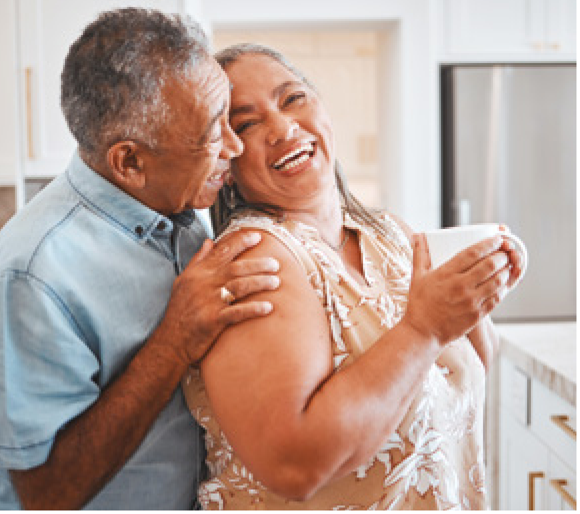

Myeloma Canada
InfoGuide Series

# Side Effects Management

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MAKING MYELOMA MATTER

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The information in this InfoGuide 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.

# Introduction

Myeloma Canada's *Side Effects Management InfoGuide* is for people living with myeloma, their families and their caregivers. It will help you learn more about common side effects of myeloma and its treatments, including the increased risk of infections, and how to manage them effectively. Understanding your symptoms and how to address them can significantly improve your treatment experience, communication with your healthcare team, and help you maintain your quality of life.

We will cover a wide range of side effects, including gastrointestinal problems (GI) like nausea, vomiting, diarrhea, and constipation; blood-related issues such as like anemia, thrombocytopenia, and neutropenia; and complications affecting your mouth, skin, nerves, and injection sites. We will also discuss side effects more commonly associated with newer immunotherapy treatments, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Additionally, we will provide practical tips for prevention and management to help you handle these side effects and improve your overall well-being.

Some of the more technical or unusual words in this Handbook appear in ***bold italics*** the first time they're used and are explained in the **Glossary** starting on page 35. Don't be afraid to ask members of your or your loved one's healthcare team to explain any terms or concepts you may have trouble understanding.

Throughout your journey with myeloma, your healthcare team will provide you with a large amount of information about your potential treatment options. Early identification, assessment and the treatment of symptoms is key. You may find it helpful to write down any questions that you have along the way and share these with your healthcare team regularly. They are the best people to help you understand what is happening and guide you to make informed decisions.

## Be an informed and cautious information consumer

Be cautious of information that comes your way. While books and the internet offer a wealth of information, not all of it is correct, it may not apply to your unique situation, and it may be confusing or misleading. Well-intended people may also try to offer you health advice without knowing the details of your condition and its treatment. Certain online support groups may also be helpful, but again be wary of possible misinformation. It's important to know that your source is reputable and to discuss what you read with your healthcare team. Never make any change to your treatment plan without checking with them first, for any symptom you're experiencing.

Be sure to visit myeloma.ca for reliable, up-to-date resources, support group information and more.

## Myeloma Canada's award-winning tools help you manage, organize and track your disease

### Myeloma Monitor

*Myeloma Monitor* is an innovative and unique application (app) created by Myeloma Canada specifically for people living with multiple myeloma and their caregivers. It's a secure (i.e., password protected) program where you can store, organize and track important health-related information, like symptoms you may be experiencing, in one centralized location.

The tool is essentiallly a patient companion, supporting you through all the important steps in managing and monitoring the disease and its symptoms. It enables patients and caregivers to become involved in informed decision-making with their healthcare providers. *Myeloma Monitor* can help you log and track:

- symptoms that directly affect daily quality of life (e.g., pain, nausea, lack of appetite, etc.);
- laboratory test results, including a graphing function to see how they change over time;
- vitals, physiological (e.g., blood pressure) and psychological changes (e.g., depression, anxiety, etc.).

*Myeloma Monitor* also helps you store and manage:

- information regarding your medications and supplements;
- medical/personal appointments, tasks and milestones;
- important contacts;
- questions for your healthcare team.

The program can generate simple to read reports that you can email and/or print and use as a resource during appointments with members of the healthcare team. *Myeloma Monitor* runs on computers and mobile devices (i.e., smart phones and tablets) and is a free download. For more information, visit myeloma.ca.

### Drug Access Navigator

Thanks to advances in research, new molecules and targeted therapies to treat myeloma are being developed at an impressive rate, with more options available than ever before. In Canada, access to, and coverage for, these new treatments varies across provinces and territories, making it often confusing and overwhelming to get the information you need.

To simplify the process of finding which drugs are available and covered within your province or territory, Myeloma Canada has created an easy-to-use, interactive online tool called the *Myeloma Drug Access Navigator.* Explore in one glance breakdown - by province and territory - of drug coverage across Canada.

### Guides for newly diagnosed and relapsed patients

You'll find many other useful resources in Myeloma Canada's Resource Library, such as *My treatment decision-making guide* and *My healthcare appointment discussion guide.* These free tools are designed to help you play an active role in, and better understand, your healthcare journey. Let us guide you through the topics you'll want to explore further, and the important issues you'll want to discuss with your healthcare team.


# About Myeloma Canada

Myeloma Canada is a registered non-profit organization created by, and for, people affected by multiple myeloma. As the only national patient organization exclusively devoted to the Canadian myeloma community, Myeloma Canada has been making myeloma matter since its founding in 2005.

Myeloma Canada works with leading national and international myeloma researchers, clinicians, as well as patient and cancer organizations to strengthen the voice of the Canadian myeloma community. We are committed to our mission: To improve the lives of all Canadians affected by myeloma by accelerating access to the best care while advancing research toward its cure and prevention so that our vision, a "life uninterrupted by myeloma" may be realized.

How we achieve this:

- **Increase awareness** of the disease and its effects on the lives of people living and supporting someone with myeloma
- **Educate** patients, families and caregivers
- **Advocate** for access to new therapies, treatment options and healthcare resources
- **Empower** patients and caregivers through community engagement
- **Advance** clinical research and promote access to new drug trials in Canada

## Myeloma Canada educational publications

For more detailed information about myeloma and living with the disease, visit myeloma.ca. From here, you can download Myeloma Canada's educational publications, watch educational videos, find a local support group and so much more.

**Whether you're downloading a copy or requesting a printed version, all Myeloma Canada publications are free of charge. To order your printed copies, email us at contact@myeloma.ca, or call us toll-free at 1-888-798-5771.**

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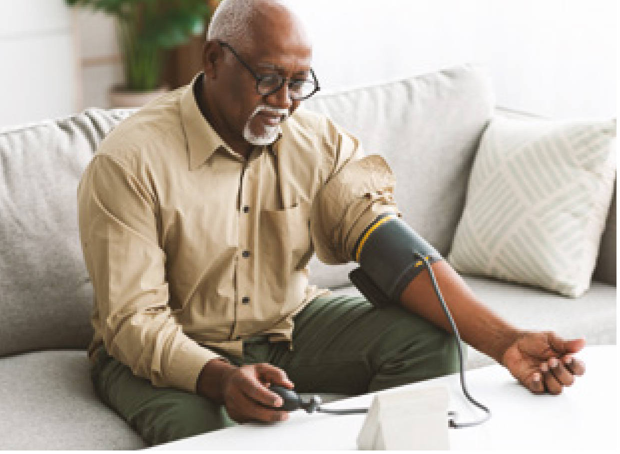

# Anemia

At least 60%-70% of patients with multiple myeloma have anemia at the time they are diagnosed, and most will experience it during the course of the disease.

This chapter addresses anemia, a common symptom associated with myeloma, which may result in the inability to carry out the activities of daily living and domestic duties. Learn to recognize the symptoms and causes of anemia, and find ways to manage this condition to enhance your quality of life.

## What is anemia?

Anemia is often the first symptom of multiple myeloma that leads patients to seek medical attention. It occurs especially when the myeloma is particularly active, i.e. at the time of diagnosis or relapse.

Anemia is typically defined as a decrease in ***hemoglobin*** to less than 100 g/L or a reduction of 20 g/L or more from the individual's normal level. It can develop either acutely (over hours to days) or chronically (over weeks to months).

Where does hemoglobin come from? In concrete terms, red blood cells (RBCs), or erythrocytes, are the elements in the blood that carry oxygen to the body's cells. Oxygen circulates on a red cell protein called hemoglobin. If the level of RBCs (and therefore hemoglobin) in the blood is reduced, for whatever reason, the body doesn’t receive enough oxygen, resulting in more rapid exhaustion, shortness of breath, and fatigue.

## Signs and symptoms of anemia

Be sure to report the following symptoms to your physician:

- Shortness of breath on light exertion
- Fatigue that does not decrease with rest
- Lack of energy and motivation
- Increased pulse, lower blood pressure
- Swelling of the legs, especially the ankles
- Dizziness
- Headache
- Paleness
- Chills
- Change in appetite
- Decreased libido

## Causes of anemia

Kidney failure is one of the two main causes of anemia in people with myeloma. This reduction in kidney function is caused by the deposition of small proteins that prevent the kidneys from playing their role as filters, and reduce the production of a kidney hormone called erythropoietin, whose role is to stimulate the bone marrow to produce RBCs.

Myeloma itself is also a cause. It is associated with the abnormal, uncontrolled growth of plasma cells (known as myeloma cells) in the bone marrow – where RBCs are also made. When too many myeloma cells are present, the bone marrow gets "crowded out", which limits the space necessary for the production of new RBCs and leads to a shortage of hemoglobin in the blood.

Nevertheless, impairment of RBC production leading to anemia can be due to a number of other reasons. A pre-existing condition not related to myeloma (for example, the result of diabetes) or a lack of iron (ferritin), vitamin B12, and folic acid required to produce hemoglobin can be responsible for this imbalance. Not to mention active bleeding that may be the result of hemorrhoids or a low platelet level (thrombocytopenia).

