About the International Myeloma Foundation

Founded in 1990, the International Myeloma Foundation (IMF) is the oldest and largest myeloma-specific charity in the world. With more than 350,000 members in 140 countries, the IMF serves myeloma patients, family members, and the medical community. The IMF provides a wide range of programs in the areas of Research, Education, Support, and Advocacy:

**RESEARCH** The IMF is the leader in globally collaborative myeloma research. The IMF supports lab-based research and has awarded over 100 grants to top junior and senior researchers since 1995. In addition, the IMF brings together the world’s leading experts in the most successful and unique way through the International Myeloma Working Group (IMWG), which is publishing in prestigious medical journals, charting the course to a cure, mentoring the next generation of innovative investigators, and improving lives through better care.

**EDUCATION** The IMF’s educational Patient & Family Seminars, Medical Center Workshops, and Regional Community Workshops are held around the world. These meetings provide up-to-date information presented by leading myeloma specialists and researchers directly to myeloma patients and their families. Our library of more than 100 publications, for patients and caregivers as well as for healthcare professionals, is updated annually and available free of charge. Publications are available in more than 20 languages.

**SUPPORT** Our toll-free InfoLine at 800-452-CURE (2873) is staffed by coordinators who answer questions and provide support and information via phone and email to thousands of families each year. The IMF sustains a network of more than 150 support groups and offers training for the hundreds of dedicated patients, caregivers, and nurses who volunteer to lead these groups in their communities.

**ADVOCACY** The IMF Advocacy program trains and supports concerned individuals to advocate on health issues that affect the myeloma community. Working both at the state and federal level, the IMF leads two coalitions to advocate for parity in insurance coverage. Thousands of IMF-trained advocates make a positive impact each year on issues critical to the myeloma community.

Learn more about the way the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure. Contact us at 800-452-CURE (2873) or 818-487-7455, or visit myeloma.org.
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The IMF is here to help

The International Myeloma Foundation (IMF) is committed to providing education and support for patients and their families. We achieve this through our website myeloma.org, telephone InfoLine, Patient & Family Seminars, Regional Community Workshops, teleconferences, and other programs and services. IMF educational publications are available as printed copies free-of-charge upon request, and can also be accessed at myeloma.org/publications.

The IMF Patient Handbook is an overview meant to help you to understand multiple myeloma – usually referred to simply as myeloma – as well as to learn medical terms and concepts you may not have encountered before. Myeloma is called “multiple” because it frequently involves multiple areas in the body. The Patient Handbook focuses on what to do when myeloma is first diagnosed, and it should also help you to communicate effectively with healthcare professionals.

In this booklet, words in bold type are explained in the “Terms and definitions” section. A more complete dictionary of myeloma-related vocabulary, the IMF’s Glossary of Myeloma Terms and Definitions, can be found at myeloma.org/publications.

Myeloma is a highly treatable disease

In the past 15 years, 9 highly effective “novel agents” have been approved for the treatment of myeloma. Ongoing clinical trials will add other promising therapies to the growing list of treatment options. Many patients lead full and productive lives for years, even decades, after diagnosis. Both survival and quality of life for myeloma patients are improving steadily. Learning about myeloma and understanding how it is treated can help reduce anxiety, gain a sense of control, and make it easier to come to terms with the diagnosis.

Why you should see a specialist

Myeloma is a very individual disease. Often, it is slow-moving. Sometimes, it can be very aggressive. A skilled myeloma specialist (a hematologist-oncologist who specializes in myeloma and other diseases of the plasma cells) will be able to determine the best approach in each patient’s individual situation. If there is no myeloma specialist nearby, we encourage you to travel for a scheduled consultation with a specialist. If this is not possible, your local physician can schedule a telephone consultation with a myeloma specialist to discuss your case, then work collaboratively with the specialist in administering your care. A local oncologist may see only a few myeloma patients per year, or none at all. Myeloma specialists at large “high-volume” treatment centers see hundreds of patients, conduct clinical trials with new drugs, develop the experience and expertise needed to make appropriate decisions, and can anticipate and prevent treatment-related problems. A large study published in 2016 shows that overall survival (OS) rates are higher for patients who are cared for at “high-volume” centers, large academic institutions where there are specialists, than in smaller medical practices.
The healthcare team
While hematologist-oncologists plan and administer treatments, a patient’s “healthcare team” will likely also include at least some of the following important members:
- a primary care physician or family doctor
- nurse or nurse practitioner
- an orthopedic surgeon (bone specialist)
- a pharmacist
- a nephrologist (kidney specialist)
- a dentist and/or oral surgeon.

Optimal care occurs when there is effective communication among every member of the healthcare team, and the patient or designated caregiver.

What is myeloma and where does it grow?
Myeloma is a cancer of plasma cells, a type of white blood cells (WBC) in the bone marrow that is responsible for making antibodies (immunoglobulins). In Greek, the language of most medical terms, “myelo” refers to the blood-producing cells in the bone marrow, and “oma” refers to a tumor or mass of cancer cells. A malignant (cancerous) plasma cell is called a myeloma cell.

Myeloma most often grows in the marrow within the bones of the spine, skull, pelvis, rib cage, shoulders, and hips. Usually, the bones of the hands and feet and lower parts of the arms and legs are not affected, preserving the function of these critical areas.

Some myeloma statistics
Currently, there are approximately 750,000 people living with myeloma worldwide, with more than 100,000 in the United States. The National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) program estimates that myeloma represented nearly 2% of all diagnosed cancers in the United States, comprising 30,330 newly diagnosed patients in 2016. The average age at diagnosis is 69 years, with 76% of patients between the ages of 55 and 84. Only 5%-10% of patients are under the age of 40. Myeloma in children has been reported, but it is extremely rare. Myeloma is more common in men than in women (the ratio is 1.44 men for every 1 woman) and among people of African-American descent. It appears that the incidence of myeloma is increasing in several parts of the world, especially in Asia.

What are the causes or triggers of myeloma?
Exposure to toxic chemicals, atomic radiation, anything that interferes with or suppresses the immune system, or infection with cancer-causing viruses have all been implicated as causes or triggers of myeloma. Toxic chemicals that have been identified include the following:
- benzene
- dioxins (such as those found in Agent Orange)
- agricultural chemicals (such as defoliants and pesticides)
- solvents
- fuels
- engine exhausts
- cleaning materials.

Several viruses have been identified, including HIV (the AIDS virus), hepatitis, and several herpes
viruses. Simian virus 40 (SV40), a contaminant in Sabin polio vaccine preparations that were used between 1955 and 1963, has also been implicated as a possible trigger for myeloma.

**Is myeloma hereditary?**

Approximately 5%–7% of myeloma diagnoses occur in a family member who has a close relative previously diagnosed with myeloma or monoclonal gammopathy of undetermined significance (MGUS). If you have a family member with myeloma or MGUS, mention this to your primary care physician so that it becomes a part of your medical record. If appropriate, your physician may want to do early screening tests. If you are a patient, your family members should inform their physicians about your diagnosis as part of their family medical history.

**MGUS, SMM, and active myeloma**

The very earliest stage of myeloma is not cancer at all, but is the benign condition called MGUS, the presence of a low level of monoclonal protein (M-protein) without any indicators of active myeloma. People with MGUS are monitored carefully to make sure the diagnosis is correct and there is no change in their status. As time goes by, if the level of monoclonal protein remains stable and there are no other health changes, the time between visits to the hematologist can be extended. All myeloma patients have MGUS before they progress to active myeloma, but the reverse is not true: only 20% of people diagnosed with MGUS

**Table 1. Definitions of MGUS and myeloma**

<table>
<thead>
<tr>
<th>NAME</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal Gammopathy of Undetermined Significance (MGUS)</td>
<td>• Monoclonal protein present but usually &lt; 3.0 g/dL</td>
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<td></td>
<td>• No CRAB features or other indicators of active myeloma</td>
</tr>
<tr>
<td></td>
<td>• Bone marrow monoclonal plasma cells &lt; 10%</td>
</tr>
<tr>
<td>Smoldering Multiple Myeloma (SMM)</td>
<td>• Higher level of disease than MGUS: serum M-component can be &gt; 3.0 g/dL</td>
</tr>
<tr>
<td></td>
<td>and/or bone marrow plasma cells between 10% and 60%, but</td>
</tr>
<tr>
<td></td>
<td>• No CRAB features or other indicators of active myeloma</td>
</tr>
<tr>
<td>Myeloma based on MDE</td>
<td>• &gt; 60% bone marrow plasma cells</td>
</tr>
<tr>
<td></td>
<td>• Free light chain ratio &gt; 100</td>
</tr>
<tr>
<td></td>
<td>• &gt; 1 MRI focal lesion</td>
</tr>
<tr>
<td>Myeloma based on CRAB</td>
<td>• Monoclonal protein present, and</td>
</tr>
<tr>
<td></td>
<td>• One or more CRAB features and/or indicators of organ damage*</td>
</tr>
</tbody>
</table>

*Organ damage classified as CRAB or any other significant clinical problem linked to myeloma progression such as recurrent infections or neuropathy unrelated to treatment

C – calcium elevation (> 10 mg/dL)
R – renal dysfunction (creatinine > 2 mg/dL or creatinine clearance < 40 ml/min)
A – anemia (hemoglobin < 10 g/dL or > 2g/dL decrease from patient’s normal)
B – bone disease (one or more osteolytic lesions detected on skeletal radiography, WBLC CT, or PET/CT)

**Figure 3. New definitions of myeloma and early myeloma**

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B – bone disease (one or more osteolytic lesions detected on skeletal radiography, WBLC CT, or PET/CT)

One or more CRAB features or other significant problem required for diagnosis of Symptomatic Myeloma
eventually get myeloma. The risk of progression from MGUS to myeloma is 1% per year.

