Myelosuppression, Bone Disease, and Acute Renal Failure

Evidence-based recommendations for oncologic emergencies

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BACKGROUND: Oncologic emergencies associated with multiple myeloma include myelosuppression (anemia, neutropenia, and thrombocytopenia), bone-related emergencies, and acute renal failure.

OBJECTIVES: This article reviews the pathophysiology of these multiple myeloma-associated oncology emergencies and provides a framework for assessment and effective intervention.

METHODS: A comprehensive review of the levels of evidence, focusing on assessment, diagnosis, comorbidities, treatment, ongoing monitoring, and patient education, are presented to support the plan of care for at-risk patients.

FINDINGS: Attention to signs and symptoms is the foundation for preventing these emergencies or managing additional escalation of symptoms.

SYMPTOM MANAGEMENT, HEALTH MAINTENANCE, AND SURVIVORSHIP in patients with multiple myeloma (MM) have been areas of focus for the International Myeloma Foundation (IMF) Nurse Leadership Board (NLB). Reviews of myelosuppression, MM bone disease, and renal complications were published in the *Clinical Journal of Oncology Nursing* in 2008. In the current article, the NLB will again review these important topics and provide evidence-based recommendations, but in the framework of oncologic emergencies (OEs). OEs have been defined as complications resulting from cancer itself, from a paraneoplastic syndrome, or from treatment of the cancer that require prompt interventions to prevent irreversible vital organ damage. OEs can be hematologic, neurologic, or metabolic in origin, but require immediate attention no matter the cause. An understanding of potential OEs, prevention, and prompt intervention is critical to organ health and survival in patients with MM.

The advent of novel therapies has affected the treatment of MM. Initial therapy typically includes a combination of three novel agents, such as an immunomodulatory agent (e.g., lenalidomide or thalidomide), a proteasome inhibitor (e.g., bortezomib or carfilzomib), and a steroid (e.g., dexamethasone or prednisone), followed by an autologous stem cell transplantation in eligible patients (Teh et al., 2014). Following transplantation (or induction therapy for transplantation-ineligible patients), most patients are treated with a reduced-intensity maintenance therapy until progression of disease. Even in patients with relapsed MM, multi-drug combinations are standard, often with the addition of the more recently approved monoclonal antibodies or histone deacetylase inhibitors (Laubach et al., 2016). This treatment paradigm of multi-drug combinations and continuous maintenance therapy has proven to be far more effective than conventional chemotherapy and has significantly improved the overall survival of patients with MM. As a result, there is an ever-increasing population of patients who have received multiple continuous types of treatment with cumulative toxicities, including a decrease in bone marrow cellularity and subsequent myelosuppression. The

novel agents for patients with MM have unique side effects and toxicities that are predictable and manageable. When used in combination, however, even mild side effects of individual drugs can be amplified and negatively impact patient quality of life (QOL).

Myelosuppression

The hematologic toxicities of anemia, neutropenia, and thrombocytopenia are a direct result of the various degrees of myelosuppression caused by treatment with immunomodulatory agents, proteosome inhibitors, or monoclonal antibodies. Myelosuppression is defined by the National Cancer Institute ([NCI], 2017) as a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. The range of these myelosuppressive hematologic toxicities can vary from minor inconveniences to life-threatening complications. If severe, consequences of under-recognized or untreated myelosupression can lead to OEs, such as life-threatening anemia, neutropenic fever, or bleeding from thrombocytopenia (Miceli, Colson, Gavino, & Lilleby, 2008). Table 1 provides a grading criteria for hematologic toxicity adverse events.

Anemia

Anemia is defined by the NCI (2017) as a condition in which the number of red blood cells is below normal. This results in a reduction in hemoglobin, which decreases the oxygen-carrying capacity of the blood (Miller, 2010). In the grading criteria outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE), grade 4 anemia is defined as life threatening or disabling and constitutes an OE (National Cancer Institute, 2010). For patients who have been diagnosed with MM, anemia is a common and expected side effect associated with the disease and its treatment. Anemia, even severe, may improve if treatment for MM is successful, but will remain or worsen if the treatment is unsuccessful (Niesvizky & Badros, 2010). Anemia may contribute to inferior outcomes, including reduced survival (Birgegård, Gascón, & Ludwig, 2006), and patients with uncorrected anemia have a diminished QOL. Therefore, understanding each patient's

> ## "Even mild side effects of individual drugs can be amplified and negatively impact patient quality of life."

risk for developing severe, disabling, or life-threatening anemia is important for its prevention and management.

About 97% of patients with MM develop anemia during the disease trajectory. More than 70% of patients present with anemia at diagnosis, with 8% classified as having severe anemia (Kyle, 1975; Kyle et al., 2003; Maes et al., 2010; Rajkumar & Kumar, 2016). In the European Cancer Anemia Survey, of the 720 patients with persistent or recurrent MM, 85% were anemic at the time of the enrollment. Of these, about 5% had severe anemia, with a hemoglobin less than 8 g/dl (Birgegård et al., 2006). The risk of becoming anemic is highest among patients with MM who initially present with anemia, have persistent or recurrent disease, are female, are older than age 60 years, or are undergoing treatment with platinum chemotherapy (Birgegård et al., 2006). In a study published by Dammacco et al. (1998), 45% of patients with MM receiving chemotherapy required a red blood cell (RBC) transfusion during their treatment.

RBCs, or erythrocytes, are produced in the bone marrow of certain bones (vertebrae, sternum, ribs, pelvis, and proximal femurs), and their production is controlled by the oxygen needs of tissues. Anemia can bring about hypoxia, which in turn triggers the body to begin the process of producing new RBCs. In response to hypoxia, the kidneys release erythropoietin, which sends a signal to erythroid progenitor cells to produce more RBCs. The role of mature RBCs is to serve as a vehicle for hemoglobin transport

TABLE 1.

GRADING CRITERIA FOR HEMATOLOGIC TOXICITY ADVERSE EVENTS

ADVERSE EVENT	UNIT OF MEASURE	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Anemia	Hemoglobin (g/dl)	Less than LLN to 10	8–10	Less than 8	Life threatening; urgent intervention indicated
Neutropenia	Absolute neutrophil count (x 10^9)	Less than LLN to 1.5	1–1.5	0.5–1	Less than 0.5
Thrombocytopenia	Platelet count (x 10^9)	Less than LLN to 75	50–75	25–50	Less than 25

LLN—lower limits of normal
Note. Based on information from National Cancer Institute, 2010.

of oxygen to the tissues and to transport carbon dioxide from the tissues to the lungs. The resulting increase in the oxygen-carrying capacity of the blood functions to downregulate further erythropoietin production (Miller, 2010). Anemia can result from a loss of RBCs from bleeding, from increased RBC destruction, from decreased RBC production, or from a combination of these etiologies. Table 2 provides a review of the etiology of anemia and its contributing factors.

Anemia in MM is caused by many factors, including replacement of bone marrow by plasma cells, which reduces erythroid precursors, leads to erythropoietin deficiency, and makes erythroblast precursors less responsive to erythropoietin; myeloma treatment (both chemotherapy and radiation); and other factors independent of myeloma or treatment itself (Niesvizky & Badros, 2010). The major cause of anemia in patients with MM is myeloma cells inducing the death of erythroblasts (RBC precursors) (Terpos et al., 2015). Cancer cells also produce signaling molecules (cytokines) that result in the sequestration of iron away from RBCs, which decreases RBC production and may shorten RBC survival (National Comprehensive Cancer Network [NCCN], 2017a). Bone marrow infiltration by plasma cells also reduces the production of hepcidin, which impairs the use of iron and increases plasma volume via paraproteins (Maes et al., 2010; Terpos et al., 2015).

SIGNS AND SYMPTOMS

Recognizing the signs, symptoms, and risks for severe anemia can mitigate potentially life-threatening anemia. Life-threatening anemia often is a preventable OE. Table 3 lists tests to establish anemia in patients with MM. Signs and symptoms of all grades of anemia severity may include pallor of the skin and mucous

TABLE 2.
ETIOLOGY OF AND CONTRIBUTING FACTORS FOR ANEMIA IN PATIENTS WITH CANCER

ETIOLOGY	CONTRIBUTING FACTORS
Relative loss of red blood cells	■ Surgical blood loss ■ Acute or chronic gastrointestinal hemorrhage ■ Excessive diagnostic phlebotomy ■ Disseminated intravascular coagulation
Increased red blood cell destruction	■ Hemolytic anemia ■ Cold agglutinin disease
Decreased red blood cell production	■ Treatment-induced myelosuppression ■ Renal impairment ■ Nutritional deficiencies ■ Anemia of chronic disease ■ Tumor infiltration of the bone marrow ■ Inherited genetic disorder (i.e., thalassemia) ■ Myeloid malignancy

Note. Based on information from Miller, 2010; National Comprehensive Cancer Network, 2017a.

membranes, shortness of breath, heart palpitations, soft systolic murmurs, lethargy, and fatigue (NCI, 2010). Fatigue, which is the most common side effect of anemia, can reduce QOL by limiting the ability to work and otherwise influence physical and emotional well-being (Miceli et al., 2008). The symptoms of anemia are likely to be pronounced if the anemia presents acutely; however, if it develops gradually, the body can compensate for the lower oxygen-carrying capacity of the blood by increasing cardiac output and coronary flow, altering blood viscosity, and adjusting oxygen consumption and extraction. The presence of preexisting cardiovascular, pulmonary, or cerebral vascular disease may interfere with these compensatory mechanisms, making the patient less able to tolerate even mild anemia and can lead to an emergency situation (NCCN, 2017a).

Neutropenia

Neutropenia is defined by the NCI (2017) as a condition in which there is a lower-than-normal number of neutrophils (a type of white blood cell). All grades of neutropenia severity can lead to OEs, such as neutropenic fever, pneumonia, and sepsis in patients who already harbor functional immunoglobulin deficiency (Miceli et al., 2008). In patients with MM, neutropenia may be caused by the disease or by its treatment. When present in high numbers, plasma cells directly interfere with normal hematopoiesis and neutrophil production. This disease-related neutropenia is common in patients at diagnosis and late in the disease (Teh et al., 2014). Beyond neutropenia, disease-related immunodeficiency also involves B-cell dysfunction; hypogammaglobulinemia; and T-cell, NK-cell, and dendritic-cell abnormalities (Teh et al., 2014). Because MM is a disease afflicting older adults, many patients have both functional and physiologic age-related comorbidities that predispose them to increased risks of infection. Given this combination of factors, patients with MM are at significantly greater risk for developing bacterial, viral, and fungal infections than matched controls, and infections are a leading contributor to morbidity and mortality. The most frequent bacterial infections (listed in order of prevalence) are pneumonia, septicemia, cellulitis, and pyelonephritis. Herpes zoster and influenza are the two most common viral infections (Blimark et al., 2015). As the disease progresses and immune dysfunction worsens, the spectrum of causative agents widens (Teh et al., 2015). Therefore, even mild neutropenia can represent an OE in patients with MM due to many factors.