Anemia can also be a side effect of treatment (anti-myeloma drugs) such as lenalidomide (e.g., Revlimid), pomalidomide (e.g., Pomalyst), carfilzomib (Kyprolis) or daratumumab (Darzalex) taken alone or in combination. Additionally, it may be caused by other medications such as:

- antibiotics taken for a long time and/or at a high dose
- ***bisphosphonates*** (e.g., Aredia and Zometa) for myeloma-related bone disease
- non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (e.g., Advil and Motrin) or naproxen (Aleve) for pain relief
- some blood pressure medications (diuretics such as Lasix)
- contrast media given for imaging studies (such as gadolinium used in some MRIs)
- ***proton pump inhibitors*** (e.g., Losec, Prevacid, Nexium)
- some supplements (such as creatine)
- laxatives and enemas containing sodium phosphate (e.g., FLEET products)

## How is anemia treated?

Treating any underlying anemia will help to relieve fatigue. Depending on whether your anemia is acute or chronic, the treatment may vary.

For newly diagnosed myeloma patients who are anemic, the first and most important thing to do is to treat the myeloma. Often, when a treatment successfully attacks and destroys myeloma cells in the bone marrow, the marrow will once again be able to make a normal number of RBCs, and your hemoglobin level will rise. On the other hand, if the anemia is a side effect of treatment, then your physician may adjust the dose and/or schedule of your therapy. Regular blood tests will help determine if the anemia treatments are working or if the doses need to be modified.

Although this is a short-term solution, some people with myeloma may be given blood transfusions to treat acute anemia by rapidly increasing the number of RBCs and hemoglobin in their blood. As the level may last only for a few weeks, you may need regular transfusions.

Incidentally, if you have chronic anemia and your kidneys are not producing a normal amount of erythropoietin (EPO), your doctor may prescribe an injection of ***erythropoiesis-regulating hormones*** (e.g. Eprex, Aranesp) to help restore normal RBC production and reduce the need for transfusions.

If anemia is caused by a pre-existing condition, your doctor may prescribe iron, vitamin B12, or folic acid supplements.

## Tips for self-management

- Have your blood tests done so that your doctor can monitor your hemoglobin levels regularly.
- Rest regularly: plan your activities to include rest periods.
- Exercise safely: avoid prolonged or intense activity.
- Follow a balanced diet rich in iron.
- Take your medication as prescribed. Side effects are possible, but don't interrupt your treatment without consulting a healthcare professional: doctor, nurse or pharmacist.

## Precautionary measures

- Discuss with your treating doctor if you are taking medications for diabetes or high cholesterol.
- Your healthcare team may change your dose or schedule of medication if needed, follow the recommendations.
- Prolonged transfusion can lead to resistance to transfused blood from other donors.
- Caution should be exercised when considering EPO agents, balancing potential benefits against risks. They have their own side effects and risks, including potential association with increased tumor growth and reduced survival in some cancer patients. Talk to your healthcare professionals.
- 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.
- Be careful when exercising. Overexertion is not recommended because your body's capacity to carry oxygen is reduced and can lead to shortness of breath, increased heart rate and fatigue.

# Gastrointestinal Problems

## Part I: Managing nausea and vomiting

Novel therapies used to treat multiple myeloma may cause complications such as gastrointestinal (GI) disturbances. Notably, nausea, vomiting, diarrhea, and constipation are very common side effects in myeloma patients.

This first section will cover nausea and vomiting issues involving your stomach, which can affect your day-to-day while you are going through treatments. We will see how they can lead to more serious conditions and learn how to prevent and manage these side effects to allow you to receive the best treatment for your multiple myeloma.

## Definition and causes of nausea and vomiting

Nausea is a feeling of queasiness, unease and discomfort in the throat and upper stomach, with a feeling like you need to vomit or actually vomiting. They can also cause symptoms such as dizziness, excessive sweating and clamminess, or dry mouth.

Nausea and vomiting are common side effects of chemotherapy drugs, such as cyclophosphamide and melphalan, other anti-myeloma drugs, such as bortezomib (e.g., Velcade), or supportive treatments, that can disrupt your digestive process.

They can be due to a number of other reasons:

- Certain bacterial and viral infections (people living with myeloma have a higher risk of developing infections);
- Strong emotions, in particular stress, anxiety and nervousness;
- Hypercalcemia (higher level of calcium in the blood);
- Pain resulting from myeloma itself or its treatment;
- Other illnesses and conditions (e.g. diabetes or travel sickness)

## Complications

Severe or persistent vomiting can lead to:

- Dehydration
- Stomach pain
- Unintended weight loss
- Damage to the throat

Note: If you find blood (either bright red or dark and sometimes could look like coffee grounds) in your vomit you should seek medical advice immediately.

## How are nausea and vomiting treated?

Nausea and vomiting are usually treated with ***antiemetics*** (e.g. metoclopramide, granisetron and ondansetron). They will be prescribed along with your myeloma treatment to prevent, reduce, or minimise these side effects.

If your nausea and/or vomiting are not directly caused by your myeloma treatment, you may be given other treatments such as painkillers, antibiotics, or relaxation aids like complementary therapies.

Your doctor may also prescribe antacid/gastric protection medication (pantoprazole or other), as some oral chemotherapy treatments can irritate the stomach.

## Tips for self-management

There are many things you can try to help prevent nausea and vomiting or reduce its severity. Here are a few suggestions, including nutritional advice to improve your appetite or reduce nausea and vomiting:

- Drink enough water and other fluids as vomiting can dehydrate you.
- Begin appropriate anti-nausea medications before chemotherapy.
- Eat small, frequent meals. Do not eat spicy, fatty, or acidic foods and avoid strong odors. Keep healthy snacks handy.
- Ask the dietician on your healthcare team for recommendations.
- Consult one of the many cancer cookbooks for patients combating side effects.
- Ginger may help settle your stomach – try ginger tea, non-alcoholic ginger beer/ale, or ginger biscuits.
- Mint can also help with nausea – try mint tea, mints, or chewing gum.
- For metal bitter taste, try marinated meat or swap beef for other protein-rich foods such as chicken, dairy products, ham, eggs, fish, nuts, seeds, legumes, tofu, or soy.
- To stimulate your appetite, take a walk or do some light exercise before your meal. Do not exercise after eating. Wear loose clothing.
- Use relaxation, breathing exercises, acupuncture, ***biofeedback***, and/or guided imagery.
- If hospital smells make you feel sick, try putting light perfume onto a handkerchief that you can use to help mask the smell. Certain scents like lavender may help.
- Get some fresh air – try sitting outside or near an open window.

## Precautionary measures

- If you vomit once, keep taking your nausea medications as prescribed.
- For 2 to 5 episodes of vomiting in 24 hours, or if you experience a decreased ability to eat or drink, see your physician for a physical examination and evaluation. New medications, oral or through the vein, may be needed.
- If vomiting is severe, fluid can be replaced by special preparations available through your GP or from a pharmacist. For example, if you can't face eating solid food, high calorie drinks may be more tolerable.
- If you are experiencing 6 or more episodes of vomiting in 24 hours, or if you are unable to eat or drink, contact your physician immediately. Hospitalization may be required to assess fluid status and to rule out bowel obstruction.
- Do not stop or adjust medications without discussing it with your healthcare provider. They may change your dose or schedule of medication to help reduce your discomfort.
- It is extremely important that you speak to your hematologist 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.

## Part II: Managing diarrhea and constipation

As seen previously, novel therapies used to treat multiple myeloma may cause complications such as gastrointestinal (GI) disturbances.

This second section focuses on diarrhea and constipation issues involving your intestines, which can affect your day-to-day while you are going through treatments. We will see how they can lead to more serious conditions and learn how to prevent and manage these side effects to allow you to receive the best treatment for your multiple myeloma.

## Definition and causes of diarrhea and constipation

Diarrhea is an abnormal increase in the frequency and the amount of fluid in the stool (more than 3 loose or watery bowel movements per day). It can last for only a short period of time or persist for long periods, typically more than 2 weeks.

Diarrhea can occur because of infection, inflammation (e.g., inflammatory bowel disease (IBD) or celiac disease), malignancy, emotional disturbances such as stress or anxiety, or be related to an autoimmune phenomenon. Bowel blockage or laxatives used to treat constipation may also be responsible for this physiologic impairment. Additionally, diarrhea is an immediate side effect of bortezomib (within 24 hours), ixazomib, lenalidomide and pomalidomide (months after treatment), and other agents prescribed for the treatment of myeloma.

To its opposite is constipation, which is rather a decreased frequency of defecation (usually less than 3 bowel movements per week) accompanied by abdominal discomfort and difficulty emptying your bowels. This is a common problem in patients with cancer who have poor oral intake or take drugs like opioids or antiemetics that slow intestinal transit time.

Some treatments for myeloma can cause more water to be removed from the feces, resulting in dry, hard stools. These treatments and supportive treatments include: thalidomide, lenalidomide (e.g., Revlimid) and bortezomib (e.g., Velcade), antiemetics (e.g., granisetron, ondansetron), and strong painkillers (e.g., codeine, tramadol, Oramorph). Constipation can be caused by a variety of other factors. These include hypercalcemia, a diet lacking in essential nutrients, dehydration, and a lack of exercise or poor mobility, which can weaken muscle tone in both the stomach area and the intestine. Change in daily routine, an emotional blow, and other illnesses and conditions and their treatments may incidentally be responsible for this imbalance.

## Complications

Both diarrhea and constipation interrupt the normal functioning of the GI tract and disrupt the intestinal flora. The consequences can be mild and transient for some, or severe and life-threatening for others. Excessive loss of water through your stools, as well as untreated constipation can both lead to more severe symptoms such as:

- Dehydration and thirst
- Swollen, painful stomach, often accompanied by stomach cramps
- Nausea or vomiting
- Fever
- Loss of appetite
- Headache

## How are diarrhea and constipation treated?

### Treatment of diarrhea

You will be asked about any history of irritable bowel syndrome, colitis, ***diverticulitis***, and medications other than routine chemotherapy. In case of acute diarrhea, a stool culture will be ordered to see whether the diarrhea is the result of an infection, and medications will be given to control frequency. Talk to your health care professional before starting anti-diarrhea treatments. Cancer therapy may be stopped for a period of time, or the dose of your cancer medication may need to be changed (see Precautionary measures below).

