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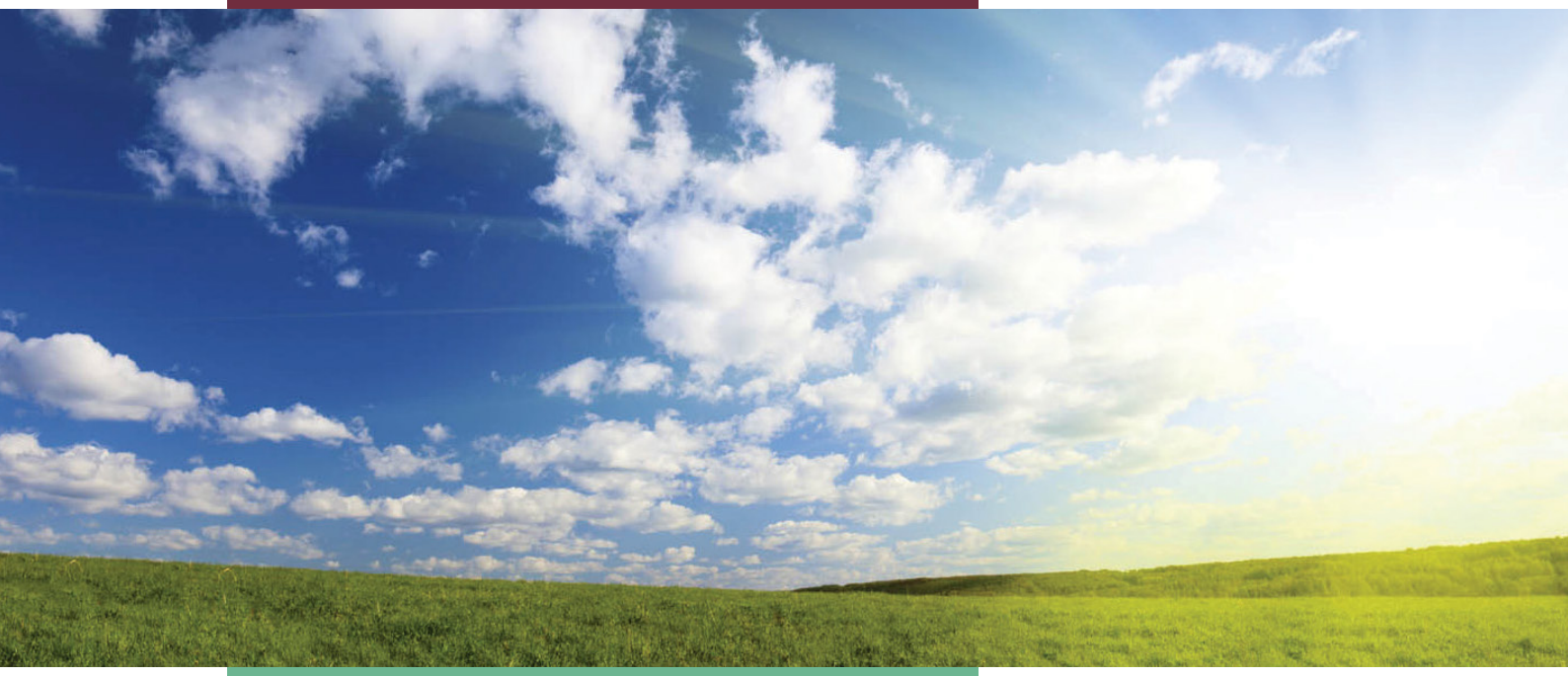

MSAG Guidelines

# Consensus clinical practice guidelines for the prevention of infection in patients with Multiple Myeloma

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# 1 INTRODUCTION

Multiple myeloma is a malignancy of plasma cells. In 2020, 2300 people were diagnosed with this disease in Australia [1]. Survival with multiple myeloma continues to increase over the last 5 years with continued expansion of new and emerging therapeutic options [1]. These options include second generation immunomodulatory drugs (IMiDs), proteasome inhibitors (PI) and monoclonal antibodies (Mabs), bispecific antibody (BsAbs), drug-antibody conjugates and cellular therapies including chimeric antigen receptor T cell therapies (CAR-T) [2].

Infection especially with bacteria and viruses is a leading contributor to morbidity and mortality in patients with myeloma[3-5]. The increased risk for infection is due to a combination of patient, disease and treatment-related factors[4]. As treatments for myeloma continue to expand and evolve, so do the patterns, risk periods and risk factors for infection[6, 7]. This guideline was developed to assist clinicians with the management of infections in patients with myeloma and encompasses screening, patterns and risk periods for infection and prevention of infection through use of prophylaxis and vaccination.

## Methodology

This clinical practice guideline was developed by the Medical Scientific Advisory Group, a sub-committee of Myeloma Australia together with infectious diseases physicians specialising in the management of infections in patients with cancer and affiliated with the National Centre for Infections in Cancer. To develop prophylaxis and vaccination recommendations, a comprehensive search was performed using PUBMED for studies published since 1980 and utilised the following terms: 'myeloma', 'plasma cell', 'haematopoietic stem cell transplantation', 'infection', 'prophylaxis', 'prevention', 'vaccination', 'vaccines', 'viral', 'virus', 'herpes' 'varicella-zoster', 'cytomegalovirus', 'hepatitis', 'tuberculosis', 'human immunodeficiency virus', 'bacteria', 'antibiotic', 'antimicrobial', 'fungus' and 'invasive fungal'. Strength of recommendation and quality of evidence supporting recommendations were made utilising established criteria below.

| **Strength of recommendation** | **Definition** |
|---|---|
| Grade A | The guideline group **strongly** supports a recommendation for use |
| Grade B | The guideline group **moderately** supports a recommendation for use |
| Grade C | The guideline group **marginally** supports a recommendation for use |
| Grade D | The guideline group supports a recommendation **against** use |
| **Quality of evidence** | **Definition** |
| Level I | Evidence from at least 1 properly designed randomised, controlled trial (orientated on the primary endpoint of the trial)<br>Note: Poor quality of planning, inconsistency of results, indirectness of evidence etc. would lower the strength of recommendation. |
| Level II | Evidence from at least 1 well-designed clinical trial (incl. secondary endpoints), without randomisation; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments |
| Level III | Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees |

# 2 EPIDEMIOLOGY OF INFECTION

In a large population-based study, patients with myeloma were noted to be at higher risk for infections compared to matched controls. This higher risk is maintained through evolution of myeloma treatment regimens from conventional chemotherapy to immunomodulatory drugs (IMiD) and proteasome inhibitors (PI)[8]. Patients had a 7-fold higher risk of any infection, 7-fold higher risk for bacterial infection and a 11-fold higher risk for viral infections compared to matched controls[8]. The risk was highest in the first year following disease diagnosis[8]. Close to 90% of the infections were bacterial with higher risk reported for clinical syndromes of pneumonia, sepsis, cellulitis, endocarditis. Higher risk for zoster and influenza viral infections were also noted[8].

The increased risk for infection varies by disease and treatment periods. Overall, 60% of patients with myeloma have had at least 1-4 infections or 1.3 infections per patient-year during their treatment course[6, 9, 10]. There are bimodal peaks of infection, predominantly around first line treatment or induction and treatment of subsequent relapse and progressive disease[6, 9]. Thirty-five percent of patients experience an infection during first line treatment and 40-50% during treatment for relapse/disease progression[9]. The highest risk periods are 4-6 months and approximately 6 years following disease diagnosis[6]. At least 60% of infections during these periods are of high severity requiring hospital admission (grade 3 or higher)[6]. For patients who are transplant-eligible, the period of myeloma suppression following conditioning chemotherapy remains a high-risk period associated with infections of high severity[6].

Overall, the respiratory tract was the most common site of infection followed by bloodstream infections (BSI)[6, 9, 10]. Across all periods, bacteria constituted the majority of microbiologically defined infections followed closely by viral infections[6]. For bacterial infections, the proportion of gram negative and gram-positive infections were 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, herpes simplex and cytomegalovirus [CMV]) were the common viral pathogens detected[6, 9, 10]. Rates of *Clostridioides difficile* infection are increasing[11]. Rates of fungal infection were low overall with *Pneumocystis jirovecii* pneumonia and Candida sp. infections reported[6].

***By treatment period (First line therapy)***

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 occurring at 4-6 months regardless of transplant eligibility [6, 12-15]. Disease burden and associated immune deficits contribute to this early increased risk which decreases once sufficient disease control and immune recovery has been achieved [4]. Up to 60% of infections are grade 3 or higher[6, 15]. Approximately 75% of infections reported during this time period are clinically diagnosed with respiratory syndromes (pneumonia), sepsis and blood stream infections noted as the most common infection syndromes [12-15]. Of the microbiologically diagnosed infections, bacterial infections with *E. coli*, *Enterococcus sp*., *Streptococcus sp* and *Clostridium sp.* were commonly reported whilst viral and fungal pathogens were less common[12-14].

***Autologous stem cell transplant***

In the period of intensive myelosuppression following conditioning chemotherapy, the rates of infection are high at 60% with the vast majority reported to be severe (grade 3 or higher) infections[6, 16, 17]. Neutropenic fever is the most common syndrome reported and only 20-40% of episodes of infection have a pathogen detected on microbiological testing [6, 17]. Blood stream infections are frequent and the proportion of gram-positive or gram-negative bacteria detected is dependent on the use of antibacterial prophylaxis [16-18]. Commensals such as coagulase negative *Staphylococcus* and Enterobacteriales from the gastrointestinal tract are dominant pathogens, likely related to breakdown of anatomical barriers through the use of long term intravenous catheters and mucosal inflammation from intensive chemotherapy [4, 16, 17].

Due to depletion of virus-specific lymphocytes, reactivation of herpes viruses in particular varicella-zoster occurs in the absence of prophylaxis[17]. CMV viraemia is often detected if weekly surveillance is performed by the centre. However, the clinical significance of CMV viraemia in the post autologous transplant setting and the need for treatment remains undefined with low rates of CMV end organ disease detected [17]. Approximately 5% of infection episodes during the post-transplant period consist of fungal infection with Candida blood stream infections occurring during the neutropenic period and *Pneumocystis jirovecii* pneumonia and invasive aspergillosis occurring within 30-100 days of transplant[16, 17, 19].

***Relapse***

Myeloma is a disease characterised by relapses necessitating additional lines of therapy to achieve disease control. This results in cumulative immune suppression which is a contributor to increased risk for infection [4]. Higher cumulative doses of corticosteroids used in most treatment regimens also contribute to increased risk [6]. Up to 15% of patients receiving first generation IMiD or PI therapy for relapse or refractory disease experience severe infection [20]. Bacterial blood stream infections, respiratory tract viral infections, CMV reactivation and invasive fungal infections are the dominant infections during this period[19, 21-23]. With advances in myeloma therapy, the patterns of infection appear to have evolved.

In patients receiving second generation IMiD, PI or monoclonal antibody (MAb) therapies (e.g daratumumab) 40- 90% had at least 1 episode of infection (30% with severe infection) with a rate of 1.7 infections per patient-year[7, 24]. Median time from commencement of therapy to first episode of infection was 3 months[7]. Although respiratory tract remains the most common site of infection, viral rather

than bacterial infections were responsible for the majority of infections[7, 24]. In particular respiratory syncytial virus, rhinovirus, influenza and reactivation of CMV and varicella were noted[7]. Close to 70% of bacterial infections were caused by gram negative pathogens such as *E. coli* and *Haemophilus influenzae*. Proven fungal infections with yeasts, namely *Cryptococcus neoformans* and *Pichia kudriavzevii (formerly Candida krusei*) were reported[7]. Infections contributed to hospitalisation and mortality in up to 50% and 70% of cases respectively [24]. The increasing burden of infection, especially with opportunistic pathogens require development and evaluation of new infection prevention measures.