Traditional chemotherapy agents, such as melphalan or cyclophosphamide, greatly increase the risk of infection through a combination of rapid, prolonged neutropenia and disruption of physical defense barriers, such as the mucosa. Such chemotherapy agents are not widely used for the treatment of MM except during an autologous stem cell transplantation and for disease control late in the disease trajectory. Although newer treatment agents (immunomodulatory drugs and proteasome inhibitors)

also negatively affect neutrophil counts, they have other effects on the immune system, some of which are beneficial. In fact, in a longitudinal study, neither class of these agents was independently associated with an increased risk of infection (Teh et al., 2015). However, these newer agents are rarely used as monotherapies and are most often combined with each other and with corticosteroids. Corticosteroids are highly immunosuppressive even when used as single agents and significantly increase the risk of developing infection (Teh et al., 2014). When corticosteroids are combined with lenalidomide or pomalidomide, neutropenia rates have been reported to be as high as 39% and 50%, respectively (Dimopoulos et al., 2014; Dimopoulos, Palumbo, et al., 2016). Therefore, in the era of combination therapy, the risk of severe neutropenia and subsequent fever has increased (Teh et al., 2014).

SIGNS AND SYMPTOMS

Like other hematologic toxicities, neutropenia is graded according to NCI CTCAE criteria. Neutropenia itself is not an OE, but the risk of developing an infection is directly related to the depth and duration of the neutropenic episode. Bodey, Buckley, Sathe, and Freireich (1966) reported that the most important risk factor for developing an infection was an absolute neutrophil count of less than 0.5×10^9. Because adequate neutrophils are necessary to mount an inflammatory reaction at the site of an active infection, fever may be the first and only sign of a bacterial infection in profoundly neutropenic patients. Fever is defined as a single oral temperature of 38.3°C (101°F) or higher, or two separate temperatures of 38°C (100.4°F) or higher, measured one hour apart (Hughes et al., 2002). Local symptoms, such as erythema, induration, or purulent discharge, may not be present in the absence of pus-generating neutrophils and monocytes. Likewise, pulmonary infiltrates are often absent in patients who are neutropenic because of a diminished and delayed inflammatory response (Lewis, Hendrickson, & Moynihan, 2011). In the absence of fever, other symptoms associated with a local or systemic infection may include chills, rigors, cough, dyspnea, nausea, diarrhea, dysuria, dizziness, fatigue, and pain. Therefore, when assessing a patient with neutropenia, a thorough review of systems is critical. In addition, a careful physical examination should focus on areas of pain and should include a careful inspection of the oral mucosa, skin, and any venous access devices.

Thrombocytopenia

Thrombocytopenia is defined by the NCI (2017) as a condition in which there is a lower-than-normal number of platelets in the blood and is the primary cause of bleeding in patients with all types of cancer. When platelet levels fall below normal levels, adult patients are considered thrombocytopenic, and their thrombocytopenia can be further subdivided into mild, moderate, and severe subgroups as per NCI (2010) CTCAE criteria. Although platelet count is the best indicator of the potential risk of bleeding, the correlation is imprecise and varies based on the underlying condition and other clinical factors (Avvisati, Tirindelli, & Annibali, 2003). Severe thrombocytopenia is considered a life-threatening OE. Because of this, the number of platelets considered "safe" lacks well-defined evidence, and there is no established threshold above which platelets should be maintained to avoid bleeding. Spontaneous bleeding rarely occurs when platelets are more than 50×10^9/L, and risk of bleeding generally increases only when platelets fall below 20×10^9/L (Avvisati et al., 2003).

In patients with MM, thrombocytopenia often is present at diagnosis and often is most severe at end-stage disease. During that time, the large numbers of MM cells present in the bone marrow play a significant role in the pathogenesis. Thrombocytopenia is also a common toxicity of proteasome inhibitors used for the treatment of MM. However, for these agents, thrombocytopenia is typically cyclical, predictable, and generally reversible. Patients who are being treated with an immunomodulatory agent or carfilzomib should also take antithrombotic agents (i.e., aspirin, enoxaparin) to reduce their risk of thrombotic events related to these drugs. Because this increases the risk of bleeding, discontinuation of anticoagulation or antiplatelet therapy needs to be considered when platelet levels decrease, particularly when platelets fall below 50×10^9/L (Noonan et al., 2017). Steroids, which are an

TABLE 3.

TESTING PROCEDURES FOR ANEMIA IN PATIENTS WITH MULTIPLE MYELOMA

DIFFERENTIAL DIAGNOSIS	TESTS TO PERFORM
Hemolysis	■ Direct antiglobulin test ■ Disseminated intravascular coagulation panel ■ Haptoglobin ■ Indirect bilirubin ■ Lactate dehydrogenase
Hemorrhage	■ Stool guaiac ■ Endoscopy
Inherited disorder	Obtain thorough family history.
Myelodysplastic syndrome	Bone marrow biopsy
Myeloid malignancy	Bone marrow biopsy
Nutritional deficiency	■ Iron, total iron-binding capacity, ferritin ■ Vitamin B_{12} ■ Folate
Radiation-induced myelosuppression	Obtain medical history.
Renal dysfunction	Glomerular filtration rate less than 60 ml/minute/1.73 m²

Note. Based on information from National Comprehensive Cancer Network, 2017a.

integral part of most anti-myeloma regimens, adversely affect the gastric mucosa, impair wound healing, and lead to an increased risk of bleeding (King & Faiman, 2017). Although onset of treatment-related thrombocytopenia may be gradual, thrombocytopenia may appear rapidly with both viral and bacterial infections related to platelet consumption, or it may be attributed to the drugs used to treat the infection. Some drugs, such as vancomycin, result in frank thrombocytopenia, whereas others increase risk of bleeding related to impaired platelet function (Aster & Bougie, 2007).

SIGNS AND SYMPTOMS

Bleeding caused by thrombocytopenia may manifest in minor signs and symptoms, such as ecchymosis or petechiae, or in more overt symptoms such as epistaxis, hemoptysis, hematuria, hematemesis, melena, vaginal bleeding, or oozing from skin lesions or vascular access lines. Hemorrhage may also occur as a catastrophic event, such as a major cerebral or gastrointestinal bleed (Damron et al., 2009). As such, nurses should conduct thorough patient histories to assess for both frank and occult bleeding. Although noting the level of thrombocytopenia identified by complete blood count (CBC) is critical to assessing risk of bleeding, noting the hemoglobin level is also of importance because the rapid development of anemia may indicate a possible hemorrhage.

Evidence-Based Recommendations for the Prevention and Management of Myelosuppression

LEVEL OF EVIDENCE I

- The prevention and management of severe anemia in MM must include treatment of the underlying malignancy, administration of erythropoiesis-stimulating agents (ESAs) if indicated, correction of additional underlying causes, and transfusions

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FIGURE 1.
PREVENTIVE MANAGEMENT OF ANEMIA FOR PATIENTS WHO REFUSE BLOOD TRANSFUSION

**PRIOR TO INITIATION OF MYELOSUPPRESSIVE CHEMOTHERAPY**
- Regard risk of anemia during treatment decision making.
- Supplement with daily folic acid and vitamin B_{12}.
- Coagulation abnormalities should be evaluated and corrected.
- Provide IV iron for treatment of iron deficiency.
- If appropriate, initiate erythropoiesis-stimulating agents in applicable patients.
- Use antifibrinolytic drugs for management of oral bleeding.
- Manage mucositis effectively.
- Incorporate proton pump inhibitors and stool softeners to decrease the risk of gastrointestinal bleeding.
- Suppress menses in applicable patients.

Note. Based on information from National Comprehensive Cancer Network, 2017a.

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with packed RBCs with or without iron supplement (NCCN, 2017a).
- Serum creatinine must also be checked, as anemia may become severe if renal function decreases (Faiman, Mangan, Spong, & Tariman, 2011).
- ESAs for patients with MM should be used after an assessment of the benefits and risks. Benefits include a potential decrease in the number of RBC transfusions. Several prospective studies have shown that ESAs can increase hemoglobin levels by 2 g/dl or more in 60%–75% of patients with MM with symptomatic anemia (Terpos et al., 2015). Potential risks of ESAs include an increase in the number of thrombotic events, hypertension, seizures, pure red cell aplasia, and possible decreased survival related to shortened time to tumor progression (NCCN, 2017a).
- Underlying causes of anemia that may not be attributable to MM should be treated. Anemia in cancer may be attributed to underlying comorbidities, such as bleeding, hemolysis, hereditary disease, renal insufficiency, nutritional deficiencies, anemia of chronic disease, or a combination of these factors (NCCN, 2017a). The mean corpuscular volume will define whether a patient has a microcytic (less than 80 fl), macrocytic (greater than 100 fl), or normocytic (80–100 fl) anemia. Microcytic anemia may be related to iron deficiency, thalassemia, anemia of chronic disease, or sideroblastic anemia. Macrocytic anemia may be related to medications, alcoholism, myelodysplastic syndrome, or vitamin B_{12} or folate deficiencies. Normocytic anemia may be a result of hemorrhage, hemolysis, bone marrow failure, anemia of chronic inflammation, or renal insufficiency (NCCN, 2017a).
- Leukocyte-reduced packed RBC is recommended for asymptomatic patients with MM at high risk for complications from anemia, such as patients who have had a progressive decline in their hemoglobin following intensive therapy or patients with comorbidities such as cardiac disease, chronic pulmonary disease, or cerebral vascular disease (NCCN, 2017a). Leukocyte-reduced blood products decrease the risk of febrile reactions, human leukocyte antigen alloimmunization, and cytomegalovirus infection (Miceli et al., 2008).
- Select patients may refuse blood transfusions because of either religious or personal preferences. Figure 1 outlines preventive management of anemia for these patients. In extreme cases of severe, life-threatening anemia, pure oxygen (400 mmHg, $SaO_2 = 1$) has been used to increase blood oxygenation (NCCN, 2017a). The benefit of an RBC transfusion in the symptomatic patient is a prompt increase in the hemoglobin and a potential for rapid improvement in anemia-related symptoms (NCCN, 2017a) (see Figure 2).
- Antibacterial and antifungal prophylaxis is recommended for patients with MM at high risk for infection, such as older adults, frail patients, or those who have a history of infections or cardiopulmonary comorbidities. Based on clinical guidelines, this same group may also benefit from the prophylactic use of

FIGURE 2.

