Teh Benjamin W (Orcid ID: 0000-0003-0213-5470)
Roberts Matthew Blake (Orcid ID: 0000-0003-0869-6463)
Chan Henry (Orcid ID: 0000-0002-0156-4655)

Executive summary of consensus clinical practice guidelines for the prevention of infection in patients with multiple myeloma

Benjamin W. Teh[1,2,3], Gemma Reynolds[1,2,4], Monica A. Slavin[1,2,3], Louise Cooley[5], Matthew Roberts[6], Eunice Liu[7], Karin Thursky[1,2,3], Dipti Talaulikar[8,9], Peter Mollee[10,11], Ferenc Szabo[12,13,14], Chris Ward[15,16], Henry Chan[17,18], H.Miles Prince[3,19], Simon J. Harrison[2,3,20] on behalf of the Medical and Scientific Advisory Group, Myeloma Australia and National Centre for Infections in Cancer.

[1]Department of infectious Diseases, Peter MacCallum Cancer Centre, Victoria
[2]National Centre for Infections in Cancer, Peter MacCallum Cancer Centre, Victoria
[3]Sir Peter MacCallum Department of Oncology, University of Melbourne, Victoria
[4]Department of Infectious Diseases, Austin Health, Victoria
[5]Department of Infectious Diseases, Royal Hobart Hospital, Tasmania
[6]Department of Infectious Diseases, Royal Adelaide Hospital, SA
[7]Department of Infectious Diseases, Royal North Shore Hospital, NSW
[8]Department of Haematology, Canberra Hospital, ACT
[9]College of Health and Medicine, Australian National University, ACT
[10]Queensland Haematology Department, Princess Alexandra Hospital, Queensland
[11]School of Medicine, University of Queensland, Queensland
[12]Royal Darwin Hospital, Haematology Department, NT
[13]Menzies School of Health Research, NT
[14] Flinders University, Adelaide, South Australia
[15] Department of Haematology, Royal North Shore Hospital, Sydney, NSW
[16]Kolling Institute, University of Sydney, NSW
[17]Department of Haematology, Waitemata District Health Board, New Zealand
[18]Faculty of Medical and Health Sciences, The University of Auckland, New Zealand
[19]Epworth Healthcare, Victoria
[20] Department of Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Victoria

Corresponding author:
A/Prof. Benjamin W. Teh
Department of Infectious Diseases
Peter MacCallum Cancer Centre
305 Grattan Street,
Melbourne 3000, Victoria, Australia

Tel: +613 8559 7994
Email: ben.teh@petermac.org

Abstract count: 139
Manuscript word count: 1585
5 tables
Keywords: myeloma; infection; prevention; guidelines

Acknowledgement
BWT is supported by the Australian Government Medical Research Future Fund Investigator Fellowship (APP1195894). MAS is supported by the National Health and Medical Research Council (NHMRC) Investigator Fellowship. The National Centre for Infections in Cancer is supported by a NHMRC Centre of Research Excellence grant (APP1116876).

Conflict of Interest
BWT is on advisory boards for CSL-Behring, Takeda (no personal fees received) and has received research funding from Merck Sharp and Dohme, Sanofi and Seqirus.

MAS has received research funding from Gilead Sciences, Merck Sharpe and Dohme (MSD), F2G She sits on advisory boards for Gilead, Takeda, CSL Behring, F2G and MSD.

DT is chair of the Haematology SWG, National Blood Authority (non remunerated) and has received research funding from Roche, Janssen and honoraria from Takeda, Roche, EUSA, Janssen, Beigene, CSL and Amgen.

PM is on advisory boards for Amgen, BMS, Janssen, Caelum, EUSA, Pfizer, SkylineDx and Takeda (no personal fees received) and has received research funding form Janssen and Pfizer.

SJH is on the advisory boards and consultant for AbbVie, Amgen, Celgene, GSK, Janssen Cilag, Novartis, Roche/Genetec, Takeda and consultant for Sanofi, EUSA and Terumo. He has received research funding from Amgen, Celgene, GSK, Janssen Cilag, Novartis and Haemalogix. He has been an investigator on studies conducted by AbbVie, Amgen, Celgene, Janssen Cilag, Novartis and Roche/Genetec. He has received honoraria from Amgen, Celgene, Janssen Cilag, Novartis, Roche/Genetec and Takeda.

Other authors have no declared conflicts of interest.

Introduction
In Australia, over 2000 people are diagnosed with multiple myeloma every year and survival continues to increase with increasing availability of new therapeutic options (1). Treatment options include second generation immunomodulatory drugs (IMiDs), proteasome inhibitors (PI) and monoclonal antibodies (Mabs), bispecific antibody (BsAbs), antibody-drug conjugates (ADC) and cellular therapies including chimeric antigen receptor T cell therapies (CAR-T) (2).

Infection remains a leading contributor to morbidity and mortality in patients with myeloma(3, 4). The increased risk for infection is due to a combination of patient, disease and treatment-related factors(3). As treatments for myeloma continue to expand and evolve, so do the patterns, risk periods and risk factors for infection(5, 6).

