# Emergencies in Hematology and Oncology

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## CME Activity

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**Statement of Need:** General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. *Mayo Clinic Proceedings* aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

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**Learning Objectives:** On completion of this article, you should be able to (1) recognize both common and uncommon hematologic and oncological emergencies in patients with cancer, (2) identify which patients need emergent or urgent initiation of therapy and admission to the hospital for an optimal outcome, and (3) promptly initiate the appropriate therapy for life-threatening complications of both the cancer itself and the therapy directed against the cancer.

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## Abstract

The development of medical emergencies related to the underlying disease or as a result of complications of therapy are common in patients with hematologic or solid tumors. These oncological emergencies can occur as an initial presentation or in a patient with an established diagnosis and are encountered in all medical care settings, ranging from primary care to the emergency department and various subspecialty environments. Therefore, it is critically important that all physicians have a working knowledge of the potential oncological emergencies that may present in their practice and how to provide the most effective care without delay. This article reviews the most common oncological emergencies and provides practical guidance for initial management of these patients.

 ■ Mayo Clin Proc. 2017;92(4):609-641

Cancer is expected to be diagnosed in more than 1.6 million people in the United States in 2017. A small percentage of these patients will experience an emergent cancer-related complication at some point during the disease course. For some patients, an emergent complication is the first manifestation of the cancer.[1] Given the large number of patients with active cancer, many practicing physicians can expect to encounter patients with a cancer-related emergency. It is therefore imperative that practitioners, especially primary and emergency care physicians, are able to rapidly recognize and effectively manage patients with these complications. Emergencies in hematology

and oncology can be broadly classified as conditions resulting from the cancer itself and complications related to therapy directed against the malignant disease, although there can be some overlap between the 2 categories. The emergencies can also be classified according to organ systems, which is the approach taken in this review.

## METABOLIC EMERGENCIES

### Hypercalcemia of Malignancy

Hypercalcemia is common in patients with advanced cancer and has been reported in up to 30% of patients with cancer.[2] The incidence varies greatly among cancer types, and hypercalcemia is most commonly associated with multiple myeloma, non–small cell lung cancer (especially squamous cell cancer), renal cell carcinoma, breast cancer, non-Hodgkin lymphoma, and leukemia but can also be seen in multiple other malignant disorders.[3] The presence of hypercalcemia in a patient with cancer is an adverse prognostic factor predicting a shorter survival, but effective therapy, both for the hypercalcemia and the underlying cancer, may improve outcomes.[4-7]

**Pathophysiology.** The pathophysiology of hypercalcemia of malignancy can be divided into 3 major categories.[8] The first category, often called humoral hypercalcemia of malignancy, usually results from tumor production of parathyroid hormone–related peptide (PTHrP) and less commonly intact parathyroid hormone (PTH). It is the most common underlying cause of hypercalcemia of malignancy. The second category is hypercalcemia from bone destruction and dissolution (osteolysis) from extensive bone metastases. The third and least common category is excess production of vitamin D analogues by the malignant cells. Humoral hypercalcemia of malignancy accounts for up to 80% of hypercalcemia that occurs in patients with cancer and is the dominant cause in patients with solid tumors.[2,9] Structurally, PTHrP is closely related to PTH and exerts many of the functions of PTH itself. It binds to receptors on osteoblasts and stimulates their activity through receptor activator of nuclear factor κB ligand (RANKL) signaling. This process in turn stimulates the osteoclasts, increasing their activation and proliferation and subsequently releases calcium into the circulation.[8,10,11] The presence of elevated PTHrP in humoral hypercalcemia of malignancy portends poorer prognosis and decreased response to therapy with bisphosphonates.[12-14] Osteolysis as a cause of hypercalcemia is commonly seen in patients with breast cancer, lung cancer, and multiple myeloma. Several cytokines have been implicated in the pathogenesis of cancer-induced osteolysis, including tumor necrosis factor, macrophage inflammatory protein 1a, and lymphotoxin.[15,16] Local production of PTHrP may also result in osteolysis, which is in part mediated through the RANKL pathway.[17,18] Extrarenal production of 1,25-dihydroxyvitamin D (calcitriol) can occur in patients with both Hodgkin and non-Hodgkin lymphomas as well as nonmalignant granulomatous diseases such as sarcoidosis.[19,20] Very rarely, ectopic production of PTH by tumors causes hypercalcemia.[21] Hypercalcemia of malignancy can also be exacerbated by factors unrelated to the malignant disorder itself such as the intake of calcium, vitamin D, lithium, and thiazides. Thiazides are thought to reduce urinary calcium excretion as a result of increased passive calcium reabsorption at the proximal tubule and increased distal reabsorption at a thiazide sensitive site.

**Clinical Presentation and Diagnosis.** Hypercalcemia is caused by either primary hyperparathyroidism or malignant disease more than 90% of the time. Therefore, it is important to distinguish between these 2 entities early on. In hypercalcemia associated with cancer, there are frequently overt signs of malignant disease at presentation. Hypercalcemia can cause a multitude of nonspecific symptoms. Lethargy, confusion, anorexia, nausea, constipation, polyuria, and polydipsia are all common symptoms of hypercalcemia, and the severity may correlate with the degree of hypercalcemia and the rapidity of onset.[22,23] Severe hypercalcemia, especially of rapid onset, may cause cardiac dysrhythmias such as bradycardia, shortening of the QT interval, and even cardiac arrest.[24] The physical examination is generally not helpful in making the diagnosis but can reveal signs of volume depletion and impaired cognitive function as well as signs of the underlying cancer such as enlarged lymph nodes.


Mayo Clin Proc. ■ April 2017;92(4):609-641 ■ http://dx.doi.org/10.1016/j.mayocp.2017.02.008
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**TABLE 1. Treatment of Hypercalcemia**

| Intervention | Dosage | Comments |
|---|---|---|
| Saline | 250-500 mL/h IV until euvolemic and 100-150 mL/h IV after volume repletion is achieved. Can start by giving an 1- to 2-L initial bolus over 1 h if hypovolemic | The rate of infusion should be adjusted for the cardiovascular status of the patient |
| Pamidronate | 60-90 mg IV over 2-4 h | Use with caution in renal insufficiency. Onset of action may take days |
| Zoledronic acid | 4 mg IV over 15 min | Use with caution in renal insufficiency. Onset of action may take days |
| Calcitonin | 4-8 IU/kg SC or IV every 12 h | Rapid onset of action but short-lived |
| Glucocorticoids | Prednisone, 60 mg/d PO; hydrocortisone, 100 mg every 6 h IV | Useful for hypercalcemia from calcitriol overproduction and in multiple myeloma |
| Denosumab | 120 mg SC weekly for 4 wk, then every 4 wk | Safe in renal insufficiency but doses should be reduced. Can cause severe hypocalcemia |
| Furosemide | 20-40 mg IV | Only for patients with volume overload after volume expansion |

IV = intravenously; PO = orally; SC = subcutaneously.

The diagnosis of hypercalcemia is confirmed by measuring the serum calcium level. Ionized calcium measurement is the preferred method of diagnosis, if available. If total serum calcium is measured, a correction needs to be made for the albumin level. The corrected calcium level is calculated as follows: corrected calcium = measured total calcium + [0.8 × (4.0 − albumin)].

Intact PTH is usually low in hypercalcemia of malignancy and can be helpful as a diagnostic tool, but the results may not be available immediately. An elevated PTH level in a patient with known malignant disease suggests either a coexisting hyperparathyroidism or a PTH-producing tumor. Measurements of PTHrP are generally not needed but may help elucidate the etiology of the hypercalcemia, and elevated levels may predict response to bisphosphonate therapy and predict inferior survival.[12-14] One study reported less response to bisphosphonates and higher risk of recurrent hypercalcemia in patients with PTHrP levels greater than 12 pmol/L.[25] A low serum chloride level (<100 mEq/L [to convert to mmol/L, multiply by 1.0]) can point to cancer as the underlying cause.[26] All patients with severe hypercalcemia should undergo electrocardiography.

**Treatment.** Untreated, severe hypercalcemia is a life-threatening entity that calls for immediate intervention for optimal results in patients who are candidates for active therapy. Physicians should not delay starting therapy while awaiting laboratory results such as PTHrP level. Not all patients with hypercalcemia need urgent treatment, and many patients with mild hypercalcemia can be managed as outpatients. Patients with more severe and symptomatic hypercalcemia are usually hospitalized for inpatient therapy. In some cases of advanced cancer, specific therapy may not be recommended if the underlying malignant disease is otherwise untreatable.[6,27] The patient's goals and wishes should always be considered before instituting therapy. Best supportive care at home, often with the help of hospice care professionals, may be appropriate for patients who have no effective treatment options remaining for their cancer or who do not wish to receive any further therapy.

The following recommendations apply to patients with severe hypercalcemia (calcium level >14 mg/dL [> 3.5 mmol/L]) and/or very symptomatic hypercalcemia. Table 1 lists the treatment options for hypercalcemia. The first step in the management is the administration of intravenous (IV) fluids because patients are often profoundly hypovolemic, often in the order of 5 to 10 L. Volume expansion will increase the renal clearance of calcium and lower calcium levels. Normal saline (0.9% sodium chloride) is the preferred IV fluid. Patients may require large volumes of normal saline, and 1000 to 2000 mL should be given in the first hour of fluid resuscitation. Larger volumes may be needed initially in hypotensive patients. After the initial bolus

of normal saline, an IV infusion of 250 to 500 mL/h can be used until urine output and euvolemia are established.

Calcitonin can lower calcium levels by inhibiting osteoclasts and can enhance urinary excretion of calcium.[28] The onset of action of calcitonin is quick, but tachyphylaxis develops within days of use.[29,30] It is therefore of most use when a prompt reduction in calcium levels is required. Calcitonin is given as a subcutaneous injection, and no dosage adjustment is needed in patients with renal insufficiency.[31] The use of loop diuretics is strongly discouraged because they may exacerbate the hypovolemia and therefore impair calcium excretion.[32] Loop diuretics should be reserved only for patients with clinical evidence of volume overload. Bisphosphonates are the mainstay of the treatment and are able to control the hypercalcemia in most patients.[33-36] Bisphosphonates block osteoclastic bone resorption, but the onset of action is slow and it may take 2 to 3 days to see a full effect. The most commonly used bisphosphonates in the United States are pamidronate (60-90 mg IV over 2-4 hours) and zoledronic acid (4 mg IV over 15 minutes), but zoledronic acid is often preferred because it can be given as a short IV infusion and may be more effective than pamidronate.[33] Ibandronate is also effective but infrequently used in the United States.[37,38] Bisphosphonates are potentially nephrotoxic and should be used with caution in patients with renal insufficiency.

Glucocorticoids are useful in patients whose hypercalcemia is driven by overproduction of calcitriol because they inhibit the conversion of calcidiol to calcitriol.[30,39] Commonly used glucocorticoids include prednisone (60 mg orally daily) and hydrocortisone (100 mg IV every 6 hours). Gallium nitrate and mithramycin (plicamycin) have been used in the past but are not readily available now and have been replaced by safer agents.[40,41] Denosumab, a humanized monoclonal antibody directed against the RANKL that inhibits osteoclast activation and function, was recently approved for use in hypercalcemia of malignancy. Denosumab has been used successfully in hypercalcemia refractory to bisphosphonate therapy.[42,43] In a single-arm trial in patients who remained hypercalcemic after bisphosphonate therapy, denosumab lowered the calcium levels in most patients and had a prolonged duration of response.[44] Denosumab was given as 120 mg subcutaneously weekly for 4 weeks and then every 4 weeks thereafter. It is well tolerated but may result in symptomatic hypocalcemia.[43,44] Denosumab can safely be given to patients with renal insufficiency, but the risk of hypocalcemia may be increased.[45] The dose should be reduced in patients with renal insufficiency, but the optimal dose has not been established. A fixed single dose of 60 mg subcutaneously has resulted in symptomatic hypocalcemia, and a weight-based dose of 0.3 mg/kg may be a safer alternative followed by careful monitoring and repeated administration in a week if needed.[45] The calcimimetic cinacalcet has been reported to lower serum calcium levels in patients with hypercalcemia secondary to PTH production of parathyroid carcinoma but is not recommended in hypercalcemia of other etiologies.[46] Hemodialysis can be used in refractory cases and situations in which other methods cannot be used safely but should be considered as a last-resort therapy.[47,48] Effective systemic therapy or radiotherapy for the underlying disease, if available, can further help decrease the serum calcium levels.

## Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a constellation of metabolic derangements resulting from the death of neoplastic cells which then release their intracellular contents into the circulation.[49] It is most commonly seen in patients with very aggressive hematologic cancers such as high-grade lymphomas and acute leukemias.[50,51] Tumor lysis syndrome is occasionally seen in patients with aggressive solid tumors such as small cell carcinoma of the lung.[52] It usually occurs after effective therapy has begun but can also occur spontaneously.[53] It is most commonly seen after the initiation of cytotoxic chemotherapy but can also result from glucocorticoid therapy for lymphoma, endocrine therapy for advanced breast cancer, various targeted agents, and radiotherapy for radiosensitive malignant diseases.[54]

**Pathophysiology.** Tumor lysis syndrome is caused by massive release of intracellular contents into the bloodstream at the time of the death of neoplastic cells.[50,55] The catabolism


Mayo Clin Proc. ■ April 2017;92(4):609-641 ■ http://dx.doi.org/10.1016/j.mayocp.2017.02.008
www.mayoclinicproceedings.org

of nucleic acids results in hyperuricemia. High concentrations of uric acid will lead to crystallization within renal tubules and tubular obstruction resulting in acute kidney injury. The renal failure is further exacerbated by hypovolemia leading to acute tubular necrosis. Elevated levels of uric acid may also lead to kidney injury independently of uric acid crystal formation, possibly secondary to alteration in the intrarenal hemodynamics.[56] The release of organic and inorganic phosphates from the neoplastic cells leads to hyperphosphatemia, which in turn leads to hypocalcemia and precipitation of calcium phosphate and nephrocalcinosis. Hyperkalemia is frequently the first manifestation of TLS, may occur within a few hours after therapy is started, and can result in life-threatening cardiac arrhythmias.[57]

**Clinical Presentation and Diagnosis.** Patients with TLS can present with symptoms (clinically evident TLS) or with abnormal laboratory test results in the absence of symptoms (laboratory TLS).[58] The presenting symptoms of TLS are nonspecific, and a high index of suspicion is needed for a timely diagnosis. Decreased urine output followed by symptoms of uremia and volume overload may occur. Seizures, arrhythmias, and even sudden death are known presentations of TLS.

Typical laboratory findings include elevated uric acid, phosphorus, potassium, and lactate dehydrogenase levels as well as low calcium concentrations. The diagnostic criteria and definition of TLS have evolved, but the most commonly used definition is the that of Cairo and Bishop[59] (Table 2).

**TABLE 2. Cairo-Bishop Classification of Laboratory and Clinical Tumor Lysis Syndrome**

| |
|---|
| Laboratory tumor lysis syndrome |
| Uric acid ≥8 mg/dL (≥476 μmol/L) or 25% increase from baseline |
| Potassium ≥6.0 mEq/L (≥6.0 mmol/L) or 25% increase from baseline |
| Phosphorus ≥4.5 mg/dL (≥1.45 mmol/L) or 25% increase from baseline |
| Calcium ≤7 mg/dL (≤1.75 mmol/L) or 25% decrease from baseline |
| Clinical tumor lysis syndrome |
| Presence of laboratory tumor lysis syndrome and one or more of the following criteria |
| Creatinine ≥1.5 times the upper limit of normal |
| Cardiac arrhythmia |
| Seizure |
| Sudden death |

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**Risk Stratification.** The risk factors for development of TLS are well known.[51] The risk is determined by the type of cancer as well as the treatment given and underlying conditions. Tumor-specific risk factors include high tumor burden, high tumor grade with rapid cell turnover, and treatment-sensitive tumor. Age, preexisting renal impairment, and concomitant use of drugs known to increase uric acid are patient-specific risk factors. Aspirin, alcohol, thiazide diuretics, and caffeine are known to increase uric acid levels. The risk can be categorized on the basis of the characteristics of the underlying malignant disease and patient characteristics (Table 3).[53]

**Prevention and Treatment.** Tumor lysis syndrome can often be prevented, and it is therefore of utmost importance to identify patients at risk and initiate prophylactic therapy because TLS is associated with increased mortality and morbidity as well as increased cost.[51,60-63] Adequate hydration and the appropriate use of uric acid—lowering (uricosuric) drugs can effectively reduce uric acid levels and reduce the risk of renal injury. The choice of uricosuric drugs depends on the risk of TLS for the given patient (Tables 3 and 4). The most commonly used drugs are allopurinol and rasburicase. Allopurinol is an inhibitor of xanthine oxidase and reduces the production of uric acid by decreasing the rate of conversion of hypoxanthine to xanthine and xanthine to uric acid. Both xanthine and hypoxanthine are more water soluble than uric acid. Allopurinol does not facilitate the breakdown of the uric acid that has already been produced. Allopurinol is an appropriate uricosuric drug in patients with low or intermediate risk of TLS. The prophylactic dose of allopurinol is 200 to 400 mg/m$^2$ daily in 1 to 3 divided doses, up to a maximum of 800 mg daily.[51] Febuxostat is a selective inhibitor of xanthine oxidase that is approved for treatment of gout. It has fewer drug-drug interactions than allopurinol, and dose adjustment is not needed in patients with mild to moderate renal impairment.[64] Febuxostat has been compared to allopurinol

**TABLE 3. Risk Stratification of Tumor Lysis Syndrome and Recommendations for Prophylaxis[a,b]**

| Risk category | Malignant disease | Prophylaxis |
|---|---|---|
| Low-risk disease | Solid tumor[c]<br>Multiple myeloma<br>CML<br>CLL[d]<br>Indolent NHL<br>Hodgkin lymphoma<br>AML (WBC <25,000/μL and LDH <2 × ULN) | Monitoring (daily laboratory tests)<br>Intravenous hydration (3 L/m$^2$ daily)<br>Consider allopurinol |
| Intermediate-risk disease | AML (WBC 25,000-100,000/μL)<br>AML (WBC <25,000/μL and LDH ≥2 × ULN)<br>Intermediate-grade NHL (LDH ≥2 × ULN)<br>ALL (WBC <100,000/μL and LDH <2 × ULN)<br>Burkitt lymphoma (LDH <2 × ULN)<br>Lymphoblastic NHL (LDH <2 × ULN) | Monitoring (laboratory tests every 8-12 h)<br>Intravenous hydration (3 L/m$^2$ daily)<br>Allopurinol for up to 7 d |
| High-risk disease | ALL (WBC ≥100,000/μL and/or LDH ≥2 × ULN)<br>Burkitt lymphoma (stages III/IV and/or LDH ≥2 × ULN)<br>Lymphoblastic NHL (stages III/IV and/or LDH ≥2 × ULN)<br>IRD with renal dysfunction and/or renal involvement<br>IRD with elevated uric acid, potassium, and/or phosphate | Monitoring (laboratory tests every 6-8 h)<br>Intravenous hydration (3 L/m$^2$ daily)<br>Rasburicase (consider 3 mg fixed dose) |

[a]ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphoid leukemia; CML = chronic myeloid leukemia; IRD = intermediate-risk disease; LDH = lactate dehydrogenase; NHL = non-Hodgkin lymphoma; ULN = upper limit of normal; WBC = white blood cell count.

[b]SI conversion factors: To convert WBC to $\times 10^9$/L, multiply by 0.001.

[c]Rare solid tumors such as small cell carcinoma, germ cell tumors, or others with bulky or advanced disease can be classified as IRD.

[d]CLL treated with fludarabine and rituximab and/or those with a high WBC (≥50 × $10^9$/L) can be classified as IRD.



for prevention of TLS. It was found to be more effective in lowering uric acid levels, but it is uncertain if it reduces clinically important TLS, at least when compared with high doses of allopurinol, and its role in management of TLS needs to be determined with further trials.[65] The dose of febuxostat is 120 mg daily. Rasburicase is a recombinant form of urate oxidase and metabolizes uric acid to allantoin, which is much more soluble than uric acid.[66] The use of rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Unlike allopurinol, rasburicase also lowers already formed uric acid. Rasburicase is generally reserved as prophylaxis for patients at high risk of TLS or patients already experiencing TLS. Rasburicase is effective as TLS prophylaxis in both adults and children.[67-71] Despite the efficacy of rasburicase in lowering uric acid levels and preventing TLS, it has not been proven to be superior to allopurinol in preventing clinical TLS and related complications.[72-74] Despite the lack of data on hard clinical end points, treatment with rasburicase is recommended in all patients with high risk of TLS. The recommended dose of rasburicase is 0.2 mg/kg once daily for up to 5 to 7 days, but lower doses and shorter duration of therapy are commonly used. A single fixed dose of 3 mg has been studied and seems to be very effective in preventing TLS, and the dose can be repeated later if needed.[75-78] Recently published guidelines from the British Committee for Standards in Haematology have endorsed the use of a single fixed 3-mg dose of rasburicase as adequate prophylactic therapy for TLS in the absence of established clinical or laboratory TLS.[51] The dose should be repeated daily if there is any evidence of progressive TLS, and if clinical TLS develops on the fixed-dose regimen, the treatment should be changed to the standard dose of 0.2 mg/kg per day. Urinary alkalinization is not recommended because it can decrease the solubility of xanthine. Normal saline is recommended as the IV fluid of choice in the management of TLS.

Patients with established TLS should receive multidisciplinary care to ensure the



Mayo Clin Proc. ■ April 2017;92(4):609-641 ■ http://dx.doi.org/10.1016/j.mayocp.2017.02.008
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**TABLE 4. Treatment of Metabolic Abnormalities Associated With Tumor Lysis Syndrome**

| Abnormality | Intervention | Dose | Comments |
|---|---|---|---|
| Renal insufficiency and hypovolemia | Intravenous fluids | NS 3 L/m$^2$/d (200 mL/kg/d) | Use with caution if history of CHF |
| | Dialysis | NA | Use in anuria and severe oliguria with volume overload |
| Hyperuricemia | Allopurinol | 200-400 mg/m$^2$/d PO in divided doses every 8-12 h | Reduce dose in renal failure |
| | | | Multiple drug interactions (6-mercaptopurine and azathioprine) |
| | | Commonly used doses include 600 mg initially followed by 300 mg daily | IV allopurinol should only be used in patients unable to take medications by mouth |
| | | IV 200-400 mg/m$^2$/d in 2-3 divided doses | Does not lower uric acid already formed |
| | Rasburicase | Flat fixed dose of 3 mg IV | Contraindicated in G6PD deficiency |
| | | 0.2 mg/kg/d IV for up to 7 d for established TLS | Transfer blood samples to the laboratory on ice |
| | | | Risk of sensitization and allergic reactions |
| | | | Expensive |
| | Febuxostat | 120 mg PO daily | Expensive |
| | | | Uncertain if more effective than allopurinol |
| | | | No need to adjust doses in mild to moderate renal insufficiency |
| Hyperphosphatemia (phosphate >6.5 mg/mL [>2.1 mmol/L]) | Minimize phosphate intake | NA | Low phosphorus diet |
| | | | Phosphorus-free IV fluids |
| | Phosphate binders (aluminum hydroxide) | PO 50-150 mg/kg/d | May interfere with drug absorption |
| | Dialysis | NA | If no response to medical therapy |
| Hyperkalemia | Insulin (regular) | IV 10 U | … |
| | Dextrose (50%) | IV 50-100 mL | … |
| | Calcium gluconate (10%; 10% = 100 mg/mL) | IV 10 mL (1000 mg) | Do not give with bicarbonate |
| | | | Use if arrhythmias or ECG changes |
| | | | Can repeat as needed |
| | Sodium bicarbonate | IV 150 mEq in 1 L of D5W over 2-4 h | Use if acidosis |
| | | | Can repeat in 30 min |
| | Sodium polystyrene sulfonate | PO 15-30 g every 6 h (can be used rectally) | Can be given with sorbitol |
| | Albuterol | Inhaled 10-20 mg | For severe hyperkalemia |
| | Dialysis | NA | Severe hyperkalemia not responsive to other measures |
| | | | Renal failure |
| | | | Volume overload |
| Hypocalcemia | Calcium gluconate (10%; 10% = 100 mg/mL) | IV 10 mL (1000 mg) as an infusion over 10-20 minutes | Only if symptomatic |
| | | | Repeat as necessary |
| | | | Caution in patients with severe hyperphosphatemia |

CHF = congestive heart failure; D5W = 5% dextrose in water; ECG = electrocardiogram; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenous; NA = not applicable; $NaHCO_3$ = sodium bicarbonate; NS = normal saline; PO = orally; TLS = tumor lysis syndrome.

best possible outcome. Frequent monitoring is essential, and patients are often transferred to intensive care units for therapy. High urine output is maintained with hydration and careful monitoring of fluid balance. The optimal rate of fluid replacement remains unknown, but 3 L/m$^2$ every 24 hours is reasonable.[50,79] Alkalinization of the urine is not recommended, and diuretics should only be used for volume overload and then with extreme caution.[55] Rasburicase is the uricosuric agent of choice in established clinical TLS and should be used in a dose of 0.2 mg/kg daily for up to 7 days.[51] Hyperkalemia should be treated aggressively. Asymptomatic hypocalcemia should not be treated, but symptomatic hypocalcemia (tetany, arrhythmia, or seizures) should be treated carefully with IV calcium gluconate with the aim of controlling the symptoms but not normalizing the serum calcium level. Restriction of phosphate intake and phosphate binders may be used for hyperphosphatemia, but severe elevations in phosphate may require hemodialysis. Other indications for dialysis are severe hyperkalemia, severe oliguria or anuria, and volume overload.