The stage of myeloma between MGUS and active myeloma is called smoldering multiple myeloma (SMM), which is characterized by a higher level of monoclonal protein than MGUS with no indicators of active myeloma. The risk of progression to active myeloma among patients with standard-risk SMM is 10% per year for the first 5 years, 3% per year for the next 5 years, and 1%–2% per year for the next 10 years. For more information about MGUS and SMM, please read the IMF publication Understanding MGUS and Smoldering Multiple Myeloma.

Plasma cells and myeloma cells

Healthy plasma cells are an important part of the immune system. They produce immunoglobulins, which are complex proteins that we call antibodies. Myeloma cells do not make normal, functioning antibodies, but instead produce an abnormal immunoglobulin known as monoclonal protein. The production of monoclonal protein rather than normal immunoglobulins results in reduced ability to fight infection. The presence of myeloma cells within the bone marrow can lead to many other medical problems within and outside the bone marrow microenvironment.

<table>
<thead>
<tr>
<th><strong>Table 2. Medical problems related to myeloma</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFECTS OF INCREASED MYELOMA CELLS IN BONE MARROW</strong></td>
</tr>
<tr>
<td>CRAB criteria</td>
</tr>
</tbody>
</table>
| C – Increase in blood Calcium | Release of calcium from damaged bone into bloodstream. | • Mental confusion  
• Dehydration  
• Constipation  
• Fatigue  
• Weakness  
• Renal or kidney damage |
| R – Renal problems – kidney damage | Abnormal monoclonal proteins produced by the myeloma cells are released into the bloodstream and can pass into the urine and produce kidney damage. High blood calcium, infections, and other factors can also cause or increase the severity of kidney damage. | • Sluggish circulation  
• Fatigue  
• Mental confusion |
| A – Anemia | Decrease in number and activity of red blood cell-producing cells in the bone marrow. | • Fatigue  
• Weakness |
| B – Bone Damage  
• Thinning (osteoporosis) or  
• Areas of more severe damage (called lytic lesions), fracture, or collapse of a vertebra | The myeloma cells activate osteoclast cells, which destroy bone, and block osteoblast cells, which normally repair damaged bone. | • Bone pain  
• Bone swelling  
• Fracture or collapse of a bone  
• Nerve or spinal cord damage |
| Additional types of organ dysfunction | Local or systemic effects of myeloma, other than CRAB features. | • Neuropathy  
• Recurrent infections  
• Bleeding problems  
• Other individual problems |
| Abnormal immune function | The myeloma cells reduce the number and activity of normal plasma cells capable of producing antibodies against infection. | • Susceptibility to infection  
• Delayed recovery from infection |
What are the criteria for diagnosing myeloma?

The most common medical problems caused by myeloma are called the CRAB criteria, defined as the following:

- an elevated level of Calcium in the blood
- kidney damage (or in medical terms, Renal damage)
- low blood counts (especially low red blood cell count, or Anemia)
- Bone damage.

For many years, the CRAB criteria were the sole basis for a diagnosis of active myeloma. Without one of these signs that myeloma had already caused what is known as “end-organ damage,” patients were monitored at regular intervals by a physician, but not treated. However, within the last few years, more effective treatments for myeloma and better methods of assessing early disease have led to changes in the treatment paradigm.

Members of the IMF’s research arm, the International Myeloma Working Group (IMWG), studied patients with asymptomatic SMM to find biological markers that could predict that end-organ damage would occur within 18 months to 2 years. After this research was completed and published, the IMWG wrote new guidelines for the diagnosis of myeloma to include three new “myeloma-defining events” that precede the CRAB criteria. Each of these events independently indicates the need for treatment before the imminent appearance of CRAB criteria. These myeloma-defining events can be identified using the results of tests that would be a part of a newly diagnosed patient’s myeloma work-up:

- bone marrow biopsy,
- Freelite® test (serum free light chain assay), and
- magnetic resonance imaging (MRI) scan.

Possible urgent problems at diagnosis

Because the bones of the spine (the vertebrae) are often affected by myeloma, and because the spinal cord runs through the vertebrae, painful vertebral fractures that in turn cause nerve compression are not uncommon. Loss of motor nerves can cause paralysis. Myeloma tumors (plasmacytomas) growing in the vertebrae can also press on spinal nerves. Breakdown of calcium from bones can result in hypercalcemia, a high level of calcium in the blood. Both hypercalcemia and high levels of monoclonal protein in the blood can seriously affect the kidneys, causing kidney failure.

Vertebral compression fractures, damage to the nerves of the spinal cord, infections, and kidney failure are all emergency medical problems that require attention before systemic therapy for myeloma begins. However, we encourage early consultation with a myeloma specialist to ensure that any treatment of urgent problems leaves all therapeuthic options open for the future. For example, radiation therapy to shrink a plasmacytoma that is pressing on nerve tissue must be weighed carefully against a surgical option; radiation may permanently damage the bone marrow and limit choices for later treatment depending on where it is focused and how much is given.

Figure 4. Bone-building anatomy

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Myeloma’s effects in the bone marrow

Myeloma cells release many proteins and other chemicals into the local bone marrow micro-environment and directly into the bloodstream. All the blood cells – white blood cells, red blood cells (RBC, erythrocytes), and platelets – are made in the bone marrow. When myeloma grows in the bone marrow, the effects include a reduction in blood cell production. Anemia, a low level of red blood cells, is an early and common sign of myeloma.

Cells in healthy bone marrow maintain our skeletons in a dynamic and balanced process of bone breakdown and bone build-up. The presence of myeloma cells in the bone marrow stimulates the cells that break down bone (osteoclasts) and suppresses cells that build new bone (osteoblasts). This upsets their balance, which results in bone pain, fractures, and the release of calcium into the blood.

Myeloma’s effects outside the bone marrow

Myeloma’s effects outside the bone marrow are due largely to the monoclonal protein produced by myeloma cells. As myeloma cells reproduce and build up in the bone marrow, monoclonal protein that is specific to the type of myeloma is released into the blood circulation. This specific immunoglobulin protein can cause tissue damage at distant sites. For example, kidney damage is quite common. Monoclonal protein can also interfere with blood clotting and/or circulation, and can potentially cause other organ or tissue damage, such as damage to nerve tissue (peripheral neuropathy, PN). Treatment for myeloma controls bone breakdown and tumor growth, as well as the diverse effects caused by myeloma proteins and the cytokines they stimulate.

Types of myeloma

There are different types and subtypes of myeloma. These are based on the type of immunoglobulin protein produced by the myeloma cells. There are 5 types of normal immunoglobulin – G, A, D, E, and M – each of which performs different functions in the body. Each immunoglobulin is made up of two heavy chains and two light chains. Light chains are smaller and weigh less than heavy chains, making it possible for them to fit through the tiny capillaries that send blood to the kidneys. The two types of light chains are kappa (κ) and lambda (λ).

The typing of myeloma is done with the immunofixation electrophoresis (IFE) test, which identifies both the heavy and the light chain type. Myeloma cells make protein monoclones, a group of identical cells from a common ancestor cell. Therefore, myeloma cells make only a single type of immunoglobulin protein. Approximately 65% of myeloma patients have immunoglobulin G (IgG) myeloma with either kappa or lambda light chains. The next most common type is immunoglobulin A (IgA) myeloma, also with either kappa or lambda light chains. IgD, IgE, and IgM myelomas are quite rare. Approximately one third of myeloma patients produce free light chains (separate from heavy chains) in addition to the complete molecule combination.
of light chains bound to heavy chains. In approximately 15%–20% of patients, the myeloma cells produce only light chains and no heavy chains. This is called light chain or Bence-Jones myeloma, named for the English doctor who first detected and identified light chains, and published his findings in 1848. Rarely, only in about 1%–2% of patients, the myeloma cells produce very little or no monoclonal protein of any type. This is called non-secretory myeloma. However, the Freelite® test can detect minute amounts of light chains in the blood of about 70% of these very low-secreting patients. A Mayo Clinic study of 124 patients with non-secretory myeloma published in 2015 found that the survival of patients with non-secretory myeloma appears superior to that of patients with secretory disease.