This clinical practice guideline (Appendix S1) was developed by the Medical Scientific Advisory

Group, Myeloma Australia together with the National Centre for Infections in Cancer. It encompasses the epidemiology of infection, and risk factors for infection; and offers recommendations on screening for infection, prophylaxis and vaccination to assist with the prevention of infections in patients with myeloma. Recommendations are graded according to established GRADE criteria. The full version of the guideline is available at the Myeloma Australia website.

Epidemiology of infection

Patients with myeloma are at higher risk for infections compared to matched controls and this higher risk is maintained despite evolution of myeloma treatment regimens (7). The majority of infections are bacterial with clinical syndromes of pneumonia and sepsis reported whilst higher risk for zoster and influenza viral infections are also observed (7).

Infection rates and patterns vary by treatment period. Between 30-65% of patients with newly diagnosed myeloma experience at least 1 episode of infection within 12 months of disease diagnosis with the peak risk period in the first 4-6 months following disease diagnosis, regardless of transplant eligibility (5, 8-10). Disease burden and associated immune deficits contribute to this increased risk (3). Up to 60% of infections were grade 3 or higher (5, 10).

For patients who are transplant-eligible, the period of intensive myeloid suppression following conditioning chemotherapy remains a high-risk period (rates up to 60%) associated with infections of high severity (5, 11, 12). Neutropenic fever is the most common syndrome reported and only 20-40% of episodes of infection have a pathogen detected (5, 12).

Myeloma is a disease characterised by relapses necessitating ongoing therapy to achieve disease control. This results in cumulative immune suppression which contributes to increased risk for infection (3). Between 40-90% of patients experience an episode of infection (30% severe infection) during treatment for disease progression with the use of second generation IMiD, PI or Mab therapies (e.g daratumumab) in combination (6, 13).

Overall, the respiratory tract is the most common site of infection followed by blood stream infections (BSI)(5, 14, 15). Potential site of infection, frequency of testing, type of assay and variable sensitivity of tests utilised can impact rates and patterns of microbiologically-defined infections. Across all time periods, bacteria constitute the majority of microbiologically defined infections followed closely by viral infections(5). For bacterial infections, the proportion of gram-negative and gram-positive infections are similar with *E. coli*, *Enterococcus sp.,* Coagulase negative *Staphylococcus* and *C. difficile* common pathogens isolated whilst respiratory viral infections and reactivation of herpes viruses (zoster [VZV], herpes simplex [HSV] and cytomegalovirus [CMV]) are the common viral pathogens detected(5, 14, 15). The morbidity and mortality from viral respiratory tract infections such as influenza and SARS-CoV-2 remains high (16, 17).Rates of invasive fungal disease (IFD) remain low overall with *Pneumocystis jirovecii* pneumonia (PJP) and *Candida sp.* more commonly reported (5). Characteristics of infection episodes by treatment period and of key pathogens are discussed in further detail in the full version of the guideline.

Risk factors for infection

In patients with myeloma, risk for infection is due to a combination of patient, disease and treatment specific factors(3, 18). Risk factors for infection by treatment stage are summarised in Table 1. It is vital that disease factors and previous treatments are taken into account when evaluating a patient's risk for infection in the setting of new generation myeloma therapies. Table 2 summarises the treatment classes and their infection rates as mostly derived from systematic review of clinical drug trials(19). Overall, disease and treatment-related risk factors can be targeted through key prevention measures to reduce burden of infection.

Screening for infection

Latent infections such as tuberculosis (LTBI), strongyloides, and Hepatitis B (HBV) can reactivate during immunosuppression (20, 21). Similarly, the natural history of untreated chronic infections, such as chronic HBV and hepatitis C (HCV) can get accelerated (22). Adverse outcomes can be prevented by early treatment or prophylaxis. Prior to commencement of active therapy, universal screening is recommended for HBV, HCV and human immunodeficiency virus (HIV) while universal screening for latent TB should be considered. Risk-based screening is recommended for latent tropical pathogens (Table 3).

Prevention of infection

Different strategies appropriately targeted to high-risk periods are required to reduce the burden of infection in patients with myeloma.

Antibacterial prophylaxis

There have been mixed findings in randomised trials of antibacterial prophylaxis during first line treatment for myeloma in the era of conventional chemotherapy (23, 24). A recent trial of levofloxacin prophylaxis for 12 weeks demonstrated a lower rate of febrile episodes and death (3% difference) at 12 weeks but no significant difference in infection-related deaths or overall survival at 12 months (25). The benefit of prophylaxis was not universal and higher rates of fluoroquinolone resistant gram-negative isolates were noted with use of levofloxacin (25). When used, trimethoprim-sulfamethoxazole as PJP prophylaxis independently reduced risk for the primary outcome of similar magnitude to levofloxacin (25).

