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ORIGINAL ARTICLE

Unmasking Infection Risks in Multiple Myeloma: Insights from a Retrospective Analysis

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Abstract Multiple myeloma (MM) has witnessed significant therapeutic advancements through the introduction of proteasome inhibitors and immunomodulators, leading to improved treatment outcomes. However, infections remain a formidable challenge for MM patients. The objective of our research is to investigate the factors that can forecast infection risk in MM patients. In pursuit of this, we conducted a thorough retrospective examination of medical records from Kidwai Memorial Institute of Oncology, Bangalore, involving 145 MM patients. Out of the 145 patients analyzed, almost half (47.5%; $n=69$) encountered at least one infection during the course of their disease. Respiratory-related infections were the most prevalent (76.2%), followed by urinary tract infections (10%) and instances of diarrhea (8.8%). Notably, gram-positive bacteria constituted the majority of identified causative organisms, accounting for 48.2% of isolated pathogens, while gram-negative bacteria comprised 37.9% of the isolated organisms. Most infections were observed either at the time of presentation or during the first month (40.5%). Overall mortality during the study period was 4.8% ($n=7$). Infections contributed to 57.1% ($n=4$ out of 7 deaths) of the mortality. Moreover, patients in advanced stages exhibited an elevated risk of infection at presentation. Infections remain a major cause of morbidity and mortality in patients with MM. Nearly half of MM patients experience an episode of infection during treatment.Gram-positive bacteria are the most common pathogens, with respiratory infections being the most common foci. Prompt identification and treatment of infections is essential, but can be challenging due to atypical or absent symptoms. Antibacterial prophylaxis is an important preventive strategy, but further research is needed to develop innovative approaches to infection prevention and targeted therapeutic interventions. We must strive to develop innovative approaches to infection prevention in MM patients. Also we need to advance our understanding of the interplay between infections and MM to improve quality of care and outcomes for these individuals. By addressing these challenges, we can aspire to offer MM patients a brighter and healthier future.

Keywords Multiple Myeloma · Respiratory Infections · Risks and Infections

Abbreviations

MM	Multiple myeloma
LDH	Lactate dehydrogenase
ICU	Intensive care unit

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NDDM	Newly diagnosed multiple myeloma
R ISS	Revised international staging system
AKI	Acute kidney injury
MRSA	Methicillin resistent staphylococcus aureus
IMid	Immunomodulators
PI	Proteasome inhibitors
ONJ	Osteonecrosis jaw
UTI	Urinary tract infections
IMWG	International myeloma working group
CART	Chimeric antigen receptor therapy
EHA ESMO	European hematology association /European society of medical oncology

Introduction

Multiple myeloma (MM) has experienced substantial advancements in their treatment outcomes with the introduction of various new therapeutic agents [1]. Till date the backbone of treatment remains proteasome inhibitors and immunomodulators. Since the advent of these molecules and newer agents, it has become a chronic disease with multiple remissions and relapses. However, infections pose a significant challenge for these patients, leading to increased morbidity and mortality rates. In fact, 50% of early deaths among MM patients have been linked to infections. The increased incidence of infections can be attributed to a combination of patient-related factors such as age and comorbidities, disease-specific issues including disease burden and the inherent immunoparesis associated with MM, as well as treatment-related factors such as the use of novel agents, immunomodulatory drugs, and steroids. All these factors collectively contribute to the heightened vulnerability of MM patients to infectious complications. Our research aims to investigate the factors that predict infection risk in MM patients and emphasize the importance of anti-infective prophylaxis in preventing infections. We examined both clinical and laboratory parameters associated with infectious complications in MM patients. Strategies must be developed to prevent infections, which can ultimately improve the prognosis for these patients. We conducted this study to determine patterns, risks, and outcomes of infections in these patients.

Patients, Materials and Methods

Place of Study

The study was conducted at Kidwai Memorial Institute of Oncology,a tertiary care centre at Bangalore, Karnataka.

Sample Size and Study Population

A comprehensive retrospective review was conducted on the medical records of 145 patients diagnosed with multiple myeloma (who had not undergone stem cell transplant, ineligible or refused) who were treated at Kidwai Memorial Institute of Oncology, Bangalore.

Study Duration

January 2020 to December 2022.

