

Steroid-Associated Side Effects in Patients With Multiple Myeloma: Consensus Statement of the IMF Nurse Leadership Board

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Steroids have been the foundation of multiple myeloma therapy for more than 30 years and continue to be prescribed as single agents and in combination with other antimyeloma drugs, including novel therapies. Steroids cause a wide range of side effects that affect almost every system of the body. Identification and prompt management of the toxicities contribute to the success of steroid-containing antimyeloma regimens. By following patients carefully and educating them and their caregivers, nurses can promote adherence to therapy and improve quality of life. The International Myeloma Foundation's Nurse Leadership Board developed this consensus statement for the management of steroid-associated side effects to be used by healthcare providers in any medical setting.

Glucocorticosteroids or corticosteroids, referred to in this article as steroids, include dexamethasone, prednisone, and prednisolone. The agents have been a backbone of therapy for multiple myeloma since the late 1960s (Alexanian et al., 1969), followed by the use of dexamethasone in combination therapy and as a single agent in the 1980s and 1990s (Alexanian, Dimopoulos, Delasalle, & Barlogie, 1992). The novel immunomodulatory drugs lenalidomide (Revlimid®, Celgene Corporation) and thalidomide (Thalomid®, Celgene Corporation) are indicated with concomitant dexamethasone (Celgene Corporation, 2007a, 2007b). The proteasome inhibitor bortezomib (Velcade®, Millennium Pharmaceuticals, Inc.), although indicated as a single agent, also may be administered in combination with dexamethasone (Millennium Pharmaceuticals, Inc., 2007).

Steroids can cause a wide range of adverse events that affect almost every system of the body (Merck & Co., Inc., 2004; Tariman & Estrella, 2005; Watson Laboratories, Inc., 2006). Identification and prompt management of the toxicities, as well as patient and caregiver education, are vital to the success of steroid-containing antimyeloma regimens. In recognition of the need for specific recommendations on managing key side effects of steroid therapy for patients with myeloma, the International Myeloma Foundation's Nurse Leadership Board developed this consensus statement for the management of steroid-associated side effects to be used by healthcare providers in any medical setting (Bertolotti et al., 2007, 2008).

Issue Statement

Dexamethasone and prednisone inhibit the expression of cytokines (e.g., interleukin-6), which are major growth factors for

At a Glance

- ◆ Steroids (glucocorticosteroids or corticosteroids), including dexamethasone, prednisone, and prednisolone, are a backbone of multiple myeloma therapy and are used as single agents and in combination regimens.
- ◆ Steroids can cause a wide range of mild to life-threatening side effects that affect almost every body system.
- ◆ Steroid-associated side effects can be managed effectively with careful patient monitoring; appropriate prophylaxis, pharmacologic, and nonpharmacologic interventions; and patient and caregiver education.

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myeloma cells, and reduce the activity of nuclear factor-kappa B, leading to apoptosis (programmed cell death) (Alexanian et al., 1992; Berenson et al., 2002). However, steroids can adversely affect multiple body systems; have a significant impact on patients' physical, social, and psychological functioning; and result in decreased quality of life and reduced treatment adherence. Adverse effects can lead to less effective dosing, which has a negative impact on treatment and survival outcomes. The management strategies described in this article may increase treatment adherence, which may result in optimal therapy responses and improved quality of life.

Strategic Recommendations

- Medical personnel should be aware of the potential side effects of steroid therapy on multiple body systems.
- Nurses should assess all patients by taking a history, performing a physical examination, and reviewing medications.
- Patients and their families should be educated about the potential side effects of steroid therapy.
- Nurses and patients' families should apply appropriate interventions if the side effects occur.
- Patients should understand the importance of informing their healthcare providers about all medications, including over-the-counter herbs and vitamins, and not self-medicating without consulting the healthcare team.

Toxicity Tool for Grading and Managing Adverse Events

Figure 1 outlines the steroid-related side effects that patients with multiple myeloma receiving steroid-based therapy are likely to experience. The severity of the adverse events can be quantified and assigned a grade of severity through the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). Table 1 lists NCI CTCAE version 3.0 toxicity grades for adverse events that correspond to the steroid side effects listed in Figure 1. The grades may be used for monitoring steroid-related toxicities, researching, and determining the need for and types of interventions. The grades also allow for consistency of evaluation among healthcare providers, which is important for patients who need referral to specialists for management of steroid-related side effects. For each system, pharmacologic, nonpharmacologic, and educational strategies are recommended as appropriate.

Constitutional Signs and Symptoms

“Let down” effect: This usually is characterized by fatigue or “weakness” and myalgia following discontinuation of steroids. It may occur when patients are receiving high-dose steroids (e.g., dexamethasone) several days each week. Pharmacologic interventions include low-dose steroids for a few days following high-dose steroid administration, tapered doses of steroids, and reduced steroid doses. Figure 2 presents a suggested dexamethasone taper schema. However, dose re-

Body Image Weight gain, increased appetite Cushingoid appearance Hirsutism or alopecia	Immune Leukocytosis Infection
Cardiovascular Edema	Musculoskeletal Proximal myopathy Osteonecrosis (avascular necrosis) Osteopenia or osteoporosis Muscle cramping
Constitutional “Let down” effect after discontinuing steroids Flushing or sweating Insomnia	Ophthalmic Blurred vision Cataracts
Dermatologic Acneform rash Thinning of skin	Psychiatric Personality changes and mood alterations (anxiety) Hyperactivity
Endocrine Steroid-induced hyperglycemia Adrenal insufficiency Hypogonadism	Sexual Dysfunction
Gastrointestinal Gastric or duodenal ulcer Heartburn (dyspepsia) Flatulence Taste alteration (dysgeusia) Hiccoughs (hiccups, singultus)	

Figure 1. Steroid-Related Side Effects

ductions for dexamethasone should be based on the clinician's experience and the patient's symptoms. Reducing the dose of dexamethasone may reduce the risk of thromboembolic events, particularly if administered in combination with other antimyeloma agents, such as lenalidomide and thalidomide (Rome et al., 2008). Patients should be advised about adjusting their activity schedules to deal with associated fatigue (Mitchell, Beck, Hood, Moore, & Tanner, 2006).