## Lactic Acidosis

Lactic acidosis is a rare complication of cancer and is most often seen in patients with aggressive hematologic cancers and less commonly with high-grade solid tumors.[80-82] The pathogenesis of lactic acidosis in cancer is poorly understood and likely involves both increased lactate production by the tumor and decreased clearance by the liver. Many, but not all, patients have extensive liver metastases, and some patients may have thiamine deficiency.[80,81,83] Therapy for cancer-associated lactic acidosis includes intensive supportive care and therapy directed at the underlying malignant disorder but is frequently ineffective, and death is usually imminent. Chemotherapy is appropriate in patients with chemotherapy-sensitive tumors, but long-term survival is rare.[80,82]

## Hyponatremia

Hyponatremia is the most common metabolic disturbance in patients with cancer, affecting up to 60% toward the end of life and associated with inferior survival.[84-86] The etiology of hyponatremia in these patients is multifactorial and includes the syndrome of inappropriate antidiuretic hormone secretion, either from the cancer itself or from drugs, hypovolemia, and salt-wasting nephropathy.[87,88] Most cases of hyponatremia in patients with cancer are mild to moderate and either require no therapy or can be treated in the outpatient setting. Symptoms of hyponatremia include headache, nausea, vomiting, lethargy, confusion, and seizures.[89] Patients are usually hypovolemic or euvolemic on examination. Severe symptomatic hyponatremia should be corrected slowly with the aim of an increase in the plasma sodium level of 4 to 6 mEq/L (to convert to mmol/L, multiply by 1.0) per day to prevent osmotic demyelination.[90,91] Patients with severe hyponatremia presenting with altered mental status or seizures are typically treated with hypertonic saline (3%) given as 3 mL/kg over 30 to 60 minutes, which will rapidly increase the serum sodium by 4 to 6 mEq/L.

## Hypoglycemia

Hypoglycemia is a rare complication of cancers seen mainly in patients with neuroendocrine tumors that produce insulin (insulinomas).[87] Patients with metastatic malignant insulinoma can have severe hypoglycemia. Small, localized benign insulinomas can cause intermittent symptomatic hypoglycemia and are often very difficult to diagnose. Hypoglycemia is rarely seen in nonneuroendocrine cancers but occasionally occurs in end-stage liver failure from extensive hepatic replacement by tumor. Typical symptoms of hypoglycemia are palpitations, tremulousness, diaphoresis, anxiety, and hunger. Further neuroglycopenic symptoms may follow, such as confusion, loss of consciousness, and seizures. If tumor-induced hypoglycemia is suspected, plasma insulin, proinsulin, C-peptide, and β-hydroxybutyrate levels should be measured in addition to glucose. The initial treatment of hypoglycemia in cancer is no different than treatment of hypoglycemia in general. Symptomatic hypoglycemia in an alert patient can be treated with oral fast-acting carbohydrates, but severe symptomatic hypoglycemia requires IV administration of dextrose. A common dose is 25 g of 50% dextrose given as a slow IV push.


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Patients with symptomatic hypoglycemia from metastatic insulin-producing neuroendocrine tumors usually require further therapy including continuous infusion of dextrose, diazoxide, and octreotide followed by tumor-directed therapy.[92]

### Adrenal Insufficiency

Adrenal insufficiency may result from a near-complete replacement of the adrenal glands by malignant tumor or secondary to therapy. Despite the adrenal glands being common sites for metastases, adrenal insufficiency from tumor replacement is rare. Iatrogenic adrenal insufficiency is much more common. Prolonged therapy with glucocorticoids will result in adrenal suppression, and a sudden cessation of such therapy can lead to acute adrenal insufficiency. Megestrol acetate, which is commonly used for cancer cachexia, can cause adrenal insufficiency while patients are taking the drug as well as an acute exacerbation when it is abruptly stopped.[93] Furthermore, megestrol acetate is associated with adrenal insufficiency in acutely ill individuals.[94] Mitotane, a rarely used adrenolytic drug indicated for the management of adrenocortical carcinoma, invariably results in adrenal insufficiency, and all patients taking mitotane also need to take replacement corticosteroids.[95] Typical signs and symptoms of adrenal insufficiency include weakness, anorexia, nausea, vomiting, and hypotension. Hyponatremia, often accompanied by hyperkalemia, is a common laboratory finding. Circulatory collapse and shock may occur, especially if there is another intercurrent illness such as an infection. If adrenal crisis is suspected, therapy should be started without delay.[96] Normal saline, 1 to 2 L in the first hour, followed by an infusion should be given. Hypotonic fluids should be avoided because they may exacerbate the hyponatremia. Glucocorticoids can reverse the adrenal crisis and should be given once the diagnosis is suspected. Dexamethasone (4 mg IV bolus) is preferred because it does not interfere with cortisol assays. Hydrocortisone at 100 mg IV can also be given but interferes with the cortisol assay. Hydrocortisone at a dose of 50 mg IV is an appropriate maintenance therapy until the situation has stabilized.

## HEMATOLOGIC EMERGENCIES

### Hyperviscosity Due to Monoclonal Proteins

Hyperviscosity is defined as an intrinsic resistance of fluid to flow. It can be seen in disorders in which there is increased production of monoclonal proteins such as in multiple myeloma and Waldenström macroglobulinemia (WM). Blood viscosity can be increased secondary to an excess of either cellular or acellular elements.[97]

**Pathophysiology.** Excessive production of immunoglobulins can lead to increased blood viscosity. Of all the dysproteinemic disorders, WM is the most likely to cause hyperviscosity. Earlier studies reported that up to 30% of patients experienced hyperviscosity.[98] The prevalence seems to be declining because the disease is now being diagnosed at earlier stages. The IgM monoclonal protein produced by WM is a large pentamer that is 80% intravascular and can therefore profoundly affect the blood viscosity.[99] IgG and IgA are much less likely to cause hyperviscosity, and hyperviscosity is uncommonly seen in multiple myeloma.[100] The levels of monoclonal protein that cause hyperviscosity symptoms can vary considerably between patients but are relatively consistent and reproducible in an individual patient. In general, symptoms of hyperviscosity are unlikely with serum viscosity of less than 4 cP, which usually corresponds to IgM levels of 3 g/dL (to convert to g/L, multiply by 10).[101-103] According to one study, most symptomatic patients had viscosity above 8 cP.[104] High concentrations of monoclonal protein result in impaired microcirculatory blood flow and subsequent ischemia causing the characteristic symptoms of hyperviscosity. Because the relationship between a monoclonal protein and symptoms of hyperviscosity is not linear, once clinical symptoms of hyperviscosity occur, even a slight further increase in the concentration of monoclonal protein can dramatically worsen symptoms, and conversely, a modest reduction in the concentration can greatly relieve symptoms.

**Clinical Presentation and Diagnosis.** The onset of the symptoms of hyperviscosity syndromes is usually insidious. Symptoms from

**TABLE 5. Clinical Manifestations of Hyperviscosity**

| |
|---|
| Central nervous system |
| Headache |
| Dizziness and vertigo |
| Seizures |
| Concentrating difficulties |
| Impaired level of consciousness |
| Tinnitus and deafness |
| Ophthalmologic |
| Blurry vision or loss of vision |
| Diplopia |
| Retinal vein occlusion |
| Papilledema |
| Retinal hemorrhage |
| Mucocutaneous |
| Epistaxis |
| Gingival bleeding |
| Cutaneous bleeding |
| Gastrointestinal bleeding |
| Other |
| Shortness of breath |
| Congestive heart failure |
| Priapism |

the central nervous system (CNS) and eyes predominate (Table 5).[99,102] Common symptoms include blurred vision, headache, vertigo, dizziness, hearing loss, and impaired mental status. Shortness of breath, chest pain from myocardial ischemia, peripheral arterial occlusion, and venous thromboembolism have been reported. The physical examination often reveals retinal venous engorgement (sausaging), retinal hemorrhages, papilledema, and retinal vein occlusion at later stages (Figure 1). The patient can also have development of localized serous detachments of the fovea, which are thought to be secondary to accumulations of the immunoglobulin and resolve with plasmapheresis. Bleeding complications can be seen, especially purpura and petechiae due to hemostatic defects.

The diagnosis of hyperviscosity requires a high index of suspicion. Most patients have a known diagnosis of a dysproteinemic disorder, but some may present with hyperviscosity as the initial manifestation. The blood smear may reveal rouleaux formation of the red blood cells, in which they stack up like coins (Figure 2). Measurements of serum viscosity may be difficult or impossible to perform in many hospitals, especially if urgently requested outside the usual office hours. Measurements of immunoglobulin levels will likely be more available in real time and can guide therapy. In patients with typical symptoms and clinical findings, especially those with a known dysproteinemic disorder, treatment can start urgently without laboratory confirmation of hyperviscosity.

**Treatment.** Therapy should be started without delay in symptomatic patients. Severely symptomatic patients with a known WM diagnosis can be treated with phlebotomy and normal saline replacement while arranging for emergent plasmapheresis. Red blood cell transfusions should be avoided before initiating therapy to prevent exacerbation of the hyperviscosity. Plasmapheresis is an effective method to lower serum viscosity, especially in patients with WM because 80% of the IgM monoclonal protein is intravascular.[99,105] Even a small reduction in the monoclonal protein concentration can have a major effect on the symptoms. Plasmapheresis does not affect the underlying disease process, and systemic therapy is always needed for durable control of the disease.

## Hyperleukocytosis and Leukostasis

Hyperleukocytosis is often defined as a total leukocyte count of $100 \times 10^9$/L or more, but symptoms of leukostasis can occur at lower leukocyte counts.[106] Hyperleukocytosis can cause microvascular obstruction leading

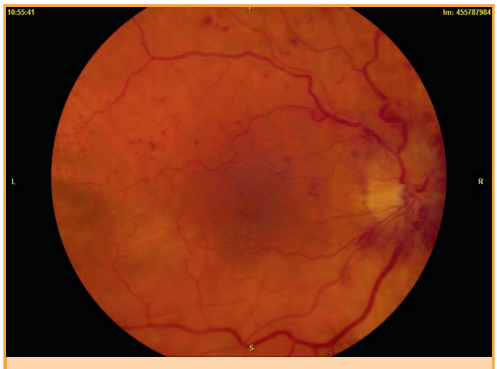

**FIGURE 1.** Retinal photograph of a patient with hyperviscosity showing dilated and tortuous retinal veins, intraretinal hemorrhages, and a cotton wool spot (infarction) by the optic disc. Image courtesy of Dr Jose Pulido, Department of Ophthalmology, Mayo Clinic.



