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Managing Patients With Oncologic Complications in the Emergency Department

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Authors

David Wacker, MD
Assistant Professor; Section of Pulmonology, Allergy, Critical Care, and Sleep Medicine; Department of Internal Medicine; University of Minnesota Medical School, Minneapolis, MN

Michael T. McCurdy, MD
Associate Professor, Pulmonary & Critical Care Medicine; Associate Professor of Emergency Medicine, University of Maryland School of Medicine, Baltimore, MD

Peer Reviewers

Karin Chase, MD
Assistant Professor of Medicine and Emergency Medicine, Departments of Medicine and Emergency Medicine, University of Rochester Medical Center, Rochester, NY

Natalie Kreitzer, MD
Assistant Professor, Emergency Medicine and Neurocritical Care, University of Cincinnati, Cincinnati, OH

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Abstract

As the prevalence of cancer continues to increase in the general population and improvements in cancer treatment prolong survival, the incidence of patients presenting to the emergency department with oncologic complications will, similarly, continue to rise. This issue reviews 3 of the more common presentations of oncology patients to the emergency department: metastatic spinal cord compression, tumor lysis syndrome, and febrile neutropenia. Signs and symptoms of these conditions can be varied and nonspecific, and may be related to the malignancy itself or to an adverse effect of the cancer treatment. Timely evidence-based decisions in the emergency department regarding diagnostic testing, medications, and arrangement of disposition and oncology follow-up can significantly improve a cancer patient's quality of life.

Case Presentations

A 67-year-old man presents to the ED with a 5-day history of constant, dull, nonradiating, mid-lower back pain. He denies any alleviating factors or any specific movements or ambulation that worsen the pain. He denies numbness or weakness to his lower extremities, fevers, or bowel or bladder problems. His past medical history is significant for low-grade prostate cancer, diagnosed 2 years ago, which was managed by active surveillance only. On exam, his strength to both lower extremities seems diminished, his patellar reflexes are brisk, and his gait is unstable. He has no range-of-motion limitations to his back, but does complain of some midline tenderness at about the L1 level. Straight-leg raise is negative on both sides. His rectal tone is normal. At the conclusion of his exam, he states: "I really just came in to get something for the pain, doc. Can you prescribe me something so I can get going?" You wonder if he needs more testing...

A 55-year-old man with non–small-cell lung cancer presents after running a temperature of 38.5°C (101.3°F) at home. The fever lasted 3 hours and he denies other symptoms. He denies oral or rectal pain. He is currently undergoing chemotherapy for non–small-cell lung cancer; his last round was about 9 days ago. His additional past medical history is significant only for hypertension, though he is not on any medications for it. Family and social history are otherwise unremarkable. On exam, his vital signs are: temperature, 37.5°C (99.5°F); heart rate, 105 beats/min; respiratory rate, 25 breaths/min; blood pressure, 105/50 mm Hg; and oxygen saturation, 92% on room air. He is in no apparent distress, HEENT exam is normal except for mildly pale conjunctiva, lungs are clear, and heart and abdominal exam are unremarkable. External exam of the anus does not reveal evidence of perianal abscess. He has an indwelling peripherally inserted central catheter, and the site is well dressed, without stigmata of infection. Labs are remarkable for a white blood cell count of 0.6 cells/mm^3 with neutrophil percentage of 10% and no bands. Hemoglobin is 7.1 g/dL, platelets are 45,000/mcL. Serum lactate is 2.9 mmol/L. Serum electrolytes, creatinine, liver function panel, and urinalysis are unremarkable. Chest x-ray shows a possible small infiltrate in the right base. The patient says he feels better overall, and asks if he needs to go home with any antibiotics, but you wonder if it is best practice to send him home...

Introduction

With increased life expectancy nationwide, the incidence and prevalence of cancer and cancer-related visits to the emergency department (ED) continues to rise. Evaluating patients for complications of malignancy or its treatment is obfuscated both by the often nonspecific presenting symptoms (eg, lethargy or encephalopathy) and the uncertainty about whether the symptoms are due to progression of the underlying disease or a complication of its therapy.[1,2] This issue of *Emergency Medicine Practice* reviews the current state of diagnosis and ED treatment for metastatic spinal cord compression (MSCC), tumor lysis syndrome (TLS), and febrile neutropenia, focusing particularly on updates since the last time this topic was reviewed, in 2010.[3,4]

Critical Appraisal of the Literature

Because of the diversity of oncologic emergencies, we performed PubMed and MEDLINE® searches using terms specific to each emergency (eg, *metastatic spinal cord compression, neutropenic fever,* and *tumor lysis syndrome*), rather than simply searching for *oncological emergencies*. Particular attention was paid to articles published in the period since the original *Emergency Medicine Practice* articles on this subject in 2010. Our search yielded significant new literature on the topics of MSCC, TLS, and neutropenic fever, including updated guidelines for each of these, as well as several meta-analyses and large prospective randomized and observational studies. Despite our focus on topics with stronger evidence, in some instances, we had to rely more heavily on weaker evidence, such as case reports and expert opinion.

Prehospital Care

Development of specific prehospital therapies is largely limited by difficulties in identification of oncologic emergencies in the prehospital setting. Cases are rare among the general population, and symptoms are often nonspecific. Furthermore, diagnostic confirmation often relies on testing that is unavailable to prehospital providers (eg, spinal magnetic resonance imaging [MRI] to confirm vertebral metastasis, or laboratory confirmation of neutropenia). Prehospital therapies remain largely supportive (eg, supplemental oxygen for hypoxia, noninvasive positive pressure ventilation or intubation for respiratory distress or failure, intravenous [IV] fluids for hypotension). Whenever possible, the patient should be transported to a facility with oncological services, ideally at the same facility as the patient's oncologist.

Metastatic Spinal Cord Compression

Epidemiology and Pathophysiology of Metastatic Spinal Cord Compression

MSCC is a devastating complication of cancer because of its potential to cause irreversible neurologic damage, such as paraplegia. Fortunately, its incidence remains low; in a retrospective study of the last 5 years of life of approximately 120,000 patients with any cancer requiring hospital admission, the incidence of MSCC was only 2.5%.[5] Nonetheless,

when it occurs, MSCC represents both a neurological threat and a marker of poor prognosis, with most observational studies showing a median life-span of 3 to 7 months after its diagnosis.[5-7]

The most common type of lesion causing spinal cord compression arises from extension of vertebral body metastases into the spinal canal.[8] In animal models, the malignancy grows in the marrow space, often without invading the cortex, and then exits the vertebral body to the anterior spinal canal via the vertebral vein foramen, where subsequent further growth results in cord compression.[9] Because the vertebral cortex is often not violated, cord compression may occur in the absence of metastatic findings on plain radiograph.[9]

Once the tumor has extended into the spinal canal, nerve insult occurs by one of two mechanisms: First (and more commonly), increasing pressures obstruct the epidural venous plexus, leading to compromised cord perfusion, breakdown of the blood-brain barrier, and vasogenic edema, which further aggravates compression.[8] Administration of corticosteroids to counter vasogenic edema can temporarily reverse this process, but neuronal damage will eventually ensue without definitive management of the offending lesion. Second (and less commonly), direct pressure on the nerves themselves will eventually lead to demyelination and axonal injury.[8]

Unsurprisingly, tumor types known for bone avidity are most likely to be responsible for MSCC, with 50% to 60% of cases attributable to breast, prostate, or lung cancer.[10-12] Consistent with the belief that vertebral metastases arise from hematologic spread, the incidence of metastatic disease within each section of the vertebral column parallels the distribution of blood supply. Most observational studies show 5% to 15% incidence of lesions in the cervical spine, 50% to 70% in the thoracic spine, and 20% to 30% in the lumbar spine.[10,11] Importantly, 2 separate observational studies reviewing imaging of patients with suspected MSCC demonstrated that 30% to 40% of patients with MSCC had identified metastatic disease at multiple levels.[13,14]

Clinical Features of Metastatic Spinal Cord Compression

Back pain is the earliest and most common presenting symptom, occurring in more than 80% of cases of MSCC.[15,16] Weakness and sensory loss are the next most common presenting symptoms, with incidences of 35% to 75% and 50% to 70%, respectively. Autonomic dysfunction, usually involving the bowel or bladder, arises latest in the progression of symptoms and is seen on presentation in only 50% to 60% of cases and almost never as the sole presenting symptom.[15,16] Physical examination for patients in whom MSCC is suspected (which should include all patients with back pain and known or suspected malignancy) should include thorough testing of strength, sensation, and reflexes in the lower extremities; palpation of the full length of the vertebral column; and assessment of rectal tone and perianal sensation.

Although back pain is the earliest and most common symptom of MSCC, it is also the least specific, often causing the diagnosis of MSCC to be delayed by weeks to months.[17,18] Maintaining a high index of suspicion can reduce this delay. In a cross-sectional study of 1975 patients with back pain in a large primary care practice, a personal history of cancer had a specificity of 98% for the diagnosis of MSCC, suggesting that this diagnosis should be assumed until proven otherwise in patients with back pain and a history of cancer.[19] The absence of cancer in the patient's history does not rule out MSCC, however, as 20% to 30% of those afflicted are previously unaware of their malignancy.[19,20] Other diagnoses that may cause back pain in patients with malignancy include vertebral fracture (benign or malignant), vertebral or epidural infection (particularly in a potentially immunocompromised patient), and musculoskeletal causes of back pain (eg, strains or sprains).

