Guideline Resource Unit
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Oncologic Emergencies

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Background

An oncologic emergency can be broadly defined as any complication related to cancer or anticancer therapy that requires immediate intervention. While some complications are insidious and may take weeks or months to develop, others manifest in a few hours and quickly lead to severe outcomes - including paralysis, coma, and death[1]. Despite the increasing incidence of cancer in the general population, cancer mortality rates are dropping due to rapid advances in treatment. The improvement in long-term survival of patients with cancer - combined with increasing use of more efficient outpatient treatment strategies – contribute to the likelihood that acute care providers will encounter oncologic emergencies in their practices more regularly [2,3]. The information below summarizes the most common oncologic emergencies one will likely encounter in the adult population.

Guideline Questions

1. What are the most common oncologic emergencies an acute care physician is likely to encounter?
2. What are the recommended management strategies for these emergencies?

Target Population

The following recommendations and management strategies apply to adult patients who are currently being treated for cancer. Different principles may apply to pediatric and elderly patients.

Search Strategy

For the 2022 guideline update, medical journal articles were searched using the PubMed database (publication date 2014 to 2019), and the references and bibliographies of articles identified through this search were scanned for additional sources. Articles were excluded from the final review if they had a non-English abstract, involved only pediatric or elderly patients, were a case report, or were published prior to January 2014.

Summary of Recommendations

Single-System Emergencies

Hemorrhage/ Bleeding:

- General Management
    - Transfuse Packed Red Blood Cells (PRBCs), correct any coagulopathy with Fresh Frozen Plasma (FFP) +/- platelets as needed.
- Disseminated intravascular coagulation (DIC)
    - Initiate anticoagulation for acute thrombosis.
    - Treat underlying malignancy – consult Primary Oncologist.
- Gross Hemoptysis
    - Protect airway, correct underlying coagulopathies, and suppress cough as needed.

        - Patient can be placed into lateral decubitus (on the bleeding side) if side of bleeding is known.
        - Selective intubation with regular endotracheal tube into the non-bleeding side, which might require help with fiberoptic guidance. Avoid double lumen tube.
    - Use of nebulized tranexamic acid 500 mg TID.
    - Arrange transfer to a centre with surgical and radiotherapy resources.
- Gastrointestinal (GI) Bleeding (overt)
    - Control vomiting/retching.
    - If gastric or duodenal source→ pantoprazole infusion (80 mg bolus, then 8mg/h).
    - If esophageal variceal source→octreotide infusion (50 µg bolus, then 50 µg/h).
    - Consult a Gastroenterologist for definitive management.
- Hematuria
    - Light bleeding: pink or cranberry juice, transparent, no clots or limited tiny clots, and patient is not in retention.
        - Encourage patient to drink fluids to dilute urine and refer to outpatient Urology.
    - Heavy bleeding: thick/opaque hematuria and/or large clots and/or clot retention.
        - Insert 3 way Foley, manually irrigate out clots with piston syringe, and initiate continuous bladder irrigation.
        - Do not insert Foley in patients with a recent radical prostatectomy (within 30 days)→call Urologist first.
    - Consult Urologist for further assessment and management.

Brain Metastases- Seizure/Change in Level of Consciousness:

- Dexamethasone (10mg IV followed by 4-8mg/dose, q6h IV or PO) and consider consultation with Neurosurgery.
- Administer anticonvulsant therapy with a short-acting benzodiazepine (midazolam 2mg or lorazepam 1mg IV) to halt seizure activity.
- Loading dose of phenytoin 15 mg/kg followed by a daily dose of 300 mg/d can be considered but consult Neurology for specific advice.

Malignant Airway Obstruction:

- Administer corticosteroids: Dexamethasone (10mg IV followed by 4-8mg/dose, q6h IV or PO) as quickly as possible.
- Administer Heliox: if patient has stridor and is not hypoxemic (21% oxygen, 79% helium- up to 30% oxygen, 70% helium).
- Contact Thoracic Surgery or Interventional Pulmonary immediately and/or arrange transfer to a center with these resources available.

Superior Vena Cava Obstruction:

- Administer corticosteroids: Dexamethasone (10mg IV followed by 4-8mg/dose, q6h IV or PO) daily.
- Arrange transfer to a centre with surgery and radiotherapy resources.

Spinal Cord Compression:

- Administer corticosteroids: Dexamethasone (10mg IV followed by 4-8mg/dose, q6h IV or PO).
- Consult Spine Service for surgical opinion.

Systemic Emergencies

Febrile Neutropenia:

- Panculture (blood/urine) and immediate antibiotic therapy with broad-spectrum antibiotics, eg: piperacillin-tazobactam 4.5 grams IV q8h (renal adjustment required) OR cefepime monotherapy: 2g IV q8h.

Hypercalcemia (Malignancy Associated):

- Fluid resuscitation with IV normal saline (250-500 mL/hour) + IV bisphosphonates (pamidronate 15-90 mg over 1-2 hours OR zoledronate 4mg over 15-30 minutes).
- May add calcitonin for severe hypercalcemia (IM/SC 4-8 units/kg q6h x2d).

Hyperviscosity Syndrome:

- Avoid transfusions if possible.
- Perform phlebotomy (remove 100-200mL whole blood) with hydration (500-1000mL of normal saline).
- Consult Hematologist for access to plasmapheresis (requires transfer to tertiary care center with apheresis capabilities).

Checkpoint Inhibitor Related Toxicities:

- Consult the Checkpoint Inhibitor prescribing physician.

Syndrome of Inappropriate Antidiuretic Hormone Secretion – Severe Hyponatremia:

- Acute duration: Fluid restrict (≤1L /day).
- Hyponatremic encephalopathy: administer IV hypertonic saline (100mL 3 % IV over 10 minutes with 1-2 repeat boluses as needed to increase plasma sodium by 4-6mEq/L).
- Chronic duration: Restrict fluids (≤1L /day). If no change after 24-38 hours: consider furosemide (20-40 mf IV or 20-80 mg orally daily) OR demeclocycline (600-1,200 mg/day orally in 3 or 4 divided doses).