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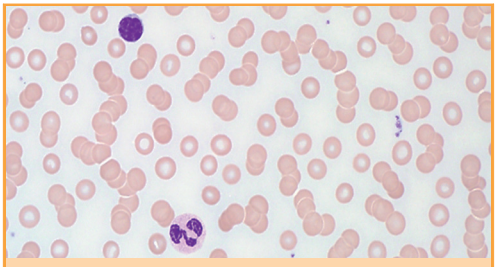

**FIGURE 2.** Red blood cell rouleaux formation in a patient with Waldenström macroglobulinemia (peripheral blood, Wright-Giemsa, original magnification ×600). Image courtesy of Dr Phuong Nguyen, Department of Laboratory Medicine and Pathology, Mayo Clinic.

to tissue hypoxia and infarction (leukostasis). Hyperleukocytosis and leukostasis are most commonly seen in acute leukemias, especially acute myeloid leukemia (AML) (5%-20% of patients).[107-109] Hyperleukocytosis secondary to AML is more common in children than adults. Acute lymphoblastic leukemia is less likely to cause leukostasis than AML. Chronic lymphocytic leukemia and chronic myeloid leukemia rarely cause symptomatic leukostasis, even despite extreme elevations in the white blood cell counts. Symptomatic hyperviscosity can also occur in patients with severe erythrocytosis and thrombocytosis.[110]

**Pathophysiology.** Rapid proliferation and disrupted cell adhesion result in the release of a large number of leukemic blasts from the bone marrow into the circulation.[107] This process can lead to microvascular occlusion resulting in tissue ischemia and infarction.[111] In addition, patients with hyperleukocytosis are at risk for development of TLS and disseminated intravascular coagulation. Two main mechanisms are thought to explain leukostasis.[107] First, the sheer quantity of immature leukocytes (Figure 3), which are frequently larger and less deformable than mature leukocytes, can lead to microvascular occlusion. Frequently, there is no clear correlation between the leukocyte count and the occurrence of leukostasis, likely due in part to a second important mechanism of abnormal interaction between the leukemic blasts and the endothelium. This abnormal interaction may be secondary to aberrant expression of adhesion molecules by the blasts.[106,112]

**Clinical Presentation and Diagnosis.** The symptoms and signs of leukostasis can resemble the presentation of hyperviscosity secondary to dysproteinemia (Table 6). Symptoms from the respiratory system and CNS including the eyes are common but can be difficult to distinguish from infectious and hemorrhagic complications.[109] Patients may present with fever, dyspnea, and pulmonary

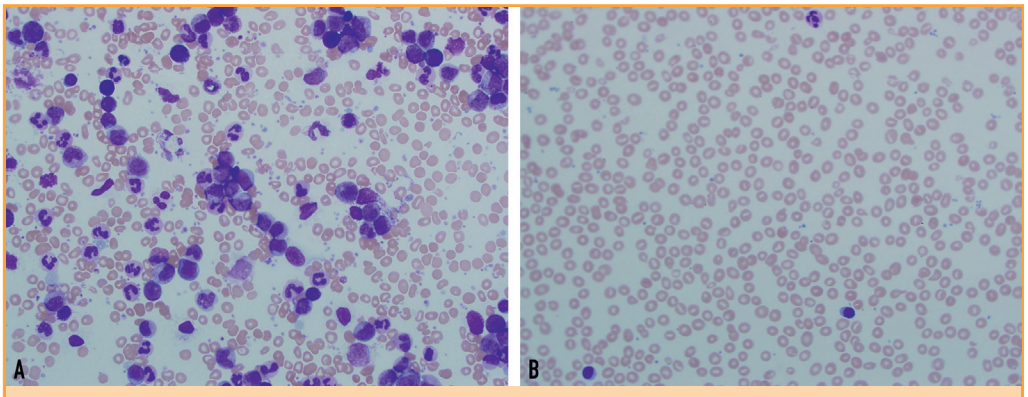


**FIGURE 3.** Photomicrographs showing hyperleukocytosis in a patient with chronic myeloid leukemia (A) and a blood smear from a normal individual (B) as a comparison (both peripheral blood, Wright-Giemsa, original magnification ×400). Images courtesy of Dr Phuong Nguyen, Department of Laboratory Medicine and Pathology, Mayo Clinic.

**TABLE 6. Clinical Manifestations of Leukostasis**

| |
|---|
| Central nervous system |
| Headache |
| Dizziness and vertigo |
| Seizures |
| Confusion and delirium |
| Impaired level of consciousness and coma |
| Focal neurologic deficits |
| Intracranial hemorrhage |
| Ophthalmologic |
| Blurry vision or loss of vision |
| Visual field defect |
| Papilledema |
| Retinal hemorrhage |
| Retinal vein thrombosis |
| Pulmonary |
| Dyspnea and tachypnea |
| Hypoxia |
| Auscultatory crackles |
| Respiratory failure |
| Pulmonary infiltrates |
| Cardiovascular |
| Chest pain |
| Myocardial ischemia/infarction |
| Other |
| Fever |
| Renal failure |
| Priapism |
| Extremity ischemia |
| Venous thrombosis |
| Disseminated intravascular coagulation |
| Tumor lysis syndrome |

infiltrates resembling symptoms of pneumonia or volume overload. Fever with neurologic symptoms can be difficult to distinguish from CNS infections. There is no single diagnostic test for leukostasis, but the diagnosis should be considered in all patients with extreme leukocytosis and typical symptoms.

**Treatment.** Hyperleukocytosis and leukostasis in patients with acute leukemia are associated with an inferior prognosis with an increase in early deaths compared with patients without these complications, and therapy should be started without unnecessary delay.[107,113] Red blood cell transfusions should be administered with caution and preferably after control of the symptoms of leukostasis given the concern of increasing viscosity.[114] Leukapheresis, a mechanical separation and removal of leukocytes from the blood, can rapidly reduce the number of leukemic blasts and reduce the likelihood of complications, but the effect of leukapheresis on early mortality is uncertain.[115-117] Despite the uncertainties, it should be strongly considered for all patients presenting with symptomatic leukostasis. The goal of leukapheresis should be resolution of symptoms, typically with reduction of the blast count to less than $100 \times 10^9$/L in AML.[106,118,119] Hydroxyurea is commonly used to provide additional control by preventing rapid reaccumulation of blasts in the initial stages of therapy, again with an uncertain effect on mortality in isolation.[115] Rapid initiation of standard induction therapy with curative intent is therefore recommended in all patients in whom intensive therapy is appropriate. Hydroxyurea can be considered as a bridging strategy while awaiting the results of diagnostic tests. Cranial radiation is no longer routinely recommended. Patients with leukostasis are at greater risk for TLS and should receive prophylactic therapy.

## NEUROLOGIC EMERGENCIES

### Malignant Spinal Cord Compression

Malignant spinal cord compression (MSCC) is a true oncological emergency. Up to 6% of patients with cancer are expected to experience MSCC at some time during the course of their illness, and the annual incidence of hospitalizations secondary to MSCC among patients with advanced cancer is 3.4%.[120-122] All cancers can cause MSCC, but the most often implicated malignant diseases are breast, lung, and prostate cancer, which account for almost two-thirds of all cases, but multiple myeloma and non-Hodgkin lymphoma have the highest cancer-specific incidence.[121-123] The prognosis of patients with MSCC is poor, especially if the presenting features include paralysis or if there is no response to therapy.[121,124] Slower onset of symptoms and the absence of neurologic deficits at diagnosis predict a better functional outcome after therapy.[125,126]

**Pathophysiology.** Most cases of MSCC are secondary to metastases to vertebral bodies that erode into the spinal canal and encroach on the spinal cord. Paravertebral tumors can extend through the neural foramina, resulting


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in cord compression.[127] Intramedullary and meningeal metastases are rare causes of spinal cord compression.[128,129] The thoracic spine is the most common location for metastases, followed by the lumbar spine and cervical spine.[120,128,130] Injury to the spinal cord can occur secondary to direct compression of the cord or from cord ischemia from vascular occlusion secondary to the tumor. Both mechanisms will eventually lead to irreversible neuronal damage resulting in neurologic deficits if untreated.

**Clinical Presentation and Diagnosis.** The literature on the natural history and early identification of MSCC is limited, but known bone metastases, high tumor burden, and recent onset of symptoms are suggestive of MSCC in patients with cancer who have back pain.[131] Most patients have back pain at diagnosis, but in 5% to 15% the pain is either absent or mild.[120,130,132-134] The pain can be localized to the spine, radicular, or both and is usually progressive.[130] The back pain is often nocturnal and can be worsened by certain movements as well as with increase in intra-abdominal pressure such as the Valsalva maneuver. Guidelines for evaluation of back pain have recommended looking for "red flags" suggestive of malignant disease, but there is limited evidence that such red flags are useful in identifying cancer as the underlying source of back pain.[135,136] Twenty percent of patients do not have a known cancer diagnosis at the time the MSCC is diagnosed.[133,134,137] Back pain in patients with cancer, especially pain of recent onset and worsening pain, should be taken very seriously and considered to be secondary to MSCC until proven otherwise. A careful history and a thorough physical examination including a neurologic examination are critical when evaluating back pain in patients with cancer. Weakness is the second most common presenting feature of MSCC, and patients may report heaviness or clumsiness of an extremity, which on examination is secondary to motor weakness. Up to 70% of patients are unable to walk at the time of presentation.[120,127,132] Sensory deficits usually occur after motor deficits, and up to 70% of patients will have sensory deficits at diagnosis.[127] Autonomic symptoms such as loss of bladder and bowel function usually occur later in the course of MSCC.[120,130] Ataxia is an unusual manifestation of MSCC.[138] Other presenting symptoms of MSCC include radicular pain and gait disturbance.[120,127,130,132]

The diagnostic method of choice is magnetic resonance imaging (MRI) because it is both sensitive and specific (Figure 4).[139-143] It is important to image the entire spine because up to 40% of patients may have multiple levels of compression or cord impingement.[144-147] If imaging of the entire spine is not feasible on initial evaluation, focused MRI of the suspected area should be performed emergently with a more complete MRI evaluation of the entire spine as soon as possible.[142] Computed tomography (CT), with or without myelography, can be used when MRI is contraindicated or not available. Plain bone radiographs and radionuclide bone scans are insensitive for spinal cord compression. Positron emission tomography with CT imaging is a useful modality to identify metastatis to the spine but lacks anatomic detail for diagnosis of MSCC.[148]

**Treatment.** Therapy should be initiated without delay in all patients with suspected MSCC to help preserve neurologic function, preferentially after imaging studies have been performed. Pretreatment motor function is an important predictor of functional outcome after therapy for MSCC.[124,125,149,150] If there is a delay in obtaining imaging studies, corticosteroid therapy may be initiated without confirmation of the diagnosis. Dexamethasone is the most commonly used glucocorticoid. A typical initial dose is 10 to 16 mg IV followed by 4 mg every 4 to 6 hours. The use of higher doses of dexamethasone (up to 100 mg) may result in a slightly better neurologic outcome but is associated with a higher risk of adverse events and is not universally supported in the literature.[151-155] High-dose dexamethasone can be considered in patients with severe and progressive neurologic deficits in whom the small potential gain may outweigh the risks.

Almost all patients with MSCC should be evaluated urgently for a decompressive surgical procedure. A randomized clinical trial evaluated surgical intervention in addition to high-dose dexamethasone and radiation therapy.[156] The trial was stopped early

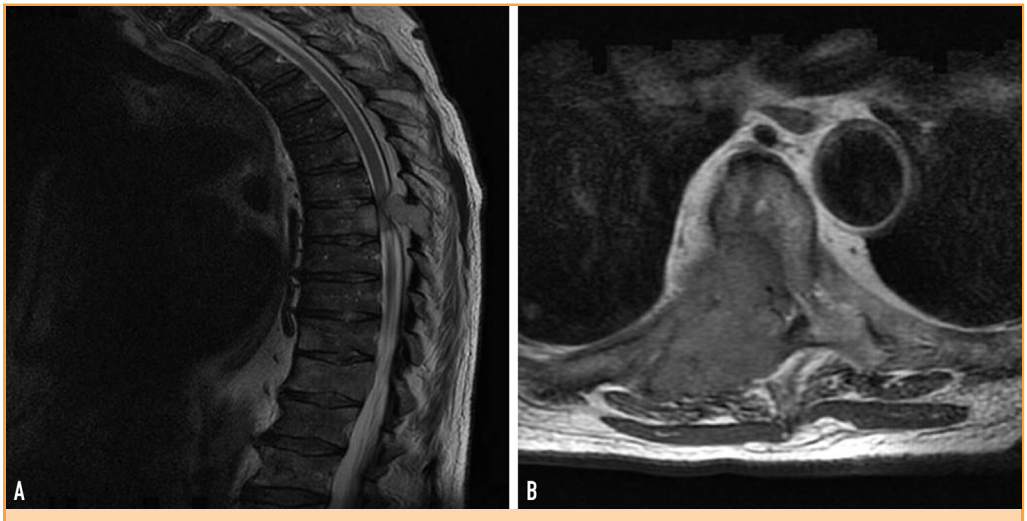


**FIGURE 4.** Metastatic spinal cord compression. Sagittal (A) and cross-sectional (B) views show metastasis to the thoracic spine in a patient with lung cancer resulting in symptomatic cord compression.