Aims and Objective

1. Study the incidence of infections in patients of multiple myeloma (who did not undergo stem cell transplant)

Study Method and Tools

The collected data encompassed demographic information of the patients including age, gender, existing health conditions, and performance status. Laboratory parameters including Hemoglobin levels, Lactate Dehydrogenase (LDH), Serum Albumin, Serum Creatinine, Serum Calcium, and Revised International Staging System (R-ISS) stage were recorded. Records of the treatment received, agents used (immunomodulators, proteasome inhibitors, steroids, cyclophosphamide, anti CD38 antibodies), duration of treatment was captured. In addition, records of infection events, timing, site of infection and clinical presentations and outcome of these infections in form of hospital admission, intensive care unit (ICU) admission, organisms isolated during these episodes, and various laboratory parameters were meticulously reviewed.

The definition of an infection for this study was based on any microbiologically confirmed infection, evidence of infection from imaging studies, or any incident of fever (oral temperature > 37 °C) with or without associated clinical symptoms such as cough, dysuria, diarrhea, or abscess formation.

Statistical Analysis

Data were entered in excel sheet and calculations by various descriptive and inferential statistics were done using SPSS software version. We utilized descriptive statistics to quantify the overall rate of infection incidents and to understand the temporal distribution of these events. By calculating the proportion of patients who experienced infections during different time periods, we were able to discern patterns in the timing of these infections. Additionally, the incidence of specific infection sites and the spread of causative pathogens

were assessed using frequency distributions. To investigate potential relationships, we used inferential statistical tests like the chi-square test. These tests helped us to explore potential links between infection rates and various factors, including LDH and hemoglobin levels, as well as patient age. Univariate analysis was performed with occurrence of infectious episode.

Through this statistical analysis, we gained crucial insights into the prevalence, timing, and properties of infections in multiple myeloma patients. This information significantly enhances our understanding of the epidemiology of infections within this patient population.

Results

Patient Characteristics

Our analysis included a total of 145 patients, encompassing both newly diagnosed multiple myeloma (NDMM) and those with relapsed myeloma. The median follow up time of the patients was 14.1 months (2–23.1 months) from the time of diagnosis. The majority, or 63.3% ($n=91$), were male, with a median age of 54 years. Most patients (93.1%; $n=134$) exhibited bone involvement, while anemia was present in 53.8% ($n=78$) of the patients. Renal involvement was observed in 42.1% ($n=61$) of the cases, and hypercalcemia in 23.4% ($n=33$). With regards to the type of myeloma, 41.4% ($n=60$) had IgG type, 13.8% ($n=20$) had IgA type, and 18% ($n=26$) presented with light chain disease. Nearly half of the patients (47.3%; $n=69$) were classified as R ISS stage I and II, while the remaining (52.7%; $n=76$) were classified as R ISS stage III.

Routine antiviral prophylaxis with Aciclovir was used for all patients. For patients in whom high dose steroids was used, additionally prophylaxis for pneumocystis jirovecii pneumonia was given.

An overview on patient characteristics is shown in Table 1.

Table 1 Patient characteristics

Variable, *n*%	Total
Total number of patients	145
Age (median, range): < 60	65.5 (94)
Age (median, range): ≥ 60	34.4 (51)
Sex: Male	63% (91)
Sex: Female	37% (53)
Myeloma isotype	
IgG	41.4% (60)
IgA	13.8% (20)
Free light chain	18% (26)

Infection Episodes and Pattern of Infections

Out of the 145 multiple myeloma patients studied, nearly half (47.5%; $n=69$) encountered at least one infection during the course of their disease, overall 102 recorded infection events. Infections were microbiologically confirmed in 60.6% of these instances. For the rest of the patients, there was clinical suspicion of infection, but cultures did not yield positive results.

The most prevalent infections were respiratory-related (76.2%), followed by urinary tract infections (10%), diarrhea (8.8%), soft tissue infections (2.9%), and bloodstream infections (2.1%). Additional clinical manifestations included mastoiditis, cellulitis, and gluteal abscess. The distribution is shown in Fig. 1.

