Oncologic Emergencies

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Oncologic Emergencies Overview

- Metabolic
  - SIADH
  - Hypercalcemia of malignancy
- Hematologic
  - Hyper viscosity syndrome
- Structural
  - Spinal cord compression
  - Superior vena cava
- 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).

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- Central Nervous System
  - Spinal cord compression
  - Brain metastases
  - Intracranial pressure
  - Seizures
- GI and Urologic
  - Bowel and urinary obstruction
  - Biliary obstruction'
  - cholangitis
  - Malignant ascites
- Cardiothoracic
  - Superior vena cava syndrome
  - Pericardial effusion; tamponade
  - Airway obstruction
  - Massive hemoptysis
  - Malignant pleural effusion
- Metabolic
  - Hypercalcemia of malignancy
  - SIADH
  - Hypoglycemia
  - Lactic acidosis
- Hematologic
  - Thromboembolic events
  - DIC
  - Leukostasis
  - Hyperviscosity Syndrome
- Chemotherapy induced
  - Febrile neutropenia
  - Tumor Lysis Syndrome
  - Diarrhea
  - Cytokine release syndrome
  - Anaphylactic hypersensitivity reactions

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Febrile Neutropenia

- 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[2]

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

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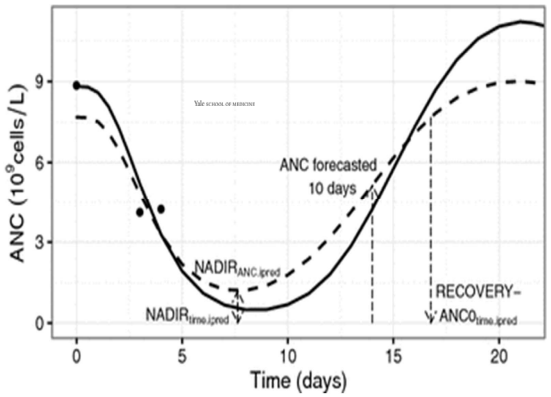
Febrile Neutropenia



- Depends on the chemo agent(s) but neutrophil nadir occurs 5-10 days after the last dose of chemo
- Regimens used to treat leukemias and lymphomas tend to cause a longer lasting and more profound neutropenia

Neutropenia	< 1.0 x 10^9/L (1000/µL)
Severe Neutropenia	< 0.5 x 10^9/L or ANC that is expected to decrease to this level in 48 hrs (500/µL)
Profound Neutropenia	< 0.1 x 10^9/L (100/µL)

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).

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Febrile neutropenia: Pathophysiology

- Few cases of FN will yield a causative organism
- Most common source of infection is patient's own flora
- **Gram positive cocci** (*Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococci viridans, Enterococcus faecalis and faecium*)
- Gram negative bacilli (*Escherichi coli*, *Klebsiella* species, *Pseudomonas aeruginosa*)
- Fungal: ***Candida**, Aspergillus, Zygomycetes*

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

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Diagnosis

- Fever may be the sole manifestation of infection
- Detailed history (ROS, antibiotic prophylaxis, history of prior infections, comorbidities)
- Physical exam: skin, catheter sites, oral cavity, lungs, abdomen, GU, perianal; avoid DRE and medications PR
- Labs: CBC with diff, CMP, UA, blood x2/urine cultures

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Febrile Neutropenia: Risk Stratification

High Risk Patients

- 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

Low Risk Patients

- 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

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Treatment

- In the absence of adequate neutrophil numbers in circulation, unopposed gram-negative bacteremia has a mortality rate of up to 70% in neutropenic patients who do not receive empiric antibiotics

THUS:

- FN should be treated as a medical emergency

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Febrile Neutropenia Tx: Antibiotics

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
  - Piperacillin-tazobactam 3.75 vs 4.5g IV every 6-8 hours
- For immediate-type hypersensitivity reaction to penicillin:
  - Aztreonam + vancomycin
  - Ciprofloxacin + clindamycin

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PJ0 Some people debate 4.5 g vs 3.75 g
Preedit, Justine, 2023-08-01T14:08:16.238

Febrile Neutropenia Tx: G-CSF

- 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 PJ0

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

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Febrile Neutropenia: When to add Vancomycin

- Suspected catheter-related infection
- Suspected soft-tissue infection
- Suspected or proven MRSA
- Known colonization with MRSA
- In case of severe mucositis
- Hemodynamically unstable

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

PJ0

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PJ0 NCCN defines which patients are appropriate for treatment with G-CSF. I would put the name of the agents & dose used somewhere

Preedit, Justine, 2023-08-01T14:08:57.536

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PJ0 Where did you find this info? I don't think this is widely accepted in NCCN/IDSA

