Oncologic Emergencies & the Role of the Pharmacist

A presentation for HealthTrust Members
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Pharmacist Objectives

- Recognize the types of oncologic emergencies and the risk factors associated with them
- Explain how to manage patients with oncologic emergencies
- Create an individualized treatment plan for patients with oncologic emergencies

Outline

- Oncologic emergencies overview
- Febrile neutropenia
- Tumor lysis syndrome
- Hypercalcemia of malignancy

Epidemiology of Cancer

- Cancer is the second leading cause of death globally
- 14.5 million persons estimated to have cancer in US
  - Could reach 19 million by 2024
- Patients with cancer account for 14-22% of all intensive care unit (ICU) admissions
- Evolution of cancer care → mortality rates decreasing by 1.5% each year (from 1991 to 2015)

Sources: J Intensive Care Med. 2018 Nov 9. Epub ahead of print.
Am Fam Physician. 2018 Jun 1;97(11):741-748.

Oncologic Emergencies

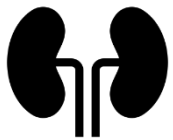
Oncologic Emergencies

Complications associated with the disease and treatment of cancer

Oncologic emergencies are frequently observed in the hospital

A better understanding of oncologic emergencies will allow pharmacists to play a more active role in the treatment and management of these patients

Oncologic Emergencies



Metabolic

- **Tumor Lysis Syndrome**
- **Hypercalcemia**

Neurologic

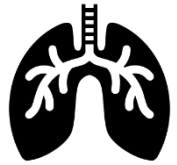
- Spinal cord compression
- Brain metastasis

Cardiovascular

- Cardiac tamponade
- Superior vena cava syndrome

Infectious

- **Febrile neutropenia**
- Sepsis



Pulmonary

- Malignant airway obstruction
- Hemoptysis
- Pulmonary embolism

Hematologic

- Hyper-viscosity syndrome
- Leukostasis

Source: J Intensive Care Med. 2018 Nov 9. Epub ahead of print.

Febrile Neutropenia

Febrile Neutropenia (FN)

- FN = Fever + decrease in absolute neutrophil count (ANC)
- A decrease in the ANC may predispose a patient to serious and life-threatening infections
  - Frequently occurs in patients receiving chemotherapy
  - Fever may be the only sign of infection
- IDSA defines fever as:
  - Single oral temperature ≥38.3ºC (101ºF) or temperature ≥38.0ºC (100.4ºF) for > 1 hour

Sources: *J Clin Oncol*. 36;14: 1443-1453.
Clin Infect Dis. 2011. 52(4):e56-93

Guidelines

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)	INFECTIOUS DISEASES SOCIETY OF AMERICA (IDSA)
ANC < 400 cells/mm^3	**ANC <500 cells/mm^3 or 1000 cells/mm AND a predicted decline to ≤500 cells/mm^3 over the next 48 hours**

Sources: *J Clin Oncol*. 36;14: 1443-1453. Clin Infect Dis. 2011. 52(4):e56-93

Epidemiology

- Rate of major complications ~25–30%
  - Hypotension, acute renal dysfunction, respiratory complications or heart failure
- Mortality rate ranges up to 11%
- In severe sepsis or septic shock, hospital mortality may be up to 50%

Source: *J Clin Oncol*. 36;14: 1443-1453.

Pathophysiology

- Due to myelosuppressive effects of cytotoxic chemotherapy
- Bone marrow infiltrated by tumor
- Direct interference with hematopoiesis

Source: *J Clin Oncol*. 36;14: 1443-1453.

Risk Factors

Low risk	High Risk
• MASCC Score ≥21 • Currently outpatient • No acute comorbid illness • Anticipated short duration of neutropenia (<100 cells/mcL for < 7 days) • Good performance status (ECOG 0-1) • No hepatic insufficiency • No renal insufficiency	• MASCC Score <21 • Inpatient at time of fever • Significant medical comorbidity • Allogeneic HCT • Anticipated prolonged severe neutropenia (<100 cells/mcL and ≥7 days) • Hepatic insufficiency • Uncontrolled/progressive cancer • Pneumonia or complex infection • Mucositis grade 3–4

Source: *National Cancer Comprehensive Network.* 2014: MS-15-MS-17.