Flushing or sweating: When flushing or sweating occur, comorbid conditions such as infection, cardiovascular abnormalities, and hyperthyroidism should be ruled out by appropriate assessments and laboratory tests. Perimenopause in women should be ruled out by appropriate assessments and laboratory tests for hormonal status, if indicated. Nonpharmacologic interventions include patient education about using cold cloths and ice packs, maintaining hydration, and layering clothes.

Insomnia: Patients may benefit from altering the timing of medications (e.g., taking steroids in the morning so they wear off by evening). Pharmacologic interventions include hypnotics and sedatives; the drug class of choice should be determined by the grade of insomnia as well as the type of insomnia (e.g., difficulty falling asleep versus difficulty staying asleep). Nonpharmacologic interventions include evaluation of sleep habits and education regarding sleep hygiene (e.g., taking a warm bath before bed, not watching television or reading in bed) (Page, Berger, & Johnson, 2006). In addition to steroid-related insomnia, other causes of sleeplessness in patients with

Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events: Steroid-Related Toxicity Grades

SYSTEM AND ADVERSE EVENT	GRADE 1 (MILD)	GRADE 2 (MODERATE)	GRADE 3 (SEVERE)	GRADE 4 (LIFE THREATENING OR DISABLING)	GRADE 5 (DEATH)
Constitutional					
"Let-down" effect (fatigue ^a)	Mild fatigue over baseline	Moderate or causing difficulty with some activities of daily living	Severe fatigue interfering with activities of daily living	Disabling	Not applicable
Flushing	Asymptomatic	Symptomatic	Not applicable	Not applicable	Not applicable
Sweating (diaphoresis)	Mild and occasional	Frequent or drenching	Not applicable	Not applicable	Not applicable
Insomnia	Occasional difficulty sleeping, not interfering with function	Difficulty sleeping; interfering with function but not interfering with activities of daily living	Frequent difficulty sleeping; interfering with activities of daily living	Disabling	Not applicable
Sexual dysfunction					
Erectile dysfunction	Decrease in erectile function (frequency or rigidity of erections) but erectile aids not indicated	Decrease in erectile function (frequency or rigidity of erections) but erectile aids indicated	Decrease in erectile function (frequency or rigidity of erections) but erectile aids not helpful; penile prosthesis indicated	Not applicable	Not applicable
Libido	Decrease in interest but not affecting relationship; intervention not indicated	Decrease in interest and adversely affecting relationship; intervention indicated	Not applicable	Not applicable	Not applicable
Psychiatric					
Personality changes	Change, but not adversely affecting patient or family	Change; adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Mood alteration ^b	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function but not interfering with activities of daily living; medication indicated	Severe mood alteration interfering with activities of daily living	Suicidal ideation; danger to self or others	Death
Immune					
Infection	Not applicable	Localized; local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	Death
Musculoskeletal					
Muscle weakness (proximal myopathy)	Asymptomatic weakness on physical examination	Symptomatic and interfering with function but not interfering with activities of daily living	Symptomatic and interfering with activities of daily living	Life threatening or disabling	Death

(Continued on next page)

^a Also see "myalgia" under "Musculoskeletal."

^b Select agitation, anxiety, depression, or euphoria.

Note. Based on information from National Cancer Institute, 2006.

Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events: Steroid-Related Toxicity Grades (Continued)

SYSTEM AND ADVERSE EVENT	GRADE 1 (MILD)	GRADE 2 (MODERATE)	GRADE 3 (SEVERE)	GRADE 4 (LIFE THREATENING OR DISABLING)	GRADE 5 (DEATH)
Osteonecrosis (avascular necrosis)	Asymptomatic; radiographic findings only	Symptomatic and interfering with function but not interfering with activities of daily living; minimal bone removal indicated (i.e., minor sequestrectomy)	Symptomatic and interfering with function but not interfering with activities of daily living; operative intervention or hyperbaric oxygen indicated	Disabling	Death
Osteoporosis	Radiographic evidence of osteoporosis or bone mineral density t score 1–2.5 (osteopenia); no loss of height	Bone mineral density t score < –2.5; loss of height < 2 cm; antiosteoporotic therapy indicated	Fractures; loss of height ≥ 2 cm	Disabling	Death
Muscle cramping	Mild	Moderate	Severe	Life threatening or disabling	Not applicable
Body image					
Weight gain	5% to < 10% of baseline	10% to < 20% of baseline	20% of baseline	≥ 20% of baseline	Not applicable
Cushingoid appearance	Not applicable	Present	Not applicable	Not applicable	Not applicable
Hair loss (alopecia)	Thinning or patchy	Complete	Not applicable	Not applicable	Not applicable
Ophthalmic					
Blurred vision	Symptomatic; not interfering with function	Symptomatic and interfering with function but not interfering with activities of daily living	Symptomatic and interfering with activities of daily living	Disabling	Not applicable
Cataracts	Asymptomatic; detected on examination only	Symptomatic with moderate decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	Not applicable	Not applicable
Gastrointestinal					
Ulcer, gastric or duodenal	Asymptomatic; radiographic or endoscopic findings only	Symptomatic; altered gastrointestinal function (e.g., altered dietary habits, oral supplements); IV fluids indicated < 24 hours	Symptomatic and severely altered gastrointestinal function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or total parenteral nutrition indicated ≥ 24 hours	Life threatening consequences	Death
Heartburn or dyspepsia	Mild	Moderate	Severe	Not applicable	Not applicable

