Consensus guidelines and recommendations for infection prevention in multiple myeloma: a report from the International Myeloma Working Group

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Infection remains the leading cause of morbidity and mortality in patients with multiple myeloma because of the cumulative effect of disease, treatment, and host-related factors. Given that infectious risk is cumulative through the course of the disease, preventing infections is paramount. Optimal preventive strategies include vaccination against common pathogens, antimicrobial prophylaxis, infection control measures, and immunoglobulin replacement in a small subset of patients; however, there are no universally accepted guidelines for infection prevention. This Review provides a consensus statement from a panel of 36 experts with global representation, which was convened by The International Myeloma Society to review existing literature and current guidelines, address issues associated with the risk of infection and prevention of infectious complications in multiple myeloma in the context of emerging therapies, and offer recommendations for preventing these complications.

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Introduction

Patients with newly diagnosed multiple myeloma have an increased susceptibility to infection because of the cumulative effect of various factors,[1,2] such as disease-related global immunoparesis and treatment-related immunosuppression (appendix p 1). Infection is the leading cause of morbidity and mortality in this patient group, particularly among older adults and individuals who are immunocompromised. Approximately 10% of patients with newly diagnosed multiple myeloma die prematurely as a result of infection, before they have had the opportunity to benefit from effective therapies.[3–6] Hence, it is crucial to understand the spectrum of infections and associated risk factors in this patient population, as well as the optimal measures to prevent and manage these complications.[7]

In this Review, we provide a consensus statement on the basis of available evidence regarding issues relating to the risk of infection and prevention of infectious complications in multiple myeloma, in the context of emerging therapies. Additionally, we also offer individualised strategies for real-world patients who represent the vast majority of those treated for multiple myeloma worldwide (panel 1). Our suggestions serve to complement the findings of clinical trials specific to multiple myeloma, keeping in mind that results might not be generalisable to all patients with the disease.

Data collection

A panel of 36 experts in multiple myeloma with global representation and a special interest in supportive care was convened by the International Myeloma Society. EA was an expert in infectious disease. The panel was asked to review existing literature and current guidelines from the Centers for Disease Control and Prevention, The Infectious Disease Society of America, and the National Comprehensive Cancer Network (NCCN); discuss various topics related to the risk of infection and prevention of infectious complications in multiple myeloma in the context of emerging therapies; and offer recommendations for preventing these complications. The panel first met at the XVI International Myeloma Workshop in New Delhi (India) between March 1 and March 4, 2017, and then at the XVII International Myeloma Workshop in Boston (MA, USA) between Sept 12 and Sept 15, 2019. The presentation and review of recommendations occurred at two workshops and through a series of three teleconferences, in which all recommendations were discussed and agreed upon. The panel used the NCCN criteria to grade the levels of recommendations. A category 1 recommendation was based on high-level evidence (usually data from phase 3 randomised controlled trials), with uniform consensus that the intervention was appropriate. A category 2A recommendation was based on low-level evidence with uniform consensus that the intervention was appropriate. A category 2B recommendation was also based on low-level evidence with consensus that the intervention was appropriate, albeit not universal. This Review summarises the panel's deliberations and recommendations in the prevention of infectious complications in patients with multiple myeloma, and provides a literature update. The scope of these recommendations does not include allogeneic haematopoietic stem-cell transplantation (HSCT). We have not included the effect of SARS-CoV-2 in patients with multiple myeloma, because a separate guideline dedicated to this topic will follow.

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See **Online** for appendix

***Panel 1*: Summary of salient features and key recommendations for infection prevention in patients with multiple myeloma**

- Infection remains the leading cause of death in patients with multiple myeloma. Several factors account for this infectious risk, including the overall state of immunosuppression from multiple myeloma, treatment, age, and comorbidities (eg, renal failure and frailty).
- The periods of highest infectious risk are during the first 3 months after diagnosis and when treating relapsed or refractory multiple myeloma.
- Patients with newly diagnosed multiple myeloma have high rates of potentially preventable infections (eg, *Streptococcus pneumoniae* or *Haemophilus influenzae*).
- Most infections in patients with multiple myeloma are caused by viruses and bacteria. Bacterial infections manifest most commonly as pneumonia and bacteraemia. Viral infections present typically as seasonal viruses, particularly influenza and herpes zoster.
- During periods of increased infectious risk, antibacterial prophylaxis with levofloxacin might be considered (NCCN level 2A). Acyclovir prophylaxis is used for patients who are seropositive for herpes simplex virus and varicella zoster virus, if tested. We also suggest use of acyclovir prophylaxis for patients receiving proteasome inhibitors or targeted monoclonal antibodies, specifically CD38-directed monoclonal antibodies (NCCN level 1). We reserve trimethoprim–sulfamethoxazole for patients at risk of *Pneumocystis jiroveccii* pneumonia, such as those with relapsed and refractory myeloma or in receipt of high doses of dexamethasone (eg, ≥40 mg/day for 4 days per week). Alternatives, such as dapsone, might be considered for patients with sulphur allergies (NCCN level 2A).
- We recommend immunising patients with multiple myeloma with inactivated influenza vaccine (preferably with a two-dose series of high-dose influenza vaccine, regardless of age) on an annual basis, and an inactivated *S pneumoniae* vaccine (PCV13) followed by PPSV23 every 5 years (NCCN level 2A).
- We only recommend inactivated vaccines in patients with multiple myeloma.
- The ability to develop a protective response after immunisation depends on the patient's state of immunosuppression (eg, disease burden, remission status, cumulative immunosuppression from antineoplastic therapies) and the timing of vaccination.
- Conventional chemotherapy considerably impairs response to vaccination in a patient with multiple myeloma.
- Protection by vaccination is best achieved when vaccines are given in early disease stages (eg, monoclonal gammopathy of undetermined significance or smouldering multiple myeloma), before the initiation of treatment or when response is reached.
- Single-agent lenalidomide improves response to vaccination in patients with multiple myeloma, provided that dexamethasone is not given concurrently. Responses to immunisation after receipt of novel agents (eg, monoclonal antibodies, panobinostat, and selinexor) are yet to be established.
- After autologous haematopoietic stem-cell transplantation (HSCT), patients with multiple myeloma might lose their immunity to the pathogens against which they were vaccinated. These patients should be revaccinated 6–24 months after HSCT. Data suggest that immunisation with the recombinant zoster vaccine is safe and effective after autologous HSCT. Therefore, we recommend recombinant zoster vaccine vaccination after autologous HSCT (NCCN level 1).
- We recommend the extension of the recombinant zoster vaccine to all patients with multiple myeloma. We recommend continued use of prophylaxis with varicella zoster vaccine where indicated, regardless of vaccination status (NCCN level 2b).
- We recommend use of passive immunisation in patients with multiple myeloma after exposure to individuals with hepatitis A, varicella, or measles (NCCN level 2b).
- We recommend that close contacts of patients with multiple myeloma receive routine vaccinations with inactivated vaccines, and that patients avoid close contact with recipients of live vaccines when possible (NCCN level 2A).
- We encourage health-care providers caring for patients with multiple myeloma to receive all indicated immunisations, particularly those for seasonal influenza viruses (NCCN level 2A).
- Use of intravenous immunoglobulin is reserved for specific situations, such as life-threatening infections and an IgG concentration below 400 mg/dL with recurrent infections (NCCN level 2A).
- For patients with multiple myeloma travelling to endemic areas of infection, we recommend travel vaccines and antimicrobial prophylaxis, as well as a consultation with an infectious disease specialist or travel clinic.

Risk factors for infection in multiple myeloma

Disease-related risk factors

Plasma-cell disorders enhance susceptibility to viral and bacterial infections, as shown in patients with monoclonal gammopathy of unknown significance[8,9] and in a large population-based study,[10] in which the investigators compared the risk of infection among 9253 patients with multiple myeloma with that of 34 931 age-matched and sex-matched controls. Compared with the control group, patients with mutiple myeloma were seven times more susceptible to bacterial infections and ten times more susceptible to viral infections.[10] Similarly, in a study of 2977 consecutive patients with invasive pneumococcal disease, the highest incidence of this condition was seen among patients with multiple myeloma, which was 154 times higher than that of

patients without multiple myeloma. Additionally, the highest rate of recurrence occurred among patients with multiple myeloma, with a case fatality rate of 18%.[11] The enhanced risk for infection in patients with newly diagnosed multiple myeloma results from the global immunoparesis that is common among this patient group, which includes dysfunction of B cells with hypogammaglobulinaemia,[12–14] disruption of global T-cell diversity,[15] and considerable alteration in the functional activity of dendritic[16] and natural killer cells, as well as of the alternative complement pathway (appendix p 2).[15] Although rare at presentation, neutropenia associated with marrow infiltration can also contribute to this increased risk.[15] Other associated comorbities, such as renal failure, are also risk factors.[1,17–21] The periods of highest infectious risk are during the first 3 months after diagnosis and when treating relapsed or refractory multiple myeloma.

