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Renal, GI, and Peripheral Nerves

Evidence-based recommendations for the management of symptoms and care for patients with multiple myeloma

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BACKGROUND: A majority of patients with multiple myeloma experience damage to the kidneys and peripheral nerves either at diagnosis or throughout the disease. Symptoms of diarrhea, nausea, vomiting, or constipation can also occur. Prevention and management of disease- and treatment-related side effects are essential to treatment adherence.

OBJECTIVES: This article aims to provide insight into prevention and management of organ health–related toxicities and give best practice recommendations for optimal nursing care.

METHODS: The authors performed a literature search, and articles were reviewed for relevance to each organ-related topic: renal, gastrointestinal, and peripheral nerves.

FINDINGS: Prevention and management strategies include close monitoring and prompt intervention when organ damage develops to reverse impairment and maintain adherence to therapy when indicated.

KEYWORDS
renal; peripheral neuropathy; gastrointestinal; multiple myeloma; side effects

DIGITAL OBJECT IDENTIFIER
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FOR MOST PATIENTS DIAGNOSED WITH MULTIPLE MYELOMA (MM), organ damage involving the kidneys, bones, or peripheral nerves has occurred at diagnosis. Organ damage contributes to a high symptom burden and low health-related quality of life. Attention to organ health at diagnosis and throughout the disease continuum is important. Patients with MM, physicians, advanced practice providers, and nurses share the responsibility of monitoring, preventing, and addressing acute or chronic organ damage. Timely correction or reversal of existing organ damage, preservation of function, and management of symptoms arising from MM or its treatment are essential goals of MM nursing care. In this article, the International Myeloma Foundation (IMF) Nurse Leadership Board (NLB) aims to highlight important findings on MM- and treatment-related symptoms. The IMF NLB believes that nurses have the ability to identify patients at risk for organ damage as a result of MM or its treatment and to institute preventive and therapeutic interventions that can minimize patient morbidity. This article reviews the most recent, significant findings about MM- and treatment-related symptoms involving the kidney, gastrointestinal (GI) tract, and peripheral nerves. The article also provides state-of-the-art, evidence-based recommendations on management of these symptoms.

Methods

To obtain highly relevant literature on organ health in MM, the authors searched the PubMed and CINAHL® Complete databases using the Medical Subject Heading (MeSH) terms *multiple myeloma*, *symptoms*, and *management* and the Boolean operator AND (*multiple myeloma* AND *symptoms* AND *management*). The search yielded 31 articles from PubMed and 53 articles from CINAHL Complete. The following inclusion criteria were used in selecting the articles for final analysis: population of patients with MM; novel therapies; supportive therapies; and symptom management for renal, GI, and peripheral neuropathy (PN)–related symptoms because of MM or its treatment. The literature search was limited to articles published in English from January 2008 to March 2017.

The IMF NLB used Melnyk and Fineout-Overholt's (2011) Levels of Evidence as a systematic framework for the appraisal and grading of the IMF NLB's consensus statements and evidence-based recommendations. The

FIGURE 1.
CLASSIFICATION OF ACUTE RENAL FAILURE

RIFLE SYSTEM

- Risk: 1.5 times or greater baseline serum creatinine level or greater than 25% decrease in GFR
  - ☐ Urine output: Less than 0.5 ml/kg per hour for greater than 6 hours
- Injury: 2 times or greater baseline serum creatinine level or greater than 50% decrease in GFR
  - ☐ Urine output: Less than 0.5 ml/kg per hour for greater than 12 hours
- Failure: 3 times or greater baseline serum creatinine level or greater than 75% decrease in GFR, or serum creatinine level greater than 4 mg/dl with a rapid increase of 0.5 mg/dl within 48 hours
  - ☐ Urine output: Less than 0.3 ml/kg per hour for greater than 24 hours or anuria for greater than 12 hours
- Loss: Dialysis greater than 4 weeks
- End-stage renal disease: Dialysis greater than 3 months

ACUTE KIDNEY INJURY NETWORK CRITERIA

- Stage 1: 1.5–1.9 times baseline serum creatinine level or rise of 0.3 mg/dl or greater within 48 hours
  - ☐ Urine output: Less than 0.5 ml/kg per hour for greater than 6 hours
- Stage 2: 2–2.9 times baseline serum creatinine level
  - ☐ Urine output: Less than 0.5 ml/kg per hour for greater than 12 hours
- Stage 3: 3 times or greater baseline serum creatinine level or serum creatinine level 4 mg/dl or greater, with a rapid increase of 0.5 mg/dl within 48 hours, or need for renal replacement therapy
  - ☐ Urine output: Less than 0.3 ml/kg per hour for 24 hours or greater or anuria for more than 12 hours

KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES STAGING

- Stage 1: 1.5–1.99 times baseline serum creatinine level or 0.3 mg/dl or greater above baseline
  - ☐ Urine output: Less than 0.5 ml/kg per hour for greater than 6 hours
- Stage 2: 2–2.99 times baseline serum creatinine level
  - ☐ Urine output: Less than 0.5 ml/kg per hour for more than 12 hours
- Stage 3: 3 times or greater baseline serum creatinine level or serum creatinine level 4 mg/dl or greater, or need for renal replacement therapy
  - ☐ Urine output: Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours or greater

GRADES 0–3 STAGING

- Grade 0: Decrease in GFR to less than 25% of baseline value
- Grade 1: Serum creatinine level increased by less than a factor of 2 with decrease in GFR from 25%–50%
- Grade 2: Serum creatinine level increased by more than a factor of 2 but no dialysis
- Grade 3: Serum creatinine level increased by more than a factor of 2 and dialysis

GFR—glomerular filtration rate
Note. To convert the values for creatinine to micromoles per liter, multiply by 88.4.
Note. Based on information from Dimopoulos, Sonneveld, et al., 2016; Hingorani, 2016; Khwaja, 2012; Thomas et al., 2015.

rating system has seven levels that are inclusive of evidence from qualitative studies, case-control and cohort studies, reports of expert committees, and opinions of authorities in the field. This article reviews organ health related to MM, including renal, GI, and PN-related symptoms, and provides evidence-based recommendations to manage renal symptoms in the care of patients with MM.

Myeloma-Induced Renal Impairment

The kidneys are vital organs that filter the blood to remove waste materials, balance fluids and electrolytes, release hormones, and eliminate harmful chemicals from the body, including chemotherapeutic drugs. The terms *renal impairment* and *renal insufficiency* are often interchangeable and refer to the kidneys' inability to function at their full capacity. Renal impairment is a relatively common presenting symptom among patients with MM and can occur throughout the duration of the disease. Mild renal insufficiency or renal failure occurs in about 50% of patients with MM at any time during the disease course (Finkel, Cohen, Shirali, & Abudayyeh, 2016; Gavriatopoulou, Terpos, Kastritis, & Dimopoulos, 2016). Multiple factors may affect renal function, including advancing age, development of new or worsening comorbid illnesses, MM disease burden, and cumulative toxicity from chemotherapy. Risk- and patient-related factors that may affect renal function should be assessed routinely at each clinic visit.

Adequate renal function in patients with MM must be safeguarded at all times because acute kidney injury (AKI), as evidenced by elevations in serum creatinine during a short period of time, is a significant factor in the development of chronic kidney disease and increases the risk of approaching end-stage renal disease and dialysis. (Hsu & Hsu, 2016). Therefore, prompt attention to new or worsening renal insufficiency and immediate identification and correction of the underlying cause are critical.

