Advanced Emergency Nursing Journal
Vol. 44, No. 2, pp. 84–102

APPLIED
PHARMACOLOGY

Column Editor: Kyle A. Weant, PharmD, BCPS, BCCCP, FCCP

NC PD

Review of Hematological and Oncological Emergencies

Stephanie Barré, PharmD
Jessica McElwee, PharmD
Chara Calhoun, PharmD, BCPS
Kyle A. Weant, PharmD, BCPS, BCCCP, FCCP
Andy Maldonado, PharmD, BCOP
Carolyn M. Bell, PharmD, BCCCP

Abstract
Patients with hematological malignancies, both treated and untreated, or solid tumors undergoing treatment are at risk of life-threatening complications, which may present in the emergency department (ED). Such emergencies are diverse in etiology and often require prompt treatment. Traditional complications, such as febrile neutropenia, have had recent guideline updates, which incorporate new evidence and a new validated risk stratification tool. In addition, newer approaches to treatment, such as chimeric antigen receptor (CAR) T-cell therapy, are becoming more widely available and have unique associated toxicities. This review discusses the management of the following hematological and oncological emergencies likely to be encountered in the ED: febrile neutropenia, CAR T-cell toxicities, differentiation syndrome, tumor lysis syndrome, hypercalcemia of malignancy, and hyponatremia. **Key words:** CAR T-cell therapy, differentiation syndrome, febrile neutropenia, hypercalcemia of malignancy, hyponatremia, tumor lysis syndrome

ONCOLOGICAL EMERGENCIES include a variety of disorders, due to both the malignancy- and treatment-associated toxicities, which require prompt medical attention. Although complications often occur with chemotherapy, patients are subject to such emergencies throughout the course of their malignancy. The intent of this review is to discuss the pathophysiology, presentation/diagnosis, and treatment of the following oncological emergencies most likely to be encountered in the emergency department (ED): febrile neutropenia, chimeric antigen receptor (CAR) T-cell therapy toxicities, differentiation syndrome, tumor lysis syndrome (TLS), hypercalcemia of malignancy (HCM), and hyponatremia. Although this review focuses on the initial emergent

Author Affiliations: *Ochsner Louisiana State University Health, Shreveport (Dr Barré); Atrium Health's Carolinas Medical Center, Charlotte, North Carolina (Dr McElwee); Medical University of South Carolina, Charleston (Drs Calhoun, Maldonado, and Bell); and Department of Clinical Pharmacy and Outcome Sciences, University of South Carolina College of Pharmacy, Columbia (Dr Weant).*

Disclosure: *The authors report no conflicts of interest.*

Corresponding Author: *Stephanie Barré, PharmD, Baylor University Medical Center, 3500 Gaston Ave, Dallas, TX 75246 (Stephanie.Barre@BSWHealth.org).*

DOI: 10.1097/TME.0000000000000399

treatment, it would be beneficial to consult the hematology and oncology service at your institution to assist with management of this patient population.

FEBRILE NEUTROPENIA

Febrile neutropenia is one of the most common complications encountered in patients with malignancy. It is defined as a temperature of 38.3 °C (101 °F) or higher, or 38 °C (100.4 °F) and higher if sustained for 1 hr with a current absolute neutrophil count (ANC) of less than 500 cells/mm^3 or an ANC of less than 500 cells/mm^3 expected within 48 hr. Profound neutropenia refers to an ANC of less than 100 cells/mm^3 and is associated with a higher risk of severe infection when anticipated to continue for more than 7 days (Freifeld et al., 2011). Documented infection is reported to occur in about 30% of patients with febrile neutropenia, and bacteremia accounts for 10%–25% of febrile neutropenia infections (Freifeld et al., 2011). Patients can experience myelosuppression as a direct effect of their primary malignancy (i.e., leukemia, lymphoma, or multiple myeloma) or as a consequence of recent chemotherapy. The nadir neutrophil count is often seen around 5–10 days after receiving chemotherapy (Brock & Cruz-Carreras, 2020). Cytotoxic agents can compromise the entire alimentary tract, including oral cavity and gastrointestinal tract, which can inadvertently cause a mucosal barrier injury. The mucosal damage, in combination with minimal host defense mechanisms, allows bacteria to translocate, leading to local infection or bacteremia (Southwick, 2020; van der Velden, Herbers, Netea, & Blijlevens, 2014). Another common source of bacteremia is the use of indwelling central venous catheters (CVCs). Other potential sources of infection include skin and soft tissue, respiratory, genitourinary, cardiovascular, and central nervous systems (Southwick, 2020).

The majority of initial infections in febrile neutropenia are caused by bacteria. The most common gram-positive blood isolates include coagulase-negative staphylococci, *Staphylococcus aureus*, viridans group streptococci, and *Enterococcus* species. However, drug-resistant gram-negative pathogens are increasingly the causative organisms, such as *Escherichia coli* and other Enterobacteriaceae, as well as *Pseudomonas* species (Cattaneo et al., 2008). Fungal infections are more likely to occur after a week of empirical antibiotics (Freifeld et al., 2011).

Diagnosis

One of the major challenges in recognizing febrile neutropenia is the lack of typical infectious signs/symptoms due to the inability to produce an inflammatory response. Therefore, fever is frequently the only sign of infection and, consequently, has the potential to go unrecognized. For example, a chest radiograph may not demonstrate an infiltrate developing due to the lack of neutrophil production. Skin and soft-tissue infections (SSTIs) may not be accompanied by erythema, warmth, pain, and/or induration (Cantwell & Perkins, 2018). Obtaining a thorough history, including cancer origin, chemotherapy regimen, and last cycle, is essential. The National Comprehensive Cancer Network (NCCN) Guidelines for Hematopoietic Growth Factors categorizes common chemotherapy regimens based on risk of febrile neutropenia, with high risk occurring in more than 20% of cases (Becker et al., 2020). Examples of such regimens include RICE (rituximab, ifosfamide, carboplatin, and etoposide) for non-Hodgkin's lymphoma or FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) for pancreatic cancer.

The American Society of Clinical Oncology (ASCO) and Infectious Diseases Society of America (IDSA) guidelines focus on risk assessment to determine which patients are at highest risk of serious complications in an effort to treat more appropriately. One common scoring system utilized is the Multinational Association for Supportive Care in Cancer (MASCC) Risk-Index Score, which

Table 1. The MASCC Risk-Index Score

Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms	5
No hypotension (systolic blood pressure greater than 90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematological malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms	3
Outpatient status	3
Age less than 60 years	2

Note. From "The Multinational Association for Supportive Care in Cancer Risk Index: A Multinational Scoring System for Identifying Low-Risk Febrile Neutropenic Cancer Patients," by J. Klastersky, M. Paesmans, E. B. Rubenstein, M. Boyer, L. Elting, R. Feld, ... J. Talcott, 2000, Journal of Clinical Oncology, 18(16), pp. 3038–3051. doi:10.1200/JCO.2000.18.16.3038. Copyright 2000 by the American Society of Clinical Oncology. Used with permission. MASCC score 21 or more: candidate for outpatient treatment. MASCC score less than 21: candidate for inpatient treatment. MASCC = Multinational Association for Supportive Care in Cancer.

categorizes patients' risk of complications/death. The scoring components are shown in Table 1. An MASCC score of 21 or greater correlates to a low risk, whereas a score of less than 21 identifies high-risk patients. There are, however, limitations of this screening tool and up to 13% of patients may be misclassified as at low risk (Carmona-Bayonas et al., 2011; Coyne et al., 2017). In 2015, the Clinical Index of Stable Febrile Neutropenia (CISNE) was validated to assess the risk of complications in patients who received chemotherapy for solid tumors and appear clinically stable (Carmona-Bayonas et al., 2015). The scoring system components are displayed in Table 2. The 2018 ASCO/IDSA guideline on outpatient management of febrile neutropenia incorporates Talcott's groups, another risk stratification tool, with the CISNE and MASCC scores to assist in determining empirical antibiotics, medication route (intravenous vs. oral), treatment location (inpatient vs. outpatient), and duration (Freifeld et al., 2011; Taplitz et al., 2018).