Treatment-related risk factors

General principles of treatment in multiple myeloma

Several treatment options are available for patients with multiple myeloma (table 1). These therapies have substantially improved patient outcomes[22] and transformed myeloma from a rapidly fatal disease to a chronic condition with several relapses that are often successfully salvaged, resulting in cumulative immunosuppression and an increased risk of infection.[23] For example, CD4 cell count decreases substantially with increasing cycles of chemotherapy, which is strongly associated with opportunistic infections.[15] However, in general, the deep and durable responses reached with combination approaches have resulted in reversal of immuneparesis and improved outcomes.

The immune status of patients with multiple myeloma is related to several factors, including disease status and treatment phase (eg, induction, remission *vs* first relapse *vs* relapsed or refractory to multiple classes and agents), extent of previous therapy (eg, single *vs* several lines), and treatment intensity (eg, triplet for induction therapy *vs* myeloablative regimen for autologous HSCT; appendix pp 1–2). Furthermore, the role of continuous therapy is associated with persistent immune paresis, resulting in increased risk of infection. Identifying whether cumulative immunosuppression is present might be facilitated by immune markers (appendix p 2).

Glucocorticoids

Dexamethasone is considered to be a backbone of mutiple myeloma therapy,[24] but is also an important contributor to infections.[7,23] In a study of 199 patients with multiple myeloma treated with various regimens, the cumulative dose of dexamethasone was an independent risk factor for infection, both during induction and at relapse.[23] Additionally, large cumulative doses of glucocorticoids (eg, ≥40 mg/day dexamethasone for 4 days per week) increase the risk of opportunistic infections, including *Pneumocystis jirovecii* pneumonia.[25]

Cytotoxic chemotherapy

Conventional chemotherapeutic agents, such as cyclophosphamide, etoposide, cisplatin, anthracyclines, melphalan, and bendamustine, enhance the susceptibility of patients with multiple myeloma to infection by inducing neutropenia, T-cell dysfunction, and mucosal damage.[26,27]

Autologous HSCT

High-dose melphalan with autologous HSCT, a standard of care in therapy for mutiple myeloma, causes severe neutropenia and alimentary tract mucositis, thus predisposing patients to severe infections (mostly bacterial). However rare, a protracted T-cell immunodeficiency after engraftment increases the risk for acquisition and reactivation of viral infections and pneumocystis.[7]

Proteasome inhibitors

Bortezomib is the first proteasome inhibitor approved for treating multiple myeloma. Bortezomib depletes T cells and impairs viral antigen presentation,[28] with a correspondingly high rate of varicella zoster virus reactivation in seropositive patients.[29] Therefore, prophylaxis with aciclovir is essential in this setting (NCCN level 1).[30] Carfilzomib, approved in 2012, and ixazomib, approved in 2015, are also potent immunosuppressants and carry the same risk of viral infections.[31] The European Myeloma Network guidelines suggest stopping antiviral prophylaxis 6 weeks after discontinuation of proteasome inhibitors.[32] We recommend adapting the duration of prophylaxis according to the patient's state of immunosuppression (appendxp 1–2) and to whether other immunosuppressive agents that increase the risk of varicella zoster virus, such as glucocorticoids or the monoclonal antibodies, are subsequently given.

Immunomodulatory drugs

Lenalidomide and pomalidomide can cause neutropenia,[33] particularly when combined with monoclonal antibodies. Granulocyte colony-stimulating factor during treatment with lenalidomide does not appear to reduce the risk of infection,[34] but might be used intermittently to combat chronic neutropenia. Single-agent thalidomide does not increase risk of infection in patients with newly diagnosed multiple myeloma, except when given in combination with other immunosuppressive agents, particularly dexamethasone.[35]

Monoclonal antibodies

Treatment with monoclonal antibodies is associated with severe lymphopenia,[36,37] pneumonia, reactivation of viral infections, particularly varicella zoster virus, and opportunistic infections, especially in heavily pretreated patients.[37,38] When these agents are combined with

	Examples of pathogens	Pathogenesis	Preventive measures
Disease-related			
Patients with active myeloma			
Bacteraemia, pneumonia, and sinusitis	Encapsulated bacteria, Gram-positive bacteria, and Gram-negative bacteria	Immunoparesis*, hypogammaglobulinaemia (especially when recurrent), and impaired lymphocyte function	Offer vaccination (encapsulated bacteria); provide prophylaxis with levofloxacin with previous invasive pneumococcal disease†
Bacteraemia, pneumonia, and urinary tract infection	*Staphylococcal aureus*, Enterobacteriaceae, and *Pseudomonas aeruginosa*	Neutropenia from bone marrow replacement (<10% of patients at diagnosis)	Consider prophylaxis with levofloxacin
Sepsis	Encapsulated organisms (eg, *Streptococcus pneumoniae* and *Haemophilus influenza*)	Anatomical or functional hyposplenism (eg, amyloid light-chain amyloidosis)	Provide prophylaxis with levofloxacin
Patients with high tumour burden			
Bacteraemia and sepsis (more frequent and severe)	*Pseudomonas* and Enterobacteriaceae	Organ dysfunction (eg, renal failure and neutropenia) and severe immunoparesis related to multiple myeloma	Consider vaccination and prophylaxis; consider immunoglobulin replacement in selective patients; manage complications; offer prompt antimicrobial therapy and multiple myeloma therapy
Patients with relapsed or refractory myeloma			
Various infections, including opportunistic infections‡	*Pneumocystis jirovecii* and aspergillus	Severe immunoparesis*	Measures depend on the history of infection, number of relapses, and lines of therapy
Patients with renal failure			
Various infections, including opportunistic infections‡	*P jirovecii* and aspergillus	Decreased number and function of lymphocytes, decreased number of dendritic cells, and loss of thymic function	Manage renal failure and start prompt and effective multiple myeloma therapy
Patients with spinal cord compression and fractures			
Pneumonia, urinary tract infection, and pressure sores	*Staphylococcus*, *Pseudomonas*, and Enterobacteriaceae	Pain, immobilisation, neurological deficit, and respiratory dysfunction from deformities related to thoracic cage fracture	Provide physical therapy and occupational therapy
Treatment-related			
Treatment with melphalan and prednisone			
Bacteraemia, pneumonia, and urinary tract infection	Enterobacteriaceae, including *Escherichia coli*, *Klebsiella*, and *Enterobacter*	Neutropenia (10–20% of patients)	Provide levofloxacin
Cumulative doses of glucocorticoids			
Oral candidiasis, *P jirovecii* pneumonia, and other opportunistic infections‡	Herpes simplex virus and varicella zoster virus	T-cell immunodeficiency and hyperglycaemia	Avoid excessive use of glucocorticoids; provide acyclovir§, fluconazole, and prophylaxis against *P jirovecii* pneumonia with trimethoprim–sulfamethoxazole¶; offer vaccination; maintain glycaemic control
Treatment with proteasome inhibitors (eg, bortezomib, carfilzomib, and ixazomib)			
Neutropenia-related infections, *P jirovecii* pneumonia, and other opportunistic infections when given with glucocorticoids (eg, thrush and shingles)	Herpes simplex virus and varicella zoster virus	Suppression of T-cell immunity and neutropenia	Provide trimethoprim–sulfamethoxazole (if at risk of *P jirovecii* pneumonia¶) and acyclovir§
Treatment with immunomodulatory drugs (eg, lenalidomide and pomalidomide)			
Bacteraemia and pneumonia	Varicella zoster virus	Neutropenia (potentially impairing stem-cell mobilisation)	Provide prophylaxis with acyclovir§ and levofloxacin; adjust dose in patients with renal dysfunction to avoid myelosuppression
Treatment with monoclonal antibodies (eg, daratumumab, elotuzumab, isatuximab, and belantamab mafodotin)			
Pneumonia and opportunistic infections‡	Herpes simplex virus and varicella zoster virus	Lymphopenia and neutropenia	Consider levofloxacin or acyclovir§, depending on history of infection
Treatment with panobinostat			
Severe infections and opportunistic infections‡	Candida, *P jirovecii*, and *Pseudomonas*	Lymphopenia and neutropenia	Provide levofloxacin and acyclovir§; avoid panobinostat if severe infection present; hold or stop agent as indicated

(Table 1 continues on next page)