Clinical Presentation and Pathogenesis

Renal impairment may be acute or chronic and may be related to the disease or treatment. To classify AKI in adults, several important classification guidelines are used: RIFLE (risk, injury, failure, loss, and end-stage renal disease) system; the Acute Kidney Injury Network criteria; Kidney Disease: Improving Global Outcomes staging; and grades 0–3 staging (Dimopoulos, Sonneveld, et al., 2016; Thomas et al., 2015) (see Figure 1). Across each of these classification guidelines, the degree of renal impairment (regardless of whether it is acute or chronic) is determined by an increased serum creatinine level and reduced glomerular filtration rate (GFR) (Dimopoulos, Sonneveld, et al., 2016; Faiman, Mangan, Spong, & Tariman, 2011).

Mild renal insufficiency is unlikely to produce symptoms, whereas anemia, fatigue, malaise, fluid and electrolyte imbalances, and decreased urination can occur with moderate to severe renal impairment. In patients who experience AKI, temporary elevations in serum creatinine or a sudden decline in GFR may

be seen in patients who are dehydrated as a result of nausea, vomiting, infection, and decreased fluid volume intake. Figure 2 presents additional conditions or drugs that lead to acute renal insufficiency. Common medications used to treat MM and renal considerations can be found in Table 1. Acute or chronic renal impairment can occur at any time and clinical presentations largely depend on the etiology or pathogenesis (Hsu & Hsu, 2016).

Distinctive Causes

Immunoglobulin light chain proteins are produced by malignant plasma cells in the bone marrow and eventually reach the nephrons where they combine with a potent immunomodulatory molecule, Tamm–Horsfall protein, and cause cast formation. Myeloma kidney (also called "cast nephropathy") can be observed microscopically when crystalline precipitates of monoclonal light chains, surrounded by multinucleated giant cells, form casts in the distal and collecting tubules. These large, dense, tubular casts may obstruct and rupture the tubular epithelium, resulting in tubulointerstitial damage that manifests clinically as increased serum creatinine levels, electrolyte imbalance, and decreased GFR (Faiman et al., 2011).

Diseases that promote glomerular injury, such as amyloid light chain amyloidosis or light chain deposition disease, should be considered in patients with MM when nephrotic-range proteinuria (defined as urine total protein levels greater than 3.5 g per 24 hours) occurs with or without significant renal impairment (Kelepouris & Rovin, 2017). Amyloid light chain amyloidosis is characterized by the deposition of fibrils consisting of monoclonal light chains in the glomeruli (Gertz, 2016). A diagnostic algorithm developed by Gertz (2016) underscores the importance of positive serum and urine immunofixation results and serum free light chain levels. A biopsy of the target organ (e.g., kidney, heart) is required if immunofixation electrophoresis of the serum or urine reveals monoclonal immunoglobulin light chains and if the clinical suspicion for amyloidosis is high (Brayer, Hussein, & Baz, 2017; Gertz, 2016). Tissue from kidney, bone marrow, or subcutaneous fat requires Congo red staining, which produces an apple-green birefringence when viewed under polarized light (Picken, 2015). The most accurate diagnosis of the presence and type of amyloidosis is obtained by mass spectroscopy. If this is not available, immunohistochemical staining is useful (Brayer et al., 2017). Determining the type of amyloid deposition patients have is essential because the selection of therapy depends on an accurate diagnosis (Picken, 2015). Light chain deposition disease is characterized by the presence of immunoglobulin light chains, usually kappa. In contrast to amyloidosis, these infiltrative light chains fail to stain with Congo red (Ardalan, 2013).

Acute Tubular Necrosis in Multiple Myeloma

Acute tubular necrosis is a common cause of acute renal impairment in MM. It may be precipitated by several factors, including dehydration or excessive diuretics, hypercalcemia (which occurs in as many as 10%–15% of patients), nonsteroidal anti-inflammatory drugs, and aminoglycoside antibiotics. Prompt diagnosis often leads to renal recovery (Doshi, Lahoti, Danesh, Batuman, & Sanders, 2016).

FIGURE 2.
HEALTH CONDITIONS OR DRUGS THAT LEAD TO ACUTE RENAL INSUFFICIENCY IN MULTIPLE MYELOMA

HEALTH CONDITIONS
- Diabetes
- Hypertension
- Advanced age
- Rhabdomyolysis (muscle injury or death leads to release of muscle contents, including creatinine, into the blood)
- Dehydration (from decreased fluid intake, fluid losses, or loop diuretics)
- Hypercalcemia
- Progressive disease or cast nephropathy (particularly light chains)

DRUGS
- Nonsteroidal anti-inflammatory agents, including cyclooxygenase-2 inhibitors
- Aminoglycoside antibiotics
- Radio-contrast dyes or IV contrast agents (e.g., for computed tomography scans)

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

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

Contributors to Chronic Kidney Disease

Adequate kidney function is required for optimal bone repair and remodeling (Wei, Yin, & Xie, 2016). In patients with chronic kidney disease and MM, bone loss and bone damage may be profound long-term consequences of CKD. Bisphosphonates, such as zoledronic acid and pamidronate, are potent inhibitors of bone resorption. However, bisphosphonate use in patients with renal insufficiency or chronic kidney disease may be toxic to the kidneys (Berenson, 1997). Bisphosphonates are generally contraindicated in stage IV chronic kidney disease, which is characterized by GFR less than 30 ml per minute (Dimopoulos, Roussou, et al., 2016). In patients with hypercalcemia, nurses should ensure that patients with monoclonal light chains (also called Bence Jones proteinuria) drink enough fluids to produce 3 liters of urine daily. A diagnosis of primary hyperparathyroidism must be excluded in patients with persistent hypercalcemia because elevated serum parathyroid hormone levels are more common in the general population (Lewis, Hendrickson, & Moynihan, 2011).

Evidence-Based Recommendations for Acute Kidney Injury

Even mild renal insufficiency or impairment can place patients with MM at risk for chronic kidney disease. It is within the nurse's scope of practice to assess and intervene when kidney health is at risk.

LEVEL OF EVIDENCE I

- The IMF NLB recommends that immediate identification and treatment of reversible causes of AKI, such as dehydration, be corrected as quickly as possible. Adequate IV or oral hydration is essential (with caution to avoid overhydration) to help reverse AKI or renal failure (Moos, van Vemde, Stoker, & Bipat, 2013; Okusa & Rosner, 2017).
- Healthcare providers must be certain that dehydration is corrected prior to oral or IV iodinated contrast dye for radiologic procedures. The risk of AKI following the use of iodinated contrast dyes is increased in patients with chronic kidney disease, diabetes, malignancy, and heart failure, and in older adults (Moos et al., 2013; Mussap & Merlini, 2014).

