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Understanding multiple myeloma

Find out the facts about the second most common blood cancer.

By Denise L. Landon, BSN, RN; Lisa Lockhart, MHA-BC, MSN, RN, NE-BC; and Charlotte Davis, BSN, RN, CCRN

Multiple myeloma is cancer of the plasma cells located within the bone marrow. According to the American Society of Clinical Oncology, in 2014 an estimated 24,050 American adults (13,500 men and 10,550 women) were diagnosed with multiple myeloma. It's estimated that 11,090 deaths (6,110 men and 4,980 women) from this disease will occur this year.

An understanding of multiple myeloma is an essential aspect of a patient's clinical outcome and quality of life after diagnosis.

Bone marrow basics

Bone marrow is the soft, spongy connective tissue within bone cavities. It contains both red and yellow bone marrow.

Red bone marrow is found in the body's flat bones, such as the skull, vertebrae, shoulder blades, hip bones, and ribs. Red marrow can also be found at the ends of long bones, such as the tibia, humerus, and femur. White blood cells (WBCs), red blood cells (RBCs), and platelets are produced in the red marrow. T cells and B cells make up approximately 5% of all bone marrow (see *B cell formation* and *T cell formation*).

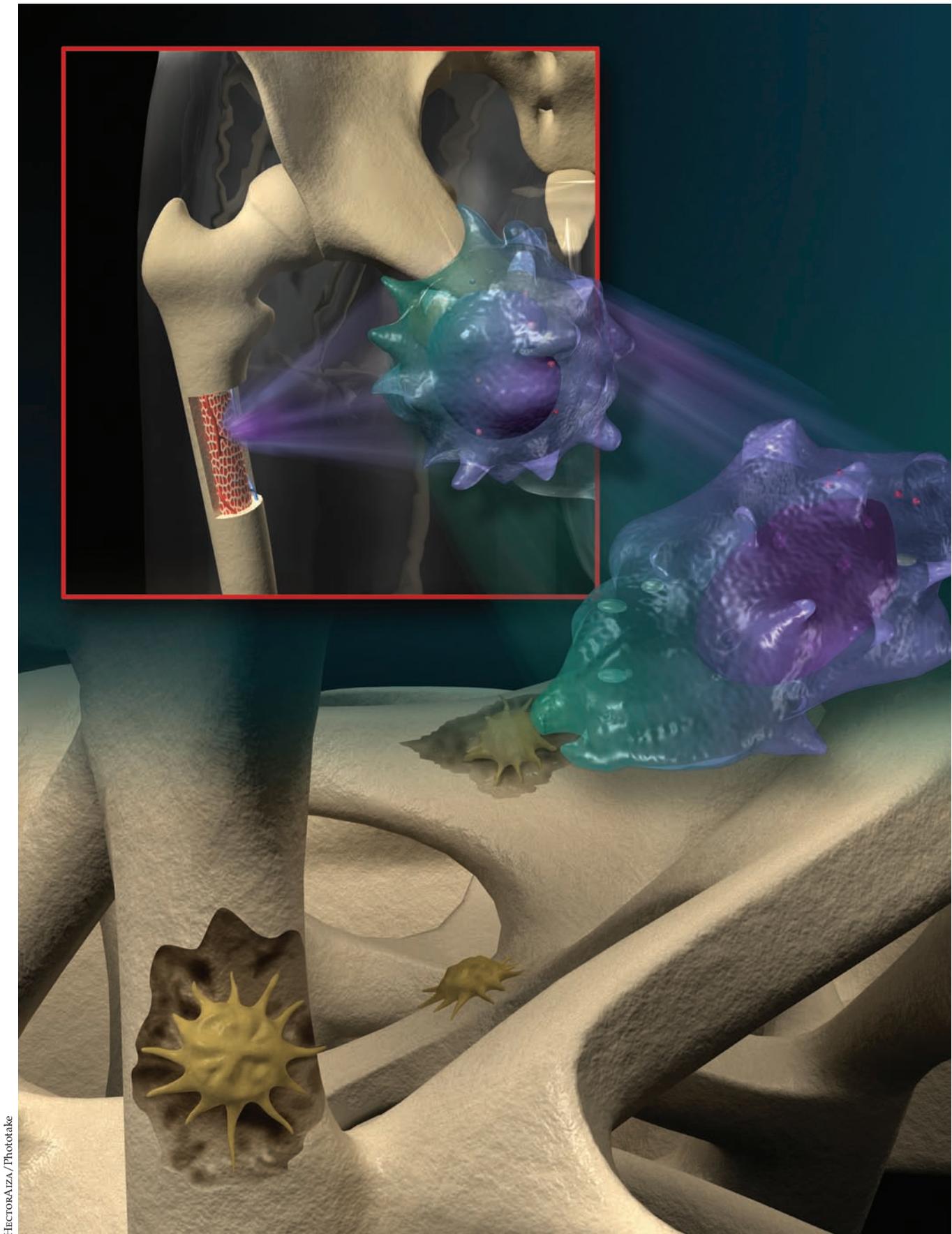
Composed mostly of fat cells, yellow bone marrow is found primarily in the middle of