Similarly, the use of antibacterial prophylaxis during the haematopoietic stem cell transplantation (HCT) period was associated with significant lower rates of neutropenic fever and BSI, no difference in mortality rates but higher rates of antibiotic resistant bacteria (26, 27). There are no studies of antibacterial prophylaxis during treatment of relapsed disease. In the absence of clear mortality benefit, routine antibacterial prophylaxis is not recommended during first-line therapy or for autologous HCT (Table 4). The use of trimethoprim-sulfamethoxazole as PJP prophylaxis could confer some concurrent antibacterial benefit.

Antiviral prophylaxis

Reactivation of latent viruses relates to depletion of cellular immunity as part of HCT conditioning, selective depletion of viral specific T-cells and disrupted viral antigen processing from PIs (3, 28). Reactivation rates of up to 80% for HSV and up to 50% for zoster occur in the absence of antiviral prophylaxis (29-31). Use of elotuzumab has been associated with higher rates of zoster reactivation (32). Antiviral prophylaxis with acyclovir and valaciclovir effectively reduces risk for HSV and VZV reactivation associated with HCT or PI treatment (28,

30, 31). In the absence of prophylaxis, rates of HBV reactivation are up to 50% and 9% for chronic HBV and resolved HBV infections respectively (33, 34). HCT, PI and high-dose corticosteroids are risk factors for HBV reactivation and prophylaxis should be considered (30). Recommendations for antiviral prophylaxis are summarised in Table 4.

Antifungal prophylaxis

In the current era, IFD rates in myeloma patients have remained below 6% (35, 36). Myelosuppression and breakdown of mucosal barriers during HCT remains a key risk period for Candida BSI supporting the need for fluconazole prophylaxis (36, 37). Treatment related factors such as cumulative high doses of corticosteroids (16-20mg of prednisolone-equivalent daily for 4 or more weeks) drive risk for PJP (38, 39). Trimethoprim-sulfamethoxazole reduces PJP risk and its use is recommended for treatment regimens that meet this corticosteroid threshold (40).

For other periods, there should be individual assessment of IFD risk, taking into consideration immune impacts of proposed treatments (e.g. prolonged neutropenia), prior number of lines of therapy, previous IFD episodes and known colonisation(41). Recommendations for antifungal prophylaxis are summarised in Table 4.

Immunoglobulin replacement

Secondary immune deficiency with hypogammaglobulinaemia is a feature of myeloma(3). In a limited number of studies, the use of immunoglobulin replacement was associated with lower rates of serious and life-threatening infection (predominantly respiratory tract infections) (42, 43). Immunoglobulin replacement should be considered in line with National Blood Authority criteria (44).

Vaccination

Patients with myeloma remain at higher risk for invasive infection with encapsulated bacteria such as *S. pneumoniae* compared to the general population while level of protective antibodies remain significantly lower (45-47). Delayed immune recovery following HCT is associated with high risk for infection with encapsulated bacteria and viral infections (reactivation, respiratory tract) in the first 12 months following HCT (3, 16, 28, 46, 48). Vaccination is an effective strategy to reduce risk and burden of key infections and is recommended. Timing of vaccination is guided by consideration of patient, disease and treatment-related factors to ensure optimal response (49). The evidence supporting vaccination recommendations is discussed in the full version of the guideline. Overall recommendations are summarised in Table 5. For SARS-CoV-2, other preventative measures such as the use of long-acting monoclonal antibodies as pre-exposure prophylaxis have been utilised in addition to vaccination. However, recommendations for their use remain dynamic and are continually updated due to emergence of new SARS-COV-2 variants of concern.

Future directions

Ongoing research is required to address significant gaps in our understanding of the epidemiology of infection with the use of new generation therapies such as Mabs, BsAbs, ADC and CAR-T therapies. New studies and trials are required to address optimal use of antimicrobial prophylaxis and to test novel vaccination strategies. Use of immune profiling

has been piloted but require validation before it can be used for personalised prediction of infection risk (50). Ongoing cross disciplinary research collaboration will help address these research gaps and generate new evidence for future guidance to reduce morbidity and mortality from infection in patients with myeloma.

Acknowledgement
BWT is supported by the Australian Government Medical Research Future Fund Investigator Fellowship (APP1195894). MAS is supported by the National Health and Medical Research Council (NHMRC) Investigator Fellowship. The National Centre for Infections in Cancer is supported by a NHMRC Centre of Research Excellence grant (APP1116876).

Conflict of Interest
BWT is on advisory boards for CSL-Behring, Takeda (no personal fees received) and has received research funding from Merck Sharp and Dohme, Sanofi and Seqirus.
MAS has received research funding from Gilead Sciences, Merck Sharpe and Dohme (MSD), F2G She sits on advisory boards for Gilead, Takeda, CSL Behring, F2G and MSD.
DT is chair of the Haematology SWG, National Blood Authority (non remunerated) and has received research funding from Roche, Janssen and honoraria from Takeda, Roche, EUSA, Janssen, Beigene, CSL and Amgen.
PM is on advisory boards for Amgen, BMS, Janssen, Caelum, EUSA, Pfizer, SkylineDx and Takeda (no personal fees received) and has received research funding form Janssen and Pfizer.
SJH is on the advisory boards and consultant for AbbVie, Amgen, Celgene, GSK, Janssen Cilag, Novartis, Roche/Genetec, Takeda and consultant for Sanofi, EUSA and Terumo. He has received research funding from Amgen, Celgene, GSK, Janssen Cilag, Novartis and Haemalogix. He has been an investigator on studies conducted by AbbVie, Amgen, Celgene, Janssen Cilag, Novartis and Roche/Genetec. He has received honoraria from Amgen, Celgene, Janssen Cilag, Novartis, Roche/Genetec and Takeda.

