

ONCOLOGIC EMERGENCIES: A GUIDE FOR FAMILY PHYSICIANS

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The recommendations contained in this guideline 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.

INTRODUCTION

An oncologic emergency can be broadly defined as any complication related to cancer or anticancer therapy that requires immediate intervention. While some oncologic complications are insidious and may take weeks or even months to develop, others can manifest in a few hours, and quickly lead to severe negative outcomes, including paralysis, coma, and death.¹ Despite the increasing incidence rate of cancer in the general population, cancer mortality rates are dropping due to rapid advances in treatment strategies. The overall improvement in long-term survival of patients with cancer combined with the increasing use of more efficient outpatient treatment strategies are both contributing factors to the high likelihood that primary health care providers will encounter oncologic emergencies in their practices on a more regular basis.^{2,3} The information provided below is a broad overview of the most common oncologic emergencies a family physician is likely to encounter.

GUIDELINE QUESTIONS

- What are the most common oncologic emergencies likely to be encountered by a family physician?
- What are the recommended management strategies for patients with an oncologic emergency related to his or her treatment for cancer?

DEVELOPMENT AND REVISION HISTORY

This comprehensive review was created by members of the Guideline Resource Unit with guidance and review from members of the Alberta Provincial Tumour Teams and Community Oncology. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#). This document was first developed in June 2010 and was revised in April 2014.

SEARCH STRATEGY

For the April 2014 guideline update, medical journal articles were searched using the Medline (2010 to April Week 1, 2014) and PubMed.gov electronic databases, as well as the Cochrane Database of Systematic Reviews (1985 to 1st Quarter, 2014); the references and bibliographies of articles identified through these searches were scanned for additional sources.

Articles were excluded from the final review if they had a non-English abstract, involved only pediatric patients, or were published prior to January 1985. A systematic search for new or updated practice guidelines published since January 2010 was also conducted. Guidelines from the National Comprehensive Cancer Network (NCCN) and Infectious Diseases Society of America (IDSA) were deemed to be most relevant and corresponded best with local context and practice.

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.

DISCUSSION AND RECOMMENDATIONS

ACUTE BLEEDING

Description. Acute bleeding in patients with cancer can be caused by the underlying malignancy, antineoplastic therapy or non-malignancy related factors. Some of the most common presentations are discussed here.

DIC: Disseminated intravascular coagulation (DIC), the result of inappropriate thrombin activation, results in the rapid formation of fibrin clots in the microcoagulation, consumption of clotting factors and clot degradation.^{4,5} Continuous bleeding and clotting continues until clotting factors are completely consumed, resulting in uncontrollable bleeding. In cancer patients, DIC is most commonly seen with acute myelocytic leukemia, adenocarcinoma, septicemia or transfusion reactions.^{4,5}

GI bleeding (overt): Upper gastrointestinal (GI) bleeding in the cancer patient can be caused by primary upper GI malignancies, a number of non-malignancy related causes (peptic ulcer disease, esophageal and gastric varices, hemorrhagic gastritis, etc.) and less commonly, by metastasis to the esophagus, stomach or duodenum; lymph node disease with invasion of overlying mucosa; and mucositis secondary to chemotherapy.⁶ Lower GI bleeding can be caused by primary upper and lower GI malignancies, non-malignancy related causes (diverticular disease, ischemic colitis, inflammatory bowel disease, hemorrhoids, etc.) and various cancer therapies (e.g., graft-versus-host disease following stem cell transplantation, radiation-induced proctosigmoiditis, etc.).⁶

Hematuria: Hematuria can result from bleeding anywhere along the urinary tract secondary to drug- or radiation-induced damage, infection or progression of cancer.^{7,8} While a number of chemotherapy agents can induce sterile hemorrhage cystitis, it is most commonly seen in patients receiving cyclophosphamide or ifosfamide, as both agents are metabolized to acrolein, a urothelial toxic metabolite.⁷ It is also seen in about 2% of patients undergoing high-dose conditioning regimens without cyclophosphamide, usually secondary to thrombocytopenia.⁷ In bone marrow transplantation, hemorrhagic cystitis can occur secondary to adenovirus or BK human polyomavirus infection.⁷ Radiation-induced cystitis results from damage to the vascular endothelium and endarteritis, resulting in progressive ischemia, inflammation, fibrosis and tissue necrosis.⁷ It is seen with pelvic irradiation (both external beam and brachytherapy) and pre-stem cell transplantation total body irradiation.⁷ Patients with previous surgery and those receiving cyclophosphamide are at greatest risk.⁷ Approximately 85% of patients who develop macrohematuria post-radiation actually have tumour recurrence.⁷

Hemoptysis: Hemoptysis is the most immediate life-threatening symptom of progressive intrathoracic disease.⁹ Massive hemoptysis (the expectoration of 100 mL of blood in a single episode or more than 600 mL in 24 hours) can lead to asphyxiation or exsanguination.¹⁰ In cancer patients, the primary causes are malignancy, infection and hemostatic abnormalities.^{9,10} In cancer patients older than 40 years, the most common cause of massive hemoptysis is bronchogenic carcinoma.¹⁰ Melanoma, breast, kidney, laryngeal and colon cancers are most commonly associated with hemoptysis secondary to lung metastases.¹⁰ Neutropenic or immunocompromised patients are at risk of necrotizing, angioinvasive fungal infections (e.g., aspergillosis, mucormycosis) with associated pulmonary hemorrhage.¹⁰ Other factors contributing to increased risk include thrombocytopenia, coagulopathy (resulting from malignancy or treatment) and radiation- or chemotherapy-induced lung damage.¹⁰

Presentation and Diagnosis.

DIC: Acute DIC classically presents with elevation in PT and PTT times, D-dimer, fibrin degradation products, and/or decreased platelet counts.¹¹ Patients with laboratory evidence of DIC may be asymptomatic, but with progression of the underlying condition, can rapidly become symptomatic.⁵ With sepsis-induced DIC, symptoms favour bleeding over thrombosis.^{4,5,11} The following signs and symptoms may be present: petechiae, ecchymosis, purpura, pallor, bleeding from multiple sites, hematuria, oliguria, abdominal distention, guaiac-positive stools, dyspnea, hemoptysis, and tachypnea.⁴ With intracranial bleeding, restlessness, confusion, lethargy and altered mental status may be seen.⁴ Cardiovascular compromise presents as tachycardia with hypotension.⁴ Purpura fulminans (DIC in association with symmetric limb ecchymosis and skin necrosis) may be seen in patients with overwhelming infection.⁵ With tumour-initiated DIC, a hypercoagulability state is favoured rather than hemorrhage. Overt manifestations include DVT, pulmonary embolus and thrombosis in the central nervous system and abdominal organs.¹¹

GI bleeding (overt): Upper GI bleeding typically presents with hematemesis and/or melena, with symptoms ranging from mild blood-streaked emesis from Mallory-Weiss tears, to frank, massive hemorrhage from bleeding varices.⁶ With lower GI bleeding, attempting to identify the site of bleeding by the characteristics of the stool is imprecise; the appearance depends on the briskness of hemorrhage and speed of passage through the GI tract.⁶ Differentiating upper from lower GI bleeding can be difficult.¹²

