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Recognition & Management of Oncologic Emergencies

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| Disclosures

The presenter has no real or perceived conflicts of interest related to this presentation

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| Learning Objectives

At the end of this session, participants should be able to:

1. Recognize common oncologic emergencies
2. Identify appropriate treatment of common oncologic emergencies
3. Recall appropriate monitoring of common oncologic emergencies

The Burden & Costs of Cancer

| Why Should I Care

If my hospital does not have an Oncology Program?

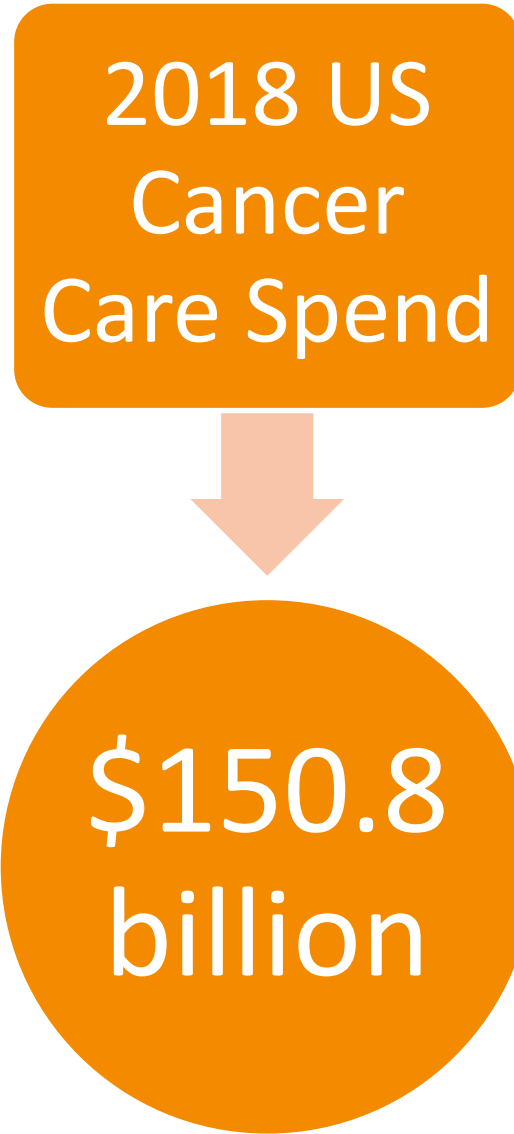
- The incidence of new cancer cases is increasing and the number of cancer survivors is rising
 - Anticipated 62% increase in new cancer cases from 2018 to 2040
 - Anticipated 72% increase in cancer-related deaths from 2018 to 2040
- In 2017, cancer-related hospitalizations in the US accounted for > 10% of all adult, nonmaternal hospitalizations and for > 13% of all hospital costs
- Cancer-related hospitalizations cost more than non-cancer hospitalizations



Sources:

Roemer M (AHRQ). Cancer-Related Hospitalizations for Adults, 2017. HCUP Statistical Brief #270. January 2021. Agency for Healthcare Research and Quality, Rockville, MD.
Cancer Statistics. NIH National Cancer Institute. Updated September 25, 2020. Accessed March 21, 2022.

| The Costs of Cancer



Sources:

Cancer Statistics. NIH National Cancer Institute. Updated September 25, 2020. Accessed March 21, 2022.

Cancer Facts & Figures 2020. American Cancer Society. Accessed March 21, 2022.

What are Common Oncologic Emergencies?

| Oncologic Emergencies to Be Discussed

Tumor lysis
syndrome

Hypercalcemia of
malignancy

Febrile neutropenia

Pseudohyperkalemia

Tumor Lysis Syndrome

Introduction

- Tumor lysis syndrome (TLS) is a constellation of metabolic abnormalities resulting from tumor cell death and the subsequent release of intracellular contents into the bloodstream
- May be spontaneous or induced by chemotherapy
- Overall mortality is not well defined
- Incidence varies based on the underlying malignancy

Sources:

Edeani A, et al. *American Society of Nephrology* 2016; 1-8.

Durani U, et al. *Oncologist*. 2017;22(12): 1506-1509.

Cancer-specific factors

Large tumor burden

White blood cells (WBC)
> 50,000

Bone marrow involvement

Liver metastasis

High proliferation rate

High sensitivity to
cytotoxic therapy

Patient-specific factors

Age

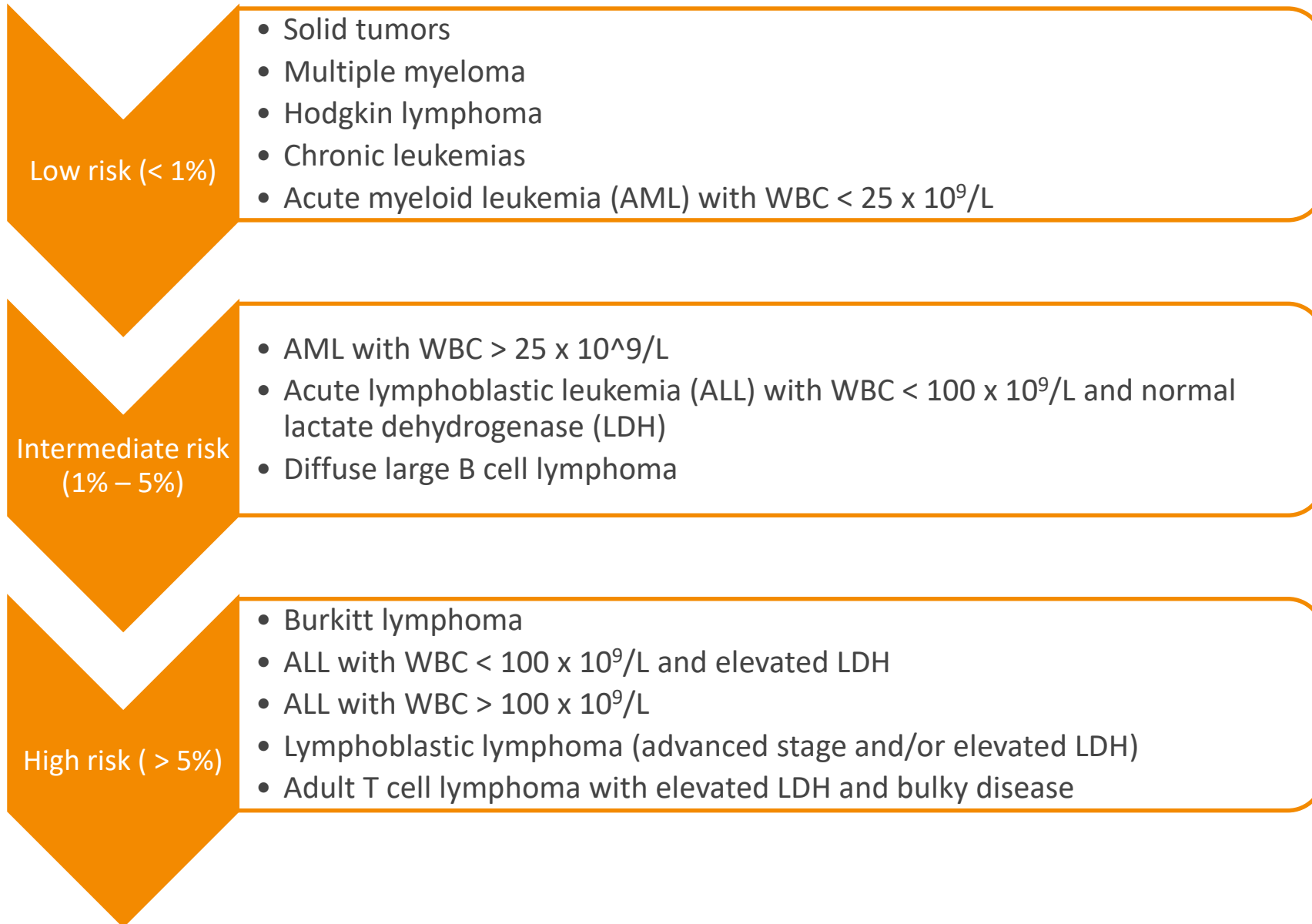
Volume depletion

Preexisting renal impairment

Hyperuricemia

Hyponatremia

Risk Classification Based on Type of Cancer



If renal dysfunction is present, low risk disease increases to intermediate risk & intermediate risk disease increases to high risk

