# Grampians Guidelines for Oncological Emergencies (other than Febrile Neutropenia – see separate guideline)

GICS gratefully acknowledges Alberta Health Services, Canada for their generous provision of evidence-based material and Stephen Brown (Medical Oncologist, Ballarat Regional Integrated Cancer Centre) for extensive revision of this document.

(Effective Date: October, 2015)

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.**

## Scope

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

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## 1. 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.

- Overt GI bleeding
- Haematuria
- Haemoptysis
- Disseminated Intravascular Coagulation

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***GI bleeding (overt):***

**Description**

Upper gastrointestinal (GI) bleeding causes

- primary upper GI malignancies,
- peptic ulcer disease
- oesophageal and gastric varices
- haemorrhagic gastritis
- Mucositis secondary to chemotherapy.

Lower GI bleeding causes

- Primary upper and lower GI malignancies
- Non-malignancy related causes (diverticular disease, ischemic colitis, inflammatory bowel disease, haemorrhoids, etc.)
- Various cancer therapies (e.g., graft-versus-host disease following stem cell transplantation, radiation-induced proctosigmoiditis, etc.).

**Presentation and Diagnosis**

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 haemorrhage from bleeding varices.

With lower GI bleeding, the appearance depends on the briskness of haemorrhage and speed of passage through the GI tract.

Differentiating upper from lower GI bleeding can be difficult.

**Management and Treatment**

In any bleeding patient, basic investigations should include:

- FBC including platelet count
- Coagulation studies including prothrombin time (PT-INR) activated partial thromboplastin time (aPTT), D-dimer and fibrinogen level.

Initial management

- 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 cross match).
- An ECG should be obtained if cardiac ischemia or electrolyte abnormalities are suspected

- Nausea and vomiting should be controlled.
- Crystalloid boluses should be used for volume resuscitation, followed by packed red blood cells if required
- For bleeds that are suspicious for a gastric or duodenal source, a pantoprazole infusion (80mg bolus and 8mg/hr) should be started
- For bleeds that are suspicious for an oesophageal 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, etc.) is indicated.
- When the cause of bleeding is known to be malignant, and the site of origin can be localised, radiotherapy is often effective for mild to moderate bleeding. However, other interventions are usually required (+/- radiotherapy) in the context of large volume haemorrhage

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***Haematuria:***

**Description**

Haematuria can result from bleeding anywhere along the urinary tract

Patients with previous surgery and those receiving cyclophosphamide are at greatest risk.

**Presentation and Diagnosis**

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,
- Long, vermiform clots usually indicate upper tract bleeding.

**Management and Treatment**

In any bleeding patient, basic investigations should include:

- FBC including platelet count,
- Coagulation studies including prothrombin time (PT-INR) activated partial thromboplastin time (aPTT), D-dimer and fibrinogen level.
- Chemotherapy-induced cystitis can be prevented by aggressive oral and/or intravenous hydration during treatment.
- With ifosfamide and high-dose cyclophosphamide, hyper-hydration and administration of prophylactic intravenous mesna are recommended.
- In the case of bladder haemorrhage with clotting, cystoscopy with evacuation of clots may be required
- Bleeding caused by recurrence of bladder tumour or invasion by other pelvic neoplasms, treatment is directed at treating the underlying malignancy and symptoms with surgery, cautery via cystoscopy, or radiation.

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***Haemoptysis:***

**Description**

Haemoptysis is a life-threatening symptom of progressive intrathoracic disease.[9] Massive haemoptysis (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. In cancer patients, the primary causes are malignancy, infection and haemostatic abnormalities. Melanoma, breast, kidney, laryngeal and colon cancers are most commonly associated with haemoptysis secondary to lung metastases.

Neutropenic or immunocompromised patients are at risk of necrotizing, angioinvasive fungal infections with associated pulmonary haemorrhage.

Other factors contributing to increased risk include thrombocytopenia, coagulopathy (resulting from malignancy or treatment) and radiation- or chemotherapy-induced lung damage.

