Consensus guidelines for Infection prophylaxis including vaccination in multiple myeloma

Indication for vaccination in MM – which vaccines to use and when

KEY Points

- Patients with multiple myeloma suffer from defects in humoral immunity and hence are at increased risk for infections with encapsulated organisms, particularly *streptococcus pneumoniae.*
- The principles that apply to vaccination of immunosuppressed cancer patients also apply to those with multiple myeloma.
- Response to vaccination is limited but one can take advantage of partial protection.
- Vaccine efficacy trials with clinical endpoint (i.e. infections) are lacking.
- The safety of some vaccines has not been tested in patients with myeloma.
- Vaccination with inactivated vaccines is safe in patients with myeloma. However, live vaccines should be avoided.
- The remission status of the underlying myeloma and the therapies applied (particularly high dose systemic corticosteroids or myeloablative chemotherapy) determine the patient's ability to develop a protective response after immunization. Response to vaccination is markedly reduced after chemotherapy. Therefore, patients should be vaccinated at earlier stages of the disease, such as MGUS or smoldering myeloma and when in remission.
- Response to vaccination after receipt of novel anti-myeloma agents (bortezomib, lenalidomide and thalidomide) remains to be determined.
- Vaccination of close contacts with inactivated vaccines is strongly recommended.

When to vaccinate patients?

- The most important vaccines for patients with MM are those against influenza and hepatitis B viruses and those deemed necessary because of the epidemiologic prevalence of a particular condition.
- Timing of vaccination should be individualized, taking into consideration the risks / benefits of vaccination including the individual susceptibility to infection and institution and country guidelines.

  Vaccination should be given as early as possible (e.g. during MGUS and smoldering phase of myeloma).

The absolute lymphocyte and CD4 counts and the plasma levels of uninvolved immunoglobulins may also be considered when planning the timing of vaccination although data in support of this approach are lacking.

Among patients scheduled to receive antimyeloma therapy, vaccination should be applied

-At least 14 days before initiation of chemotherapy or

-Before stem cell mobilization among patients undergoing this procedure.

-Upon achievement of best response or

-3 – 6 months after completion of chemotherapy or 6-12 months after receipt of high dose therapy.

-Vaccination may be given between cycles of chemotherapy although its effectiveness is significantly reduced.

- **Live vaccines** include vaccines for measles, mumps, and rubella (MMR), varicella (Varivax), Zoster (Zostavax), *Bacillus* Calmette-Geurin (BCG), oral typhoid and yellow fever, influenza virus (intranasal live) and oral polio (live). Effective inactivated alternative vaccines exist for influenza and polio viruses. Hence live vaccines against these viruses should not be used.
- No safety and efficacy data are available for the live influenza and typhoid vaccines in immunocompromised patients including those with MM. Similarly, no data exist regarding the safety of the varicella and zoster vaccines.
- Live vaccines are contraindicated in patients undergoing immunosuppressive therapy but may be considered in patients with MGUs and smoldering myeloma.
- Live vaccines may be given to at-risk patients in remission 3 – 6 months after completion of chemotherapy. Timing of vaccination should always be individualized (as above).
- Nonimmune close contacts of patients may be vaccinated for:
    - For measles, mumps, and rubella (MMR) if they are older than one year and are not pregnant or immunocompromised. No evidence exists to suggest that live-attenuated vaccine-strain viruses in MMR vaccine can be transmitted from person to person
    - For varicella if they are older than one year and are not pregnant or immunocompromised and have a negative or uncertain history of varicella disease with a negative serologic screen.
    - Where possible, nonimmune close contacts of patients should avoid direct contact with patients for 4- 6 weeks after vaccination with live vaccines. The time period during which nonimmune close contacts should avoid direct contact with immunosuppressed patients may be individualized according to institution and country guidelines and social settings.

- If a close contact develops a postvaccination varicella rash within 6 weeks of vaccination, the individual should avoid direct contact with the patient until all rash lesions have crusted or the rash has resolved. Affected areas of the skin should be covered.
- If polio vaccination is considered, the inactivated vaccine should be used. If a close contact inadvertently receives the oral polio vaccine, the vaccinee should avoid close contact with the patient for 4-6 weeks after vaccination; careful hand hygiene should be practiced after any contact with feces from the vaccinee (e.g., after changing the diaper of a vaccinated child) and contact with saliva should be avoided (e.g., shared food or utensils).