Laboratory TLS

Two or more of the following:

- Uric acid \geq 8 mg/dL or 25% increase from baseline
- Potassium \geq 6 mEq/dL or 25% increase from baseline
- Phosphorus \geq 4.5 mg/dL or 25% increase from baseline
- Calcium \geq 25% decrease from baseline

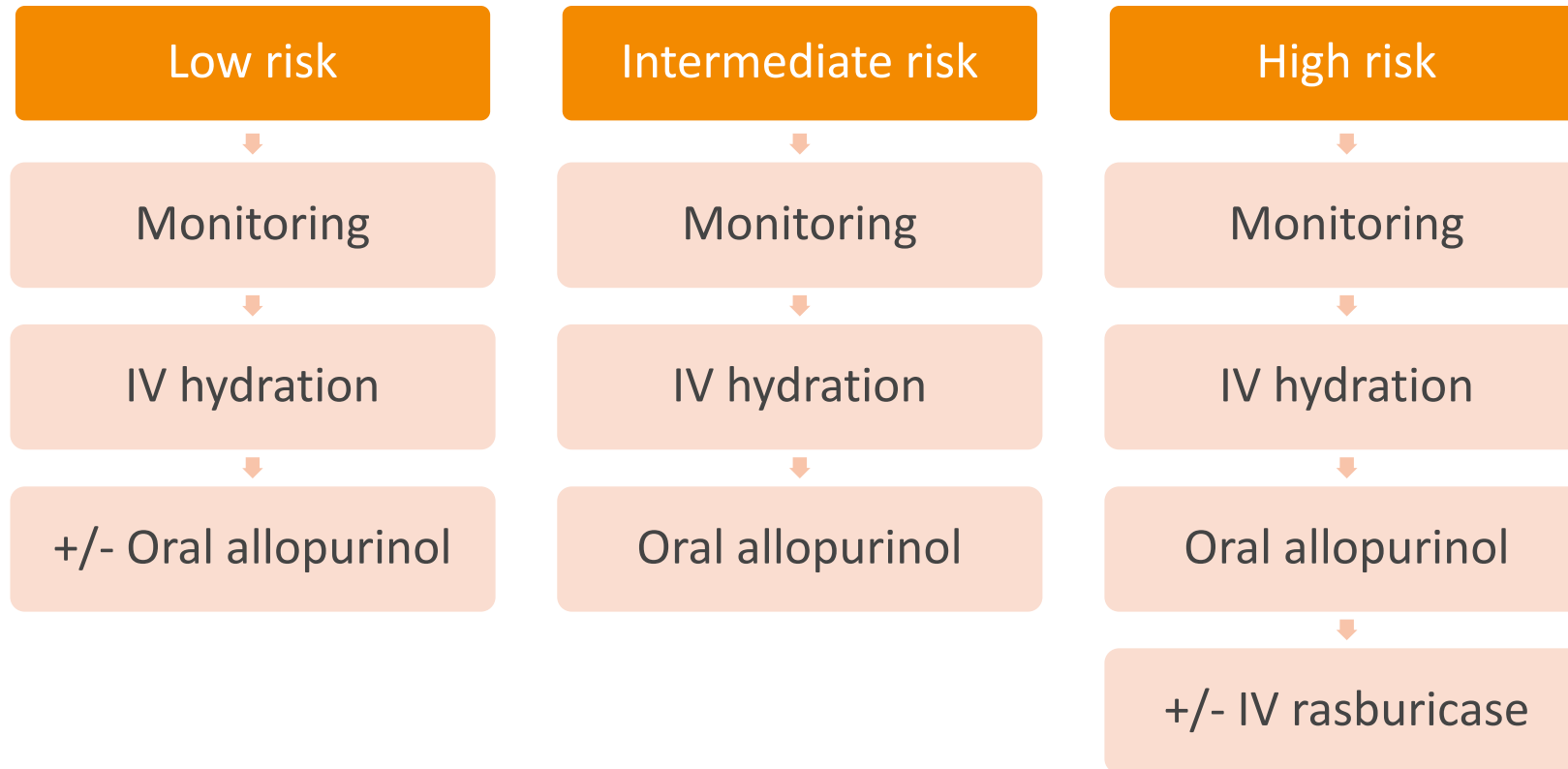
Clinical TLS

Laboratory TLS plus at least one of the following:

- Creatinine \geq 1.5 times the upper limit of normal
- Cardiac arrhythmia
- Seizure

Prevention of TLS

The best treatment of TLS is prevention



| Hydration

- IV fluids at a rate of 80 – 125 mL/hr
- Common IV fluids:
 - 0.9% sodium chloride
 - 5% dextrose
 - 0.45% sodium chloride + 5% dextrose
- Alkaline fluids such as sodium bicarbonate were used in the past, but this practice has fallen out of favor

Allopurinol

- Inhibits xanthine oxidase, the enzyme responsible for formation of uric acid
- Dosing:
 - Typical dosing is 300 mg by mouth once daily
 - Frequency may be increased to 2 – 3 times daily in high risk patients
 - Renal dose adjustments are recommended if the patient has renal impairment
- Prevents the formation of **new** uric acid only
- Prevents an increase in uric acid levels in 93% of adults and 92% of children when used as prophylactic therapy



Rasburicase

- Enzyme that converts uric acid to a more soluble metabolite called allantoin, which is more easily excreted by the kidneys than uric acid
- Rapidly lowers pre-existing uric acid levels but does not inhibit the formation of uric acid
- May be used as:
 - Treatment of TLS
 - Prevention in high risk patients with uric acid ≥ 4 mg/dL
 - Prevention in patients with baseline uric acid ≥ 8 mg/dL
- Adverse effects are very rare
- Has been proven to lower uric acid levels in 100% of adults and 99% of children

Rasburicase Dosing — Weight-Based or Fixed Dose?

Weight-Based

- FDA approved dosing of rasburicase is 0.2 mg/kg IV once daily for up to 5 days
- Rasburicase is **\$951.31** per 1.5 mg vial
- For an 80 kg male, a weight-based dose of 0.2 mg/kg = 16 mg
- 16 mg requires eleven 1.5 mg vials = **\$10,464.41** for one dose
- If completing a 5-day course, total cost = **\$52,322.05**

Fixed Dose

- Fixed dosing of rasburicase ranging from 3 mg to 7.5 mg as a single dose has been studied for efficacy and cost savings
- A meta-analysis of 10 studies evaluated single-dose rasburicase (SDR) compared to daily dosing rasburicase (DDR) and plasma uric acid level reduction at 24, 48, and 72 hours
 - Uric acid was maintained below 7.5 mg/dL in 88.15% of SDR patients vs. 90.18% of DDR patients (P = 0.542)
 - Average cost in SDR group was **\$4,456.45** vs. **\$36,024** in DDR group

Sources:

Boutin A, et al. J Oncol Pharm Practice. 2019; 25(3):577-583.

