MYELOMA CANADA
MAKING MYELOMA MATTER

InfoSheet

MANAGING INFECTIONS AND NEUTROPENIA ASSOCIATED WITH MYELOMA AND ITS TREATMENT

A healthy immune system is the body's natural defence against threats such as infections (e.g., bacteria, viruses, fungi), foreign particles, and even cancer.

People with multiple myeloma are more prone to infections than those without the condition. This is due to both the myeloma itself, and the effects of anti-myeloma treatments.

Through this InfoSheet, you will learn more on how to identify the symptoms and causes of infections, and find preventive strategies to improve quality of life and patient outcomes.

Definition and causes of infections

Infections occur when a harmful organism enters the body and multiplies, causing illness. These organisms, often called “germs”, do not belong in the body and might enter through a cut, breathing them in, or touching something then touching your eyes, nose, or mouth. Once these germs get into your body they can multiply and spread, which is what makes you feel sick. Typically, the body's immune system will quickly kill and then remove the invader, however sometimes these organisms are too strong, or the immune system is too weak, leading to infections.

Infections are a significant cause of morbidity and mortality in people with multiple myeloma. Studies show that approximately 10% of individuals die due to infections at the time of diagnosis, even before starting treatment[1]. Most infections in myeloma patients are caused by viruses and bacteria, although fungal and parasitic infections can also occur.

[1] Raje et al. Lancet Haematology, 2022.

Infections are graded from 1 to 5, mild stages corresponding to 1 and 2, while grades 3 to 5 are considered more severe and require closer attention.

There are four types of infections:

- **Bacterial** infections: urinary tract, lung (pneumonia), mouth, gastrointestinal (e.g., E. coli, salmonella) or other infections like meningitis.
- **Viral** infections: influenza, COVID-19, gastrointestinal (e.g., rotavirus), shingles and chickenpox, and cold sores.
- **Fungal** infections: yeast infections, lung condition called Aspergillosis, and fungal infections on the skin or nails.
- **Parasitic** infections: toxoplasmosis, trichinosis, malaria, and scabies.

Causes of infections in myeloma and role of antibodies in fighting infections

The abnormal accumulation of myeloma cells in your bone marrow has both direct and indirect effects on your blood, bone and kidneys. It disrupts the normal production of antibodies and reduces white blood cell counts, weakening the immune system's ability to fight infection. This can leave a person susceptible to repeated infections or illness, especially respiratory infections, from which it may take a long time to recover.

Antibodies (immunoglobulins) are special proteins made by plasma cells, a type of white blood cell, to help protect the body from infections. Antibodies are Y-shaped molecules that have heavy and light chains. These chains act like lock and keys, attaching to bacteria, viruses, toxins, tumours, or other harmful substances to destroy them. In myeloma, the body's ability to make these protective antibodies is disrupted. Instead of producing healthy antibodies, myeloma cells create large amounts of abnormal proteins, called M proteins. These M proteins do not fight infection. This weakens the immune system and makes it harder for the body to protect itself.

Multiple myeloma can also impair other parts of our immune system. In addition to plasma cell dysfunction, there is a reduction in immune cells, including neutrophils, lymphocytes, and natural killer (NK) cells. Neutropenia (not enough neutrophils), caused by the invasion of myeloma cells in the bone marrow weakens the body's defences against infection caused by bacteria and fungi. Although common in multiple myeloma, neutropenia can be potentially serious. Lymphopenia (not enough lymphocytes) impairs the body’s ability recognize and attack specific infections. Natural killer cells, which are responsible for killing abnormal or infected cells, also become less active. T-cells, another crucial part of our immune system, lose their diversity and function, which further reduces the body’s ability to fight off infections.