the body's long bones. It stores fat and has no hematopoietic properties except in the event of severe blood loss.

What happens in multiple myeloma?

In multiple myeloma, the plasma cells abnormally multiply at an accelerated rate, producing abnormally elevated levels of protein (a combination of monoclonal paraprotein [M protein] and other compounds such as immunoglobulins). Unhealthy levels of immunoglobulins are released into the bones and blood. Excessive immunoglobulins accumulate throughout the body, causing organ damage. Multiple myeloma plasma cell growth can result in bone destruction, soft tissue mass development, impaired immune system function, and pain from collapsing bone.

Multiple myeloma cells damage the bone by reducing the activity of osteoblasts, which usually helps rebuild new bone. The reduced activity of osteoblasts causes increased activity of osteoclasts, which usually breaks down old bone. In addition, the abnormal plasma cells may form masses in the bone marrow that further damages the structure of the bone.



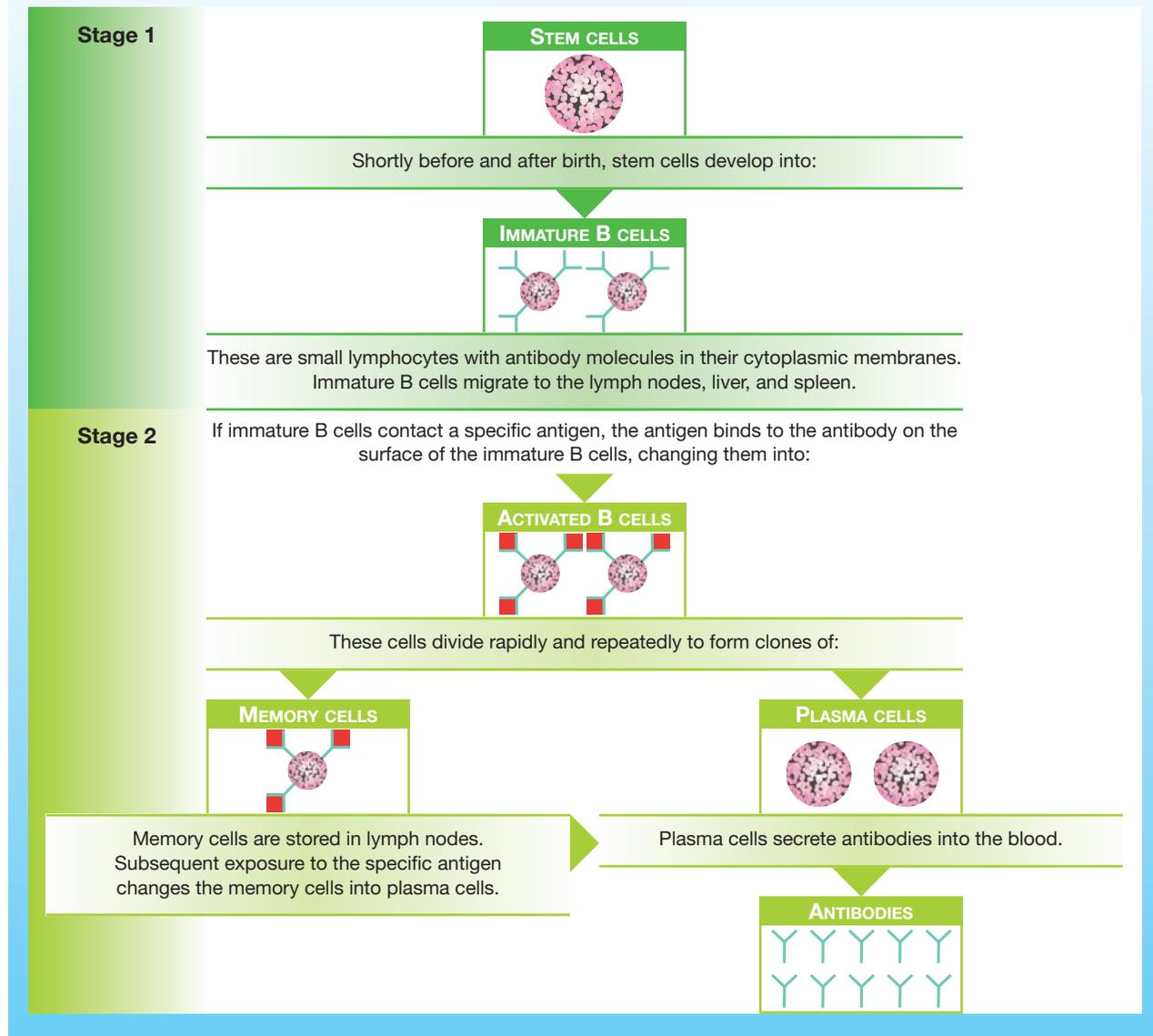
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As the plasma cells rapidly multiply, they crowd out healthy cells within the bone marrow, such as RBCs that are vital for carrying oxygen to the body's tissues and organs. This decreased RBC distribu-

