Oncologic Emergencies: Diagnosis and Treatment

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Patients with malignancies are subject to developing a unique set of complications that require emergent evaluation and treatment. With the increasing incidence of cancer in the general population and improved survival, these emergencies will be more frequently encountered. Physicians must be able to recognize these conditions and institute appropriate therapy after a focused initial evaluation. The approach to definitive therapy is commonly multidisciplinary, involving surgeons, radiation oncologists, medical oncologists, and other medical specialists. Prompt interventions can be lifesaving and may spare patients considerable morbidity and pain. In this review, we discuss the diagnosis of and initial therapy for common emergencies in hematology and oncology.

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CT = computed tomography; MRI = magnetic resonance imaging; MSCC = malignant spinal cord compression; PTH = parathyroid hormone; PTHrP = PTH-related protein; SVCS = superior vena cava syndrome; TLS = tumor lysis syndrome; WM = Waldenström macroglobulinemia

Because of the increasing incidence of cancer in the general population, combined with improved survival and increasing reliance on outpatient treatment strategies, it is imperative that primary care and emergency department physicians understand and are able to treat emergencies associated with malignancies. In this review, we discuss the diagnosis of and initial therapy for common emergencies in hematology and oncology. Oncologic emergencies can be broadly classified as those resulting from the disease itself and those resulting from therapy directed against the cancer; however, we categorize such emergencies according to organ system to facilitate the recognition and management of oncologic emergencies.

METABOLIC EMERGENCIES

HYPERCALCEMIA

Hypercalcemia is a common problem in advanced malignancies and has been reported in 10% to 30% of patients with cancer at some time during their disease.[1,2] Hypercalcemia may be a presenting feature but is more commonly seen in patients with an established diagnosis. The most common malignancies associated with hypercalcemia are breast and lung cancer and multiple myeloma.[2] Hypercalcemia often portends a poor prognosis, particularly if associated with elevated parathyroid hormone–related protein (PTHrP) levels.[3-7]

Pathophysiology. The pathophysiology of hypercalcemia can be divided into 3 types: humoral hypercalcemia of malignancy, often mediated by production of PTHrP; local bone destruction that results in release of cytokines, including osteoclast activating factors; and tumor production of vitamin D analogues.[1] Humoral hypercalcemia of malignancy is the most common mechanism that produces cancer-induced hypercalcemia, and one study reported that 35 (88%) of 40 patients with solid tumors and 3 (33%) of 9 patients with hematologic malignancies with hypercalcemia had an elevated PTHrP level.[8] As a result of close structural similarities between parathyroid hormone (PTH) and PTHrP, PTHrP can simulate many of the actions of PTH, specifically bone resorption and distal tubular calcium reabsorption. In some patients serum levels of PTHrP are high, suggesting a systemic effect, whereas in other patients local production of PTHrP may be responsible.[9,10] Induction of osteolysis by malignant cells occurs commonly with breast and lung cancer and multiple myeloma. Secreted cytokines (eg, tumor necrosis factor, interleukin 1, interleukin 6, macrophage inflammatory protein 1a, and lymphotoxin) can stimulate local macrophages to differentiate into osteoclasts, resulting in bone destruction and hypercalcemia.[11,12] A recent study has demonstrated that inhibition of osteoblastic differentiation may also play a role in the etiology of myeloma bone disease.[13,14] Overproduction of vitamin D analogues, including calcitriol, is a common mechanism of hypercalcemia in lymphomas, particularly Hodgkin disease, and nonmalignant granulomatous disorders, particularly sarcoidosis.[15]

Clinical Presentation and Diagnosis. The symptoms of hypercalcemia are multiple and nonspecific.[16] Classic symptoms include lethargy, confusion, anorexia, nausea, constipation, polyuria, and polydipsia. These symptoms correlate to some degree with the degree of the hypercalcemia and the rapidity of onset.[17] A physical examination is seldom helpful in making the diagnosis of hypercalcemia. The patient is often severely hypovolemic due to

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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	The rate of infusion should be adjusted for the cardiovascular status of the patient
Furosemide	20-40 mg IV	Loop diuretics generally avoided in the absence of heart and renal failure until after volume correction
Pamidronate	60-90 mg IV for 2-4 h	Use cautiously in patients with renal insufficiency; onset of action is within a few days
Zoledronic acid	4 mg IV for 15 min	
Glucocorticoids	Prednisone, 60 mg/d orally; hydrocortisone, 100 mg every 6 h IV	May cause immunosuppression and hyperglycemia and should be used only temporarily if possible
Calcitonin	4-8 IU/kg SC or IV every 12 h	Rapid onset of action (hours) but short lived; can cause flushing
Mithramycin†	25 μg/kg administered over 4-6 h as a single dose	Multiple adverse effects, including thrombocytopenia, renal failure, abnormalities in liver chemical test results, and coagulation
Gallium nitrate†	100-200 mg/m^2 of BSA daily IV given continuously for 5 d	Renal failure; inconvenient to give because of the slow infusion rate; rapid onset of action but short lived; can cause flushing

*BSA = body surface area; IV = intravenously; SC = subcutaneously.
†These drugs are uncommonly used to treat hypercalcemia.
Adapted from *N Engl J Med*,[1] with permission.

excessive fluid losses and impaired fluid intake. Nonetheless, hypercalcemic patients without a preexisting cancer diagnosis should be examined carefully for evidence of malignancy.

