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# Infections in Patients with Multiple Myeloma: Epidemiology, Risk Prediction, and Prevention Strategies - A Review

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## ABSTRACT

Infections are a leading cause of morbidity and premature mortality in patients with multiple myeloma (MM). Patients with MM face a 5–7-fold increased risk of bacterial infections and even a 10-fold higher risk of viral infections compared with the general population. Impaired humoral responses, lymphocyte dysfunction, or hypogammaglobulinemia contribute to secondary immunodeficiency. The risk of infections is particularly high during the first months after diagnosis and remains elevated while receiving treatment. The introduction of novel therapies, including targeted agents such as bortezomib, daratumumab, as well as CAR-T and bispecific antibodies, has changed the management of MM by bringing new infection related challenges. Risk prediction tools, antimicrobial prophylaxis, vaccination strategies and monitoring viral infections are essential in a preventive approach. This review summarizes current evidence on the epidemiology, risk factors, pathogenic mechanisms, and recommendations for the prevention and management of infectious complications in patients with MM.

**Keywords:** multiple myeloma, infections, treatment strategies, epidemiology, prophylaxis

## 1. INTRODUCTION

One of the most common malignancies in hematology is Multiple Myeloma (MM). It is known as the second most frequent disease in hemato-oncology, described as the proliferation of plasma cells, mostly in the bone marrow, connected with the monoclonal protein secretion. It has been reported to be around 5 to 7 cases per 100000 people globally (Teh et al., 2015).

Infections are still the great majority cause of mortality among patients with MM and have a variety of origins. Not only because of the disease itself, due to impaired function of lymphocytes B, causing a reduction in levels of immunoglobulins, but also due to the variety of treatments the patients are receiving. On the other hand, an important change in the infection profile has been observed in association with the introduction of new therapies. In particular, CAR-T

cell therapy or bispecific antibodies result in an increase in viral infections (Akhmedov et al., 2024).

The aim of our article is to review and summarize the knowledge about epidemiology, sources of infections, and their hypothetical complications in patients with MM. Also, we would like to discuss possible strategies and guidelines on this topic, along with an indication of the most common sources of infections.

## 2. REVIEW METHODS

Our review was based on studies identified through searches of major scientific databases such as PubMed and PubMed Central. The research focused on infection epidemiology in MM, prophylaxis, treatment and prevention strategies. We analyzed the articles and summarized in this review. In our database research we used the following keywords: multiple myeloma, infections, treatment strategies, epidemiology, prophylaxis. The time covered by this review included articles published between January 2010 and August 2025. What is more, case reports, conference abstracts, non-peer-reviewed materials, and studies written that were not directly associated with infections in MM were excluded from further analysis as shown in PRISMA diagram (Figure 1).

