Oncologic Emergencies, Part II: Neutropenic Fever, Tumor Lysis Syndrome, And Hypercalcemia Of Malignancy

It is your Friday evening shift in a suburban emergency department (ED), and the waiting room is full, as usual. The nurse hands you the chart of a 22-year-old man who is reporting profound weakness and palpitations. He had been triaged as low priority on the basis of his age and stable vital signs (temperature, 37°C [98.6°F]; heart rate, 96 beats/minute; blood pressure, 102/64 mm Hg; respiratory rate, 16 breaths/minute; and SaO₂, 98% on room air). As you enter the room, you see that he appears pale and quite fatigued. His symptoms are nonspecific, so you order basic laboratory tests and an electrocardiogram (ECG) for his palpitations. There is something about this patient that is not right.

As you leave the man’s room, a nurse calls your attention to an ill-appearing woman she has placed in one of the back rooms. As you walk into the room, you see that the patient is noticeably cachectic and lethargic. Her vital signs include a rectal temperature of 36.7°C (97.9°F); heart rate, 112 beats/minute; blood pressure, 90/64 mm Hg; respiratory rate, 22 breaths/minute; and SaO₂, 98% on room air. Her husband tells you she is being treated for lung cancer and her last chemotherapy session was 3 days ago. She has had poor oral intake since then and has reported abdominal pain and vomiting. He states that she does not have any other medical problems. You instruct the nurse to begin intravenous (IV) fluid resuscitation with 500 mL of normal saline while...
Of the 3 topics reviewed, neutropenic fever has the best evidence supporting its management. Evidence regarding management of the other conditions is largely based on case reports and observational cohort studies.

**Neutropenic Fever**

Neutropenic fever (also known as febrile neutropenia) remains one of the most commonly encountered oncologic emergencies, with ED presentations for evaluation of this disorder increasing as the number of cancer patients continues to grow. The survival of patients with neutropenia hinges on the expeditious recognition and appropriate treatment of infection; however, because of their impaired immune systems, neutropenic patients often do not exhibit typical signs and symptoms of infection, so subtle clues in their presentation should always be vigorously pursued.

**Definition Of Neutropenic Fever**

Neutropenic fever is defined as a single temperature measurement \( \geq 38.3^\circ C (101^\circ F) \) or a sustained temperature \( \geq 38^\circ C (\geq 100.4^\circ F) \) for more than 1 hour in a patient with an absolute neutrophil count (ANC) of either \(< 500 \text{ cells/µL} \) or \(< 1000 \text{ cells/µL} \), with a predicted nadir of \(< 500 \text{ cells/µL} \) over the subsequent 48 hours. This ANC cutoff was derived from a prospective study of 747 patients and is important because the incidence of serious infection greatly increases as the ANC declines, resulting in higher morbidity and mortality.\(^3\) The rate and time frame of the decline vary according to the chemotherapy used, but nadirs generally occur 7 to 10 days after chemotherapy. In a review of 160 patients with non-Hodgkin lymphoma and neutropenic fever, half experienced ANC declines within 14 days after their first cycle of chemotherapy.\(^4\)

The anticipated duration of neutropenia also largely depends on the type of cancer treatment received. For example, most solid tumor chemotherapy regimens cause neutropenia that lasts 5 days or less. However, intensive regimens for hematologic malignancies can result in neutropenia lasting longer than 14 days. Moreover, despite elevated total white blood cell (WBC) counts, the ANC in patients with active hematologic malignancy may actually be low. The duration of neutropenia is also an important consideration in determining likely organisms that may cause infection.

**Epidemiology And Costs Of Neutropenic Fever**

Chemotherapy-induced neutropenia is very costly, both financially and in terms of patient mortality. The inpatient mortality rate for neutropenic fever is 9% to 20%, and the average cost per hospitalization for its treatment often exceeds $19,000 (not factor-
ing in expenses affiliated with required discharge follow-up).\textsuperscript{5,6,7} Approximately 4\% of patients with leukemia require hospitalization for neutropenia after each round of chemotherapy.\textsuperscript{8} As the population grows and chemotherapy regimens become more effective, the number of individuals living with leukemia in the United States, estimated at almost 900,000 in 2008, will continue to increase, as will corresponding costs and mortality surrounding their care.\textsuperscript{9}

### Pathophysiology Of Neutropenic Fever

Neutropenia most commonly results from insults to the bone marrow, such as malignant invasion, therapeutic irradiation, or chemotherapy. Leukemias and lymphomas, which are malignancies of the hematopoietic system, are associated with a particularly high incidence of neutropenia. Chemotherapy is a double-edged sword, because it targets the rapidly dividing cells of both the malignancy and the host. Mucosal breakdown is also conducive to infection. The high cell turnover of the gastrointestinal mucosa makes this normally effective barrier to infection susceptible to the invasion of infectious organisms, and the weakened hematopoietic system cannot generate enough WBCs to fight their proliferation. From mouth to anus, endogenous bacterial flora can translocate across the damaged mucosal barrier to the bloodstream. Patients with cancer typically have other potential entry points for infection, including IV catheters, sites of surgical manipulation, and areas of abnormal anatomic architecture created by the tumors themselves, which can establish a milieu favoring bacterial growth.

Neutropenic patients are vulnerable to numerous infectious organisms. Endogenous flora account for approximately 80\% of infections in neutropenic patients\textsuperscript{10}, however, a definite infectious source is identified in only about a third of patients with neutropenic fever.\textsuperscript{11} The most frequently cultured organisms arise from the gut (eg, \textit{Escherichia coli}, \textit{Enterobacter}, anaerobes), skin (eg, \textit{Staphylococcus}, \textit{Streptococcus}), and respiratory tract (eg, \textit{Streptococcus pneumoniae}, \textit{Klebsiella}, \textit{Corynebacterium}, \textit{Pseudomonas}) as well as from other areas that are susceptible to opportunistic colonization (eg, by \textit{Clostridium difficile}, \textit{Mycobacterium}, \textit{Candida}, \textit{Aspergillus}).

The chemotherapy landscape that has evolved over the past 30 years has brought about a shift in the etiologic organisms for most infections. Gram-negative bacteria, in particular, \textit{Pseudomonas}, were once the most common infectious cause of neutropenic fever. Now, gram-positive infections predominate as a result of permanent IV access, an increased incidence of vancomycin-resistant \textit{Enterococcus} and methicillin-resistant \textit{Staphylococcus aureus}, the use of antibiotic prophylaxis, and the increased efficacy of antimicrobial agents against gram-negative organisms.\textsuperscript{12} Although fungi and viruses are important contributors to infection in neutropenic patients, with a few exceptions, they rarely need to be treated in the ED because of their typically indolent courses.

Some viruses and fungi do deserve mention because of their lethality, high incidence in particular neutropenic individuals, and response to treatment with appropriate antimicrobials. The Human herpesviruses (eg, simplex and zoster) and influenza viruses are lethal in this patient population and potentially treatable with acyclovir and a neuraminidase inhibitor, respectively. In addition to their susceptibility to these and other common viruses (eg, parainfluenza virus, respiratory syncytial virus [RSV]), patients who have undergone hematopoietic stem cell transplantation are at particular risk for cytomegalovirus, Epstein-Barr virus, and Human herpesvirus 6\textsuperscript{13}; however, treatment in the ED is generally not initiated for these patients without discussion with an oncologist. Furthermore, those patients receiving the aforementioned transplants often receive fluconazole prophylaxis because of their high risk of candidemia; thus, when these high-risk individuals present, it is important to consider the possibility of alternative fungal etiologies (eg, \textit{Aspergillus}, \textit{zygomycosis}) and broaden the coverage appropriately.\textsuperscript{14} Overall, the clinical scenario should guide the ensuing antimicrobial regimen in the ED setting.

### Differential Diagnosis For Neutropenic Fever

Causes of fever other than infection must be considered. The differential diagnosis includes transfusion reactions, medication allergies and toxicities, and tumor-related fever.

### History And Physical Examination For Neutropenic Fever

The classic manifestations of infection seen in immunocompetent hosts may not be evident in infected neutropenic patients because of host immunodeficiency. Therefore, a thorough history and physical examination are essential so that clinicians can identify subtle clues to guide the diagnosis and workup. (See Table 1.) Because mucosal and skin barriers are particularly affected by chemotherapy, sites of even mild erythema on the skin or slight erosion in the oropharynx or perianal area should be regarded

### Table 1. Pertinent Historical Features In Patients With Neutropenic Fever

<table>
<thead>
<tr>
<th>Important Topics For The Patient History</th>
</tr>
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<tbody>
<tr>
<td>• Comorbidities</td>
</tr>
<tr>
<td>• Current medications</td>
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<tr>
<td>• Time since last chemotherapy treatment</td>
</tr>
<tr>
<td>• Chemotherapeutic regimen</td>
</tr>
<tr>
<td>• Recent antibiotic use</td>
</tr>
<tr>
<td>• Recent exposure to infections at home</td>
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</table>
with suspicion. A mild cough may be indicative of serious underlying pathology. Elderly patients and those on corticosteroids may be unable to mount a fever in response to an infection.