Feng X, et al. J Clin Pharm Ther. 2013;38(4):301-308. doi: 10.1111/jcpt.12061

Rasburicase Dosing at Swedish Medical Center

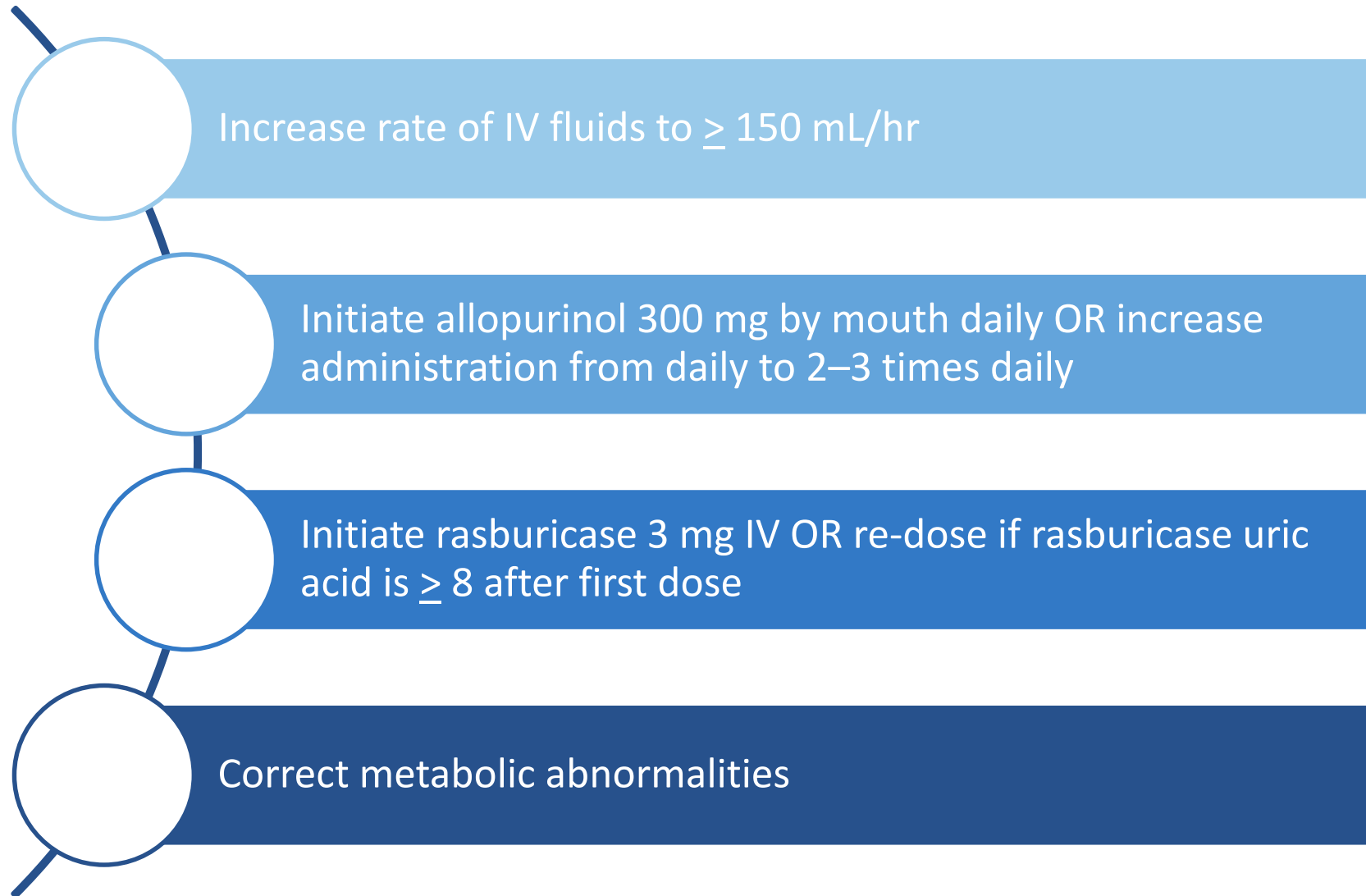
- Swedish Medical Center implemented a rasburicase dosing and monitoring policy allowing pharmacists to automatically substitute all doses of rasburicase to 3 mg IV once
- An additional 3 mg dose may be repeated in 24 hours if uric acid still ≥ 8 mg/dL

Rasburicase Monitoring

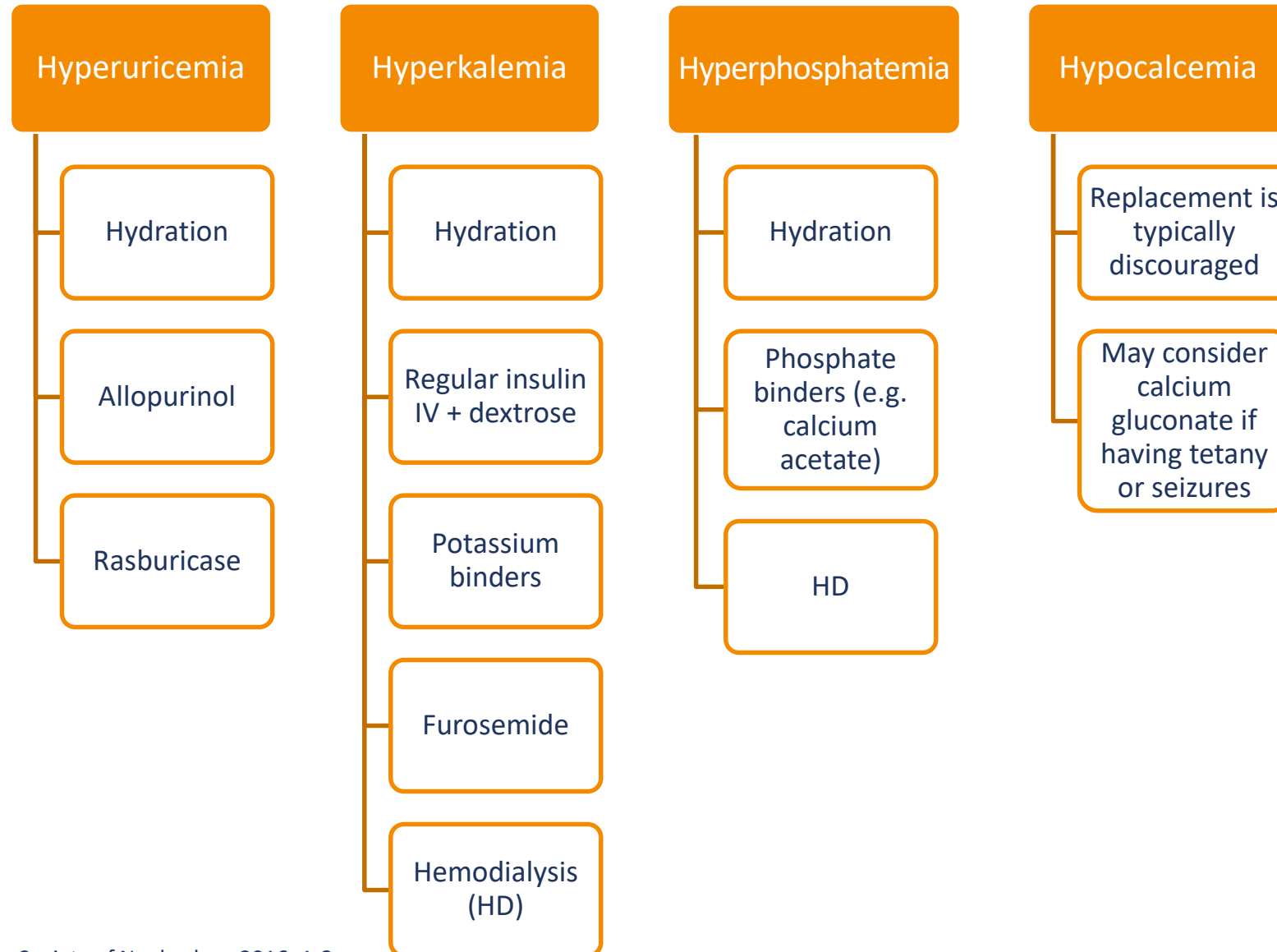
- Monitor uric acid level \geq 4 hours after administration of rasburicase
- Obtain a plasma sample in pre-chilled tubes containing heparin anticoagulant
- Immediately immerse sample in an ice bath
- Analyze the sample in a pre-cooled centrifuge within 4 hours of collection
- Sample is ordered as **“rasburicase uric acid”** at Swedish Medical Center instead of “uric acid” to differentiate from the standard uric acid sample process