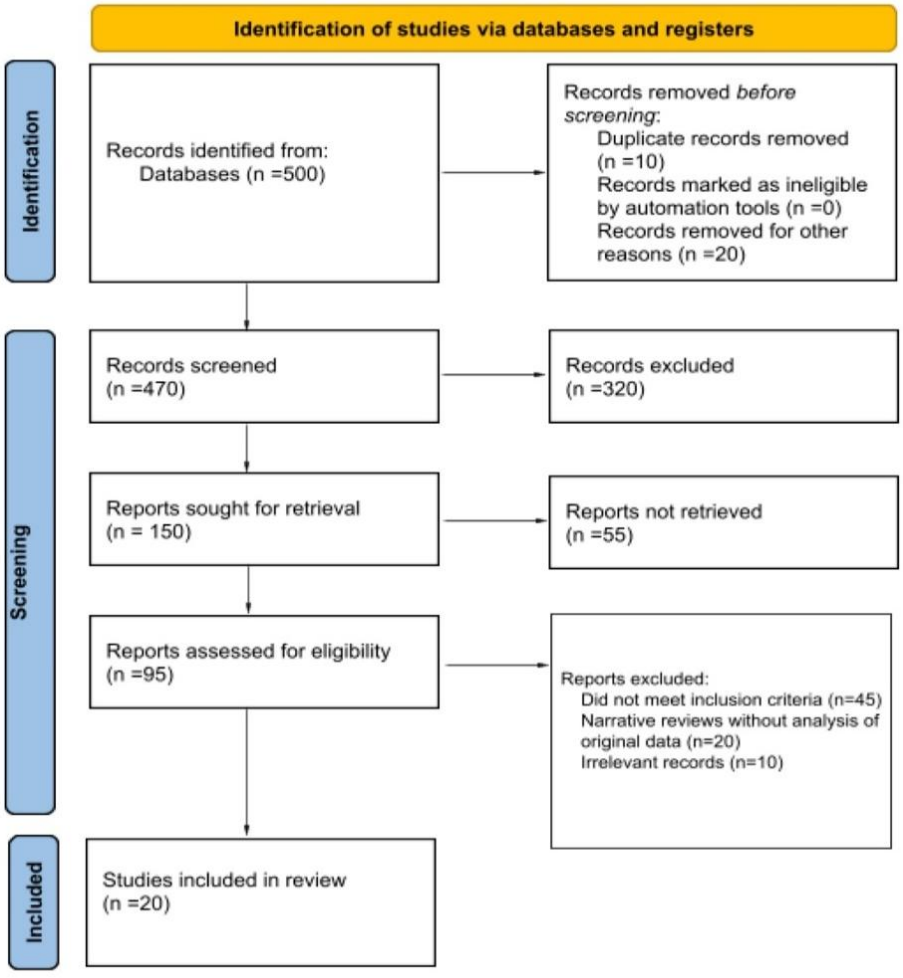


**Figure 1**. PRISMA flow diagram

## 3. RESULTS & DISCUSSION

**Epidemiology of infectious complications**

The population-based study from Sweden described that the risk of any infection is 7 times remarkably increased compared to the control group, with an 11 times higher risk for developing bacterial infection and 18 times for viral infection (Blimark et al., 2015). Additionally, in MGUS, a condition that might precede MM, the risk of infection has been elevated. Also, the risk of infection is constantly increasing despite the introduction of new therapies.

**Spectrum of infections in Multiple Myeloma**

Bacterial infections are the great majority among patients with MM. The most common pathogens are Gram-positive bacteria, mostly Streptococcus pneumoniae and Staphylococcus aureus, but also Gram-negative bacteria such as Escherichia coli. Sepsis and pneumonia are the most common manifestations of bacterial infection in the first months after diagnosis.

Viral infections, especially reactivation of latent viral infections, are a big concern in patients with MM. It is observed that the varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), or hepatitis B virus is the most common one (Teh et al., 2015). Fungal infections, although are not very frequent, might also become a life-threatening issue. The most common pathogens are Candida species, mainly because of observed neutropenia, or Aspergillus species (Raje et al., 2022).

**Mechanisms of immunodeficiency in Multiple Myeloma**

MM is characterized by hypogammaglobulinemia. This dysfunction is present in a great majority of patients with newly diagnosed MM and results from many mechanisms. One of them is suppression of normal immunoglobulins. Pathological plasma cells inhibit the correct antibody production. Moreover, an increased immunoglobulin G catabolism is observed. Another one refers to impaired B-cell lymphocytes maturation that led to a reduction in number and damaged function. Hypogammaglobulinemia leads to a significant decrease in the ability to fight pathogens, especially opportunistic ones (Li et al., 2019).

Despite the dominance of humoral immune defects, cellular immunity is also significantly impaired. For example, there is a reduced CD4+ T-cells lymphocyte count or CD8+ T-cells lymphocyte impairment, effectively reducing the ability to kill infected cells. What is more, Natural Killer (NK) cells are also impaired in function and reduced in count (Li et al., 2019).

Finally, there is a dysfunction of dendritic cells, causing reduced ability to present the antigens, a necessary process in the activation of T lymphocytes. Also, neutropenia lowers the ability to fight infections. At the end, there is a slower inflammatory response caused by decreased production of pro-inflammatory cytokines. All these things are caused by impaired innate immune dysfunction (Allegra et al., 2021).