tion can cause symptoms such as fatigue or shortness of breath due to tissues and organs receiving inadequate oxygenation. The abnormal plasma cells compress WBCs, placing the patient at an

B cell formation

The formation of B cells consists of two stages. The first stage occurs shortly after birth; the second stage occurs when an immature B cell encounters its specific antigen.



increased risk for infection and resulting in lower platelet levels (thrombocytopenia) that put the patient at risk for bleeding disorders.

Types of multiple myeloma

There are two types of multiple myeloma: oligosecretory and nonsecretory.

Oligosecretory multiple myeloma is characterized by the increased production of plasma B cells. This plasma secretes a large amount of paraprotein, which is expelled into the blood and urine. This makes it easier to track the efficacy of treatments; if protein levels decrease, the treatment or therapy is effective.

Nonsecretory multiple myeloma refers to a lack of protein secretion. This occurs in

approximately 5% of cases. Diagnosis is reliant on symptomatology, which is indicative of advanced disease process, and indicators of success or response are more difficult to ascertain.

Risk factors for multiple myeloma include:

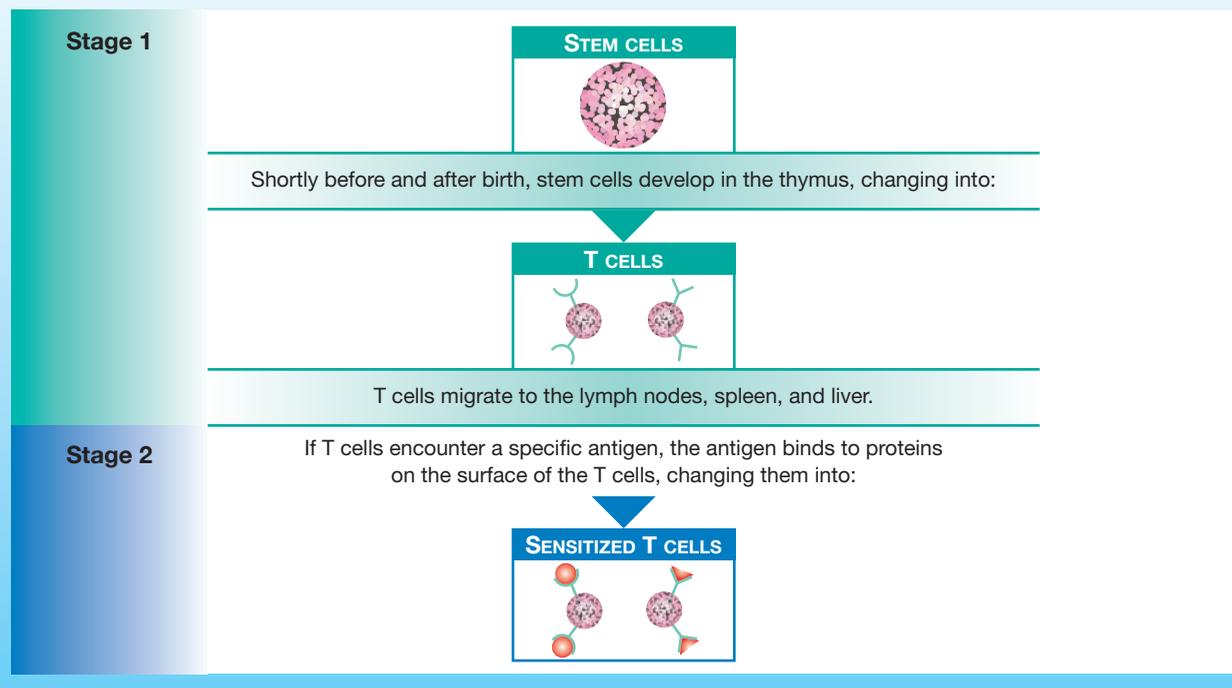
- age—over age 65
- sex—males appear to be at greater risk
- ethnicity—risk is highest among African Americans and lowest for Asian Americans
- genetics—relatives of people who've had the disease are at a higher risk.

Clinical presentation on notice

Symptoms may vary in severity based on the stage of the disease. In the very early

T cell formation

T cells are lymphocytes that have undergone their first stage of development in the thymus. The second stage of development occurs when they contact an antigen.



stages of multiple myeloma, the patient may be asymptomatic; this is commonly referred to as *smoldering multiple myeloma*. Many patients aren't diagnosed until the late stages of the disease.

Common symptoms include:

- bone pain ranging from mild to severe in one or multiple joints
- confusion
- constipation