TLS Treatment



How to Correct Metabolic Abnormalities



| Summary of TLS

- TLS is a constellation of symptoms resulting from tumor cell death and release of intracellular components into the bloodstream
- Most often occurs within 3 days prior to or 7 days after the initiation of chemotherapy
- Cancers with the highest risk of TLS include Burkitt lymphoma and acute leukemias with elevated WBC and LDH
- The best treatment of TLS is prevention
 - IV fluids
 - Allopurinol
 - Consider rasburicase in select patients
- If TLS occurs, rapidly correct electrolyte abnormalities and lower uric acid to minimize morbidity and mortality

Hypercalcemia of Malignancy

| Hypercalcemia of Malignancy

- Hypercalcemia is defined as an increase in serum calcium above the upper limit of normal (8.5 – 10.3 mg/dL)
- Hypercalcemia of malignancy affects up to 44% of patients with cancer
- Most often occurs in:
 - Breast cancer
 - Lung cancer
 - Multiple myeloma
 - Renal cell carcinoma
- Patients with hypercalcemia of malignancy often have limited survival of several months

Confirming Hypercalcemia: Ionized Calcium vs. Serum Calcium?

- Ionized calcium measures the amount of **free calcium** in the blood (normal range: 1.12 – 1.32 mmol/L)
- Serum calcium measures the **total amount** of calcium in the blood
- Serum calcium must be corrected if albumin is low (normal range 3.4 – 5 g/dL)
 - Corrected calcium = serum calcium + [0.8 x (4 – serum albumin)]
- Ionized calcium is often thought to be the gold standard when compared to serum calcium, however:
 - A study of 188 patients with solid tumors compared serum calcium and ionized calcium and found no difference in clinical usefulness, prediction of hypercalcemia, or clinical prognosis between the two measurements
 - Measuring ionized calcium is more expensive than measuring serum calcium and correcting for low albumin, if required

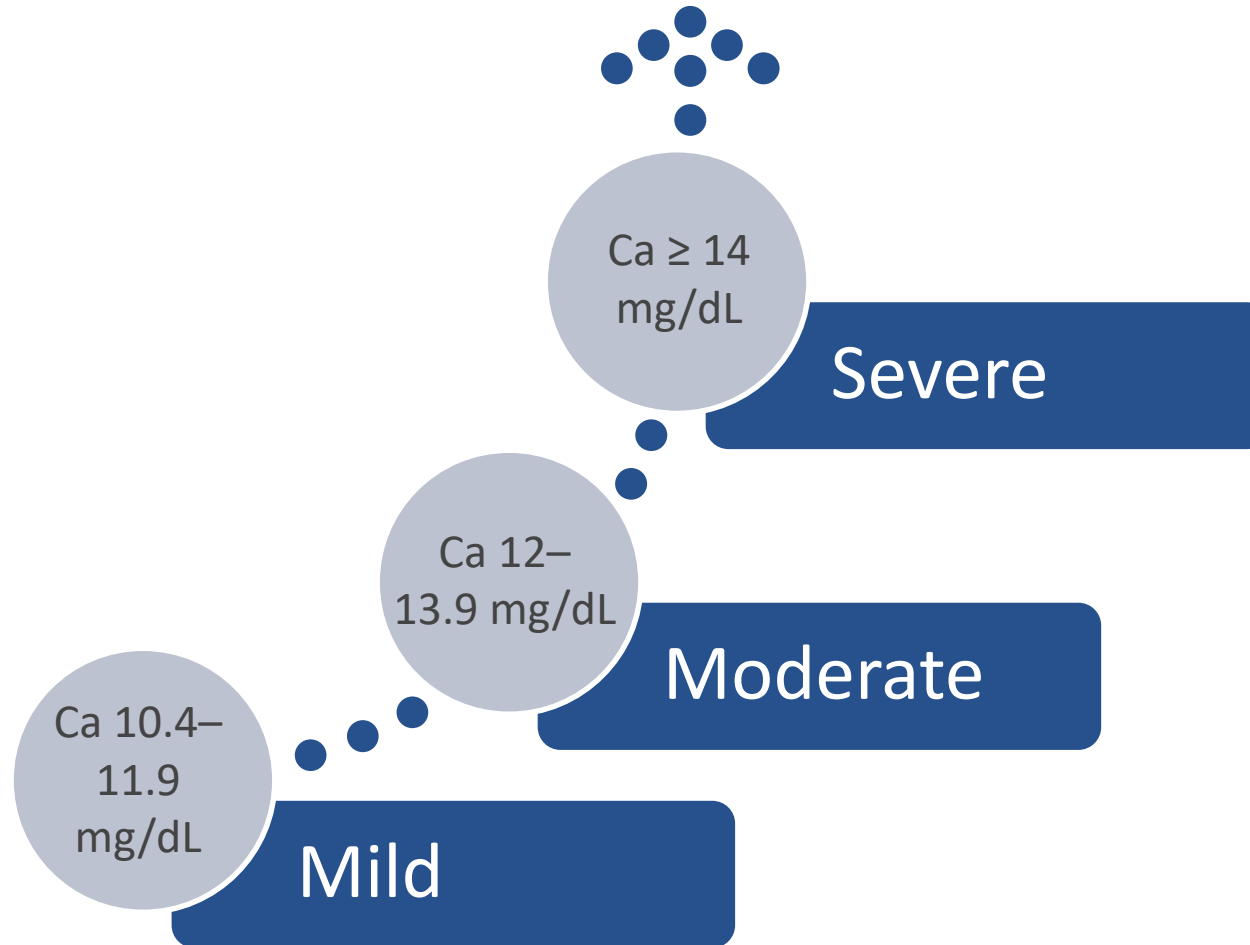
Sources:

Riancho JA, et al. Postgraduate Medical Journal. 1991; 67: 350-353.

Calvi LM, et al. JASN. 2008; 19(7): 1257-1260.

Classifying the Severity of Hypercalcemia of Malignancy

Note: Serum calcium ranges corrected for albumin are reflected



| Symptoms of Hypercalcemia of Malignancy

Mild

- Asymptomatic
- Constipation
- Fatigue

Moderate

- Polyuria & polydipsia
- Nausea
- Anorexia
- Muscle weakness

Severe

- Lethargy
- Confusion
- Stupor
- Coma
- Arrhythmias

Treatment of Hypercalcemia of Malignancy

Mild



- Treat the underlying malignancy
- Discontinue aggravating medications
- Hydration