INDICATIONS FOR RED BLOOD CELL TRANSFUSION IN PATIENTS WITH ANEMIA
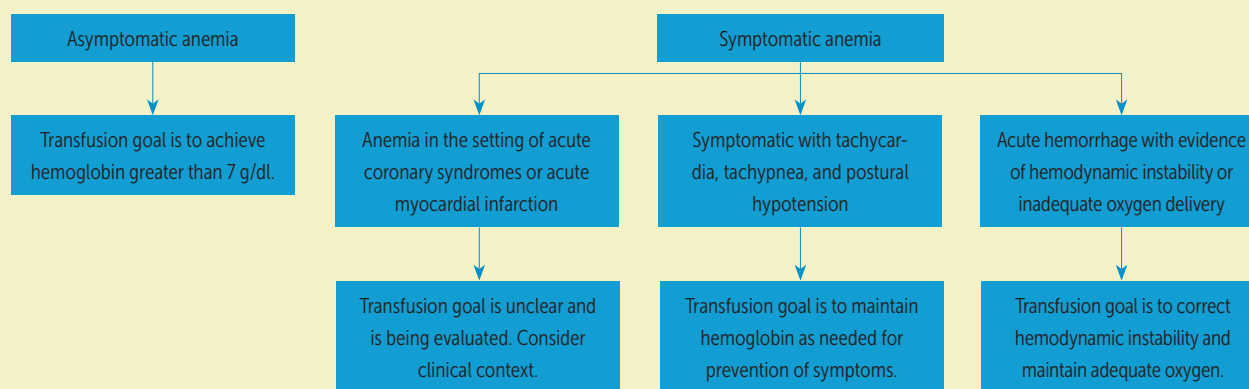
Note. Based on information from National Comprehensive Cancer Network, 2017a.

hematopoietic growth factors, such as filgrastim or newer biosimilars (NCCN, 2017a; Smith et al., 2015).

■ It is recommended that all patients receive vaccination against influenza, *Haemophilus influenza,* and *Streptococcus pneumoniae,* although vaccine efficacy is not guaranteed because patients with MM may not mount a robust immune response. Live vaccines, such as the varicella-zoster virus vaccine, should not be given to patients with MM, as live vaccines have the potential to cause the disease they are meant to prevent (Flowers et al., 2013; Freifeld et al., 2011; NCCN, 2017c; Snowden et al., 2011).

LEVEL OF EVIDENCE II

■ All patients receiving therapy for MM should have their CBC closely monitored, with specific frequency and timing of monitoring based on the prescribing information for each drug or combination of drugs. Dose modifications or treatment delays should be considered if grade 3 anemia, neutropenia, or thrombocytopenia occurs (Amgen Inc., 2016a; Bristol-Myers Squibb, 2015; Celgene, 2016, 2017a, 2017b; Janssen Biotech, 2017; Millennium Pharmaceuticals, 2017; Novartis, 2016; Takeda Oncology, 2016).

■ Patients undergoing treatment with anti-myeloma therapy should observe the hematologic outcomes achieved solely through tumor reduction prior to considering the use of ESAs. If anemia does not improve with anti-myeloma therapy, treatment with ESAs may be considered, beginning with the lowest possible dose (Rizzo et al., 2010; Terpos et al., 2015).

■ The use of ESAs during chemotherapy is recommended, particularly in patients with renal impairment, when the hemoglobin concentration is less than 10 g/dl and no improvement is noted in anemia despite MM disease response (Palumbo et al., 2014).

■ Caution should be exercised when using ESAs with other chemotherapeutic agents (i.e., immunomodulatory drugs, doxorubicin, or high-dose corticosteroids) that increase the risk of thromboembolic complications (Rizzo et al., 2010). A few randomized studies have evaluated the impact of ESAs on outcomes in patients with MM. One randomized study showed no evidence of inferior outcome following ESA treatment; however, the trial was small and statistically underpowered (Richardson et al., 2011).

■ To minimize the risk of infection, the use of neutropenic precautions is recommended in patients with MM (see Figure 3). Patients and their caregivers should be educated to promptly recognize and act on signs and symptoms of infection and should be given specific written instructions on how and when to contact a healthcare provider (Flowers & Karten, 2013).

■ Prophylactic antivirals are recommended for patients receiving proteasome inhibitors (Amgen Inc., 2016a; Millennium Pharmaceuticals, 2017; Takeda Oncology, 2016) and following autologous stem cell transplantation.

■ For patients receiving high-dose corticosteroids, prophylaxis with trimethoprim-sulfamethoxazole should also be considered (Flowers et al., 2013). The use of prophylactic immunoglobulin replacement is not uniformly recommended, although it may be useful in subsets of patients with hypogammaglobulinemia and recurrent infections.

■ All healthcare workers and caregivers should follow hand hygiene guidelines and respiratory and cough etiquette guidelines to reduce pathogen exposure. In addition, healthcare personnel who access central venous catheters should follow well-established guidelines to prevent infection through these devices (NCCN, 2017c; O'Grady et al., 2011; Schiffer et al., 2013).

■ For patients who develop fever and neutropenia, urgent action is required because these patients may quickly become hemodynamically unstable. Paired blood cultures should be obtained prior to starting antibiotics, and if clinical signs or symptoms are present, cultures of the nares, urine, or diarrheal stools may be obtained. All patients should receive initial empirical antibiotic therapy within an hour of triage to cover gram-positive and gram-negative pathogens. Although most patients with febrile neutropenia will be admitted to the hospital, a select low-risk group may be managed safely in the outpatient setting (Flowers et al., 2013; Freifeld et al., 2011).

FIGURE 3.

PATIENT TIP SHEET: NEUTROPENIC PRECAUTIONS, SIGNS, AND SYMPTOMS OF INFECTION

PREVENTING INFECTION
■ Clean your hands frequently and ask others to do the same.
■ Shower or bathe daily.
■ Use an unscented lotion to keep your skin moist.
■ Avoid direct contact with pet waste.
■ Wash your hands after touching animals.
■ Use gloves when gardening.
■ Brush your teeth and gums with a soft toothbrush.
■ Avoid crowded places or people who are sick.
■ Do not share food utensils and cups.
■ Do not share personal items like toothbrushes.
■ Keep household surfaces clean.
■ Cook meat and eggs thoroughly.
■ Wash raw fruits and vegetables.
■ Get a seasonal flu vaccine.

SIGNS AND SYMPTOMS
■ Fever of 100.4°F or higher for more than one hour or a one-time temperature of 101°F or higher
■ Chills or sweats
■ New cough or change in cough
■ Shortness of breath
■ Sore throat, new mouth sores, or nasal congestion
■ Stiff neck
■ Diarrhea or vomiting
■ Burning, pain, or increased urination
■ Unusual vaginal discharge
■ New onset pain
■ Redness, soreness, or swelling in any area, particularly around ports and surgical wounds
■ Change in mental status

Note. Based on information from Centers for Disease Control and Prevention, 2017; Hughes et al., 2002.

■ Platelet transfusion practices should follow established guidelines, such as those provided by the American Society of Clinical Oncologists (Schiffer et al., 2001). Although invasive procedures should be minimized in patients with thrombocytopenia, a platelet count of 40×10^9/L to 50×10^9/L is considered acceptable for proceeding with invasive procedures in the absence of other coagulation abnormalities.

LEVEL OF EVIDENCE VII
■ Beyond platelet transfusions, patients should avoid using drugs that adversely affect platelet function, such as aspirin, ibuprofen, or naproxen, unless medically necessary and directed by their healthcare provider to take them for thromboprophylaxis (Miceli et al., 2008).
■ When platelets are low, patients should avoid activities that may result in bleeding or bruising, such as contact sports and tattooing, and they should be instructed to use soft sponges and nonabrasive toothpaste for their oral care (Miceli et al., 2008).

Bone Disease

About 90% of people will, at some point in the disease continuum, have lytic lesions visible by radiographic imaging. At the time of diagnosis, about 80% of patients will have bone disease and 60% of patients will present with bone pain (Kyle et al., 2003; Terpos, Dimopoulos, & Moulopoulos, 2016). The most common bones affected are the vertebrae, long bones, and flat bones (Roodman, 2008). This high incidence of bone disease leads to an increased risk of two significant OEs in the MM population, hypercalcemia of malignancy (HOM) and spinal cord compression (SCC), both at time of diagnosis and at fulminant relapse.

Hypercalcemia of Malignancy

Calcium is an abundant mineral in the body and a common nutrient in dairy and some green leafy vegetables. Among its many functions, calcium is essential for bone development and maintenance, muscle contractility, and transmission of nerve impulses. Normal calcium levels range from 8.5–10.5 mg/dl, with hypercalcemia being defined as serum levels greater than 10.5 mg/dl. Hypercalcemia can result from hyperparathyroidism, but HOM is related to bone metastasis from a malignant process (Terpos et al., 2015).

HOM is not unique to MM, occurring in about 20% of patients with advanced solid tumors (Kaplan, 2012a; Pace, 2015). However, with the high incidence of bone disease in MM, HOM is a potential OE at time of diagnosis and relapse, and 15%–40% of patients with MM present with HOM (Kaplan, 2012a; Roodman, 2008). In MM, bone disease is closely connected to the bone marrow microenvironment, and an imbalance of osteoclast and osteoblast formation results in decreased bone formation, calcium resorption, and lytic lesions (Galson, Silbermann, & Roodman, 2012).

The greatest concentration of the body's calcium is held in the bone. The remaining 1% of calcium is found in the serum,

with a high concentration primarily bound to albumin (Kaplan, 2012a; Pace, 2015). This is particularly important in MM because many patients will have an abnormally low albumin level with active disease (Greipp et al., 2005). Therefore, when reviewing for hypercalcemia in a patient with MM, albumin must also be taken into consideration. A serum calcium level adjusted for hypoalbuminemia is higher than the reported level (Kaplan, 2012a). About 20% of newly diagnosed patients with MM will present with a calcium level less than 10.5 mg/dl (Faiman & Bilotti, 2014; Pace, 2015; Shane & Berenson, 2015; Thomas & Chung, 2016).

SIGNS AND SYMPTOMS

Treatment of HOM is directed by patient symptoms and serum calcium level. If treated, there is an 80% rate of reversal; if untreated, hypercalcemia can result in renal failure and death (Terpos et al., 2015). Hypercalcemia can be mild (less than 12 mg/dl), moderate (12–14 mg/dl), or severe (greater than 14 mg/dl). Lethargy, constipation, dysuria, polydipsia, confusion, muscle weakness, and cardiac dysrhythmias are symptoms that patients may exhibit as calcium levels rise. Not all patients are symptomatic, or their symptoms may be attributed to the underlying malignancy or treatment (Terpos et al., 2015) (see Figure 4).

Astute nursing assessment and rapid nursing interventions are important when reducing high calcium levels and reversing the signs and symptoms associated with HOM. The primary focus is to reduce serum calcium quickly and safely and then to identify and treat the underlying cause of HOM (see Figure 5). Administration of prescribed calcium-reducing medications in a timely manner is essential. Dialysis may be needed if HOM is associated with acute renal failure. Additional diagnostic testing and disease reassessment should be anticipated, as HOM likely indicates active or relapsed disease. While hospitalized, patients should be monitored closely for risk of falls and wandering related to lethargy and confusion. Fluid volume overload

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FIGURE 4.

CORRECTED CALCIUM LEVEL CALCULATION

Total calcium (mg/dl) + 0.8 x (4.0 – serum albumin [g/dl])

- Example: A person with a mildly elevated calcium level of 11 mg/dl and a normal albumin of 4.2 g/dl has a corrected ionized calcium level of 10.8 mg/dl.
- Example: A person with a mildly elevated calcium level of 11 mg/dl and a low serum albumin of 2.5 g/dl has a corrected ionized calcium level of 12.2 mg/dl.