**Presentation and Diagnosis.**

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.

In addition to obvious haemoptysis, patients may be hypotensive, tachycardic, centrally cyanotic and clammy, and may experience dyspnoea or chest pain.

**Management and Treatment**

In any bleeding patient, basic investigations should include:

- FBC including platelet count,
- Coagulation studies including prothrombin time (PT-INR) activated partial thromboplastin time (aPTT), D-dimer and fibrinogen level.

**Haemoptysis:**

The airway must be protected

- Intubation is warranted with rapid bleeding, haemodynamic instability, ventilatory impairment, severe dyspnoea or hypoxia.
- The site of bleeding must be identified
- Volume resuscitation, supplemental oxygen, correction of underlying coagulopathies and cough suppressants may be required.
- With unilateral bleeding, lateral decubitus positioning with the affected lung in the dependent position may help to minimize aspiration to the unaffected lung.
- Bronchoscopic treatments include administration of topical thrombin and/or fibrinogen/thrombin, iced saline lavage, endobronchial tamponade, laser photocoagulation and electrocautery.
- Surgical intervention is usually reserved for patients with haemoptysis refractory to other treatments and patients with life-threatening cardiovascular compromise.

***Disseminated Intravascular Coagulation:***

**Description**

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. Continuous bleeding and clotting continues until clotting factors are completely consumed, resulting in uncontrollable bleeding.

**Presentation and Diagnosis**

Acute DIC classically presents with elevation in PT and PTT times, D-dimer, fibrin degradation products, and/or decreased platelet counts.

- Patients with laboratory evidence of DIC may be asymptomatic, but with progression of the underlying condition, can rapidly become symptomatic. With sepsis-induced DIC, symptoms favour bleeding over thrombosis.

Signs and symptoms include:

- Petechiae, ecchymosis, purpura, pallor, bleeding from multiple sites, Haematuria, oliguria, abdominal distention, guaiac-positive stools, dyspnoea, haemoptysis, and tachypnoea.
- With intracranial bleeding, restlessness, confusion, lethargy and altered mental status may be seen.
- Cardiovascular compromise presents as tachycardia with hypotension.

With tumour-initiated DIC, a hypercoagulability state is favoured rather than haemorrhage.

- Overt manifestations include DVT, pulmonary embolus and thrombosis in the central nervous system and abdominal organs.11

**Management and Treatment**

In any bleeding patient, basic investigations should include:

- FBC including platelet count,
- Coagulation studies including prothrombin time (PT-INR) activated partial thromboplastin time (aPTT), D-dimer and fibrinogen level.

**DIC:**

Do not delay definitive treatment (even if invasive), as DIC will not improve until the underlying cause is treated.

- Coagulation and vital organ function must be supported.
- The need for large transfusions of platelets (a reasonable platelet target is 50-75 x $10^9$/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.

At this point, the advice of a haematologist should be sought.

## 2. MALIGNANCY ASSOCIATED HYPERCALCAEMIA (MAH)

**Description**

Malignancy associated hypercalcemia (MAH) is defined as a ***corrected*** serum calcium > 2.65 mmol/L. 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%). 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 hyper-albuminemia 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).

**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.

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 leukaemia/lymphoma). Humoral hypercalcemia 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).Osteolytic bone metastases account for 20% of cases, and other causes (such as ectopic PTH section, vitamin D secreting lymphomas, etc.) account for less than 1%. Many cancer therapies (e.g., antineoplastic agents, vitamin D analogues) can induce or exacerbate hypercalcemia, particularly when used in combination.