(Continued on next page)

^a Also see “myalgia” under “Musculoskeletal.”

^b Select agitation, anxiety, depression, or euphoria.

Note. Based on information from National Cancer Institute, 2006.

Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events: Steroid-Related Toxicity Grades (Continued)

SYSTEM AND ADVERSE EVENT	GRADE 1 (MILD)	GRADE 2 (MODERATE)	GRADE 3 (SEVERE)	GRADE 4 (LIFE THREATENING OR DISABLING)	GRADE 5 (DEATH)
Flatulence	Mild	Moderate	Not applicable	Not applicable	Not applicable
Taste alteration (dysgeusia)	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	Not applicable	Not applicable	Not applicable
Hiccoughs (hiccups, singultus)	Symptomatic; intervention not indicated	Symptomatic; intervention indicated	Symptomatic; significantly interfering with sleep or activities of daily living	Not applicable	Not applicable
Endocrine					
Hyperglycemia	> upper limit of normal to 160 mg/dl	> 160 to 250 mg/dl	> 250 to 500 mg/dl	> 500 mg/dl	Death
Adrenal insufficiency	Asymptomatic; intervention not indicated	Symptomatic; intervention indicated	Hospitalization	Life threatening or disabling	Death
Cardiovascular					
Edema	Mild	Moderate	Severe	Life threatening or disabling	Death
Dermatologic					
Acne or acneform rash	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	Not applicable	Death
Atrophy	Detectable	Marked	Not applicable	Not applicable	Not applicable

^aAlso see "myalgia" under "Musculoskeletal."

^bSelect agitation, anxiety, depression, or euphoria.

Note. Based on information from National Cancer Institute, 2006.

myeloma should be considered, such as pain and obstructive sleep apnea, which may result from steroid-related weight gain. Nurses should ask patients what keeps them up at night and whether they have trouble falling asleep or staying asleep. The questions will help to identify whether insomnia is steroid related or caused by a different issue.

Sexual Dysfunction

In men, rule out other causes by checking testosterone levels and evaluate for neuropathy and other comorbidities. Evaluate for pharmacologic interventions, including hormone supplementation if needed, and phosphodiesterase-5 inhibitors if indicated. Nonpharmacologic interventions include patient education and support as deemed advisable by the clinician and possible referral to a urologist if pharmacologic interventions fail (National Library of Medicine & National Institutes of Health, 2007).

Sexual dysfunction related to steroids is not well described in women. Signs and symptoms may include lack of sexual desire, difficulty becoming aroused, lack of orgasm, vaginal dryness,

or painful vaginal intercourse. If such conditions exist, consider referral to an appropriate specialist.

Psychiatric Signs and Symptoms

Personality changes or mood alterations: Patients should be evaluated with a predetermined depression tool (MacArthur Initiative on Depression and Primary Care, 2003–2006; National Institutes of Mental Health, 2007). Patients should be asked about suicidal ideation. Patients and their families should receive counseling and education regarding the potential for steroid-associated mood changes that may be severe. Referrals to support groups and psychosocial services (e.g., social worker, psychiatrist) should be considered. Pharmacologic interventions include dose reduction and discontinuation of steroids and dosing in the morning versus later in the day. The use of selective serotonin reuptake inhibitors or mood stabilizers (e.g., citalopram, escitalopram, olanzapine) may help not only with mood alterations but also with insomnia and hyperactivity (Badger, Fulcher, Gunter, Marrs, & Reese, 2006; Cerullo, 2006).

- If taking dexamethasone 40 mg PO daily, days 1–4, 9–12, 17–21, consider 50% dose reduction if any grade 2 or grade 3 steroid toxicity occurs.
 - If dose is already reduced, consider reducing dose frequency days 1–4 and 15–18, at a dose of dexamethasone 20 mg PO each day if grade 2 or grade 3 toxicity persists.
 - Consider further reduction to days 1–4 each month if grade 2 or grade 3 toxicity persists.
 - Consider dexamethasone 40 mg at weekly intervals.
 - Consider stopping steroids if grade 2 or grade 3 toxicity persists despite dose reductions.
- If taking dexamethasone 40 mg PO daily, days 1–4 and 15–18, follow dose reduction schedule as above, starting with 50% dose decrease with the first evidence of grade 2 or grade 3 toxicity.
 - Consider further reduction to days 1–4 each month if grade 2 or grade 3 toxicity persists.
 - Consider stopping steroids if grade 2 or grade 3 toxicity persists despite dose reductions.
- If taking dexamethasone 40 mg PO daily, days 1–4, consider steroid taper if grade 2 or grade 3, such as
 - 40 mg PO days 1–3, then 20 mg PO day 4, 12 mg PO day 5, 8 mg PO day 6, and 4 mg PO day 7
- If taper is ineffective and grade 2 or grade 3 toxicities persist, consider dexamethasone 20 mg PO daily days 1–4.