Hypercalcemia is diagnosed by measuring ionized serum calcium. If total serum calcium is measured, one has to correct for the albumin level. The corrected calcium is calculated according to the following formula: corrected calcium = measured total calcium + [0.8 × (4.0 – albumin)]. The level of creatinine, other electrolytes, and alkaline phosphatase should be checked. A low serum chloride level (<100 mEq/L) is suggestive of hypercalcemia of malignancy.[18] Intact PTH is usually low in hypercalcemia of malignancy. Measuring levels of PTHrP is not necessary for diagnosis but may be helpful in understanding the mechanism of hypercalcemia and assessing prognosis and response to bisphosphonates.[6,7] One study reported that patients with serum PTHrP levels higher than 12 pmol/L were less responsive to bisphosphonate therapy and that such levels were associated with a greater risk of recurrent hypercalcemia within 14 days.[19]

Treatment. Untreated, symptomatic hypercalcemia is a life-threatening entity that needs immediate intervention (Table 1). Hypercalcemia occurs commonly in patients with advanced cancer, and it may be appropriate, ethical, and humane to institute only comfort measures in circumstances in which patients have specified that no further active therapy be undertaken for the treatment of their malignancy. Severe hypercalcemia is usually associated with pronounced hypovolemia, and the first step in treatment is intravenous hydration with normal saline. The patient may require large volumes of fluids, and 500 to 1000 mL of normal saline can be given during the first hour and continued at a lower rate until intravascular volume repletion is achieved and urine output established. Care must be taken in hydrating persons with a history of congestive heart failure. Milder hypercalcemia may be treated without intravenous hydration. Loop diuretics should be avoided until euvolemia is achieved because hypovolemia that results in renal hypoperfusion may further decrease the renal excretion of calcium. Serum calcium should be measured frequently until responses are seen. Care should be taken in eliminating sources of calcium and discontinuing the use of medications that may increase the calcium level, such as thiazide diuretics and vitamin D.

Bisphosphonates block osteoclastic bone resorption and have revolutionized the treatment of hypercalcemia of malignancy.[20,21] The bisphosphonates most commonly used for hypercalcemia of malignancy are pamidronate and zoledronic acid. These drugs control the hypercalcemia in most cases.[22-24] Zoledronic acid may be more potent, but the clinical importance of the increased potency is of uncertain significance.[1,23] Zoledronic acid should be used cautiously in patients with renal insufficiency, and the dose should be adjusted according to the calculated creatinine clearance.

Subcutaneous or intramuscular calcitonin can quickly lower calcium levels to a modest degree, but the effect is usually short lived.[25,26] Nasal administration is not effective for the treatment of hypercalcemia.[27] Other medications include mithramycin (plicamycin) and gallium nitrate, both of which are associated with serious adverse effects and, in the case of gallium nitrate, are cumbersome to administer.[26,28-31] These drugs have fallen out of favor since the introduction of bisphosphonates. Glucocorticoids are par-

ticularly effective in cases in which the hypercalcemia is caused by elevated levels of vitamin D ($1,25(OH)_2D$), such as some lymphomas, particularly Hodgkin disease.[32,33] Dialysis may be appropriate for patients with renal failure or congestive heart failure when aggressive hydration and bisphosphonates cannot be used safely.[34,35] Taking measures to reduce the risk of recurrent hypercalcemia is important. Sources of oral phosphate should be eliminated, and the use of medications known to raise serum calcium levels should be discontinued. Adequate hydration should be provided, and some patients may benefit from intermittent use of bisphosphonates, especially those with metastatic bone disease. Treatment of the underlying disease with chemotherapy and radiation can successfully control the hypercalcemia in many cases in which effective therapy exists.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is characterized by several metabolic derangements that may be life-threatening. It is most commonly seen after therapy for aggressive hematologic malignancies, such as high-grade lymphomas and acute leukemias. In addition, TLS may be seen after the treatment of kinetically active solid tumors and may occur spontaneously.[36,37]

Pathophysiology. Tumor lysis syndrome is caused by massive release of intracellular contents after tumor cell death. The nucleic acid products released result in hyperuricemia. The high concentration of uric acid can lead to crystallization within the renal tubules, resulting in obstruction of tubular flow and acute renal failure. The renal failure is further exacerbated by hypovolemia. The release of intracellular potassium along with decreasing renal function lead to hyperkalemia that may cause life-threatening arrhythmias. Increasing levels of phosphorus result in hypocalcemia and sometimes tetany, seizures, and arrhythmias.

TABLE 2. **Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome 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 mmol/L) or 25% increase from baseline
Phosphorus ≥6.5 mg/dL (≥2.1 mmol/L) or 25% increase from baseline
Calcium ≤7 mg/dL (≤1.75 mmol/L) or 25% decrease from baseline
Clinical tumor lysis syndrome
Creatinine ≥1.5 times upper limit of normal
Cardiac arrhythmia or sudden death
Seizure

Adapted from *Br J Haematol*,[36] with permission from Blackwell Publishing Group. Copyright © 2004. All rights reserved

Clinical Presentation and Diagnosis. Tumor lysis syndrome was defined as either clinical TLS or laboratory TLS by Hande and Garrow.[38] This classification has been refined further by Cairo and Bishop (Table 2 and Table 3).[36]

The symptoms and signs of TLS are usually nonspecific. Generally, patients have recently started chemotherapy. Urine output may decrease, and the patient may manifest symptoms of uremia or volume overload. Seizures and arrhythmias can occur. A high index of suspicion is necessary for the timely diagnosis of TLS. Laboratory studies usually show elevated uric acid, phosphorus, potassium, and lactate dehydrogenase levels and a low calcium level. An electrocardiogram should be obtained in all patients with pronounced electrolyte abnormalities to rule out serious arrhythmias and conduction abnormalities.

Treatment. Every attempt should be made to anticipate and prevent TLS in patients at risk. The risk of TLS can be reduced by administering allopurinol for 2 to 3 days before

TABLE 3. **Cairo-Bishop Grading Classification of Tumor Lysis Syndrome***

	Grade 0†	Grade I	Grade II	Grade III	Grade IV	Grade V
LTLS	No	Yes	Yes	Yes	Yes	Yes
Creatinine‡	≤1.5 × ULN	1.5 × ULN	>1.5-3.0 × ULN	>3.0-6.0 × ULN	>6 × ULN	Death§
Cardiac arrhythmia‡	None	Intervention not needed	Nonurgent intervention needed	Symptomatic and incompletely controlled medically or controlled with a device	Life-threatening (eg, arrhythmia associated with CHF, hypotension, or shock)	Death§
Seizures‡	None	None	One brief, generalized seizure, seizures controlled with anticonvulsant drugs, or infrequent motor seizures	Seizures with impaired consciousness, poorly controlled seizures, generalized seizures despite medical interventions	Status epilepticus	Death§

*CHF = congestive heart failure; LTLS = laboratory tumor lysis syndrome; ULN = institutional upper limit of normal adjusted for age and sex.
†No LTLS.
‡Not attributable to a therapeutic drug or an intervention.
§Attributable probably or definitively to clinical tumor lysis syndrome.
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TABLE 4. **Treatment of Metabolic Abnormalities Associated With Tumor Lysis Syndrome***