**Behavior of the different types of myeloma**

Because it is the most common type of myeloma, the behavior of IgG myeloma conforms to the usual CRAB features.

IgA myeloma can sometimes be characterized by tumors outside of the bone.

<table>
<thead>
<tr>
<th>Table 4. Types of myeloma and related diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISEASE TYPE</td>
</tr>
<tr>
<td>Myeloma:</td>
</tr>
<tr>
<td>IgG κ or λ</td>
</tr>
<tr>
<td>IgA κ or λ</td>
</tr>
<tr>
<td>Rarer subtypes:</td>
</tr>
<tr>
<td>Light Chain only or Bence Jones (BJ) myeloma:</td>
</tr>
<tr>
<td>κ or λ types</td>
</tr>
<tr>
<td>Non-secretory myeloma:</td>
</tr>
<tr>
<td>κ or λ types</td>
</tr>
<tr>
<td>IgM myeloma:</td>
</tr>
<tr>
<td>κ or λ subtypes</td>
</tr>
<tr>
<td>Amyloidosis:</td>
</tr>
<tr>
<td>AL or immunoglobulin light chain type κ or λ subtypes</td>
</tr>
<tr>
<td>Light Chain Deposition Disease (LCDD):</td>
</tr>
<tr>
<td>κ or λ subtypes</td>
</tr>
<tr>
<td>POEMS syndrome:</td>
</tr>
<tr>
<td>Usually IgG or IgA λ (rarely κ subtype)</td>
</tr>
</tbody>
</table>
IgD myeloma can be accompanied by plasma cell leukemia, which is characterized by high levels of myeloma cells circulating in the blood. IgD myeloma is also known to cause kidney damage.

Light chain myeloma is most likely to cause kidney damage and/or lead to deposits of light chains in the kidneys and/or on nerves or other organs. Depending upon the characteristics of the light chain deposits, this condition is called either amyloid light-chain amyloidosis (AL amyloidosis) or light chain deposition disease (LCDD).

Two other related diseases of the plasma cells are Waldenström’s macroglobulinemia (WM), which is associated with IgM monoclonal protein, and POEMS syndrome, a rare disease associated with neuropathy, enlarged organs, endocrine disorders, monoclonal protein, and skin changes.

**Staging of myeloma**

When myeloma is diagnosed, the stage of the disease varies from patient to patient. The most commonly used clinical staging system, the Durie-Salmon Staging System, demonstrates the correlation between the amount of myeloma and the damage it has caused, such as bone disease or anemia.

The “measured myeloma cell mass” for the Durie-Salmon Staging System was calculated from studies in which the amount of myeloma protein per myeloma cell was measured. Studies of body metabolism of monoclonal protein were also conducted, which allowed calculation of the exact number of myeloma cells in the body. This led to the understanding that for some patients who produce a lot of protein, the number of myeloma cells can be quite low. Conversely, in patients with low protein production, the number of myeloma cells can be high.

Staging of myeloma can also be done according to prognosis, or expected survival. The most commonly-used staging system for myeloma that is based on prognostic factors is the International Staging System (ISS).

The ISS is the result of the collaboration of more than 20 research institutions worldwide. Analysis of their joint data identified which of the many tests to assess disease behavior were most predictive

<table>
<thead>
<tr>
<th>STAGE</th>
<th>CRITERIA</th>
<th>MEASURED MYELOMA CELL MASS (myeloma cells in billions/m²)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAGE I (low cell mass)</td>
<td>All of the following: • Hemoglobin value &gt; 10 g/dL • Serum calcium value normal or &lt; 10.5 mg/dL • Bone x-ray, normal bone structure (scale 0), or solitary bone plasmacytoma only • Low M-component production rates IgG value &lt; 5 g/dL; IgA value &lt; 3 g/dL • Urine light chain M-component on electrophoresis &lt; 4 g/24h</td>
<td>600 billion*</td>
</tr>
<tr>
<td>STAGE II (intermediate cell mass)</td>
<td>Fitting neither Stage I nor Stage III</td>
<td>600 to 1,200 billion*</td>
</tr>
<tr>
<td>STAGE III (high cell mass)</td>
<td>One or more of the following: • Hemoglobin value &lt; 8.5 g/dL • Serum calcium value &gt; 12 mg/dL • Advanced lytic bone lesions (scale 3) • High M-component production rates IgG value &gt; 7 g/dL; IgA value &gt; 5 g/dL • Urine light chain M-component &gt;12 g/24h</td>
<td>&gt; 1,200 billion*</td>
</tr>
<tr>
<td>SUBCLASSIFICATION (either A or B)</td>
<td>• A: relatively normal renal function (serum creatinine value) &lt;2.0 mg/dL • B: abnormal renal function (serum creatinine value) &gt;2.0 mg/dL Examples: Stage IA (low cell mass with normal renal function); Stage IIIB (high cell mass with abnormal renal function)</td>
<td></td>
</tr>
</tbody>
</table>
of aggressive myeloma. The ISS is based on four highly predictive markers of aggressive disease, all of which are blood-borne proteins: serum beta 2 microglobulin (S β2M), serum albumin (S ALB), C-reactive protein (CRP), and serum lactate dehydrogenase (LDH).

Inexpensive laboratory tests can be used to assess these markers of aggressive myeloma. In general, abnormal test results indicate more active myeloma as well as, possibly, less likelihood of having a long response to treatment. For more detailed information, please read the IMF publication Understanding Your Test Results.

**Genetic studies of disease risk**

In addition to the four predictive markers used in ISS, standard bone marrow cytogenetics (karyotyping) and fluorescence in situ hybridization (FISH) are studies that also assess disease risk. These two chromosomal studies are performed on bone marrow aspirate samples. We strongly recommend that these chromosomal studies be done on bone marrow samples taken at the time of diagnosis.

**Cytogenetics**

Cytogenetics is the assessment of the chromosomes in dividing myeloma cells after brief culture in the laboratory. Since the active growth rate of myeloma cells is usually very low (fewer than 3%, and often fewer than 1%, of the cells are proliferating), this provides an incomplete assessment of any chromosomal changes present. Nonetheless, if abnormalities are noted, they are important, because they appear on the few cells that are actually growing.

**FISH**

FISH is the assessment of the chromosomes of all myeloma cells in a bone marrow sample. FISH allows detection of changes whether myeloma cells are growing or not. Special gene probes that

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**Table 6. Prognostic factors**

<table>
<thead>
<tr>
<th>TEST</th>
<th>SIGNIFICANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum β2 microglobulin (S β2M)</td>
<td>The higher the level the more advanced the stage.</td>
</tr>
<tr>
<td>Serum Albumin (S ALB)</td>
<td>The lower the level the more advanced the stage.</td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td>Increased with active disease.</td>
</tr>
<tr>
<td>Serum lactate dehydrogenase (LDH)</td>
<td>Increased with active disease.</td>
</tr>
<tr>
<td>Abnormal chromosomes on bone marrow cytogenetics and Fluorescence In Situ Hybridization (FISH)</td>
<td>Several chromosome deletions or translocations are considered high-risk; can be associated with shorter duration of remission.</td>
</tr>
</tbody>
</table>

**Table 7. International Staging System (ISS) for myeloma**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>VALUES</th>
</tr>
</thead>
</table>
| STAGE 1 | β2M < 3.5  
ALB ≥ 3.5                                    |
| STAGE 2 | β2M < 3.5  
ALB < 3.5  
or  β2M 3.5 – 5.5                               |
| STAGE 3 | β2M > 5.5                                    |

Note: β2M = Serum β2 microglobulin in mg/L  
ALB = Serum albumin in g/dL
fluoresce (glow) are added to the bone marrow sample. These probes track genetic material after cell division and signal the presence or absence of chromosomal abnormalities that are known to occur in myeloma. Each chromosome is given probes of a different color. If, for example, genetic material from chromosome 4 is wrongly connected to chromosome 14, then the differently colored dots of genetic material from these chromosomes appear together, indicating the high-risk abnormality t(4;14), which is shorthand for “translocation of genetic material between chromosomes 4 and 14.” Other abnormalities that are considered high-risk are t(14;16), t(14;20), 17p-, which stands for “loss of the short arm (upper part) of chromosome 17,” and 1q+, which stands for “an additional long arm (lower part) of chromosome 1.” The presence of translocations, missing pieces, extra pieces, and loss of chromosomes can all be detected by FISH testing.

The presence of abnormal chromosomes generally suggests poor prognosis, but this is a trend, not a guaranteed outcome. For example, approximately one third of patients with any of the so-called high-risk abnormalities can do well and have normal outcomes with standard, current approaches to treatment, including induction therapy followed by autologous stem cell transplant. Prompt and effective treatment is essential for any myeloma patient, and especially so for those with features of high-risk disease.