Medications that may be ordered by your healthcare team to treat diarrhea include: loperamide (Imodium), diphenoxylate, cholestyramine, octreotide, or bismuth subsalicylate may be recommended.

### Treatment of constipation

You will be asked about any abdominal pain, bloating, nausea, vomiting, inability to urinate, confusion, and diarrhea alternating with constipation. Severe bowel obstruction should be assessed by a healthcare provider so that medication changes and referral to a gastrointestinal specialist may be arranged.

For constipation, your physician may prescribe docusate, senna, magnesium sulfate, magnesium citrate, lactulose, or bisacodyl. Yet there are many over-the-counter remedies available at your local drug store. If your constipation is not relieved by oral laxatives, then you may need to have a suppository or an ***enema*** (under the advice of your doctor or nurse).

## Tips for self-management

### What helps diarrhea?

- Drink more liquids. Avoid caffeinated, carbonated, heavily sugared beverages, and alcohol.
- Dietary changes may be needed, such as a decrease in fiber, greasy, fried, acidic, or spicy foods. Eat smaller, more frequent, lactose-free, low-fat meals. Favour a BRAT diet (bananas, rice, applesauce, and toast).
- Consider adding probiotics if diarrhea persists.
- Discontinue high osmolar foods such as cheese and milk, sesame seeds, watercress and sardines, or supplements.

### What helps constipation?

- For mild constipation, increase your fluid and fiber intake, do physical activity, and start stool softeners. For example, drink 2-3 litres of water a day, eat bran-based cereals, fruit and vegetables, prunes and other dried fruits, and limit the amount of refined food. Hot decaffeinated drinks may help to stimulate a bowel movement.
- For moderate constipation, speak with a dietician about your food intake and consider laxatives and stimulants.
- For severe constipation, your physician may discuss treatment for an impacted colon or assess if your bowel is obstructed.

## Precautionary measures

- Change in your normal bowel habits should be reported to your doctor or nurse. If you feel awkward or embarrassed discussing your bowel habits, try to remember your doctor and nurse will be used to talking about it and they are there to help prevent and manage any side effects of myeloma and its treatment.
- People living with myeloma have a higher risk of developing infections. It is important to tell your doctor if you suspect that your diarrhea is caused by an infection as bacterial and viral infections are often contagious.
- If you are experiencing 4 to 6 stools per day for over 24 hours, it's important to inform your healthcare provider. They should recommend medications and you might require fluids and salts.
- An increase of 7 or greater stools per day over your regular amount may necessitate hospitalization to address dehydration, as it often requires fluid replenishment through an IV. Beyond that level, urgent intervention is indicated as it could have life-threatening consequences.
- Do not stop or adjust medications without discussing it with your healthcare provider. They may change your dose or schedule of medication to help reduce your discomfort.
- As mentionned in part I, it is extremely important that you speak to your hematologist before taking any kind of supplement or alternative treatment that they have not prescribed.
- Keep the rectal area clean, take very good care of your skin, and use disposable pads or diapers.

# Peripheral neuropathy

Multiple myeloma and novel therapies used to treat this blood cancer may affect the nerves in the peripheral nervous system. In myeloma, the nerves most affected are those in the hands and feet.

This chapter will give you more information about peripheral neuropathy and the way it can affect your body. We will learn how to recognize the signs and symptoms, and to help manage this side effect.

## Definition and causes of peripheral neuropathy

Peripheral neuropathy affects the nerves in the peripheral nervous system (PNS), one of the two main parts of the nervous system:

- **Central Nervous System (CNS):** Includes the brain and spinal cord.
- **Peripheral Nervous System (PNS):** Includes all nerves outside the CNS, such as those in the face, arms, legs, torso, hands, and feet.

The PNS is further divided into two systems:

1. **Autonomic Nervous System (ANS):** Controls automatic functions like heart rate and blood pressure by connecting the brain to internal organs.
2. **Somatic Nervous System (SNS):** Manages voluntary actions and consists of:
   a. **Motor neurons:** Transmit signals from the brain to muscles for movement.
   b. **Sensory neurons:** Send sensory information (pain, temperature, touch) from the body to the brain.

Medications and medical conditions associated with multiple myeloma can be a cause of peripheral neuropathy. Additionally, factors that aren't related to myeloma such as diabetes, vitamin deficiency and a history of high alcohol consumption can cause or contribute to peripheral neuropathy. When our peripheral nerves become damaged or inflamed, this can change how the nerves function. Symptoms may vary from person to person and depend on which nerves are affected.

Some myeloma patients experience peripheral neuropathy at the time of diagnosis, while many others develop it later as a complication of the disease or its treatment. The causes of peripheral neuropathy in myeloma are diverse and can result from multiple factors. Treatments (such as thalidomide, bortezomib, and vincristine) are the most common cause, as these drugs can damage nerve cells, especially at high doses or with prolonged use. Paraproteins produced by myeloma cells may harm nerves directly as high paraprotein levels can lead to hyper viscosity which reduces blood flow and contributes to nerve damage. Other causes include spinal cord compression from vertebral fractures, kidney damage, and complications such as diabetes, vitamin deficiencies, high alcohol use, or shingles. These factors may occur alone or in combination, increasing the risk and severity of neuropathy in myeloma patients.

## Symptoms of peripheral neuropathy

The symptoms of peripheral neuropathy can vary and depend on the nerves that have been affected.

Sensory nerve neuropathy symptoms include:

- Numbness, tingling; prickling or "pins and needles" sensation; vibrations in limbs
- The feeling of sand or stones in your shoes
- The sensation of burning and/or freezing
- Throbbing sensation in the hands and feet
- Altered or unusual sensations (light touch causing pain; touching something cold and feeling heat)
- Ringing in the ears or trouble hearing
- Reduction or loss of ***proprioception*** (for example the feeling of not knowing where your feet are)
- Loss of balance
- Reduction or loss of reflexes

Motor nerve neuropathy symptoms include:

- Muscle weakness and cramping
- Decrease in muscle mass
- Decrease in reflexes and coordination
- Difficulty with fine motor movements and writing

Autonomic nerve neuropathy symptoms include:

- Intolerance to heat
- Difficulty adjusting to dark lighting
- Digestive issues, bowel or bladder issues
- ***Orthostatic hypertension***
- Sexual dysfunction

The above lists highlight common symptoms but is not exhaustive. It is important to report any new or worsening symptoms to your healthcare team promptly.

## How is peripheral neuropathy treated?

Managing peripheral neuropathy will involve treating the symptoms experienced and involve identifying the cause(s). If the cause is determined to be the myeloma itself, it may improve as the myeloma is treated. If it is being cause by a medication or treatment your doctor will discuss your options, which could include continuing treatment with close monitoring, changing the schedule/frequency, the way the medication is given, decreasing the dose, or even stopping the treatment. Treatment related neuropathy may be reversible, but it may also be permanent. For many patients with multiple myeloma these neuropathies are at least partially reversible.

Treatment depends on what is causing your neuropathy and which symptoms you have. Neuropathies do not typically respond to ordinary pain relievers such as acetaminophen but there are medications that are known to help. It should be noted that myeloma patients in general should avoid the use of non-steroidal-anti-inflammatory drugs (for example, ibuprofen).

Treatment for neuropathies may include:

- Medication applied to the skin – These include topical creams, gels, or patches designed to target localized areas of pain. For example, a lidocaine patch or ointment can offer local relief to a particular area of pain, as can a capsaicin cream.
- Anti-seizure or antidepressant medications – Certain medications in these categories can effectively reduce neuropathic pain by altering how the nervous system processes pain signals. For example, duloxetine, amitriptyline, gabapentin and pregabalin.
- Physical therapy – For those experiencing muscle weakness, numbness, or coordination issues, physical therapy can improve mobility, strength, and overall function.
- Assistive devices – Tools such as hand or foot braces, canes, walkers, or wheelchairs can provide support and enhance independence for individuals with significant mobility challenges.
- TENS therapy – Transcutaneous electrical nerve stimulation (TENS) involves placing small adhesive patches (electrodes) on the skin. These electrodes deliver a low-level electric current that can help alleviate pain by interrupting nerve signals.
- Nerve blocks – Injections of medications close to targeted nerves to help relieve the pain symptoms by altering the pain signals to the brain.

- Electrolytes – May help ease stiffness, cramping, and nerve pain. For example, magnesium (taken orally, or applied as a spray) and Epsom salts baths may be effective.
- Specialized treatments – Interventions may also be needed to address complications affecting eating, sexual health, or bladder and bowel function, ensuring these essential systems are managed effectively.
- Complementary therapies – these may include acupuncture, massage, counselling, occupational and/or physical therapy, referral to a pain clinic.

There are many treatments and interventions available to help with peripheral neuropathy. If one is not a good fit for you, please discuss alternatives with your healthcare team.

## Tips for self-management

There are many things you can try to help make living with peripheral neuropathy more manageable or reduce its severity. Here are a few suggestions:

- Care for hands and feet – Keep feet clean and dry, and toenails trimmed as ingrown toenails can cause infections and neuropathy may reduce your ability to feel pain. Regularly check your feet for sores or signs of infection, especially if you have diabetes. Wear protective, well-fitting shoes. Keep your hands and feet warm, as cold can worsen symptoms. Ask for help or consult your doctor if needed.
- Limit alcohol – Excessive alcohol consumption can worsen peripheral neuropathy. Consult your doctor about safe limits.
- Quit smoking – Smoking reduces blood flow to peripheral nerves, potentially worsening symptoms. Your healthcare provider can offer support to help you quit.
- Prevent falls – Weakness, balance issues, or numbness can increase your risk of falling. Reduce hazards by removing clutter, loose rugs and cords, and ensure your home is well-lit, especially in hallways and on stairs. Store frequently used items within easy reach to avoid climbing or stretching.
- Engage in regular gentle exercise – Light exercise can help maintain muscle tone, improve circulation, and reduce symptoms. Consult your healthcare team for guidance before beginning any new exercise routine.
- Avoid burns and cuts – Peripheral neuropathy can impair your ability to feel temperature changes or pain. Always check water temperature before bathing or showering and handle hot objects or sharp items with extra care to prevent injury.
- Eat a well-balanced diet – Focus on a diet rich in essential vitamins and minerals, including vitamins B6, B12, D, E, folate, and healthy fats to support your nervous system. Include plenty of fresh fruits, vegetables, whole grains, and omega-3 rich fish. Stay well hydrated with water and non-alcoholic beverages, and limit sugar intake to prevent damage to peripheral circulation and nerves.