	Examples of pathogens	Pathogenesis	Preventive measures
(Continued from previous page)			
Treatment with selinexor			
Neutropenia-related infection	Candida, *P jirovecii*, and *Pseudomonas*	Neutropenia	Provide levofloxacin and acyclovir§
Treatment with standard chemotherapy (eg, cytoxan)			
Neutropenia-related infection	Candida, *P jirovecii*, and *Pseudomonas*	Neutropenia	Provide levofloxacin and acyclovir§
Treatment with intensive chemotherapy (eg, bortezomib–dexamethasone–thalidomide–cisplatin–adriamycin–cyclophosphamide–etoposide)			
Bacteraemia, pneumonia, colitis, and *Clostridioides difficile* colitis	Herpes simplex virus and varicella zoster virus	Severe neutropenia and mucositis	Provide levofloxacin and acyclovir§
Treatment with chemotherapy-based stem-cell mobilisation			
Bacteraemia, pneumonia, colitis, and *C difficile* colitis	Herpes simplex virus and varicella zoster virus	Neutropenia	Control viral infections (eg, HBV and HCV) before starting chemotherapy; avoid trimethoprim–sulfamethoxazole
Treatment with high-dose therapy with autologous HSCT			
Bacteraemia, pneumonia, colitis, and *C difficile* colitis	Herpes simplex virus and varicella zoster virus	Severe neutropenia, mucositis, prolonged humoral and T-cell immunodeficiency after autologous HSCT	Depends on individual patients: provide levofloxacin, acyclovir§, and fluconazole and perform baseline dental consultation; in patients who are seropositive for cytomegalovirus after autologous HSCT, consider monitoring by quantitative PCR and measuring HBV and HCV viral load, if applicable; provide prophylaxis against *P jirovecii* pneumonia with trimethoprim–sulfamethoxazole¶; offer revaccination
Treatment with bisphosphonate-induced osteonecrosis of jaw			
Bacterial infections	Anaerobes and *Actinomyces* spp	Local infection and impairment of local host defences	Perform baseline dental evaluation and encourage optimal oral hygiene
Treatment with vertebroplasty or kyphoplasty			
Skin infections	Gram-positive bacteria (eg, *S aureus* or *Streptococcus* spp)	Breach of anatomical barrier	Consider prophylaxis in patients with relapsed or refractory myeloma
Host-related factors			
Patients aged >75 years, with frailty, poor performance status, or comorbidities			
Shingles, pneumonia, and urosepsis	Varicella zoster virus, *Pseudomonas*, and *E coli*	Immune senescence and defects associated with renal and liver dysfunction	Provide risk-adapted therapy for multiple myeloma (including dose reduction) and provide prophylaxis with acyclovir to help prevent infection
Pathogen exposure			
Patients with history of infection			
Viral and fungal infections, *C difficile* colitis, and opportunistic infections‡	Herpes simplex virus, varicella zoster virus, HBV, HCV, and cytomegalovirus	Not applicable	Take history of infection and immunisation and provide targeted prophylaxis *vs* monitoring-based pre-emptive therapy
Colonisation with pathogens			
Pathogen-specific infections	*S aureus*	Not applicable	Provide therapy targeting decolonisation (eg, *S aureus*)
Environmental exposure			
Respiratory infections and gastrointestinal infections	Water and food-borne pathogens (eg, *Steptococcus* and salmonella)	Not applicable	Offer pneumococcal vaccinations and deliver patient education

HBV=hepatitis B virus. HCV=hepatitis C virus. HSCT=haematopoietic stem-cell transplantation. *Immunoparesis might include dysfunction of B cells and T cells, natural killer cells, dendritic cells, or the alternative complement pathway; decreased concentrations of uninvolved serum immunoglobulins; serum-specific antibody titres in response to immunisation (eg, polysaccharide antigen responses) or to infection; and impaired neutrophil and lymphocyte functions. †Invasive pneumococcal disease is defined as isolation of *S pneumoniae* from a normally sterile site (eg, blood or cerebrospinal fluid), but not sputum. ‡Opportunistic infections include *P jirovecii* pneumonia, tuberculosis, endemic mycoses, *Strongyloides stercoralis*, *Listeria monocytogenes*, and malaria. §Prophylaxis with acyclovir, valacyclovir, or famciclovir for patients who are seropositive for herpes simplex virus or varicella zoster virus. ¶Trimethoprim–sulfamethoxazole: 160 mg or 800 mg twice a day, 2–3 days per week. Because of increased risk of severe skin toxicity in patients receiving an immunomodulatory agent, consider the following alternative agents: aerosolised pentamidine (300 mg once per month), dapsone (50 mg twice a day), or atovaquone (1500 mg once daily).

Table 1: **Risk factors, infections, pathogens, pathogenesis, and preventive measures for infection in patients with multiple myeloma**

	Recommended recipients	Dose schedule and comments
Vaccines against *Streptococcus pneumoniae*		
Pneumococcal conjugate vaccines (eg, PCV13 and PCV 10) and pneumococcal polysaccharide vaccine (eg, PPSV23)	All patients, particularly survivors of invasive pneumococcal disease and patients with asplenia, which might be present with amyloid light-chain amyloidosis	Vaccinate as early as possible, ideally before starting multiple myeloma therapy. PCV13 is more immunogenic than PPSV23, and the response to PPSV23 is reduced after immunosuppression. If not previously vaccinated, provide one dose of PCV13 at diagnosis followed by one dose of PPSV23 ≥8 weeks later; if previously vaccinated with at least one dose of PPSV23 (but not PCV13), provide one dose of PCV13, 1 year after the last PPSV23 treatment; for severely immunocompromised patients, consider a dose of PPSV23 every 5 years once they reach age 65 years. In patients with recurrent pneumococcal infections and previous invasive pneumococcal disease, consider antibiotic prophylaxis* because the response to the pneumococcal vaccine might be suboptimal. PCV10 is used in some regions, including Europe
Vaccines against influenza viruses		
High-dose inactivated vaccine (ie, fluzone), trivalent inactivated vaccine (ie, fluad), recombinant quadrivalent haemagglutinin vaccine (ie, flublok), quadrivalent inactivated vaccine, and egg-free and cell-cultured inactivated vaccines	All patients, non-immune close contacts (eg, household members and family), and health-care workers	Vaccinate annually before the onset of influenza activity in the community. Provide two doses of high-dose fluzone (separated by ≥30 days) to all patients, regardless of age. During influenza season, provide antiviral prophylaxis (eg, oseltamivir or zanamivir) to patients at risk of severe complications (eg, during autologous HSCT); if a nosocomial outbreak occurs with a strain not contained in the vaccine, close contacts and health-care workers should be offered prophylaxis with standard vaccination; in patients aged ≥65 years, the high-dose inactivated vaccine, recombinant quadrivalent haemagglutinin influenza vaccine, and trivalent adjuvanted vaccine are more protective than the standard vaccine; avoid the live attenuated influenza vaccine (nasal spray) in all patients
Vaccines against varicella zoster virus		
Recombinant glycoprotein E vaccine (ie, recombinant zoster vaccine)	All patients, including autologous HSCT recipients	Provide two doses of vaccine; in autologous HSCT recipients, provide the first dose 50–70 days after autologous HSCT and the second dose 1–2 months later; revaccinate all autologous HSCT recipients according to published guidelines[66,67]

For all patients with multiple myeloma, live vaccines should be avoided and inactivated vaccines only should be used. HSCT=haematopoietic stem-cell transplantation. *For prophylaxis against *S pneumoniae*, penicillin is the standard of care; however, increasing resistance to penicillin worldwide might require alternative agents (eg, fluoroquinolone, azithromycin, or second-generation penicillin or cephalosporin) on the basis of susceptibility to strains causing previous invasive pneumococcal disease and local resistance patterns.

Table 2: **Active immunisation of patients with multiple myeloma**

lenalidomide or pomalidomide, clinically significant neutropenia might develop, requiring dosage adjustments. CD38-directed monoclonal antibodies have a higher incidence of neutropenia than does elotuzumab; therefore, the risk of associated infections will differ on the basis of specific monoclonal antibodies in clinical use.

Panobinostat

Panobinostat, a histone deacetylase inhibitor, causes severe lymphopenia and neutropenia, putting patients at substantial risk of acute bacterial, fungal, and viral infections, and the reactivation of opportunistic infections.[37,39]

Selinexor

Selinexor, a nuclear export inhibitor, might cause neutropenia-related infections.[40]

Novel immune approaches

Since 2016, there have been several methods for targeting B-cell maturation antigen, including cellular therapy (eg, chimeric antigen receptor T cells), bispecific T-cell engagers, and antibody drug conjugates (eg, belanatmab mafodotin). All of these strategies result in immunosuppression, because they target antibody-producing B cells and plasma cells. Therefore, patients with multiple myeloma receiving this therapy might require immunoglobulin replacement. Furthermore, these therapies can lead to neutropenia and myelosuppression, which require prophylactic use of antibiotics, antiviral coverage, and antifungal coverage in some cases.