Note. The formula will help determine the free or ionized calcium, will correct for low albumin, and give a more accurate assessment of the serum calcium level. The lower the albumin, the higher the corrected serum calcium.
Note. Based on information from Focus Information Technology, 2017; Kaplan, 2012a.

FIGURE 5.

THREE-PRONGED APPROACH TO MEDICATION MANAGEMENT OF SEVERE HYPERCALCEMIA OF MALIGNANCY

CALCITONIN
- 4 IU/kg subcutaneous every 12 hours; dose may be increased to 6–8 IU/kg.
- Rapid but short acting
- Concomittent corticosteroid use can prolong effect.

HYDRATION
- 200–300 cc per hour infusion
- Goal is euvolemia to abragate effects of nausea and renal dysfunction.
- Concomitant use of loop diuretic for renal and cardiac dysfunction

BISPHOSPHONATE THERAPY
- Zoledronic acid 4 mg or pamidronate 60–90 mg, via IV, every four weeks
- Denosumab 120 mg, subcutaneous, every four weeks. Not restricted by renal function.

Note. Based on information from Amgen Inc., 2016b; Faiman & Bilotti, 2014; National Comprehensive Cancer Network, 2017b; Pace, 2015; Thomas & Chung, 2016.

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is possible during times of active hydration; intake and output need to be closely monitored, particularly in patients with renal dysfunction and cardiac comorbidities. If patients have not previously received IV bisphosphonate therapy, they should be monitored for first-infusion reaction of fever, chills, and body aches (Miceli, Colson, Faiman, Miller, & Tariman, 2011). If adjunct steroids are administered to a patient with diabetes, glucose levels should be monitored frequently. HOM may be associated with generalized bone and/or fracture pain. Analgesia may be needed (Rome, Noonan, Bertolotti, & Miceli, 2017), but both HOM and opioid analgesics can cause constipation. Patient education should include the caregiver and should be reinforced with the patient when their calcium levels decrease to normal range (Faiman & Bilotti, 2014; Kaplan, 2012a; Pace, 2015; Shane & Berenson, 2015) (see Table 4).

Spinal Cord Compression

Patients with MM are at risk for SCC, another bone disease–related OE. In MM, SCC can be caused by a destructive lesion involving the vertebrae or by an extra-osseous plasmacytoma. In both circumstances, the spinal cord is compromised, resulting in back pain with progression to neurologic deficit if untreated (Ha, Kim, & Kim, 2013; Kaplan, 2012b; Roodman, 2008).

The spine is the part of the skeletal structure that provides stability and movement. It is made up of individual vertebrae identified in sections by their anatomical location—cervical (7), thoracic (12), lumbar (5), and the sacrum and coccyx. The vertebrae act as a skeletal protector of the spinal cord. The spinal cord is part of the central nervous system and has spinal nerve

branches. These branches become peripheral nerves and supply motor and sensory fibers to areas of muscle (myotomes) and skin (dermatomes) (Clemente, 1985; Kaplan, 2012b).

As previously discussed, MM bone disease is a frequent occurrence at time of diagnosis (60%–80%) and during the course of the disease (90%) (Kyle et al., 2003; Terpos, Christoulas, et al., 2016). About 50% of people with bone disease will have spinal involvement (Roodman, 2008). Spinal involvement occurs on a spectrum from focal lesions to osteolytic lesions to osteoporosis, any of which can lead to vertebral compression fracture (Hussein et al., 2008). An estimated 30% of patients with spinal MM bone disease will experience vertebral compression fracture, whereas the incidence of SCC is less than 5% (Dispenzieri & Kyle, 2005; Hussein et al., 2008; Roodman, 2008). However, MM accounts for 11% of all neoplastic incidence of SCC complications (Terpos et al., 2015). SCC is more commonly a result of an extradural destructive vertebral lesion, or bone plasmacytoma, and less commonly related to an extra-osseous (or soft tissue) plasmacytoma, which is seen more often later in the disease (Dispenzieri & Kyle, 2005; Ha et al., 2013).

SIGNS AND SYMPTOMS

Presenting symptoms of SCC include back pain and neurologic symptoms that depend on the level and extent of the cord compression (Ha et al., 2013; Kaplan, 2012b; Roodman, 2008). Pain onset may be acute and followed by progression of neurologic deficits to paralysis in hours. The thoracic region is the most common area of spinal cord involvement, with symptoms experienced distal to the area of involvement (Dispenzieri & Kyle, 2005). Therefore, neurologic symptoms may include weakness and paresthesia extending from the abdomen to the lower extremities; bowel, bladder, and sexual dysfunction; and paralysis (Kaplan, 2012b). Symptoms that may indicate a higher level of spinal involvement should not be ignored and may include upper body weakness and/or paresthesia, respiratory insufficiency, and the Lhermitte sign or Horner Syndrome (Kaplan, 2012b).

If a patient presents with symptoms concerning for SCC, a thorough neurologic evaluation should be performed. Interview the patient regarding personal history (cancer, previous vertebral compression fracture); symptoms, particularly pain and neurologic changes (onset, duration, intensity); and any interventions

TABLE 4.

HEALTHCARE PROVIDER TIP SHEET: ASSESSMENT, INTERVENTION, AND PATIENT EDUCATION FOR HYPERCALCEMIA OF MALIGNANCY

METHOD	ASSESSMENT	INTERVENTION	PATIENT EDUCATION
Patient and caregiver interview	■ Has there been a change in mental status, physical function, or bathroom patterns? ■ New onset of pain? ■ Current medications including supplements?	■ Interview the patient and the caregiver. If the patient is experiencing confusion, a caregiver may be able to provide more accurate answers. ■ Discontinue vitamin D and calcium supplements. Review for thiazide or lithium use.	■ Patient education should include the caregiver. Repeat patient education as the calcium level decreases and mental status improves.
Review of systems	■ General: increased fatigue, somnolence, lethargy ■ Gastrointestinal/genitourinary: nausea, vomiting, constipation; increased urine output to no urine output ■ Neurologic: restlessness, confusion, seizure activity ■ Pain: acute onset or new pain indicating fracture	■ Depending on degree of symptoms, patient may be at risk for falls, seizures, or aspiration. ■ Reassurance and reorientation. ■ Anti-emetics and stool softeners for gastrointestinal symptoms. Monitor for rectal bleeding and frequent assessment for acute abdominal pain indicating obstipation or ileus. ■ Pain medication for comfort	■ Explain symptoms related to increasing level of calcium; explain that acute pain may indicate new disease activity. ■ Weight-bearing activity is important to reduce bone resorption. ■ Provide rationale for instituting fall, seizure, or aspiration precautions.
Laboratory values	■ Ionized calcium greater than 12 mg/dl (correct for low albumin) ■ Elevated creatinine from baseline ■ Potassium ■ Sodium ■ Magnesium ■ Complete blood count ■ Echocardiogram changes ■ Multiple myeloma disease workup	■ Calcitonin with or without corticosteroids, hydration with or without loop diuretics, and bisphosphonates to reduce serum calcium ■ Thiazide diuretics should be avoided. ■ Hydrate to euvolemia to correct for dehydration and renal insufficiency ■ Monitor for treatment-related sequelae, including first infusion reaction to bisphosphonates, fluid overload, hyperglycemia, and electrolyte imbalance. ■ Hypercalcemia of malignancy is related to active disease; therefore, treat as indicated.	■ Explain rationale for close monitoring, medication use, and the urgency of the medical situation. ■ Educate regarding change in MM therapy as needed, including side effect monitoring and prevention.

Note. Based on information from Faiman & Bilotti, 2013; Kaplan, 2012a; Pace, 2015; Shane and Berenson, 2015.

TABLE 5.

HEALTHCARE PROVIDER TIP SHEET: ASSESSMENT, INTERVENTION, AND PATIENT EDUCATION FOR SPINAL CORD COMPRESSION

METHOD	ASSESSMENT	INTERVENTION	PATIENT EDUCATION
Patient and caregiver interview	■ Back pain: location, intensity, and duration ■ Sensory/motor changes ■ Weakness; paresthesia; changes in bowel, bladder, or sexual function ■ Review current medications and interventions already attempted.	■ Interview the patient and the caregiver. ■ Institute pain management and safety measures.	■ Patient education should include the caregiver.
Review of systems	■ General: acute onset of back pain ■ Gastrointestinal/genitourinary: bladder or bowel incontinence or retention, sexual dysfunction ■ Neurologic: paresthesia, muscle weakness, progressive sensory/motor changes	■ Pain medication for comfort ■ Monitor and maintain bladder and bowel output. ■ Depending on degree of symptoms, patient may be at risk for falls. ■ Physical therapy and mobility, if no additional risk for further cord compromise	■ Explain symptoms related to spinal cord compression; explain that acute pain may indicate new disease activity. ■ Provide rationale for instituting fall precautions and mobility restrictions, if needed.
Diagnostic workup	■ Magnetic resonance image of full spine ■ Multiple myeloma disease workup	■ Premedicate before magnetic resonance imaging for patients who are claustrophobic and for pain. ■ Spinal cord compression may be related to active disease; therefore, treat as indicated. ■ If radiation therapy, manage side effects related to field of radiation. ■ If surgery, postoperative care is needed.	■ Explain rationale for close monitoring and urgency of the medical situation. ■ Neurologic changes may improve with time. ■ Educate regarding change in multiple myeloma therapy as needed, including side effect monitoring and prevention.

Note. Based on information from Kaplan, 2012b.

already attempted (pain medication, physical therapy). Comorbid or preexisting conditions need to be considered when interviewing the patient. For example, urinary incontinence, paresthesia, and neuropathy may be preexisting and not related to current symptoms. Physical examinations should include spinal palpation and a full neurologic assessment (Kaplan, 2012b).

Diagnostic evaluation may start with plain radiographs because of their availability and cost; however, they are less reliable for evaluating SCC than other diagnostic imaging modalities. Imaging techniques have become more sensitive and, therefore, the preferred methods to assess MM bone disease have evolved. Without controversy, the preferred imaging for the spine is magnetic resonance imaging (MRI) (Dimopoulos et al., 2015; Terpos, Christoulas, et al., 2016). Spinal MRI should be performed to evaluate for SCC because it clearly defines the area of compression, which will aid in developing a plan for intervention (see Table 5).

SCC is an OE requiring immediate intervention to prevent progression of symptoms and nerve damage. Educate patients on signs and symptoms of SCC and the need to contact a healthcare provider if back pain occurs with acute onset. For a diagnosis of SCC, nursing assessment is needed for pain, safety, and sensory and motor function. Interventions are focused on safety and pain management, and based on a plan of care. If radiation is prescribed, manage side effects based on the field of radiation.

Evidence-Based Recommendations for the Management of Bone-Related Oncologic Emergencies
LEVEL OF EVIDENCE I

■ Treating HOM concurrently with treatment of its underlying cause, such as active myeloma, is recommended (Faiman & Bilotti, 2014; Kaplan, 2012a; NCCN, 2017b; Pace, 2015; Shane & Berenson, 2015; Thomas & Chung, 2016).