## Precautionary measures

- It’s important to prevent and address problems early, especially with neuropathy. Symptoms often start gradually but can worsen over time, affecting your quality of life, sleep, and daily activities. In severe cases, permanent nerve damage can occur. Early communication with your healthcare team is key — inform them as soon as you notice any new or worsening symptoms. Early diagnosis and intervention can make peripheral neuropathy more manageable and can help prevent further complications.
- Do not stop or adjust medications without discussing it with your healthcare provider as some medications should be tapered down. Your healthcare team may change your dose or medication schedule to help reduce your discomfort.
- It is extremely important that you speak to your hematologist before taking any kind of supplement or alternative treatment that they have not prescribed. These treatments may include herbal, traditional or natural medicines and remedies, vitamins [1] or supplements as they have the potential to cause complications when taken alongside your prescribed regimen.
- 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.

[1] Nathan P Staff, Anthony J Windebank (2014). *Peripheral Neuropathy Due to Vitamin Deficiency, Toxins, and Medications. The American Academy of Neurology.* https://pmc.ncbi.nlm.nih.gov/articles/PMC4208100/#:~:text=6%20Since%20many%20patients%20with,6%20and%20worsening%20their%20disease.

## When to seek immediate medical attention?

Contact your healthcare team if you experience any of the following red flags for peripheral neuropathy:

- A fever of 38°C (100.4°F) or higher, with or without chills
- A wound that won't heal; a wound with swelling, redness, warmth, foul smell, or discharge (yellow/green/blood)
- New numbness or weakness in your foot, leg, or other areas
- Worsening symptoms or increased pain
- Dizziness, lightheadedness, or fainting
- Double vision or confusion
- Trouble breathing or chest pain/discomfort

These could indicate serious complications that need prompt medical attention.

# Infections and neutropenia

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.

You will now 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 [2]. Most infections in myeloma patients are caused by viruses and bacteria, although fungal and parasitic infections can also occur.

[2] 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 (e.g. 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
- Diarrhoea 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 and prevention

### 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 [3]. 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.

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[3] 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, USA.

## 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.

# Thrombocytopenia

Multiple myeloma and novel therapies used to treat this blood cancer may affect the normal production of blood cells or cause an extensive range of side effects in myeloma patients.

This section will give you more information about thrombocytopenia and the way it affects your body. We will learn how to recognize its signs and symptoms, and to better manage this side effect.

## Definition and causes of thrombocytopenia

Thrombocytopenia is a decrease in platelets (also called thrombocytes) preventing your blood from clotting normally after an injury. A low platelet count can lead to bruising or prolonged and excessive bleeding, while high levels may increase the risk of clotting (thrombosis).

The normal number of platelets (in adults) is between about 150 million and 400 million per millilitre. A person is then considered to be suffering from thrombocytopenia if they have less than 150 million platelets per millilitre of blood.

### How can this happen?

In myeloma, abnormal plasma cells (known as myeloma cells) multiply and spread in an uncontrolled manner within the bone marrow, eventually crowding out the normal blood cells and preventing the bone marrow from working properly. This means the bone marrow produces fewer blood cells, including platelets.

Not only myeloma itself may be responsible for this imbalance, but medications used to treat it can also interfere with the production of red blood cells (RBCs), white blood cells (WBCs) and platelets, which, in this case, increase the risk of infections and bleeding.

Anti myeloma treatments causing thrombocytopenia include immunomodulatory agents like lenalidomide (e.g., Revlimid), pomalidomide (e.g., Pomalyst), proteasome inhibitors such as bortezomib (e.g., Velcade) and carfilzomib (e.g., Kyprolis), and high-dose chemotherapy such as cyclophosphamide and melphalan.

It is important to note that some myeloma treatments may also increase the risk of developing a blood clot, such as a pulmonary embolism or deep vein thrombosis.

Mild thrombocytopenia does not always cause symptoms. Some of the more common signs and symptoms of moderate to severe thrombocytopenia are:

- Easy or excessive bruising
- Prolonged bleeding from cuts that does not stop with pressure
- Spontaneous bleeding from your gums or nose
- Excessively heavy menstrual bleeding or spotting
- Blood in your urine or stool, which may appear dark red or black and tarry
- Freckle-like red or purple spots under the skin due to leaking blood vessels (petechiae)

## How is thrombocytopenia treated?

Treatment depends on the severity and underlying cause. Thrombocytopenia, as a complication of the myeloma, normally begins to improve with anti-myeloma treatment. As treatment begins to bring myeloma under control, the bone marrow is often able to recover and will start producing normal amounts of platelets and other blood cells. If thrombocytopenia is a side effect of anti-myeloma treatment, platelet levels will usually improve during the non-treatment days of your treatment cycle. However, in some cases, particularly if thrombocytopenia is severe, it may be necessary to temporarily reduce your dose or postpone treatment until your platelet levels begin to return to normal.

If thrombocytopenia is graded as severe or you have signs of bleeding, you may require a platelet transfusion. A platelet transfusion is when you are given platelets from someone else (a donor). It is administered into the vein for a period of 15 to 30 minutes. Your platelet levels will increase immediately but may only last for a few days. Another transfusion could be necessary.

## Tips for self-management

There are many things you can try to reduce your risk of bruising or bleeding. Here are a few suggestions:

- Have your blood tests done so that your doctor can monitor your blood counts.
- Your doctor may make changes in the choice, dosing, or scheduling of your medications or other treatments.
- Exercise safely: avoid activities that can result in bruising or bleeding e.g. contact sports, body piercing or tattooing.
- Take care when brushing your teeth to avoid bleeding of the gums e.g. use a soft toothbrush and take care when flossing.
- Take extra care not to cause cuts or wounds to the skin.
- Avoid constipation. If you need treatment for constipation, talk to your pharmacist or another member of your healthcare team.
- Limit your alcohol intake. Alcoholic beverages may lead to a deficiency of folate (needed for platelet production), and increase the chance of bleeding.
- Drink 6 to 8 glasses of water per day and follow a balanced diet.
- Avoid tonic water which usually contains quinine. Quinine is a cause of drug-induced thrombocytopenia.

## Precautionary measures

- Advise your healthcare team if you experience bruises, small red spots under the skin, or a rash with no known cause, fever or signs of infection, headaches, joint pain, fatigue or weakness.
- Blood in stools (poo), urine or vomit can be a sign of spontaneous or internal bleeding and requires immediate medical attention.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin, ibuprofen or naproxen are painkillers which have an anti-platelet effect which may increase the risk of bleeding. Do not take these drugs. Ask your doctor or pharmacist which painkiller is right for you.
- Your doctor may prescribe aspirin or anticoagulants for other reasons, which are valid despite thrombocytopenia. Do not stop these treatments without discussing it with your doctor. However, advise your healthcare team and pharmacist if your platelet count is low.
- 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 interact with your prescribed treatment or, in this case, contribute to poor platelet function or bleeding risk.

# Injection site reactions

Novel therapies used to treat Multiple Myeloma, and other associated conditions can be injected in one of three ways; subcutaneously (directly under the skin), intramuscularly (into the muscle tissue) or intravenously (directly into the veins). These administration methods, however, may result in the occurrence of injection site reactions.

These reactions can vary in severity and type depending on factors such as the route of administration, the medication being used, and the individual patient's sensitivity.

This part will give you more information about injection site reactions – including how they can affect your body. It will also cover how to recognize its signs and symptoms, as well as ways to better manage this side effect.

## Definition and causes of injection site reactions

**Localized injection site reactions** are responses that may occur at or near the injection site. These reactions can arise from subcutaneous, intramuscular, or intravenous medication administration. Any medication, including vaccinations, have the potential to cause a local injection site reaction.

Localized injection site reactions typically range from mild and transient symptoms to more severe complications, though they are usually mild and resolve quickly. Common symptoms include redness (erythema), swelling, pain, tenderness, itching, bruising, and, in rare cases, infection or abscess formation. These reactions are often caused by the mechanical insertion of the needle, the properties of the medication (e.g., irritants), or an inflammatory or allergic response [4].

[4] Cole, B. *Injection-Site Reactions and How to Manage Them. Pharmacy Times,* 2019
https ://www.pharmacytimes.com/view/injection-site-reactions-and-how-to-manage-them

Intravenous (IV) therapy is widely used to deliver fluids, nutrients, and medications directly into a patient's bloodstream. While highly effective, IV therapy carries risks, including two common complications: IV infiltration and IV extravasation.

**Infiltration** occurs during the intravenous administration of a medication. It is an adverse reaction when a non-irritating medication escapes from the veins or intravenous catheter and the medication gets into the surrounding tissues. These drugs do not cause blisters or tissue necrosis. Common symptoms include pain, swelling, coolness, tight skin, or skin appearing pale around the IV site. These reactions cause minimal tissue damage and like localized injection site reactions are typically mild and short-term.

**Extravasation** is an adverse reaction when an irritating medication escapes from the veins or intravenous catheter and gets into the surrounding tissues. These are more serious, as these medications can cause tissue damage, which can lead to necrosis, or tissue death. The common symptoms include severe pain, swelling, redness, skin discoloration, blistering, and a feeling of heat near the IV site [5].