Pathogens Causing Infection

The analysis of the causative organisms revealed that gram-positive bacteria (48.2%) were the most commonly isolated, followed by gram-negative bacteria (37.9%) and Candida/fungal hyphae (13.7%). The pathogens identified

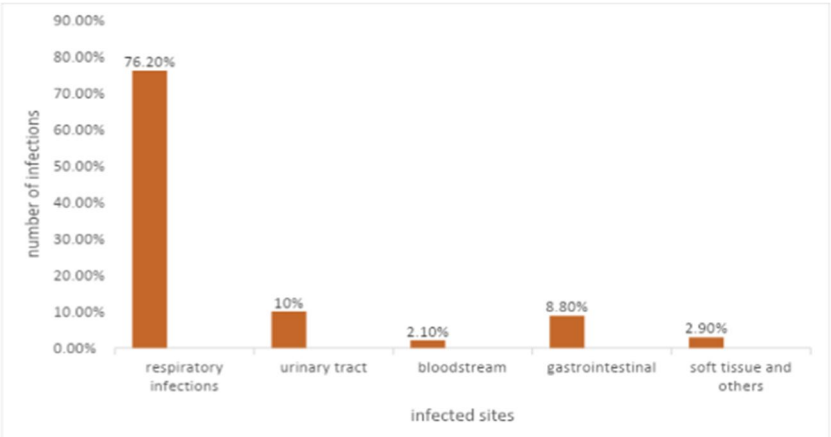

Fig. 1 Distribution of infected sites in patients with multiple myeloma

encompassed beta-hemolytic streptococci, MRSA, H. Influenza, K. pneumoniae, E. coli, A. baumannii, along with a single case of tuberculosis reactivation. In our patient cohort, there were no documented instances of viral infections.

One individual within the study group died due to sepsis after an extended stay in the Intensive Care Unit (ICU). This patient had MRSA-positive sputum, was diagnosed with sepsis, and experienced acute kidney injury (AKI) that necessitated dialysis.

Infection Timeline

Most infections were observed either at the time of presentation or during the first month (40.5%), succeeded by the second month (10.14%), third month (8.6%), and fourth month (7.2%). Infections that occurred beyond the five-month mark accounted for 21.4% of cases. The distribution is shown in Fig. 2.

Factors Influencing Risk of Infection

In our univariate analysis (Table 1), we identified several factors linked with an increased risk of infections, including age, disease stage, LDH levels, hemoglobin level, and hypoalbuminemia.

In our patient cohort, 42.8% ($n=38$ out of 91 male patients in the cohort) of the male patients experienced at least one infection, compared to 81.2% (43 out of 53 female patients) of female patients. However, this gender difference was not statistically significant ($p=0.07$).

We found that patients aged over 60 years were more prone to infection episodes. Infections occurred in 42.5% ($n=40$) of patients aged under 60, compared to 58% ($n=29$) of those aged over 60, a difference that was statistically significant ($p=0.02$).

Patients in stage III of the disease had a significantly higher number of infectious events compared to those in stages I/II, with 52.7% ($n=76$) in stage III and 47.3% ($n=69$) in stages I/II.

LDH levels, indicative of disease burden, showed a significant correlation with the risk of infectious complications in our study ($p=0.007$). High LDH levels represent a high-risk disease as per R ISS classification.

Further, a low haemoglobin level was associated with an increased incidence of infections, with 84.7% ($n=66$) of infections occurring in patients with low haemoglobin compared to 68.3% ($n=45$) in patients with haemoglobin levels above 10. This difference was statistically significant ($p=0.014$).

Hypoalbuminemia also significantly increased the risk of infections, with an infection incidence of 81.1% (73 out of 90 patients with hypoalbuminemia) in patients with hypoalbuminemia versus 69.3% (38 out of 55 patients without hypoalbuminemia) in patients without it ($p=0.076$).

We found no significant association between infection risk and hypercalcemia, renal function abnormalities, or the type of heavy chain or light chain involvement.

Majority of the patients received triplet regimen consisting of PI, IMiDs and steroids. Among patients who experienced infectious complicatins, 53.6% ($n=77$) received PI and IMiD-based chemotherapy, 5.7% ($n=8$) received only IMiD and steroids, and 36.2% ($n=52$) received cyclophosphamide and PI-based therapy. We could not establish a significant association between any class of drugs and the occurrence of infection.

Table 2 depicts the univariate analysis of clinical and treatment factors with risk of infection in patients with multiple myeloma.

