Waldenstrom's Macroglobulinemia

Frequently Asked Questions

IWMF

International Waldenstrom's Macroglobulinemia Foundation

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This booklet is dedicated to the memory of IWMF Trustee, Dr. Glenn Howard Cantor, who was lost to us in a tragic accident. Glenn, a veterinarian by training, had a long career as a respected pharmaceutical research scientist. His background and experience were instrumental in helping IWMF support and advance WM research and translate dense scientific concepts into language and illustrations we could all understand. Glenn had many avocations: outdoor adventurer, birdwatcher, nature photographer, bicyclist, and volunteer (Peace corps in Ecuador). He was a loving husband, caring father, and adoring grandfather and will be missed by his family, friends, and the WM community he served so well.

Table of Contents

Introduction

Frequently Asked Questions is designed to support newly diagnosed and veteran patients with Waldenstrom's macroglobulinemia (WM) and their caregivers. Answering questions about this disease requires the use of terms that may not be familiar to some readers. Terms related to WM are defined in the booklet, Glossary: Useful Words to Know When You Have WM, which can be found on the IWMF website at **iwmf.com/publications.**

Initial Key Questions

What is WM?

Waldenstrom's macroglobulinemia (WM) is a slow growing (indolent) type of non-Hodgkin lymphoma, a blood cancer. It occurs in a type of white blood cell called a B lymphocyte or B cell, which normally matures into a plasma cell whose job is to manufacture immunoglobulins (antibodies) to help the body fight infection. In WM, there is a malignant change to the B cell in the late stages of maturing and it continues to multiply over and over as a clone of identical cells, primarily in the bone marrow. These cells produce too much of the same immunoglobulin (Ig), called monoclonal IgM, which can be detected in the blood. WM can also cause enlargement of the lymph nodes and spleen and the cancer cells can accumulate in other tissues and organs (lung space, brain, or spine). WM is also referred to as lymphoplasmacytic lymphoma (LPL) because the cancer cells have the appearance of both B lymphocytes and plasma cells under a microscope. For WM to be diagnosed, the LPL cancer cells in the bone marrow and the monoclonal IgM in the blood must both be present.

What's the difference between WM and LPL (lymphoplasmacytic lymphoma)? Are they the same disease?

Sometimes WM and LPL (lymphoplasmacytic lymphoma) are used interchangeably, although WM is really a type of LPL—the most common type, comprising about 90-95% of all people with LPL. The LPL cancer cells, when viewed by a pathologist under a microscope, have the appearance of both B lymphocytes (also called B cells) and plasma cells, hence the term lymphoplasmacytic. B cells and plasma cells, including the LPL cancer cells, typically make proteins, known as immunoglobulins or antibodies (referred to as IgM, IgA, IgG, IgE or IgD), but LPL cells that produce IgM of one kind (monoclonal IgM) are found in patients with WM. In short, the clinical diagnosis of WM is made in cases where LPL cells are present in the bone marrow, and monoclonal IgM is present in the blood.

My doctor said WM was a rare disease. How rare is it? What does that mean for me?

WM is a rare cancer diagnosed only in approximately three to four people per million people per year, with about 1,500-3,000 new cases diagnosed in the US and in Europe each year. Overall, WM comprises only 1-2% of all blood cancers. This disorder is age-dependent and is quite unusual in anyone under the age of 50 (less than 10% of people with WM), while 25% are younger than 60 years of age. Typically, people with WM are diagnosed between the ages of 60 and 70. For reasons that are unclear, approximately 60% are males, and it is more common in Caucasians, compared with other ethnic groups. Specifically, it is very uncommon in Blacks, who make up approximately 5% of cases, and in people of Asian ancestry. There is a familial predisposition to WM, with most studies suggesting that up to 25%

of people with WM have a first-degree relative (parent, sibling, or child) or second-degree relative (grandparent, aunt, uncle, cousin) with WM or other B cell disorders, such as other lymphomas or multiple myeloma. A small number of families exist with parents and children, as well as siblings, having WM. WM is a such rare disease that most community hematologist/oncologists see few, if any, people with WM in their careers. This is why it is so important to have a second opinion on diagnosis and/or treatment from a hematologist/oncologist at a large academic medical center that sees a lot of people with WM.

Is there a cure for WM?

No, WM is incurable, although quality of life and survival for people with WM are continuing to improve because of newer treatments that are better, safer, and more effective. Today, many people with WM have a cause of death unrelated to their diagnosis of WM.

> ***"At the end of the day, do I believe there is a cure in sight for WM? Absolutely."***
>
> *- Dr. Steven P. Treon, Dana-Farber Cancer Institute*

How long do I have to live?

Although WM is incurable, in most cases it can be effectively treated to provide a good quality of life for many years. In most people, WM is a slow growing (indolent), chronic disease. The median survival after diagnosis has varied in studies, from 5-10 years in the past to 15-20 years now. Another way to answer this question is to look at the five-year survival rate, which indicates what percentage of people live at least five years after cancer is found. The current five-year survival rate for people with WM is about 78%. In other words, nearly four out of five people live for at least five years after being diagnosed with WM. However, it is important to note that survival rates vary based on individual factors, including the person's age and whether there are other medical problems. It is also important to remember that statistics on the survival rates for people with WM are an estimate. As newer, safer, and more effective drugs become available, the life expectancy will continue to increase. The main causes of death because of WM include disease progression, transformation to an aggressive lymphoma, or complications from therapy. What is most important is that the time frame for living with WM has increased dramatically and is continuing to increase, and people with WM will likely die from something unrelated to WM.

How often should I see my hematologist/oncologist?

This depends greatly on the disease status and whether treatment is underway. If someone has smoldering (asymptomatic) WM and is stable, a visit to the hematologist/oncologist may not be necessary more than once or twice a year. If someone is newly diagnosed or has progressive disease, a hematologist/oncologist may want to follow at more frequent intervals, perhaps once every 2-3 months. If someone is currently being treated, a hematologist/oncologist may choose to monitor even more frequently during this period because some treatments can cause side effects, which need to be recognized early and managed appropriately.

Should I get a second opinion? If so, when?

It is not unusual for newly diagnosed people or people needing treatment to get a second opinion from a recognized WM expert or from a hematologist/oncologist who has an interest in and experience with the diagnosis and treatment of

WM. WM is a rare disease, and as a result, many hematologist/oncologists may have little experience dealing with people who have WM.

The IWMF magazine, the *Torch*, has published an article on this subject, "Should I Get a Second Opinion" by Dr. Morie A. Gertz, which can be found at **iwmf.com/wp-content/uploads/2022/02/GertzSecond-Opinion-revised-2022.pdf.**

How do I find a good doctor for a second opinion?

Large academic teaching hospitals tend to see more people with WM, and their staff physicians have more experience with it. The IWMF website maintains a list of such physicians at **iwmf.com/directory-of-wm-physicians/.**

When should I get treatment?

The course of WM can vary significantly from person to person. Not all people newly diagnosed with WM need immediate treatment. People who do not have symptoms (asymptomatic) requiring treatment but have a detectable amount of monoclonal IgM (usually a low level) in the blood may be actively monitored at regular intervals by their hematologist/oncologist. These individuals are on "watch-and-wait" or medical surveillance (starting on page 17 for more information on watch-and-wait).

Some people are symptomatic with low levels of IgM while others continue to do well with a higher level. Hematologist/oncologists will consider starting treatment when people begin having significant symptoms, such as progressive fatigue, weight loss, swollen lymph nodes, infections, or when blood test results suggest a health risk, such as low levels of red blood cells, white blood cells, or platelets. To some extent, the decision to begin treatment is dependent on a particular patient's tolerance of symptoms and how they are affecting quality of life. The IgM level in and of itself is not an indication for treatment, but if the level of IgM in the blood is increasing rapidly or if the blood becomes significantly thickened because of the increased IgM (hyperviscosity), then hematologist/oncologists will consider treatment.

Other indications for treatment can be found at **iwmf.com/when-is-treatment-needed-for-wm**. Additionally, the *IWMF Torch* magazine has published an article on this subject, written by Dr. Stephen Ansell and called "Who Needs Treatment for Waldenstrom's Macroglobulinemia and When?" The article is located at **https://tinyurl.com/Torch-0415-Ansell**

What are my treatment options for WM?

Today, there are many treatment options for WM. Treatment can be with oral medication(s) that may need to be taken indefinitely or with an infusion into a vein or an injection under the skin that is taken for a limited time. Most treatments were derived from therapies used for similar diseases, such as follicular lymphoma, chronic lymphocytic leukemia, and multiple myeloma. More specific information about treatment for people with newly diagnosed or recurrent WM can be found in this booklet on starting on page 17.

There are more treatment options available for people with WM today, and information regarding many of them (IWMF Treatment Guides and Fact Sheets) can be accessed at **iwmf.com/publications**. Also, several major academic cancer centers have developed guidelines for the treatment of WM. These are available at: **iwmf.com/publications-about-wm-from-iwmf-partners**, or through the National Comprehensive Cancer Network Guidelines for Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma at **nccn.org/patients/guidelines/content/PDF/waldenstrom-patient.pdf** The treatment landscape continues to evolve, with novel therapies being discovered

and tested in clinical trials. For an updated list of trials, go to the US government website, **clinicaltrials.gov**, which contains trials in the US and many other countries.