Note. Dose reductions for dexamethasone should be based on clinician experience and the most current clinical data available. A recent Eastern Cooperative Oncology Group clinical trial in patients with newly diagnosed multiple myeloma showed that patients treated with lenalidomide plus low-dose dexamethasone experienced less toxicity and had improved survival compared with patients treated with lenalidomide plus high-dose dexamethasone (Rajkumar, 2007; Rajkumar et al., 2006, 2007). However, no evidence exists concerning toxicity or survival in newly diagnosed patients treated with lower doses of dexamethasone in combination with other agents, such as thalidomide or liposomal doxorubicin, nor are any data available concerning toxicity or survival for patients with relapsed or refractory myeloma treated with lower doses of dexamethasone in combination with lenalidomide, thalidomide, liposomal doxorubicin, or other agents.

Figure 2. Suggested Dexamethasone Taper

Hyperactivity: Nonpharmacologic interventions include patient education regarding taking steroids in the morning, avoiding divided doses, and negotiating activity schedules to correspond with energy levels. In addition to altering medication schedules, relaxation techniques and exercise may be effective in decreasing hyperactivity. Pharmacologic interventions include benzodiazepines and mood stabilizers (Ceruleo, 2006).

Immune System Signs and Symptoms

Leukocytosis: If a patient's white blood cell count is elevated, ask about and assess for any signs or symptoms of infection or the use of granulocyte growth factors. Patients should be educated to be aware of signs and symptoms of infection. Pharmacologic interventions include prophylaxis and treatment with antibacterial, antiviral, or antifungal agents.

Infection: Patients and caregivers should be educated to look for signs and symptoms of infection, which may be subtle because of the immunosuppressive effect of steroids (for example, chills, rigors, and aching rather than a high fever). Obtain blood, urine, sputum, and stool cultures as indicated per institutional protocol, along with chest radiograph and complete blood count with differential. Instruct the patient and his or her caregiver to call the clinician if body temperature is higher than 100.5°F (38°C). Pharmacologic interventions include antibiotics, antiviral agents, or antifungal agents as indicated based on dose and duration of steroid therapy. Prophylactic anti-infective agents for opportunistic infections such as herpes simplex virus, varicella zoster virus, and *Pneumocystis carinii* should be considered. Although prophylaxis against *Pneumocystis carinii* pneumonia and fungal infections is accepted practice, antiviral prophylaxis is controversial (Zitella et al., 2006). Recommendations in the context of neutropenia are discussed in the Nurse Leadership Board's consensus statement on myelosuppression (Miceli et al., 2008).

Musculoskeletal Signs and Symptoms

Proximal myopathy: Proximal myopathy is caused by the breakdown of proteins in muscles. Patients should be assessed to determine whether they are candidates for physical therapy, exercises that use large muscle groups, or aquatic therapy if symptoms are mild to moderate. If symptoms are severe, hold steroids until myopathy improves, then restart at a decreased dose. Patients with myeloma also are at risk for spinal cord compression because of spinal cord compromise from plasmacytoma or vertebral compression fractures. If patients are experiencing an acute onset of myopathy and loss of bowel or bladder control, immediate medical evaluation is needed to rule out spinal cord compression. Patients should check with their healthcare providers about the use of weights and appropriate weight limits for exercises because of bone involvement in the spine and the risk of compression fracture.

Avascular necrosis: Avascular necrosis or osteonecrosis results from the temporary or permanent loss of blood supply to bones. Although its incidence is low, it is a concern (Talamo et al., 2005). Obtain radiographs or magnetic resonance imaging of the affected and contralateral joints; a high probability exists that the contralateral joint may be affected. Pain assessment with appropriate pharmacologic intervention is needed frequently. Refer promptly to an orthopedist for evaluation, which may result in recommendations for conservative (nonsurgical) or surgical approaches. Consider discontinuation of steroid use.

Osteopenia and osteoporosis: Steroids increase bone loss in several ways. They reduce bone formation by inhibiting osteoblasts and increasing osteoblast apoptosis, stimulating bone resorption, inhibiting intestinal absorption of calcium, and increasing urinary excretion of calcium (Lindsay & Cosman, 2005).

A baseline bone density scan should be obtained if other risk factors for osteoporosis are present (e.g., older age, postmenopausal status in women, history of smoking, presence of lytic lesions).

The following are recommendations for the general use of bisphosphonates and calcium supplementation in individuals

with multiple myeloma, as well as some helpful education tips (Dawson-Hughes, Harris, Krall, & Dallal, 1997; Guise, 2006; Jackson et al., 2006; Lips, Graafmans, Ooms, Bezemer, & Bouter, 1996; Sambrook, 2005).

- Calcium supplementation is advised for patients taking bisphosphonates, particularly zoledronic acid. Nurses should be aware that calcium supplementation is contraindicated in patients with hypercalcemia or significant renal dysfunction, either of which may be present in patients with myeloma.
- The National Osteoporosis Foundation makes the following recommendations for vitamin D intake.
 - Adults younger than 50 need 1,000 mg of calcium and 400–800 IU of vitamin D₃ daily.
 - Adults 50 or older need 1,200 mg of calcium and 800–1,000 IU of vitamin D₃.
- Patients taking bisphosphonates should continue with current treatment guidelines.
- Patients should make sure their dental care providers are aware that they are taking bisphosphonates.