Mortality

Overall mortality in our study group patients was 4.8% ($n=7$). Out of 7 patients, 4 patients died of sepsis; with repiratory infection being the cause of sepsis in 3 patients

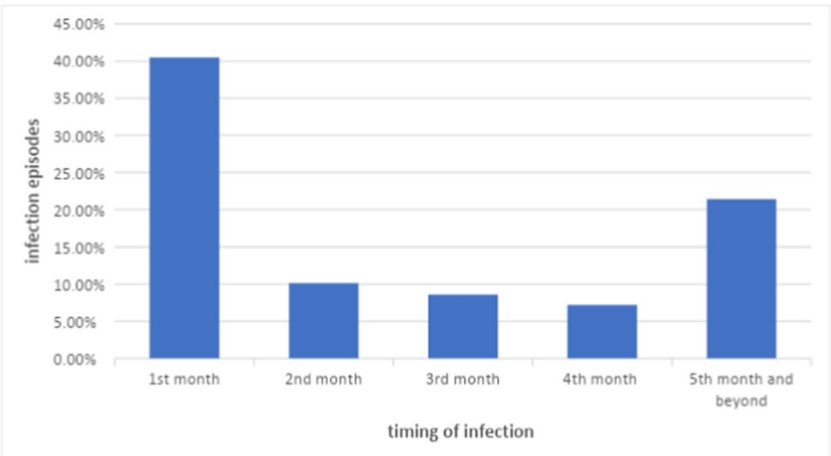

Fig. 2 Timing of Infections at presentation and beyond

Table 2 Univariate analysis of clinical and treatment factors with risk of infection in patients with multiple myeloma

Factors	Number	Group with infection	Group without infection	Univariate	
				Chi-square	*P*
Total number	145	47.5% (69)	52.5 (76)	3.2	0.07
Male	63% (91)	42.8% (38)	57.2% (53)		
Female	37% (53)	81.2% (43)	18.8% (10)		
Age				5.12	0.02
< 60	65.5% (95)	42.5% (40)	57.8% (55)		
≥ 60	34.4% (50)	58% (29)	42% (21)		
LDH				11.3431	0.007
≥ 210	37.9% ($n=55$)	65.4% (36)	34.6% (19)		
< 210	62.06%($n=90$)	36.6% (33)	63.4% (57)		
Type				0.67	0.880
lgG	41.4% (60)	70% (42)	30% (18)		
lgA	13.8% (20)	71.1% (14)	28.9% (6)		
Light chain	18% (26)	80% (20)	20% (6)		
Non-secretory	1.4% (2)	50% (1)	50%(1)		
Stage				16.9	0.0038
I/II	47.3% (69)	28.9% (20)	71.1%(48)		
III	52.7% (76)	64.4% (49)	35.6% (28)		
Hb				6.09	0.014
< 10	54.1% (78)	84.7% (66)	15.3% (12)		
≥ 10	45.9 (67)	68.3% (45)	31.7(22)		
Albumin				3.155	0.076
< 3.5	62.06% (90)	81.1% (73)	18.9% (17)		
≥ 3.5	37.94% (55)	69.3% (38)	30.6% (17)		
S.Creatinine				0.450	0.502
< 1.2	57.5% (84)	76.9% (65)	23.1(19)		
≥ 1.3	42.5 (61)	81.8% (50)	18.2% (11)		
S. Calcium				0.651	0.420
< 11	76.7% (111)	77.2% (85)	22.8% (26)		
≥ 11	23.3% (34)	91.7% (31)	8.3% (3)		

and one individual within the study group died due to sepsis after an extended stay in the Intensive Care Unit (ICU). This patient had MRSA-positive sputum, was diagnosed with sepsis, and experienced acute kidney injury (AKI) that necessitated dialysis. The other 3 deaths were attributed to cardiac event and AKI at diagnosis. So infections contributed to 57.1% of the overall mortality.

Discussion

Dealing with infections is a significant aspect of managing multiple myeloma patients, as they significantly contribute to increasing rates of morbidity and mortality. A study by Augustson et al. found that 10% of these patients die prematurely due to infections, even before they undergo definitive treatment [2]. Multiple myeloma patients are more prone to infections—around seven times more likely for bacterial infections and ten times for viral ones, as per a study by Blimark et al. [3, 4]. This research sought to explore the range and epidemiology of infections in multiple myeloma patients, offering insights into the timing, causative organisms, focus, and associated factors. The results provide valuable information about the clinical pattern and range of infections in multiple myeloma patients.

Nearly half (47.5%) of the multiple myeloma patients experienced at least one infection during their disease course, with 69 out of 145 patients affected. Respiratory tract infections were the most common type of infection, accounting for 76.2% of cases. This aligns with existing studies which highlight the propensity of multiple myeloma patients towards respiratory infections due to compromised immune function and respiratory defenses [5].