TABLE 1.
COMMON MEDICATIONS USED TO TREAT MM AND RENAL CONSIDERATIONS AS OF SEPTEMBER 2017

DRUG	INDICATION	RENAL CONSIDERATIONS	CLINICAL TRIAL DATA
Bortezomib	Newly diagnosed MM; relapsed, refractory MM	■ No dose reduction required ■ Give after dialysis on dialysis days.	Bridoux et al., 2016; Chanan-Khan et al., 2007; Dimopoulos, Roussou, et al., 2016; Palumbo et al., 2016; San Miguel et al., 2008; Zanetti et al., 2015; Ziogas et al., 2017
Carfilzomib	Newly diagnosed MM; relapsed MM	■ Increased creatinine may result. ■ Hydration before and after treatment	Badros et al., 2013; Kwon & Niesvizky, 2013; Mikhael et al., 2015; Shah, 2013; Stewart, 2015; Stewart et al., 2015
Daratumumab	Relapsed, refractory MM	■ No dose reduction required	Laubach et al., 2017
Elotuzumab	Relapsed, refractory MM	■ No dose reduction required	Jakubowiak et al., 2016; Lonial et al., 2015; Mateos et al., 2016
Ixazomib	Relapsed MM	■ Dose reduction for GFR less than 30 (3 mg on days 1, 8, and 15 every 28 days) ■ Not dialyzable	Richardson et al., 2015
Lenalidomide	Newly diagnosed MM; relapsed, refractory MM	■ Dose reduction according to the degree of renal insufficiency (days 1–21 of each 28-day cycle) ■ CrCl greater than 60 ml/min, 25 mg/day ■ CrCl 30–60 ml/min, 10 mg/day ■ CrCl less than 30 ml/min (not requiring dialysis), 15 mg alternate days ■ CrCl less than 30 ml/min (requiring dialysis), 5 mg/day after dialysis	Dimopoulos, Cheung, et al., 2016; Weber et al., 2007
Melphalan	Newly diagnosed MM; relapsed, refractory MM	■ No dose reduction for conditioning treatment ■ Dose reduction of as much as 50% for renal insufficiency (BUN 30 mg/dl or greater) for palliative treatment	Palumbo et al., 2007, 2014; Roy et al., 2015
Panobinostat	Relapsed, refractory MM	■ Mild to severe renal impairment does not affect plasma concentration. Effect in patients with end-stage renal disease or on dialysis is not known.	Libby et al., 2015; Richardson et al., 2016; San-Miguel et al., 2014
Pomalidomide	Relapsed, refractory MM	■ Dose reduction for renal insufficiency or dialysis: 3 mg daily for days 1–21 every 28 days ■ Give after dialysis on dialysis days.	Conticello et al., 2017; Richardson et al., 2014; Siegel et al., 2016
Thalidomide	Newly diagnosed MM; relapsed, refractory MM	■ No dose reductions required	Palumbo et al., 2008; Rajkumar et al., 2006; Singhal et al., 1999
Valacyclovir, acyclovir	Herpes zoster or shingles prevention	■ Dose reduction for reduced CrCl	Kim et al., 2011; Swaika et al., 2012

BUN—blood urea nitrogen; CrCl—creatinine clearance; GFR—glomerular filtration rate; MM—multiple myeloma
Note. Renal considerations were based on prescribing information for the agents.

FIGURE 3.

HEALTHCARE PROVIDER TIP SHEET: RENAL CARE PLAN FOR PATIENTS WITH STABLE MM

Comorbidities (e.g., diabetes, hypertension, increased age), dehydration, hypercalcemia, progressive disease, and cast nephropathy (particularly light chains) can all contribute to a decline in renal function. Acute renal failure because of disease progression or acute tubular necrosis is generally reversible if corrected early. Avoid drugs that can worsen preexisting kidney disease.

HISTORY AND PHYSICAL EXAMINATION

- Quarterly review of medications, changes in medical history, and physical examinations are recommended.

BLOOD TEST

- Perform CBC, CMP, SPEP, SIFE, 24-hour UPEP, UIFE, LDH, serum FLC assay, beta-2-microglobulin every three months if stable.
- Vitamin D deficiency (vitamin D 1-25, vitamin D 25 hydroxy), hyperparathyroidism (serum PTH-intact) should be assessed at baseline and periodically.

BONE SURVEYS

- Perform metastatic skeletal survey annually or earlier if new skeletal symptoms occur.

URINALYSIS

- Perform urinalysis quarterly if on bisphosphonates to assess for albuminuria.

NEPHROLOGIST FOLLOW-UP

- See nephrologist annually or as needed if decline in GFR is less than 30.

DIAGNOSTIC IMAGING

- Perform renal ultrasound to rule out hydronephrosis with new onset renal insufficiency. Avoid the use of IV dye or contrast with PET-CT or MRI scans if possible.

MEDICATIONS

- Avoid the use of NSAIDs, aminoglycosides, COX-2 inhibitors. Many over-the-counter supplements and medications can contribute to worsening renal dysfunction, but others can be given safely with dose reduction. Consult a trusted website, such as Medicines Complete, to evaluate safety.
- Bisphosphonates must be used with caution, and serum creatinine must be obtained prior to each dose.
- ESAs must be used with caution with recent safety concerns (e.g., stroke).

CALCULATION OF MEDICATION DOSE

- Many drugs to treat MM require a dose decrease for patients with renal insufficiency based on GFR or creatinine clearance.
- Many medications used to treat MM are safe to give after dialysis on a dialysis day.
- Drugs that require dose reduction based on GFR
  - ☐ Lenalidomide
  - ☐ Ixazomib
  - ☐ Carfilzomib
  - ☐ Melphalan
- Supportive care drugs that may require dose reduction based on GFR
  - ☐ Amoxicillin clavulante
  - ☐ Acyclovir
  - ☐ Low-molecular-weight heparins and factor inhibitors (e.g., rivaroxaban)
- Drugs that are potentially nephrotoxic
  - ☐ NSAIDs, including COX-2 inhibitors
  - ☐ Vancomycin, aminoglycoside antibiotics
  - ☐ Radio-contrast IV dye

GENERAL PREVENTIVE RULES TO PROTECT KIDNEY FUNCTION

- Be aware of the nephrotoxic potential of specific drugs.
- Be aware of the increased risk in the elderly.
- Assess the risk–benefit ratio for treatment with any drug.
- Avoid dehydration.
- Limit dose and duration of treatment, particularly if the drug is known to be nephrotoxic.
- Adjust dose based on GFR.
- Avoid combining potentially nephrotoxic drugs.

CBC—complete blood count; CMP—comprehensive metabolic panel; COX—cyclooxygenase; ESA—erythropoiesis-stimulating agent; FLC—free light chain; GFR— glomerular filtration rate; LDH—lactate dehydrogenase; MM—multiple myeloma; MRI—magnetic resonance imaging; NSAID—nonsteroidal anti-inflammatory drug; PET-CT—positron-emission tomography–computed tomography; PTH —parathyroid hormone; SIFE—serum immunofixation; SPEP—serum protein electrophoresis; UIFE—urine immunofixation; UPEP—urine protein electrophoresis

Note. From "Renal Complications in Multiple Myeloma and Related Disorders: Survivorship Care Plan of the International Myeloma Foundation Nurse Leadership Board," by B.M. Faiman, P. Mangan, J. Spong, & J.D. Tariman, 2011, *Clinical Journal of Oncology Nursing, 15,* pp. 71–72. Copyright 2011 by Oncology Nursing Society. Adapted with permission.

- The IMF NLB recommends measurement of serum creatinine prior to any radiologic procedure that requires an 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, which accounts for the patient's age, creatinine level, gender, and race (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDKD], 2015).
- The IMF NLB recommends that contrast-induced nephropathy risk assessment and prophylactic strategies should be based on estimated GFR using the CKD-EPI equation (Faiman et al., 2011) rather than solely relying on the absolute value of creatinine. The European Renal Best Practice Ad-Hoc Working Group on contrast-induced nephropathy (Fliser et al., 2012) and a study by Terpos et al. (2013) showed better detection of stages III–V chronic kidney disease (stage III with estimated GFR 30–60 ml per minute per 1.73 m^2) in patients with newly diagnosed MM with the CKD-EPI equation than with the absolute creatinine value alone.

LEVEL OF EVIDENCE II

- The IMF NLB recommends plasmapheresis in conjunction with anti-MM therapies and the use of high-cutoff dialyzers.

FIGURE 4.
PATIENT EDUCATION TIP SHEET: RENAL CARE PLAN FOR PATIENTS WITH MM

HISTORY AND PHYSICAL EXAMINATIONS
- Regular review of medications, changes in medical history, and physical examination
- Call your primary care provider for annual physical examination.
- Your hematology-oncology practitioner will review medications at each visit.