Weight-bearing exercise is essential for all patients with osteopenia or osteoporosis and should be advised for most days. Exercise may improve quality of life, muscle strength, and cardiorespiratory function in patients with myeloma (Groeneveldt et al., 2007).

Muscle cramping: Although the mechanism of steroid-related muscle cramping is unknown, the symptom may be caused by water retention and fluid or electrolyte shifts. Assess for electrolyte imbalances (sodium, potassium, calcium, and magnesium, which may be altered with the fluid shifts associated with steroids) and replace as needed. Assess for dehydration and replace fluids orally if possible; consider IV fluids if necessary. Muscle relaxants such as baclofen may be considered. L-glutamine has been noted to be beneficial for muscle cramping in doses ranging from 1–3 g per day in divided doses (Colson, Doss, Swift, Tariman, & Thomas, 2004).

Guidelines for the use of quinine sulfate in the treatment of leg cramps: Serious adverse reactions, including death, have been reported in patients who had taken quinine sulfate. Quinine is an older drug that is approved for the treatment of malaria. In the past, some practitioners have prescribed the drug off label to treat leg cramps and similar conditions. Malaria is life threatening; therefore, the risks associated with quinine use are justified for that condition. However, according to the U.S. Food and Drug Administration (2006), the drug should not be used to prevent or treat leg cramps because of its serious risks.

Body-Image Signs and Symptoms

Obesity and cushingoid appearance: Central obesity, Cushingoid facies, increased appetite, and weight gain are common side effects of steroid therapy. They may lead to steroid-induced diabetes and insulin resistance, as well as body-image issues. Nonpharmacologic interventions include evaluating diet, referring to a dietician and support group, encouraging physical activity, managing diabetes if it occurs, and providing psychological support.

Changes affecting hair: Hirsutism (excessive hairiness), alopecia (loss of hair), or hair thinning may occur in patients on

steroid therapy. Therefore, patients should be informed about the possibility of the two conditions. If one of the conditions does occur, rule out endocrinopathies, such as hypothyroidism. Patients with alopecia or thinning hair should avoid excessive hair coloring or permanent straightening or curling of the hair because such activities may cause scalp irritation and damage hair.

Ophthalmic Signs and Symptoms

Blurred vision: Transient blurry vision may occur with steroid use because of fluid shifts in the aqueous humor or uncontrolled hyperglycemia. It generally is reversible.

Cataract formation: Cataracts are a long-term adverse event associated with steroid therapy. Patients should have a baseline eye examination if possible.

General ophthalmic recommendations include not changing eyeglass prescriptions often and performing refraction (determining defects in vision and prescribing corrective lenses) only when patients are taking low-dose or no steroids. Decreasing the dose or holding steroids may be necessary until toxicity resolves to grade 2 or lower; restart once symptoms are resolved.

Gastrointestinal Signs and Symptoms

Recommendations for management of the gastrointestinal toxicities of nausea, vomiting, constipation, and diarrhea associated with the use of the novel antimyeloma agents lenalidomide and thalidomide and the proteasome inhibitor bortezomib are discussed in a separate consensus statement (Smith et al., 2008).

Ulcers and heartburn (dyspepsia): Steroids can cause gastric or duodenal (peptic) ulcers (Merck & Co., Inc., 2004; Watson Laboratories, Inc., 2006). Symptoms that resemble gastroesophageal reflux disease (GERD) or indigestion may occur. Concomitant medications should be evaluated. Patients with indigestion or symptoms of reflux may benefit from lifestyle changes. They should be advised to take their steroids with food in the morning and to avoid greasy, fried, and highly acidic foods. If reflux occurs more commonly at night, consider elevating the head of the patient's bed on blocks to raise the esophagus over the stomach. In addition, chewing gum may increase the amount of bicarbonate-containing saliva and neutralize acid. Patients and nurses, however, must be aware that symptoms of acid reflux or indigestion that worsen or do not improve should be evaluated properly (upper GI series, a test for *H. pylori*, or evaluation as indicated by a gastroenterologist). Pharmacologic recommendations include gastrointestinal prophylaxis with over-the-counter or prescription medications, including antacids, H₂ receptor inhibitors, and proton pump inhibitors (Del Valle, 2005).

Flatulence: Evaluate medications that might contribute to flatus (gas). Suggest that patients take steroids with food in the morning. Evaluate patients' diets, and consider restricting high fiber intake, because an abrupt increase in fiber can cause gas. Pharmacologic interventions include over-the-counter medications such as simethicone and bismuth subsalicylate.

Increased appetite: See "Body-Image Signs and Symptoms."

Changes in taste: Taste changes are common with steroid use, but nurses should be aware that they also may occur secondary to oral or sinus infection, decreased or absent saliva production (xerostomia), or GERD. Medications, such as certain antihypertensives, anxiolytics, chemotherapy agents, antibiotics, and zinc, also may cause taste changes, and patients with prior surgery or radiation to the neck may be at increased risk. Removing the underlying cause, if possible, is the treatment of choice, but good oral hygiene and lozenges to stimulate salivary secretions may produce palliative benefit (Doty & Bromley, 2004).

Hiccoughs: Hiccoughs (hiccups, singultus) may respond to well-known home remedies such as holding the breath while drinking water, swallowing a teaspoon of sugar, or drinking from the opposite side of a glass. Pharmacologic interventions include baclofen, chlorpromazine, and phenytoin (Woo-Ming, 2007). When hiccoughs persist, patients should be evaluated for other causes.