■ Local external-beam radiation should be used at a palliative dose of 10–30 Gy as part of frontline treatment for SCC, particularly when neurologic symptoms are present. A therapeutic dose of 40–50 Gy may be used, and is potentially curative, if the cause of SCC is a solitary plasmacytoma, which is rare (Dispenzieri & Kyle, 2005; Hussein et al., 2008; NCCN, 2016; Terpos, Morgan, et al., 2013).

LEVEL OF EVIDENCE II

■ For symptomatic and severe hypercalcemia, immediate intervention is recommended, which likely involves hospitalization. Calcitonin and saline hydration can reduce serum calcium levels within 48 hours. Adjunct use of bisphosphonate therapy (IV zoledronic acid or pamidronate) as part of frontline therapy becomes effective in days, providing later calcium control. Mild to moderate hypercalcemia that is asymptomatic is not an OE, but does require intervention. Patients should be instructed on how to administer oral hydration and be educated

about weight-bearing activity. In addition, patient medications that may contribute to higher levels of blood calcium should be identified, including lithium, vitamin D, and calcium supplements, (Kaplan, 2012a; Faiman & Bilotti, 2014; Pace, 2015; Shane & Berenson, 2015; Thomas & Chung, 2016).

■ Denosumab, a monoclonal antibody against eceptor activator of nuclear factor kappa-B ligand, can be used for patients not responding to bisphosphonate treatment and is not restricted by renal function (Shane & Berenson, 2015; Thomas & Chung, 2016)

■ Calcitonin has a rapid but short-term effect with onset of action within four to six hours. Corticosteroids such as hydrocortisone or prednisone can be added to prolong the effectiveness of calcitonin, but neither corticosteroids nor calcitonin should not be used as single agents (Sternlicht & Glezerman, 2015).

■ The goal of hydration is currently to achieve euvolemia by replacing volume loss from nausea and renal dysfunction that can contribute to hypercalcemia. Aggressive hydration with concomitant use of loop diuretics (i.e., furosemide) is less favored because of the availability of bisphosphonate agents (Shane & Berenson, 2015) and the desire to avoid complications that can arise from electrolyte imbalance and comorbid conditions.

■ Regardless of the cause, SCC should be considered an OE that requires immediate intervention to prevent irreversible nerve

damage. First-line therapy includes a high-dose steroid infusion, and although no consensus exists on dose and type, use of dexamethasone, as much as 100 mg IV bolus, followed by a tapering oral dose for days to weeks, is reported in the literature (Dispenzieri & Kyle, 2005; Kaplan, 2012b).

■ MM tends to be very radiosensitive, and external beam radiation results in improvement in motor function in 75% of patients. Surgical intervention is less common but may be warranted, particularly if vertebral bone fragments compromise the spinal cord, or plasmacytoma is resistant to radiation. An orthopedic specialist should be consulted (Terpos, Morgan, et al., 2013). The use of spinal augmentation with vertebroplasty or kyphoplasty is contraindicated in spinal cord compression (Hussein et al., 2008).

Acute Renal Failure

The kidneys are vital organs, responsible for flushing out toxins and ridding the body of waste products. When the kidneys are unable to function properly because of acute or chronic insults, patients may be forced to begin dialysis, an artificial method of waste product removal. In addition, if acute renal failure and acute kidney injury occur, the individual may be unable to receive future anti-myeloma therapies. Severe and permanent renal failure can follow acute renal failure, making treatment decisions more difficult and affecting overall survival for patients with MM. Chronic or acute insults to the kidney can place patients at risk for end-stage renal disease, which requires acute or chronic dialysis. However, prompt diagnosis and reversal of renal toxicity can lead to renal recovery, and the poor prognostic significance of acute kidney injury for future MM treatment options can lessen over time (Doshi, Lahoti, Danesh, Batuman, & Sanders, 2016; Hsu & Hsu, 2016).

Therefore, it is well within the scope of nurses to participate in the routine assessment and monitoring of kidney function in patients with MM. With education focused on primary prevention and prompt identification of acute kidney injury and appropriate nursing management, renal function can be recovered. In contrast, a lack of attention to these measures can lead to grave outcomes for patients (Hsu & Hsu, 2016).

Definition and Etiology of Acute Renal Failure

As a potential OE, acute renal failure is defined as an acute elevation in serum creatinine levels, which is accompanied by a decrease in glomerular filtration rate (GFR) levels within a short time period (Dimopoulos, Sonneveld, et al., 2016). Many criteria exist with regards to acute renal failure severity; however, any rapid decline in renal function can be considered an OE, particularly among patients with active MM (Terpos et al., 2015). Identifying the underlying cause of renal injury and employing prompt and appropriate interventions to address the renal failure are crucial steps towards reversing the injury and preventing further damage.

FIGURE 6.

HEALTH CONDITIONS, DRUGS, AND RISK FACTORS FOR ACUTE KIDNEY FAILURE

HEALTH CONDITIONS
■ Diabetes
■ Hypertension
■ Advanced age
■ Rhabdomyolysis (muscle breakdown of creatinine, leading to increased blood creatinine)
■ Dehydration (from decreased fluid intake, fluid losses, or loop diuretics)
■ Hypercalcemia
■ Progressive multiple myeloma disease or cast nephropathy (particularly light chains)
■ Amyloid light chain amyloidosis or light chain deposition disease

DRUGS
■ Nonsteroidal anti-inflammatory agents, including cyclooxygenase-2 inhibitors
■ Aminoglycoside antibiotics
■ Radio-contrast dyes or IV contrast agents
■ Loop diuretics, other medications (such as ACE inhibitors)

OTHER FACTORS
■ Increased intake of creatinine (high protein meal)
■ Sepsis, infection

Note. Based on information from Faiman et al., 2011; Thomas et al., 2015.

The etiology of acute renal failure in MM includes active infections, dehydration, the use of nephrotoxic medications, as well as comorbidities such as uncontrolled diabetes and hypertension. In MM, acute tubular necrosis is a common cause of acute renal failure that may be caused by dehydration in the presence of urinary light chains, which overwhelm the distal tubules. Diuretic medications, such as furosemide, can lead to urinary cast formation, increased serum creatinine levels, and possibly acute kidney injury. Hypercalcemia, a common symptom of MM when the disease is active, can lead to vasoconstriction (Terpos, Christoulas, et al., 2013). Nonsteroidal anti-inflammatory drugs (NSAIDs) and aminoglycoside antibiotic use can also decrease blood flow to and from the kidneys (Faiman et al., 2011). Given these risk factors for renal failure, active myeloma remains a common cause of renal failure. The pathogenesis of acute renal failure and cast nephropathy, which is the most common type of renal injury in MM, is reviewed in Faiman et al. (2017).

When disease-related acute renal failure occurs, it is important to promote hyper-hydration, with close attention to the patient's risk of fluid volume overload (Faiman et al., 2011). Rapid control of the disease is necessary to give the kidney the best chance at returning to the baseline function and preventing additional impairment. As such, prompt treatment of active MM disease with corticosteroids, bortezomib, and other effective treatment strategies can assist with renal recovery (Dimopolous, Sonneveld, et al., 2016).

SIGNS AND SYMPTOMS

Patients should be counseled to avoid nephrotoxic agents, such as over-the-counter pain medications like NSAIDs, which can decrease renal blood flow and, in the presence of immunoglobulin light chains, obstruct the tubules of the kidneys, causing a decrease in creatinine clearance and severe renal failure (Faiman et al., 2011).

Adequate oral hydration is also very important for patients. Dehydration can happen quickly and result in acute kidney injury, which can lead to permanent kidney failure if uncorrected. Assessing the patient's oral intake at each appointment is necessary in helping to prevent dehydration from occurring. Encouraging patients to drink plenty of hydrating fluids and to avoid excessive amounts of caffeinated beverages are key tools in protecting the kidney from dehydration and/or injury. Treatment of the underlying cause of renal failure with effective anti-myeloma therapies may be needed. Common drugs to treat MM and their considerations in regards to dose reduction is located in Fairman et al. (2017) in this supplement.

Evidence-Based Recommendations for the Prevention and Management of Acute Kidney Injury
LEVEL OF EVIDENCE I
- Identify and correct the causes of acute kidney injury, including dehydration, hypovolemia, hypotension, loop diuretics, angio-

tensin-converting enzyme inhibitors, angiotensin II receptor inhibitors, NSAIDs, aminoglycoside antibiotics, hypercalcemia, infection, sepsis, or iodinated contrast dye. This must be a top priority action for the nurse clinician to prevent long-term and permanent renal complications. In many cases, adequate IV or oral hydration (with caution to avoid overhydration) can help to reverse acute kidney injury or acute renal failure related to dehydration, hypovolemia, hypotension, and an acute tubular necrosis-type of kidney injury (Gavriatopoulou, Terpos, Kastritis, & Dimopoulos, 2016; Moos, van Vemde, Stoker, & Bipat, 2013).
- Clinicians should assess patients for reversible and nonmodifiable acute kidney injury risk factors before any use of oral or IV iodinated contrast dye for radiologic studies. The nonmodifiable factors that can increase the risk of acute kidney injury following iodinated contrast dye include chronic kidney disease (CKD), diabetes, heart failure, low body mass index, and aging (Faiman et al., 2011) (see Figure 6).
- A serum creatinine measurement should be obtained through a basic chemistry panel prior to any radiologic procedure that would require an oral or IV iodinated contrast dye. Once a creatinine level is available, an estimated GFR can be calculated by using the Chronic Kidney Disease–Epidemiology (CKD-EPI) equation (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDKD], 2016), which accounts for the patient's age, creatinine level, gender, and race (Terpos, Christoulas, et al., 2013).
- Contrast-induced nephropathy risk assessment and prophylactic strategies should be based on GFR estimated from the CKD-EPI equation rather than solely relying on the absolute creatinine value. The European Renal Best Practice Ad-Hoc Working Group (Fliser et al., 2012) on contrast-induced nephropathy and a study by Terpos, Christoulas, et al. (2013) demonstrated better detection of stage III–V CKD (stage III with estimated GFR 30–60 ml/minute/173 m^2) using the CKD-EPI equation than using the creatinine value alone in newly diagnosed myeloma.

LEVEL OF EVIDENCE II
- High-cutoff dialyzers for plasmapheresis are recommended in conjunction with anti-myeloma therapies. Plasmapheresis can effectively, albeit temporarily, remove damaging paraproteins and has been shown to improve or reverse acute renal failure based on data from a few small studies (Burnette, Leung, & Rajkumar, 2011; Clark, 2007). Temporary or permanent hemodialysis is indicated if the patient's GFR is critically low and if symptomatic uremia becomes an issue. The use of high-cutoff dialyzers may

effectively remove serum free light chains and can lead to improved renal function (Finkel, Cohen, Shirali, & Abudayyeh, 2016; Hutchison et al., 2007, 2009) or independence from hemodialysis among patients receiving a bortezomib-based regimen (Bridoux et al., 2016).