The best method and location for taking a patient’s temperature have not been established. Despite the absence of supporting evidence, many oncologists advise against rectal measurements because of concerns about an increased risk of mucosal tearing, with a subsequent increased risk of bacterial seeding.

**Diagnostic Studies For Neutropenic Fever**

Extensive initial laboratory and radiologic investigations are usually required to properly begin the ED workup of the patient with neutropenic fever. However, clinicians should remember that diagnosis is not the goal. Instead, the goals are to clinically stabilize the patient, initiate an appropriate diagnostic work-up, and promptly administer empiric antibiotics. As mentioned, a definitive cause of neutropenic fever is found in only about 30% of cases by the time of discharge. However, 1 retrospective study in a Philadelphia ED of febrile patients with ANC < 1000 cells/µL found that of 26 individuals with neutropenic fever who had a specific infection during hospitalization, the source was identified in 21 of the patients while they were in the ED via a thorough history, physical examination, chest radiograph, and urinalysis. The remaining 5 patients were found to have bacteremia during their hospital course.¹⁵

The initial laboratory workup should include basic chemistries, liver function tests, a complete blood cell count (CBC) with differential, a urinalysis and urine culture, a sputum Gram stain and culture, and 2 sets of blood cultures. Although the IDSA recommends blood cultures from both the central venous catheter and the periphery, or 2 cultures from the periphery, recent evidence suggests that 2 samples from the central venous port alone are sufficient.¹⁶ Successful identification of the infecting organism mostly depends on the quantity of blood drawn, and the best yield is achieved when at least 20 to 30 mL of blood is obtained.¹⁷ Per expert opinion, site-specific studies should also be obtained, depending on the level of suspicion for particular infections.² For example, a nasopharyngeal wash specimen should be obtained from patients with symptoms consistent with an upper respiratory tract infection, and it should be screened for RSV and influenza, or a sample of drainage from any site should be taken for Gram stain and culture. Also, the emergency clinician should note that neutropenia may preclude the presence of leukocytes or leukocyte esterase in the urine, making urinalysis an unreliable diagnostic modality for a urinary tract infection.

Despite evidence demonstrating that chest radiographs are unnecessary in people with normal findings on physical examination and no respiratory symptoms, and that they frequently yield normal results even in the setting of active infection, expert consensus recommends radiographic evaluation as part of the standard workup.²¹⁸ Because no formal guidelines address the use of computed tomography (CT), the emergency clinician must use clinical judgment when deciding whether to obtain CT imaging for highly suspicious findings on the history, physical examination, and/or plain films or with abnormal laboratory results. For example, a sinus CT for sinus tenderness, chest CT for respiratory abnormalities, or abdominal CT for diarrhea and abdominal pain may be appropriate. Orders for further tests should be guided by the level of suspicion for a particular infection (eg, a lumbar puncture for neurologic abnormalities or C difficile) toxin, microscopic analysis for ova and parasites, or a stool culture for diarrhea). (See Table 2.)

**Treatment For Neutropenic Fever**

All patients meeting the criteria for neutropenic fever should be treated promptly and aggressively. Even afebrile neutropenic patients who present with signs or symptoms consistent with possible infection should receive antibiotics.¹

In the ED, timely evaluation of patients with neutropenic fever and initiation of antibiotics are crucial. Nirenberg and colleagues found that for patients with neutropenic fever, the mean time from patient-reported onset of fever to the patient’s arrival in the ED was 21 hours, and the median times from the patient’s ED arrival until examination, antibiotic administration, and hospital admission were 75 minutes, 210 minutes, and 330 minutes, respectively.¹⁹

Based on the need for broad-spectrum bactericidal coverage against numerous potential organisms, particularly S aureus, S epidermidis, E coli, Pseudomonas aeruginosa, and Klebsiella spp., the IDSA guidelines recommend prompt initiation of coverage with a third- or fourth-generation cephalosporin (cefepime or ceftazidime) or a carbapenem (imipenem or meropenem). (See Table 3.) However, in a

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**Table 2. Recommended Basic Diagnostic Tests For Patients With Neutropenic Fever**

<table>
<thead>
<tr>
<th>Baseline Diagnostic Tests</th>
<th>CBC with differential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal function tests</td>
<td>Basic chemistries</td>
</tr>
<tr>
<td>Liver function tests</td>
<td></td>
</tr>
<tr>
<td>2 sets of blood cultures</td>
<td>Adults: 20-30 mL total</td>
</tr>
<tr>
<td></td>
<td>Children: 1-5 mL total</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Chest radiograph</td>
</tr>
<tr>
<td>Other tests as indicated</td>
<td></td>
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</tbody>
</table>

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meta-analysis of randomized controlled trials (RCTs) that included more than 5500 patients receiving empiric monotherapy antibiotic regimens for neutropenic fever, cefepime was associated with increased mortality, bringing into question its current role in the treatment of neutropenic fever. In the same meta-analysis, initial monotherapy with the antipseudomonal β-lactam piperacillin/tazobactam was found to be as effective as other agents; however, because only 6 large trials existed at the time the study was published, no recommendations were made regarding use of this monotherapy. \(^2\) \(^2\) \(^3\) A subsequent RCT of 528 patients confirmed the noninferiority of piperacillin/tazobactam to cefepime, leading to its recent inclusion in the updated IDSA guidelines for the treatment of neutropenic fever.1, \(^2\) \(^2\) \(^2\)

The IDSA guidelines allow the addition of an aminoglycoside to 1 of the drugs listed above for a theoretical synergistic effect against bacteria, a reduction of emerging resistant organisms, and broader coverage against increasingly resistant bacteria. \(^2\) However, a recent meta-analysis of 47 trials that included more than 7800 patients demonstrated that this addition was accompanied by an increase in adverse side effects and did not enhance the overall efficacy of monotherapy. \(^2\) \(^3\) \(^3\) Alternatively, the use of an antipseudomonal fluoroquinolone (eg, moxifloxacin, levofloxacin, ciprofloxacin) as part of the 2-drug regimen has been proposed by some experts, although the literature supporting this regimen is limited. \(^1\) \(^1\) \(^1\) One randomized, double-blind, multicenter study of 471 cases of neutropenic fever did demonstrate that ciprofloxacin plus piperacillin was as safe and effective as tobramycin plus piperacillin. \(^2\)-safe\) Similar to aminoglycosides, this additive antibiotic is usually considered in the setting of suspected multidrug resistance or for critically ill patients.

Primarily out of concern for growing antibiotic resistance patterns, many experts discourage the use of vancomycin unless certain criteria are met. \((\text{See Table 4.})\) According to an RCT of 747 patients, although vancomycin shortens the duration of fever in adults, it does not confer a benefit in mortality. \(^2\) \(^5\) A recent meta-analysis of RCTs supports deferring treatment with vancomycin until a gram-positive infection is documented. \(^2\) \(^6\) However, evidence of decreased mortality rates does support its use in children. \(^2\) \(^7\) When vancomycin cannot be used or when vancomycin-resistant gram-positive pathogens are present, quinupristin/dalfopristin, daptomycin, and linezolid can be used; these are the only current indications for the drugs because of their various toxicities and limitations in efficacy. \(^2\) \(^8\) Although no data exist regarding the use of tigecycline in lieu of vancomycin in the setting of neutropenic fever, the principles listed above should hold true regarding its use. For low-risk patients who are allergic to penicillin, treatment options include levofloxacin, moxifloxacin, ciprofloxacin plus azithromycin, or ciprofloxacin plus clindamycin. \(^1\) \(^9\) Updated IDSA guidelines for the management of neutropenic fever are planned for release in 2010. \(^1\) \(^9\) \((\text{See the Clinical Pathway For The Initial Management Of Neutropenic Fever, page 6.})\)

Currently, no strong evidence supports the use of empiric antifungal or antiviral agents on the basis of fever alone during a patient’s initial presentation. This therapy is usually initiated on hospital days 4 through 7 if fever persists or if other evidence of a fungal source is present. \(^1\) \(^1\) \(^1\) However, if other clues indicate the presence of a viral infection (eg, physical examination findings consistent with herpes zoster) or a fungal infection (eg, outpatient blood cultures yielding Candida albicans), treatment for that particular infection should, of course, be initiated in the ED.