Tumour Lysis Syndrome:

- Administer IV saline (250cc/hour or more), + rasburicase (6mg given as a 30 min infusion).
    - Avoid rasburicase in patients with known glucose-6-phosphate dehydrogenase (G6PD) deficiency; use allopurinol (100 mg/m^2 q8h to maximum 800 mg per day) for these patients.
- Refer to tertiary centre for additional management and possible dialysis.

Recommendations and Discussion: Single System Emergencies

Management of oncologic emergencies should include communication with the patient or alternate decision maker about treatment benefits and drawbacks, with respect to disease status and goals of care.

Hemorrhage/ Bleeding

Acute bleeding in patients with cancer can be due to the underlying malignancy, antineoplastic therapy, or non-malignancy related factors. The most common presentations are DIC, hemoptysis, overt gastrointestinal (GI) bleeding, and hematuria.

- **General Bleeding Recommendations:**
  - In any bleeding patient, basic investigations should include complete blood count (CBC), blood smear, prothrombin time (PT-INR), activated partial thromboplastin time (aPTT), D-dimer and fibrinogen level[4].
  - Management initial steps: Transfuse Packed Red Blood Cells (PRBCs), correct any coagulopathy with Fresh Frozen Plasma (FFP 15-30 mL/kg) ± platelets (a reasonable target is 50 x10^9/L) as needed[5-8].

1. Disseminated intravascular coagulation (DIC):

DIC Management Summary:
Initiate anticoagulation for acute thrombosis; Treat underlying malignancy –consult Primary Oncologist.

DIC is an abnormal bleeding and clotting cascade due to inappropriate thrombin activation. It causes rapid formation of fibrin clots in the microcoagulation, consumption of clotting factors, and clot degradation[5,9]. Continuous bleeding and clotting then continues until clotting factors are completely consumed – this can manifest as uncontrollable bleeding.

- *Etiology.*
  - Most commonly seen with acute promyelocytic leukemia, mucin-producing solid tumours (pancreatic, gastric, ovarian, breast) and brain tumours[4,5,7,9].
- *Presentation.*
  - Can present with bleeding, thrombosis or both[7,10].
  - Malignancy-associated DIC is usually more subacute than that seen in sepsis/trauma.
    - DIC associated with brain malignancies is usually associated with surgery and self-limited.
- *Diagnosis.*
  - The diagnosis can be established with laboratory evidence of thrombocytopenia, fibrinolysis and coagulation factor consumption[6,10]:
    - prolonged PT, aPTT, thrombin time
    - low plasma fibrinogen
    - increased plasma D-dimer
    - microangiopathic changes on peripheral blood smear (helmet cells, fragmented red cells, microspherocytes)

        - reduced platelet count
- *Management.*
    - Supportive measures:
        - see General Bleeding Management
    - Initiate anticoagulation for acute thrombosis
    - Consult Primary Oncologist to treat the underlying cancer[7,11].

2. Hemoptysis:

Hemoptysis is the most immediate life-threatening symptom of progressive intrathoracic disease[12]. Life-threatening hemoptysis (the expectoration of 250mL-600mL of blood over 24 hours) can lead to asphyxiation or exsanguination[13].

> **Hemoptysis Management Summary:**
> Protect airway, correct underlying coagulopathies, suppress cough as needed; patient can be placed into lateral decubitus (on bleeding side) if side of bleeding is known; selective intubation with regular endotracheal tube into non-bleeding side (might require fiberoptic guidance); avoid double lumen tube; arrange transfer to a centre with surgical and radiotherapy resources.

- *Etiology.*
    - In cancer patients, the primary causes are malignancy, infection, and hemostatic abnormalities[12,13].
    - Bronchogenic carcinoma is the most common cause of life-threatening hemoptysis in cancer patients over 40 years of age[13]; lung metastases from primary melanoma, breast, kidney, laryngeal and colon cancers are another common cause [13].
    - Other factors contributing to increased risk of hemorrhage include thrombocytopenia, coagulopathy (due to either the malignancy itself or its treatment) and radiation- or chemotherapy-induced lung damage[13].
- *Presentation.*
    - Symptom severity is dependent on the rate and duration of bleeding, the degree of airway obstruction and pulmonary involvement, and the patient's underlying performance status and concurrent comorbidities[13].
    - In addition to hemoptysis, patients may be hypotensive, tachycardic, centrally cyanotic and clammy, and may experience dyspnea or chest pain from underperfusion[13].
- *Diagnosis.*
    - Initial diagnostic efforts will often need to occur simultaneously with management[14].
        - Chest radiography and routine laboratories.
        - Rigid bronchoscopy (expertise required, can be performed bedside in unstable patient).
        - Bronchoscopy and chest computed tomography (CT) ideally performed within first 12-14 hours.
- *Management.*
    - Protect the airway: Intubation is warranted with rapid bleeding, hemodynamic instability, ventilatory impairment, severe dyspnea or hypoxia[13,14].

        - Patient can be placed into lateral decubitus (on the bleeding side) if side of bleeding is known.
        - Selective intubation with regular endotracheal tube into the non-bleeding side, which might require help with fiberoptic guidance. Avoid double lumen tube.
    - see General Bleeding Management
    - Use of nebulized tranexamic acid 500 mg TID[15]
    - Admit to Intensive Care Unit (ICU) if appropriate.

3. GI bleeding (overt):

> **GI Bleeding Management Summary:**
> Control vomiting/retching; gastric or duodenal source→ pantoprazole infusion (80mg bolus, then 8mg/h); esophageal variceal source→ octreotide infusion (50µg bolus, then 50µg/h); consult a Gastroenterologist for definitive management.