Hematuria: The type of bleeding can assist in determining the origin of bleeding. Bright red blood without clots that partially clears during urination usually indicates a lower tract bleed, as do less common broader clots (which can be difficult to evacuate and may cause renal colic).⁷ Long, vermiform clots usually indicate upper tract bleeding.⁷

Hemoptysis: In addition to obvious hemoptysis, patients may be hypotensive, tachycardic, centrally cyanotic and clammy, and may experience dyspnea or chest pain.¹⁰ 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.¹⁰

Management and Treatment. In any bleeding patient, basic investigations should include hematocrit, platelet count, prothrombin time (PT-INR), activated partial thromboplastin time (aPTT), D-dimer and fibrinogen level.⁵

DIC: Do not delay definitive treatment (even if invasive), as DIC will not improve until the underlying cause is treated.¹³ In the meantime, coagulation and vital organ function must be supported.^{4,5,13} The need for large transfusions of platelets (a reasonable platelet target is $50-75 \times 10^9/L$), cryoprecipitate (a reasonable fibrinogen target is 50-100 mg/dL), fresh frozen plasma, clotting factors and/or packed red blood cells should be anticipated.^{5,11} Heparin may be used to slow clot formation, but there is little evidence supporting its effectiveness, it carries the obvious risk of increasing bleeding and is generally reserved for patients with large vessel thrombosis.^{4,5,13} However, cancer patients with chronic DIC (e.g., Trosseau syndrome) may require long-term heparin therapy.⁵ At this point, the advice of a hematologist should be sought.

GI Bleeding (overt): For all acute GI bleeding, rapid assessment with a focused history should accompany any initial resuscitation. Information should be obtained on: nature and duration of bleeding, history of pharmaceutical anticoagulation, bleeding diatheses, NSAID use, prior GI bleeding, chemo- and radiotherapy treatments, stool habits, nature of any recent emesis, and history of comorbid conditions that may impact evaluation or treatment decisions.^{6,14} Initial management should focus on rapid assessment of airway, breathing and circulation, establishment of large bore IV access and laboratory collection (CBC,

chemistry panel, coagulation panel, liver function tests, blood type and crossmatch).⁶ An ECG should be obtained if cardiac ischemia or electrolyte abnormalities are suspected.⁶ Vomiting and retching should be controlled.⁶ NG aspiration with lavage may help confirm the source and briskness of bleeding.⁶ If needed, crystalloid boluses should be used for volume resuscitation, followed by packed red blood cells.⁶ For bleeds that are suspicious for a gastric or duodenal source, a pantoprazole infusion (80mg bolus and 8mg/hr) should be started and for bleeds that are suspicious for an esophageal variceal bleed, an octreotide infusion (50 µg bolus and 50 µg/hr) should be started. Referral to a gastroenterologist for definitive management (e.g., endoscopic evaluation, radionuclide scintigraphy, selective angiography and embolization) is indicated.^{6,12,14}

Hematuria: Chemotherapy-induced cystitis can be prevented by aggressive oral and/or intravenous hydration during treatment.⁷ With ifosfamide and high-dose cyclophosphamide, hyperhydration and administration of prophylactic intravenous mesna are recommended.⁷ In the case of bladder hemorrhage with clotting, cystoscopy with evacuation of clots may be required.^{7,8} If bleeding is caused by recurrence of bladder tumour or invasion by other pelvic neoplasms, disease may be advanced and treatment is usually palliative and directed at treating the underlying malignancy and symptoms with surgery, cauterization via cystoscopy, or radiation.⁷

Hemoptysis: The airway must be protected, and intubation is warranted with rapid bleeding, hemodynamic instability, ventilatory impairment, severe dyspnea or hypoxia.¹⁰ The site of bleeding must be identified, and the best and most direct way to do so is via bronchoscopy.^{9,10} Volume resuscitation, supplemental oxygen, correction of underlying coagulopathies and cough suppressants may be required.¹⁰ With unilateral bleeding, lateral decubitus positioning with the affected lung in the dependent position may help to minimize aspiration to the unaffected lung.¹⁰ Bronchoscopic treatments include administration of topical thrombin and/or fibrinogen/thrombin, iced saline lavage, endobronchial tamponade, laser photocoagulation and electrocautery.¹⁰ With hemorrhage from the bronchial circulation, selective angiography and embolization of the bleeding vessel with foam, coils, isobutyl-2-cyanoacrylate or absorbable gelatin pledgets may resolve the bleeding.¹⁰ Once the acute bleed is stabilized, radiotherapy should be initiated as soon as possible.⁹ By causing vascular thrombosis and necrosis of contributing vessels, radiotherapy controls bleeding and prevents further hemoptysis.^{9,10} Surgical intervention is usually reserved for patients with hemoptysis refractory to other treatments and patients with life-threatening cardiovascular compromise.¹⁰

BRAIN METASTASES, INCREASED INTRACRANIAL PRESSURE, AND SEIZURES

Description. Brain metastases represent the most common type of brain malignancy, and occur in approximately 10-30% of all adult patients with cancer.¹⁵⁻¹⁷ Although any primary tumour can metastasize to the brain, lung cancer, breast cancer, and melanoma are the most common, collectively accounting for approximately 70-90% of all cases of brain metastases in adult patients.¹⁸ Other common primary tumours include colorectal cancer and renal cell carcinoma.^{16,17} 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.¹⁹ Brain metastases can lead to neurologic deficits and seizures, and become an oncologic emergency in cases of increased intracranial pressure and status epilepticus.¹⁹ In addition, patients with a primary brain tumour and patients with edema resulting from treatment with whole-brain radiotherapy or some chemotherapeutic agents can also show signs of increased intracranial pressure.

Presentation and Diagnosis. Patients with brain metastases may experience a variety of neurological symptoms, the most common of which is subacute onset of headache, which occurs in approximately 50%

of cases. Other common symptoms include altered mental status, hemiparesis, impaired cognition, increased intracranial pressure, and seizures.^{18,19} Increased intracranial pressure and seizures lasting longer than 30 minutes (status epilepticus) are considered oncologic emergencies.

Patients with increased intracranial pressure due to brain metastases or a primary brain tumour classically present with headache, nausea, and vomiting, all of which may be most severe in the morning and when supine. In addition, papilledema is detected on physical examination almost always indicates increased intracranial pressure.¹⁹ Status epilepticus is defined as more than 30 minutes of continuous seizure activity or two or more sequential seizures without full recovery between seizures.