- dizziness
- excessive thirst
- recurrent infections
- weakness
- fatigue
- bruising or purple-colored rash
- shortness of breath
- loss of appetite
- weight loss
- hypercalcemia
- anemia
- osteolytic lesions
- nontrauma-related bone fractures.

Difficult diagnosis

Multiple myeloma is often difficult to detect. At this time, there's no screening test that can identify it in the early stages.

Typically, when multiple myeloma is discovered during an early phase of the disease by a healthcare practitioner, it's after common lab tests have revealed abnormally high levels of protein in the blood. There are four pathways to diagnose multiple myeloma: lab studies, imaging studies, pathology, and genetic studies.

Lab studies

Common diagnostic lab studies include:

- *serum protein electrophoresis (SPEP)*.

The immunoglobulin produced by myeloma cells is abnormal because it has monoclonal antibodies. A SPEP test separates the blood proteins and can detect the presence of monoclonal proteins; this is commonly referred to as an "M spike," which is indicative of multiple myeloma.

- *urine protein electrophoresis (UPEP)*. A UPEP is an evaluation of a 24-hour urine sample. Immunoglobulins are made up of protein chains: two long (heavy) chains and two shorter (light) chains. Sometimes, the kidneys excrete pieces of the monoclonal protein into the urine, which may indicate multiple myeloma. Only monoclonal light chains, not heavy chains, are found in urine. Approximately 30% of patients have light chain protein in their urine, as well as heavy and light chains in the blood. Approximately 10% of patients have myeloma cells that produce only light chains and no heavy chains.

- *serum free light chain assay*. This test is utilized to measure the number of free kappa or lambda light chains (fragments of the monoclonal protein) if it isn't possible to quantify heavy chains with SPEP or light chains with UPEP. Some patients' myeloma cells secrete very little or no monoclonal protein that can be detected with SPEP or UPEP. The majority of these patients can be tested adequately with the serum free light chain assay.