Problem	Intervention	Dosages	Comments
Renal insufficiency and hypovolemia	Intravenous fluids	Normal saline, 3 L/m^2 daily (200 mL/kg daily)	Use with caution if history of CHF
	Dialysis		Patients with oliguric renal failure not responding to IV fluids or patients with CHF
Hyperuricemia	Allopurinol	100 mg/m^2 per dose orally every 8 h (10 mg/kg/day divided in 3 doses) or 200-400 mg/m^2 per day IV in divided doses every 8-12 h; commonly used dosages include 600 mg initially followed by 300 mg/d	Reduce dose in renal failure; multiple drug interactions (6-mercaptopurine and azathioprine); IV allopurinol should be used only in patients unable to take oral medications
	Rasburicase	0.05-0.2 mg/kg IV	Contraindicated in G6PD deficiency; transfer blood samples on ice to the laboratory; risk of sensitization and allergic reactions; expensive
Hyperphosphatemia (phosphate level >6.5 mg/mL [>2.1 mmol/L])	Minimize phosphate intake		Low phosphorus diet; phosphorus-free IV fluids
	Phosphate binders (aluminum hydroxide)	50-150 mg/kg daily orally	May interfere with drug absorption
	Dialysis		If no response to medical therapy
Hyperkalemia	Insulin (regular)	10 units IV	
	Dextrose (50%)	50-100 mL IV	
	Calcium gluconate (10%)	10-20 mL (100-200 mg) IV	Do not give with bicarbonate; use if arrhythmias or ECG changes; can repeat as needed
	Sodium bicarbonate	45 mEq IV (1 ampule of 7.5% $NaHCO_3$)	Use if acidosis; can repeat in 30 min
	Sodium polystyrene sulfonate (Kayexalate)	15-30 g every 6 h orally (can be used rectally)	Can be given with sorbitol
	Albuterol	Inhaled 2.5 mg	For severe hyperkalemia
	Dialysis		Severe hyperkalemia not responsive to other measures; renal failure; volume overload
Hypocalcemia	Calcium gluconate (10%)	5-20 mL (50-200 mg) IV	Only if symptomatic; repeat as necessary; use with caution in patients with severe hyperphosphatemia

*CHF = congestive heart failure; ECG = echocardiogram; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenously.

planned chemotherapy and by maintaining good hydration status. Allopurinol can be administered intravenously in patients unable to take oral medications.[39,40] Patients at high risk, such as those with tumors of high proliferative rate, high baseline uric acid, large tumor burden (white blood cell count $>50 \times 10^9$/L, high low-density lipoprotein cholesterol level, and large tumors), and chemosensitive disease, may benefit from intravenous recombinant urate oxidase (rasburicase).[36,41,42] Rasburicase is currently approved only for pediatric patients. Patients with established TLS need hospital admission and may need cardiac monitoring. Intravenous fluids should be given to maintain a urine output of 100 mL/m^2 per hour or greater. An infusion rate of 3 L/m^2 per day (200 mL/kg per day if ≤10 kg) is appropriate if cardiovascular status allows. Aggressive treatment of hyperkalemia is indicated as outlined in Table 4. Calcium gluconate and sodium bicarbonate should be used in addition to insulin, dextrose, and sodium polystyrene sulfonate (Kayexalate) in severe hyperkalemia and hyperkalemia associated with cardiac conduction disturbance. Patients with hyperkalemia and renal insufficiency or volume overload may need hemodialysis. Alkalinization of the urine has been recommended in the past, but usefulness remains controversial. Uric acid is more soluble in alkaline urine, but the solubility of xanthine and hypoxanthine decreases with alkalinization of the urine. Urine alkalinization could possibly lead to formation of urinary xanthine crystals, resulting in obstruction of renal tubules if allopurinol is used concurrently.[36] Diuretics such as furosemide can be used cautiously to increase urine output if the patient is not hypovolemic. Hyperphosphatemia can be treated by restricting phosphate intake and with phosphate binders such as aluminum hydroxide. Dialysis is indicated in severe cases, including patients with oliguric renal failure, congestive heart failure, or severe hyperkalemia or patients who do

not respond to medical therapy. Hypocalcemia should not be treated unless symptomatic. Hyperkalemia is treated conventionally with restriction of potassium intake and appropriate medications (Table 4).

NEUROLOGIC EMERGENCIES

Malignant Spinal Cord Compression

Malignant spinal cord compression (MSCC) is a relatively common problem and a true oncologic emergency. Early diagnosis is extremely important to prevent further neurologic compromise and to maintain functional status and quality of life. Between 2.5% and 6% of patients with cancer have MSCC as a complication of their disease.[43,44] All cancers can cause MSCC, but breast, lung, and prostate cancers account for almost two thirds of all cases.[45] Survival after the diagnosis of MSCC is poor, especially if paralysis is present or there is no clinical response to therapy.[43,46] The neurologic status at diagnosis and the time to development of symptoms are important prognostic factors for outcome.[47,48] Functional outcome is better if the development of symptoms is slow.[47,48] Overall survival depends on the tumor type, and patients with hematologic malignancies have better survival than patients with solid tumors. Patients with lung cancer have an especially poor prognosis.[43]

Pathophysiology. Most spinal cord compressions develop from tumors metastatic to the vertebral bodies that subsequently erode into and encroach on the spinal cord. The thoracic spine is the most common location for metastases that cause MSCC.[49] Less commonly, tumors such as lymphomas, sarcomas, and lung cancers that occupy the paraspinous space may enter the spinal canal through the intervertebral foramen and cause cord compression. Such tumors are important to recognize because, although they will not cause bony destruction, they can lead to spinal cord damage. Rarely, metastases occur directly at the spinal cord or meninges.