A non-contrast computed tomography (CT) scan should be performed in order to rule out brain hemorrhage.¹⁰ Magnetic resonance imaging (MRI) is superior to CT scanning in terms of sensitivity and specificity, but if a patient is unstable or if MRI is not immediately available, CT scanning is a safer and timelier option.^{10,19}

Management and Treatment. Initial treatment of elevated intracranial pressure is with the steroid dexamethasone, because it is the most lipid-soluble of all the steroids. Despite its common use, however, there have been few prospective clinical trials to determine the optimal dose and schedule for dexamethasone in patients with primary or metastatic brain tumours, and subsequently fewer clinical practice guideline recommendations. Dexamethasone and all steroids are associated with a variety of side effects, therefore the risks and benefits must be weighed carefully for each patient. The Alberta Provincial CNS Tumour Team has developed a comprehensive clinical practice guideline outlining consensus-based recommendations for dexamethasone dosing in patients with brain tumours and cerebral edema. Further details can be found in the [Use of Dexamethasone in Patients with High Grade Gliomas](#) guideline. In the most severe cases, mannitol in addition to intubation and controlled hyperventilation may be used to decrease cerebral edema, but this is reserved for critical cases in patients with rapidly declining clinical states.^{2,19}

Status epilepticus is a medical emergency requiring the immediate assessment of airway, breathing, and circulation. Anticonvulsant therapy with a short-acting benzodiazepine such as lorazepam or diazepam should be administered intravenously to halt seizure activity. Patients with status epilepticus may also require further treatment with other anticonvulsants such as phenytoin or phenobarbital.^{2,10} Anticonvulsants are associated with significant adverse effects however, and are therefore not recommended as prophylactic therapy in patients with brain metastases *without* a history of seizures.²⁰

For select patients with a good performance status and well-controlled systemic disease, more definitive treatments of brain metastases may include surgery, whole brain radiotherapy, stereotactic radiosurgery or a combination. Further details and recommendations can be found in the [Palliative Radiotherapy: Brain Metastases Clinical Practice Guideline](#).

FEBRILE NEUTROPENIA

Description. Febrile neutropenia is one of the most common complications related to cancer therapy, and is considered a potentially life-threatening medical and oncologic emergency. 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.^{21,22} In addition, the development of febrile neutropenia in a patient with cancer can lead to the decision to reduce or delay subsequent chemotherapy cycles, thereby leading to negative outcomes for patients being treated with curative intent.

Febrile neutropenia is defined as fever higher than 38.3°C OR higher than 38.0°C for more than 1 hour, in a patient who has received chemotherapy in the past month, AND an absolute neutrophil count (ANC) less than 0.5×10^9 cells/L.^{23,24} Patients actively being treated with chemotherapy should be instructed to promptly contact the on-call oncologist or go to the nearest emergency department if they develop an oral temperature equal to or higher than 38.3°C or a sustained oral temperature of 38.0°C for more than one hour. For a comprehensive review of the literature and treatment recommendations, refer to the Alberta provincial clinical practice guideline on the [Management of Febrile Neutropenia in Adult Cancer Patients](#).

Many chemotherapy drug regimens can have adverse effects on the mucosal barrier, and seeding of the bloodstream by endogenous bacteria from the gastrointestinal tract is thought to be responsible for the most cases of febrile neutropenia. Blood cultures are positive in about 30% of cases, and gram-positive organisms are isolated more commonly than gram-negative organisms; the latter, however, are associated with more severe infections, including sepsis.^{24,25}

The risk for development of febrile neutropenia is approximately 25-40% in adult patients with cancer, and is usually based on the type, duration, and intensity of the chemotherapy regimen.^{25,26} Older age, female sex, low performance status, low albumin level, low body surface area, low baseline counts, low lymphocyte counts, low hemoglobin level, high lactate dehydrogenase level, and bone marrow involvement are all common risk factors that have been associated with the development of febrile neutropenia in adult patients with both solid tumours and hematologic malignancies.²⁶⁻²⁹

Presentation and Diagnosis. Given the inability of most immunocompromised hosts to mount an adequate response to infection, the classic signs and symptoms of infection, other than fever, may be minimal.³⁰ A careful history and detailed examination is therefore required for all patients with cancer suspected of having febrile neutropenia. The examination should include assessments of mental status, hydration status, oral and pharyngeal mucosa, the skin (including any indwelling IV sites), the respiratory system, the abdomen, the peri-anal area, and the cardiovascular system (including signs of sepsis). Clinicians should also be aware of the increased risk for meningitis, sinusitis, herpes simplex, herpes zoster, and thrush in patients with prolonged neutropenia. A rectal exam should be avoided, but a perirectal inspection for abscesses should be done.^{23,24}

A complete hematological profile and chemistry profile should also be completed. The latter is done to assess for co-morbidities or any end-organ effects of sepsis, and to determine if any antibiotic dose modifications or contraindications may apply.^{23,24,31} These laboratory tests should include:

- CBC and differential
- Transaminases, bilirubin, alkaline phosphatase
- Electrolytes
- Creatinine and urea
- Blood cultures
 - aerobic and anaerobic
 - peripheral and from any indwelling IV lines
- Urinalysis and urine culture (absence of pus cells on urinalysis does not rule out a urinary tract infection in the setting of neutropenia)
- Sputum gram stain and culture if productive
- AST
- Nasopharyngeal swab for viral respiratory panel PCR, if respiratory symptoms are present

A lumbar puncture and cerebrospinal fluid analysis **should not** be routinely done.

A chest x-ray should also be obtained, even in the absence of pulmonary symptoms or signs. Pulmonary infiltrates may not develop until the neutropenia begins to recover. Thoracic CT can be considered in the setting of clinical abnormalities and a normal chest x-ray. Other imaging tests should be guided by the clinical picture.

Supplementary historical information (e.g., major comorbid illness, time since last chemotherapy administration, history of prior documented infections, recent antibiotic therapy/prophylaxis, medications, HIV status, and recent exposures) as well as site-specific cultures (e.g., diarrhea, skin lesions) and viral cultures (e.g., vesicular/ulcerated skin lesions, respiratory virus symptoms) should also be obtained, as necessary.

Management and Treatment. Febrile neutropenia is considered a true medical and oncologic emergency with high mortality rates in patients with cancer if untreated. Empiric broad-spectrum antibiotics must therefore be administered immediately.^{24,25,32,33} **Patients transferred from the emergency department to a ward should already be receiving antibiotic therapy.** Allergies, prior antibiotic history, clinical picture and local flora should be considered as guides.^{33,34}

The initial antibiotic regimen for the treatment of patients with cancer who develop febrile neutropenia should be one of the following broad-spectrum regimens:^{23,24}

1. **Combination Therapy:**

- Piperacillin-tazobactam 4.5 grams IV every 8 hours is the treatment of choice
- β -Lactam plus an aminoglycoside plus vancomycin is recommended until C&S results are available in patients who are hemodynamically unstable or have septic shock
 - In such circumstances, vancomycin 15 mg per kg IV every 12 hours should be administered, in combination with either gentamicin 5-7 mg/kg IV every 24 hours or tobramycin 7 mg/kg IV every 24 hours.

2. **Monotherapy:**

- Cefipime (2 grams IV every 8 hours)
- Carbapenem monotherapy is an alternative to piperacillin-tazobactam. In order to prevent the selection of carbapenem resistance, carbapenems should not be used in first line unless there is a known or suspected infection with ESBL/Amp C cephalosporinase-producing organisms or a penicillin allergy.

3. **Empiric Vancomycin:**

- Should not be used routinely, but should be considered for patients with a major β -lactam allergy, evidence of an IV catheter/tunnel infection, a positive gram-positive culture with organisms not yet identified, known colonization with MRSA or penicillin-resistant *S. pneumoniae*, a history of recent quinolone antibiotic prophylaxis, skin or soft-tissue infection, pneumonia, or who are hemodynamically unstable.
- Vancomycin therapy should be stopped on day 2 or 3 if cultures are negative for β -lactam resistant Gram positive organisms.