- *beta-2 microglobulin (B2M) test*. This test is commonly referred to as a tumor

The international staging system

This system is commonly utilized to stage the severity of multiple myeloma. It divides myeloma into three stages based only on the serum B2M and serum albumin levels.

Stage I

- The serum B2M level is less than 3.5 mg/L and the serum albumin level is greater than 3.5 g/L.

Stage II

- Neither stage I nor III, meaning that either:
 - the serum B2M level is less than 3.5 mg/L, but the serum albumin level is less than 3.5 mg/L

OR

- the serum B2M level is between 3.5 and 5.5 mg/L, with any serum albumin level.

Stage III

- The serum B2M is greater than 5.5 mg/L.

Source: International Myeloma Foundation. International staging system. <http://myeloma.org/ArticlePage.action?articleId=889>.



key points

Nursing considerations

- Bleeding precautions
- Fracture precautions
- Falls precautions
- Infection prevention
- Pain management

marker for blood cell cancers such as multiple myeloma. It isn't diagnostic for a specific disease, but it provides a way to assess how many cancer cells the patient has. This assists the healthcare team in determining the patient's prognosis. A serum B2M test and often a urine test may be ordered to help determine the severity and stage of cancers such as multiple myeloma.

- **complete blood cell (CBC) count.** A CBC count is used to measure the levels of RBCs, WBCs, and platelets in the blood. If there are too many myeloma plasma cells in the bone marrow, some of these blood cell levels will be low. The most common finding is a low RBC count (anemia).

- **serum calcium levels.** High levels of calcium in the blood (hypercalcemia) occur when calcium leeches from the weakened bone structure into the bloodstream. Combined with the clinical presentation of the patient and other diagnostic tests, serum calcium levels can be beneficial in diagnosing multiple myeloma.

- **immunofixation.** This test provides information about the presence or absence of monoclonal proteins, as well as the type of myeloma protein (heavy chain [G, A, D, or E] and/or light chain [kappa or lambda]).

- **quantitative immunoglobulins.** This test shows the total amount of the immunoglobulins IgG, IgA, IgD, IgE, and IgM. Elevated levels of IgM are typically seen in cancers that involve the lymphocytes or plasma cells. In multiple myeloma, the level of one type of immunoglobulin may be high whereas the others may be low.

Imaging studies

Common imaging studies include:

- **X-ray.** Total body X-rays are typically performed if multiple myeloma is suspected. This is commonly referred to as a "skeletal survey" and will display bone integrity or damage areas. In multiple myeloma, the

most common finding is osteolytic lesions that appear to be "punched out" areas indicative of bone loss.

- **computed tomography (CT) scan.** Used primarily for the purpose of biopsy, the CT scan will illuminate the area and facilitate in the accuracy of sample retrieval. It can also be beneficial in diagnosing other areas of metastasis.

- **magnetic resonance imaging.** This imaging study is used to locate the extent of bone damage caused by multiple myeloma. It can also help identify plasmacytomas that aren't visible with X-ray.

- **positron emission tomography (PET) scan.** Using radioactive glucose via injection, a PET scan identifies cancer cells that have an affinity for the dye and readily attach to it. Areas of cancer cell concentration can then be visualized. A PET scan is also useful in identifying other areas of metastasis.

Pathology and genetic studies

Common invasive pathology tests include:

- **bone marrow biopsy.** After a bone marrow sample is obtained, the pathologist looks at the size and shape of the plasma cells and how they're arranged. A plasma cell count of 10% to 30% can potentially be useful in diagnosing multiple myeloma when used in combination with other diagnostic tools. However, a plasma cell count of greater than 30% is indicative of multiple myeloma, according to the World Health Organization diagnostic criteria. The aspirate may also be sent for other tests, including immunohistochemistry and flow cytometry, and chromosome analyses, including karyotype and fluorescent in situ hybridization (FISH).

FISH is a genetic test that looks for specific changes in chromosomes that may indicate multiple myeloma. It can be used on regular blood samples, as well as bone marrow samples. It's accurate and because the cells don't have to grow in a dish first,



did you know?