### Table 3. Standard Antibiotic Doses For The Initial Treatment Of Neutropenic Fever In Adults With Normal Renal Function\(^2\)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>First Dose In Adults, IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>2 g</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2 g</td>
</tr>
<tr>
<td>Imipenem</td>
<td>500 mg</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 g</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>2 g</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>4.5 g</td>
</tr>
<tr>
<td>Ticarcillin/clavulanate</td>
<td>3.1 g</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2-5 mg/kg</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>1-1.7 mg/kg</td>
</tr>
<tr>
<td>Amikacin</td>
<td>7.5 mg/kg</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1 g</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>900 mg</td>
</tr>
</tbody>
</table>

Abbreviation: IV, intravenously.

Adapted with permission from Hughes et al. 2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients With Cancer, ©The University of Chicago Press.

### Table 4. Indications For Vancomycin In Patients With Neutropenic Fever\(^2\)

- Hypotension
- Preliminary cultures showing gram-positive flora
- Known history of methicillin-resistant Staphylococcus aureus or β-lactam-resistant pneumococci
- Prior prophylaxis with a fluoroquinolone or trimethoprim/sulfamethoxazole\(^2\)
- Probable catheter-related infection

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Clinical Pathway For The Initial Management Of Neutropenic Fever

Fever (temperature ≥ 38.3°C [≥ 101ºF]) plus neutropenia (ANC < 500 cells/μL)

At risk for severe infection? (See Table 5, page 8) (Class II)

IV monotherapy (See Table 3, page 5) (Class I)

Vancomycin indicated? (See Table 4, page 5)

Add vancomycin (Class I)

Is patient critically ill or at risk for multidrug-resistant organisms?

Add an aminoglycoside or a fluoroquinolone (Class II)

Admit

Tolerates oral medications?

Meets MASCC criteria for outpatient management? (See Table 6, page 8) (Class I)

Consider outpatient management with oral ciprofloxacin and amoxicillin/clavulanate (Class I)

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Special Circumstances For Neutropenic Fever

High-Risk Infections
Two infections—neutropenic enterocolitis (typhlitis) and zygomycosis (mucormycosis)—deserve mention because of their particularly high mortality rates.

Neutropenic enterocolitis is a life-threatening necrosis of the bowel wall, resulting from microbial invasion. It usually involves the cecum and typically occurs 10 to 14 days after cytotoxic chemotherapy. Provoking symptoms of fever, right-lower-quadrant pain, nausea, and vomiting, it can mimic appendicitis. A CT scan of the abdomen often shows cecal distention and wall thickening, warranting medical management that includes bowel rest, nasogastric suction, IV fluids, and broad-spectrum antibiotics. However, even in the absence of clinical or radiographic evidence of bowel perforation, surgical consultation is appropriate for evaluation of a right hemicolectomy in the event the patient’s condition deteriorates. Despite appropriate treatment, the overall mortality rate associated with neutropenic enterocolitis remains around 50%.

Mucormycosis is an infection of fungal hyphae into the vasculature of immunocompromised individuals, rapidly leading to tissue necrosis and destruction. Although the fungus has been associated with infections of the lungs, gastrointestinal tract, and central nervous system (CNS), the most common site of infection is the paranasal sinuses (rhinocerebral mucormycosis). Even when the infection is consolidated entirely within the sinuses, mortality estimates range from 30% to 90%.

Low-Risk Groups
The 2002 IDSA guidelines detail various clinical factors associated with a low risk for serious infection in neutropenic patients. The Multinational Association for Supportive Care in Cancer (MASCC) risk index was prospectively derived in 756 individuals to determine the likelihood of successful outpatient treatment of those with neutropenic fever. A score of 21 or higher identifies a low-risk individual, with a positive predictive value of 94%, a sensitivity of 80%, and a specificity of 71%. A subsequent validation study of 178 patients confirmed the utility of the MASCC risk index to safely discharge patients.
who are receiving oral antibiotics after an in-hospital observation period of less than 48 hours. The ciprofloxacin (500 mg 3 times per day) and amoxicillin-clavulanate (500 mg 3 times per day) combination resulted in successful outpatient treatment of 96% of patients; the remaining 4% required readmission to the hospital but had no serious complications.\textsuperscript{35} Prior fluoroquinolone prophylaxis prohibits the subsequent use of that drug as initial therapy in low-risk patients with neutropenic fever.\textsuperscript{1}

These studies demonstrate the safety, efficacy, and economic savings associated with treating select patients with oral antibiotics in the outpatient setting. Financial incentives certainly exist for patients and hospitals to pursue outpatient management. For each episode of neutropenic fever, the average cost per inpatient hospitalization exceeds $12,000 for those with solid tumors and $19,000 for those with lymphoma.\textsuperscript{36} In contrast, the estimated cost for outpatient care ranges from $2000 to $7500 per episode.\textsuperscript{37,38}

### Controversies And Cutting Edge For Neutropenic Fever

Despite the publication of clear guidelines by the IDSA in 2002,\textsuperscript{2} antibiotic use in hospitals varies significantly and trials continue, in order to identify the best regimens. The upcoming IDSA guidelines will likely address additional issues surrounding antibiotic treatment of neutropenic fever (eg, the formal addition of piperacillin/tazobactam to the antibiotic armamentarium).\textsuperscript{1}

The IDSA and various cancer societies have emphasized the importance of developing more effective ways of identifying patients at risk for serious infection. Current studies have preliminarily identified C-reactive protein, procalcitonin, and interleukin 6 (IL-6) as important prognostic markers.\textsuperscript{39}

### Summary Of Neutropenic Fever

As a result of their impaired immune systems, patients with neutropenic fever are primed for the development of fulminant sepsis if they are not evaluated and treated quickly. The number of individuals with neutropenic fever presenting to EDs is increasing throughout the country, ensuring that most emergency clinicians will encounter this disease. Therefore, it is imperative that clinicians are comfortable appropriately treating these patients.

### Disposition Of Patients With Neutropenic Fever

The vast majority of patients presenting to the ED with neutropenic fever should be admitted to the hospital. Most will be clinically stable for transfer to the floor, while a few will require higher levels of care based on their vital signs and comorbid conditions. Because these patients have the potential to become ill rapidly, the oncologist may occasionally request a higher level of care than appears to be warranted based on the potential for severe illness. If the hospital has a designated oncologic floor, this option is usually preferred, as nurses there have experience treating patients with neutropenic fever.

Only select patients who are clinically well-appearing and have excellent follow-up should even be considered for discharge home. The patient has to be high-functioning, have excellent family support, and be motivated to go to the outpatient oncologic clinic daily. The oncologist should be the one who suggests a discharge plan, as he or she will be the one following up once the patient returns home.

### Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a rare oncologic emergency that also requires rapid identification and

### Table 5. Factors Associated With Low Risk For Severe Infection In Patients With Neutropenic Fever\textsuperscript{2}

<table>
<thead>
<tr>
<th>Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute neutrophil count ≥ 100 cells/mm\textsuperscript{3}</td>
<td></td>
</tr>
<tr>
<td>Absolute monocyte count ≥ 100 cells/mm\textsuperscript{3}</td>
<td></td>
</tr>
<tr>
<td>Normal results on chest radiograph</td>
<td></td>
</tr>
<tr>
<td>Normal hepatic and renal function</td>
<td></td>
</tr>
<tr>
<td>Neutropenia duration &lt; 7 days</td>
<td></td>
</tr>
<tr>
<td>Neutropenia expected to resolve in &lt; 10 days</td>
<td></td>
</tr>
<tr>
<td>No IV catheter site infection</td>
<td></td>
</tr>
<tr>
<td>Early evidence of bone marrow recovery</td>
<td></td>
</tr>
<tr>
<td>Malignancy in remission</td>
<td></td>
</tr>
<tr>
<td>Peak temperature &lt; 39.0°C (&lt; 102.2°C)</td>
<td></td>
</tr>
<tr>
<td>Normal results on neurologic examination</td>
<td></td>
</tr>
<tr>
<td>Not ill-appearing</td>
<td></td>
</tr>
<tr>
<td>No abdominal pain</td>
<td></td>
</tr>
<tr>
<td>No concomitant comorbidities (eg, shock, hypoxia, deep organ infection, vomiting, diarrhea)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 6. MASCC Risk Index For Patients With Neutropenic Fever\textsuperscript{34}

<table>
<thead>
<tr>
<th>Patient Clinical Factors</th>
<th>Score\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of illness</strong></td>
<td></td>
</tr>
<tr>
<td>No symptoms or mild symptoms</td>
<td>5 points</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>3 points</td>
</tr>
<tr>
<td>No hypotension</td>
<td>5 points</td>
</tr>
<tr>
<td>No chronic obstructive pulmonary disease</td>
<td>4 points</td>
</tr>
<tr>
<td>Solid tumor or no fungal infection</td>
<td>4 points</td>
</tr>
<tr>
<td>No dehydration</td>
<td>3 points</td>
</tr>
<tr>
<td>Outpatient at onset of fever</td>
<td>3 points</td>
</tr>
<tr>
<td>Age &lt; 60 years</td>
<td>2 points</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Validated in individuals older than 16.