Evidence-Based Recommendations for Treatment of Renal Injury
LEVEL OF EVIDENCE I

- Prompt initiation of effective MM therapy is recommended. This is critical for long-term kidney health.
- In line with the International Myeloma Working Group (IMWG) recommendations for treating patients with renal injury with bortezomib-based regimens (Dimopoulos, Sonneveld, et al., 2016), the IMF NLB recommends bortezomib as the cornerstone in the management of patients with renal injury.

LEVELS OF EVIDENCE I–III

- Prompt treatment using classes of drugs approved by the U.S. Food and Drug Administration (FDA) is recommended to treat patients with relapsed or refractory myeloma and renal injury. The FDA-approved drugs that can be used for patients with simultaneous renal injury and active MM include immunomodulatory agents such as thalidomide (level I [Picot, Cooper, Bryant, & Clegg, 2011]); lenalidomide and pomalidomide (level III [Celgene, 2016, 2017a]); proteasome inhibitors such as bortezomib (level I [Picot et al., 2011]), carfilzomib (level III [Amgen Inc., 2016a]), and ixazomib (level III [Takeda Oncology, 2016]); and monoclonal antibodies such as elotuzumab (level III [Bristol-Myers Squibb, 2015]), and daratumumab (level III [Janssen Biotech, 2017]).

Evidence-Based Recommendations for Bone Health in Patients With Kidney Disease
LEVEL OF EVIDENCE I

- Bisphosphonate therapy is recommended to prevent skeletal-related events, but not in patients with GFR of less than 30 ml per minute (Terpos, Roodman, & Dimopoulos, 2013).
- Bisphosphonates, such as zoledronic acid and pamidronate, are potent inhibitors of bone resorption that promote bone formation. However, bisphosphonate use in patients with renal injury or CKD may be toxic to the kidneys (Berenson, 1997). In patients with grade 1 or 2 CKD, the serum creatinine level should be monitored and the GFR should be estimated using the CKD-EPI calculator prior to each dose, as well as periodic monitoring with 24-hour urine to assess for albuminuria (NIDDKD, 2016).
- For patients who are taking bisphosphonates, it is recommended that they also take calcium 1,000 mg per day and vitamin D 400 IU per day. However, calcium supplementation remains contraindicated in patients with hypercalcemia (Faiman et al., 2011; Miceli et al., 2011).

LEVEL OF EVIDENCE III

- The use of ESAs is recommended. Anemia, defined in patients with MM as a hemoglobin value 2 g/dl below the institutional limits of normal, often is present in patients with moderate-to-severe renal dysfunction. The use of ESAs in renal disease is common practice related to decreased renal production of erythropoietin. The use of ESAs to manage chemotherapy-induced anemia remains controversial because of concerns related to shortened survival seen in other cancers. An increased risk of stroke and thromboembolic events can be observed in patients with MM on ESA for prophylactic use (Anaissie et al., 2012. Interventions that minimize this risk should be initiated prior to use of ESA, such as employing general venous thromboembolic event precautions (ambulation, antiplatelet, and anticoagulation treatment when appropriate). According to the NCCN (2016d), CKD is not a contraindication for receiving ESAs. Obtaining baseline serum iron, ferritin, and serum total iron binding capacity are recommended prior to initiating oral iron therapy (NCCN, 2017c).

Evidence-Based Recommendations for Monitoring Multiple Myeloma and Renal Function
LEVEL OF EVIDENCE V

- Close monitoring of a patient's MM disease burden and renal injury is recommended by ensuring that the patient obtain routine blood chemistry, CBC, and myeloma-specific biomarker tests as part of every clinic visit (Faiman et al., 2017; Faiman, Mangan, Spong, & Tariman, 2011; Kurtin et al., 2016).
- Laboratory monitoring should be performed monthly or based on institutional routine clinic follow-up for stable disease (Kurtin et al., 2016). Myeloma-specific biomarkers should include serum and urine protein electrophoresis, quantitative immunoglobulins, 24-hour urine for protein electrophoresis, and serum free light chain assay (Kurtin, Bertolotti, Brigle, & Verina, 2016). The frequency of laboratory testing may change depending on the degree of renal failure and the patient's response to therapy (Dimopoulos, Sonneveld, et al., 2016; Kurtin et al., 2016).

Evidence-Based Recommendations: Patient Education About Multiple Myeloma Oncology Emergencies
LEVEL OF EVIDENCE V

- Patients and their caregivers should be taught about the additional burden of comorbid conditions on renal function. The National Kidney Foundation identifies risk factors for CRD, including diabetes, cardiovascular disease, hypertension, age (older than 60 years), U.S. racial or ethnic minority status, and family history of CKD (Levey et al., 2013).
- Comorbid conditions should be monitored closely and managed effectively in partnership with patients, caregivers, and nephrologists to avoid any additional injury to the kidney.

Patients with MM are at increased risk for renal failure, not only from MM but also from aging itself (Palumbo et al., 2014). Diabetes and hypertension are the leading causes of end-stage renal disease, and diabetes mellitus is the number one cause of kidney failure. Almost half of all new patients on dialysis have diabetes, making it the fastest growing risk factor for kidney disease. Uncontrolled hypertension is both a cause and complication of CKD and should be carefully treated and controlled in all patients (Song, Cong, & Wilson, 2016).

LEVEL OF EVIDENCE VI

- Oncology clinicians should address weight control, exercise, smoking cessation, and medications for adequate blood pressure or blood sugar control. Adequate health maintenance and preventive screenings for hypertension, diabetes, obesity, and smoking-related health conditions may prevent or slow the progression to kidney failure (Faiman et al., 2011; Tariman et al., 2016).

Conclusion

Patients with MM are living longer through advances in treatment and supportive measures. Nurses play pivotal roles in the education about, assessment of, and early intervention for OEs that can lead to mortality and morbidity in the myeloma survivor. Implementing evidence-based recommendations can reduce morbidity and mortality and increase patient QOL.

Hematologic toxicity is an expected but manageable side effect of the novel therapies that are used to treat MM. A combination of patient and caregiver education, careful monitoring of the patient's CBC, and a comprehensive patient review of systems are all necessary to aid in the prevention of serious side effects. Early intervention is often the key to promoting patient adherence to therapeutic regimens and enhancing patient outcomes.

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REFERENCES

Amgen Inc. (2016a). *Kyprolis® (carfilzomib)* [Package insert]. Retrieved from http://pi.amgen .com/~/media/amgen/repositorysites/pi-amgen-com/kyprolis/kyprolis_pi.ashx

Amgen Inc. (2016b). *Xgeva® (denosumab)* [Package insert]. Retrieved from http://pi.amgen .com/united_states/xgeva/xgeva_pi.pdf

Anaissie, E.J., Coleman, E.A., Goodwin, J.A., Kennedy, R.L., Lockhart, K.D., Stewart, C.B., . . . Barlogie, B. (2012). Prophylactic recombinant erythropoietin therapy and thalidomide are predictors of venous thromboembolism in patients with multiple myeloma: Limited effectiveness of thromboprophylaxis. *Cancer, 118*, 549–557. https://doi.org/10.1002/cncr.26302

Aster, R.H., & Bougie, D.W. (2007). Drug-induced immune thrombocytopenia. *New England Journal of Medicine, 357*, 580–587. https://doi.org/10.1056/NEJMra066469

Avvisati, G., Tirindelli, M.C., & Annibali, O. (2003). Thrombocytopenia and hemorrhagic risk in cancer patients. *Critical Reviews in Oncology/Hematology, 48*(Suppl.), S13–S16.

Berenson, J.R., Rosen, L., Vescio, R., Lau, H.S., Woo, M., Sioufi, A., . . . Seaman, J.J. (1997). Pharmacokinetics of pamidronate disodium in patients with cancer with normal or impaired renal function. *Journal of Clinical Pharmacology, 37,* 285–290.

Birgegård, G., Gascón, P., & Ludwig, H. (2006). Evaluation of anaemia in patients with multiple myeloma and lymphoma: Findings of the European Cancer Anaemia Survey. *European Journal of Haematology, 77*, 378–386. https://doi.org/10.1111/j.1600-0609.2006.00739.x

Blimark, C., Holmberg, E., Mellqvist, U.H., Landgren, O., Björkholm, M., Hultcrantz, M., . . . Kristinsson, S.Y. (2015). Multiple myeloma and infections: A population-based study on 9253 multiple myeloma patients. *Haematologica, 100*, 107–113. https://doi.org/10.3324/ haematol.2014.107714

Bodey, G.P., Buckley, M., Sathe, Y.S., & Freireich, E.J. (1966). Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Annals of Internal Medicine, 64*, 328–340. https://doi.org/10.7326/0003-4819-64-2-328

Bridoux, F., Pegourie, B., Augeul-Meunier, K., Royer, B., Joly, B., Lamy, T., . . . Fermand, J-P. (2016). Treatment of myeloma cast nephropathy (MCN): A randomized trial comparing intensive haemodialysis (HD) with high cut-off (HCO) or standard high-flux dialyzer in patients receiving a bortezomib-based regimen. *Blood, 128,* 978.

Bristol-Myers Squibb. (2015). *Empliciti® (elotuzumab)* [Package insert]. Retrieved from http:// packageinserts.bms.com/pi/pi_empliciti.pdf

Burnette, B.L., Leung, N., & Rajkumar, S.V. (2011). Renal improvement in myeloma with bortezomib plus plasma exchange. *New England Journal of Medicine, 364*, 2365–2366. https://doi .org/10.1056/NEJMc1101834

Celgene. (2016). *Pomalyst®* (pomalidomide) [Package insert]. Retrieved from http://www .celgene.com/content/uploads/pomalyst-pi.pdf

Celgene. (2017a). *Revlimid® (lenalidomide)* [package insert]. Retrieved from http://www .celgene.com/content/uploads/revlimid-pi.pdf

Celgene. (2017b). *Thalomid® (thalidomide)* [Package insert]. Retrieved from http://www .celgene.com/content/uploads/thalomid-pi.pdf

Centers for Disease Control and Prevention. (2017). *Cancer, infection, and sepsis fact sheet.* Retrieved from https://www.cdc.gov/sepsis/pdfs/cancer-infection-and-sepsis-fact-sheet .pdf

Clark, W.F. (2007). Correction: Plasma exchange when myeloma presents as acute renal failure. *Annals of Internal Medicine, 146*, 471. https://doi.org/10.7326/0003-4819-146-6-2007 03200-00024

Clemente, C.D. (1985). The back, vertebral column, and spinal cord. In, *Anatomy: A regional atlas of the human body* (3rd ed., pp. 517–573). Baltimore, MD: Urban and Schwarzenberg.

Dammacco, F., Silvestris, F., Castoldi, G.L., Grassi, B., Bernasconi, C., Nadali, G., . . . Resegotti, L. (1998). The effectiveness and tolerability of epoetin alfa in patients with multiple myeloma refractory to chemotherapy. *International Journal of Clinical and Laboratory Research, 28*, 127–134.