- *Etiology.*
    - Upper GI bleeding is most commonly caused by primary upper GI malignancies and common non-malignancy related GI pathology.
        - Less commonly, it is related to metastases to the esophagus, stomach, or duodenum, lymph node disease with invasion of overlying mucosa, and mucositis secondary to chemotherapy[16].
    - Lower GI bleeding can be from primary GI malignancies, non-malignancy related GI pathology and indirectly by various cancer therapies (e.g., graft-versus-host disease following stem cell transplantation, radiation-induced proctosigmoiditis, etc.)[16].
- *Presentation.*
    - Upper GI bleeding typically presents with hematemesis and/or melena[16].
    - Appearance of lower GI bleeding depends on the briskness of hemorrhage and speed of heme passage through the GI tract[16] but can range from frank red blood per rectum to melena.
    - Attempting to identify the site of bleeding by the characteristics of the stool is imprecise.
- *Diagnosis.*
    - Obtain information on: nature/duration of bleeding, nature of any recent emesis, stool habits, bleeding diatheses, prior GI bleeding, history of pharmaceutical anticoagulation, NSAID use, chemo- and radiotherapy treatments, history of comorbid conditions that may impact evaluation or treatment decisions[16,17].
    - Collect essential labs (CBC, chemistry panel, coagulation panel, liver function tests, blood type and crossmatch)[16].
    - NG aspiration with lavage may help confirm the source and briskness of bleeding[16].
- *Management.*
    - Initial management should focus on[16]:
        - Rapid assessment of airway, breathing and circulation.
        - See General Bleeding Management.
    - Control vomiting and retching[16].

- For bleeds that are suspicious for a gastric or duodenal source, a pantoprazole infusion (80mg bolus, then 8mg/h) should be started.
- For bleeds that are suspicious for an esophageal variceal source, an octreotide infusion (50µg bolus, then 50 µg/h) should be started[16,18].
- Refer to a Gastroenterologist for definitive management (e.g., endoscopy, radionuclide scintigraphy, selective angiography, and embolization)[16,17,19].

4. Hematuria:

- *Etiology.*
  - Urothelial carcinoma, renal cell carcinoma and metastases to the kidney, prostate cancer, urethral or vascular invasion of penile cancers, previous instrumentation/ catheter trauma, radiation cystitis (related to pelvic irradiation)[20,21].

> **Hematuria Management Summary:**
> Light Bleeding: fluids and Outpatient Urology referral; Heavy Bleeding: Foley irrigation and consult with Urology.

- *Presentation.*
  - The appearance of bleeding can assist in determining its origin:
    - Long, worm like clots usually indicate upper tract bleeding[22].
    - Bright red blood without clots that partially clears during urination usually indicates a lower tract bleed, as do broader clots (less common), which can be difficult to evacuate[22].
  - Light bleeding: pink or cranberry juice, transparent, no clots or limited tiny clots, and patient is not in retention.
  - Heavy bleeding: thick/opaque hematuria and/or large clots and/or clot retention.
- *Diagnosis.*
  - Complete history and physical exam[22].
  - Urinalysis[22] ± urine culture if concerned about infection.
  - Urinary tract imaging via ultrasound or CT scan, alongside referral for cystoscopy, are required for definitive diagnosis.
- *Management*.
  - see General Bleeding Management.
  - If bleeding is light, encourage patient to drink fluids and refer to Outpatient Urology
  - If bleeding is heavy, bladder irrigation[23,24]:
    1. Insert 22Fr 3-way Foley
    2. Manually irrigate out clots with piston syringe
    3. Initiate continuous bladder irrigation

    *Do not insert Foley in a patient who recently underwent radical prostatectomy (within 30 days). Call Urology first.
  - Discontinue medications that increase bleeding risk (anti-inflammatories or anticoagulants)[23].

- Consult Urology for further assessment and management.
  - Surgery, radiation, embolization[23,24].

Brain Metastases- Seizure/Change in Level of Consciousness

Brain metastases represent the most common type of brain malignancy and occur in approximately 30% of all adult patients with cancer[25-27].

Brain Mets Management Summary:
Dexamethasone (10mg IV followed by 4-8mg/dose, q6h IV or PO) and consider consultation with Neurosurgery; Administer anticonvulsant therapy with a short-acting benzodiazepine (midazolam 2mg or lorazepam 1mg IV) to halt seizure activity; Loading dose of phenytoin (15mg/kg followed by a daily dose of 300mg/d) can be considered but consult Neurology for specific advice.

- **Etiology:**
  - Any primary tumour can metastasize to the brain.
    - Lung cancer (40-50%), breast cancer (15-25%), and melanoma (5-20%) are the most common[28].
    - Other common primary tumours include colorectal cancer and renal cell carcinoma[29,30].
    - Melanoma and lung cancer are most frequently associated with multiple brain metastases, whereas breast, colorectal, and renal cancers are more likely to be associated with a solitary metastasis[31].
- **Presentation:**
  - Patients with brain metastases may experience a variety of neurological symptoms, the most common of which is subacute onset of headache - this occurs in approximately 50% of cases.
  - Other common symptoms include hemiparesis, altered mental status, impaired cognition, increased intracranial pressure, and seizures[28,31].
  - Increased intracranial pressure and seizures lasting longer than 30 minutes (status epilecticus) are considered oncologic emergencies.
- **Diagnosis:**
  - Contrast enhanced MRI is the preferred diagnostic tool[31].
    - CT can be used but is less sensitive.
- **Management:**
  - Treat elevated intracranial pressure initially with dexamethasone (10mg IV followed by 4-8mg/dose, q6h IV or PO) and consider consultation with Neurosurgery).
  - Administer anticonvulsant therapy with a short-acting benzodiazepine to halt seizure activity (midazolam 2mg or lorazepam 1mg IV).
  - No current trials establishing 1 medication over another[32].
  - Loading dose of phenytoin (15mg/kg followed by a daily dose of 300mg/d) can be considered but consult Neurology for specific advice
  - For more information, see Cancer Care Alberta's Brain Mets Guideline[33].