The ASCO/IDSA guidelines recommend the initial diagnostic approach and evaluation include the following: complete blood cell count with leukocyte differential count,

Table 2. The Clinical Index of Stable Febrile Neutropenia

Explanatory variable	Points
Eastern Cooperative Oncology Group performance status of 2 or greater	2
Chronic obstructive pulmonary disease	1
Chronic cardiovascular disease	1
National Cancer Institute Common Toxicity Criteria mucositis of Grade 2 or higher	1
Monocytes less than 200 μl	1
Stress-induced hyperglycemia	2

Note. CISNE score less than 3: candidate for outpatient treatment. CISNE score 3 or more: candidate for inpatient treatment. From "Prediction of Serious Complications in Patients With Seemingly Stable Febrile Neutropenia: Validation of the Clinical Index of Stable Febrile Neutropenia in a Prospective Cohort of Patients From the FINITE Study," by A. Carmona-Bayonas, P. Jiménez-Fonseca, J. Virizuela Echaburu, M. Antonio, C. Font, M. Biosca, ... F. Ayala de la Peña, 2015, Journal of Clinical Oncology, 33(5), pp. 465–471. doi:10.1200/JCO.2014.57.2347. Copyright 2015 by the American Society of Clinical Oncology. Used with permission. CISNE = Clinical Index of Stable Febrile Neutropenia.

complete metabolic panel, and serum lactate concentration (Taplitz et al., 2018). Guidelines recommend obtaining two or more sets of blood cultures from different sites, including a CVC, if applicable and cultures from other sources as clinically indicated. Because many patients have central venous access, such as ports or peripherally inserted central catheters, it is important to ensure only appropriately trained individuals access these catheters.

Treatment

Before selecting antimicrobial therapy, it is important to identify which patients are appropriate for inpatient, compared with outpatient, treatment using risk stratification (Taplitz et al., 2018). Patients with most of the following factors are classified as at low risk: outpatient at time of fever, no acute comorbid illness, expected duration of profound neutropenia less than 7 days, no hepatic or renal insufficiency, and an MASCC score of greater than 21 or a CISNE score of less than 3 (Baden et al., 2020). For those with low risk of complications, outpatient treatment with oral antibiotics may be appropriate. However, any patient with colonization or suspected methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), or *Stenotrophomonas maltophilia* should be considered for inpatient treatment (Taplitz et al., 2018).

For patients appropriate for outpatient treatment, the first dose of antibiotics is recommended to be given in the ED after cultures are obtained and the patient should be observed for at least 4 hr thereafter. Empirical treatment with a fluoroquinolone, such as ciprofloxacin or levofloxacin, plus amoxicillin/clavulanate is recommended. Clindamycin can be used as an alternative to amoxicillin/clavulanate in patients with a true penicillin allergy (Taplitz et al., 2018). Fluoroquinolones as monotherapy are not recommended for empirical treatment despite studies demonstrating similar efficacy in low-risk patients, likely due to increasing resistance (Kern et al., 2013; Taplitz et al., 2018). Antibiotic dosing recommendations are shown in Table 3. Patients treated outpatient who return with ongoing signs or symptoms after 2–3 days of treatment should be considered for inpatient therapy. The treatment duration should be based on site of infection and organism, if known, or until resolution of neutropenia (Freifeld et al., 2011).

Table 3. Antibiotic dosing guide

Outpatient antibiotic dosing
Ciprofloxacin 500 mg orally twice daily[a]
Levofloxacin 500–750 mg orally once daily[a]
Amoxicillin/clavulanate 875 mg orally twice daily[a]
Clindamycin 600 mg orally three times daily
Inpatient standard antibiotic dosing
Cefepime 2 g IV every 8 hr[a]
Piperacillin/tazobactam 3.375 g IV every 6 hr or 4.5 g IV every 8 hr[a]
Meropenem 1–2 g IV every 8 hr[a]
Imipenem/cilastatin 500 mg IV every 6 hr[a]
Inpatient additional antibiotic dosing
Vancomycin 20–30 mg/kg IV loading dose x1, then dosing based on weight/renal function
Daptomycin 6–10 mg/kg IV once daily[a] depending on suspected source
Linezolid 600 mg IV every 12 hr

Note. From Lexicomp Online Database (Lexicomp, 2020; Rybak et al., 2020). IV = intravenous.
[a]Requires dose or frequency adjustment for renal dysfunction.

Patients are considered at high risk if any of the following factors are present: MASCC score is less than 21 or CISNE score of 3 or greater, inpatient at time of fever occurrence, allogeneic hematopoietic stem cell transplantation, anticipated profound neutropenia for at least 7 days, hepatic or renal insufficiency, uncontrolled or progressive cancer, pneumonia or complex infections at presentation, use of alemtuzumab, and mucositis Grade 3 or 4 (Baden et al., 2020). In addition, any patient who has significant medical comorbidities or is clinically unstable, with features such as hypotension, hypoxemia, or altered mental status, is considered at high risk. Such patients are candidates for inpatient treatment with intravenous antibiotics. Intravenous antibiotics should be administered within 1 hr of initial presentation of fever (Taplitz et al., 2018).

Inpatient antimicrobial recommendations are adopted from the 2010 update to the IDSA guidelines, which recommend standard treatment with an antipseudomonal β-lactam such as cefepime, piperacillin/tazobactam, or a carbapenem (excluding ertapenem). Additional gram-positive coverage with vancomycin or other anti-MRSA agent is not recommended as part of the standard regimen; however, it can be considered for patients with suspected CVC-related infections, SSTIs, pneumonia, hemodynamic instability, or risk factors for resistant organisms. Risk factors are defined as a previous infection or colonization with a resistant gram-positive organism and treatment in a facility with high rates of endemicity (Freifeld et al., 2011; Taplitz et al., 2018).

For patients with a history of MRSA infection, consideration should be given to adding vancomycin, linezolid, or daptomycin based on the suspected source of infection. For those with previous VRE isolates, the addition of linezolid or daptomycin is indicated. If there is a history of an extended-spectrum β-lactamase-producing organism, empirical initiation of a carbapenem is warranted. Other empirical antimicrobial therapy is generally not necessary. Antiviral therapy is not indicated unless the patient has documented evidence of an acute viral illness. Antifungal therapy should be considered in patients who are persistently febrile despite at least 4 days of antibiotic therapy and are expected to be neutropenic for more than 7 days (Freifeld et al., 2011).

CHIMERIC ANTIGEN RECEPTOR T-CELL TOXICITIES

CAR T-cell therapy is a novel immunotherapy that has yielded impressive outcomes for hematological malignancies. It is created directly from the patient's own blood. After leukapheresis, the patient's T cells are genetically engineered to express CARs to recognize specific antigen tumor cells. Before reinfusion, the patient undergoes lymphodepleting chemotherapy to allow space for CAR T-cell expansion (Frey & Porter, 2019). There are three current U.S. Food and Drug Administration (FDA)-approved agents available, all of which target CD19 (Kite Pharma, Inc., 2020; Novartis Pharmaceutical Corporation, 2018). Tisagenlecleucel (Kymriah), the first approved CAR T-cell therapy, has FDA indications for adult patients with relapsed or refractory large B-cell lymphoma or B-cell acute lymphoblastic leukemia (ALL) (Novartis Pharmaceutical Corporation, 2018). Axicabtagene ciloleucel (Yescarta) has an FDA indication for relapsed or refractory large B-cell lymphoma (Kite Pharma, Inc., 2020). Brexucabtagene autoleucel (Tecartus) was recently FDA-approved for relapsed or refractory mantle cell lymphoma (Kite Pharma, Inc., 2020). CAR T-cell therapy is currently being investigated with additional malignancies, including multiple myeloma. Despite successes, CAR T-cell therapy is not without risks and can cause several serious side effects that have warranted black box warnings including cytokine release syndrome (CRS) and neurotoxicity, for which the management of each is discussed further. When administered as an outpatient, patients should remain within the proximity of the certified facility for at least 4 weeks and report to the ED for CAR

T-cell-associated toxicities (Kite Pharma, Inc., 2020; Novartis Pharmaceutical Corporation, 2018).

Cytokine Release Syndrome

CRS is the most common toxicity of CAR T-cell therapy. It occurred in 58%–93% of patients in clinical trials, and up to 47% were reported at a Grade 3 level of severity, requiring vasopressor administration and/or high-flow nasal cannula placement (Maude et al., 2018; Neelapu et al., 2017; Schuster et al., 2019). CRS is defined as a heightened response due to immune system activation from CAR T-cell expansion, causing elevations in cytokines (e.g., interleukin [IL]-6, IL-10, IL-2) and inflammatory markers, such as C-reactive protein and ferritin (Shimabukuro-Vornhagen et al., 2018). Although CRS has been largely linked to CAR T-cell therapy, it can occur following administration of other medications such as blinatumomab (Blincyto), a bispecific T-cell engager monoclonal antibody used in the treatment of B-cell ALL (Frey & Porter, 2019).

Diagnosis

The presentation is highly nonspecific as many patients exhibit mild to moderate symptoms including fever, hypotension, rigors, and malaise. CRS may also present with severe symptoms including hypotension requiring vasopressor support, capillary release syndrome, hypoxia, and organ failure such as acute kidney injury or acute liver failure (Lee et al., 2019). Fever may not always be present, as it may be masked by an antipyretic, anticytokine therapy, or corticosteroids (Frey & Porter, 2019). Most CRS cases present within 14 days of CAR T-cell infusion. Because of the high risk of CRS, CAR T-cell products are limited to availability through a Risk Evaluation and Mitigation Strategy (REMS) program, which mandates that the certified health care facility have two patient-specific doses of tocilizumab (Actemra), an IL-6 receptor antagonist, on hand for treatment of toxicities related to CAR T-cell therapy and all relevant staff members involved in prescribing, dispensing, and administering CAR T-cell therapy must be trained (Kite Pharma, Inc., 2020; Novartis Pharmaceutical Corporation, 2018).