Myeloma can also weaken the spleen (hyposplenia), an organ that helps to filter out bacteria from the body and fight infection or cause the absence of a functional spleen all together (asplenia). Additionally, myeloma cells in the bone marrow will crowd out the healthy cells, reducing the number of white blood cells the body can produce. Kidney issues, which are common in myeloma, will further reduce the body’s white blood cell counts. For example, patients receiving hemodialysis (used in advanced kidney disease) have an increased risk of developing an invasive infection caused by Staphylococcus aureus bacteria. This type of bacteria lives on our skin and is usually responsible for minor skin infections such as boils. However, the hemodialysis process can allow the bacteria to enter the body where they can cause a more serious, invasive infection known as sepsis or blood poisoning. Sepsis may lead to multiple organ failure.

Impacts of myeloma treatments on the immune system

Treatment-related immune suppression further exacerbates these vulnerabilities. Anti-myeloma treatments, including chemotherapy (for example, cyclophosphamide and melphalan), proteasome inhibitors (bortezomib and ixazomib), immunomodulatory agents (e.g. lenalidomide and pomalidomide), monoclonal antibodies (daratumumab). CAR-T cell therapies, bispecific antibodies and steriods, contribute to immunosuppression by lowering neutrophils and lymphocyte counts, reducing antibody production.

In addition, some of these treatments damage the body's natural barriers, such as the lining of the mouth (mucositis). This damage creates openings that allow bacteria, viruses, and other pathogens to enter the body more easily to cause infections. Together these treatment effects increase both the risk of frequent and severe infection.

Anti-myeloma treatments have shown remarkable success in improving outcomes and extending survival for individuals affected by the disease. While these therapies can affect the immune system, ongoing advancements in treatment are targeting the disease more precisely, hopefully making the side effects more manageable.

Signs and symptoms of infections

Be sure to report the following signs and symptoms of infection to your healthcare team:

- Fever (temperature above 38°C)
- Chills and sweating
- Change in cough or a new cough
- Swollen lymph nodes that may last for weeks
- Sore mouth and throat.
- Muscle aches or any new onset of pain.
- Burning sensation or pain when passing urine, or a frequent need to urinate
- Diarrhea or pain in the abdomen
- Nausea or vomiting
- Skin rash
- Redness, heat or swelling (injection site reaction)

How are infections treated?

Individualized treatment plans, timing of immunization, and diagnostic tests are crucial in reducing the burden of infectious complications in multiple myeloma patients.

Depending on the type, location, and severity of the infection different treatments will be considered. Topical treatments can be used for superficial infections on your skin, oral treatments for infections inside your body and intravenous treatment for more serious infections. Other medications may be chosen by your healthcare team to help control fever and pain , a topical cream for itch, anti-diarrheal or anti-nausea medications, to ensure you receive the best treatment for your multiple myeloma, while managing all other conditions.

Infection caused by bacteria is typically treated using antibiotics, which will help to kill the bacteria. Alongside of the antibiotics, plenty of rest and staying hydrated are very important to allow the body to heal.

An example of a common infection is a kidney infection. This can be very painful and unpleasant; it usually happens when bacteria travel up from the bladder into one or both kidneys. If treated promptly with antibiotics, a kidney infection does not cause serious harm. If a kidney infection is not treated, it can get worse and cause permanent kidney damage.

It is important to understand that antibiotics are not effective against all infections, particularly those caused by viruses. Some viral infections can be treated with antiviral drugs (e.g. valacyclovir). Another well-known example to reduce serious complications in myeloma patients is Paxlovid (taken by mouth twice a day for five days), an antiviral medication that works well against the COVID-19 infection.

Minor fungal infections, such as those infecting the skin, can typically be treated using topical antifungal treatments like creams or sprays. Superficial yeast infections are often managed with oral antifungal medications (e.g. fluconazole) , whereas more serious fungal infections will need intravenous antifungal medications (directly into a vein).

Prolonged neutropenia is relatively rare, but manageable with antibiotics and antifungal medications. In some cases, a drug called granulocyte-colony stimulating factor (G-CSF) can be used to help your bone marrow make more white blood cells.