Other authors have no declared conflicts of interest.

Treatment stage	**Risk factors**
First line	ECOG ≥2 Higher ISS BM plasma cell percentage > 70% Higher LDH Anaemia Lymphopenia Higher creatinine Conventional chemotherapy

	Cumulative corticosteroid dose
First line – transplant ineligible	ECOG, Serum beta-2 microglobulin, LDH, haemoglobin 1 point each ECOG ≥2 LDH≥200 U/L Hb≤11g/dL 2 points Beta-2 microglobulin ≥6 mg/L Score 2-5 pts = high risk
Autologous transplant	Increasing time for disease diagnosis Beta-2 microglobulin >3.5 Prior use of bortezomib Use of chemotherapy as mobilising regimen More prior chemotherapy Higher Karnofsky performance status lower risk
Relapse	Neutropenia Lymphopenia Lower CD56+ cells Receipt of PI, IMID and PI, Mabs-based therapies Increasing lines of therapy (>4)

ECOG: Eastern Cooperative Oncology group; BM: bone marrow; ISS: international staging system; LDH: lactate dehydrogenase; Hb: haemaglobin; PI: proteasome inhibitor; IMID: immunomodulatory drug; Mabs: monoclonal antibody.
References in the full version of guideline.

Table 1: Risk factors for infection in patients with myeloma by treatment stage

Treatment class	Treatment stage	Rates of infection
Immunomodulatory drugs		

Thalidomide, Lenalidomide	First-line HCT	Severe infection 15-22%
Thalidomide, Lenalidomide	First line non-HCT	Severe infection 11-13%
Thalidomide, Lenalidomide	Maintenance	All grade infection 50% Severe infection 10%
Thalidomide, Lenalidomide	Relapse/Refractory	Severe infection 7-23%
Pomalidomide	Relapse/Refractory	Severe infection 30%
Proteasome inhibitor		
Bortezomib	First-line HCT	Severe infection 20%
Bortezomib with lenalidomide, dexamethasone	First-line HCT	All grade infection 28% Severe infection 9%
Bortezomib	First line non-HCT	Severe infection 10%
Carfilzomib with lenalidomide or thalidomide, dexamethasone	First-line HCT	All grade infection 74% Severe infection 11-22%
Bortezomib	Relapse/Refractory	Severe infection Pneumonia 8%
Carfilzomib	Relapse/Refractory	Severe infection Pneumonia 8-10%
Ixazomib With lenalidomide, dexamethasone	Relapse/Refractory	All grade URTI 23%
Ixazomib With pomalidomide or bendamustine, dexamethasone	Relapse/Refractory	All grade infection 50-60% Severe infection 14-22%
Monoclonal antibody		

Daratumumab With bortezomib, thalidomide, dexamethasone	First-line HCT	All grade infection 65% Severe infection 22%
Daratumumab With bortezomib, lenalidomide, dexamethasone	First-line HCT Complete single course	All grade infection 91% Severe infection 23%
Daratumumab With bortezomib, melphalan, prednisolone	First-line non HCT	All grade infection 67% Severe infection 23%
Daratumumab	Maintenance	Severe infection 11%
Daratumumab With bortezomib, dexamethasone	Relapse/Refractory	Severe infection 21%
Daratumumab With lenalidomide, dexamethasone	Relapse/Refractory	Severe infection 28%
Daratumumab With pomalidomide, dexamethasone	Relapse/Refractory	All grade infection 76% Severe infection 31%
Isatuximab with pomalidomide, dexamethasone	Relapse/Refractory	All grade URTI 28-42% Severe infection 16-18%
Elotuzumab with lenalidomide, dexamethasone	Relapse/Refractory	All grade infection 81%
Elotuzumab with pomalidomide, dexamethasone	Relapse/Refractory	All grade infection 65% Severe infection 13%
Drug-antibody conjugate		

Belantamab	Relapsed/refractory	All grade infections 14-23%
Bi-specific antibody therapy		
AMG 420	Relapse/Refractory	All grade infection 33% Severe infection 29%
BCMA chimeric antigen receptor T-cell therapy		
Idecabtagene	Relapse/Refractory	All grade infection 67-75%
Selective inhibitor of nuclear export		
Selinexor with carfilzomib, dexamethasone	Relapse/Refractory	All grade infection 29% Severe infection 24%
BCL-2		
Venetoclax with bortezomib, dexamethasone	Relapse/Refractory	All grade infection 80% Severe infection 28%

HCT: haematopoietic stem cell transplant; URTI: upper respiratory tract infection; BCMA: B-cell maturation antigen; BCL-2: B cell lymphoma-2; AMG 420: anti-B-cell maturation antigen bi-specific T-cell engager molecule

References in the full version of guideline.