Endocrine Signs and Symptoms

Steroid-induced hyperglycemia: Patients should be educated about the signs and symptoms of hyperglycemia and hypoglycemia. Healthcare providers must conduct baseline assessments (Pogach et al., 2004) and refer patients to a primary care physician or endocrinologist if necessary (American Diabetes Association, 2007). Whether strict glycemic control in patients with myeloma has a significant effect on overall outcome is unknown.

- If hyperglycemia is mild, with a postprandial serum blood glucose < 200 mg/dl, and patients do not have a history of diabetes, a nonpharmacologic approach may be adequate. This includes receiving nutrition counseling to avoid simple carbohydrates and sugars, losing weight if overweight, and increasing physical activity.
- If serum glucose is > 200 mg/dl at any time, glucose monitoring with possible oral hypoglycemic agents may be needed.
- If serum glucose is > 300 mg/dl, patients may need insulin therapy at least in the short term, as well as the nonpharmacologic approaches.

Adrenal insufficiency: Acute adrenal insufficiency is characterized by dehydration, hypotension, hypoglycemia, or altered mental status and may occur from rapid cessation of long-term steroid use. Educate patients that it is a potentially life-threatening side effect; tapering steroids after long-term use is suggested. Emergent evaluation by a physician and restarting steroids are essential. Cortisol levels should be obtained (Arlt & Allolio, 2003; Wilson & Speiser, 2007).

Hypogonadism: Hypogonadism occurs when the sex glands produce little or no hormones. This is noted most symptomatically in men who experience a loss of normal male hormone production, with resulting decreases in beard and body hair, muscle loss, and breast enlargement. Women can notice hypogonadism as well, with typical postmenopausal symptoms, such as loss of menstruation, decreased libido, hot flashes, and loss of body hair. Replacing estrogen hormones in women and testosterone in men is controversial but may be a good treatment option depending on the severity of symptoms. Educate patients about the potential for this side effect. Endocrinologists are most appropriate for referral if necessary.

Cardiovascular Signs and Symptoms

Edema: Nonpharmacologic approaches include salt restriction, elevation of limbs, elastic compression stockings, and increased physical activity. If edema is moderate to severe, pharmacologic approaches include diuretics such as hydrochlorothiazide, spironolactone, and furosemide.

Dermatologic Signs and Symptoms

Acneform rashes: Acne-like rashes may occur. When they are mild, recommend that patients wash their faces twice daily with an exfoliant and keep affected areas clean. When rashes are moderate to severe with cystic or infected papules, pharmacologic treatment should be considered (e.g., topical antibiotics such as clindamycin or cephalixin, oral antibiotics).

Thinning of skin: Skin thinning, skin tearing, and bruising may occur secondary to long-term steroid use. If they occur, suggest good hygiene practices and cleansing of affected areas with sterile water. Patients should be instructed to avoid hydrogen peroxide solutions because they might impair wound healing. Instead, patients should apply triple antibiotic ointment, cover the areas with nonstick gauze for the first five days, and then allow the areas to remain exposed to air to promote healing. Patients also should be advised to avoid trauma by wearing long sleeves and to be cautious during activities to decrease the risk of skin tears.

Conclusions

Corticosteroid therapy can cause mild to severe adverse events that affect almost every body system. However, when patients are followed carefully, and when they and their caregivers are educated about what to expect during treatment, the side effects can be managed effectively to promote adherence to therapy and improve quality of life.

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References

- Alexanian, R., Dimopoulos, M.A., Delasalle, K., & Barlogie, B. (1992). Primary dexamethasone treatment of multiple myeloma. *Blood*, 80(4), 887-890.
- Alexanian, R., Haut, A., Khan, A.U., Lane, M., McKelvey, E.M., Migliore, P.J., et al. (1969). Treatment for multiple myeloma. Combination chemotherapy with different melphalan dose regimens. *JAMA*, 208(9), 1680-1685.
- American Diabetes Association. (2007). All about diabetes. Retrieved October 23, 2007, from <http://www.diabetes.org/about-diabetes.jsp>
- Arlt, W., & Allolio, B. (2003). Adrenal insufficiency. *Lancet*, 361(9372), 1881-1893.
- Badger, T.A., Fulcher, C.D., Gunter, A.K., Marrs, J., & Reese, J. (2007).