## Characteristics and patterns of key pathogens

***Blood stream infections***

BSI with encapsulated organisms such as *S. pneumoniae* have classically been described in patients with newly diagnosed myeloma[4]. With the introduction of IMiD and PIs, overall 36% of patients with myeloma will experience a BSI through their treatment courses with two peak periods (4-6 months and 6 years) following disease diagnosis[21, 25]. At least 10% of patients receiving first line therapy will experience a BSI[25, 26].

There are differences in patients who have undergone an autologous haematopoietic cell transplantation (autoHCT) compared to those who are not transplant eligible. The proportion of patients with BSI is lower in non-transplanted patients, with most pathogenic isolates being Gram negative bacteria [21]. In contrast, in auto HCT patients the proportion of Gram negative, Gram positive and mixed pathogens were approximately a third each [21]. *E. coli*, *Pseudomonas* sp., *Streptococcus* sp., *S. aureus* and *Enterococcus* sp. were common pathogens isolated and 10% of BSI isolates were multi-drug resistant [21, 25, 26]. *S. pneumoniae*, a classic pathogen of interest in multiple myeloma, is now responsible for less than 10% of BSI overall but remains a significant pathogen during first line treatment and during treatment for disease relapse[21]. Poor functional status, higher disease stage and activity (LDH), and recent HCT were factors associated with higher risk for BSI whilst use of trimethoprim-sulfamethoxazole for PJP prophylaxis was protective [21, 25, 26].

***Viral respiratory tract infection***

In the early era of IMiDs and PI-based therapies, viral respiratory tract infections impacted up to 20% of patients with myeloma with 40% presenting with lower respiratory tract infection and 30-40% requiring hospital admission[23, 27]. These infections were acquired in the community and were more common in patients with myeloma compared to other B-cell malignancies such as non-Hodgkin lymphoma[27]. The common respiratory viruses detected by nucleic acid testing (NAT) were picornaviruses, RSV and influenza [23, 27]. Infection with influenza virus was often more severe, leading to hospital admission, ICU admission and mortality in 67%, 42% and 33% respectively[23, 28]. This highlights the need for seasonal influenza vaccination and evaluation of new influenza vaccination approaches to reduce the burden and impact of influenza on patients with myeloma. Recent autologous HCT and more than 3 lines of therapy were associated with increased risk for viral respiratory tract infection. Evolving knowledge of risk factors for viral infection potentially allows for a risk-stratified approach to prevention measures[23, 27].

Infection with SARS-CoV-2 virus (COVID-19 infection) was the dominant viral respiratory tract infection in 2020 and is likely to develop into an endemic respiratory viral infection[29]. In 2020, the incidence of COVID-19 in patients with myeloma appears to be 16 times higher than the general population and 80% and 15% of myeloma patients with COVID-19 required hospital and ICU admission [30-32]. Patients with underlying malignancy have higher SARS-CoV-2 viral loads and significantly prolonged viral shedding of up to 60 days, especially following HCT and cellular therapies [33, 34]. This adds to the complexity of patient management, especially infection prevention measures such as duration of isolation. Close to 80% had moderate to severe disease presentation, 20% and 9% needed non-invasive and invasive ventilation respectively [35]. Across different countries, mortality rates from COVID-19 have ranged between 30-55% [32, 35-39]. In myeloma, patient and disease related factors drive increased risk for mortality from COVID-19. The type of active treatment does not appear to impact mortality once a patient develops the infection[35, 36]. Increasing age (above 65 years), renal co-morbidity, high-risk myeloma (cytogenetics), poor disease control (progressive disease, not in complete remission) were associated with higher risk for mortality with COVID-19 infection [32, 35, 36]. Multiple vaccines based on different platforms are now available for prevention of SARS-CoV-2 infection and severe complications; these are discussed in further detail in sections to follow [40].

***Reactivation of varicella-zoster virus***

Depletion of varicella zoster specific T-cells and interruption to viral antigen processing and presentation increases the risk of reactivation of zoster[4, 41]. For patients with myeloma, the period of risk is in the setting of proteasome inhibitor-based therapy and during cellular recovery following HCT[42]. Up to 20% of patients experience reactivation of zoster; only a very small proportion of cases (less than 5%) are disseminated [42]. Antiviral prophylaxis is very effective in reducing risk of zoster reactivation with the majority of episodes occurring in the absence of prophylaxis[42]. Strategies to reduce the burden of zoster, such as the use and duration of antiviral prophylaxis and inactivated zoster vaccination, are discussed in further detail in later sections of these guidelines.

***Reactivation of CMV***

Assessment and management of cytomegalovirus (CMV) infection in the non-allogeneic HCT setting remains challenging. In patients with myeloma, studies have predominantly focussed on patients receiving bortezomib-based therapies[43, 44]. Routine screening for CMV via PCR every 1-2 weeks in PI-treated and autoHCT patients has detected high rates CMV reactivation of up to 40% with most episodes being CMV DNAemia [43, 45]. In the post autoHCT setting, episodes have occurred within 30 days of transplant [46]. Utilising various viral load thresholds, over half these episodes were treated [43, 46]. Proven CMV end organ disease remains uncommon with first line treatment

or following autoHCT with rates of less than 5% [43, 45]. With a symptom-driven diagnostic strategy, the rate of CMV reactivation is lower and the proportion with CMV disease is similar (3%) [44]. In patients on first line therapy or following autoHCT, it remains unclear if early detection and treatment of CMV DNAemia through routine screening leads to a clinically meaningful difference in outcomes compared to a symptom-driven diagnostic strategy.

However, with more lines of therapy utilised for management of relapsed disease, there have been case reports of CMV disease with high mortality rates in the setting of combination myeloma therapies containing daratumumab[47]. Episodes of CMV infection have also been reported with the use of newer generation IMiD, PI and MoAbs for relapsed and refractory disease[7]. In this heavily treated patient group, it is often challenging to determine the impact of specific types of therapy such as daratumumab on the risk of CMV reactivation[47]. In patients with relapsed disease, there should be a low clinical threshold to investigate for CMV reactivation in the setting of compatible symptoms.

***Hepatitis B virus***

In patients with chronic hepatitis B (HBV), rate of reactivation in the setting of myeloma therapy is as high as 50% in the absence of prophylaxis[48, 49]. Antiviral prophylaxis, especially in the post-HCT period is effective in reducing risk for reactivation with rates of 5-9% reported with the use of lamivudine prophylaxis [50]. In myeloma patients with resolved HBV (HBsAg negative, HBcAb positive) managed on IMiDs/PI and HCT, rates of HBV reactivation are 5-9% in the absence of prophylaxis[51-54]. Definitions of HBV reactivation reported vary between detection of HBV by PCR or reappearance of HBsAg [52-54]. HBV reactivation was associated with biochemical hepatitis in 90% of cases but fortunately did not result in hepatic failure [54]. In patients managed on BCMA CAR-T, HBV reactivation occurred in 16% of patients with chronic or resolved HBV in the absence of prophylaxis[55]. Absence of HBsAb levels, HCT, and PI appear to be associated with higher risk for reactivation whilst use of lenalidomide is associated with lower risk[51, 52, 54]. HBV is not endemic in Australia; it can be managed effectively with complications prevented if detected early. Screening for infections that are associated with higher risk for reactivation is discussed in more detail in later sections of this guideline.

***Invasive fungal disease***

Overall rates of invasive fungal disease (IFD) in patients in myeloma are low at between 2-6% and are associated with periods of intensive myelosuppression following an autoHCT or with treatment for disease relapse and progression[19, 22, 56-58]. Infections with yeasts, in particular Candida BSI were more common than invasive mould infections[19, 56]. *Lomentospora prolificans*, *Aspergillus fumigatus* and other *Aspergillus* sp. are common moulds reported [19]. IFD tend to commonly involve the respiratory tract and blood stream[19, 57]. Although rates of IFD are low, these infections are still associated with significant morbidity, intensive care admission and mortality of between 40-70%[19, 22, 56]. Following introduction of IMiD and PI-based therapies, the majority of patients with IFD had established risk factors such as prolonged neutropenia and concurrent use of high-dose corticosteroids[19]. A recent study of heavily treated patients on second generation IMiD, PI and MoAb based therapies confirmed a low IFD rate of 3% with high mortality rate of 40%, emergence of cryptococcal infection and the absence of neutropenia as a risk factor [59]. Increasing lines of therapy is also associated with risk for IFD [19, 59]. Previous episode of IFD is associated with higher risk of subsequent episodes[57]. Despite the high mortality rate from IFD, there remains significant evidence gaps in the approach to diagnosis and prevention of IFD in myeloma patients with relapsed or refractory disease.

# 3 RISK FACTORS FOR INFECTION

## Summary of patient/disease factors by disease stage

In patients with myeloma, risk for infection is due to a combination of patient, disease and treatment specific factors[4, 60]. While patient-specific factors such as age are not modifiable, disease and treatment risk factors are often interrelated and can be targeted through key prevention measures. The relative importance of these factors change as a patient progresses through myeloma treatments.

During first-line treatment, disease burden and its associated immune suppressive effects (including impairment of monocyte function, complement activation, suppression of immunoglobulin levels and reduction of cellular immune cell function) drives risk for infection[4, 60]. Patients with higher disease burden (bone marrow plasma cells, LDH), higher disease stage (>2), evidence of end organ damage (e.g. anaemia, lymphopenia) and poor functional status are associated with increased risk for infection and serious infection during this early treatment period[6, 9, 12, 14]. In earlier studies, cumulative dose of corticosteroids and use of conventional chemotherapy as first-line induction therapy was also associated with increased risk[6, 9]. In non-transplant eligible patients, similar disease risk factors have been identified[13, 15]. Based on the analysis of data from the FIRST trial, a predictive model utilising ECOG, beta-2 microglobulin, LDH and haemoglobin was identified and was able to predict high vs. low risk for grade 3 or higher treatment emergent infections during first 4 months of therapy [13]. It was externally validated against three other clinical datasets and performed well except in 1 trial with low rates of infection [13]. Risk factors are summarised in Table 1.

During HCT, although some disease factors have been identified including increasing duration from disease diagnosis and increased disease activity (beta-2 microglobulin), treatment related factors dominate risk for infection[16, 17]. Myelosuppression from intensive treatment results in increased risk for bacterial infection in early (0-30 days) and progressive immune recovery mediates risk for viral infections in the later (day 30 or longer) post-HCT periods[4, 60]. In addition to conditioning chemotherapy, pre-transplant treatment factors such as use of bortezomib-based induction, use of chemotherapy as the mobilising regimen and cumulative cycles of chemotherapy were associated with increased risk for neutropenic fever, BSI and clinically diagnosed infections in the post-transplant period [16, 17].