Diagnostic Workup of Metastatic Spinal Cord Compression

Magnetic Resonance Imaging

The diagnosis of MSCC is confirmed or refuted with spinal imaging. MRI has the highest sensitivity (93%) and specificity (97%) for the diagnosis.[21,22] An MRI including all 3 sections of the spine can provide valuable information even when symptoms are localized to a single section or the diagnosis of MSCC has already been established. Two retrospective observational studies comparing findings of full-spine MRI with clinical findings demonstrated that one-quarter of patients had a cord-affecting lesion that was > 3 vertebral levels away from the clinically suspected location,[13] and half of the patients had treatment changes (usually changes to the radiotherapy field) based on information provided by the scan.[13,23] Further highlighting the need for full-spine MRI, 4 separate studies of patients with symptomatic MSCC have demonstrated that full-spine MRI will identify an additional asymptomatic site of cord compression in 25% to 40% of patients.[11,13,14,24] However, because of the low incidence of metastasis to the cervical spine, only 1% of these additional sites were discovered there.[25]

For these reasons, all patients with suspected MSCC should undergo MRI imaging of at least the thoracic and lumbar segments of the spine, and ideally all 3 segments. Because MRI is an expensive and time-consuming resource, completion of a full-spine MRI need not be completed prior to disposition. However, because management of cord compression is time-sensitive, every effort should be made to image the affected segment of the spine as quickly as possible.

If not all segments are imaged initially, the remaining segments should be scanned nonemergently.

Computed Tomography

If MRI is unavailable or contraindicated (eg, in patients with MRI-incompatible pacemakers), a computed tomography (CT) scan is the test of choice. A CT scan without contrast may be performed initially and, if evidence of vertebral metastasis is present, a CT myelogram (in which dye is injected into the subarachnoid space just prior to the scan) should be conducted to evaluate for cord impingement.[26] Two observational, head-to-head comparisons of CT myelography and MRI involving a total of 101 patients have demonstrated similar sensitivity of the 2 techniques.[27,28] Although rarely performed because of the widespread availability of MRI, CT myelogram is still widely available. It entails 3 basic steps: (1) lumbar puncture; (2) infusion of contrast dye into the intrathecal space; and (3) subsequent CT scanning. Depending on the radiologist's comfort with the lumbar puncture procedure, the ED physician may be asked to perform the lumbar puncture in the CT suite to facilitate contrast administration. Contraindications to CT myelography include allergy or known adverse reaction to the contrast media and standard contraindications to lumbar puncture (eg, severe thrombocytopenia, coagulopathy, cellulitis at the injection site). Historical concerns about spinal coning, in which changes in the pressure gradient across a complete subarachnoid obstruction lead to paralysis below the obstruction, have not been borne out in patients undergoing myelography.[29]

Plain Radiography

Plain radiographs may be helpful in demonstrating vertebral metastases, but negative radiographs are insufficient to rule out MSCC because a malignant lesion may still compress the cord without involving cortical bone.[9] In an observational study of 60 patients, two-thirds of patients with normal radiographs were found to have metastatic vertebral disease by alternative imaging methods.[26] Two other observational studies have shown that plain films failed to identify an epidural tumor in up to 20% of cases,[30,31] and a prospective observational trial of over 300 patients demonstrated that plain films predict the correct vertebral level of spinal involvement in only 20% of cases.[17]

Radionuclide Scanning

Radionuclide scanning, which utilizes a radioactive tracer to localize sites of increased bone turnover, has a sensitivity and specificity similar to MRI for detecting sites of vertebral metastasis;[32] however, it cannot provide information about the spinal canal or cord itself. Furthermore, its usefulness to the emergency clinician is limited by availability and the duration of time required to perform the test (eg, absorption of the tracer may take up to 4 hours).

Management of Metastatic Spinal Cord Compression

Corticosteroids

In addition to appropriate analgesia, the immediate therapy for proven or suspected MSCC with neurological symptoms is corticosteroids, which can slow or reverse development of vasogenic edema in order to reduce mass effect on the spinal cord.[8] In a randomized controlled trial of 57 patients comparing only radiotherapy and/or surgery with the same therapy plus high-dose dexamethasone (96 mg IV immediately, then 96 mg orally for 3 days, then a taper), patients in the corticosteroid group retained the ability to ambulate at the completion of treatment, and at 6 months post completion, at higher rates than those in the noncorticosteroid group (81% vs 63%, and 59% vs 33%, respectively, $P < .05$ in both cases).[33] An observational trial of 83 patients similarly demonstrated decreased pain in patients receiving a single dose of 100 mg of IV dexamethasone.[34]

In a subsequent randomized controlled trial of 37 patients receiving a bolus IV dose of either 10 mg or 100 mg of dexamethasone, no differences in either ambulatory function or pain control existed between the groups.[35] Current clinical guidelines recommend immediate treatment with 10 mg of IV dexamethasone for any patient with known or suspected vertebral metastasis and neurological symptoms (eg, weakness, numbness, autonomic dysfunction), (grade 1B; strong recommendation, moderate-quality evidence).[36] Because a single dose of corticosteroids carries little risk of adverse effect, poses minimal logistical burden, and does not require knowledge of the affected anatomy, this treatment can be initiated while awaiting further imaging (MRI) or more definitive treatment (eg, surgery or radiation). Patients with severe deficits, such as dense paraplegia, should receive the higher dexamethasone dose of 100 mg IV.[36] Patients with asymptomatic vertebral metastases or back pain only[37] do not require immediate corticosteroids.[36]

Surgery and Radiation

Corticosteroids decrease pressure on the spinal cord by mitigating vasogenic edema; however, compression will continue until definitive treatment of the vertebral lesion is achieved. The roles of surgical excision and radiation therapy are often debated, but a randomized controlled trial of 101 patients found that patients undergoing surgery plus radiotherapy retained ambulatory function longer and experienced less pain than patients undergoing radiation only.[38] Three observational studies arrived at similar conclusions,[11,39,40] but equivalence between surgery plus radiation and radiation alone has been noted

in 1 observational study[41] and 1 meta-analysis.[42] Recently, 2 observational studies of patients with lymphoma[43] and multiple myeloma[44]—tumor types specifically known for radiation sensitivity— have shown good outcomes with radiation therapy alone; however, these studies do not compare outcomes with patients receiving surgery.

Current guidelines recommend surgical intervention for any patient with MSCC and neurological symptoms who can tolerate the procedure (grade 1B; strong recommendation, moderate-quality evidence).[36,45] However, because 30-day mortality and overall complication rates can be as high as 13% and 54%, respectively,[46] a patient's presurgical functional status should be a consideration. Without existing specific guidelines, expert opinion from consultants (eg, spine surgeon, radiation oncologist, or medical oncologist) usually weigh heavily in guiding this decision. Surgery may particularly benefit patients with direct cord compression by bony fragments, spinal column instability, sphincter dysfunction, known radiation-insensitive tumor histology, or compression in an area that has already received a maximum allowable radiation dose.[45] Immediate surgical management should precede radiation therapy in appropriate patients. Delayed surgery following radiation leads to decreased rates of continence and ambulation at 30 days and wound healing complications.[47]

Recurrence of Spinal Cord Compression

Cord compression recurs in approximately 20% of patients undergoing management for MSCC, with about half of recurrences occurring at the same vertebral level as the original lesion.[48] Recurrence further complicates treatment plans because the threat of radiation myelopathy limits the lifetime dose of radiation that can be delivered to a single area of the spinal cord. In these cases, management should favor surgery, when possible,[36,49] or radiation therapy as allowed within the limits of neurotoxicity.[50,51] More recent techniques in radiation therapy, such as radiosurgery and stereotactic body radiation therapy, employ multiple radiation beams and high-precision coordinate maps of the patient's tumor location to provide a tight focus of radiation and limit collateral tissue exposure,[52-54] making them attractive therapeutic options.

Palliative Care and Prognosis

Although MSCC generally represents a late-stage manifestation of malignancy, with median survival of 3 to 7 months after occurrence,[7] timely management can preserve motor function and improve the quality of the remaining life for those affected. For patients who are not surgical candidates, emergency radiotherapy should be pursued when compatible with goals of care. A purely palliative approach may also be reasonable, especially for patients for whom cancer treatments have already failed or who desire palliation only. This is a complicated and nuanced decision for which no firm guidelines exist, so it should be made in conjunction with the patient, the patient's family, and the patient's oncologist.

Tumor Lysis Syndrome

Epidemiology and Pathophysiology of Tumor Lysis Syndrome

TLS occurs when cancer cell turnover outpaces the body's normal regulatory mechanisms for metabolizing serum electrolytes and cellular waste products. This metabolic imbalance results in excess serum levels of intracellular contents, which primarily include potassium, phosphorus, and uric acid. Meanwhile, excess phosphorus depletes available serum calcium by crystallizing into the poorly soluble calcium phosphate.[55] Bulky tumors, advanced metastatic disease, and hematologic tumors are all risk factors; however, with more effective chemotherapy regimens, TLS is increasingly seen with other tumor types, including solid tumors.[56-58] Although TLS can occur spontaneously,[59] it is far more likely to arise when an anticancer therapy triggers large-scale turnover of malignant cells. Pre-existing renal failure and spontaneous TLS at the time of antitumor therapy initiation are both risk factors for development or worsening of TLS.[56]

Among the complications of TLS, acute kidney injury (AKI) is associated with high morbidity and mortality because the kidneys are the primary organs responsible for restoring metabolic homeostasis. Uric acid and calcium phosphate crystal accumulation in the renal tubules leads to crystal nephropathy,[60] but elevated serum uric acid levels can also cause AKI by crystal-independent mechanisms, which are still poorly understood but are likely driven by renal vasoconstrictive and proinflammatory effects of soluble uric acid.[61,62] When present, a downward spiral may ensue, in which worsening metabolic derangements lead to AKI, and worsening AKI augments metabolic derangements. In an observational study of 63 patients with hematologic malignancies and TLS, those who also had AKI had an in-hospital mortality rate of 51%, compared to just 7% for those who had TLS alone.[63]

Clinical Features of Tumor Lysis Syndrome

Most symptoms of TLS arise due to electrolyte disturbances that cause a varied and nonspecific presentation. Presenting symptoms can include nausea, vomiting, muscle cramps, myalgias, tetany, edema, cardiac dysrhythmias, and neurological symptoms such as lethargy, confusion, seizures, or coma.[56,64] Specific physical examination findings are rare in TLS and are mainly limited to those findings caused

by electrolyte derangements (eg, Chvostek sign or Trousseau sign due to hypocalcemia). Electrocardiographic (ECG) findings are similarly driven by electrolyte derangements and may include T-wave peaking, P-wave flattening, PR- and QRS-interval lengthening due to hyperkalemia, or QT-interval lengthening due to hypocalcemia.[65]

Diagnostic Workup of Tumor Lysis Syndrome

The formal diagnosis of TLS in a patient with known or suspected malignancy is established by measurement of serum values of uric acid, potassium, phosphorus, and calcium.