Intravenous Immunoglobulin (IVIg), derived from blood plasma of donors, and Subcutaneous Immunoglobulin (SCIg) infusions, help increase the immunoglobulin (antibody) levels in the body and support the immune system to fight the infection. These treatments are typically used for life-threatening or recurrent infections, particularly when IgG concentration is low.

For more severe infections, such as sepsis, hospitalization and intravenous antibiotics are required.

Tips for self-management

In prevention of infections, vaccination is key.

Vaccines are preparations made from killed microorganisms (inactivated), living but weakened organisms (live attenuated), small pieces of the pathogen (recombinant, subunit, conjugate) or messenger mRNA or DNA vaccines delivering a small piece of information to the cells, all designed to produce or artificially increase immunity to a particular disease.

Annual seasonal flu vaccination is a yearly vaccine strongly recommended for all myeloma patients, as well as for any family members or contacts living in the same household. However, live nasal flu vaccines are not recommended for myeloma patients, as they can lead to an influenza infection. As mentioned above, live vaccines use a weakened form of the pathogen. In patients who have weakened immune systems, they may not be able to control the weakened version, potentially leading to an infection of what we are trying to vaccinate against. That is why live vaccines are often avoided in myeloma patients.

Another important vaccination to consider is pneumococcal vaccination, which protects against certain strains of S. pneumoniae bacteria. Depending on age, stem cell transplant status and previous vaccination status, your healthcare team will help choose a product and dosing schedule most appropriate for you.

Although COVID-19 levels of infection in the community have dropped to lower levels, people with myeloma remain at risk of serious infection. If you have myeloma, follow your healthcare providers' vaccination recommendations for immunosuppressed individuals. It is important to stay informed about any new variants of concern and follow the guidance of your healthcare team.

Vaccination to help prevent shingles infection (painful blistering rash) caused by the varicella zoster virus (VZV) is recommended with an inactivated VZV vaccine (i.e., Shingrix). Revaccination is also recommended 6-24 months after a high-dose therapy and stem cell transplantation (HDT-SCT).

Careful consideration should be given to vaccinations and health when travelling. A travel consultation should be done when travelling internationally. Travel vaccines and other infection prevention treatment are recommended for multiple myeloma patients traveling to endemic areas with specific local disease risk.

There are other things you can try to reduce your risk of infection.

Here are a few suggestions:

- Exercise safely: Avoid prolonged or intense activity, and avoid higher risk activities such as swimming in a lake or heated public pool, gardening, and large gym classes.
- Follow a balanced diet and stay hydrated.
- Remove all natural plants: Plants and flowers can carry microbes such as bacteria and/or fungi.
- Avoid using razors or scissors as they can lead to bleeding and infections.
- Do not eat raw or undercooked meat and shellfish that are known carriers of a parasite. Unpasteurized milks and untreated drinking water also may be carriers of pathogens.
- Wash the surface of fruits and vegetables carefully.
- Wash kitchen utensils and cutting boards thoroughly after contact with raw meats or unwashed fruits and vegetables.
- Wear gloves and a face mask when cleaning a litter box, or have someone else clean it, as cat feces may carry parasites.
- Regularly wash your hands with warm water and soap or use sanitising hand gel if washing is not possible. Shower daily and change bedding on a regular basis.
- Good oral health is important at all times, and even more so when you are undergoing myeloma treatment. Infections from the teeth can drain into the lymph glands in the neck, and if your teeth and gums are not kept clean, large quantities and varieties of bacteria can colonize the gums.
- When possible, hold consultations by telephone or video call instead of in person so you don't have to visit the hospital as often.

- Avoid crowded public spaces and public transport if possible. It is still recommended to mask while indoors (especially when in crowded situations).
- Do not share towels, drinks, toothbrushes or other items of a similar nature.