**Treatment options for newly diagnosed myeloma**

Whether or not treatment is necessary is the most important initial decision. Baseline testing, staging, and prognostic classification are essential. Treatment is recommended for active, symptomatic myeloma. Treatment is recommended for smoldering, asymptomatic myeloma with myeloma-defining events (MDE). The urgency of treatment depends upon the exact problems faced by an individual patient. This is why the experience and expertise of a myeloma specialist is of great benefit.

Many studies have demonstrated the superiority of three-drug combination therapies over two-drug combinations for fit, newly-diagnosed myeloma patients. In the United States, the most commonly-used induction therapy for fit, transplant-eligible patients is the combination of Velcade® (bortezomib) + Revlimid® (lenalidomide) + low-dose dexamethasone (VRd). Other induction therapy options include:
- Velcade + cyclophosphamide + dexamethasone (VCD or CyBorD)
- Velcade + thalidomide + dexamethasone (VTD)
- Revlimid + dexamethasone (Rd)
- Velcade + dexamethasone (Vd)
- VRd Lite (reduced dose and schedule of VRd)

After maximum response to induction therapy has been achieved, your physician may recommend a maintenance regimen. The benefit of continuous therapy until disease progression has been amply demonstrated to improve survival, but is not necessary or appropriate for every patient. The financial, physical, and emotional implications of continuous therapy must be taken into consideration along with the characteristics of each patient’s myeloma.

The IMF’s Understanding series of booklets includes information about the individual drugs used to treat myeloma. (https://www.myeloma.org/imf-publications/understanding-series)

In addition to baseline test results, one must consider a number of important issues in selecting a treatment regimen:

- **Day-to-day functioning:** Will treatment affect the ability to perform daily activities?
- **Work:** Will any changes or interruptions be required?

- **Age:** Is this a factor in treatment selection and expected outcomes?
- **Treatment side effects:** How significant will these be?
- **Other medical issues:** Will they affect treatment choices and tolerance of treatment?
- **Transplant:** Is high-dose chemotherapy with transplant of blood-making stem cells recommended?
- **Speed of response:** How rapidly will the treatment work, and how will that be assessed?
- **Initial and later decisions:** How much needs to be decided right away?
- **Financial considerations:** Which part of my treatment will be covered by my insurer, and what will my financial responsibility be? Are there resources to help me pay for my treatment?

**Figure 9. Initial treatment of myeloma**

Key point: If one treatment does not work, this does not mean that another treatment cannot work extremely well and provide an excellent remission.

If a particular induction therapy is not working, there are numerous treatment options available beyond the scope of this introductory handbook. However, it is not advisable to skip rapidly from one treatment regimen to another without exhausting available options.
### Table 8. Baseline testing

<table>
<thead>
<tr>
<th>TEST</th>
<th>PURPOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone marrow biopsy</strong>&lt;br&gt;Special testing is done to assess prognosis (e.g., chromosomes, immune typing, staining for amyloid)</td>
<td>This is the single most critical test to determine both the presence and the percentage of myeloma cells in the bone marrow. In Stage I disease or for a solitary plasmacytoma, direct biopsy of the tumor mass may be necessary. Chromosome analysis (cytogenetic testing) can reveal good or poor chromosomal features using direct (Giemsa stained for banding) and/or FISH analysis. A fresh sample is needed for this type of testing.</td>
</tr>
<tr>
<td><strong>Blood Testing</strong>&lt;br&gt;Complete blood count (CBC)</td>
<td>• To assess presence/severity of anemia (low hemoglobin)&lt;br&gt;• To assess for low white cell count&lt;br&gt;• To assess for low blood platelet count</td>
</tr>
<tr>
<td>Chemistry panel</td>
<td>Used to assess kidney function (creatinine and BUN), liver functions, albumin, calcium level, and LDH</td>
</tr>
<tr>
<td>Special protein testing</td>
<td>This shows the presence of the monoclonal myeloma protein “spike”</td>
</tr>
<tr>
<td>Serum protein electrophoresis (SPEP)</td>
<td>The amount of the abnormal myeloma heavy chain protein</td>
</tr>
<tr>
<td>Immunofixation electrophoresis (IFE)</td>
<td>Shows the heavy chain (G, A, D, E, and M) and light chain (kappa [κ], lambda [λ]) types of the myeloma protein</td>
</tr>
<tr>
<td>Freelite® assay</td>
<td>Can be used to measure the amount of free kappa or lambda light chains if no SPEP or UPEP abnormality discovered</td>
</tr>
<tr>
<td>Hevylite® assay</td>
<td>Can be used to measure normal and abnormal levels of intact immunoglobulins</td>
</tr>
<tr>
<td><strong>Urine Testing</strong>&lt;br&gt;Special protein testing similar to serum above:&lt;br&gt;• Urine Protein Electrophoresis (UPEP)&lt;br&gt;• Immunofixation</td>
<td>Shows the presence, amount, and type of abnormal myeloma protein in urine.</td>
</tr>
<tr>
<td><strong>Bone Testing</strong>&lt;br&gt;To assess the presence, severity, and location of any areas of bone damage:</td>
<td></td>
</tr>
<tr>
<td><strong>X-Rays</strong>&lt;br&gt;X-rays are still used in searching for myeloma bone damage. In a majority of patients, x-rays show characteristic myeloma bone disease (lytic lesions or “holes” in the bones). However, x-rays can be negative in approximately 25% of patients with active myeloma and further imaging with whole-body MRI, whole-body low-dose CT, or PET/CT is needed to rule out possible bone involvement. A full skeletal survey for myeloma using a series of x-rays is needed to show loss or thinning of bone (osteoarthritis or osteopenia caused by myeloma bone destruction), lytic lesions, and/or any fracture or collapse of bone.</td>
<td></td>
</tr>
<tr>
<td>MRI&lt;br&gt;(Magnetic Resonance Imaging)</td>
<td>Used when x-rays are negative and/or for more detailed testing of particular areas such as spine and/or brain. Can reveal the presence and distribution of disease in the bone marrow when x-rays show no bone damage. Can also reveal disease outside of bone, which may be pressing on nerves and/or the spinal cord.</td>
</tr>
<tr>
<td>CT Scan&lt;br&gt;(Computed Tomography)</td>
<td>Used when x-rays are negative and/or for more detailed testing of particular areas. Especially useful for detailed evaluation of small areas of possible bone damage or nerve pressure.</td>
</tr>
<tr>
<td>Nuclear Medicine Scans</td>
<td>Routine bone scans used for other cancers. Not useful in myeloma and should not be performed unless ruling out other diagnoses.</td>
</tr>
<tr>
<td>FDG/PET Scan or PET/CT Scanning</td>
<td>A much more sensitive whole body scanning technique. Useful for disease monitoring, especially for non-secretory disease. CT used to assess sites of PET-positive disease.</td>
</tr>
<tr>
<td><strong>Bone Density Testing</strong></td>
<td>Helpful to assess the severity of diffuse bone loss in myeloma and to measure the serial improvement with bisphosphonate therapy.</td>
</tr>
</tbody>
</table>
### Drugs in current use for myeloma

**Table 9.** Drugs in current use for myeloma

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>BRAND NAME</th>
<th>DISEASE SETTINGS</th>
<th>ADMINISTRATION: DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alkylating agent</strong></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| melphalan | Alkeran® | • Induction in non-transplant-eligible patients  
• One to three prior relapses  
• Relapsed/refractory | • IV (intravenous injection): 200 mg/m²  
• Oral: 6 mg (three tablets) daily |
| cyclophosphamide | Cytoxan® | • Induction  
• One to three prior relapses  
• Relapsed/refractory | • IV: 40–50 mg/kg divided over 2–5 days  
• Oral: 300 mg/m² once weekly |
| **Anthracycline** | | | |
| pegylated liposomal doxorubicin | Doxil® (plus Velcade® + dexamethasone) | • One to three prior relapses  
• Relapsed/refractory | IV: 30 mg/m² on day 4 following bortezomib |
| **Corticosteroid** | | | |
| dexamethasone | Decadron® | • Induction  
• One to three prior relapses  
• Relapsed/refractory | • Can be given IV  
• Usually given weekly at 40 mg orally (10 pills) (“low-dose” dexamethasone)  
• As monotherapy, given orally at 40 mg four days on, four days off |
| **Immunomodulatory drug** | | | |
| thalidomide | Thalomid® (plus dexamethasone) | • Induction  
• One to three prior relapses  
• Relapsed/refractory  
• Maintenance | Oral: approved at 200 mg daily, but is rarely given above 100 mg daily because it is effective at lower doses and higher doses are generally not well tolerated. |
| lenalidomide | Revlimid® (plus dexamethasone) | • Induction  
• One to three prior relapses  
• Relapsed/refractory  
• Maintenance | Oral: 25 mg days 1–21 of a 28-day cycle. |
| pomalidomide | Pomalyist® (plus dexamethasone) | • One to three prior relapses  
• Relapsed/refractory | Oral: 4 mg days 1–21 of a 28-day cycle. |
### SIDE EFFECTS