- Putting Evidence Into Practice®: Depression. Retrieved September 10, 2007, from <http://www.ons.org/outcomes/volume2/depression.shtml>
- Berenson, J.R., Crowley, J.J., Grogan, T.M., Zangmeister, J., Briggs, A.D., Mills, G.M., et al. (2002). Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. *Blood*, 99(9), 3163–3168.
- Bertolotti, P., Bilotti, E., Colson, K., Curran, K., Doss, D., Faiman, B., et al. (2007). Nursing guidelines for enhanced patient care. *Haematologica*, 92(Suppl. 2), 211.
- Bertolotti, P., Bilotti, E., Colson, K., Curran, K., Doss, D., Faiman, B., et al. (2008). Management of side effects of novel therapies for multiple myeloma: Consensus statements developed by the International Myeloma Foundation's Nurse Leadership Board. *Clinical Journal of Oncology Nursing*, 12(3, Suppl.), 9–12.
- Celgene Corporation. (2007a). Revlimid® (lenalidomide) [Package insert]. Summit, NJ: Author.
- Celgene Corporation. (2007b). Thalomid® (thalidomide) [Package insert]. Summit, NJ: Author.
- Cerullo, M.A. (2006). Corticosteroid-induced mania: Prepare for the unpredictable. *Current Psychiatry*, 5(6), 43–50.
- Colson, K., Doss, D.S., Swift, R., Tariman, J., & Thomas, T.E. (2004). Bortezomib, a newly approved proteasome inhibitor for the treatment of multiple myeloma: Nursing implications. *Clinical Journal of Oncology Nursing*, 8(5), 473–480.
- Dawson-Hughes, B., Harris, S.S., Krall, E.A., & Dallal, G.E. (1997). Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *New England Journal of Medicine*, 337(10), 670–676.
- Del Valle, J. (2005). Peptic ulcer disease and related disorders. In D.L. Kasper, E. Braunwald, D. Longo, J.L. Jameson, A.S. Fauci, & S.L. Hauser (Eds.), *Harrison's principles of internal medicine* (16th ed.). New York: McGraw-Hill.
- Doty, R.L., & Bromley, S.M. (2004). Effects of drugs on olfaction and taste. *Otolaryngologic Clinics of North America*, 37(6), 1229–1254.
- Groeneveldt, L.J., Garrod, R., Yong, K.L., Dangwa, F., Jewell, A.P., van Someren, K., et al. (2007). An exercise training programme produces significant improvements in quality of life (QoL), muscle strength and cardiorespiratory function in patients with myeloma [Abstract]. *Blood*, 110(11), 3323.
- Guisse, T.A. (2006). Bone loss and fracture risk associated with cancer therapy. *Oncologist*, 11(10), 1121–1131.
- Jackson, R.D., LaCroix, A.Z., Gass, M., Wallace, R.B., Robbins, J., Lewis, C.E., et al. (2006). Calcium plus vitamin D supplementation and the risk of fractures. *New England Journal of Medicine*, 354(8), 669–683.
- Lindsay, R., & Cosman, F. (2005). Osteoporosis. In D.L. Kasper, E. Braunwald, D. Longo, J.L. Jameson, A.S. Fauci, & S.L. Hauser (Eds.), *Harrison's principles of internal medicine* (16th ed.). New York: McGraw-Hill.
- Lips, P., Graafmans, W.C., Ooms, M.E., Bezemer, P.D., & Bouter, L.M. (1996). Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. *Annals of Internal Medicine*, 124(4), 400–406.
- MacArthur Initiative on Depression and Primary Care at Dartmouth and Duke. (2003–2006). Depression tool kit. Retrieved September 25, 2007, from <http://www.depression-primarycare.org/clinicians/toolkits/>
- Merck & Co., Inc. (2004). Decadron® (dexamethasone) [Package insert]. Whitehouse Station, NJ: Author.
- Miceli, T., Colson, K., Gavino, M., Lilleby, K., & the IMF Nurse Leadership Board. (2008). Myelosuppression associated with novel therapies in patients with multiple myeloma: Consensus statement of the IMF Nurse Leadership Board. *Clinical Journal of Oncology Nursing*, 12(3, Suppl.), 13–19.
- Millennium Pharmaceuticals, Inc. (2007). Velcade® (bortezomib) [Package insert]. Cambridge, MA: Author.
- Mitchell, S., Beck, S., Hood, L., Moore, K., & Tanner, E. (2006). Putting Evidence Into Practice®: Fatigue. Retrieved September 10, 2007, from <http://www.ons.org/outcomes/volume1/fatigue.shtml>
- National Cancer Institute. (2006). *Common Terminology Criteria for Adverse Events v.3.0*. Retrieved December 28, 2007, from <http://ctep.cancer.gov/forms/CTCAEv3.pdf>
- National Institutes of Mental Health. (2007). Health and outreach topics: Depression. Retrieved September 25, 2007, from <http://www.nimh.nih.gov/healthinformation/depressionmenu.cfm>
- National Library of Medicine & National Institutes of Health. (2007). Erectile dysfunction. Retrieved September 25, 2007, from <http://www.nlm.nih.gov/medlineplus/erectiledysfunction.html>
- Page, M.S., Berger, A.M., & Johnson, L.B. (2006). Putting Evidence Into Practice®: Sleep-wake disturbances. Retrieved September 10, 2007, from <http://www.ons.org/outcomes/volume1/sleep.shtml>
- Pogach, L.M., Brietzke, S.A., Cowan, C.L., Conlin, P., Walder, D.J., & Sawin, C.T. (2004). Development of evidence-based clinical practice guidelines for diabetes: The Department of Veterans Affairs/Department of Defense guidelines initiative. *Diabetes Care*, 27(Suppl. 2), B82–B89.
- Rajkumar, S.V. (2007). The role of lenalidomide in myeloma patients eligible for high dose therapy. *Haematologica*, 92(Suppl. 2), 30–32.
- Rajkumar, S.V., Jacobus, S., Callander, N., Fonseca, R., Vesole, D., & Griep, P. (2006). A randomized phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): A trial coordinated by the Eastern Cooperative Oncology Group [Abstract]. *Blood*, 108(11), 799.
- Rajkumar, S.V., Jacobus, S., Callander, N., Fonseca, R., Vesole, D., Williams, M., et al. (2007). Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): A trial coordinated by the Eastern Cooperative Oncology Group [Abstract]. 2007 ASCO Annual Meeting Proceedings Part I. *Journal of Clinical Oncology*, 25(18, Suppl.), 8025.
- Rome, S., Doss, D.S., Miller, K.C., Westphal, J., & the IMF Nurse Leadership Board. (2008). Thromboembolic events associated with novel therapies in patients with multiple myeloma: Consensus statement of the IMF Nurse Leadership Board. *Clinical Journal of Oncology Nursing*, 12(3, Suppl.), 21–27.
- Sambrook, O.N. (2005). How to prevent steroid induced osteoporosis. *Annals of the Rheumatic Diseases*, 64(2), 176–178.
- Smith, L.C., Bertolotti, P., Curran, K., Jenkins, B., & the IMF Nurse Leadership Board. (2008). Gastrointestinal side effects associated with novel therapies in patients with multiple myeloma: Consensus statement of the IMF Nurse Leadership Board. *Clinical Journal of Oncology Nursing*, 12(3, Suppl.), 37–51.
- Talamo, G., Angtuaco, E., Walker, R.C., Dong, L., Miceli, M.H., Zangari, M., et al. (2005). Avascular necrosis of femoral and/or humeral heads in multiple myeloma: Results of a prospective study of patients treated with dexamethasone-based regimens