Moderate



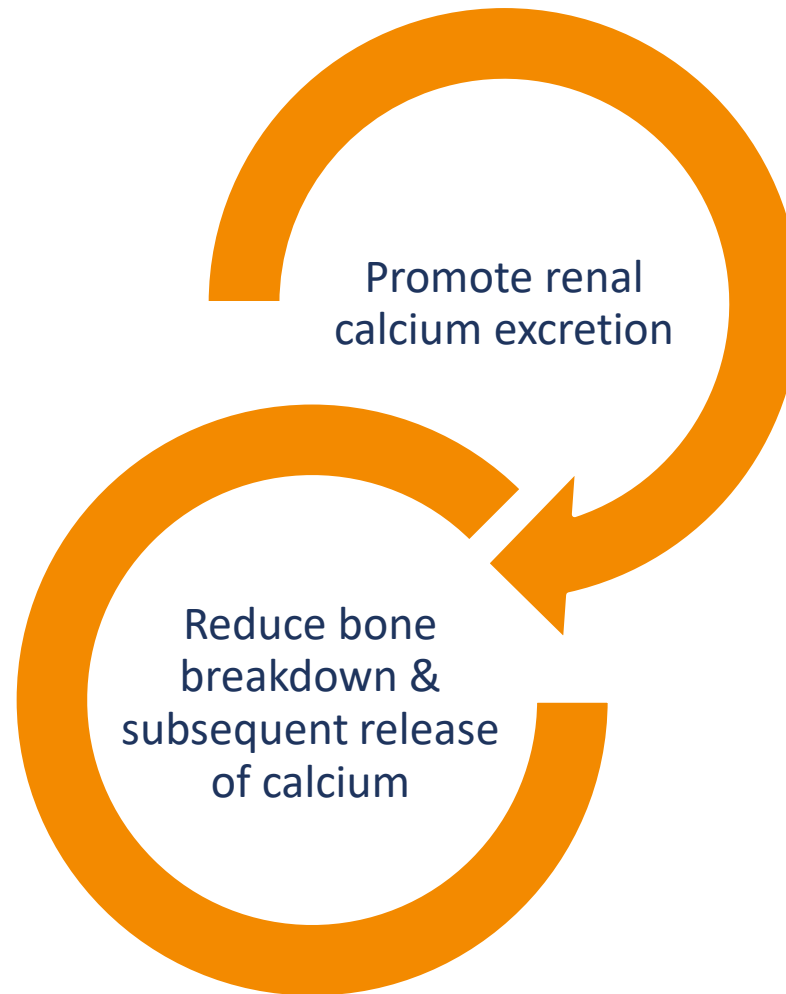
- Treat the underlying malignancy
- Discontinue aggravating medications
- Hydration
- IV bisphosphonate

Severe



- Treat the underlying malignancy
- Discontinue aggravating medications
- Hydration
- IV bisphosphonate
- Calcitonin
- Denosumab

Mechanisms of Calcium Reduction



| Promoting Renal Calcium Excretion

- Normal saline
 - 1 – 2 L initial bolus
 - 150 – 300 mL/hour for 2-3 days
- Loop diuretics (e.g. furosemide)
 - Should be reserved for patients with heart failure or who need diuresis

Sources:

Goldner W. *Journal of Oncology Practice*. 2016;12(5):426-432.

Mirрахimov AE. *North Am J Med Sci*. 2015;7:483-93.

Reducing Bone Breakdown & Release of Calcium



IV Bisphosphonates

- First-line therapy for moderate and severe hypercalcemia of malignancy
- Options:
 - Pamidronate 60 – 90 mg IV over at least 2 hours
 - Zoledronic acid 4 mg IV over at least 15 minutes
- Administer within 48 hours of diagnosis and wait at least 7 days prior to re-dosing

Sources:

Goldner W. Journal of Oncology Practice. 2016 12:5, 426-432.

Mirрахimov AE. N Am J Med Sci 7:483-493, 2015.

| Choice of Bisphosphonate

- A pooled analysis of 2 randomized controlled trials of 287 patients evaluated zoledronic acid 4 mg, zoledronic acid 8 mg, and pamidronate 90 mg in regard to safety and efficacy of treatment of moderate to severe (corrected serum Ca ≥ 12) hypercalcemia of malignancy
- Clinical end points included rate of complete response by day 10, response duration and time to relapse
- Conclusion: zoledronic acid is superior to pamidronate
 - Significantly higher percentage of patients achieving complete response
 - Significantly longer median time to relapse
 - Significantly longer median duration of complete response

| Calcitonin

- Increases renal calcium excretion and decreases bone breakdown
- Dosing: 4 units/kg every 12 hours for a maximum of 48 hours
- Should be used in combination with pamidronate or zoledronic acid
- Costs \$998.20 per 400 unit vial

Calcitonin Cost Savings

- Restrict use to severe hypercalcemia (serum calcium ≥ 14) and/or symptoms such as altered mental status, arrhythmias, lethargy, coma
- Draw up patient-specific doses in a syringe in the sterile IV room so any remainder in the vial can be used later, instead of sending the entire vial up to the nursing unit with each dose and discarding excess
- Swedish Medical Center is in the process of implementing this practice after realizing it could have saved **11 vials** (estimated cost savings of **\$10,980**) over a 6-month span



| Denosumab

- Monoclonal antibody that leads to decreased bone breakdown and increased bone mass
- Administer 120 mg subcutaneously once every 4 weeks
- Median time to response is 9 days
- Should be restricted for use in the outpatient setting only
 - May consider select use in the inpatient setting if patient has hypercalcemia refractory to IV fluids, IV bisphosphonate and calcitonin



Summary of Hypercalcemia of Malignancy

- Typically occurs in advanced cancers and may be mild, moderate or severe based on calcium level and presence or absence of symptoms
- May use ionized calcium or serum calcium corrected for low albumin to monitor, depending on facility preference
- Manage by:
 - Treating underlying malignancy
 - Discontinuing medications that may increase calcium
 - Starting IV hydration
 - Considering the use of an IV bisphosphonate, calcitonin or denosumab, depending on calcium level and severity of symptoms

Sources:

Goldner W. Journal of Oncology Practice. 2016;12(5):426-432.

Mirrakhimov AE. North Am J Med Sci. 2015;7:483-93

Febrile Neutropenia

Febrile Neutropenia

- One of the most common complications of cancer treatment
 - 10% – 50% of patients with solid tumors
 - > 80% of patients with hematologic malignancies
- Often the only sign of severe underlying infection
- Definition of febrile neutropenia:
 - Single temperature of $\geq 101^{\circ}\text{F}$ (38.3°C) **or** temperature of $\geq 100.4^{\circ}\text{F}$ (38°C) sustained over 1 hour
 - Absolute neutrophil count (ANC) of < 500 cells/ mm^3 **or** ANC that is expected to decrease to < 500 cells/ mm^3 within the next 48 hours



| What is Absolute Neutrophil Count (ANC)?

- ANC measures the number of neutrophils (WBCs that kill bacteria) in the blood
- Used as an estimate of the body's ability to fight infections
- The lower the ANC, the higher the risk of getting an infection
 - Normal: $\text{ANC} > 2500 \text{ cells/mm}^3$
 - Neutropenia: $\text{ANC} < 500 \text{ cells/mm}^3$
 - Profound neutropenia: $\text{ANC} < 100 \text{ cells/mm}^3$



Etiology of Febrile Neutropenia

- Most often thought to occur due to translocation of gut bacteria into extraintestinal sites
- The majority of patients with fever and neutropenia will have no infectious cause documented
- Clinically documented infections occur in only 20 – 30% of febrile neutropenia episodes
- Common sites of documented infections include:
 - Intestinal tract
 - Bloodstream
 - Lungs
 - Skin