Myeloma is characterised by disease relapse and increasing lines of therapy to achieve disease control[4]. During this later phase and in the setting of disease relapse, disease burden and cumulative immune suppression from previous treatments including corticosteroids mediate risk for infection[4, 6, 24]. A reduction in corticosteroid dosing in myeloma treatment regimens has been associated with lower toxicities including lower risk for infection [61]. In a recent cohort study, increasing lines of therapy and use of second-generation proteasome inhibitor-based and MoAb-based treatment regimens have been associated with increased risk for infection on multivariable analysis[7]. 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.

| Treatment stage | Risk factors | References |
|---|---|---|
| First line | ECOG ≥2<br><br>Higher ISS<br>BM plasma cell percentage > 70%<br>Higher LDH<br>Anaemia<br>Lymphopenia<br>Higher creatinine<br><br>Conventional chemotherapy<br>Cumulative corticosteroid dose | [6, 9, 10, 14] |
| First line – transplant ineligible | ECOG, Serum beta-2 microglobulin, LDH, haemoglobin<br><br>1 point each<br>ECOG ≥2<br>LDH≥200 U/L<br>Hb≤11g/dL<br><br>2 points<br>Beta-2 microglobulin<br>≥6 mg/L<br><br>Score 2-5 pts = high risk, -3 to 1 = low risk | [13, 15] |

*table continues next page*

| Treatment stage | Risk factors | References |
|---|---|---|
| Autologous transplant | Increasing time for disease diagnosis<br>Beta-2 microglobulin >3.5<br>Prior use of bortezomib<br>Use of chemotherapy as mobilising regimen<br>More prior chemotherapy<br>Higher Karnofsky performance status lower risk | [16, 17] |
| Relapse | Neutropenia<br>Lymphopenia<br>Lower CD56+ cells<br>Receipt of PI, IMID and PI, Mab-based therapies<br>Increasing lines of therapy (>4) | [7, 24] |

ECOG: Eastern Cooperative Oncology group; BM: bone marrow; ISS: international staging system; LDH: lactate dehydrogenase; Hb: haemaglobin; PI: proteasome inhibitor; IMID: immunomodulatory drug; Mab: monoclonal antibody

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

# Treatment (drug)-related factors associated with infection

The impact of anti-myeloma treatments on the immune system and its associated risks for infection have been covered by published reviews[4, 20]. The following section covers the rates of infection associated with particular classes of drugs and their comparative infection rates (Table 2). Infection risks associated with the use of various therapies were predominantly derived by systematic review and analysis of clinical trials [20]. However, most trials report limited details on the patterns and timing of infection.

***Immunomodulatory drugs (IMiDs)***

Currently IMiDs thalidomide, lenalidomide and pomalidomide are an essential component of myeloma treatment regimens and part of the standard of care. For first line therapy in an earlier era, rates of severe infection (grade 3 or higher) with IMiD (thalidomide/lenalidomide) use were 11-13% for non-HCT and 15-22% for HCT patients and they were associated with lower risk for infection compared to conventional chemotherapy [20, 62]. When used for first line treatment in combination with cyclophosphamide and dexamethasone, there were similar rates of infection with thalidomide or lenalidomide [63].

When used for maintenance, the overall rate of severe infection was 11% and risk was higher when compared to use of prednisolone alone or observation[20, 62]. Treatment pathways incorporating the use of lenalidomide maintenance reported rates of 50% (all grade) compared to 34% for observation and approximately 10% of infections were severe [64]. In a meta-analysis of earlier studies (up to 2015), the use of lenalidomide as maintenance therapy was associated with higher risk for infection compared to thalidomide [20].

For treatment of relapsed or refractory disease, the serious infection rate was 7-23% for thalidomide and lenalidomide [20, 62]. For pomalidomide, its addition to bortezomib and dexamethasone was associated with a higher rate of severe infection (31% vs. 18%) with longer duration of drug exposure [65]. A pooled analysis of three randomised clinical trials reported a similar rate of severe infections of around 30% which included pneumonia, lower respiratory tract infections and sepsis[66]. The use of daratumumab with pomalidomide and dexamethasone was associated with an infection rate of 76%, severe infection rate of 31% and notable rates of neutropenic fever (10%) and influenza (5%)[67].

***Proteasome inhibitors***

The use of first-generation proteasome inhibitor bortezomib as first-line therapy was associated with rates of severe infection in non-HCT and HCT patients of 10 and 20% respectively[20]. Although risk for infection was not higher than conventional chemotherapy its use was associated with higher risk for severe infection compared to thalidomide [20]. The use of bortezomib in combination with lenalidomide and dexamethasone as first-line therapy was associated with overall rates of infection and severe infection of 28% and 9% respectively[68].

In contrast, the second-generation PI carfilzomib, in combination with lenalidomide or thalidomide and dexamethasone for first-line treatment was associated with higher rates of all grade (74%) and severe infections (11-22%)[69, 70]. When carfilzomib was used for relapsed or refractory disease, there was no major difference in rates of severe pneumonia compared to bortezomib[71]. When carfilzomib dosing was once weekly, rates of severe infection appeared to be marginally higher likely due to longer duration of drug exposure [72]. In a recent meta-analysis, the use of carfilzomib for first line therapy and relapsed or refractory myeloma was associated with a 40% higher risk for severe infections and 30% higher risk for respiratory tract infections compared to non-carfilzomib containing regimens[73]. Two-thirds of infections involved the respiratory tract[73].

Ixazomib, an oral PI, appears to have a favourable infection profile with slightly higher rates of all grade upper respiratory tract infection and similar rates of severe infection when added to lenalidomide and dexamethasone for treatment of relapsed or refractory myeloma despite longer duration of drug exposure[74]. In addition, when it is used in combination with pomalidomide or bendamustine and dexamethasone, rates of all grade infection (50-60%) and severe infection (14-22%) are consistent with other trials involving patients with relapsed or refractory disease [75, 76].

***Monoclonal antibody therapies***

Combination therapy improves progression-free survival in multiple myeloma. Synergistic combinations incorporating the use of anti-CD38 (daratumumab, isatuximab) and SLAMF7 (elotuzumab) monoclonal antibody therapies have been evaluated in large clinical trials for first-line therapy as well as for relapsed or refractory myeloma.

Higher rates of all-grade (by 19%) and severe infections (by 8%) were reported when daratumumab was added to bortezomib, melphalan and prednisolone as first line therapy for patients who were not transplant eligible [77]. The increase in infections was largely due to higher rates of pneumonia and upper respiratory tract infection[77]. When continued as maintenance therapy, daratumumab was associated with a severe infection rate of 11%[78]. In transplant eligible patients, its use in addition to either bortezomib, thalidomide and dexamethasone was associated with 8% higher rate for all grade infections but no difference in rates for severe infections[79]. In the same patient group, its addition to bortezomib, lenalidomide and dexamethasone as part of a complete first line single course of treatment (induction, transplant, consolidation and maintenance) was associated with a higher rate of all grade infections of 91% (29% higher) but similar rates of severe infection of 23% (1% higher)[80]. Episodes of upper respiratory tract infection contributed to the higher rates seen[80].

When used for treatment of relapsed or refractory myeloma, the addition of daratumumab to lenalidomide or bortezomib and dexamethasone improved progression-free survival but was associated with 2-6% higher rate of severe infection [81, 82]. Similar higher rates (by 2%) of severe infection (18-20%) were reported when isatuximab was used in combination with pomalidomide and dexamethasone for treatment in the same patient group[83, 84].

The use of SLAMF7 monoclonal antibody therapy elotuzumab in addition to lenalidomide or pomalidomide and dexamethasone has been evaluated in patients with relapsed or refractory disease (median 2-3 prior lines of therapy)[85, 86]. When combined with lenalidomide, the incidence of infections was similar (197 events per 100 patient years) after accounting for duration of drug exposure[85]. In contrast, a lower incidence was noted when it was combined with pomalidomide (182 vs 230 events per 100 patient years)[86]. In both trials, higher incidence of zoster was noted with the addition of elotuzumab suggesting the need for antiviral prophylaxis with this therapy [85, 86].

***New generation therapies including cellular therapies***

Despite advances with combination therapies, survival remains limited in patients with myeloma refractory to IMiD, PI and MoAbs. New generation therapies such as antibody-drug conjugate (i.e. Belantamab mafadotin mafadotin), bispecific antibody therapies (BsAb), anti-BCMA chimeric antigen receptor T cell (CAR-T) therapy, new drug classes such as selective inhibitor of nuclear export (selinexor) and BCL-2 inhibitor (venetoclax) have been evaluated in clinical trials for this patient cohort.

When Belantamab mafadotin mafadotin was used, rates of infection were not higher than expected for a heavily treated cohort (median 5 or more prior lines of therapy)[87-89]. In single arm studies rates of all grade infection were 14-23%, mostly infections involving the respiratory tract (upper respiratory tract infections, pneumonia) and blood stream (bacteraemia, sepsis)[87-89]. Details of microbiological diagnosis were not routinely reported but where available, influenza was a viral pathogen identified[87, 88]. In contrast, for BsAb (AMG420) therapy rates of all-grade and severe infections were higher at 33% and 29% respectively [90]. Rate of cytokine release syndrome (CRS) was 38% but only 1 patient required tocilizumab [90]. Line-related infection was the dominant severe infection type and deaths were due to infection with influenza and invasive aspergillosis (n=1) and adenovirus hepatitis (n=1) [90].

The use of idecabtagene (BCMA CAR-T) at 3 dose levels was evaluated in a heavily-treated patient cohort (median 6 prior lines of therapy, over 90% previous HCT) resistant to IMiD, PI and anti-CD38 MoAb[91]. Over 80% developed CRS with up to 50% of patients requiring tocilizumab [91]. The severity and treatment of CRS is associated with higher risks for infection [92]. Although type of prophylaxis was not directly reported, it appears patients received antibacterial, antiviral and PJP prophylaxis [91]. Rates of all grade infections were 67-75% across the 3 dose levels evaluated [91]. Rates of all-grade viral, bacterial and fungal infections were 24-75%, 9-25% and 7-9% respectively with the highest risk period for bacterial/fungal infection occurring 8 or less weeks following infusion [91]. For viral infections, the highest risk period was between 8 weeks to 6 months and CMV pneumonia was a common cause of death [91]. This pattern of infection is consistent with expected immune recovery and the pattern seen in patients following HCT.

In similar heavily-treated refractory cohort of patients, the use of selinexor with dexamethasone was associated with all-grade respiratory tract infections of 20% and severe infection of 10% consisting of pneumonia and sepsis [93]. All-grade infection rate of 29% and severe infection rate of 24% was reported when selinexor was used in addition to carfilzomib and dexamethasone [94]. Aciclovir prophylaxis was used due to the inclusion of carfilzomib. Current trial data suggests rates are consistent with heavily-treated relapsed disease status but more data from trials and cohort studies are required to determine if particular patterns of infection emerge.