Assessing response to vaccination

- The immune response to specific vaccinations may serve as a surrogate marker for patient's ability to resist infections. Hence, vaccination may not provide protection unless response is confirmed. Assessing serologic response to vaccination may be considered after certain vaccines to document level of response to vaccine and/or assess for the maintenance of antibody responses over time. However, it may not be feasible to measure response in the majority of patients and against all vaccine serotypes. Assessing response to tetanus and Hepatitis B vaccines is relatively simple and inexpensive when compared to testing for other vaccines.
- Non-responsiveness to vaccines may be limited to polysaccharide antigens only or may include both polysaccharide and protein antigens. Hence, assessing response to vaccination typically includes response to both protein antigens (e.g., tetanus and diphtheria) and polysaccharide antigens (typically pneumococcal). Evaluation of responsiveness to the latter includes measuring ≥ 14 serotypes to pneumococcal polysaccharides (although titers to serotypes in the conjugate vaccine are not relevant to polysaccharide responsiveness). If the age-appropriate protective titers are achieved, the patient is considered to be responsive to polysaccharide antigens and no further evaluation is required. If the titers are not protective, then the patient may be revaccinated with the polysaccharide vaccine and the titers repeated one to two months later.
  The role of baseline assessment of protective antibody titers against specific vaccines appears to be limited.
- Assessing response to vaccination suffers several limitations:
  - Testing methods:
    - High costs
    - Limited availability in many countries
    - Large technical variability; specifically, the evaluation of pre- and post- vaccination titers should be performed by the same laboratory, applying the same method on pre-

and post- vaccination samples and the assay should be standardized to WHO standards.

- Vaccine responsiveness:
    - Serologic response to a polysaccharide antigen does not automatically imply responsiveness to all polysaccharide antigens; this principle extends to protein antigens as well.
    - Potential loss of response following additional immunosuppressive therapies

Additional comments on vaccination

Pneumococcal vaccine

The CDC/ACIP guidelines recommend the polysaccharide vaccine PPSV23 and should be considered for patients with MM. However, the conjugate pneumococcal vaccine PCV13 is more immunogenic than PPSV23. PCV13 contains the seven serotypes included in PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) and six additional serotypes (serotypes 1, 3, 5, 6A, 7F, and 19A). However, PPSV23 protects against 23 strains while PCV protects against 13 strains only and PCV 13 is not FDA-approved for use in adults.

The protective titer for *S. pneumoniae* is unknown and may vary by serotype. If a breakthrough pneumococcal infection develops after vaccination, identifying the strain serotype helps to know whether the breakthrough serotype was included in the vaccine (i.e. vaccine nonresponsivness). Additional doses of pneumococcal vaccine may be considered with the vaccine (i.e., PCV-13 or PPSV23) which includes the strain identified.

Travelers

Travel to areas of endemicity should be strongly discouraged for severely immunosuppressed myeloma patients. In the event that a travel is scheduled, vaccination should be given according to **Table 1.** Before travel, we recommend a consultation with a travel medicine specialist and researching the CDC website for specific recommendations including protective clothing, food and water precautions, prophylactic agents, patterns of resistance for certain pathogens and travel vaccinations.

Selection of travel vaccines should be individualized based on the host and the travel itinerary and may include typhoid, polio, *meningococcus*, rabies, tick-borne encephalitis, Japanese encephalitis, *salmonella* and others. However, data regarding the safety and efficacy of some of these vaccines in immunosuppressed patients are lacking.

Immunoglobulin may provide protection against measles, mumps, rubella, varicella, hepatitis A and rabies when vaccination is contraindicated or there is insufficient time to develop immunity.

