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

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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.

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

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

ECOG: Eastern Cooperative Oncology group; BM: bone marrow; ISS: international staging system; LDH: lactate dehydrogenase; Hb: haemoglobin; 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).		
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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 (<i>N. meningitidis</i> , <i>H. influenzae B</i> , hepatitis B, diphtheria, 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

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