Preedit, Justine, 2023-08-01T14:09:26.302

PJ0

Spinal Cord Compression

Definition: Compressive indentation, displacement, or encasement of the thecal sac that surrounds the spinal cord or cauda equina by cancer

Possible Etiologies:

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

Associated with breast, prostate, lung, multiple myeloma

Lawton AJ, et al. Assessment and Management of Patients with Metastatic Spinal

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Cord Compression Signs and Symptoms

- Most common presenting symptom is **back pain**
- Back pain may worsen gradually and precedes neurologic symptoms
- Timeline occurs over weeks to months
- Neurologic symptoms: motor weakness, sensory impairment, autonomic dysfunction
- Cauda equina syndrome: urinary retention, overflow incontinence, decreased sensation (buttocks, posterior thighs, perineal regions)

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PJ0 Recommend a pic here
Preedit, Justine, 2023-08-01T14:14:33.763

Spinal Cord Compression Workup

- Gold standard for diagnosis is **MRI** and should include entire thecal sac
  - Sensitivity of 93% and specificity of 97%.
- MRI of the entire spine because 20% to 35% of patients have multiple, noncontiguous levels of compression
- When MRI is unavailable or contraindicated, CT scan maybe considered

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Treatment of Spinal Cord Compression

- Dexamethasone 10mg or 16mg IV bolus followed by 4mg Q 6 hours (16mg daily in divided doses)
  - DO NOT WAIT FOR MRI prior to giving steroids
- Pain Management
- Consider DVT ppx
- Consults:
  - Radiation Oncology
  - Neurosurgery
  - Medical Oncology

Lawton AJ, et al. Assessment and Management of Patients with Metastatic Spinal

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External Beam RT	Chemotherapy	Surgery
• Lymphoma and multiple myeloma respond well • Prostate and breast CA respond well • Responsiveness of other solid tumors vary	• Lymphoma and multiple myeloma respond well	• Prior spinal irradiation • Unknown primary 10% of spinal cord compression occurs with no known cancer diagnosis • Spinal instability • Compression fracture/bony impingement on cord

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Hypercalcemia of Malignancy

Experienced by up to 30% of patients with cancer

Among hospitalized patients with hypercalcemia, malignancy is most common cause

Breast, **lung**, and renal cell carcinomas; **multiple myeloma**, T-cell leukemia/lymphoma

Prostate cancer, though it often metastasizes to bones, rarely causes hypercalcemia

JAMA Oncol. 2023;9(3):430-431. doi:10.1001/jamaoncol.2022.7941

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Pathophysiology

- Three mechanisms:
  - Secretion of parathyroid related peptide hormone (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

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Signs and Symptoms of Hypercalcemia

- Symptoms tend to be nonspecific; "painful bones, renal stones, abdominal groans, and psychic moans"
- Bone pain usually related to discrete metastases
- Nephrolithiasis can occur
- Abdominal pain from impaired intestinal motility, pancreatitis, constipation, nausea, anorexia
- Changes in mental status from lethargy to coma
- Shortened QT interval → arrhythmias

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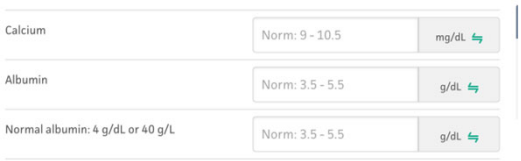
Grading Hypercalcemia of Malignancy

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



Screen grab from MD Calc

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Severe Hypercalcemia Management

- Cornerstone of treatment is IV fluids
- For severe hypercalcemia in a patient with no cardiac or renal disease:
  - Vigorous hydration with isotonic saline (i.e., 0.9% NaCl, LR)
  - IV NS at 200-250 mL/hr for 3-4 hours (if tolerated)
  - Maintain urine output 100-150 mL/hour

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General Considerations for treatment of HCM

Management considerations:
- Degree of hypercalcemia
- Acuity of Ca++ increase

Asymptomatic patients with mild or moderate chronic hypercalcemia may not need immediate treatment.

Goal: restore GFR and promote excretion of Na+ and Ca++

Monitor volume and electrolyte status closely

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Severe Hypercalcemia Management

- Calcitonin
  - Initial dose 4 IU/kg (intramuscularly or subcutaneously)
  - Repeat serum calcium in 4-6 hours
  - If calcium decreases, can repeat every 12 hours
- Benefits:
  - 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
  - High Cost

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PJ0 Disadvantage: $$$$
Preedit, Justine, 2023-08-01T14:18:14.940

PJ0

Bisphosphonates

- Osteoclast Inhibitors, Onset of action is 48 hours
- Calcium nadir in 7-10 days
  - Zoledronic acid 4 mg IV over > 15 minutes