> ***"The generous past support of IWMF has set the stage for an acceleration of research towards a cure."***
>
> *-- Dr. Stephen M. Ansell, Mayo Clinic*

In-Depth Disease Information

Where did the name "Waldenström" come from? What does "macroglobulinemia" mean?

Dr. Jan Waldenström (1906-1996) was a Swedish physician who in 1944 first described two patients with symptoms of what is now known as Waldenström's macroglobulinemia. "Macroglobulinemia" is a compound word—"macro" meaning large and "globulinemia" meaning protein in the blood. In the case of WM, the WM cancer cells over-produce a large immunoglobulin (antibody) protein of one type that circulates in the blood and is called monoclonal IgM.

What is IgM and how does it relate to WM?

Immunoglobulin M, or IgM for short, is one of five basic antibody proteins (IgG, IgA, IgM, IgD and IgE) that are produced by B cells and plasma cells (which are types of white blood cells). IgM is by far the largest antibody in the human circulatory system. It is the first antibody to appear in response to initial exposure to an infection. WM occurs in B cells when they are in the process of developing into plasma cells. They become abnormal "lymphoplasmacytic (LPL) cells," sometimes referred to as "WM cells," in the bone marrow, and they produce large amounts of only one kind of IgM. Although they are of no use to the body, these WM cells keep multiplying over and over again.

As the number of WM cells increase, they build up in the bone marrow, lymph nodes, spleen, and other organs and affect their functions. In the bone marrow, the result of this build-up is that the normal blood cells are "crowded out" or suppressed, and this leads to a gradual reduction of normal blood counts. Substantial amounts of IgM in the blood can cause it to become thick and syrupy (hyperviscosity). Hyperviscosity can lead to blood vessels bursting in the retina, mucosa (lining) of the nose/mouth, or brain. Sometimes, the IgM may wrongly recognize the body's tissues as foreign and attach to them, causing inflammation and damage. If they attach to nerves and cause damage, this is known as neuropathy. If the IgM attaches to and destroys red blood cells, it is known as autoimmune hemolytic anemia.

For a deeper understanding of basic immunology and immunoglobulins, read the IWMF booklet, *Basic Immunology*, at **iwmf.com/publications.**

What is an M-spike?

M-spike stands for monoclonal spike. The word "monoclonal" refers to an immunoglobulin (antibody) protein of one kind produced by the cells of certain blood cancers such as WM and multiple myeloma. The word "spike" is used because this monoclonal protein produces a spike pattern on the tracing of its electrical charge on the serum protein electrophoresis, which is an important test used to evaluate the types of proteins (normal and abnormal) in the blood. In the case of WM, the monoclonal immunoglobulin protein or M-spike produced by the WM cells is IgM.

What risk factors cause WM? Is there an environmental cause?

The specific cause(s) of WM are unknown. Male sex, Caucasian race, increasing age, a family history of WM or other B cell disorders, hepatitis C virus infection, AIDS infection, occupations such as farming, and exposure to pesticides, solvents, and wood dust are possible risk factors for the disease. More studies are needed to determine if there is a causal relationship between any of these factors and WM.

What is IgM MGUS?

WM is preceded by a condition known as monoclonal gammopathy of undetermined significance (MGUS) of the IgM type and is the very early stage when there are very few WM cells in the bone marrow. These cells are often barely visible in tissues samples, but there is a detectable amount of monoclonal IgM (usually a low level) in the blood. IgM MGUS may be picked up on a blood sample done for an unrelated reason, and at this point, people generally have no symptoms. Up to 25% of people with WM, excluding those with IgM MGUS, may be asymptomatic at diagnosis; such patients are considered to have smoldering WM. The cause of IgM MGUS and smoldering WM (and hence the potential future diagnosis of active or symptomatic WM) is not known, but it is more common as people get older. Over time (usually years), these WM cells may gradually accumulate. As they accumulate, symptoms such as fatigue, weight loss, night sweats, nerve damage (neuropathy), fever, or recurrent infections may develop, and symptomatic WM may eventually be diagnosed. The risk of IgM MGUS turning into symptomatic WM requiring therapy is 1-2% per year. There are other types of MGUS associated with immunoglobulins, such as IgG, IgA or rarely, IgD.

The IWMF magazine, the *Torch*, has published an article on this subject, "From Precursors to Progression: The Need for More Research" by Dr. Irene Ghobrial, et al. This article can be found at **iwmf.com/wp-content/uploads/2020/10/Ghobrial-WM-Torch-Article.pdf**. Another very useful article from the *Torch* is "IgM MGUS, Smoldering Waldenstrom's Macroglobulinemia and Waldenstrom's Macroglobulinemia" by Dr. Robert Kyle, located on page 6 at **iwmf.com/wp-content/uploads/2020/10/Torch_October2018.pdf**.

Is there a familial predisposition to WM? Do I have to worry about my kids getting it?

There is a slightly increased familial predisposition to WM, with most studies suggesting that up to 25% of people with WM have a history of the disease or related B cell disorders in their families. At this time, there is no test that will predict which, if any, family members of someone with WM will ultimately also develop WM, although those family members with IgM MGUS (monoclonal gammopathy of undetermined significance) are at greater risk of developing WM. Although the risk of developing WM is slightly greater in families with familial disease, the absolute risk is still extremely low because of the rarity of the disease. Experts do not recommend testing children or young adults since their risk of developing WM is so low.

The IWMF magazine, the *Torch*, has published "Family Matters in Waldenstrom Macroglobulinemia" by Dr. Mary McMaster, which can be found at **iwmf.com/wp-content/uploads/2020/10/Familial-WM-Torch-20.1.pdf.**

If I have WM, do I have a greater risk for other cancers?

Several studies have suggested that people with WM can get any type of cancer, but they have an increased risk of acute myeloid leukemia (AML),

diffuse large B cell lymphoma, melanoma, other skin cancers, and thyroid cancer. People with WM should continue routine screening with their healthcare providers for other types of cancer and should do their best to stay away from all tobacco products and tobacco smoke, as smoking increases the risk of many cancers. Wearing sunscreen during sun exposure can decrease the risk of melanoma and other skin cancers.

What is MYD88 and what is the MYD88 mutation I've heard about in people with WM?

MYD88 is a normal protein coded by a gene called myeloid differentiation primary response 88. When B cells are exposed to bacteria or viruses, MYD88 initiates several downstream cell pathways that result in the expression of factors critical to the development and activation of B cells, one of which is Bruton tyrosine kinase (BTK). A single specific mutation in the MYD88 gene, designated as MYD88 L265P, was found to have a much higher prevalence in WM (approximately 90-95%) than in other kinds of blood cancers. The MYD88 L265P mutation is also seen in approximately 50% of people with IgM MGUS (monoclonal gammopathy of undetermined significance), a precursor condition to WM.

The IWMF magazine, the *Torch*, has published an article on this subject, called "Mutation MYD88 L265P," written by Dr. Steven Treon. This article is at **iwmf.com/wp-content/uploads/2020/10/Treon.pdf.**

What is the significance of the MYD88 L265P mutation in WM?

Its significance is still not fully understood. Although it is prevalent in WM (at approximately 90-95%), at this point researchers do not believe it causes the disease. However, it does appear to play a role in the growth and survival of WM cells by leading to over-expression of proteins such as BTK that are involved in B cell development and activation. Because of its prevalence in WM, its presence or absence becomes useful as part of the diagnostic workup of people with suspected WM or related diseases, and it can impact subsequent treatment choices.

Are there other gene mutations that are important in WM? What are CXCR4 and TP53?

Researchers are looking at several other gene mutations found in people with WM. Mutations in the gene CXCR4 are found in approximately 30-40% of people with WM. CXCR4 mutations may lead to more bone marrow and less lymph node involvement, higher IgM, and greater likelihood of hyperviscosity (thicker blood) and acquired von Willebrand disease, a deficiency in the body's blood clotting process. CXCR4 mutations have been likened to the "GPS" of the WM cell, in that they cause WM cells to home to the bone marrow and stick there. CXCR4 mutations have not been associated with worse survival but are associated with lower efficacy when treated with ibrutinib.

The IWMF continues to sponsor research studying CXCR4 mutations. The TP53 gene is also altered in 20-30% of people with WM, particularly those who were previously treated. Zanubrutinib shows greater response activity and/or improved progression-free survival (the time from initiation of treatment to the occurrence of disease progression or death) in people without the MYD88 mutation (MYD88WT), with mutated CXCR4 (CXCR4Mut), or with the altered TP53 (TP53Alt) gene, compared to ibrutinib. Experts note the necessity of a bone marrow biopsy (starting on page 15) when making the initial diagnosis of WM to avoid confusing it with other diseases. Experts also recommend that when bone marrow biopsies are performed, samples should

be sent to specialized academic medical centers for diagnostic workup. The molecular studies should include testing for mutations in MYD88, CXCR4, TP53, and an assessment of portions of two chromosomes, called 6q and 17p, which are sometimes deleted in WM. CXCR4 testing is particularly recommended when considering ibrutinib treatment, since patients with certain CXCR4 mutations, such as the S338X mutation, have lower odds of responding well to ibrutinib.