Venetoclax is a pro-apoptotic BCL-2 targeting agent that has improved outcomes for patients with chronic lymphocytic leukaemia; its use was evaluated in patients with relapsed and refractory myeloma in a recent clinical trial [95]. While all-grade infection rates were similar, and the addition of venetoclax to bortezomib and dexamethasone was associated with higher rates of severe pneumonia, neutropenic fever, sepsis and septic shock [95]. Close to 60% of treatment emergent deaths were associated with infection, mainly around the time of disease progression [95]. As a result, venetoclax, bortezomib and dexamethasone combination treatment had lower overall survival in patients without t(11;14), even though it had longer progression-free survival. Particular patterns of infections were notable, mainly higher rates of influenza, herpes zoster and PJP were reported with venetoclax treated arm [95]. The use of antiviral, antibacterial and PJP prophylaxis was subsequently made mandatory [95]. This study highlights the need for detailed reporting of infectious complications beyond severity and site in large clinical trials.

| Treatment class | Treatment stage | Rates of infection | References |
|---|---|---|---|
| **Immunomodulatory drugs** | | | |
| Thalidomide, Lenalidomide | First-line HCT | Severe infection 15-22% | [20, 62] |
| Thalidomide, Lenalidomide | First line non-HCT | Severe infection 11-13% | [20, 62] |
| Thalidomide, Lenalidomide | Maintenance | All grade infection 50%<br>Severe infection 10% | [20, 62, 64] |
| Thalidomide, Lenalidomide | Relapse/Refractory | Severe infection 7-23% | [20, 62] |
| Pomalidomide | Relapse/Refractory | Severe infection 30% | [65, 66] |
| **Proteasome inhibitor** | | | |
| Bortezomib | First-line HCT | Severe infection 20% | [20] |
| Bortezomib with lenalidomide, dexamethasone | First-line HCT | All grade infection 28%<br>Severe infection 9% | [68] |
| Bortezomib | First line non-HCT | Severe infection 10% | [20] |
| Carfilzomib<br>with lenalidomide or thalidomide, dexamethasone | First-line HCT | All grade infection 74%<br>Severe infection 11-22% | [69, 70] |
| Bortezomib | Relapse/Refractory | Severe infection<br>Pneumonia 8% | [71] |
| Carfilzomib | Relapse/Refractory | Severe infection<br>Pneumonia 8-10% | [71, 72] |
| Ixazomib<br>With lenalidomide, dexamethasone | Relapse/Refractory | All grade URTI 23% | [74] |
| Ixazomib<br>With pomalidomide or bendamustine, dexamethasone | Relapse/Refractory | All grade infection 50-60%<br>Severe infection 14-22% | [75, 76] |
| **Monoclonal antibody** | | | |
| Daratumumab<br>With bortezomib, thalidomide, dexamethasone | First-line HCT | All grade infection 65%<br>Severe infection 22% | [79] |
| Daratumumab<br>With bortezomib, lenalidomide, dexamethasone | First-line HCT<br>Complete single course | All grade infection 91%<br>Severe infection 23% | [80] |
| Daratumumab<br>With bortezomib, melphalan, prednisolone | First-line non HCT | All grade infection 67%<br>Severe infection 23% | [77] |
| Daratumumab | Maintenance | Severe infection 11% | [78] |
| Daratumumab<br>With bortezomib, dexamethasone | Relapse/Refractory | Severe infection 21% | [81] |

*table continues next page*

| Treatment class | Treatment stage | Rates of infection | References |
|---|---|---|---|
| Daratumumab<br>With lenalidomide,<br>dexamethasone | Relapse/Refractory | Severe infection 28% | [82] |
| Daratumumab<br>With pomalidomide,<br>dexamethasone | Relapse/Refractory | All grade infection 76%<br>Severe infection 31% | [67] |
| Isatuximab<br>with pomalidomide,<br>dexamethasone | Relapse/Refractory | All grade URTI 28-42%<br>Severe infection 16-18% | [83, 84] |
| Elotuzumab<br>with lenalidomide,<br>dexamethasone | Relapse/Refractory | All grade infection 81% | [85] |
| Elotuzumab<br>with pomalidomide,<br>dexamethasone | Relapse/Refractory | All grade infection 65%<br>Severe infection 13% | [86] |
| **Drug-antibody conjugate** | | | |
| Belantamab mafadotin<br>mafadotin | Relapsed/refractory | All grade infections 14-23% | [87-89] |
| **Bi-specific antibody therapy** | | | |
| AMG 420 | Relapse/Refractory | All grade infection 33%<br>Severe infection 29% | [90] |
| **BCMA CAR-T** | | | |
| Idecabtagene | Relapse/Refractory | All grade infection 67-75% | [91] |
| **Selective inhibitor of nuclear export** | | | |
| Selinexor<br>with carfilzomib,<br>dexamethasone | Relapse/Refractory | All grade infection 29%<br>Severe infection 24% | [94] |
| **BCL-2** | | | |
| Venetoclax<br>with bortezomib,<br>dexamethasone | Relapse/Refractory | All grade infection 80%<br>Severe infection 28% | [95] |

HCT: haematopoietic stem cell transplant; URTI: upper respiratory tract infection; BCMA: B-cell maturation antigen; BCL-2: B cell lymphoma-2

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

# 4 SCREENING FOR INFECTION

Screening cancer patients for latent and undiagnosed infections prior to the commencement of cancer therapy is considered standard of care [96]. Latent infections such as tuberculosis, strongyloides, and HBV can reactivate during immunosuppression [97-101]. Similarly, the natural history of untreated chronic infections, such as chronic HBV, hepatitis C (HCV) and human immunodeficiency virus (HIV) can accelerate [102-104]. Adverse outcomes can be prevented by early treatment or prophylaxis. Entecavir effectively prevents HBV reactivation [99, 105]. Latent tuberculosis infection (LTBI) treatment prior to, or concurrently with immunosuppression, reduces reactivation risk [106]. Anti-retroviral therapies for HIV and antiviral therapy for HCV improve long-term outcomes [107, 108]. Endemic tropical infections can be successfully eradicated prior to chemotherapy [98]. Recommendations for screening and detection of common latent infections prior to commencement of treatment is outlined in this section and summarised in Table 3.

| Disease | Guidelines Promoting Universal Screening | Guidelines Promoting Risk-Based Screening | Recommendations | Screening tests |
|---|---|---|---|---|
| HBV | ASID[99]<br>ASHM[246]<br>APASL[247]<br>ECIL-5[248] | ASCO[249]<br>AASLD[250] | All MM patients undertaking active treatment | Hepatitis surface antigen (HBsAg), surface antibody (anti-HBsAb) and core antibody (anti-HBcAb)<br>HBV viral load if HBsAg positive and/or anti-HBcAb positive |
| HCV | ECIL-5[248]<br>NCCN[96] | EASL[117]<br>AASLD[251]<br>ASHM[118]<br>CDC[115] | | Hepatitis C core Antibody |
| HIV | CDC[252]<br>NCCN[96]<br>ASHM[122] | | | HIV 1 & 2 Antibody |
| HSV | N/A | N/A | Consider prior to PI-based therapy and autoHCT and in heavily pre-treated myeloma patients | HSV 1/2 IgG |
| VZV | N/A | N/A | | VZV IgG |
| CMV | N/A | N/A | | CMV IgM/IgG |
| Latent TB | ECIL-5[248] | NICE[253]<br>ATS[128] | High-risk patients (TB endemic country or known smear-positive, close-contact), diagnosis with HIV; in consultation with infectious diseases specialist | IGRA (Quantiferon-Gold™) |
| Other tropical pathogens | N/A | Expert group [143] | High risk patients (e.g. country of birth, lived for prolonged periods in region of high prevalence), screening in consultation with infectious diseases specialist | Testing guided by country of birth/risks. Examples include Schistosomiasis serology, Strongylodies serology |

HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HSV: herpes simplex virus; VZV: varicella-zoster virus; CMV: cytomegalovirus; TB: tuberculosis

HBsAg: Hepatitis B surface antigen; anti-HBcAb: anti hepatitis B core antibody; anti-HBsAb: hepatitis B surface antibody; IGRA: interferon gamma release assay

ASID: Australasian Society for Infectious Diseases; ASHM: Australasian Society for HIV, Viral Hepatitis & Sexual Health Medicines; APASL: Asian Pacific Association for the Study of the Liver; ECIL: European Conference on Infections in Leukemia; NCCN: National Comprehensive Cancer Network; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Diseases; ASCO: American Society of Clinical Oncology; CDC: Centres for Disease Control; NICE: National Institute for Health and Care Excellence; ATS: American Thoracic Society

**Table 3: Summary of screening recommendations**

***Hepatitis B Infection***

Since the introduction of novel agents, 5 to 8 percent of myeloma patients with resolved HBV infection (HBsAg negative, Anti-HBcAb positive), without prophylaxis, will experience an HBV reactivation within 12 months of therapy [109]. Universal HBV screening of patients with multiple myeloma is likely advantageous for several reasons. Firstly, it identifies patients who would be missed by targeted screening practices. A recent analysis of screening in 3092 cancer patients across multiple US centres, identified that 7 percent of patients (N=21) diagnosed with HBV infection at the time of cancer diagnosis, had no classical risk factors for HBV [97]. Additionally, screening practices focusing on the likelihood of reactivation increase decision-making complexity for the treating clinician [110]. Finally, universal screening has been shown to reduce reactivation rates following cancer therapies, reducing overall patient morbidity [99, 111]. In 2019, the Australian Society of Infectious Diseases (ASID) endorsed universal HBV screening for all cancer patients [99]. Universal screening is also endorsed by the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM), the Asia Pacific Association for the Study of Liver, and the European Conference of Infections in Leukaemia (ECIL-5) [99]. In line with national recommendations, all myeloma patients should be screened for HBV infection and immunity prior to commencement of active treatment with HBV serology (HBsAg, anti-HBcAb and anti-HBsAb) and HBV viral load testing should be performed if HBsAg positive and/or anti-HBcAb positive. Patients with chronic HBV should be managed in conjunction with an expert in hepatitis management and have routine screening for complications of HBV such as hepatocellular carcinoma.

***Hepatitis C Infection***

Significant contention surrounds the approach to HCV testing in haematology patients. Case reports have identified reactivation of hepatitis C in the context of myeloma therapies, leading to acute liver injury and interruption to therapy [112, 113]. However, meta-analyses have failed to identify a higher proportion of HCV positive patients amongst myeloma cohorts [114]. The Centre for Disease Control recommends universal testing for adults born between 1945 and 1965, as well as patients with risk factors such as incarceration or intravenous drug-use [115]. Overseas guidelines, including ECIL-5 and NCCN, recommend universal HCV screening [96]. Conversely, Australian National Testing Policy, along with the European Association for Society of Liver (EASL) recommend a risk-based approach [104, 116-118]. In a multi-centre analysis of 3092 US oncology patients 2.4 percent had newly diagnosed HCV infection at the time of screening, and 31 percent lacked classical risk factors [97]. A large retrospective analysis of data from MD Anderson Cancer Centre demonstrated a 2.1 percent prevalence of cleared or chronic HCV amongst 13 718 oncology patients [119]. However, 30 percent were outside the birth years recommended by the CDC, and 83 percent of patients lacked risk factors. Prospective studies have demonstrated that combined screening of birth year and risk factors offered higher sensitivity (95 percent) than either factor alone (80% and 68% respectively), but still missed cases and increased decision-making burden for the treating clinicians [120]. Based on the challenges of risk-guided testing, universal screening for HCV with a Hepatitis C antibody (HCV-Ab) is recommended. In the event of a positive result, a qualitative or quantitative (viral load) nucleic acid test (HCV PCR) should be performed to determine active viraemia. Treatment of active hepatitis C should be undertaken in consultation with an expert in hepatitis management and will depend on stage of liver disease and proposed myeloma treatment.

***Human Immunodeficiency Virus (HIV)***

Since 2006, the Centre of Disease Control has recommended HIV testing in all US health-care settings based on the mortality benefit derived from early diagnosis and treatment [121]. This was supported by the National Comprehensive Cancer Network, advocating for HIV testing in anyone undertaking chemotherapy [96]. The Australian National HIV Testing Policy recommends a risk-based approach, with no specific recommendations for oncology populations [122]. However, Australian oncology guidelines recommend HIV testing in HIV-associated malignancies, such as Non-Hodgkin Lymphoma, Kaposi's sarcoma and cervical cancer [123, 124]. Overseas data suggests that HIV screening uptake is typically low (5-18%), with low prevalence of the disease (<2%) [97, 110, 121, 125]. However, patients diagnosed at time of cancer screening were likely to present late, be older, be migrant patients and have multiple barriers to healthcare with high HIV-associated morbidity [125]. Given the high associated morbidity, a prevalence of greater than 0.1% in oncology populations is required to make screening cost effective [102]. A recent Australian study examining HIV screening in haematology and oncology patients at a quaternary referral centre identified a 0.2% HIV prevalence, suggesting cost effectiveness of universal screening [126]. All patients should be screened with a fourth-generation immunoassay that detects anti-HIV 1& 2 antibody and p24 antigen prior to planned commencement of treatment.