Antiresorptive therapy

Antiresorptive therapy is used in most patients with multiple myeloma to prevent bone disease. Rarely, the mandibular and maxillary bones become infected, resulting in osteonecrosis of the jaw.[41] The pathogenesis of this condition involves chronic local infection and reduced bone turnover associated with antiresorptive therapy.[42] Poor dental hygiene, poorly fitting dentures, advanced periodontal disease, and recent dentoalveolar surgery are known risk factors.[41,43–45]

If infection develops in the context of osteonecrosis of the jaw, we recommend initiating treatment with broad-spectrum antibiotics that are active against anaerobes, including *Actinomyces* spp[46] and resistant *Bacteroides fragilis*.[47] Examples include clindamycin, a carbapenem, or a β-lactam or β-lactamase inhibitor. We also recommend obtaining a biopsy of the lesion with stains and cultures if the response to antibiotics is slow or suboptimal, or if osteomyelitis is suspected. Limited debridement might be needed; however, surgical resection should be reserved for refractory cases of multiple myeloma.[48]

Kyphoplasty and vertebroplasty

Kyphoplasty and vertebroplasty are generally well tolerated and are crucial for controlling the pain

associated with involvement of multiple myeloma in vertebral bodies. Rarely, spondylitis with Gram-positive bacteria (eg, *Staphylococcal aureus*) can develop[49] and evolve into a paravertebral abscess.[50] When planning such procedures for patients at high risk of infection (appendix pp 1–2), we recommend use of antimicrobial prophylaxis 24 h before and during the procedure.

Host-associated factors

Multiple myeloma mainly affects older individuals (aged ≥65 years) with a senescent immune system, who have reduced antibody responses to pneumococcal and influenza vaccines[51] and increased likelihood of having clinically significant comorbidities.[1] In a study of 801 consecutive patients with multiple myeloma, five independent risk factors predicted reduced overall survival: renal and pulmonary dysfunction, poor Karnofsky Performance Status, frailty, and advanced age (aged ≥65 years). Combining these elements in a weighted revised Myeloma Comorbidity Index[52] allowed for the identification of three risk groups: fit, with a median overall survival of 10·1 years; intermediate fit, with a median overall survival of 4·4 years; and frail, with a median overall survival of 2·1 years.

Host exposure to pathogens

Current and previous exposure to pathogens is another factor contributing to the risk of infection in patients with multiple myeloma.[1]

Factors predictive of early and severe infections in patients with multiple myeloma

A substantial proportion of patients with newly diagnosed multiple myeloma die prematurely, primarily as a result of infections, before they have had the opportunity to benefit from effective therapies.[3] Reports have identified predictors of early and severe infection among patients with newly diagnosed multiple myeloma, including a high tumour burden (International Staging System [ISS] score II–III), abnormally elevated concentrations of serum lactic dehydrogenase, poor performance status, and renal dysfunction.

A prognostic model was developed in 2018 that categorised patients into high risk (24% incidence of grade 3 treatment-emergent infections) and low risk (7% incidence) for severe early infection.[53] Investigators also evaluated the risk factors for severe infection during the first 6 months following diagnosis of multiple myeloma in a cohort of 2557 patients.[54] Of a total of 1981 reported infections, pneumonia developed in 548 (28%) patients and sepsis developed in 353 (18%) patients. Multivariate analyses identified male sex and high tumour burden (ISS score II–III and elevated serum lactic dehydrogenase) as risk factors for pneumonia. A high tumour burden (ISS score II–III) and elevated concentration of serum creatinine independently predicted the risk of sepsis.

Immune reconstitution following successful therapy

Effective control of multiple myeloma commonly results in improved immunity. For example, when investigators examined time to immune reconstitution in 42 patients with multiple myeloma after autologous HSCT, a robust negative correlation was shown between the incidence of infections and recovering serum concentrations of IgG and IgA.[55] This period of immune reconstitution might provide a window of opportunity for vaccinations that are likely to generate a protective response. Although an increased risk of infection during maintenance therapy with lenalidomide was not shown in early studies,[56] this finding has since been convincingly shown, probably because of neutropenia induced by lenalidomide.[57]

The spectrum of infections in patients with multiple myeloma

The type, severity, and timing of infectious complications in patients with multiple myeloma have evolved with the introduction of novel therapies. These complications develop during the first several months of induction therapy, peaking at 4–6 months, predominantly as a result of Gram-positive (eg, coagulase-negative staphylococci, *S aureus*, *Streptococcus pneumoniae*, and *Enterococcus fecalis*) and Gram-negative bacteria (eg, *Haemophilus influenzae* and *Escherichia coli*). Tracheobronchitis and pneumonia from respiratory viruses (eg, influenza and respiratory syncytial virus) are also common.[58–60]

Infections peak again during the treatment of relapsed disease,[23] when the immunity of a patient with multiple myeloma is severely impaired. Infections not typically seen in patients with multiple myeloma might develop, including invasive pulmonary aspergillosis[61] and viral infections, such as cytomegalovirus,[62] hepatitis B virus (HBV) or hepatitis C virus (HCV), and parvovirus B19.[63] Tuberculosis[64] and other opportunistic infections are also seen rarely.[65]

Strategies to prevent and manage infections in patients with multiple myeloma

The key to reducing the burden of infectious complications in patients with multiple myeloma is an individualised treatment plan adapted by risk after comprehensive staging at diagnosis and relapse. Staging includes taking clinical history (particularly of vaccination and previous infections), examining physical health, and evaluating functional status for patients older than 65 years (ie, fit, intermediate fit, or frail).

We recommend optimising dose intensity in patients at high risk of severe infection (ie, with high disease burden or elevated serum lactic dehydrogenase) and of clinically significant comorbidities (particularly renal dysfunction).[54,55] Additionally, we suggest considering the state of immunosuppression when treating a relapsed patient with multiple previous lines of therapy.

Panel 2: Timing of immunisation with inactivated vaccines only in patients with multiple myeloma

Patients with monoclonal gammopathy of undetermined significance, smouldering myeloma, or asymptomatic multiple myeloma

- Response to immunisation in these patients has been documented[68–70]
- Vaccination might be more effective in patients with monoclonal gammopathy of undetermined significance with a lower concentration of M-protein and might not be persistent in smouldering myeloma, unless vaccinations are repeated[71]

Patients with multiple myeloma requiring therapy

This disease status is associated with inadequate response to immunisation with the following caveats:

As early as possible

- Vaccinate patients (preferably) 14 days before starting therapy

Partial response (especially with immune reconstitution)

- A good response is usually associated with immune reconstitution with normalisation of uninvolved immunoglobulins[55,68,72]
- Suppression of uninvolved immunoglobulins is a risk factor for inadequate response to vaccination[68]

Treatment with immune modulatory agent alone or with a proteasome inhibitor

- Treatment with an immune modulatory agent alone or with a proteasome inhibitor[68] is associated with an increased likelihood of a serological response
- Maintenance with a single immune modulatory agent (ie, lenalidomide) augments immunity against some pathogens,[58,68,73,74] but not when combined with dexamethasone[75]

Non-influenza respiratory infection during the influenza season

- Avoid immunisation temporarily because response to vaccine is unlikely to be adequate and a subgroup of patients with active multiple myeloma might be at increased overall risk of infection[68]

Conventional chemotherapy

- Avoid vaccination until disease control is reached because response is likely to be inadequate in patients with cancer,[69,70,76] which is compatible with the evidence that higher multiple myeloma burden increases risk of infection[53,54,68]

High-dose myeloablative therapy with autologous HSCT

- Avoid immunisation before autologous HSCT because response to vaccine is unlikely to be adequate
- Revaccinate patients 6–12 months after autologous HSCT,[58] because patients develop severe humoral and cell-mediated immunodeficiency but rapid immune reconstitution after autologous HSCT
- Recovery of CD4 cell count is considered to be a reasonable guide to immune recovery[77–79]

Relapse or resistant multiple myeloma

- Avoid immunisation during active disease, because response to vaccine is unlikely to be adequate, particularly in patients with several previous lines of therapy

Cumulative immunosuppression from extensive treatments increases the net state of immunosuppression and the risk of severe infections

Likelihood of response is decreased with descending order. No data exist regarding any vaccine response to the recently approved monoclonal antibodies, panobinostat and selinexor.

HSCT=haematopoietic stem-cell transplantation.

Preventive strategies include vaccination against common pathogens (table 2), with attention to the timing of vaccination (panel 2) and the education of patients and caregivers about measures to reduce exposure to potential sources of pathogens, including when travelling (panel 3; appendix p 3). Furthermore, we recommend risk-adapted antimicrobial prophylaxis (table 3) and consideration of immunoglobulin replacement, and possibly myeloid growth factor support, in a small subset of patients. Careful surveillance during highly immunosuppressive therapies and after autologous HSCT might help to anticipate the likelihood and type of infection.

Tests for infection

Fever should always be considered as a marker of infection in patients with multiple myeloma. A high index of suspicion in patients without a fever should be maintained, especially in patients on corticosteroids. We suggest obtaining the patient's history of vaccination and previous infection, viral serostatus, disease status, most recent therapy, and associated comorbidities to identify the probable causative pathogens (appendix pp 1–2).[1] Additionally, we suggest considering local epidemiology.