| Suppression of blood cell counts, hypersensitivity reactions, gastrointestinal toxicity, pulmonary toxicity, infertility, secondary malignancies (leukemia). | • Used as high-dose therapy in autologous transplant.  
• Used in combination with prednisone ± third drug for non-transplant patients (MPV, MPR). |
| Suppression of blood cell counts, infections, urinary tract and renal toxicity, cardiotoxicity, pulmonary toxicity, secondary malignancies, fever, alopecia (IV), nausea, vomiting, diarrhea. | • Sometimes used to mobilize stem cells from the marrow to the peripheral blood for harvest prior to ASCT.  
• Used orally in combination therapies such as CyBorD.  
• Used IV in combination therapies such as DCEP and DVPACE. |
| Cardiotoxicity, infusion reactions, decreased blood cell counts, hand-foot syndrome, mouth sores, nausea and vomiting, tiredness, weakness. | New US manufacturer approved last year to alleviate supply problems. See doxilsupply.com |
| Infections, cardiac conditions/fluid retention, acne, rash, elevated blood glucose, GI disorders, weight gain, coughing, hoarseness, osteoporosis, muscle pain, ophthalmologic disorders, psychiatric effects, sleeplessness. | • Caution about drug interactions. For details, read IMF publication Understanding Dexamethasone and Other Steroids. Several studies have demonstrated that reducing dexamethasone dose in combination therapy improves tolerance, extending treatment duration and overall survival.  
• ASH 2015 Karolinska Institute study demonstrated that on achieving at least a partial remission with Revlimid + dexamethasone second-line therapy, continuing with dexamethasone in addition to Revlimid does not add benefit. |
| Embryo-fetal toxicity, venous and arterial thromboembolism, peripheral neuropathy, constipation, drowsiness, dizziness, low white blood cell counts, rash. | • Patients must participate in a risk evaluation and mitigation strategies (REMS) program.  
• Both partners must use contraception.  
• Causes irreversible peripheral neuropathy.  
• Increased risk of thromboembolism when combined with dexamethasone, requiring use of a blood thinner. |
| Embryo-fetal toxicity, low white blood cell counts, low platelet counts, venous and arterial thromboembolism (blot clot that can travel to the lung), diarrhea, fatigue, anemia, constipation, rash. | • Patients must participate in a risk evaluation and mitigation strategies (REMS) program.  
• Both partners must use contraception.  
• FIRST trial demonstrated the benefit of continuous Revlimid in newly diagnosed myeloma patients who are not candidates for transplant.  
• Increased risk of thromboembolism when combined with dexamethasone, requiring use of a blood thinner. |
| Embryo-fetal toxicity, low white blood cell counts, low red blood cell counts, low platelet counts, venous and arterial thromboembolism, fatigue, weakness, dizziness and confusion, constipation, nausea, diarrhea, neuropathy. | • Patients must participate in a risk evaluation and mitigation strategies (REMS) program.  
• Both partners must use contraception.  
• Increased risk of thromboembolism when combined with dexamethasone, requiring use of a blood thinner. |

(Table 9 continues on next page)
<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>BRAND NAME</th>
<th>DISEASE SETTINGS</th>
<th>ADMINISTRATION: DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proteasome inhibitor</strong></td>
<td></td>
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<tr>
<td>bortezomib</td>
<td>Velcade® (plus dexamethasone)</td>
<td>• Induction</td>
<td>IV or SQ (subcutaneous) injection at 1.3 mg/m² days 1, 4, 8, 11 of every 21-day cycle.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• One to three prior relapses</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>• Relapsed/refractory</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Maintenance</td>
<td></td>
</tr>
<tr>
<td>carfilzomib</td>
<td>Kyprolis® (alone or plus Revlimid + dexamethasone)</td>
<td>• One to three prior relapses</td>
<td>IV: 10-minute infusion twice-weekly on 2 consecutive days for 3 weeks out of every 4-week cycle.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Relapsed/refractory</td>
<td></td>
</tr>
<tr>
<td>ixazomib</td>
<td>Ninlaro® (plus Revlimid + dexamethasone)</td>
<td>One to three prior relapses</td>
<td>Oral: 4 mg on days 1, 8, 15 of a 28-day cycle.</td>
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<tr>
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<tr>
<td><strong>Monoclonal antibody (mAb)</strong></td>
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<tr>
<td>daratumumab</td>
<td>Darzalex®</td>
<td>Relapsed/refractory</td>
<td>IV: 16 mg/kg weekly cycles 1 &amp; 2, every 2 weeks cycles 3–6, every 4 weeks cycle 7 onward.</td>
</tr>
<tr>
<td>elotuzumab</td>
<td>Empliciti® (plus Revlimid + dexamethasone)</td>
<td>One to three prior relapses</td>
<td>IV: 10 mg/kg cycles 1 + 2 once weekly, days 1, 8, 15, 22 of a 28-day cycle; thereafter every other week, days 1 and 15, every 28 days.</td>
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<tr>
<td><strong>HDAC Inhibitor (histone deacetylase inhibitor)</strong></td>
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<tr>
<td>panobinostat</td>
<td>Farydak® (plus Velcade + dexamethasone)</td>
<td>• One to three prior relapses</td>
<td>Oral: 20 mg every other day for 3 doses per week (days 1, 3, 5, 8, 10, 12) of weeks 1 and 2 of each 21-day cycle, for 8 cycles.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Relapsed/refractory</td>
<td></td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>REMARKS</td>
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<tr>
<td>Peripheral neuropathy, fatigue, nausea, diarrhea, thrombocytopenia, hypotension.</td>
<td>• Increased incidence of herpes zoster virus (shingles). Discuss with doctor the use of anti-viral medication as preventive measure while on Velcade. • Shown to be effective in patients with the t(4;14) high-risk cytogenetic abnormality. • Safe for patients with renal (kidney) insufficiency. • Subcutaneous and/or once-weekly administration reduces the risk of peripheral neuropathy.</td>
<td></td>
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</tr>
<tr>
<td>Fatigue, anemia, thrombocytopenia, shortness of breath, diarrhea, fever, low blood pressure, cardiac failure and other cardiac events, infusion reactions.</td>
<td>• Patients with pre-existing heart conditions may be at greater risk for cardiac complications. • Outperformed Velcade + dexamethasone in relapsed myeloma for PFS, OS (regardless of age, cytogenetics, prior treatment). • Anti-viral therapy for prevention of herpes zoster virus (shingles) is recommended.</td>
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<tr>
<td>Thrombocytopenia, neutropenia, diarrhea, constipation, nausea, vomiting, peripheral neuropathy, peripheral edema (swelling of the feet), rash, liver toxicity, back pain, upper respiratory tract infection.</td>
<td>• Dose should be 3 mg for patients with moderate to severe liver or kidney impairment. • Causes embryo-fetal toxicity. • Discuss with doctor use of anti-viral therapy for prevention of herpes zoster virus (shingles). • Take one hour before or two hours after eating. • In combination with Revlimid + dexamethasone (Rd), increased risk of thromboembolism requiring use of a blood thinner.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion reactions, fatigue, nausea, back pain, fever, cough, low blood cell counts.</td>
<td>• Clinical trial in progress to test new SQ administration. • In combination with Velcade + dexamethasone or Revlimid + dexamethasone after at least one prior therapy. • Darzalex may cause embryo-fetal toxicity. • Patients must be medicated before and after infusions with a corticosteroid, an anti-fever medication, and an antihistamine to prevent infusion reactions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion reactions, low blood counts, infections, fatigue, diarrhea, fever, constipation, muscle spasms, decreased appetite.</td>
<td>• Anticoagulation is advised for the combination with Revlimid due to high incidence of deep vein thrombosis and pulmonary embolism. • Patients must be pre-medicated with dexamethasone, antihistamine, ranitidine, and acetaminophen prior to each dose of elotuzumab to prevent infusion reactions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low blood counts, diarrhea, nausea or vomiting, cardiac toxicity, hemorrhage (due to low platelets), infections, liver toxicity, embryo-fetal toxicity, fatigue.</td>
<td>• Patients with a history of recent myocardial infarction or unstable angina should not receive Farydak. • Patients with severe hepatic impairment should not receive Farydak; dose should be lowered for those with mild or moderate impairment. • Reduce dose to 10 mg if given with strong CYP3A inhibitors, including clarithromycin (Biaxin®).</td>
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</tbody>
</table>
Stem cell transplant

It’s best to keep the door open for stem cell transplantation if you and your doctor feel it can be an option for you. The current consensus of the IMWG is that all transplant-eligible patients should store stem cells for possible future need. In general, patients who are younger than 65 years (and have no other medical conditions that would put them at risk) are considered candidates for stem cell transplant. Although definitive clinical trial results with overall survival data are not yet available, studies indicate that deeper responses and longer duration of remission – known as progression-free survival (PFS) – occur among patients who have autologous stem cell transplant as a planned part of their initial therapy for myeloma.