**Presentation and Diagnosis**

Mild hypercalcemia may be asymptomatic. Moderate to severe hypercalcemia may be associated with various symptoms:

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

| | Early manifestations | Later manifestations |
|---|---|---|
| Neurological | • weakness/fatigue<br>• memory/concentration difficulty | • drowsiness/confusion<br>• delirium → coma |
| Cardiovascular | • shortened $QT_c$ interval<br>• enhancement of digitalis effects | • ST segment elevation<br>• hypotension<br>• bradyarrhythmias → heart block → cardiac arrest |
| Gastrointestinal | • anorexia<br>• constipation | • nausea<br>• vomiting |
| Genitourinary | • polyuria and nocturia | • 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.

Hypercalcemia 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.

**Management and Treatment**

Antihypercalcemic therapy is an interim measure, and long term resolution depends on prompt antitumour therapy. 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.

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.

First line therapy should include fluid resuscitation with IV normal saline and initiation of intravenous bisphosphonates.

- 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.
- Bisphosphonates are the most efficacious agents for treating MAH.
    - Pamidronate, zoledronate and ibandronate should be considered the drugs of choice.
- Frusemide should be restricted to managing fluid overload and should only be considered after euvolemia and sodium diuresis has been achieved.
- Thiazide diuretics stimulate renal calcium reabsorption and should not be used.
- 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.
- Sedatives, hypnotics and analgesics that impair cognitive function should be withheld, as they may worsen the neurologic effects of hypercalcemia.
- Hypophosphatemia frequently occurs with hypercalcemia, and phosphorous should be replaced orally or via NG tube as neutral phosphate. Intravenous phosphorous replacement is contraindicated.

## 3. BRAIN METASTASES: INCREASED INTRACRANIAL PRESSURE, AND SEIZURES

### Description

Brain metastases are far more common than primary brain malignancy, and occur in approximately 10-30% of all adult patients with cancer. Most common tumours to metastasize to the brain include lung cancer, breast cancer, and melanoma, collectively accounting for approximately 70-90% of all cases of brain metastases in adult patients. Other common primary tumours include colorectal cancer and renal cell carcinoma. Brain metastases can lead to neurologic deficits and seizures, and become an oncologic emergency in cases of increased intracranial pressure and status epilepticus.

### 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.

Patients with increased intracranial pressure classically present with headache, nausea, and vomiting, all of which may be most severe in the morning and when supine. In addition, papilledema detected on physical examination almost always indicates increased intracranial pressure.

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 haemorrhage. Magnetic resonance imaging (MRI) is recommended in the case of brain metastases and 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.

### Management and Treatment

Raised intracranial pressure:

- 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, the optimal dose and schedule for dexamethasone isn't universally agreed upon.
- 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 most common dose used is 8-16 mg in single or two divided doses.
- In the most severe cases, mannitol in addition to intubation and controlled hyperventilation may be used to decrease cerebral oedema, but this is reserved for critical cases in patients with rapidly declining clinical states.

Status epilepticus:

- 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 phenytoin or phenobarbital.
- Anticonvulsants are associated with significant adverse effects however, and are therefore not routinely recommended as prophylactic therapy in patients with brain metastases without a history of seizures.

For select patients with a good performance status and well-controlled systemic disease, more definitive treatments of brain metastases may include surgery orstereotactic radiosurgery, with or without whole brain radiotherapy

In patients with a poor performance status, poorly controlled systemic disease, or a large volume of brain metastases, whole brain radiotherapy or best supportive care are usually appropriate.

## 4. MALIGNANT SPINAL CORD/CAUDA EQUINA COMPRESSION

**Description**

- Common neurological complication ~ 5% of adult patients with cancer
    - Breast, prostate, lung cancer most common primary sites
    - Thoracic > lumbosacral > cervical location, but multiple levels common
- Usually in setting of widespread metastatic disease
- Invasion of epidural space by bony metastatic deposit most common (~90%).
- True oncologic emergency - requires rapid diagnosis and treatment.
- If untreated, can lead to progressive pain, sensory loss, incontinence, and irreversible paralysis
- Early diagnosis and treatment essential to preserve neurologic function and quality of life
- Most important determinant of outcome is pre-treatment motor function