Treatment

Treatment of CRS, which is dependent on grade, has been challenging to standardize due to variations in grading scales between clinical trials and institutions. Recently, the American Society of Blood and Marrow Transplantation (ASBMT) released formalized grading scales for CRS and neurotoxicity to allow for a more consistent approach to management, although practice still may differ between institutions (Lee et al., 2019). Patients experiencing Grade 2–4 CRS will warrant prompt pharmacological intervention with tocilizumab with or without high-dose corticosteroids. Full ASMBT assessment criteria and management recommendations are described in Table 4 (Lee et al., 2019). Tocilizumab was investigated and approved for CRS after the discovery that serum IL-6 was elevated in patients with CRS (Shimabukuro-Vornhage et al., 2018). It exerts its effect through IL-6 inhibition, with minimal impact on T-cell function, making it an effective treatment option (Maude, Barrett, Teachey, & Grupp, 2014). For adults, tocilizumab should be dosed at 8 mg/kg of actual body weight (maximum dose of 800 mg) and given by intravenous infusion over 1 hr (Genentech, Inc., 2010). Tocilizumab dosing can be repeated every 8 hr as needed, for a maximum of three doses per 24-hr period, and a maximum of four total doses (Genentech, Inc., 2010). Once diluted, tociluzimab is stable for 24 hr, should be protected from light, and not be infused concomitantly in the same intravenous line as other medications (Genentech, Inc., 2010). The most common adverse reactions include upper respiratory tract infections, hypertension, hypersensitivity reactions, headache, and liver dysfunction (Genentech, Inc., 2010). Essential laboratory monitoring includes neutrophils, platelets,

Table 4. ASBMT cytokine release syndrome grading and management

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	**Temperature 38 °C or more (not attributed to another cause)**			
			+	
Hypotension	N/A	No vasopressor requirement	Requiring vasopressors (with or without vasopressin)	Requiring multiple vasopressors (excl. vasopressin)
			AND/OR	
Hypoxia	N/A	Requiring low-flow nasal cannula (defined as 6 L or less of NC)	Requiring high-flow nasal cannula	Requiring positive pressure (CPAP, BiPAP, intubation, mechanical ventilation)
Example management	Symptomatic treatment only	Tocilizumab 8 mg/kg (dose cap at 800 mg) IV over 1 hr If no improvement, manage per Grade 3 if no improvement within 24 hr after starting tocilizumab	Tocilizumab 8 mg/kg (dose cap at 800 mg) IV over 1 hr Methylprednisolone 1 mg/kg IV twice daily Continue corticosteroids until event is Grade 1 or less and then taper over 3 days	Tocilizumab 8 mg/kg (dose cap at 800 mg) IV over 1 hr Methylprednisolone 1,000 mg IV per day for 3 days; if improves, manage as above

Note. From "ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated With Immune Effector Cells," by D. W. Lee, B. D. Santomasso, F. L. Locke, A. Ghobadi, C. J. Turtle, J. N. Brudno, … S. S. Neelapu, 2019, *Biology of Blood and Marrow Transplantation, 25*(4), pp. 625–638. doi:10.1016/j.bbmt.2018.12.758. Copyright 2018 by the American Society for Bone and Marrow Transplantation. Used with permission. ASBMT = American Society for Transplantation and Cellular Therapy; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; IV = intravenous; NC = nasal cannula.

lipids, and liver function tests (Genentech, Inc., 2010). Although package labeling does suggest dose modifications for serious laboratory abnormalities, these adjustments are not applicable when used for CRS (Genentech, Inc., 2010). Corticosteroids are typically reserved for tocilizumab refractory cases because they have been found to suppress T cells, potentially interfering with CAR T-cell activity (Lee et al., 2019). However, recent literature suggests that corticosteroids do not impact efficacy and kinetics of CAR T cells, as there was no difference in complete remission found in those who received corticosteroids as first-line treatment compared with those who did not (Liu et al., 2020). Corticosteroid use remains controversial, and many institutions will only allow administration following direct approval from a hematologist. Other agents, such as siltuximab, are currently being evaluated for patients refractory to the aforementioned therapies (Leyfman, 2018).

Neurologic Toxicity

Neurotoxicity is another potentially serious adverse effect that can occur in up to 64% of patients (Kite Pharma, Inc., 2020). The exact mechanism of neurotoxicity in CAR T-cell

patients has not been elucidated; however, it is thought to be due to systemic inflammation and cytokine production that causes endothelial activation, coagulopathy, and blood–brain barrier disruption (Frey & Porter, 2019). It can be a separate entity from CRS or occur concomitantly.

Diagnosis

Immune effector cell-associated neurotoxicity syndrome (ICANS) can present as a tremor, speech difficulty, and/or delirium in more mild stages; however, it can potentially cause agitation, seizures, and, in rare cases, cerebral edema (Frey & Porter, 2019). Because of the high incidence of neurotoxicity, patients should be counseled to avoid driving or operating dangerous machinery for at least 8 weeks following CAR T-cell infusion (Kite Pharma, Inc., 2020; Novartis Pharmaceutical Corporation, 2018). Medications including prochlorperazine and haloperidol that may lower the seizure threshold should be avoided. Often, inpatient providers will initiate a nonsedating, prophylactic antiepileptic medication such as levetiracetam. The earliest characteristic feature of neurotoxicity is often deficits in expressive speech, including naming of objects, and may quickly progress to global aphagia (Frey & Porter, 2019). Usually, it has a later onset than CRS, with a median onset of 4–6 days compared with 2–3 days for CRS (Kite Pharma, Inc., 2020; Novartis Pharmaceutical Corporation, 2018).

Treatment

Both tocilizumab and high-dose steroids are appropriate for patients with CRS and neurotoxicity concurrently (Kite Pharma, Inc., 2020; Novartis Pharmaceutical Corporation, 2018). However, tocilizumab should not be given to patients without concomitant CRS because tocilizumab does not effectively penetrate the blood–brain barrier and thus is not effective for neurotoxicity (Genentech, Inc., 2010). Tables 5 and 6 provide further guidance on grading and management of neurotoxicity.

DIFFERENTIATION SYNDROME

Differentiation syndrome can be a life-threatening oncological emergency. It is associated with rapid proliferation and differentiation of myeloid cells and has historically been identified in patients receiving all-*trans* retinoic acid (ATRA) and/or arsenic trioxide (ATO) for the treatment of acute promyelocytic leukemia (APL). Yet, this syndrome has been identified with the use of more recently FDA-approved therapies for the management of newly diagnosed and relapsed acute myelogenous leukemia (AML). These newer agents include the isocitrate dehydrogenase inhibitors, ivosidenib (Tibsovo) and enasidenib (IDHIFA), and the kinase inhibitor, gilteritinib (Xospata).

Diagnosis

The features of differentiation syndrome may include rapid weight gain (5 kg or more), dyspnea, hypoxia, peripheral edema, unexplained fever, hypotension, acute renal or hepatic failure, and pulmonary infiltrates on chest radiograph or pleural/pericardial effusion. If left uncontrolled, multiorgan failure may ensue (Stahl & Tallman, 2019). The incidence of differentiation syndrome ranges anywhere from 2% to 48% in patients with APL and from 3% to 25% in patients with AML (Astellas Pharma Inc., 2019; Fathi et al., 2018; Norsworthy et al., 2020; Pollyea et al., 2019; Roboz et al., 2020; Stahl & Tallman, 2019). The timing can also vary on the basis of the agents being used. In patients receiving ATRA and/or ATO, it has a bimodal distribution and can be seen most commonly during the first and third weeks of treatment (Stahl & Tallman, 2019). For patients receiving gilteritinib or ivosidenib, it can occur as early as 1 day and up to 3 months after the start of treatment and in patients receiving enasidenib, it may occur as early as 1 day and up to 5 months after the start of treatment (Astellas Pharma Inc., 2019; Fathi et al., 2018; Norsworthy et al., 2020; Roboz et al., 2020).