BLOOD TESTS
- Perform CBC, CMP, SPEP, SIFE, 24-hour UPEP, UIFE, LDH, serum FLC assay, and beta-2 microglobulin every three months. Special tests for bone loss may be ordered on an individual basis.
- Contact your treating hematology-oncology provider for monitoring.

BONE IMAGING
- Long-term or late effects of chronic kidney disease include osteoporosis.
- Talk with your primary care provider or hematology/oncology provider about bone density scans to monitor your bone health.

URINALYSIS
- Check annually if not on pamidronate or zoledronic acid. Check quarterly if you are receiving one of these drugs.
- Contact your treating hematology-oncology provider for monitoring.

NEPHROLOGIST OR KIDNEY SPECIALIST FOLLOW-UP
- See nephrologist annually or as needed if change in creatinine or GFR occurs.
- Call your nephrologist or kidney specialist.

DIAGNOSTIC IMAGING
- Avoid the use of IV dye or contrast with PET, CT, or MRI scans.
- Any provider may order one of these tests. You should alert whoever is ordering these tests that you have a diagnosis of MM and that IV dye may not be safe.

MEDICATIONS
- Avoid the use of NSAIDs, such as ibuprofen. Many medications and over-the-counter supplements (including Chinese herbs) can worsen renal impairment, but others can be given safely at lower doses.
- Bisphosphonates (zoledronic acid and pamidronate) are often used to prevent bone fractures and can be used with caution. Your provider should check your kidney function before each dose.
- ESAs, such as darbepoetin alfa and erythropoietin, are used to treat anemia. These must be used with caution, and a CBC must be obtained before each dose.
- All medications should be reviewed with your provider before starting, including herbal and over-the-counter medications.

DOSE ADJUSTMENTS
- Tell your providers if you have a decrease in kidney functioning. Certain medications to treat your cancer or other health conditions, such as antibiotics, will require a dose reduction or change in the way the medicines are given (e.g., days of the week).
- Contact your healthcare team for monitoring.

OTHER FACTORS
- Maintain adequate hydration; 2.5 liters of fluid per day is recommended. It is important to avoid dehydration, particularly during hot days or if you have a raised temperature.

CBC—complete blood count; CMP—comprehensive metabolic panel; CT—computed tomography; ESA—erythropoiesis-stimulating agent; FLC—free light chain; GFR— glomerular filtration rate; LDH—lactate dehydrogenase; MM—multiple myeloma; MRI—magnetic resonance imaging; NSAID—nonsteroidal anti-inflammatory drug; PET—positron-emission tomography; SIFE—serum immunofixation; SPEP—serum protein electrophoresis; UIFE—urine immunofixation; UPEP—urine protein electrophoresis

Note. From "Renal Complications in Multiple Myeloma and Related Disorders: Survivorship Care Plan of the International Myeloma Foundation Nurse Leadership Board," by B.M. Faiman, P. Mangan, J. Spong, & J.D. Tariman, 2011, *Clinical Journal of Oncology Nursing, 15,* pp. 71–72. Copyright 2011 by Oncology Nursing Society. Adapted with permission.

Plasmapheresis removes damaging monoclonal light chains and has been shown to improve or reverse renal failure (Burnette, Leung, & Rajkumar, 2011; Clark, 2007; Finkel et al., 2016; Hutchison et al., 2007). The use of high-cutoff dialyzers may effectively remove serum free light chains and can lead to improved renal function (Finkel et al., 2016; Hutchison et al., 2007, 2009) or independence from hemodialysis among patients receiving a bortezomib-based regimen (Bridoux et al., 2016). Temporary or permanent hemodialysis is indicated if symptomatic uremia becomes an issue.

Evidence-Based Recommendations for Simultaneous Renal Impairment and Active Multiple Myeloma

LEVEL OF EVIDENCE I

- The IMF NLB recommends prompt initiation of effective MM therapy. In line with International Myeloma Working Group recommendations that renal impairment should be treated with bortezomib-based regimens (Dimopoulos, Sonneveld, et al., 2016), the IMF NLB recommends the use of bortezomib as the cornerstone treatment in the management of these patients.

LEVELS OF EVIDENCE I–III

- The IMF NLB recommends prompt treatment using classes of drugs approved by the U.S. Food and Drug Administration to treat patients with relapsed or refractory MM and renal impairment. These include immunomodulatory agents like the following:
  - Level of evidence I: Thalidomide; proteasome inhibitors, such as bortezomib (Dimopoulos, Sonneveld, et al., 2016; Picot, Cooper, Bryant, & Clegg, 2011)
  - Level of evidence III: Lenalidomide and pomalidomide; carfilzomib and ixazomib; monoclonal antibodies, such as elotuzumab and daratumumab

Evidence-Based Recommendations for Supportive Care

LEVEL OF EVIDENCE I

- The IMF NLB recommends bisphosphonate therapy to prevent skeletal-related events, with caution paid to serum creatinine levels (Mhaskar et al., 2010). In patients with chronic kidney disease, the IMF NLB recommends monitoring of the serum creatinine level and estimated GFR using the CKD-EPI calculator (NIDDKD, 2015) prior to each dose, in addition to periodic monitoring with 24-hour urine to assess for albuminuria.
- The IMF NLB recommends that patients who are taking bisphosphonates should also take daily calcium and vitamin D supplementation. Recommendations vary according to vitamin D status and nutritional intake, but supplements of 600 mg calcium and 800 IU vitamin D daily are generally accepted (Body et al., 2016). Calcium supplementation remains contraindicated in patients with hypercalcemia (Body et al., 2016; Dimopoulos, Sonneveld, et al., 2016; Faiman et al., 2011; Mhaskar et al., 2010).

LEVEL OF EVIDENCE III

- The IMF NLB recommends the use of erythropoiesis-stimulating agents (ESAs). Anemia, defined in patients with MM as having a hemoglobin value 2 g/dl below the institutional limits of normal, is often present in patients with moderate to severe renal dysfunction, as well as MM itself. The use of erythropoiesis-stimulating agents in renal disease is common practice. However, the use of these drugs in MM and chronic kidney disease remains controversial. An increased risk of stroke and thromboembolic events may occur in patients with MM receiving ESAs (Anaissie et al., 2012). Interventions to minimize this risk, such as venous thromboembolism precautions (e.g., ambulation, antiplatelet and anticoagulant therapy when appropriate), should be initiated prior to use of ESAs. According to the National Comprehensive Cancer Network (2016) clinical practice guidelines for patients with MM, chronic kidney disease is not a contraindication for receiving ESAs. Obtaining baseline serum iron, ferritin, and serum total iron binding capacity is recommended prior to initiating oral iron therapy (Khwaja, 2012).

Evidence-Based Recommendations for Monitoring of Disease Status and Renal Function

LEVEL OF EVIDENCE V

- The IMF NLB recommends close monitoring of a patient's MM disease burden and renal insufficiency by ensuring that they obtain routine complete blood count, blood chemistries, and measurement of monoclonal protein levels. In patients with stable disease, laboratory monitoring should be performed either monthly or according to institutional schedules for routine clinic follow-up. During laboratory monitoring, MM-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 (Kurtin et al., 2016). See Figures 3 and 4 for renal care plans, including patient monitoring.

"Renal impairment is a relatively common presenting symptom among patients with multiple myeloma and can occur throughout the duration of the disease."