***Latent Tuberculosis***

Cancer and cancer therapies are established risk-factors for TB reactivation, but there is no standardized approach to screening for LTBI in cancer patients. The World Health Organization recommends screening high-risk groups in middle- to high-income countries with low background TB incidence [106]. However, a universal approach has not been adopted by the National Institute for Health and Care Excellence, American Thoracic Society and Infectious Diseases Society of America guidelines [127, 128]. These guidelines instead recommend screening in haematological malignancy, due to risk of reactivation with profound immunosuppression, as well as head and neck, and gastric malignancies, due to the compromise of local immune control [127, 129]. Screening studies in US haematology populations report incidences of LTBI between 3 and 8 percent, depending on testing modality and proportion of patients recruited with epidemiological risks [130, 131]. Several small case series have demonstrated increased risk of TB reactivation and progression with cytotoxic regimens [129, 132, 133]. Recent studies suggest that newer immunotherapies, may also be associated with increased TB reactivation [134-137]. Recent data suggests that Australian centres typically under-screen for LTBI in haematology patients, but have identified prevalence rates comparable to the US [126]. Based on availability, the use of interferon-gamma release assays (IGRA) such as Quantiferon-Gold assays for detection of LTBI is recommended. Universal screening for latent TB should be considered. Patients should be assessed for risk factors for LTBI including country of birth, current and previous residence, Australian First Nations peoples [138] and close contact with patients with TB. Positive results should be interpreted in conjunction with infectious diseases colleagues to help exclude active TB.

***Additional Tropical Pathogens***

Endemic tropical pathogens including melioidosis, leishmania, Chagas disease, strongyloidiasis and schistosomiasis, have gained increasing attention as risk of reactivation of latent infection in solid-organ transplants [139-142]. In non-endemic settings, expert groups have recommended screening for strongyloides in patients who are immune suppressed or candidates for immune suppression if they have high or intermediate risks for exposure (country of birth, time spent in an endemic setting)[143]. Formal screening recommendations amongst oncology patients, however, are yet to be formalised. from  In Australia, patients from refugee backgrounds demonstrated a prevalence between 5-8 percent of schistosomiasis, malaria and strongyloidiasis [144]. In addition, strongyloides is endemic in Northern and tropical regions of Australia [145]. Furthermore, a Spanish prospective study screening infection in migrants receiving cancer therapies found 71 percent of patients had at least one latent infection [146]. For patients born or who have lived for prolonged periods in region of high prevalence, screening is recommended in conjunction with infectious diseases consultation.

## Prior to haematopoietic stem cell transplantation

***Varicella Zoster Virus (VZV) / Herpes Simplex Virus (HSV)***

More than 80 percent of myeloma patients demonstrate past exposure to VZV or HSV, with positive IgG demonstrated on serology [147]. As outlined above, the risk of reactivation is highest following autoHCT [42]. Prophylaxis with valaciclovir aciclovir or aciclovir is associated with significantly reduced risk of VZV and HSV reactivation, and is now standard of care for many myeloma regimens; however,  it is most effective when targeted appropriately [96]. Screening for IgG positivity for VZV or HSV may assist to guide need for antiviral prophylaxis during periods of increased risk.

***Cytomegalovirus (CMV)***

Close to 80% of Australian adults have been exposed to CMV and are seropositive (CMV IgG positive)[148]. As discussed above, the incidence of CMV reactivation amongst MM patients largely depends on the method of surveillance, with higher incidence recorded amongst centres pre-emptively measuring CMV viraemia compared to centres auditing end-organ disease [149, 150]. The role of early intervention in CMV viraemia is unclear with overall low rates of end-organ involvement but there are increasing reports of end-organ disease in heavily pre-treated myeloma patients who have experienced multiple lines of therapy, including autologous transplantation [43, 45, 151, 152]. While there is insufficient evidence to recommend routine screening of myeloma patients for CMV seropositivity, CMV serology could be considered prior to HCT and/or prior to commencement of treatment for relapsed or refractory disease, particularly those undergoing CAR-T and bispecific antibody therapy. This would establish a useful baseline in future assessments should patients develop symptoms compatible with CMV reactivation.

***Summary of screening recommendations prior to commencement of myeloma therapy:***

1) Universal screening for HBV with HBsAg, anti-HBcAb and anti-HBsAb serology is recommended prior to commencement of myeloma therapy (Strong recommendation, Level II evidence)
2) Universal screening for HCV with a Hepatitis C antibody is recommended (Moderate recommendation, Level III evidence)
3) Universal screening for HIV with HIV 1 & 2 antibody-p24 combination assay (Moderate recommendation, Level III evidence).
4) Universal screening for latent TB is should be considered. Patients should be assessed for risk factors for LTBI including country of birth, close contact with TB (Strong recommendation, Level II evidence).
5) Screening for endemic tropical pathogens is recommended on the basis of risk factors including country of birth, refugee status and area of residence (Marginal recommendation, Level III evidence)
6) Universal screening for VZV or HSV seropositivity (IgG) is recommended prior to planned HCT to guide need for post-HCT prophylaxis (Moderate recommendation, Level II evidence).
7) 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 recommendation, Level II evidence).

# 5 PREVENTION OF INFECTION

Different strategies are required to reduce the burden of infection in patients with myeloma and need to be appropriately targeted to period of highest risk. Measures include use of antimicrobial prophylaxis, immunoglobulin replacement and vaccination.

***Antibacterial prophylaxis***

Coinciding with commencement of first line treatment, the first 6 months following disease diagnosis is a high-risk period for infection and the target period for several randomised trials of antibacterial prophylaxis [6, 13]. In a small trial conducted during the era of conventional chemotherapy, use of trimethoprim-sulfamethoxazole prophylaxis at a dose of 1 tablet twice a day for first 2 months resulted in lower rates of bacterial and serious bacterial infection compared to observation alone[153]. There was no significant difference in rates of death[153]. In contrast, a subsequent trial involving larger number of patients treated with conventional chemotherapy and use of trimethoprim-sulfamethoxazole or ciprofloxacin prophylaxis for 8 weeks resulted in no significant difference in rates of serious bacterial infection or any infection compared to observation alone[154].

Recently, Drayson et. al. conducted a randomised clinical trial of levofloxacin prophylaxis 500mg daily compared to placebo for a longer period of 12 weeks[155]. Utilising a composite outcome of febrile episode or death within 12 weeks of treatment, an 8% lower rate was observed with the use of levofloxacin prophylaxis mainly driven by lower rates of febrile episodes [155]. While there was a 3% difference in survival at 12 weeks, there was no significant difference in deaths due to infection at 12 weeks or overall survival at 12 months [155]. Interestingly, there was a 35% higher rate of death due to progressive disease in the levofloxacin prophylaxis group and the reasons for this observation remain unclear[155]. Potential negative impact on microbiome and subsequent response to treatment has been raised as a possibility[156].

Unsurprisingly use of levofloxacin prophylaxis resulted in fewer episodes of fever and gram-negative bacterial infection [155]. The trial monitored for emergence of complications such as *Clostridiodes difficile* for a short period of 4 weeks following completion of prophylaxis and noted no difference between the treatment arms[155]. However, use of levofloxacin was not without issue with 100% of the Gram-negative isolates in the prophylaxis group resistant to fluoroquinolone and episodes of drug-related tendonitis[155]. In this study, around 30% of patients received trimethoprim-sulfamethoxazole as *Pneumocystis jirovecii* prophylaxis and its use was independently associated with reduced risk for the primary composite outcome of similar magnitude to use of levofloxacin[155]. In addition, the benefit of levofloxacin prophylaxis was not universal with no benefit seen in patients 65 years and younger, in those undergoing HCT, with higher International Staging Score (ISS) and in patients receiving trimethoprim-sulfamethoxazole[155].

A meta-analysis of these trials confirm non-significantly lower rates of infection within 3 months with the use of fluroquinolone (RR 0.79, $p$=0.049) or trimethoprim-sulfamethoxazole prophylaxis (RR 0.70, $p$=0.45) and no difference in mortality[157]. With the growing threat posed by multi-drug resistant bacteria, antibacterial prophylaxis should be used judiciously and in a calibrated approach. In the absence of clear mortality benefit, routine antibacterial prophylaxis with fluoroquinolones is not recommended during first-line therapy for myeloma. The use of trimethoprim-sulfamethoxazole as PJP prophylaxis could be optimised through daily dosing to confer some concurrent antibacterial benefit based on its pharmacokinetics[158].

The nadir of neutrophils as a result of conditioning chemotherapy for autoHCT results in increased risk for infection, in particular neutropenic fever and BSIs[4, 21]. The benefit of using routine antibacterial prophylaxis during the HCT period remains intensely debated and the need for early recognition and optimal management of sepsis during this high-risk period is highlighted [159]. In observation studies of fluoroquinolone (levofloxacin or ciprofloxacin) prophylaxis in myeloma patients undergoing autoHCT, use of prophylaxis was associated with significantly lower rates of neutropenic fever and BSI especially with gram-negative bacterial infections[160-164]. Unfortunately, this benefit did not translate to better outcomes with no significant difference in mortality rates. The use of prophylaxis was found to lead to the emergence of antibiotic resistant bacteria with 60-90% of isolated gram-negative bacteria resistant to fluoroquinolones and 40% found to be multi-drug resistant[160-164]. Therefore, any short-term benefits is offset by complexity of future management and risks encountered by limited antibiotic treatment options for serious bacterial infection. At this stage, routine use of antibacterial prophylaxis during HCT is not recommended. Its use may be reasonable in patients with a history of recurrent and severe bacterial infections. Outpatient transplant programs may wish to provide patients with antibiotics for pre-emptive emergency use in the setting of sepsis symptoms prior to presentation for acute medical care. This should be in conjunction with an established system to ensure complete work-up for an infective cause and timely access to acute care.