Table 2: Summary of rates of infection by drug class and treatment stage

Screening for infections prior to commencement of therapy		
Recommendations	Strength of recommendation	Quality of evidence
Universal screening for HBV with HBsAg, anti-HBcAb and anti-HBsAb serology is recommended prior to commencement of myeloma therapy.	Strong	Level II
Universal screening for HCV with a Hepatitis C antibody is recommended.	Moderate	Level III

Universal screening for HIV with HIV 1 & 2 antibody-p24 combination assay.	Moderate	Level III
Universal screening for latent TB (IGRA) should be considered. Patients should be assessed for risk factors for LTBI including country of birth, close contact with TB.	Strong	Level II
Screening for endemic tropical pathogens on the basis of risk factors including country of birth, refugee status and area of residence is recommended.	Marginal	Level III
Universal screening for VZV or HSV seropositivity (IgG) is recommended prior to planned HCT to guide need for post-HCT prophylaxis.	Moderate	Level II
Universal screening for CMV seropositivity (IgG) could be considered prior to planned HCT and/or prior to commencement of treatment of relapsed/refractory disease to potentially assist with assessment for CMV reactivation.	Moderate	Level II

HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen, anti-HBcAb: anti-hepatitis B core antibody; anti-HBsAb: anti-hepatitis B surface antibody; HCV: hepatitis C; HIV: human immunodeficiency virus; TB: tuberculosis; IGRA: interferon gamma release assay; VZV: varicella-zoster virus; HSV: herpes simplex virus; CMV: cytomegalovirus; HCT: haematopoietic stem cell transplantation; LTBI: Latent tuberculosis infection
References in the full version of guideline.

Table 3: Screening recommendations prior to commencement of therapy

Antibacterial prophylaxis		
Recommendations	Strength of recommendation	Quality of evidence
During first-line therapy, routine antibacterial prophylaxis is not recommended due to absence of clear universal, mortality benefit.	Strong	Level I
During HCT, routine antibacterial prophylaxis is not recommended due to absence of clear mortality	Strong	Level I

benefit. It can be considered in patients with recurrent and severe bacterial infections.		
During treatment for relapsed/refractory disease, antibacterial prophylaxis should only be considered based on an individual assessment of future risk for infection.	Marginal	Level III
Antiviral prophylaxis: HCT		
Recommendations	Strength of recommendation	Quality of evidence
For prevention of HSV, antiviral prophylaxis with aciclovir (400-800mg BD) or valaciclovir (500mg daily to BD) is recommended for a period of 30 days following HCT.	Strong	Level I
For prevention of VZV, antiviral prophylaxis aciclovir (400-800mg BD) or valaciclovir (500mg daily to BD) is recommended for a period of at least 12 months following HCT.	Strong	Level I
Patients with chronic HBV should receive prophylaxis with entecavir or tenofovir, which is recommended to continue until 18-24 months following HCT.	Strong	Level II
Patients with chronic HBV with baseline viral load above 2000 IU/ml should be treated for HBV with entecavir or tenofovir, likely lifelong and referred to a hepatitis specialist for ongoing management.	Strong	Level I
Patients with resolved HBV should receive antiviral prophylaxis in setting of HCT, which is recommended for a period of 18-24 months following HCT.	Strong	Level II
Antiviral prophylaxis: Treatment risk		
Recommendations	Strength of recommendation	Quality of evidence
For prevention of VZV during PI-based therapy, antiviral prophylaxis with aciclovir (200-400mg BD) or valaciclovir (500mg daily) is recommended during duration of therapy and up to 1 month post.	Strong	Level II
For prevention of VZV with therapies containing elotuzumab, antiviral prophylaxis with aciclovir (200-400mg BD) or valaciclovir (500mg daily) is recommended during duration of therapy and up to 1 month post.	Moderate	Level II

Patients with chronic HBV with baseline viral load above 2000 IU/ml should be treated for HBV with entecavir or tenofovir, likely lifelong and referred to a hepatitis specialist for ongoing management.	Strong	Level I
For patients with resolved HBV, antiviral prophylaxis should be considered with the use of PI-based regimens and high dose corticosteroids, which is recommended for a period of 6-12 months following completion of therapy.	Strong	Level II
Antifungal prophylaxis		
Recommendations	Strength of recommendation	Quality of evidence
During autoHCT, antifungal prophylaxis with fluconazole (400mg daily) is recommended.	Moderate	Level II
With new generation anti-myeloma therapies, routine antifungal prophylaxis is not recommended. Individual risk assessment is recommended.	Marginal	Level III
With regimens causing prolonged and severe neutropenia and other concurrent risk factors for IFD, use of anti-mould prophylaxis could be considered.	Marginal	Level III
Trimethoprim-sulfamethoxazole (160/800mg 1 tablet daily) as PJP prophylaxis is recommended in the setting of prednisolone-equivalent 16-20mg daily for 4 or more weeks*. Prophylaxis during therapy and up to 6 weeks following completion.	Strong	Level II
Trimethoprim-sulfamethoxazole (160/800mg 1 tablet daily) as PJP prophylaxis is recommended in the setting of HCT and continued until 3-6 months following HCT.	Strong	Level II
Immunoglobulin replacement		
Recommendations	Strength of recommendation	Quality of evidence
Immunoglobulin replacement should be considered for patients with severe hypogammaglobulinaemia (IgG < 4g/L) irrespective of presence, frequency or severity of infections, or hypogammaglobulinaemia (IgG < normal) with at least 1 life threatening in 12 month period or recurrent severe infections requiring	Strong	Level I

more than standard course of antibiotics (at least 2 in 6 months).		