Table 1. Recommendations for Active Immunization of Patients with Multiple Myeloma and their Close Contacts (Inactivated vaccines only)			
VACCINE	**Individuals Who Should Receive the Vaccine**	**Doses**	**Antibody testing after vaccination (if planned) and comments**
BACTERIAL			
Streptococcus pneumoniae Pneumococcal 23-Valent polysaccharide (PPSV23) Pneumococcal 13-valent conjugate (PCV13)	All patients	1 Repeat in 3 years	PPSV23 is recommended by the CDC. An alternative strategy relies on using 3 doses of PCV 13 with an additional dose of PPSV23 at 12 months to broaden the immune response. For severely immunocompromised patients who are likely to respond poorly to PPSV23, a fourth PCV dose may be used instead. May test ≥ 1 month after last dose then every 2 years. Consider antibiotic prophylaxis for patients who fail to mount a serologic response or who develop pneumococcal infections despite vaccination. According to epidemiological patterns of resistance, choices may include penicillin or a fluoroquinolone.
Haemophilus influenza type b conjugate	All patients	1	May test ≥ 1 month later after last dose
Meningococcal conjugate	-Patients at increased risk for meningococcal infection (asplenia and travel to areas of high endemicity). -Non-immune close contacts at risk (younger individuals and military)	1	
Tetanus, diphtheria toxoids and pertussis combined (Tdap♣)	-Patients who did not receive complete a primary vaccination for Tdap and those who did not have a booster dose of tetanus and diphtheria toxoid-containing vaccine in the previous10 years. May limit vaccination to Tetanus only based on epidemiological prevalence. -Non-immune close contacts and HCWs.	3♣	May test for tetanus antibody titers at baseline and ≥ 1 month after last dose May retest every 4 to 5 years. Booster dose of Td every 10 years
VIRAL			
Influenza (inactivated) (Seasonal and 2009 H1N1)	∆ All patients, non-immune close contacts and HCWs.	1, yearly	Testing not needed. Consider antiviral prophylaxis for patients undergoing intensive chemotherapy∆. Intranasal influenza vaccine (live) is contraindicated.
Recombinant Hepatitis B☼	Patients and nonimmune close contacts at increased risk (HBsAg (+) close contacts, travel to areas of high endemicity, behavioral/occupational exposure, chronic liver disease, end stage renal disease /hemodialysis, others).	3	May test ≥ 1 month after last dose, then every 6-12 months. Consider revaccinating nonresponders, preferably after the cause for non-responsiveness has resolved. Consider booster dose if antibody level falls <10 IU/L. May retest every 4-5 years.
Hepatitis A	TRAVELERS ONLY. Patients and nonimmune close contacts at increased risk (travel to areas of high endemicity, behavioral and occupational exposure, chronic liver disease, others)	2	May test ≥ 1 month after last dose. Hepatitis A-susceptible patients who are exposed or anticipate exposure to hepatitis A should receive prophylaxis with intravenous immunoglobulins.
Polio (inactivated)	All patients and nonimmune close contacts at increased risk	3	Vaccination not routinely recommended

HBsAg (+) = hepatitis B surface antigen–positive; CDC: Centers for Disease Prevention and Control. HCWs: healthcare workers. IU: international unit. ☼ May be used in conjunction with hepatitis B immunoglobulin prophylaxis. ∆ If close contacts and HCWs are vaccinated during an influenza outbreak, they should also receive ~ 2 weeks of chemoprophylaxis with oseltamivir or zanamivir based on strain susceptibility. If a nosocomial outbreak occurs with an influenza strain that is not contained in the available vaccine, close contacts and HCWs, should be administered influenza chemoprophylaxis based on strain susceptibility until the end of the outbreak.
♣Tdap should replace a single dose of Td for adults who have not received a prior dose of Tdap. Adults with uncertain history of primary vaccination series with tetanus and diphtheria toxoid-containing vaccines should begin or complete a primary vaccination series i.e. 3 doses of tetanus and diphtheria toxoid-containing vaccines; the first 2 doses at least 4 weeks apart and the third dose 6–12 months after the second.
Optional vaccines include varicella live vaccine –Varivax-but data on safety and efficacy are limited; Human papillomavirus; rabies

(consider if at risk such as occupational exposure); tick-borne encephalitis, Japanese B encephalitis and others.

IMMUNOGLOBULIN REPLACEMENT

Limited data: It is however important to recognize that no level of serum immunoglobulin has been shown to be protective and that no data exist to support the protective effect of IVIG with novel anti-myeloma agents or the optimal dosage-schedule and duration of IVIG therapy.

Protective effects: Immunoglobulin replacement may be useful in selected myeloma patients. In one study, prophylactic intravenous immunoglobulin (IVIG) (400 mg/kg every 4 weeks) prevented serious infection during the plateau phase of myeloma. However, antibiotic prophylaxis was not given in that study, and chemotherapy was mildly immunosuppressive as given in the early 90's.

Potential candidates: Because of the lack of data supporting the protective effects of IVIG with novel anti-myeloma agents, their high cost, the good protection conferred by antimicrobial agents, and the risk for IVIG-related renal dysfunction among myeloma patients, IVIG should be reserved for patients with significant hypogammaglobulinemia who, despite appropriate antimicrobial prophylaxis and immunization, suffer serious and/or recurrent infections likely to respond to IVIG (i.e. preparation with specific antibodies titers against target pathogen (s); e.g. encapsulated bacteria or common viral pathogens. The use of IVIG may possibly be considered in patients with poor antibody production especially to pneumococcal vaccines. Although IVIG preparations are not routinely tested for titers of specific antibodies except for measles, poliovirus, and hepatitis B surface antigen, various preparations are likely to have equivalent therapeutic efficacy.