MASCC Scoring System

- Maximum score: 26

- ≥ 21 = low risk for FN
- < 21 = high risk for FN

Multinational Association of Supportive Care in Cancer (MASCC)	
Characteristic	**Score**
Burden of FN with no or mild symptoms	5
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of FN with moderate symptoms	3
Outpatient status	3
Age <60 years	2
Age > 60 years	0
Severe symptoms	0

Source: *J Clin Oncol*. 36;14: 1443-1453.

Chemotherapy Drugs Associated with FN

Anthracyclines
Taxanes
Topoisomerase inhibitors
Platinum-based agents
Gemcitabine
Vinorelbine
Certain alkylators (cyclophosphamide, ifosfamide)

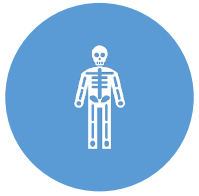
Source: J Intensive Care Med. 2018 Nov 9. Epub ahead of print.

Considerations for Initial Antibiotics

Infection risk assessment

Potential pathogens

Colonization with methicillin-resistant Staphylococcus aureus (MRSA)



Site of infection

Broad-spectrum coverage

Local antibiogram

Allergies

Organ dysfunction

Common Causative Organisms of FN

Gram-positive Organisms	Gram-negative Organisms	Fungal Organisms
Staphylococcus aureus *Staphylococcus Epidermidis* *Streptococcus Pneumoniae* *Streptococcus pyogenes* *Streptococci viridans* *Enterococcus faecalis* *Enterococcus faecium* *Corynebacterium*	*Escherichia coli* *Klebsiella pneumoniae* *Pseudomonas aeruginosa*	Candida species

Source: J Intensive Care Med. 2018 Nov 9. Epub ahead of print.

Initial Antibiotic Regimens

IV antibiotics - Monotherapy

- Cefepime
- Imipenem/cilastatin
- Meropenem
- Piperacillin/tazobactam
- Ceftazidime
- ± vancomycin or linezolid

Low risk patients may receive PO antibiotics

- Ciprofloxacin + amoxicillin/clavulanate
- Moxifloxacin
- Levofloxacin
- Not recommended if patient prophylactically received quinolones

Combination regimens may be considered if resistance is suspected

Source: Clin Infect Dis. 2011. 52(4):e56-93

Management of FN

- Adjust initial antibiotic regimen based on clinical and microbiological results
- If no evidence of gram-positive infection, stop vancomycin after 2 days
- Unexplained persistent fever in a patient who is otherwise stable would rarely need escalation of therapy
- If hemodynamically unstable, escalate and broaden coverage

Source: Clin Infect Dis. 2011. 52(4):e56-93

Management of FN

- Duration of therapy
  - Based on particular organism and site
  - At least the duration of neutropenia (longer if clinically necessary)
- If appropriate treatment course completed and all signs of infection resolved, but patient is still neutropenic – resume oral fluoroquinolone prophylaxis until recovered

Source: Clin Infect Dis. 2011. 52(4):e56-93

Fluoroquinolone Prophylaxis

- For high risk patients with expected duration of ANC ≤100 cells/mm for >7 days
  - Levofloxacin and ciprofloxacin
- Not recommended for low-risk patients with expected duration of neutropenia < 7 days

Source: Clin Infect Dis. 2011. 52(4):e56-93

Anti-fungal prophylaxis

For patients with persistent or recurrent fever after 4-7 days of antibiotics with overall duration of neutropenia >7 days

Discontinue if no indicators of possible invasive fungal infection (clinically stable, no clinical or chest computed tomography signs of fungal infection, no fungi growth from any site)

Source: Clin Infect Dis. 2011. 52(4):e56-93

Anti-Viral Prophylaxis

Herpes simplex virus (HSV)-seropositive undergoing allogeneic hematopoietic stem cell transplant or leukemia induction therapy should receive acyclovir

Yearly influenza vaccine

Source: Clin Infect Dis. 2011. 52(4):e56-93

Use of Granulocyte-colony Stimulating Factor (G-CSF)

- Most benefit if given prior to neutropenia
- American Society of Clinical Oncology (ASCO) recommends against routine use as adjunctive treatment for febrile neutropenia
- May be used if high risk
  - Persistent fever despite antibiotics
  - Prolonged neutropenia (>10 days)
  - Severe neutropenia (ANC <100 cells/mcL)
  - Age >65 years