A diagnosis of *laboratory TLS* is made by 1 or more of the following:[56]

- Uric acid level > 8 mg/dL
- Potassium level > 6 mEq/L
- Phosphorus level > 4.5 mg/dL (6.5 mg/dL in children)
- Calcium level < 7 mg/dL
- A 25% or greater change from baseline for any of those values

Clinical TLS is established when a patient who meets criteria for laboratory TLS also has at least 1 clinical manifestation of the disorder, such as:[56]

- A neurological symptom (eg, seizure, confusion, coma)
- Cardiac dysrhythmia
- AKI requiring hemodialysis

Diagnosing TLS requires clinical suspicion. Because of the nonspecificity of presenting symptoms and partial overlap of laboratory findings between laboratory TLS and other syndromes, TLS may masquerade as sepsis, prerenal azotemia, or malignancy-associated hypercalcemia. Further complicating this picture, lysis of tumor cells may release abnormally high levels of proinflammatory proteins, creating systemic inflammatory response syndrome.[66]

Once the diagnosis is established, patients with TLS should be evaluated further by measuring serum ionized calcium, creatinine, blood urea nitrogen (BUN), and lactate dehydrogenase levels. For patients with AKI, placing a Foley catheter ensures accurate measurement of urine output. A urinalysis should be performed as well as renal imaging (eg, sonography) to rule out obstructive pathology; however, this does not usually need to be completed prior to admission. For patients with AKI and oliguria who have not received a loop diuretic, a fraction of excreted sodium (FeNa) may be calculated to differentiate prerenal etiologies from intrinsic renal etiologies (eg, crystal nephropathy). Contrary to early reports,[67] a urine uric acid-to-creatinine ratio > 1.0 is not a reliable method to diagnose a crystalline etiology of renal failure.[68] Any additional symptom-specific workup (eg, head CT or MRI for neurological symptoms, abdominal imaging for gastrointestinal symptoms) may also be performed.

Management of Tumor Lysis Syndrome

Intravenous Fluids

First-line therapy for TLS is aggressive IV administration of 0.9% sodium chloride (normal saline). This optimizes renal perfusion and mitigates formation of urate and calcium phosphate crystals by diluting their serum concentrations. While the optimal regimen for volume repletion is unknown, guidelines suggest initial administration of isotonic crystalloid at a rate of 3 L/m^2/day for children and adults, and 200 mL/kg/day for infants.[56] These fluids should be titrated to maintain a urine output > 100 mL/m^2/hr for children and adults, and 4 mL/kg/hr for infants.[69] Diuresis does not directly improve TLS, but it should be judiciously employed to avoid volume overload in patients receiving high rates of IV fluid hydration. Care should be taken to avoid diuresis prior to sufficient fluid resuscitation or in patients with urinary obstruction.[64] Management of TLS in patients with acute oliguria or anuria can be challenging, due to concerns for volume overload. While little direct evidence exists to guide management in this situation, we advise proceeding with aggressive IV crystalloid fluid administration and initiating diuresis once euvolemic. If the patient remains oliguric, plans for renal replacement therapy and early nephrology consultation should commence.

Adjunctive Therapies

Despite the lack of evidence to support the practice, for many years, urine alkalization had been touted as an effective means of promoting uric acid clearance. More recently, however, expert opinion has steered away from this, citing both the lack of evidence and the potential danger of causing serum acid-base derangements in patients who often have underlying acute renal dysfunction.[70] Additionally, an alkaline environment promotes formation of both calcium phosphate[60] and xanthine crystals,[64,66] thus potentiating kidney damage. The most recent guidelines advise against urine alkalinization, grading the recommendation as 1C (strong recommendation; low-quality evidence).[69]

Although cancer cell turnover is the primary driver of the electrolyte derangements of TLS, unintentional administration of exogenous potassium or phosphorus may further contribute to electrolyte derangements. Emergency clinicians should pay specific attention for potassium- or phosphate-containing IV fluids and medications (both oral and intravenous) being administered to the patient to avoid unnecessary delivery of these electrolytes.[64]

Hyperkalemia associated with TLS should be managed just as hyperkalemia from any other

source. For patients at immediate risk for life-threatening dysrhythmias (eg, widened QRS complex on ECG or potassium level > 6.0 mEq/L), administration of IV calcium will temporarily stabilize cardiac myocytes (for < 1 hour),[71] allowing time for more definitive therapies to take effect. IV insulin (10 units regular insulin with 25 g D50 [50% dextrose in water]), IV sodium bicarbonate (50 mEq), and 10 mg nebulized albuterol are typical starting doses that may then be employed to shift excess potassium intracellularly.

Ultimately, systemic elimination of potassium occurs in 3 ways: (1) via the kidneys (with or without assistance from a loop diuretic); (2) in the gastrointestinal tract, with administration of potassium-eliminating medication (eg, patiromer or sodium polystyrene sulfonate [72]); or (3) by hemodialysis. Of note, sodium polystyrene sulfonate should be employed with care, as cases of associated bowel necrosis have been reported, particularly in patients with renal compromise.[73]

Hypocalcemia occurs in TLS as a secondary effect of hyperphosphatemia, which drives formation of the poorly soluble compound, calcium phosphate, and contributes to crystal nephropathy. Repletion of hypocalcemia provides further raw material for calcium phosphate formation, and should therefore be avoided except in patients with neurological symptoms (eg, seizure or coma) or cardiac dysrhythmias believed to be due to hypocalcemia. For all other patients, monitoring of serum calcium levels should occur without repletion. Normal calcium concentration will be restored upon resolution of TLS and normalization of phosphorus concentration.[56]

Xanthine Oxidase Inhibitors and Rasburicase

Elevated uric acid level (hyperuricemia) results from the metabolism of purine nucleic acids released from dying cancer cells. Adenosine and guanine are both metabolized to xanthine then to uric acid prior to renal elimination. Hyperuricemia can be mitigated by aggressive hydration, but uric acid generation can also be pharmacologically inhibited.

Allopurinol, a hypoxanthine analog often used to prevent gout, competitively inhibits xanthine oxidase, the enzyme that converts xanthine to uric acid. **(See Figure 1.)** While it does not eliminate existing uric acid, allopurinol can prevent further generation of it, and thus may be used as a preventative measure against worsening of hyperuricemia.

More recently, febuxostat, a noncompetitive inhibitor of xanthine oxidase, has been shown in a multicenter randomized controlled trial of 100 patients to be noninferior to allopurinol in regulating uric acid levels in patients at risk for TLS.[74] Though a feasible alternative for patients in whom allopurinol is contraindicated (eg, in medication allergy), the steep cost differential between allopurinol and febuxostat[75] renders allopurinol the preferred agent for most patients.

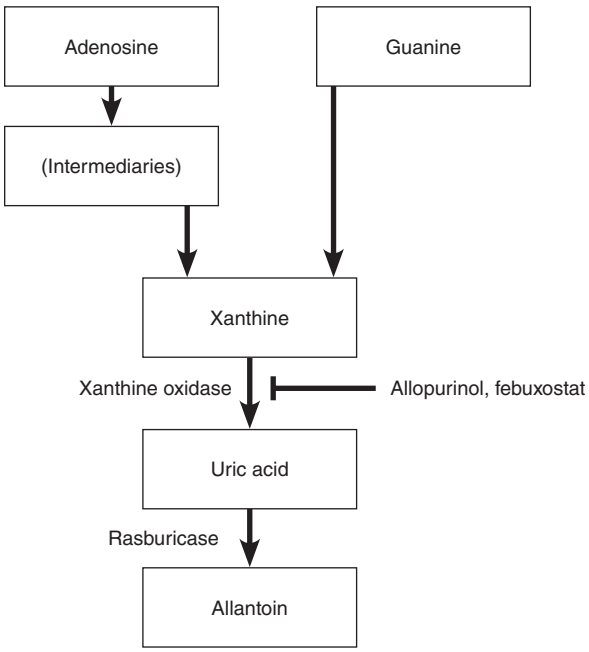
Allopurinol must be renally dosed, and alterations to the metabolism of purine analog chemotherapy agents (eg, 6-mercaptopurine, azathioprine) often mandates a dose reduction of these agents upon initiation of allopurinol or febuxostat.[56,64]

Rasburicase

Two limitations hinder the ability of xanthine oxidase inhibitors to treat hyperuricemia: First, these medications do not lower pre-existing levels of uric acid. Second, inhibition of xanthine oxidase causes elevation of serum xanthine levels, which itself can cause crystal nephropathy. The development of rasburicase has provided a means to overcome these limitations.

Rasburicase is a recombinant version of the enzyme urate oxidase (found in most nonhuman mammals), and it metabolizes uric acid to the far more soluble compound, allantoin, which is then renally eliminated.[56] **(See Figure 1.)** Rasburicase has been shown in at least 1 randomized controlled trial[76] and several observational studies[77-80] to effectively lower uric acid levels, though at least 1 meta-analysis failed to show a benefit for prevention of mortality or AKI in children.[81]

Figure 1. Flow Diagram of Purine Metabolism



Under normal circumstances, purine metabolism terminates at uric acid, which the kidney eliminates. Exogenous administration of rasburicase allows further metabolism to the more soluble compound, allantoin. Xanthine oxidase inhibitors (such as allopurinol or febuxostat) prevent metabolism of xanthine to uric acid.

