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 myelosuppression 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 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**

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>UNIT OF MEASURE</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Hemoglobin (g/dl)</td>
<td>Less than LLN to 10</td>
<td>8–10</td>
<td>Less than 8</td>
<td>Life threatening; urgent intervention indicated</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Absolute neutrophil count (x 10⁹)</td>
<td>Less than LLN to 1.5</td>
<td>1–1.5</td>
<td>0.5–1</td>
<td>Less than 0.5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Platelet count (x 10⁹)</td>
<td>Less than LLN to 75</td>
<td>50–75</td>
<td>25–50</td>
<td>Less than 25</td>
</tr>
</tbody>
</table>

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).

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

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

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

Thrombocytopenia is defined by the NCI (2017) as a condition in which the absolute neutrophil count falls below normal levels. However, the risk of developing an infection may not be the first and only sign of a bacterial infection in patients with MM. The large numbers of MM cells present in the bone marrow can be further subdivided into mild, moderate, and severe subgroups based on the underlying condition and other clinical factors (Avvisati et al., 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 x 10^9/L, and risk of bleeding generally increases only when platelets fall below 20 x 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 x 10^9/L (Noonan et al., 2017). Steroids, which are an

<table>
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<tr>
<th>TABLE 3. TESTING PROCEDURES FOR ANEMIA IN PATIENTS WITH MULTIPLE MYELOMA</th>
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<tbody>
<tr>
<td>DIFFERENTIAL DIAGNOSIS</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Hemolysis</td>
</tr>
<tr>
<td>■ Disseminated intravascular coagulation panel</td>
</tr>
<tr>
<td>■ Haptoglobin</td>
</tr>
<tr>
<td>■ Indirect bilirubin</td>
</tr>
<tr>
<td>■ Lactate dehydrogenase</td>
</tr>
<tr>
<td>Hemorrhage</td>
</tr>
<tr>
<td>■ Endoscopy</td>
</tr>
<tr>
<td>Inherited disorder</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
</tr>
<tr>
<td>Myeloid malignancy</td>
</tr>
<tr>
<td>Nutritional deficiency</td>
</tr>
<tr>
<td>■ Vitamin B12</td>
</tr>
<tr>
<td>■ Folate</td>
</tr>
<tr>
<td>Radiation-induced myelosuppression</td>
</tr>
<tr>
<td>Renal dysfunction</td>
</tr>
</tbody>
</table>

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 le-
sions 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 thor-
ough 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 bleed-
ing, 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, administra-
tion of erythropoiesis-stimulating agents (ESAs) if indicated, correction of additional underlying causes, and transfusions

**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 B₁₂.
- 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.*

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, sei-
zures, pure red cell aplasia, and possible decreased survival re-
lated 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, heredi-
tary 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 pa-
tient 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 B₁₂ 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 asympto-
tomatic 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 dis-
ease, or cerebral vascular disease (NCCN, 2017a). Leukocyte-
reduced blood products decrease the risk of febrile reactions,
human leukocyte antigen alloimmunization, and cytomegalovi-
rus 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,
SaO₂ = 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 car-
diopulmonary comorbidities. Based on clinical guidelines, this
same group may also benefit from the prophylactic use of
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 influenzae, 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 antibiologic 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).

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 $40 \times 10^9/L$ to $50 \times 10^9/L$ 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 non-abrasive 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,

**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.
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 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).

**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.

**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
- Concomitant corticosteroid use can prolong effect.

**HYDRATION**

- 200–300 cc per hour infusion
- Goal is euvolemia to abrogate 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.

**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).

**TABLE 4.**
**HEALTHCARE PROVIDER TIP SHEET: ASSESSMENT, INTERVENTION, AND PATIENT EDUCATION FOR HYPERCALCEMIA OF MALIGNANCY**

<table>
<thead>
<tr>
<th>METHOD</th>
<th>ASSESSMENT</th>
<th>INTERVENTION</th>
<th>PATIENT EDUCATION</th>
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| 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 obstruction 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 euvoolemia 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

<table>
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<th>METHOD</th>
<th>ASSESSMENT</th>
<th>INTERVENTION</th>
<th>PATIENT EDUCATION</th>
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| 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 receptor 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 (Dispensieri & 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 (Dimopoulos, 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, angiotensin-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/1.73 m²) 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, & Abudayeh, 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

CJON.ONS.ORG SUPPLEMENT TO VOLUME 21, NUMBER 5 CLINICAL JOURNAL OF ONCOLOGY NURSING 73
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