**Presentation and Diagnosis**

- Back pain the earliest and most common symptom (90%)
    - Often crescendo pain, not responding to analgesia
    - May be localized to spine, or radicular pain due to nerve root compression
    - High index of suspicion in all patients with a history of cancer and new-onset back/neck pain
- Other symptoms include motor weakness and sensory impairment, bladder/bowel dysfunction (late)
- Neurological impairment may be subtle, e.g. ataxia (proprioceptive) without obvious motor/sensory deficit
- MRI the preferred imaging study, whole spine should be imaged (multilevel involvement common)
- A CT scan can be used if MRI is contraindicated or not available, but lacks sensitivity
- A plain radiograph is insufficient to exclude the diagnosis

**Management and Treatment**

- Goals of treatment
    - decrease pain, preserve neurological function
- Initial management
    - Analgesia – opioids required in many patients
    - Corticosteroids – 16mg daily (8mg mane/midi), as soon as diagnosis strongly suspected/confirmed
    - Urgent referral to neurosurgeon/oncologist for definitive management
    - Bed rest not necessary in most cases
- Definitive management
    - Depends on several factors, including life expectancy, tumour type, extent of disease, prior treatment, and degree of motor impairment
    - Most commonly radiotherapy +/- surgery

- A neurosurgical opinion should generally be sought - decompressive surgery followed by postoperative radiotherapy has been shown to be superior to radiotherapy alone for select patients
- In patients who are not candidates for surgery, radiotherapy alone is the recommended treatment for most patients. Radiotherapy will typically be delivered daily over 1-2 weeks
- Chemotherapy alone is occasionally used to treat malignant spinal cord/cauda equine compression from particularly chemosensitive histologies

## 5. MALIGNANT AIRWAY OBSTRUCTION

### Description

Airway obstruction in patients with cancer is most commonly caused by direct extension from an adjacent tumour, or a primary tumour of the head and neck.[48] Airway obstruction secondary to metastatic malignancies has also been reported. Airway obstruction may also be caused by tumour encroachment and by tumour-associated airway oedema or haemorrhage.

### Presentation and Diagnosis

The most common presenting symptoms of malignant airway obstruction are nonspecific and include dyspnoea, haemoptysis, wheezing, hoarseness, difficulty clearing secretions, and cough. 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. 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. A CT scan of the neck and chest is the most effective initial study to assess the location and extent of airway obstruction.

### 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.

- Rigid bronchoscopy provides a means of immediate airway control and initial stabilization in patients with acute and malignant airway obstructions.
- Lasers, in combination with rigid bronchoscopy, can also be used to urgently open the airway in patients with malignant intrinsic airway obstruction.
- 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.
- Short course, multi-fractionated external-beam radiotherapy at a dose of 20 Gy/5 fractions is often used for the palliation of intrathoracic symptoms, and is preferred over single-fraction treatment.

## 6. 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. In addition, an increasing number of cases of SVCO in cancer patients are due to thrombosis of indwelling central venous catheter devices.

### 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. Symptoms of SVCO more typically present insidiously over a period of day to weeks.

- Worrisome signs include stridor, which may indicate laryngeal oedema, and headache or confusion, which may indicate cerebral oedema.
- Cough, dyspnoea, and orthopnoea are also common symptoms that can often mimic congestive heart failure or pericardial disease.
- 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 oedema, intracranial thrombosis or bleeding, and death.

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 – this will aid in the decision of whether a definitive curative course of therapy versus palliative treatment is most appropriate.

- 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.
- Venography is considered when an intervention such as stent placement or surgery is planned.

### Management and Treatment

Management is guided by the severity of the symptoms and the underlying malignancy, as well as by the anticipated response to the treatment.

- 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.
- Stent insertion can provide rapid relief of associated symptoms, particularly for patients who are unlikely 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
- Radiotherapy is often the 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 relatively insensitive to chemotherapy, such as non-small cell lung cancer.
- 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

## 7. SIADH (syndrome of inappropriate antidiuretic hormone)

SIADH results from inappropriate production and secretion of antidiuretic hormone (ADH, also known as arginine vasopressin) which leads to water retention/intoxication, hyponatremia and hypo-osmolality.