Nonetheless, the most recent guidelines from the British Committee for Standards in Haematology recommend giving rasburicase at a dose of 0.2 mg/kg/day IV for any patient with established laboratory TLS.[69] Two observational studies have shown that a single, fixed dose of rasburicase 6 mg IV is successful in reducing elevated uric acid levels[82,83] and that a single, fixed dose of 3 mg IV may also be effective.[84]

Patients who have received rasburicase should stop receiving xanthine oxidase inhibitors such as allopurinol, as these will unnecessarily elevate xanthine concentrations, rather than allowing metabolism to allantoin. Though generally safe, rasburicase should be avoided in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as hydrogen peroxide is a byproduct of enzymatic activity and may trigger a hemolytic crisis.[56] Methemoglobinemia has also been reported as an adverse effect of rasburicase administration.[85]

Renal Replacement Therapy

Although IV fluids and medical management of electrolyte derangements and hyperuricemia are often sufficient management for TLS, in cases of oliguria despite fluid resuscitation, recalcitrant electrolyte abnormalities, or worsening AKI, renal replacement therapy may become necessary. In a recent cross-sectional study of 22,785 patients with laboratory TLS, 12% developed AKI requiring dialysis.[86] In another observational study of patients with hematologic malignancy and AKI prior to chemotherapy, 50% of patients required dialysis.[87] While intermittent hemodialysis or continuous renal replacement therapies may be employed for patients with TLS, guidelines advise against peritoneal dialysis, as this method corrects metabolic abnormalities too slowly to be of use in TLS.[69]

Disposition of Patients With Tumor Lysis Syndrome

Any patient with established TLS should be admitted for further management, and intensive care unit admission should be considered for patients with clinical TLS. Prior to admission, adequate IV access for fluid resuscitation as well as access for hemodialysis, if emergently indicated, should be established. Although guidelines exist to predict TLS risk during initiation of chemotherapy and recommend prophylactic measures,[55] implementing these measures is seldom necessary in the ED unless in conjunction with an oncologist.

Neutropenic Fever

Epidemiology and Pathophysiology of Neutropenic Fever

Neutropenia can arise from 2 main sources in cancer patients. First, in patients with hematologic malignancies, overgrowth of malignant cells in the bone marrow may crowd out functional blood cell precursors. Thus, despite the appearance of leukocytosis on laboratory measurement, functional leukocytes, including neutrophils, may be deficient. Second, and more commonly, blood cell precursors suffer collateral damage from cytotoxic anticancer agents, which, by design, are particularly lethal to cells with rapid turnover.

The loss of neutrophils and the resulting deficiency in innate immunity causes patients to be susceptible to life-threatening infection. Therefore, the development of neutropenic fever (febrile neutropenia) or other infectious symptoms may mark the development of a serious complication. Unfortunately, neutropenic fever is a relatively common occurrence, with rates as high as 50% for patients with solid tumors and as high as 80% for hematologic cancer patients.[88] A recent prospective study assessing the use of the ED by patients with acute leukemia found similar incidence, with 81% of these patients visiting the ED at least once in the year following administration of induction chemotherapy. Of those, 55% presented for neutropenic fever.[89]

Absolute Neutrophil Count

The severity of neutropenia for a given patient can be determined by calculating the absolute neutrophil count (ANC), which is obtained by multiplying the total white blood cell count by the sum of the percentages of granulocytes and band cells, and then dividing this product by 100.

An online calculator for ANC, along with more information about the uses of this test, is available at MDCalc.com.

- Absolute Neutrophil Count Calculator: www.mdcalc.com/absolute-neutrophil-count-anc

The risk of infection begins to elevate once the ANC falls below 1000 cells/mm^3, and risk continues to increase, approximately linearly, as ANC decreases from this threshold. Patients with an ANC of < 100 cells/mm^3 have a daily infection risk of more than 50%.[90] Reflecting this, neutropenia is often referred to as *mild* (ANC 1000-1500 cells/mm^3), *moderate* (500 to < 1000 cells/mm^3), or *severe* (< 500 cells/mm^3). For simplicity, the most current guidelines do not emphasize these gradations, but rather define neutropenic patients as those who have an ANC of ≤ 500 cells/mm^3, or are expected to fall below this threshold within 48 hours.[91,92]

Signs and Symptoms of Neutropenic Fever

The most common sites of infection in neutropenic patients are the lung (pneumonia), anorectal area, skin (cellulitis- or central line-associated infection), oropharynx, and urinary tract.[93] Because of impaired innate immunity, presenting symptoms may vary. Fever, defined by the current guidelines as a single temperature of ≥ 38.3°C (100.9°F) or a sustained temperature of ≥ 38.0°C (100.4°F) for over 1 hour, may be the sole presenting symptom.[91,92] Conversely, the absence of fever does not indicate the absence of infection, and afebrile neutropenic patients with signs or symptoms of infection should be managed according to guidelines for neutropenic fever. In fact, a large observational study demonstrated that hypothermia on presentation has a higher correlation with mortality than fever among neutropenic sepsis patients.[94]

Pathogens among neutropenic patients are frequently from the patient's own microbiome.[93] An observational study using high-throughput PCR techniques to identify pathogens in bacteremic neutropenic patients revealed that 65% were normal human flora; however, a total of 30 genera from 5 phyla were identified.[95] Two observational studies of blood cultures from neutropenic patients similarly identified *Escherichia coli* and coagulase-negative *Staphylococcus*, both normal flora, as the most common bloodstream pathogens.[96,97]

Clinical Features of Neutropenic Fever

ED evaluation of patients with neutropenic fever should begin with a thorough history of the present illness and review of systems focusing on infectious symptoms such as cough, shortness of breath, headache, neck stiffness, abdominal pain, nausea, vomiting, diarrhea, dysuria, ear or sinus pain, pharyngitis, rashes, and upper respiratory symptoms. Physical examination should include lung auscultation, neck range-of-motion testing, skin examination, abdominal examination, testing for sinus tenderness, and an ear and throat examination. Oral examination should be performed, looking especially for mucositis, and external perianal examination should be performed, looking specifically for perianal abscess.[98] Absent supporting evidence, experts recommend against digital rectal examination so as to prevent translocation of rectal flora to the bloodstream via induced microperforations.[91] Inventory should be made of indwelling lines, and line sites should be examined for evidence of cellulitis.

Fever in cancer patients may be due to various causes, including infection, venous thromboembolism, and inflammatory effects of the cancer itself. However, given the high mortality associated with neutropenic infection, any patient with neutropenia and fever should be empirically treated for infection.

Diagnostic Workup of Neutropenic Fever

Diagnostic workup should begin with blood cultures, and at least 2 sets of 2 bottles each should be drawn. The first should come from a peripheral phlebotomy site. If the patient has no indwelling lines, the second set should be peripheral as well, preferably from a site independent of the first set. If the patient does have an indwelling line or port, additional sets should be drawn off the port or line, at least 1 set per lumen.[91,92,98] Sending blood cultures in this fashion can provide evidence for or against venous catheter infection. In at least 1 prospective study, growth in catheter-drawn blood cultures occurring 2 hours or more before growth in peripherally drawn cultures carried a 100% positive predictive value for catheter infection.[99] Catheter-drawn cultures growing out within 2 hours of or after peripherally drawn cultures carried a negative predictive value of 89% to 96%.[99]

Additional elements of laboratory workup should include complete blood cell count (CBC) with differential to assess the severity of neutropenia, urinalysis, urine culture, and renal and hepatic function testing.[91,98] Other testing should be ordered as directed by the clinical scenario.[91,98] For patients with respiratory symptoms, this should involve sputum culture and respiratory viral testing. Bronchoscopy with bronchoalveolar lavage has a diagnostic yield approaching 50% in patients with a pulmonary infiltrate and is particularly helpful in diagnosing fungal pneumonia;[100,101] however, this procedure may be performed following admission and need not be pursued in the ED. Those with diarrhea and abdominal pain should be tested for *Clostridium difficile*, even in the absence of other traditional risk factors (eg, recent antibiotics), as neutropenia itself may be sufficient to trigger colitis in a colonized patient. Patients with hypotension and concern for shock should have serum lactic acid levels trended.[102]

Imaging Studies for Neutropenic Fever

Imaging should be similarly directed by clinical scenario. Though not unreasonable to perform, chest x-ray has a low yield for identifying the infectious etiology in those without respiratory symptoms. In a prospective study of 109 patients lacking respiratory symptoms, only 2 patients had chest x-ray findings helpful in diagnosing the etiology of fever.[103] More advanced chest imaging, such as CT scan, may be performed in patients with respiratory symptoms whose chest x-ray is inconclusive or in those who have been febrile for ≥ 72 hours without a clear source and may be harboring an occult fungal infection.[92] Sinus imaging is also unlikely to be helpful in patients without sinus-specific symptoms,[103] but may be considered as part of a workup for occult fungal infection in patients with fever without source for 72 hours.[92] In general, CT scans of the chest and sinuses are low-yield in the ED.

Management of Neutropenic Fever

Risk Stratification

Management of neutropenic fever varies depending on risk stratification of the presentation, but all risk levels mandate immediate empiric antibiotics even in the absence of culture results. Three sets of criteria for risk stratification exist. The Infectious Diseases Society of America (IDSA) identified high-risk criteria, and any patient meeting at least 1 criterion is considered to be at high risk:

- Expected duration of neutropenia > 7 days
- Expected nadir in ANC < 100 cells/mm^3
- Hypotension, pneumonia, abdominal pain, neurologic changes
- Existence of significant comorbidities[91]

The European Conference on Infections in Leukemia (ECIL) also identifies current or prior infections with resistant organisms, or treatment at a center with known prevalence of such organisms.[104] Separately, the Multinational Association for Supportive Care in Cancer (MASCC) risk index was developed to identify patients with low-risk features who may be eligible for outpatient treatment with oral antibiotics. **(See Table 1.)** A score of ≥ 21 identifies low-risk patients with an approximately 90% chance of uncomplicated resolution of fever within 5 days.