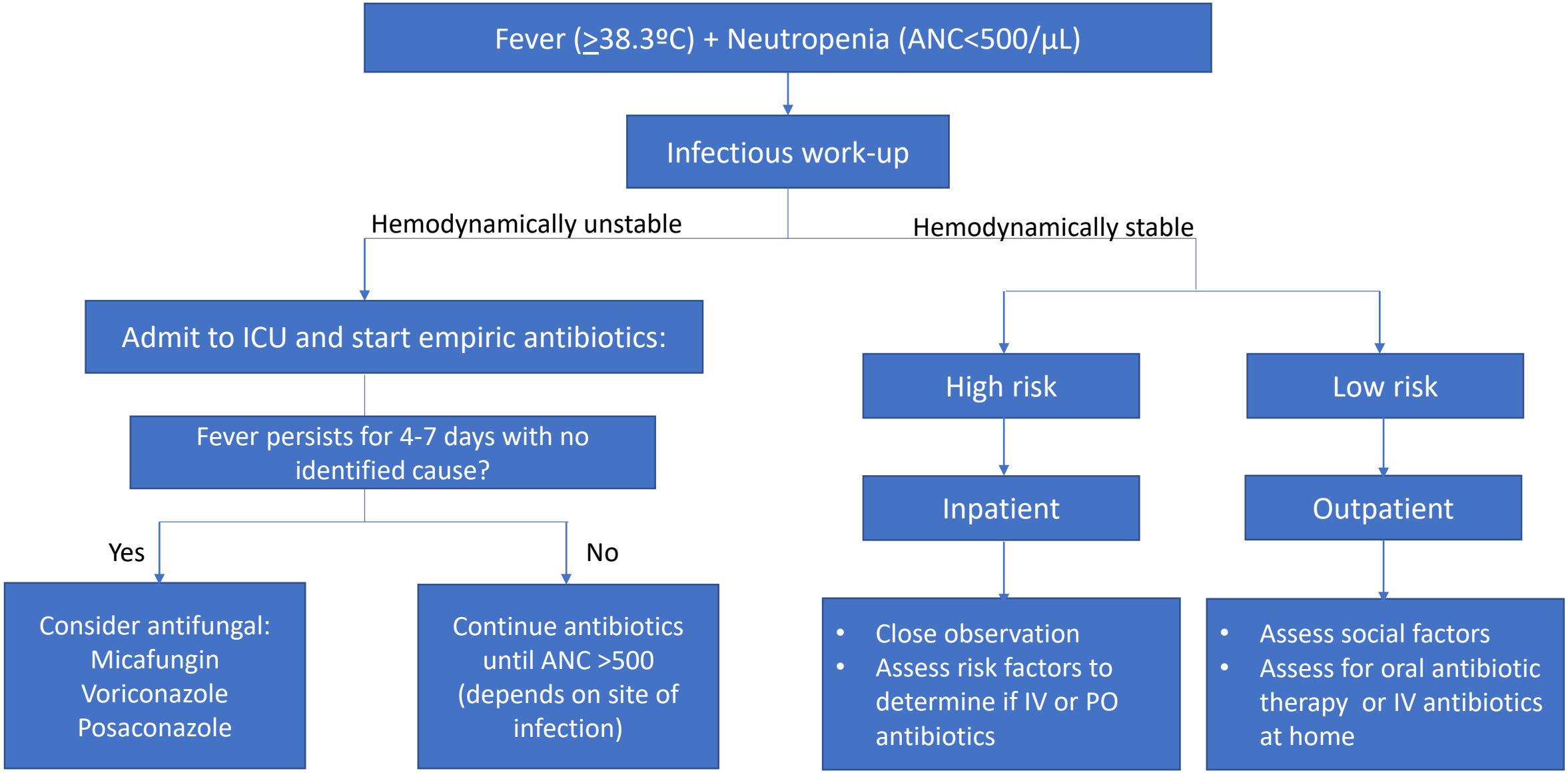
Source: J Clin Oncol. 2015;33(28):3199-3212

Chemotherapy-induced neutropenia/febrile neutropenia prophylaxis with biosimilar filgrastim in solid tumors versus hematological malignancies: MONITOR-GCSF study

Design	Population	Intervention	Outcomes	Results
• Prospective real-world observational study • 140 centers in 12 European countries	• 1447 cancer patients • 77.2% solid tumor • 22.8 hematological malignancy	• Patients received biosimilar filgrastim; observed for up to 6 cycles of chemotherapy	• Prophylaxis patterns and clinical outcomes among patients receiving FN prophylaxis with biosimilar filgrastim	• No differences in rates of chemotherapy induced neutropenia of any grade • Hematologic group had higher rate of FN (9.1% v 5%) • More patients in solid group were "over-prophylacted" (p= 0.009)

Source: Future Oncol. 2019 Mar;15(8):897-907.