SIADH can be caused by malignant and non-malignant conditions. Small cell lung cancer is the malignancy most often associated with SIADH. Drugs like Opioid analgesics, tricyclic antidepressants, selective serotonin reuptake inhibitors, NSAIDs, thiazide diuretics, barbiturates, aesthetic agents and chemotherapy drugs can cause SIADH. Other causes include CNS disorders, pulmonary diseases, HIV and hormonal disorders like hypopituitarism and hypothyroidism.

Hyponatremia alone is not sufficient to diagnose SIADH. Three laboratory tests provide important initial information in differential diagnosis of hyponatremia

- Serum osmolality
- Urine osmolality
- Urine sodium, potassium, and chloride concentrations

SIADH should be suspected in any patient with hyponatremia, hypo-osmolality, and urine osmolality above 100 mosmol/kg. In SIADH, urine sodium concentration is usually above 40 meq/L, serum potassium concentration is normal, there is no acid-base disturbance, and serum uric acid concentration is frequently low and other hormonal levels normal

**Symptoms**

- Patients with chronic hyponatremia are frequently asymptomatic or may have subclinical impairments in mentation and gait.
- **Mild to moderate symptoms** –include headache, nausea, vomiting, fatigue, gait disturbances, and confusion. In patients with acute hyponatremia, such symptoms may evolve without warning to seizures, respiratory arrest, and herniation.
- **Severe symptoms** – Severe symptoms of hyponatremia include seizures, obtundation, coma, and respiratory arrest.

**Treatment**

Three components to the treatment of hyponatremia in SIADH:

- Treatment of the underlying disease, if possible
- Initial therapy to raise serum sodium
- Prolonged therapy in patients with persistent SIADH

**Patient risk stratification** according to duration, severity of hyponatremia, and whether or not patients are symptomatic

Fluid restriction is mainstay of therapy in most patients with SIADH; with suggested goal intake of less than 800 mL/day .The associated negative water balance initially raises the serum sodium concentration toward normal and, with maintenance therapy in chronic SIADH, prevents further reduction in serum sodium.

The choice of therapy in patients with hyponatremia due to SIADH varies with the severity of hyponatremia and symptoms. The maximum rate of correction of chronic hyponatremia should be less than 10 meq/L at 24 hours and less than 18 meq/L at 48 hours. Overly rapid correction of severe can lead to a severe and sometimes irreversible neurologic disorder -osmotic

demyelination syndrome .Serum sodium concentration should be checked at two to three hours initially and then every three to four hours until the patient is stable.

1. Severe symptomatic hyponatremia presenting with seizures or other severe neurologic abnormalities, or symptomatic hyponatremia in patients with intracerebral diseases requires urgent intervention with hypertonic saline to prevent potentially fatal cerebral oedema. 100 mL of 3 %saline given as an intravenous bolus, If neurologic symptoms persist or worsen, 100 mL bolus of 3 percent saline can be repeated one or two more times at ten-minute intervals. Once symptoms resolve, careful monitoring with measurement of serum sodium every two to three hours is required.
2. Patients with less severe neurologic manifestations and serum sodium concentration below 120 meq/L that develops over more than 48 hours, lesser degree of hyponatremia that develops over less than 48 hours, or chronic moderate hyponatremia (serum sodium 120 to 129 meq/L). Initial therapy in these patients depends in part upon the severity of symptoms.
    - For patients with confusion and lethargy, initial administration of hypertonic saline therapy to raise the serum sodium .Once stabilised maintenance therapy included fluid restriction and oral tablets may be required.
    - For patients who have only mild symptoms (e.g. forgetfulness, gait disturbance), we suggest initial therapy with fluid restriction and oral salt tablets rather than hypertonic saline.