[5] Lee, S. (2016). Side effects of chemotherapy. Canadian Cancer Society.
https ://cancer.ca/fr/treatments/treatment-types/chemotherapy/side-effects-of-chemotherapy

## How are injection site reactions treated?

It is important not to try to treat injection site reactions caused by intravenous administration yourself, unless instructed by your healthcare provider. Both infiltration and extravasation are treated by immediately stopping the treatment and cleaning the area around the IV site to prevent any further damage. Next steps will depend on the medication that was being administered.

Localized injection site reactions are easier to treat and can be treated by:

- Applying a cold compress to decrease pain and swelling
- Gentle massage of the injection site to encourage blood flow
- Using oral analgesics for pain or oral antihistamines for itch (consult your healthcare provider for advice on the most appropriate medication for you)
- Warm compresses to help soothe your muscle if it is irritated
- Moving the affected body part regularly to increase blood flow and promote faster healing
- Avoid using scented products on the location

## Tips for self-management and prevention

There are a few things you and your healthcare team can do to reduce your risk of injection site reactions, such as:

- Prior to your treatment appointment, make sure you are well hydrated.
- Your treatment administration nurse will select the appropriate needle size and injection site to minimize the risk of reaction. They will consider the type of treatment you are receiving and assess the veins in your arms to find one that is large, straight, and any free from bruises, cuts, or other recent injection sites.
- For subcutaneous and intramuscular injections, it is especially important to rotate the injection site to prevent the formation of lumps and ensure the body absorbs the medication equally each time. This means rotating injection sites to give treatment. For subcutaneous injections, this might mean using a different side of the abdomen, the upper arms, or the outer thighs. For intramuscular injections, rotation might involve alternating between the upper arms and outer thighs.
- Your treatment administration nurse will also help select the best site for each administration. Depending on quality of veins and frequency of treatment administration, ***central venous access device (CVAD)*** can be useful, notably PICCs/Ports/Hickmans.

## Precautionary measures

During or after your intravenous treatment, if you notice any pain, redness, blistering, or itching around or nearby the injection site, alert your nurse or healthcare provider right away.

### When to seek immediate medical attention?

While many injection site reactions are mild, certain symptoms may indicate serious complications that require urgent care:

- Rapid swelling, tightness, or discoloration near the injection or IV site.
- Fever, chills, or other signs of infection.
- Severe pain or blistering that worsens over time.

**If experiencing difficulty breathing, swelling of the face or throat, widespread hives, or other symptoms of anaphylaxis, you should call 911 and proceed to the nearest Emergency Department.**

# Osteonecrosis of the jaw (ONJ) and other mouth issues

Good oral health is always important, and even more so when you are undergoing myeloma treatment. Thus, it is best to identify and treat dental problems and oral infections before you start chemotherapy, undergo stem cell transplant, or start taking bone protector drugs.

We will cover now some common oral infections and mouth issues associated with myeloma and its treatment, as well as a less frequent side effect known as osteonecrosis of the jaw (ONJ). See how you can prevent and manage these undesirable effects appropriately.

## Definition and causes of ONJ and other mouth issues

Myeloma patients are at an increased risk of developing a variety of mouth problems resulting from a weakened immune system and/or the side effects of treatment. Common issues include sore or inflamed mouth, fungal or viral infection, bleeding gums, and a dry mouth. Infections from the teeth can drain into the lymph nodes in the neck, and if your teeth and gums are not kept clean, large quantities and varieties of bacteria can colonize the gums. Good oral care is important to keep your mouth clean, moist, and free from infection.

Some of the chemotherapy drugs used to treat myeloma can cause a variety of mouth problems, especially inflammation of the oral mucosa (known as mucositis). The lining of the mouth becomes redder, thinner and more fragile, which can lead to ulcers, a burning sensation and altered taste (called dysgeusia). This is because chemotherapy attacks the rapidly dividing cells in the body, such as those in the lining of the mouth. Patients receiving high-dose melphalan given as part of a high-dose therapy and stem cell transplantation (HDT-SCT) are particularly at risk of developing oral mucositis.

Some myeloma treatments can also temporarily lower your platelet count. Platelets are the blood cells involved in clotting. As a result of a lowered platelet count, you may notice that you bleed more easily, especially from your gums or the corners of your mouth, which can sometimes lead to painful cracks. In addition, some myeloma treatments can affect saliva production and cause a sore or dry mouth in some patients.

Saliva is our natural protection against tooth decay. When the quantity and quality of saliva are altered, teeth are more vulnerable to acidity (which can come from diet, gastric reflux, etc.) and the self-cleaning of teeth by saliva is reduced, increasing the risk of cavities.

Although unpleasant and uncomfortable, most mouth problems are usually temporary and improve once treatment has finished or once your myeloma is brought back under control.

Osteonecrosis of the jaw (ONJ) is a relatively rare, undesirable effect in which one or more parts of the jawbone becomes exposed to the inside of the mouth. Bone dies due to a lack of blood supply. Some bone-densifying drugs unfortunately reduce the blood supply to the bone. The jawbone dies (known as avascular necrosis) and covered only by a thin layer of tissue, eventually breaks through the mucosa and becomes exposed in the mouth. It then becomes at risk of infection, which could lead to pain, swelling, and bone damage that can affect the teeth. In more advanced cases, the exposed bone may form bone spurs or bone sequestration (a small piece of bone that breaks off).

ONJ can thus be observed in a small percentage of people taking bone protector drugs, called bisphosphonates, and is more common when the bisphosphonates are given intravenously (into the vein) or after prolonged periods of treatment. Bisphosphonates are drugs used in myeloma to strengthen and protect patients' bones. They help to reduce fractures, relieve pain, and improve quality of life. It has been suggested ONJ occurs because bisphosphonate drugs disrupt normal bone remodelling, and affect the healing process after any trauma (the bone loses its ability to heal). Bisphosphonates, like denosumab, another type of medication used to strengthen bones, may increase the risk of ONJ by reducing the blood supply to the bone.

Medications often used in myeloma to strengthen bones include the following:
- Denosumab (e.g. Xgeva) : subcutaneous injection every 4 weeks.
- Disodium pamidronate (e.g. Aredia): intravenous infusion taken over 90–120 minutes, once a month, repeated every 4 weeks.
- Zoledronic acid (e.g. Zometa): intravenous infusion over 15–30 minutes, once a month, repeated every 3–4 weeks. Zoledronic acid appears to carry the highest risk.

ONJ can occur spontaneously but appears to be more likely following particularly traumatic dental work such as extractions (since the bone is no longer able to heal without sufficient blood supply). It is also more common in people with a history of gum disease (e.g. periodontitis) or mouth infections, those who wear dentures (because prostheses can rub, injure the mucosa and expose the underlying bone) or have a history of smoking (because nicotine also reduces blood supply) and poor oral hygiene. There is also evidence of possible genetic risk factors, but further research is needed before a link can be definitively established.

## Signs and symptoms of ONJ and oral infection

You should contact your doctor, pharmacist or dentist for advice if you experience any of the signs and symptoms below (particularly if you are currently on bisphosphonate or denosumab treatment):
- Non-healing of a tooth socket after extraction
- An area of exposed bone in the mouth
- A heavy or numb feeling in the jaw
- Loosening of teeth
- Discharge of pus
- Unusual dryness of the mouth
- Pain, redness or swelling of the tongue, lips, gums or the lining of the mouth
- Gums that bleed easily or are inflamed
- Sores on the lips or at the corners of the mouth
- Mouth ulcers
- Altered taste or sensation in the mouth
- White plaque coating the tongue and the lining of the mouth

## How is ONJ treated?

If you develop ONJ, your doctor will prescribe one of the following treatments to relieve symptoms, prevent secondary infections, prevent the development of new areas of necrosis and maintain myeloma treatment as much as possible.
- Mouthwash made from table salt and baking soda (homemade recipe) [6]
- Antibacterial mouthwash (e.g. chlorhexidine) – to reduce the risk of infection
- Anaesthetic mouthwash (e.g. lidocaine) or other drugs – to relieve pain
- Follow-up with an oral specialist every 8 weeks
- Antibiotics
- Antifungal mouthwash (e.g. nystatin) – to treat and prevent oral thrush
- Artificial saliva spray – to help relieve the discomfort of a dry mouth
- Pain killers (e.g. codeine or morphine) may sometimes be required (often in liquid form or via a syringe driver) for severe mucositis
- Mouth rinse (e.g. Biotène) – to help moisten a dry mouth caused by mucositis. It may be given as a 30ml solution at the start of HDT-SCT

Note: In more serious cases of ONJ, an oral surgeon may remove some of the dead tissue or bone from the area with a small operation called debridement, or by using low-level lasers to remove necrotic cells.

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[6] Homemade mouthwash: ¼ teaspoon salt (1.25 ml) + ¼ teaspoon baking soda (1.25 ml) + 1 cup water (250 ml)

## Tips for self-management

There are many things you can do to reduce your risk and help manage mouth problems (especially once you've started taking bone protectors):

- Practice good oral hygiene to reduce the odds of needing dental care.
- Visit your dentist regularly (every 6 months) for dental check-ups to catch problems when they are small.
- Keep your doctor informed on your dental health and report any side effects as quickly as possible.
- Take all of your medications as prescribed.
- Brush your teeth after each meal and at bedtime with a soft-bristle toothbrush and use alcohol-free mouthwashes prescribed.
- Floss at least once a day with waxed floss to minimize gum trauma. If flossing causes bleeding gums that doesn't stop after 2 minutes, consult your health care team.
- Keep your mouth moist and fresh and try to drink plenty of clear fluid – at least 6 to 8 glasses a day. Water-based lubricants can also be used.
- If you wear dentures, make sure these fit properly and don't cause irritation before starting treatment to strengthen your bones. Keep them clean, remove them at night and soak them in a rinse solution.
- Avoid smoking and drink alcohol in moderation.
- Avoid soft drinks and spicy, acidic or salty foods as they can increase irritation in your mouth.
- If you are going through high-dose therapy and autologous stem cell transplantation (HDT-SCT), ask for some ice or an ice lolly to suck on when high-dose melphalan is being administered. This can help reduce the risk of mucositis or lessen its severity, and can also soothe a sore mouth or relieve dryness.