Optimal dosage – schedule: No data exist to guide the optimal dosage-schedule of Ig replacement in patients with MM. A sensible target dose schedule of immunoglobulin replacement is that dose schedule which keeps that individual patient free from serious infections. Measuring antibodies against specific pathogens (e.g., pneumococcal polysaccharides) may help determining whether the selected Ig dosing maintains protective levels.

Based on experience with common variable immunodeficiency disorders, some have suggested targeting trough serum IgG concentrations (of uninvolved IgG) of > 400 mg/dL. However, this approach may not be applicable to the majority of myeloma patients (who have IgG Myeloma), is not practical and may result in excessive IVIG use.

Duration of therapy: The optimal duration of IVIG therapy in myeloma patients has not been examined and should be individualized taking into consideration the risks / benefits of IVIG. Potential variables to consider prior to stopping IVIG may include the absolute lymphocyte and/or CD4 counts, the plasma levels of uninvolved immunoglobulins, the remission status and whether the patient is still receiving severely immunosuppressive therapies. A six month trial of IVIG followed by an observation period during which the rate of serious infections is assessed may also be considered.

Route of administration: Immunoglobulin replacement can be given intravenously, subcutaneously or intramuscularly.

Intravenous route:

The half-life of IVIG is approximately three weeks among healthy adults but is significantly shorter among patients with fever and infection (likely as a result of hypercatabolism) and particularly among recipients of hematopoietic cell transplantation (HCT) in whom it ranges between 1 to 10 days only. IVIG are generally well tolerated and most reactions are related to the rate of administration. A potentially serious complication in MM patients is acute renal failure, usually with sucrose-containing preparations, but also reported with other IVIG products (**Table 2**). Patients with congenital IgA deficiency should receive IgA-depleted IVIG preparations (**Tables 2 and 3**). Where possible, use of local IVIG products is recommended.

Table 2: IgA and sucrose content by selected brands of Intravenous Immune globulins.
Other commercially available preparation should be evaluated for their IgA and sucrose content.

Brand	IgA Content µg/mL	Sucrose gram/gram of protein
Carimune® NF	720	1.67
Flebogamma®	<50	None
Gammagard® Liquid	37	None
Gammagard® S/D	≤2.2	None
Gamunex®	46	None
Octagam®	<200	None
Privigen®	≤25	None
Gammaplex	<10	None

Premedications

Premedications should be given to prevent /reduce the severity of IVIG infusion-related symptoms; 30 minutes prior to the infusion:

1) Acetaminophen (650 to 1000 mg orally) and
2) H1 antihistamines: Diphenhydramine (25 to 50 mg orally/IV/IM) or Cyproheptadine 4 mg orally
3) Glucocorticoids (particularly before the initial infusion, or when changing IVIG products).
    a. Intravenous: Methylprednisone 40 to 60 mg or dexamethasone 10-20 mg or
    b. Oral: must be given 1-2 hours before the infusion).
        1. Prednisone or Prednisolone 40 to 60 mg (oral corticosteroids

Hydration: Hydration with normal saline 10-20 mL/Kg before starting IVIG. Hydration is particularly important for patients with hyperviscosity, those receiving sucrose–containing IVIG **(Table 2)** and

patients with risk factors for renal complications including preexisting renal insufficiency, hypercalcemia, diabetes mellitus, older age (>65), concomitant nephrotoxins.

Infusion rates: to decrease infusion rate -related adverse effects, IVIG should be started at a slow rate of 0.01 mL/kg/min with progressive increase of the infusion rate at 15 or 30 min intervals under constant monitoring of symptoms and vital signs until the maximum rate of 0.08 mL/kg/min is reached. The rate of infusion can be individualized (shorter intervals to rate increases) with subsequent doses if a patient tolerated well the same IVIG product during the initial infusion.

Monitoring: signs and symptoms, vital signs**,** serum creatinine, complete blood count with differential (to monitor for neutropenia and anemia) and direct Coombs' test after the first dose (to check for hemolysis) in patients scheduled to receive high-dose IVIG over ≥ 2 days.

Other routes of administration:

Immunoglobulin replacement can also be given **subcutaneously (SCIG)** or **intramuscularly (IMIG)**.

SCIG is as effective as IVIG in protecting patients with primary immune deficiency from infection.

The SCIG offer several advantages over IVIG including**:**

- Fewer systemic reactions (<1% vs. ~ 5% for IVIG); SCIG is tolerated by most patients who had previous serious systemic reactions to IVIG or IMIG.
- Safely in most patients with IgA deficiency
- More consistent serum levels of IgG because SCIG is given in smaller, more frequent doses than IVIG
- Convenience of home-infusion
- No need for venous access
- No requirement for premedication in most patients
- Less expensive than IVIG.

