The intent of this handout is to provide background information regarding the risks of infections in multiple myeloma and management guidelines. This handout is not intended to provide treatment guidance for patients.

INFECTION RISK IN MULTIPLE MYELOMA

Risk factors for infection in multiple myeloma include:[1]

Patient-related

- Age ≥65 years
- Male sex
- Neutropenia
- Elevated serum lactic dehydrogenase levels
- Pathogen exposure history
- High tumor burden
- Disease stage
- Immune cell dysfunctions (eg, B cells, natural killer cells)
- Comorbidities (eg, renal dysfunction)

Treatment-related

- Lines of therapy
- Therapy type
- Antigen target
- Regimen combinations
- Treatment intensity (eg, cycles, dosage)

Consider advising patients receiving treatment for multiple myeloma about the risk of infection, as well as the signs and symptoms associated with it.

Treatments may increase risk of infection[1-4]

Anti–multiple myeloma treatments result in cumulative immunodeficiencies that can increase the risk of infections.[1,2] Anti-myeloma therapies that specifically target the B-cell compartment are associated with higher-grade infections, including grade ≥3 infections[3,4]

Stem cell transplant[1]
Chemotherapy[1]
Glucocorticoids[1]
Immunomodulators[1]
Checkpoint inhibitors*[5]
Small-molecule inhibitors (eg, SINEs, PIs)[1]
Antibody-drug conjugates*[1]
T cell–engaging therapies (bispecifics, CAR-T)[1]

*Not currently available[6,7]

Some multiple myeloma therapies may be associated with adverse reactions that increase risk of infection including:[8-12]

- Cytopenia
- Hypogammaglobulinemia
- Cytokine release syndrome
- Immune effector cell-associated neurotoxicity syndrome
- Deficient humoral immunity

Types of infections may include:[1,9]

- COVID-19
- Cytomegalovirus infection
- Fungal infections
- Gram-negative bacterial infection
- Gram-positive bacterial infection
- Hepatitis B
- Hepatitis C
- Herpes zoster
- Respiratory virus

Because different multiple myeloma treatments can provide unique infection management recommendations, it is important to consult individual product labeling to familiarize yourself with what to expect and what to do when infections occur.

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CONSIDERATIONS FOR INFECTION PROPHYLAXIS AND MANAGEMENT[1]

Prophylaxis[1]

Consider the following:

- Updating patient's immunization status[1,10]
  - SARS-CoV-2 vaccine (mRNA-based)
  - Influenza (inactivated)
  - Pneumococcal conjugate
  - Pneumococcal polysaccharide
  - Diphtheria/tetanus/acellular pertussis
  - Haemophilus influenzae type B
  - Hepatitis A
  - Hepatitis B
  - Varicella zoster (non-live adjuvant) in VZV seropositive patients, >50 years
- Using inactivated vaccines in patients with multiple myeloma[1]
- Immunoglobulin replacement[1]
- Patient education to avoid pathogen exposure[1]

Immunosuppressed patients may have diminished vaccine responses and increased risk of viral shedding (eg, for COVID-19).[8,13]

Monitoring[1]

Consider cytokine release syndrome (CRS) when patient presents with fever. CRS and infections may present similarly and it is important to consider CRS when assessing for infection.

Management[14]

Consider drug interactions when managing infections in patients undergoing anti-multiple myeloma treatments (eg, CYP450 competitors/inducers).

IMWG recommendations for risk-adapted antimicrobial prophylaxis in patients with multiple myeloma[1]

Risk level	Bacterial	Fungal	Viral
Low	None	None	None unless prior herpes simplex virus episode, in which case use acyclovir
Intermediate	Consider levofloxacin* 500 mg once daily	Consider fluconazole† or micafungin in the setting of severe mucositis and prolonged neutropenia (absolute neutrophil count ≤100 cells per µL for ≥7 days)	For patients who are seropositive for herpes simplex virus or herpes zoster virus, provide acyclovir (400 mg or 800 mg orally twice daily for herpes simplex virus, and 800 mg orally twice daily for herpes zoster virus) or valacyclovir (500 mg orally twice daily)
High	Consider levofloxacin* 500 mg once daily	Consider fluconazole† or micafungin in the setting of prolonged neutropenia (absolute neutrophil count ≤100 cells per µL for ≥7 days) and severe mucositis; consider prophylaxis with voriconazole† or posaconazole† for patients with an absolute neutrophil count ≤100 cells per µL for >7 days; consider prophylaxis against *Pneumocystis jirovecii* pneumonia with trimethoprim–sulfamethoxazole or alternative agents, as clinically indicated‡	For patients who are seropositive for herpes simplex virus or herpes zoster virus: Provide acyclovir (400 mg or 800 mg orally twice daily for herpes simplex virus and 800 mg orally twice daily for herpes zoster virus) or valacyclovir (500 mg orally twice daily) For patients who are seropositive for HBV, the risk of reactivation depends on HBV serostatus and type and duration of immunosuppressive therapies For patients at intermediate to high risk of HBV reactivation, consider prophylaxis; for patients at low risk, consider early preemptive treatment.§ Use tenofovir or entecavir, rather than lamivudine, for treatment and preemptive purposes and select tenofovir in patients with previous exposure to lamivudine; maintain antiviral therapy for several months and monitor HBV viral load. Consider stopping antiviral agents when HBV viral load normalizes and stopping immunosuppressive agents

*Levofloxacin is preferred because the trial showing effective infection prevention in this setting used this agent. Additionally, drug-drug interactions exist between ciprofloxacin and pomalidomide, causing a significantly increased drug exposure of pomalidomide and potential toxicity. For patients who are intolerant to levofloxacin and other fluoroquinolones, consider trimethoprim–sulfamethoxazole.

†Monitor for drug-drug interactions between antifungal triazoles and agents against multiple myeloma: fluconazole, itraconazole, voriconazole, and posaconazole with bortezomib and itraconazole, voriconazole, and posaconazole with panobinostat. The dose of levofloxacin (and other fluoroquinolones), trimethoprim–sulfamethoxazole, acyclovir, and valacyclovir might require a reduction in the presence of renal dysfunction.

‡Trimethoprim–sulfamethoxazole (160 mg or 800 mg twice a day, 2–3 days per week) is the agent of choice for prophylaxis against *P. jirovecii* pneumonia. Alternative agents include aerosolized pentamidine (300 mg once monthly), dapsone (50 mg twice a day), or atovaquone (1,500 mg daily). Consider alternative options for patients receiving immunomodulators (eg, thalidomide) because of potentially increased risk of severe skin toxicity with trimethoprim–sulfamethoxazole.

§Intermediate to high risk of HBV reactivation (>1% risk): HBsAg-positive or -negative but anti–HBc-positive. Low risk of HBV reactivation (<1%): HBsAg-negative and anti–HBc-negative. Patients with evidence of a low circulating viral load of HBV DNA can be given antiviral therapy or closely monitored and treated if there is evidence of increasing viremia, regardless of serum concentrations of alanine aminotransferase.

CAR-T, chimeric antigen receptor T-cell; COVID-19, coronavirus disease 2019; CRS, cytokine release syndrome; CYP450, cytochrome P450; DNA, deoxyribonucleic acid; HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IMWG, International Myeloma Working Group; mRNA, messenger ribonucleic acid; PI, proteasome inhibitors; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SINE, selective inhibitor of nuclear export; VZV, varicella zoster virus.

Table adapted from Raje NS, Anaissie E, Kumar SK, et al. *Lancet Haematol*. 2022;9(2):e143-e161. With permission from Elsevier.

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