Malignant Upper Airway Obstruction

Airway obstruction in patients with cancer is caused by tumour encroachment and by tumour-associated airway edema or hemorrhage[13].

> **Airway Obstruction Management Summary:**
> Administer dexamethasone as soon as possible (10mg IV followed by 4-8mg/dose, q6h IV or PO); Administer Heliox: if patient has stridor and is not hypoxemic (21% oxygen, 79% helium); Contact Thoracic Surgery or Interventional Pulmonary immediately and/or arrange transfer to a center with these resources available.

- **Etiology:**
  - Most commonly related to direct extension from an adjacent tumour (usually inoperable or recurrent) in the mediastinum (i.e. lung cancer, thymoma), or a primary head and neck tumour [34].
  - Less commonly from local extension of metastatic tumour from esophageal, thyroid, breast, or renal primaries[31,34].
- **Presentation:**
  - Symptoms of malignancy-associated airway obstruction are not specific to malignancy; it is critical that the provider consider this diagnosis in their differential for this presentation.
    - The most common presenting symptoms include dyspnea, hemoptysis, wheezing, hoarseness, difficulty clearing secretions, and cough[31,34,35].
    - Stridor is also a common presenting complaint; the effect is most marked on inspiration, and can progress to a near-complete obstruction as a result of infection, inflammation, or manipulation of the airway[35].
    - Progressive symptoms represent a true medical emergency.
- **Diagnosis:**
  - For most patients, the physical examination (which may be aided by direct visualization with a laryngoscope or bronchoscope) is sufficient for diagnosis - depending on the location of the lesion[13].
  - A CT scan or x-ray[36] of the neck and chest is the best initial study to assess the location and extent of the obstruction[35], if the patient can tolerate lying flat.
- **Management:**
  - Use dexamethasone immediately upon diagnosis (10mg IV followed by regular doses q6h, 4-8mg IV)
  - Administer Heliox: if patient has stridor and is not hypoxemic (21% oxygen, 79% helium-up to 30% oxygen, 70% helium)
  - Laryngoscopy or bronchoscopy may be necessary to guide the placement of an endotracheal tube[13].
  - Rigid bronchoscopy provides the safest and most effective means of immediate airway control and initial stabilization; Interventional Pulmonary Medicine is on call 24 hours/7 days a week at specific centres.

- Consult surgical services urgently if there is concern that the above measures are insufficient, and a surgical airway will be required.
- Contact Thoracic Surgery or Interventional Pulmonary immediately and/or arrange transfer to a center with these resources available.

Superior Vena Cava Obstruction

Superior vena cava obstruction (SVCO) results from partial or complete obstruction of blood flow from the superior vena cava to the right atrium. The obstruction may be caused by vessel compression, invasion, thrombosis, or fibrosis[13].

> **SVCO Management Summary:**
> Administer dexamethasone (10mg IV followed by 4-8mg/dose, q6h IV or PO); Arrange transfer to a centre with surgery and radiotherapy resources.

- **Etiology:**
  - Both lung cancer (small cell and non-small cell) and non-Hodgkin lymphoma account for approximately 85% of SVCO cases[37].
    - Approximately 10% of patients with small cell lung cancer, 2-4% of patients with non-small cell lung cancer, and 2-4% of patients with non-Hodgkin lymphoma will develop SVCO at some point during their disease course[37,38].
  - An increasing number of cases of SVCO in cancer patients are also due to thrombosis of indwelling central venous catheter devices and/or pacemaker leads[31,37,39].
- **Presentation:**
  - Symptoms:
    - The most common are facial or neck swelling, arm swelling, and dilated chest vessels[2,37].
    - Cough, dyspnea, and orthopnea are also common symptoms that can often mimic congestive heart failure or pericardial disease[40].
    - Worrisome signs include: stridor, which may indicate laryngeal edema, and headache or confusion, which may indicate cerebral edema[37].
  - Sudden onset of SVCO causes rapid elevation of pressure in the superior vena cava, resulting in increased intracranial pressure and cerebral edema, intracranial thrombosis or bleeding, and even death[13].
- **Diagnosis:**
  - Accurate diagnosis via imaging should always be obtained.
    - A contrast-enhanced CT scan of the chest wall is the most useful study, as it clearly identifies the level and extent of the blockage, and delineates collateral drainage pathways [37].
    - MRI is useful for patients who cannot tolerate the contrast medium[37,41].
    - Venography is generally only warranted when an intervention such as stent placement or surgery is planned[41].
  - If a patient presents with SVCO without a prior diagnosis of malignancy, every effort should be made to obtain biopsies and histologic diagnosis after patient stabilization[31].

        - This aids the decision on whether curative versus palliative treatment is most appropriate[37].
- **Management:**
    - Acute management involves securing the airway and administering corticosteroids
        - Dexamethasone 10mg IV followed by 4-8mg/dose, q6h IV or PO
        - Transfer to a center with surgery and radiotherapy resources.
    - Definitive management is guided by the severity of the symptoms and the underlying malignancy, as well as by the anticipated response to the treatment[41-43].

Spinal Cord Compression

Malignant epidural spinal cord compression (SCC) is a common complication that affects approximately 5%-10% of all adult patients with cancer, and most commonly occurs in the setting of widespread metastatic disease[27]. The most common site of cord compression is in the thoracic spine (60% of cases), followed by the lumbosacral spine (25% of cases), and finally the cervical spine (15% of cases). Multiple sites of spinal cord compression also occur in up to 35% of patients[44].

SCC Management Summary:
Administer dexamethasone 10mg IV followed by 4-8mg/dose, q6h IV or PO; Consult Spine Service for surgical opinion.