Common Bacterial Pathogens in Neutropenic Patients

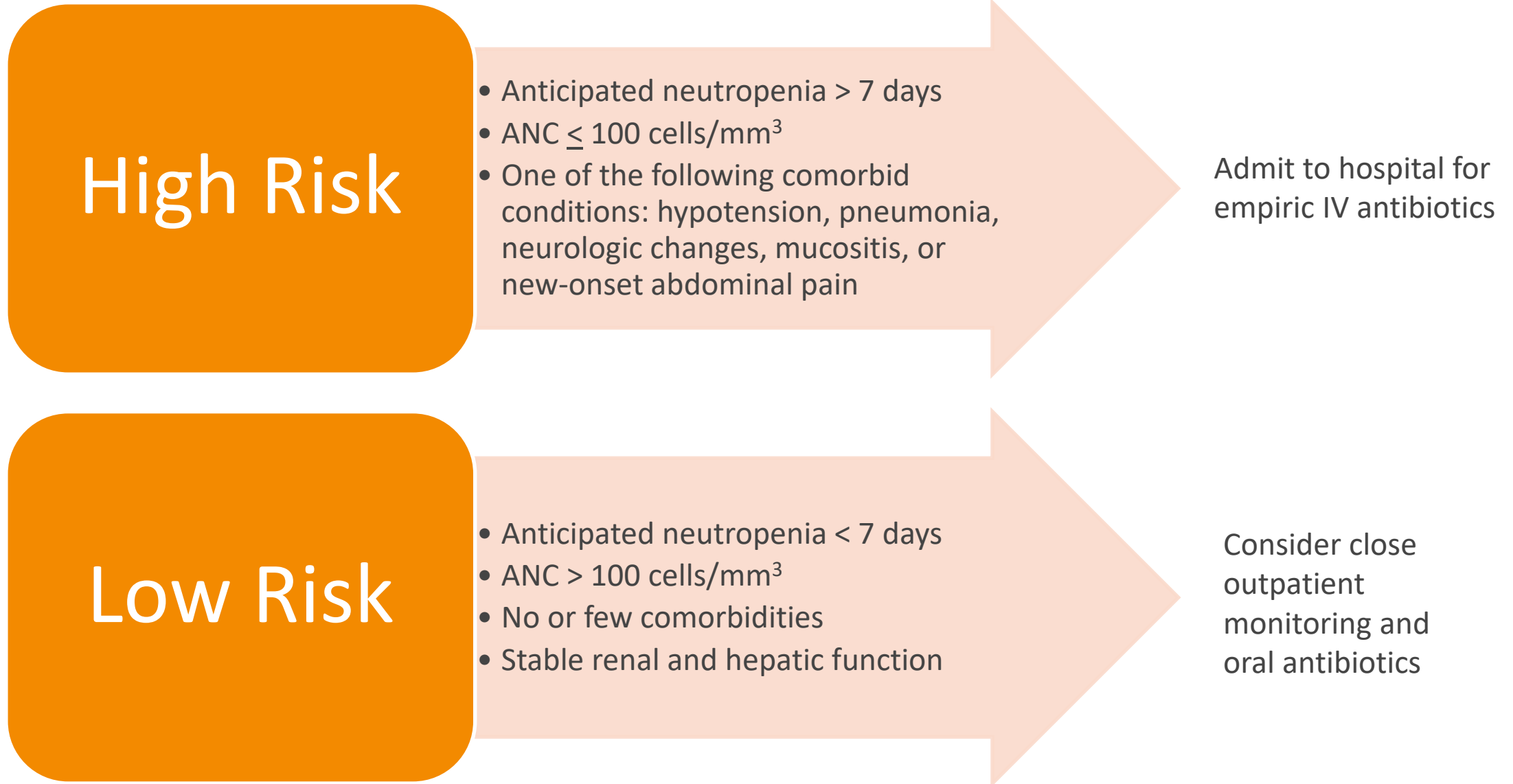
Gram-positive Pathogens

- Coagulase-negative staphylococci (CONS)
- *Staphylococcus aureus*, including methicillin-resistant strains (MRSA)
- *Enterococcus* species, including vancomycin-resistant strains (VRE)
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- Viridans group streptococci

Gram-negative Pathogens

- *Escherichia coli*
- *Klebsiella* species
- *Enterobacter* species
- *Pseudomonas aeruginosa*
- *Citrobacter* species
- *Acinetobacter* species
- *Stenotrophomonas maltophilia*

Risk Assessment of Febrile Neutropenia



Management of High Risk Febrile Neutropenia

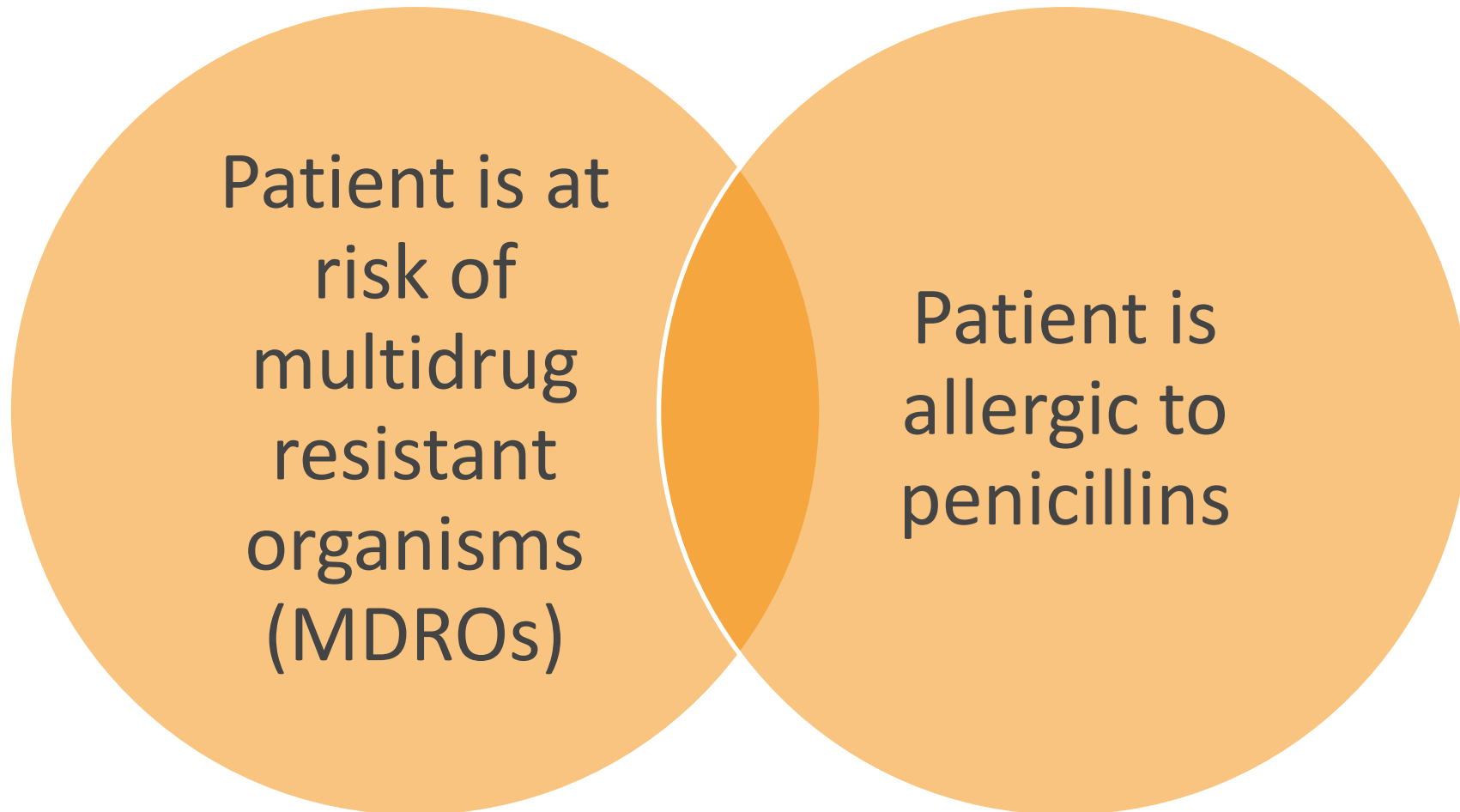
- Admit to hospital and monitor vital signs, CBC with differential, CMP and LFTs
- Obtain at least 2 sets of blood cultures prior to starting antibiotics
 - A set from each lumen of an existing central venous catheter (if present) + from a peripheral site
 - 2 sets from separate venipunctures if no central catheter is present
- Obtain cultures from other sites of suspected infection, if indicated
- Obtain a chest radiograph in patients with respiratory signs and symptoms