Urinary tract infections (UTIs), being the second most common infection, affected 10% of patients. UTIs are a well-known issue in multiple myeloma patients, often linked to urinary tract obstruction, catheterization, or immunosuppression. Early diagnosis and treatment of UTIs in this group

are vital to prevent further complications like pyelonephritis and sepsis.

The infection timeline showed a high proportion of infections occurring at presentation or during the first month (40.5%), indicating the vulnerability of newly diagnosed multiple myeloma patients. This early susceptibility could be due to disease-related immune dysfunction and the effects of initial treatments [6]. Infections beyond the first month remained a concern, underlining the need for continuous vigilance and preventive measures throughout the disease course. The risk of infection tends to decrease with increasing duration, partly due to immune recovery after start of therapy [7].

The identified causative organisms in this study predominantly consisted of gram-positive bacteria, accounting for 48.2% of isolated pathogens. This is consistent with prior studies reporting a higher incidence of gram-positive infections in multiple myeloma patients, including species like beta-hemolytic streptococci and methicillin-resistant Staphylococcus aureus (MRSA) [8, 9]. The prevalence of gram-positive infections emphasizes the importance of suitable empiric antibiotic therapy targeting these organisms.

Gram-negative bacteria made up 37.9% of the isolated organisms, highlighting their role in causing infections in multiple myeloma patients. Notable among the identified gram-negative species were H. Influenza, K. pneumoniae, and E. coli. The existence of gram-negative infections underscores the necessity for broad-spectrum antibiotic coverage to effectively manage infections in this patient group.

Our study found that fungal infections, notably those caused by Candida species and fungal hyphae, occurred in 13.7% of the cases. This highlights the vulnerability of multiple myeloma patients to such pathogens due to weakened immune defenses, extensive use of broad-spectrum antibiotics, and long-term immunosuppression. Early detection and timely antifungal treatment are vital for managing these infections and reducing related morbidity and mortality. One patient in our group experienced jaw osteonecrosis (ONJ) complicated by mucor mycosis, which was managed conservatively.

An intriguing case in our study involved a multiple myeloma patient who experienced a reactivation of tuberculosis. Such reactivation is a known complication in immunocompromised individuals, and multiple myeloma patients are at heightened risk due to disease-related immunosuppression and the use of immunomodulatory agents [10]. Therefore, vigilance for tuberculosis in endemic areas and implementing appropriate prophylactic measures are crucial in managing multiple myeloma patients.

Infection related mortality was seen in 2.7% patients with overall mortality being 4.8%. 57.1% of the deaths were attributed to infections. In a Danish study, 50.9% of the deaths were attributed to infections. Juan et al., in a retrospective study observed infections as a cause of death in 46.4% newly diagnosed MM patients compared to those that did not have infections.

No viral infections were recorded in our study, possibly due to the routine use of antiviral prophylaxis in all our patients treated with PI-based therapy. Previous studies have documented a very high incidence of viral infections, with the APEX study showing an increased incidence of herpes zoster virus infection in patients on Bortezomib therapy [11]. A study conducted by Lim et al. found a very high incidence 58% cases who were hospitalised and 17.2% cases had ICU admission among these [12].

In terms of therapy type, we found no significant association between chemotherapy regimen and occurrence of infections. Brioli et al. concluded that use of IMiDs and PIs were not associated with a significantly increased risk of infection (1). In a recent study, Lim et al. reported that use of PIs-based therapy and increasing lines of therapy (> 4) were independently associated with an increased risk of infection. However, IMiDs-based therapy was not associated with an increased risk.

Despite conflicting results from previous studies regarding the risk of infections with the use of IMiDs and PIs, our study couldn't establish a significant correlation.

Our study identified significant associations between the incidence of infection and laboratory parameters such as LDH, haemoglobin, and patient age. Elevated LDH levels have been linked to aggressive disease and a higher risk of infections in multiple myeloma patients. Low haemoglobin levels can indicate disease-related bone marrow suppression, leading to compromised immune function and increased infection susceptibility. Furthermore, older age is a known risk factor for infections due to immune senescence and comorbidities.

Patients in advanced stages were at increased risk of infection at presentation. Our findings align with previous studies showing a statistically significant difference in the incidence of infections in patients with R ISS III versus R ISS stage I/II.