- **Etiology:**
    - Metastatic prostate, breast, and lung cancer each cause approximately 15-20% of cases.
    - Other associated cancers include non-Hodgkin lymphoma, myeloma, renal-cell carcinoma, colorectal cancer, and sarcoma, each of which account for approximately 5-10% of cases[44,45].
- **Presentation:**
    - Back or neck pain with any associated leg weakness should trigger investigations (including physical exam) to exclude SCC.
        - Red flags including: motor weakness, loss of bowel or bladder control, and reduced peri-anal sensation[31,44].
- **Diagnosis:**
    - A full MRI spine is the preferred imaging study.
        - CT scan, plain radiograph, or myelography with or without accompanying CT can also be used if MRI is contraindicated or not available[13].
- **Management:**
    - Corticosteroids should be administered as soon as SCC is suspected or confirmed, as the most important prognostic indicator for ambulatory outcome is pre-treatment motor function[31,46].
        - Dexamethasone rapidly reduces spinal cord edema and back pain and may also improve neurologic functioning[27,31,47-49].

        - The typical dose of dexamethasone is 10mg IV followed by 4-8mg/dose, q6h IV or PO.
    - The Spinal Service should also be consulted for a surgical opinion.

Recommendations and Discussion: Systemic Emergencies

Febrile Neutropenia

Febrile neutropenia is one of the most common complications related to systemic cancer therapy and is considered a potentially life-threatening medical and oncologic emergency. Spontaneous bacterial infection can occur in the setting of severe neutropenia (neutrophils less than $0.5x10^9$/L). The primary source of pathogens is the patient's endogenous flora[50]. The mortality rate associated with febrile neutropenia in patients with cancer is between 5 and 20%; therefore, timely recognition of symptoms and administration of antibiotics is critical for the prevention of sepsis and death[51,52].

> **Febrile Neutropenia Management Summary:**
> Panculture (blood/urine) and immediate antibiotic therapy with broad-spectrum antibiotics, e.g.: piperacillin-tazobactam 4.5g IV q8h (renal adjustment required) OR cefepime monotherapy: 2g IV q8h.

- **Presentation:**
    - Fever higher than 38.3°C OR higher than 38.0°C for more than 1 hour, in a patient who has received systemic cancer therapy in the past month AND has an absolute neutrophil count (ANC) less than 0.5 x 10^9 cells/L[53,54].
- **Diagnosis:**
    - Testing[55]:
        - Investigate for source of infection through history, physical exam.
        - Panculture to identify the pathogen (blood cultures, urine cultures, nasopharyngeal swab if respiratory symptoms, Chest Xray).
        - Assess for signs of sepsis and initiate aggressive fluid resuscitation as required.
- **Management:**
    - Provide initial antibiotic therapy with piperacillin-tazobactam 4.5g IV q8h (renal adjustment required) OR cefepime monotherapy: 2g IV q8h, plus IV fluids[55].
    - For more information see Cancer Care Alberta's Febrile Neutropenia Guideline[55].

Malignancy Associated Hypercalcemia

Hypercalcemia is defined as a ***corrected*** serum calcium > 2.6 mmol/L[3,56]. **Note:** While unexpected hypercalcemia of unknown etiology may be an indicator of malignancy, the information that follows focuses on the identification and management of hypercalcemia in the patient already known to have cancer.

Hypercalcemia Management Summary:
Fluid resuscitation with IV normal saline (250-500 mL/hour) + IV bisphosphonates (pamidronate 15-90mg over 1-2 hours OR zoledronate 4mg over 15-30 minutes); May add calcitonin for severe hypercalcemia (IM/SC 4-8units/kg q6h x2d).

Note: corrected Ca^{2+} (mmol/L) = measured total Ca^{2+} (mmol/L) + (0.02 x [40 – measured albumin (g/L)])

Corrected values are approximations and may not be precise or reliable. Serum ionized Ca^{2+} should be measured when the validity of measured total calcium is in doubt[57-60].

- **Etiology:**
  - Malignancy-associated hypercalcemia (MAH) occurs in up to 30% of patients with cancer.
    - Most commonly in those with solid breast, lung, head/neck tumours, and hematologic malignancies (especially multiple myeloma and adult T-cell leukemia/lymphoma)[57-59].
  - Humoral hypercalcemia accounts for the majority of MAH cases (80%)[3,59].
  - Osteolytic bone metastases account for the other 20% of MAH cases; other causes (such as ectopic PTH secretion, vitamin D secreting lymphomas, etc.) account for less than 1%[3,59].
  - Many cancer therapies (e.g., antineoplastic agents, vitamin D analogues) can also induce or exacerbate hypercalcemia, particularly when therapies are combined[57].
- **Presentation and Diagnosis:**
  - Mild hypercalcemia may be asymptomatic and does not require therapy.
  - Moderate to severe hypercalcemia is typically symptomatic (see below)[3,56,57,60] and requires therapy:

Table 1. Symptoms of moderate to severe hypercalcemia associated with cancer and anticancer treatments.

	Early Manifestations	Later Manifestations
Neurological	• weakness/fatigue • memory/concentration difficulty	• drowsiness/confusion • delirium → coma
Cardiovascular	• shortened QT_c interval • enhancement of digitalis effects	• ST segment elevation • hypotension • bradyarrhythmias → heart block → cardiac arrest
Gastrointestinal	• anorexia • constipation	• nausea • vomiting
Genitourinary	• polyuria and nocturia	• dehydration → oliguria

- Hypercalcemic crisis is an emergency usually associated with a serum calcium >3.5mmol/L.
- It may present with life threatening complications such as acute pancreatitis, acute renal failure, and coma[3,57].