- and high-dose chemotherapy. *Journal of Clinical Oncology*, 23(22), 5217-5223.
- Tariman, J.D., & Estrella, S.M. (2005). The changing treatment paradigm in patients with newly diagnosed multiple myeloma: Implications for nursing [Online exclusive]. *Oncology Nursing Forum*, 32(6), E127-E138. Retrieved March 26, 2008, from <http://www.ons.org/publications/journals/ONF/Volume32/Issue6/32061098.asp>
- U.S. Food and Drug Administration. (2006). FDA advances effort against marketed unapproved drugs. Retrieved October 23, 2007, from <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01521.html>
- Watson Laboratories, Inc. (2006). Prednisolone (prednisolone) [Package insert]. Corona, CA: Author.
- Wilson, T.A., & Speiser, P. (2007). Adrenal insufficiency. Retrieved October 23, 2007, from <http://www.emedicine.com/PED/topic47.htm>
- Woo-Ming, M.A. (2007). Hiccups. Retrieved September 25, 2007, from http://www.emedicinehealth.com/hiccups/article_em.htm
- Zitella, L., Friese, C., Gobel, B.H., Woolery-Antill, M., O'Leary, C., Hauser, J., et al. (2006). Putting Evidence Into Practice®: Prevention of infection. Retrieved October 23, 2007, from <http://www.ons.org/outcomes/PEPcard/prevention.shtml>

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Patient Education Sheet: Managing Steroid-Associated Side Effects of Novel Agents for Multiple Myeloma

KEY POINTS

Steroids have been an effective treatment for multiple myeloma, alone and in combination with other drugs, for many years and still are used as an important part of treatment with newer drugs known as novel therapies (thalidomide, lenalidomide, and bortezomib). Steroids cause a wide range of side effects, affecting nearly every system of the body. Identifying the side effects early and managing them quickly will contribute to successful treatment and ultimately improve overall quality of life. Do not stop or adjust your medications without discussing it with your healthcare provider.

Steroids commonly prescribed include dexamethasone, prednisone, prednisolone, and solumedrol.

POTENTIAL SIDE EFFECTS

- "Let down" or withdrawal effect
- Flushing and sweating
- Difficulty sleeping (insomnia)
- Sexual dysfunction
- Personality changes or mood alterations
- Hyperactivity and jitters
- Difficulty concentrating
- Increased numbers of white blood cells
- Infection
- Muscle weakness (myopathy)
- Death of bone tissue (avascular necrosis)
- Decrease in bone strength (osteopenia or osteoporosis)
- Muscle cramps
- Weight gain in body or face
- Changes affecting hair
- Blurred vision
- Cataract formation
- Ulcers and heartburn (dyspepsia)

Note. For more information, please contact the International Myeloma Foundation (1-800-452-CURE; www.myeloma.org). The foundation offers the Myeloma Manager™ Personal Care Assistant™ computer program to help patients and healthcare providers keep track of information and treatments. Visit <http://manager.myeloma.org> to download the free software.

Note. Patient education sheets were developed in June 2008 based on the International Myeloma Foundation Nurse Leadership Board's consensus guidelines. They may be reproduced for noncommercial use.

- Gas (flatulence)
- Increased appetite
- Changes in taste
- Hiccoughs
- Higher blood sugar levels
- Temporary diabetes or thyroid issues
- Temporary decrease in testicular size
- Swelling of the hands, legs, or feet
- Acne or rashes
- Thinning of skin

STRATEGIES FOR CONTINUING TREATMENT

Steroids should be taken with food.

Steroids can cause sleeplessness and therefore should be taken early in the morning.

Signs and symptoms of infection: fever of more than 100.5°F (38°C), shaking chills even without fever, dizziness, shortness of breath, and low blood pressure

Patients should take an over-the-counter or prescription medication to prevent gastrointestinal issues.

Medications to prevent infection, shingles (small blister-like rash anywhere on the body; usually painful with or without rash), and thrush (white coating on tongue, bad taste, and painful swallowing) also may be prescribed.

Know the signs and symptoms of high and low blood sugar: aggressiveness, confusion, difficulty waking, increased thirst, and frequent urination. If you have known diabetes, consult with your endocrinologist or diabetes educator prior to starting treatment with steroids.

Always report symptoms to your healthcare team as soon as they occur.