Management of High Risk Febrile Neutropenia

- Initiate broad-spectrum IV antibiotic therapy; ideally after drawing cultures and within 1 hour of presentation
- Most patients should receive monotherapy with an anti-pseudomonal beta-lactam:
 - Cefepime 2g IV q8h
 - Piperacillin-tazobactam 4.5g IV q8h
 - Meropenem 2g IV q8h
- May add vancomycin to initial therapy if patient has at least one of the following:
 - Hemodynamic instability
 - Pneumonia
 - Suspected catheter-related infection
 - Skin or soft-tissue infection

Modifications to Initial Empiric Therapy for High Risk Patients

Consider modifications to initial empiric therapy if:



| How to Modify Antimicrobial Therapy During the Course of Fever & Neutropenia

Use clinical & microbiologic data to guide modifications to the initial antibiotic regimen

Adjust antibiotics accordingly if an infection is identified

Discontinue vancomycin or other gram-positive coverage after 48 hours if there is no evidence of a gram-positive infection

| Duration of Empiric Antibiotic Therapy

- Continue antibiotics in all patients at least until $ANC \geq 500$ cells/mm³
- If no infectious source is identified, continue antibiotics until patient is afebrile for ≥ 48 hours
- If an infectious source is identified, tailor duration of therapy for the particular organism and site

Management of Neutropenic Fever in Patients on Prophylactic Antimicrobials

- Discontinue antibacterial prophylaxis and initiate broad spectrum empiric antibiotics using a different agent(s)
 - Usual antibacterial prophylaxis: levofloxacin 500 mg by mouth once daily
- Continue viral and fungal prophylaxis (unless those pathogens are suspected as the causal agent)
 - Usual viral prophylaxis: acyclovir 400 mg by mouth twice daily or valacyclovir 500 mg by mouth twice daily
 - Usual fungal prophylaxis: fluconazole 400 mg by mouth once daily, posaconazole 300 mg by mouth once daily, or voriconazole 200 mg by mouth twice daily
- Once neutropenia resolves and the appropriate duration of antimicrobial therapy is completed, initiate a different prophylactic agent than the prior agent the patient was on

| Do hematopoietic growth factors play a role in managing fever & neutropenia?

- Therapeutic use is controversial
- Two types of growth factors:
 - Pegfilgrastim (or biosimilar): Long acting and dosed once per chemotherapy cycle
 - Filgrastim (or biosimilar): Short acting and dosed daily through ANC recovery to normal
- Consider whether or not patient already received prophylactic growth factor with their chemotherapy cycle. If patient received:
 - Prophylactic pegfilgrastim: No additional growth factors should be used
 - Prophylactic filgrastim: May choose to continue
 - Prophylactic growth factor: May consider initiating daily filgrastim

Summary of Febrile Neutropenia

- Definition:
 - ANC < 500 cells/mm³ **or** anticipated to decrease to < 500 cells/mm³ within the next 48 hours
 - Single temperature of $\geq 101^\circ\text{F}$ (38.3°C) **or** temperature of $\geq 100.4^\circ\text{F}$ (38°C) sustained over 1 hour
- Most patients can be started on monotherapy with cefepime, piperacillin-tazobactam, or meropenem
 - Add vancomycin if hemodynamically unstable or suspected pneumonia, catheter-related infection, or skin and soft tissue infection
 - Consider further therapy modifications and/or an infectious diseases consult if patient at risk of or with prior history of MDROs
- Tailor duration of therapy to suspected or confirmed organism/site, and continue at least until patient is afebrile for ≥ 48 hours and ANC increased to ≥ 500 cells/mm³

Pseudohyperkalemia

| Pseudohyperkalemia

- Elevated serum potassium level (normal range 3.5 – 5.1 mmol/L) despite concurrently normal physiologic potassium level
- Most commonly seen secondary to red blood cell hemolysis
- Occasionally seen in cases of acute and chronic leukemias with extreme leukocytosis
 - WBC most often > 100,000 cells/mm³

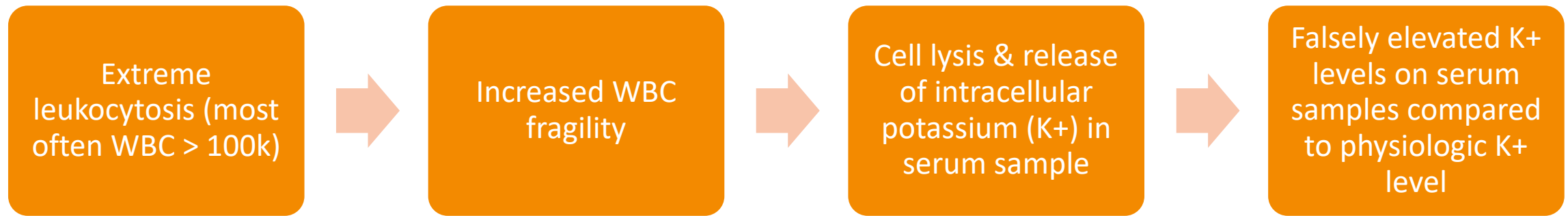


Sources:

Rifkin S. Int J Nephrol. 2011; 759749:1-3.

Jain AG, et al. Cureus. 2018 Nov;10(11):e3570.