Table 5. ASBMT-based grading for ICANS

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
ICE (orientation, naming, attention, writing, commands) score	7–9 (mild)	3–6	0–2 (severe)	Unable to assess
Depressed level of consciousness	Awaken spontaneously	Awakens to voice	Awakens only to tactile stimuli	Unarousable or requires vigorous tactile stimuli; coma; stupor
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local cerebral edema	Diffuse cerebral edema
Seizures	N/A	N/A	N/A	+
Motor findings	N/A	N/A	N/A	Deep focal motor weakness → hemiparesis/ paraparesis

Note. From "ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated With Immune Effector Cells," by D. W. Lee, B. D. Santomasso, F. L. Locke, A. Ghobadi, C. J. Turtle, J. N. Brudno, … S. S. Neelapu, 2019, *Biology of Blood and Marrow Transplantation, 25*(4), pp. 625–638. doi:10.1016/j.bbmt.2018.12.758. Copyright 2018 by the American Society for Bone and Marrow Transplantation. Used with permission. ASBMT = American Society for Transplantation and Cellular Therapy; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy; ICP = intracranial pressure.

Table 6. Treatment example for ICANS

Grading	Concurrent CRS	No concurrent CRS
Grade 2	Administer tocilizumab per CRS Grade 2 management If no improvement within 24 hr after starting tocilizumab, continue therapy and add on dexamethasone	Dexamethasone 10 mg IV every 6 hr Continue until event is Grade 1 or less and then taper over 3 days
Grade 3	Administer tocilizumab per CRS Grade 2 management In addition, administer dexamethasone 10 mg IV with first dose of tocilizumab and repeat every 6 hr. Continue until grade 1 event or less and then taper over 3 days	
Grade 4	Administer tocilizumab per CRS Grade 2 management Administer methylprednisolone 1,000 mg IV per day with first dose of tocilizumab and continue methylprednisolone 1,000 mg IV per day for 2 more days; if improves, manage as above	Methylprednisolone 1,000 mg IV per day for 3 days; if improves, manage as above

Note. From "ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated With Immune Effector Cells," by D. W. Lee, B. D. Santomasso, F. L. Locke, A. Ghobadi, C. J. Turtle, J. N. Brudno, … S. S. Neelapu, 2019, Biology of Blood and Marrow Transplantation, 25(4), pp. 625–638. doi:10.1016/j.bbmt.2018.12.758. Copyright 2018 by the American Society for Bone and Marrow Transplantation. Used with permission. CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; IV = intravenous.

Treatment

Management generally consists of the use of corticosteroids combined with increased hemodynamic monitoring. Dexamethasone 10 mg intravenously every 12 hr (or an equivalent dose of an oral or intravenous corticosteroid) should be initiated as soon as differentiation syndrome is suspected. The dose may be increased to 10 mg intravenously every 6 hr if there is no clinical improvement noted in 24 hr. The corticosteroid is usually continued for a minimum of 3 days or until symptoms resolve. For patients receiving ATRA and/or ATO, the medication is held in severe cases of differentiation syndrome (those patients exhibiting severe organ dysfunction) or for patients requiring admission to the intensive care unit (Sanz & Montesinos, 2014). The newer agents all have long half-lives ranging from 4 to 8 days, so discontinuation of the agent does not usually lead to quick improvement of differentiation syndrome symptoms and may do away with any gains made in controlling the disease (Agios Pharmaceuticals, Inc., 2019; Astellas Pharma Inc., 2019; Celgene Corporation, 2019). It is recommended to interrupt therapy if severe signs/symptoms persist for more than 48 hr after the initiation of corticosteroids, and in the case of enasidenib, for any severe pulmonary symptoms requiring intubation or ventilator support (Celgene Corporation, 2019).

TUMOR LYSIS SYNDROME

TLS is characterized by the breakdown of malignant cells and rapid release of intracellular contents into the blood. This causes metabolic abnormalities such as hyperuricemia, hyperkalemia, hyperphosphatemia, uremia, and hypocalcemia, which can lead to acute renal failure, cardiac dysrhythmias, and sudden death (Jones et al., 2015). TLS may present with one or more of the following: vomiting, diarrhea, anorexia, lethargy, edema, fluid overload, hematuria, congestive heart failure, seizure, muscle cramps, tetany, and syncope (Will & Tholouli, 2011).

TLS occurs most commonly 12–72 hr postchemotherapy but can occur before chemotherapy is initiated in patients with high disease burden (Davidson et al., 2004; Ribiero & Pui, 2003). Risk of TLS depends on factors such as tumor type, tumor/disease burden, baseline renal function, baseline uric acid, and response to chemotherapy. It is more common in patients with leukemia, lymphoma, and solid tumors with high proliferative rates and/or rapid response to chemotherapy. Incidence is also higher with bulky diseases (tumor greater than 10 cm), lactate dehydrogenase elevation more than two times the upper limit of normal (ULN), and a white blood cell count greater than 25,000 cells/mm^3. Patients with preexisting renal failure and those with a baseline uric acid level greater than 7.5 mg/dl are also at an increased risk.

Diagnosis

Patients can have either laboratory TLS, defined as metabolic abnormalities only, or clinical TLS, defined as laboratory abnormalities with associated clinical symptoms (Jones et al., 2015). Laboratory TLS is defined as two or more of the following within 3 days before or 7 days after initiation of treatment: uric acid 8 mg/dl or more or 25% increase from baseline, potassium of 6 mg/L or more or 25% increase from baseline, phosphorus 6.5 mg/dl or more or 25% increase from baseline, or calcium less than 7 mg/dl or 25% decrease from baseline. Clinical TLS is defined as laboratory TLS plus one or more of the following: serum creatinine 1.5 times or more the ULN, cardiac arrhythmias/sudden death, and/or seizures (Cairo & Bishop, 2004).

Prophylactic measures such as intravenous fluid administration and allopurinol play a key role in preventing TLS. All patients who receive chemotherapy should have a risk assessment for TLS and receive appropriate prophylaxis (Jones et al., 2015). Unfortunately,

many patients presenting to the ED have not had a risk assessment and are not on prophylaxis because they have aggressive malignancy and spontaneous TLS before initiating chemotherapy (Galardy et al., 2013).

Treatment

TLS management includes treatment of each metabolic abnormality, including hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia.

Hyperuricemia

Aggressive hydration and diuresis are a mainstay of both the prevention and treatment of TLS. Hydration and increased urine output help excrete uric acid and phosphorus, therefore preventing uric acid crystallization and calcium phosphate deposits in the renal tubules (Coiffier, Altman, Pui, Younes, & Cairo, 2008). Fluids should be used to maintain a urine output of 100 ml/m^2/hr (Coiffier et al., 2008; Jones et al., 2015).

Allopurinol is a xanthine oxidase inhibitor, which reduces the production of uric acid (Casper Pharma LLC, 2018). Although allopurinol has demonstrated efficacy in preventing hyperuricemia, it does not break down uric acid that is already formed (de Bont & Pieters, 2004). The effects of allopurinol are not seen for 24–72 hr and therefore it is considered an option for prophylaxis but is not the drug of choice in the acute treatment of TLS (Coiffier et al., 2008; Jones et al., 2015).

Rasburicase is a recombinant urate oxidase that metabolizes uric acid to allantoin, a more soluble compound (Pui, 2002; Sanofi-aventis, 2019). Therefore, rasburicase can break down uric acid deposits and reduce uric acid levels (Goldman et al., 2001; Jeha et al., 2005). Rasburicase should be given if a patient has hyperuricemia with laboratory or clinical TLS unless there are contraindications. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency and women who are pregnant or breastfeeding (Sanofi-aventis, 2019). The recommended dose of rasburicase is 0.15–0.2 mg/kg once daily over 30 min for 5 days (Sanofi-aventis, 2019). Lower doses of 0.05–0.2 mg/kg once have been used successfully in clinical trials and were not inferior to higher or multiple daily doses (Hutcherson, Gammon, Bhatt, & Faneuf, 2006, McBride et al., 2013, McDonnell et al., 2006; Reeves & Bestul, 2008; Trifilio et al., 2006). In practice, doses are typically rounded to 3–6 mg. Available data suggest that one dose of rasburicase 6 mg is sufficient to lower uric acid and creatinine levels in adult patients with TLS (Feng et al., 2013; Yu et al., 2017). Furthermore, the NCCN Guidelines on Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma support the use of a fixed, single dose of rasburicase 3–6 mg, with repeat dosing individualized on the basis of response (Wierda et al., 2020). Administer as an infusion over 30 min in a dedicated intravenous line or flush with 0.9% sodium chloride prior to and after infusion. Uric acid levels should be monitored to guide the need for repeat rasburicase dose(s) and duration of therapy (Coiffier et al., 2008; Jones et al., 2015). In practice, uric acid concentrations are often monitored every 8 hr during initial treatment. Of note, rasburicase causes breakdown of uric acid in blood samples at room temperature. To limit interference with accurate measurements, blood samples for monitoring uric acid levels should be placed on ice until the assay is run and testing should be completed within 4 hr of collection (Coiffier et al., 2008).