Dosing recommendations available in the full version of guideline.

*common treatment regimens containing 20-40mg dexamethasone weekly will fulfil this criteria.

HBV: hepatitis B virus; VZV: varicella-zoster virus; HSV: herpes simplex virus; HCT: haematopoietic stem cell transplantation; auto: autologous; PJP: *Pneumocystis jirovecii pneumonia*

References in the full version of guideline.

Table 4: Summary of recommendations for antimicrobial prophylaxis

Vaccination recommendations		
Recommendations	Strength of recommendation	Quality of evidence
In unvaccinated patients with myeloma, Pneumococcal vaccination is recommended with PCV13 followed by PPV23 at least 2 months later.	Strong	Level II

Post-HCT, Pneumococcal vaccination is recommended with PCV13 at 6, 8, 12 months followed by PPV23 12 months later.	Strong	Level II
Annual seasonal influenza vaccination is recommended. In patients 65 years and above should receive the adjuvant IIV while two IIV doses (1 month apart) could be considered taking into account national immunisation program criteria.	Strong	Level I
In the first 12 months following autoHCT, two doses of IIV is recommended.	Strong	Level I
Vaccination against SARS-CoV-2 is recommended with 3-doses of any registered vaccine. Revaccination with 3 doses recommended commencing at least 3 months post-HCT. Use, formulation and timing of additional (booster) dose as per national guidance	Moderate	Level II
Post-HCT, vaccination with recombinant subunit zoster vaccination should be considered especially if planned duration of antiviral prophylaxis is less than 12 months.	Moderate	Level I
Post-HCT, vaccination for other vaccine preventable infections (*N. meningitidis*, *H. influenzae B*, hepatitis B, diptheria, tetanus, pertussis, polio) is recommended.	Moderate	Level II

PCV13: Pneumococcal conjugate 13 vaccine; PPV23: Pneumococcal polysaccharide 23 vaccine; IIV: inactivated influenza vaccine HCT: haematopoietic stem cell transplantation; auto: autologous

References in the full version of guideline.

Table 5: Summary recommendations for vaccination of patients with myeloma

References

1. Welfare AIoHa. Cancer data in Australia. Canberra: Australian Government; 2020.
2. Hang Quach MP, Medical Scientific Advisory Group. Clinical Practice Guideline: Multiple Myeloma. Myeloma Foundation of Australia. 2019.
3. Teh BW, Harrison SJ, Pellegrini M, Thursky KA, Worth LJ, Slavin MA. Changing treatment paradigms for patients with plasma cell myeloma: impact upon immune determinants of infection. Blood Rev. 2014;28(2):75-86.