The IWMF magazine, the *Torch*, has published an article on this subject, called "A Guide to CXCR4 Mutations and Their Importance in Waldenstrom's Macroglobulinemia," written by Dr. Steven Treon. This article can be found on page 1 at **iwmf.com/wp-content/uploads/2021/04/Final-pdf-Torch-April-2021.pdf.**

Is WM different when you are young and get the diagnosis?

Less than 10% of people with WM are younger than 50 years, and 25% are younger than 60 years at diagnosis; thus, they have been often underrepresented in scientific literature and clinical trials. Younger people generally have better organ and functional reserve, or the ability to successfully return to their original physiological state after periods of stress, as compared to older individuals, and thus can better tolerate therapy. Therefore, the disease and treatment course of WM is different in those who are younger than in older patients, who often have a higher rate of comorbidities or other health conditions and are unable to tolerate more aggressive treatment regimens.

The estimated survival of younger patients with WM is much longer than for older patients. In patients with symptomatic WM requiring treatment, one study showed that ten years after first-line treatment, 86% of people younger than 45 years and 74% of those younger than 50 years were alive, compared to 31% of older people (greater than 65 years). Overall, young people with WM have an excellent prognosis with chemoimmunotherapy treatment regimens (less than 2% patients were treated with BTK inhibitors in this study). Most young people with WM (less than 45 years) did not need treatment at the time of diagnosis but required treatment initiation at a median time of 2.5 years from diagnosis. Despite differences in outcomes, the optimal treatment strategy for younger individuals is not well defined. In younger people with a longer life expectancy ahead, it is vital to consider a long-term treatment strategy to maximize treatment-free intervals while minimizing the risk of persistent or late side effects from therapy. The simplest way of achieving these goals is by ensuring that treatment is only given when absolutely necessary (spacing/delaying treatments as much as possible).

The management of WM in younger patients has been referred to as a marathon, not a sprint. IWMF has published a Fact Sheet called "Young Patients with Waldenstrom's Macroglobulinemia," which is located at **iwmf.com/publications.**

Signs and Symptoms

What are the common signs and symptoms of WM? What is the connection between WM and fatigue?

WM can cause a wide variety of signs and symptoms. The effects of WM vary from person to person. People with WM may experience some or none of these symptoms. The most common are slowly progressing fatigue (extreme tiredness and weakness) and shortness of breath or breathlessness with exertion because of an underlying anemia. The anemia is the result of a decrease in the number of red blood cells, typically caused by the increased number of WM

cells in the bone marrow that "crowd out" or suppress normal blood cells. Other typical symptoms are easy bruising or bleeding (including abnormal bleeding from gums and nose), dizziness, headaches, blurred vision, confusion or poor concentration, swollen glands (enlarged lymph nodes), enlarged spleen or liver, weight loss, unexplained fevers, and drenching night sweats. There may be neurological symptoms such as nerve damage in the hands and feet (peripheral neuropathy). Most symptoms are attributable to the buildup of the WM cells in the bone marrow and other tissues or because of the secretion and accumulation of abnormal monoclonal IgM in the body.

What kind of skin problems are related to WM?

Skin problems are uncommon with WM. Rarely, WM cells can infiltrate the skin, or the IgM secreted by WM cells can deposit in the skin. Symptoms may include skin thickening, nodules, or rashes. If you have these symptoms, you should see a dermatologist to rule out other causes of your skin problems. Occasionally, people with WM may have low platelets (thrombocytopenia) or their high IgM may cause bleeding problems in the skin, leading to easy bruising, tiny red or purple spots (petechiae), or small red or purple areas (purpura). Treatment with ibrutinib or zanubrutinib (and other BTK inhibitors) and chemotherapy (i.e., bendamustine) can cause skin problems, such as rashes, bruising, and brittle nails.

What is the cause of night sweats in WM?

Unexplained fevers, drenching night sweats (with the need to change bed clothes and sheets because of these soaking sweats), and significant weight loss may be a feature of WM in a very active disease period. They are sometimes referred to as B cell symptoms. Researchers do not have a definitive answer as to the cause, but one possible mechanism is that the progression of lymphoma and the body's way of fighting infection have some things in common—both may lead to the mobilization of WM cells and associated proteins called cytokines, and their activities may account for these physically noticeable symptoms. Treatment may need to be started, so informing one's healthcare team as soon as these symptoms start is prudent.

How can WM affect my eyes?

WM can affect the eyes in several ways, especially when the IgM in the blood increases to a high level (over 3,000-4,000 mg/dL), making the blood thicker (hyperviscosity). Symptoms of hyperviscosity syndrome include bleeding from the nose and gums, headaches, blurred vision, and dizziness. A test for blood thickness (serum viscosity level or SV) will be ordered, and treatment will probably be recommended.

The IWMF magazine, the *Torch*, has published an excellent article on this subject, called "I Have Waldenstrom Macroglobulinemia – Why Should I Get My Eyes Checked?" by Dr. Maureen Hanley. This article is at **iwmf.com/wp-content/uploads/2020/10/Maureen-Hanley.-July-2020-Torch-Article.pdf.**

What is peripheral neuropathy? What does it feel like?

The IgM protein in WM can cause peripheral neuropathy (PN). It is estimated that approximately 20-30% of people with WM have PN caused by the IgM immunoglobulin antibody mistakenly targeting the nerves in the hands and feet (peripheral nerves). This antibody causes a dysfunction of nerves that extend from the spinal cord out to the peripheral portions of the body (arms, hands, legs, and feet). PN can also be a consequence of certain WM treatments, such

as bortezomib. The symptoms of PN include tingling or prickling, numbness, cold sensation, tightness, burning, shooting or stabbing pains, and increased sensitivity to contact. These symptoms usually begin in both feet and can eventually extend upward so that both hands may be affected. PN can also affect motor nerves and involuntary (autonomic) nerves, causing symptoms such as difficulty in rising from a sitting position, lightheadedness upon standing, and decreased grip strength.

The IWMF magazine, the *Torch*, has published an article on this subject, called "Peripheral Neuropathy in IgM-MGUS and Waldenstrom Macroglobulinemia," written by Tom Hoffmann, MD. This article is available at **iwmf.com/wp-content/uploads/2020/10/Hoffmann-Peripheral-Neuropathy-.pdf.**

How can I treat my peripheral neuropathy? Will it improve with treatment?

First, the cause of the peripheral neuropathy (PN) should be determined if possible. If WM is the cause, treating the disease may cause some improvement. It is difficult to restore nerve function once it has been damaged. The presence of neuropathy alone is not an immediate indication for treatment, given the slowly progressive nature of the IgM-associated peripheral neuropathies. When treatment is warranted, the goal is to try to keep the neuropathy stable and prevent it from becoming worse. There are many therapies often used to relieve the symptoms of neuropathy, but there is no general agreement as to which may be more effective. They range from over-the-counter remedies to prescribed medications. It is important to tell one's healthcare team about any of these symptoms, especially if they are getting worse over time. People with WM who have a progressing IgM-associated peripheral neuropathy are typically treated with rituximab alone, dexamethasone-cyclophosphamide-rituximab, or bendamustine-rituximab. BTK inhibitors like ibrutinib, acalabrutinib, and zanubrutinib can also be considered.

What is hyperviscosity syndrome? What is plasmapheresis? Why is plasmapheresis done? What should I do before, during, and after plasmapheresis?

Hyperviscosity syndrome caused by WM occurs when extremely high levels of the IgM protein cause thickening of the blood which, if extreme, can cause problems with bleeding, most typically from the gums or nose, and eye problems. Plasmapheresis (PP) is often used for hyperviscosity syndrome to provide temporary relief for the patient. During plasmapheresis for WM, patients are connected to a special machine through a needle inserted into a vein (intravenous or IV) in the arms or through a tube (intravenous catheter) in the upper chest area. Blood is then processed through the machine where the plasma (which contains the IgM) is removed and discarded, and the remaining blood is returned to the patient. The removed plasma is typically replaced with albumin or fresh frozen plasma to maintain the appropriate blood volume. Improvement of symptoms is usually rapid. PP does not reduce the number of WM cells in the bone marrow, only the amount of IgM; therefore, these cells continue to make monoclonal IgM, and the relief is temporary. The underlying disease of WM must be treated for longer-lasting results.

The IWMF magazine, the *Torch*, has published an article called "Hyperviscosity Syndrome" by Dr. Shirley D'Sa, which can be found at **iwmf.com/wp-content/uploads/2020/10/DSa.pdf.** Another resource is the IWMF Fact Sheet on Plasmapheresis at **iwmf.com/publications**.

Diagnosis and Tests

How is WM diagnosed?