| Pathophysiology of Pseudohyperkalemia

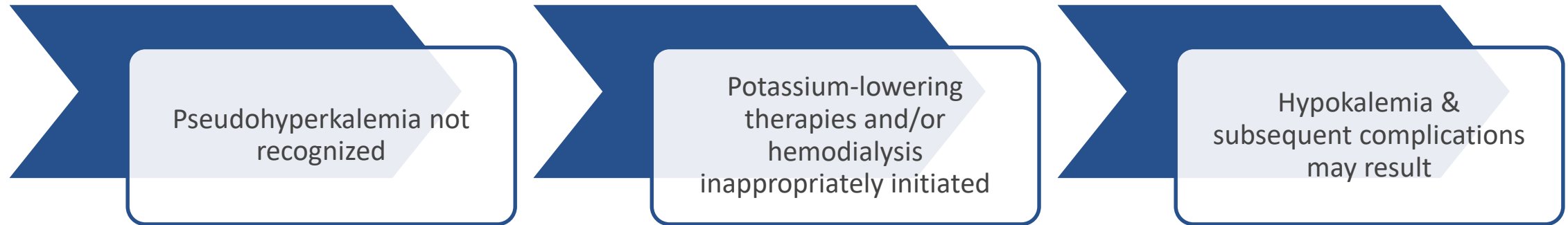


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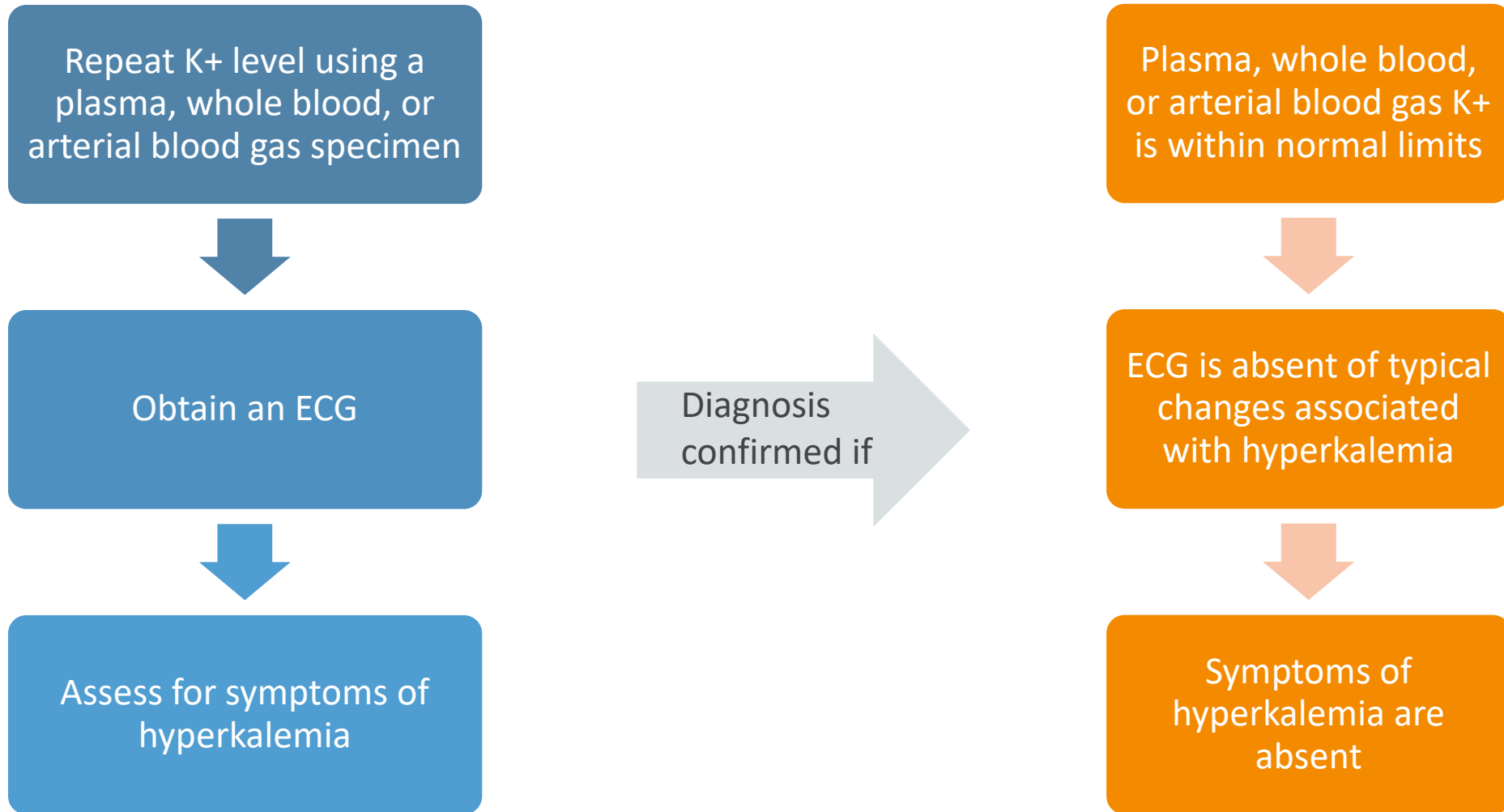
Possible Adverse Outcomes Secondary to Pseudohyperkalemia



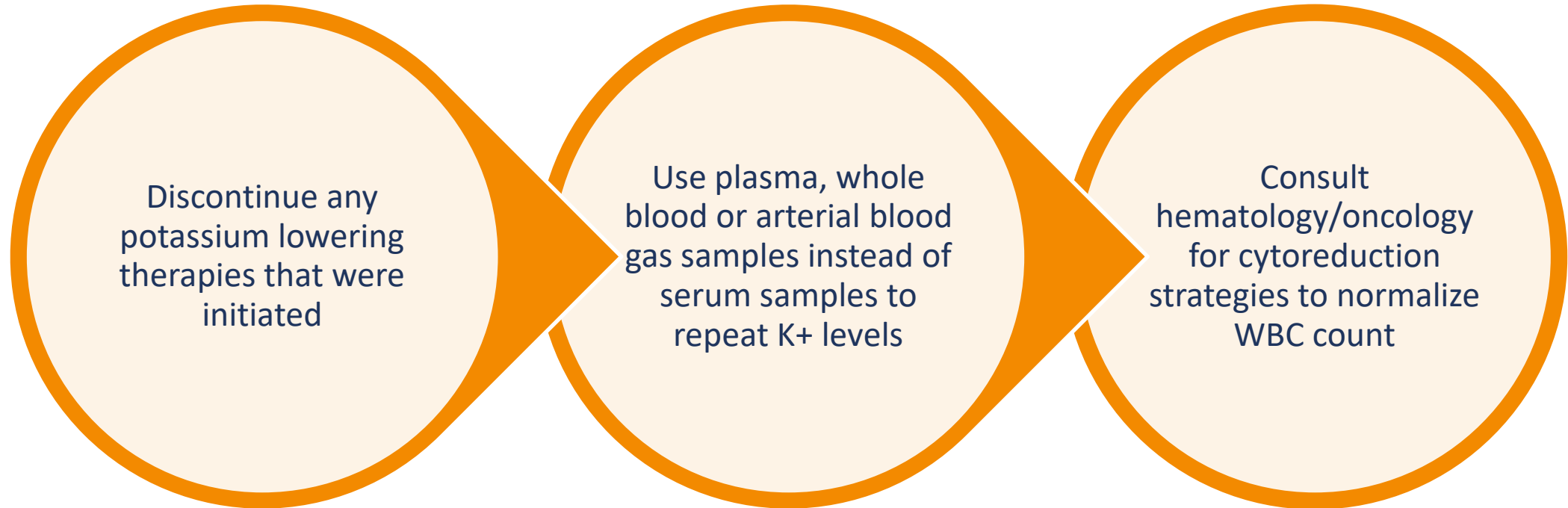
Source:

Meng QH, et al. *Critical Reviews in Clinical Laboratory Sciences*. 2014;52(2):45-55.
Kardalas E, et al. *Endocr Connect*. 2018;7(4):R135-R146.

Diagnosis



| What to Do if Diagnosis Is Confirmed



Sources:

Rifkin S. Int J Nephrol. 2011; 759749:1-3.

Jain AG, et al. Cureus. 2018 Nov;10(11):e3570.

| Patient Case

- A 50-year-old female with no significant past medical history presented to the Swedish Medical Center emergency department in September 2021 with a 3-week history of malaise, nausea, loss of appetite, and shortness of breath
- Notable labs included WBC 410,000 cells/mm³ and platelets 36 cells/mm³ → patient admitted due to concern for acute leukemia
- Serum K⁺ was 6.7 mmol/L on admit → potassium lowering therapies were initiated
- Repeat serum K⁺ was 7 mmol/L → nephrology was consulted and planned to initiate HD
- The possibility of pseudohyperkalemia was mentioned prior to HD initiation → whole blood K⁺ and ECG were obtained
- Whole blood potassium was 2.1 mmol/L
- ECG showed conduction abnormalities consistent with hypokalemia

Recommendations to Alert Workers to the Possibility of Pseudohyperkalemia

- Literature recommends using the hospital information system to flag the possibility of pseudohyperkalemia in patients with serum potassium level > 6 mmol/L and WBC $> 100,000$ cells/mm³
- At Swedish Medical Center, we:
 - Created a rule in our clinical pharmacy monitoring system to alert pharmacists to the possibility of pseudohyperkalemia
 - Are working with lab to create an alert in the electronic medical record system to alert all staff to the possibility of pseudohyperkalemia



Sources:

Rifkin S. Int J Nephrol. 2011; 759749:1-3.

Jain AG, et al. Cureus. 2018 Nov;10(11):e3570.

Summary of Pseudohyperkalemia

- Pseudohyperkalemia is a rise in serum potassium despite concurrently normal plasma potassium level
- Occasionally seen in acute and chronic leukemias when WBC > 100,000 cells/mm³
- Inappropriate initiation of potassium lowering medications may result in hypokalemia and subsequent complications
- Diagnose by obtaining a plasma, whole blood, or arterial blood gas K⁺ level; an ECG; and assessing for symptoms of hypokalemia
- If diagnosis is confirmed, discontinue any potassium lowering therapies that were initiated and consult hematology/oncology to cytoreduce and/or initiate treatment of leukemia

Source:

Rifkin S. Int J Nephrol. 2011; 759749:1-3.

Jain AG, et al. Cureus. 2018 Nov;10(11):e3570.

| Oncologic Emergencies Discussed Today

Tumor lysis
syndrome

Hypercalcemia of
malignancy

Febrile neutropenia

Pseudohyperkalemia

References

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Thank you...

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