The mechanism of injury to the spinal cord from an epidural tumor is due to direct compression of the neural elements interrupting axonal flow or a vascular mechanism. Venous plexus obstruction can cause marked cord edema, whereas tumor occlusion of the arterial blood supply to the spinal cord creates an acute infarction, leading to abrupt and irreversible cord ischemia.[50] Multiple inflammatory mediators and cytokines can increase the edema and the ischemia. The ischemia finally results in irreversible neuronal injury.[50]

Clinical Presentation and Diagnosis. Ninety percent of patients with MSCC have back pain.[51] Eighty percent of all cases of MSCC occur in patients with a preceding diagnosis of malignancy.[52] Back pain in a patient with known cancer should be considered secondary to MSCC until proved otherwise. Other symptoms include radicular pain, motor weakness, gait disturbance, and dysfunction of bladder and bowel function.[44,51,53,54] Because neurologic deficits may not improve with treatment, it is imperative to not wait until neurologic dysfunction develops before considering the possibility of spinal cord compression. Multiple and synchronous spinal metastases are common, occurring in up to one third of patients.[55-58]

Magnetic resonance imaging (MRI) is the imaging study of choice in diagnosing MSCC.[59-61] If the history and clinical findings do not suggest metastases to the cervical spine, it is appropriate to obtain an MRI of the thoracolumbar spine only. Computed tomography (CT) myelography can be used if MRI is contraindicated or not available. Plain radiographs of the spine and radionuclide bone scans have limited sensitivity and specificity and are therefore less useful than MRI or CT in suspected cases of cord compression.[50] Plain radiographs are easy to obtain in most hospitals and emergency departments and may provide valuable information because abnormal findings have been reported in more than 80% of patients with symptomatic spinal metastases.[62,63]

Treatment. Therapy should be initiated as soon as possible but preferentially after the imaging studies have been obtained. Glucocorticoids should be given immediately if there is a delay in performing the imaging studies. Dexamethasone is the most commonly used corticosteroid and is typically given as an initial intravenous dose of 10 to 16 mg followed by 4 mg every 4 hours. Higher doses of dexamethasone (up to 100 mg) may be associated with slightly better outcome but have a higher incidence of adverse effects.[61,64-66] Patients without motor deficits or massive invasion of the spine on imaging studies may do well without corticosteroids.[67] Radiation therapy has been the mainstay of the treatment, but recent studies have challenged that belief.[49,63,68] Several radiation regimens are available, but there is no evidence that one is superior to the others.[61] A recent study by Patchell et al[68] showed that in patients who present with neurologic deficits, functional outcome, including the ability to ambulate and maintain continence, is better in patients who undergo radical tumor resection followed by radiation compared with patients who receive radiation therapy alone. Despite the findings of that study, the indications for surgical treatment continue to be debated and have to be carefully considered for each case. It seems reasonable to consider surgery in highly selected cases, especially in patients who maintain a good performance status, including the ability to withstand an extensive operation; when there is gross instability of the spine, rapidly progressive symptoms, or progressive symptoms during radiation therapy; or when tissue for

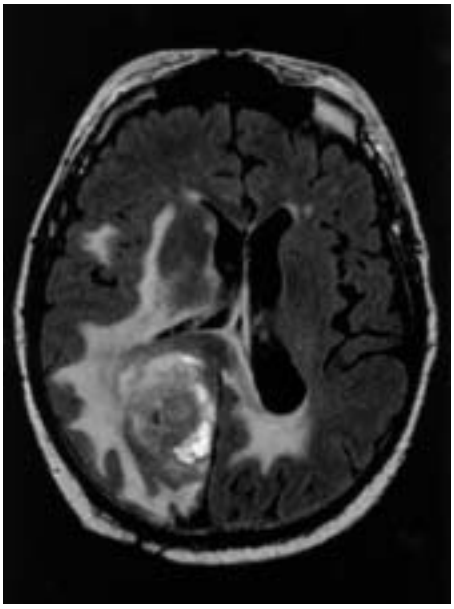

FIGURE 1. Patient with glioblastoma multiforme. The magnetic resonance image shows a contrast-enhancing tumor, edema of the adjacent brain tissue, and distortion of the ventricle.

diagnosis is needed. A surgeon experienced in spinal surgery should be consulted if there is any doubt regarding the need for a surgical intervention. Surgery may become even more feasible with the advent of less invasive surgical techniques.[49,63]

Brain Metastases and Increased Intracranial Pressure

Intracranial metastases occur in up to one fourth of patients dying of cancer.[69] Any cancer can metastasize to the brain, but lung cancer, breast cancer, and melanoma are the most common culprits.[70]

Pathophysiology. Brain metastases arise from hematogenous spread of the tumor, and the distribution within the brain is in accordance with the regional blood flow.[71] Approximately 90% of brain metastases are found in the supratentorial region. The metastases are commonly located at the junction of the gray and white matter and in the so-called watershed areas of the brain.[71] Brain edema and tumor expansion commonly result in increased intracranial pressure.

Clinical Presentation and Diagnosis. Most patients who present with brain metastases are known to have cancer. Less commonly, brain metastases are the initial presentation of a malignancy. In rare cases, the brain metastases are the only known site of disease (brain metastases of unknown primary tumor).[72] Symptoms can be focal or generalized and depend on the location of the lesion or lesions within the brain. Brain metastases are usually associated with gradual appearance of symptoms that may be subtle, and only 50% of patients have headaches.[73] Patients may present with acute seizures or symptoms of increased intracranial pressure. Magnetic resonance imaging is the most sensitive and specific diagnostic modality (Figure 1).[71,74] Computed tomographic scans are less sensitive, especially for metastases in the posterior fossa.

Treatment. Brain metastases portend a poor prognosis for most patients with solid tumors and often occur in the setting of advanced systemic disease. Thus, it may be appropriate to treat only to alleviate symptoms, or in other patients it may be appropriate to provide aggressive treatment directed at the tumor. In this review, we focus on symptom management (Table 5). Elevated intracranial pressure is most commonly treated with steroids, specifically dexamethasone, because it is the most lipid soluble of all the steroids.[75] A commonly used regimen consists of an initial dose of 16 to 24 mg intravenously, followed by 4 mg every 6 hours. Lower doses (4 mg/d) may be as effective as higher doses and associated with fewer adverse effects.[76] Asymptomatic patients may not need corticosteroids. Seizures are treated with anticonvulsants, but patients with brain metastases and no history of seizures do not generally