The duration of antibiotic coverage depends on the early clinical course and the results of any cultures. If a definite source of infection is identified, such as a urinary tract infection or pneumonia, the treatment duration should be appropriate for those infections. If a pathogen is identified in the blood cultures, especially gram-negative bacilli, a 10 to 14 day course of antibiotics is recommended. If no source of infection is identified either clinically or in blood cultures, antibiotics can be stopped if the patient is afebrile

and the ANC has recovered to 0.5×10^9 cells/L, although some recommend a minimum of 7 days of therapy. If the fever resolves but the ANC is still low, there is no consensus on duration of antibiotics but a reasonable strategy would be to continue the antibiotics for 5 to 10 days, depending on the clinical picture. If the still neutropenic patient is unstable or has significant mucositis, antibiotics should be continued for at least 14 days even if the patient is afebrile.^{23,24,35}

Be aware that fever in the patient with cancer can be due to the disease itself but a persisting fever in the neutropenic patient usually suggests an ongoing infection not adequately treated by the current antibiotic regimen. The clinical picture must be thoroughly re-evaluated. Blood or other culture results should be verified and repeat cultures obtained if fever persists for more than three days. Empirically, vancomycin (1 gram IV every 12 hours) is usually added at this point. Fungal cultures should be obtained and empiric antifungal therapy is recommended if the fever persists beyond 5 days of appropriate antibacterial therapy. Please consult a medical oncologist or infectious disease specialist for advice regarding the most appropriate agent. Viral infections can also commonly occur in the patient with febrile neutropenia. Severe oral herpes can look like severe mucositis. Viral swabs and empiric antiviral therapy should be considered.

Patients who have rapidly improved on IV antibiotics and who are afebrile, stable, and no longer neutropenic can be switched to an appropriate oral regimen for the balance of the chosen antibiotic duration.³⁶ Such patients can also be discharged if they are stable (non-septic presentation, mucositis resolving, neutrophils $>0.1 \times 10^9/L$, adequate GI absorption), have no unmanaged comorbidities, and have a safe and reliable home environment. If the patient was treated with prophylactic quinolone prior to the episode of febrile neutropenia, quinolone should be avoided on discharge. Ciprofloxacin (750mg twice daily) plus amoxicillin–clavulanate (875mg twice daily) or levofloxacin (500mg once daily) are reasonable step-down regimens.²⁴ Culture and sensitivity results can also guide therapy, and should be reviewed prior to discharge.

Granulocyte colony stimulating factors (G-CSF) can decrease the duration of neutropenia, fever, and hospitalization, but these benefits are modest and mortality is unaffected.²⁴ Therapy with G-CSF can be considered for use in a hospitalized patient with pneumonia, hypotension/sepsis, or organ dysfunction, or for a patient being treated with a chemotherapy regimen that is known to cause prolonged neutropenia.^{37,38}

HYPERVISCOSITY SYNDROME

Description. Hyperviscosity syndrome refers to a group of clinical symptoms related to increases in blood viscosity, which in turn, lead to adverse effects on tissue perfusion. Causes of elevated viscosity include increased protein content and large molecular size, abnormal polymerization, and abnormal shape of immunoglobulin molecules.³⁹ Hyperviscosity syndrome can occur secondary to a variety of hematologic malignancies, the most common being Waldenström macroglobulinemia, which accounts for as many as 80% of cases of hyperviscosity in patients with cancer.⁴⁰ Waldenström macroglobulinemia is a relatively rare B-cell lymphoproliferative disorder characterized by bone marrow infiltration and production of monoclonal immunoglobulin M (IgM).⁴¹ Less frequently, hyperviscosity syndrome can also occur in patients with multiple myeloma, leukemia, polycythemia, and the myelodysplastic disorders.^{39,42}

There is no concise relationship between serum viscosity and the appearance of symptoms.¹⁹ Most commonly however, symptoms of hyperviscosity will appear when the normal serum viscosity of 1.4 to 1.8 centipoise (cp) reaches 4 to 5 cp, corresponding to a serum IgM level of at least 3 g/dL; a normal serum IgM concentration is approximately 1.5 g/dL.^{2,40,43}

Presentation and Diagnosis. Hyperviscosity syndrome should be suspected in patients with a known hematologic malignancy who present with classic symptoms of bleeding, visual disturbances, and/or focal

neurologic signs. However, symptoms may be vague, and this triad of classic symptoms is not always present in all patients, therefore making the diagnosis and workup challenging in many cases.⁴³ Bleeding typically arises from oozing mucosal sites, including epistaxis, bleeding gums, and gastrointestinal bleeding.^{42,43} Visual disturbances may include diplopia, retinal vein thrombosis, papilledema and retinal hemorrhage. Fundoscopic examination commonly reveals dilation or engorgement of retinal veins, resembling the appearance of “sausage links”.^{42,43} Neurologic manifestations often include headache, dizziness, vertigo, ataxia, encephalopathy, hearing impairment, seizures, and altered mental status.^{42,43} Hyponatremia and hypercalcemia are often also present in patients with hyperviscosity syndrome.¹⁹ In rare cases, congestive heart failure, stroke, and coma may also occur in patients with hyperviscosity syndrome, leading to multiorgan system failure and death if treatment is not initiated in a timely manner.^{19,40}

The diagnosis of hyperviscosity syndrome is based on the presence of clinical symptoms in combination with a measure of serum viscosity levels using an Ostwald tube.⁴⁰ 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, and will vary depending on the urgency of the presenting symptoms.^{19,43}

Management and Treatment. Short-term management of symptomatic hyperviscosity syndrome is directed at immediately reducing blood viscosity, which is most effectively accomplished using plasmapheresis. The effect of plasmapheresis is usually rapid in IgM-related cases, as most IgM is intravascular.¹⁹ Typically, one to two plasmapheresis procedures, each involving an exchange of 1 to 1.5 calculated plasma volumes, will reduce the plasma viscosity to near normal levels for several weeks.⁴⁴ If plasmapheresis is not readily available, or if the patient presents with severe neurologic symptoms such as seizures or coma, phlebotomy of 100 to 200 mL of whole blood can also be used to rapidly reduce acute symptoms.^{19,42}

Long-term management of patients with hyperviscosity syndrome is directed at controlling the underlying disease, and patients should be referred to a hematologist or medical oncologist following short-term management of symptoms. For patients with symptomatic Waldenström macroglobulinemia, treatment with systemic agents is indicated to prevent recurrent symptoms; alkylating agents, purine analogues, and rituximab are all appropriate choices.⁴⁴ Plasmapheresis may be indicated as long-term management for hyperviscosity syndrome in patients who are drug-resistant, have a poor performance status, or cannot tolerate chemotherapy.^{39,44}

MALIGNANCY ASSOCIATED HYPERCALCEMIA

Description. 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. Malignancy associated hypercalcemia (MAH) is defined as a **corrected** serum calcium > 2.6 mmol/L.³ Calcium circulates in the blood in a biologically active ionized form (50%), a protein-bound (biologically inactive) fraction (40%) and in a form complexed to assorted anions (10%).⁴⁵ Accordingly, changes in albumin levels can alter total calcium levels. Most laboratories measure total serum calcium (rather than ionized calcium), which must be “corrected” in the setting of hypo- or hyperalbuminemia to compare total calcium values against the normal range (every 10 g/L decrease in albumin corresponds to a 0.2 mmol/L increase in calcium).^{45,46}