- **Management:**
  - **Note:** Acute antihypercalcemic therapy should be considered an interim solution only; long term resolution is dependent on prompt antitumour therapy[56,59,60].
  - Principles of treatment:
    - Avoidance/discontinuation of medications that can exacerbate MAH (eg. Thiazides, NSAIDs, cimetidine, calcitriol, drugs containing calcium (antacids) or vitamin D or vitamin A)[56,58-60].
    - First line therapy should include fluid resuscitation with IV normal saline, and initiation of IV bisphosphonates[3,56,57,59-62].
      - IV saline is usually administered at 250-500 mL/hour, depending on degree of dehydration, renal function, cardiovascular status and degree of cognitive impairment and severity of hypercalcemia[3,56-60].
      - Bisphosphonates include, pamidronate 15-90mg over 1-2 hours (dependent on renal function) or zoledronate acid 4mg over 15-30 minutes (preferred) should be considered the drugs of choice.
      - Patients suffering from severe MAH can be given calcitonin (IM/SC 4-8 units/kg q6h x2d) concurrently with bisphosphonates to briefly reverse hypercalcaemia while waiting for the bisphosphonate's therapeutic effect[56].
  - The table below details specific treatment recommendations based on degree of hypercalcemia.

Table 2: Management of MAH based on serum calcium concentration[56,60].

Serum Calcium Concentration	Management of MAH
Mild MAH: 2.6-2.9 mmol/L	No treatment **OR** Outpatient treatment: Ensure adequate oral fluid and salt intake, Corticosteroids, PO phosphate (if serum phosphate is low), monitoring
Moderate MAH: 3.0-3.4 mmol/L	IV Saline **+** IV Pamidronate 15- 90 mg over 1-2 hour **OR** IV Zoledronic acid 4 mg over 15-30 minutes
Severe MAH: ≥ 3.5 mmol/L	IV Saline **+** IV Pamidronate: 15-90 mg over 1-2 hour **OR** IV Zoledronic acid: 4 mg over 15-30 minutes
Sever MAH: ≥4 mmol/L	IV Saline **+** IM/SC Calcitonin: 4-8 unit/kg q6h x2d **+** IV Pamidronate (started concurrently with calcitonin): 90 mg over 1-2 hour **OR** IV Zoledronic acid (started concurrently with calcitonin): 4 mg over 15-30 minutes

Hyperviscosity Syndrome

Hyperviscosity syndrome refers to symptoms from increases in blood viscosity, which then decrease tissue perfusion. Causes of elevated viscosity include increased protein content, large molecular size, abnormal polymerization, and abnormal shape of immunoglobulin molecules[63].

> **Hyperviscosity Management Summary:**
> Avoid transfusions if possible; Perform phlebotomy (remove 100-200mL whole blood) with hydration (500-1000mL of normal saline); Consult Hematologist.

- **Etiology:**
  - Hyperviscosity syndrome can occur secondary to a variety of hematologic malignancies.
    - The most common is Waldenström macroglobulinemia, which accounts for up to 80% of cases[64].
    - Waldenström macroglobulinemia is a relatively rare lymphoma that produces a monoclonal immunoglobulin M (IgM) protein[65].
  - Less frequently, hyperviscosity syndrome may occur in patients with multiple myeloma (also from very high monoclonal protein production) or from hyperleukostasis in acute leukemia or erythrocytosis from polycythemia[63,66].
- **Presentation:**
  - The triad of bleeding, visual disturbances, and/or focal neurologic signs[67].
    - Bleeding typically arises from mucosal sites, most commonly occur in the lining of the nose, gums, the retina and the lumen of the gastrointestinal tract and the surface of the brain[66-68].
    - Visual changes may manifest as diplopia, blurred vision and are associated with papilledema and retinal hemorrhages or thrombosis[68].
      - Fundoscopic examination commonly reveals dilation or engorgement of retinal veins, resembling the appearance of “sausage links”[66,67].
    - Neurologic manifestations often include headache, dizziness, vertigo, ataxia, encephalopathy, hearing impairment, seizures, somnolence, cerebral hemorrhage, and altered mental status[66-69].
  - Hyponatremia and hypercalcemia may also be present [31].
- **Diagnosis:**
  - Based on clinical symptoms plus serum viscosity levels and should be suspected in patients with marked elevation of total protein (greater than 110) [64]
  - Symptoms typically appear when the viscosity reaches 4 to 5 centipoise (cp) (normal viscosity is 1.4-1.8cp) - corresponding to a serum IgM level of at least 30g/L (normal serum IgM level is ~15g/L[2,64,67]).
    - There is no linear relationship between serum viscosity and the appearance of hyperviscosity symptoms[31].
    - Asymptomatic patients with an elevation in the serum viscosity do not require treatment[68].

- Additional laboratory evaluations such as an electrolyte panel, peripheral blood smears, measurement of quantitative Ig levels, and imaging studies should be used to rule out other causes of the presenting symptoms.

- **Management:**
  - Short-term management is directed at immediately reducing blood viscosity –most effectively accomplished via plasmapheresis.
  - If the patient presents with severe neurologic symptoms (seizures or coma), or plasmaphresis is not readily available - phlebotomy of 100 to 200mL of whole blood can also be used to rapidly reduce acute symptoms[31,66,70] (and may be aided by hydration post-phlebotomy – ex 150cc/hr to 500-1000mL).

Checkpoint Inhibitor Related Toxicities

CPI Related Toxicities Management Summary:
Consult with the CPI prescribing physician; online guidance is available in emergent situations.

Immune checkpoint inhibitors (CPIs) are antibodies that increase anti-tumour activity by inhibiting natural regulators of immunity. By modulating the activity of the immune system, CPIs can cause inflammatory side effects called immune-related adverse events (irAEs) that present like new auto-immune disorders[71]. irAEs are toxicities caused by non-specific activation of the immune system.