because the predetermined criteria were met, with surgical patients more likely to be able to walk after therapy compared with those who received radiation and dexamethasone alone (84% vs 57%; $P$=.003). Furthermore, patients in the surgical group remained ambulatory for a longer period (122 days vs 13 days) and had better survival. An unplanned subgroup analysis suggested that the benefit was related to age, with younger patients being more likely to benefit.[157] Other researchers have questioned the generalizability of the results of the trial to a broader cohort of patients because the study patients were highly selected. Moreover, the outcome in the nonsurgical group was inferior to that found in other studies. A matched pair analysis comparing patients who underwent surgical intervention plus radiotherapy with patients receiving radiotherapy alone did not show a benefit from surgical intervention.[158] Until more data become available, it is appropriate to have most patients evaluated for a decompressive surgical procedure, especially younger patients and those with better performance status, evidence of spinal instability, or rapidly progressive symptoms. A scoring system has been proposed to predict the prognosis of patients with MSCC, and those in the poorest prognosis group may best be served with corticosteroids, short-course radiation therapy, and best supportive care.[159]

Radiation therapy remains the mainstay of the treatment for most patients with MSCC, whether they do or do not undergo a decompressive surgical procedure. Multiple radiation regimens are in use, but none has emerged as the standard.[155,160,161] Shorter courses of radiation therapy may be as effective as longer courses, especially for patients with poor prognosis.[162-164] Stereotactic radiosurgical procedures may be considered in selected cases, especially after resection.[165-167]

## Brain Metastases

Brain metastases are a common complication in cancer, occurring in up to 20% of patients.[168] The incidence of symptomatic brain metastases is not well known, but autopsy studies have found that the prevalence of brain metastases is higher than clinically appreciated antemortem.[169,170] The cancers most likely to metastasize to the brain are lung cancer (both non–small cell and small cell), breast cancer, renal cell cancer, and malignant melanoma.[171,172] About 50% of brain metastases are solitary.[171]

**Pathophysiology.** Brain metastases arise secondary to hematogenous dissemination of tumor cells to the brain. The biology of brain metastases is complex.[173] The distribution within the brain reflects the distribution of blood flow, with 80% of brain metastases


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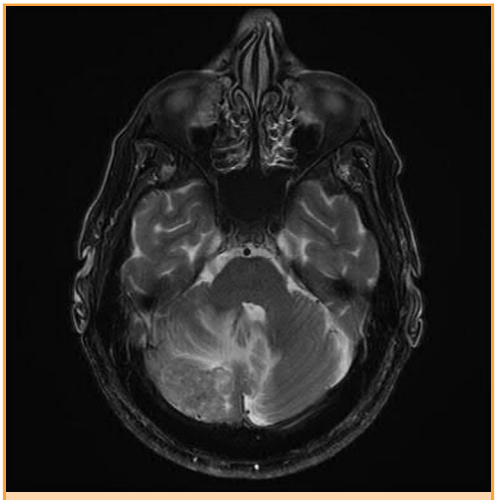

**FIGURE 5.** Contrast-enhanced T2-weighted magnetic resonance image showing symptomatic cerebellar metastasis with associated cerebellar edema and distortion of the fourth ventricle in a patient with esophageal adenocarcinoma.

occurring in the cerebral hemispheres,[169] 15% in the cerebellum, and 3% in the brain stem. Brain metastases are frequently located in the watershed areas of the arterial circulation and at the junction of gray and white matter.[174] Brain metastases frequently result in cerebral edema and subsequently elevated intracranial pressure. The etiology of the edema is complex and includes vasogenic edema secondary to leaky capillaries, stasis from impaired venous drainage, and obstruction of cerebrospinal fluid by the tumor.[175]

**Clinical Presentation and Diagnosis.** Most patients presenting with brain metastases have a known diagnosis of cancer, and the highest incidence is in patients with advanced malignant disease.[176] Brain metastases can also be the first presentation of a malignant disorder. The presenting features of brain metastases are variable, but headache is the most common symptom.[174,177] Other symptoms depend on the location of the lesion within the brain. Common symptoms include motor and sensory deficits, speech disturbance, unsteadiness, and cognitive decline. Up to 10% of patients have seizures, usually when there are multiple brain metastases.[174] A hemorrhage into a brain metastasis can result in sudden and severe symptoms.

Contrast-enhanced MRI is the most sensitive imaging modality for brain metastases (Figure 5).[178,179] Contrast-enhanced CT can be used when MRI is either unavailable or contraindicated but is less sensitive for smaller tumors and posterior fossa tumors. Noncontrast CT is helpful when an intracranial hemorrhage is suspected.

**Treatment.** The prognosis of most patients with brain metastases is poor, and other factors in addition to the presence of brain metastases determine the prognosis. Those factors include the tumor type, age at diagnosis, the performance score, and the presence of extracranial disease. Several scoring systems have been proposed, and one useful and accurate system is the Graded Prognostic Assessment, which is easily applied in clinical practice.[180] Patients with poor performance may be best served with supportive care alone. Table 7 lists treatment options for intracranial hypertension and seizures. Glucocorticoids are indicated in all symptomatic patients with cerebral edema secondary to metastases, and the effect of therapy occurs within several hours.[175] A commonly used glucocorticoid is dexamethasone, but others are likely as effective as long as they are given in equipotent doses.[181] Dexamethasone is generally preferred because it has a long half-life and less mineralocorticoid activity.[181] The optimal dose is unknown, but one trial reported no benefit of higher doses of dexamethasone (16 mg/d) vs lower doses (4-8 mg/d) in patients with no signs of impending brain herniation.[182] Therefore, a reasonable starting dose is 4 to 8 mg/d unless the patient has severe symptoms, in which case 16 mg/d can be considered.[183] Dexamethasone has excellent oral bioavailability and can therefore be given orally in patients with intact mentation and a functioning gastrointestinal tract. The dexamethasone should be tapered over 3 to 4 weeks after more definitive therapy. Patients with asymptomatic brain metastases and minimal edema do not need glucocorticoids. Seizures occur in 10% to 20% of patients and should be treated aggressively.[184] Prophylactic anticonvulsant therapy is not recommended for patients who have not had seizures.[185-188]

**TABLE 7. Management of Intracranial Hypertension and Seizures**

| Disorder | Intervention | Dosage and comments |
|---|---|---|
| Intracranial hypertension | Dexamethasone | 4-8 mg/d in divided doses; a higher dose can be used with severe symptoms (10-16 mg IV followed by 4 mg IV every 6 h) |
| Seizures | Lorazepam | 2-4 mg IV (or 0.1 mg/kg up to 4 mg maximum) at 2 mg/min; total dose capped at 4 mg |
| | Phenytoin | 20 mg/kg IV at 50 mg/min (25 mg/min in elderly patients and patients with cardiovascular disorders) |
| | Fosphenytoin | 20 mg/kg PE at 150 mg/min |

IV = intravenous; PE = phenytoin equivalent.

The treatment of refractory seizures in patients with cancer is no different than that in patients without cancer.[189] More definitive therapy for brain metastases, including resection, radiation, and chemotherapy, is offered to patients with good performance status and more favorable prognosis.[168,190] Surgical resection can rapidly decrease the intracranial pressure, especially in patients with tumors in the posterior fossa. A neurosurgeon should be consulted for all cases in which an operative intervention may be indicated.

## CARDIOVASCULAR EMERGENCIES

### Malignant Pericardial Effusion and Cardiac Tamponade

Pericardial effusions are commonly seen in patients with advanced and metastatic malignant diseases, but most patients are asymptomatic and do not require urgent therapy. Pericardial effusions in patients with cancer are not always related to the malignant disease itself and may also be secondary to cancer therapy, especially radiotherapy, or a manifestation of either an infection or an autoimmune process.[191,192]

**Pathophysiology.** Pericardial effusions in patients with cancer can be secondary to metastases to the pericardium, tumor invasion of the pericardium, or treatment related. Large effusions, especially if they accumulate rapidly, can impair ventricular filling and reduce cardiac output.[193] Patients with slowly accumulating effusions are frequently asymptomatic despite large effusions.

**Clinical Presentation and Diagnosis.** Small pericardial effusions are often asymptomatic. Typical symptoms of large or rapidly accumulating effusions include dyspnea, cough, and chest pain. A physical examination may reveal tachycardia, hypotension, distant heart sounds, fixed jugular venous distention, peripheral edema, and pulsus paradoxus. In addition, patients with tamponade can have hypotension and shock.[193,194] Electrocardiography frequently reveals low-voltage and nonspecific ST-T changes. Electrical alternans (beat-to-beat variations in the QRS complex size and shape) is thought to be caused by the heart moving within the enlarged and fluid-filled pericardium but can be seen in other cardiac conditions (Figure 6).[195] The diagnosis of pericardial effusions and tamponade is best made by echocardiography, which confirms the presence of the effusion but also provides hemodynamic information (Figure 7).[196] Computed tomography and MRI can also provide valuable information, especially regarding tumor invasion and metastases to the pericardium.[197] Cytological examination of the pericardial fluid may reveal malignant cells, but occasionally a pericardial biopsy is needed to establish the diagnosis.

**Treatment.** Small and asymptomatic pericardial effusions do not need to be treated. Patients with symptomatic effusions, especially with rapidly developing symptoms and hemodynamic instability, may need urgent interventions. Therapeutic echocardiographically guided pericardiocentesis is a safe procedure that can immediately relieve symptoms and improve hemodynamics, but a more durable treatment is usually needed.[198] A pericardial drain can be placed for drainage, and in selected cases, surgical procedures or instillation of a sclerosing agent may be used.[199,200]


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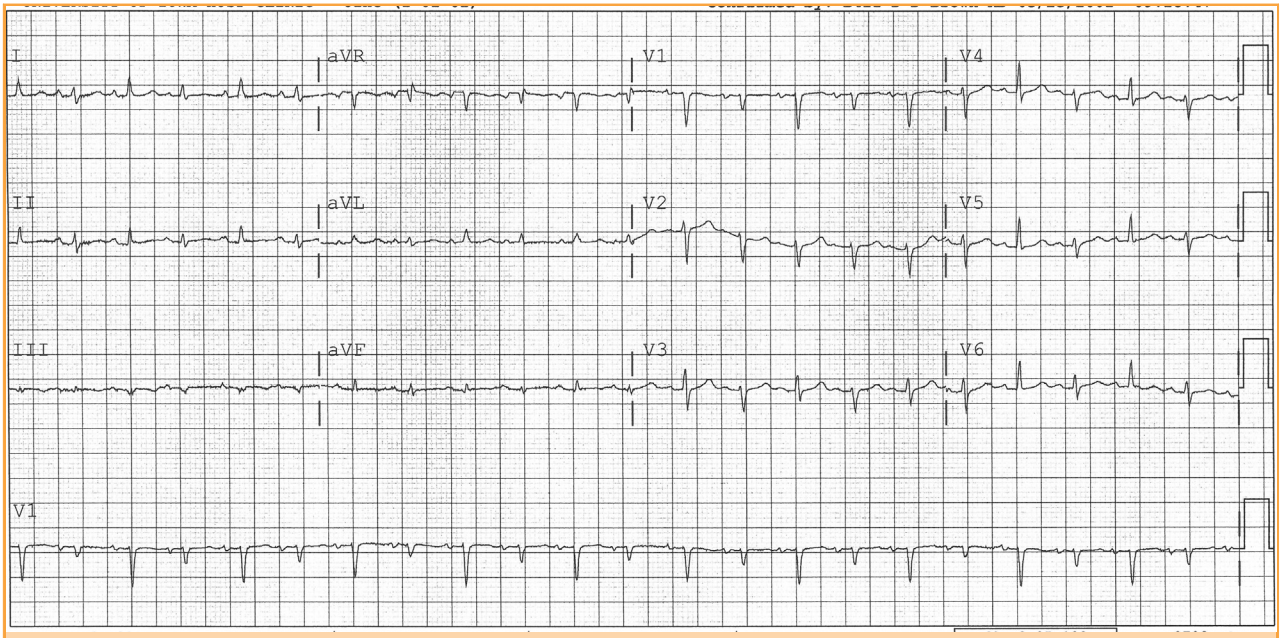


**FIGURE 6.** Electrocardiogram showing electrical alternans in a patient with malignant pericardial effusion. Image courtesy of Dr Donald Brown, Division of Cardiology, University of Iowa Hospitals and Clinics.