## Precautionary measures

While dentists who work at cancer centres are familiar with the special requirements that people with myeloma have, some community dentists may not be. Therefore, as a person affected by myeloma, it is crucial to speak to your dentist and clearly outline what drugs you are taking (including intravenous therapies), where you are in your therapy, and what the plans may be for the future.

Myeloma patients are advised to take the following precautions:

- It is important to have a complete dental examination before you begin any myeloma treatment. Because people with myeloma have an increased risk of infection, you may require antibiotics before having any dental work.
- Make sure your dentist and your pharmacist know if you are on a bisphosphonate or denosumab treatment.
- Before starting bone protector therapy, it is recommended that you have a routine dental examination and X-ray done, and to perform major dental procedures such as oral surgery or tooth extractions in advance. Restorative work such as fillings, bridges, crowns and root canals are likely safe after starting bone protector drugs, provided that the wounds are small, and all the rough edges are carefully smoothened.
- Avoid invasive dentistry (e.g. tooth extractions, insertion of tooth implants and periodontal surgery) during treatment, as this is likely to greatly reduce the incidence of ONJ. Ideally, all extractions should be performed before starting bone protector drugs. If invasive treatment is absolutely necessary after taking these medications, this should be done in collaboration with an experienced oral and maxillofacial surgeon. You may be taken off bone protector drugs for a period and restarted once healing is complete (but even when the drug is stopped, its effect remains in the patient's system for a very long time, and the risk of complications remains, especially with IV bisphosphonates).
- You and your doctor can consider which bone protector drug is most appropriate for your situation. They will discuss the best option with you.
- Ask your dentist to speak with your doctor about any other special precautions you may require, especially when receiving treatment.
- Many vitamins, supplements and herbal therapies can interact with your cancer medications. Before taking any vitamin, supplement or herbal therapy, talk to your physician and/or your pharmacist.
- Ask to be referred to a dietician if you are having problems eating – they can prescribe supplements to boost your nutritional intake.
- Your healthcare team, pharmacist, and nutritionist are also there to support you. It's important to share your symptoms with them.

# Cytokine release syndrome (CRS)

Unlike chemotherapy, myeloma immunotherapy better targets myeloma cells and spares most healthy cells. It helps your immune system recognize and destroy myeloma cells.

Because of the way myeloma immunotherapy works in the body, some of the side effects that may occur are different from those seen in conventional myeloma treatments. These may include, among others: infusion or injection-related reactions, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), other neurologic events, infections, gastrointestinal problems, damage to nerves (peripheral neuropathy), lower blood cell counts, abnormal levels of minerals, and other potential more specific side effects such as temporary vision or skin problems.

This chapter will give you more information about the cytokine release syndrome and the way it affects your body. We will learn how to recognize its signs and symptoms, better manage its undesirable effects on the body and limit the damages.

## Definition and causes of cytokine release syndrome

Cytokine release syndrome, or namely CRS, is a severe and sudden inflammatory syndrome caused by a large, rapid and excessive release of cytokines into the blood. Cytokines are small proteins that play a crucial role to combat infections. However, the presence of too many cytokines can cause inflammation and an overreaction of the immune system.

This reaction often happens after an infection (e.g. COVID-19) but it is also observed with certain treatments associated with cancers. More precisely, such complication can occur after certain T-cell-engaging (TCE) immunotherapies such as Chimeric Antigen Receptor (CAR) T-cell therapies, like idecabtagene vicleucel and ciltacabtagene autoleucel, and bispecific antibody therapies, notably elranatamab, talquetamab and teclistamab, being investigated for myeloma. In this regard, the infusion of CAR-T cells or the injection of bispecific T-cell engagers trigger the activation the T-cells (also called T lymphocytes) binding them to the tumour cells.

CRS usually occurs within the first few doses of bispecifics or CAR-T (most frequently within the first 14 days) and typically happens before or at the same time as the neurotoxicity syndrome. The degree of CRS is graded on a scale of 1 to 4, based on the key symptoms and signs of fever and blood pressure. Grades 1 and 2 are considered mild, while Grades 3 and 4 are severe to life-threatening and require admission to the hospital in an intensive care unit to ensure patients are given medications to boost their blood pressure. Fortunately, most cases of CRS are Grades 1-2, and generally respond very well to treatments designed to reduce inflammation while calming immune system activation.

## Signs and symptoms of CRS

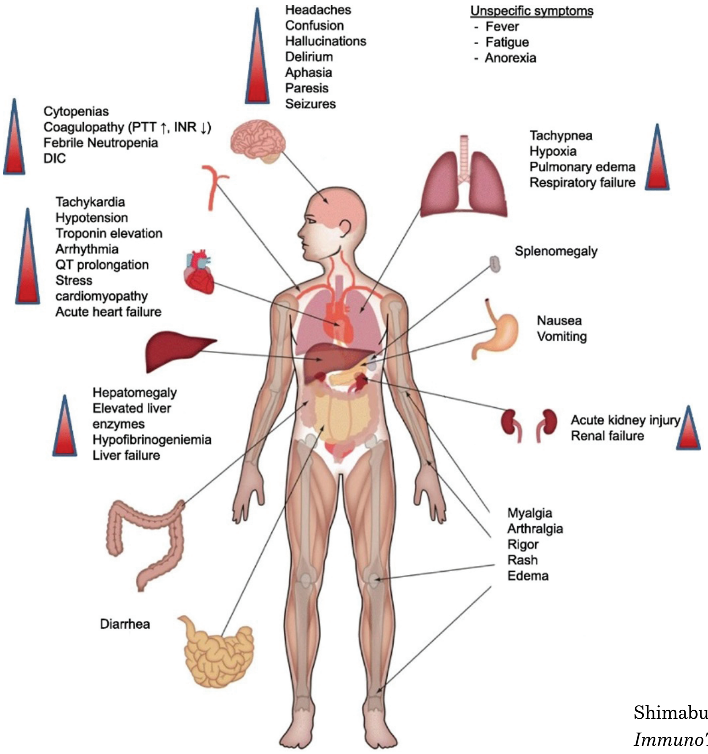
You should inform your healthcare team if you experience any of the signs and symptoms below (particularly if you are currently on CAR-T cell or on a bispecific antigen treatment):

- Fever, chills and aches (similar to flu symptoms)
- Difficulty breathing
- Dizziness
- Nausea
- Tachycardia (fast heartbeat)
- Low blood pressure
- Low blood oxygen concentration (desaturation)
- Fatigue
- Multi-organ failure

Most often CRS is characterized by fever, a drop in blood pressure and/or a reduction in blood oxygen concentration (desaturation). These signs and symptoms will enable the healthcare team to establish a diagnosis of CRS.

The impact of this syndrome on the body can be visualized as follows:

Figure 1



Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. *Cytokine release syndrome. Journal for ImmunoTherapy of Cancer.* 2018;6:56. doi: 10.1186/s40425-018-0343-9

## How is CRS treated?

Though most CRS cases are manageable, prompt diagnosis and management of symptoms are essential to prevent serious complications and improve patient outcomes.

Management is based on the type of symptoms (grade of CRS) and how severe they are.

At first, supportive care (e.g. acetaminophen, etc.) is provided to bring down the temperature and manage the inflammation. Intravenous fluids can also be given if needed (Grade 1-2).

If symptoms become more severe or life-threatening (Grade 3-4), for instance if you have trouble breathing, oxygen replacement treatment and a drug named tocilizumab to actually treat the CRS may be necessary to act against the inflammatory mediators and make the response less severe. Tocilizumab is an interleukin-6 (IL-6) receptor inhibitor that can be given alone or combined with steroids (e.g. dexamethasone) when CRS progresses.

Beyond this point, if you need more oxygen support or if the blood pressure drops too low and you need to get medication to bring it back up, monitoring will be necessary.

## Tips for self-management and prevention

The best preventative measure is to optimize your health as much as possible ahead of time. Be in optimal physical shape prior to going into CAR-T cell therapy or bispecifics.

Prophylactic measures, such as using tocilizumab and/or administering steroids (e.g. dexamethasone) prior to each dose of bispecific antibodies and CAR T-cell therapy to prevent CRS are being tested in research projects. Preliminary results from these research projects seem to demonstrate a reduction in the incidence of CRS with these preventive treatments [7].

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[7] Rosinil L et al. IMS 2024 Brazil; Trudel S, el al. ASH 2022

Also, in attempt to minimize the side effects and reduce the likelihood of CRS or ICANS, bispecific antigen therapy uses a step-up dosing strategy. This means that the patient will receive an initial reduced dose of the drug to allow the person's immune system to slowly become familiar with the new medication. The step-up schedule given over several days helps prevent an overreaction of the immune system and therefore reduces the risk of CRS. These first progressive doses can be given on an outpatient basis, or the patient can be hospitalized.

These treatments, like other anti-myeloma drugs, may also increase your risk of infections on a long-term basis. Here are some other considerations to take in order to prevent infections:

- Complete any outstanding vaccinations at least 2 weeks before starting therapy to prevent influenza, pneumococcal infection, zoster or COVID-19.
- Consider intravenous gamma globulin (IVIg) supplementation for infection control.
- Consider an anti-virus treatment (e.g. valacyclovir) to prevent shingles.
- Myeloma patients have an increased risk of developing *Pneumocystis jirovecii* pneumonia (PJP) than the general population. Prophylaxis with a drug such as trimethoprim-sulfamethoxazole (Septra) or other alternatives is recommended.
- As ***Cytomegalovirus*** (CMV) can occur in people with weakened immune systems, it is preferable to check its viral load on a regular basis using blood tests.

## Precautionary measures

- Inform your healthcare team of any new or concerning aforementioned symptoms, especially if you have fever or if your pressure drops.
- Some of these side effects can be potentially serious. Patients need to be monitored frequently for early indications of side effects and given rapid intensive care and supportive treatment if needed.
- Infection prophylaxis with granulocyte colony-stimulating factors (G-CSFs), used for treating chemotherapy-induced neutropenia, should be used with caution during step-up phase and in case of CRS.
- Your healthcare team may hold treatment in case of active infection or if significant CRS and/or ICANS occur.
- Do not stop or adjust medications without discussing it with your healthcare provider. They may change your dose or schedule of medication to help reduce your discomfort.