However, SCIG require more frequent infusions (but may change from weekly to every other week injection) and local reactions may occur although they typically improve with time and their severity can be decreased with diphenhydramine premedication in patients who develop these reactions.

A 100 mg/kg SCIG per week is an adequate starting dose for most patients. However, and because therapeutic plasma levels are not attained as rapidly with SCIG, compared with IVIG, SCIG-naïve patients who need immediate protection from immunoglobulins can be given one loading dose of IVIG (400 mg/Kg), followed within seven days by 100 mg/kg of SCIG; alternatively, five consecutive daily doses of 100 mg/kg of SCIG can be administered, before starting the 100 mg/kg weekly dose.

To convert a patient from IVIG to SCIG, the same total monthly IVIG dose is divided by four and that amount is given weekly as SCIG, an approach which yields trough IgG levels that are approximately 10-20% higher than those achieved with IVIG.

To avoid wastage, the dose can be rounded to the nearest full vial or the dose adjusted slightly upwards or downwards on alternate weeks. Alternative doses can be used (e.g. 200 mg/kg every two weeks, or 50mg/kg twice a week) although the latter are not in the US FDA-approved labeling for SCIG products. Because bioavailability of SCIG may be decreased in obese individuals, monitoring serum IgG levels may be considered in such patients with dose – adjustment as needed.

The use of **IMIG** at 100-150 mg/kg/week is limited by the pain at site of administration and the risk of local tissue injury, such as bleeding in thrombocytopenic patients or nerve damage.

Table 3. **Subcutaneous and Intramuscular Immunoglobulins available in the U.S.**

Several additional products are available in the European Union. Use local product where possible.

Brand	Route	Concentration	IgA Content µg/mL
Hizentra	Subcutaneous	20%	≤25
Vivaglobin	Subcutaneous	16%	Not provided
GamaSTAN S/D	Intramuscular	15-18%	Not provided

Ten percent IVIG products are also well tolerated when given subcutaneously but none of these intravenous products is licensed for subcutaneous administration.

Post exposure prophylaxis for immunosuppressed myeloma patients at risk

Varicella and Zoster

Because attack rates after exposure to varicella and zoster are very high (higher risk with varicella), it is important to determine the risk following exposure. Risk assessment includes:

-whether the patient is susceptible (e.g., recent bortezomib therapy, no prior vaccination and no history of varicella),

-whether the exposure is significant enough to result in infection (prolonged face-to-face contact or close indoor contact lasting ≥one hour) and

-whether the patient is at higher risk for complications from the infection (ie, severe immunosuppression).

All immunocompromised patients with a history of varicella can be considered immune, with the exception of BMT recipients.

Post-exposure prophylaxis relies on acyclovir and VariZIG IM within 96 h of exposure. One dose of IVIG (400 mg/kg) should be administered if VariZIG cannot be given within this time frame. Patients given VariZIG should be monitored for varicella for 28 days after exposure because passive immunization may prolong the incubation period. These patients should also receive varicella vaccine five months after VariZIG unless the vaccine is contraindicated.

Hepatitis A

Hepatitis A-susceptible patients who anticipate exposure to hepatitis A (travel to endemic areas) and those who are exposed to hepatitis A should receive IVIG prophylaxis.

Hepatitis B

It is suggested that if the postvaccination anti-HBs titer is < 10 IU/L, hepatitis B Immunoglobulins (HBIG at 0.06 ml/kg) should be administered immediately prior to commencing highly immunosuppressive chemotherapy. However, antiviral prophylaxis with lamivudine is highly effective and obviates the need for HBIG.

Infection Prophylaxis in Patients with Multiple Myeloma

The decision to provide antimicrobial prophylaxis starts by an individualized assessment of the risk factors for infection with stratification into high and low-risk groups. The risk factors for serious infections in patients with MM result from the combined effects of a) exposure to pathogens; b) organ dysfunction (comorbidities) and c) the net state of immunosuppression.

The organ dysfunctions which place the MM patient at higher risk for infection include most importantly the presence of chronic renal disease (especially when requiring dialysis), but also diabetes mellitus, heavy smoking, iron overload, chronic liver disease, and others.

The net state of immunosuppression is determined by several factors including:

- Older age (> 70 years).
- Prior therapy type and extent (stem cell transplantation within the preceding two years, particularly if allogeneic, corticosteroids with >14 mg/kg prednisone equivalent in the preceding month, and combination myelosuppressive chemotherapy).
- Disease activity (refractory myeloma).