When monoclonal proteins are found in urine, they're referred to as Bence-Jones proteins.

results are often available within a couple of days.

- **bone core biopsy.** This sample is typically obtained during a bone marrow biopsy to count myeloma cells and check questionable areas that may be plasmacytomas.
- **flow cytometry.** For this test, a sample of cells is treated with special antibodies that stick to the cells only if certain substances are present on their surfaces. The cells are then passed in front of a laser beam. If the cells have antibodies attached to them, the laser will make them give off light, which can be measured and analyzed by a computer. Groups of cells, specifically abnormal cells that are indicative of multiple myeloma, can be separated and counted by these methods.

Appearing on stage

The International Staging System for Multiple Myeloma is used worldwide. It utilizes a combination of serum B2M and serum albumin levels to categorize multiple myeloma into three stages (see *The international staging system*).

Stage I criteria:

- serum B2M level is less than 3.5 mg/L
- serum albumin level is greater than 3.5 g/L.

Stage II criteria:

- neither stage I nor III, meaning that either:
 - serum B2M level is less than 3.5 mg/L, but the serum albumin level is less than 3.5 mg/L or
 - serum B2M level is between 3.5 and 5.5 mg/L, with any serum albumin level.

Stage III criteria:

- serum B2M is greater than 5.5 mg/L.

Another staging methodology is the Durie-Salmon Staging System. This system is based on four factors:

- amount of abnormal monoclonal immunoglobulin in the blood or urine
- amount of calcium in the blood
- severity of bone damage based on X-rays
- amount of hemoglobin in the blood.

The system utilized is based on the healthcare provider's preference.

A plethora of treatments

There are many different treatment options for multiple myeloma, and healthcare teams often use a combination of treatments rather than one single treatment. Options include chemotherapy, biologic therapy, radiation therapy, stem cell transplant, and plasmapheresis. Treatment may be administered in phases, including induction therapy (initial), consolidation therapy, and, lastly, maintenance therapy.

Chemotherapy

Chemotherapy can be used to stop the cancer from metastasizing, slow the growth of the cancer cells or mass, and kill or eradicate cancer cells that may have traveled to different areas of the body. Chemotherapy can also be used to relieve or minimize symptoms, such as pain, that are often experienced by patients with multiple myeloma. Common chemotherapy drugs used to treat multiple myeloma include melphalan, cyclophosphamide, vincristine, doxorubicin, and liposomal doxorubicin. Typically, chemotherapy and medications such as corticosteroids or immunomodulating agents are used in combination.

Immunomodulating agents change a patient's immune response by modifying or regulating one or more immune response functions. The three main immunomodulating agents used to treat multiple myeloma are thalidomide, lenalidomide, and pomalidomide. The use of these drugs can increase the risk of serious blood clots; for this reason, these medications are typically administered with aspirin or an anticoagulant. Patient teaching includes information about signs and symptoms of blood clots, such as chest pain or pressure; shortness of breath; and pain, warmth, or swelling in the arms or legs. Patients should contact their healthcare provider immediately if



Risk factors

cheat

sheet

- over age 65
- male
- African American
- Relative diagnosed with multiple myeloma

any of these symptoms are experienced. Thalidomide and its related drugs carry a high risk of birth defects and, therefore, careful family planning education should be conducted with all female patients of childbearing age.

Corticosteroids are also used to help regulate the immune system to control inflammation. The most commonly used corticosteroids to treat multiple myeloma are dexamethasone and prednisone. These are often used to treat the nausea and vomiting associated with chemotherapy. Long-term use of corticosteroids may contribute to immunosuppression and result in adverse reactions, such as weakened bones, avascular necrosis, and age-accelerated osteoporosis.

Biologic therapy

Proteasome inhibitors work by preventing certain enzyme complexes (proteasomes) in cells from breaking down the proteins that are important for keeping abnormal cell division under control. Proteasome inhibitors are typically administered I.V. or subcutaneously once or twice a week.