\textsuperscript{b} A score ≥ 21 out of a possible 26 points indicates that the patient is likely at low risk for significant bacterial illness.
management. Most patients who develop TLS have a lymphoproliferative or hematopoietic malignancy and have recently started a course of chemotherapy. However, if a large tumor burden exists, TLS can present following chemotherapy for solid tumors, or it can present spontaneously in certain lymphoproliferative malignancies before they are diagnosed. As the survival rate of oncologic patients increases and more therapeutic regimens become available, emergency clinicians will likely see an increased number of patients presenting with TLS. Because these patients may deteriorate quickly and have the potential for significant morbidity if the syndrome is not recognized and promptly treated, emergency clinicians should be familiar with its presentation and management.

**Etiology For TLS**

Although TLS was first described in 1929 as a collection of metabolic abnormalities seen in patients with acute leukemia, experts have yet to reach consensus on how to define it. Tumor lysis syndrome is often described as the massive release of intracellular products from malignant cells after antitumor treatment (or spontaneously), resulting in hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and acute kidney injury. Tumor lysis syndrome is frequently categorized according to its tumor classification (hematologic malignancy vs solid tumor) and relationship to antitumor treatment (spontaneous vs treatment-associated).

In 1993, Harde and Garrow classified TLS into laboratory tumor lysis syndrome (LTLS) and clinical tumor lysis syndrome (CTLS). However, since LTLS required a 25% worsening in baseline laboratory values (eg, creatinine clearance), it could not accurately account for patients with LTLS and preexisting abnormal values (eg, those with chronic kidney disease) who did not experience the case-defining 25% change in laboratory data. In 2004, Cairo and Bishop modified the criteria so that a more-inclusive definition of LTLS included patients with abnormal baseline laboratory values prior to chemotherapy and those who develop TLS within the 3 days preceding and during the 7 days following treatment. (See Table 7.)

Cairo and Bishop also developed a grading system based on the severity of end-organ complications associated with TLS (ie, acute kidney injury, cardiac dysrhythmia, or seizure). Regardless of which definition of TLS is used, uniformity among studies is necessary to better track the true incidence and mortality rate of the disease as well as the efficacy of the various treatment modalities for TLS.

**Epidemiology Of TLS**

The exact incidence of TLS for each tumor type is unknown, partly because of the lack of universal diagnostic criteria. The disorder is most common among patients with non-Hodgkin lymphoma (especially Burkitt lymphoma), acute leukemia, or chronic leukemia who have undergone recent chemotherapy. In 1993, Hande and Garrow calculated the incidence of TLS among patients with non-Hodgkin lymphoma after combination chemotherapy. All 102 patients were treated with IV fluids and allopurinol but still developed LTLS at a rate of 42% and CTLS at a rate of 6%. The overall mortality associated with CTLS has been reported to range from 29% to 79%, but the risk of dying largely varies on the basis of the patient’s underlying functional status. Older patients have higher TLS-related morbidity and mortality rates, likely related to preexisting kidney disease and other comorbidities. TLS occurs in patients with solid tumors but much less frequently than in those with lymphoproliferative malignancies. Such solid malignancies include metastatic carcinoma of the breast, small cell and non–small cell lung cancer, seminoma, invasive thymoma, metastatic medulloblastoma, Merkel cell carcinoma, ovarian carcinoma, rhabdomyosarcoma, metastatic melanoma, and vulvar carcinoma. Although TLS is rare in patients with solid malignancies, emergency clinicians should be aware of its possible presentation in their practice.

**Pathophysiology And Clinical Presentation Of TLS**

Tumor lysis syndrome is actually a constellation of metabolic derangements resulting from the massive release of intracellular metabolites from lysed tumor cells. Nucleic acid metabolites, phosphorus, and

| Table 7. Cairo-Bishop Definitions Of Laboratory Tumor Lysis Syndrome And Clinical Tumor Lysis Syndrome |
| Laboratory Tumor Lysis Syndrome  |
| 2 or more of the following criteria within 3 days prior to or 7 days after initiation of chemotherapy: |
| • Uric acid level: ≥ 8 mg/dL or 25% increase from baseline |
| • Potassium level: ≥ 6.0 mEq/L or 25% increase from baseline |
| • Phosphorus: ≥ 6.5 mg/dL for children |
| • Phosphorus concentration: ≥ 4.5 mg/dL for adults or 25% increase from baseline |
| • Calcium level: ≤ 7 mg/dL or 25% decrease from baseline |

| Clinical Tumor Lysis Syndrome  |
| Laboratory tumor lysis syndrome plus 1 or more of the following criteria: |
| • Creatinine > 1.5 times upper limit of age-adjusted reference range |
| • Cardiac dysrhythmia or sudden death |
| • Seizure |

potassium are among the intracellular contents that spill into the circulation. Consequently, manifestations of TLS reflect hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcemia. Hyperuricemia and calcium phosphate formation from hyperphosphatemia can lead to acute kidney injury, which is the primary mechanism for morbidity and mortality. Electrocardiographic changes may show sudden derangements in electrolyte balance. Metabolic acidosis that is not explained solely by renal compromise may also occur.45

Hyperkalemia
Roughly 98% of the body’s potassium stores are located in the intracellular compartment. Release of potassium from tumor cells into the circulation can cause acute hyperkalemia, which may lead to dysrhythmias. Acute hyperkalemia should be the first concern when TLS is suspected, as it poses the most immediate threat to the patient’s life. Patients with concurrent kidney disease, which is commonly present in TLS, have a higher risk of hyperkalemia from impaired renal excretion of excess potassium.

Hyperuricemia
After cell lysis, nucleic acids degrade into purine metabolites, which are then processed by xanthine oxidase into uric acid. (See Table 8.) Uric acid is subsequently excreted into the urine. If the urine becomes an acidic environment (as is the case with TLS), uric acid can precipitate into crystals, which may cause an obstructive uropathy with resultant kidney injury. Hyperuricemia may also cause nausea, vomiting, and lethargy.40

Hyperphosphatemia And Secondary Hypocalcemia
Most of the body’s stores of phosphorus reside in the intracellular compartment and the bony matrix. Malignant hematologic cells may contain up to 4 times more phosphate than normal mature lymphoid cells contain, and the rapid turnover of these cells releases large quantities of phosphorus.40 Excess phosphate binds to serum calcium, leading to hypocalcemia. Calcium phosphate crystals may also precipitate in the renal tubules and microvasculature. This crystal deposition can cause urinary obstruction and a local inflammatory response, potentially leading to acute kidney injury, which further impairs phosphorus elimination.42 Calcium phosphate deposition may also cause iritis, acute arthritis, and gangrenous skin lesions. Hypocalcemia is often asymptomatic in milder cases; however, with increasing severity, it can cause anorexia, vomiting, neuromuscular irritability, seizures, and cardiac arrest.40

Risk Factors For TLS
Tumor characteristics and host factors make some patients more susceptible to TLS than others. Tumor-related factors include a high cell proliferation rate, a large tumor burden (lactate dehydrogenase [LDH] > 1500 IU/L, WBC count ≥ 50 × 10^9 cells/L), extensive bone marrow involvement, tumor infiltration of the kidney, and high tumor sensitivity to chemotherapeutic agents.42,46 Examples of malignancies that share these characteristics are Burkitt leukemia/lymphoma, high-grade lymphoma, and acute leukemia with significant leukocytosis. Host risk factors include low urinary output, preexisting hyperuricemia, chronic kidney disease, dehydration, and acidic urine.42,47 Recognition of these risk factors for the development of TLS facilitates a more rapid diagnosis and initiation of appropriate care.

Diagnostic Studies For TLS

Laboratory Tests
All patients with suspected TLS should have a comprehensive metabolic profile performed that includes measurement of uric acid, LDH, phosphorus, total calcium, and ionized calcium levels; a CBC; a peripheral smear; and a urinalysis. A spot urine uric-acid-to-urine-creatinine ratio greater than 1 indicates uric acid nephropathy, while a ratio less than 0.65 suggests other causes of kidney injury such as nephrotoxic medications (the chemotherapeutic agents being given to the patient should be reviewed), hypercalcemia, recent contrast administration, infection, or urinary obstruction from direct tumor invasion.40

ECG
Electrolyte derangements are associated with certain ECG changes.

- Hyperkalemia: peaked T wave → wide QRS complex → loss of P wave → ventricular tachycardia/ventricular fibrillation
- Hypocalcemia: prolonged QT interval → ventricular tachycardia / torsades de pointes

Imaging Studies
Routine imaging is not generally needed to assess TLS. Instead, studies to assess concomitant disease entities should be based on the history and physical examination. Studies requiring IV contrast should be avoided, if possible, because crystal uropathy and volume depletion can predispose the kidney to significant injury.