The treatment of MM is also an important source of immune dysfunction. Proteasome inhibitors such as Bortezomib have cytotoxic effects on cancer cells and lead to much more sensitivity to apoptosis-inducing mechanisms than on healthy cells. Although it might be the reason for additional hypogammaglobulinemia, reactivation of latent infections, and worsen the T lymphocytes' function. Lenalidomide, the immunomodulatory drug, has antitumor, antiangiogenic, immunomodulatory, and proerythropoietic effects. At the same time, it may result in neutropenia and affect lymphocytes, leading to their dysfunction. Daratumumab, a monoclonal antibody anti-CD38 targeting human immunoglobulin G kappa. It is suggested that CD38 plays a role in the regulation of pro-inflammatory responses in immune cells by affecting leukocyte recruitment, macrophage activity, and dendritic cell migration, ultimately leading to impaired T- and B-cell function. It might be an explanation for the observed immunosuppression in some patients during the treatment. As a result, there is an increased risk of viral infections or bacterial infections (Mikulski et al., 2024). The newest therapies, such as Bispecific Antibodies and CAR-T, bring new challenges. Both viral and bacterial infections have a significant greater risk. During the treatment, cytokine release syndrome (CRS) or Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) additionally increases sensitivity to infections. This is the reason close monitoring is required (Mohan et al., 2023).

**Risk Factors for infection in multiple myeloma**

In patient- related risk factors, we can include older age (over 80 years old) but in general age over 65 is independed risk factor, sex (man have a higher risk of infection than women), patient's functional status rating by ECOG scale in oncology. While an ECOG higher than 1 is an independent risk factor, an ECOG 2-4 is associated with a 3-fold higher risk (Raje et al., 2022).

In disease-related risk factors, there are plasma cell disorders clearly increasing the chance of any infection, advancement of the disease, measured by the ISS international staging system (ISS), where ISS III is a general risk of infection. Additionally, biological markers such as elevated lactate dehydrogenase (LDH), C-reactive protein (CRP), or decreased levels of hemoglobin also increase the chance of infection. At the end, renal failure with a glomerular filtration rate (GFR) with creatine level higher than 2 mg/dl is also a factor for a higher chance of infection (Raje et al., 2022).

Treatment-related risk factors are also important. Glucocorticoids, cytotoxic chemotherapy, immunomodulatory drugs, and autologous Hematopoietic Stem Cell Transplantation (aHSCT) affect the immune system and significantly decrease the immune system's response to fight infections. (Raje et al., 2022). Especially patients undergoing aHSCT should be under a careful observation.

The GEM-PETHEMA score is a clinical tool used in MM to predict an early risk of severe infection. It contains four simple factors: albumin level (less than 30 g/L), ECOG score higher than 1, male sex, and myeloma type (non- IgA myeloma). Scores 0 to 2 indicate low risk of infection, scores 3 indicate intermediate risk, and scores 4 indicate high risk (Encinas et al., 2022).

Also, there are a couple of risk factors connected with premature mortality, such as male sex, hypoalbuminemia, elevated calcium levels, and elevated LDH levels (Hsu et al., 2015).

**Prevention Strategies**

***Antibiotics***

Antibiotic prophylaxis is not routinely recommended in all patients with MM. However, there are a few cases in which it might be considered. For example, patients with neutropenia, especially prolonged neutropenia, patients who were classified as high risk of infection, or patients with a history of recurrent bacterial infection. In first-line options, we should consider an antibiotic with a wide spectrum of action, such as Levofloxacin with 500 mg once per day dosing (a preferred therapy) or Norfloxacin with 400 mg three times per day as an alternative option. Antibiotics should be used during the first 3 to 4 months after diagnosis or until the neutrophil count returns to a normal level. Clinical studies show that antibiotics used in prevention can significantly reduce the chance of infection. At the same time, careful monitoring of the patient's clinical state and bacteria's resistance to antibiotics should be provided (Jung et al., 2014).

***Anti-viral medicaments***

Viral infection prevention is also essential, especially for VZV or HSV viruses. It should be considered in patients with cases like: patients receiving proteasome inhibitor-based therapy, patients treated with bispecific antibodies, and patients with positive serology for HSV or VZV. Acyclovir with a daily dose of 400 mg is a standard option (patients with renal failure should have a reduced dose up to 200 mg per day). Alternative options are Valacyclovir with 250-500 mg per day and Famciclovir with 500 mg once a day. Viral infections prevention should be continued for the whole time while being under MM treatment and should be considered even after, if necessary (Raje et al., 2023).