Evidence-Based Recommendations for Patient Education

LEVEL OF EVIDENCE V

- The IMF NLB recommends that patients and their caregivers be taught about the additional burden of certain comorbidities on renal functions and that comorbidities 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 an increased risk of renal failure not only from MM itself, but also from aging, because MM occurs in older adults (Zweegman, Palumbo, Bringhen, & Sonneveld, 2014). Diabetes and hypertension are the leading causes of end-stage renal disease, and diabetes mellitus is the number one cause of kidney failure (United States Renal Data System, 2016). About half of all new patients receiving dialysis have diabetes, making it the fastest-growing risk factor for kidney disease. Uncontrolled hypertension is a cause and complication of chronic kidney disease and should be carefully treated and controlled in all patients (Song, Cong, & Wilson, 2016). Other factors that may increase the risk of renal failure include racial or ethnic minority status in the United States and family history of chronic kidney disease.

LEVEL OF EVIDENCE VI

- The IMF NLB recommends that oncology clinicians advise all patients, including those with MM, to actively engage in weight

control, exercise, smoking cessation, and taking 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 progression to kidney failure (Faiman et al., 2011; Tariman et al., 2016).

Gastrointestinal Symptoms

GI symptoms are commonly experienced among patients who undergo active treatment of MM, particularly with novel therapies. Inadequately addressed symptoms, such as constipation, diarrhea, nausea, vomiting, or anorexia, can negatively affect the patient physically and psychologically. Adequate management of GI symptoms has the potential to increase patient adherence to treatment regimens, decrease physiologic impairment, and improve quality of life (Smith, Bertolotti, Curran, & Jenkins, 2008). The following evidence-based recommendations address the GI toxicities of constipation, diarrhea, nausea, and vomiting and will allow the healthcare provider, as part of an interprofessional team, to be better prepared to manage these toxicities associated with novel therapies for MM.

Clinical Presentations and Pathophysiology

The GI tract is a complex system responsible for the disintegration of solid foods, bioavailability of nutrients, and excretion of unnecessary waste (Faiman, 2016; Kong & Singh, 2008). Multiple factors can contribute to abnormal functioning of the GI tract and include disruption of the normal intestinal flora (by chemotherapy or autoimmunity) or changes to GI motility, which allows for excretion of foods (Nitzan, Elias, Chazan, Raz, & Saliba, 2013). For patients with MM, medications used for disease management or supportive care can interrupt the normal functioning of the GI system and lead to diarrhea, constipation, nausea, or vomiting.

The incidence of GI toxicities in patients with MM varies greatly with type of therapy. Diarrhea, defined as an abnormal increase in the amount of fluid in stool, is the most common GI symptom that patients with MM experience. Diarrhea can occur because of infection, inflammation, malignancy, or an autoimmune

FIGURE 5.
HEALTHCARE PROVIDER TIP SHEET: ASSESSMENT AND DIFFERENTIAL DIAGNOSIS OF DIARRHEA

ASSESSMENT OF DIARRHEA

- Determine if a change in bowel habits is present.
- Determine the severity grade of diarrhea, and rule out contributing factors.
- Determine the duration of symptoms by calculating the number of stools over normal baseline, nocturnal diarrhea, stool consistency (watery or soft), urgency, and frequency with bowel movements.

GRADING OF DIARRHEA SEVERITY

- Grade 1: Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline
- Grade 2: Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline
- Grade 3: Increase of 7 or greater stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated

DIFFERENTIAL DIAGNOSIS AND POTENTIAL CAUSES

- Careful analysis of causative agent(s) is essential to appropriate management and intervention.
- Infection: Diagnosed based on symptoms, history (such as travel or close contact with diarrheal illness), and stool culture to rule out viral or bacterial causes
- Inflammation: Intestinal inflammatory disorders, such as Crohn's disease, ulcerative colitis, and irritable bowel syndrome, will predispose patients to develop diarrhea.
- Malignancy: Can occur in certain types of cancers, such as colon, endometrial, ovarian, and sarcoid, as well as T-cell lymphoma
- Immunodeficiency: Immunoglobulin A deficiency
- Graft-versus-host disease: Immune-related diarrhea, which usually occurs after donor allogeneic hematopoietic cell transplantation in hematologic cancers and blood disorders
- Radiation therapy: Cancer treatment–induced diarrhea
- Identify any associated symptoms and potential complicating factors.
- Abdominal pain, gas, cramping, and signs and symptoms of dehydration
- Signs of fever, orthostatic symptoms, abdominal pain, weakness (denotes complicated diarrhea)
- Assess current medications (chemotherapy or targeted therapy) and diet (high fiber, lactose intolerance, and laxative use).
- Anxiety, malnutrition, and severe constipation might contribute to diarrhea.

PRELIMINARY INVESTIGATIONS

- Conduct a physical assessment to evaluate abdominal pain and localized abdominal tenderness and to rule out bowel obstruction.
- Consider abdominal x-ray to rule out obstruction or perforation.
- Evaluate complete blood count with differential to evaluate for neutropenia.
- Obtain a comprehensive metabolic panel to assess for electrolyte abnormalities (primarily magnesium and potassium).
- Order stool culture to rule out viral pathogens (e.g., *Clostridium difficile*, salmonella, shigella, giardia).
- Determine a severity grade of diarrhea.

Note. Based on information from Benson et al., 2004; Kinnebrew et al., 2014; Oncology Nursing Society, 2017; Smith et al., 2008; Tam et al., 2013.

FIGURE 6.

PATIENT EDUCATION TIP SHEET: MANAGEMENT OF GASTROINTESTINAL SIDE EFFECTS IN MULTIPLE MYELOMA

KEY POINTS

Many of the drugs used to treat multiple myeloma may be associated with gastrointestinal side effects, including nausea, vomiting, diarrhea, and constipation. Managing side effects can reduce your discomfort and can allow you to receive the best treatment for your multiple myeloma. Your healthcare provider may change your dose or schedule of medication to help manage your symptoms. Do not stop or adjust medications without discussing it with your healthcare provider.

TYPES OF GASTROINTESTINAL SYMPTOMS

- Nausea: An unpleasant feeling in the throat and stomach
- Vomiting: A forceful emptying of the stomach contents
- Constipation: Decreased frequency of defecation accompanied by discomfort and difficulty
- Diarrhea: An abnormal increase in the frequency and the amount of fluid in the stool

Always report symptoms early to your healthcare team. Keep skin clean and dry with good hygiene to prevent skin breakdown.

MANAGEMENT OF NAUSEA

You may be asked about the circumstances surrounding episodes, upper abdominal pain, pain when swallowing, hiccups or heartburn, weight loss, dizziness upon standing, and your medication history.

- General dietary and lifestyle recommendations for nausea: Eat small, frequent meals; do not eat fatty or fried foods; avoid strong odors; do not exercise after eating; wear loose clothing; begin appropriate medications before chemotherapy; and use relaxation, acupuncture, biofeedback, and guided imagery.
- Loss of appetite, still able to eat normally: Adjust dosages of medications, drink enough water and other fluids, and keep track of effects of medications in a daily diary.
- Decreased ability to eat or drink: Consider asking for different medications, and see your physician for physical examination and evaluation should the medications be causing you to feel sick.
- Inability to eat or drink: You may need hospitalization or medications through a vein. Contact your healthcare provider immediately.
- Medications that may be ordered by your healthcare team include lorazepam, prochlorperazine, promethazine, metoclopramide, ranitidine, famotidine, and dexamethasone.

MANAGEMENT OF VOMITING

You will be asked about the appearance of the fluid (whether digested or undigested), whether a trigger was involved, and whether it was new or different from other times.

- 1 episode in 24 hours: This is usually self-limiting; continue medications for nausea.
- 2–5 episodes in 24 hours: New medications, oral or through a vein, may be needed. Contact a physician immediately.
- 6 or more episodes in 24 hours: This may require hospitalization to assess fluid status and rule out bowel blockage. Contact your healthcare provider immediately.
- Medications that may be ordered by your healthcare team include aprepitant, ondansetron, and granisetron.