TABLE 5. **Management of Brain Metastases and Increased Intracranial Pressure***

Problem	Intervention	Dosages and comments
Intracranial hypertension	Dexamethasone; other corticosteroids can be used in equipotent doses	4-16 mg daily in divided doses; higher doses can be used initially, especially if patients are very symptomatic
	Mannitol	1 g/kg IV; can follow with 0.25-0.5 mg/kg every 3-6 h; not recommended for routine use unless patient is critical and going to operating room for debulking
Seizures (status epilepticus)	Lorazepam	0.1 mg/kg IV at 2 mg/min up to 4 mg
	Phenytoin	20 mg/kg IV at 50 mg/min
	Fosphenytoin	20 mg/kg PE at 150 mg PE per minute
Intracranial tumor	Radiation therapy	Whole-brain radiation; stereotactic radiosurgery
	Surgery	Especially if solitary metastases, oligometastases (<3), or metastases in the posterior fossa

*IV = intravenously; PE = phenytoin equivalents.

need anticonvulsant drugs.[77] Reviews of the treatment of status epilepticus have been published.[78,79] More definitive treatment, such as surgery and radiotherapy, is usually offered to selected patients who have oligometastatic disease, maintain a good performance status, and have relatively well-controlled or minimal systemic disease.[71,74] Whole-brain radiation is still the mainstay of treatment for brain metastases, but stereotactic radiosurgery is emerging as a new option for selected patients with brain metastases.[80,81]

CARDIOVASCULAR EMERGENCIES

Malignant Pericardial Effusion

Pericardial effusions are commonly seen in patients with advanced cancer and are frequently asymptomatic. The presence of malignant pericardial effusions portends a poor prognosis, with most patients dying within 1 year.[82]

Pathophysiology. Pericardial effusions can result from metastases to the pericardium, direct invasion of the cancer, or therapy.[83] Large or rapidly accumulating effusions may lead to compression of the heart chambers and cardiac tamponade.[84]

Clinical Presentation and Diagnosis. Small pericardial effusions are frequently asymptomatic. Symptoms of pericardial effusions include dyspnea, cough, chest pain, dysphagia, hiccups, and hoarseness.[85] The onset of symptoms can be slow, but occasionally these patients present with acute symptoms. Physical findings include tachycardia, distant heart sounds, fixed jugular venous distention, upper and lower extremity edema, and pulsus paradoxus. The presenting features of cardiac tamponade commonly include exaggeration of these symptoms in addition to hypotension and shock.[84] An electrocardiogram may reveal low-voltage, nonspecific ST-T changes and electric alternans.[85,86] The preferred diagnostic method is echocardiography, which may both confirm the presence of a pericardial effusion and provide hemodynamic information, including presence of tamponade physiology.[85,87] Both CT and MRI can be used to diagnose pericardial effusions and may in addition be valuable in assessing structural abnormalities, such as intracardiac tumors or tumors that invade the pericardium.[88]

Treatment. Asymptomatic effusions do not need to be treated. If patients are symptomatic or deteriorating, they may need an urgent intervention. Echocardiographically guided pericardiocentesis is a safe and effective procedure.[87] Malignant pericardial effusions can also be managed surgically for palliation of symptoms by placement of a percutaneous pericardial drain or by resection of the pericardium.[86,89] Systemic and intrapericardial chemotherapy may provide palliation of symptoms in chemotherapy-sensitive tumors.[86,90] Radiation therapy may provide palliation in selected cases.

Superior Vena Cava Syndrome

Superior vena cava syndrome (SVCS) occurs when the superior vena cava becomes occluded or compressed, restricting blood return to the heart. Malignancies are the most common cause of SVCS, but multiple benign disorders can also cause the condition. The most common malignancies that cause SVCS are lung cancer and lymphoma.[91] Intraluminal thrombus can also cause SVCS by occluding the superior vena cava.[91,92] Indwelling central venous catheters are increasingly found as a cause of SVCS in patients with cancer, and they may present atypically with predominantly unilateral findings.[93-95]

Pathophysiology. The thin-walled superior vena cava is easily compressed by tumors, resulting in impaired venous drainage from the head, neck, and upper extremities. If the occlusion occurs gradually, collaterals may form and mitigate the symptoms.

Clinical Presentation and Diagnosis. The onset of SVCS is usually insidious but may occur rapidly, especially if the underlying cause is a rapidly growing tumor or thrombosis. The most common symptoms are dyspnea, facial swelling, and cough that may be aggravated by bending forward or stooping. The most common signs are distended neck and chest wall veins, facial edema and plethora, and edema of the upper extremities.[91,92,96] The diagnosis is usually made with CT with or without venography, but MRI can also be used.[97]

Treatment. Usually, SVCS is not a true medical emergency unless neurologic symptoms are present; therefore, in patients who present without a preceding diagnosis of malignancy, biopsies should be performed before instituting therapy. Mediastinoscopy, bronchoscopy, and biopsy can be safely performed in the setting of SVCS.[98] Stenting of the superior vena cava has been shown to be effective and feasible in relieving the symptoms of SVCS.[99-101] Radiotherapy is a standard treatment modality for sensitive tumors but may take a few weeks to show effect.[102,103] Chemotherapy and corticosteroids can also be used, especially in tumors that are sensitive.[104]

HEMATOLOGIC EMERGENCIES

Hyperviscosity Due to Dysproteinemia (Monoclonal Gammopathy)

Hyperviscosity is defined as an increased intrinsic resistance of fluid to flow. It can be seen in a variety of disorders, including monoclonal gammopathies such as Waldenström macroglobulinemia (WM) and acute leukemias.[105] In this review, we discuss hyperleukocytosis related to leukemia separately.

TABLE 6. **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

Pathophysiology. The hyperviscosity seen in association with WM is related to high levels of the large IgM molecule.[106] Symptoms of hyperviscosity are rare with monoclonal gammopathies other than IgM, and patients with myeloma that produces IgA monoclonal protein appear to be more prone to develop symptomatic hyperviscosity than patients with IgG myeloma due to the tendency of the IgA to polymerize.[105] Less than 7% of patients with newly diagnosed myeloma have hyperviscosity.[107] The clinical symptoms are primarily related to increased stasis of blood flow, resulting in ischemia and hemorrhages. Patients with WM are unlikely to develop symptoms if the serum viscosity is less than 4 cP and if the serum concentration of IgM is less than 4 g/L.