In the United States, Medicare insurance will cover a single autologous stem cell transplant for eligible patients of any age, as long as they have Durie-Salmon stage II or III myeloma. Their myeloma must be either newly diagnosed or must still be responsive to treatment, and they must have adequate heart, liver, lung, and kidney function. Medicare will not cover tandem or two back-to-back autologous transplants.

If a patient has a transplant that is covered by Medicare and then relapses after a remission of two years or longer, Medicare may cover another transplant at that time. Eligibility for stem cell transplant must be evaluated on an individual basis, taking into account health status, other illnesses, and treatment history. Many older patients are in excellent physical health and would be considered fit and transplant-eligible.

Clinical trials

Although clinical trials for induction therapy are available, patients must be completely comfortable that they might be randomly assigned to one treatment versus another, depending on the trial’s design. This might result in a patient being locked into future randomization and treatments. It’s vital
to understand the full scope of the treatment trial protocol. For a more complete discussion of clinical trials, see the IMF publication *Understanding Clinical Trials*.

**Supportive care**

Treatments are available to alleviate the physical and emotional impact of the disease. Early use of supportive care measures is just as important as initiating induction therapy. Beyond the management of specific symptoms, a whole range of supportive measures is critically important:

- **Physical activity:** Patients should check with their physicians to clarify if full physical activity is feasible or if adjustments must be made due to bone disease or particular areas of bone damage. Usually, some physical activity can be planned, such as walking or swimming, flexibility and strengthening exercises, and/or a personalized yoga program.

- **Diet:** No specific diet has been developed for myeloma patients, although research has clearly demonstrated the link between obesity and myeloma. We recommend that patients eat a healthy, Mediterranean-type diet emphasizing fruits, vegetables, fish, other lean animal proteins, whole grains, and unprocessed “real” foods. We recommend that patients avoid foods that include processed sugars and artificial trans fats. Caution should be used in two areas:
  - **Vitamin C:** Doses greater than 1000 mg per day may be counter-productive in myeloma and can increase the risk of kidney damage.
  - **Herbal and vitamin supplements:** Talk to your physician or pharmacist about using supplements at the same time as treatment for myeloma. Some supplements can prevent treatments from working effectively. Drug-supplement interactions can also create

### Table 11. Drugs in current use for supportive care – April 2017

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>BRAND NAME</th>
<th>DISEASE SETTINGS</th>
<th>ADMINISTRATION: DOSE</th>
<th>SIDE EFFECTS</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bisphosphonate</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>pamidronate</td>
<td>Aredia®</td>
<td>For the treatment of myeloma bone disease</td>
<td>IV: 90 mg infused over 2–4 hours once monthly.</td>
<td>Renal toxicity, fever, vein irritation, general aches and pains, osteonecrosis of the jaw.</td>
<td>• Long-term use (5+ years) can lead to atypical fractures of the femur. • Patients without documented myeloma-related bone disease should not take bisphosphonates.</td>
</tr>
<tr>
<td>zoledronate, zoledronic acid</td>
<td>Zometa®</td>
<td>For the treatment of myeloma bone disease</td>
<td>IV: 4 mg over no less than 15 minutes every 3–4 weeks; usually 30–45 minutes once monthly.</td>
<td>Renal toxicity, fever, vein irritation, general aches and pains, osteonecrosis of the jaw.</td>
<td>• Long-term use (5+ years) can lead to atypical fractures of the femur. • Patients without documented myeloma-related bone disease should not take bisphosphonates. • Dose should be reduced for patients with renal impairment. • 500 mg calcium and 400 IU vitamin D should be taken daily.</td>
</tr>
</tbody>
</table>

| **Stem cell mobilizer** |
| plerixafor | Mozobil® | For use in combination with GCSF to mobilize hematopoietic stem cells prior to ASCT | IV: at 0.24 mg/kg body weight. | Nausea, vomiting, diarrhea, tiredness, headache, dizziness, joint or muscle pain, injection site reaction, low platelets. | May cause embryo-fetal harm. |
serious medical problems. Many pharmacies have computer programs that can identify potential interactions between medications and/or supplements.

**Mental health:** Your mental health is critical as you move forward with planned treatment. Make sure you’re comfortable with the treatment plan. Schedule an appointment with a mental health professional if you believe that you might be depressed, or if others are concerned that you might be depressed. This is a normal response to a cancer diagnosis, and most patients will need some help at one time or another. A myeloma support group can also be helpful in this context. Gathering information and support among peers is vital at this time. For a referral to a myeloma support group in your area, call the IMF InfoLine or visit myeloma.org.

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>TREATMENT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue and weakness due to anemia</td>
<td>• Blood transfusion (packed red blood cells: leukoreduced, virus screened) if anemia severe&lt;br&gt;• Erythropoietin if anemia mild to moderate and induced by therapy</td>
<td>The treatments are simple, usually highly beneficial, and improve feelings of well-being.</td>
</tr>
<tr>
<td>Bone pain</td>
<td>• Bisphosphonate (e.g., Aredia® 90 mg IV over 2–4 hrs monthly; Zometa® 4 mg IV over 15–45 minutes monthly)&lt;br&gt;• Pain medication as needed (e.g., acetaminophen, oral morphine derivatives, fentanyl)</td>
<td>Relief of bone pain is important in itself and improves physical activity, which in turn promotes bone strength and healing and improves emotional well-being. Potential damage to kidneys and jaws, though rare, can result from chronic bisphosphonate therapy. Awareness is the key to prevention.</td>
</tr>
<tr>
<td>Fever and/or evidence of infection</td>
<td>• Appropriate antibiotics&lt;br&gt;• Neupogen® if necessary to boost low white blood cell count&lt;br&gt;• Intravenous gamma globulin for severe infections&lt;br&gt;• Tests as needed to diagnose the exact type of infection should be performed (except for dangerous biopsies/cultures)</td>
<td>Although antibiotics should be selected and used with care, it is extremely important that infections be brought under control promptly. Having an antibiotic on hand for emergency use (especially if traveling) is recommended.</td>
</tr>
<tr>
<td>Gastrointestinal side effects</td>
<td>• Appropriate medications to treat nausea, vomiting, constipation, or diarrhea&lt;br&gt;• Maintain adequate fluid intake and nutrition</td>
<td>Discuss symptoms with healthcare providers; severe symptoms may require hospitalization.</td>
</tr>
<tr>
<td>Blood clots and thromboembolic events</td>
<td>• Clotting events are medical emergencies; treatment based on event and patient risk factors&lt;br&gt;• Aspirin or anti-clotting medications may be prescribed</td>
<td>Risk may be reduced by exercise, weight loss, not smoking.</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>• Pain medications&lt;br&gt;• Adjustment of dose, schedule, and/or route of administration&lt;br&gt;• Physical therapy, vitamin and other supplements</td>
<td>Discuss symptoms with healthcare providers. Early intervention can prevent permanent damage and allow continued treatment. Do not adjust doses on your own. Do not take supplements without discussing with doctor.</td>
</tr>
<tr>
<td>Steroid side effects</td>
<td>• Take with food early in the morning&lt;br&gt;• Be aware of signs and symptoms of infection, changes in blood sugar&lt;br&gt;• Medications to prevent shingles and yeast infections</td>
<td>Report side effects and symptoms to healthcare providers. Do not stop or adjust doses on your own.</td>
</tr>
</tbody>
</table>

Please visit myeloma.org or contact the IMF for patient education sheets on preventing blood clots and thromboembolic events, managing steroid-associated side effects, managing myelosuppression, preventing peripheral neuropathy, and managing gastrointestinal side effects.
myeloma.org/support-groups to search for a group near you.

- **Regular sleep:** This is very important for your immune system.

- **Make adjustments:** As much as possible, reduce or eliminate stress in job, family, or social situations. Avoid close contact with school-age children. Avoid crowds as much as possible. Wash hands frequently. Your immune system is compromised both by the disease and the treatments. Management of the myeloma is the top priority until remission or a stable situation has been reached.

**In closing**

While a diagnosis of cancer is something you cannot control, gaining knowledge that will improve your interaction with your doctors and nurses is something you can control, and it will have a significant impact on how well you do throughout the disease course.

This booklet is not meant to replace the advice of your doctors and nurses who are best able to answer questions about your specific healthcare management plan. The IMF intends only to provide you with information that will guide you in discussions with your healthcare team. To help ensure effective treatment with good quality of life, you must play an active role in your own medical care.