# Immune effector cell-associated neurotoxicity syndrome (ICANS)

Immunotherapies used to treat myeloma, more specifically Chimeric Antigen Receptor (CAR) T-cell therapies and bispecific antibodies, are T-cell-engagers that have the ability to target and destroy myeloma cells.

While they play an important role with the cells in your immune system, they unfortunately come with their load of side effects. These may include, among others: infusion or injection-related reactions, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), other neurologic events, infections, gastrointestinal problems, damage to nerves (peripheral neuropathy), lower blood cell counts, abnormal levels of minerals, and other potential more specific side effects such as temporary vision or skin problems.

This section informs how the healthcare team monitors for a potential case of neurotoxicity syndrome after an immunotherapy is administered to a patient. It helps recognize its signs and symptoms, and understand its management to make sure the patient is in a safe environment.

## Definition and causes of ICANS

Immune effector cell-associated neurotoxicity syndrome, known under the acronym ICANS, is an inflammatory reaction of the immune system that is somewhat related to CRS, but it actually occurs when that inflammatory response goes into the nervous system. That happens when the immune proteins, cytokines and some of the immune cells, leak into the nervous system and cause damage and inflammation to the brain. In other words, they cross the blood brain barrier, which usually protects us from a lot of this kind of damage to the nervous system.

ICANS is less common than CRS, and severe ICANS is also less common than severe CRS. People who have a higher burden of disease (have more cancer in their body) and get higher dose of treatment, particularly older patients, are at higher risk of this toxicity. This syndrome occurs mainly with CAR T-cell therapies and more rarely with bispecific antibodies. According to Dr. Joseph Mikhael, IMF Chief Medical Officer, in his presentation on the ***"Early Side Effects of Bispecific Antibodies",*** less than 10% of patients receiving bispecific antibodies experience ICANS.

This neurological complication usually occurs in the days or weeks following a myeloma immunotherapy treatment that activates T-cells. It typically happens after or at the same time as CRS. Although it can be quite frightening and it needs to be treated aggressively, most patients do really well.

## Signs and symptoms of ICANS

ICANS manifests itself as any of these neurological symptoms:
- Headaches or migraines
- Confusion

- Disorientation
- Loss of consciousness
- Vision impairment
- Partial loss of the ability to speak or write
- Concentration issues
- Tremor
- Lethargy
- Muscle weakness
- Seizures
- ***Cerebral edema***

Close monitoring by the healthcare team and the caregiver is key. There are many ways to measure this toxicity as it develops. The healthcare teams uses a scoring system to determine how severe the ICANS is. The patients are being asked basic questions such as "what is your name" and "where are you", and undergo simple mental tasks. The doctor will look if there are damages to their sensations and how they move, as well as evidence of seizure activity or swelling in the brain.

## How is ICANS prevented and treated?

There is not really a great way to prevent ICANS.

Like for CRS, a step-up dosing strategy of bispecific antibodies may be considered to minimize the side effects and reduce the likelihood of ICANS by preventing an overreaction of the immune system. In this case, the patient receives an initial reduced dose of drug followed by a gradual increase in the dose to allow the immune system to slowly become familiar with the new medication that is being introduced to the body.

Though most ICANS cases are manageable, prompt diagnosis and management of symptoms are essential to prevent serious complications and improve patient outcomes.

Steroids (e.g. dexamethasone) often given in combination with myeloma treatments, alone or combined with anakinra (Kineret), help to control and regulate toxicity syndrome when mild.

Moreover, the doctor involves the neurologist to perform brain imaging (CT scan or MRI of the brain) or an electroencephalogram (EEG) to measure the electrical activity of the brain. This will help determine the need to start anti-seizure medication as prevention or if they see early signs of seizure in order to manage this condition. He may also order a lumbar puncture to ensure that there is no infection or underlying problem, or order tests to check that the patient is not suffering from epilepsy.

In more severe cases, the intensive care unit colleagues are involved early in the process in case the patient needs to be transferred to the ICU, where supportive care and intravenous fluids can be dispensed. The dose and frequency of steroids can be increased, such as those of anakinra, or other agents may be introduced to block inflammation in the brain and solve the problem when ICANS progresses.

## Precautionary measures

- It is extremely important that you speak to your healthcare team if you suspect signs of neurotoxicity syndrome as complications can lead to neurological disorders such as convulsions and even paralysis.
- Caregivers must remain attentive to signs of confusion or unusual changes in the patient's behavior, and notify the medical team accordingly.
- Patients need to be monitored frequently for early indications of side effects and given rapid care and supportive treatment if needed.
- Your healthcare team may hold treatment in case of active infection or if significant CRS and/or ICANS occur.
- Do not stop or adjust medications without discussing it with your healthcare provider. They may change your dose or schedule of medication to help reduce your discomfort.

# Toxicities associated with GPRC5D-targeted therapies used to treat myeloma

Targeting GPRC5D represents an important advancement in expanding treatment options for relapsed/refractory multiple myeloma patients. While very promising in research, GPRC5D-targeted therapies cause their own set of risks and a combination of side effects.

This last topic gives more information on this new ***antigen*** target and explains how it is expressed on myeloma cells and other tissues. Learn how it affects your body and discover ways to manage the undesirable effects.

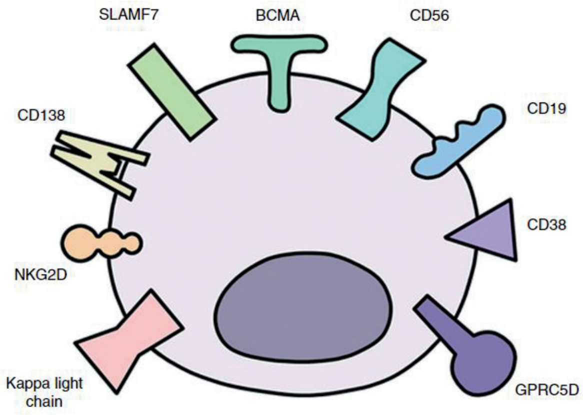
## Definition and causes of GPRC5D-related toxicities

GPRC5D (G protein-coupled receptor class C group 5 member D) is another antigen target that is being used to develop new treatment approaches for multiple myeloma. Because this receptor is heavily expressed on myeloma cells, it makes it an effective target for myeloma drugs while limiting complications in other tissues. Explored as an alternative target to BCMA (B-cell maturation antigen), several new therapies are being developed to target GPRC5D. Notably, talquetamab (Talvey), a bispecific antibody that targets GPRC5D on myeloma cells and CD3 on T-cells, as well as AZD0305, an antibody-drug conjugate that targets GPRC5D on myeloma cells, or other CAR T-cell therapies and bispecific antibodies in development.

### More on antigen targets:

For myeloma immunotherapy to work at its best, the goal is for the treatment to target antigens that are generally more numerous on the surface of myeloma cells, but not present on most healthy cells. Some antigens may also be on the surface of other cells, so they may not all be possible targets for myeloma immunotherapy. Several new immunotherapy approaches have been developed to target CD38 (clusters of differentiation 38) and BCMA (B-cell maturation antigen) because they are heavily expressed by nearly all myeloma cells but not by healthy plasma cells. There are also specific antigens on the surface of T-cells that could be helpful to “recruit” other T-cells and enhance myeloma cell destruction. Figure 2 illustrates some myeloma cell antigen targets that have been studied or are being investigated (at the time of writing), in clinical trials..

Figure 2 – Myeloma cell antigen targets



In his presentation entitled ***"Using Different Targets to Destroy Multiple Myeloma",*** Dr. Joseph Mikhael, IMF Chief Medical Officer, explains how different bispecific antibodies work to destroy myeloma by attaching to antigens on myeloma cells.

New antigens like GPRC5D have been discovered on myeloma cells, expanding treatment options for patients. Since myeloma is still incurable to date, it is important that we discover new targets and develop drugs to attack those targets. We learned that diversifying targets helps combat myeloma's resistance to drugs and improves treatment outcomes, allowing for more time in remission. Over time, myeloma cells become resistant to the drugs we use. Thus, it is crucial to expand the ways we can treat this disease. *"Early work with these drugs shows that, much like teclistamab, they can be effective in achieving response rates of over 60% in heavily-pretreated patients"* says Dr. Mikhael.

## Side effects of GPRC5D-targeted therapies

Key side effects of GPRC5D-targeted therapies, such as talquetamab, include:

- Cytokine Release Syndrome (CRS) – Refer to the Cytokine release syndrome (CRS) InfoSheet
- Skin peeling or rashes
- Hair thinning
- Nail changes or nail loss
- Taste changes (dysgeusia) including complete loss of taste, loss of appetite and weight loss
- Hematological effects such as neutropenia and thrombocytopenia – Refer to the Infections and neutropenia Infosheet and Thrombocytopenia Infosheet
- Risk of infections (slightly lower compared to BCMA-directed bispecific antibodies) – Refer to the Infections and neutropenia Infosheet
- Neurological effects such as Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS) – Refer to the Neurotoxicity syndrome (ICANS) InfoSheet
- Fatigue
- Nausea – Refer to the Nausea and vomiting InfoSheet

As we have seen, treatment for multiple myeloma targeting the GPRC5D on the myeloma surface has incidentally a direct impact on other tissues where this antigen is expressed. Let's learn more about the impact on skin, hair, nails and taste buds.

Dysgeusia is an abnormal or reduced sense of taste due to GPRC5D expression on taste buds. Results from studies [8] show that dysgeusia occurs in 71-72% of patients treated with talquetamab and its duration varies from 57 to 109 days for most patients.