Clinical Presentation and Diagnosis. Waldenström macroglobulinemia occurs predominantly in elderly patients, with a median age at onset of 60 years. The onset of hyperviscosity is usually gradual and commonly results from effects of impaired perfusion on the central nervous system and the eyes (Table 6). Impaired hemostasis that manifests primarily as mucocutaneous bleeding may be prominent. Common symptoms include mental status changes, visual changes, retinal hemorrhage, papilledema, and engorged retinal veins. Purpura is common because of quantitative or qualitative defects of platelets.

Treatment. When hyperviscosity secondary to a monoclonal gammopathy is diagnosed, it is important to exercise caution with red blood cell transfusions for anemic patients because increasing the hematocrit may greatly increase plasma viscosity. The fastest method to decrease plasma viscosity is plasmapheresis, which is a relatively safe procedure in experienced hands. Plasmapheresis is especially effective in patients with WM because most of the IgM monoclonal protein is within the intravascular space.[108] A single plasmapheresis can successfully decrease the hyperviscosity and associated clinical improvement, whereas it usually takes several therapies to achieve the same benefit for patients with IgA or IgG myeloma.[108] Ultimately, control of the underlying disease with glucocorticoids and chemotherapeutic agents, such as alkylating agents (melphalan, chlorambucil, cyclophosphamide) or nucleoside analogues (cladribine or rituximab), are required to prevent recurrent symptoms.

Hyperleukocytosis and Leukostasis

Increased viscosity secondary to leukocytosis is a well-recognized complication associated with acute leukemias.[109] Hyperviscosity has also been reported in patients with erythrocytosis and severe thrombocytosis.[110,111] Hyperleukocytosis is seen in up to 13% of patients with acute myelogenous leukemia and may even be more common in the pediatric population. Symptomatic hyperleukocytosis is less common in acute lymphoblastic leukemia.[109] Hyperleukocytosis that results in leukostasis is much less common in chronic lymphocytic and myelogenous leukemias, despite extremely elevated cell counts.

Pathophysiology. Earlier reports had suggested that an increased number of circulating leukocytes was the major factor that resulted in sluggish capillary blood flow (leukostasis).[112] More recently, investigators have suggested that abnormal expression of adhesion molecules is a crucial element in the pathophysiology of leukostasis.[113]

Clinical Presentation and Diagnosis. The clinical manifestations of hyperleukocytosis and leukostasis are in many ways similar to the manifestations of hyperviscosity due to a monoclonal protein discussed previously, but pulmonary symptoms such as dyspnea are also common. Pulmonary symptoms of leukostasis may be difficult to distinguish from infection because patients may have pulmonary infiltrates and fever. Fever is common in patients with hyperleukocytosis and is uncommonly related to an infection. Most patients have severely elevated leukocyte counts, but occasional patients have symptoms with leukocyte counts less than 100×10^9/L.[113] Thrombocytopenia and coagulopathy are commonly seen in association with acute leukemia and hyperleukocytosis.

Treatment. Prompt leukoreduction is the mainstay of therapy for hyperleukocytosis and can be achieved quickly with leukapheresis. In patients with acute myelogenous leukemia, leukapheresis therapy is commonly begun when the leukocyte count is above 1.0×10^9/L, and the goal is to reduce the count to at least 0.5×10^9/L.[113]

Although leukapheresis may reduce early mortality in patients with acute myelogenous leukemia, the improvement in overall survival is less certain.[114,115] Leukapheresis alone is never sufficient as therapy however, and chemotherapy needs to be initiated as soon as possible. Hydroxyurea in a dosage of 50 to 100 mg/kg daily can be used while awaiting more definitive chemotherapy.[116] These patients should also receive prophylactic therapy for TLS as described previously. Transfusions need to be used with caution because the transfused red blood cells may substantially increase the blood viscosity. Cranial irradiation is occasionally considered in patients with acute neurologic changes, although its role is controversial and no controlled series confirm benefit. Similarly, little evidence is available to support a clear role for pulmonary irradiation for leukostasis that results in hypoxia.

INFECTIOUS COMPLICATIONS

Neutropenic Fever

Infections in cancer patients are common and a significant cause of morbidity and mortality, especially in patients with leukemia undergoing chemotherapy. Fever is defined as a single oral temperature in excess of 38.3ºC (101.3ºF) or a sustained temperature of more than 38ºC (100.4ºF) for more than 1 hour.[117] For this review, we consider an absolute neutrophil count less than 1.0×10^9/L as neutropenia. A neutrophil count less than 0.5×10^9/L is considered severe neutropenia.

Pathophysiology. Most episodes of febrile neutropenia occur in patients receiving chemotherapy. Less commonly, patients with acute leukemias, myelodysplastic syndromes, or other diseases that create leukopenias may present de novo with febrile neutropenia. Most patients currently being treated with chemotherapy now receive treatment in the outpatient setting. The risk of developing febrile neutropenia depends on both the depth and the duration of the neutrophil nadir, as well as comorbid conditions or complications such as mucositis. The timing of the neutrophil nadir depends on the type of chemotherapy given, but for most outpatient chemotherapy, the neutrophil nadir typically occurs 5 to 10 days after the last dose. Most often, white blood cell recovery occurs within 5 days of this nadir. Certain regimens, especially those used to treat leukemias and lymphomas, produce a longer-lasting and more profound neutropenia.

Microbiology. Multiple gram-positive and gram-negative bacteria can cause infections in neutropenic patients, but frequently no organisms are recovered. Enteric gram-negative bacilli have historically been the bacteria most commonly recovered from the bloodstream of febrile neutropenic patients. Gram-positive bacteria are assuming more importance.[118,119]

TABLE 7. **Initial Antibiotic Therapy of Neutropenic Fever***

Monotherapy	Cefepime
	Ceftazidime
	Carbapenem (eg, imipenem or meropenem)
	Piperacillin/tazobactam
Dual therapy	Aminoglycoside plus 1 of the following drugs
	Piperacillin
	Cefepime or ceftazidime
	Carbapenem

*Some patients may require additional antibiotics for gram-positive bacteria. See text for indications regarding additional coverage directed against gram-positive bacteria.