Initial Management of Febrile Neutropenia



Source: J Clin Oncol. 2015;33(28):3199-3212

Question 1: A 47-year old who recently completed cisplatin-based chemotherapy with presents was admitted to the ICU with temperature of 38.5ºC and ANC 350. He has no known allergies. What should be your initial course of action?

A. Initiate piperacillin-tazobactam

B. Initiate meropenem

C. Initiate cefepime

D. Initiate meropenem + vancomycin

Response 1: A 47-year old who recently completed cisplatin-based chemotherapy with presents was admitted to the ICU with temperature of 38.5ºC and ANC 350. He has no known allergies. What should be your initial course of action?

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Tumor Lysis Syndrome

Tumor Lysis Syndrome (TLS)

- Oncologic emergency characterized by metabolic abnormalities caused by the rapid and abrupt release of intracellular cellular contents into the blood after rapid lysis of malignant cells
- Untreated TLS can lead to profound metabolic changes, which can result in: cardiac arrhythmias, seizures, loss of muscle control, acute renal failure, and death

Source: *Journal of Clinical Oncology.* 2008; 26: 2767-2778.
NCCN Clinical Practice Guidelines in Oncology. 2014

Metabolic Disturbances

Hyperkalemia	• Potassium ≥ 6 mEq/L or 25% decrease from baseline
Hypocalcemia	• Calcium ≤7 mEq/dL or ionized calcium <1.12 mg/dL • or 25% decrease from baseline
Hyperphosphatemia	• Phosphorus ≥ 4.5 mg/dL (≥ 6.5 mg/dL in children) or 25% increase from baseline
Hyperuricemia	• Uric acid ≥ 8 mg/dL or 25% increase in baseline

Source: Am Fam Physician. 2018 Jun 1;97(11):741-748.

Classifications

Laboratory TLS:

- 2 or more abnormal serum values of uric acid, potassium, phosphorus, calcium are present
- Or if 25% increase in the levels of serum uric acid, potassium, or phosphorus or a 25% decrease in calcium levels
- Considered either present or absent
- Monitor serum creatinine (SCr) for signs of renal failure

Clinical TLS

- Presence of laboratory TLS PLUS one or more clinical complication(s)
- Clinical complication: renal insufficiency, cardiac arrhythmia/sudden death, or seizures

Source: *Journal of Clinical Oncology.* 2008; 26: 2767-2778.

Epidemiology

- 42% of patients with high-grade non-Hodgkin's lymphoma (NHL) laboratory TLS
  - 6% of these patients has life-threatening emergencies
- 17% of patients with acute myeloid leukemia (AML) developed clinical or laboratory TLS
  - Found no correlation between laboratory TLS and death rate
  - However, clinical TLS was associated with statistically significant increased death rate
- TLS occurs in more aggressive disease: leukemias (ALL, AML), small cell lung cancer, high tumor burden in solids

Source: *Journal of Clinical Oncology.* 2008; 26: 2767-2778.

Pathophysiology

The release of intracellular contents overwhelms normal homeostatic mechanisms, which leads to electrolyte abnormalities

Crystallization of uric acid or calcium phosphate in renal tubules may impair renal function, possibly to the point of acute renal failure or death

Source: *Journal of Clinical Oncology.* 2008; 26: 2767-2778.

High Risk Features

- Cancer type
- Spontaneous TLS
- Elevated WBC
- Bone marrow involvement
- Pre-existing hyperuricemia
- Ineffectiveness of allopurinol
- Renal disease or renal involvement by tumor

Source: National Cancer Comprehensive Network 2014: MS-15-MS-17.

Clinical Presentation

Usually observed after 12-24 hours after chemotherapy

Spontaneous TLS may occur in patients with bulky disease even prior to chemo

Symptoms: Nausea/vomiting, shortness of breath, irregular heartbeat, cloudy urine, lethargy, and/or joint discomfort

Source: National Cancer Comprehensive Network 2014: MS-15-MS-17.

Prevention and Management

- Due to potential severity of complications due to TLS, prevention and prompt treatment is necessary in high risk patients
- Best managed if TLS is anticipated and treatment is started prior to chemo
- Cornerstone of TLS:
  - Hydration
  - Management of hyperuricemia
  - Electrolyte management

Source: *Journal of Clinical Oncology.* 2008; 26: 2767-2778.