We recommend commencing empirical broad-spectrum antibiotics while performing diagnostic tests in patients with febrile neutropenia[82] and in those with manifestations of infection. Furthermore, we suggest selecting agents active against *S pneumoniae* and Gram-negative pathogens, particularly *E coli* and *Pseudomonas aeruginosa*.[1] We recommend targeted antimicrobial agents depending on the clinical, radiological, and microbiological findings.[1]

Diagnostic tests for infection include a complete blood cell count with differential renal and liver function tests, electrolyte tests, and microscopy or cultures from blood and other sites as clinically indicated. We also suggest obtaining the rapid pneumococcal antigen test in urine, blood, and cerebrospinal fluid samples[83] when indicated.

For patients with respiratory manifestations, we suggest obtaining a CT scan of chest and sinuses, a nasopharyngeal sample for a panel for respiratory pathogens, microscopy or cultures of respiratory secretions, and a urine antigen test for legionella. For persistent fever beyond 3–4 days with pulmonary infiltrates, we suggest considering bronchoscopy with bronchoalveolar lavage or transbronchial biopsy to identify opportunistic pathogens. Markers of fungal infection, such as galactomannan and β glucan, can be used where clinically indicated.

For abdominal symptoms and diarrhoea, we recommend starting broad-spectrum antibiotics. We suggest obtaining stool samples for *Clostridioides difficile* infection.[1] If this infection is documented, we suggest adding oral vancomycin because of its superior activity over metronidazole. Evidence indicates that fidaxomicin is at least as effective as oral vancomycin for confirmed *C difficile* infection[84] and could be associated with a lower risk of recurrent infection, particularly when used as extended-pulsed therapy for 25 days.[85] Empirical treatment should be considered in the presence of severe colitis, particularly with a high index of suspicion of *C difficile* infection, pending results of diagnostic testing.

We suggest considering a CT scan of the abdomen and pelvis for severe focal signs and symptoms. Depending on the local epidemiology, we suggest obtaining stool cultures and PCR for enteric pathogens, and other tests for intestinal parasites (eg, Giardia and Cryptosporidium).[1]

If fever persists with undetermined cause, despite comprehensive investigation, we recommend further diagnostic imaging to identify the presence, location, and extent of infected sites.[86,87] Once an infectious cause has been excluded, we suggest consideration of other causes of febrile illness associated with multiple myeloma, such as tumour fever, venous thromboembolism, adrenal insufficiency, or an engraftment syndrome coinciding with marrow recovery following autologous HSCT.[1,88] Non-infectious causes should be considered when fever persists, despite optimal investigation and antimicrobial therapy in a patient who is otherwise clinically stable. Tumour fever should be considered when serum concentrations of lactic dehydrogenase and other blood and urine markers of multiple myeloma are abnormally elevated.[89,90] Fever associated with venous thromboembolism should be ruled out with an extremity doppler or ultrasonography, ventilation or perfusion scan, or a protocol CT scan for pulmonary embolism, particularly in patients at risk of venous thromboembolism—eg, those receiving immunomodulatory imide drug therapy or recombinant erythropoietin,[91] those who are immobilised (due to fractures or spinal cord compression),[92] or those with other known risk factors.[93] Drug-induced fevers should always be considered in patients with fevers of undetermined origin. Fevers in the context of novel immune strategies might be a symptom of cytokine release syndrome and should be appropriately managed.

***Panel 3:* Travel precautions for patients with multiple myeloma**

- Obtain a pre-travel consultation with an clinician in infectious disease or travel medicine specialist familiar with the patient's immunocompromised state and medications
- Review the Centers for Disease Control and Prevention's website[80] for continuous updates on regional disease transmission patterns and outbreaks

Consultant's counselling and region-specific advice for patients with multiple myeloma

- Assess immune status and advise severely immunocompromised patients against travel to areas where potentially severe infections are endemic
- Update the patient's immunisation status and review medications
- Advise the patient to use general protective measures, repellents, bed nets, and protective clothing to minimise risk of infection from mosquito bites (eg, malaria, dengue virus, chikungunya, Zika virus, and West Nile encephalitis) and from ticks (eg, Lyme borreliosis, tick-borne encephalitis, and relapsing fever)
- Provide relevant country-specific and region-specific vaccinations according to risks, including those against *Neisseria meningitidis*, hepatitis A virus and hepatitis B virus, and poliovirus
- Provide country-specific and region-specific antimicrobial prophylaxis, including for malaria and tuberculosis
- Provide an antibiotic supply (eg, a fluoroquinolone or a macrolide antibiotic) for self-administration for persistent diarrhoea with fever (>48 h) and actively encourage the patient to seek medical advice for such a condition
- Consider immunoglobulins for hepatitis A virus in select individuals who are seronegative and at high risk of hepatitis A virus infection, including those travelling to areas where hepatitis A virus is endemic
- Educate the patient and caregivers about:
  - Region-specific risks, with an emphasis on malaria and tuberculosis
  - Avoiding raw foods, eating fruits and vegetables that can be peeled to prevent traveller's diarrhoea, and drinking bottled or boiled beverages only
  - Avoiding suboptimal cooking of meat
  - Avoiding close contact or prolonged time with patients with tuberculosis in crowded and enclosed environments (eg, hospitals or clinics); if the traveller anticipates such exposure, obtain a tuberculosis test (skin or blood) before their departure and after their return
  - Avoiding activities associated with increased risk of fungal infection (eg, excavation) to prevent endemic fungal pneumonia (southeast Asia: penicilliosis with *Talaromyces marneffei*; USA: histoplasmosis, blastomycosis, and coccidioidomycosis; and Latin America: histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis)

Special considerations for managing infections according to disease status and treatment phase

Newly diagnosed multiple myeloma

Because *S pneumoniae* is a prevalent pathogen when multiple myeloma is first diagnosed, we recommend administering the pneumococcal vaccination as early as possible (table 2) and starting a broad-spectrum antimicrobial agent active against *S pneumoniae* for fever or other manifestations of infection.[1]

	Bacterial prophylaxis	Fungal prophylaxis	Viral prophylaxis
Low risk	None	None	None, unless a previous episode of herpes simplex virus; in which case, use acyclovir
Intermediate risk	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 risk	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 for 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 pre-emptive treatment.§ Use tenofovir or entecavir, rather than lamivudine, for treatment and pre-emptive 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 normalises and stopping immunosuppressive agents.

HBV=hepatitis B virus. *Levofloxacin is preferred because the trial[81] 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 aerosolised pentamidine (300 mg once monthly), dapsone (50 mg twice a day), or atovaquone (1500 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 viraemia, regardless of serum concentrations of alanine aminotransferase.

Table 3: **Recommendations for risk-adapted antimicrobial prophylaxis in patients with multiple myeloma**

Induction therapy for patients with newly diagnosed multiple myeloma

A considerable proportion of patients with newly diagnosed multiple myeloma die within the first several months after diagnosis,[94] mainly as a result of infectious complications.[3] Therefore, we recommend applying an aggressive approach to managing infection in this setting by initiating rapidly active agents and treating complications related to multiple myeloma, such as renal failure.[95] Use of antimicrobial prophylaxis with levofloxacin during the first 3 months of therapy can be considered,[81] particularly in patients at high risk of early infection,[54,55] although its benefit in current triplet and quadruplet combinations (eg, lenalidomide–bortezomib–dexamethasone with or without daratumumab, and carfilzomib–lenalidomide–dexamethasone) remains unknown (NCCN level 2A). The benefits of fluoroquinolone use (eg, levofloxacin) should be weighted, because these drugs have been rarely associated with tendinopathy with rupture, particularly of the Achilles tendon. Risk factors for tendinopathy include older age (aged >60 years), concomitant use of corticosteroids, and the presence of renal dysfunction,[96] a setting common among patients with multiple myeloma. Other recommendations for antimicrobial prophylaxis according to disease stage and type of antineoplastic treatment are listed in table 3. Consideration for the use of a quinolone should be based on degree and duration of neutropenia.[82]

Consolidation with autologous HSCT

Patients with multiple myeloma who undergo autologous HSCT are at risk of severe infections (mostly bacterial), and we suggest use of antimicrobial prophylaxis. Immune deficiency develops after autologous HSCT and might cause clinically significant infectious morbidity. We recommend monitoring for infections and providing prophylaxis for pneumocystis for 3 months and herpes simplex virus or varicella zoster virus for 1 year on the basis of global guidelines (NCCN level 2A).[66] Given that antibacterial prophylaxis is not routine for all transplantation centres worldwide, it should be noted that, although its use has reduced incidence of fever and bloodstream infections, this has not translated into reduction of mortality. Another caveat to consider with antimicrobial prophylaxis is the risk of development of resistant pathogens.

Maintenance therapy

Severe infections during maintenance therapy are mostly attributed to neutropenia; however, the risk is low with a fatality rate of less than 1%.[97] This rate can change depending on what agents are used during maintenance therapy, such as monoclonal antibodies and proteasome inibitors.

Treatment of relapsed multiple myeloma

Relapsing multiple myeloma is a heterogeneous disease, ranging from an indolent biochemical relapse to a rapidly progressive disease. At this stage, patients might still be able to tolerate various treatments or might have become frail from advanced age, cumulative toxicities, and immunosuppression.