Clinical Presentation and Diagnosis. Fever is commonly the only symptom, but patients may also have localizing symptoms and physical findings. Common infections may present atypically due to the lack of neutrophils. Skin infections may manifest as subtle rash or erythema, patients with meningitis may not have the typical physical findings such as nuchal rigidity, and urinary tract infections may be asymptomatic. Moreover, because of profound neutropenia, patients can have lung infections without pulmonary infiltrates and no pyuria despite having a urinary tract infection. A thorough physical examination should be performed. The oral cavity should be examined carefully, looking for erythema and mucosal ulcers. All sites of intravenous catheters and tunneled catheters should be inspected, looking for erythema, tenderness, and purulent exudate. The perianal area should be inspected and palpated gently. Digital rectal examination or any other rectal manipulations are discouraged.

Blood cultures should be obtained as soon as possible. One sample should be drawn from a peripheral vein and another from a central venous catheter if one is in place.[117,120] Samples for urine cultures should be collected, and sputum should be sent for cultures if there is productive cough. Stool samples and cerebrospinal fluid should be cultured, but only if there is clinical suspicion of infections in these sites.[118] Chest radiographs are commonly normal or show nonspecific findings. High-resolution CT may be helpful in patients with suspected lung infection and a normal chest radiograph.[121]

Treatment. Once febrile neutropenia is diagnosed, instituting therapy should not be delayed. Broad-spectrum antibiotics should be administered once the necessary cultures have been obtained. Commonly used antibiotics and antibiotic combinations for infectious complications are listed in Table 7. Patients with fever but no other symptoms should be treated even if the physical examination and the initial laboratory studies and radiographs show no evidence of infection. Afebrile patients should be treated as well if an infection is strongly suspected. Use of broad-spectrum an-

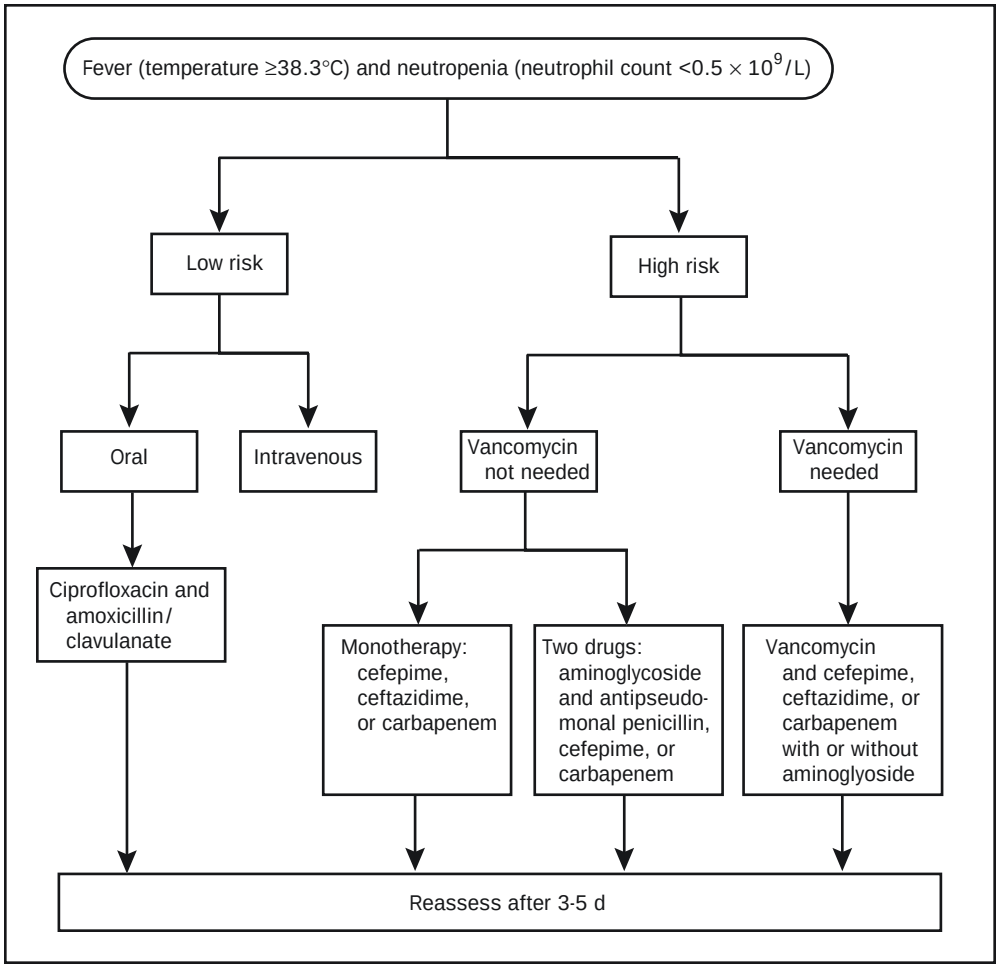

FIGURE 2. Initial management of patients with neutropenic fever. Adapted from *Clin Infect Dis*,[117] with permission from the University of Chicago Press, copyright © 2006 by the Infectious Diseases Society of America. All rights reserved.

tibiotics is essential, and in certain circumstances, a drug active against gram-positive bacteria is recommended. Such circumstances include known colonization with gram-positive bacteria, suspected infection of a central venous line or device, and severe sepsis with or without hypotension. Gram-positive coverage should also be considered in patients with suspected skin infection or severe mucosal damage and when prophylactic antibiotics against gram-negative bacteria have been used. Vancomycin is the most commonly used drug for suspected infections with gram-positive bacteria. Single-drug therapy with a broad-spectrum antibiotic appears to be as effective as double gram-negative coverage in most circumstances, is associated with fewer adverse effects, and is generally recommended over 2-drug therapy (dual therapy). Antifungal or antiviral drugs are usually not needed as a part of initial therapy. The following approach is commonly used (Figure 2).