MANAGEMENT OF CONSTIPATION

You will be asked about any abdominal pain, bloating, nausea, vomiting, inability to urinate, confusion, and diarrhea alternating with constipation.

- Mild: Increase fluid and fiber intake, increase physical activity, and start stool softeners.
- Moderate: You may need to speak with a dietitian about your food intake; consider laxatives and stimulants.
- Severe: Bowel obstruction should be assessed by a healthcare provider. Dehydration may require fluids through a vein. Treatment for a blocked colon may be discussed. Medication changes may be ordered by a physician. Referral to a gastrointestinal specialist may be arranged by a physician.
- Medications that may be ordered by your healthcare team include docusate, senna, magnesium sulfate, magnesium citrate, lactulose, and bisacodyl.

MANAGEMENT OF DIARRHEA

You will be asked about any history of irritable bowel syndrome, colitis, diverticulitis, and medications other than routine chemotherapy. Your healthcare provider will want to know whether you have gas and whether the diarrhea is a leakage or sudden occurrence.

- Fewer than 4 stools a day: Drink more liquids. Avoid caffeinated, carbonated, heavily sugared beverages. Dietary changes may be needed, such as a decrease in fiber, greasy, or fried food. Discontinue any medications, such as over-the-counter herbal medications, that cause diarrhea. Keep the rectal area clean. Loperamide, cholestyramine, or bismuth subsalicylate may be recommended to treat the diarrhea after each loose bowel movement.
- 4–6 stools per day: Medications should be recommended, and you may need fluids and salts. Your healthcare provider must be notified if you have more than 4–6 stools per day for more than 24 hours.
- 7–9 stools per day: Hospitalization may be considered for fluid replacement. A stool culture will be ordered to see whether the diarrhea is the result of an infection, and medications will be given to control frequency. You should take very good care of your skin and use disposable pads or diapers. Cancer therapy may be stopped for a period of time, or the dose of your cancer medication may need to be changed.
- Medications that may be ordered by your healthcare team include loperamide, diphenoxylate, cholestyramine, and octreotide.

Note. Based on information from Amgen, 2016; Faiman et al., 2013; Millennium Pharmaceuticals, 2017; National Comprehensive Cancer Network, 2016; Novartis, 2015; Smith et al., 2008; Takeda Pharmaceutical Company, 2015, 2016.

FIGURE 7.

HEALTHCARE PROVIDER TIP SHEET: MANAGEMENT OF DIARRHEA IN MULTIPLE MYELOMA

INITIAL MANAGEMENT OF MILD DIARRHEA

- Counseling on dietary modifications and ensuring adequate oral hydration
- Eat smaller, more frequent, lactose-free, low-fat meals.
- BRAT diet (bananas, rice, applesauce, and toast)
- Avoid caffeine and alcohol.
- Avoid greasy, fried, acidic, or spicy foods.
- Discontinue high osmolar food supplements.
- Consider adding probiotics if diarrhea persists.

PHARMACOLOGIC INTERVENTIONS WITH HIGHEST LEVELS OF EVIDENCE

- For grade 1 diarrhea (an increase of less than 4 stools daily over baseline or mild increase in ostomy output as compared with baseline but not interfering with activities of daily living) and not responding to dietary intervention
  - ☐ Initiate loperamide 4 mg following first loose bowel movement and then 2 mg every 4 hours.
  - ☐ Alternatively, patients can be instructed to take 4 mg after initial loose bowel movement and then 2 mg after each subsequent loose bowel movement.
- For persistent grades 1–2 diarrhea (after 24 hours of loperamide)
  - ☐ Begin high-dose loperamide at an initial dose of 4 mg followed by 2 mg every 2 hours and 4 mg every 4 hours at night.
  - ☐ Consider atropine-diphenoxylate, 1–2 tablets every 6–8 hours.
  - ☐ If diarrhea persists for more than 24 hours, start oral antibiotics.
- For grade 2 diarrhea (increase of 4–6 stools daily over baseline, moderate increase in ostomy output compared with baseline) or if unresponsive to 48 hours of high-dose loperamide
  - ☐ Stop loperamide and start octreotide, 100–150 mcg subcutaneously three times daily or other second-line agents (tincture of opium).
  - ☐ Expert opinion considers tincture of opium 0.6 ml orally every 4–6 hours useful. Because of lack of randomized, controlled trials, it cannot be unequivocally recommended for practice.
  - ☐ Patient should be seen for further evaluation, including complete stool, blood work, and skin assessment.
  - ☐ IV hydration is recommended if unable to take adequate fluids orally.
- For complicated grade 2 diarrhea and grades 3–4 diarrhea (increase of 7 stools daily over baseline or a severe increase in ostomy output over baseline)
  - ☐ Consider hospital admission.
  - ☐ Administer octreotide 100–150 mcg subcutaneously every 8 hours or 25–50 mcg per hour via IV.
  - ☐ Initiate IV fluids as needed for at least 24 hours.
  - ☐ Initiate total parenteral nutrition as indicated.
  - ☐ Initiate antibiotics (if an infectious cause is suspected).
  - ☐ Perform stool workup (for pathogens), laboratory studies, and skin assessment.
- For patient experiencing significant diarrhea, hold chemotherapy until complete resolution of symptoms for at least 24 hours without antidiarrheal therapy.

EVIDENCE-BASED DOSE MODIFICATIONS FOR CANCER

- Many targeted agents can cause diarrhea. Dose modifications are at the discretion of the treating provider and are dependent upon the type of cancer, goals of cure versus control of the cancer, and diarrhea severity.

MANAGEMENT OF DIARRHEA IN TARGETED AGENTS OF INTEREST

Common causes of moderate to severe chemotherapy-induced diarrhea by class and incidence include the following:

- Histone deacetylase inhibitors: Panobinostat (overall incidence 68%, with grades 3 and 4 incidence of 25%)
  - ☐ At first sign of abdominal cramping, loose stools, or onset of diarrhea, begin antidiarrheal medication.
  - ☐ Grade 2 (moderate diarrhea, 4–6 stools per day): Interrupt panobinostat until resolved and then restart at the same dose.
  - ☐ Grade 3 (severe diarrhea, 7 or more stools per day, IV fluids, or hospitalization required): Interrupt panobinostat treatment until resolved and then restart at a reduced dose.
  - ☐ Grade 4 (life-threatening): Permanently discontinue panobinostat.
- Immunomodulatory drugs: Lenalidomide (29%) and pomalidomide (35%)
  - ☐ At onset, rule out other causes of infection and begin antidiarrheal medication.
  - ☐ For lenalidomide and pomalidomide, the manufacturer recommends holding the medication for moderate to severe diarrhea and resuming when the diarrhea returns to grade 2.
  - ☐ Symptomatic management with cholestyramine or loperamide is recommended.
  - ☐ Lenalidomide-induced diarrhea typically occurs after 17.7 months of therapy; diarrhea occurs in 46% of patients with continuous lenalidomide/dexamethasone.
- Proteasome inhibitors: bortezomib (52% with monotherapy; less common with combined therapy), carfilzomib (25%), ixazomib (42%, with 6% grade 3)
  - ☐ Administer antidiarrheal for grade 1 diarrhea associated with proteasome inhibitor use.
  - ☐ Management of proteasome inhibitor–associated diarrhea: Withhold therapy until symptoms of toxicity have resolved to grade 1 or baseline, and rule out other causes of diarrhea.
    - If bortezomib or carfilzomib: Resume with one dose level reduction at the discretion of the provider.
    - If ixazomib: Diarrhea rarely leads to treatment discontinuation; symptomatic management with loperamide is recommended.
- Selinexor (XPO1 inhibitor; 42% diarrhea overall and 3% grade 3): Administer antidiarrheal for mild grade 1 toxicity, and encourage dietary strategies.
  - ☐ Weight loss and anorexia are unique side effects of selinexor. Dose modification for severe grade 3 toxicities, such as weight loss and anorexia, should be considered.