Fluids and Hydration

- Aggressive hydration and diuresis for prevention and management
- Improves intravascular volume, renal blood flow, and glomerular filtration, which promotes excretion of uric acid and phosphate
- Diuretics may be used to maintain adequate urine output
  - Contraindication: patients with hypovolemia or obstructive uropathy

Source: *Journal of Clinical Oncology.* 2008; 26: 2767-2778.

Alkalinization

- Sodium bicarbonate to alkalinize urine
- Not recommended with recombinant urate oxidase (rasburicase)
- Due to potential effects of alkalinization (metabolic alkalosis and calcium phosphate precipitation), alkalinization currently not recommended

Source: *Journal of Clinical Oncology.* 2008; 26: 2767-2778.

Allopurinol

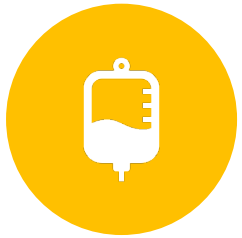
- Blocks conversion of xanthine to uric acid
- Decreases uric acid formation and precipitation and reduces the risk of obstructive uropathy
- Alternative: febuxostat
  - If intolerant to allopurinol or not a candidate for rasburicase

Source: *Journal of Clinical Oncology.* 2008; 26: 2767-2778.

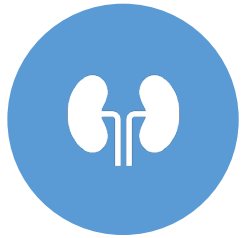
Rasburicase (Recombinant Urate Oxidase)

Presence of any high-risk feature

Urgent need to initiate therapy in a high-bulk patient



Situations where adequate hydration may be difficult or impossible



Acute renal failure, renal insufficiency

Not responsive to allopurinol

Sources: *Journal of Clinical Oncology.* 2008; 26: 2767-2778.
National Cancer Comprehensive Network 2014: MS-15-MS-17.

Fluids

MOA	Dosing	Renal Adjustment	Adverse Effects	Notes
Promotes excretion of uric acid and phosphate by improving intravascular volume, renal blood flow and GFR	NS 125 mL/hr to maintain urine output of 80-100 $mL/m^2/h$ ASCO guidelines recommends hydration at 2-3 $L/m^2/d$ (maintain at approximately 1-2 times maintenance)	None	Hyperchloremia, hypervolemia	Diuretics may be used to maintain urine output (80-100 $mL/m^2/h$)

Allopurinol

MOA	Dosing	Renal Adjustment	Adverse Effects	Notes
Xanthine analog that competitively inhibits xanthine oxidase, which blocks the conversion of purine metabolites to uric acid resulting in decreased formation of uric acid production (no effect on existing uric acid)	In patients without pre-existing hyperuricemia: PO: 300 mg/m^2/d or 10 mg/kg/d in 3 divided doses q8h (max 800 mg/d) IV: 200-400 mg/m^2/d in a single daily or 2-3 divided doses (max 600 mg/d) Start: 1-2 days prior to chemotherapy Continue: up to 3-7 days after chemotherapy until normalization of labs	Chemotherapy induced hyperuricemia: dose reduction of 50% CrCl 10-20: 200 mg/d CrCl 3-10: 100 mg/d CrCl<3: 100 mg/d, may need to extend dosing interval	May lead to accumulation of xanthine crystals in renal tubules→ obstructive uropathy	Can take several days to normalize uric acid levels DDIs: reduced clearance of 6-MP/AZA (reduce 6-MP/AZA doses by 65-75%) and high-dose methotrexate Rash (SJS/TEN) [HLA-B*58:01] - Asians at higher risk

Febuxostat

MOA	Dosing	Renal Adjustment	Adverse Effects	Notes
Decreases uric acid by selectively inhibiting xanthine oxidase	40 mg daily (max 120 mg daily)	CrCl < 30: 40 mg/day (max)	Skin rash, nausea, LFT abnormalities, arthralgias	Used if intolerant to allopurinol or not a candidate for rasburicase

Sources: *Journal of Clinical Oncology.* 2008; 26: 2767-2778.
National Cancer Comprehensive Network 2014: MS-15-MS-17.