An online calculator for the MASCC risk index, along with more information about its uses, is available at MDCalc.com:

- MASCC Risk Index for Febrile Neutropenia Calculator: www.mdcalc.com/mascc-risk-index-febrile-neutropenia

Recent retrospective[106] and prospective[107] studies have identified additional high-risk features. These features include poor baseline performance status, underlying chronic obstructive pulmonary disease or cardiovascular dysfunction, stress-induced hyperglycemia, monocyte count < 200/mm^3, platelet count < 50,000/mm^3, total serum protein level < 6 g/dL, respiratory rate of ≥ 24 breaths/min, and presence of pulmonary infiltrate. Overall, neutropenic infection carries a mortality rate approaching 20%.[108]

Table 1. Components of the Multinational Association of Supportive Care in Cancer (MASCC) Risk Index[105]

Clinical Feature	Point value
Absence of hypotension	5
Asymptomatic or overall mild symptom burden	5
No history of chronic obstructive pulmonary disease	4
No prior fungal infections or solid tumor type	4
Absence of dehydration	3
Overall moderate symptom burden	3
Onset of fever while outpatient	3
Age < 60 years	2

A score of ≥ 21 implies a 90% chance of uncomplicated resolution of fever within 5 days.

Antimicrobial Therapy for Neutropenic Fever

Patients at high risk should be managed with intravenous broad-spectrum antibiotics. Current guidelines recommend single coverage with a broad-spectrum, antipseudomonal beta-lactam agent such as cefepime, piperacillin-tazobactam, meropenem, or imipenem.[91,92] Prior guidelines have recommended empiric double coverage of *Pseudomonas* with a fluoroquinolone or aminoglycoside, which may be done at the discretion of the treating physician.[104] However, a recent meta-analysis failed to show survival benefit from double coverage with a beta-lactam and aminoglycoside, and instead suggested an increased rate of complications such as renal failure and fungal superinfection when compared to beta-lactam monotherapy.[109] Selection of a specific broad-spectrum beta-lactam should be done in reference to local antibiograms; however, most head-to-head studies have shown little or no benefit from one to another.[110-117] Only 1 meta-analysis suggested a small survival benefit to piperacillin-tazobactam when compared with cefepime.[118]

Many emergency clinicians are inclined to empirically add gram-positive bacterial coverage; specifically, vancomycin.[119] Despite increasing rates of bacteremia with gram-positive organisms,[96,120] multiple studies have failed to show a survival benefit from empiric addition of vancomycin; conversely, they suggest increased complication rates, such as AKI.[121-123] Similarly, a retrospective study of vancomycin-resistant *Enterococcus*-colonized patients with neutropenic fever failed to demonstrate a survival benefit from empiric therapy with linezolid.[124] Clinically unstable patients (eg, those with septic shock) and those with cellulitis, suspected catheter-associated infection, or pneumonia should receive empiric gram-positive-specific coverage (eg, vancomycin or linezolid).[91,92] For all others, gram-positive coverage should be initiated according to culture data.

Additional antimicrobial therapy should be tailored to the clinical presentation. Patients with abdominal pain and diarrhea should receive metronidazole for empiric *C difficile* coverage; this addition to beta-lactam coverage alone for patients with gastrointestinal symptoms has, in fact, conferred a survival benefit in 1 randomized controlled trial.[125] Patients with community-acquired pneumonia should be covered for atypical pathogens with azithromycin or a respiratory fluoroquinolone (levofloxacin or moxifloxacin), and consideration should be given to empiric influenza treatment and

empiric pneumocystis pneumonia treatment as well, depending on symptoms, time of year, and duration and severity of neutropenia.[92] Patients with vesicular rash should be considered for empiric acyclovir.[92] Nuchal rigidity with mental status changes should trigger coverage for meningeal pathogens.

Empiric antifungal coverage is rarely employed and is generally not initiated in the ED, except as directed by specific clinical data or in cases of extreme clinical instability. One randomized controlled trial failed to show survival benefit associated with empiric initiation of voriconazole.[126] In lieu of empiric antifungal agents, some oncology wards have adopted a protocol for pre-emptive screening for fungal infection in neutropenic patients, including regular high-resolution chest CT scans, scheduled measurement of galactomannan levels, and bronchoscopy with bronchoalveolar lavage. These programs have reduced patient exposure to complication-laden antifungal agents without increasing mortality.[127,128] Informed selection between antifungal agents is hindered by systemic problems in existing studies[129] and equivalency between empiric agents;[130,131] however, a meta-analysis did favor liposomal amphotericin B.[132]

Several observational studies in patients with neutropenic fever have examined the effect of time to administration of antibiotics on mortality. While some have shown a correlation between delays in antibiotics and mortality,[133,134] others have shown no correlation.[135,136] Nonetheless, we recommend patients at high risk receive IV broad-spectrum antibiotics as soon as reasonably possible after blood cultures are obtained. Two recent ED studies have demonstrated expedited time to antibiotic administration by employing clinical protocols for patients with neutropenic fever. In the first study, patients at high risk for neutropenia were given identification cards by their oncologists, which cued emergency clinicians to order antibiotics for fever and high-risk features without having to wait for a CBC with differential.[137] Other changes in this study included implementation of an electronic order set for neutropenic fever, introduction of neutropenic fever as a specific chief complaint in triage, and storage of common neutropenic fever antibiotics in the ED rather than in the pharmacy. These changes decreased the average time to antibiotic administration from 235 minutes to 81 minutes. In the second study, bedside nurses were empowered to order protocoled antibiotics without waiting for a provider. This resulted in > 95% of patients with neutropenic fever receiving appropriate antibiotics within 60 minutes.[138]

Disposition of Patients With Neutropenic Fever

Disposition depends on the risk of mortality or complication. Hemodynamically unstable patients or those likely to become unstable should be admitted to an intensive care unit. Most patients will be admitted to a floor bed (ideally in an oncology unit) for IV broad-spectrum antibiotics; however, a small portion may be managed with oral antibiotics, usually ciprofloxacin plus amoxicillin/clavulanate, as outpatients.[139]

In order to be eligible for outpatient treatment, the patients should:

- Meet low-risk MASCC criteria (score ≥ 21; **see Table 1, page 10**)
- Have reliable daily oncology follow-up
- Demonstrate stability during ≥ 4-hour ED observation
- Have no evidence of cellulitis, line infection, pneumonia, or organ failure[139-142]

Perhaps because of the rarity of patients meeting these criteria, the majority of emergency physicians (77%) were unaware of them when surveyed.[143] Furthermore, in a retrospective study of the dispositions of 173 neutropenic patients with fever, 120 of 129 high-risk patients were admitted in accordance with guidelines, but 43 of 44 low-risk patients who met criteria for discharge were also admitted.[144] Identification of such discharge-eligible patients will become increasingly important as the mandate for cost-conscious care strengthens. Because of the importance of follow-up, a febrile neutropenic patient should generally only be discharged after direct consultation with the patient's oncologist.

Controversies and Cutting Edge

Decades of research have come to fruition in recent years with novel therapies for cancer, including monoclonal antibodies targeting cancer-specific antigens, development of techniques to invigorate the host's immune response against tumor (ie, immunotherapy), and engineering of viruses designed to seek and destroy cancer cells (ie, virotherapy). These new therapies are in their relative infancy, and they may also bring new complications.

Monoclonal Antibody Therapy

As cancer-causing mutations continue to be identified, novel monoclonal antibodies targeting their corresponding peptide products are developed. Because of the targeted nature of these therapies, they tend to carry fewer adverse effects than traditional chemotherapeutics. However, they still may cause hypersensitivity reactions, cytokine release syndromes, and, in rare cases, progressive multifocal leukoencephalopathy.[145] Cases of TLS following administration of monoclonal antibody therapy have also been reported.[146,147]

Immunotherapy

Immunotherapy recognizes that tumor cells express non–self-tolerant neoantigens, and attempts to bol-

ster the patient's own immune system against these neoantigens. Immunotherapy is accomplished by directly stimulating T cells or inhibiting checkpoints of T-cell activation and development.[148] Currently, therapies achieving the latter are more developed, with 4 monoclonal antibodies to T-cell checkpoint proteins currently approved in the United States (ipilimumab, nivolumab, pembrolizumab, and atezolizumab). Inhibiting T-cell checkpoints can lead to failures of self-tolerance, causing a specific set of immune-related adverse events, including diarrhea (11%-33% of patients receiving therapy), colitis (1%-12%), hepatitis (1%-7%), skin toxicity (9%-35%), thyroid dysfunction (3%-17%), and pituitary inflammation (hypophysitis, 1%-4%).[149,150] Hypophysitis is particularly important for emergency clinicians to identify, as secondary adrenal insufficiency may cause life-threatening hypotension that can be easily managed with exogenous corticosteroids.[151]

Virotherapy

Virotherapy involves the design and delivery of viruses that specifically target and destroy tumor cells while sparing noncancerous tissue.[152] The first such commercially available treatment in the United States, talimogene laherparepvec (T-Vec) was approved by the United States Food and Drug Administration (FDA) in 2015 for melanoma treatment. T-Vec targets tumor cells by relying on tumor-specific transcription factors for replication. Tumor cell death is achieved by lysis as part of the viral reproductive cycle.[152] Common side effects during phase 3 testing of T-Vec included fatigue, fever, and chills, and 2.1% of participants developed cellulitis.[153] Additionally, animal tests using other oncolytic viruses have generated tumor cell death rates rapid enough to induce TLS.[154]

Summary

Continued strides in the field of cancer treatment ensure that the number of people living with cancer and complications of cancer will rise in coming years. Until future therapies that more tightly target malignant cells lessen the severity of complications and adverse effects, toxicities of traditional treatments will continue to manifest in patients presenting to the ED. Therefore, it is incumbent upon the emergency clinician to remain vigilant for these complications of cancer and its treatment.