Treatment For TLS

Hydration
All patients who have or are at risk for TLS should be treated with aggressive IV hydration with normal saline to achieve a urinary output of 3 L/24 hours. Adequate hydration decreases uric acid concentration in both serum and renal tubules and reduces uric acid precipitation.40,46
Diuretics
Although no study has determined the efficacy of diuretics in the management of TLS, the agents are used occasionally to maintain urinary output and excretion of uric acid. Diuretic use should be considered only after the patient achieves euvoledia via adequate fluid resuscitation.

Allopurinol
Allopurinol is converted to oxypurinol by xanthine oxidase. Oxypurinol effectively inhibits xanthine oxidase, blocking production of uric acid. Inhibition of xanthine oxidase can last 18 to 30 hours. Because allopurinol is cleared by the kidneys, it should be administered with caution to patients with decreased renal function. Allopurinol may cause xanthine crystal nephropathy through its action of increasing xanthine levels; however, the clinical significance of this effect remains controversial. If the patient cannot tolerate oral allopurinol, an IV formulation with similar efficacy can be used. Allopurinol acts slowly and only against future production of uric acid. These features limit its utility in the ED setting.

Urine Alkalization
Uric acid solubility increases in an alkaline environment, which has led to the routine use of urine alkalization as part of the standard treatment for TLS. However, the efficacy of this treatment has been questioned, as it may crystallize calcium phosphate and worsen kidney injury. Experimental studies suggest that urine alkalization is no better than saline hydration in preventing uric acid precipitation. Unless future RCTs demonstrate a benefit of routine urine alkalization, the currently available evidence does not support its use and therefore it is not recommended.

Urate Oxidase Therapy
In humans, uric acid is the final product of purine metabolism; it is also intricately involved in TLS and gout. In most other mammals, the enzyme urate oxidase converts uric acid to allantoin. Allantoin is 5 to 10 times more soluble than uric acid. Uricozyme, an Aspergillus-derived form of nonrecombinant urate oxidase that converts uric acid to allantoin, has been used extensively in Europe for almost 3 decades as a treatment for TLS.

Two European studies compared the efficacy of allopurinol with that of rasburicase, a recombinant form of urate oxidase, in treating pediatric patients with non-Hodgkin lymphoma or acute lymphoblastic leukemia. The same chemotherapeutic agents were used in each trial, and the results heavily favored the use of rasburicase. Hemodialysis was eventually required in 16% of those receiving allopurinol vs 2.6% of those receiving rasburicase. Rasburicase was approved by the US Food and Drug Administration (FDA) in 2002 for children with leukemia, lymphoma, or solid tumors and anticipated TLS and hyperuricemia from antitumor therapy. A multicenter, randomized, open-label trial compared allopurinol with rasburicase in 52 pediatric patients with leukemia or lymphoma at high risk of TLS. Rasburicase significantly reduced serum uric acid levels; however, the sample size was too small to determine if there was a difference in the incidence of kidney injury.

Rasburicase is promising and generally well-tolerated in the treatment of TLS. It has, however, been associated with a 4.5% risk of allergic reactions (e.g., urticaria, bronchospasm) and rare (< 2%) mild side effects (e.g., headache, fever, rigors). Patients with severe allergies, asthma, and known glucose-6-phosphate dehydrogenase deficiency have an increased risk of anaphylaxis with use of the drug.

In contrast to allopurinol, rasburicase may be used for both prevention and treatment of TLS. Although the high cost of rasburicase remains an issue, its rapid onset, high efficacy, and low toxicity make it an intervention that emergency clinicians must be familiar with. FDA approval for rasburicase was extended to adults in October 2009.

Electrolyte Correction
Management of the electrolyte abnormalities associated with TLS is summarized in Table 9 (page 13). Asymptomatic hypocalcemia should not be treated, as treatment could increase the deposition of calcium phosphate crystals. Control of hyperphosphatemia is usually adequate for such patients. Dialysis should be considered early in patients with persistent or worsening electrolyte abnormalities, acidemia, fluid overload, or uremia despite optimal medical treatment.

Summary For TLS
Tumor lysis syndrome results from multiple metabolic derangements that are usually caused by antitumor treatment for lymphoproliferative or hematologic malignancies. Although TLS is widely recognized and certainly feared in the oncologic field, its relatively rare occurrence makes it difficult for the emergency clinician to diagnose and treat comfortably. Without a careful history and diligent attention to abnormal laboratory results, this diagnosis could easily be overlooked. The emergency clinician must act quickly once this diagnosis is suspected and work to correct life-threatening electrolyte abnor-
Clinical Pathway For Management Of Tumor Lysis Syndrome

Suspected clinical tumor lysis syndrome?

Signs/symptoms: seizure, lethargy, vomiting, dysrhythmia, dehydration, oliguria

Risk factors: lymphoproliferative or chemosensitive malignancy, large tumor burden, recent antitumor therapy, preexisting acute kidney injury, or hyperuricemia

Perform the following diagnostic studies: chemistries; ionized calcium, uric acid, phosphate, LDH, and lactate levels; complete blood cell count, peripheral smear; urinalysis; ECG

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
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust RCTs
- 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


Abbreviations: ECG, electrocardiogram; IV, intravenously; PR, per rectum.
mic therapy alone has no effect on overall survival. Consequently, treatment should be viewed as a temporizing measure until definitive therapy for the underlying malignancy can be instituted. Hypercalcemia associated with cancer is different from hypercalcemia due to other causes (see Table 10, page 14), not only because of its prognostic significance but also because of its unique mechanisms of action. Multiple etiologies can be present simultaneously and should be considered.

Hypercalcemia of malignancy can be better understood by reviewing 3 general physiologic processes that increase serum calcium levels.

1. Parathyroid hormone (PTH) and the active form of vitamin D, also called calcitriol (1,25-[OH]2D), enhance intestinal calcium absorption (See Figure 3, page 14.)

2. Osteoclastic stimulation by various hormones (eg, PTH and parathyroid hormone–related protein [PTHrP]) and cytokines (eg, interleukin 1, IL-6, tumor necrosis factor, tumor growth factor α) promotes bone resorption to elevate calcium levels.

### Hypercalcemia of Malignancy

Hypercalcemia occurs in approximately 25% of patients with cancer, and approximately half of these patients die within a month after diagnosis. Hypercalcemia of malignancy is diagnosed in more than a third of all patients with hypercalcemia who present to the ED, and despite best efforts, antihypercalce-
3. Enhanced resorption (induced by either PTH or PTHrP) or decreased excretion of calcium through the renal tubules (as a result of volume depletion) raises calcium levels.

In the setting of cancer, hypercalcemia falls into the following 4 categories:

1. Local osteolysis associated primarily with bone metastasis.
2. Humoral hypercalcemia of malignancy (HHM) associated with PTHrP.
3. Lymphoma-associated secretion of calcitriol, which increases intestinal calcium absorption and bone resorption by osteoclasts.
4. Ectopic secretion of PTH, which is extremely rare (usually with parathyroid carcinomas).

Local osteolytic hypercalcemia causes about 20% of cancer-related hypercalcemia by inducing nearby osteoclastic bone resorption via cytokines and chemokines, which are released primarily from bone metastases. Breast cancers, multiple myelomas, and lymphomas work mainly in this fashion to raise serum calcium levels.

Eighty percent of patients with solid tumors and hypercalcemia have elevated levels of PTHrP. Although PTHrP is not the sole mediator of HHM and the protein has been identified in normal host tissue, it is associated with the vast majority of cases of HHM. Similar to PTH, PTHrP increases osteoclastic bone resorption; however, it is most active in the renal tubule, where it enhances active calcium resorption and inhibits renal tubular phosphate resorption. Squamous cell carcinoma (particularly of the head and neck); renal, endometrial, and breast cancers; and Human T-Lymphotropic Virus (HTLV)-associated lymphomas have all been implicated in the development of HHM.

Calcitriol-secreting lymphomas are responsible for less than 1% of all cases of hypercalcemia associated with cancer. By releasing 1,25-(OH)₂D, the active form of vitamin D, certain lymphomas stimulate increased calcium uptake from the gut and enhance osteoclastic bone resorption. Nearly all cases of Hodgkin-associated hypercalcemia and 30% to 40% of non-Hodgkin lymphoma–associated hypercalcemia occur through this process.

PTH is secreted uncontrollably in parathyroid cancers, but it is also produced ectopically in certain cancers of the ovary, lung, and primitive neuroectoderm. This type of hypercalcemia in malignancy occurs in less than 1% of cases.