We encourage you to visit myeloma.org for up-to-date information about myeloma, and to contact the IMF InfoLine with your myeloma-related questions and concerns. The IMF InfoLine consistently provides callers with the best information about myeloma in a caring and compassionate manner. IMF InfoLine specialists can be reached at InfoLine@myeloma.org, or 800-452-CURE (2873) or 818-487-7455.

**Terms and definitions**

**Albumin (ALB):** Simple water-soluble protein that is found in blood serum. Production is inhibited by interleukin-6 when myeloma is very active.

**Amyloid light-chain amyloidosis (AL amyloidosis):** A condition in which myeloma light chains cross-link with each other in a beta-pleated fashion and then are deposited in tissues and organs throughout the body, such as the heart, nerves, and kidneys, rather than being excreted through the kidneys. This condition is also known as primary amyloidosis.

**Anemia:** A decrease in hemoglobin contained in red blood cells that carry oxygen to the body’s tissues and organs. Anemia is usually defined as hemoglobin below 10 g/dL, with over 13–14 g/dL considered normal, and/or a decrease of ≥ 2 g/dL from the normal level for an individual.

**Antibody:** A protein produced by white blood cells called plasma cells that helps fight infection and disease.

**Asymptomatic myeloma:** Myeloma that presents no signs or symptoms of disease; early-stage myeloma. See “Smoldering multiple myeloma (SMM).”

**Bence-Jones myeloma:** Myeloma characterized by the presence of Bence-Jones protein, an abnormal protein in urine made up of free kappa or lambda light chains.

**Bence-Jones protein:** A myeloma monoclonal protein. The protein is composed of either free kappa or free lambda light chains. Because of their small size, Bence-Jones light chains pass freely into the urine. The amount of Bence-Jones protein in the urine is expressed in terms of grams per 24 hours. Normally, a very small amount of protein (<0.1 g/24 h) can be present in the urine, but this is albumin rather than Bence-Jones protein. The presence of any Bence-Jones protein in the urine is abnormal.

**Beta-2 microglobulin (also called β2-microglobulin, β₂M, or β2M):** A small protein found in the blood. High levels occur in patients with active myeloma. Low or normal levels occur in patients with early myeloma and/or inactive disease. Approximately 10% of patients have myeloma that does not produce β2M. At the time of relapse, β2M can increase before there is any change in the myeloma protein level. Factors such as viral infection can sometimes produce elevated serum β2M levels.
Bone marrow: The soft, spongy tissue in the center of bones that produces white blood cells, red blood cells, and platelets. This is the tissue within which abnormal plasma cells build up to cause myeloma.

C-reactive protein (CRP): A protein made in the liver that rises when there is inflammation throughout the body.

Calcium: A mineral found mainly in the hard part of bone matrix or hydroxyapatite. If produced or released in excess, it can build up in the bloodstream. See “Hypercalcemia.”

Clinical trial: A research study of new treatment that involves patients. Each study is designed to find better ways to prevent, detect, diagnose, or treat cancer and to answer scientific questions.

*Control group* – The arm of a randomized clinical trial that gets the standard treatment or placebo (no treatment).

*Experimental group* – The arm of a randomized trial that gets the new treatment.

*Randomized clinical trial* – A research study in which subjects are randomly assigned to receive a particular treatment or not.

*Arm* – One of the treatment groups of a randomized trial. The majority of randomized trials have two, but some have more.

*End point* – The goal of the trial; what a clinical trial is trying to measure or find out. Typical end points include measurements of toxicity, response rate, and survival.

*Double blind* – Aspect of a randomized trial in which neither the participant nor the investigator knows the arm of the trial to which the patient is assigned. The purpose is to eliminate any bias in the reporting of results.

*Phase I trial* – A trial designed to determine the maximum-tolerated dose (MTD) of a new drug or a new combination of drugs. It is usually the first human testing of a new treatment, although in phase I trials of combination therapies, the individual elements may already have been well tested. Patients in phase I trials generally have advanced cancer that is refractory to all standard treatment. In a typical phase I trial, successive groups (“cohorts”) of 3 to 6 patients are given the treatment. All patients in a cohort get the same dose. The first cohort typically gets a very low dose, and the dose is raised in each subsequent cohort until a set number of patients experience dose-limiting toxicity (DLT). The dose level used for the previous cohort is then taken to be the MTD. This dose is then used in a phase II trial.

*Phase II trial* – A trial designed to determine the response rate of a new therapy that has already been tested in phase I trials. Typically, 14 to 50 patients with one type of cancer are treated to see how many have a response. Patients are usually required to have advanced cancer that is refractory to any standard treatment, and in addition, they must have measurable disease. If results from a phase II trial are promising enough, the treatment may then be tested in a phase III trial. If the results are obviously much better than the standard treatment, then it may not be necessary to do a phase III trial, and the treatment may become standard-based on phase II trial results.

*Phase III trial* – A trial designed to compare two or more treatments for a given type and stage of cancer. The end point of a phase III trial is usually survival or disease-free survival. Phase III trials are usually randomized, so patients don’t choose which treatment they receive. A typical phase III trial has 50 to thousands of patients. Some phase III trials compare a new treatment that has had good results in phase II trials with an older, well known, standard treatment. Other phase III trials compare treatments that are already in common use. Some treatments in phase III trials may be available outside the clinical trial setting.

*Phase IV trial* – Even after a drug has been approved by the United States Food and Drug Administration (FDA) for use in a particular indication, there may be need for additional studies. Phase IV clinical trials may be required by regulatory authorities or may be undertaken by the sponsoring company for a variety of reasons. For example, safety surveillance is designed to detect any rare or long-term side effects over a larger patient population and longer time period than was possible during the phase I–III clinical trials.
Cytokines: Proteins secreted by cells which can stimulate or inhibit growth/activity in other cells. Cytokines are produced locally (i.e., in the bone marrow) and circulate in the bloodstream. They are normally released in response to infection.

Extramedullary plasmacytoma: A tumor made up of monoclonal plasma cells that is found in soft tissue outside of the bone marrow and separate from bone.

Fluorescence in situ hybridization (FISH): A procedure that allows researchers to locate the positions of specific DNA sequences on chromosomes.

Free light chain: A portion of the monoclonal protein that is of low molecular weight. It may be bound to a heavy chain or it may be unbound, or free. Free light chains can be measured in a sensitive assay called the Freelite® test.

Hypercalcemia: A higher than normal level of calcium in the blood. In myeloma patients, it usually results from bone breakdown with release of calcium from the bone into the bloodstream. This condition can cause a number of symptoms, including loss of appetite, nausea, thirst, fatigue, muscle weakness, restlessness, and confusion.

See “Calcium.”

IgG, IgA: The two most common types of myeloma. The G and the A refer to the type of protein produced by the myeloma cells. The myeloma protein, which is an immunoglobulin, consists of two heavy chains, (for example, of a G type) combined with two light chains, which are either kappa or lambda. Therefore, the two most common subtypes of myeloma have identical heavy chains (i.e., IgG kappa and IgG lambda). The terms “heavy” and “light” refer to the size or molecular weight of the protein, with the heavy chains being larger than the light chains.

IgD, IgE: Two types of myeloma that occur less frequently. See “IgG, IgA.”

IgM: Usually associated with Waldenström’s macroglobulinemia. In rare cases, IgM can be a type of myeloma.

Immune system: The complex group of organs and cells that produces antibodies, cellular responses to defend the body against foreign substances such as bacteria, viruses, toxins, and cancers.

Immunofixation electrophoresis (IFE): An immunologic test of the serum or urine used to identify proteins. For myeloma patients, it enables the doctor to identify the M-protein type (IgG, IgA, kappa, or lambda). The most sensitive routine immunostaining technique, it identifies the exact heavy- and light-chain type of M-protein.

Immunoglobulin (Ig): A protein produced by plasma cells; an essential part of the body’s immune system. Immunoglobulins attach to foreign substances (antigens) and assist in destroying them. The classes (also called isotypes) of immunoglobulins are IgG, IgA, IgD, IgE, and IgM. The non-medical word for immunoglobulin is “antibody.”

Induction therapy: The initial treatment used in an effort to achieve remission in a newly diagnosed myeloma patient. Sometimes called “frontline” therapy.

Lactate dehydrogenase (LDH): An energy-producing enzyme that is present in almost all of the tissues in the body. LDH levels in the bloodstream rise in response to cell damage. LDH may be used to monitor myeloma activity.

Lesion: An area of abnormal tissue. A lump or abscess that may be caused by injury or disease, such as cancer. In myeloma, “lesion” can refer to a plasmacytoma or a hole in the bone.

Light chain: An immunoglobulin light chain is the smaller of two units of an antibody (immunoglobulin). The light chains are bound by chemical bonds to the ends of the heavy chains, but we make extra light chains that enter the bloodstream. These are called “free light chains.” There are two types of light chains: kappa and lambda.

Lytic (lysis): Dissolution or destruction of cells or tissues.