Time- and Cost-Effective Strategies

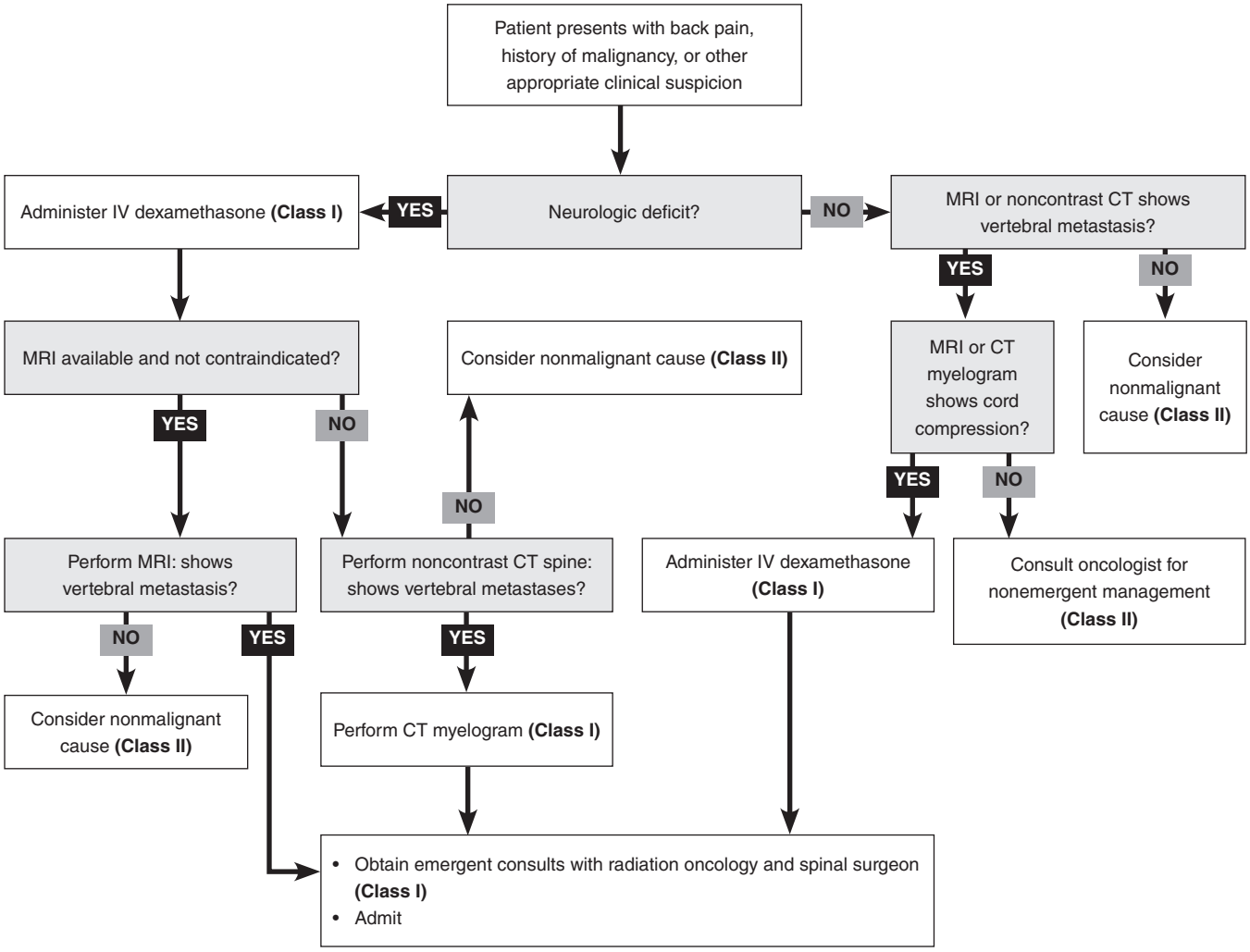
- If MSCC is suspected but MRI unavailable, initial imaging should be noncontrasted CT scan of the spinal column. If this does not reveal evidence of bony metastasis and clinical suspicion is low, other diagnoses are more probable. CT myelography needs to be pursued only if bony metastases appear or clinical suspicion for cord compression is high.
- In the treatment of TLS, a single dose of rasburicase 6 mg IV has been shown to successfully reduce uric acid levels and may be considered in place of the 0.2 mg/kg IV daily dose.
- In the treatment of neutropenic fever, effective coverage is provided by monotherapy with a broad-spectrum, antipseudomonal beta-lactam. Addition of a second antipseudomonal agent, empiric vancomycin coverage, or empiric antifungal coverage does not improve outcomes and may cause complications (eg, AKI). Exceptions may be driven by individual clinical circumstances (eg, known methicillin-resistant *Staphylococcus aureus* colonization, suspected line infection, or known history of fungal pneumonia).

Case Conclusions

Given the high clinical suspicion for metastatic disease in your 67-year-old patient with prostate cancer and back pain in addition to the neurologic findings on exam, you administered IV dexamethasone and arranged for an MRI of the thoracic and lumbar spine. The thoracic region was included as well because of the high incidence of additional asymptomatic metastases. The MRI revealed lesions to the T8, L1, and L2 vertebrae that were suspicious for malignant disease, with compression of the spinal cord at the L1 level. Oncology, radiation oncology, and a spinal surgeon were emergently consulted. The patient was taken for anterior laminectomy, followed by radiation therapy, and his symptoms had improved markedly by hospital discharge.

With the 55-year-old man who presented with lung cancer and fever, you recognized the patient's neutropenia, as well as high-risk features that included profound neutropenia (ANC, 60 cells/mm^3), possible pneumonia, and relatively low blood pressure (given his history of hypertension). You also noted lab abnormalities, including thrombocytopenia and lactic acidosis, which could portend a complicated course. He was started on cefepime 2 g IV, and blood, urine, and sputum cultures were sent. Large-bore IV access was established and 30 mL/kg of crystalloid fluid was administered, with improvement in his pulse and blood pressure. He was admitted to the oncology ward for continued broad-spectrum antibiotic coverage. Within hours, his blood cultures grew gram-negative rods, with the cultures from the line turning positive more than 2 hours before the peripheral cultures, suggesting a catheter-related infection.

Clinical Pathway for Emergency Department Management of Metastatic Spinal Cord Compression



Abbreviations: CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging.

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

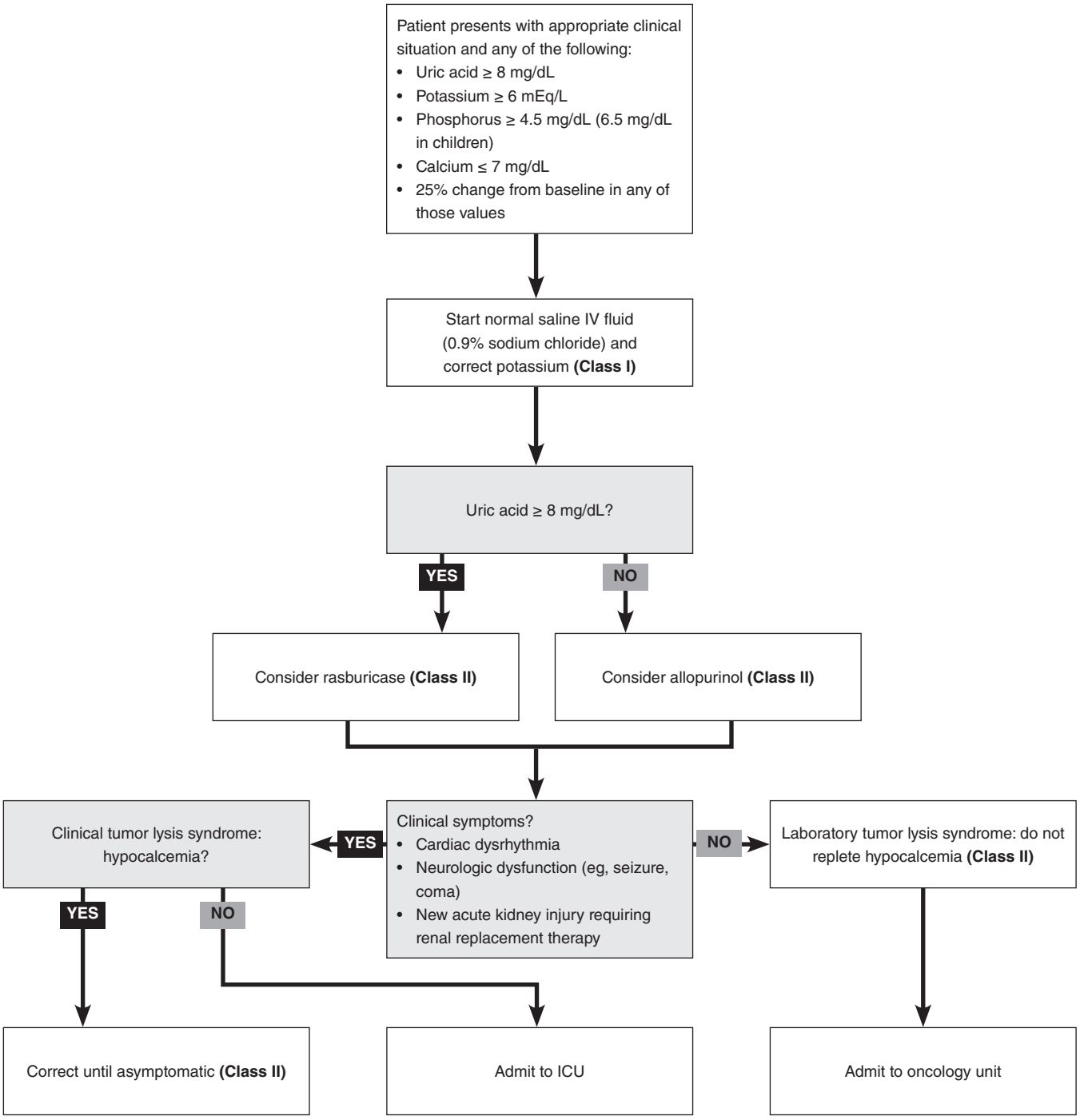
Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