Note. Based on information from Amgen, 2016; Faiman et al., 2013; Millennium Pharmaceuticals, 2017; National Comprehensive Cancer Network, 2016; Novartis, 2015; Smith et al., 2008; Takeda Pharmaceutical Company, 2015, 2016.

phenomenon (Faiman, 2016). Diarrhea is also an immediate side effect of bortezomib, ixazomib, and other agents prescribed for the treatment of MM. Late-onset diarrhea occurs in as many as 45% of individuals from exposure to oral lenalidomide, possibly because of an immune effect and a fairly common long-term side effect (Celgene Corporation, 2010; Faiman, 2016; Tariman, 2017). The consequences of diarrhea can be mild and transient or, for some, severe and life-threatening. Figure 5 presents the approach to assessment and differential diagnosis of diarrhea in patients with MM.

Constipation is defined as a decreased frequency of defecation, usually less than three bowel movements per week, with accompanying abdominal discomfort. This is a common problem in patients with cancer who have poor oral intake or take drugs like opioids or antiemetics that slow intestinal transit time (Smith et al., 2008).

Nausea is an uncomfortable feeling that occurs in the throat or stomach and may or may not result in vomiting. Acute nausea usually occurs within a few minutes to several hours after administration of anticancer agents and often resolves within the first 24 hours. Delayed nausea occurs more than 24 hours after administration of anticancer agents, peaks 48–72 hours after treatment, and can last 6–7 days. Patients may also experience anticipatory nausea, which is a conditioned response that occurs before they receive an anticancer treatment. Once a patient has been determined to have or to be at risk for nausea, it is appropriate to recommend prophylactic and therapeutic interventions and to implement an effective nausea management plan.

Some antiemetic therapies may be helpful for nausea and vomiting (see Figure 6). Antiemetics for older adult patients should have a low risk of drug–drug interactions and a simple, convenient dosing regimen (Smith et al., 2008).

Vomiting is a separate act from nausea and often a result of an episode of nausea (Smith et al., 2008). Fortunately, outside of transplantation with high-dose chemotherapy, vomiting is rare among patients with MM who receive newer classes of drugs.

Anorexia and weight loss are common and unique GI side effects of an emerging therapy currently in clinical trials, selinexor (Vogl et al., 2016). Selinexor is a first-in-class exportin 1 (XPO1) inhibitor that induces nuclear retention and activation of tumor suppressor proteins and the glucocorticoid receptors and suppresses oncoprotein expression (Turner et al., 2016; Vogl et al., 2016). In a clinical trial, selinexor was found to be effective in combination with corticosteroids in patients who were no longer responding to treatment with five prior therapies (i.e., lenalidomide, bortezomib, carfilzomib, daratumumab, and isatuximab). Despite premedication with a 5-HT3 receptor antagonist, patients in the study experienced nausea (72% overall, 6% for grade 3), anorexia (49% overall, 3% for grade 3), vomiting (43% overall, 4% for grade 3), diarrhea (42% overall, 5% for grade 3), and weight loss (33% overall, 1% for grade 3) (Vogl et al., 2016). Although management of diarrhea, nausea, and vomiting has been associated with newer agents, it is important to emphasize that anorexia and weight loss with selinexor are unique side effects that can occur, and patients taking this drug should be effectively monitored.

Guidance for strategies to manage GI side effects of selinexor can be modeled from clinical trials experience. For patients who experience nausea, ensure they are taking proton pump inhibitor drugs, such as omeprazole, lansoprazole, or esomeprazole. For moderate to severe nausea, vomiting, anorexia, diarrhea, or weight loss, holding selinexor until the symptom improves and resuming at a lower dose level are recommended. Nurses can intervene if anorexia and weight loss are observed by advising patients to eat small, high-caloric meals consisting of food that is not greasy, acidic, fried, or spicy to minimize stomach upset. Patients can proceed to appetite stimulants if initial dietary interventions are not successful. As with any severe toxicity, such as weight loss of greater than 10% (can be more than 20–40 lbs depending on the size of the individual), dietary supplements for weight gain and holding of the drug until the symptom improves or resolves should be considered (Vogl et al., 2016).

Smith et al. (2008) previously presented patient characteristics and clinical features of GI complications in patients with MM treated with typical agents (http://bit.ly/2wEzJ2d). Figure 7 contains information for managing GI side effects with novel agents used to treat MM.

Evidence-Based Recommendations for Gastrointestinal Symptoms

LEVEL OF EVIDENCE II

- The IMF NLB recommends dose modifications of causative agents when GI symptoms from MM therapies, such as uncontrolled nausea, vomiting, diarrhea, constipation, and weight loss, persist despite employing best practices in preventive and supportive care.
- Selinexor represents a new class of drugs with weight loss, anorexia, nausea, vomiting, and diarrhea as common side effects. Optimizing antiemetic, antidiarrheal, and dietary strategies is the best recommended first-line management. If side effects persist and affect quality of life, holding or decreasing the dose of selinexor may allow patients to stay on therapy longer.

Peripheral Neuropathy Symptoms

PN is commonly cited as a major side effect of MM therapy that can negatively affect a patient's quality of life (Richardson et al., 2012; Sonneveld et al., 2013). PN symptoms can occur in as many as 75% of individuals secondary to disease progression or after prolonged exposure to neurotoxic therapies, such as thalidomide and bortezomib (Richardson et al., 2012). Patients with PN experience a variety of symptoms, such as mild discomfort, loss of sensation, painful burning, muscle cramping, heightened sensitivity to temperature variations, impaired fine-motor skills, and paralysis in the most severe cases (Hershman et al., 2014; Richardson et al., 2012; Tariman, Love, McCullagh, & Sandifer, 2008). These deleterious

effects can be cumulative over time and can cause significant morbidity, limit a patient's ability to receive the appropriate doses of anticancer medication, and lead to decreased cancer treatment compliance (Kaplan, Torcun, Grune, Ozer, & Karademir, 2017). Paying attention to the drugs and conditions that can cause PN and preserving nerve function are critical (Richardson et al., 2012).

Clinical Presentations and Pathophysiology

To understand the pathology of PN, the normal neurophysiologic function of the peripheral nervous system must be reviewed. Each neuron consists of a cell body, dendrites that synapse with other nerves, and an axon that is often surrounded by Schwann cells that form a myelin sheath. The cell bodies of sensory neurons are bundled together within the dorsal root ganglia. Motor nerve cell bodies are in the ventral spinal cord. The motor and sensory neurons are responsible for different actions. Motor neurons carry signals from the central nervous system to muscles and glands. Large, myelinated sensory neurons are responsible for the perception of vibration, proprioception (body position), and light touch, whereas small, myelinated sensory neurons transmit impulses for temperature. Pain impulses can be transmitted by either small myelinated or unmyelinated nerve fibers (Poncelet, 1998).

PN occurs when peripheral nerves are damaged or inflamed or when degeneration has occurred, leading to changes in the way the

FIGURE 8.
HEALTHCARE PROVIDER TIP SHEET: PERIPHERAL NEUROPATHY EVALUATION AND MANAGEMENT

PRIOR TO START OF THERAPY

- Baseline neurosensory examination of extremities (based on the use of neurotoxicity assessment)
  - ☐ For preexisting neuropathy, rule out other possible causes.
- Take B-complex vitamins, including B_1, B_6, B_{12} (based on anecdotal evidence).
- Take folic acid.
- Provide patient education on signs and symptoms of peripheral neuropathy.