Bispecific antibodies and antibody-drug conjugates that targets GPRC5D can also cause negative effects on nails. Incidence rates for nail toxicities associated with talquetamab are between 54-55% and the symptoms generally last for 74-89 days. Patients may experience different types of toxicities like separation of the nail from the nail bed, shedding, breakage or deformation of the nail, or even nail ridges or discoloration.

Hair-related side effects are common because GPRC5D is expressed in hair follicles. Patients may notice hair thinning or hair loss (alopecia) during treatment.

Furthermore, we observe several skin-related side effects in 30-73% of patients treated with talquetamab due to GPRC5D expression in skin tissue. These skin toxicities include rash, dry skin, peeling and itching. The duration of the inflammation or irritation usually lies between 26-39 days for most patients.

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[8] Catamero, D. Practical Management of Patients with Relapsed/Refractory Multiple Myeloma Receiving Talquetamab. *International Myeloma Society (IMS),* Athens, Greece, 2023

## How are GPRC5D-related toxicities treated?

Clinical trials show that the undesirable effects of GPRC5D-targeted therapies are generally manageable, with low rates of treatment discontinuation.

Dysgeusia and other oral side effects, can be temporarily relieved using artificial saliva spray, mouth rinses, and vitamin support. When persistent, strategies to help patients maintain interest in food could be required. In this case, your nutritionist may suggest foods to stimulate your texture and taste functions. Make sure you are well hydrated by increasing your liquids intake.

Nails typically return to normal once myeloma treatment is completed. Your doctor may prescribe topical corticosteroids if needed. Nail-related toxicities may cause discomfort; using moisturizers and over-the-counter nail lacquer or vitamin E oil will help during the healing process. Make sure you wear comfortable shoes that that don't pinch your toes too tightly, along with soft and loose-fitting stockings. It is important to maintain good nail hygiene at all times.

Most GPRC5D-related side effects affecting hair, are generally mild to moderate in severity. There is no specific management strategy for hair-related side effects, but hair normally grows back after treatment. Close monitoring and supportive care are likely recommended.

Inflammation, irritation, and redness caused by skin-related side effects can be treated using topical corticosteroids. In more severe cases, your doctor may prescribe oral corticosteroids. Drink 6 to 8 glasses of water per day and use heavy moisturizers to help restore your skin's natural properties.

## Precautionary measures

- If you experience skin-related side effects, communicate with your healthcare team to find the appropriate treatment strategy. Ask a dermatologist for their guidance on how to control and manage your discomfort.
- It is important to communicate any hair-related changes to your healthcare team during treatment. Although the hair loss may be shocking and make you feel anxious or distressed, these side effects are usually not severe enough to require discontinuation of treatment and are often manageable with appropriate care. Support from a dermatologist is also suggested.
- In case of dysgeusia, patients will be monitored for weight loss (a few times per week), as taste changes can affect appetite and food intake. Your healthcare team will help find strategies to ensure proper nutrition is maintained during treatment and adapt or hold doses if needed.
- Avoid the use of artificial nails due to risk of infection.
- Do not stop or adjust medications without discussing it with your doctor or nurse. They may change your dose or schedule of medication to help reduce your discomfort and manage some side effects.
- Some of these side effects, notably CRS, can be potentially serious. Patients need to be monitored frequently for early indications of side effects, especially during initial treatment, and given rapid care and supportive treatment if needed.

## Concluding remarks

You may experience side effects that are not covered in this InfoGuide. Some of these might include fatigue or difficulty sleeping (insomnia) due to therapies such as corticosteroids, weight changes, changes in appetite, or, in some cases, rare but serious side effects like pulmonary embolism associated with certain treatments. Members of your healthcare team, including your doctor, nurse, pharmacist, dentist, dermatologist, and nutritionist can offer expert guidance tailored to your specific situation. It's important to share any new or concerning symptoms with them.

In order to better prepare for your medical appointments, use Myeloma Canada's Myeloma Monitor on a day to day basis to store, organize, and track your symptoms. Access the Myeloma Monitor App here!

To learn more about side effects associated with myeloma and its treatment, or have access to an extensive library of informative material to help you understand the complexities of living with the disease and what you can expect from various treatment options, consult Myeloma Canada's publications available in the Resource Library at www.myeloma.ca.

# Beyond family and friends: Myeloma support groups and programs

## Local support groups and programs

Talking to people outside your immediate circle may be easier than talking to family and close friends. Meeting and speaking to others with shared experiences through support groups can truly provide you with invaluable information and support. Other patients may be, or have already been, in a similar situation to yours. They understand what you're going through and how to help from a different perspective. Sometimes relief can be found just by speaking to people that can personally identify and relate to you, your experiences and your feelings.

Visit myeloma.ca to find a support group near you. If a physical support group doesn't exist in your area, consider forming one yourself. Myeloma Canada can help you get started.

## Virtual, online support groups

You may also be able to meet and connect with other patients through an online support group. Myeloma Canada has created, and is the lead administrator of many online, virtual patient support groups on Facebook. These closed groups offer a safe environment for myeloma patients to connect and exchange experiences with others facing similar challenges. Thanks to the Facebook "translate" button, language barriers can be overcome, enabling you to communicate, in your mother tongue, with people nation-wide. Moreover, the information shared on the page is private and can't be viewed by the public. All members must request to join the group to gain access.

## Myeloma peer support

In addition to joining a support group, you may want to talk with someone who has first-hand experience either living with myeloma, or as a caregiver to someone with the disease. Myeloma Canada's *Myeloma Peer Support* program provides you with this opportunity.

## You are not alone

Visit myeloma.ca, "Find support", to find the support resources you need.

Myeloma Canada's *MC Assistance* is a personalized information service for people with myeloma, their families and friends. Our myeloma information specialists are here to help you navigate life with myeloma and can be reached by phone or over e-mail, the choice is yours.

Whether you're looking for information on the disease, its treatments and side effects, or searching for cancer-related community services in your area, MC Assistance information specialists can help you find the answers and resources you need. Perhaps you're looking for someone outside your circle to lend a supportive ear or listen to your concerns? Our information specialists are specially trained to listen and support you, in full confidentiality, throughout the many phases of the disease. To request information or contact an MC Assistance information specialist, simply fill out the request form on our website (here) or call 1-888-798-5771.

# Glossary

**Antigen:** Foreign substance that can be recognized by cells of the immune system leading to the production of protective antibodies.

**Antiemetics:** Medications used to prevent or control nausea and vomiting caused by chemotherapy or other treatments. They can be given orally, intravenously, or as suppositories, depending on the specific medication and patient needs.

**Biofeedback:** A safe, non-invasive technique that helps individuals gain conscious control over typically unconscious bodily functions. This method uses sensors attached to the body to measure physiological processes such as heart rate, blood pressure, muscle tension, skin temperature, and brain waves.

**Bisphosphonates:** Laboratory-produced antibodies that target two antigens (one on myeloma cells and one on T-cells to link them together).

**Central venous access device (CVAD) or central venous catheter (CVC):** A thin, flexible tube that's placed in a blood vessel (usually in the upper chest) and can be kept there for the long-term administration of medications, fluids, or blood products, and from which blood samples can be taken.

**Cerebral edema:** A serious condition in which fluid accumulates in the brain, increasing pressure inside of the skull (also called brain swelling). It can lead to significant neurological complications and, if untreated, may be life-threatening.

**Cytomegalovirus (CMV):** A virus belonging to the herpesvirus family, also known as Human Herpesvirus type 5 (HHV-5). CMV can cause illness in immunocompromised individuals, transplant recipients, and people with blood cancers. It is often asymptomatic but can present with mild symptoms such as fever or fatigue. In immunocompromised people, CMV may lead to severe complications, including pneumonia, hepatitis, retinitis, brain inflammation, or seizures. CMV spreads through contact/exchange of bodily secretions containing the virus: saliva, sneezes, urine, tears, etc).

**Diverticulitis:** Inflammation or infection of small bulging pouches (also called diverticula) in the colon (large intestine) wall, leading to severe pain, fever, nausea, and changes in bowel habits.

**Enema:** The injection of fluid into the rectum to relieve constipation or cleanse the bowel.

**Erythropoiesis-regulating hormones:** Substances, such as erythropoietin (EPO), that regulate/control the production of red blood cells (erythrocytes). These hormones are given as injections to help manage anemia in myeloma patients by stimulating red blood cell production in the bone marrow. Erythropoiesis refers to the process of forming and developing red blood cells in the bone marrow.

**Hemodialysis:** A medical procedure used to treat kidney failure or severe kidney dysfunction in myeloma patients. It involves filtering waste products and excess fluids from the blood using a machine before returning the cleansed blood back to the body.

**Hemoglobin:** The substance in the red blood cell that contains iron and transports oxygen. Commonly used to monitor anemia.

**Orthostatic hypertension:** A sudden drop in blood pressure that causes dizziness or lightheadedness when changing position, such as moving from lying down to sitting or standing.

**Prophylaxis:** Preventive measures taken prior or during treatment to reduce the risk of disease or complications, such as infections. Your healthcare team will tailor prevention strategies based on specific risk factors, treatment regimens, and overall health status.

**Proprioception:** The body's ability to sense its position and movement in space. This awareness arises from sensory receptors in the skin, joints, and muscles and plays a crucial role in balance, coordination, and force control.

**Proton pump inhibitor (PPI):** A type of medication that reduces stomach acid production by blocking an enzyme in the stomach lining. PPIs are used to treat acid reflux, heartburn, and stomach ulcers and help manage gastrointestinal side effects from certain myeloma therapies or steroids.

**Toxoplasmosis:** An infection caused by a parasite called *Toxoplasma gondii*, often linked to undercooked meat or exposure to cat feces. Symptoms may include flu-like illness, muscle aches, and swollen lymph nodes.

**Trichinosis:** A parasitic infection caused by the *Trichinella* species, typically contracted by consuming raw or undercooked infected meat. Symptoms include digestive disturbances (abdominal cramps, nausea, diarrhea, vomiting), fever, muscle pain, headaches, facial swelling, and itching. Severe cases may involve complications such as myocarditis (heart inflammation) and encephalitis (brain inflammation), and, in rare cases, can be fatal.

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