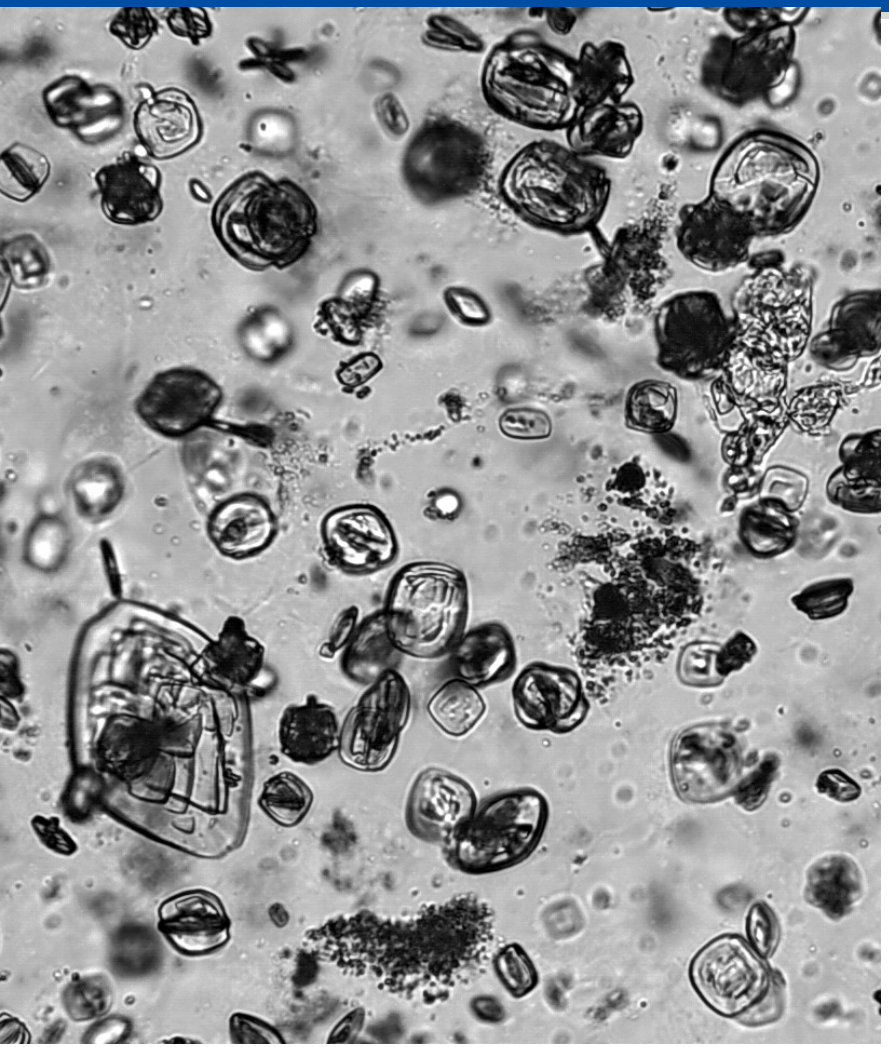
HYPERkalemia
HYPERuricemia
HYPERphosphatemia



HYPOcalcemia

- Hyperkalemia » cardiac arrhythmias » death
- Hyperuricemia » urine becomes acidic » uric acid crystals deposited » renal failure » oliguria/anuria
- Hyperphosphatemia » causes HYPOcalcemia » tetany/seizures & arrhythmias » renal failure

Tumor Lysis Syndrome: Pathophysiology



Uric acid crystals in urine

Renal Failure in Tumor Lysis Syndrome

- Multifactorial etiology
  - Volume depletion/dehydration
  - Uric acid crystals
  - Calcium phosphate crystals
  - Previous—and possibly undetected—kidney damage

Tumor Lysis Syndrome: Risk Factors

- Bulky disease (tumors or lymphadenopathy larger than > 10 cm)
- Elevated WBC count (> 25,000)
- Elevated LDH (2x ULN)
- Elevated uric acid (>7.5 mg/dL)
- Prior renal insufficiency
- Dehydration/volume depletion

Tumor Lysis Syndrome: Cairo-Bishop Classification

Laboratory Definition
(in adults)

25% **increase** from baseline or:

- Uric acid ≥ 8.0 mg/dL
- Potassium ≥ 6.0 mEq/L
- Phosphorous ≥ 4.5 mg/dL

25% **decrease** from baseline or:

- Calcium ≤ 7.0 mg/dL

Clinical Definition

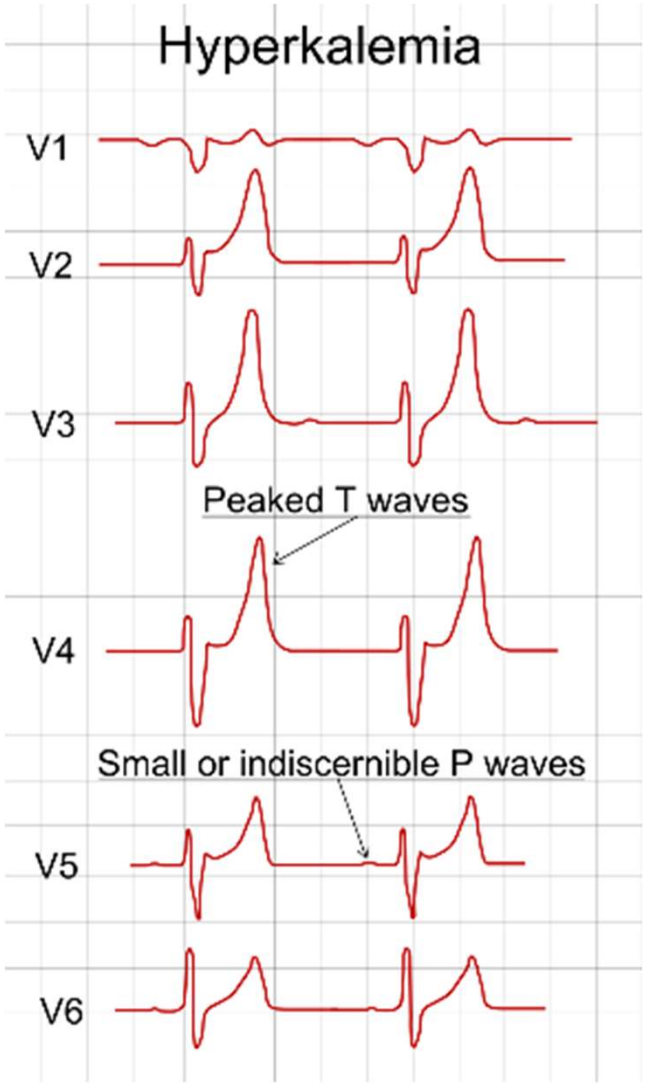
- Creatinine ≥ 1.5 x upper limit of normal
- Cardiac arrhythmia or sudden death
- Seizure