Vesol et al. conducted a study on the role of prophylaxis for infection for newly diagnosed multiple myeloma. The study emphasized the use of prophylactic antibiotics (3 arm study with ciprofloxacin vs cotrimoxazole vs observation) for the first two months of treatment in myeloma patients. They concluded that routine use of prophylactic antibiotics should not be mandated as rate and risk of infections was comparable in patients receiving or not receiving antibiotics [13].

A phase III TEAMM study performed on 977 patients with NDMM showed that addition of prophylactic levofloxacin during the first 12 weeks of therapy significantly reduced febrile episodes and deaths compared with placebo without increasing health care-associated infections [14].

Prophylactic measures to prevent anticipated infections can significantly decrease morbidity and mortality. We routinely follow antimicrobial prophylaxis with acyclovir in all patients planned for proteasome inhibitor therapy, and cotrimoxazole in patients receiving high-dose steroids.

Recommendations for infection prevention have been laid by IMWG [15] and EHA ESMO [16]. Both stress on the role of antibacterial, antiviral prophylaxis. The prophylactic use of levofloxacin is now incorporated in NCCN guidelines (level 2A). Aciclovir prophylaxis is indicated for seropositive herpes simplex virus and varicella zoster virus. It is also indicated for patients receiving proteasome inhibitors or targeted monoclonal antibodies (NCCN level 1). Pneumocystis jiroveccii prophylaxis is indicated for patients with relapsed /refractory myeloma, and those receiving high dose dexamethasone. Also recommended is vaccination, protection is best achieved when given in earlier stages. Use of immunoglobulins is reserved for situations like life threatening infections or an IgG concentration below 400 mg/dl.

EHA ESMO recommend the use of levofloxacin prophylaxis during the first 3 months of initiation of therapy, especially in patients receiving lenalidomide or pomalidomide, or in patients at high risk of infections (previous serious infections or neutropenia). Influenza, Varicella zoster (inactivated vaccine) and pneumococcal vaccinations are recommended, while acyclovir or valacyclovir for Herpes zoster virus prophylaxis is recommended for patients receiving PI-based and daratumumab-based therapies. Intravenous IgG prophylaxis is not routinely recommended although highly recommended in patients receiving CAR-T cells, however they recommend it to be used in patients with low IgG levels (< 400-500 mg IgG) and atleast two severe infections requiring hospitalization during the last year.

Despite the insights from this study, it's important to consider its limitations, including its retrospective design and potential selection bias. The study also focused on a specific patient population at a single center, limiting its generalizability. Future work could involve prospective multicenter studies with larger sample sizes to validate and expand upon these findings.

Conclusion

The management of infections in patients with multiple myeloma represents a formidable hurdle, significantly impacting their overall well-being and survival rates. Notably, respiratory and urinary tract infections emerge as the most prevalent culprits in this vulnerable population, often stemming from gram-positive bacteria. It is imperative to underscore the paramount importance of promptly identifying these infections, initiating swift and tailored treatment strategies, and implementing proactive preventive measures to mitigate their adverse consequences.

We need to identify and give adequate antibacterial prophylaxis to the patients at high risk of infections to prevent morbidity and mortality associated with infections.

Moreover, the existing body of knowledge emphasizes the pressing need for further research endeavors in this domain. These future studies should delve into innovative approaches for infection prevention and explore targeted therapeutic interventions to effectively reduce the infection-related risks faced by multiple myeloma patients. By continuing to advance our understanding of this intricate interplay between infections and multiple myeloma, we can aspire to enhance the quality of care and outcomes for these individuals, ultimately offering them a brighter and healthier future.

Clinical Practice Points

Nearly half of the patients with MM experience an episode of infection during the course of their treatment.

Infections from gram positive organisms are the most common type with respiratory infections being the most common foci of infection.

This study underscores the importance of antibacterial, antiviral prophylaxis in patients of MM treated with proteasome inhibitors and immunomodulating agents.

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Authors' Contributions LAJ and SKC contributed to the conception of the study. LAJ, SB and SKC were responsible for the acquisition. SKC, LKN, RAH, RLK, SS drafted the work. AH, VBM performed the statistical analysis. LAJ and SBMC substantively revised it. All authors have read and approved the manuscript.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations Ethics approval and consent to participate obtained from Kidwai Memorial Institute of Oncology Medical Ethics Committee: No. KMIO/MEC/011/24.08.2021. Written informed consent was obtained from all the participants.

Consent for Publication Not applicable.

Competing Interests The authors declare that they have no competing interests.

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