MILD SYMPTOMS OR GRADE 1

- Neurosensory examination of extremities (based on the use of neurotoxicity assessment)
- Continue therapy and educate patient to notify clinicians immediately if peripheral neuropathy worsens.

MODERATE SYMPTOMS OR GRADE 2

- Neurosensory examination of extremities based on the use of neurotoxicity assessment
- If symptoms are intermittent, continue therapy.
- If continuous, stop therapy and see if symptoms continue.
- If symptoms resolve, restart therapy at a reduced dose.
- Consider amitriptyline.
- Try using amino acids, such as acetyl-L-carnitine and alpha-lipoic acid, on an empty stomach (based on anecdotal evidence).
- For intermittent symptoms, try gently massaging areas with cocoa butter.

SEVERE SYMPTOMS OR GRADE 3

- Hold therapy until resolution to baseline.
- Perform nerve conduction studies.
- Make sure patient is on amino acids (based on anecdotal evidence).
- Consider using gabapentin or pregabalin.
- Try lidocaine patch on affected area every 12 hours.
- Provide education on decreased sensation in extremities and safety issues.
- Assess need for assistance with ADLs.

NEUROTOXICITY ASSESSMENT

Ask patients to rate the following items on a scale from 0 (not at all) to 4 (very much). Healthcare providers may find discussion of patients' responses helpful in determining the grade of neuropathy as defined by the National Cancer Institute CTCAE. However, there is no direct correlation between assessment scores and toxicity grades.

- I have numbness or tingling in my hands.
- I have numbness or tingling in my feet.
- I feel discomfort in my hands.
- I feel discomfort in my feet.
- I have joint pain or muscle cramps.
- I feel weak all over.
- I have trouble buttoning buttons.
- I have trouble feeling the shape of small objects when they are in my hand.
- I have trouble walking.

CTCAE GRADING

Peripheral sensory neuropathy

- 1: Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function
- 2: Sensory alteration or paresthesia (including tingling); interfering with function but not ADLs
- 3: Objective sensory alteration or paresthesia; interfering with ADLs
- 4: Disabling or life-threatening
- 5: Death

Neuropathic pain

- 1: Mild pain not interfering with function
- 2: Moderate pain; pain or analgesics interfering with function but not ADLs
- 3: Severe pain; pain or analgesics severely interfering with ADLs
- 4: Disabling; referral to neurology or pain management
- 5: Death

ADL—activity of daily living; CTCAE—Common Terminology Criteria for Adverse Events
Note. Based on information from Calhoun et al., 2003; Cella et al., 1993; National Cancer Institute, 2010.

nerves function (Ferrier, Pereira, Busserolles, Authier, & Balayssac, 2013). The mechanism of PN in MM is not well characterized but is thought to be because of a combination of direct damage to nerve cells, toxicity to the dorsal root ganglion, and decreased nerve blood flow (Ferrier et al., 2013; Richardson et al., 2012).

IMPLICATIONS FOR PRACTICE

- Encourage patients to assess for trouble buttoning shirts or walking and to alert the healthcare team if increased numbness or tingling occurs.
- Increase detection of neurologic effects by becoming aware of drugs that can cause the effects.
- Hold or reduce dose of the offending chemotherapy agent to allow patients to remain on therapy longer to control multiple myeloma.

Diagnosis

There is no gold standard for the diagnosis or measurement of chemotherapy-induced PN; however, patient self-report of symptoms remains the most common diagnostic technique (Tofthagen & Irwin, 2014; Visovsky et al., 2012). Electromyography is a technique that involves the placement of a needle into various muscles to record different stages of muscle activity, including rest, contraction, and activity. This technique can be useful in detecting motor neuropathy but is less accurate in detecting the sensory changes most commonly encountered in MM; however, detection methods for PN, including electromyography, are lacking (Preston & Shapiro, 2005).

Nerve conduction studies can also be performed to diagnose PN and distinguish from other disorders. These studies measure the velocity and size of the signal along a nerve, allowing neurologists to evaluate nerve myelination and muscle contraction amplitude. This procedure can aid in categorizing the pathophysiology of the PN as demyelinating, axonal, or mixed (Preston & Shapiro, 2005).

PN assessment and monitoring are largely based on patient self-report of symptoms, which commonly include pain, numbness, tingling, or all three of those symptoms. The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity is an 11-item questionnaire that addresses patient-reported concerns likely to be associated with chemotherapy-induced PN (Calhoun et al., 2003; Cella et al., 1993; Cella & Webster, 1999). This instrument, with scores ranging from 0–44 on a continuous scale (with higher scores indicating greater impairment), has been validated in patients with neurotoxicity associated with ovarian cancer chemotherapy, and has been used in several MM studies (Richardson et al., 2012).

Evidence-Based Recommendations for Management of Peripheral Neuropathy

The IMF NLB has reviewed over-the-counter preventive and treatment strategies for PN. These recommendations can be found in Figure 8.

LEVEL OF EVIDENCE II

- The IMF NLB recommends dose reduction of the causative agent or a change to subcutaneous route of administration, and discontinuation of bortezomib with the onset of moderate PN (Richardson, Sonneveld, et al., 2009). To date, few interventions have been documented to prevent or treat neuropathy in patients with MM (Faiman et al., 2013; Moreau et al., 2011; Richardson et al., 2012; Richardson, Xie, et al., 2009; Takeda Pharmaceutical Company, 2016; Tsubaki et al., 2015; Velasco et al., 2010). However, dose reduction or discontinuation may come at the expense of inferior disease control.

LEVEL OF EVIDENCE III

- The IMF NLB recommends to consider the use of glutamine for prevention of PN in patients with MM receiving a neurotoxic agent, such as bortezomib. Glutamine, a naturally occurring nonessential amino acid, is easy to use, well absorbed, and cost effective. Two key studies (Hall, Heel, & McCauley, 1996; Klimberg et al., 1992) support the safety and efficacy of oral glutamine in preventing cancer treatment–induced PN. The glutamine group had a lower incidence of severe (grades 3–4) PN than the placebo group and, therefore, less need to reduce the chemotherapy dose. In one small trial of patients with colorectal cancer, response rates for the glutamine and nonglutamine groups (52.4% and 47.8%, respectively) were not significantly different, suggesting that glutamine does not interact with the efficacy of the chemotherapy regimen (Wang et al., 2007). A second randomized pilot study of oral glutamine in MM demonstrated a medium effect size (0.43) of glutamine on neuropathy symptoms and a large effect on quality of life (1.09). In this study, diarrhea and nausea were mild (grade 1) in both study groups. Drug-related grade 3 or 4 toxicities did not occur in any study participant (Faiman, Zhang, Moore, Daly, & Reu, 2015).
- The IMF NLB recommends the use of the most widely studied over-the-counter supplements with varying suggested benefits for CIPN. In addition to glutamine, these include B vitamins, magnesium, potassium, and glutathione (Cascinu et al., 2002; Hershman et al., 2014; Vahdat et al., 2001), alpha-lipoic acid (Ziegler, Nowak, Kempler, Vargha, & Low, 2004); acetyl-L-carnitine (Bianchi et al., 2005); and vitamin E (Pace et al., 2003). These supplements may have activity in the prevention and treatment of PN.

Conclusion

Symptoms related to renal, GI, or peripheral nerve organ damage in patients with MM should be assessed and treated promptly if they are present at initial diagnosis and throughout therapy. Preventive measures should be initiated at diagnosis and continue throughout the disease course. Evidence-based recommendations for the management of organ damage–related symptoms should be updated as the need arises. The prevention of acute and long-term organ damage gives patients with MM more therapeutic options

and offers them the opportunity to achieve a longer overall survival and a better quality of life.

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