While treatment for relapsed or refractory myeloma is associated with high risk for BSI with poor outcomes, there are no studies evaluating the use of antibacterial prophylaxis for this treatment period [21]. Increasing lines of treatment for episodes of disease progression is a risk factor for infection but the period and duration at-risk is not well defined[6]. Use of trimethoprim-sulfamethoxazole during this period may potentially be of benefit but studies evaluating the use of prevention measures including prophylaxis are required [6]. At this stage, use of antibacterial prophylaxis during treatment for relapsed or refractory myeloma should only be considered based on an individual assessment of future risk for infection. Recommendations for antibacterial prophylaxis are summarised in Table 4.

| Type of prophylaxis | Treatment stage | Recommendation |
|---|---|---|
| **Antibacterial** | | |
| | First line treatment | Not routinely recommended |
| | Autologous HCT | Not routinely recommended |
| | Relapse or refractory | Could be considered in the setting of recurrent severe bacterial infection |
| **Antiviral** | | |
| HSV | Autologous HCT | Prophylaxis recommended<br>Aciclovir 400-800mg BD<br>Valaciclovir 500mg daily to BD<br>Duration 30 days following HCT |
| VZV | Autologous HCT | Prophylaxis recommended<br>Aciclovir 400-800mg BD<br>Valaciclovir 500mg daily to BD<br>Duration 12 months following HCT |
| | Proteasome inhibitor therapy | Prophylaxis recommended<br>Aciclovir 200-400mg BD<br>Valaciclovir 500mg daily<br>During PI therapy and up to 1 month post |
| | Other therapies | Prophylaxis should be considered with the use of elotuzumab<br>Aciclovir 200-400mg BD<br>Valaciclovir 500mg daily<br>Individual assessment of risk including previous episode of zoster, recent prior therapies (e.g. HCT) |
| HBV | Autologous HCT | Chronic HBV<br>Prophylaxis recommended<br>Entecavir 0.5mg daily or<br>Tenofovir 300mg daily<br>Duration 18-24 months following HCT<br>If viral load > 2000 IU/ml at baseline, life-long treatment<br>Resolved HBV<br>Prophylaxis recommended<br>Entecavir 0.5mg daily or<br>Tenofovir 300mg daily<br>Duration 18-24 months following HCT<br>Duration of prophylaxis should be extended if ongoing immune suppression planned |
| | Proteasome inhibitor therapy | Chronic HBV<br>Prophylaxis recommended<br>Entecavir 0.5mg daily or<br>Tenofovir 300mg daily<br>Duration 6-12 months following completion of therapy<br>If viral load > 2000 IU/ml at baseline, life-long treatment<br>Resolved HBV<br>Prophylaxis recommended<br>Entecavir 0.5mg daily or<br>Tenofovir 300mg daily<br>Duration 6-12 months following completion of therapy<br>Duration of prophylaxis should be extended if ongoing immune suppression planned |

| Type of prophylaxis | Treatment stage | Recommendation |
|---|---|---|
| **Antifungal prophylaxis** | | |
| | Autologous HCT | Prophylaxis recommended<br>Fluconazole 400mg daily<br><br>*Pneumocystis jirovecii* pneumonia prophylaxis recommended<br>Trimethoprim-sulfamethoxazole 160/800mg 1 tab/daily<br>Duration 3-6 months following HCT |
| | Corticosteroids | *Pneumocystis jirovecii* pneumonia prophylaxis recommended if more than 16-20mg prednisolone equivalent daily for 4 weeks utilised<br>Trimethoprim-sulfamethoxazole<br>160/800mg 1 tab/daily<br>Duration up to 6 weeks following completion of therapy |
| | Other therapies | Mould active prophylaxis could be considered if prolonged and severe neutropenia anticipated with proposed therapy<br><br>Individual assessment of risk including risk of myelosuppression, use of high-dose corticosteroids, recent prior therapies (e.g. HCT), prior fungal colonisation, previous episode of invasive fungal disease |

HCT: haematopoietic stem cell transplant; HSV: herpes simplex virus; VZV: varicella-zoster virus, HBV: hepatitis B virus

**Table 4: Recommendations for antimicrobial prophylaxis**

***Summary of recommendations for antibacterial prophylaxis:***

1) During first-line therapy, routine antibacterial prophylaxis is not recommended due to absence of clear mortality benefit (Strong recommendation, Level I evidence).
2) During HCT, routine antibacterial prophylaxis is not recommended due to absence of clear mortality benefit. It can be considered in patients with recurrent and severe bacterial infections (Strong recommendation, Level I evidence).
3) During treatment for relapsed/refractory disease, antibacterial prophylaxis should only be considered based on an individual assessment of future risk for infection (Marginal recommendation, Level III evidence).

***Antiviral prophylaxis***

Herpes viruses such as herpes simplex (HSV) and varicella-zoster (VZV) are commonly encountered and establish latency in 60-80% of patients undergoing treatment for haematological malignancy with rates of reactivation of up to 80% for HSV and up to 50% for zoster in the absence of antiviral prophylaxis [50, 165, 166]. Reactivation of latent viruses relates to the immune impact of drugs and treatment modalities integral to the management of patients with myeloma [4]. In particular, depletion of cellular immunity as part of myeloablative conditioning for HCT, selective depletion of viral specific T-cells and disrupted viral antigen processing from proteasome inhibitors results in high risk period for viral reactivation[4, 42].

For herpes simplex, this period of risk appears to be the first 30 days following HCT whilst for herpes zoster the period of risk extends to at least 12 months following HCT [50, 165, 167]. Antiviral prophylaxis with intravenous or oral aciclovir effectively reduce risk of HSV reactivation by 85% in the post HCT period [165, 166]. Different doses of aciclovir and dosing schedules (400-800mg BD to 200mg QID) were utilised in clinical trials for 28-30 days[165, 166]. Rates of HSV reactivation were not significantly different when valaciclovir 500mg daily to BD were utilised instead of aciclovir[50]. Therefore, antiviral prophylaxis with either aciclovir (cumulative daily dose 800-1600mg) or valaciclovir (500mg to 1g daily) is recommended for a period of 30 days following HCT for prevention of HSV reactivation.

However, aciclovir or valaciclovir prophylaxis is also very effective in preventing zoster reactivation[42]. Cumulative incidence of zoster reactivation is 19% following autoHCT [168]. Unsurprisingly cumulative incidence and risk for zoster reactivation varies according to duration of follow-up and duration of antiviral prophylaxis[168]. For a similar follow up period, cumulative incidence of zoster is higher at 15-40% for HCT patients receiving less than 12 months or no prophylaxis compared to 10% or less for patients who receive 12 or more months of antiviral prophylaxis[168]. Commonly used doses of aciclovir and valaciclovir in the HCT setting are 800mg BD and 500mg BD respectively [50, 167, 168]. However, lower doses including aciclovir 400mg daily, 400mg BD and valaciclovir 500mg daily have been utilised effectively (similar zoster reactivation rates) as post-HCT prophylaxis[169-172].

For myeloma patients undergoing autoHCT, use of aciclovir 400mg-800mg BD or valaciclovir 500mg daily or BD is recommended for a period of 12 months following transplant. The potential role of recombinant zoster vaccination for prevention and shortening of duration of prophylaxis is discussed in the vaccination section to follow.

The use of proteasome inhibitor bortezomib is associated with at least double the rate of zoster reactivation and based on common mechanism of action and impact on the cellular immunity, this is likely to be a drug class effect [173]. Antiviral prophylaxis reduces the risk of zoster reactivation in the setting of bortezomib therapy by at least 60%[174]. Low rates of reactivation of between 0-4% have been reported with the use of low dose aciclovir (200-400mg daily) or valaciclovir 500mg daily during duration of bortezomib therapy [50, 174-176]. Prevention of zoster reactivation with the use of aciclovir (200-400mg daily) or valaciclovir (500mg daily) prophylaxis is highly recommended for patients receiving proteasome inhibitor-based treatment regimens for the entire duration of therapy. It would be reasonable to cease prophylaxis 1 month after completion of PI-based therapy. Amongst the new generation therapies, higher rates of zoster reactivation have been reported in clinical trials involving the use of elotuzumab which strongly suggests the concurrent need for specific zoster prophylaxis with this agent [85, 86].

In the absence of prophylaxis, rates of HBV reactivation are up to 50% and 9% for chronic HBV and resolved HBV respectively [48, 49, 51]. HCT, PI and high-dose corticosteroids are associated with higher risk for HBV reactivation and prophylaxis effectively reduces risk and should be considered in the presence of these risk factors[50, 51, 54]. Multi-disciplinary national consensus guidance has been developed for the management of HBV in patients with haematological malignancy[177]. Antiviral prophylaxis with a nucleoside analogue with a high barrier to resistance such as entecavir or tenofovir is strongly recommended for patients with chronic HBV and recommended to continue until 18-24 months following HCT or B-cell depleting therapies [177]. Ongoing immune suppression such as use of consolidative regimens or PI-based regimens for disease progression may require extended use of HBV prophylaxis. Of note, patients with chronic HBV and viral load above 2000 IU/ml at baseline require treatment for HBV utilising the same antivirals regardless of myeloma treatment and the duration is likely to be life-long and be referred to a hepatitis specialist for follow up [50].

For patients with resolved HBV (HBsAg negative, anti-HBcAb positive), prophylaxis is recommended in the setting of HCT and should be considered with the use of PI-based regimens and high dose corticosteroids, especially if HBV surface antibodies (anti-HBsAb) are not present [50, 177]. Prophylaxis should be commenced prior to myeloma therapy and continued until 6-12 months following completion of myeloma treatment (non-HCT) or 18-24 months after HCT[50, 177]. Continuation of prophylaxis should be considered if there is ongoing immune suppression. Serial measurement of HBV viral load and liver function tests every 3-6 months is recommended during duration of prophylaxis[177]. There is insufficient evidence to recommend routine prophylaxis for myeloma patients with resolved HBV managed on new generation therapies (e.g. MoAb) and need for prophylaxis should be assessed taking into account previous types and lines of therapy, cumulative dose of corticosteroids and ongoing risk of immune suppression. Recommendations for antiviral prophylaxis are summarised in Table 4.

***Summary of recommendations for antiviral prophylaxis:***

**Patients undergoing HCT**

1) For prevention of HSV, antiviral prophylaxis is recommended for a period of 30 days following HCT (Strong recommendation, Level I evidence).
2) For prevention of VZV, antiviral prophylaxis is recommended for a period of 12 months following HCT (Strong recommendation, Level I evidence)
3) Patients with chronic HBV should receive prophylaxis with entecavir or tenofovir, which is recommended to continue until 18-24 months following HCT (Strong recommendation, Level II evidence).
4) 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 recommendation, Level I evidence).
5) 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 recommendation, Level II evidence).

**Other periods at risk or receiving at-risk treatments**

1) For prevention of VZV during PI-based therapy, antiviral prophylaxis is recommended until 1-month post-therapy (Strong recommendation, Level II evidence).
2) For prevention of VZV with therapies containing elotuzumab, antiviral prophylaxis is recommended during duration of therapy and for 1-month post-therapy (Moderate recommendation, Level II evidence).
3) 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 recommendation, Level I evidence).
4) 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 recommendation, Level II evidence).

***Antifungal prophylaxis***

In the setting of routine use of anti-yeast prophylaxis during autoHCT and overall low use of anti-mould prophylaxis, IFD rates in patients with myeloma have remained below 6%, even in the era of new generation PI, IMiD and MoAbs[19, 57, 59]. Use of antifungal prophylaxis should be targeted to high-risk periods. Intensive myelosuppression and breakdown of mucosal barriers during HCT remains a key risk period for IFD with Candida BSI [19, 58]. Therefore, the use of fluconazole prophylaxis during the HCT period until neutrophil recovery is recommended. There is insufficient evidence to recommend routine use of antifungal prophylaxis during treatment with other or new generation regimens in the absence of established risk factors. For regimens leading to prolonged and severe neutropenia (<0.5 x $10^9$/L) with concurrent risk factors for IFD such as high cumulative dose of corticosteroids, use of anti-mould prophylaxis could be considered [178]. To determine need and type of antifungal prophylaxis, individual assessment of IFD risk should take into account immune impacts of planned treatment, prior number of lines of therapy, previous episodes of IFD and known colonisation[19, 56, 57, 59].

The epidemiology of IFD in patients with myeloma continues to evolve with the emergence of cryptococcal infection and the absence of established risk factors in patients managed on increasing lines of therapy challenges patient management and targeting of antifungal prophylaxis[59]. Studies to address these gaps in patients with relapsed or refractory disease are vital.