### History For Hypercalcemia of Malignancy

A history of symptoms consistent with hypercalcemia, including anorexia, polydipsia, polyuria, weakness, bone pain, gastrointestinal symptoms (nausea, vomiting, and constipation), psychiatric symptoms (memory loss, apathy), lethargy, and fatigue can suggest an early diagnosis while laboratory confirmation is pending. Eliciting a history of any relative contraindications to aggressive fluid administration (eg, congestive heart failure, chronic kidney disease) and identifying potentially correctable causes (eg, inciting medications, calcium-containing supplements) are critical to subsequent management decisions. The severity of symptoms is related to both the degree of hypercalcemia and the rate at which the calcium level increases. An acutely rising serum calcium concentration often results in severe

### Table 10. Nonmalignant Causes Of Hypercalcemia

**Medications**
- Thiazide diuretics
- Calcitriol
- Vitamin D
- Lithium
- Estrogen
- Theophylline (supratherapeutic dose)

**Endocrine**
- Hyperparathyroidism
- Hyperthyroidism
- Myxedema
- Milk-alkali syndrome
- Adrenal insufficiency
- Pheochromocytoma
- Vasoactive intestinal polypeptide tumors (VIPomas)
- Acromegaly

**Other**
- Granulomatous disease (tuberculosis, histoplasmosis, sarcoidosis)
- Paget disease
- Familial hypocalciuric hypercalcemia
- Immobilization
- Hypervitaminosis (vitamins A and D)
- Benign monoclonal gammopathy
- Periostitis

### Figure 3. Sources Of Calcitriol

```
Endogenous precursors → Sun → D₃ → Hepatic metabolism → D₂ → Plants

Parathyroid hormone → 25-OHD (25-hydroxycholecalciferol) → Renal metabolism → Calcitriol (1,25-dihydroxycholecalciferol)
```
symptoms, whereas a chronic, slowly rising level is better-tolerated but often presents with vague signs and symptoms.

**Physical Examination For Hypercalcemia of Malignancy**

Physical examination findings are generally non-specific but reflective of the underlying mechanisms of action of the disease process. For example, bony tenderness is frequently found in areas of osteolysis. Signs of volume depletion are typically evident, consistent with the patient’s decreased oral intake and the kidneys’ inability to concentrate urine with such a high osmolar gradient. Abnormal psychiatric findings, ranging from slight forgetfulness to coma, can also be encountered on examination. Finally, as with the history, it is important to search for signs of congestive heart failure, kidney disease, and other potential impediments to the aggressive administration of IV fluids.

**Diagnostic Studies For Hypercalcemia of Malignancy**

Although a history and physical examination can guide management decisions until laboratory confirmation is obtained, an elevated calcium level is what clinches the diagnosis of hypercalcemia of malignancy. Attempts have been made to categorize hypercalcemia as mild (total calcium level, 10.5-11.9 mg/dL), moderate (total calcium level, 12.0-13.9 mg/dL), and severe (total calcium level ≥ 14.0 mg/dL). Unfortunately, this system may not be clinically helpful as it does not account for the acuity in the rise of the calcium level or the patient’s symptoms. Because about half of serum calcium is protein-bound, ionized calcium level is a more accurate measure of the true degree of hypercalcemia, but this test may not be available in many clinical settings. Instead, the corrected serum calcium level is calculated with the following formula:

\[
\text{Corrected calcium level} = \text{Measured calcium level} + (0.8 \times (4.0 - \text{Serum albumin level (g/dL)})
\]

In patients with identical total calcium levels, the patient with hypoalbuminemia has a greater proportion of free total calcium in the plasma. This distinction is important because of the high frequency of low protein levels in this patient population.

Other laboratory data that are helpful in the analysis of hypercalcemia are potassium (half of patients with HHM are hypokalemic), phosphorus (hypophosphatemia is frequent; goal level should be 2.5-3.0 mg/dL), creatinine (to gauge renal function), alkaline phosphatase (to help identify bony invasion), and magnesium values. Measurement of PTH can be useful because of the increased incidence of primary hyperparathyroidism in cancer inpatients, and PTHrP may be valuable in assessing response to treatment, however, these tests are not indicated in the emergent setting.

Electrocardiographic analysis may identify various associated abnormalities such as a prolonged PR interval, widened QRS complex, shortened QT interval, bundle branch block, or bradydysrhythmia and even cardiac arrest (typically with calcium levels > 15 mg/dL).

An overall assessment of the patient’s clinical situation, which includes the corrected calcium level, comorbidities, ECG findings, and signs and symptoms that cause concern, should be used to classify an individual as having either mild or severe hypercalcemia of malignancy.

**Management Of Hypercalcemia of Malignancy**

Whether induced by distant hormonal influences or by local bone invasion, increased bone resorption by hyperactive osteoclasts ultimately causes hypercalcemia of malignancy. Release of high levels of calcium into the blood causes excessive urinary loss, anorexia, and nausea, which all worsen volume depletion. Renal blood flow subsequently diminishes, and any meaningful calcium excretion is negligible. Therefore, properly managing hypercalcemia of malignancy requires a 2-pronged approach that entails aggressive fluid administration and the reduction of excess bone resorption.

Because of varied clinical findings in patients with the same calcium measurements, no formal guidelines exist to definitively guide treatment to correct a particular calcium level. Expert opinions vary, but treatment is generally based on clinical severity. Mild hypercalcemia of malignancy is generally considered to be a serum calcium level < 12 mg/dL along with very mild, if any, clinical findings. This diagnosis does not necessarily warrant admission to the hospital, and it should ideally be managed with the patient’s primary physician or oncologist, who should provide prompt follow-up. In fact, simple cessation of an inciting factor such as supplemental calcium and encouraging increased weight-bearing activity, oral hydration, and salt intake may be sufficient to control many cases of mild hypercalcemia. Nevertheless, most patients with hypercalcemia of malignancy presenting with significant symptoms have severe hypercalcemia and usually require admission.

The serum calcium level can be lowered via 3 general mechanisms: (1) limiting calcium uptake into the body; (2) decreasing its availability through chelation and decreased bone resorption; and (3) increasing its excretion. Measures should be taken to both minimize oral intake and decrease intestinal and renal absorption. As described previously, an important first step is to halt the administration of
Clinical Pathway For The Management Of Hypercalcemia Of Malignancy

Hypercalcemia (Using corrected* or ionized serum calcium level)

10.3-11.2 mg/dL
- No symptoms?
  - Contact oncology and discharge home (Class III)
- Symptoms?
  - Initiate treatment with IVF, consider discharge home (Class II)

11.3-13.5 mg/dL
- No symptoms?
  - Begin treatment and contact oncology (See Table 11, page 17)
- Symptoms?
  - Arrange emergent hemodialysis (Class III)

13.5-17.9 mg/dL

>18 mg/dL or >13.5 with neurological symptoms, renal failure, or CHF
  - Aggressive IVF (Class II);
  - Loop diuretics when euvolemic (Class III);
  - Consider bisphosphonate (Class I)

*Corrected calcium level = Measured calcium level + 0.8 x (4.0 - Serum albumin level)

Abbreviations: CHF, congestive heart failure; IVF, intravenous fluids.

Class Of Evidence Definitions

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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
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust RCTs
- 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
- 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.

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medications that contain calcium or promote calcium reabsorption (eg, thiazides). Phosphorus administration (in either oral or IV form) may bind and thereby decrease the amount of free calcium available; however, because of the risk of precipitation of calcium phosphate crystals in various tissues in the body, this treatment should not be used. For a hypercalcemic patient with known lymphoma, prednisone 40 to 100 mg may be appropriate to decrease calcitriol production,62 which limits intestinal calcium absorption. Since steroids are often administered in conjunction with a particular chemotherapeutic protocol, they should be given only after discussion with the patient’s oncologist.