Laboratory evaluation of immune status in patients with multiple myeloma includes evaluation of:

- Innate immunity with absolute neutrophil count (ANC)
- Cellular immunity with absolute lymphocyte count (ALC) and CD4 cell count (routine testing of CD4 count is not recommended)
- Humoral immunity with the serum level of uninvolved serum Immunoglobulins. Specific antibody responses (usually IgG) in response to immunization (e.g. polysaccharide antigen responses) or to infection are however much better markers of humoral immunity although routine testing for specific antibody responses is not recommended.
- Severe immunosuppression is considered to be present if the ANC is <100 cells/μL (particularly if > 10-14 days), the ALC is < 300 cells/μL, the CD4 cell count is <200cells/μL or the serum level of uninvolved Immunoglobulins is markedly decreased/undetectable.

These laboratory parameters of immune status are not accurate surrogate markers that can determine the relative risk of infection for individual patients and hence cannot always be applied to individualize infection prophylaxis.

A high net state of immunosuppression places the MM patient at a high risk for severe infection.

In general, the risk for infection after non myelosuppressive therapies is related to the depth and duration of defects in humoral and cell-mediated immunity (CMI) (e.g. prolonged therapy with adrenal corticosteroids or bortezomib).

The risk for early infection following myelosuppressive therapies is closely related to depth and duration of neutropenia and regimen-induced mucosal damage. A higher risk for late infection is known to be

present in the setting of profound and prolonged immunosuppression of humoral and CMI (e.g. grade III-IV acute graft vs. host disease (GVHD) or extensive chronic GVHD).

Table 4. Risk factors for and strategies to prevent infection in patients with multiple myeloma. Also see tables 4 and 5 for risk stratification.

Risk factor	Pathogen / infection	Prevention / management
Disease-related		
Hypogammaglobulinemia	Encapsulated bacteria; *S. aureus*, GNB. Bacteremia, pneumonia, sinusitis, otitis, meningitis	IVIG, antibiotics, immunizations
Renal failure	Various	Prevention of conditions that result in renal failure†
Treatment-related		
Corticosteroid-induced T-cell immunodeficiency	Various bacteria Viruses (CMV, HSV, VZV, Influenza) Fungi (mucosal candidiasis, *P. jirovecii pneumonia)* Mycobacteria (tuberculosis) Endemic infections	Control of glycemia Immunizations Prophylaxis for *P. jirovecii pneumonia* (TMP-SMX)* *Candida* species (clotrimazole, fluconazole), influenza viruses (consider neuraminidase inhibitor during influenza season), HSV, VZV (acyclovir, valacyclovir, famciclovir) isoniazid if PPD positive or prior history of tuberculosis
Bortezomib	Herpes virus infections particularly HSV and VZV	Same as active disease and dexamethasone-based regimens, with emphasis on prophylaxis against HSV and VZV; closely monitor for skin lesions suggestive of VZV
Lenalidomide	Neutropenia – related infections	Adjust lenalidomide dose in presence of renal dysfunction to avoid excessive and prolonged myelosuppression. Consider G-CSF
Iron overload	Various infections	Erythropoietin instead of transfusions, consider iron chelation though no data exist to support its routine use
Bisphosphonates-induced osteonecrosis of the jaw	Oral bacteria (aerobic and anaerobic including actinomycosis)	Intensive oral hygiene Early diagnosis (pain, exposed bone) Prompt antibiotic therapy Consider avoiding bisphosphonates 3 months before and 3 months after major dental surgery
Chemotherapy-induced neutropenia	Gram-positive and gram negative bacteria, yeasts.	Antimicrobial prophylaxis, high dose (>5 x 10^6 CD34+ cells/kg) infused after high-dose therapy, G-CSF
Related to exposure		
History of infection	Various (e.g. fungal, viruses, *P. jirovecii*, tuberculosis)	Antimicrobial prophylaxis / pre-emptive therapy
Environmental exposure	Respiratory viruses, water- or food-borne pathogens	Immunizations; patient education and appropriate infection control measures;
Travel to endemic areas	Various including malaria and tuberculosis	Consultation, before travel, with an infectious disease physician and / or researching the CDC website for specific recommendations including prophylactic agents, patterns of resistance for certain pathogens and vaccination needed

IVIG = Intravenous immunoglobulin; TMP-SMX = trimethoprim-sulfamethoxazole; CMV = cytomegalovirus; *P. jirovecii = Pneumocystis jirovecii;* HSV = herpes simplex virus; VZV = varicella-zoster virus; GNB = gram negative bacilli (enterobacteriaceae, *P. Aeruginosa).* G-CSF = granulocyte colony-stimulating factor; Ig = immunoglobulin; TMP-SMX = trimethoprim-sulfamethoxazole; IVIG = intravenous immunoglobulin; IgG = immunoglobulin G; CMV = cytomegalovirus; HSV = herpes simplex virus; VZV = varicella-zoster virus; PCR = polymerase chain reaction; ESA = Erythropoietin-stimulating agents.