  OR
  - Pamidronate 60-90 mg IV over > 2 hours
- Adverse Events:
  - Nephrotoxicity/nephrotic syndrome
  - Unusual fractures
  - Osteonecrosis of the jaw

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TLS pathophysiology

Hyperkalemia » cardiac arrhythmias » death

Hyperuricemia » urine becomes acidic » uric acid crystals deposited » renal failure » oliguria/anuria

Hyperphosphatemia » causes HYPOcalcemia » tetany/seizures & arrhythmias » renal failure

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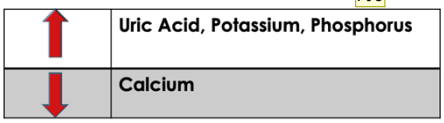
PJ0 To be complete, you should probably mention denosumab (not used in hypercalcemia of malignancy unless refractory to bisphos)
Preedit, Justine, 2023-08-01T14:19:48.508

Tumor Lysis Syndrome (TLS)

- Definition: Tumor lysis syndrome (TLS) is an oncologic emergency as a result of tumor cell lysis with the release of intracellular potassium, nucleic acids, and phosphorus into the systemic circulation.
- More common in rapidly proliferating hematologic malignancies, such as ALL, AML, and aggressive lymphomas

PJ0



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

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Cario-Bishop laboratory diagnosis of TLS

Element	Value	Change from baseline
Uric acid	≥476 micromol/L (8 mg/dL)	25% increase
Potassium	≥6.0 mmol/L (or 6 mEq/L)	25% increase
Phosphorus	≥2.1 mmol/L (6.5 mg/dL) for children or ≥1.45 mmol/L (4.5 mg/dL) for adults	25% increase
Calcium	≤1.75 mmol/L (7 mg/dL)	25% decrease

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PJ0 I would say "aggressive lymphomas." Did you define ALL/AML yet?
Preedit, Justine, 2023-08-01T14:20:17.462

Presentation

- Signs and symptoms include:
  - Nausea and/or vomiting
  - Anorexia
  - Fatigue
  - Dark urine or decrease urine output
  - Change in mentation
  - Seizures; hallucinations
  - Muscle cramps
  - Heart arrythmias and palpitations

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Prophylaxis of TLS

- Hydration, hydration, hydration! Hydration is the mainstay for TLS prophylaxis PJ0
  - Ideally 2-3L/m^2 /day IV fluid
- Allopurinol given up to 48 hours before treatment, only prevents new uric acid formation
  - Doses around 300 mg daily, may need dose reduction depending on CrCL
- Rasburicase, a recombinant urate oxidase, converts uric acid into water-soluble allantoin
  - 3mg (1/2 dose) vs 6 mg (full dose) @ Allina Hospital systems
  - Uric acid levels drawn on ice for 72 hours following administration of rasburicase PJ1

Sarno J. Prevention and Management of Tumor Lysis Syndrome in adults with Malignancy. J Adv Pract Oncol. 2013;4(2):101-6

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Slide 30

PJ0 Recommend discussing who is candidate for each of these (risk stratifying)
Preedit, Justine, 2023-08-01T14:21:46.682

PJ1 Heading says "prophylaxis of TLS" - I would never use 6mg of rasburicase for prophylaxis. Also mention $$$
Preedit, Justine, 2023-08-01T14:22:05.151

Management of TLS

- **Hypocalcemia**
- Asymptomatic
  - No treatment
- Symptomatic – i.e., seizure
  - Calcium gluconate
- **Hyperphosphatemia**
- Severe
  - Dialysis
- Moderate
  - Restrict phosphate intake
  - Phosphate binders

Treat underlying metabolic abnormalities

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

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TLS treatment

- **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[6]

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PJ0 SPS?
Preedit, Justine, 2023-08-01T14:22:31.886

TLS Management:

- **Hyperuricemia**
- Continue IV hydration goal to maintain high urine output
- Start allopurinol if not started already
- Rasburicase
  - Breaks down uric acid into more soluble allantoin
  - Not cleared by the kidneys
  - Contraindicated in G6PD deficiency and pregnancy
  - Uric acid level drawn on ice for 72 hours following administration [6]

Adult Rasburicase Dosing

Indication	Rasburicase dose (mg)
TLS Prophylaxis or Treatment	**3 mg**
Weight ≥120 kg or uric acid ≥12 mg/dL	**6 mg**

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

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Oncologic Emergencies Summary

- Oncologic emergencies require prompt identification and intervention
- Prompt management can improve quantity and/or quality of life
- Febrile neutropenia requires prompt blood cultures and initiation of empiric antibiotics
- When spinal cord compression is suspected, steroids should be started immediately
- Hypercalcemia is managed with aggressive hydration and bisphosphonate therapy
- The keys to managing tumor lysis syndrome are prevention, vigilant monitoring of electrolytes, and intervention when needed

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References

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

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