Risk-adapted antineoplastic and antimicrobial strategies can minimise infection-related morbidity

and mortality in this setting (appendix pp 1–2). Patients with relapsed and refractory myeloma are at high risk of life-threatening infections from a broad spectrum of pathogens, including bacterial and viral infections (eg, herpes simple virus or varicella zoster virus, cytomegalovirus, HBV, and HCV).[1,23] Fungal pneumonia, including invasive pulmonary aspergillosis[98] and pulmonary pneumocystis,[25] might also develop.

Screening for infections

We suggest testing patients with relapsed and refractory myeloma who are seropositive for cytomegalovirus, HBV with cytomegalovirus antigenaemia or quantitative PCR, or circulating HBV DNA,[15,99] before starting therapy (NCCN level 2B). We suggest considering serum antigen testing for *Aspergillus* galactomannan to detect invasive pulmonary aspergillosis before symptoms arise[98] in patients with a high index of suspicion. The role of serum (1,3)-β-D-glucan for invasive pulmonary aspergillosis is unclear, but it could be a useful adjunct for diagnosing pneumocystosis.[100]

Depending on the serostatus of the patient, HBV reactivation and disease can lead to severe complications and death in patients with multiple myeloma, typically following autologous HSCT.[101] Furthermore, HBV reactivation has been seen rarely after CD38-directed monoclonal antibody therapy. We suggest managing patients according to their HBV serostatus and the type and duration of immunosuppressive therapies (table 3). We recommend using antiviral prophylaxis for patients at intermediate-to-high risk of HBV reactivation or disease, or early pre-emptive treatment for patients at low risk. Treatment for cytomegalovirus viraemia should only be given in the presence of clinically relevant conditions (eg, cytopenias and cytomegalovirus disease).

The effect of chronic HCV infection on the course of multiple myeloma is not well understood, although reactivation is known to occur following chemotherapy and can require dose reduction or discontinuation.[102] However, unlike HBV, acute liver failure or death are not features of chronic HCV infection. We suggest evaluating HCV serostatus when multiple myeloma is diagnosed, and use of a regimen without interferon alpha, such as direct-acting antiviral agents (eg, sofosbuvir, simeprevir, and ledipasvir) throughout therapy, with close monitoring of serum alanine transaminase and HCV viral load. Monitoring HCV viral load and treating infection is crucial before stem-cell mobilisation. Chronic HCV infection might cause trilineage cytopenia[103] and result in suboptimal mobilisation. Loss of HCV seropositivity might occur rarely in patients with cancer,[104] and we recommend measuring HCV viral load when the patient's serostatus is not known. In all complex situations, the expertise of an infectious disease specialist is recommended.

Vaccination

General principles of vaccination in multiple myeloma

Vaccination has a prominent role in preventing infection in the setting of multiple myeloma due to its safety, cost-effectiveness, and ability to avert serious infection. However, efficacy trials with clinical endpoints and data on the surrogate markers of efficacy are limited in this setting.

Although the response to vaccination is frequently minimal, there could be a benefit of partial protection with decreased rates of infection and hospitalisation.[76,105–108] Despite recommendations to vaccinate patients with multiple myeloma, the rate of vaccination (eg, for *S pneumoniae*) remains low.[72] The duration of the benefit is not known and could vary on the basis of vaccination timing.[76,109]

Although the safety of most vaccines has not been tested in patients with multiple myeloma, both influenza and pneumococcal vaccinations are safe,[107] as are other inactivated vaccines.[110] Vaccines against *S pneumonia* and seasonal influenza viruses are highly recommended for patients with multiple myeloma, as well as those deemed necessary by epidemiological prevalence (eg, HBV). *H influenzae* vaccination is also recommended in patients with asplenia, as seen in amyloid light-chain amyloidosis.[111]

We recommend *S pneumoniae* vaccination because of the risk of infections with encapsulated organisms in patients with multiple myeloma.[112,113] We recommend one dose of the pneumococcal conjugate vaccine (PCV13), followed by one dose of the polysaccharide vaccine (PPSV23) at least 8 weeks later. If the patient was previously vaccinated with PPSV23, then we recommend vaccination with PCV13 1 year later (NCCN level 2A; table 2).[112] The protective titre for *S pneumoniae* is unknown and might vary by serotype. If a breakthrough pneumococcal infection develops after vaccination, we suggest an attempt at identifying the strain serotype to report non-responsiveness to the vaccine if possible. The purpose of identifying the serotype is to identify whether it is not one included in the PCV13 vaccine—eg, in a patient who was immunised with PCV7 or PCV10. In such a setting, we consider immunisation with PCV13 vaccine.

Because antibody response to pneumococcal vaccines might be suboptimal, extended antibiotic prophylaxis might be useful in patients with recurrent *S pneumoniae* infections and in those with an episode of invasive pneumococcal disease. Although penicillin G is the standard of care,[114] an antibiotic based on the susceptibility of the strains that caused previous invasive pneumococcal disease and the local patterns of resistance might be used. A fluoroquinolone (eg, levofloxacin), azithromycin, or second-generation penicillin or cephalosporin could be considered as reasonable alternatives (NCCN level 2B).[115]

Vaccination for seasonal influenza viruses is necessary because patients with cancer have increased risk of infection and mortality.[116] Immunogenicity for influenza

vaccines might be weak in patients with multiple myeloma. In one study, 51 patients with monoclonal gammopathies (49 had multiple myeloma) received two doses of the high-dose, inactivated trivalent influenza vaccine. There was significant production of antibodies in 24 (47%) after the first dose and in 35 (65%) after the second,[68] which was significantly higher than the 20% response rate with a single standard vaccine[76] and 33% with two doses of the standard vaccine.[117] Furthermore, the prevalence of influenza infections was only 6% compared with an expected rate of at least 20%. The investigators also identified five clinical risk factors that predicted a reduced likelihood of reaching total seroconversion. These findings are particularly relevant to the timing of vaccination in patients with plasma-cell disorders, including multiple myeloma, smouldering multiple myeloma, and monoclonal gammopathy of unknown significance (panel 1).

Therefore, we recommend two doses of the high-dose inactivated quadrivalent influenza vaccine for all patients with multiple myeloma instead of the standard vaccine, regardless of age (NCCN level 2A). The intial dose should be given as early as possible in the influenza season and the second high-dose booster should be provided 1 month later. For patients who have severe adverse events to inactivated influenza vaccines, two doses of recombinant vaccine can be considered.[68]

HBV vaccination is universally recommended, particularly for patients at high risk of contracting the virus (NCCN level 2A). Other potentially useful vaccines for patients with multiple myeloma include those against *Neisseria meningitides*, tetanus, diphtheria, and pertussis and the inactivated poliovirus vaccine.

Because of the increased risk of reactivation of varicella zoster virus during treatment of multiple myeloma, vaccination should be considered to decrease the risk of developing this virus and postherpetic neuralgia. Two types of vaccines are available: a non-live recombinant glycoprotein E vaccine (ie, the recombinant zoster vaccine, approved for use in the USA in October, 2017) and a live attenuated vaccine (ie, the zoster vaccine live, approved for use in the USA in 2005). The zoster vaccine live continues to be used in most countries given that the recombinant zoster vaccine is not yet widely available. However, since July 1, 2020, the zoster vaccine live is no longer available in the USA.

We recommend the recombinant zoster vaccine rather than the zoster vaccine live for patients with multiple myeloma because it is safe (ie, non-live) and provides higher and more durable protection against herpes zoster and, therefore, postherpetic neuralgia (NCCN level 1). In one study, the recombinant zoster vaccine was safe and immunogenic in patients with multiple myeloma and solid tumours, showing persistence of humoral and cell-mediated immunity 1 year after vaccination.[117]

The Advisory Committee on Immunization Practices recommends the recombinant zoster vaccine as the preferred vaccine for preventing shingles in healthy adults aged 50 years and older, including those who previously received zoster vaccine live.[118] Data from 2017 support the use of the recombinant zoster vaccine in patients with multiple myeloma. Even if vaccinated, patients receiving a proteasome inhibitor or CD38-directed monoclonal antibody therapy should continue with acyclovir prophylaxis, because the degree of protection afforded by vaccination is difficult to assess (NCCN level 2A). Specifically, patients with multiple myeloma have variable immune responses that are reliant on their immune status and, therefore, cannot rely on vaccination alone for prevention. In a phase 1 and 2 trial, the recombinant zoster vaccine was immunogenic in recipients of autologous HSCT.[119] Additionally, a phase 3 randomised trial evaluating this vaccine in recipients of autologous HSCT, 53% of whom had multiple myeloma, showed clinical benefit for this patient population compared with placebo.[120] In this trial, the recombinant zoster vaccine was well tolerated and reduced episodes of varicella zoster virus, postherpetic neuralgia, and other complications associated with the virus, compared with placebo. Another randomised trial compared the immunogenicity of the recombinant zoster vaccine with that of a placebo in 1846 patients with haematological malignancies, of whom 983 individuals had multiple myeloma. Only two cases of varicella zoster virus developed among the 490 participants who had received the vaccine, compared with 12 cases among the 493 participants who were given placebo.[121] The recombinant zoster vaccine was also tested in a trial that included 69 patients with multiple myeloma at various stages of disease, with a median number of previous lines of therapy of one (IQR 1–7), including previous autologous HSCT.[122] The vaccine resulted in high rates of seroconversion from baseline (81% after one dose and 90% after two doses). Taken together, data from these studies suggest that the recombinant zoster vaccine is effective and safe in patients with multiple myeloma. Therefore, we recommend vaccinating this patient group with the recombinant zoster vaccine at the same dose schedule used in these trials[120,121]—ie, first dose 50–70 days after autologous HSCT and second dose 1–2 months later). For patients who have previously received the zoster vaccine live, we recommend revaccination with the recombinant zoster vaccine with the two-dose series, which should be initiated at least 8 weeks after administration of the zoster vaccine live.