Disease and treatment related factors drive risk for *Pneumocystis jirovecii* pneumonia (PJP) in patients with haematological malignancy[179]. For patients with myeloma, treatment related factors dominate risk for PJP. Cumulative high doses of corticosteroids (20-40mg dexamethasone weekly), the backbone of most myeloma treatment regimens is an established risk factor for PJP. The threshold corticosteroid dose for increased risk appears to be 16-20mg of prednisolone-equivalent daily for 4 or more weeks[179-181]. Therefore, PJP prophylaxis is recommended for treatment regimens that meet this corticosteroid threshold regardless of the specific class of myeloma therapy. Intense immune suppression of cellular immunity associated with conditioning chemotherapy and HCT is also associated with higher risk for PJP in the absence of prophylaxis with the period at risk estimated to be 6 months[180]. The use of prophylaxis is associated with PJP rate of less than 2% with duration of prophylaxis of up to 3 months [155, 182].

Trimethoprim-sulfamethoxazole is effective in reducing risk for PJP and various schedules such as 1 tablet (160/800mg) daily and 2 tablets twice or 3 times per week have been utilised [179]. As the optimal dosing schedule has not been established, daily dosing could be considered as it could potentially offer concurrent anti-bacterial protection based on its pharmacokinetics[158]. Trimethoprim-sulfamethoxazole remains first line agent for PJP prophylaxis but alternative second-line options include dapsone (100mg daily), pentamidine (inhaled, 300mg 4 weekly) and atovaquone (1500mg daily)[179]. Duration of prophylaxis has been suggested to be 6 weeks following completion corticosteroid therapy and 3-6 months following HCT. CD4 cell count guided duration of prophylaxis has been utilised in the HIV setting but its utility in non-HIV patients require further evaluation.

***Summary of antifungal recommendations:***

1) During autoHCT, antifungal prophylaxis with fluconazole is recommended (Moderate recommendation, Level II evidence).
2) With new generation anti-myeloma therapies, routine antifungal prophylaxis is not recommended. Individual risk assessment is recommended (Marginal recommendation, Level III evidence).
3) With regimens causing prolonged and severe neutropenia and other concurrent risk factors for IFD, use of anti-mould prophylaxis could be considered (Marginal recommendation, Level III evidence).
4) Trimethoprim-sulfamethoxazole as PJP prophylaxis is recommended in the setting of prednisolone-equivalent dosing of 16-20mg daily for 4 or more weeks. Prophylaxis during therapy and up to 6 weeks following completion (Strong recommendation, Level II evidence).
5) Trimethoprim-sulfamethoxazole as PJP prophylaxis is recommended in the setting of HCT and continued until 3-6 months following HCT (Strong recommendation, Level II evidence).

***Immunoglobulin replacement***

Secondary immune deficiency with hypogammaglobulinaemia is a feature of myeloma[4]. There are limited number of studies evaluating the use of immunoglobulin replacement in patients with myeloma and most were conducted prior to the use of IMiDs and PI as standard of care[183, 184]. Intravenous immunoglobulin replacement for a period of 6 to 12 months for myeloma patients with IgG levels below the limit of normal or with recurrent infections was associated with lower rates of serious and life-threatening infections but showed no difference in rates of minor infections[183, 185].

In a randomised trial of a 12-month period of IVIG replacement for patients in plateau phase of myeloma during the era of conventional chemotherapy, lower rates of serious infection such as sepsis, meningitis and pneumonia and recurrent infections were reported [184]. Approximately 60% of patients received pneumococcal polysaccharide vaccination and patients who were poor vaccine responders appeared to derive benefit from IVIG replacement[184]. Rate of adverse reaction was higher with IVIG replacement[184]. In a more recent randomised trial, lower annual rates of serious and minor infections were reported with the use of subcutaneous immunoglobulin replacement in patients with IgG < 5g/L in the absence of HCT [186]. Lower annual rates of serious and all infections were noted with the

use of IVIG in hypogammaglobulinaemic patients (IgG <7g/L) treated with daratumumab for a median of 22 months[187]. There were predominantly lower rates of respiratory tract infection with immunoglobulin replacement [184-186]. In contrast, IVIG replacement in the peri-autoHCT period (-30 to +30 days) was not associated with a significant difference in rates of infections of various categories[188].

Overall, use of immunoglobulin replacement should be considered for patients with severe hypogammaglobulinaemia (serum IgG < 4g/L) or hypogammaglobulinaemia (IgG < normal) with at least 1 life threatening infection in a 12-month period, or recurrent (at least 2 in a 6 month period) severe infections requiring more than standard antibiotics in line with National Blood Authority criteria[189].

**Recommendation: Immunoglobulin replacement should be considered for patients with severe hypogammaglobulinaemia (IgG < 4g/L) or hypogammaglobulinaemia (IgG < normal) with at least 1 life threatening in 12 month period or recurrent severe infection (at least 2 in 6 months) (Strong recommendation, Level I evidence).**

# 6 VACCINATION

Whilst encapsulated bacteria such as *S. pneumoniae* now constitute a smaller proportion of serious bacterial infection in patients with myeloma, patients overall remain at higher risk for invasive infection with these pathogens compared to the general population [21, 190]. At disease diagnosis and with first line therapy, the level of protective antibodies against encapsulated bacteria remains significantly lower than healthy controls[191]. The morbidity and mortality from viral respiratory tract infections such as influenza remains high in the era of IMiDs and PI [23]. AutoHCT remains a vital treatment strategy for patients with myeloma and high intensity conditioning chemotherapy and associated slow post-HCT immune recovery is associated with high risk for infection with encapsulated bacteria, reactivation of viral infections and new respiratory tract infections in the first 12 months following HCT [4, 23, 42, 190, 192]. Vaccination is an effective strategy to reduce risk and burden of key infections in patients with myeloma and is recommended regardless of transplant eligibility. Timing of vaccination is guided by consideration of patient, disease and treatment-related factors to ensure optimal response [193]. Recommendations are summarised in Table 5.

Most studies evaluating utility and vaccination schedules in haematology patient groups have utilised primary immune, commonly serological endpoints as surrogate marker for clinical efficacy. These endpoints only offer a glimpse of potential breadth of immune response and more studies are required to improve our understanding of the depth and breadth of immune response to vaccination, to identify new markers that correlate with clinical protection against infection and to evaluate new vaccination strategies to improve outcomes for patients with myeloma.

| Vaccination | Type of vaccine | Timing |
|---|---|---|
| *S. pneumoniae* | | |
| Transplant ineligible patients | PCV 13 followed by PPV 23, at least 8 weeks later | If feasible prior to commencement of treatment or during treatment with IMiDs |
| HCT patients | Three doses of PCV 13 followed by PPV23 | Commence vaccination 6 months following HCT<br>6, 8 and 12 months followed by 24 months following HCT |
| Influenza | | |
| Transplant ineligible patients | Annual vaccination with inactivated influenza vaccine<br>If under 65 years, standard dose QIV IIV<br>If 65 years and above, adjuvant QIV IIV<br>Consider 2 doses | If feasible, vaccinate prior to commencement of therapy |
| HCT patients | Annual vaccination with inactivated influenza vaccine<br>2 standard QIV IIV recommended for first 12 months following HCT<br>Consider 2 doses for subsequent years | Vaccinate 2 or more months following HCT |
| SARS-CoV-2 | | |
| Transplant ineligible patients | Three doses of SARS-CoV-2 vaccine<br>mRNA vaccines in preference as third dose<br>Use, formulation and timing of additional (booster) dose as per national guidance | If feasible, vaccinate prior to commencement of therapy |
| HCT patients | Three doses of SARS-CoV-2 vaccine<br>Use, formulation and timing of additional (booster) dose as per national guidance | Vaccinate 3 or more months following HCT |
| *Zoster* | | |

*table continues next page*

| Vaccination | Type of vaccine | Timing |
|---|---|---|
| Transplant ineligible patients | Two doses, recombinant subunit zoster vaccine | Not available on national immunisation program.<br>1-2 month interval between doses |
| HCT patients | Two doses, recombinant subunit zoster vaccine | Not available on national immunisation program.<br>50-70 days following HCT (median 2 months)<br>1-2 month interval between doses |
| *N. meningitidis* | | |
| Transplant ineligible patients | Two doses, Meningococcal conjugate ACWY vaccine<br>Two doses, Meningococcal B vaccine | If feasible, vaccinate prior to commencement of therapy<br>2 month interval between doses |
| HCT patients | Two doses, Meningococcal conjugate ACWY vaccine<br>Two doses, Meningococcal B vaccine | Commence vaccination 6 months following HCT<br>6 and 8 months following HCT |
| Other vaccines | | |
| HCT patients | 3 doses of *Haemophilus influenzae* B vaccine<br>3 doses of dTP-IPV vaccine | Commence vaccination 6 months following HCT<br>6, 8 and 12 months following HCT |
| | 3 doses of high-dose hepatitis B vaccine | 6, 7 and 12 months following HCT |

PCV13: Pneumococcal conjugate 13 vaccine; PPV23: Pneumococcal polysaccharide 23 vaccine; QIV: Quadrivalent influenza vaccine; IIV: inactivated influenza vaccine; dTP-IPV: diptheria-tetanus-pertussis-inactivated polio vaccine; HCT: haematopoietic stem cell transplantation; IMiD: immunomodulatory drug

**Table 5: Summary of recommendations for vaccination in patients with myeloma**

***Pneumococcal vaccination***

Currently there are two vaccines available for pneumococcal vaccination; pneumococcal conjugate 13 (PCV13) vaccine and pneumococcal polysaccharide 23 (PPV23). Overall the pneumococcal conjugate vaccines (initially 7-valent and now 13-valent) which elicits T-cell dependent responses achieves higher serological and longer lasting memory response compared to the polysaccharide vaccines which trigger predominantly B-cell responses [194-196]. PPV 23 covers more pneumococcal serotypes[197]. Only 40-55% of myeloma patients responded to single dose PPV vaccination alone[184, 198]. The use of PCV13 alone resulted in response rates similar to controls but only one third of myeloma patients maintained this response[199]. Serological response does not appear to be sustained with single dose of either vaccine and is negatively impacted by ongoing therapy [196, 200]. The two vaccines work synergistically when used in combination to improve depth and breadth of immune responses especially following HCT [197, 201].

In a recent study, the use of PCV13 followed by PPV23 4-12 weeks later in largely newly diagnosed patients commencing PI-based therapy was associated with response of 85% and 55% to 1 and 3 antibody subtypes respectively[202]. Highest increase in antibody concentration was seen in patients who received PPV23 more than 30 days following PCV13[202]. In addition, vaccination in the setting of lenalidomide therapy augments PCV-specific humoral and cellular responses[203]. While most studies have relied on serological endpoints, a recent small clinical trial reported significantly lower rates of clinically diagnosed pneumonia with the use 3 doses of PCV13, 1 month apart but optimal timing of vaccination was not defined [204]. Based on available studies, pneumococcal vaccination is recommended for patients with myeloma utilising PCV13 followed by PPV23 at least 1 month later. National vaccination guidelines recommend a 2-month interval between PCV13 and PPV23 [205]. Vaccination prior to commencement of active therapy or during IMiD-based therapy is associated with higher responses and would be an optimal period to target pneumococcal vaccination.

In allo-HCT patients, pivotal trials conducted by Cordonniere et. al. established the timing and pneumococcal vaccination schedule[197, 201, 206]. The use of 3 monthly doses of PCV (7-valent) followed by a dose of PPV23 6 months later was associated with serological response rates of 80%[201]. There was no significant difference in response rates between patients vaccinated at 3 compared to 9 months following HCT[201]. The addition of PPV 23 improved depth of response with conversion of 42% of non-responders and increased breadth with additional response to serotypes not contained in PCV vaccine[201]. A similar schedule with 3 doses of PCV13 commencing 3-6 months after HCT followed by PPV23 6 months later resulted in serological response in over 90% of patients[206].