The diagnosis of WM requires two components. The first is the presence in the blood of a monoclonal IgM antibody protein, the so-called "macroglobulin." The second is the presence of an abnormal cell population in the bone marrow. These abnormal cells (lymphoplasmacytic or LPL cells) in the bone marrow are responsible for the production of the IgM protein. When LPL cells produce IgM, they are commonly called WM cells. To make that diagnosis, a doctor will begin with a series of questions or medical history. He or she will then perform an examination to look for signs and symptoms of disease (SIGNS AND SYMPTOMS, starting on page 12). Based on this information, a series of blood and other medical tests will be ordered.

If WM is suspected, a bone marrow biopsy is necessary. Experts recommend that when bone marrow biopsies are performed, samples should be sent to specialized academic centers for diagnostic workup. The molecular studies should include testing for mutations in the genes MYD88, CXCR4, TP53, and an assessment of portions of two chromosomes, called 6q and 17p, which are sometimes deleted in WM. For more information on how WM is diagnosed, please refer to the IWMF booklet, *Medical Tests,* which is located at **iwmf.com/publications.**

The IWMF magazine, the *Torch*, has published an article on this subject, called "How Is Waldenstrom's Macroglobulinemia Diagnosed" by Dr. Morie A. Gertz, which is found at **iwmf.wpengine.com/wp-content/uploads/2020/10/Gertz4.pdf**. Another helpful *Torch* article called "Laboratory Diagnosis and Monitoring of Waldenstrom's Macroglobulinemia" by Dr. Janis Atkinson is at **iwmf.wpengine.com/wp-content/uploads/2020/10/Atkinson-LABORATORY-DIAGNOSIS-AND-MONITORING-OF.pdf.**

What is a bone marrow biopsy? What should I expect?

A bone marrow biopsy is performed to look for abnormalities in the bone marrow, which is the spongy tissue inside the larger bones where blood cells are produced. This procedure can be performed in a physician's office or a hospital using local anesthetic, with or without light sedation. The specimen is usually obtained from the posterior iliac crest (back of the hip bone) by using a special needle. Both a fine needle aspiration (a very thin needle on a syringe collects cells, tissue and/or fluid from the bone marrow) and a solid bone marrow sample (biopsy) may be taken. There may be some discomfort or a feeling of pressure even when a local anesthetic is given. The biopsy site may be bruised and sore for a few days following the procedure. A pathologist examines the bone marrow cells under a microscope and performs additional testing with special staining of the cells to identify the presence of an abnormality. Again, experts recommend that when bone marrow biopsies are performed, samples should be sent to specialized academic centers for diagnostic workup. The molecular studies should include testing for mutations in the genes MYD88, CXCR4, TP53, and an assessment of portions of two chromosomes, called 6q and 17p, which are sometimes deleted in WM.

For more information on the bone marrow and WM, please refer to the IWMF booklet, "A Basic Guide to Understanding Your Bone Marrow and Waldenstrom's Macroglobulinemia," at **iwmf.com/publications.**

How often do I need to have a bone marrow biopsy?

A bone marrow biopsy is necessary to establish the diagnosis of WM. Frequent bone marrow biopsies are not usually recommended for disease monitoring because this is a costly and invasive

technique and normally not necessary to monitor the disease. There may be situations, however, where one's hematologist/oncologist may decide that an additional biopsy is warranted to help determine if a someone needs treatment, to learn how someone's bone marrow is responding to therapy, or as part of a clinical trial requirement.

What is the purpose of measuring the IgM level and SV (serum viscosity)?

Since the IgM monoclonal protein in WM comes from the abnormal WM cells, the quantity of IgM can be used to monitor disease activity. As the disease progresses, more cells are produced, and the amount of IgM in the blood goes up. Conversely, as the disease responds to treatment, the IgM declines. The monoclonal IgM protein measurement can be made by serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE). If too much IgM with one specific charge is present, it produces a "spike" pattern on the tracing of the protein's electrical charge, and, in combination with the tissue sample findings, a diagnosis of WM can be made. While SPEP and IFE are good screening tests for monoclonal protein, additional testing called quantitative serum immunoglobulins is used to detect and monitor the levels of the three major immunoglobulin classes (IgG, IgA, and IgM). In quantitative serum immunoglobulin testing, the IgM total includes both normal IgM and monoclonal IgM, and the normal range of IgM in this test is 37-287 mg/dL. Many people with WM never develop high serum viscosity (thick blood) but more often have other symptoms associated with their disease (anemia, fatigue, peripheral neuropathy, etc.). However, the serum viscosity (SV) measurement is important for those people with WM who have a high IgM level, usually more than 3,000-4,000 mg/dL.

For more information about laboratory diagnosis and monitoring of WM, please refer to the IWMF publication, "Laboratory Diagnosis of Waldenstrom's Macroglobulinemia Fact Sheet," at **iwmf.com/publications.**

Are IgG and IgA levels important measurements to follow too?

People with WM usually have low levels of either IgG (normal range of IgG is 767-1,590 mg/dL) or IgA (normal range of IgA is 61-356 mg/dL) or both because of treatment for WM and/or for reasons that are not known but appear to be related to having WM. If a patient has recurrent infections (sinus infections or bronchitis, for example), then low IgG and IgA levels may be playing a role, and treatment could possibly include IVIG (intravenous IgG) or subcutaneous IgG (injected under the skin of the abdomen or thigh). If a WM patient is not experiencing recurrent infections, the IgG and IgA levels are of little importance.

What are the key numbers in my blood testing?

Most hematologist/oncologists look at trends in test results more than a specific number. The IgM level, in and of itself, is not an indication for treatment. If there are no symptoms associated with rising IgM, treatment may not be needed. Generally speaking, the most important blood tests to monitor are the serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE), and quantitative serum immunoglobulins test to detect and monitor IgM and other major immunoglobulins.

Another important blood test is the complete blood count (CBC). Several components of the CBC are carefully monitored in patients with WM, including the white blood cell (WBC) count, hemoglobin (Hgb or Hb), and platelet (Plt) count. These are important because anemia, infection, and bleeding may be complications of WM or

treatments for it. The comprehensive metabolic panel (CMP) is another useful series of tests that provide information about how the body uses food and energy (the body's metabolism) and the balance of certain chemicals in the body. People with amyloidosis, cryoglobulinemia, cold agglutinin disease, Bing-Neel syndrome, enlarged lymph nodes, or, rarely, WM-related kidney disease may need to monitor their disease progression with additional tests.

More about these special conditions and testing is explained in the IWMF booklet *Medical Tests* at **iwmf.com/publications**.

Treatment

Why am I on watch-and-wait and not being treated if I have cancer?

Treating asymptomatic (smoldering) WM does not save lives, nor does it improve the quality of life, cure the disease, or change the long-term outlook. Furthermore, there may be side effects from the medications as well as increased costs and inconvenience. People without significant symptoms affecting quality of life receive no benefit from early treatment and may suffer from side effects of the treatment without adding any years of life. A high IgM does not justify treatment (if the IgM level is not critically high or there are no other major blood problems), and a low IgM does not mean that treatment is not required. Frequent monitoring of blood values and symptoms is important. The rule of thumb is that symptoms, not the IgM level, should be the determining factor to decide if treatment is necessary.

The IWMF magazine, the *Torch*, has published an article on this subject, "When to Move from Watch and Wait to Treatment" by Dr. Morie A. Gertz, which is at **iwmf.com/wp-content/uploads/2020/10/Gertz6WW.pdf.**

Since I am newly diagnosed, what can I expect from treatment for WM?

There is currently no treatment that cures WM. The goal of treatment is to reduce or relieve the severity of symptoms, to improve quality of life, and to maintain that state for an extended period. While undergoing treatment and for a while afterward, one may experience symptoms related to treatment side effects. If drug delivery through a vein (intravenous) is chosen for the administration of treatment, some side effects may occur during the infusion and may be alleviated by certain pre-medications. Other side effects may remain throughout the course of the treatment and for a short while afterward. These may include fatigue, nausea, hair and weight loss, low blood counts, and infections, to name a few. Treatment side effects vary according to the specific type of treatment, and one should consult their physician to determine exactly what to expect.

Frequently encountered side effects from WM chemotherapeutics are covered under the drug name in the IWMF Fact Sheets, written in several languages, at **iwmf.com/publications**. The IWMF magazine, the *Torch*, has an article on side effects, "WM: Managing the Side Effects" by Dr. Jeffrey V. Matous, at **iwmf.com/wp-content/uploads/2020/10/Matous.pdf.** Also for the *Torch*, Dr. Jonas Paludo has written a helpful article, "Beyond Remission: Understanding the Goals of Therapy in WM," available on page 1 at **iwmf.com/wp-content/uploads/2024/01/N52606-Torch-January-2024_web.pdf.**

When the first treatment is needed, many people with WM ask which is best, the bendamustine-rituximab combination (BR or Benda-R, also called chemoimmunotherapy or CIT) or pills such as ibrutinib or zanubrutinib, which are BTK inhibitors. A panel of experts from the International Workshops on WM concluded that either BR or

a BTK inhibitor is suitable for first-time (treatment-naïve) patients. They are both reasonable choices with similar efficacy. The experts also said that a third option, dexamethasone, cyclophosphamide, and rituximab (a chemoimmunotherapy called DRC) is suitable, especially for less fit patients with lower tumor burden. Both chemoimmunotherapy regimens, BR or DRC, are effective, of fixed duration (which is important to many patients), generally well-tolerated, and less costly. The BTK inhibitors are also generally well-tolerated and are especially useful if patients are unsuitable for BR or DRC because they have too many other medical problems. BTK inhibitors are an important option for young patients, since BR may carry the risk of damaging DNA and causing additional blood cancers in the future. The experts pointed out that zanubrutinib, a second-generation BTK inhibitor, shows less risk for causing atrial fibrillation than ibrutinib and induces deeper improvements (responses).