Systemic chemotherapy and/or radiotherapy may prevent reaccumulation in some patients.[192]

## Superior Vena Cava Syndrome

Superior vena cava syndrome (SVCS) occurs in the setting of an extrinsic compression or other occlusion of the superior vena cava (SVC). It is a common complication of cancer, and thoracic malignant disorders are the most common cause of SVCS.[201,202] Superior vena cava syndrome can also be seen as a complication of benign conditions such as SVC thrombosis secondary to indwelling venous lines or pacemaker leads as well as a complication of fibrosing mediastinitis and histoplasma infection.[201,203,204]

**Pathophysiology.** The thin-walled SVC can easily be compressed by tumors outside of the vessel, resulting in impaired venous drainage from the head, neck, and upper extremities. The compressing tumors are frequently in the middle or anterior mediastinum and the right paratracheal and precarinal nodal regions. The compression results in the formation of venous collaterals, including the azygos vein. Superior vena cava syndrome secondary to a compression below the azygos vein can result in more severe symptoms, highlighting the importance of the azygos vein as a collateral vessel.[205]

**Clinical Presentation and Diagnosis.** Superior vena cava syndrome can be acute, subacute, or more insidious and sometimes occurs with minimal symptoms. Very highly proliferative tumors and SVC thrombosis can result in a rapid onset of symptoms. Common symptoms include dyspnea, orthopnea, cough, sensation of fullness in the head and face, and headache, often exacerbated by stooping. Less common symptoms are chest pain, hemoptysis, hoarseness, dizziness, light-headedness, and even syncope. The most common physical findings are facial and neck swelling, arm swelling, and dilated veins in the chest (Figure 8, A), neck, and proximal part of the arms. Stridor and mental status changes are worrisome signs and indicate laryngeal edema and increased intracranial pressure, respectively. A grading system for SVCS has been proposed that can easily be applied in clinical practice (Table 8).[206] Computed tomography with IV contrast is the most useful method of diagnosing SVCS (Figure 8, B).[202,207] A plain chest

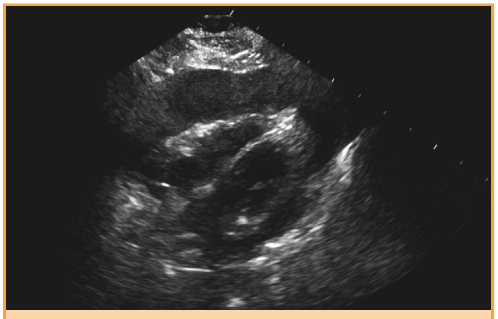

**FIGURE 7.** Transthoracic echocardiographic subcostal 4-chamber view showing a large circumferential pericardial effusion. Image courtesy of Dr S. Allen Luis, Division of Cardiovascular Diseases, Mayo Clinic.

radiograph may suggest SVCS, usually by showing a right hilar mass. Magnetic resonance imaging is particularly helpful in cases in which the administration of IV contrast is contraindicated.

**Treatment.** Although SVCS is commonly considered an oncological emergency, most cases are not.[206,208,209] Patients with symptoms and signs concerning for cerebral and/or airway edema and circulatory instability need urgent initiation of therapy (Table 8). In cases in which the etiology is not yet known, there is usually time to establish a diagnosis before starting therapy. Endovascular stenting of the SVC can promptly relieve symptoms of SVCS and is the treatment of choice in very symptomatic patients (Figure 9).[210,211] Radiation therapy is effective for many patients, but the relief of symptoms may be slow. Tissue diagnosis should be established before initiating radiation therapy. Adjunctive supportive therapy may be useful, such as elevation of the head of the bed, supplemental oxygen, and cautious use of diuretics and glucocorticoids in cases of laryngeal edema. Glucocorticoids administered for SVCS secondary to lymphoma relieve symptoms but should typically not be given until the diagnosis has been established with a biopsy because corticosteroids may obscure the pathologic diagnosis. Corticosteroids have little or no role in SVCS secondary to lung cancer.[212] Anticoagulation should be reserved for patients with evidence of an SVC thrombus or other venous thromboembolic complications and considered for patients who undergo a stent placement. Catheter-directed thrombolysis can be useful in SVCS secondary to a thrombus.[213] More definitive therapy, such as systemic therapy and radiation therapy, is dictated by the underlying cancer, which also is the primary determinant of the patient's prognosis.

## PULMONARY EMERGENCIES

### Acute Airway Obstruction

Malignant thoracic and mediastinal tumors can erode into the major airways or cause extrinsic compression leading to airway obstruction. The most common cause of cancer-related airway obstruction is lung cancer, and up to one-third of patients may experience airway obstruction during the course of the illness.[214] Other cancers, including anaplastic thyroid cancer,

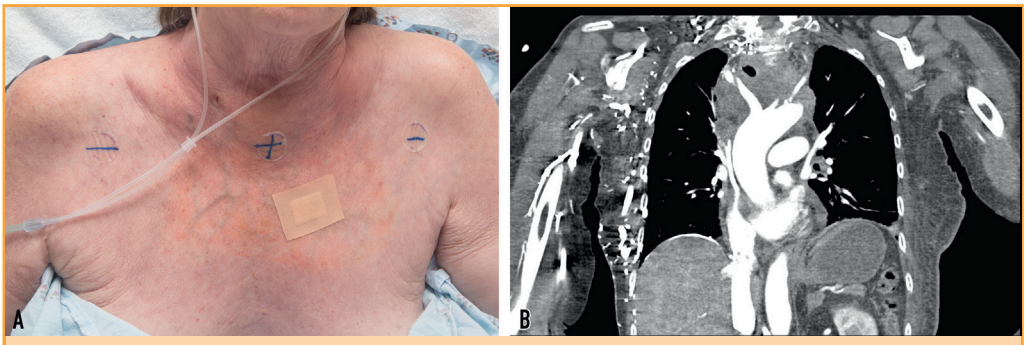


**FIGURE 8.** Superior vena cava syndrome in a patient with a large malignant mediastinal mass. A, Extensive venous collaterals can be seen on the right side of the chest wall and the right arm. B, Computed tomogram shows dilated superficial veins in the anterior chest wall.


Mayo Clin Proc. ■ April 2017;92(4):609-641 ■ http://dx.doi.org/10.1016/j.mayocp.2017.02.008
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**TABLE 8. Grading of Superior Vena Cava Syndrome**

| Grade | Category | Definition | Urgent treatment needed |
|---|---|---|---|
| 0 | Asymptomatic | Radiographic superior vena cava obstruction in the absence of symptoms | No |
| 1 | Mild | Edema of the head or neck (vascular distention), cyanosis, plethora | No |
| 2 | Moderate | Facial and neck edema with functional impairment (mild dysphagia, cough, mild or moderate impairment of head, jaw, or eyelid movements, visual disturbances caused by ocular edema) | No |
| 3 | Severe | Mild or moderate cerebral edema (headache, dizziness) or mild/moderate laryngeal edema or diminished cardiac reserve (syncope after bending) | Yes |
| 4 | Life-threatening | Severe cerebral edema (confusion, obtundation), laryngeal edema (stridor), or hemodynamic compromise (syncope without precipitating factors, hypotension, renal insufficiency) | Yes |
| 5 | Fatal | Death | Not applicable |

Adapted from *J Thorac Oncol*,[206] with permission from the International Association for the Study of Lung Cancer.

squamous cell cancers of the head and neck, and mediastinal malignant diseases such as lymphoma and germ cell tumor, can also cause airway obstruction. Primary tracheal tumors are a rare cause of airway obstruction.

**Clinical Presentation and Diagnosis.** The most common symptoms include dyspnea, cough, wheezing, hemoptysis, and stridor, and the manifestations depend on the severity and location of the obstruction.[215,216] The symptoms of airway obstruction can resemble symptoms of worsening chronic obstructive pulmonary disease, which is a common comorbidity in patients with lung cancer. The physical examination frequently reveals focal wheezing on auscultation and inspiratory stridor. Computed tomography is the preferred method of evaluation and provides information on the extent of the cancer as well as the airway involvement. The obstruction can be visualized with bronchoscopy, and biopsies can be performed at the same time if needed.

**Treatment.** The treatment of airway obstruction requires good visualization of the larger airways, which usually necessitates the use of rigid bronchoscopy.[216] The goal of therapy is to restore airway patency, which can be achieved with a variety of modalities.[217] Supplemental oxygen should be given to patients awaiting interventions, and bronchodilator therapy may be indicated in patients with coexisting obstructive small airways disease. Airway stenting, laser therapy, argon plasma coagulation, photodynamic therapy, and brachytherapy have all been used in the management of central airway obstruction and result in substantial relief of symptoms in most patients.[218,219] Interventions such as stent placement can have severe negative consequences such as subsequent airway infections.[220,221] External beam radiation therapy and systemic chemotherapy play an important role in the subsequent management of malignant airway occlusion.

## Acute Airway Hemorrhage

The etiologies of hemoptysis are diverse and vary with anatomic location. Malignant disease is among the most common causes of hemoptysis. Tumors eroding into the airways can cause hemoptysis, which usually is not an emergency. Substantial airway hemorrhage leads to hypoxemia and can be fatal.[222,223] The definition of massive hemoptysis is not well established, and definitions of 100 to 600 mL of bloody expectoration over 24 hours have been used.[224] Airway hemorrhage is commonly divided into proximal and distal airway bleeding, and the causes and management differ according to the anatomic location.[225] Lung cancer is the most common cause of massive hemoptysis, but other cancers, especially squamous cell carcinoma of the head and neck, can bleed profusely into the airways.

**Clinical Presentation and Diagnosis.** Patients usually present with expectoration of bloody

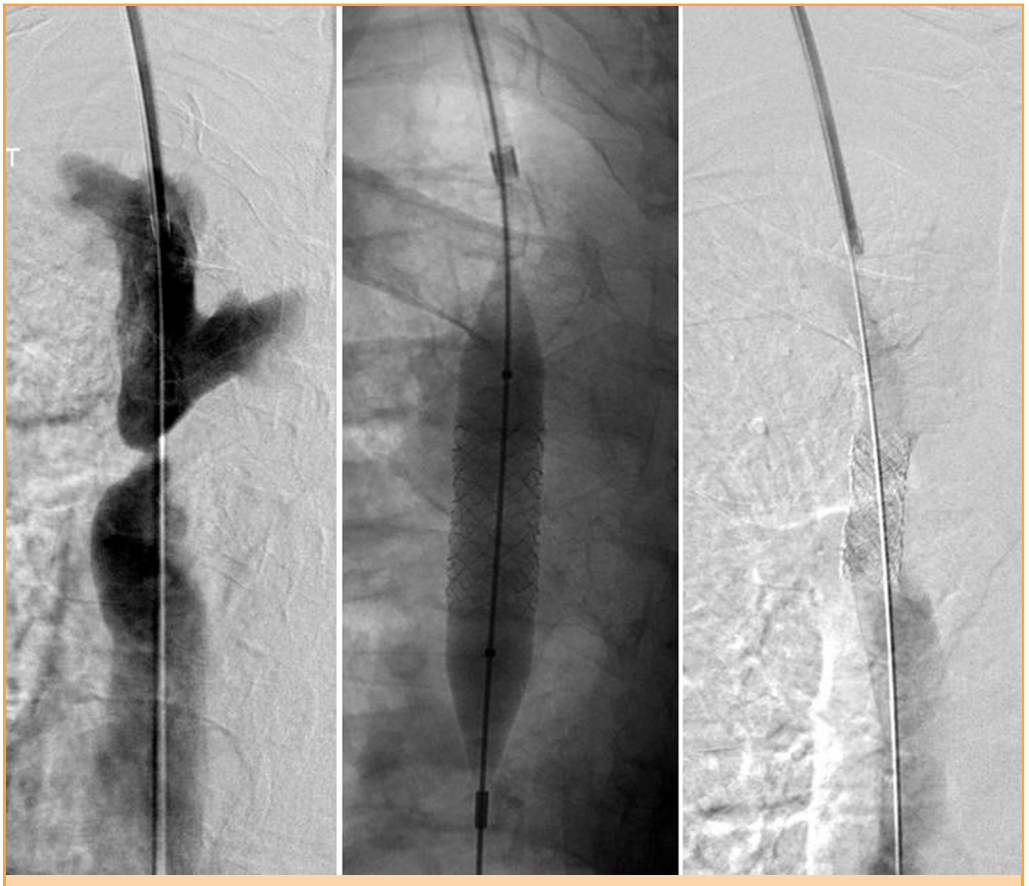

**FIGURE 9.** Insertion of a stent in the SVC can promptly improve the symptoms of superior vena cava syndrome. Images courtesy of Dr Haraldur Bjarnason, Department of Radiology, Mayo Clinic.

mucus or frank blood. Other symptoms and signs include dyspnea, respiratory distress, hypoxia, and hemodynamic instability. It is important to promptly identify the source of bleeding in patients with hemoptysis who are considered for more aggressive therapy. Computed tomography, especially CT angiography, can provide important information regarding the location of the bleeding and may help select an appropriate treatment strategy.[226,227] Bronchial artery angiography frequently reveals the bleeding location, and therapeutic embolization can be performed at the same time.