Damron, B.H., Brant, J.M., Belansky, H.B., Friend, P.J., Samsonow, S., & Schaal, A. (2009). Putting Evidence Into Practice: Prevention and management of bleeding in patients with cancer. *Clinical Journal of Oncology Nursing, 13,* 573–583. https://doi.org/10.1188/09.CJON .573-583

Dimopoulos, M.A., Cheung, M.C., Roussel, M., Liu, T., Gamberi, B., Kolb, B., . . . Facon, T. (2016). Impact of renal impairment on outcomes with lenalidomide and dexamethasone treatment in the FIRST trial, a randomized, open-label phase 3 trial in transplant-ineligible patients with multiple myeloma. *Haematologica, 101*, 363–370. https://doi.org/10.3324/haematol .2015.133629

Dimopoulos, M.A., Hillengass, J., Usmani, S., Zamagni, E., Lentzsch, S., Davies, F.E., . . . Terpos, E. (2015). Role of magnetic resonance imaging in the management of patients with multiple myeloma: A consensus statement. *Journal of Clinical Oncology, 33*, 657–664. https://doi .org/10.1200/JCO.2014.57.9961

Dimopoulos, M.A., Palumbo, A., Corradini, P., Cavo, M., Delforge, M., Di Raimondo, F., . . . Moreau, P. (2016). Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): A phase 3b study in refractory multiple myeloma. *Blood, 128*, 497–503. https://doi.org/10.1182/blood-2016-02-700872

Dimopoulos, M.A., Sonneveld, P., Leung, N., Merlini, G., Ludwig, H., Kastritis, E., . . . Terpos, E. (2016). International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. *Journal of Clinical Oncology, 34*, 1544–1557. https://doi.org/10.1200/jco.2015.65.0044

Dimopoulos, M.A., Swern, A.S., Li, J.S., Hussein, M., Weiss, L., Nagarwala, Y., & Baz, R. (2014). Efficacy and safety of long-term treatment with lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma. *Blood Cancer Journal, 4*, e257. https:// doi.org/10.1038/bcj.2014.77

Dispenzieri, A., & Kyle, R.A. (2005). Neurological aspects of multiple myeloma and related disorders. *Best Practice and Research Clinical Haematology, 18*, 673–688. https://doi.org/ 10.1016/j.beha.2005.01.024

Doshi, M., Lahoti, A., Danesh, F.R., Batuman, V., & Sanders, P.W. (2016). Paraprotein-related kid- ney disease: Kidney injury from paraproteins—What determines the site of injury? *Clinical Journal of the American Society of Nephrology, 11*, 2288–2294. https://doi.org/10.2215/ cjn.02560316

Faiman, B., & Bilotti, E. (2014). Multiple myeloma. In M. Olsen & L.J. Zitella (Eds.), *Hematologic malignancies in adults* (pp. 445–498). Pittsburgh, PA: Oncology Nursing Society.

Faiman, B., Doss, D., Colson, K., Mangan, P., King, T., Tariman, J., & IMF NLB. (2017). Renal, GI, and pe- ripheral nerves: Evidence-based recommendations for the management of symptoms and care for patients with multiple myeloma. *Clinical Journal of Oncology Nursing, 21*(Suppl., 5), 19–36.

Faiman, B.M., Mangan, P., Spong, J., & Tariman, J.D. (2011). Renal complications in multiple myeloma and related disorders: Survivorship care plan of the International Myeloma Foun- dation Nurse Leadership Board. *Clinical Journal of Oncology Nursing, 15*(Suppl.), S66–S76. https://doi.org/10.1188/11.CJON.S1.66-76

Finkel, K.W., Cohen, E.P., Shirali, A., & Abudayyeh, A. (2016). Paraprotein-related kidney disease: Evaluation and treatment of myeloma cast nephropathy. Clinical Journal of the American Society of Nephrology, 11, 2273–2279. https://doi.org/10.2215/cjn.01640216

Fliser, D., Laville, M., Covic, A., Fouque, D., Vanholder, R., Juillard, L., & Van Biesen, W. (2012). A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: Part 1: Defini- tions, conservative management and contrast-induced nephropathy. *Nephrology, Dialysis, Transplantation, 27*, 4263–4272. https://doi.org/10.1093/ndt/gfs375

Flowers, C.R., & Karten, C. (2013). Communicating safe outpatient management of fever and neutropenia. *Journal of Oncology Practice, 9*(4), 207–210. https://doi.org/10.1200/ JOP.2012.000815

Flowers, C.R., Seidenfeld, J., Bow, E.J., Karten, C., Gleason, C., Hawley, D.K., . . . Ramsey, S.D. (2013). Antimicrobial prophylaxis and outpatient management of fever and neutro- penia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *Journal of Clinical Oncology, 31*, 794–810. https://doi.org/10.1200/ JCO.2012.45.8661

Focus Information Technology. (2017). Corrected calcium calculator. Retrieved from http:// www.perinatology.com/calculators/Corrected%20Calcium.htm

Freifeld, A.G., Bow, E.J., Sepkowitz, K.A., Boeckh, M.J., Ito, J.I., Mullen, C.A., . . . Wingard, J.R. (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*, 427–431. https://doi.org/10.1093/cid/ciq147

Galson, D.L., Silbermann, R., & Roodman, G.D. (2012). Mechanisms of multiple myeloma bone disease. *BoneKEy Reports, 1*, 135. https://doi.org/10.1038/bonekey.2012.135

Gavriatopoulou, M., Terpos, E., Kastritis, E., & Dimopoulos, M.A. (2016). Current treatments for renal failure due to multiple myeloma. *Expert Opinion on Pharmacotherapy, 17*, 2165–2177.

Greipp, P.R., San Miguel, J., Durie, B.G., Crowley, J.J., Barlogie, B., Bladé, J., . . . Westin, J. (2005). International staging system for multiple myeloma. *Journal of Clinical Oncology, 23*, 3412–3420. https://doi.org/10.1200/JCO.2005.04.242

Ha, K.Y., Kim, Y.H., & Kim, H.W. (2013). Multiple myeloma and epidural spinal cord compression: Case presentation and a spine surgeon's perspective. *Journal of Korean Neurosurgical Society, 54*, 151–154. https://doi.org/10.3340/jkns.2013.54.2.151

Hsu, R.K., & Hsu, C.Y. (2016). The role of acute kidney injury in chronic kidney disease. *Seminars in Nephrology, 36*, 283–292. https://doi.org/10.1016/j.semnephrol.2016.05.005

Hughes, W.T., Armstrong, D., Bodey, G.P., Bow, E.J., Brown, A.E., Calandra, T., . . . Young, L.S. (2002). 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clinical Infectious Diseases, 34*, 730–751. https://doi.org/10.1086/339215

Hussein, M.A., Vrionis, F.D., Allison, R., Berenson, J., Berven, S., Erdem, E., . . . Durie, B.G. (2008). The role of vertebral augmentation in multiple myeloma: International Myeloma Working Group consensus statement. *Leukemia, 22*, 1479–1484. https://doi.org/10.1038/ leu.2008.127

Hutchison, C.A., Bradwell, A.R., Cook, M., Basnayake, K., Basu, S., Harding, S., . . . Cockwell, P. (2009). Treatment of acute renal failure secondary to multiple myeloma with chemother- apy and extended high cut-off hemodialysis. *Clinical Journal of the American Society of Nephrology, 4*, 745–754. https://doi.org/10.2215/cjn.04590908

Hutchison, C.A., Cockwell, P., Reid, S., Chandler, K., Mead, G.P., Harrison, J., . . . Bradwell, A.R. (2007). Efficient removal of immunoglobulin free light chains by hemodialysis for multiple

myeloma: In vitro and in vivo studies. *Journal of the American Society of Nephrology, 18*, 886–895. https://doi.org/10.1681/asn.2006080821

Janssen Biotech. (2017). *Darzalex® (daratumumab)* [Package insert]. Retrieved from https://www.darzalexhcp.com/shared/product/darzalex/darzalex-prescribing-information.pdf

Kaplan, M. (2012a). Hypercalcemia of malignancy. In M. Kaplan (Ed.), *Understanding and managing oncologic emergencies: A resource for nurses* (2nd ed., pp 103–156). Pittsburgh, PA: Oncology Nursing Society.

Kaplan, M. (2012b). Spinal cord compression. In M. Kaplan (Ed.), *Understanding and managing oncologic emergencies: A resource for nurses* (2nd ed., pp 337–384). Pittsburgh, PA: Oncology Nursing Society.

King, T., & Faiman, B. (2017). Steroid-associated side effects: A symptom management update on multiple myeloma. *Clinical Journal of Oncology Nursing, 21*, 240–249. https://doi.org/10.1188/17.CJON.240-249

Kyle, R.A. (1975). Multiple myeloma: Review of 869 cases. *Mayo Clinic Proceedings, 50*, 29–40.

Kyle, R.A., Gertz, M.A., Witzig, T.E., Lust, J.A., Lacy, M.Q., Dispenzieri, A., . . . Greipp, P.R. (2003). Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clinic Proceedings, 78*, 21–33. https://doi.org/10.4065/78.1.21

Kurtin, S., Bertolotti, P., Brigle, K., & Verina, D. (2016). Updates in the diagnosis and monitoring of multiple myeloma. *Journal of the Advanced Practitioner in Oncology, 7*, 59–70. https://doi.org/10.6004/jadpro.2016.7.2.15

Laubach, J., Garderet, L., Mahindra, A., Gahrton, G., Caers, J., Sezer, O., . . . Richardson, P.G. (2016). Management of relapsed multiple myeloma: Recommendations of the International Myeloma Working Group. *Leukemia, 30*, 1005–1017. https://doi.org/10.1038/leu.2015.356

Levey, A.S., Coresh, J., Balk, E., Kausz, A.T., Levin, A., Steffes, M.W., . . . Eknoyan, G. (2013). National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. A*nnals of Internal Medicine, 139*, 137–147.

Lewis, M.A., Hendrickson, A.W., & Moynihan, T.J. (2011). Oncologic emergencies: Pathophysiology, presentation, diagnosis, and treatment. *CA: A Cancer Journal for Clinicians, 61*, 287–314. https://doi.org/10.3322/caac.20124

Maes, K., Nemeth, E., Roodman, G.D., Huston, A., Esteve, F., Freytes, C., . . . Ganz, T. (2010). In anemia of multiple myeloma, hepcidin is induced by increased bone morphogenetic protein 2. *Blood, 116*, 3635–3644. https://doi.org/10.1182/blood-2010-03-274571

Miceli, T., Colson, K., Gavino, M., & Lilleby, K. (2008). Myelosuppression associated with novel therapies in patients with multiple myeloma: Consensus statement of the IMF Nurse Leadership Board. *Clinical Journal of Oncology Nursing, 12*(Suppl. 3), S13–S20. https://doi.org/10.1188/08.CJON.S1.13-19

Miceli, T.S., Colson, K., Faiman, B.M., Miller, K., & Tariman J.D. (2011). Maintaining bone health in patients with multiple myeloma: Survivorship care plan of the International Myeloma Foundation Nurse Leadership Board. *Clinical Journal of Oncology Nursing, 15*(Suppl.), S9–S23. https://doi.org/10.1188/11.S1.CJON.9-23

Millennium Pharmaceuticals. (2017). *Velcade®* (bortezomib) [Package insert]. Retrieved from http://www.velcade.com/files/PDFs/VELCADE_PRESCRIBING_INFORMATION.pdf

Miller. (2010). Anemia. In C. Brown (Ed.), *Guide to oncology symptom management* (pp. 29–47). Pittsburgh, PA: Oncology Nursing Society.