Other chemotherapy treatments used in the past, including R-CHOP, R-CVP, fludarabine, or cladribine-based treatments, are not preferred in first-line treatment of WM because of higher toxicity, without evidence of long-term benefit, compared with BR or DRC. If therapy with ibrutinib or zanubrutinib is chosen, the experts recommended testing the mutational status of MYD88 and CXCR4, if possible, since that information is helpful in predicting how quickly the treatment will start to work and how well the therapy will work. For example, if CXCR4 is mutated, zanubrutinib results in faster and deeper responses than ibrutinib. There has been increased attention recently on mutations in another gene, called TP53. The experts concluded that the impact of TP53 mutations on treatment outcomes for newly diagnosed WM patients is not yet known.

Rituximab is a targeted therapy classified as a monoclonal antibody. It is given as an infusion into a vein (intravenous, IV) or injected under the skin (subcutaneously) as Rituxan Hycela. Medications are given before intravenous rituximab to reduce the occurrence of side effects associated with the administration of the drug. A short-term increase in IgM levels following rituximab therapy is well documented in WM; it occurs in 30% to 70% of patients. This “IgM flare” occurs soon after initiating rituximab, with IgM levels returning to baseline in about four months. Some people require a medical procedure called plasmapheresis to reduce their IgM level on a short-term basis before or after starting therapy with rituximab. For more information about plasmapheresis, starting on page 14. Alternatively, rituximab may be started later in the treatment regimen. Rituximab given by itself (solo) is suitable in certain medical situations but does not typically provide the best and longest responses. It is usually given in combination with many other drugs used to treat WM.

The panel of experts also considered proteasome inhibitor-based therapy, such as bortezomib or the newer drugs, ixazomib or carfilzomib. These drugs are often used in combination with other drugs like rituximab and dexamethasone. A problem with bortezomib is that it can cause neurotoxicity, especially peripheral neuropathy, and possibly lead to increased infections. The use of bortezomib injection just under the skin (subcutaneous), rather than through a needle or tube into a vein (intravenous or IV) bortezomib, reduces the risk of peripheral neuropathy. Carfilzomib or ixazomib, in combination with rituximab and dexamethasone, are effective in newly diagnosed patients. This type of regimen may be appropriate for patients with WM who also have amyloidosis (starting on page 22). Carfilzomib should be avoided in patients with heart and lung (cardiopulmonary) disease.

The experts addressed treatment for WM-associated cryoglobulinemia (starting on page 23), cold agglutinins (starting on page 23), Bing-

Neel syndrome (starting on page 24), peripheral neuropathy (starting on page 13), and hyperviscosity (starting on page 14) and said that the basic practice should be to treat WM to reduce the tumor burden and the IgM level rapidly and deeply. In Bing-Neel, ibrutinib can be highly active and produce deep, long-lasting responses. For amyloidosis (starting on page 22), another complication of WM, BTK inhibitors are not recommended.

What if my treatment requires the use of multiple intravenous (IV) infusions and a port is recommended? What is a port?

Intravenous (IV) infusion of bendamustine often causes irritation to the veins and may result in permanent damage, even when all precautions are taken. This is an important concern for patients with WM who are administered bendamustine-rituximab. Dilution of the IV infusion may reduce injury to the vein, although a port may be recommended if the medical providers feel the veins cannot be safely used for IV infusions. A port (otherwise known as a port-a-cath) is an intravenous (IV) line that is surgically implanted and resides completely under the skin. It consists of a one inch (or two and one-half centimeters) in diameter round piece of metal with a soft silicone top called the port and a catheter, which is the thin, flexible tube attached to the port. A port provides a more comfortable way for the patient to receive IV medications, such as chemotherapy, directly into a larger vein located within the chest rather than using a smaller vein in the arm. It can be removed when treatment is finished.

My WM has recurred, or I am not responding to therapy. What should I do?

Patients who have relapsed are those who respond initially to treatment but then develop active disease again. Patients who are refractory are those who do not respond to their treatment. Taken together, these people are classified by the experts as having relapsed/refractory (RR) WM. There is no single treatment recommendation for people with WM who are RR. The therapies BR, DRC, or BTK inhibitors are all important options. Proteasome inhibitors, such as bortezomib, carfilzomib, and ixazomib, are another type of therapy used to treat RR WM. These therapies are often used in combination with dexamethasone and rituximab. Often, choice is guided by what the patient was treated with before, how well they responded to their prior treatment, and what type of toxicities they encountered. Many other factors need to be considered, including the nature of the relapse (rapid vs. more gradual onset), biological age (not just year of birth, but how old a patient looks and feels), other medical problems (called comorbidities), overall fitness, symptoms, blood values, and whether there are WM-related complications. The choice also depends on guidelines and reimbursement arrangements in different countries. Patient preferences are important, and it is helpful for doctors to have a detailed discussion with patients of the advantages and disadvantages of the various treatment options.

When thinking about using a BTK inhibitor, doctors should consider cardiovascular problems, such as atrial fibrillation or other disturbances of heart rhythm; bleeding risk; and other medications that the patient is also taking. The MYD88 and CXCR4 mutational status should be considered since some types of CXCR4 mutations reduce the response to ibrutinib. New data from the experts in WM have discussed mutations in

another gene called TP53. TP53 mutations are much more common in WM patients than previously appreciated; the impact of TP53 mutations require further study and cannot guide treatment choices at this time. Several other treatment options are possible: switching to a treatment that the patient has not been exposed to before; adding rituximab to a BTK inhibitor regimen; switching to a newer BTK inhibitor such as zanubrutinib or pirtobrutinib; using proteasome inhibitors such as bortezomib, ixazomib, or carfilzomib; or using BCL-2 inhibitors such as venetoclax (Venclexta). In some patients with iron deficiency, IV iron may correct anemia and improve well-being, which reduces the urgency to start treatment. The experts also emphasize that all patients with WM who are relapsed or refractory to conventional treatments should be encouraged to participate in clinical trials.

What if subsequent treatments still do not work?

Some treatments work faster than others, so adequate time should be allowed for treatment to work. Just because one doesn't see immediate results doesn't mean there is treatment failure. Furthermore, certain treatments work better for some people than for others. Since WM is usually slow growing, it is frequently not necessary to achieve immediate results (although with symptomatic hyperviscosity, treatment should be initiated urgently). The same treatment used previously may be recommended again along with a different medication, or a new class of therapy may be prescribed. Treatment options are being tested in clinical trials all the time, and if treatment has truly failed, a hematologist/oncologist will be able to suggest an alternate course of therapy. It may be desirable to obtain the advice of an expert in WM.

The IWMF website maintains a list of experts that are available for consultation at **iwmf.com/directory-of-wm-physicians/**.

What are clinical trials?

Clinical trials have become the backbone for testing all new drugs and are the cornerstone of progress in disease treatment. They determine safety profiles, appropriate dosing, correct usage, and efficacy or benefit. To get a drug cleared to start a clinical trial, it must first be tested vigorously in basic science projects. These include everything from test tubes to animal testing to human tissue testing. This is the kind of research that IWMF supports. Many drugs are dropped from production at the basic science level and never enter clinical trials.

There are many reasons that could make clinical trials appropriate for someone with WM. The drug(s) in any given trial may be the best fit if available therapies have not been successful or if one is unable to tolerate conventional drugs because of past treatments or other health conditions. Also, the financial aspects of some conventional drug regimens may be a burden that cannot be handled, while trial drugs are free. There are many more prospective drugs in the pipeline than ever before. As researchers learn more about the mutations occurring in WM, they are finding that newer drug regimens can target the mutation(s) in WM while causing fewer side effects. Newer trial drugs may be focused more on a particular mutation, disease location, or physical situation than current proven drugs.

The Cancer Support Community/Gilda's Club offers a collection of resources to help patients, caregivers, and their healthcare team find clinical trials at **cancersupportcommunity.org/article/find-clinical-trial**. The Leukemia and Lymphoma Society (LLS) also provides free one-on-one sessions with a registered nurse with expertise in adult blood cancers who will help identify clinical trial options for each unique situation. To request clinical trial support from LLS, go to **lls.org/support-resources/clinical-trial-support-center-ctsc**.

Why would I want to enter a clinical trial?

- Current drugs don't work.
- There is concern about the side effects of currently approved drugs.
- Drug companies cover the cost of trial drugs and a lot (but perhaps not all) of the other trial expenses.
- One's disease is familial, so this helps one's family.
- It provides access to new treatments.
- One's doctor thinks a trial would be best.
- The new drug is potentially a better fit.
- One wants to contribute to science.