Hyperkalemia

Hyperkalemia should be verified with repeat sampling to rule out hemolysis as the cause (Coiffier et al., 2008). Patients should be monitored with electrocardiogram (ECG). For asymptomatic patients, consider administering sodium polystyrene sulfonate 1 g/kg orally or rectally (rectal route not recommended in patients who are neutropenic and/or thrombocytopenic). For symptomatic patients with ECG abnormalities consistent with hyperkalemia, consideration should be given to administering 1 g of

calcium gluconate, 5 units of regular insulin intravenously, 25 g of intravenous dextrose, and sodium bicarbonate 50 mEq intravenous push. Calcium and sodium bicarbonate should not be administered via the same line without flushing between administrations. Life-threatening hyperkalemia may require dialysis (Coiffier et al., 2008).

Hyperphosphatemia

The treatment of acute hyperphosphatemia is primarily focused on adequate hydration. Phosphorus binders such as aluminum hydroxide, sevelamer hydroxide, and lanthanum carbonate can be utilized to prevent further absorption of phosphorus (Coiffier et al., 2008). Aluminum hydroxide, if used, should be limited to 1–2 days to prevent toxicity. Severe hyperphosphatemia may require renal replacement therapy (Coiffier et al., 2008).

Hypocalcemia

Hypocalcemia should only be treated if the patient is symptomatic (Cario & Bishop, 2004). Treatment with calcium can lead to precipitation of a calcium phosphate product that can deposit in the kidneys. Symptomatic patients with cardiac arrhythmias, seizures, or tetany should be given calcium gluconate intravenous push over 5 min and have ECG monitoring in place (Cario & Bishop, 2004).

HYPERCALCEMIA OF MALIGNANCY

As nearly 30% of patients with a malignancy will develop hypercalcemia, it is one of the most common causes of hypercalcemia in patients presenting to the ED (Klemencic & Perkins, 2019). Calcium homeostasis is mediated by the actions of parathyroid hormone (PTH), vitamin D metabolites, and calcitonin on the gastrointestinal tract, kidneys, and bones. Increased serum calcium occurs through multiple mechanisms including the following: intestinal absorption occurs with increased 1,25-dihydroxyvitamin D_3 (calcitriol), reabsorption in the kidney via PTH and calcitriol, and, finally, decreased kidney excretion with PTH. Both PTH and calcitriol mediate increased bone resorption, whereas calcitonin inhibits bone resorption (Maier & Levine, 2013).

Diagnosis

Patient presentations may range from asymptomatic to the following symptoms alone or in combination: nausea, vomiting, anorexia, lethargy, weakness, hyporeflexia, confusion, and bone pain (Dellay & Groth, 2016). These symptoms correspond with the rate of serum calcium increase and not necessarily the level. Supratherapeutic calcium levels can act as an osmotic diuretic causing polyuria and polydipsia resulting in volume depletion (Klemencic & Perkins, 2019). Cardiac abnormalities include prolonged PR interval and QRS, shortened QT, and ventricular dysrhythmias. Cardiac arrest may occur with calcium levels above 15 mg/dl (Maier & Levine, 2013).

Hypercalcemia is determined by total corrected serum calcium levels using the following calculation: measured calcium (mg/dl) + 0.8[4 – albumin (g/dl)]. The corrected calcium level can be classified as mild hypercalcemia, 10.5–11.9 mg/dl; moderate, 12–13.9 mg/dl; or severe, 14 mg/dl or higher (Goldner, 2016; Maier & Levine, 2013). Confirmation of calcium elevation is necessary as patients with hypoalbuminemia may actually have an elevated ionized calcium level due to reduced protein-bound calcium (Maier & Levine, 2013). Ionized serum calcium may be used to confirm hypercalcemia; however, it is greatly affected by pH levels. Patient evaluation should include an ECG to assess for potential cardiac abnormalities, and frequent neurological assessments may be necessary depending on presentation.

Treatment

The degree of hypercalcemia and associated symptoms determines the treatment regimen. Asymptomatic patients with mild hypercalcemia may not require intervention, whereas moderate to severe hypercalcemia or the presence of renal or neurological

symptoms warrants prompt treatment. The initial management of HCM in the ED includes intravenous fluid resuscitation, as dehydration is common. Often, 1–2 L of 0.9% sodium chloride, followed by a maintenance rate of 150-250 ml/hr, is a common starting regimen (Pi et al., 2016). However, it is important to avoid aggressive fluid resuscitation in patients with cardiac or renal insufficiency. The use of furosemide or other diuretics is no longer recommended as they have poor efficacy and may counteract attempts at fluid resuscitation (Goldner, 2016).

Bisphosphonate medications reduce osteoclast and increase osteoblast activity (Goldner, 2016). Bisphosphonate therapy is needed intravenously for calcium reduction in HCM, as oral therapy does not achieve concentrations necessary to reduce osteoclast activity (Zagzag, Hu, Fisher, & Perrier, 2018). However, these agents have limited utility in the acute management of this condition in the ED as the delayed onset of action occurs 1–3 days later and peak calcium reduction is observed after 4–7 days with an effect lasting up to 3 weeks (Zagzag et al., 2018). The two bisphosphonate regimens utilized for HCM are zoledronic acid 4 mg intravenously given over 15–30 min and pamidronate 60–90 mg intravenously administered over 2–6 hr, with zoledronic acid demonstrating greater efficacy in studies (Major et al., 2001; Pi et al., 2016).

It is prudent to ensure adequate volume resuscitation prior to bisphosphonate therapy because these agents may cause renal toxicity (Zagzag et al., 2018). Dose adjustments are required for renal dysfunction. To bridge the gap until the effects of bisphosphonates are present, calcitonin is a potential option to acutely reduce calcium levels, which is dosed 4–8 units per kilogram administered subcutaneously or intravenously every 8–12 hr (Pi et al., 2016). Intranasal calcitonin is not used for this indication. Calcitonin is expected to result in a mild calcium reduction of 1–2 mg/dl, but when used in conjunction with aggressive fluid resuscitation the synergistic calcium reduction may be sufficient to avoid severe toxicity from hypercalcemia (Maier & Levine, 2013). It is important to understand the aforementioned therapies only temporarily reduce serum calcium and the underlying cause, malignancy, must be addressed to prevent relapse following admission to the hospital.

HYPONATREMIA

One of the most common electrolyte disorders encountered in the ED is hyponatremia (Anderson, Chung, Kluge, & Schrier, 1985; Hawkins, 2003; Upadhyay, Jaber, & Madias, 2006). Hyponatremia can present within the context of hypervolemia, euvolemia, or hypovolemia. The etiology in those with malignancy can be multifactorial including gland dysfunction, paraneoplastic production of antidiuretic hormone (ADH), chemotherapy-induced dysfunction, and iatrogenic, secondary to the use of aggressive hydration as a part of chemotherapy regimens (Onitilo, Kio, & Doi, 2007). The most frequent cause of hyponatremia is the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and is associated with solid tumors, including a particularly high incidence among those with small cell lung cancer (Adrogue & Madias, 2000; Allan et al., 1990; Berghmans, Paesmans, & Body, 2000; Hansen, Sorensen, & Hansen, 2010; Lassen et al., 1995; Onitilo et al., 2007; Osterlind & Andersen, 1986). In patients with cancer receiving chemotherapy, such as vincristine and cyclophosphamide, the incidence of hyponatremia can be up to 47% (Liamis, Milionis, & Elisaf, 2008; Pi et al., 2016; Robertson, Bhoopalam, & Zelkowitz, 1973; Stuart, Cuaso, Miller, & Oski, 1975). At baseline, ADH is released from the posterior portion of the pituitary gland and allows for increased reabsorption of water in the kidney (Verbalis, Goldsmith, Greenberg, Schrier, & Sterns, 2007). An imbalance of this hormone can lead to an excess of total body water, without a corresponding rise in sodium, and result in hypervolemic hyponatremia. Hyponatremia can have a variety of presentations, ranging from asymptomatic to

life-threatening. The most severe symptoms include confusion, hallucinations, seizures, coma, and death (Ellison & Berl, 2007).

Treatment

When assessing hyponatremia, it is important to note the severity, duration, volume status of the patient, and presence of clinical symptoms (Berl, 1990; Decaux & Soupart, 2003). In patients who have severe hyponatremia (typically defined as a serum sodium less than 125 mmol/L) and associated symptoms that have developed within the previous 48 hr, rapid correction can be attempted with a target rise in serum sodium of 1–2 mmol/L/hr, usually with 3% sodium chloride or higher concentrations (Adrogue & Madias, 2000). Although limited data exist regarding the volume of 3% sodium chloride to administer in this setting, consensus recommendations suggest repeated 150-ml infusions every 20 min until symptoms abate (Spasovski et al., 2014). The total correction is generally recommended not to exceed 8–12 mmol/L over 24 hr and not more than 18–25 mmol/L over the first 48 hr (Adrogue & Madias, 2000; Janicic & Verbalis, 2003; Palmer, Gates, & Lader, 2003). However, if patients present with life-threatening symptoms (e.g., seizures), the correction of sodium should be done as rapidly as necessary to relieve the symptoms and thereafter reducing the correction rate (Decaux & Soupart, 2003). One of the primary concerns that exist with the overcorrection of hyponatremia is the occurrence of osmotic demyelination syndrome. This disorder encompasses myelinolysis of various regions of the brain including the pontine region and can lead to lethargy, dysarthria, quadriparesis, and pseudobulbar palsy (Laureno & Karp, 1997).