3. Patients with chronic moderate hyponatremia (serum sodium 120 to 129 meq/L) are usually asymptomatic, initiate therapy with fluid restriction.

## 8. TUMOUR LYSIS SYNDROME

Tumour Lysis Syndrome (TLS) is a life-threatening complication that arises when the rapid lysis of tumour cells leads to the release of excessive quantities of cellular contents into the systemic circulation resulting in a metabolic disturbance characterised by:-

- Hyperuricemia
- Hyperkalemia
- Hyperphosphatemia
- Hypocalcemia

This can lead to acute oliguric renal failure, seizures, cardiac arrhythmias and death. TLS can occur spontaneously in patients with tumours of a high proliferative rate, but is more commonly seen following initiation of chemotherapy

**Classification TLS:**

**Laboratory TLS (LTLS)** - patients that have laboratory evidence of TLS

**Clinical TLS (CTLS)**- patients experiencing life-threatening abnormalities requiring specific intervention

Cairo and Bishop Definition

**Laboratory TLS**

- the presence of greater than or equal to 2 of the below metabolic abnormalities at presentation **OR**
- change of 25% from baseline within 3 days prior to or 7 days post commencement of therapy:

| | |
|---|---|
| Uric Acid | greater than or equal to 0.476 mmol/L or 25% increase from baseline |
| Potassium | greater than or equal to 6.0 mmol/L or 25% increase from baseline |
| Phosphorus | greater than or equal to 1.45 mmol/L or 25% increase from baseline |
| Calcium | less than or equal to 1.75 mmol/L or 25% decrease from baseline |

**Clinical TLS**

Laboratory evidence of TLS plus 1 or more of:

- Cr > 1.5 x ULN
- Cardiac arrhythmia / sudden death
- Seizures

**Principles of Management of Acute Tumour Lysis Syndrome**

- Identify patients at risk, initiate preventative measures prior to chemotherapy, and monitor for clinical and laboratory features of TLS.
- Detect features of TLS promptly and initiate supportive therapy early.

**Risk factors for developing tumour lysis syndrome include:**

- 1st cycle of chemotherapy
- high tumour cell proliferation rate
- bulky disease (greater than 10 cm)
- increased WCC (greater than 25 x109/L)
- increased LDH (greater than 2 xULN)
- chemosensitive malignancies

**Malignancies associated with a higher risk of TLS include:**

- Burkitt's lymphoma
- Acute lymphoblastic leukaemaia (ALL)
- Lymphoblastic lymphoma
- Non Hodgkins lymphoma (eg: Diffuse large-cell lymphoma)
- Hodgkin’s Disease
- chronic myeloid leukaemia (CML)
- multiple myeloma (multi-agent systemic chemotherapy)
- extensive germ cell tumour
- extensive small cell carcinoma
- solid tumours with high proliferative rate and rapid response to therapy

**Additional conditions that may predispose patients to developing TLS:**

- renal insufficiency or renal failure
- dehydration
- decreased urinary flow

- pre-existing uraemia or hyperuricaemia
- pre-existing hyperphosphaemtemia

**Prevention and Management of TLS**

1. Aggressive hydration and diuresis
2. Adminstration of hypouricaemic agents
3. Correction of metabolic abnormalities

- IV hydration with **3 L/m$^2$/day** of IV fluid
- Maintain a urine output of **≥ 100 mL/m$^2$/hour** and a urine specific gravity of less than or equal to 1.010 g/mL
- Diuretics may be used to maintain urine output and prevent fluid overload (used only if there is no evidence of obstructive uropathy or hypovolaemia)

Urinary alkalinisation with sodium bicarbonate is NOT currently recommended (risk of precipitation of calcium phosphate)

If oliguria, the measurement of urine specific gravity or osmolality may be useful in defining the hydration status

**Hypouricaemic Agents**
Should be initiated 12-24 hours before anti-cancer therapy

**Allopurinol:**

Reduce dose in renal failure

Allopurinol is not thought to be necessary after initial treatment with rasburicase, though there is no evidence to support or refute this opinion

**Rasburicase:**

Treatment of choice for all patients with TLS-associated hyperuricemia

Initial prophylaxis in patients at high risk of TLS.