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.^{45,47,48}

MAH occurs in up to 30% of patients with cancer, most commonly among those with breast, lung and head/neck tumours, as well as those with hematologic malignancies (especially multiple myeloma and adult T-cell leukemia/lymphoma).^{45,47,48} Humoral hypercalcemia accounts for the majority of cases (80%).^{3,48} It results from secretion of parathyroid hormone related protein (PTHrP) or other cytokines which bind to the PTH receptor and mimics the physiological effects of PTH (i.e., increased bone resorption, enhanced renal retention of calcium).^{3,47,48} Osteolytic bone metastases account for 20% of cases, and other causes (such as ectopic PTH secretion, vitamin D secreting lymphomas, etc.) account for less than 1%.^{3,48} Further, many cancer therapies (e.g., antineoplastic agents, vitamin D analogues) can induce or exacerbate hypercalcemia, particularly when used in combination.⁴⁵

Presentation and Diagnosis. Mild hypercalcemia may be asymptomatic. Moderate to severe hypercalcemia may be associated with various symptoms:^{3,45}

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

	Early Manifestations	Later Manifestations
Neurological	<ul style="list-style-type: none"> weakness/fatigue memory/concentration difficulty 	<ul style="list-style-type: none"> drowsiness/confusion delirium → coma
Cardiovascular	<ul style="list-style-type: none"> shortened QT_c interval enhancement of digitalis effects 	<ul style="list-style-type: none"> ST segment elevation hypotension bradyarrhythmias → heart block → cardiac arrest
Gastrointestinal	<ul style="list-style-type: none"> anorexia constipation 	<ul style="list-style-type: none"> nausea vomiting
Genitourinary	<ul style="list-style-type: none"> polyuria and nocturia 	<ul style="list-style-type: none"> dehydration → oliguria

In general, neurologic and renal complications worsen with increasing hypercalcemia, but it is also important to consider the rate of Ca^{2+} increase. Rapid onset moderate hypercalcemia usually causes marked neurological dysfunction, while chronic severe hypercalcemia may result in only mild neurological symptoms.⁴⁸ Hypercalcemic crisis, an emergency usually associated with serum Ca^{2+} > 3.5 mmol/L, may present with life threatening complications such as acute pancreatitis, acute renal failure and coma.^{3,45}

Management and Treatment. Antihypercalcemic therapy is an interim measure, and long term resolution depends on prompt antitumour therapy.⁴⁸ Most patients with moderate MAH can be managed on a medical ward without the involvement of oncology. Patients with life threatening complications warrant ICU admission. In patients who are on (or are candidates for) anticancer therapy, dialysis should be initiated in the presence of acute or chronic renal failure.^{45,48} It should be noted that when all curative cancer therapies have failed and treatment is entirely palliative, withholding antihypercalcemic therapy (which will eventually lead to coma and death) may be appropriate.⁴⁸

Patients with MAH become dehydrated as a result of hypercalcemia-induced nephrogenic diabetes insipidus and reduced oral hydration secondary to anorexia, nausea and vomiting.⁴⁷ As dehydration worsens, the glomerular filtration rate falls, further impairing renal excretion of calcium.⁴⁷ First line therapy should include fluid resuscitation with IV normal saline and initiation of intravenous bisphosphonates.^{3,45,48,49} Intravenous saline is usually administered at 250-500 mL/hour, depending on

degree of dehydration, renal function, cardiovascular status, degree of cognitive impairment and severity of hypercalcemia.^{3,45,47,48} Bisphosphonates are the most extensively studied and most efficacious agents for treating MAH. At present, pamidronate, zoledronate and ibandronate should be considered the drugs of choice.⁵⁰ Older agents such as mithramycin, calcitonin and gallium nitrate are no longer widely used because of their limited activity and extensive side effects (particularly renal).⁵⁰

While furosemide is frequently recommended for emergency hypercalcemia management, there is no good evidence supporting its use, which should be restricted to managing fluid overload and should only be considered after euvolemia and sodium diuresis have been achieved.^{45,47,49} Premature and/or excessive use of loop diuretics can deplete sodium stores relative to calcium, resulting in intravascular contraction and worsening hypercalcemia.⁴⁵ Thiazide diuretics stimulate renal calcium reabsorption and should **not** be used.⁴⁸ Sources of calcium supplementation (TPN, oral feeding solutions, tablets) and medications that exacerbate hypercalcemia (e.g., calcitriol, vitamin D, thiazides, lithium, antacids, etc.) should be discontinued if possible.^{47,48} Sedatives, hypnotics and analgesics that impair cognitive function should be withheld, as they may worsen the neurologic effects of hypercalcemia.⁴⁷ Hypophosphatemia frequently occurs with hypercalcemia, and phosphorous should be replaced orally or via NG tube as neutral phosphate.⁴⁸ Intravenous phosphorous replacement is contraindicated.^{45,48}

MALIGNANT AIRWAY OBSTRUCTION

Description. Airway obstruction in patients with cancer is most commonly caused by direct extension from an adjacent tumour, particularly an inoperable or recurrent tumour in the mediastinum (i.e. lung cancer, thymoma) or a primary tumour of the head and neck.⁵¹ Airway obstruction secondary to metastatic malignancies has also been reported, particularly from esophageal, renal, breast, or thyroid cancers.^{19,51} Airway obstruction may also be caused by tumour encroachment and by tumour-associated airway edema or hemorrhage.¹⁰ Although rare in non-thoracic malignancies, airway compromise or obstruction will develop in approximately 20-30% of patients with lung cancer during the course of their disease.^{52,53}

Presentation and Diagnosis. The most common presenting symptoms of malignant airway obstruction include, dyspnea, hemoptysis, wheezing, hoarseness, difficulty clearing secretions, and cough.^{19,51,53} These symptoms are nonspecific and may be mistaken for more common conditions, such as an exacerbation of chronic obstructive pulmonary disease, asthma, infections, bronchitis, or heart disease.¹⁹ 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.⁵³ Progressive symptoms of malignant airway obstruction represent a true medical emergency. For most patients with an upper airway obstruction, the physical examination, often accompanied by direct visualization with a laryngoscope or bronchoscope is sufficient to make a diagnosis, depending on the location of the lesion.¹⁰ Laryngoscopy or bronchoscopy may also be necessary to guide the placement of an endotracheal tube.¹⁰ A CT scan of the neck and chest is the most effective initial study to assess the location and extent of airway obstruction.⁵³

Management and Treatment. The management of patients with a malignant airway obstruction depends on factors such as the histologic type, stage and location of the tumour, as well as the urgency of presentation and performance status of the patient. The primary and most urgent goal of treatment is to establish a patent airway to allow for proper gas exchange.¹⁹ Rigid bronchoscopy provides the safest and most effective means of immediate airway control and initial stabilization in patients with acute and malignant airway obstructions.^{19,51,53} In patients with potentially resectable primary tumours, bronchoscopy may also optimize the preparation of patient for airway surgery.⁵¹ The majority of patients with malignant airway obstruction will be unresectable however, due to locally advanced disease, metastatic disease, or

comorbidities. In these patients, therapeutic bronchoscopy provides a prompt and reliable palliation of the airway obstruction. Neodymium-yttrium-aluminum-garnet (Nd:YAG) lasers, in combination with rigid bronchoscopy, can also be used to urgently open the airway in patients with malignant intrinsic airway obstruction. Following the establishment of a patent airway, more definitive tumour control measures should follow, including airway surgery, stenting, radiotherapy, and endobronchial brachytherapy.