- CPIs are currently approved in the setting of melanoma, non-small cell lung cancer, renal cell cancer and bladder cancer[72].
- Common irAEs include dermatitis, colitis/diarrhea, hepatitis and arthritis.
- Immune-related endocrinopathies may occur with CPI treatment, including thyroiditis (and associated hyper and hypothyroidism), hypophysitis (and associated secondary adrenal insufficiency) and diabetes.
- Serious irAEs suchas pneumonitis or myocarditis are rare but may be life threatening.
- For more information please see CCA's guideline on Follow-up and Management of Checkpoint Inhibitor Related Toxicities in Cancer Patients[71].

Syndrome of Inappropriate Antidiuretic Hormone Secretion -Severe Hyponatremia

SIADH Management Summary:
Acute duration: Fluid restrict (≤1L/day); Hyponatremic encephalopathy: administer IV hypertonic saline (100mL 3 % IV over 10 minutes with 1-2 repeat boluses as needed to increase plasma sodium by 4-6 mEq/L).

Chronic duration: Restrict fluids (≤1L/day). If no change after 24-38 hours: consider furosemide (20-40 mf IV or 20-80 mg orally daily) OR demeclocycline (600-1200 mg/day orally in 3 or 4 divided doses).

Syndrome of inappropriate antidiuretic hormone (SIADH) results from the inappropriate production and secretion of antidiuretic hormone (ADH, also known as arginine vasopressin or AVP) which leads to water retention/intoxication, hyponatremia and hypoosmolality[73].

- **Etiology:**

- In cancer patients, SIADH can be caused by:
  - The ectopic production of ADH by tumour tissue[73,74].
    - Most common: small cell lung cancer
  - The inappropriate production and release of ADH from the posterior pituitary gland[73,74].
  - Cytotoxic chemotherapy and other pharmacologic agents.
    - Opioid analgesics, tricyclic antidepressants, and selective serotonin reuptake inhibitors can also increase ADH production.
    - NSAIDs, thiazide diuretics, barbiturates and anesthetic agents can increase the effects of ADH on the renal tubules[73].

- **Presentation:**
  - Despite the water intoxication caused by SIADH, signs and symptoms of fluid overload (hypertension, peripheral edema, ascites, heart failure) are rarely observed as much of the excess water diffuses into intracellular fluid -only a portion is retained in the intravascular and interstitial spaces[73].
  - The main symptoms are neurological dysfunction secondary to water intoxication that leads to swelling of the brain cells.

Table 3: Symptoms and Signs of SIADH[73,75].

System	Symptoms	Signs
General	-weakness -fatigue -malaise	n/a
Neurological	-altered metal status -headache -lethargy -irritability -delirium -psychosis -personality change	-ataxia -tremors -focal neurological signs -seizures -coma -obtundation -confusion -disorientation
Cardiovascular	n/a	-usually normal blood pressure -usually normal pulse -normal skin turgor -no edema
Gastrointestinal	-anorexia -nausea -vomiting -diarrhea -thirst -abdominal cramping	-moist mucous membranes
Renal	n/a	-oliguria (<400 cc/24 hours) -weight gain -incontinence
Musculoskeletal	-muscle cramps	-hypoactive reflexes -myoclonus

- **Diagnosis:**
  - SIADH is diagnosed after other conditions are excluded[76].
    - Rule out: Pseudohyponatremia due to hyperglycemia, hyperlipidemia, hyperproteinemia, renal failure, adrenal insufficiency, hypovolemia, or hypervolemia[75,77,78].
  - Labs in keeping with SIADH:
    - serum sodium (result <135 mmol/L)
    - serum osmolality (<270 mmol/kg H_2O)
    - serum urea (<3.6 mmol/L)
    - urine osmolality (>100mmol/kg H_2O)
    - urine sodium (>30mmol/L)[78,79]
- **Management:**
  - Treatment should be guided by symptoms and the severity and duration of hyponatremia[77].
    - Acute (<48 hours duration): restrict fluids (≤ 1L /day).
    - Management of hyponatremic encephalopathy: prompt sodium chloride 3% IV [513 mmol/L].
      - 100ml 3% sodium chloride IV bolus over 10 minutes with 1-2 repeat boluses as needed to increase plasma sodium by 4-6mEq/L[73,75,77-80].
      - Goal: to increase plasma sodium levels by 8-12mEq/L over 24 hours
      - Considered to have limited risk of overcorrection and osmotic demyelination.
    - Chronic (≥48 hours duration): Restrict fluids (≤ 1L /day); if after 24-28 hours serum sodium isn't corrected, or urine results indicate low renal electrolyte-free water excretion- consider pharmacological therapies.
      - Slow correction recommended to avoid osmotic demyelination[75,79].

Tumour Lysis Syndrome

Tumour lysis syndrome (TLS) is a complication of cellular breakdown in rapidly proliferating, bulky, or highly chemo-radiosensitive tumours - and the subsequent release of intracellular contents into the bloodstream[81,82]. TLS is characterized by hyperuricemia and major electrolyte disturbances (hyperkalemia, hyperphosphatemia and hypocalcemia)[82,83]. Without timely intervention, TLS can lead to oliguric renal failure, seizures, cardiac arrhythmias, and death[81,82].

TLS Management Summary:
Administer IV saline (250cc/hour or more), + rasburicase (6mg given as a 30-min infusion); Avoid rasburicase in patients with known G6PD deficiency; use allopurinol (100 mg/m2 q8h to maximum 800 mg per day) for these patients; Refer to tertiary centre for additional management and possible dialysis.

- **Etiology:**
  - Most frequently occurs in hematologic malignancies, and very rare in solid tumours[83,84].