For the treatment of less acute presentations of unclear duration, particularly in the absence of clinical symptoms, the targeted correction rate is somewhat less clear, although general recommendations suggest an increase in serum sodium of 0.5–1 mmol/L/hr with a 24-hr limit of 8 mmol/L and a 48-hr limit of 18 mmol/L (Decaux & Soupart, 2003). Monitoring is critical in the treatment of all hyponatremia presentations and is recommended every 2–3 hr to prevent overcorrection. Fluid restriction also plays a key role in the treatment of hypervolemic hyponatremia, as well as the encouragement of adequate dietary protein and salt consumption (Schwartz, Bennett, Curelop, & Bartter, 1957). For euvolemic and hypervolemic hyponatremia, fluid restriction may be instituted between 500 and 1,000 ml per day (Adrogue & Madias, 2000; Onitilo et al., 2007). Although less common, patients presenting with hypovolemic hyponatremia should have their fluid status optimized, as well as increase their sodium concentration, with fluid replacement using 0.9% sodium chloride at approximately 0.5–1 ml/kg/hr (Verbalis et al., 2007).

CONCLUSION

Complications of malignancy and chemotherapy are frequently seen in the ED and often require emergent treatment. A fundamental understanding of the disease process and the appropriate acute management strategies in critical situations is important for all Emergency Medicine personnel. In addition, it is important to consult with the hematology and oncology service to ensure patients receive appropriate inpatient or outpatient management and follow-up.

REFERENCES

Adrogue, H. J., & Madias, N. E. (2000). Hyponatremia. *The New England Journal of Medicine*, *342*(21), 1581–1589. doi:10.1056/NEJM200005253422107

Agios Pharmaceuticals, Inc. (2019). *TIBSOVO: Full prescribing information*. Cambridge, MA: Author.

Allan, S. G., Stewart, M. E., Love, S., Cornbleet, M. A., Smyth, J. F., & Leonard, R. C. (1990). Prognosis at presentation of small cell carcinoma of the lung. *European Journal of Cancer*, *26*(6), 703–705. doi:10.1016/0277-5379(90)90121-9

Anderson, R. J., Chung, H. M., Kluge, R., & Schrier, R. W. (1985). Hyponatremia: A prospective analysis of its epidemiology and the pathogenetic role of

vasopressin. *Annals of Internal Medicine*, *102*(2), 164–168. doi:10.7326/0003-4819-102-2-164

Astellas Pharma, Inc. (2019). *XOSPATA: Full prescribing information.* Northbrook, IL: Author.

Baden, L. R., Swaminathan, S., Angarone, M., Blouin, G., Camins, B. C., Casper, C., … Smith, C. (2020). Prevention and treatment of cancer-related infections, Version 1.2020, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*, *14*(7), 882–913.

Becker, P. S., Griffiths, E. A., Alwan, L. M., Bachiashvili, K., Brown, A., Cool, R., … Pluchino, L. A. (2020). NCCN guidelines insights: Hematopoietic growth factors, Version 1.2020. *Journal of the National Comprehensive Cancer Network*, *18*(1), 12–22. doi:10.6004/jnccn.2020.0002

Berghmans, T., Paesmans, M., & Body, J. J. (2000). A prospective study on hyponatraemia in medical cancer patients: Epidemiology, aetiology and differential diagnosis. *Supportive Care in Cancer*, *8*(3), 192–197. doi:10.1007/s005200050284

Berl, T. (1990). Treating hyponatremia: What is all the controversy about? *Annals of Internal Medicine*, *113*(6), 417–419. doi:10.7326/0003-4819-113-6-417

Brock, P., & Cruz-Carreras, M. T. (2020). Emergency complications of malignancy. In J. E. Tintinalli & O. J. Ma (Eds.), *Tintinalli's emergency medicine: A comprehensive study guide* (9th ed. pp. 9-11). New York, NY: McGraw-Hill Education.

Cairo, M. S., & Bishop, M. (2004). Tumour lysis syndrome: New therapeutic strategies and classification. *British Journal of Haematology*, *127*(1), 3–11.

Cantwell, L., & Perkins, J. (2018). Infectious disease emergencies in oncology patients. *Emergency Medicine Clinics of North America*, *36*(4), 795–810. doi:10.1016/j.emc.2018.06.009

Carmona-Bayonas, A., Gómez, J., González-Billalabeitia, E., Canteras, M., Navarrete, A., Gonzálvez, M. L., … Ayala de la Peña, F. (2011). Prognostic evaluation of febrile neutropenia in apparently stable adult cancer patients. *British Journal of Cancer*, *105*(5), 612–617. doi:10.1038/bjc.2011.284

Carmona-Bayonas, A., Jiménez-Fonseca, P., Virizuela Echaburu, J., Antonio, M., Font, C., Biosca, M., … Ayala de la Peña, F. (2015). Prediction of serious complications in patients with seemingly stable febrile neutropenia: Validation of the Clinical Index of Stable Febrile Neutropenia in a prospective cohort of patients from the FINITE study. *Journal of Clinical Oncology*, *33*(5), 465–471. doi:10.1200/JCO.2014.57.2347

Casper Pharma LLC. (2018). *Zyloprim (allopurinol): Full prescribing information*. East Brunswick, NJ: Author.

Cattaneo, C., Quaresmini, G., Casari, S., Capucci, M. A., Micheletti, M., Borlenghi, E., … Rossi, G. (2008). Recent changes in bacterial epidemiology and the emergence of fluoroquinolone-resistant *Escherichia coli* among patients with haematological malignancies: Results of a prospective study on 823 patients at a single institution. *Journal of Antimicrobial Chemotherapy*, *61*(3), 721–728. doi:10.1093/jac/dkm514

Celgene Corporation. (2019). *IDHIFA: Full prescribing information*. Summit, NJ: Author.

Coiffier, B., Altman, A., Pui, C.-H., Younes, A., & Cairo, M. S. (2008) Guidelines for the management of pediatric and adult tumor lysis syndrome: An evidence-based review. *Journal of Clinical Oncology*, *26*, 2767–2778.

Coyne, C. J., Le, V., Brennan, J. J., Castillo, E. M., Shatsky, R. A., Ferran, K., … Vilke, G. M. (2017). Application of the MASCC and CISNE Risk-Stratification Scores to identify low-risk febrile neutropenic patients in the emergency department. *Annals of Emergency Medicine*, *69*(6), 755–764. doi:10.1016/j.annemergmed.2016.11.007

Davidson, M. B., Thakkar, S., Hix, J. K., Bhandarkar, N. D., Wong, A., & Schreiber, M. J. (2004). Pathophysiology, clinical consequences, and treatment of tumor lysis syndrome. *The American Journal of Medicine*, *116*(8), 546–554. doi:10.1016/j.amjmed.2003.09.045

de Bont, J. M., & Pieters, R. (2004). Management of hyperuricaemia with rasburicase review. *Nucleosides, Nucleotides & Nucleic Acids*, *23*(8–9), 1431–1440.

Decaux, G., & Soupart, A. (2003). Treatment of symptomatic hyponatremia. *The American Journal of the Medical Sciences*, *326*(1), 25–30. doi:10.1097/00000441-200307000-00004

Dellay, B., & Groth, M. (2016). Emergency management of malignancy-associated hypercalcemia. *Advanced Emergency Nursing Journal*, *38*(1), 15–25. doi:10.1097/tme.0000000000000093

Ellison, D. H., & Berl, T. (2007). Clinical practice. The syndrome of inappropriate antidiuresis. *The New England Journal of Medicine*, *356*(20), 2064–2072. doi:10.1056/NEJMcp066837

Fathi, A. T., DiNardo, C. D., Kline, I., Kenvin, L., Gupta, I., Attar, E. C., … AG221-C-001 Study Investigators. (2018). Differentiation syndrome associated with enasidenib, a selective inhibitor of mutant isocitrate dehydrogenase 2: Analysis of a Phase 1/2 study. *JAMA Oncology*, *4*(8), 1106–1110. doi:10.1001/jamaoncol.2017.4695

Feng, X., Dong, K., Pham, D., Pense, S., Inciardi, J., & Bhutada, N. S. (2013). Efficacy and cost of single-dose rasburicase in prevention and treatment of adult tumour lysis syndrome: A meta-analysis. *Journal of Clinical Pharmacy and Therapeutics*, *38*(4), 301–308.