4. Bringhen S, Offidani M, Palmieri S, Pisani F, Rizzi R, Spada S, et al. Early mortality in myeloma patients treated with first-generation novel agents thalidomide, lenalidomide, bortezomib at diagnosis: A pooled analysis. Crit Rev Oncol Hematol. 2018;130:27-35.
5. Teh BW, Harrison SJ, Worth LJ, Spelman T, Thursky KA, Slavin MA. Risks, severity and timing of infections in patients with multiple myeloma: a longitudinal cohort study in the era of immunomodulatory drug therapy. Br J Haematol. 2015;171(1):100-8.
6. Lim C, Sinha P, Harrison SJ, Quach H, Slavin MA, Teh BW. Epidemiology and Risks of Infections in Patients With Multiple Myeloma Managed With New Generation Therapies. Clin Lymphoma Myeloma Leuk. 2021.
7. Blimark C, Holmberg E, Mellqvist UH, Landgren O, Bjorkholm M, Hultcrantz M, et al. Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients. Haematologica. 2015;100(1):107-13.
8. Lin C, Shen H, Zhou S, Liu M, Xu A, Huang S, et al. Assessment of infection in newly diagnosed multiple myeloma patients: risk factors and main characteristics. BMC Infect Dis. 2020;20(1):699.
9. Dumontet C, Hulin C, Dimopoulos MA, Belch A, Dispenzieri A, Ludwig H, et al. A predictive model for risk of early grade >/= 3 infection in patients with multiple myeloma not eligible for transplant: analysis of the FIRST trial. Leukemia. 2018;32(6):1404-13.
10. Djebbari F, Panitsas F, Eyre TA, Prodger C, Davies F, Burton K, et al. Infection-related morbidity in a large study of transplant non-eligible newly diagnosed myeloma patients treated with UK standard of care. Haematologica. 2020.
11. Rahman S, Rybicki L, Ky Hamilton B, Pohlman B, Jagadeesh D, Cober E, et al. Early infectious complications after autologous hematopoietic cell transplantation for multiple myeloma. Transpl Infect Dis. 2019;21(4):e13114.
12. Park H, Youk J, Kim HR, Koh Y, Kwon JH, Yoon SS, et al. Infectious complications in multiple myeloma receiving autologous stem cell transplantation in the past 10 years. Int J Hematol. 2017;106(6):801-10.
13. Johnsrud AJ, Johnsrud JJ, Susanibar SA, Kamimoto JJ, Kothari A, Burgess M, et al. Infectious and immunological sequelae of daratumumab in multiple myeloma. Br J Haematol. 2019;185(1):187-9.
14. Brioli A, Klaus M, Sayer H, Scholl S, Ernst T, Hilgendorf I, et al. The risk of infections in multiple myeloma before and after the advent of novel agents: a 12-year survey. Ann Hematol. 2019;98(3):713-22.
15. Hyun SY, Han SH, Kim SJ, Jang JE, Kim Y, Cho H, et al. Pretreatment Lymphopenia, Poor Performance Status, and Early Courses of Therapy Are Risk Factors for Severe Bacterial Infection in Patients with Multiple Myeloma during Treatment with Bortezomib-based Regimens. J Korean Med Sci. 2016;31(4):510-8.
16. Teh BW, Worth LJ, Harrison SJ, Thursky KA, Slavin MA. Risks and burden of viral respiratory tract infections in patients with multiple myeloma in the era of immunomodulatory drugs and bortezomib: experience at an Australian Cancer Hospital. Support Care Cancer. 2015;23(7):1901-6.
17. Cook G, John Ashcroft A, Pratt G, Popat R, Ramasamy K, Kaiser M, et al. Real-world assessment of the clinical impact of symptomatic infection with severe acute respiratory syndrome coronavirus (COVID-19 disease) in patients with multiple myeloma receiving systemic anti-cancer therapy. Br J Haematol. 2020;190(2):e83-e6.
18. Nucci M, Anaissie E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. Clin Infect Dis. 2009;49(8):1211-25.

19. Teh BW, Harrison SJ, Worth LJ, Thursky KA, Slavin MA. Infection risk with immunomodulatory and proteasome inhibitor-based therapies across treatment phases for multiple myeloma: A systematic review and meta-analysis. Eur J Cancer. 2016;67:21-37.
20. Ramsey SD, Unger JM, Baker LH, Little RF, Loomba R, Hwang JP, et al. Prevalence of Hepatitis B Virus, Hepatitis C Virus, and HIV Infection Among Patients With Newly Diagnosed Cancer From Academic and Community Oncology Practices. JAMA Oncology. 2019;5(4):497-505.
21. Kurizky PS, dos Santos Neto LL, Aires RB, da Mota LMH, Gomes CM. Opportunistic tropical infections in immunosuppressed patients. Best Practice & Research Clinical Rheumatology. 2020:101509.
22. MacLachlan JH, Romero N, Higgins N, Coutts R, Chan R, Stephens N, et al. Epidemiology of chronic hepatitis B and C in Victoria, Australia: insights and impacts from enhanced surveillance. Aust N Z J Public Health. 2020;44(1):59-64.
23. Oken MM, Pomeroy C, Weisdorf D, Bennett JM. Prophylactic antibiotics for the prevention of early infection in multiple myeloma. Am J Med. 1996;100(6):624-8.
24. Vesole DH, Oken MM, Heckler C, Greipp PR, Katz MS, Jacobus S, et al. Oral antibiotic prophylaxis of early infection in multiple myeloma: a URCC/ECOG randomized phase III study. Leukemia. 2012;26(12):2517-20.
25. Drayson MT, Bowcock S, Planche T, Iqbal G, Pratt G, Yong K, et al. Levofloxacin prophylaxis in patients with newly diagnosed myeloma (TEAMM): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial. Lancet Oncol. 2019;20(12):1760-72.
26. Satlin MJ, Vardhana S, Soave R, Shore TB, Mark TM, Jacobs SE, et al. Impact of Prophylactic Levofloxacin on Rates of Bloodstream Infection and Fever in Neutropenic Patients with Multiple Myeloma Undergoing Autologous Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2015;21(10):1808-14.
27. Yeshurun M, Vaxman I, Shargian L, Yahav D, Bishara J, Pasvolsky O, et al. Antibacterial prophylaxis with ciprofloxacin for patients with multiple myeloma and lymphoma undergoing autologous haematopoietic cell transplantation: a quasi-experimental single-centre before-after study. Clin Microbiol Infect. 2018;24(7):749-54.
28. Teh BW, Harrison SJ, Worth LJ, Slavin MA. Antiviral prophylaxis for varicella zoster virus infections in patients with myeloma in the era of novel therapies. Leuk Lymphoma. 2016;57(7):1719-22.
29. Glenny AM, Fernandez Mauleffinch LM, Pavitt S, Walsh T. Interventions for the prevention and treatment of herpes simplex virus in patients being treated for cancer. Cochrane Database Syst Rev. 2009(1):CD006706.
30. Teh BW, Slavin MA, Harrison SJ, Worth LJ. Prevention of viral infections in patients with multiple myeloma: the role of antiviral prophylaxis and immunization. Expert Rev Anti Infect Ther. 2015;13(11):1325-36.
31. McKay SL, Guo A, Pergam SA, Dooling K. Herpes Zoster Risk in Immunocompromised Adults in the United States: A Systematic Review. Clin Infect Dis. 2020;71(7):e125-e34.
32. Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, Hori M, et al. Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. N Engl J Med. 2018;379(19):1811-22.
33. Mya DH, Han ST, Linn YC, Hwang WY, Goh YT, Tan DC. Risk of hepatitis B reactivation and the role of novel agents and stem-cell transplantation in multiple myeloma patients with hepatitis B virus (HBV) infection. Ann Oncol. 2012;23(2):421-6.