Moos, S.I., van Vemde, D.N., Stoker, J., & Bipat, S. (2013). Contrast induced nephropathy in patients undergoing intravenous (IV) contrast enhanced computed tomography (CECT) and the relationship with risk factors: A meta-analysis. *European Journal of Radiology, 82*(9), e387–e399. https://doi.org/10.1016/j.ejrad.2013.04.029

National Cancer Institute. (2010). *Common terminology criteria for adverse events* [v.4.03]. Retrieved from https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

National Cancer Institute. (2017). NCI dictionary of cancer terms: Myelosuppression. Retrieved from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=44173

National Comprehensive Cancer Network. (2016). *NCCN Guidelines for Patients®: Multiple myeloma* [v.1.2016]. Retrieved from https://www.nccn.org/patients/guidelines/content/PDF/myeloma.pdf

National Comprehensive Cancer Network. (2017a). *NCCN Clinical Practice Guidelines in Oncology: Cancer- and chemotherapy-induced anemia* [v.1.2017]. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/anemia.pdf

National Comprehensive Cancer Network. (2017b). *NCCN Clinical Practice Guidelines in Oncology: Multiple myeloma* [v.3.2017]. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf

National Comprehensive Cancer Network. (2017c). *NCCN Clinical Practice Guidelines in Oncology: Prevention and treatment of cancer-related infections* [v.2.2017]. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf

National Institute of Diabetes and Digestive and Kidney Diseases. (2016). CKD-EPI adults (conventional units). Retrieved from https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/adults-conventional-unit-ckd-epi/Pages/default.aspx

National Institute of Diabetes and Digestive and Kidney Diseases. (2017). Anemia in chronic kidney disease. Retrieved from https://www.niddk.nih.gov/health-information/kidney-disease/chronic-kidney-disease-ckd/anemia

Niesvizky, R., & Badros, A.Z. (2010). Complications of multiple myeloma therapy, part 2: Risk reduction and management of venous thromboembolism, osteonecrosis of the jaw, renal complications, and anemia. *Journal of the National Comprehensive Cancer Network, 8*(Suppl. 1), S13–S20.

Noonan, K., Rome, S., Faiman, B., Verina, D., & the IMF NLB. (2017). Heart and lung complications: Assessment and prevention of venous thromboembolism and cardiovascular disease in patients with multiple myeloma. *Clinical Journal of Oncology Nursing, 21*(Suppl. 5), 37–46.

Novartis. (2016). *Farydak® (panobinostat)* [Package insert]. Retrieved from https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/farydak.pdf

O'Grady, N.P., Alexander, M., Burns, L.A., Dellinger, E.P., Garland, J., Heard, S.O., . . . Saint, S. (2011). Guidelines for the prevention of intravascular catheter-related infections. *Clinical Infectious Diseases, 52*(9), e162–e193. https://doi.org/10.1093/cid/cir257

Pace, A.F. (2015). Electrolyte imbalances, syndrome of inappropriate antidiuretic hormone, and tumor lysis syndrome. In C. Brown (Ed.), *A guide to oncology symptom management* (2nd ed., pp 319–368). Pittsburgh, PA: Oncology Nursing Society.

Palumbo, A., Rajkumar, S.V., San Miguel, J.F., Larocca, A., Niesvizky, R., Morgan, G., . . . Orlowski, R.Z. (2014). International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *Journal of Clinical Oncology, 32*, 587–600. https://doi.org/10.1200/JCO.2013.48.7934

Picot, J., Cooper, K., Bryant, J., & Clegg, A.J. (2011). The clinical effectiveness and cost-effectiveness of bortezomib and thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma: A systematic review and economic evaluation. *Health Technology Assessment, 15*(41), 1–204. https://doi.org/10.3310/hta15410

Rajkumar, S.V., & Kumar, S. (2016). Multiple myeloma: Diagnosis and treatment. *Mayo Clinic Proceedings, 91*, 101–119. https://doi.org/10.1016/j.mayocp.2015.11.007

Richardson, P., Schlag, R., Khuageva, N., Dimopoulos, M., Shpilberg, O., Kropff, M., . . . San Miguel, J.F. (2011). Characterization of haematological parameters with bortezomib-melphalan-prednisone versus melphalan-prednisone in newly diagnosed myeloma, with

evaluation of long-term outcomes and risk of thromboembolic events with use of erythropoiesis-stimulating agents: Analysis of the VISTA trial. *British Journal of Haematology, 153*, 212–221. https://doi.org/10.1111/j.1365-2141.2011.08569.x

Rizzo, J.D., Brouwers, M., Hurley, P., Seidenfeld, J., Arcasoy, M.O., Spivak, J.L., . . . Somerfield, M.R. (2010). American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood, 116*, 4045–4059. https://doi.org/10.1182/blood-2010-08-300541

Rome, S., Noonan, K., Bertolotti, P., Tariman, J.D., Miceli, T., & IMF NLB. (2017). Bone health, pain, and mobility: Evidence-based recommendations for patients with multiple myeloma. *Clinical Journal of Oncology Nursing, 21*(Suppl. 5), 47–59.

Roodman, G.D. (2008). Skeletal imaging and management of bone disease. *Hematology: American Society of Hematology Education Program, 2008*, 313–319. https://doi.org/10.1182/asheducation-2008.1.313

Schiffer, C.A., Anderson, K.C., Bennett, C.L., Bernstein, S., Elting, L.S., Goldsmith, M., . . . Wagnon, A.H. (2001). Platelet transfusion for patients with cancer: Clinical practice guidelines of the American Society of Clinical Oncology. *Journal of Clinical Oncology, 19*, 1519–1538. https://doi.org/10.1200/JCO.2001.19.5.1519

Schiffer, C.A., Mangu, P.B., Wade, J.C., Camp-Sorrell, D., Cope, D.G., El-Rayes, B.F., . . . Levine, M. (2013). Central venous catheter care for the patient with cancer: American Society of Clinical Oncology clinical practice guideline. *Journal of Clinical Oncology, 31*, 1357–1370. https://doi.org/10.1200/JCO.2012.45.5733

Shane, E., & Berenson, J.R. (2015). Treatment of hypercalcemia. *UpToDate*. Retrieved from http://www.uptodate.com/contents/treatment-of-hypercalcemia

Smith, T.J., Bohlke, K., Lyman, G.H., Carson, K.R., Crawford, J., Cross, S.J., . . . Armitage, J.O. (2015). Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology, 33*, 3199–3212. https://doi.org/10.1200/JCO.2015.62.3488

Snowden, J.A., Ahmedzai, S.H., Ashcroft, J., D'Sa, S., Littlewood, T., Low, E., . . . Bird, J.M. (2011). Guidelines for supportive care in multiple myeloma 2011. *British Journal of Haematology, 154*, 76–103. https://doi.org/10.1111/j.1365-2141.2011.08574.x

Song, X., Cong, Z., & Wilson, K. (2016). Real-world treatment patterns, comorbidities, and disease-related complications in patients with multiple myeloma in the United States. *Current Medical Research and Opinion, 32,* 95–103. https://doi.org/10.1185/03007995.2015.1105202

Sternlicht, H., & Glezerman, I.G. (2015). Hypercalcemia of malignancy and new treatment options. *Therapeutics and Clinical Risk Management, 11*, 1779–1788.

Takeda Oncology. (2016). *Ninlaro® (ixazomib)* [Package insert]. Retrieved from https://www.ninlarohcp.com/pdf/prescribing-information.pdf

Tariman, J.D., Gleason, C., Faiman, B., Doss, D., Catamero, D., Bishop-Royse, J., . . . Moran, D. (2016). Lack of health maintenance examinations and risk in myeloma patients. *Cancer Medicine, 5*, 1425–1435. https://doi.org/10.1002/cam4.716

Teh, B.W., Harrison, S.J., Pellegrini, M., Thursky, K.A., Worth, L.J., & Slavin, M.A. (2014). Changing treatment paradigms for patients with plasma cell myeloma: Impact upon immune determinants of infection. *Blood Reviews, 28*, 75–86. https://doi.org/10.1016/j.blre.2014.01.004

Teh, B.W., Harrison, S.J., Worth, L.J., Spelman, T., Thursky, K.A., & Slavin, M.A. (2015). Risks, severity and timing of infections in patients with multiple myeloma: A longitudinal cohort study in the era of immunomodulatory drug therapy. *British Journal of Haematology, 171*, 100–108. https://doi.org/10.1111/bjh.13532

Terpos, E., Christoulas, D., Kastritis, E., Katodritou, E., Pouli, A., Michalis, E., . . . Dimopoulos, M.A. (2013). The Chronic Kidney Disease Epidemiology Collaboration cystatin C (CKD-EPI-CysC) equation has an independent prognostic value for overall survival in newly diagnosed patients with symptomatic multiple myeloma: Is it time to change from MDRD to CKD-EPI-CysC equations? *European Journal of Haematology, 91*, 347–355.

Terpos, E., Dimopoulos, M.A., & Moulopoulos, L.A. (2016). The role of imaging in the treatment of patients with multiple myeloma in 2016. *American Society of Clinical Oncology Educational Book, 35*, e407–e417. https://doi.org/10.14694/EDBK_159074

Terpos, E., Kleber, M., Engelhardt, M., Zweegman, S., Gay, F., Kastritis, E., . . . Palumbo, A. (2015). European Myeloma Network guidelines for the management of multiple myeloma-related complications. *Haematologica, 100*, 1254–1266.

Terpos, E., Morgan, G., Dimopoulos, M.A., Drake, M.T., Lentzsch, S., Raje, N., . . . Roodman, G.D. (2013). International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *Journal of Clinical Oncology, 31*, 2347–2357. https://doi.org/10.1200/JCO.2012.47.7901

Terpos, E., Roodman, G.D., & Dimopoulos, M.A. (2013). Optimal use of bisphosphonates in patients with multiple myeloma. *Blood, 121*, 3325–3328. https://doi.org/10.1182/blood-2012-10-435750

Terpos, E., Christoulas, D., Kastritis, E., Bagratuni, T., Gavriatopoulou, M., Roussou, M., . . . Dimopoulos, M.A. (2016). High levels of periostin correlate with increased fracture rate, diffuse MRI pattern, abnormal bone remodeling and advanced disease stage in patients with newly diagnosed symptomatic multiple myeloma. *Blood Cancer Journal, 6*(10), e482. https://doi.org/10.1038/bcj.2016.90

Thomas, S.A., & Chung, S. (2016). Management of hypercalcemia of malignancy. *Journal of Hematology Oncology Pharmacy, 6*, 18–21.

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