Stent placement, particularly self-expanding metal stents, is indicated for the relief of acute airway obstruction in patients with extrinsic tumour compression or with tracheoesophageal fistulas. In addition, stents can be used as a supplemental therapy to laser ablation or photodynamic therapy, or as a second line therapy following failure of local control with laser, photodynamic, or radiation therapy.^{19,53}

Short course, multi-fractionated external-beam radiotherapy at a dose of 20 Gy/5 fractions is recommended for the palliation of intrathoracic symptoms, and is preferred over single-fraction treatment.⁵⁴ Endobronchial brachytherapy may be considered as an adjuvant to external beam radiotherapy, and also in select patients with lung cancer previously treated with external beam radiotherapy who become obstructed due to secondary disease.^{55,56} Endobronchial brachytherapy is not associated with a higher risk of massive hemoptysis compared to radiotherapy alone if brachytherapy fraction sizes less than 7.5Gy to 10Gy are used.⁵⁷

MALIGNANT EPIDURAL SPINAL CORD COMPRESSION

Description. Malignant epidural spinal cord compression (SCC) is a common neurological complication that affects approximately 5% of all adult patients with cancer, and most commonly occurs in the setting of widespread metastatic disease.⁵⁸ Malignant epidural SCC is a true oncologic emergency that needs rapid diagnosis and treatment. If left untreated, it can lead to progressive pain, sensory loss, incontinence, and irreversible paralysis.⁵⁸ The early diagnosis and treatment of patients with malignant epidural SCC is essential to preserving neurologic function and quality of life.

In adult patients, prostate, breast, and lung cancer each account for approximately 15-20% of cases of malignant epidural SCC; other cancers associated with malignant epidural SCC include non-Hodgkin lymphoma, myeloma, renal-cell carcinoma, colorectal cancer, and sarcoma, which each account for approximately 5-10% of cases.^{58,59} The most common location of malignant epidural SCC is in the thoracic spine in 60% of cases, the lumbosacral spine in 25% of cases, and the cervical spine in 15% of cases; multiple sites of spinal cord compression also occur in up to 35% of patients with malignant epidural SCC.⁵⁸

Presentation and Diagnosis. Back pain is the earliest and most common symptom and is present in over 90% of patients with malignant epidural SCC. Pain is often an early indicator of malignant epidural SCC, and may be present for several months before a diagnosis is made.^{10,58} Patients may present with pain localized to the spine, or with radicular pain due to neural compression. The pain may worsen with movement, or when the patient lies down, coughs, sneezes, or strains. Pain that worsens when the patient lies down should increase the suspicion of epidural metastasis.¹⁰ Other presenting symptoms include motor weakness and sensory impairment; autonomic dysfunction usually occurs later in the progression of metastatic epidural SCC, and is a poor prognostic indicator for preservation of neurologic functioning.^{19,58}

The initial diagnosis should involve a medical history and physical examination: all new-onset back or neck pain in a patient with a history of cancer should increase suspicion of malignant epidural SCC.⁵⁸ MRI is the preferred imaging study, if readily available. If the history and clinical findings do not suggest metastasis to the cervical spine, it is appropriate to obtain an MRI of the thoracic and lumbosacral spinal regions only.² A CT scan or a plain radiograph of the spine can also be used if MRI is contraindicated or not available.

However, although plain radiographs of the spine can identify abnormalities in 85-90% of patients with malignant epidural SCC, epidural metastasis should not be excluded on the basis of normal spine films, due to a high likelihood of a false-negative result.¹⁰ Conventional myelography techniques, with or without CT, can also be used if MRI is contraindicated or unavailable.⁵⁸

Management and Treatment. The goals of treatment for patients with malignant epidural SCC are to decrease pain, maintain ambulation, and if possible, decrease tumour bulk. This is achieved through the use of corticosteroids, radiation therapy, surgery, or a combination of these modalities, and will depend on the life expectancy of the patient, extent of disease, and degree of motor impairment. Corticosteroids should be administered as soon as malignant epidural SCC is strongly suspected or confirmed. Because the most important prognostic indicator for ambulatory outcome is the pre-treatment motor function, immediate initiation of therapy is critical.¹⁹ The corticosteroid dexamethasone rapidly reduces spinal cord edema and back pain, and may also improve neurologic functioning. The optimal dose of dexamethasone is still unclear, however, and is debated because of the significant side effects associated with higher doses.¹⁹ One common option is to administer an IV bolus of dexamethasone at 10 to 16 mg, followed by 4 to 6 mg every 4 hours, with a taper during, or immediately after, completion of radiotherapy.

The spinal service should also be consulted for a surgical opinion. Decompressive surgery followed by postoperative radiotherapy has been shown to be superior to radiotherapy alone for select patients with malignant epidural SCC. In patients who are not candidates for surgery, radiotherapy alone is the recommended treatment, although the optimum dose and treatment regimen varies widely within the published literature. For patients with a short estimated lifespan, hypofractionated radiotherapy at a dose of 20Gy/5 fractions or 30Gy/10 fractions could be considered.

SUPERIOR VENA CAVA OBSTRUCTION

Description. Superior vena cava obstruction (SVCO), which is a common complication of malignancy, refers to a constellation of signs and symptoms resulting from partial or complete obstruction of blood flow through the superior vena cava to the right atrium. The obstruction may be caused by compression, invasion, thrombosis, or fibrosis of this vessel.¹⁰ Lung cancer, both small cell and non-small cell, and non-Hodgkin lymphoma combined account for approximately 85% of all cases of SVCO.⁴⁶ At some point during their disease course, 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.^{46,60} In addition, an increasing number of cases of SVCO in cancer patients are due to thrombosis of indwelling central venous catheter devices and/or pacemaker leads.^{19,46,61}

Presentation and Diagnosis. Patients with SVCO may present with a variety of signs and symptoms, the most common being facial or neck swelling, arm swelling, and dilated chest vessels.^{2,46} Worrisome signs include stridor, which may indicate laryngeal edema, and headache or confusion, which may indicate cerebral edema.⁴⁶ Cough, dyspnea, and orthopnea are also common symptoms that can often mimic congestive heart failure or pericardial disease.⁶² Sudden onset of SVCO is rare, but is considered a true oncologic emergency because the rapid elevation of pressure in the superior vena cava causes increased intracranial pressure, resulting in cerebral edema, intracranial thrombosis or bleeding, and death.¹⁰ However, symptoms of SVCO more typically present insidiously over a period of day to weeks.^{10,63}

If patient presents with SVCO without a prior tissue diagnosis of malignancy, every effort should be made to obtain biopsies and histologic diagnosis before any treatment decisions are made,¹⁹ this will aid in the decision of whether a definitive curative course of therapy versus palliative treatment is most appropriate.⁴⁶ Accurate diagnosis via imaging should always be obtained. A contrast-enhanced CT scan of the chest wall is the most useful imaging study, as it clearly identifies the level and extent of the blockage, as well as an

evaluation of collateral pathways of drainage.⁴⁶ MRI is useful for patients who cannot tolerate the contrast medium.^{46,63} Venography is generally only warranted when an intervention such as stent placement or surgery is planned.⁶³