Other viruses such as Influenza, respiratory syncytial virus (RSV), HBV, parainfluenza, or CMV should also be considered as a potential threat (Teh et al., 2015). Among patients with daratumumab therapy, the chance of CMV reactivation was reported to be 33%, compared with 4% in the control group. It shows why viral infection prevention is very important (De Novellis et al., 2024).

***Protective vaccinations***

Vaccination strategies are another essential thing. In general, vaccinations should be administered before the start of any MM therapy, especially while the disease is well controlled. Otherwise, a response to the vaccine might often not be optimal during already administered treatment. What is more, it is important to know that after autologous stem cell transplantation, patients might be vaccinated again. The highly recommended vaccine is the annual inactivated influenza vaccine. Another one is pneumococcal vaccination with 23-valent pneumococcal polysaccharide vaccine (PPSV23) or 13-valent pneumococcal conjugate vaccine (PCV13). The recommended schedule is PCV 13 followed by PPSV23 after a one-year interval. Along with the COVID-19 pandemic, vaccination for this viral infection should be considered. It is preferred to use mRNA vaccines, and the best option is a series of 2-3 doses and then another booster dose. Vaccination against VZV is also recommended, and the recombinant vaccines are preferred over the live attenuated, most likely administered as two doses given up to six months apart (Ludwig et al., 2022).

Despite not optimal reaction due to plasma cells malfunction and low antibody responses, vaccination provides protection against severe infections. Also, it is important to know that live vaccines and vaccination during severe periods of immunosuppression are not recommended (Ludwig et al., 2022).

***Immunoglobulin replacement therapy***

Intravenous immunoglobulin (IVIg) therapy should be considered in indications like patients who experience recurrent infections and have hypogammaglobulinemia (IgG level less than 400-500 mg/dL), patients who received CART-T cell or bispecific antibodies therapy and developed a severe hypogammaglobulinemia. Also, patients with interrupted treatment due to infectious complications should receive IVIg. The administration of IVIg should be 200-400 mg/kg every three to four weeks. The alternative option is subcutaneous immunoglobulin (SCIg) with a dose of 100-200 mg/kg administered weekly (O'Donnell et al., 2025).

Real-world studies showed that immunoglobulin replacement therapy is associated with a meaningful improvement in immunoglobulin levels, a reduction in the incidence of severe and hard to heal infections, and decreased use of any antipathogen medications (O'Donnell et al., 2025).

*Hematopoietic Support*

Granulocyte Colony-Stimulating Factors (G-CSF) might be helpful thing during the neutropenia period. It is recommended for patients who develop grade three or four neutropenia, febrile neutropenia (FN), or are expected to have a long neutropenia time longer than ten days. Filgrastim, a short acting G-CSF, should be administered with a 5 μg/kg/day dose subcutaneously and Pegfilgrastim a long acting G-CSF, with a dose of 6 mg as a single injection per chemotherapy cycle (Cerchione et al., 2021).

Available clinical data show that long acting G-CSF preparations are associated with fewer early infectious complications and a lower risk of treatment delays when compared with conventional short-acting G-CSF formulations (Cerchione et al., 2021).

At the end, it is important to mention that not only doctors but also patients should receive recommendations about prevention strategies. Detailed explanations about this issue may increase compliance and be helpful in managing infections in MM.

*Management of Infectious Complications*

The possible diagnostics of bacterial infections include taking a blood culture in patients with fever, chest imaging while suspecting pneumonia, and laboratory tests including basic biochemistry and morphology. The treatment in acute infection when the pathogen is not yet identified should be focused on a wide spectrum of antibiotics, such as fluoroquinolones orally, plus a beta-lactam agent, for example, piperacillin or tazobactam intravenously, or carbapenems. When the pathogen is identified, it is recommended to de-escalate the antibiotic therapy. It should always be guided by an antimicrobial susceptibility test (Freifeld et al., 2011).

For viral infections, most likely VZV or HSV, it is recommended Valacyclovir with a 1000 mg dose three times a day for at least 7-10 days. Another option is acyclovir intravenously with a dose of 10-15 mg/kg 3 time a day if there is a situation of severe infection (Gnann Jr et al., 2007).

CMV infection requires Ganciclovir or Valganciclovir therapy to prevent severe and potentially life-threatening disease (Tan et al., 2014).