**Treatment.** As with acute airway obstruction, securing the airway is of utmost importance. The patient should be positioned in the lateral decubitus position with the bleeding side down, if known, to preserve alveolar exchange in the unaffected lung. If the patient is intubated, the bronchial main stem of the affected side can also be selectively intubated to avoid bleeding into the unaffected side. Administration of IV fluids and blood products may be needed for stabilization, especially in patients with hemodynamic instability or thrombocytopenia. Coagulation abnormalities should be corrected as indicated with blood products and reversal of anticoagulants if needed. Recombinant factor VII has been used to treat massive hemoptysis in patients with cancer and can be considered when other measures fail.[228,229] Rigid bronchoscopy is the preferred method for control of airway hemorrhage, but other treatments are frequently needed.[225] Bronchial artery angiography can identify the bleeding vessel(s), and embolization can be performed during the procedure, often with successful control of the bleeding.[230-232]



Mayo Clin Proc. ■ April 2017;92(4):609-641 ■ http://dx.doi.org/10.1016/j.mayocp.2017.02.008
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Massive hemoptysis is extremely distressing to both patients and their caregivers and is often a terminal event in the disease course. Best supportive care without further interventions may be appropriate in selected cases. Intravenous administration of opioids and benzodiazepines may provide substantial relief but with the risk of suppressing respiratory drive. Darkly colored bed sheets, pillowcases, and towels may decrease the psychological trauma associated with massive hemoptysis.

## INFECTIOUS EMERGENCIES

### Febrile Neutropenia

Infections are common in patients with cancer and a major contribution to both morbidity and mortality. Most infections in patients with cancer are not emergencies and can be treated in the outpatient setting. Febrile neutropenia is a common complication in patients undergoing therapy for malignant disease. Prompt diagnosis and initiation of therapy are of key importance in decreasing morbidity and mortality and can also decrease costly hospitalizations. For the purpose of this review, we use the definitions of the Infectious Diseases Society of America. Fever is defined as a single oral temperature higher than 38.3°C or a temperature higher than 38.0°C sustained for more than 1 hour.[233] Neutropenia is defined as an absolute neutrophil count (ANC) of less than $0.5 \times 10^9$/L or an ANC that is expected to decrease to less than $0.5 \times 10^9$/L during the next 48 hours.[233,234] An ANC level of less than $0.1 \times 10^9$/L is defined as profound neutropenia.[233]

**Pathophysiology.** Febrile neutropenia is most common in patients receiving cytotoxic chemotherapy, especially patients with acute leukemia. Febrile neutropenia is much less common in patients undergoing therapy for solid tumors given the less intensive therapy. Some malignant disorders, especially sarcomas and germ cell tumors, require high-intensity chemotherapy, which increases the risk of febrile neutropenia (Table 9).[235] The risk of febrile neutropenia depends on both the severity and duration of neutropenia. The neutrophil nadir usually occurs 5 to 10 days from initiation of therapy, and neutrophil recovery begins about 5 days later, but there are substantial variations depending on the regimens used and the patient characteristics. Preexisting comorbidities such as liver or kidney dysfunction as well as concurrent use of certain drugs can increase the severity and duration of the neutropenia (Table 9). Patients with bone marrow dysfunction, especially acute leukemia, myelodysplastic syndromes, and aplastic anemia, as well as drug- or radiation-induced neutropenia can present with febrile neutropenia in the absence of cytotoxic chemotherapy. Factors other than the neutropenia itself play a role in the pathogenesis of febrile neutropenia. Chemotherapy can disrupt mucosal barriers, making the risk of gram-negative sepsis greater. Indwelling vascular devices can serve as the port of entry for organisms that colonize the skin such as gram-positive cocci. Hematologic cancers are often associated with defects in both humoral and cellular immunity, further adding to the immunosuppressive effects of the cancer-directed therapy.

**Microbiology.** Most patients with febrile neutropenia will not have a specific microbial pathogen isolated during their illness, and a focus of an infection may not be identified. A bacterial pathogen is isolated in less than 30% of patients during an episode of febrile neutropenia and is more common in patients with prolonged or profound neutropenia.[233] The epidemiology of bacterial infections during neutropenia has changed markedly in recent decades. Gram-negative bacteria were the most commonly identified cause of febrile neutropenia in the past, but more recently, the incidence of gram-positive infections has surpassed those caused by gram-negative bacteria.[236,237] In recent years, an increase in the incidence of gram-negative bacteria has been observed, but infections with gram-positive bacteria are still in the majority.[238,239] The most common gram-positive bacteria are coagulase-negative staphylococci. Among the gram-negative bacteria, *Escherichia coli*, *Klebsiella,* and *Pseudomonas aeruginosa* are the most commonly isolated. Fungal and viral infections are also frequently encountered. The risk of fungal infections increases with the duration and severity of the neutropenia and is a common etiology of persistent neutropenic fever in patients treated empirically with

**TABLE 9. Risk Factors for Febrile Neutropenic Episodes**

| Risk factors | Effect on risk | Reported febrile neutropenia rate |
|---|---|---|
| Patient characteristics | | |
| Advanced age | Increased risk if age ≥65 y | NA |
| ECOG performance status | Increased risk if ≥2 | NA |
| Nutritional status | Increased risk if albumin <35 g/L (3.5 g/dL) | NA |
| Prior febrile neutropenia | Increased risk if FN during the first cycle | NA |
| Comorbidities | FN odds increase by 27%, 67%, and 125%, respectively, for 1, 2, or 3 comorbidities | NA |
| Underlying malignant disorder | | |
| Acute leukemia/MDS | NA | 85%-95% |
| Soft tissue sarcoma | NA | 27% |
| NHL/myeloma | NA | 26% |
| Germ cell tumors | NA | 23% |
| Hodgkin lymphoma | NA | 15% |
| Ovarian carcinoma | NA | 12% |
| Lung cancer | NA | 10% |
| Colorectal cancer | NA | 5% |
| Breast cancer | NA | 5% |
| Prostate cancer | NA | 1% |
| Cancer stage | Increased risk if stage II or higher | NA |
| Remission status | Increased risk if not in remission | NA |
| Treatment response | Increased risk in patients not responding to therapy | NA |
| Treatment characteristics | | |
| Cytotoxic regimen | Increased risk with higher doses of chemotherapy | NA |
| Degree and duration of mucositis | Higher risk with more severe mucositis | NA |
| Neutropenia | Absolute neutrophil count $<0.5 \times 10^9$/L for ≥7 d | NA |
| Lymphopenia | Absolute lymphocyte count $<0.7 \times 10^9$/L | NA |
| Monocytopenia | Absolute monocyte count $<0.15 \times 10^9$/L | NA |
| Prophylactic use of growth factors | Reduces the risk in selected populations | NA |

ECOG = Eastern Cooperative Oncology Group; FN = febrile neutropenia; MDS = myelodysplastic syndrome; NA = not available; NHL = non-Hodgkin lymphoma.
Adapted from Flowers CR et al. *J Clin Oncol*. 2013;31(6):794-810.[235] Reprinted with permission. ©2013 American Society of Clinical Oncology. All rights reserved.

broad-spectrum antibiotics. A more detailed review of the microbiology of febrile neutropenia is outside the scope of this review, but it is important to understand that there are substantial geographic variations, both in the type of pathogens implicated and in their resistance patterns regarding antimicrobial therapy.

**Clinical Presentation and Diagnosis.** The predominant sign at diagnosis is fever, but patients may also present with localizing symptoms and signs. A thorough history and physical examination are essential in the initial evaluation of patients with febrile neutropenia, even though a focus of infection is frequently not found. Emphasis should be placed on the oral cavity and oropharynx, skin, lungs, abdomen, and perianal area. Because of the lack of neutrophils, clinical and laboratory findings may be atypical. Purulence and swelling are frequently absent, and the only sign of a soft tissue infection may be erythema. The oral cavity should be examined for the presence of mucosal ulcers and periodontal disease. The skin should be carefully evaluated. All sites of indwelling venous devices should be thoroughly examined for erythema and tenderness. For example, port sites and line exit sites should be gently palpated and all dressings removed if needed for better visualization. Abdominal examination may reveal tenderness suggestive of enterocolitis, and examination of the lungs can identify focal abnormalities or tachypnea. The perianal region should be examined for erythema and tenderness, but a digital rectal examination should be avoided. Central nervous system infections may present with nonspecific symptoms of confusion or subtle focal findings. Patients should undergo risk assessment at presentation, as factors such as advanced age, poor performance status, and comorbidities may increase the risk of serious complications.


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A complete blood count with differential, liver chemistry tests, electrolyte panels, lactic acid measurements, coagulation tests, and creatinine measurements should be performed at presentation. At least 2 sets of blood specimens should be collected for cultures, with one from a peripheral vein. If the patient has an indwelling venous access device, specimens for culture should be obtained from each lumen in addition to a culture specimen from a peripheral vein. Other samples should be collected as clinically indicated, such as urine and stool samples. Very neutropenic patients may not have pyuria, pulmonary infiltrates, or cerebrospinal fluid leukocytosis. Samples should be obtained from skin lesions and sent for cultures, fungal stains, and virologic examation as indicated. Discharge from any line exit sites should be submitted for bacterial cultures. A lumbar puncture should be performed in patients with suspected meningitis, but platelet transfusion should be administered to patients with a platelet count of less than $50 \times 10^9$/L before the procedure. Chest radiography should be done in all patients with respiratory signs and symptoms, and CT imaging should be considered in patients with high risk of complications. Given its greater sensitivity, high-resolution CT should be performed in patients with suspected respiratory infection but no abnormalities on chest radiography.[240] The role of circulating blood markers such as C-reactive protein and procalcitonin is unclear. Procalcitonin may have a role when used with other predictors in risk stratification of patients with febrile neutropenia.[241,242]

**Treatment.** Early recognition and treatment of febrile neutropenia are key to successful management (Figure 10). Not all patients with neutropenic fever need to be admitted to the hospital. Empirical antibiotic therapy should be initiated without delay once samples for microbial cultures have been obtained. Delays in the initiation of antimicrobial therapy have been associated with inferior outcomes in patients admitted to the hospital with sepsis.[243,244] A systemic and algorithmic method to identify patients with febrile neutropenia and start appropriate therapy has been found to reduce the time from triage to initiation of antibiotics.[245,246]

Patients with low risk can be considered for outpatient IV or possibly oral antibiotic therapy assuming they meet certain criteria.[234,235,247] A useful risk stratification tool is the Multinational Association for Supportive Care in Cancer risk index score (Table 10).[248] Other risk stratification models exist, such as the National Comprehensive Cancer Network guidelines for management of cancer-related infections[249] and the Clinical Index of Stable Febrile Neutropenia.[250] Patients with anticipated longer duration and greater severity of neutropenia (>7 days, ANC $<0.5 \times 10^9$/L) as well as patients with major comorbidities are considered to be at high risk and should be hospitalized for therapy. Other indications for an admission include the presence of renal or hepatic insufficiency, hypotension, severe mucositis, pneumonia, hypoxia, new-onset abdominal pain, neurologic changes including mental status abnormalities, and suspected line infections. Patients with afebrile neutropenia who have new or worsening signs and symptoms of an infection should be evaluated and treated as being at high risk and be admitted to the hospital. For outpatient antibiotic therapy to be successful, the patient must have prompt access to health care professionals for evaluation as needed; have reliable transportation and access to a telephone; and have a reliable caregiver who is with them all the time. If there are any doubts regarding the safety of outpatient therapy, the patient should be hospitalized. A recommended outpatient oral regimen is a combination of amoxicillin/clavulanic acid and ciprofloxacin, but this regimen will depend on many factors including clinical presentation, absence of comorbidities, access to rapid advanced health care, antimicrobial prophylaxis, and resistance patterns.[251,252] Patients previously taking a prophylactic fluoroquinolone antibiotic should not receive fluoroquinolone-based empirical antibiotic therapy.[234] Low-risk patients with hematologic cancers can be treated as outpatients with IV chemotherapy, often in a hospital-based outpatient environment.