The IWMF magazine, the *Torch*, has published an article called "Clinical Trials – The Cornerstone for Better Treatments" by Dr. Tom Hoffmann, which can be found on page 1 at **iwmf.com/wp-content/uploads/2020/10/torch-oct-2020.pdf.**

What is a generic drug? Are generics the same as biosimilar drugs?

A generic drug is an exact copy of a brand name drug. Generic drugs work the same way and can be used to treat the same things as their brand name counterparts. A biosimilar is a drug that is very close in structure and function, but not exactly the same, as an original biologic brand name drug, with biologic drugs being products like vaccines, hormones, and monoclonal antibody therapies like rituximab. Biologic drugs are large and complex molecules synthesized by living cells, usually in a fermentation process, and are very difficult to reproduce exactly. However, a biosimilar behaves in much the same way, and there are no meaningful differences between it and its brand name medicine. This means that the biosimilar is also considered as safe and effective as the brand name treatment. Both generic and biosimilar drugs are tested and compared to brand name drugs (that already have US Food and Drug Administration approval) in clinical trials. Also, both types of drugs might be less expensive treatment options than their brand name drugs.

To read more about biosimilars, go to page 1 at **iwmf.com/wp-content/uploads/2020/10/Torch_April2020.pdf.**

What is a patient registry?

A quote from John M. Mandrola, MD, is very useful here, "Science tells us what we can do, clinical trials tell us what we should do, and patient registries tell us what we are doing." A patient registry for WM collects patient-derived data on WM and manages and analyzes this information over time to help researchers better understand outcomes from the patients' perspectives and tailor better treatments. There are two patient registry projects for WM: the IWMF WhiMSICAL global patient-derived WM registry, and the Rory Morrison Registry Project of WMUK in the United Kingdom (an IWMF affiliate).

Information from the IWMF WhiMSICAL project can be found at **iwmf.com/wp-content/uploads/2021/05/WhiMSICAL-IWMF-international-affiliates-meeting-presentation_20210429.pdf**. Data from the Rory Morrison Registry Project in the UK is at **iwmf.com/wp-content/uploads/2022/01/Rory-Morrison-Report-2021-2-11-21-Final-Version.pdf.**

"Rare" Complications

What are some of the "rare" complications of WM?

Transformation to Diffuse Large B Cell Lymphoma (DLBCL) or Richter's Syndrome

In a small proportion of people with WM, some of the WM cells may change or transform into a

faster growing type of lymphoma called diffuse large B cell lymphoma, which has a more aggressive course with a new set of symptoms. Since all the WM cells do not transform, people have coexisting WM and DLBCL. Signs of transformation may include a sudden and rapid enlargement of a single lymph node, and/or the development of nighttime fevers or drenching sweats, and/or decreased IgM levels. The blood test levels for lactate dehydrogenase can rapidly rise. A tissue biopsy is required to establish the presence of transformation. Often, a PET (positron emission tomography) scan will show enhanced uptake in a transformed lymph node. Fortunately, diffuse large B cell lymphoma is a treatable form of lymphoma. One possible complication may arise because many people with WM have been exposed to various treatments over the years for their disease; for such people, there is the potential that some preferred drug treatments may not work any longer (inherent chemotherapy resistance). Treatment of people with diffuse large B cell lymphoma usually requires more intensive chemoimmunotherapy or possibly stem cell transplant.

Purine nucleoside analogs such as fludarabine and cladribine have been implicated as a potential risk factor for the development of DLBCL transformation. Fortunately, the risk is low, and it often occurs late. People with WM and their hematologist/oncologists should discuss this risk before reaching a decision to proceed with fludarabine or cladribine therapy. Treatment with purine nucleosides analogs is highly effective in the management of WM, and all treatments carry side effects and toxicities, so that a risk-versus-benefit assessment is warranted. DLBCL transformation can also occur in people with WM who have never been treated. Cancer cells are genetically unstable and, thus, can change over time. Therefore, it is possible for lymphomas to change from slow growing (WM) to aggressive (DLBCL) even in the absence of therapy; however, this risk is only for a very small percentage of people with WM.

The *IWMF Torch* magazine has published an article on DLBCL called "Late (and Rare!) Complications of Waldenstrom Macroglobulinemia by Dr. Morie A. Gertz, MD. This article is located at **iwmf.wpengine.com/wp-content/uploads/2020/10/Gertz3.pdf.**

Amyloidosis

Amyloidosis, when associated with WM, is a rare disorder characterized by organ dysfunction (usually kidneys and nerves, but also possibly heart, lung, and lymph node involvement) because of the buildup of misfolded protein deposits in these organs. There are characteristic signs and symptoms of amyloidosis in people with WM. When kidneys are affected by amyloidosis, elevated protein in the urine (proteinuria) may develop. This protein is not the typical monoclonal protein (i.e., IgM) that is seen in WM but is an increase in albumin (a healthy protein) that is being spilled into the urine because of dysfunctional kidneys caused by the amyloid deposits. This loss of albumin can lead to swelling (edema) in the legs or around the eyes. It can also lead to significant fatigue, low blood pressure, and an increased risk of blood clotting. Nerve damage related to amyloidosis can include peripheral neuropathy, such as numbness, tingling, and pain in the toes that moves upward to the feet, legs, hands, and arms. Nerve damage can also occur to the autonomic nervous system, which controls the inner workings of the body, including the regulation of blood pressure, the movement of the intestinal tract, and control of the bladder. When the autonomic nervous system is affected, the development of orthostasis (symptoms related to low blood pressure such as lightheadedness), new diarrhea or constipation, or changes in urination may occur. Amyloid deposits can be caused by conditions other than WM and are never normally found

in the body. Their presence always indicates an abnormal process. Treatment for amyloidosis associated with WM includes therapies that are like those used in WM, with some modifications.

The IWMF magazine, the *Torch*, has published an article called "IgM-Related Amyloidosis" by Dr. Shayna Sarosiek, which can be found on page 1 at **iwmf.com/wp-content/uploads/2022/01/Torch-Jan-2022_final_web.pdf.**

Cold Agglutinin Hemolytic Anemia

Rarely, the monoclonal IgM protein develops the unusual ability to bind to the surface of red blood cells. The red blood cell is the packet that carries hemoglobin through the circulation and delivers oxygen to all the tissues. On a routine blood count, you will notice that both the hemoglobin level and the red blood cell count are reported—these two measurements go hand in-hand. In individuals who develop cold agglutinin hemolytic anemia, the IgM protein, which is usually at a very low level (often under 1,000 mg/dL), will bind to the red blood cell surface, and the protein changes the red blood cell so that it becomes recognized by the body's immune system as being "different." Because it is "different," the red blood cell is subsequently removed from the circulation and destroyed, resulting in lowering of the red blood cell count and consequent anemia. The term "cold" in cold agglutinin is derived from the testing for this condition, which takes place on blood placed in the refrigerator at 38° Fahrenheit (less than 4° Celsius). "Agglutinin" or "agglutination" means that the red blood cells stick together and are seen as clumps in this refrigerated tube of blood. Confusion may arise if anemia is seen in a person with a monoclonal IgM protein. Both active WM cells in the bone marrow as well as cold agglutinin disease from IgM in the blood can cause a person to be anemic. Specialized testing is required to determine which disorder is causing the anemia.

When severe, the anemia of cold agglutinin disease can cause profound symptoms of weakness, shortness of breath, and fatigue. The severity of this anemia is quite variable, and there are many patients with this disorder who are candidates for watch-and-wait. However, when the anemia is severe and interferes with quality of life, treatment is appropriate. Previously, the most common treatments were identical to those used for WM. Recently, a new medication has been introduced that acts by blocking the protein from sticking to the red blood cell surface and therefore prevents the red blood cell from being removed from the circulation and destroyed. This medication is called sutimlimab (Enjaymo) and is given as an injection under the skin that can be self-administered at home.

The IWMF *Torch* magazine has published an article by Dr. Morie Gertz called "Overview of Cold Agglutinin Hemolytic Anemia and Cryoglobulinemia," located on page 1 at **iwmf.com/wp-content/uploads/2022/08/N27358-Torch-July-2022_web.pdf.**

Cryoglobulinemia ("Cryo")

This literally means "cold antibody protein in the blood" and refers to the fact that the IgM protein can combine with other proteins and form a single unit which can gel (precipitate) in the bloodstream, like Jell-O. These gel complexes, called cryoglobulins, can deposit in the linings of blood vessels and cause inflammation at a temperature below 37° Celsius (body temperature) and then re-dissolve upon warming. Cryoglobulinemia may develop for unknown reasons or may be associated with an underlying disease such as WM. Testing requires placing a sample of serum (non-clotting part of the blood) in the refrigerator for seven days to observe the formation of a gel. Treatment for cryoglobulinemia involves treating the underlying issue, the WM, and the inflamed blood vessels will improve.