Freifeld, A. G., Bow, E. J., Sepkowitz, K. A., Boeckh, M. J., Ito, J. I., & Mullen, C. A., … Infectious Diseases Society of America. (2011). Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*, *52*(4), e56–e93. doi:10.1093/cid/cir073

Frey, N., & Porter, D. (2019). Cytokine release syndrome with chimeric antigen receptor T cell therapy. *Biology of Blood and Marrow Transplantation*, *25*(4), e123–e127. doi:10.1016/j.bbmt.2018.12.756

Galardy, P. J., Hochberg, J., Perkins, S. L., Harrison, L., Goldman, S., & Cairo, M. S. (2013). Rasburicase in the prevention of laboratory/clinical tumour lysis syndrome in children with advanced mature B-NHL: A Children's Oncology Group Report. *British Journal of Haematology*, *163*(3), 365–372. doi:10.1111/bjh.12542

Genentech, Inc. (2010). *Actemra: Full prescribing information.* South San Francisco, CA: Author.

Goldman, S. C., Holcenberg, J. S., Finklestein, J. Z., Hutchinson, R., Kreissman, S., Johnson, F. L., … Cairo, M. S. (2001). A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood*, *97*(10), 2998–3003.

Goldner,, W. (2016). Cancer-related hypercalcemia. *Journal of Oncology Practice*, *12*(5), 426–432. doi:10.1200/JOP.2016.011155

Hansen, O., Sorensen, P., & Hansen, K. H. (2010). The occurrence of hyponatremia in SCLC and the influence on prognosis: A retrospective study of 453 patients treated in a single institution in a 10-year period. *Lung Cancer*, *68*(1), 111–114. doi:10.1016/j.lungcan.2009.05.015

Hawkins, R. C. (2003). Age and gender as risk factors for hyponatremia and hypernatremia. *Clinica Chimica Acta*, *337*(1–2), 169–172. doi:10.1016/j.cccn.2003.08.001

Hutcherson, D. A., Gammon, D. C., Bhatt, M. S., & Faneuf, M. (2006). Reduced-dose rasburicase in the treatment of adults with hyperuricemia associated with malignancy. *Pharmacotherapy*, *26*(2), 242–247. doi:10.1592/phco.26.2.242

Janicic, N., & Verbalis, J. G. (2003). Evaluation and management of hypo-osmolality in hospitalized patients. *Endocrinology and Metabolism Clinics of North America*, *32*(2), 459–481, vii. doi:10.1016/s0889-8529(03)00004-5

Jeha, S., Kantarjian, H., Irwin, D., Shen, V., Shenoy, S., Blaney, S., … Pui, C. H. (2005). Efficacy and safety of rasburicase, a recombinant urate oxidase (Elitek™), in the management of malignancy-associated hyperuricemia in pediatric and adult patients: Final results of a multicenter compassionate use trial. *Leukemia*, *19*(1), 34–38.

Jones, G., Will, A., Jackson, G., Webb, N., Rule, S., & British Committee for Standards in Haematology. (2015). Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. *British Journal of Haematology*, *169*(5), 669–671.

Kern, W. V., Marchetti, O., Drgona, L., Akan, H., Aoun, M., AkovaRobrecht de Bock, M., … Calandra, T. (2013). Oral antibiotics for fever in low-risk neutropenic patients with cancer: A double-blind, randomized, multicenter trial comparing single daily moxifloxacin with twice daily ciprofloxacin plus amoxicillin/clavulanic acid combination therapy—EORTC Infectious Diseases Group Trial XV. *Journal of Clinical Oncology*, *31*(9), 1149–1156. doi:10.1200/JCO.2012.45.8109

Kite Pharma, Inc. (2020). *Tecartus and Yescarta: Full prescribing information*. Santa Monica, CA: Author.

Klastersky, J., Paesmans, M., Rubenstein, E. B., Boyer, M., Elting, L., Feld, R., … Talcott, J. (2000). The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *Journal of Clinical Oncology*, *18*(16), 3038–3051. doi:10.1200/JCO.2000.18.16.3038

Klemencic, S., & Perkins, J. (2019). Diagnosis and management of oncologic emergencies. *Western Journal of Emergency Medicine*, *20*(2), 316–322. doi:10.5811/westjem.2018.12.37335

Lassen, U., Osterlind, K., Hansen, M., Dombernowsky, P., Bergman, B., & Hansen, H. H. (1995). Long-term survival in small-cell lung cancer: Posttreatment characteristics in patients surviving 5 to 18+ years—An analysis of 1,714 consecutive patients. *Journal of Clinical Oncology*, *13*(5), 1215–1220. doi:10.1200/JCO.1995.13.5.1215

Laureno, R., & Karp, B. I. (1997). Myelinolysis after correction of hyponatremia. *Annals of Internal Medicine*, *126*(1), 57–62. doi:10.7326/0003-4819-126-1-199701010-00008

Lee, D. W., Santomasso, B. D., Locke, F. L., Ghobadi, A., Turtle, C. J., Brudno, J. N., … Neelapu, S. S. (2019). ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biology of Blood and Marrow Transplantation*, *25*(4), 625–638. doi:10.1016/j.bbmt.2018.12.758

Lexicomp. (2020, May 15). *Lexicomp Online database*. Hudson, OH: Wolters Kluwer Clinical Drug Information, Inc.

Leyfman, Y. (2018). Chimeric antigen receptors: Unleashing a new age of anti-cancer therapy. *Cancer Cell International*, *18*, 182. doi:10.1186/s12935-018-0685-x

Liamis, G., Milionis, H., & Elisaf, M. (2008). A review of drug-induced hyponatremia. *American Journal of Kidney Diseases*, *52*(1), 144–153. doi:10.1053/j.ajkd.2008.03.004

Liu, S., Deng, B., Yin, Z., Pan, J., Lin, Y., Ling, Z., … Tong, C. (2020). Corticosteroids do not influence the efficacy and kinetics of CAR-T cells for B-cell acute lymphoblastic leukemia. *Blood Cancer Journal*, *10*(2), 15. doi:10.1038/s41408-020-0280-y

Maier, J. D., & Levine, S. N. (2013). Hypercalcemia in the intensive care unit. *Journal of Intensive Care Medicine*, *30*(5), 235–252. doi:10.1177/0885066613507530

Major, P., Lortholary, A., Hon, J., Abdi, E., Mills, G., Menssen, H. D., … Seaman, J. (2001). Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: A pooled analysis of two randomized, controlled clinical trials. *Journal of Clinical Oncology*, *19*(2), 558–567. doi:10.1200/JCO.2001.19.2.558

Maude, S. L., Barrett, D., Teachey, D. T., & Grupp, S. A. (2014). Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer Journal (Sudbury, Mass.)*, *20*(2), 119–122. doi:10.1097/PPO.0000000000000035

Maude, S. L., Laetsch, T. W., Buechner, J., Rives, S., Boyer, M., Bittencourt, H., … Grupp, S. A. (2018). Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *The New England Journal of Medicine*, *378*(5), 439–448. doi:10.1056/nejmoa1709866

McBride, A., Lathon, S. C., Boehmer, L., Augustin, K. M., Butler, S. K., & Westervelt, P. (2013). Comparative evaluation of a single fixed dosing and weight-based dosing of rasburicase for tumor lysis syndrome. *Pharmacotherapy*, *26*, 806–812.

McDonnell, A. M., Lenz, K. L., Frei-Lahr, D. A., Hayslip, J., & Hall, P. D. (2006). Single-dose rasburicase 6 mg in the management of tumor lysis syndrome in adults. *Pharmacotherapy*, *26*(6), 806–812.

Neelapu, S. S., Locke, F. L., Bartlett, N. L., Lekakis, L. J., Miklos, D. B., Jacobson, C. A., … Go, W. Y. (2017). Axicabtagene Ciloleucel CAR T-Cell therapy in refractory large B-cell lymphoma. *The New England Journal of Medicine*, *377*(26), 2531–2544. doi:10.1056/NEJMoa1707447

Norsworthy, K. J., Mulkey, F., Scott, E. C., Ward, A. F., Przepiorka, D., Charlab, R., … Pazdur, R. (2020). Differentiation syndrome with ivosidenib and enasidenib treatment in patients with relapsed or refractory IDH-mutated AML: A U.S. Food and Drug Administration systematic analysis. *Clinical Cancer Research*. Retrieved from https://clincancerres.aacrjournals.org/content/early/2020/05/09/1078-0432.CCR-20-0834

Novartis Pharmaceutical Corporation. (2018). *Kymriah: Full prescribing information*. East Hanover, NJ: Author.