34. Tsukune Y, Sasaki M, Odajima T, Isoda A, Matsumoto M, Koike M, et al. Incidence and clinical background of hepatitis B virus reactivation in multiple myeloma in novel agents' era. Ann Hematol. 2016;95(9):1465-72.
35. Lim C, Sinha P, Harrison SJ, Quach H, Slavin MA, Teh BW. Low rates of invasive fungal disease in patients with multiple myeloma managed with new generation therapies: Results from a multi-centre cohort study. Mycoses. 2020.
36. Teh BW, Teng JC, Urbancic K, Grigg A, Harrison SJ, Worth LJ, et al. Invasive fungal infections in patients with multiple myeloma: a multi-center study in the era of novel myeloma therapies. Haematologica. 2015;100(1):e28-31.
37. Tisi MC, Hohaus S, Cuccaro A, Innocenti I, De Carolis E, Za T, et al. Invasive fungal infections in chronic lymphoproliferative disorders: a monocentric retrospective study. Haematologica. 2017;102(3):e108-e11.
38. Cooley L, Dendle C, Wolf J, Teh BW, Chen SC, Boutlis C, et al. Consensus guidelines for diagnosis, prophylaxis and management of Pneumocystis jirovecii pneumonia in patients with haematological and solid malignancies, 2014. Intern Med J. 2014;44(12b):1350-63.
39. Yale SH, Limper AH. Pneumocystis carinii pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. Mayo Clin Proc. 1996;71(1):5-13.
40. Chen CS, Boeckh M, Seidel K, Clark JG, Kansu E, Madtes DK, et al. Incidence, risk factors, and mortality from pneumonia developing late after hematopoietic stem cell transplantation. Bone Marrow Transplant. 2003;32(5):515-22.
41. Teh BW, Yeoh DK, Haeusler GM, Yannakou CK, Fleming S, Lindsay J, et al. Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2021. Intern Med J. 2021;51 Suppl 7:67-88.
42. Musto P, Brugiatelli M, Carotenuto M. Prophylaxis against infections with intravenous immunoglobulins in multiple myeloma. Br J Haematol. 1995;89(4):945-6.
43. Chapel HM, Lee M, Hargreaves R, Pamphilon DH, Prentice AG. Randomised trial of intravenous immunoglobulin as prophylaxis against infection in plateau-phase multiple myeloma. The UK Group for Immunoglobulin Replacement Therapy in Multiple Myeloma. Lancet. 1994;343(8905):1059-63.
44. Authority NB. Criteria for the clinical use of immunoglobulin in Australia In: Authority NB, editor. 2018.
45. Teh BW, Harrison SJ, Slavin MA, Worth LJ. Epidemiology of bloodstream infections in patients with myeloma receiving current era therapy. Eur J Haematol. 2017;98(2):149-53.
46. Kumar D, Humar A, Plevneshi A, Siegal D, Franke N, Green K, et al. Invasive pneumococcal disease in adult hematopoietic stem cell transplant recipients: a decade of prospective population-based surveillance. Bone Marrow Transplant. 2008;41(8):743-7.
47. Chicca IJ, Heaney JLJ, Iqbal G, Dunn JA, Bowcock S, Pratt G, et al. Anti-bacterial antibodies in multiple myeloma patients at disease presentation, in response to therapy and in remission: implications for patient management. Blood Cancer J. 2020;10(11):114.
48. Youssef S, Rodriguez G, Rolston KV, Champlin RE, Raad, II, Safdar A. Streptococcus pneumoniae infections in 47 hematopoietic stem cell transplantation recipients: clinical characteristics of infections and vaccine-breakthrough infections, 1989-2005. Medicine (Baltimore). 2007;86(2):69-77.
49. W. TB. Vaccination Schedules: Springer; 2020.

50. Teh BW, Harrison SJ, Allison CC, Slavin MA, Spelman T, Worth LJ, et al. Predicting Risk of Infection in Patients with Newly Diagnosed Multiple Myeloma: Utility of Immune Profiling. Front Immunol. 2017;8:1247.