## Monitoring

Monitor laboratory and clinical TLS parameters for at least 72 hours after initiation of cytotoxic chemotherapy:

- Strict monitoring of weight, blood pressure,fluid input and urine output
- Serum chemistry (creatinine, sodium, potassium, calcium, phosphate, uric acid)
- Daily LDH
- Urinalysis

### Guide for Management of Electrolyte Abnormalities

| Abnormality | Management Recommendations |
|---|---|
| Hyperphosphataemia<br>Moderate>2.1mmol/l | Adminster phosphate binders (e.g., aluminium hydroxide) for up |

| | |
|---|---|
| Severe>3.33mmol/l | to 2 days (longer treatment carries the risk of aluminium toxicity). Calcium infusions should be withheld.<br><br>Peritoneal dialysis, haemodialysis, or continuous venovenous hemofiltration (CVVH) |
| Hypocalcemia<br><br>Asymptomatic<1.75mmol/l<br><br>Symptomatic (paraesthesia,muscle cramps,tetany,Long QT on ECG) | <br><br>Treatment is not recommended (risk of precipitating metastatic calcifications especially with hyperphosphatemia)<br><br>IV calcium gluconate<br>If phosphate is also high, a renal consult should be considered. |
| Hyperkalaemia<br><br>Asymptomatic<br><br>Symptomatic | ECG –cardiotoxicity<br><br>oral or rectal sodium polystyrene sulphonate<br><br>insulin and dextrose infusion<br>Calcium gluconate<br>Haemolysis |

## 9. HYPERVISCOSITY SYNDROME

### Description

Hyperviscosity syndrome (HVS) refers to the clinical sequelae of increased blood viscosity. Increased serum viscosity usually results from increased circulating serum immunoglobulins and can be seen in such diseases as Waldenström macroglobulinemia and multiple myeloma. HVS can also result from increased cellular blood components (typically white or red blood cells) in hyperproliferative states such as the leukemias, polycythemia, and the myeloproliferative disorders.

### Presentation and Diagnosis

The clinical presentation in HVS consists principally of the triad of mucosal bleeding, visual changes, and neurologic symptoms. However, this triad of classic symptoms is not always present in all patients. Bleeding typically arises from mucosal sites, including epistaxis, bleeding gums, and gastrointestinal bleeding. Visual disturbances may include diplopia, retinal vein thrombosis, papilloedema and retinal haemorrhage. Neurologic manifestations often include headache, dizziness, vertigo, ataxia, encephalopathy, hearing impairment, seizures, and altered mental status. 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.

The diagnosis of HVS is confirmed by measurement of elevated serum viscosity in a patient with characteristic clinical manifestations of HVS. The normal value for serum viscosity is 1.8 centipoise (CP), but hyperviscosity symptoms are rarely present unless the viscosity is >4 CP.

### Management and Treatment

The hyperviscosity syndrome is a clinical emergency resulting in decreased flow and impaired microcirculation of the central nervous system. Although the diagnosis is established by measuring serum viscosity, the clinician should make the decision to initiate treatment with plasmapheresis on the basis of the patient's symptoms and physical findings rather than on the magnitude of the viscosity measurement.

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. 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.

Long-term management of patients with hyperviscosity syndrome is directed at controlling the underlying disease.

# GLOSSARY OF TERMS

| Acronym | Description |
|---|---|
| ADH | antidiuretic hormone |
| AHS | Alberta Health Services |
| AKI | acute kidney injury |
| ANC | absolute neutrophil count |
| Ca2+ | 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 *Staphylococcus Aureus* |
| Nd:YAG | neodymium-yttrium-aluminium-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 |

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