Management and Treatment. Treatment approaches for patients with SVCO can vary widely: management is guided by the severity of the symptoms and the underlying malignancy, as well as by the anticipated response to the treatment.⁶³ Radiotherapy is the preferred initial treatment for the majority of patients with SVCO resulting from malignancy, particularly those with SVCO caused by recurrent disease after chemotherapy or with tumours insensitive to chemotherapy, such as non-small cell lung cancer.¹⁰ Emergency treatment with radiotherapy is also indicated if a histologic diagnosis cannot be established in a timely manner, and in rare life-threatening situations, such as airway obstruction, spinal cord compression, or increased intracranial pressure.¹⁰ While there is insufficient evidence to guide practice on radiotherapy dose fractionation, a retrospective review of SVCO due to any histology reported that an initial dose greater than or equal to 3Gy/fraction yields a higher rate of symptomatic relief in less than two weeks than a conventional dose of 2Gy/fraction.⁶⁴

Chemotherapy can also be used as the initial treatment of SVCO caused by malignancies sensitive to chemotherapy, such as small cell lung cancer and non-Hodgkin lymphoma.^{63,65}

Stent insertion appears to provide rapid relief of associated symptoms, particularly for patients who fail to respond to chemotherapy or radiotherapy. Because the stent can be placed before a histologic diagnosis is made, it is a useful and effective option for patients with severe symptoms such as respiratory distress.⁶³

Although corticosteroids such as dexamethasone may be useful in the presence of airway compromise or increased intracranial pressure, their role in the management of patients with SVCO has not been clearly established at the present time.⁶⁵

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

Description. SIADH (syndrome of inappropriate antidiuretic hormone) results from the inappropriate production and secretion of antidiuretic hormone (ADH, also known as arginine vasopressin) which leads to water retention/intoxication, hyponatremia and hypoosmolality.⁶⁶ In cancer patients, SIADH can be caused by the ectopic production of ADH by tumour tissue.^{50,66} Small cell lung cancer is the malignancy most often associated with SIADH; less common malignancies include non-small cell lung cancer; head and neck, prostate, pancreatic, breast, ovarian, duodenal and esophageal cancers; lymphoma and leukemia; thymoma, neuroblastoma and carcinoid tumours.⁶⁶ Other possible causes of SIADH include cytotoxic chemotherapy and other pharmacologic agents. The chemotherapy agents most frequently implicated in SIADH include cyclophosphamide, ifosfamide, vincristine, vinblastine, cisplatin and melphalan.⁴⁵ Opioid analgesics, tricyclic antidepressants, and selective serotonin reuptake inhibitors can cause also increase ADH production, and NSAIDs, thiazide diuretics, barbiturates and anesthetic agents can increase the effects of ADH on the renal tubules.⁶⁶

Presentation and Diagnosis. Despite the water intoxication of 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 and only a portion is retained in the intravascular and interstitial spaces.⁶⁶ Early symptoms of SIADH can include headache, difficulty concentrating, muscle cramps and weakness, hypoactive reflexes, lethargy, irritability, ataxia, anorexia, nausea, vomiting, diarrhea, thirst, oliguria and abdominal cramping.^{66,67} Severe hyponatremia (serum sodium < 125 mmol/L) has serious and potentially life threatening consequences, particularly if onset is rapid (within 1-3

days).^{66,67} These include confusion, hallucinations, delirium, seizures, coma, decerebrate posturing and respiratory arrest. If SIADH has a slower onset, patients can remain asymptomatic.^{66,67}

Hyponatremia alone is not sufficient to diagnose SIADH. Essential features include decreased effective serum osmolality (< 275 mOsm/kg of water), urine osmolality > 100 mOsm/kg of water during hypotonicity, clinical euolemia (no evidence of volume depletion or excessive volume of extracellular fluid), urinary sodium > 40 mmol/L with normal dietary salt intake and normal thyroid and adrenal function.⁶⁷ With diagnostic uncertainty, volume contraction of the extracellular fluid can be ruled out by infusing 2 liters of 0.9% saline over 24-48 hours. Though not the preferred treatment, normal saline infusion is usually safe when baseline urine osmolality is less than 500 mOsm/kg of water, and correction of the hyponatremia suggests underlying extracellular volume depletion.⁶⁷

Management and Treatment. The only definitive treatment is elimination of the underlying cause. Antineoplastic therapy that causes regression of chemosensitive tumours usually resolves SIADH.^{66,67} If brain metastases are an underlying cause, corticosteroids and radiation therapy may be effective.⁶⁶ If other pharmacologic agents are the cause, their discontinuation usually quickly resolves the syndrome.⁶⁷

Treatment decisions should be guided by the severity and duration of hyponatremia, and the presence or absence of symptoms. Rapid treatment is indicated for symptomatic patients with severe hyponatremia known to have developed within 48 hours.⁶⁷ The goal of therapy is to increase serum sodium by 1-2 mmol/L per hour by infusing 3% hypertonic saline.^{66,67} Most experts believe sodium correction should not exceed 8-10 mmol/L or 18-25 mmol/L during the first 24 and 48 hours of treatment, respectively.⁶⁷

Patients with hyponatremia of unknown duration and nonspecific or absent symptoms require more cautious management. Rapid correction of serum sodium may cause osmotic demyelination characterized by lethargy and affective changes, mutism or dysarthria, spastic quadraparesis and pseudobulbar palsy.⁶⁷ More modest correction (0.5 to 1.0 mmol/L per hour, to a maximum of 8 mmol/L in 24 hours and 18 mmol/L in 48 hours) via slower saline infusion is recommended.⁶⁷ In all patients, frequent monitoring of serum sodium (as often as every 2-3 hours) is indicated to avoid overcorrection.⁶⁷

Asymptomatic patients with chronic hyponatremia have a low risk of serious neurological complications but a high risk of osmotic demyelination if sodium levels are rapidly corrected.⁶⁷ Fluid restriction (ranging from < 500 mL to < 1000 mL per day, based on urine electrolytes and serum sodium) is the primary therapy and usually normalizes sodium gradually over 3-10 days.^{66,67} Adequate dietary protein and sodium intake should be encouraged to increase osmotic load. If fluid restriction is ineffective, demeclocycline (300 to 600 mg twice daily) can be considered, but its effectiveness is variable and it carries the risk of nephrotoxicity.^{66,67}

TUMOUR LYSIS SYNDROME

Description. Tumour lysis syndrome (TLS) is a complication of massive cellular breakdown in rapidly proliferating, bulky or highly chemo-radiosensitive tumours and the subsequent release of intracellular contents into the bloodstream.^{68,69} TLS is characterized by hyperuricemia and major electrolyte disturbances (hyperkalemia, hyperphosphatemia and hypocalcemia).^{69,70} Without timely intervention, it can quickly lead to oliguric renal failure, seizures, cardiac arrhythmias and death.^{68,69}

While common in hematologic malignancies, TLS is relatively rare in solid tumours.^{70,71} Patients most at risk are those with acute lymphoproliferative disorders with a high proliferative rate and high tumour sensitivity to chemotherapy (e.g., Burkitt's lymphoma, B-cell acute lymphoblastic leukemia).^{68,69} Predisposing comorbidities include pre-treatment elevations in serum uric acid levels, pre-existing renal

disease, tumour infiltration in the kidney, obstructive uropathy and advanced age.⁶⁸ Highly active, cycle specific drugs (e.g., cytarabine, etoposide, cisplatin) are most frequently associated with TLS, as are corticosteroids (likely implicated because they are used as primary therapy for highly proliferating lymphoid disease).⁶⁸ TLS has also been reported after treatment with other agents, including intrathecal methotrexate, monoclonal antibodies (e.g., rituximab), radiotherapy, interferon, thalidomide, hydroxyurea, fludarabine, imatinib and bortezomib.⁶⁸ TLS may also arise spontaneously prior to the initiation of anti-tumour therapy.⁶⁹