† Sepsis, hypovolemia, drugs (non-steroid anti-inflammatory drugs, others), tumor lysis, obstruction, hypercalcemia.

Table 5. Dosage-schedule of antimicrobial agents used for prophylaxis and treatment of infection in patients with multiple myeloma. *Regional patterns of susceptibility should dictate the selection antimicrobial agents.*

Disease	Prophylaxis	Treatment
Bacterial infections		
Neutropenic	Fluoroquinolone† (FQ)	Antipseudomonal β-lactam antibiotic‡
Non neutropenic	FQ †, TMP-SMX – 800 mg/160 mg PO daily or Amoxacillin	Broad spectrum antibiotic (FQ †, β-lactam, other). If FQ† not used in prophylaxis, add a FQ† or macrolide§ if pneumonia is present
Clostridium difficile colitis	Consider prophylaxis with metronidazole PO (500 mg TID) only if prior history of C. difficile colitis.	Metronidazole – 500 mg PO TID or vancomycin – 125 mg PO QID; Treat for 2-4 weeks
Tuberculosis	Isoniazid – 300 mg PO daily	Various regimens
Fungal infections		
Oropharyngeal candidiasis	Clotrimazole troches (10 mg, five times daily) or fluconazole – 100-200 mg PO daily	Fluconazole – 200-400 mg PO daily for 7-10 days
Pneumocystis jirovecii	TMP-SMX –160 mg/800 mg PO daily or twice a week, pentamidine – 300 mg aerosol monthly, or dapsone – 100 mg PO daily, or atovaquone 1500 mg PO daily	TMP-SMX – 15-20 mg/kg of TMP IV daily (severe infection) or atovaquone 1500 mg PO daily (mild-moderate infection); treat for 3 weeks and give secondary prophylaxis
Viral infections		
Herpes simplex	Acyclovir – 200 - 400 mg PO BID or TID, valacyclovir – 500 mg PO TID or famciclovir – 500 mg PO TID	7-14 days of acyclovir – 250 mg/m^2 IV TID, valacyclovir – 1 g PO TID or famciclovir – 500 mg PO BID
Herpes zoster	Acyclovir – 400 mg PO BID or TID, valacyclovir – 500 mg PO TID or famciclovir – 500 mg PO TID	7-14 days of acyclovir – 500 mg/m^2 IV TID, valacyclovir – 1 g PO TID or famciclovir – 500 mg PO BID
Cytomegalovirus	Ganciclovir - 5 mg/kg IV BID or valganciclovir - 900 mg/d PO or foscarnet – 60 mg/kg IV BID	14-21 days of ganciclovir IV- 5 mg/kg IV BID or valganciclovir PO - 900 mg/d BID or foscarnet – 90 mg/kg IV BID
Influenza virus	Oseltamivir – 75 mg PO daily for the duration of the Influenza season; ZanamivirΔ	Oseltamivir – 75 mg PO BID for 5-7 days. ZanamivirΔ

Unless otherwise stated, the duration of treatment depends on clinical response and persistence or resolution of immunosuppression; Antibiotic choices should be dictated by local epidemiological factors. TMP-SMX = trimethoprim-sulfamethoxazole; PO = per os; TID = three times a day; QID = four times a day; BID = twice a day

†Includes ciprofloxacin – 500 mg PO BID, levofloxacin – 500 mg PO daily, moxifloxacin – 400 mg PO daily, others.

‡Antipseudomonal β-lactam antibiotics: ceftazidime, cefepime, piperacillin-tazobactam, imipenem or meropenem.

§ Macrolides: erythromycin 500 mg PO BID, azithromycin 400 mg/d PO/IV or clarithromycin 500 mg BID PO or IV.

Δ Zanamivir: Two 5-mg inhalations (10 mg total) once per day for prophylaxis or twice a day (20 mg total) for treatment.

Table 6. Preventive measures in severely immunosuppressed patients with myeloma

GENERAL MEASURES

MAINTAINING GOOD PERSONAL HYGIENE

Handwashing, frequent, preferably with liquid soap, before eating and after contact with contaminated materials.