The IWMF magazine, the *Torch*, has published an article called "Overview of Cold Agglutinin Hemolytic Anemia and Cryoglobulinemia" by Morie Gertz, MD. The article is located on page 1 at **iwmf.com/wp-content/uploads/2022/08/N27358-Torch-July-2022_web.pdf.**

Hypogammaglobulinemia

About 70% of people with WM have low levels of IgG and/or IgA immunoglobulins even at the time of diagnosis. Most WM-directed treatments bring down the IgG and IgA to an even lower level. Whether because of WM itself or as a side effect of treatment, the functions of the immune system are decreased, and that makes many people with WM more prone to repeated and/or serious infections. People with WM who have repeated, serious sinus or bronchial infections requiring antibiotics benefit the most from human intravenous immunoglobulin IgG (IVIG) replacement therapy. The IV stands for intravenous and the IG for immunoglobulin G (IgG or gammaglobulin). Replacement IgG can also be given subcutaneously (under the skin). It cannot be overemphasized that not all patients with low levels of IgG and/or IgA have repeated or severe infections. Furthermore, repeated, or serious infections can occur without low levels of IgG or IgA but for other reasons, such as neutropenia (low levels of another type of white blood cell that fights infection) or suppression of T cells (another important group of lymphocytes that play a vital role in active immunity).

The IWMF has published a Fact Sheet called "Human Intravenous Immunoglobulin (IVIG) Replacement Therapy," found at **iwmf.com/publications.**

Bing-Neel Syndrome (BNS)

When WM cells move out of the bone marrow, they tend to collect in certain organs, usually the liver, spleen, and lymph nodes. The presence of WM is generally restricted to these organs because the cells have a peculiar "stickiness" that keeps them within those specific sites. In rare instances (1% of people with WM), the WM cells can lose this "sticky" quality, gain access to the brain and spinal cord (central nervous system, or CNS), and cause symptoms associated with this involvement. How or why the WM cells access the CNS in some people, but not in others, is not well understood. In some people, Bing-Neel syndrome can occur as the first sign of WM, and in others, BNS occurs as a late development, usually after people have received multiple treatments for WM. Very rarely, BNS can be present in the absence of WM. The symptoms of BNS are diverse and can include brain-related symptoms (headaches, facial paralysis, seizures), spine-related symptoms (weakness or numbness in limbs, unsteady gait), or a combination of these. Rarely, the optic nerve can be involved, causing visual disturbances.

The definitive diagnosis of BNS is made by detecting WM cells in the patient's spinal fluid by means of a lumbar puncture (spinal tap). Brain and spine magnetic resonance imaging (MRI) are recommended in suspected cases of BNS, although in 10-20% of patients with suspected BNS, the brain and MRI tests might not show abnormalities, and the diagnosis is made solely on the presence of WM cells in the spinal fluid. In a portion of patients suspected to have BNS, the spinal fluid might not show abnormalities, and in this situation, the diagnosis of BNS is not definitive. In rare cases, the symptoms that prompted the initial evaluation resolve, and it is reasonable to observe without intervention. For patients who are symptomatic from BNS, treatment options should be discussed.

In theory, any treatment option for WM should be beneficial in BNS. However, the vessels in the CNS have an additional layer of protection called the blood-brain barrier (BBB), which prevents some molecules in the blood from reaching the CNS. Treatment options for BNS include chemoim-

munotherapy agents with easy access to the CNS (methotrexate, cytarabine, fludarabine, bendamustine) and BTK inhibitors. Ibrutinib is the BTK inhibitor most studied for BNS and is becoming the preferred initial therapy because of its high benefit and limited harmful side effects. Bendamustine can also be used and is effective. The aim of treatment for BNS is clinical improvement.

The IWMF magazine, the *Torch*, has published an article, "Bing Neel Syndrome" by Dr. Jorge J. Castillo, located on page 1 at **iwmf.com/wp-content/uploads/2022/03/Final-pdf.pdf**

Health Maintenance

Which vaccines should I get?

In the words of Stephen Ansell, MD, a hematologist/oncologist from Mayo Clinic, people with WM should "vaccinate, vaccinate, and then vaccinate" but be sure they are not live virus vaccines. Live virus vaccines use the weakened (attenuated) form of the virus, for example rotavirus, smallpox, measles, mumps, and rubella (MMR), intranasal form of influenza, and the chickenpox (varicella) vaccines; even though they are weakened, these live virus vaccines have the potential to cause the disease in people who are immunocompromised (including people with blood cancers). Non-live (inactivated) vaccines are fine to use as they are made from a protein, or other small pieces taken from a virus or bacteria. The shingles vaccine called Shingrix, the RSV vaccine, influenza shots, and the COVID -19 vaccines are not live virus vaccines, rather they are made from parts of the virus.

Should I get a COVID-19 vaccine?

Yes. Vaccination against COVID-19 is the most important preventive strategy against getting sick with the virus. People who have compromised immune systems from blood-based cancers, such as WM, are more susceptible to COVID-19 and are at a higher risk of severe complications, compared with the general population. Even with COVID-19 vaccination and boosters, patients with symptomatic and asymptomatic WM tend to produce lower titers (amounts) of antibodies against the virus, so getting every available vaccine and booster is considered essential, and if possible, should be performed before receiving treatment for WM. If a new vaccine or booster is offered during treatment, a temporary interruption before vaccination might be considered. Self-protection measures, such as N95 or KN95 mask wearing, social distancing, frequent hand washing, and avoiding crowds during periods when the immune system is especially compromised (low white blood counts, including neutrophils, and low IgG) or while undergoing treatment are highly recommended.

People with WM are candidates for pre-exposure antivirals if they are available, depending on the COVID-19 variants in the community. With few exceptions, oral antiviral drugs, such as Paxlovid, should be offered to patients with WM who have mild-to-moderate COVID-19 symptoms, regardless of vaccination status, WM status, or treatment, as soon as possible after a positive test and within five days of symptom onset. Co-administration of ibrutinib or venetoclax with Paxlovid should be avoided. Zanubrutinib should be stopped, or the dose adjusted during Paxlovid administration. If Paxlovid use is not desirable for a particular patient, other antiviral treatment alternatives should be explored. People with asymptomatic COVID-19 should not interrupt treatment with a BTK inhibitor, such as ibrutinib, zanubrutinib, acalabrutinib, tirabrutinib, or pirtobrutinib. In those with symptomatic COVID infections, these treatments should only be interrupted temporarily as needed due to interactions with specific antivirals.

Should I get the RSV vaccine?

RSV (respiratory syncytial virus) vaccines are safe for people with WM who are eligible to get the shot. The US Centers for Disease Control and Prevention (CDC) recommends RSV vaccines to protect adults ages 60 and older from severe RSV infections. The vaccines are non-live virus vaccines that contain a protein that is part of the RSV virus. The RSV vaccine cannot cause an infection in people with a weakened immune system, rather it recognizes the actual RSV virus and, if/when it encounters it, helps prevent severe disease. For now, one dose of the vaccine is recommended and appears to provide some protection for at least two RSV seasons. Additional evaluation is planned to assess how long the protection lasts and whether additional doses will be needed.

Should I get the shingles vaccine?

Yes. The non-live virus shingles vaccine called Shingrix should be considered after consultation with your doctor. It is given as two shots, with the second shot administered 2-6 months after the first one. Current guidelines do not recommend re-vaccination with Shingrix. In some cases, it may be preferable to stay on prophylactic oral anti-viral medication, such as acyclovir, to help prevent shingles.

Should I get a flu shot? What about the nasal mist vaccination?

You should get a flu (influenza) shot at least annually. This is a non-live virus vaccine and is therefore safe to use. The nasal mist vaccination called FluMist is a live virus vaccine and is not recommended for people with WM. Experts in WM may also recommend that people with WM should receive two high-dose quadrivalent influenza shots, separated by at least 30 days, rather than a single influenza shot. This can help people with WM have a stronger immune response against the flu.

Should I get the pneumonia vaccine?

In the US, the Centers for Disease Control and Prevention recommends that all adults over the age of 65 receive the pneumococcal polysaccharide vaccine (PPSV) and that adults younger than 65 receive it if they have a condition that lowers the body's resistance to infection. Lymphoma, including WM, is listed as one of these conditions. Re-vaccination is recommended five years after the first dose for individuals under the age of 64 who are at high risk for pneumococcal infection or rapid antibody loss.

What should I do to protect my immune system?

Wash hands frequently and avoid touching hands to the face, especially during cold and flu season. Keep up to date on COVID-19, flu, RSV, and pneumonia vaccinations and boosters. Self-protection measures, such as N95 or KN95 mask wearing, social distancing, frequent hand washing, and avoiding crowds during periods when the immune system is especially compromised (low white blood counts, including neutrophils, and low IgG) or while undergoing treatment are highly recommended. Eat a healthy, well-balanced diet and get the proper amount of sleep. Avoid close contact with people who are exhibiting obvious symptoms of colds, flu, or other diseases. Be sure to wash raw fruits and vegetables before eating and make sure that meat and seafood are cooked to the proper temperature.

Will I still be able to travel?