Lytic lesions: The damaged area of a bone that shows up as a dark spot on an x-ray when at least 30% of the healthy bone in any one area is eaten away. Lytic lesions look like holes in the bone and are evidence that the bone is being weakened.

Malignant: Cancerous; capable of invading nearby tissue and spreading to other parts of the body.
Monoclonal: A clone or duplicate of a single cell. Myeloma develops from a single malignant plasma cell (monoclonal). The type of myeloma protein produced is also monoclonal; a single form rather than many forms (polyclonal). The important practical aspect of a monoclonal protein is that it shows up as a sharp spike (M-spike) in the serum electrophoresis test.

Monoclonal gammopathy of undetermined significance (MGUS): A category of plasma cell disorder characterized by comparatively low levels of monoclonal protein in the blood and/or urine. Bone marrow plasma cell levels are low (<10%). Myeloma-related symptoms (i.e., anemia, renal failure, hypercalcemia, and lytic lesions) are absent.

Monoclonal protein (M-protein): An abnormal protein produced by myeloma cells that accumulates in and damages bone and bone marrow. A high level of M-protein indicates that myeloma cells are present in large numbers.

Myeloma-defining events (MDE): Biologic markers that indicate progression to symptomatic myeloma that occur within 18 months to 2 years.

Non-secretory myeloma: Approximately 1% of myeloma patients do not have detectable M-protein in the blood (serum) and urine. Some of these patients can be successfully monitored using the serum free light chain assay; others may be monitored with bone marrow biopsy and/or PET/CT scan. Patients with non-secretory myeloma are treated in the same fashion as those with M-protein-secreting disease.

Osteoblast: A bone cell that is associated with production of bone tissue. Osteoblasts produce osteoid, which becomes mineralized with calcium to form new hard bone.

Osteoclast: A cell found in bone and bone marrow at the junction between the bone marrow and the bone. It is responsible for breaking down or remodeling old bone tissue. In myeloma, the osteoclasts are overstimulated, while osteoblast activity is blocked. The combination of accelerated bone resorption and blocked new bone formation results in lytic lesions.

Overall survival (OS): For a group of individuals suffering from a cancer, this term denotes the chances of staying alive. It denotes the median number of individuals in the group who are likely to be alive after a particular duration of time. At a basic level, OS is representative of cure rates. OS is often used as a measure of treatment efficacy in clinical trials.

Peripheral neuropathy (PN): Numbness, tingling, and/or pain in the hands, feet, legs, and/or arms.

Plasma cells: Special white blood cells that produce antibodies (immunoglobulins). Myeloma is a cancer of the plasma cells. Malignant plasma cells are called myeloma cells. In myeloma, malignant plasma cells produce large amounts of abnormal antibodies that lack the capability to fight infection. These abnormal antibodies are the monoclonal protein, or M-protein, that functions as a tumor marker for myeloma. Plasma cells also produce other chemicals that can cause organ and tissue damage (i.e., anemia, kidney damage, and nerve damage).

Plasmacytoma: See “Extramedullary plasmacytoma” and “Solitary plasmacytoma of the bone (SPB).”

Platelets: One of the three major blood elements, others being the red blood cells and white blood cells. Platelets plug up breaks in the blood vessel walls and release substances that stimulate blood clot formation. Platelets are the major defense against bleeding. Also called thrombocytes.

Progression-free survival (PFS): The improved survival of a patient that can be directly attributed to the treatment given for the myeloma. The time period during which the patient survives, and the myeloma does not regrow or relapse. See “Progressive disease.”

Progressive disease: Myeloma that is becoming worse or relapsing, as documented by tests. Defined as an increase of ≥ 25% from lowest confirmed response value in the myeloma protein level and/or new evidence of disease.
Red blood cells (RBC, erythrocytes): Cells in the blood that contain hemoglobin and deliver oxygen to and take carbon dioxide from all parts of the body. Red cell production is stimulated by a hormone (erythropoietin) produced by the kidneys. Myeloma patients with damaged kidneys don’t produce enough erythropoietin and can become anemic. Myeloma patients can also become anemic because of myeloma cells’ effect on the ability of the bone marrow to make new red blood cells.

Smoldering multiple myeloma (SMM): SMM is a higher level of disease than MGUS, but is still not active myeloma with CRAB features indicating organ damage. Patients with standard-risk SMM do not require treatment, but should be observed at regular intervals by a hematologist-oncologist. Patients with high-risk SMM may choose to participate in a clinical trial.

Solitary plasmacytoma of bone (SPB): A discreet, single mass of monoclonal plasma cells in a bone. The diagnosis of SBP requires a solitary bone lesion, a biopsy of which shows infiltration by plasma cells; negative imaging results for other bone lesions; absence of clonal plasma cells in a random sample of bone marrow; and no evidence of anemia, hypercalcemia, or renal involvement suggesting systemic myeloma.

Transplant (transplantation): There are several different types of transplantation.

• Peripheral blood stem cell (PBSC) transplant – Doctors remove healthy stem cells from a patient’s circulating blood system (not from the bone marrow) and store them before the patient receives high-dose chemotherapy to destroy the cancer cells. The stem cells are then returned to the patient, where they can produce new blood cells to replace cells destroyed by the treatment. Using PBSC for autologous transplantation allows for easier and safer collection of stem cells and faster recovery after the transplant than bone marrow transplant.

• Autologous transplant – A procedure in which stem cells are removed from a patient’s blood and then are given back to the patient following intensive treatment.

• Bone marrow transplant – This term refers to the process of collecting stem cells from the bone marrow and infusing them into a patient. This term is used less frequently today in myeloma as stem cells are now collected from the peripheral or circulating blood.

• Allogeneic (allograft) transplant – The infusion of bone marrow or stem cells from one individual (donor) to another (recipient). A patient receives bone marrow or stem cells from a compatible, though not genetically identical, donor. An HLA blood test is done to determine if a patient has a potential donor match. A donor may be a family member or may be obtained through a donor registry such as the National Marrow Donor Program (NMDP). Rarely, donor cells may be obtained from an umbilical cord blood bank.

• Reduced-intensity conditioning (RIC) allo transplant – A newer and, for myeloma, safer technique than an allogeneic transplant. RIC is a non-myeloablative, reduced-intensity “mini-allo” transplant performed within 180 days after a standard autologous transplant.

• Tandem transplant – A term used to indicate two transplants. This may be two autologous transplants or an autologous transplant followed by an allogeneic (donor) transplant. Tandem transplants are usually planned with 3- to 6-month intervals between transplants. Tandem transplantation has become less common in the era of effective novel therapies.

• Matched unrelated donor (MUD) transplant – Refers to a stem cell transplantation procedure in which the patient and the stem cells are genetically matched but are not from family members. This procedure is not recommended for myeloma patients because it carries an acceptably high mortality rate.

• Syngeneic transplant – The infusion of bone marrow or stem cells from one identical twin into another.

• Umbilical cord blood transplant – Stem cells obtained from the umbilical cords of newborns. These are frozen and stored in cord blood banks.

Tumor: An abnormal mass of tissue that results from excessive cell division.
Vaccine: A preparation of killed microorganisms, living attenuated organisms, or living fully virulent organisms that is administered to produce or artificially increase immunity to a particular disease.

Virus: A small living particle that can infect cells and change how the cells function. Infection with a virus can cause a person to develop symptoms. The disease and symptoms that are caused depend on the type of virus and the type of cells that are infected.

Waldenström’s macroglobulinemia (WM): A rare type of indolent lymphoma that affects plasma cells. Excessive amounts of IgM protein are produced. Not a type of myeloma.

White blood cells (WBC): General term for a variety of cells responsible for fighting invading germs, infection, and allergy-causing agents. These cells begin their development in the bone marrow and then travel to other parts of the body. Specific white blood cells include neutrophils, granulocytes, lymphocytes, and monocytes.

Notes
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One of the most daunting aspects of being diagnosed with multiple myeloma is learning about – and understanding – an unfamiliar disease that is quite complicated. From diagnosis to long-term survival, the 10 Steps to Better Care® will guide you through the myeloma journey:

1. Know what you’re dealing with. Get the correct diagnosis.
2. Tests you really need.
3. Initial treatment options.
4. Supportive care and how to get it.
5. Transplant: Do you need one?
6. Response Assessment: Is treatment working?
7. Consolidation and/or maintenance.
9. Relapse: Do you need a change in treatment?

Visit 10steps.myeloma.org to gain a better understanding of the disease and diagnosis, and proceed through the steps to learn the best tests, treatments, supportive care, and clinical trials currently available.

As always, the International Myeloma Foundation (IMF) urges you to discuss all medical issues thoroughly with your doctor. The IMF is here to equip you with the tools to understand and better manage your myeloma. Visit the IMF website at myeloma.org or call the IMF InfoLine at 800-452-CURE (2873) or 818-487-7455 to speak with our trained information specialists about your questions or concerns. The IMF is here to help.