Selected patients with neutropenic fever can be treated in the outpatient setting. Close follow-up and unrestricted access to health care personnel are essential when patients are receiving outpatient therapy for neutropenic fever (Figure 3). Certain social situations are contraindications to outpatient therapy, including history of noncompliance, inability to care for oneself, lack of caregivers, no telephone, or lack of reliable transportation. Several patient-related factors favor lower risk of severe infection in these patients (Table 8).[117]

The Multinational Association for Supportive Care in Cancer has introduced a prediction device to assess patients suitable for outpatient antibiotic therapy (Table 9).[122] The initial evaluation focuses on assessing the burden of illness. Several factors are evaluated and assigned a score. Individual scores are totaled, and the patient is given a total score. A total score of 21 or higher indicates

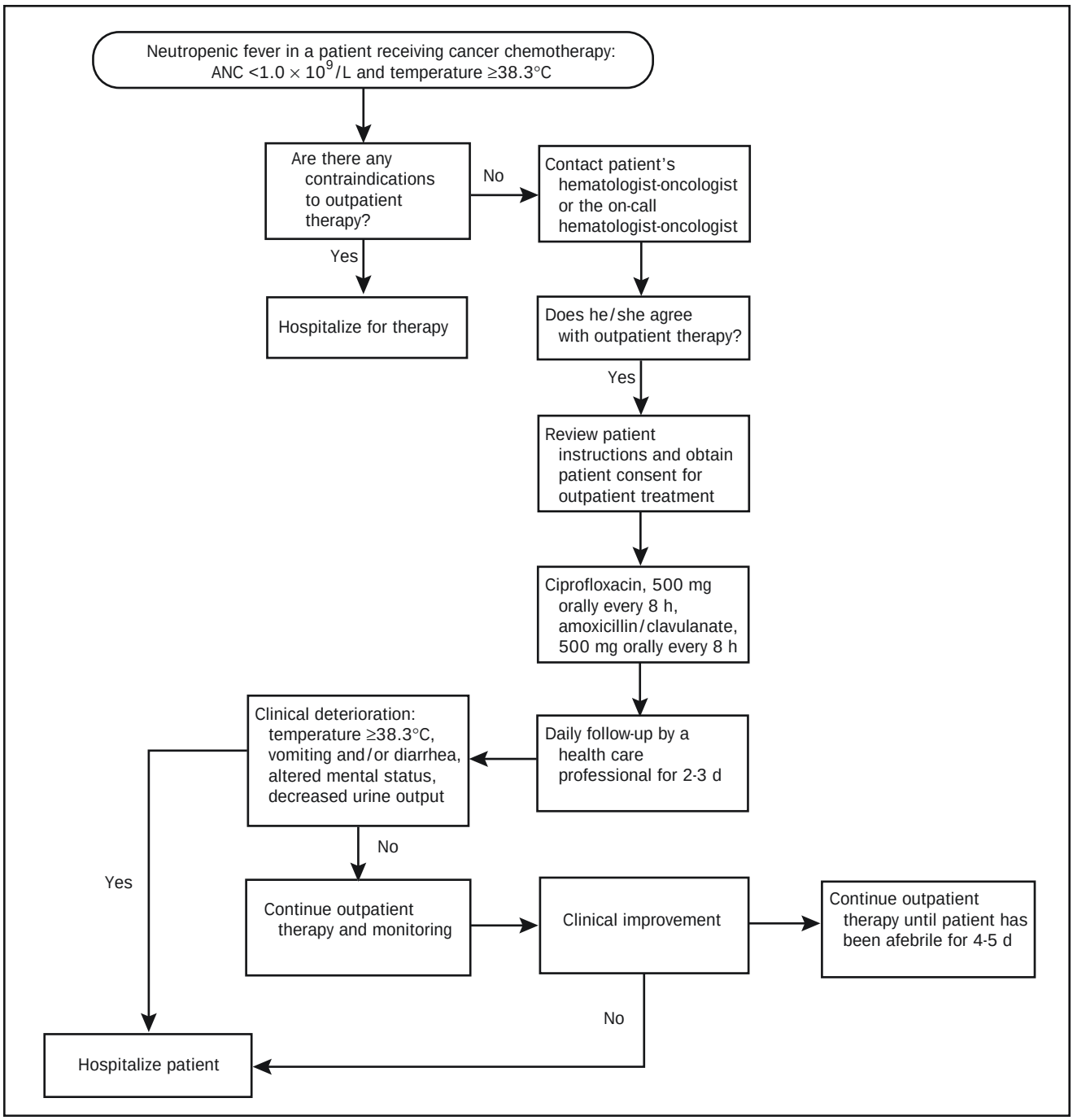

FIGURE 3. Outpatient therapy for neutropenic fever. ANC = absolute neutrophil count.

patients with low risk of a serious infection (Table 9). The best studied regimen used in outpatient therapy of neutropenic fever is a combination of ciprofloxacin (500 mg every 8 hours) and amoxicillin/clavulanate (500 mg every 8 hours). Daily assessment by a health care professional is recommended for the first 3 days to assess response, tolerability, and compliance to therapy. A recent meta-analysis has shown that the use of myeloid growth factors in patients with established neutropenic fever can reduce the length of hospitalization and the neutrophil recovery time, but these reductions are minimal.[123] The effects of myeloid growth factors on infection-related

TABLE 8. **Factors That Favor Low Risk for Severe Infection in Patients With Neutropenic Fever**

Absolute neutrophil count ≥1.0×10^9/L
Absolute monocyte count ≥1.0×10^9/L
Normal chest radiograph
Normal or only minimally abnormal renal and liver chemical test results
Duration of neutropenia <7 d
Resolution of neutropenia expected in <10 d
No intravenous catheter-site infection
Early evidence of bone marrow recovery
Malignancy in remission
Peak temperature of <39°C
No mental or neurologic changes
No appearance of illness
No abdominal pain
No comorbidity complications (eg, shock, hypoxia, pneumonia, deep-organ infection, vomiting, or diarrhea)

TABLE 9. **Multinational Association for Supportive Care in Cancer Scoring System for Patients With Neutropenic Fever***

Characteristic	Score
Burden of illness: no or mild symptoms	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

*Patients with a total score of ≥21 have a low risk of having serious medical complications. Points attributed to the variable "burden of illness" are not cumulative. Therefore, the maximum theoretical score is 26.

mortality are uncertain. In general, these drugs should not be used unless consulting with a specialist in hematology and oncology or infectious diseases.

CONCLUSION

Emergencies are common in patients with cancer, and these patients frequently seek help in emergency departments and offices of primary care physicians. Prompt evaluation that leads to a diagnosis and urgent institution of therapy can be lifesaving or essential to prevent irreversible loss of function. With timely intervention and a multidisciplinary approach to therapy, many of these patients can return to their previous level of function and independence. Therefore, it is important that all health care professionals likely to encounter patients with cancer have a sound knowledge of the most common oncologic emergencies.

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