Rasburicase

MOA	Dosing	Renal Adjustment	Adverse Effects	Notes
Recombinant urate oxidase that catalyzes the oxidation of uric acid to a highly soluble, non-toxic metabolite that is readily excreted	Weight-based regimens: High risk (uric acid>7.5): 0.2 mg/kg IV over 30 min Intermediate risk (uric acid < 7.5): 0.15 mg/kg IV Low risk (clinical judgement): 0.1 mg/kg IV Duration: usually 2 d, but can vary from 1-7 d Single dose regimens: 0.15 mg/kg or 3-7.5mg as single dose, may repeat doses based on serum uric acid level	None	Hypersensitivity reaction, Peripheral edema, headache, anxiety, hypophosphatemia, hyperphosphatemia	Monitor uric acid levels 4 hrs after administration, then q6-8h Gives inaccurate results after giving rasburicase (uric acid level will be falsely low) Draw blood and put it in ice so rasburicase is not activated Contraindication: G6PD deficiency

The optimal single-dose regimen of rasburicase for management of tumor lysis syndrome in children and adults: a systematic review and meta-analysis.

Design	Population	Intervention	Outcomes	Results

• Meta-analysis	• Meta-analysis
	  • 15 adult reports
	  • 4 pediatric reports
	• 906 adult patients (2006 to 2016)
	• 92 pediatric patients (2013-2016)
		• Adults
		  • Rasburicase 1.5-7.5 mg fixed doses and weight-based doses
		• Pediatrics:
		  • 1.5 mg dose
		  • 0.15 mg/kg dose
			• Response rates
			• Uric acid levels
				• Response rates superior in single dose 6 mg, 7.5 mg and 0.15 mg/kg clinically (RR=0.88, 0.83-0.93)
				• 6 mg and 0.15 mg/kg had greater efficacy overall (UA reduction=7.01 mg/dL, 5.84-8.18)

Conclusion	Single dose 6 mg rasburicase to normalize and sustain uric acid Pediatric patients: 1.5 mg and 0.15 mg/kg single doses

Source: Yu X, et al. The optimal single-dose regimen of rasburicase for management of tumor lysis syndrome in children and adults: a systematic review and meta-analysis. Journal of Clinical Pharmacy and therapeutics 2017; 42: 18-26.

Question 2: A 40-year-old man was recently diagnosed with acute myeloid leukemia. He presents with white blood cell count (WBC 14,000). He is scheduled to start chemotherapy tomorrow. Which of the following is the best prevention strategy for tumor lysis syndrome (TLS)?

A. Hydration with 5% dextrose 100 mL/hour 24 hours before chemotherapy PLUS allopurinol 300 mg daily
B. Hydration with 0.9% sodium chloride 250 mL/hour starting at least 24 hours before chemotherapy PLUS allopurinol 300 mg daily
C. Hydration with 0.9% sodium chloride 250 mL/hour starting at least 24 hours before chemotherapy PLUS rasburicase 6 mg
D. Hydration with 0.9% sodium chloride 250 mL/hour starting at least 24 hours before chemotherapy plus sodium bicarbonate 500 mg orally every 6 hours