Maintaining good dental hygiene: brushing teeth with soft bristle toothbrush after meals, and flossing daily. Not sharing toothbrushes and changing toothbrush every three months, particularly in patients treated with bisphosphonates.

Unprotected sexual encounters including oral and anal sex are associated with the risk of transmitting viruses such as HIV, *Human papillomavirus*, *Herpes simplex*, *Hepatitis B, others* and hence should be avoided. Kissing is less likely to transmit these viruses but must also be avoided in the setting of mucositis or in patients with oral ulcers or lesions or if a patients partner has had a history of herpetic outbreaks

AVOIDING AT RISK ENVIRONMENTAL EXPOSURE

Individuals (visitors, household members/caregivers and health care workers)

Avoiding exposure to individuals with any of the following:

-Signs and symptoms of infection including respiratory infections (fever, cough, etc.)

-Skin lesions (herpes simplex, varicella zoster, other)

-Infectious conjunctivitis

-Recent vaccination with live vaccines (e.g. the oral polio vaccine)

-In endemic areas: exposure to individuals with tuberculosis, hepatitis A infection, measles, others.

-Encouraging influenza virus vaccination of close contacts before the influenza season

Food and water

Food should be thoroughly cooked and fruits and vegetables washed before eating.

Avoiding drinking potentially contaminated water.

Recreational activities

Avoiding swimming in public places, particularly in stagnant water.

Avoiding outdoor activities at risk for infections (e.g. exploring caves)

Pets and livestock

Pets may also pose an infectious disease risk to severely immunosuppressed myeloma patients and thus the following measures must be taken to mitigate these risks

--Pets must have updated and appropriate vaccinations specific to their locality

--Avoid handling the droppings of pets especially birds and cats

-- Skinning and birthing of wild game /animals should be avoided

--Animal bites should addressed promptly for initiation of appropriate antibiotics and local wound care

-- DEET / insect repellant use in case of a potential exposure to insect bites (e.g. risk for *West Nile* virus, arthropod-borne illnesses).

Occupational settings

Avoiding working in settings that may cause exposure to pathogens

Travel to endemic areas (see Table 7)

Consultation, before travel, with a travel medicine specialist♠ and / or researching the CDC website for specific recommendations including prophylactic agents, patterns of antimicrobial resistance for certain pathogens and vaccination needed when traveling with particular emphasis on malaria and tuberculosis.

HIV = Human immunodeficiency virus; CDC: Centers for Disease Control and Prevention.

♠ Travel medicine specialists include infectious disease physicians and clinicians practicing in travel clinics (family physicians, internists, others).

Table 7. Travel precautions for immunocompromised patients with multiple myeloma

Prior to travel, a consultation with a travel medicine specialist ♠is recommended with focus on:

1. Assessing immune status as discussed above; severely immunocompromised patients should be advised against travel to areas where potentially serious infections are endemic.
2. Updating immunization **(Table 1)** and reviewing patient's medications♦.
3. Educating patient about the travel region-specific risks including the need to apply DEET / insect repellant to prevent potential exposure to insect bites (e.g. risk for *West Nile* virus, malaria, arthropod-borne illnesses).
4. Providing additional protection depending on travel plans (countries / regions)
    a. Vaccination: additional vaccination for country-specific risks§
    b. Malaria
        i. Minimize insect bites (insect repellents, bed nets and protective clothing).
        ii. Antimicrobial prophylaxis (country/region – specific) §.
    c. Traveler's diarrhea
        i. Food precautions (only bottled or boiled beverages allowed; avoidance of raw foods; however, fruit and vegetables that can be peeled are safe).
        ii. Antibiotic supply for self administration if diarrhea persists > 48 hours or is associated with fever (fluoroquinolone or macrolide antibiotic) §. Where possible, consultation with a physician is strongly recommended.
    d. Respiratory fungal infection
        i. Southeast Asia: penicilliosis *(Penicillium marneffei*).
        ii. USA: histoplasmosis, blastomycosis and coccidioidomycosis.
        iii. Latin American: same plus paracoccidioidomycosis
        iv. Worldwide: cryptococcosis

        Avoid activities associated with increased risk for these infections (e.g. excavation)
    e. Other infections:
        i. Tick-borne diseases, babesiosis, others (use of insect repellant).
5. Intravenous immune globulins offer protection against hepatitis A, measles and varicella and should be considered for seronegative patients traveling to areas where these infections are endemic.

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§ Data available on the website of the Centers for Disease Control and Prevention.

♠ Travel medicine specialists include infectious disease physicians and clinicians practicing in travel clinics (family physicians, internists, others).

♦ Myeloma therapy (current and recent) and other medications taken by the patient.