The proteasome inhibitor bortezomib is typically used in combination with dexamethasone, another antimyeloma drug, or as part of a three-drug combination. Examples of commonly used three-drug combinations include revlimid-velcade-dexamethasone and velcade-cyclophosphamide-dexamethasone.

Carfilzomib is a newer proteasome inhibitor that can be used in patients with multiple myeloma who've already used bortezomib and an immunomodulating agent. The medication is generally administered I.V. in a 4-week cycle.

Radiation therapy

Radiation is used in the treatment of multiple myeloma to control the growth of tumors in the bone, as well as an adjunctive therapy to relieve associated pain. Radiation therapy can last 1 to 3 weeks. Common

adverse reactions include changes to the skin at the area being treated (redness and blistering), nausea, fatigue, and low blood cell counts.

Stem cell transplant

A stem cell transplant is used to replace diseased bone marrow with new, healthy bone marrow. The transplant is typically performed after the patient receives chemotherapy, often in conjunction with radiation therapy, which kills both cancerous and healthy cells. Bone marrow contains immature cells called hematopoietic stem cells. These cells divide, forming more blood-forming stem cells or maturing into RBCs, WBCs, or platelets. Stem cell transplants were first performed by harvesting stem cells from bone marrow and were referred to as bone marrow transplants. Now, stem cells are often gathered from the blood in a process known as peripheral blood stem cell transplant (PBSCT).

PBSCT is used to replace blood-forming cells that have been destroyed by cancer treatment, such as chemotherapy and/or radiation therapy. Immature blood cells (stem cells) in the bloodstream are administered to the patient after chemotherapy and/or radiation treatment. This helps the bone marrow recover and continue to make healthy blood cells. Transplantation may be autologous (an individual's own stem cells saved before treatment), allogeneic (stem cells donated by someone else, including a relative or unrelated donor), or syngeneic (stem cells donated by an identical twin). It typically takes up to 10 million stem cells to

complete a PBST; this may require multiple harvesting procedures to acquire an adequate amount of stem cells.

Plasmapheresis

Plasmapheresis is a procedure that removes the blood from the body and spins it in a centrifuge to filter out the plasma. The RBCs are returned to the body and the plasma may be treated and reintroduced or replaced, depending on the condition which the plasmapheresis is designed to treat. Often, treatment for multiple myeloma consists of a combination of these therapies (filtered, treated, reintroduced, and replaced).

It's complicated

Complications of multiple myeloma include acute renal failure, anemia, bone damage, intractable pain, and recurrent infections.

Patients with multiple myeloma are vulnerable to the nephrotoxic effects of chemotherapy medications and the imaging contrast exposure needed to monitor disease progress and treatment efficacy. Patients may develop acute tubular necrosis related to chemotherapy or contrast media. They may also develop collapsing focal segmental glomerulosclerosis related to bisphosphonates that are given to slow bone loss. Renal damage can also occur due to high levels of abnormal monoclonal proteins. Urinalysis may reveal an elevated protein level and a serum blood test may show an elevated creatinine level and glomerular filtration rate indicative of kidney damage. As damage occurs to the kidneys, they're no longer able to filter waste products and rid the body of excess salt and fluids. This can cause weakness, shortness of breath, itching, and swelling in the legs.

Fatigue related to anemia occurs when there's a reduced number of RBCs. In severe cases, this can lead to emergent conditions such as hypovolemic shock. The reduced

volume of circulating RBCs may evolve over the course of days, weeks, or months and the symptoms will slowly increase as the circulating RBC volume is reduced. This typically occurs as the abnormal myeloma cells replace oxygen-carrying RBCs in the bone marrow.

Bones invaded by myeloma cells are damaged, resulting in a destructive process called osteolytic lesion formation. This is a result of the invading myeloma cells overpowering the healthy bone marrow and slowly destroying it, causing a weakened bone matrix structure. This damage can result in bone pain or tenderness, often in the back, ribs, hips, and skull; fractures or breaks from minor injuries; and osteoporosis. Myeloma cells can dissolve, weaken, and even break bones. Bisphosphonates, such as alendronate and risedronate, may be used to help bones stay strong by slowing down osteonecrosis or bone loss.