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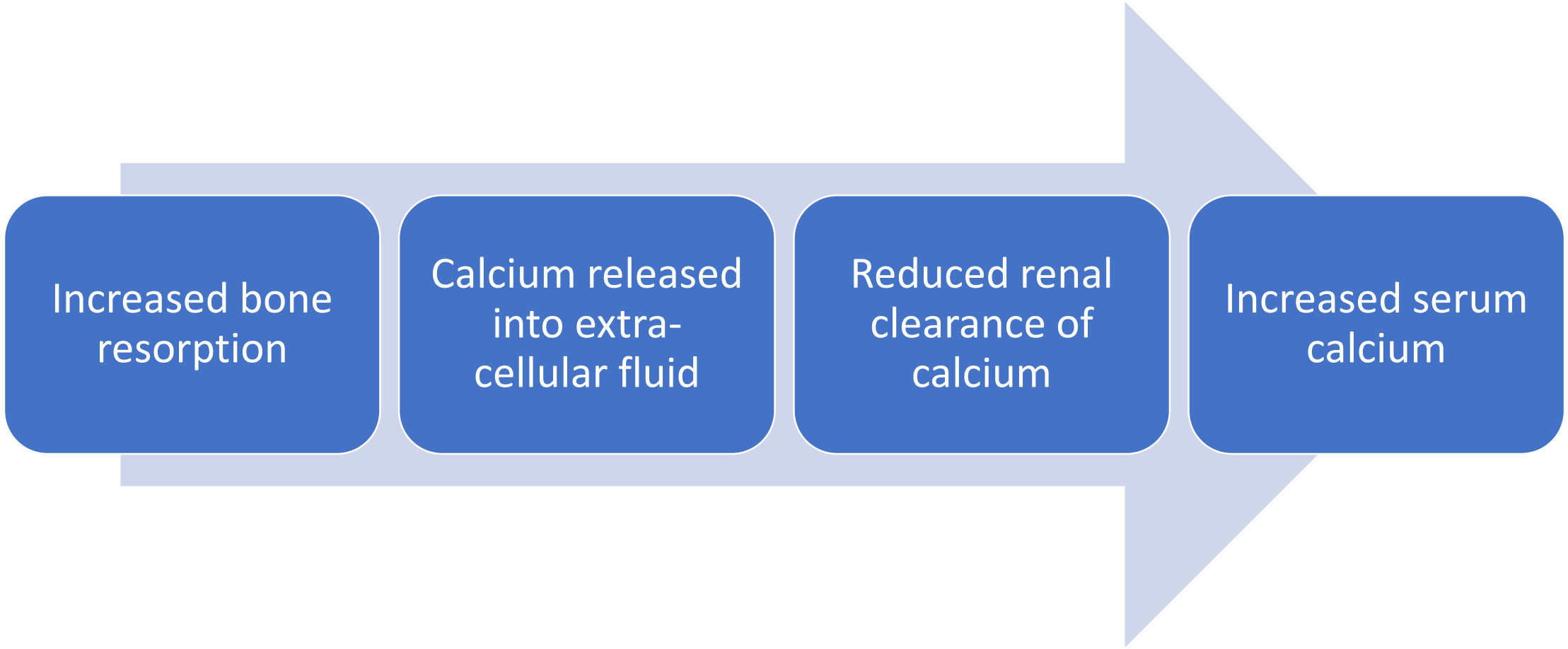
Hypercalcemia of Malignancy

Pathophysiology



Source: Elder, C. ACCP Updates in Therapeutics. 2018. 2-141-2-181.

Types of Cancer with Higher Risk

Lung

Breast

Multiple myeloma

Head and neck

Renal cell

Non-Hodgkin lymphoma

Source: Elder, C. ACCP Updates in Therapeutics. 2018. 2-141-2-181.

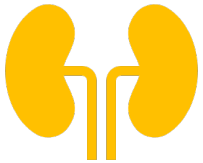
Other Risk Factors

Medications

Hormonal therapies

Thiazide diuretics

Immobility



Renal impairment

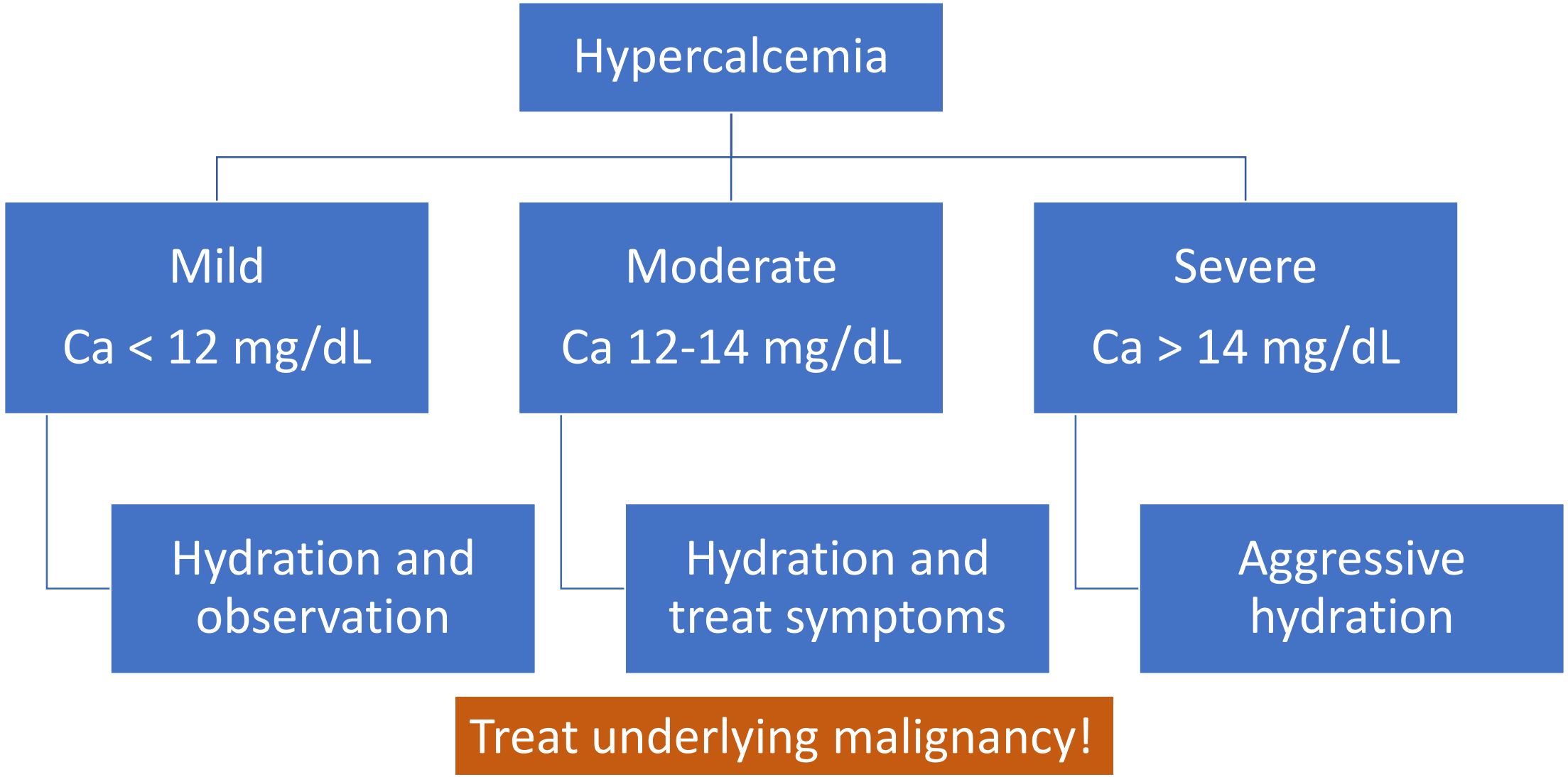
Source: Elder, C. ACCP Updates in Therapeutics. 2018. 2-141-2-181.