        - TLS can rarely occur spontaneously in highly proliferative diseases (Burkitt Lymphoma or Acute Lymphoblastic Leukemia) but is usually triggered by therapy and occurs early (within days) of treatment initiation/change in therapy.
- **Diagnosis:**
    - TLS is often divided into laboratory TLS and clinical TLS.
    - Laboratory TLS can be defined by: 2 or more of the following metabolic abnormalities that arise within 7 days after the initiation of chemotherapy[85]:
        - serum uric acid >476µmol/L (or 25% increase from baseline)
        - serum potassium ≥6.0mmol/L (or 25% increase)
        - serum phosphorous ≥1.45mmol/L in adults (or 25% increase)
        - hypocalcemia (serum calcium ≤1.75mmol/L or 25% decrease)
    - Clinical manifestations of TLS are variable and may include nausea, vomiting, decreased urine output, renal failure, fluid overload, congestive heart failure, arrhythmias, lethargy, paresthesias, muscle cramps, tetany, syncope, seizures, and sudden death[82,85].
    - In patients with obstructive uropathy secondary to hyperuricemia- hematuria, flank or back pain and hypertension may be present[82].
- **Management:**
    - Aggressive hydration with normal saline should immediately be initiated for suspected TLS (250cc/hour or more).
    - If TLS is confirmed, rasburicase 6mg IV as a 30min infusion should be provided to reduce the uric acid and prevent further renal injury (usually requires transfer to a tertiary care centre).
    - Avoid rasburicase in patients with known glucose-6-phosphate dehydrogenase (G6PD) deficiency.
        - Use allopurinol (100 mg/m^2 q8h to maximum 800 mg per day).
    - Severe or worsening TLS may warrant hemodialysis so urgent transfer to a dialysis centre should be organized.
- **Specific management strategies for TLS laboratory abnormalities:**
    1. *Hyperuricemia.*
        - Rasburicase 6mg IV as a 30 min infusion is recommended for treatment of TLS.
            - Avoid rasburicase in patients with G6PD deficiency, use allopurinol (100 mg/m^2 q8h to maximum 800 mg per day) in these patients[86,87].
    2. *Hyperkalemia.*
        - For severe hyperkalemia, rapid acting insulin and a dextrose infusion should be administered[87].
            - Recommended dose is regular insulin (10 units) IV plus 100mL of a 50% dextrose solution (D50).
            - May be repeated after 30-60 minutes (monitor finger prick glucose closely).

- Calcium gluconate via slow infusion (and with continuous ECG monitoring for bradycardia) may be used for life-threatening arrhythmias[82,88-90].
    - Recommended dose is 1g (10 mL of 10 percent solution).
- Sodium bicarbonate can be given IV push to induce the influx of potassium (K) into cells, in addition to the above treatments if patient is acidemic.
    - Should not be administered in same line as calcium solutions.
    - Recommended dose 45-50mEq slow IV infusion over 5-20 minutes[87].
- Albuterol can also be used to help shift potassium into the intracellular space.
    - Recommended dose 10-20mg in 4mL saline nebulized over 20 minutes or 10 to 20 puffs per metered dose inhaler over 10-20 minutes[87].
- Potassium levels should be rechecked in 4 to 6 hours[87].
- Oral or rectal sodium polystyrene sulphonate will help with excretion of K.
    - Recommended dose is 15-30g orally repeated every 4-6 hours up to 4 times daily as needed based on repeat serum K+ level[87].

3. *Hyperphosphatemia.*
    - There are no therapies to ‘shift’ phosphate and the only acute method to reduce phosphate levels in the blood is via renal dialysis. This is rarely indicated for phosphate levels alone but for management of the syndrome of TLS.
4. *Hypocalcemia.*
    - Severe hypocalcemia may cause muscular (cramps, spasms), cardiovascular (ventricular arrhythmias, heart block, hypotension) and neurological (confusion, delirium, hallucinations, seizures) signs.
    - If hyperphosphatemia is also present, calcium replacement may precipitate calcium phosphate crystals and worsen renal dysfunction.
    - A renal consult for consideration of dialysis should be initiated prior to any attempts at IV calcium replacement in TLS.

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Development and Revision History

This guideline was reviewed and endorsed by members of multiple Alberta Provincial Tumour Teams. Members include medical oncologists, hematologists, respirologists, nephrologists, urologists, nurses and acute care physicians. Evidence was selected and reviewed by a working group comprised of members from multiple Alberta Provincial Tumour Teams, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2010 and updated in 2014 and 2022.

Maintenance

A formal review of the guideline will be conducted in 2025. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

aPTT, activated partial thromboplastin time; ADH, antidiuretic hormone; ANC, absolute neutrophil count; AVP, arginine vasopressin; Ca2+, calcium; CBC, complete blood count; CCA, Cancer Care Alberta; d, day(s); cp, centipoise; CPIs, checkpoint inhibitors; CT, computed tomography scan; DIC, disseminated intravascular coagulation; D50, 50% dextrose solution; ECG, electrocardiogram; FFP, fresh frozen plasma; G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal; h, hour(s); ICU, Intensive care unit; IgM, immunoglobulin M; IM, intramuscular; irAEs, immune-related adverse events; IV, intravenous; K, potassium; MAH, malignancy associated hypercalcemia; MRI, magnetic resonance imaging; NG, nasogastric; NSAID, non-steroidal anti-inflammatory drug; PO, per os/by mouth; PRBCs, packed red blood cells; PTH, parathyroid hormone; PT(-INR), prothrombin time; q, every; SC, subcutaneous; SCC, spinal cord compression; SVCO, superior vena cava obstruction; TID, ter in die/ three times a day; TLS, tumour lysis syndrome.

Disclaimer

The recommendations contained in this guideline are a consensus of members of multiple Alberta Provincial Tumour Teams and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

Dr. Bettina Lott reports payment for committee work for Alberta Health outside the submitted work

***Dr. Carolyn Owen** reports honoraria from AbbVie, AstraZeneca, Janssen, Roche, Merck, Incyte and Gilead.

Rachel Vanderploeg has nothing to disclose.

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