Onitilo, A. A., Kio, E., & Doi, S. A. (2007). Tumor-related hyponatremia. *Clinical Medicine Research*, *5*(4), 228–237. doi:10.3121/cmr.2007.762

Osterlind, K., & Andersen, P. K. (1986). Prognostic factors in small cell lung cancer: Multivariate model based on 778 patients treated with chemotherapy with or without irradiation. *Cancer Research*, *46*(8), 4189–4194.

Palmer, B. F., Gates, J. R., & Lader, M. (2003). Causes and management of hyponatremia. *Annals of Pharmacotherapy*, *37*(11), 1694–1702. doi:10.1345/aph.1D105

Pi, J., Kang, Y., Smith, M., Earl, M., Norigian, Z., & McBride, A. (2016). A review in the treatment of oncologic emergencies. *Journal of Oncology Pharmacy Practice*, *22*(4), 625–638. doi:10.1177/1078155215605661

Pollyea, D. A., Tallman, M. S., de Botton, S., Kantarjian, H. M., Collins, R., Stein, A. S., … Stein, E. M. (2019). Enasidenib, an inhibitor of mutant IDH2 proteins, induces durable remissions in older patients with newly diagnosed acute myeloid leukemia. *Leukemia*, *33*(11), 2575–2584. doi:10.1038/s41375-019-0472-2

Pui, C.-H. (2002). Rasburicase: A potent uricolytic agent. *Expert Opinion in Pharmacotherapy*, *3*(4), 433–452.

Reeves, D. J., & Bestul, D. J. (2008). Evaluation of a single fixed dose of rasburicase 7.5 mg for the treatment of hyperuricemia in adults with cancer. *Pharmacotherapy*, *28*(6), 685–690. doi:10.1592/phco.28.6.685

Ribiero, R. C., & Pui, H.-C. (2003). Recombinant urate oxidase for the prevention of hyperuricemia and tumor lysis syndrome in lymphoid malignancies. *Clinical Lymphoma*, *3*(4), 225–232.

Robertson, G. L., Bhoopalam, N., & Zelkowitz, L. J. (1973). Vincristine neurotoxicity and abnormal secretion of antidiuretic hormone. *Archives of Internal Medicine*, *132*(5), 717–720.

Roboz, G. J., DiNardo, C. D., Stein, E. M., de Botton, S., Mims, A. S., Prince, G. T., … Stone, R. M. (2020). Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. *Blood*, *135*(7), 463–471. doi:10.1182/blood.2019002140

Rybak, M. J., Le, J., Lodise, T. P., Levine, D. P., Bradley, J. S., Liu, C., … Lomaestro, B. M. (2020). Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *American Journal of Health-System Pharmacy*, *77*(11), 835–864. doi:10.1093/ajhp/zxaa036

Sanofi-aventis. (2019). *Elitek: Full prescribing information*. Bridgewater, NJ: Author.

Sanz, M. A., & Montesinos, P. (2014). How we prevent and treat differentiation syndrome in patients with acute promyelocytic leukemia. *Blood*, *123*(18), 2777–2782. doi:10.1182/blood-2013-10-512640

Schuster, S. J., Bishop, M. R., Tam, C. S., Waller, E. K., Borchmann, P., McGuirk, J. P., … JULIET Investigators. (2019). Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *The New England Journal of Medicine*, *380*(1), 45–56. doi:10.1056/NEJMoa1804980

Schwartz, W. B., Bennett, W., Curelop, S., & Bartter, F. C. (1957). A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. *The American Journal of Medicine*, *23*(4), 529–542. doi:10.1016/0002-9343(57)90224-3

Shimabukuro-Vornhagen, A., Gödel, P., Subklewe, M., Stemmler, H. J., Schlößer, H. A., Schlaak, M., … von Bergwelt-Baildon, M. S. (2018). Cytokine release syndrome. *Journal for ImmunoTherapy of Cancer*, *6*(1), 56. doi:10.1186/s40425-018-0343-9

Southwick, F. S. (2020). Infections in the immunocompromised host. In J. Malley & K. J. Davis (Eds.), *Infectious disease: A clinical short course* (4th ed, chapter 15). New York, NY: McGraw-Hill.

Spasovski, G., Vanholder, R., Allolio, B., Annane, D., Ball, S., Bichet, D., … Hyponatraemia Guideline Development Group. (2014). Clinical practice guideline on diagnosis and treatment of hyponatraemia. *European Journal of Endocrinology*, *170*(3), G1–G47. doi:10.1530/EJE-13-1020

Stahl, M., & Tallman, S. (2019). Differentiation syndrome in acute promyelocytic leukaemia. *British Journal of Haematology*, *187*, 157–162.

Stuart, M. J., Cuaso, C., Miller, M., & Oski, F. A. (1975). Syndrome of recurrent increased secretion of antidiuretic hormone following multiple doses of vincristine. *Blood*, *45*(3), 315–320.

Taplitz, R. A., Kennedy, E. B., Bow, E. J., Crews, J., Gleason, C., Hawley, D. K., … Flowers, C. R. (2018). Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America clinical practice guideline update. *Journal of Clinical Oncology*, *36*(14), 1443–1453. doi:10.1200/JCO.2017.77.6211

Trifilio, S., Gordon, L., Singhal, S., Tallman, M., Evens, A., Rashid, K., … Mehta, J. (2006). Reduced-dose rasburicase (recombinant xanthine oxidase) in adult cancer patients with hyperuricemia. *Bone Marrow Transplantation*, *37*(11), 997–1001. doi:10.1038/sj.bmt.1705379

Upadhyay, A., Jaber, B. L., & Madias, N. E. (2006). Incidence and prevalence of hyponatremia. *The American Journal of Medicine*, *119*(7, Suppl. 1), S30–S35. doi:10.1016/j.amjmed.2006.05.005

van der Velden, W. J., Herbers, A. H., Netea, M. G., & Blijlevens, N. M. (2014). Mucosal barrier injury, fever and infection in neutropenic patients with cancer: Introducing the paradigm febrile mucositis. *British Journal of Haematology*, *167*(4), 441–452. doi:10.1111/bjh.13113

Verbalis, J. G., Goldsmith, S. R., Greenberg, A., Schrier, R. W., & Sterns, R. H. (2007). Hyponatremia treatment guidelines 2007: Expert panel recommendations. *The American Journal of Medicine*, *120*(11, Suppl. 1), S1–21. doi:10.1016/j.amjmed.2007.09.001

Wierda, W. G., Byrd, J. C., Abramson, J. S., Awan, F., Bilgrami, S. F., Bociek, G., … Wagner-Johnston, N. (2020). Chronic lymphocytic leukemia/small lymphocytic lymphoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*, *18*(2), 185–217.

Will, A., & Tholouli, E. (2011). The clinical management of tumour lysis syndrome in haematological malignancies. *British Journal of Haematology*, *154*(1), 3–13.

Yu, X., Lui, L., Nie, X., Li, J., Zhang, J., Zhoa, L., & Wang, X. (2017) The optimal single-dose regimen of rasburicase for management of tumour lysis syndrome in children and adults: A systematic review and meta-analysis. *Journal of Clinical Pharmacy and Therapeutics*, *42*(1), 18–26. doi:10.1111/jcpt.12479

Zagzag, J., Hu, M. I., Fisher, S. B., & Perrier, N. D. (2018). Hypercalcemia and cancer: Differential diagnosis and treatment. *CA: A Cancer Journal for Clinicians*, *68*(5), 377–386. doi:10.3322/caac.21489

For more than 175 additional continuing professional development articles related to Advanced Pharmacology Hours, go to NursingCenter.com/ce.

Lippincott® NursingCenter®

NCPD Nursing Continuing Professional Development

TEST INSTRUCTIONS

- Read the article. The test for this nursing continuing professional development (NCPD) activity is to be taken online at **www.nursingcenter.com/CE/AENJ**. Tests can no longer be mailed or faxed.
- You'll need to create an account (it's free!) and log in to access My Planner before taking online tests. Your planner will keep track of all your Lippincott Professional Development online NCPD activities for you.
- There's only one correct answer for each question. A passing score for this test is 7 correct answers. If you pass, you can print your certificate of earned contact hours and access the answer key. If you fail, you have the option of taking the test again at no additional cost.
- For questions, contact Lippincott Professional Development: 1-800-787-8985.
- Registration deadline is March 7, 2025.

PROVIDER ACCREDITATION

Lippincott Professional Development will award 3.0 contact hours and 3.0 pharmacology contact hours for this nursing continuing professional development activity.

Lippincott Professional Development is accredited as a provider of nursing continuing professional development by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is also provider approved by the California Board of Registered Nursing, Provider Number CEP 11749 for 3.0 contact hours. Lippincott Professional Development is also an approved provider of continuing nursing education by the District of Columbia, Georgia, West Virginia, New Mexico, South Carolina, and Florida, CE Broker #50-1223. Your certificate is valid in all states.

Payment: The registration fee for this test is $27.95.