Fungal infections also might be a big challenge. For candidemia, it is recommended to use Fluconazole intravenously or orally. Invasive Aspergillosis is treated with voriconazole or liposomal amphotericin B if treatment is insufficient or fluconazole resistance. Pneumocystis jirovecii Pneumonia (PCP) is a unique and very serious infection treated with Trimethoprim and sulfamethoxazole for a prolonged period (for 14-21 days). Lower doses might be used for the prevention (Liu et al., 2016).

**Other important issues**

It is important to mention opportunistic infections as a severe and life-threatening problem. One of them is Tuberculosis (TB). Patients with MM have a 3–4 times higher risk of developing TB compared with the general population, with a key risk factor including older age or corticosteroid therapy. It is a recommendation to screen for latent TB with the tuberculin skin test (TST) before starting therapy and then a chest X-ray if the TST is positive, along with intensive antibiotic therapy before MM treatment. PCP is also one of them, especially when CD4 plus lymphocytes count is under 200 cells/μL or when receiving high dose corticosteroid treatment (Raje et al., 2022).

Early infection monitoring might be an essential thing to deal with complications and avoid severe infections. Routine laboratory test before each chemotherapy cycle, Screening for viral antigens, taking cultures from blood and urine seems to be a key solution (Raje et al., 2022). To conclude, the summary of our study regarding infectious complications in MM along with epidemiology, risk prediction and prevention strategies is presented in Table 1.

**Table 1**. Study summary of infectious complications in multiple myeloma.

| Category | Key Information |
|---|---|
| **Population** | Multiple Myeloma patients |
| **Infection Risk** | 7-fold increased (any), 11-fold (bacterial, 18-fold (viral) |
| **Bacterial Pathogens** | S. pneumoniae, S. aureus, E. coli |
| **Viral Pathogens** | VZV, CMV, EBV, HBV |

| | |
|---|---|
| **Fungal Pathogens** | Candida spp., Aspergillus spp. |
| **Risk Factors** | Age >65, male sex, ECOG >1, ISS III, elevated LDH/CRP |
| **Risk Score** | GEM-PETHEMA: 0-2 (low), 3 (intermediate), 4 (high) |
| **Antibiotic Prophylaxis** | Levofloxacin 500 mg/day x 3-4 months |
| **Antiviral Prophylaxis** | Acyclovir 400 mg/day for VZV/HSV |
| **Vaccinations** | Influenza, PCV13 + PPSV23, COVID-19 mRNA, VZV |
| **G-CSF Support** | Pegfilgrastim 6 mg per cycle |

## 4. CONCLUSION

Infections remain a leading cause of morbidity and mortality in patients with MM. Despite major advances in cancer therapy, infectious complications continue to be a significant clinical challenge and need a complex approach to prevention, monitoring and treatment. There is a need for risk stratification by using a scoring system, for example the GEM-PENTHEMA to identify patients with a high risk of infection. The introduction of CAR-T cell therapy and bispecific antibodies presents new challenges for infection profiles, underscoring the need for further research and optimized preventive strategies. Future directions should focus on developing more precise risk prediction tools. Therefore, targeted prophylaxis for each bacterial, viral and fungal infection must be provided. A proper vaccination strategy is also essential. Regular screening for pathogens, particularly opportunistic pathogens, is recommended in patients with newly diagnosed MM or those receiving the latest therapies. Immunoglobulin replacement by IVIg should be considered in patients with hypogammaglobulinemia and recurrent infection. At the end, hematopoietic support by using G-CSF should be administered to prevent a prolonged neutropenia. Additionally, we believe that education in this area is needed for both patients and doctors of other specialties. Adopting this strategy can improve patient management and may lead to better overall treatment results for patients with MM.

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**Authors' Contributions**

Conceptualization & Methodology: Kacper Kopeć, Małgorzata Gasińska-Franas
Formal Analysis: Gabriela Szubert, Marta Ciszewska, Kacper Kopeć
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Writing – Review & Editing: Kacper Kopeć, Gabriela Szubert
All authors have read and agreed with the published version of the manuscript.

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**Ethical approval**

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**Conflict of interest**

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

**Data and materials availability**

All data associated with this study will be available based on reasonable request to the corresponding author.

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