Monotherapy with a broad-spectrum cephalosporin such as cefepime, a carbapenem, or an antipseudomonal β-lactam such as piperacillin/tazobactam is recommended as initial therapy by the Infectious Diseases

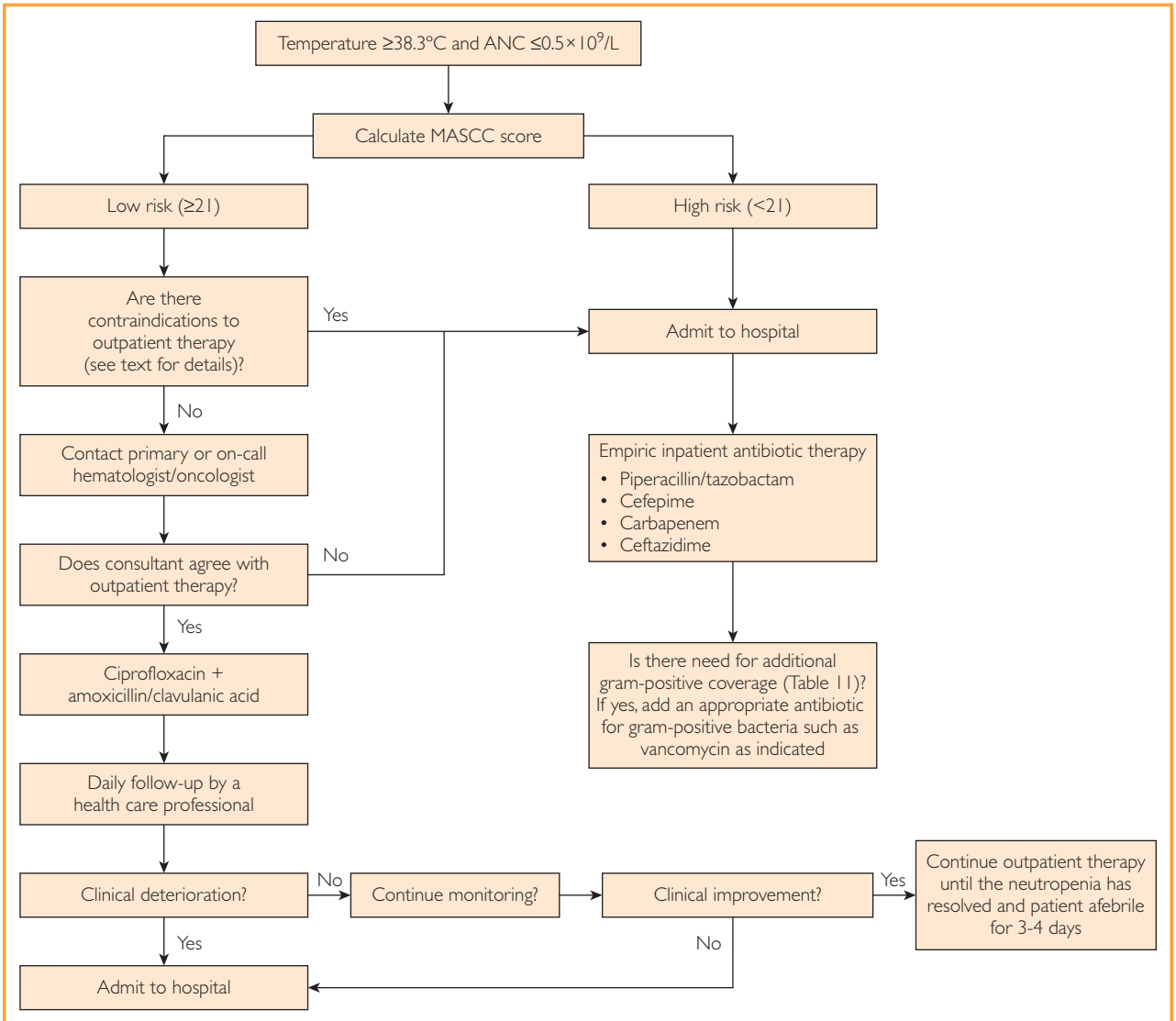


**FIGURE 10.** Algorithm for initial management of febrile neutropenia. ANC = absolute neutrophil count; MASCC = Multinational Association for Supportive Care in Cancer.

Society of America.[233] Gram-positive coverage should be considered in selected patients and not employed routinely for all patients. Patients with hypotension, sepsis, or suspected catheter-related infection should receive an antibiotic with adequate gram-positive activity such as vancomycin. Table 11 lists other indications for gram-positive coverage. Knowledge of the susceptibility patterns in the community and within institutions and hospitals is important when selecting the appropriate initial therapy. Empirical antifungal or antiviral therapy is not routinely recommended unless there is a high risk for or suspicion of a fungal or viral infection. The role of myeloid growth factors is uncertain. They may reduce the duration of hospital stay but do not seem to improve mortality.[253] Myeloid growth factors can be considered in patients with neutropenic fever who are at risk of severe complications. Such patients include those with expected prolonged (>10 days) and profound neutropenia, pneumonia, hypotension, uncontrolled primary cancer and multiorgan dysfunction, or sepsis and those who are older than 65 years.[254]


Mayo Clin Proc. ■ April 2017;92(4):609-641 ■ http://dx.doi.org/10.1016/j.mayocp.2017.02.008
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**TABLE 10. MASCC Scoring System for Patients With Neutropenic Fever[a,b]**

| Characteristic | Score |
|---|---|
| Burden of febrile neutropenia: no or mild symptoms[c] | 5 |
| No hypotension | 5 |
| No chronic obstructive pulmonary disease | 4 |
| Solid tumor or no previous fungal infection | 4 |
| No dehydration | 3 |
| Burden of illness: moderate symptoms | 3 |
| Outpatient status | 3 |
| Age <60 y | 2 |

[a]MASCC = Multinational Association for Supportive Care in Cancer.

[b]Patients with a total score of ≥21 have a low risk of having serious medical complications.

[c]Burden of neutropenia reflects the clinical status of the patient and is scored on the following scale: no or mild symptoms, score of 5; moderate symptoms, score of 3; severe symptoms or moribund, score of 0. Points attributed to the variable "burden of febrile neutropenia" are not cumulative. Therefore, the maximum theoretical score is 26.

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### Fever in Patients Without a Functional Spleen

Patients who have either undergone a splenectomy or have functional asplenia are at increased risk of fulminant infections with encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*.[255,256] The risk of severe infections in asplenic patients is the highest in the first few years after splenectomy when it may be as high as one infection per 14 patient-years, but the risk persists for decades.[257,258] Sepsis in asplenic patients has a high risk of mortality.[259] Asplenic and hyposplenic patients with fever should be evaluated immediately, and empirical antibiotic therapy should be initiated once blood has been drawn for cultures. Patients who are not acutely ill can be treated with ceftriaxone or cefotaxime. More severely ill patients should receive dual therapy with a combination of ceftriaxone or cefotaxime and vancomycin because of concerns for penicillin-resistant pneumococci or β-lactamase–producing *H influenzae*. A combination of moxifloxacin or levofloxacin and vancomycin can be used in patients with allergy to β-lactam antibiotics.

## UNIQUE EMERGENCIES RELATED TO SYSTEMIC TUMOR-DIRECTED THERAPY

Cytotoxic chemotherapy has a relatively predictable range of toxicities, most commonly associated with the dose-related cytotoxic effect on normal cells. Cytotoxic chemotherapy can result in life-threatening complications that can present as emergencies, such as thrombotic microangiopathy with mitomycin C and gemcitabine, pulmonary toxicity with bleomycin and gemcitabine, and coronary vasospasms from fluoropyrimidines. Many of the newer targeted agents and immunotherapeutic drugs are associated with unique and sometimes life-threatening toxicities.[260] Cardiotoxicity of targeted therapies is increasingly being recognized as a major clinical problem, often with acute presentations.[261] With the increasing use of immunotherapy for cancer, we are likely to encounter more patients with unusual complications of such therapy. Immunotherapy can adversely affect multiple organs, most commonly the skin, gastrointestinal tract, endocrine system, and lungs, and patients may present in an emergent manner—for example, with adrenal insufficiency or severe diarrhea leading to hypovolemia and shock.[262] Newer immunologic technologies such as bispecific antibodies (blinatumomab) or chimeric antigen receptor T cells are frequently associated with serious or life-threatening cytokine release syndrome (CRS).[263] A CRS grading system has been described by Lee et al.[263] Specific therapies such as tocilizumab, an anti–interleukin 6 receptor inhibitor, have efficacy in treating CRS but require experience and judgment as to timing of use to minimize the impairment of efficacy while maximizing safety.

**TABLE 11. Indications for the Addition of a Gram-Positive Antibiotic in the Empirical Management of Febrile Neutropenia**

| |
|---|
| Hypotension or hemodynamic instability |
| Sepsis syndrome |
| Radiographically documented or strongly suggested pneumonia |
| Known colonization with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, or penicillin-resistant streptococci |
| Blood cultures positive for gram-positive bacteria |
| Skin or soft tissue infections |
| Severe mucositis |
| Previous use of fluoroquinolones as prophylactic therapy |
| Suspected catheter-related infection |

**TABLE 12. Emergencies and Other Urgent Adverse Events Related to Targeted Cancer Therapies**

| Organ system affected | Class of drug | Example |
|---|---|---|
| Cardiovascular | | |
| Congestive heart failure | HER2-directed therapy | Trastuzumab, pertuzumab |
| | Immunotherapy | Ipilimumab, nivolumab, pembrolizumab |
| Arterial thromboembolism | VEGF-directed therapy | Bevacizumab, aflibercept, ramucirumab |
| | Kinase inhibitors | Ponatinib, pazopanib |
| Venous thromboembolism | Immunomodulatory drugs | Thalidomide, lenalidomide |
| Arrhythmia | Kinase inhibitors | Dasatinib, vandetanib, ibrutinib, lenvatinib |
| | Antiemetics | Ondansetron, metoclopramide |
| | Protesome inhibitors | Bortezomib, carfilzomib |
| Pulmonary | | |
| Pneumonitis | mTOR inhibitors | Everolimus, temsirolimus |
| | Kinase inhibitors | Erlotinib, gefitinib, crizotinib, idelalisib |
| Pleural effusions | Kinase inhibitors | Dasatinib |
| Gastrointestinal | | |
| Bowel perforation | VEGF inhibitors | Bevacizumab |
| Diarrhea | Kinase inhibitors | Multiple TKIs |
| | Immunotherapy | Ipilimumab, nivolumab, pembrolizumab |
| Acute liver failure | Multiple targeted agents | |
| Endocrine | | |
| Adrenal insufficiency | Immunotherapy | Ipilimumab, nivolumab, pembrolizumab |
| Hypophysitis | Immunotherapy | Ipilimumab, nivolumab, pembrolizumab |
| Hyperglycemia | mTOR inhibitors | Everolimus, temsirolimus |
| Hematologic | | |
| Hemorrhage | VEGF inhibitors | Bevacizumab, aflibercept, ramucirumab |
| Neutropenia | Multiple targeted agents | |
| Thrombocytopenia | Multiple targeted agents | |

HER2 = human epidermal growth factor receptor 2; mTOR = mammalian target of rapamycin; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

A detailed discussion of the emergent toxicities secondary to noncytotoxic systemic therapy is outside the scope of this review. Table 12 lists examples of targeted therapies associated with acute and life-threatening complications.

## CONCLUSION

Patients with cancer commonly present with emergent complications of either the malignant disease itself or the therapy they are receiving. Practicing clinicians can therefore expect to encounter such patients in emergency departments or outpatient offices. Prompt evaluation and accurate diagnosis followed by the institution of appropriate therapy can be lifesaving and may prevent irreversible loss of organ function. A sound knowledge of oncological and hematologic emergencies is therefore very important for all health care professionals involved in direct patient care.

**Abbreviations and Acronyms:** **AML** = acute myeloid leukemia; **ANC** = absolute neutrophil count; **CNS** = central nervous system; **CRS** = cytokine release syndrome; **CT** = computed tomography; **IV** = intravenous; **MRI** = magnetic resonance imaging; **MSCC** = malignant spinal cord compression; **PTH** = parathyroid hormone; **PTHrP** = PTH-related peptide; **RANKL** = receptor activator of nuclear factor κB ligand; **SVC** = superior vena cava; **SVCS** = SVC syndrome; **TLS** = tumor lysis syndrome; **WM** = Waldenström macroglobulinemia

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