Cairo MS, Bishop M. *Br J Haematol* 2004;127(1):3-11

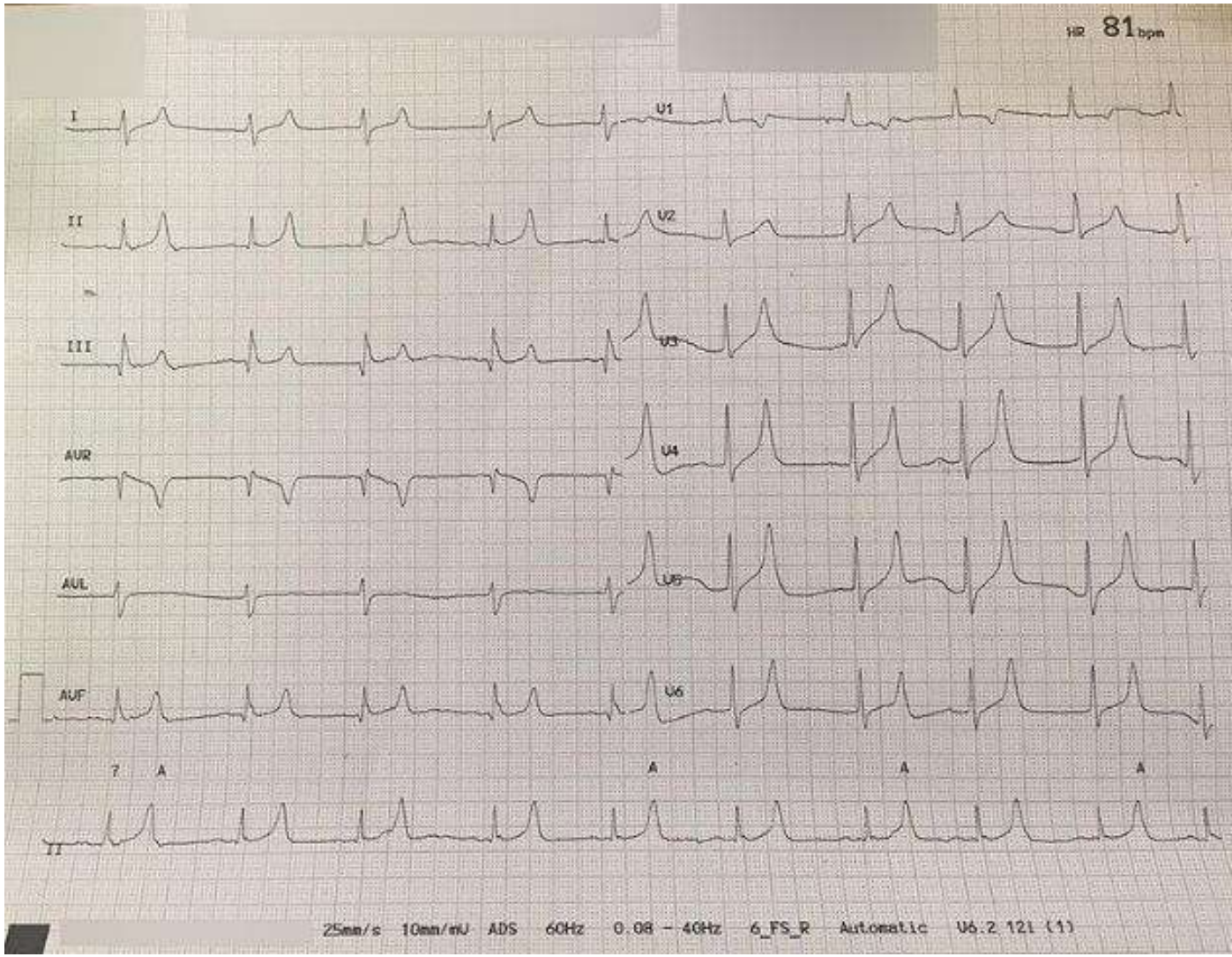
Tumor Lysis Syndrome: Presentation

- Nausea and/or vomiting
- Anorexia
- Fatigue
- Dark urine or decrease urine output
- Change in mentation; seizures; hallucinations
- Muscle cramps
- Heart arrythmias and palpitations

Tumor Lysis Syndrome: ECG Changes



Mikael Häggström, used with permission



Patient with renal disease and potassium of 8.2 mmol/L
Dr. Michael-Joseph F. Agbayani and Dr. Eddieson Gonzales (Manila, Philippines)

Tumor Lysis Syndrome: Management

- Goal is to treat electrolyte abnormalities
- Hyperkalemia
  - Constant cardiac monitoring
  - Frequent serum potassium (every 4-6 hours)
  - Severe (≥ 7.0 mmol/L) or symptomatic:
    - Calcium gluconate (IV) to reduce the risk of cardiac dysrhythmia
    - IV insulin + glucose to drive extracellular potassium into cells
    - Hemodialysis

Howard SC. The Tumor Lysis Syndrome. *N Engl J Med*. 2011; 364:1844-1854.

Tumor Lysis Syndrome: Management

- Hyperuricemia
  - Fluid and electrolyte management

  - IV Hydration with normal saline (200-250 mL/hr)
  - Maintain high urine output
  - Decrease uric acid levels:
    - rasburicase 0.2 mg/kg once daily x 5-7 days
      - Breaks down uric acid into more soluble allantoin
      - Not cleared by the kidneys
      - Contraindicated in G6PD deficiency and pregnancy
    - allopurinol 100 mg/m2 every 8 hours (max 800 mg/day)
      - Used in prophylaxis
      - Only prevents **new** uric acid formation

Howard SC. The Tumor Lysis Syndrome. *N Engl J Med*. 2011; 364:1844-1854.

Tumor Lysis Syndrome: Management

- Hyperphosphatemia
  - Moderate
    - Restrict phosphate intake
    - Phosphate binders (i.e., calcium carbonate)
  - Severe
    - Dialysis
- Hypocalcemia
  - Asymptomatic
    - No treatment
  - Symptomatic (i.e., seizure)
    - Calcium gluconate

Howard SC. The Tumor Lysis Syndrome. *N Engl J Med*. 2011; 364:1844-1854.

Summary

- Maintain elevated index of suspicion when managing patients with cancer who present with unexplained symptoms:
  - Consider occult infection in an unstable patient, especially in the setting of neutropenia
  - Consider cord compression in a patient who presents with unusual back pain, especially in the thoracic spine and in the setting of neurological deficits
  - Consider hypercalcemia and tumor lysis syndrome in a patient with dehydration, mental status changes, and/or cardiac arrhythmias

Summary (continued)

- In a patient who is undergoing active treatment for cancer, always ask about the:
  - specific chemo agents
  - cycle of treatment, when the last treatment was given
  - if they received G-CSF support

- With prevention and high suspicion, PAs make a difference.

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Thank you!

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