In an observational study involving myeloma patients on maintenance lenalidomide post-autoHCT, a variable 3-dose PCV13 dosing schedule (1-3 monthly) commencing 12 months post-HCT was associated with a 60% serological response[207]. PPV23 was only utilised in non-responders[207]. There remains a lack of dedicated clinical trials of pneumococcal vaccination in autoHCT patients. As such, findings

from alloHCT trials are extrapolated to autoHCT patients to help guide timing and the vaccination schedule. Overall, studies support pneumococcal vaccination and its commencement 3-6 following autoHCT. A schedule involving 3 doses of PCV13 (monthly) followed by PPV 23 is recommended. Although slight variation in timing of PPV23 exist between various specialist guidelines, Australian vaccination guidelines recommend PCV13 at 6, 8, 12 months post-HCT followed by PPV23 12 months later[205, 208-210].

***Influenza vaccination***

The influenza season in Australia is between the months of May to October, peaks in July and August and every year, the composition of the inactivated influenza vaccine (IIV) is updated to best match the anticipated circulation strains for the respective hemisphere[211, 212]. As such, annual influenza vaccination is required [211].

A single dose of IIV was associated with seroprotection rates of 60-75% for patients with haematological malignancy and higher responses were seen in patients not on treatment [213, 214]. Immune response continues to mature over the next 3 months [213]. In heavily treated patients with myeloma, seroprotection rate of 15-30% were noted [215]. In predominantly alloHCT patients, seroprotection rates were 30-50% depending on the influenza strain and higher level of response was associated with increasing interval between vaccination and HCT [216-218]. Although most studies of influenza vaccination have relied on serological endpoints, some studies have demonstrated lower rates of hospitalisation and respiratory tract infection with influenza vaccination [219, 220].

Different strategies such as use of additional dose, high-dose or adjuvant IIV have been evaluated to improve vaccination responses. In patients with myeloma the use of two doses of high-dose IIV was associated with seroprotection rates to all three influenza strains of 49% after a single dose and 65% after 2 doses. Seroconversion rate was approximately 70% for the influenza virus strains[221]. The same strategy was evaluated against the standard of care approach (single dose of IIV, high dose if 65 years and above) and had significantly higher rates of seroprotection against all 3 influenza strains (87% vs. 63%) and higher rates of seroconversion (55% vs 34%)[222]. Although the rate of seroprotection declined with time, it remained significantly higher at the end of influenza season with the 2 high-dose IIV strategy[222]. Although this strategy is very promising, the high-dose formulation of IIV is not currently available in Australia and it is unclear if substitution with the available adjuvant IIV will result in the same benefit. In addition, use of two doses of adjuvant IIV is not current approved under the national immunisation program. Further evaluation of adjuvant IIV in myeloma patients is required.

In alloHCT patients, use of high-dose or adjuvant IIV have been utilised with mixed success[223, 224]. A dedicated randomised trial of influenza vaccination strategies in autoHCT patients found no difference in seroprotection or seroconversion rates with the use of high-dose followed by standard dose IIV compared to two standard dose IIVs [225]. Regardless of the vaccine type, a two dose IIV strategy resulted in high rates of seroprotection of 76 to 97% across vaccine strains despite vaccination at a median of 2 months following HCT [225]. This study supports the utility of early vaccination in autoHCT patients and the use of two doses of IIV in the first 12 months following HCT. In addition, IMiD was associated with higher odds of seroconversion[225].

Influenza vaccination is highly recommended for patients with myeloma at least 1 month prior to start of influenza season to allow sufficient time for maturation of immune response.

Vaccination of household members is also advisable. In line with national recommendations, patients 65 years and above should receive the adjuvant IIV. The use of two IIV doses could be considered taking into account national immunisation program criteria. In the first 12 months following autoHCT, two doses of IIV is recommended and could commence as early as 2 months following HCT. As seroprotection is not universal, patients should be counselled about the need for testing in the setting of influenza-like illness and use of oseltamivir as post-exposure prophylaxis if there is direct exposure to laboratory confirmed case of influenza.

***SARS-CoV-2 vaccination***

In the last 12 months several vaccines have been developed and proven highly effective in preventing symptomatic COVID-19 infection (70-95%) and severe infection, hospitalisation or deaths (above 90%) in clinical trials and in real-world settings[226-230]. The vaccines that have been ordered or available in Australia are the mRNA-based vaccines, Pfizer BNT162b2 and Moderna mRNA1273, the adenovirus-vectored vaccine Astra-Zeneca ChAdOx1 vaccine and the recombinant subunit protein adjuvanted Novavax NVX-CoV2372 vaccine[231]. The clinical trials of these vaccines have excluded patients with cancer but studies evaluating the immune response to these vaccines have been increasingly reported. Following a single dose of BNT162b2, the rate of humoral response was 25% in elderly myeloma patients but was 56% in patients on median of 1 prior line of therapy with no difference between BNT162b2 or ChAdOx1 vaccines [232, 233]. Response rate was 75% if vaccinated within 12 months of HCT [233].

However, following two doses of COVID-19 vaccine the overall humoral response rate was higher at around 80% with most studies utilising the BNT162b2 vaccine [234-236]. Response rates varied according to type of concurrent myeloma therapy ranging from 50-60% for anti-CD38 based therapy, 80-90% for PI and/or IMiD-based therapies to 100% during lenalidomide maintenance therapy[235, 236]. Overall, higher age, progressive disease or poor response, receipt of active therapy, increasing exposure to novel therapies and certain types of therapy (BCMA CAR-T, anti-CD38) were associated with lower response to COVID-19 vaccination [233-236]. It should be noted that studies published so far have largely reported humoral responses to vaccination which may not correlate with cellular responses and their correlation with clinical efficacy remains undefined [237]. Due to lower immune response rates to two doses compared to normal health cohorts, expert advisory groups have recommended the use of third dose of COVID-19 vaccine with mRNA vaccines in preference as part of the primary vaccination schedule based on data extrapolated from other immune compromised patients[238, 239]. Following a 3-dose primary vaccination course, an additional dose is recommended as a booster dose to combat waning immunity [240]. A repeat of 3 doses is recommended following autoHCT commencing at 3-6 months [238]. Guidance on the need for booster doses, their formulation and timing will continue to evolve with the emergence of new SARS-CoV-2 variants and are continually updated by national expert vaccination

advisory groups. Patients should be counselled about the importance of maintaining general prevention measures and the need for testing in the setting of symptoms to guide use of early treatments.

***Zoster vaccination***

Vaccination utilising live attenuated vaccines are not recommended in the setting of ongoing immune suppression and for 24 months post-HCT due to concerns around immune control of live vaccine-associated virus [205, 208]. Although its use more than 24 months after autoHCT was not associated with significant adverse events, the live zoster vaccine (Zostavax©) is contraindicated for a majority of patients with myeloma [241]. A recombinant subunit zoster vaccine (Shingrix©) is now licensed for use in autoHCT patients for the prevention of zoster. Two doses of the recombinant zoster vaccine separated by a month and given a median of 2 months following autoHCT resulted in significantly lower incidence of zoster (incidence risk ratio of 0.3) with close to half the cumulative incidence (10% vs. 20%) compared to placebo[242]. Patients received less than 6 months of antiviral prophylaxis [242]. Risk reduction was highest in patients not on antiviral prophylaxis post HCT and overall vaccination efficacy was 68% [242]. Immune response was 70% and 90% for humoral and cellular response respectively which declined over 2 years [242]. Rates of adverse events were high with close to 90% of participants reporting injection site pain, 75% systemic symptoms and 20% fever[242].

The duration of immunity, need for booster doses and ongoing antiviral prophylaxis with subsequent PI-based therapy remains unanswered. The recombinant subunit zoster vaccination is effective in reducing risk for zoster reactivation post-autoHCT but is not available under the national immunisation program and at this stage only available via private script with associated cost. Clinicians and transplant centres could consider its use for patients post autoHCT who are intolerant of antiviral prophylaxis or in place of 12 months of antiviral prophylaxis after consideration of clinical benefit and cost to patient and health service.

***Meningococcal and other encapsulated bacteria***

Whilst there are no dedicated trials evaluating meningococcal vaccination in patients with myeloma, they remain at increased risk for meningococcal infection and other encapsulated bacteria due to underlying disease-related immune deficits impacting complement and humoral immunity[4, 8]. The impact of immune deficits following autoHCT is also associated with increased risk for infection with data largely extrapolated from alloHCT [208]. Despite differences in conditioning chemotherapy and expected rate of immune recovery, the recommended vaccination schedule is similar regardless of the type of HCT[208].

Considering high morbidity from meningitis and good vaccine safety profile, vaccination against all 5 strains of *N. meningitidis* and *Haemophilus influenzae* B is recommended.

*Other vaccines*

Myeloma patients post autoHCT are able to respond effectively to diptheria, tetanus and pertussis vaccination (60-76%)[207]. Response to HBV vaccination is poor at 40%[207]. As part of a holistic approach to reducing risk of infection in the post-HCT setting, a program of revaccination against a wide range of vaccine preventable infections (including human papilloma virus if risk factors present) should be adopted. Its incorporation into a dedicated vaccination service can improve uptake and coverage[243]. The proposed schedule, in line with national recommendations are summarised in Table 5 [205].

***Summary of vaccination recommendations:***

1) In unvaccinated patients with myeloma, Pneumococcal vaccination is recommended with PCV13 followed by PPV23 at least 2 months later (Strong recommendation, Level II evidence).
2) Post-HCT, Pneumococcal vaccination is recommended with PCV13 at 6, 8, 12 months followed by PPV23 12 months later (Strong recommendation, Level II evidence).
3) Annual seasonal influenza vaccination is recommended (Strong recommendation, Level II evidence). Patients 65 years and above should receive the adjuvant inactivated influenza vaccine (IIV) while two IIV doses (1 month apart) could be considered taking into account national immunisation program criteria (Strong recommendation, Level I evidence).
4) In the first 12 months following autoHCT, two doses of IIV is recommended (Strong recommendation, Level I evidence).
5) Vaccination against SARS-CoV-2 is recommended with 3-doses of any registered vaccine. Revaccination with 3 doses recommended commencing at 3-6 months post-HCT (Moderate recommendation, Level II evidence).
6) Post-HCT, vaccination with recombinant subunit zoster vaccination should be considered especially if planned duration of antiviral prophylaxis is less than 12 months (Moderate recommendation, Level I evidence).
7) Post-HCT, vaccination for other vaccine preventable infections is recommended (Moderate recommendation, Level II evidence).

## Future directions

While significant advances have been made in the treatment of myeloma in recent years, infection associated morbidity and mortality can nullify benefits. There remain significant gaps in our understanding of the epidemiology of infection with the use of new generation therapies such as BCMA CAR-T and BisAb therapies, defining risk periods and risk factors for infection in patients with relapsed or refractory disease, optimal use (type, duration) of antimicrobial prophylaxis with relapsed or refractory disease and immune correlates of clinical vaccination efficacy need to be addressed through new studies. Concurrent collection and reporting of detailed data on infection episodes as part of myeloma treatment trials will also assist with the management of infection with next generation myeloma therapies.

In addition, new and novel vaccination and prophylaxis strategies should continue to be trialled to reduce the burden of infections in patients with myeloma. Cumulative immune suppression with increasing lines of myeloma treatment increases complexity and uncertainty in infection risk assessment[4, 244]. While pilot studies have been conducted that demonstrate utility of immune profiling[245], personalised infection risk prediction to assist targeting of prevention measures remain a holy grail and require further translational research that can only be achieved through ongoing cross disciplinary collaboration.

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