Aggressive pain management is typically needed to adequately control the patient's pain. Extended-release opioids in combination with anti-inflammatory medications are often called for to maintain adequate pain management. The pain management regimen must be followed to ensure that a consistent dosage is maintained to diminish the likelihood of intractable pain.

Frequent and repeated infections, such as pneumonia, skin infections, sinusitis, kidney infections, and bladder infections, are common in patients with multiple myeloma due to reduced neutrophil counts. As myeloma cells proliferate, they crowd out neutrophils and reduce the body's defense system against infections. Without a healthy immune response, the patient is at risk for bacteremia, sepsis, septic shock, and hemodynamic collapse.

For your consideration

When caring for a patient with multiple myeloma, careful consideration of

treatment and symptoms will guide your care. Protecting your patient from infection exposure during chemotherapy regimens, bleeding precautions, and fall prevention are essential elements of care for these patients.

Multiple myeloma predisposes the patient to infection because the abnormal plasma cells produce a large amount of M protein, an antibody that doesn't fight infection. The abnormal myeloma cells build up in the bone marrow and crowd out healthy WBCs that usually fight infection; this increases the risk of infection for patients with multiple myeloma 15 times more than a patient without multiple myeloma. Chemotherapy also increases the risk of infection because it impairs the immune system.

To minimize the risk of infection, advise the patient to:

- avoid large crowds of people to reduce the risk of exposure to bacterial or viral pathogens
- avoid friends or family members who may show signs of being sick, such as an elevated temperature, cough, or chills.
- cook foods thoroughly and wash fruits and vegetables well
 - wash his or her hands with an antiseptic soap.

Keep in mind that a patient with multiple myeloma who does acquire an infection will often respond very slowly to treatments because of an impaired immune system and the disease process.

In addition to infection prevention, it's extremely important to have a pain management plan in place. Ongoing pain assessment and reassessment are essential for success when managing acute and chronic pain. Education of the patient, family, and main caregivers is vital to maintain quality of life and safety.

During discharge planning, encourage the patient to:

- keep a pain diary to document the location, severity, relief measures attempted, and any activity that may have preempted

on the web

To read the International Myeloma Working Group's updated criteria for the diagnosis of multiple myeloma, visit <http://www.myelomabeacon.com/news/2014/10/26/new-multiple-myeloma-diagnostic-criteria/>.



the pain so that he or she can discuss the pain management regimen with the health-care provider

- make changes to his or her home environment to minimize the risk of injury or falls, such as securing loose rugs, installing handrails, or adding nonskid rugs to bathroom floors
- consult with the oncologist or primary care provider immediately if he or she experience a temperature over 100.5° F, chills, flu-like symptoms, cough, shortness of breath, dyspnea, dysuria, or drainage from a cut or sore
- consult with the oncologist or primary care provider before beginning exercise programs to strengthen bones to ensure that the exercises are safe.

Inform the patient to notify the health-care provider immediately if he or she experiences sudden severe pain, numbness, or muscle weakness because the bones in the spine may become weak, collapse, or press on spinal nerves as their structure weakens.

Aim for a positive prognosis

Many factors can affect the prognosis of a patient with multiple myeloma, including the stage of the disease at initial diagnosis, whether certain antibodies are present, whether the kidneys are damaged, the response to treatment regimens, and the patient's age and overall health. Many patients live fulfilling lives for 10 years or longer with lifestyle modifications and combination maintenance therapy. Armed with knowledge, you can reduce patient and caregiver anxiety, and improve their healthcare experience. ■

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Denise L. Landon is a Clinical Nurse for the Department of Veterans Affairs in Clarksville, Tenn. Lisa Lockhart is a Nurse Manager, Specialty Clinics, at Alvin C. York VA Medical Center in Murfreesboro, Tenn. Charlotte Davis is a CCU/CVICU Clinical Nurse at Heritage Medical Center in Shelbyville, Tenn., and a Clinical Nurse/Charge Nurse/CCRN Review Program Coordinator at Alvin C. York VA Medical Center in Murfreesboro, Tenn. She is also a *Nursing made Incredibly Easy!* Editorial Advisory Board Member.

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