In the ED, prompt and aggressive IV administration of normal saline is the most important treatment for patients with symptomatic or severe hypercalcemia. Restoration of adequate intravascular volume promotes renal calcium excretion by improving the glomerular filtration rate (GFR) and decreasing the kidneys’ need to reabsorb sodium, an electrolyte that is passively absorbed along with calcium in the proximal tubule.57 Although no strong evidence or professional society guidelines have been issued on the topic, various expert opinions recommend that in the absence of contraindications to large volumes of fluid, normal saline should be infused at 200 to 300 mL/h and then adjusted to maintain a target urine output of 100 to 150 mL/h.68 Although it has been shown to decrease serum calcium levels by only 1 mg/dL,53 saline’s ease of administration and efficacy make it an important first step in the ED management of hypercalcemia. Most texts recommend loop diuretics once the patient is euvolemic to further inhibit calcium reabsorption in the ascending loop of Henle.60,69 However, loop diuretic administration exacerbates the hypokalemia present in approximately half of patients with hypercalcemia of malignancy.59 Because of the risks of worsening concomitant electrolyte abnormalities and of further volume loss, more recent literature suggests that this therapy be withheld unless volume overload is a concern.62

Pamidronate and zoledronate, the only 2 bisphosphonates approved by the FDA for hypercalcemia of malignancy, are pyrophosphate analogues that bind to hydroxyapatite to inhibit bone crystal dissolution and therefore osteoclastic resorption.70 In well-designed studies,71,72 these medications have demonstrated superiority over all other treatment modalities for cancer-associated hypercalcemia and are regarded as current standards of care in its management. Calcium levels begin to decrease 2 to 4 days after administration of IV bisphosphonates, reach a nadir between 4 and 7 days, and typically remain within the reference range for 1 to 4 weeks. In RCTs that included more than 300 patients, 60% to 90% of patients who received IV bisphosphonates for hypercalcemia of malignancy attained normal serum calcium levels within a week.71,72 This relatively prolonged duration of calcemic control affords the opportunity to explore additional cancer treatment options or at least temporize adverse symptoms. In a head-to-head comparison of zoledronate (4 mg) versus pamidronate (90 mg), zoledronate had the benefit of a shorter administration time (15 minutes vs 2 hours, respectively) and a statistically significant difference (p 0.001) of 0.7 mg/dL in the calcium level at its nadir (9.8 mg/dL vs 10.5 mg/dL, respectively).71 It is unclear whether the small but statistically significant difference in calcium levels is clinically significant. Pamidronate is less expensive than zoledronate ($41 vs $681, respectively [Ian Watt, pharmacist, University of Maryland Medical Center, oral communication, November 1, 2009]), but longer treatment time and the additional nursing care associated with its administration must be factored into the overall cost comparison. In conclusion, despite slight differences, zoledronate and pamidronate are both appropriate treatments for hypercalcemia of malignancy.

Because of its negligible toxicity and relatively rapid onset of peak activity within 12 to 24 hours, calcitonin remains a useful adjunct for lowering serum calcium levels. Although calcium levels usually return to pretreatment range within a few days, calcitonin’s value, albeit small, is its ability to lower these levels by approximately 1.0 mg/dL until the effects of bisphosphonates are fully realized.71 Calcitonin exerts this effect by inhibiting osteoclastic resorption and inducing calciuresis.74

### Table 11. Treatment According To Degree Of Hypercalcemia

<table>
<thead>
<tr>
<th>Calcium level</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 12 mg/dL (mild or chronic)</td>
<td>Oral hydration, High-salt diet, Avoid medications that cause hypercalcemia</td>
</tr>
<tr>
<td>≥ 12 mg/dL (severe or symptomatic)</td>
<td>Normal saline: initially 200-300 mL/h until patient is euvolemic, then adjust to maintain urine output of 100-150 mL/h, Loop diuretics only after volume repletion in patients with congestive heart failure or chronic kidney disease, Calcium, 4 IU/kg subcutaneously or intramuscularly; repeat every 6-12 hours only if patient is responsive, Intravenous bisphosphonate, Zoledronic acid: 4 mg over 15 minutes; 8 mg if second dose is required (not FDA approved), Pamidronate: given over 2-24 hours, either as 60 mg (calcium level, 12-13.5 mg/dL) or 90 mg (calcium level &gt; 13.5 mg/dL), Cardiac monitoring, Hemodialysis for patients with acute or chronic kidney disease (GFR &lt; 10-20 mL/min), Congestive heart failure</td>
</tr>
</tbody>
</table>

*GFR = glomerular filtration rate; ED = emergency department.*
Although no quality evidence has demonstrated exactly when hemodialysis should be initiated, the procedure is generally indicated in the setting of hypercalcemia and congestive heart failure, severe kidney injury (GFR < 10-20 mL/min),60 neurologic symptoms, or calcium concentration ≥ 18 mg/dL.68

**Summary Of Hypercalcemia Of Malignancy**

Hypercalcemia of malignancy is a relatively common problem encountered in the ED; however, its diagnosis portends a poor prognosis. A focused history and physical examination identify signs and symptoms consistent with hypercalcemia, but the diagnosis is secured with laboratory confirmation. The mainstays of treatment are aggressive rehydration and administration of a bisphosphonate and calcitonin. After discussion with the patient’s oncologist, admission to the hospital is usually warranted. (See Clinical Pathway For Management of Hypercalcemia Of Malignancy, page 16.)

**Disposition Of Patients With Hypercalcemia Of Malignancy**

Patients with symptomatic or severe hypercalcemia (calcium level ≥ 12 mg/dL) should generally be admitted to the hospital. Most of these patients will be significantly dehydrated and will require IV fluid resuscitation. In addition, these patients will require adjunctive IV medications to help lower the serum calcium level over the course of their hospital stay. The majority of patients requiring admission can be safely transferred to a floor bed (ideally on the oncologic floor); however, changes in ECG findings may require admission to a telemetry unit. Asymptomatic oncologic patients who are found to have mild hypercalcemia (< 12 mg/dL) may be considered for discharge after a discussion with their oncologist regarding a plan of care in the outpatient setting. (See Table 11, page 17.)

**Summary**

Emergency clinicians must familiarize themselves with the presentation and management of oncologic

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**Risk Management Pitfalls For Oncologic Emergencies (continued on page 19)**

1. “Although this cancer patient said he had a fever at home today, he doesn’t have one here. Plus, results of his chest radiograph are normal, his urine is clean, and his physical examination doesn’t show any infection. I’m going to send him home.”

   Patients with neutropenic fever often have subtle or no signs of infection other than the fever, and only about 30% have an infectious cause identified by the time of hospital discharge. Neutropenic fever results in high morbidity and mortality if not treated aggressively and early. Additionally, neutropenic individuals who are afebrile in the ED but report fevers at home need to be evaluated and treated just as aggressively as those who have a fever in the ED.

2. “I read EM Practice, so I knew that this leukemic patient who recently received chemotherapy needed antibiotics promptly. It looked like she had a urinary tract infection, so I gave her sulfamethoxazole-trimethoprim right away!”

   Prompt and appropriate antibiotic administration is fundamental in the treatment of patients with neutropenic fever. Except in very rare instances, broad IV antimicrobial coverage (eg, cefepime, imipenem, piperacillin/tazobactam) is necessary.

3. “I’m not worried about neutropenic fever because the patient’s ANC is 800 cells/µL, which doesn’t meet the criterion of less than 500 cells/µL for a diagnosis.”

   Although an ANC of < 500 cells/µL is what most physicians recognize as neutropenia, another defining characteristic is an ANC of < 1000 cells/µL with a predicted nadir of < 500 cells/µL over the ensuing 48 hours.

4. “I thought TLS only occurred in patients with leukemia.”

   Although TLS is much more common with lymphoproliferative malignancies, it certainly occurs with solid tumors as well, especially in metastatic and therapy-sensitive cancers. The high 36% mortality rate associated with solid tumor TLS can be partially attributed to the lack of anticipation and delayed recognition of TLS following chemotherapy.45

5. “The patient did not have a recent history of chemotherapy. I didn’t think TLS could occur without it.”

   If a patient has electrolyte abnormalities in the setting of an underlying malignancy, one should consider TLS in the differential diagnosis. Patients with a large tumor burden can present with TLS even in the absence of antitumor treatment (eg, chemotherapy, radiotherapy, surgery, endocrine therapy, corticosteroids).
Case Conclusions

The 22-year-old male patient is doing better after administration of IV fluids, IV calcium, insulin, dextrose, and sodium polystyrene. The ECG changes have resolved, and his urine output has increased. Someone from Hematology calls you in the interim to report numerous blasts on the patient’s peripheral smear, most likely indicating acute leukemia. You begin vigorous saline IV fluid administration and initiate rasburicase in consultation with the hematologist to treat the evolving TLS with uric acid of 14 mg/dL. You arrange for an intensive care unit bed and for a nephrologist to see the patient in consultation.

In the meantime, the woman who was cachectic has been moved to the resuscitation room, where you order basic blood work, a chest radiograph, and an emergent noncontrast CT scan of her head. Her systolic blood pressure is now above 100 mm Hg after the 500-mL normal saline bolus, but she is still lethargic and unable to cooperate with a full physical examination. Findings from the CT scan are unremarkable, and the portable chest radiograph does not reveal an infiltrate to explain her

Risk Management Pitfalls For Oncologic Emergencies (continued from page 18)

6. “This patient with TLS has a creatinine value of 2.4 mg/dL, so I am going to gently hydrate him to avoid volume overload.”
Most patients with TLS are intravascularly depleted and will require aggressive volume resuscitation to prevent significant kidney injury and severe electrolyte abnormalities. An abnormal serum creatinine value in a patient with previously normal renal function is a red flag that kidney injury is imminent if fluid resuscitation is not aggressive. Aggressive IV fluid administration is the cornerstone of treatment for TLS, so large volumes of fluid must be given to induce forced diuresis unless the patient is clinically fluid overloaded or has congestive heart failure.