Presentation and Diagnosis. The syndrome is often divided into laboratory TLS and clinical TLS. While there is no universally accepted specific definition or grading system for laboratory TLS, the commonly cited 2004 Cairo and Bishop grading scale defines laboratory TLS as 2 or more of the following metabolic abnormalities within 3 days before or 7 days after the initiation of chemotherapy:⁷²

- serum uric acid > 476 $\mu\text{mol/L}$ (or 25% increase from baseline)
- serum potassium ≥ 6.0 mmol/L (or 25% increase)
- serum phosphorous ≥ 1.45 mmol/L in adults (or 25% increase)
- secondary hypocalcemia (serum calcium ≤ 1.75 mmol/L or 25% decrease)

The 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.^{69,72} In patients with obstructive uropathy secondary to hyperuricemia, hematuria, flank or back pain and hypertension may be present.⁶⁹

Routine evaluation and diagnostic workup should include.⁶⁹

- strict monitoring of weight, blood pressure and urine output
- serum chemistry (creatinine, sodium, potassium, calcium, phosphorus, uric acid) before any anticancer therapy and up to q6h during the first 2-3 days of treatment
- daily LDH concentrations
- ECG
- Urinalysis
- renal ultrasound to rule out obstructive uropathy may be considered

Management and Treatment. The basic principles of TLS management are aggressive prophylaxis and early recognition and correction of metabolic abnormalities to prevent or minimize clinical manifestations.^{69,71} In the absence of acute renal dysfunction and oliguria, vigorous IV hydration (3 L/m² per day) and diuresis (≥ 100 mL/m²/hour) should be maintained. Diuretics (furosemide, mannitol) may be required to maintain urine output and prevent fluid overload, but should only be used if there is no evidence of acute obstructive uropathy or hypovolemia. Urine specific gravity should be kept below 1.010. Potassium, calcium and phosphate should not initially be added to hydration fluids.^{69,71}

Dose modifications of drugs that are primarily renally cleared may be required during acute TLS. Hemodialysis or hemofiltration may be required with increasing renal dysfunction; uncontrolled hyperphosphatemia, hyperkalemia, hyperuricemia, hypocalcemia, volume overload or hypertension; severe acidosis and/or severe uremia with pericarditis or CNS toxicity.^{69,71}

It is important to note that while rare, TLS associated with solid tumours has a higher mortality rate compared to that observed with hematological malignancies.⁷⁰ This may be due, in part, to time of onset. While TLS associated with hematological malignancies generally occurs soon after treatment begins, TLS in solid tumours can occur days or weeks later. Awareness and vigilance are essential to preventing a delay in or omission of effective prophylaxis.

Hyperuricemia: Acute kidney injury (AKI) secondary to precipitation of uric acid in renal tubules is a potential complication of hyperuricemia. Urine alkalinization via sodium bicarbonate administration has historically been a mainstay of treatment, but is no longer recommended given accumulating evidence of ineffectiveness and the potential to actually induce AKI.^{50,69,73}

Allopurinol and rasburicase are two therapeutic options. Both reduce the formation of new uric acid, and rasburicase also degrades uric acid formed prior to treatment initiation.^{69,74} Guidelines published by an international panel of clinical oncologists recommend allopurinol for patients with no hyperuricemia at intermediate risk of TLS.⁷³ It should be initiated 12-24 hours before anti-cancer therapy and continued until the patient can be classified as low risk. Rasburicase for 1 to 7 days is the treatment of choice for all patients with TLS-associated hyperuricemia and for initial prophylaxis in patients at high risk of TLS.⁷⁴ Allopurinol is not thought to be necessary after initial treatment with rasburicase, though there is no evidence to support or refute this opinion.⁷⁴

Hyperkalemia: Potassium levels should be immediately verified with a second sample to rule out hemolysis during phlebotomy. Close evaluation of ECG, cardiac rhythm and electrolytes is warranted. Oral and IV supplemental potassium should be discontinued. In asymptomatic patients, the preferred treatment is oral or rectal sodium polystyrene sulphonate. In symptomatic patients, rapid acting insulin and a 25% dextrose infusion should be administered. Sodium bicarbonate can be given IV push to induce the influx of potassium into cells. Calcium gluconate via slow infusion (and with continuous ECG monitoring for bradycardia) may be used for life-threatening arrhythmias.^{69,73}

Hyperphosphatemia: Initial management includes removing phosphate from IV fluids and administering oral or nasogastric phosphate binders (e.g., aluminum hydroxide) for up to 2 days (longer treatment carries the risk of aluminum toxicity). Calcium infusions should be withheld. In severe cases, continuous peritoneal dialysis, hemodialysis, or continuous venovenous hemofiltration (CVVH) may be required.^{69,73}

Hypocalcemia: Treatment is not recommended in asymptomatic patients as the risk of precipitating metastatic calcifications is high, especially with hyperphosphatemia, and hypocalcemia will generally resolve as tumour lysis improves. Severe hypocalcemia is one of the most critical manifestations of TLS and may cause muscular (cramps, spasms), cardiovascular (ventricular arrhythmias, heart block, hypotension) and neurological (confusion, delirium, hallucinations, seizures) signs. Symptomatic hypocalcemia is treated with IV calcium gluconate, though patients must be monitored for acute obstructive uropathy. If phosphate is also high, a renal consult should be considered.^{69,73}

GLOSSARY OF TERMS

Acronym	Description
ADH	antidiuretic hormone
AHS	Alberta Health Services
AKI	acute kidney injury
ANC	absolute neutrophil count
AST	aspartate aminotransferase test
Ca ²⁺	calcium
CBC	complete blood count
CNS	central nervous system
CT	computed tomography scan
CVVH	continuous venovenous hemofiltration
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
ECG	electrocardiogram
G-CSF	granulocyte-colony stimulating factor
GI	gastrointestinal
GU	genitourinary
Gy	gray
ICU	intensive care unit
Ig	immunoglobulin
IV	intravenous
LDH	lactate dehydrogenase
MAH	malignancy associated hypercalcemia
MRI	magnetic resonance imaging
MRSA	methicillin-resistant <i>Staphylococcus Aureus</i>
Nd:YAG	neodymium-yttrium-aluminum-garnet laser
NG	nasogastric
NSAID	non-steroidal anti-inflammatory drug
PT	prothrombin time
PTH	parathyroid hormone
PTT	partial thromboplastin time
SCC	spinal cord compression
SVCO	superior vena cava obstruction
TLS	tumour lysis syndrome
TPN	total parenteral nutrition

DISSEMINATION

- Present the document at relevant local and provincial tumour team meetings and weekly rounds.
- Post the document on the AHS website.
- Include links to the document in relevant clinical practice guidelines posted on the AHS website.

MAINTENANCE

A formal update of this review will be conducted in April 2016; however if new evidence is brought forward before that time, the document will be changed accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Tumour Teams in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Tumour Teams are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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