Travel should still be possible but perhaps with some limitations or additional precautions. Enclosed places like airplanes, crowded airports, and public transportation are sources of infection, especially during COVID-19, cold, and flu season. If WM is progressing to a point where it requires treatment or if someone is currently on treatment

that can adversely affect the immune system, a hematologist/oncologist should be consulted for any travel restrictions that are necessary. Consultation is suggested if travel is planned to unusual or exotic destinations where specific disease alerts might be in effect or where additional vaccinations are required. It is important to keep up to date on recommended vaccinations and boosters and exercise common sense by frequent hand washing, wearing N95 or KN95 masks in crowded areas, social distancing, and being careful about eating fruits and vegetables in areas that are prone to food- and water-borne diseases.

Quality of Life

What can I do to help myself and improve my quality of life?

Upon receiving the diagnosis of WM, many questions often surface, such as: *Why me? How did this happen? How long will I live? How will my life, work, relationships change? Will I be around to see my children grow up?* Experiencing many different feelings—even all at once—is an expected part of having cancer. People often face an array of emotions as they cycle through the adjustment process. When starting treatment, many emotions may arise and continue even after it ends. Finding the right kind of support that best fits your personal needs is key. Joining a support group, calling a friend or family member, reaching out to a spiritual or community leader, or seeking professional help from a licensed therapist can be important coping strategies.

IWMF offers many support resources, including 1:1 phone calls/emails, support groups, wellness programs, and online discussion groups for which you will find links below, along with helpful resources from other organizations that have been vetted by IWMF. With IWMF, you are never alone!

The IWMF Education Committee has curated many useful references to help the newly diagnosed take charge of the diagnosis of WM through a holistic approach to care. From emotional and physical wellness to helping manage financial issues, these resources can assist in self-healing, improve the quality of life, and foster health promotion so that treatments can be more effective with fewer side effects. These resources can be found on the IWMF website at **iwmf.com/wellness-resources.**

Fitness

There is increasing evidence that people who are fit (as opposed to frail) do better with treatment. People who are fit can tolerate their treatment with fewer complications, and this hopefully will translate into better outcomes. Daily activity in the form of walking, as briskly as is physically possible without the risk of falls, is strongly encouraged. There is also increasing evidence that obesity is linked with the development of cancer.

Diet

There is no evidence that special diets are beneficial for WM. In general, a varied and wide-ranging diet with protein and lots of varied fruits and vegetables is the best way to obtain needed nutrients. At times, a diet change is necessary. Some medications that are used to treat WM may have reduced effectiveness if taken with certain foods, such as Seville oranges or grapefruit. One should consult their healthcare team if there is uncertainty about what to eat. Certain vitamin deficiencies are common in WM, for reasons unknown. These vitamins (B12, folate, vitamin D) are easy to replace. If someone is developing anemia that cannot be accounted for by a buildup of WM cells in the bone marrow, it is worth checking vitamin B12 and folate levels. If they are low, they can be replaced by pills or injections through a vein. Another correctable cause of anemia in WM is iron deficiency. This can be remedied by intravenous infusions of iron.

Any diet or supplement that recommends amounts more than the recommended daily allowance (RDA) should be avoided unless they are prescribed for a specific reason by a doctor. Such excesses can affect WM in ways that cannot be predicted, and they can interfere with treatment for the WM. Attention to diet (reducing total non-nutritive calories and fat) is important for overall health, and maintaining a normal weight contributes to being fit. Many people ask about sugar. There is no evidence that sugar feeds cancer. However, consumption of sugar is calories wasted and has little nutritive value. Sugar raises insulin levels which contribute to the deposition of fat in the body and merely adds to the total caloric intake in a day. Eating well-balanced meals, maintaining normal body weight, and aerobic activity are important for improving outcomes with WM.

Are there any foods that are beneficial or harmful to eat while in treatment? Are there any alternative medicine treatments for WM?

People considering complementary and alternative medicines should be very careful about their use. Mega-vitamins, over-the-counter medications, and so-called health food remedies should always be discussed with one's physician. Some of these substances may alter the effectiveness of conventional treatments for the disease or may worsen treatment side effects. While some complementary and alternative therapies, such as yoga or meditation, are helpful in dealing with the psychological issues associated with a chronic health situation, other so-called alternative therapies have the potential to be harmful. For more information about complementary and alternative treatments, visit the IWMF website at **iwmf.com/complementary-alternative-and-integrative-medicine/.**

Sleep/Stress

It is also important to get adequate amounts of sleep (eight hours is optimal) and to pay attention to stress level and emotional state when coping with a diagnosis of WM. Fatigue is a very common symptom in WM and has many causes that can change over time, depending on general health, medications associated with treatment, and the status of the disease.

Support

There are many sources of support from IWMF, such as local support groups (US and international), online discussion forums (IWMF Connect and the Facebook WM Support Group), and LIFELINE, a one-on-one connection with peer volunteers for specific treatments and WM-related issues. These services can be found on the IWMF website at **iwmf.com/get-support.** Psychological counseling can be very helpful for anyone whose emotional distress is impacting their quality of life.

Organization

What types of medical records should I keep?

Keeping an organized file of medical information is an important element of being an engaged and informed patient. It is one way to improve one's quality of care, particularly if being seen by more than one doctor, seeking a second opinion, or changing doctors. It helps ensure safe and effective management of WM, as well as general health. One should keep information pertaining to general medical history, including health history with information on past procedures/surgeries, illnesses, and injuries; family history, including significant medical issues, such as cancer, heart disease, diabetes, etc.; current medications or supplements; allergies

(including drug, food, latex, and/or seasonal allergies); and immunizations (with dates and types). With WM, there are certain pieces of information that should also be in a file:

- Medical report when initially diagnosed with WM.
- Pathology reports from bone marrow and/or other biopsies.
- Imaging test results (X-rays, CT, PET scans) – Include both the written report and the actual images, which are stored digitally and can be obtained as a digital file from the medical facility performing the imaging. These images may not be required for patients who are asymptomatic.
- Drug treatments – List the drug(s), dosage(s), frequency, duration, and start and stop dates; note any side effects experienced.
- Other therapies or procedures, such as plasmapheresis with dates and side effects.
- All blood and other laboratory test results – For example, complete blood count (CBC) and further breakdown of values (differential), comprehensive metabolic panel (CMP), 24-hour urine tests, genetic results from the bone marrow aspirate (MYD88, CXCR4, TP53), free light chains (kappa and lambda and the kappa/lambda free light chain ratio), immunoglobulin levels, serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE), serum viscosity (SV) if performed for symptomatic hyperviscosity, urine protein electrophoresis (UPEP), beta-2 microglobulin, lactate dehydrogenase, iron, B12, folate , cryoglobulins, cold agglutinins (if performed), amyloid results (if performed), and CD4 counts (if performed).

What about organizing my medical bills?

It is also important to keep organized records of medical bills, payments, and insurance claims. Access to online tracking and other tools may be provided by one's insurance company, employer, Medicare, or Medicaid. Organizing records becomes essential if one has questions about insurance coverage or billing disputes. Copies should be kept of the following information related to medical treatment, including:

- Itemized bills
- Payment receipts
- Insurance explanations of benefits (EOBs)
- Correspondence with insurance companies
- Letters of medical necessity
- Prescription cost/payments
- Receipts for out-of-pocket expenses (parking fees, meals, travel, lodging, etc.)

Being able to easily retrieve information when, where, and how it's needed can lower the stress of having WM, so it's important to keep these files from the start of diagnosis. There are a wide variety of organizations that provide financial assistance to patients with cancer. For information about financial assistance for the expenses associated with WM, go to **iwmf.com/financial-assistance-2.**

International Waldenstrom's Macroglobulinemia Foundation

Website: **iwmf.com**
Email: **info@iwmf.com**
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IWMF, the only international organization dedicated solely to Waldenstrom's macroglobulinemia (WM), is a patient-founded and patient-driven nonprofit with a simple but compelling vision and mission.

VISION: A world without WM.

MISSION: Support and educate everyone affected by WM to improve patient outcomes while advancing the search for a cure.

IWMF is committed to creating a world without WM by finding a cure. Since 1999, IWMF has invested more than $30 million USD in WM research projects throughout the world. Thanks to this research, WM patients are living longer and have better treatment options that can lead to longer-lasting remissions with fewer side effects.

Visit the IWMF website to:

- Download a free Newly Diagnosed Info Pak.
- Learn about WM and download free publications available in multiple languages.
- Find curated resources to help support your mental, physical, and financial health.
- Join a local IWMF Support Group or IWMF International Affiliate.
- Refer to the IWMF Directory of Physicians available for consultations or second opinions.
- Subscribe to the IWMF *Torch*, our free quarterly magazine.
- Participate in the annual IWMF Educational Forum or our online webinars.
- Join IWMF Connect, an online community offering a wide variety of moderated WM-related email discussions, or the IWMF Support Group on Facebook.
- Find contact information for our partner organizations.

IWMF relies on donor contributions to fulfill its mission, and we welcome your support. You can contribute to the organization by visiting our website or by mailing a check to:

International Waldenstrom's Macroglobulinemia Foundation
6144 Clark Center Avenue
Sarasota, FL 34238

IWMF is a 501(c)(3) tax-exempt nonprofit organization, Fed ID #54-1784426

Notes

IWMF

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