Clinical Presentation

- Lethargy
- Confusion
- Anorexia
- Nausea
- Constipation
- Polyuria, polydipsia

Source: Elder, C. ACCP Updates in Therapeutics. 2018. 2-141-2-181.

Management: Hydration



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Pharmacologic Management

IV Bisphosphonate

Mechanism: Binds to hydroxyapatite in calcified bone, which inhibits bone resorption

Onset of action: 3-4 days

Calcitonin

Mechanism: Inhibits effects of parathyroid hormone (PTH)

Onset of action: rapid, but short duration

Additional considerations: tachyphylaxis, injection

Denosumab

Mechanism: monoclonal antibody which binds to nuclear factor-kappa ligand (RANKL) and prevent osteoclast formation

For acute hypercalcemia of malignancy

Steroids

Mechanism: Lowers calcium in patients with steroid-responsive tumors (lymphoma and myeloma)

Phosphate

Reserved for hypo-phosphatemia

Seldom-used due to risk of precipitation in soft tissue

Dialysis

Patients with hypercalcemia and renal failure

Question 3: A 63-year-old man with metastatic non-small-cell lung cancer is admitted to the ICU with a two day history of symptoms of abdominal pain, nausea/vomiting, and lethargy. *Lab values: Ca: 15 mg/dL, SCr: 2.3*

After aggressive hydration with fluids, which agent would be most appropriate to initiate?

A. Zoledronic acid
B. Alendronate
C. Sodium bicarbonate and insulin
D. Allopurinol

Response 3: A 63-year-old man with metastatic non-small-cell lung cancer is admitted to the ICU with a two day history of symptoms of abdominal pain, nausea/vomiting, and lethargy. *Lab values: Ca: 15 mg/dL, SCr: 2.3*

After aggressive hydration with fluids, which agent would be most appropriate to initiate?

A. **Zoledronic acid**
B. Alendronate
C. Sodium bicarbonate and insulin
D. Allopurinol

Key Takeaways

- **Oncologic emergencies** can be caused by chemotherapy or the cancer itself and requires immediate identification and management
- Management of **febrile neutropenia** depends upon patient's risk factors and presentation, and typically requires broad-spectrum antimicrobials and monitoring of symptom resolution
- **Tumor lysis syndrome** is associated with metabolic disturbances which is best managed with adequate hydration and management of hyperuricemia
- **Hypercalcemia of malignancy** is best managed with appropriate hydration depending on severity

Thank you!

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