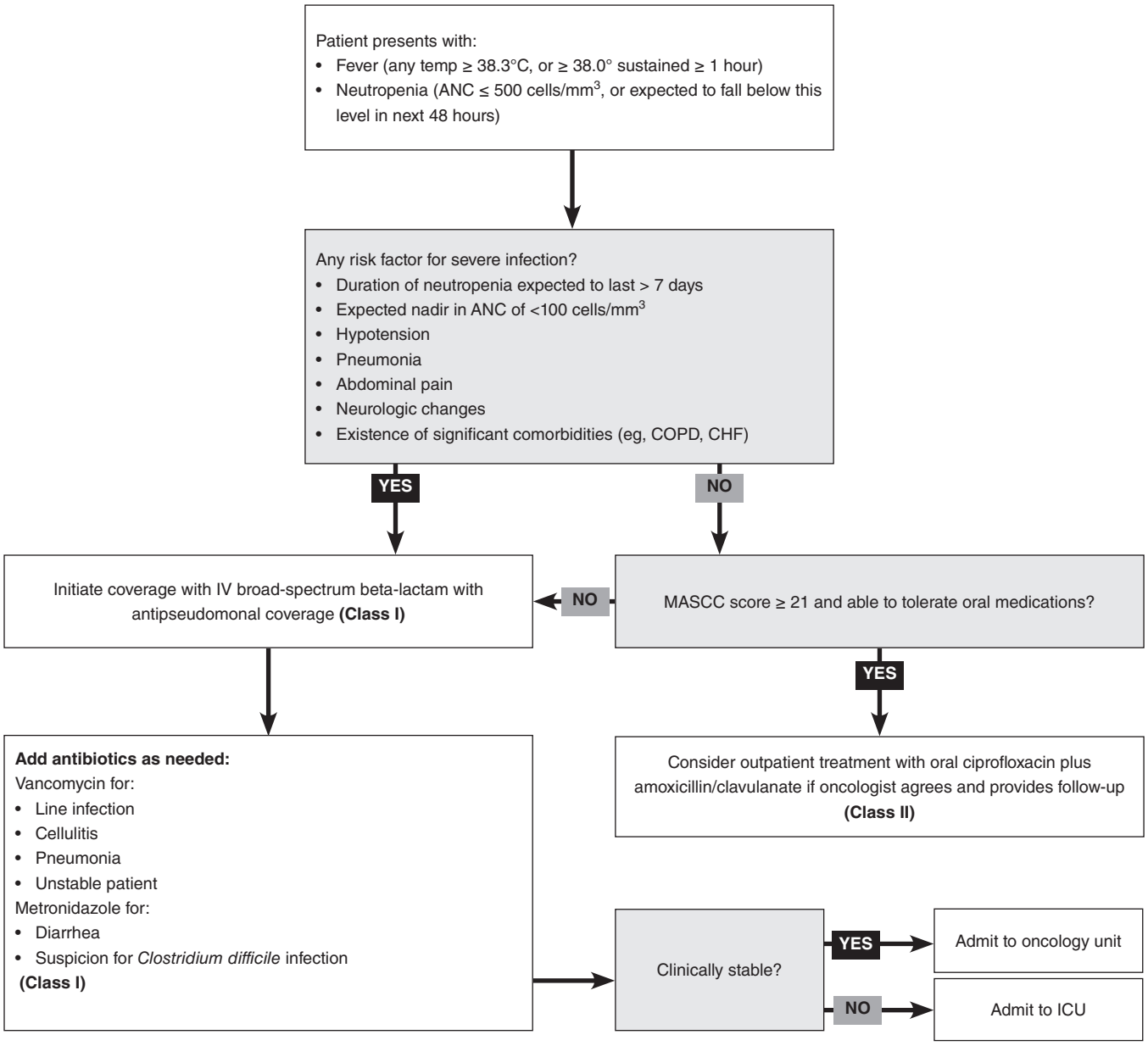
Clinical Pathway for Emergency Department Management of Tumor Lysis Syndrome



Abbreviations: ICU, intensive care unit; IV, intravenous.

For Class of Evidence definitions, see page 13.

Clinical Pathway for Emergency Department Management of Neutropenic Fever



Abbreviations: ANC, absolute neutrophil count; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IV, intravenous; MASCC, Multinational Association for Supportive Care in Cancer.

For Class of Evidence definitions, see page 13.

Risk Management Pitfalls for Oncologic Emergencies

1. **"He's already getting treatment for his prostate cancer, so his back pain is probably just from lifting something heavy."**
   In patients with known cancer, specificity of a complaint of back pain for metastatic spinal disease approaches 100%. This diagnosis should be assumed until proven otherwise.

2. **"The spinal x-rays look normal. If she doesn't have any metastasis, she couldn't have cord compression."**
   Normal spinal plain films do not rule out metastatic spinal cord compression. Often, the invading tumor will spread from the vertebral bone marrow to the spinal canal prior to invading cortical bone, therefore remaining undetected on x-ray.

3. **"Call a surgeon? I've always treated metastatic spinal cord compression with radiation. If the oncologists want a surgeon, they can consult after they try radiation."**
   Surgical management of metastatic spinal cord stenosis should precede radiation therapy unless contraindicated. This leads to better outcomes than radiation therapy alone or surgery following radiation therapy.

4. **"Whoa, that patient with TLS has a calcium level of 8.0 mg/dL. He seems fine, but I'd better give him a little just to be sure."**
   Avoid repletion of hypocalcemia in patients with TLS except in cases of cardiac arrhythmia or central nervous system involvement. Repletion of hypocalcemia in a setting of hyperphosphatemia will drive calcium phosphate crystal nephropathy.

5. **"Normal saline? No, this patient has TLS. We need to use a sodium bicarbonate drip to alkalinize the urine."**
   Avoid urine alkalization when treating TLS. This has not been shown to improve uric acid clearance, and may cause acid/base complications.

6. **"The oncologist said we need to test for G6PD deficiency before we give rasburicase, but that test takes a day to come back and his uric acid level is 14 mg/dL. What's the worst that could happen?"**
   Rasburicase should not be administered to patients with G6PD deficiency. It can trigger a hemolytic crisis.

7. **"I know she has TLS, but she's not making any urine. I don't want to risk giving any IV fluids."**
   For patients with TLS, first-line therapy is aggressive hydration with normal saline IV fluid. This should be performed even for oliguric or anuric patients; however, plans should be made for renal replacement therapy if urine output does not improve with hydration. A Foley catheter should be placed to evaluate the response to fluids.

8. **"The oncologist said to admit him for high-risk neutropenic fever because his ANC is so low and he has infiltrates on chest x-ray, but he looks fine now and wants to go home. I think we can discharge on oral antibiotics."**
   For patients with neutropenic fever, the following findings define high risk: duration of neutropenia expected to last > 7 days, expected nadir in ANC of < 100 cells/mm^3, hypotension, pneumonia, abdominal pain, neurologic changes, existence of significant comorbidities, current or prior infections with resistant organisms, or treatment at a center with known prevalence of such organisms. Patients with high-risk neutropenic fever should be admitted for IV antibiotics and monitoring.

9. **"He has neutropenic fever, but he's hemodynamically stable. I'd rather not start antibiotics until we know what it is we're treating."**
   In the treatment of patients with febrile neutropenia, empiric broad-spectrum antibiotic therapy should begin immediately, even if a specific diagnosis has not yet been made. For patients with high-risk features, a parenteral beta-lactam with antipseudomonal properties (such as cefepime or piperacillin-tazobactam) should be used. Additional antibiotics can be added specific to clinical suspicions (eg, metronidazole if *C difficile* is suspected).

10. **"Her oncologist sent her in for neutropenia with cough and sputum production and there are infiltrates on chest x-ray, but she hasn't actually been febrile. I'm not sure she really needs IV cefepime for this. Maybe she can go home on oral azithromycin."**
    Neutropenic patients who display signs or symptoms of infection even in the absence of fever should be treated immediately and aggressively with broad-spectrum IV antibiotics.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of patients. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study is included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, are noted by an asterisk (*) next to the number of the reference.

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CME Questions

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1. For patients with suspected metastatic spinal cord compression, which spinal segment(s) are most likely to contain an offending lesion?
   a. Cervical only
   b. Cervical and thoracic
   c. Cervical and lumbar
   d. Thoracic and lumbar

2. Which of these imaging studies will demonstrate the presence of spinal cord compression?
   a. Magnetic resonance imaging (MRI)
   b. Noncontrast computed tomography (CT)
   c. Plain films
   d. Radionuclide scanning

3. For patients with metastatic spinal cord compression, which sequence of treatments is most likely to lead to the best possible neurologic outcome, assuming no surgical contraindications?
   a. Immediate IV corticosteroid, then radiation therapy
   b. Immediate IV corticosteroid, then radiation therapy, then IV corticosteroid
   c. Immediate IV corticosteroid, then surgery, then radiation therapy
   d. Immediate surgery, then IV corticosteroid, then radiotherapy

4. Which of the following patients with vertebral metastatic disease may be managed without dexamethasone administration?
   a. 53-year-old man with left-leg weakness, but still able to walk
   b. 67-year-old woman with dulled sensation to both legs
   c. 61-year-old man with back pain only
   d. 72-year-old woman with new urinary incontinence

5. Which of the following constitutes appropriate first-line treatment for tumor lysis syndrome?
   a. IV furosemide
   b. IV 0.9% sodium chloride
   c. IV pamidronate
   d. IV sodium bicarbonate

6. Which of the following medications administered for tumor lysis syndrome will alter the metabolism of purine-analog chemotherapeutic agents, potentially requiring dose modification of the chemotherapeutic?
   a. Allopurinol
   b. Calcium gluconate
   c. Furosemide
   d. Insulin

7. Rasburicase is contraindicated in a patient with which of the following comorbidities?
   a. Factor V Leiden
   b. Glucose-6-phosphate dehydrogenase deficiency
   c. Pernicious anemia
   d. Von Willebrand disease

8. Which of the following diagnostic tests should be ordered for all patients with neutropenic fever in the ED, regardless of symptoms?
   a. Blood cultures
   b. Bronchoscopy with lavage
   c. *Clostridium difficile* antigen testing
   d. CT of the chest

9. Which of the following is an acceptable empiric antibiotic regimen for a neutropenic patient with fever and high-risk features?
   a. IV cefepime
   b. IV clindamycin
   c. IV ampicillin-sulbactam
   d. IV vancomycin

10. For which of the following neutropenic fever patients do guidelines recommend empiric addition of IV vancomycin to the antibiotic regimen?
   a. 57-year-old man with fever and no other specific symptoms
   b. 63-year-old woman with dysuria and urinalysis positive for nitrite and bacteria
   c. 45-year-old man with erythema noted around his Mediport site
   d. 72-year-old woman with oral pain and mucositis on examination

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Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

Learning Objectives: Upon completion of this article, the reader should be able to: (1) identify conditions due to cancer or cancer therapy that have the potential to cause death or organ damage; (2) initiate treatment for oncologic emergencies, including providing immediate therapies in the emergency department and establishing plans for definitive management; and (3) make disposition decisions appropriate to patient condition and expected prognosis.