7. “Intravenous fluid is really the only significant treatment for TLS.”
Although IV fluids are very important, rasburicase is a very effective and increasingly common adjunctive medication for TLS. It works by converting uric acid to allantoin, a substance that is 5 to 10 times more soluble than uric acid in the blood, facilitating its urinary excretion. Because of rasburicase’s high cost, however, it should be given only after discussion with the oncologist.

8. “The patient has hypercalcemia, most likely due to hyperparathyroidism or another metabolic problem. I’ll give her some fluids and tell her to avoid milk and other calcium-containing products, and she’ll be ready for discharge and outpatient follow-up in the next 2 to 3 weeks.”
Hypercalcemia occurs in a quarter of cancer patients, and half die within a month after diagnosis of this metabolic complication. More than a third of all hypercalcemic patients presenting to the ED have a malignancy. In patients with mild hypercalcemia, it is important to stress the need for close follow-up to ensure adequate screening for potential cancer.

9. “This patient doesn’t have hypercalcemia. Her calcium level is only 9.5 mg/dL.”
Although the total calcium level may appear normal in the laboratory results, a serum albumin level or an ionized calcium level is needed to more accurately assess the true degree of hypercalcemia. Remember that for every 1 g/dL decrease in albumin, the corrected calcium level should increase by 0.8 mg/dL.

10. “She has breast cancer, and now she’s here with hypercalcemia. To lower her calcium level, she needs some furosemide ASAP.”
Loop diuretics exacerbate hypokalemia, which is present in approximately half of patients with hypercalcemia of malignancy. Additionally, most patients with hypercalcemia of malignancy are significantly volume depleted. Unless volume overload is already a concern, furosemide should be held until the patient is euvelemic.

emergencies. What were once thought to be relatively unusual clinical problems in the ED are now becoming more frequent, as patients with cancer live longer and receive a broad array of chemotherapeutic treatments. The presentation of neutropenic fever, TLS, and hypercalcemia of malignancy can be subtle and easily missed if the clinician does not consider these diagnoses. Additionally, individuals presenting with these problems often have serious comorbidities unrelated to their malignancy that contribute to their poor clinical status. However, due to the potential lethality of these conditions, prompt diagnosis and intervention are essential to achieve a favorable outcome. Once a particular diagnosis is established, it is important to avoid an anchoring bias that may prevent the identification of concomitant — but just as lethal — conditions related to the underlying malignancy. The 3 complications discussed in this review highlight the importance of taking a thorough history and considering a broad differential diagnosis for all patients presenting to the ED with a diagnosis of malignancy.
change in mental status. You instruct the nurse to place a Foley catheter to obtain a urine sample and monitor urine output. Just then, a laboratory employee calls you with a panic calcium level of 15.4 mg/dL. You order another 1-L bolus of normal saline and place a call to the patient’s oncologist. The oncologist confirms that the patient has no history of heart failure or chronic kidney disease but is being treated for small-cell lung cancer, which could cause paraneoplastic syndrome. You agree a 40-mg furosemide IV bolus should be administered when the patient’s tachycardia resolves, her blood pressure returns to her normal baseline level, and she begins to produce a urine output of 0.5 mL/kg/h. The oncologist also advises you to administer pamidronate 60 mg IV over 2 hours and admit the patient to the intermediate care unit for her change in mental status. A second ECG after 1.5 L of fluid shows sinus bradycardia at 56 bpm, with resolution of the ST depression and a normalization of the QT interval.

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References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. 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, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

1. Freifeld AG. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2007 update. Proceedings of the 49th Annual Infectious Disease Society of America Meeting; October 6, 2007; San Diego, CA. (Expert panel recommendations; guideline publication pending)
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CME Questions

1. Which of the following values is included in the definition of neutropenic fever?
   a. Absolute lymphocyte count of 1000 cells/µL
   b. ANC of 1000 cells/µL
   c. Single temperature reading of 38.3°C (101.3°F)
   d. Temperature of 38°C (100.4°F) for 30 minutes
   e. WBC count < 1000 cells/µL

2. Which antibiotic regimen is NOT recommended as monotherapy for adults with neutropenic fever?
   a. Cefepime, 2 g IV
   b. Ceftazidime, 2 g IV
   c. Ceftriaxone, 2 g IV
   d. Imipenem, 500 mg IV
   e. Piperacillin/tazobactam, 4.5 g IV

3. Which of the following options is NOT an indication for vancomycin administration in patients with neutropenic fever?
   a. Hypotension
   b. Known history of methicillin-sensitive Staphylococcus aureus
   c. Likely catheter-related infection
   d. Preliminary cultures showing gram-positive flora
   e. Prior antibiotic prophylaxis with ciprofloxacin or levofloxacin
4. Which laboratory test reflects a high tumor burden for patients with a solid tumor?
   a. D-dimer level
   b. Erythrocyte sedimentation rate
   c. Lactate level
   d. Lactate dehydrogenase level
   e. Phosphorus concentration

5. Which of the following abnormal laboratory results is NOT consistent with a diagnosis of TLS?
   a. Total calcium level > 11 mg/dL
   b. Creatinine > 1.5 times the upper limit of normal
   c. Phosphorus concentration ≥ 4.5 mg/dL
   d. Potassium level ≥ 6.0 mEq/dL
   e. Uric acid level ≥ 8 mg/dL

6. Which of the following medications generally should NOT be used early in the treatment of symptomatic hypercalcemia?
   a. Calcitriol
   b. Furosemide
   c. Normal saline
   d. Pamidronate
   e. Zoledronic acid

7. Which of these symptoms is commonly observed in patients with severe hypercalcemia?
   a. Confusion
   b. Gastrointestinal symptoms (eg, nausea, constipation)
   c. Weakness
   d. Polydipsia
   e. All of the above

8. Which mechanism is the most common cause of hypercalcemia of malignancy?
   a. Ectopic secretion of PTH
   b. HHM
   c. Local osteolysis associated primarily with bone metastasis
   d. Lymphoma-associated secretion of calcitriol

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**Key Points**

| Comments | 
|------------------|------------------|
| In neutropenic fever, subtle clues of infection are the rule; fever is frequently the only sign of serious infection. | Because mucosal and skin barriers are particularly affected by chemotherapy, sites of even mild erythema on the skin or slight erosion in the oropharynx or perianal area should be regarded with suspicion. A mild cough may be indicative of serious underlying pathology. Elderly patients and those on steroids may be unable to mount a fever in response to infection. |
| According to IDSA guidelines for treatment of neutropenic fever, monotherapy should be initiated using cefepime, ceftazidime, a carbapenem, or piperacillin/tazobactam. | Endogenous flora account for approximately 80% of infections in neutropenic patients; however, a definite source is identified in only about a third of the patients. The most frequently cultured organisms arise from the gut, skin, and respiratory tract, as well as from other areas that are susceptible to opportunistic colonization. |
| Patients with TLS need repeated laboratory work to monitor their electrolyte levels because the disease process may worsen even after proper initial treatment. | Asymptomatic hypocalcemia should not be treated, as treatment could increase the deposition of calcium phosphate crystals. Control of hyperphosphatemia is usually adequate for such patients. Dialysis should be considered early in patients with persistent or worsening electrolyte abnormalities, acidemia, fluid overload, or uremia, despite optimal medical treatment. |
| In the ED, the most important treatment for TLS is aggressive hydration with isotonic fluid; allopurinol and rasburicase should also be considered. | Rasburicase’s rapid onset, high efficacy, and low toxicity make it an intervention that emergency clinicians must be familiar with. It has, however, been associated with 4.5% risk of allergic reactions. Patients with severe allergies, asthma, and known G6PD deficiency have an increased risk of anaphylaxis. |
| Patients presenting with multiple vague symptoms should prompt a simple workup for metabolic derangements of hypercalcemia of malignancy. | The severity of symptoms is related to both the degree of hypercalcemia and the rate at which the calcium level increases. An acutely rising serum calcium concentration often results in severe symptoms, whereas a chronic, slowly rising level is better tolerated, but often presents with vague signs and symptoms. |
| The basics of treatment for hypercalcemia of malignancy include aggressive administration of isotonic fluids, calcitriol, and an IV bisphosphonate ( pamidronate or zoledronate); furosemide may be indicated once euvolemia or hypervolemia is achieved. | Because of varied clinical findings in patients with the same calcium measurements, no formal guidelines exist to definitively guide treatment to correct a particular calcium level. Treatment is generally based on clinical severity. |
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1. Freifeld AG. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2007 update. Proceedings of the 45th Annual Infectious Disease Society of America Meeting; October 6, 2007; San Diego, CA. (Expert panel recommendations; guideline publication pending)


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