Precautionary measures

- Take your medication as prescribed. Side effects are possible, but don't interrupt your treatment without consulting a healthcare professional: doctor, nurse or pharmacist.
- Antibacterial prophylaxis with levofloxacin may be considered during periods of increased infectious risk, especially in case of neutropenia.
- As the risk of virus reactivation is increased when following treatments for myeloma, anti-viral prophylaxis is given to reduce this risk.
- Valacyclovir prophylaxis is recommended for prevention of herpes simplex virus and varicella zoster virus, especially in patients receiving certain targeted monoclonal antibodies.
- Neutropenia can be prevented or reduced using a synthetic hormone called G-CSF (e.g., Neupogen).
- IVIg prophylaxis is being studied in clinical trials[2]. Studies show that patients given IVIg as primary prophylaxis, rather than being used as a reactive strategy, present a much lower risk of grade 3-5 infections.
- After an HDT-SCT, prophylaxis with antifungal, antiviral and antibacterial drugs are needed to support the immune system.
- Trimethoprim-sulfamethoxazole (Septra) or dapsone may be considered for patients at risk of *Pneumocystis jirovecii* pneumonia (PJP).
- It's very important to discuss any new or persistent pain with your healthcare team as quickly as possible as it may be associated with an infection.
- Take your temperature if you think you might have an infection.
- It is extremely important that you speak to your hematologist and pharmacist before taking any kind of supplement or alternative treatment that they have not prescribed, including herbal, traditional or natural medicines and remedies, and vitamins or wellbeing supplements. They have the potential to cause problems when taken alongside your prescribed treatment.
- Patients and close contacts of multiple myeloma patients should receive routine vaccinations with inactivated vaccines. Speak to your doctor before having "live" vaccines because they may not be safe for you.
- If your anti-myeloma treatment is lowering your white blood cell counts, it may be necessary to temporarily postpone treatment or reduce your treatment dose until your white blood cell levels begin to return to normal. Your doctor will advise you.
- Some common non-medical strategies are used to help treat or relieve pain. People living with myeloma are at increased risk of infection and should consult their doctor before undergoing acupuncture.

[2] Guido Lancman, MD MSc. Infections and Severe Hypogammaglobulinemia in Multiple Myeloma Patients Treated with Anti-BCMA Bispecific Antibodies. Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, É-U.

When to seek immediate medical attention?
Contact your healthcare team if you experience any of the following red flags for infection:

- Sepsis, or what we call blood poisoning, is a serious bacterial infection which can lead to organ failure. This life-threatening infection requires urgent medical assistance. It is crucial to report any signs of fever of 38°C (100.4°F) or more, difficulties to breathe, to speak or are confused, extreme muscle pain, if your skin is pale or if you have not had a pee all day.
- Urine that is a dark brown colour may be a sign of a problem, such as infection in the urinary tract, kidney disease, injury or bleeding disorders. Consult with your healthcare team if this occurs.
- Central line (central venous catheter) can become infected and, if left untreated, lead to even more serious infections and complications. If you notice any redness or swelling around your catheter or are experiencing tenderness or pain, inform your doctor or nurse immediately.

To learn more about infections and the importance of vaccination, consult Myeloma Canada's "**Multiple Myeloma Patient Handbook**", "**Myeloma and the Kidney**" and "**Managing Pain and Fatigue**" InfoGuides in the Resource library at www.myeloma.ca.

Your healthcare team, pharmacist, and nutritionist are also there to support you. It's important to share your symptoms with them.

Myeloma Canada wishes to acknowledge the contribution of Stephanie Valkenier, Community Pharmacist and PharmD candidate for her contribution. The information disclosed in this InfoSheet is based on existing Myeloma Canada publications reviewed by healthcare professionals and other publications from our sister myeloma organizations: the International Myeloma Foundation (IMF) and Myeloma UK. This information is not meant to replace the advice of a medical professional; they are the best people to ask if you have questions about your specific medical/social situation.