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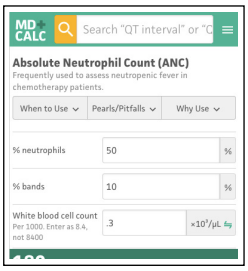

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Absolute Neutrophil Count

Introduction: The Absolute Neutrophil Count is frequently used to assess neutropenic fever in chemotherapy patients.

Points & Pearls

- Absolute Neutrophil Count (ANC) calculation is not a static measurement done only once upon hospital admission. Rather, it is often measured daily in critically ill patients (for example, to assess the bone marrow's response after chemotherapy).
- Recall that the ANC is dynamic; it is an absolute value and is **expected** to drop during the patient's nadir after chemotherapy.

Critical Actions

If the clinical scenario is suggestive of neutropenic fever, appropriate cultures and infectious disease workup should be instituted along with prompt initiation of empiric broad-spectrum antibiotics to cover mostly endogenous flora.

Evidence Appraisal

Al-Gwaiz et al (2007) tested the application of ANC to predict bacterial infections. They examined 105 peripheral blood smears and determined ANC, as well as the sensitivity of predicting bacterial infections. They determined that the ANC and toxic granulations are more sensitive than band count in predicting bacterial infections. Rivera et al (2003) performed a cross-validation study of Silber et al's 1998 findings to test if the first-cycle nadir ANC predicted the risk of febrile neutropenia. An ANC of $\leq 0.5 \times 10^9$/L was associated with a relative odds ratio of 4.8. The goal of this study was to provide a foundation for which dose adjustments in chemotherapy can be made to provide maximal anti-neoplastic therapy while minimizing side effects.

CALCULATOR REVIEW AUTHOR

Sagar Patel, MD

Department of Hematology and Medical Oncology
Cleveland Clinic, Cleveland, OH

Instructions

Use in neutropenic patients with a fever of at least 38°C (100.4°F). Do not use in patients with acute leukemia who are undergoing induction chemotherapy or allogeneic hematopoietic stem cell transplant conditioning, per IDSA guidelines.

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Calculator Creator

Layla A. Al-Gwaiz, MD, FCAP
Click here to read more about Dr. Al-Gwaiz.

References

Original/Primary Reference

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Why to Use

The ANC can be calculated with a routine complete blood cell (CBC) count and differential. No additional laboratory work is needed to complete the calculation. It is a tool that provides rapid risk stratification.

When to Use

- The ANC can be critical in assessing an immunocompromised patient's risk for developing opportunistic infections. It is commonly used in the hospital setting, clinic, and emergency department.
- If a patient undergoing active myelosuppressive chemotherapy presents with a sustained fever (with or without localizing symptoms), there is a risk of progression to sepsis. Thus, it is imperative to calculate the ANC to help decide whether empiric antibiotics should be initiated.

Next Steps

- Neutropenic fever (without a source of infection found) is typically the result of direct toxic effects of chemotherapy on mucosal surfaces and the immune system, in addition to the impact of the underlying malignancy. It is defined as a single oral temperature of ≥ 38.3°C (100.9°F), or a sustained temperature of > 38°C (100.4°F) for over 1 hour in a patient with neutropenia. Neutropenic fever is typically seen in those who have received anticancer therapies in the last 6 weeks. Filgrastim (Neupogen®, Zarxio®), also known as G-CSF, can stimulate production of neutrophils, but is rarely indicated in the evaluation and treatment of neutropenic fever.
- Additional tools to risk stratify a neutropenic fever patient and predict complications include the Clinical Index of Stable Febrile Neutropenia (CISNE) score and the Multinational Association for Supportive Care in Cancer (MASCC) score.
- Obtain a complete blood count with differential.
- ANC is calculated as 10 x WBC count in 1000s x (% PMNs + % bands)
- Classify neutropenia as mild, moderate, or severe according to the following:
  Neutropenia: ANC < 1500 cells/mm³
  - Mild neutropenia: 1000-1500 cells/mm³
  - Moderate neutropenia: 500-999 cells/mm³
  - Severe neutropenia: < 500 cells/mm³
- ANC values also can be interpreted by NCI risk categories, as in the table below:

NCI Risk Category	ANC
0	Within normal limits
1	≥ 1500 to < 2000 cells/mm³
2	≥ 1000 to < 1500 cells/mm³
3	≥ 500 to < 1000 cells/mm³
4	< 500 cells/mm³

Other References

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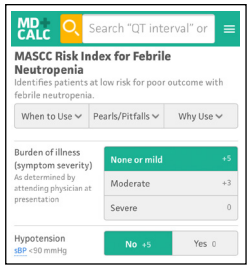
Related Calculator

- Click here to access the Clinical Index of Stable Febrile Neutropenia (CISNE).



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MASCC Risk Index for Febrile Neutropenia

Introduction: The MASCC risk index for febrile neutropenia identifies patients who are at low risk for poor outcomes with febrile neutropenia.

Points & Pearls

- The Multinational Association for Supportive Care in Cancer (MASCC) risk index applies only to adult patients.
- It is validated as a dichotomous outcome: low-risk versus not-low-risk. Obviously, patients who are "not-low-risk" have varying degrees of risk.

Critical Actions

The Infectious Diseases Society of America (IDSA) recommends admission for empiric antibiotics for high-risk patients who are not already admitted to the hospital.

Evidence Appraisal

The derivation study for the MASCC risk index was performed in the late 1990s (1994-1997) and included 756 patients in the derivation cohort and 383 patients in the validation cohort. While many claim that the MASCC risk index cannot be applied to patients with hematologic malignancies, over 40% of the patients included in the study had a hematologic malignancy. Logistic regression analysis was used to determine a weighted risk score with a positive predictive value (PPV) of 91%, specificity of 68%, and sensitivity of 71%.

Of note, patients were only included in the study for a single episode of febrile neutropenia and were not allowed to re-enter the study for subsequent episodes; thus, it is unclear whether the score should be applied to patients with multiple episodes of febrile neutropenia, although this is routinely done in clinical practice.

There have been at least 8 external validation studies showing a PPV from 83% to 98% with sensitivity from 59% to 95%. Studies that included more patients with hematologic malignancies had lower PPV and sensitivity, suggesting a poorer performance of the score in that population.

CALCULATOR REVIEW AUTHOR

Justin Taylor, MD

Leukemia Service, Division of Hematologic Oncology
Memorial Sloan Kettering Cancer Center, New York, NY

Instructions

Use in neutropenic patients with a fever of at least 38°C (100.4°F). Do not use in patients with acute leukemia who are undergoing induction chemotherapy or allogeneic hematopoietic stem cell transplant conditioning, per IDSA guidelines.

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Calculator Creator

Jean Klastersky, MD
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References

Original/Primary Reference

- Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol.* 2000;18(16):3038-3051.

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Why to Use

Febrile neutropenia is a potentially life-threatening complication of chemotherapy, but some patients are at low risk for serious complications. The MASCC risk index is an internationally validated scoring system that identifies these low-risk patients who can potentially be treated as outpatients with early antibiotics.

When to Use

- Use at onset of fever, to assess the risk of complications in febrile neutropenia for patients undergoing chemotherapy treatment.
- Use after addressing immediate concerns, to identify patients who may not need to be admitted to the hospital or could be discharged early.

Next Steps

- Higher scores indicate lower risk, with a maximum of 26 points. Using a cutoff value of ≥ 21 points discriminates patients with low risk from those with high risk (< 21 points) for serious complications of febrile neutropenia, eg, death, admission to the intensive care unit, or hypotension.
- The MASCC score has been endorsed by the IDSA since 2002 with Level B (moderate) evidence supporting its use. However, most experts consider high-risk patients to be those with anticipated prolonged neutropenia (> 7 days), profound neutropenia (absolute neutrophil count < 100), and/or comorbid conditions (in addition to chronic obstructive pulmonary disease) – Level A evidence – that are not necessarily accounted for in the MASCC score. Therefore, clinical judgment by specialists (in infectious disease, hematology/oncology, or emergency medicine/internal medicine/critical care) with knowledge of predicted disease-specific chemotherapy effects may override the MASCC score.
- High-risk patients require admission for intravenous antibiotics.
- Carefully selected low-risk patients should receive oral or intravenous empiric antibiotics in a clinic or hospital setting, and may be transitioned to outpatient regimens if they meet certain criteria.

- Carmona-Bayonas A, Gómez J, González-Billalabeitia E, et al. Prognostic evaluation of febrile neutropenia in apparently stable adult cancer patients. *Br J Cancer.* 2011;105(5):612-617.

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