In general, we do not advise use of live vaccines to immunise patients with multiple myeloma owing to the scarcity of safety or efficacy data. Besides the zoster vaccine live, live vaccines are available for measles, mumps, rubella, varicella, BCG, oral typhoid and yellow fever, intranasal influenza virus, and oral poliovirus. Effective inactivated vaccines are available for influenza and poliovirus. Live vaccines might be considered in patients with monoclonal gammopathy of unknown significance

and smouldering myeloma, given that they have a relatively healthy immune system. The measles, mumps, and rubella vaccine and the zoster vaccine live have been used following HSCT and might be considered in specific situations if patients are in remission.

Vaccination of non-immune close contacts

Patients with multiple myeloma, especially those receiving treatment, might not be able to mount an immune response to a pathogen, and immunisation of close contacts with inactivated vaccines might offer herd immunity for the patient. Thus, we recommend vaccination of non-immune close contacts with the vaccines usually indicated for immunocompetent individuals on the basis of vaccination history, age, and exposure history, with an emphasis on the use of inactivated vaccines only (NCCN level 2A).[118] We encourage health-care providers caring for patients with multiple myeloma to receive all indicated immunisations, particularly those for seasonal influenza viruses.

Timing of vaccinations

The timing of vaccination should be individualised on the basis of the risks and benefits of immunisation, including individual susceptibility to a specific infection, the patient's immune status (panel 2), and institutional and country guidelines.[12] Multiple studies with specific vaccines and existing guidelines have resulted in the recommendations outlined in panel 2.[68–79] The timing of vaccination has a role in maximising immune responses, such that patients with monoclonal gammopathy of unknown significance or smouldering multiple myeloma are more likely to have a robust immune response than are patients with active relapse.[70,71] The type of antineoplastic therapy given to the patient should also be considered, despite the challenges surrounding the use of combination regimens and the cumulative immunosuppression that develops during the disease.[73,74,123–125] For example, data suggest that immunomodulatory drugs (eg, lenalidomide and pomalidomide) cause increased immune responses, whereas the addition of dexamethasone can have a negative effect on immune responses.[73–75,124]

Assessing response to vaccination

The immune response to specific vaccinations might serve as a surrogate marker for the patient's ability to resist infections. Hence, vaccination might not be protective unless a serological response is confirmed. Assessing serological response might be considered after some vaccines to document the level and duration of response. For instance, measuring response to tetanus and HBV vaccines is relatively inexpensive and simple. However, a serological response to one vaccine does not imply response to other vaccines, and response to a polysaccharide or protein antigen in a polyvalent vaccine does not automatically imply responsiveness to all antigens. For example, responsiveness to one of at least 14 serotypes of pneumococcal polysaccharides does not ensure protection from all pneumococcal infections.

Assessing response to vaccination has several limitations, and it might not be feasible in most patients and against all vaccine serotypes. High costs, scarce availability in many countries, large technical variability, and absence of universal standardisation are additional limitations. Furthermore, non-responsiveness to vaccines might be limited to polysaccharide antigens only or might include polysaccharide and protein antigens. Therefore, assessing response to vaccination typically includes response to both protein antigens (eg, tetanus and diphtheria) and polysaccharide antigens (typically pneumococcal). Loss of serological immunity can also occur following additional immunosuppressive therapies.[125] Thus, we do not recommend routine assessment of response to vaccination (NCCN level 2A).

Travelling

We discourage patients with multiple myeloma to travel to areas of endemicity and we recommend vaccination, as well as prophylactic antimicrobials and immunoglobulins, as indicated (appendix p 3). A selection of travel vaccines should be individualised on the basis of the patient and the travel itinerary, and might include typhoid, polio, meningococcus, rabies, tick-borne encephalitis, Japanese encephalitis, and salmonella. Vaccination for yellow fever, BCG, and typhoid (oral) is contraindicated in patients with multiple myeloma.[118] Data regarding the safety and efficacy of some of these vaccines, such as yellow fever and BCG, in immunosuppressed patients are scarce. Before travel, we recommend that the patient attends a consultation with a travel medicine specialist or travel clinic and researches the Centers for Disease Control and Prevention website for updated country and region-specific recommendations,[126] including protective clothing, food and water precautions, prophylactic agents, patterns of resistance for specific pathogens, and travel vaccinations (panel 2). Country-specific guidelines should be obtained before travel from the countries themselves. Immunoglobulin might protect against measles, mumps, and rubella; varicella; hepatitis A; and rabies when vaccination is contraindicated, or if there is insufficient time to develop immunity before the trip.

Immunoglobulin replacement

Immunoglobulin replacement can be given intravenously, subcutaneously, or intramuscularly. For simplicity, we will refer to immunoglobulin replacement as intravenous immunoglobulin. A single study conducted in 1994 supported the use of intravenous immunoglobulin in patients with multiple myeloma. The trial enrolled 82 patients with plateau-phase (ie, stable) multiple myeloma, who were randomly assigned to receive either intravenous immunoglobulin at 0·4 g/kg or placebo every month for 1 year.[127] The chemotherapy used was only mildly immunosuppressive and given without antibiotic prophylaxis. Treatment with intravenous immunoglobulin

resulted in a significantly lower incidence and recurrence of severe infections than did treatment with placebo. As part of the study, 54 patients received Pneumovax before antineoplastic therapy, and their specific IgG responses were measured. An inadequate response to pneumococcal IgG antibody identified the patients who benefited the most from intravenous immunoglobulin. As such, intravenous immunoglobulin was recommended for patients with plateau-phase multiple myeloma who had hypogammaglobulinaemia and recurrent bacterial infections, and did not respond to pneumococcal immunisation. However, this trial took place before the era of autologous HSCT and novel treatments. The spectrum of infections in patients with multiple myeloma has changed considerably since, and more potent antimicrobial agents are now available that probably obviate the need for immunoglobulin prophylaxis. Additionally, two studies of prophylactic intravenous immunoglobulin in patients with multiple myeloma undergoing autologous HSCT did not show a reduction in viral and bacterial infections when intravenous immunoglobulin was given during the transplantation[128] or following the procedure,[129] suggesting that this therapy might not be protective in these settings.

Several factors refute the use of immunoglobulin replacement, such as the scarcity of supporting contemporary data, high cost, limited availability, and the potential for complications (including acute renal failure[130] and cardiovascular events).[131] We suggest a targeted approach, limiting replacement therapy to patients with serum IgG concentrations that are less than 400 mg/dL and who have severe and recurrent infections by encapsulated bacteria (or other pathogens reasonably thought to be due to hypogammaglobulinaemia), despite appropriate antimicrobial prophylaxis and immunisation (NCCN level 2A).

Another potential consideration includes patients with inadequate antibody production, especially to pneumococcal vaccines.[131] The use of immunoglobulin replacement can only benefit patients infected with pathogens that are likely to respond on the basis of specific antibody titres against target pathogens in the intravenous immunoglobulin preparation; for example, its use for infections caused by severe parvovirus B19 in patients with multiple myeloma.[63]

When planning to use intravenous immunoglobulin, it is essential to assess the patient's immune status and history of infections (especially recurrent ones), and to perform laboratory examinations of immune parameters (including specific antibody responses) to identify patients who could benefit from early intervention with intravenous immunoglobulin. The optimal dosage schedule of intravenous immunoglobulin is unclear. Ideally, the target dose schedule should be one that keeps the individual free from infection.[132] Targeting through IgG concentrations, as done in common variable immunodeficiency disorders or allogeneic HSCT, is limited by the scarcity of evidence in patients with multiple myeloma and is not usually applicable given that most of these patients have IgG multiple myeloma.

The infusion is typically well tolerated, and most reactions are rate-dependent. However, severe complications can occur, including acute renal failure and, rarely, cardiovascular events (eg, myocardial infarction, stroke, or venous thromboembolism).

We suggest the use of standard premedications to reduce the severity of infusion-related reactions. We also suggest hydration before the infusion, particularly in the presence of hyperviscosity, risk factors for renal complications, and in patients due to receive a sucrose-containing formulation. We suggest starting intravenous immunoglobulin treatment at a slow rate of 0·01 mL/kg per min and progressively increasing, as tolerated, to a maximum speed of 0·08 mL/kg per min. If serum IgA concentrations are undetectable, we suggest use of IgA-depleted intravenous immunoglobulin.[132] The subcutaneous and intramuscular formulations[133] are as protective as the intravenous formulation, and we suggest use of similar doses regardless of the route of administration.[134]

Post-exposure prophylaxis for immunosuppressed patients with multiple myeloma

Immunoglobulin prophylaxis might be protective for immunosuppressed patients with multiple myeloma after exposure to varicella, herpes zoster, and hepatitis A (NCCN level 2B). Severe illness after exposure to herpes zoster and, in particular, varicella are very high, and it is essential to establish the level of risk. The period of contagiousness begins 1–2 days before the onset of a rash,[135] so patients can present several days after their exposure. All immunocompromised patients with a history of varicella infection can be considered to be immune, except for recipients of autologous HSCT. For patients without a history of varicella infection, risk assessment includes establishing the susceptibility of the patient and duration of exposure. Risk factors include recent use of a proteasome inhibitor, no previous vaccination for varicella, severe immunosuppression, and face-to-face or close indoor contact lasting for more than 1 h. Post-exposure prophylaxis relies on varicella zoster immunoglobulins, ideally within 96 h of exposure, although the benefit could extend up to 10 days.[130] If varicella zoster immunoglobulins are not readily available, we recommend use of acyclovir following exposure. The typical incubation period for varicella is 14–16 days.[135] However, because varicella zoster immunoglobulins might prolong the incubation period,[136] we suggest monitoring recipients of this therapy for evidence of varicella up to 28 days after exposure.

For patients with multiple myeloma travelling to areas that are endemic for hepatitis A virus, we suggest a 0·02 mL/kg dose of hepatitis A immunoglobulin within 2 weeks of travel, and an initial dose of hepatitis A

Search strategy and selection criteria

We searched PubMed on Aug 15, 2021, without date restrictions, using the search terms "myeloma", "infection", "prophylaxis", "vaccination", and "therapy". We included articles that were published in English and deemed relevant to current practice after summary data were reviewed by panel members. The panel also reviewed and included existing guidelines from the Centers for Disease Control and Prevention, The Infectious Disease Society of America, and the National Comprehensive Cancer Network.

vaccine.[137] We also suggest a dose of hepatitis A immunoglobulin for patients who have a known exposure. For patients who are not immunised for HBV or who have an anti-HBV titre of less than 10 IU/L after vaccination, we suggest use of prophylaxis with tenofovir or entecavir, which obviates the need for HBV immunoglobulin. Occasionally, patients might require tetanus immunoglobulin[138] or human rabies immunoglobulin,[139] following specific high-risk exposures. For patients at risk of respiratory syncytial virus infection during the viral season, we do not recommend the use of either intravenous immunoglobulin or palivizumab, the humanised monoclonal antibody against the respiratory syncytial virus F glycoprotein.

Myeloid growth factors

Prophylactic granulocyte macrophage colony-stimulating factor or, preferably, granulocyte colony-stimulating factor are recommended in afebrile patients, in whom the anticipated risk of fever and neutropenia is at least 20% (NCCN level 2A).[82] This patient group would include individuals receiving autologous HSCT, chimeric antigen receptor T cells, and conventional chemotherapy (eg, dexamethasone–cisplatin–doxorubicin–cyclophosphamide–etoposide and dexamethasone–cyclophosphamide–etoposide–cisplatin). The decision to use granulocyte colony-stimulating factor to prevent treatment delays, such as those associated with lenalidomide, should be individualised.[140] Occasionally, growth factor support is required for chronic neutropenia.

Conclusions

Despite continued improvement in the response rates and survival of patients with multiple myeloma, infectious complications remain a clinically significant cause of morbidity and mortality. The general principles and recommendations provided in this Review provide a template from which an individualised patient-specific plan can be derived.

Contributors

NSR, EA, and NCM contributed equally to data collection, data analysis, data interpretation and manuscript writing. All other authors contributed equally to data interpretation and manuscript writing. All authors approved the final version and NSR had final responsibility for the decision to submit for publication.

Declaration of interests

NSR reports grants and consulting fees from Bristol Myers Squibb–Celgene, Bluebird Bio, Amgen, Janssen, GlaxoSmithKline, Caribou Biosciences, and Immuneel; and personal fees from Research to Practice, Karyopharm, Takeda, Amgen, and Janssen, outside the submitted work. SKK reports grants and consulting fees from Bristol Myers Squibb–Celgene, Takeda, Abbvie, Roche, and Janssen; grants from Medimmune, Tenebio, and Carsgen; and personal fees from Oncopeptides, Beigene, and Antengene, outside the submitted work. SL reports personal fees from Celgene, Janssen, Takeda, Novartis, Bristol Myers Squibb, GlaxoSmithKline, and Amgen, outside the submitted work. TM reports personal fees from GlaxoSmithKline; and grants from Sanofi, Janssen, and Amgen, outside the submitted work. MAG reports personal fees from Abbvie, Celgene, Akcea, i3Health, Prothena, Research to Practice, Alnylym, Ambry Genetric, Amgen, Janssen, Celgene, Aurora Bio, Ionis, Karyopharm, and Sanofi; and grants from Pfizer, outside the submitted work. PH reports grants and personal fees from Bristol Myers Squibb, Takeda, Amgen, Janssen, and Legend Biotech, outside the submitted work. HL reports personal fees from Janssen, Bristol Myers Squibb–Celgene, and Seattle Genetics; and grants and personal fees from Amgen and Takeda, outside the submitted work. JLK reports grants from Abbvie; personal fees from TG Therapeutics and Incyte; and grants and personal fees from Janssen, Bristol Myers Squibb, Amgen, and Takeda, outside the submitted work. ADC reports personal fees from Bristol Myers Squibb–Celgene, Janssen, Takeda, AstraZeneca, Genentech–Roche, Oncopeptides, and Seattle Genetics; grants from Novartis; and grants and personal fees from GlaxoSmithKline, outside the submitted work. LG reports personal fees from Amgen, Takeda, Novartis, Bristol Myers Squibb, Janssen, and Sanofi, outside the submitted work. ET reports personal fees from Bristol Myers Squibb; grants and personal fees from GlaxoSmithKline, Janssen, and Sanofi; and grants, personal fees, and consulting fees from Amgen, Genesis Pharma, and Takeda, outside the submitted work. RN reports personal fees from Takeda, Amgen, Celgene, Janssen, Karyopharm, GlaxoSmithKline, and Bristol Myers Squibb, outside the submitted work. NL reports consulting fees from AbbVie, Takeda, and Omeros; and grants from Omeros and Alnylam, outside the submitted work. ME reports grants from Amgen, Bristol Myers Squibb, Janssen, Takeda, Sanofi, and GlaxoSmithKline, outside the submitted work. AB reports personal fees from BeiGene, Sanofi Genzyme, Pharmacyclics, and Karyopharm, outside the submitted work. AC reports personal fees from Bristol Myers Squibb, Karyopharm, Sanofi, Oncopeptides, Antengene, GlaxoSmithKline, Secura Bio, and Shattuck Labs; grants from Pharmacyclics; and grants and personal fees from Janssen, Celgene, Novartis Pharmaceuticals, Amgen, Seattle Genetics, and Millenium–Takeda, outside the submitted work. BL reports personal fees from Karyopharm, Bristol Myers Squibb, Janssen, and GlaxoSmithKline; grants from Cellectar; and grants and personal fees from Amgen, outside the submitted work. JR reports personal fees from Bristol Myers Squibb, Takeda, Karyopharm, Oncopeptides, AstraZeneca, Adaptive Biotechnologies, Janssen, Secura Bio, and Sanofi, outside the submitted work. JSM reports personal fees from Amgen, Bristol Myers Squibb, Celgene, Janssen, Merck, Novartis, Takeda, Sanofi, Roche, GlaxoSmithKline, Abbvie, Karyopharm, and SecuraBio, outside the submitted work. KCA reports personal fees from Amgen, Pfizer, Janssen, AstraZeneca, Precision Biosciences, Windmill, Mana, Starton, Raqia, Oncopeptides, and C4 Therapeutics, outside the submitted work. PLM reports personal fees from BlueBird Biotech, Bristol Myers Squibb, Fate Therapeutics, Janssen, Juno, Karyopharm, Magenta Therapeutics, Takeda, and Medscape; grants from Celgene; and non-financial support from Sanofi, outside the submitted work. NCM reports personal fees from Bristol Myers Squibb, Oncopeptides, Janssen, Amgen, Novartis, Takeda, Abbvie, and C4 Therapeutics, outside the submitted work. All other authors declare no competing interests.

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